

# World Journal of *Cardiology*

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## Endothelial progenitor cells: Exploring the pleiotropic effects of statins

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### Abstract

Statins have become a cornerstone of risk modification for ischaemic heart disease patients. A number of studies have shown that they are effective and safe.

However studies have observed an early benefit in terms of a reduction in recurrent infarct and or death after a myocardial infarction, prior to any significant change in lipid profile. Therefore, pleiotropic mechanisms, other than lowering lipid profile alone, must account for this effect. One such proposed pleiotropic mechanism is the ability of statins to augment both number and function of endothelial progenitor cells. The ability to augment repair and maintenance of a functioning endothelium may have profound beneficial effect on vascular repair and potentially a positive impact on clinical outcomes in patients with cardiovascular disease. The following literature review will discuss issues surrounding endothelial progenitor cell (EPC) identification, role in vascular repair, factors affecting EPC numbers, the role of statins in current medical practice and their effects on EPC number.

**Key words:** Statins; Endothelial progenitor cells; Pleiotropic effects; Ischaemic heart disease; Pleiotropic mechanisms

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**Core tip:** Statin therapy is a cornerstone of current management in coronary artery disease. Conventional thinking of stain therapy is for reduction of low-density lipoproteins. However a number of studies have observed an early benefit prior to any significant change in lipid profile. Therefore alternative pleiotropic mechanisms to account for this have been proposed. One such proposed mechanism is the ability of statins to augment both number and function of endothelial progenitor cells (EPCs). The following literature review discusses issues surrounding EPC identification, role in vascular repair, the role of statins in current medical practice and their effects on EPCs.

Sandhu K, Mamas M, Butler R. Endothelial progenitor cells: Exploring the pleiotropic effects of statins. *World J Cardiol*

## INTRODUCTION

The maintenance of endothelial integrity is essential for the preservation of a healthy vasculature<sup>[1]</sup>. This integrity results from a balance between on-going endothelial damage and the rate of vascular repair. Disruption of endothelial integrity or impairment of endothelial repair mechanisms is a central step in both the initiation and progression of atherosclerosis<sup>[2]</sup>. Endothelial repair is dependent on undifferentiated cells migrating to sites of vascular injury<sup>[3-5]</sup> then differentiating into mature endothelial cells<sup>[6-13]</sup>. These undifferentiated cells are called endothelial progenitor cells (EPCs) have a central role in vascular repair by virtue of their ability to proliferate, migrate to site of vascular injury and then differentiate into mature vascular endothelium<sup>[13,14]</sup>. EPCs perpetuate this cycle by secreting pro-angiogenic cytokines<sup>[15]</sup>.

Statins form the corner stone of treatment of coronary artery disease. The safety and efficacy of statins in reducing cardiac events by decreasing serum LDL-cholesterol has been well described<sup>[16-18]</sup>. Recently however studies have shown the early beneficial effect of statins occurs before any significant change in lipid profile. This led to the hypothesis that cardiovascular benefits of statins may occur *via* alternative mechanisms other than reduction of LDL-cholesterol alone<sup>[19,20]</sup>. One such proposed mechanism is the ability of statins to augment both number and function of EPCs.

The following literature review discusses issues surrounding EPC identification, role in vascular repair, factors affecting EPC numbers, the role of statins in current medical practice and their effects on EPC number.

## RESEARCH AND LITERATURE

We performed a review of various studies within the literature available on endothelial progenitor cell and statins. The authors searched various databases (EMBASE, OVID, PubMed) using the keywords: "Endothelial progenitor cells", "statin", "pleiotropic effects". We studied the various publications that we obtained from the search results. Full text manuscripts were obtained. We only included papers in the English language.

## EPCS

Cellular identification and staging of differentiation has been made possible by specific surface receptors called epitopes that allow immunophenotyping. This

process allows identification of subset of cellular surface molecule termed cluster of differentiation (CD). Cellular subtypes may be defined by the presence or absence of a particular CD molecule. Therefore "CD" may be "+ "or "-" denoting either presence or absence of a particular CD, and is used to describe stem cells rather than fully differentiated cell types. Certain cell types may have variable CD marker expression during maturation for example, and therefore classed as bright (high), mid (mid) or dim (low) denoting intensity of expression<sup>[21,22]</sup>.

Vascular repair had previously been thought to be due to migration and proliferation of fully differentiated endothelial cells, in a process called angiogenesis<sup>[23]</sup>. Asahara *et al*<sup>[24]</sup> identified putative cells with cell surface marker CD34<sup>+</sup>, alternately named kinase insert domain receptor (KDR/VEGFR) markers capable of differentiating into endothelial cells both *in vitro* and *in vivo*<sup>[24-26]</sup>. Subsequent studies recognised that in fact undifferentiated cells subsequently termed EPCs migrated to sites of neovascularization and then differentiate into endothelial cells<sup>[24,26]</sup> in a process called vasculogenesis<sup>[27]</sup>. EPCs are derived from pluripotential stem cells within the bone marrow. These then evolve into mature endothelial cells<sup>[24]</sup> accounting for only 0.001%-0.0001% of peripheral blood cells in an unstressed state<sup>[28]</sup>. Circulating EPCs may be isolated from bone marrow or the circulation as mononuclear cells<sup>[24,29,30]</sup>, expressing a variety of endothelial surface markers<sup>[31]</sup>. However, there currently remains a lack of consensus on phenotypic and functional definition of endothelial precursor cells<sup>[32,33]</sup>.

EPCs are a diverse group of cells of different lineages that have angiogenic potential, but are not always necessarily able to differentiate into functional endothelial cells as would be suggested from their name<sup>[32]</sup>. EPCs are derived from CD34<sup>+</sup> hematopoietic progenitor cells<sup>[6,24,29,31]</sup>, with the subset of EPCs characterized by co-expression of endothelial marker proteins<sup>[6,29,31]</sup>. Studies have identified 3 markers associated with early functional EPCs including CD133, CD34, and the vascular endothelial growth factor receptor-2 (VEGFR-2) also known as kinase insert domain receptor (KDR, Flk-1 or CD309)<sup>[7,31]</sup>. Therefore EPCs express markers of both hematopoietic stem cells (CD34 and CD133) and endothelial cells (CD146, vWF, and VEGFR2)<sup>[26,28,29,31,34-37]</sup>. The presence of certain cell surface markers are depend on the stage of maturations of the EPC. For example the cell surface marker CD133, a 120-kDa trans-membrane polypeptide, is expressed on bone marrow derived hematopoietic stem and progenitor cells in peripheral blood<sup>[37]</sup>. The expression of CD133 on EPCs declines during maturation within the peripheral circulation. Currently there remains some uncertainty as to when EPCs lose the CD133 surface marker, whether during transmigration from bone marrow to circulation or later whilst in the peripheral blood system<sup>[38]</sup>. Nevertheless the loss of CD133 represents the transformation into more mature EPCs that are endothelial-like cells<sup>[37]</sup>.

**Table 1** Table to show cell markers during development of endothelial progenitor cell

	Endothelial progenitor cells		
	Bone marrow	Circulation	
		Early EPCs	Mature EPCs
CD133 <sup>+</sup>	+	+/-	-
CD34 <sup>+</sup>	+	+	+
VEGFR2 <sup>+</sup>	+	++	+++
CD31 <sup>+</sup>	-	+	+
VE-cadherin	-	+	+
vWF	-	+	+

EPC: Endothelial progenitor cell; VEGFR: Vascular endothelial growth factor receptor.

Whereas the expression of CD34 a cell surface marker found on immature pluripotential stem cells<sup>[31]</sup> that acts as an adhesion molecule, although the precise function remains unclear, gradually increases as the CD133 decreases as the EPC matures<sup>[37]</sup>. During the course of maturity EPCs begin to have increased expression of other markers specific to endothelial cells such as VEGFR-2, VE-cadherin, and von Willebrand factor (vWF)<sup>[37]</sup>.

The expression of CD34<sup>+</sup>, CD133<sup>+</sup>, and/or VEGF2<sup>+</sup> has been used as identifying markers of EPCs in a number of studies<sup>[28,32,39-41]</sup>. Whereas as other studies advocate the use of CD133<sup>+</sup> either alone or in combination with CD34<sup>+</sup>/VEGFR-2<sup>+</sup> cells for identification of EPCs<sup>[31,42]</sup>. In contrast, other studies have suggested that CD133<sup>+</sup> are haematopoietic cell lines and have not been identified in and therefore unable to form endothelial phenotypic EPCs<sup>[7,40,43]</sup>. Ingram *et al.*<sup>[28]</sup> proposed that CD45<sup>-</sup> cells incorporated "true" circulating EPCs and verified by other studies<sup>[28,39,40,43]</sup>. Interestingly, CD34<sup>+</sup>/VEGFR2<sup>+</sup> and diminished (dim) CD45 (CD45<sup>dim</sup>) cells have been found to have greater correlation with coronary heart disease severity and response to statin therapy<sup>[44,45]</sup>.

In summary, the maturity of the EPC is marked by the gradual loss of CD133, gradual increased expression of CD34<sup>+</sup> and the appearance of CD31, VE-cadherin and vWF cell surface markers (Table 1).

## EPCS AND CORONARY ARTERY DISEASE

Endothelial integrity is essential for healthy vasculature, and can be thought of as a balance between continued endothelial damage and the capacity to repair by a pool of EPCs<sup>[9,46]</sup>. It is now generally accepted that cardiovascular risk correlates with EPC numbers. Highlighting the integral relationship between endothelium and atherosclerosis<sup>[47-51]</sup>, disruption of endothelial integrity by endothelial cell injury has been shown to be a stimulus for the development of atherosclerosis<sup>[2]</sup>, but also as a stimulus for augmentation of EPC number and function<sup>[9,52,53]</sup>. Continued endothelial damage<sup>[54]</sup> may lead to an eventual reduction of the number of EPCs. Elevated EPC numbers have been shown to be

associated with augmented formation of collaterals in coronary artery disease<sup>[55]</sup> and restoration of endothelial vasodilator function<sup>[9]</sup>. A reduction in EPC numbers may lead to deficient endothelial repair and progression of atherosclerosis, with further EPC depletion and perpetuation of atherosclerosis<sup>[9,56]</sup>. However, it is uncertain whether low numbers of circulating EPCs represents enhanced usage by vascular repair processes, or reduced production by bone marrow.

CD34<sup>+</sup> VEGFR2<sup>+</sup> EPCs cells have been shown to be reduced in patients with atherosclerotic coronary and peripheral disease<sup>[57]</sup>. Vasa *et al.*<sup>[56]</sup> found not only reduced numbers, but also impaired function of EPCs in patients with coronary artery disease. Elevated numbers of EPC have been associated with freedom from myocardial infarction, hospitalization, revascularization and cardiovascular death in patients with coronary artery disease<sup>[56,58]</sup>. Furthermore the predictive value of EPC count has been shown to be independent of traditional cardiovascular risk factors<sup>[9,46,59]</sup>. In fact, the extent of the reduction in EPC numbers has been associated not only with coronary artery disease burden<sup>[60]</sup>, but also the presence of symptoms<sup>[61,62]</sup>.

Finally, elevated numbers of circulating CD34<sup>+</sup>/CD133<sup>+</sup>/VEGFR2 EPCs have been observed after an acute myocardial infarction<sup>[42,63]</sup>. This may be regarded as a consequence of cardiac ischaemia together with raised inflammatory and haematopoietic cytokines stimulating EPC mobilisation from the bone marrow<sup>[64-66]</sup>. A similar response is seen following coronary angioplasty<sup>[67]</sup>, and interestingly, the combination of an acute coronary syndrome (ACS) treated by angioplasty provoked an enhanced EPC response<sup>[68]</sup>. Therefore, EPC may have a central role not only in repairing coronary vessels after plaque rupture, but also after any coronary intervention.

## STATIN THERAPY

Statins act by competitively inhibiting 3 hydroxy-3-methylglutaryl Coenzyme A (HMG CoA) reductase, the rate limiting step in the mevalonate pathway producing isoprenoids including cholesterol. The competitive inhibition of HMG CoA reductase induces the expression of LDL receptors within the liver, thereby increasing the catabolism of plasma LDL, with a consequent decrease in LDL-cholesterol levels<sup>[69]</sup>.

The safety and efficacy of statins in reducing cardiac events by decreasing serum LDL-cholesterol has been well described<sup>[16-18]</sup>. Statin therapy has been shown to reduce death and cardiovascular events in primary prevention of atherosclerosis<sup>[70]</sup>, stable coronary artery disease<sup>[16,71-73]</sup>, ACS<sup>[74,75]</sup> and secondary prevention<sup>[72]</sup>. Statins also appear to reduce development of atherosclerotic lesions<sup>[76,77]</sup> and decrease plaque burden<sup>[13,78]</sup>.

The beneficial effect of intensive statin therapy was studied in a prospective meta-analysis of 90056 patients from 14 randomised trials and found greater

cholesterol reduction was associated with better patient outcomes<sup>[19]</sup>. The study found that the 5-year incidence of major adverse cardiac events, coronary revascularization and stroke was reduced by one fifth for every millimoles per liter reduction in LDL cholesterol, which was irrespective of the initial lipid profile<sup>[19]</sup>.

Another meta-analysis found aggressive statin therapy was associated with reduced peri-procedural myocardial infarction and a 44% risk reduction in major adverse cardiovascular events at 30-d irrespective of clinical presentation<sup>[79]</sup>. Moreover, the ARMYDA-RECAPTURE study<sup>[80]</sup> found reloading of the high dose statin, atorvastatin 80 mg in 383 NSTEMI and stable angina patients on chronic therapy prior to percutaneous coronary intervention (PCI) had a 50% reduction in 30-d major adverse cardiac events in both group with a greater reduction in NSTEMI group<sup>[80]</sup>.

These studies led to the universal adoption of statin therapy in patients with coronary artery disease irrespective of presentation from stable angina to ACSs<sup>[81,82]</sup>.

## THE EFFECT OF STATIN THERAPY ON EPCS

Several studies have shown the early beneficial effect of statins occurs before any significant change in lipid profile. This led to the hypothesis that cardiovascular benefits of statins may occur *via* alternative mechanisms other than reduction of LDL-cholesterol alone<sup>[19,20]</sup>. These potential beneficial effect(s) may represent a potential therapeutic target for ischemic heart disease patients, and therefore is of great interest. There have been a number of mechanisms proposed to account for pleiotropic effects of statin therapy. These include reduction in vascular inflammation<sup>[83]</sup>, reduction of platelet aggregability and thrombus deposition<sup>[77,84-86]</sup>, enhancement of fibrinolysis<sup>[87]</sup> and increased endothelium derived NO production<sup>[88-90]</sup>. However the mechanism that has evoked the most interest is the impact of statins on EPCs<sup>[70]</sup>.

Statin therapy has been associated with greater numbers of circulating EPCs by enhancing mobilization, differentiation, increasing longevity, enhance homing to sites of vascular injury with augmentation of re-endothelisation by enhancing expression of adhesion molecules on EPC cell surface membrane<sup>[3,70,91-94]</sup>.

However, the duration of the effect on EPC number by statin therapy continues to remain contentious.

In one study, atorvastatin therapy was shown to significantly increase circulating EPC as soon as 1 wk with plateauing after 3-4 wk with a 3-fold increase of EPCs from baseline in a stable angina population was also observed<sup>[70]</sup>. Whereas Deschaseaux *et al*<sup>[95]</sup> investigated whether EPCs could be firstly detected and secondly characterized in patients receiving long-term statin therapy defined as 4 wk. The group found a significantly greater number of CD34<sup>+</sup>, CD34<sup>+</sup>/CD144<sup>+</sup>

circulating EPC in patients receiving statin therapy compared to statin naïve patients. Interestingly two types of EPCs were detected, early and late EPCs. The early EPCs were found to form elongated cells whereas the late EPC population gave rise to cobblestone-like colonies with strong proliferation capacities seen *in-vitro* cell culture. The numbers of early EPCs were significantly higher in patients not receiving statin therapy whereas late EPCs were significantly higher in patients receiving statin therapy. The study also observed that long term statin therapy specifically maintained late EPCs in circulation with a CD34<sup>+</sup>/CD144<sup>+</sup> phenotype. Rodent studies have found rosuvastatin resulted in a greater than 3 fold increase in EPC numbers when compared with placebo as long as 10 wk after myocardial infarction<sup>[56]</sup>. Long-term atorvastatin 10 mg for 12 mo markedly increased EPC number with an associated decrease in oxidative DNA damage<sup>[35]</sup>. However to the contrary, Hristov *et al*<sup>[96]</sup> found reduced numbers of circulating EPCs in CHD patients on long-term statin treatment.

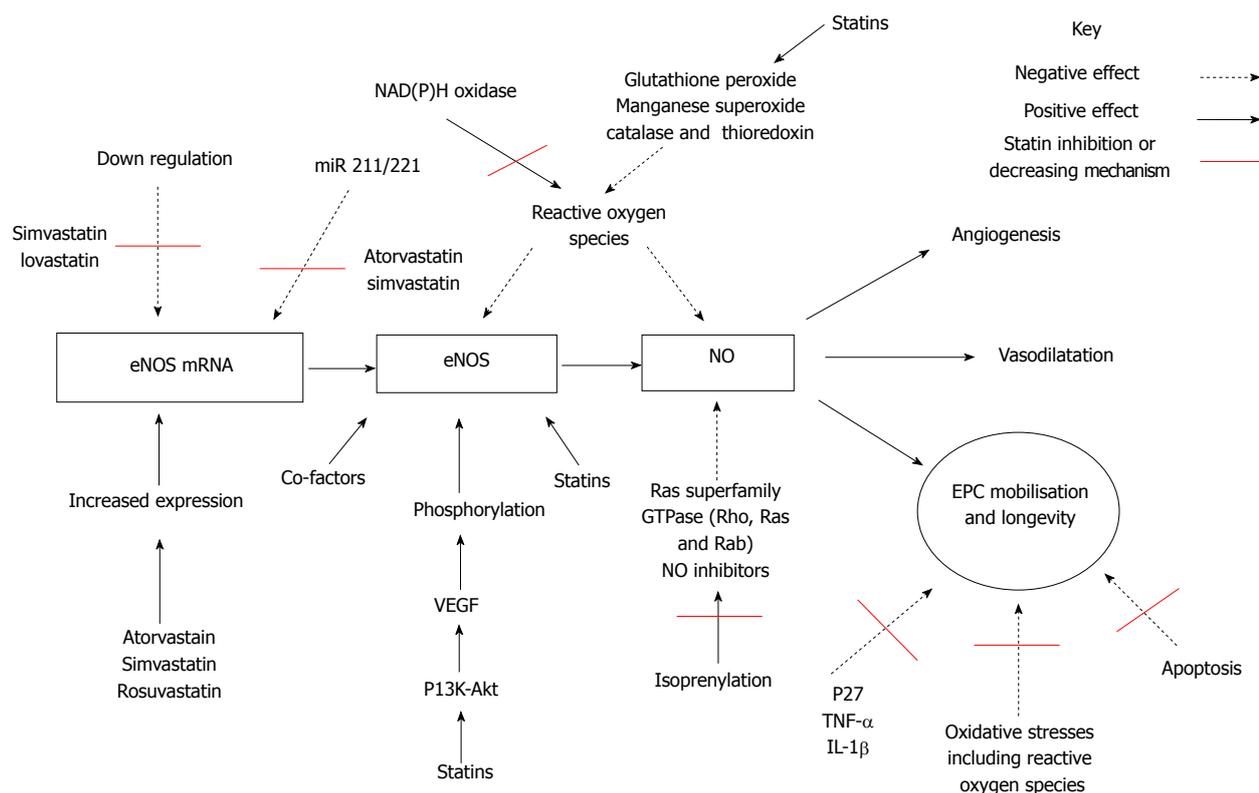
Statins appear to have a dose dependant effect on EPC count. A double blinded randomised pilot study found greater number of circulating CD34<sup>+</sup> VEGFR-2<sup>+</sup> EPCs after 12 wk of therapy with pravastatin 20 mg when compared to atorvastatin 10 mg<sup>[97]</sup>. Similarly, in ACS patients' intensive statin therapy with atorvastatin 80 mg after primary or rescue PCI was associated with greater EPC count at 4-mo follow up as compared to 20 mg atorvastatin. The authors found no beneficial effect in an improvement of LV function<sup>[98]</sup>. Furthermore statin reloading in patients on moderate statin therapy undergoing percutaneous coronary intervention has been shown to increase EPC count<sup>[99,100]</sup> this correlates with the beneficial effect of statin reloading of high dose statin in patients on chronic therapy<sup>[80]</sup> mentioned above.

## PLEIOTROPIC EFFECTS OF STATIN THERAPY

Several proposed intracellular signaling mechanisms accounting for the pleiotropic effect of statin therapy have been put forward. Figure 1 below summarizes the positive and negative effects on EPC proliferation, mobilisation and longevity but also the effect of statin therapy.

### Nitric oxide pathway

The first proposed intracellular signaling mechanisms involves nitric oxide pathway. The endothelium releases nitric oxide (NO), a primary mediator of smooth muscle tone that causes vasodilatation through the activity of endothelial-type nitric oxide synthase (eNOS)<sup>[101-104]</sup>. NO has an central role in vascular homeostasis with its bioavailability dependent on expression of endothelial eNOS<sup>[105]</sup>, presence of eNOS substrate and or co-factors<sup>[106]</sup>, phosphorylation of eNOS<sup>[107,108]</sup> or due to excessive depletion of NO such as seen with presence of



**Figure 1** Simplified diagram illustrating the positive and negative effects on endothelial progenitor cell proliferation, mobilisation and longevity together with proposed mechanisms of action of statin therapy. EPC: Endothelial progenitor cell; NO: Nitric oxide; eNOS: Endothelial nitric oxide synthase; VEGF: Vascular endothelial growth factor; mRNA: Messenger ribonucleic acid; TNF: Tumor necrosis factor alpha; IL-1: Interleukin 1; P13k-AKT: Phosphoinositide 3-kinase - protein kinase B pathway; NAD(P)H oxidase: Nicotinamide adenine dinucleotide phosphate-oxidase; miR : Micro non-coding ribonucleic acid.

excessive reactive oxygen species<sup>[109]</sup>. However the main functions of NO is as a cellular signaling molecule<sup>[101]</sup>, an angiogenic factor involved in stimulation, promotion, and stabilization of new blood vessels together with VEGFs, FGFs, Angiopoietins, PDGF, MCP-1, TGF, various integrins, VE-cadherin<sup>[110-113]</sup>. Statin therapy has been proposed to both enhance expression and activity of eNOS<sup>[114]</sup> a prerequisite stage for statin-mediated EPC mobilisation<sup>[115]</sup>. Statins are known to augment eNOS activity<sup>[116-118]</sup>, increase eNOS expression and restoration of endothelial function<sup>[104,119-121]</sup>. Statins have also been associated with increased EPC longevity *via* several pathways including inhibition of p27<sup>[122]</sup>, down regulating TNF- $\alpha$  or IL-1 $\beta$  expression<sup>[123]</sup> and prolonging eNOS expression<sup>[122]</sup> and finally by increasing eNOS mRNA half-life<sup>[124,125]</sup>. Kosmidou *et al*<sup>[126]</sup> found simvastatin and rosuvastatin prolonged expression by increasing 3' polyadenylation of eNOS mRNA. Laufs *et al*<sup>[88,124]</sup> firstly noted simvastatin and lovastatin reversed the down-regulation of eNOS expression caused by hypoxia and secondly simvastatin reversed down regulation of eNOS expression induced by oxidized LDL<sup>[88,124]</sup> a recognised cause of atherosclerosis.

#### **miR 221 and miR 222 levels**

A second observed pleiotropic mechanism of statin therapy has been a decreased level of micro non-coding RNAs called miR 221 and miR 222. These negatively

regulate protein expression at post-transcriptional stage<sup>[127]</sup>. This down regulating effect occurs by targeting 3' untranslated regions resulting in either degradation of target mRNA or impairing translation<sup>[128]</sup>. Furthermore miR-221 and miR-222 have been observed to regulate proliferation and differentiation of CD34-positive haematopoietic progenitor cells by reducing expression of *c-kit* receptor factor impairs haematopoietic progenitor cell proliferation<sup>[129]</sup>. Increased miR-221 and or miR-221 expression in EPC down regulates EPC differentiation and mobilisation *via* *c-kit* and or eNOS pathways in coronary artery disease patients<sup>[127]</sup>. Atorvastatin has been shown firstly to decrease miR 221 and miR 222, and secondly increase EPC numbers<sup>[127]</sup>. Cerda *et al*<sup>[130]</sup> found both atorvastatin and simvastatin increased NO levels and NOS3 mRNA expression, whereas ezetimibe did not. Atorvastatin, simvastatin and ezetimibe have all been shown to down-regulate the expression of miR-221, whereas miR-222 was reduced only after atorvastatin treatment. The magnitude of the reduction of miR-221 and miR-222 after treatment with statins correlated with an increment in NOS3 mRNA levels<sup>[130]</sup>. The eNOS and miR221/222 are thought likely to be components of the same pathway<sup>[131]</sup>.

#### **The PI3K/Akt/mTOR pathway**

The third proposed pleiotropic mechanism involves the phosphoinositide 3-kinase (PI3K)/protein kinase B

(Akt)/mammalian target of rapamycin (mTOR) signaling pathway plays. The PI3K/Akt/mTOR pathway plays a central role in multiple cellular processes, including cell proliferation, angiogenesis, metabolism, differentiation and longevity<sup>[132,133]</sup>. PI3K generates phosphatidylinositol 3,4,5-triphosphate (PIP3) an important lipid secondary messenger which in turn plays a central role in several signal transduction pathways<sup>[134,135]</sup> including activation of the serine/threonine kinases PDK1 and Akt. Akt controls protein synthesis and cell growth *via* the phosphorylation of mTOR<sup>[136]</sup>. The PI3K/Akt pathway has been associated with angiogenesis through the regulation of the NO signaling pathway<sup>[137]</sup>. The PI3K pathway releases a group of angiogenic factors including VEGF. VEGFR2 has a central role in VEGF-induced angiogenesis<sup>[138]</sup>. VEGF is required for the migration of endothelial cells and *via* PI3K-Akt dependent manner allows formation of capillary like structures<sup>[139]</sup>. Studies have shown that NO production may be induced by VEGF and appears to be attenuated by the inhibition of PI3K<sup>[140]</sup>. This is thought to occur *via* phosphorylation of eNOS at the serine 1177 residue by Akt<sup>[107,141]</sup>, required for the VEGF induced endothelial cell migration<sup>[142]</sup>. Factors that stimulate the PI3K/Akt protein kinase pathway, including statins, have been shown also to activate eNOS<sup>[87,141,143]</sup>. In turn, the expression of eNOS appears to be fundamental for mobilization of EPC and any impairment in PI3K/Akt/eNOS/NO signaling pathway may result in decreased EPC number<sup>[91,92]</sup>.

The PI3K/Akt/mTOR intracellular pathway *via* inhibition of the Rho kinase has also been shown to preserve mitochondrial permeability transition pore preventing mitochondrial apoptosis, and therefore death, while conserving cardiomyocyte function<sup>[144,145]</sup>.

These proposed mechanisms may account for difference in the effect of statin therapy in acute or chronic therapy. Statins given during acute ischaemic stress have been shown to firstly potentiate adenosine receptors<sup>[146,147]</sup> eventually leading to downstream regulation of eNOS and therefore increases NO production. Secondly statins augment activation of the reperfusion injury salvage kinase (RISK) pathway<sup>[148]</sup>. This results in enhanced activity of the PI3K/Akt/mTOR intracellular signal pathways<sup>[149]</sup>, leading to preservation of mitochondrial function and cardio-protection. Short-term high dose statin therapy have shown an increase in both EPC mobilisation from bone marrow and augmented function<sup>[92,150-154]</sup>.

Whereas chronic statin therapy has been linked to a phenomenon termed pre-ischaemic conditioning, protecting the myocardium against ischaemia<sup>[155]</sup>. This is believed to be secondary to statin induced NO availability by up regulation of eNOS and stabilisation of eNOS mRNA. Secondly, by increased production of NO and superoxide radicals improves vascular function and reducing vascular inflammation respectively<sup>[88,156]</sup>. Statins also inhibit isoprenylation of a number of Ras superfamily GTPase including Rho, Ras and Rab<sup>[157]</sup> NO inhibitors resulting in increased NO bioavailability.

Thirdly, by preventing mitochondrial apoptosis and preservation of cardiomyocyte function *via* the up-regulation of the PI3K/Akt/mTOR intracellular signalling pathway by inhibition of Rho kinase<sup>[144,145]</sup>. However, the RISK pathway has been shown the down regulated with chronic statin therapy<sup>[158]</sup> and has been shown to become reactivated by statin re-loading<sup>[159]</sup>. The latter may account for the increase in EPC count in patients on chronic statin therapy reloaded with statin therapy<sup>[80,99,100]</sup>.

### **Oxidative stresses**

Finally, EPC mobilisation and or function may also be affected by oxidative stress<sup>[153,160]</sup>. Oxidative stresses occur secondary to generation of oxygen free radicals or reactive oxygen species (ROS). Oxidative stress has a central role in cardiovascular disease, and a pivotal role in atherosclerosis<sup>[161]</sup>. Cellular oxidative stress seen with oxidized low-density lipoprotein (ox-LDL) has a central role in the pathogenesis of atherosclerosis. LDL is oxidised by reactive oxygen species from both circulating cells and cells on vascular walls<sup>[162,163]</sup>. In essence, LDL oxidation is a result of a chain reaction of free radicals converting polyunsaturated fatty acids into lipid peroxides and as a consequence, formation of active aldehydes<sup>[164]</sup>. The biochemical reaction forming ox-LDL have been found to cause senescence of EPCs<sup>[165]</sup>. Whereas high density lipoprotein is regarded as atheroprotective due to some part of its antioxidant properties also has a positive effect on EPC number and function<sup>[166]</sup>. There are a number of endogenous antioxidants exerting protective effects by scavenging ROS. An indirect way ROS effects EPCs includes ROS reacting with NO forming a potent oxidant<sup>[167]</sup> with a consequent decrease in NO. Decrease in NO either by excessive oxidation or impaired production reduces EPC mobilisation and/or function<sup>[161,168]</sup>. Secondly, direct exposure to oxidative stresses or in disease conditions with high oxidative stress, for example diabetes, is associated with induced EPC apoptosis with significant reduction in EPC numbers<sup>[168,169]</sup>, mobilisation, function<sup>[170]</sup> and reduced ability to migrate and or integrate into vasculature<sup>[161,171]</sup>.

In an attempt to counteract the effects of oxidative stress EPCs produce superoxide dismutase<sup>[172]</sup>. Interestingly, cardiovascular risk factors have been found to alter and or reduce the EPC antioxidant ability. Healthy volunteers have found to express higher levels of antioxidative enzyme catalases including glutathione peroxidase and manganese superoxide dismutase when comparing patients with cardiovascular disease<sup>[173,174]</sup>. The underlying pathophysiological mechanism currently remains undetermined. The antioxidant pleiotropic effect of statins may include indirect mechanism increasing NO bioavailability accounting for antioxidant properties contributing to an increase in EPC mobilisation and or function<sup>[114,175]</sup>. Secondly statin therapy has also been shown to inhibit activation of NAD(P)H oxidase and ROS release<sup>[176]</sup> but also activate catalase and thioredoxin

ROS scavenging mechanisms<sup>[176,177]</sup>. Finally, statins appear to have a direct effect by significantly reducing peroxide induced apoptosis of EPCs<sup>[169]</sup> and decreasing the oxidative damage to DNA in EPCs<sup>[178]</sup>.

### G proteins and G protein-coupled receptors

G protein-coupled receptors (GPCR) are comprised of seven trans-membrane domain proteins and are a super family consisting of a large and diverse number of proteins encoded by approximately 5% of human genes<sup>[179]</sup>. There have been a number of classification systems proposed the most recent "GRAFS" (Glutamate, Rhodopsin, Adhesion, Frizzled/Taste2 and Secretin)<sup>[180]</sup>. In mammals there are five main families<sup>[181]</sup>. GPCRs have an integral role in transfer of extracellular stimuli to within the cell by conformational changes in trans-membrane domain structure<sup>[182-185]</sup>. They regulate physiological responses to a myriad of endogenous ligands including amines, glycoproteins, peptides and lipids. Therefore, not surprisingly that GPCRs have been implicated in regulation of cellular maintenance, differentiation, proliferation and migration of various stem cells<sup>[186-189]</sup>.

GPCRs modulate activity of intracellular signaling *via* G proteins. There are currently four known G protein subfamilies each able to potentiate a number of downstream effectors triggering a number of signaling pathways<sup>[182]</sup>. These include activation of Rho associated kinases<sup>[190,191]</sup>, activation or inhibition of cyclic AMP production<sup>[192]</sup> and PI3Ks and therefore modulate the PI3K/Akt pathway<sup>[193,194]</sup>. The aforementioned have been implicated in EPC proliferation and function as described above. GPCRs have evoked great interest as a possible target for novel drug therapy<sup>[195]</sup> as an estimated 50% of all currently prescribed drugs target only a small proportion of GPCRs<sup>[196]</sup>. They are also becoming increasingly recognised as having a major role in stem cell signaling<sup>[197]</sup>. The role of GPCR in regulation and function of EPCs and the effect of statin therapy remains yet to be elucidated however current evidence suggests that they may have a pivotal role.

### CONCLUSION

EPCs have a pivotal role in the maintenance of vascular integrity. However, factors that influence EPC number, migration and function are now becoming recognised and have potentially a significant role in management of ischaemic heart disease patients. Statins once thought to modify cardiovascular risk only by lowering LDL-cholesterol are now being acknowledged as having alternative mechanisms that appear to have beneficial pleiotropic effects. One such mechanism may be mediated by EPCs. A number of studies have shown positive pleiotropic effect of statins on EPCs, both function and number. There appears to be a complex interaction between statins and EPC that is only now becoming recognised. Despite great progress since Asahara's pioneering work, there remain gaps within our

knowledge regarding the pleiotropic effect(s) of statins on EPCs. Further studies are required to elucidate and fully understand any pleiotropic effect and this may guide future beneficial therapeutic interventions.

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## Vitamin D and acute myocardial infarction

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### Abstract

Vitamin D deficiency is a prevalent condition, cutting across all ethnicities and among all age groups, and occurring in about 30%-50% of the population. Besides vitamin D established role in calcium homeostasis, its deficiency is emerging as a new risk factor for coronary artery disease. Notably, clinical investigations have suggested that there is an association between

hypovitaminosis D and acute myocardial infarction (AMI). Not only has it been linked to incident AMI, but also to increased morbidity and mortality in this clinical setting. Moreover, vitamin D deficiency seems to predispose to recurrent adverse cardiovascular events, as it is associated with post-infarction complications and cardiac remodeling in patients with AMI. Several mechanisms underlying the association between vitamin D and AMI risk can be involved. Despite these observational and mechanistic data, interventional trials with supplementation of vitamin D are controversial. In this review, we will discuss the evidence on the association between vitamin D deficiency and AMI, in terms of prevalence and prognostic impact, and the possible mechanisms mediating it. Further research in this direction is warranted and it is likely to open up new avenues for reducing the risk of AMI.

**Key words:** Vitamin D; Acute myocardial infarction; Incidence; Prognosis

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**Core tip:** Vitamin D deficiency is a prevalent condition and it is emerging as a new risk factor for coronary artery disease. Notably, hypovitaminosis D has been reported to be common in patients with acute myocardial infarction, and preliminary studies indicate a possible association with short-term and long-term morbidity and mortality. Although these observational initial proofs, interventional trials with supplementation of vitamin D have yielded controversial results. We herein discuss the current evidence suggesting an association between acute myocardial infarction and vitamin D deficiency, in terms of prevalence and prognostic impact, and the possible underlying mechanisms.

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## INTRODUCTION

Cardiovascular disease, and specifically acute myocardial infarction (AMI), is the main cause of morbidity and mortality in western countries, despite current preventive and therapeutic strategies<sup>[1,2]</sup>.

Besides the traditional, most recognized risk factors for AMI development, new risk factors are emerging with potential relevant therapeutic implications. Among them, hypovitaminosis D has been the focus of recent interest. It is well known that vitamin D insufficiency, or deficiency, is highly prevalent in the general population<sup>[3-7]</sup>. Traditionally, the most characterized consequences of vitamin D depletion have involved bone metabolism and calcium homeostasis<sup>[8]</sup>. However, its close association with major cardiovascular risk factors, such as diabetes, hypertension, and chronic kidney disease, and the detection of nuclear vitamin D receptors (VDR) on vascular endothelial cells and cardiomyocytes have paved the way to studies investigating the intriguing link between hypovitaminosis D and cardiac disease<sup>[9-11]</sup>.

Deficiency of vitamin D was shown to be common in AMI, and preliminary studies indicate a possible association with their short-term and long-term prognosis<sup>[12-14]</sup>. Indeed, vitamin D deficiency seems to predispose to in-hospital and recurrent adverse cardiac events, since it is associated with the number of affected coronary arteries, AMI complications, and cardiac remodeling in patients with AMI<sup>[12-14]</sup>.

In this review, we provide an overview on the currently available evidence supporting the relationship between hypovitaminosis D and AMI, its prognostic relevance, and the possible underlying mechanisms. Finally, we will try to identify challenges and future investigative perspectives in this field.

### Vitamin D metabolism

There are two major forms of vitamin D: Vitamin D<sub>2</sub>, which is contained in plants and fortified foods, and vitamin D<sub>3</sub>, which is obtained from aliments or through the conversion of dehydrocholesterol in the skin<sup>[11,15]</sup>. Of note, the cutaneous synthesis of vitamin D<sub>3</sub> from sunlight exposure is the main source of vitamin D in humans. Vitamin D undergoes hydroxylation in the liver to 25-hydroxyvitamin D - its main circulating form in the blood - and then in the kidney to 1,25-dihydroxyvitamin D. The 1,25(OH) vitamin D<sub>3</sub> reaches the nucleus where, by binding to its receptors, it regulates the transcription and function of more than 200 genes<sup>[16,17]</sup>. The VDR, which are expressed in enterocytes, osteoblasts, parathyroid glands, distal renal tubule cells, regulate calcium homeostasis and bone metabolism. Recent investigations have also demonstrated their presence on endothelial cells, lymphocytes, macrophages,

**Table 1 Most relevant risk factors for vitamin D deficiency**

Age
Increased distance from the equator
Winter season
Darkly pigmented skin
Institutionalized/housebound
Sunscreens and cover-up clothing
Air pollution
Smoking
Obesity
Physical inactivity
Malabsorption
Chronic kidney disease
Liver disease
Drugs (glucocorticoids, antirejection medications, human immunodeficiency virus medications, antiepileptic drugs, <i>etc.</i> )

smooth vascular muscle cells, beta-pancreatic cells and cardiomyocytes, through which vitamin D<sub>3</sub> mediates cardiovascular effects<sup>[18-20]</sup>.

There is no consensus on how to define vitamin D deficiency, and this introduces significant difficulties in conducting epidemiological studies in this field<sup>[21-24]</sup>. The most widely accepted definition for normal vitamin D serum levels, according to the United States Endocrine Society guideline recommendations, is  $\geq 30$  ng/mL. Vitamin D insufficiency is characterized by levels of 21-29 ng/mL, while its deficiency by levels  $\leq 20$  ng/mL<sup>[25]</sup>. Vitamin D deficiency is the most common nutritional deficiency worldwide in both children and adults<sup>[26]</sup>. In the United States and Europe, > 40% of the adult population has low vitamin D levels<sup>[26]</sup>. The Third National Health and Examination Survey (NHANES III) reports a high prevalence of vitamin D deficiency and its rapid increase, going from 55% in the period 1988-1994 to 77% in the years 2001-2004<sup>[27,28]</sup>. The main causes of vitamin D deficiency are listed in Table 1.

### Rationale for the link between vitamin D and AMI

A growing amount of data has highlighted the potential link between vitamin D and cardiovascular disease. Firstly, VDR have been found in the myocardium, as well as in vascular cells<sup>[18,29,30]</sup>. Secondly, epidemiological studies demonstrated that the incidence of coronary artery disease, diabetes, hypertension, and hypovitaminosis D, increase in proportion to distance from the equator<sup>[31]</sup>. Cardiac death and prevalence of vitamin D deficiency have also been reported to be at their highest during periods of decreased sunlight exposure (*i.e.*, winter months)<sup>[32]</sup>. Thirdly, new evidence suggests that vitamin D deficiency has a role in the development of different cardiovascular risk factors, in particular hypertension<sup>[33,34]</sup>, metabolic syndrome<sup>[35]</sup>, and diabetes mellitus<sup>[36-38]</sup>. Finally, patients with conditions known to be associated with vitamin D deficiency, such as chronic kidney disease and primary hyperparathyroidism, die more frequently from cardiovascular causes than from those related to their underlying disease<sup>[39]</sup>.

Taken together, these findings strongly support the

notion that vitamin D is involved in cardiac risk factor development, finally leading to an increased burden in coronary artery disease and to a worse short-term and long-term outcome in AMI patients.

### **Clinical studies on vitamin D in AMI**

An initial Danish report in 1978 examined vitamin D levels in 75 patients with stable angina, in 53 patients with AMI, and in 409 healthy subjects, and it found that vitamin D levels were significantly lower in patients with angina or AMI than in controls<sup>[40]</sup>. In 1990, a case control study showed that AMI patients had lower vitamin D levels than controls, and this difference was more pronounced in the winter-spring period<sup>[41]</sup>. Of note, the relative risk of AMI decreased across increasing quartiles of vitamin D, suggesting an inverse correlation between vitamin D levels and AMI risk<sup>[41]</sup>. These figures have also been confirmed in more contemporary cohorts. Among 1739 Framingham Offspring Study healthy participants, the rates of major cardiovascular events were 50% and 80% higher in those with vitamin D insufficiency and deficiency, respectively<sup>[42]</sup>. In particular, subjects with no history of coronary artery disease and vitamin D levels < 10 ng/mL experienced a hazard ratio of 1.8 for developing a first cardiovascular event during a 5-year follow-up compared with subjects with levels > 15 ng/mL<sup>[43]</sup>. Finally, in 18225 men in the Health Professionals Follow-up Study, low vitamin D levels were associated with a higher risk of AMI, even after controlling for other cardiovascular risk factors and, at 10-year follow-up, subjects with normal vitamin D levels (> 30 ng/mL) had approximately half the risk of AMI<sup>[43]</sup>. These findings have been recently confirmed in a large meta-analysis that showed an adjusted pooled relative risk of 1.52 for total cardiovascular events when comparing the lowest to the highest categories of baseline circulating vitamin D concentration<sup>[44]</sup>. Thus, there is growing evidence suggesting that vitamin D deficiency represents a novel risk factor for AMI.

In agreement with these epidemiological data, prospective reports have found a high prevalence of vitamin D deficiency in patients hospitalized with AMI. A multicenter study performed in 239 acute coronary syndrome patients showed that 96% of them had vitamin D levels < 30 ng/mL at hospital presentation<sup>[45]</sup>. In line with this, Ng *et al.*<sup>[13]</sup> demonstrated that 74% of AMI patients had low vitamin D levels and, of note, 36% of them had a severe deficiency. Correia *et al.*<sup>[46]</sup> reported a median serum concentration of vitamin D of 18.5 ng/mL in a cohort of 206 AMI patients (7% with STEMI), and a severe deficiency in 10% of the sample analyzed. Similar findings were also observed by De Metrio *et al.*<sup>[12]</sup> and Aleksova *et al.*<sup>[14]</sup>, who reported a prevalence of hypovitaminosis D in AMI patients of 89% and 68%, respectively.

Low vitamin D levels seem to be not only a prevalent independent risk factor for AMI, but also to be associated with a worse outcome when it occurs (Table 2). Correia

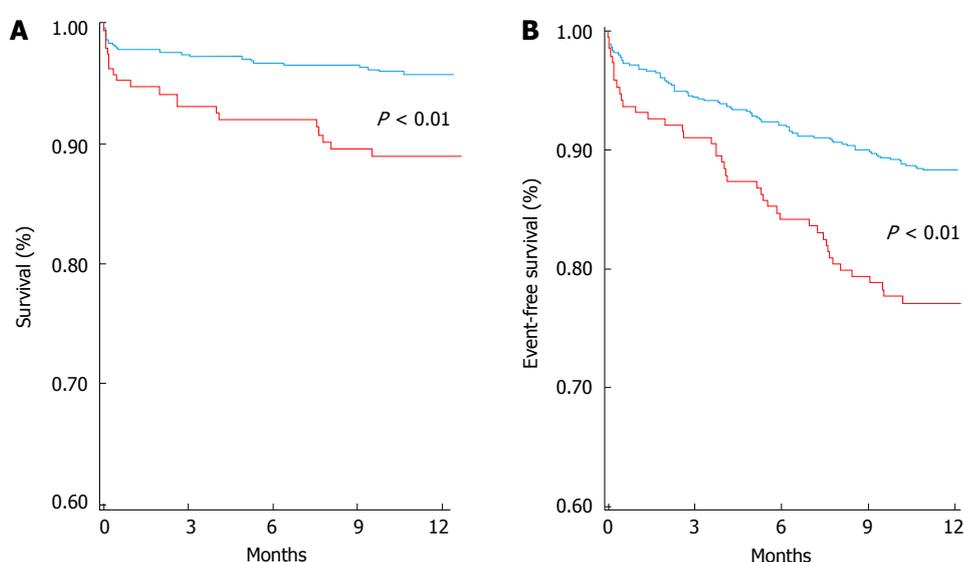
*et al.*<sup>[46]</sup> provided the first evidence of the potential independent association between severe deficiency of vitamin D and in-hospital mortality in patients with acute coronary syndromes. Indeed, patients with vitamin D levels < 10 ng/mL had a 24% in-hospital cardiovascular mortality rate, significantly higher than that observed in the remaining patients (4.9%, with a relative risk 4.3). A possible association between hypovitaminosis D and higher in-hospital mortality was also reported by Khalili *et al.*<sup>[47]</sup> in 139 STEMI patients. However, the study was underpowered to show statistically significant difference in in-hospital mortality between patients with normal and low vitamin D<sup>[48]</sup>. More robust data have been provided on the long-term clinical implications of low vitamin D levels in AMI. Thus far, the largest study assessing vitamin D and prognosis in 1259 acute coronary syndrome patients is that by Ng *et al.*<sup>[13]</sup>. In their study, the lowest vitamin D quartile (< 7.3 ng/mL) was associated with long-term major adverse cardiovascular events. Notably, the association was predominantly with re-hospitalization for acute decompensated heart failure or for successive acute coronary syndrome<sup>[13]</sup>. In agreement with these findings, in our cohort of AMI patients, the lowest quartile of vitamin D was a strong predictor of 1-year mortality (Figure 1)<sup>[12]</sup>. Of note, vitamin D deficiency was again a borderline independent predictor of in-hospital mortality, possibly due to the relatively low in-hospital mortality rate of our population, and it was associated with the highest risk of several in-hospital major adverse cardiac events. Interestingly, the lowest vitamin D quartile was associated with a higher incidence of bleeding requiring transfusion, although similar baseline hemoglobin values<sup>[12]</sup>. This is a crucial issue in the setting of AMI, as potent antithrombotic therapy is the mainstay of treatment, and bleeding and transfusions have a detrimental role on outcomes. We also found an association between the lowest vitamin D quartile and acute respiratory insufficiency rate<sup>[12]</sup>. The higher occurrence of these threatening complications might have contributed to the higher in-hospital mortality risk found in AMI patients and low vitamin D levels.

The causal relationship between vitamin D status and outcomes in AMI remains to be elucidated. Indeed, in more than 3000 patients undergoing coronary angiography, a significant association between hypovitaminosis D and lower left ventricular function was shown<sup>[49]</sup>. Of note, in this report, vitamin D deficiency was associated with deaths due to heart failure and with sudden cardiac deaths<sup>[50]</sup>. This highlights the possible relevance of vitamin D contribution to several aspects of AMI, such as acute ventricular dysfunction, heart failure progression, post-AMI ventricular remodeling, inflammation, thrombotic/bleeding balance and arrhythmias, which should be more deeply investigated through well-designed studies. Taking together, these considerations, along with older age, higher incidence of well-known cardiovascular risk factors, and lower rate of

**Table 2** Main prospective studies on serum vitamin D levels in patients with acute myocardial infarction

Ref.	Study population (n)	Definitions of vitamin D levels (ng/mL)	Prevalence	End points considered	Major findings
Lee <i>et al</i> <sup>[45]</sup>	NSTEMI STEMI (n = 219)	Normal > 30 insufficiency 21-29 deficiency < 20	4% were normal 75% were insufficient 21% were deficient	Prevalence and vitamin D correlates	Vitamin D deficiency was more commonly observed in non-Caucasian patients, in diabetics patients, and in those with a higher body mass index
Khalili <i>et al</i> <sup>[47]</sup>	STEMI (n = 139)	Deficiency < 30	73% were deficient	In-hospital mortality correlation with MMP-9 levels at 72 h	Inverse correlation between vitamin D and MMP-9 levels
Correia <i>et al</i> <sup>[46]</sup>	UA NSTEMI STEMI (n = 206)	Severe deficiency < 10	10% were severely deficient	In-hospital mortality long-term mortality (mean FU 635 d)	A significant higher incidence of in-hospital and long-term mortality in patients with severe vitamin D deficiency
Ng <i>et al</i> <sup>[13]</sup>	NSTEMI STEMI (n = 1259)	Deficiency < 20	74% were deficient	long-term incidence of mortality and MACE (median FU 550 d)	A significant higher incidence of MACE in patients with deficient vitamin D levels
De Metrio <i>et al</i> <sup>[12]</sup>	NSTEMI STEMI (n = 814)	Normal > 30 Insufficiency 21-29 Deficiency < 20	11% were normal 19% were insufficient 70% were deficient	In-hospital mortality and in-hospital MACE 1-yr mortality and 1-yr re-admission for acute coronary syndrome and acute decompensated heart failure	A higher incidence of in-hospital mortality, mechanical ventilation, and major bleeding in patients with the lowest quartile of vitamin D levels A significant higher incidence of 1-yr mortality and re-hospitalization for acute decompensated heart failure in patients with the lowest quartile of vitamin D levels
Aleksova <i>et al</i> <sup>[14]</sup>	NSTEMI STEMI (n = 478)	Sufficient > 30 Insufficiency 21-30 Deficiency ≤ 20	10% were sufficient 22% were insufficient 68% were deficient	Independent predictors of vitamin D deficiency	Older age, female gender, higher body mass index, autumn/winter sampling, and lower GFR predicted vitamin D deficiency

HR: Hazard ratio; FU: Follow-up; GFR: Glomerular filtration rate; MACE: Major adverse cardiac event; MMP-9: Matrix metalloproteinase-9; NSTEMI: Non-ST-elevation myocardial infarction; STEMI: ST-elevation myocardial infarction; UA: Unstable angina.



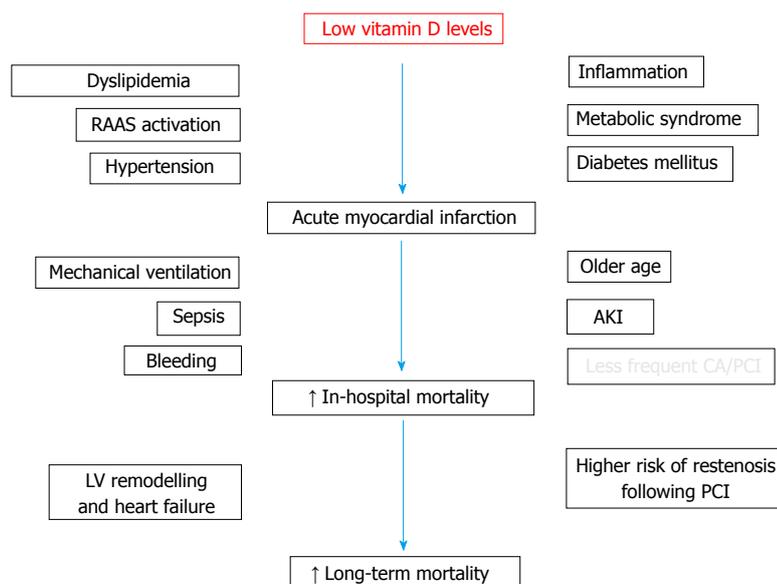
**Figure 1** Kaplan-Meier curve analysis stratified according to vitamin D levels. The lowest quartile (red line) vs the other three quartiles pooled together (blue line) for 1-year mortality (A), and for the combined end point<sup>1</sup> (B), in the whole study population. *P* value by Log rank test. Reproduced from De Metrio *et al*<sup>[12]</sup>.  
<sup>1</sup>Combined end point: death, major bleeding (requiring blood transfusion), acute pulmonary edema, cardiogenic shock, clinically significant tachyarrhythmias and bradyarrhythmias, and acute kidney injury.

reperfusion strategy, might explain the worse outcome of AMI patients presenting with low vitamin D levels (Figure 2). A similar prognostic relevance has also been reported in critically ill patients, in whom a low vitamin D status was significantly associated with disease severity and

mortality<sup>[50-52]</sup>.

#### Potential therapeutic implications

Although many studies suggest a higher cardiovascular risk associated with low vitamin D levels, the data



**Figure 2** Potential factors impacting on acute myocardial infarction occurrence and outcome associated with low vitamin D levels. AKI: Acute kidney injury; CA/PCI: Coronary angiography/percutaneous coronary intervention; LV: Left ventricular; RAAS: Renin-angiotensin-aldosterone system.

regarding vitamin D supplementation are more sparse and controversial, in terms of primary prevention<sup>[53-57]</sup>. The potential benefit of vitamin D administration in the early phase of AMI has not been investigated yet. From a clinical point of view, vitamin D levels can be rapidly determined by blood testing and treated by supplementation. It has been demonstrated that a single oral ultra-high dose of vitamin D is able to restore normal levels in 2 d in critically ill patients, with no adverse effects, potentially providing an easy-to-administer dosing regimen for intervention trials in acute cardiovascular settings<sup>[58]</sup>. Although this evidence was not focused on AMI patients, it may pave the way for new investigations based on the use of a high oral loading dose regimen of vitamin D for restoration of adequate levels within few days. Notably, a dose-response association with cardiovascular risk and mortality has been demonstrated by Wang *et al.*<sup>[44]</sup>, and this was particularly true when short-term outcomes were considered.

Data on vitamin D supplementation in the setting of secondary prevention of AMI are also lacking. Yet, it has been recently demonstrated that high-dose vitamin D supplementation for 1-year in patients with chronic heart failure due to left ventricular systolic dysfunction and vitamin D deficiency, on contemporary optimal medical therapy, resulted in a significant improvement in left ventricular structure and function<sup>[59]</sup>. Of note, in almost 60% of these patients, the etiology was ischemic heart disease, suggesting a possible beneficial effect on post-AMI ventricular dysfunction<sup>[59]</sup>.

Some studies have also proposed a possible association between low vitamin D and increased levels of cholesterol and of inflammatory markers, in particular C-reactive protein, in the setting of AMI<sup>[12,46]</sup>. Interestingly, 1-year atorvastatin treatment in patients with AMI determined a marked decrease in cholesterol and an unexpected increase in vitamin D levels, reinforcing the interplay among inflammation, low vitamin D and

dyslipidemia<sup>[60,61]</sup>.

### Future perspectives and conclusions

Thus far, evidences in this field have been mainly driven by observational cohort studies, and these data are hypothesis-generating. Therefore, whether vitamin D is a risk factor or marker in this clinical setting cannot be inferred from the current literature. Larger studies are needed in order to shed lights on this issue. Because of their health status, frail patients with a high cardiovascular risk burden may spend mostly of their time indoors, which leads to low levels of vitamin D. This is also supported by the fact that such a similar observation has been found in patients with cancer, multiple sclerosis, and psychiatric diseases, potentially supporting the notion that hypovitaminosis D may be simply a marker of health<sup>[62]</sup>. However, even when adjusted for major confounders, vitamin D status still remains an independent risk factor, as it is significantly linked to incident AMI, worse short-term outcome, and recurrent major adverse cardiovascular events.

Whether vitamin D supplementation can counteract this increased risk in AMI patients is still an unanswered question, which should be investigated in large, well-designed, adequately powered interventional trials.

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## Ambulatory pulmonary artery pressure monitoring in advanced heart failure patients

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### Abstract

Heart failure (HF) is an emerging epidemic associate with significant morbidity, mortality, and health care expenditure. Although there were major advances in pharmacologic and device based therapies for the management of HF, mortality of this condition remains high. Accurate monitoring of HF patients for exacerbations is very important to reduce recurrent hospitalizations and its associated complications. With the failure of clinical signs, tele-monitoring, and laboratory bio-markers to function as early markers of HF exacerbations, more sophisticated techniques were sought to accurately predict the circulatory status in HF patients in order to execute timely pharmacological intervention to reduce frequent hospitalizations. CardioMEMS™ (St. Jude Medical, Inc., Saint Paul, Minnesota) is an implantable, wireless pulmonary arterial pressure (PAP) monitoring system which transmits the patient's continuous PAPs to the treating health care provider in the ambulatory setting. PAP-guided medical therapy modification has been shown to significantly reduce HF-related hospitalization and overall mortality. In advanced stages of HF, wireless access to hemodynamic information correlated with earlier left ventricular assist device implantation and shorter time to heart transplantation.

**Key words:** CardioMEMS; Heart failure; Remote heart failure monitoring; Pulmonary arterial pressure monitoring; Left ventricular assist device

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**Core tip:** Traditional heart failure monitoring methods have failed to accurately and timely identify worsening heart failure. Remote pulmonary artery pressure monitoring *via* CardioMEMS™ heart failure system identified heart failure exacerbations earlier and more accurately than clinical signs, and timely medical

interventions resulted in reduced hospitalizations and mortality. Remote pulmonary artery pressure monitoring appears to have positive clinical implications in patients with mechanical circulatory support.

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## INTRODUCTION

Heart failure (HF) is a chronic debilitating condition which impairs the ability of the heart to effectively pump the blood to the body to meet its metabolic requirements. HF is an emerging epidemic with an estimated prevalence of 5.8 million in the United States, and over 23 million worldwide<sup>[1]</sup>. Within the United States, the incidence of HF exceeds 650000 each year with an estimated annual financial burden of around 30.7 billion dollars<sup>[2,3]</sup>. Although there were major advances in pharmacologic and device based therapies for the management of HF which improved the overall survival over time, mortality of this condition remains high. The estimated survival after the diagnosis of HF is 50% at 5 years and 10% at 10 years<sup>[1]</sup>. Hospitalization for acute decompensated HF serves as a poor prognostic indicator with an approximate 30% and 50% readmission rates at 1-mo and 6-mo, respectively<sup>[1,3]</sup>. With improved survival of patients after acute myocardial infarction, a growing elderly population, and frequent hospitalizations in the HF population owing to acute exacerbations, HF continues to be one of the leading causes of morbidity, mortality, and health care expenditures in the United States and worldwide.

Around 150000-250000 Americans suffer from advanced stage HF<sup>[4]</sup>. Although cardiac transplantation is the gold standard treatment in such patients, limited organ availability restricts the number of heart transplants to around 2500 per year ([https://www.unos.org/data/transplant-trends/#transplants\\_by\\_organ](https://www.unos.org/data/transplant-trends/#transplants_by_organ)). More than 4000 patients are currently on the waiting list for a cardiac transplant ([www.unos.org/data/transplant-trends/#waitlists\\_by\\_organ](http://www.unos.org/data/transplant-trends/#waitlists_by_organ)), a number which is expected to increase significantly because of the increasing number of patients living with advanced HF and an increasing elderly population. Left ventricle assist device (LVAD) has emerged as a life-saving option for these patients as either bridge to transplant, bridge to decision, bridge to recovery or as destination therapy. Around 15000 HF patients across the world are currently supported with LVADs<sup>[5]</sup>. LVAD serves as destination therapy in more than 45% of the patients living with the device<sup>[5]</sup>.

## PREVIOUSLY TESTED METHODS FOR MONITORING HF PATIENTS

Identification of physical manifestations such as weight gain, extremity edema, fatigue, shortness of breath, orthopnea, paroxysmal nocturnal dyspnea, jugular venous distention, third heart sounds, and rales, *etc.* have poor to moderate sensitivities and are often late manifestations of worsening HF, thereby, relying on these markers have limited impact on reducing HF hospitalizations<sup>[6]</sup>. Also, such efforts largely employ patient self-management strategies, including diuretic dose adjustments based on clinical worsening, and are unsuccessful in patients with poor self-care skills and compliance<sup>[6]</sup>. Two large trials which investigated the benefits of tele-monitoring in HF population failed to show any significant decrease in the all-cause mortality and HF hospitalizations in the tele-monitored group<sup>[6]</sup>. A smart-phone based electrocardiographic monitoring of HF has been recently proposed, but there is not much data exploring this idea<sup>[7]</sup>.

Lainchbury *et al.*<sup>[8]</sup> compared N-terminal pro-B-type natriuretic (NT-proBNP) guided titration of medical therapy in HF patients with intensive clinical management and with usual care in a randomized sample of 564 patients. There was a reduction in the 3-year mortality in the NT-proBNP-guided group compared to the clinically-guided group (30.9%;  $P = 0.048$ ) and to those with usual care (31.3%;  $P = 0.021$ ). These benefits were selectively seen in patients  $\leq 75$  years of age. However, there was no statistically significant difference in the overall hospitalizations for HF and the secondary outcomes among all the groups<sup>[8]</sup>. Another study monitored plasma B-type natriuretic peptide (BNP) levels in up to 558 chronic stable HF patients in an ambulatory setting to predict imminent decompensation<sup>[9]</sup>. The study showed that both symptomatic and asymptomatic HF patients had a wide range of plasma BNP levels. Interestingly, 21% of symptomatic decompensated HF patients had BNP levels below the diagnostic threshold of  $< 100$  pg/mL<sup>[9]</sup>.

## REMOTE HEMODYNAMIC MONITORING IN HF PATIENTS

With the failure of reliable clinical symptoms/signs, tele-monitoring, and laboratory bio-markers to help reduce the hospitalizations, and health care expenditure in the HF population, more sophisticated techniques were sought to accurately predict the circulatory status in HF patients in order to execute timely pharmacological intervention to prevent the primary onus of this disease, *i.e.*, hospitalizations. Echocardiography is being used as a monitoring system in the hospitalized and ambulatory population, but it is associated with significant costs, less accuracy, and observer variability. Traditionally, in hospitalized HF patients, right heart catheterization

(RHC) provides invaluable information regarding the volume status and filling pressures which can form the basis of successful medical management. However, RHC is not routinely recommended to aid in the management of hospitalized decompensated HF patients owing to its invasive nature and associated risks. We had no such accurate monitoring systems in the ambulatory setting until scientific advances led to the development of implantable hemodynamic monitors (IHMs) which provided hemodynamic information comparable to the information obtained from a RHC<sup>[10]</sup>. The idea of IHM based monitoring and necessary interventions in HF patients was innovative and exiting.

Earlier trials of implantable hemodynamic monitoring in HF patients did not show significant clinical benefit or were unable to adequately assess clinical efficacy. The COMPASS-HF (Chronicle Offers Management to Patients with Advanced Signs and Symptoms of Heart Failure) trial using Chronicle (Medtronic Inc., Minneapolis, Minnesota) to estimate right ventricular pressures and guide medical therapy, did not show a significant reduction in HF-related events when compared to the control group<sup>[11]</sup>. The Reducing Decompensation Events Utilizing Intracardiac Pressures in Patients With Chronic Heart Failure (REDUCEhf) study employed a device combining IHM and implantable cardioverter-defibrillator technology to measure right ventricular pressures and guide medical therapy<sup>[12]</sup>. The REDUCEhf study was unable to test clinical efficacy end points adequately and findings from this study did not show a difference in the rate of HF-equivalents when medical therapy was guided based on the information obtained from the IHM<sup>[12]</sup>.

The Hemodynamically Guided Home Self-Therapy in Severe Heart Failure Patients (HOMEOSTASIS) trial is a small study of 40 patients in which the benefit of physician-directed patient self-management of left atrial pressures as measured with the implantable HeartPOD (St. Jude Medical Inc, Minneapolis, Minnesota) was investigated<sup>[13]</sup>. Left atrial pressure guided medical therapy was associated with an improved event-free survival (death or hospitalization for acute decompensated HF), reduced mean daily left atrial pressures, improved New York Heart Association (NYHA) functional class, improved left ventricular ejection fraction, increased doses of neuro-hormonal antagonists, and reduced diuretic doses<sup>[13]</sup>. Encouraging results from this smaller study formed the basis of the larger and currently ongoing LAPTOP-HF trial which will investigate the role of implantable left atrial pressure monitoring in conjunction with a new HF treatment paradigm across the spectrum of HF patients<sup>[14]</sup>.

pressure monitoring system. It measures PA pressures from a battery free capacitive electromechanical sensor which is permanently implanted with a delivery system in the distal pulmonary artery with a RHC *via* transvenous access. An electronic system transmits the generated data to a secure network where it is readily available for interpretation by the treating clinician. Verdejo *et al*<sup>[15]</sup> showed that wireless PA pressure monitoring using the CardioMEMS sensor correlated with Swan-Ganz catheter and echocardiographic PA pressure measurements. The outcomes of remote management of HF patients guided by wireless PA pressure monitoring was investigated in the landmark CHAMPION (CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in NYHA Class III Heart Failure Patients) trial<sup>[16]</sup>.

The CHAMPION trial is a randomized, controlled, multi-center, single-blind trial in which 550 NYHA class III HF patients were implanted with the wireless CardioMEMS HF pressure sensor system<sup>[16]</sup>. Physicians had access to the PA pressures of the patients in the treatment group only, in which medications were adjusted based on the generated data. The control group received traditional HF management. The primary efficacy endpoint was the rate of HF-related hospitalizations at 6 mo. In comparison to the control group, there was a remarkable 28% reduction in HF-related hospitalizations at 6 mo, and 37% at 15 mo in the treatment group (Hazard ratio 0.63,  $P < 0.0001$ )<sup>[17]</sup>. There were no pressure sensor failures and 98.6% of the study population was free from device-related or system-related complications<sup>[17]</sup>. A sub-analysis of the original trial in HF with preserved ejection fraction (HFpEF) patients showed that there was a 50% reduction ( $P < 0.0001$ ) in HF-related hospitalizations at 17 mo in the treatment group<sup>[18]</sup>. These landmark findings led to the Food and Drug Administration approval of the CardioMEMS™ HF system for ambulatory hemodynamic monitoring in NYHA class III HF with reduced ejection fraction (HFrEF) and HFpEF patients, who are on optimal medical therapy, and had a HF hospitalization in the previous year<sup>[19]</sup>. In the 2016 European society of Cardiology guidelines, CardioMEMS received a Class IIb recommendation for directed therapy management and monitoring tool in HF patients<sup>[20]</sup>.

Numerous sub-analyses supported the encouraging results obtained from the original CHAMPION trial. The reduced HF-related hospitalization rate was postulated to be from physician controlled effective changes in diuretic dosing in the treatment group ( $P < 0.0001$  for more frequent diuretic dose changes in treatment group compared to control)<sup>[21]</sup>. Wireless PA pressure-guided HF management was superior to clinical signs-guided management with a 67% relative risk reduction ( $P = 0.0007$ ) in HF hospitalizations when diuretic doses were adjusted based on PA pressure alone vs clinical signs alone<sup>[22]</sup>. At 6 mo, the target group experienced a higher frequency of medication adjustments with significant increases in the doses of diuretics, vasodilators, and

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## CARDIOMEMS™ AND REMOTE PULMONARY ARTERIAL PRESSURE MONITORING

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CardioMEMS™ (St. Jude Medical, Inc., Saint Paul, Minnesota) is a wireless pulmonary arterial (PA)

neuro-hormonal antagonists with preserved renal function despite intensification of diuretic therapy<sup>[23]</sup>. Remote PA pressure-guided treatment resulted in similar reductions in HF hospitalization in HFrEF patients with and without a cardiac resynchronization therapy (CRT) device, suggesting that HF management guided by PA pressures may provide additive benefits to CRT<sup>[24]</sup>.

Wireless PA-pressure monitoring on top of guideline-directed medical therapy and CRT or ICD, had an additive effect in improving HF hospitalizations and mortality<sup>[25]</sup>. There were significant reductions in all-cause hospitalization ( $P < 0.0032$ ), and in the number of deaths or all-cause hospitalization in the treatment group ( $P = 0.0017$ )<sup>[26]</sup>. Interestingly, it was observed that measurement of PA pressures using RHC alone may result in under-diagnosing pulmonary hypertension related to HF. Of the 217 patients who did not meet criteria for pulmonary hypertension during implantation RHC, 49% met criteria for pulmonary hypertension based in the first week IHM data<sup>[27]</sup>. Alam *et al.*<sup>[27]</sup> compared 34 HF patients who had an implanted CardioMEMS HF system with 32 HF patients without an IHM, and reported a three-fold improvement in the Kansas City Cardiomyopathy Questionnaire scores ( $P < 0.001$ ) and increased 6-min walk distance ( $P < 0.001$ ) in the CardioMEMS group. These findings represent improved quality of life and exercise capacity. Results from the CHAMPION trial and subsequent sub-analysis confirmed that early and appropriate medical interventions following early detection of elevated PA pressures resulted in a significant reduction of HF-related hospitalizations, readmission rates and mortality.

There is an increasing trend in the number of HF patients living with LVADs and an increasing use of LVAD as destination therapy for advanced HF patients. Feldman *et al.*<sup>[29]</sup> conducted a sub-analysis of the CHAMPION trial to determine the validity of remote PA pressure directed therapy on optimization of medications, pump parameters, and timing of heart transplantation in patients receiving a LVAD. Of the 27 patients who received an LVAD, 15 patients were assigned to the treatment group where their medical therapy was modified based on PA pressures and 12 patients in the control group received standard care. The data obtained from CardioMEMS HF system led to significantly more medication changes in the treatment arm ( $P = 0.025$ ). Wireless access to hemodynamic information correlated with earlier LVAD implantation ( $P = 0.001$ ) and shorter time to transplantation ( $P = 0.001$ ) in the treatment arm<sup>[29]</sup>.

Over the last few decades, efforts have been directed at reducing recurrent hospitalizations for worsening HF in this patient population. A variety of markers varying from clinical symptoms and signs to laboratory testing have been investigated to identify acute decompensated HF early enough to prevent hospitalizations, subsequent morbidity, and health care expenditure. Daily weight monitoring is a cornerstone for managing HF patients. It has been shown that increases in body weight begin at

least 1 week before a HF hospitalization<sup>[30]</sup>. However, less than a half of the HF patients including those recently discharged after a hospitalization for HF exacerbation check their weight on a daily basis<sup>[31]</sup>. Daily electronic body weight transmission to a HF clinic in patients with severe HF who had a recent HF hospitalization did not show any benefit in reducing HF re-hospitalization or death<sup>[32]</sup>.

## CONCLUSION

HF continues to be a major public health problem with a significant financial burden. As more and more people are living with HF, it is important have a simple, reliable, and valid monitoring system to aid in the early identification and appropriate management of worsening HF in the ambulatory setting. IHM is an innovative and exciting monitoring system for HF management. CardioMEMS has steered HF research into a new direction which will serve as the gateway to future therapies and innovations in the management of chronic HF patients. Also with increasing number of people living with LVADs and LVAD being used as destination therapy in a large percentage of the LVAD population, CardioMEMS will be a promising monitoring system to better manage HF as well as the LVAD device in this population. However, given the small number of participants involved in many of the available trials, large multicenter randomized clinical trials are needed to make valid recommendations in an effort to lower mortality and improve quality of life in the chronically sick HF population. Wireless left atrial pressure-guided and PA pressure-guided management of HF can have a substantial positive effect on reducing the financial burden of HF and improving the overall morbidity and mortality in this population.

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## Retrospective Cohort Study

## Does heart rate variability correlate with long-term prognosis in myocardial infarction patients treated by early revascularization?

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### Abstract

#### AIM

To assess the prevalence of depressed heart rate variability (HRV) after an acute myocardial infarction (MI), and to evaluate its prognostic significance in the present era of immediate reperfusion.

#### METHODS

Time-domain HRV (obtained from 24-h Holter recordings) was assessed in 326 patients ( $63.5 \pm 12.1$  years old; 80% males), two weeks after a complicated MI treated by early reperfusion: 208 ST-elevation myocardial infarction (STEMI) patients (in which reperfusion was

successfully obtained within 6 h of symptoms in 94% of cases) and 118 non-ST-elevation myocardial infarction (NSTEMI) patients (percutaneous coronary intervention was performed within 24 h and successful in 73% of cases). Follow-up of the patients was performed *via* telephone interviews a median of 25 mo after the index event (95%CI of the mean 23.3-28.0). Primary end-point was occurrence of all-cause or cardiac death; secondary end-point was occurrence of major clinical events (MCE, defined as mortality or readmission for new MI, new revascularization, episodes of heart failure or stroke). Possible correlations between HRV parameters (mainly the standard deviation of all normal RR intervals, SDNN), clinical features (age, sex, type of MI, history of diabetes, left ventricle ejection fraction), angiographic characteristics (number of coronary arteries with critical stenoses, success and completeness of revascularization) and long-term outcomes were analysed.

## RESULTS

Markedly depressed HRV parameters were present in a relatively small percentage of patients: SDNN < 70 ms was found in 16% and SDNN < 50 ms in 4% of cases. No significant differences were present between STEMI and NSTEMI cases as regards to their distribution among quartiles of SDNN ( $\chi^2 = 1.536$ ,  $P = 0.674$ ). Female sex and history of diabetes maintained a significant correlation with lower values of SDNN at multivariate Cox regression analysis (respectively:  $P = 0.008$  and  $P = 0.008$ ), while no correlation was found between depressed SDNN and history of previous MI ( $P = 0.999$ ) or number of diseased coronary arteries ( $P = 0.428$ ) or unsuccessful percutaneous coronary intervention (PCI) ( $P = 0.691$ ). Patients with left ventricle ejection fraction (LVEF) < 40% presented more often SDNN values in the lowest quartile ( $P < 0.001$ ). After > 2 years from infarction, a total of 10 patients (3.1%) were lost to follow-up. Overall incidence of MCE at follow-up was similar between STEMI and NSTEMI ( $P = 0.141$ ), although all-cause and cardiac mortality were higher among NSTEMI cases (respectively: 14% *vs* 2%,  $P = 0.001$ ; and 10% *vs* 1.5%,  $P = 0.001$ ). The Kaplan-Meier survival curves for all-cause mortality and for cardiac deaths did not reveal significant differences between patients with SDNN in the lowest quartile and other quartiles of SDNN (respectively:  $P = 0.137$  and  $P = 0.527$ ). Also the MCE-free survival curves were similar between the group of patients with SDNN in the lowest quartile *vs* the patients of the other SDNN quartiles ( $P = 0.540$ ), with no difference for STEMI ( $P = 0.180$ ) or NSTEMI patients ( $P = 0.541$ ). By the contrary, events-free survival was worse if patients presented with LVEF < 40% ( $P = 0.001$ ).

## CONCLUSION

In our group of patients with a recent complicated MI, abnormal autonomic parameters have been found with a prevalence that was similar for STEMI and NSTEMI cases, and substantially unchanged in comparison to what reported in the pre-primary-PCI era. Long-term outcomes did not correlate with level of depression of

HRV parameters recorded in the subacute phase of the disease, both in STEMI and in NSTEMI patients. These results support lack of prognostic significance of traditional HRV parameters when immediate coronary reperfusion is utilised.

**Key words:** Heart rate variability; Autonomic nervous system; Primary percutaneous coronary intervention; Myocardial infarction; ST-elevation myocardial infarction; Non-ST-elevation myocardial infarction; Left ventricle ejection fraction; Long-term prognosis

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**Core tip:** Depressed heart rate variability (HRV) is usually considered a negative long-term prognostic factor after an acute myocardial infarction (MI). Anyway, most of the supporting research was conducted before the era of immediate reperfusion by percutaneous coronary intervention. In our study, in MI patients treated by early reperfusion abnormal values of HRV are present in a low percentage of cases. Low HRV does not correlate with long term-prognosis, both in ST-elevation and non-ST-elevation MI patients. Abnormal HRV seems to have lost prognostic significance in the present era of primary percutaneous revascularization.

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## INTRODUCTION

The first clinical evidence that one measure of heart rate variability (HRV), the standard deviation of all normal RR intervals (SDNN), was a powerful predictor of cardiac mortality after an acute myocardial infarction (AMI) was given by the wide longitudinal study by Kleiger *et al*<sup>[1]</sup> in 1987. Since then, marked abnormalities of various parameters of HRV, indicating profound derangement of the cardiac autonomic system, have been often described after AMI and have been confirmed to be reliable predictors of poor long-term prognosis<sup>[2,3]</sup>. The large multicentre ATRAMI study conducted in 1998 demonstrated that 15% of AMI patients observed during the first 4 week of the acute event, presented a SDNN < 70 ms, and that among the group with depressed SDNN long-term mortality was 5 times higher than in the patients with better preserved HRV parameters<sup>[4]</sup>. These results confirmed the findings of previous studies, such as the GISSI-2 study that used similar evaluation parameters<sup>[5]</sup>. Other studies used various and different methods to assess HRV (time and frequency domain

measures, discriminant analysis, fractal and other non-linear HRV analysis, with both short-term and long-term evaluations) and observed AMI patients at variable periods of time after the index event; they reported a wide range of prevalence of reduced HRV parameters (ranging from 7% to 34%)<sup>[6,7]</sup>, and different incidence of long-term mortality (ranging from 0% to 45%)<sup>[8-10]</sup>. Despite this, the cited studies mainly confirmed that abnormal HRV holds a negative predictive value on both short and long-term prognosis, with HRV parameters holding high specificity, but poor sensitivity<sup>[11]</sup>.

A limitation of the reported studies is that the majority of them did not provide data of how patients with ST-elevation myocardial infarction (STEMI) behave separately from non-ST-elevation myocardial infarction (NSTEMI) patients. Furthermore, the majority of studies on HRV in patients with a recent AMI have been conducted in an era prior to that of immediate reperfusion by percutaneous coronary intervention (PCI). Among 21 papers analyzed in the recent review by Brateanu *et al.*<sup>[10]</sup>, patients had been treated by primary PCI only in 5 studies and in widely variable percentages (ranging from 18% up to 95% of cases)<sup>[6,12]</sup>, so, little information is currently available on prevalence and prognostic significance of depressed HRV in present day AMI patients.

Aims of this study were to assess the prevalence of severely decreased HRV in patients during the subacute phase of a STEMI treated by primary PCI, and to evaluate if HRV maintains a prognostic value in the current era of immediate percutaneous reperfusion, comparing results with those of NSTEMI cases.

## MATERIALS AND METHODS

### **Design of the study**

We retrospectively reviewed the clinical files of 326 consecutive patients which were part of a larger study on the effects of cardiac rehabilitation (CR) after AMI. All had suffered a complicated AMI (208 STEMI, 118 NSTEMI) and had been admitted to our CR unit for a period of residential, exercise-based rehabilitation, a median of 13.5 d (95%CI of the mean 15.2-17.3) after the index event. All patients had undergone coronary angiography on initial admission to the Intensive Coronary Care Unit, within 24 h from beginning of AMI symptoms: 194 (94%) STEMI underwent successful PCI of the culprit coronary artery within 6 h of symptoms<sup>[13]</sup>, while only a small percentage of them (14 cases, 6%) could not be revascularized due to unfavourable coronary anatomy and had to be placed on medical therapy; NSTEMI patients underwent coronary angiography within 24 h<sup>[14]</sup>, with successful PCI in 86 cases (73%) and medical therapy in the remaining 32 cases. Of the primary-PCI STEMI patients, 67 (32%) had also been immediately treated on non-culprit coronary lesions; 42 (36%) NSTEMI patients were similarly also immediately treated on non-culprit

coronary lesions. Eight (4%) STEMI and 4 (3%) NSTEMI patients received further elective percutaneous revascularization during the initial stay in the Cardiology Department. Overall, at the time of transferral to the CR unit, 121 (58%) STEMI patients and 54 (46%) NSTEMI patients had a complete revascularization, while 87 STEMI and 64 NSTEMI patients were still incompletely revascularized.

Patients were selected for referral to our CR program if they suffered a complicated AMI (cardiogenic shock or pulmonary edema, episode of cardiac arrest, complex ventricular arrhythmias), or if they had incomplete revascularization (because of unfavorable coronary anatomy or technical failure)<sup>[15]</sup>. Low risk patients were referred as out-patients to a CR program in a different centre and excluded from this study.

Echo- or cardiac MRI- documented intracavitary thrombosis, extreme thinning or intra-myocardial bleeding and/or suspected rupture of the ventricular wall were other exclusion criteria from referral to the CR program.

The following clinical variables were recorded for each patient: Age, gender, body mass index, cardiovascular risk factors, site of infarction, culprit coronary artery vessel, number of diseased coronary artery vessels (defined as presence of diameter stenosis > 50%), history of previous PCI or coronary or valvular surgery, presence of ancillary diseases (renal failure, thyroid dysfunction, known diabetes or abnormal glucose metabolism, pulmonary diseases, history or presence of neoplastic diseases, carotid and peripheral vascular disease) and previous and concurrent drug therapy. During their hospitalisation in CR, all patients without previous diagnosis of diabetes underwent an oral glucose tolerance test to identify subclinical abnormal glucose metabolism. Left ventricular ejection fraction (LVEF) was measured before discharge by 2-D echocardiography, following the Simpson method.

### **Holter monitoring**

On the day of admittance to CR, all patients underwent 24-h ECG Holter recording, using 3-channel digital recorders (Lifecard CF, Del Mar Reynolds, Irvine, CA, United States), monitoring chest leads CM5, CM3 and modified aVF. Recordings were analyzed using a commercial Holter device system (Del Mar-Reynolds Impresario Holter Analysis System, vers. 2.8.0024; Time-domain HRV Analyzer, vers. 1.0.8.4, CENTUM and Del Mar Reynolds Medical Inc., Irvine, CA, United States; sampling rate of 128 Hz).

After cleansing of arrhythmias and artefacts, the usual time domain HRV variables were assessed including: Standard deviation of all normal-to-normal (NN) intervals (SDNN), standard deviation of all 5-min mean NN intervals (SDANN), root mean square of successive differences (RMSSD), and mean of the standard deviations of all RR intervals of all 5-min segments in the 24 h (SDNN-i). For the purposes of

this study, the main variable that was considered in the correlations with other clinical parameters was the SDNN, as it is usually considered a measure of total variance in heart rate; it is also the variable most widely used in previous studies<sup>[10]</sup> and more strongly associated with mortality compared to other variables<sup>[11]</sup>. SDNN parameters were analyzed for the entire 24 h period; analysis of day and night hours was also done separately. "Day" was defined as the time period between 06:00 and 22:59 and "night" as the period between 23:00 and 05:59.

Patients with atrial fibrillation, or rhythm disturbances that could interfere with accurate HRV analysis (e.g., frequent ectopic beats, rhythm induced by pacemaker) were excluded from the study, as were patients with inadequate/inaccurate recordings.

### End points and follow-up

The primary outcome measure was the occurrence of cardiac death; the secondary end-point was occurrence of major clinical events (MCE), defined as death (all-cause mortality, cardiac mortality) or readmission for a new AMI, new revascularization, episodes of heart failure or stroke. At the time of follow-up, the clinical status of the patients was assessed by telephonic interviews, performed either by a doctor or a trained team nurse. In case of clinical events, detailed information was obtained from the patient or his/her relatives. Outcomes were analyzed by intention to treat.

### Statistical analysis

Continuous variables were expressed as a mean  $\pm$  standard deviation (SD) and compared using an unpaired *t* test; otherwise, variables were expressed with median and interquartile range (IQR) and compared using a Wilcoxon-Mann-Whitney test. Categorical variables were expressed as frequencies and percentages and were compared between groups by a  $\chi^2$  test. The relationships between continuous variables were evaluated by Pearson's correlation coefficient. A Cox regression multivariate analysis was also performed to determine the influence of different factors on HRV parameters, including in the multivariable model only variables with a *P* value  $\leq$  0.1 at univariate analysis. HRV variables were initially analyzed as continuous variables; subsequently, HRV variables that showed a significant association with other factors at multivariate analysis were dichotomized and analyzed according to the lowest quartile value. Kaplan-Meier estimates of the distribution of times from baseline to death were computed, and Mantel-Cox Log-Rank analysis was performed to compare the survival curves between the groups. All reported probability values are two-tailed and the significance level was set at 0.05. Statistical analyses were performed using SPSS 18 software package (SPSS Inc, Chicago, IL, United States).

### Statement

During CR hospitalization, all participants had been fully

informed on the procedures they were undergoing; a written consent was obtained from all patients before performance of the medical procedures. The routine diagnostic examinations and follow-up protocol for CR were applied; no special tests or treatments were performed. The research was conducted in accordance with the ethical guidelines of the 1975 Declaration of Helsinki. This study is part of a larger follow-up study on patients admitted to CR; approval of the Provincial Ethics Committee (Provincial Health Directorate, Belluno, Italy) was obtained for the main research.

## RESULTS

### General findings and HRV parameters

Main patients' characteristics are presented in Table 1, together with the medical therapy prescribed at the time of discharge from hospital. Patients with NSTEMI were older than those with STEMI, and presented more often history of hypertension, previous MI and coronary revascularization procedures, and clinical signs of metabolic syndrome. Patients with NSTEMI had greater number of critical coronary stenoses, revascularization was more often incomplete, and such patients presented more often with symptoms of heart failure on initial admission to the coronary care unit.

In the same Table 1, time-domain HRV parameters are also reported. In spite of the above described clinical differences, all main HRV parameters did not show significant differences between STEMI and NSTEMI patients, except for mean heart rate that was lower in NSTEMI cases.

In a total of 52 patients (16% of the whole group; 16% of STEMI and 15% of NSTEMI:  $\chi^2 = 0.067$ , *P* = 0.796), SDNN was  $< 70$  ms, and in 13 (4% of the whole group; STEMI 5.3%, NSTEMI 1.7%:  $\chi^2 = 2.539$ , *P* = 0.111) it was  $< 50$  ms. When subdivided into 4 quartiles according to the value of SDNN, the 81 patients in the lowest quartile presented a mean SDNN of  $63.7 \pm 11.8$  ms (vs a mean of  $119.4 \pm 35.0$  ms of the other quartiles; *P*  $< 0.001$ ). Patients with STEMI or NSTEMI were equally distributed between quartiles of SDNN ( $\chi^2 = 1.536$ , *P* = 0.674).

On average, SDNN was higher during night hours than during day-time (*P*  $< 0.001$ ), although in 109 patients the day-night variation was insignificant or negative; patients with STEMI or NSTEMI behaved in the same way as regards day vs night SDNN.

Female patients presented on average lower values of SDNN than male patients ( $97.1 \pm 42.2$  ms vs  $107.9 \pm 38.1$  ms; *P* = 0.046), and in 24 out of 65 cases they presented SDNN values in the lower quartile (females 37% vs males 17%;  $\chi^2 = 6.723$ , *P* = 0.010).

SDNN values in the lower quartile were present more frequently in patients older than 65 years ( $\chi^2 = 4.478$ , *P* = 0.034), as well as in patients with known diabetes ( $\chi^2 = 10.859$ , *P* = 0.001) but not in patients with abnormal glucose metabolism detected during the rehabilitation period ( $\chi^2 = 0.762$ , *P* = 0.383). Patients

**Table 1** Main data of patients, reported for the whole group and for patients with ST-elevation myocardial infarction and non-ST-elevation myocardial infarction

	All patients (n = 326)	STEMI (n = 208)	NSTEMI (n = 118)	P <sup>1</sup>	P <sup>2</sup>
Age, yr	63.5 ± 12.1	61.3 ± 12.5	67.4 ± 10.4	< 0.001	
Male, n (%)	261 (80)	171 (82)	90 (76)		0.197
History and cardiovascular risk factors					
Known diabetes, n (%)	82 (25)	45 (22)	37 (31)		0.055
Abnormal glucose metabolism, n (%)	106 (32)	68 (33)	38 (32)		0.733
Hypertension, n (%)	238 (73)	134 (64)	104 (88)		< 0.001
Smoking habit, n (%)	106 (32)	81 (39)	25 (21)		0.001
Family history, n (%)	179 (55)	111 (53)	68 (58)		0.367
Previous CABG, n (%)	26 (8)	7 (3)	19 (16)		< 0.001
Previous PCI, n (%)	43 (13)	13 (6)	30 (25)		< 0.001
Previous AMI, n (%)	60 (18)	21 (10)	39 (33)		< 0.001
Previous stroke, n (%)	11 (3)	5 (2)	6 (5)		0.193
Total cholesterol (under treatment), mg/dL	124.3 ± 26.0	123.4 ± 26.3	125.8 ± 25.5	0.424	
Metabolic syndrome, n (%)	204 (62)	124 (60)	80 (68)		0.011
BMI	27.2 ± 4.3	26.9 ± 3.7	27.9 ± 5.2	0.090	
AMI characteristics					
Anterior, n (%)	171 (52)	138 (66)	33 (28)		< 0.001
Inferior, n (%)	86 (26)	66 (32)	20 (17)		0.003
Other, n (%)	69 (21)	4 (2)	65 (55)		< 0.001
Coronary vessels with critical lesions, n	2.05 ± 0.85	1.94 ± 0.84	2.25 ± 0.85	0.002	
1-vessel disease, n (%)	105 (32)	75 (36)	30 (26)		0.014
2-vessels disease, n (%)	97 (30)	68 (33)	29 (25)		
3-vessels disease, n (%)	124 (38)	66 (31)	58 (49)		
Coronary arteries treated by PCI, n	1.29 ± 0.82	1.34 ± 0.72	1.20 ± 0.97	0.141	
Incomplete revascularization, n (%)	151 (46)	87 (42)	64 (54)		0.031
Left ventricle ejection fraction, %	47.2 ± 10.3	47.8 ± 9.2	46.4 ± 12.0	0.222	
Patients with LVEF < 40%, n (%)	85 (26)	43 (21)	41 (35)		0.006
Patient with heart failure at initial admission, n (%)	37 (11)	15 (7)	22 (19)		0.002
Time before Holter, d	16.2 ± 9.6	15.6 ± 9.5	17.4 ± 9.8	0.117	
Therapy at time of discharge from hospital (number of cases, %)					
Aspirin	314 (96)	202 (97)	112 (95)		0.469
Clopidogrel	302 (93)	192 (92)	110 (93)		0.458
Warfarin	38 (12)	22 (11)	16 (14)		0.399
β-blocker	290 (89)	189 (91)	101 (86)		0.198
Ca-antagonist	38 (12)	18 (9)	20 (17)		0.022
ACE-inhibitor	264 (81)	180 (86)	84 (71)		0.001
AT-II-antagonist	43 (13)	16 (8)	27 (23)		< 0.001
Statin	314 (96)	201 (97)	113 (96)		0.893
Diuretic(s)	140 (43)	75 (36)	65 (55)		0.001
HRV parameters					
Mean heart rate, bpm	68.1 ± 10.0	69.1 ± 10.1	66.2 ± 9.7	0.016	
pNN50	10.1 ± 12.0	9.5 ± 10.5	11.1 ± 14.3	0.245	
Triangular Index	18.6 ± 29.9	19.6 ± 44.4	17.0 ± 26.6	0.567	
SDNN, ms	105.7 ± 39.1	105.7 ± 39.2	105.7 ± 39.2	0.990	
SDNN day, ms	95.8 ± 35.4	95.2 ± 33.9	96.8 ± 37.9	0.688	
SDNN night, ms	103.5 ± 41.0	102.8 ± 41.6	104.8 ± 40.1	0.671	
RMSSD, ms	45.0 ± 37.7	42.2 ± 30.6	49.9 ± 47.4	0.079	
SDANN, ms	92.1 ± 33.1	93.5 ± 35.1	89.7 ± 29.4	0.331	
SDNN-i, ms	41.4 ± 22.5	40.7 ± 18.9	42.6 ± 27.7	0.444	

<sup>1</sup>Level of significance from unpaired *t* tests for STEMI and NSTEMI patients; <sup>2</sup>Level of significance from  $\chi^2$  tests for STEMI and NSTEMI patients. ms: Milliseconds; STEMI: ST-elevation myocardial infarction; NSTEMI: Non-ST-elevation myocardial infarction; CABG: Coronary artery by-pass graft; PCI: Percutaneous coronary intervention; AMI: Acute myocardial infarction; BMI: Body mass index; LVEF: Left ventricle ejection fraction; ACE: Angiotensin converting enzyme; AT-II: Angiotensin II receptor type 2; HRV: Heart rate variability; SDNN: Standard deviation of all normal-to-normal intervals; RMSSD: Root mean square of successive differences between normal-to-normal intervals.

with known diabetes presented also absence of the day/night variation of SDNN (SDNN day: 85.2 ± 32.2 ms in diabetic patients vs 99.5 ± 35.7 ms in non-diabetics,  $P = 0.002$ ; SDNN night: 85.3 ± 31.0 ms in diabetic patients vs 109.8 ± 42.2 ms in non-diabetic patients,  $P < 0.001$ ; SDNN day vs night:  $P = 0.975$  in diabetic vs  $P < 0.001$  in non-diabetic patients).

Patients with history of previous MI, or previous CABG or previous PCI were equally distributed among quartiles of SDNN (respectively:  $\chi^2 = 0.017$ ,  $P = 0.999$ ;  $\chi^2 = 1.306$ ,  $P = 0.728$ ;  $\chi^2 = 1.729$ ,  $P = 0.631$ ).

No correlation was found between number of diseased coronary arteries and quartiles of SDNN (whole group:  $\rho -0.044$ ,  $P = 0.428$ ; STEMI:  $\rho 0.001$ ,  $P = 0.985$ ;

NSTEMI:  $\rho$  -0.120,  $P = 0.199$ ). Patients with complete or incomplete coronary revascularization did not differ as regards distribution among quartile of SDNN ( $\chi^2 = 0.059$ ,  $P = 0.807$ ).

Similarly, no correlation was found between quartile of SDNN and successful vs unsuccessful primary PCI (whole group:  $\chi^2 = 0.158$ ,  $P = 0.691$ ; STEMI:  $\chi^2 = 0.031$ ,  $P = 0.861$ ; NSTEMI:  $\chi^2 = 0.684$ ,  $P = 0.408$ ). Overall, patients with unsuccessful primary PCI presented markedly reduced variation of SDNN values between day and night (SDNN day  $94.7 \pm 39.3$  ms; SDNN night  $102.9 \pm 37.9$  ms;  $P = 0.092$ ); by the contrary, such variations persisted in patients with successful primary PCI (SDNN day  $96.2 \pm 34.6$  ms; SDNN night  $103.9 \pm 41.5$  ms;  $P < 0.001$ ).

In the whole group of patients, a linear correlation was found between LVEF and the values of some HRV parameters (SDNN:  $\rho$  0.168,  $P = 0.002$ ; SDANN:  $\rho$  0.225,  $P < 0.001$ ), but not with other HRV parameters such as RMSSD, SDNN Index, Triangular Index and pNN50. Patients with lower LVEF ( $< 40\%$ ) presented more often values of SDNN in the lowest quartile ( $\chi^2 = 12.668$ ;  $P < 0.001$ ). Mean heart rate during the 24 h of Holter recording was lower in patients with higher LVEF ( $\rho$  -0.310,  $P < 0.001$ ).

The 37 patients that presented symptoms of heart failure during the acute phase of AMI showed SDNN values in the lower quartile more often than the remaining patients ( $\chi^2 = 7.884$ ;  $P = 0.005$ ), with SDNN  $< 70$  ms in 32% of cases (vs 14% of the patients without initial symptoms of heart failure;  $\chi^2 = 8.457$ ;  $P = 0.004$ ).

At multivariate Cox regression analysis, a significant correlation with the lowest quartile of SDNN was maintained only by female sex, history of diabetes mellitus and LVEF  $< 40\%$  (respectively:  $\beta = -0.143$ ,  $P = 0.008$ ;  $\beta = 0.146$ ,  $P = 0.008$ ;  $\beta = -0.179$ ,  $P = 0.001$ ).

### Clinical features and outcome

Ten (3.1%) patients were lost to follow up, which occurred a median of 25.0 mo after the index event (95%CI of the mean: 23.3-28.0).

Of the 316 patients which could be interviewed, MCE occurred in 56 (17.2%) of which 20 deaths (6.3%; 14 cardiac deaths), 9 cases of new non fatal AMI (3.0%), 5 patients with stroke (1.6%) and 17 cases of successful elective revascularization (5.4%: 4 CABG, 13 elective PCI); 21 (6.6%) patients had one or more hospital readmissions for heart failure.

No significant difference in overall incidence of MCE at follow-up was evident between cases with STEMI vs NSTEMI ( $\chi^2 = 2.166$ ,  $P = 0.141$ ), although all-cause mortality was higher among NSTEMI patients (14% vs 2%;  $\chi^2 = 17.863$ ,  $P < 0.001$ ) as well as cardiac mortality (10% vs 1.5%;  $\chi^2 = 11.471$ ,  $P = 0.001$ ). Only after one and a half year of follow-up, the Kaplan-Meier MCE-free survival curves begin to diverge, with NSTEMI patients presenting worse outcomes (Mantel-Cox Log-

Rank:  $\chi^2 = 5.525$ ,  $P = 0.019$ ); Figure 1A.

Patients with a 3-vessel disease and those who received an incomplete revascularization had a greater incidence of MCE during the period of follow-up (respectively:  $\chi^2 = 14.369$ ,  $P = 0.006$ ; and  $\chi^2 = 6.987$ ,  $P = 0.008$ ). A significant correlation was evident between all-cause deaths or cardiovascular deaths and number of diseased vessels (respectively:  $\chi^2 = 19.218$ ,  $P = 0.001$ ; and  $\chi^2 = 13.077$ ,  $P = 0.011$ ). Incomplete revascularization showed a correlation with all-cause deaths ( $\chi^2 = 4.732$ ,  $P = 0.030$ ) but not with cardiac deaths ( $\chi^2 = 1.859$ ,  $P = 0.173$ ) at follow-up.

The 234 patients that maintained a better preserved myocardial function, as suggested by LVEF  $> 40\%$ , had lower number of MCE (32) and cardiovascular deaths (3) in the follow-up, than patients with more compromised LVEF, that suffered 24 MCEs and 11 cardiovascular deaths among 82 patients (for MCE:  $\chi^2 = 10.126$ ,  $P = 0.001$ , and OR = 0.383, 95%CI: 0.209-0.701; for cardiovascular deaths:  $\chi^2 = 21.110$ ,  $P < 0.001$ , and OR = 0.084, 95%CI: 0.023-0.309).

At multivariate Cox regression analysis, the variables that showed predictive value for MCE were presence of a three-vessel disease ( $\beta = 0.062$ ,  $P = 0.013$ ), elective PCI ( $\beta = 0.250$ ,  $P = 0.021$ ), known diabetes mellitus ( $\beta = 0.124$ ,  $P = 0.013$ ) and LVEF  $< 40\%$  ( $\beta = -0.114$ ,  $P = 0.017$ ), while no significant correlation was found with age, sex, number of vessels treated by PCI ( $\beta = -0.032$ ,  $P = 0.229$ ), history of incomplete revascularization, STEMI vs NSTEMI ( $\beta = -0.002$ ,  $P = 0.970$ ), site of infarction or presence of signs of heart failure during initial admission.

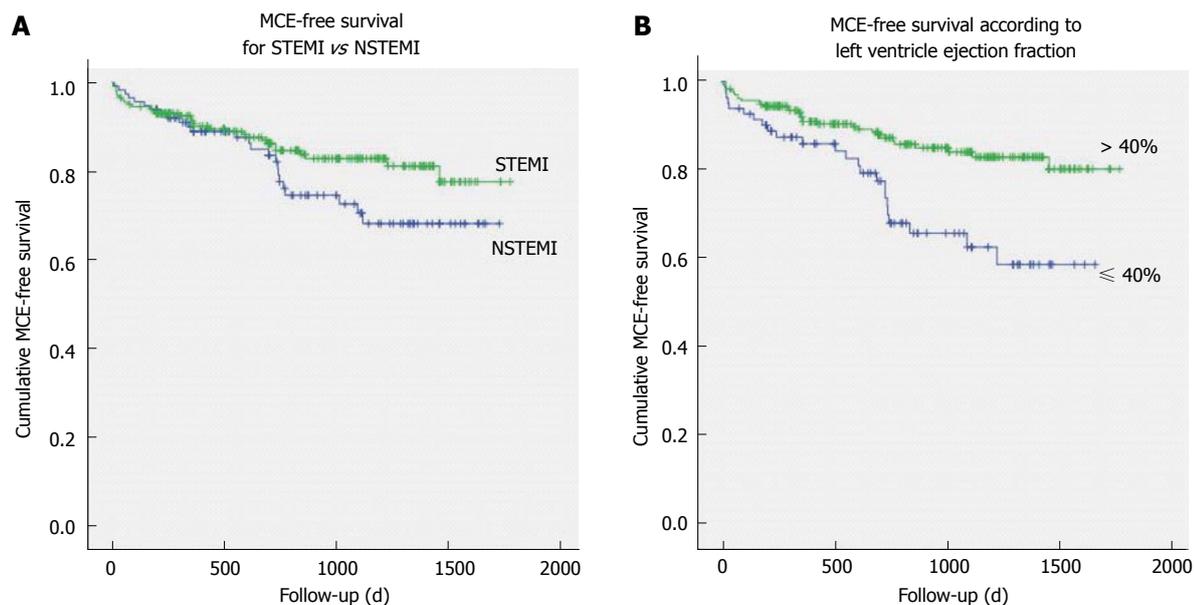
In Figure 1B, the Kaplan-Meier events-free survival curves are presented for patients stratified according to LVEF  $\leq 40\%$  vs LVEF  $> 40\%$ ; the Mantel-Cox Log-Rank demonstrated statistically significant differences between the curves ( $\chi^2 = 10.896$ ,  $P = 0.001$ ).

### HRV and outcome

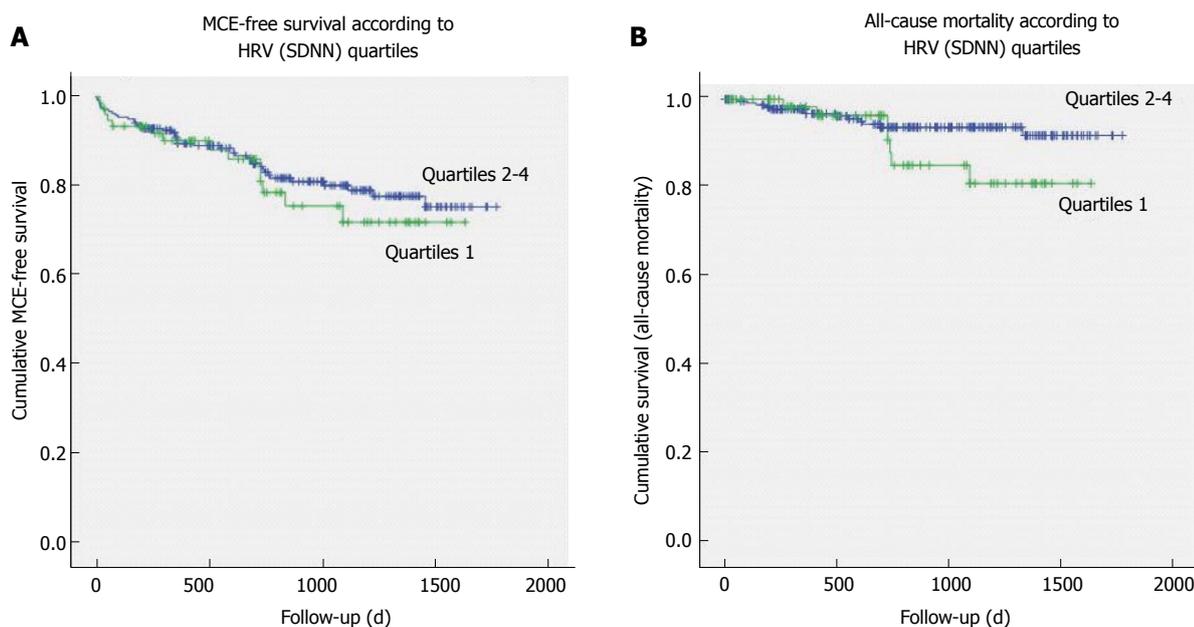
Even in the subgroup in the lower quartile of SDNN, no difference was found in incidence of MCE (14/76 cases) in comparison with other subgroups (42/240 cases), ( $\chi^2 = 0.034$ ,  $P = 0.855$ ); this finding was similar for STEMI and NSTEMI patients (respectively: 10 MCE among 52 STEMI patients with lower quartile of SDNN vs 21/150 of the other quartiles,  $\chi^2 = 0.813$ ,  $P = 0.367$ ; and 4 MCE among 24 NSTEMI patients with lower quartile of SDNN vs 21/90 of the other quartiles,  $\chi^2 = 0.492$ ,  $P = 0.483$ ).

Patients with negative day-night variations of SDNN presented long-term events similar to patients with positive SDNN day-night variations ( $\chi^2 = 2.107$ ,  $P = 0.147$ ).

The Kaplan-Meier MCE-free survival curves were similar between the group of patients with SDNN in the lowest quartile vs the patients of the other SDNN quartiles (Log-Rank  $\chi^2 = 0.376$ ,  $P = 0.540$ ; Figure 2A), with no difference for STEMI (Log-Rank  $\chi^2 = 1.801$ ,  $P =$



**Figure 1** Kaplan-Meier major clinical events-free survival curves for: Patients with recent ST-elevation myocardial infarction vs patients with recent non-ST-elevation myocardial infarction (A), patients with preserved left ventricle ejection fraction (> 40%) vs patients with depressed left ventricle ejection fraction ( $\leq$  40%) (B). STEMI: ST-elevation myocardial infarction; NSTEMI: Non-ST-elevation myocardial infarction; MCE: Major clinical events.

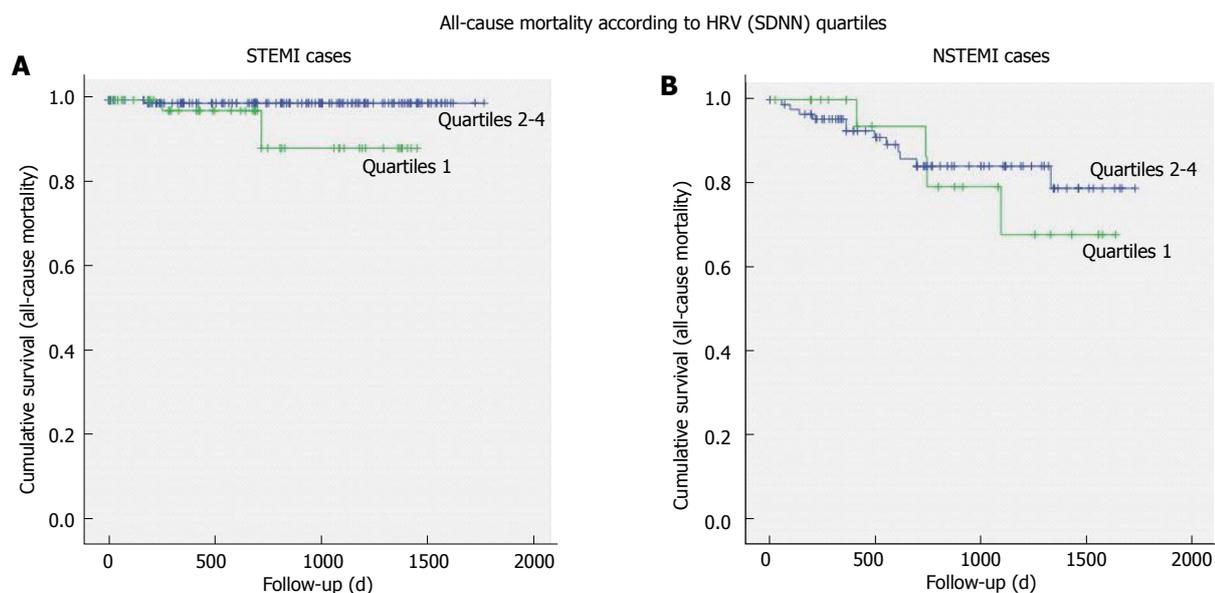


**Figure 2** Kaplan-Meier survival curves for patients with lowest quartile of standard deviation of all normal-to-normal intervals vs patients in the other standard deviation of all normal-to-normal intervals quartiles: Major clinical events-free survival curves (A), all-cause mortality curves (B). HRV: Heart rate variability; SDNN: Standard deviation of all normal-to-normal intervals; MCE: Major clinical events.

0.180) or NSTEMI patients (Log-Rank  $\chi^2 = 0.373$ ,  $P = 0.541$ ). In particular, no correlation was found between quartile of SDNN and recurrence of MI during the follow-up period ( $\chi^2 = 0.489$ ,  $P = 0.484$ ).

As regards to death for all causes, 7 out of 20 deaths occurred among patients with lowest quartile of SDNN ( $\chi^2 = 1.401$ ,  $P = 0.236$ ); analyzing the whole group of AMI patients, the Kaplan-Meier survival curves for all-cause mortality (Figure 2B) and for cardiac deaths did not evidence significant differences between patients

with SDNN in the lowest quartile and other quartiles of SDNN (Mantel-Cox log rank, respectively:  $\chi^2 = 2.207$ ,  $P = 0.137$ ; and  $\chi^2 = 0.399$ ,  $P = 0.527$ ). After separating STEMI from NSTEMI patients, different survival curves have been observed only for all-cause mortality (Figure 3), but not for cardiac mortality: STEMI patients with SDNN in the lowest quartile presented 3 out of 4 all-cause deaths (Mantel-Cox log rank  $\chi^2 = 6.591$ ,  $P = 0.010$ ) and 2 out of 3 cardiac deaths (Log-Rank  $\chi^2 = 3.685$ ,  $P = 0.055$ ), while among NSTEMI patients no



**Figure 3** Kaplan-Meier all-cause mortality curves for ST-elevation myocardial infarction patients (A) and non-ST-elevation myocardial infarction patients (B) divided between cases with lowest quartile of standard deviation of all normal-to-normal intervals vs cases in the other standard deviation of all normal-to-normal intervals quartiles. HRV: Heart rate variability; SDNN: Standard deviation of all normal-to-normal intervals; STEMI: ST-elevation myocardial infarction; NSTEMI: Non-ST-elevation myocardial infarction.

difference in the survival curves was observed between patients with SDNN in the lowest quartile vs the other quartiles (all-cause mortality: Log-Rank  $\chi^2 = 0.195$ ,  $P = 0.659$ ; cardiac deaths: Log rank  $\chi^2 = 0.040$ ,  $P = 0.842$ ).

Analysis of the long term outcomes of patients with low values of RMSSD gave similar results as those described for low SDNN values: Kaplan-Meier events free survival did not differ between patients with RSDNN in lowest quartile vs the other quartiles, both for incidence of MCE ( $\chi^2 = 0.849$ ,  $P = 0.357$ ) and all-cause or cardiac mortality (respectively:  $\chi^2 = 0.060$ ,  $P = 0.806$ ; and  $\chi^2 = 0.245$ ,  $P = 0.621$ ).

#### Patients lost to follow-up

Patients' main clinical parameters (age, sex, time from STEMI to CR, site of infarction, number of diseased vessels, fasting glucose, HbA1c, haemoglobin level at admission, LVEF) and HRV values (SDNN, RMSSD, SDNNi, SDANN) have been compared between the 10 cases lost to follow-up and the 314 patients that completed the study. Patients lost to follow-up presented more elevated average values of HbA1c ( $7.2\% \pm 2.0\%$  vs  $6.4\% \pm 1.1\%$ ;  $P = 0.022$ ) but not of fasting glucose ( $109.5 \pm 37.9$  mg/dL vs  $95.2 \pm 22.5$  mg/dL;  $P = 0.085$ ) at admission. All the other clinical and HRV parameters were not significantly different in comparison to followed-up patients.

## DISCUSSION

In studied patients with STEMI, treatment by primary PCI did not demonstrate a clear effect in reduction of the prevalence of marked depression of HRV in comparison to what was reported in studies performed

in the pre-primary-PCI era: The prevalence of 16% of STEMI patients with SDNN < 70 ms at 2 wk from the acute event is the same as that recorded in the GISSI-2 and the ATRAMI studies, in which patients had been treated conservatively or by thrombolysis<sup>[4,5]</sup>. It is however much lower than that reported by Wiliński *et al*<sup>[7]</sup> in patients treated by primary PCI (21% in patients < 65 years old and 34% in those  $\geq 65$  years old), as well as in other smaller dimension studies in which patients had also been treated by primary PCI<sup>[9,16]</sup>. When considering the subgroup of patients with even more depressed HRV (using the cut-off of SDNN < 50 ms, as in the pivotal study by Kleiger *et al*<sup>[11]</sup>), the prevalence of this abnormal parameter was lower in our STEMI patients (5% in our study vs 15% in Kleiger's study), being somehow similar to that observed also by Erdogan *et al*<sup>[6]</sup> (7%) in patients treated by immediate revascularization. A number of other studies investigating HRV in the post-acute phase of MI have been conducted in the last 15 years. In such studies the percentage of patients treated by primary PCI varied between 18% and 70%, so that their results about the effects of early revascularization on HRV parameters are not easily comparable between them and with our ones<sup>[11,12,17-19]</sup>.

Even if the percentage of patients with markedly depressed SDNN was not clearly reduced by the immediate reperfusion strategy, the overall derangement of HRV parameters in our cases was limited, in spite of our study population being constituted by patients that suffered a complicated AMI: On average, mean HRV values were only slightly lower than those reported in literature for healthy persons of the same age group<sup>[20]</sup>. In fact, in previous studies, it has been observed that

autonomic function is better preserved in patients treated by primary PCI, in comparison to patients who receive fibrinolysis or are treated conservatively<sup>[21]</sup>. It must also be added that all our patients were under treatment with ACE-inhibitors and beta-blockers, drugs that may impact on HRV in post-infarction patients<sup>[22-25]</sup>.

Patients with NSTEMI did not show significant differences in the analyzed HRV parameters in comparison to STEMI patients, even though they presented various factors that may have lead to more depressed HRV (older age, greater prevalence of previous AMI, multiple risk factors, heart failure complicating the initial phase of AMI, often a 3-vessel disease and incomplete revascularization). To the best of our knowledge, before the present study no information was available in the literature regarding HRV in NSTEMI patients, when considered separately.

In 13 follow-up studies conducted between 1987 and 1999 where HRV was analyzed in AMI patients not treated with immediate PCI reperfusion, the reported incidence of long-term mortality ranged widely between 3.4% and 45% of study cases; from the data provided in the papers mortality can be estimated on average to be around 10%<sup>[1,4,5,8,26-34]</sup>. Almost all these studies included both STEMI and NSTEMI patients. More recently, only STEMI patients have been analysed, following treatment by primary PCI: Their long-term mortality rate was reported to be substantially lower than in the pre-primary-PCI era, being possible to calculate it on average around 5% of cases<sup>[6,9,16]</sup>.

In spite of our patients having experienced various kinds of major complications during the initial phase of MI, in STEMI cases both the overall mortality and cardiac mortality at long-term follow-up were rather low, and significantly lower than the long-term mortality of NSTEMI patients. The timely reperfusion strategy, with consequent reduction of infarct size and salvage of more heart muscle, as well as the multiple pharmacological therapy used, may have contributed to the better long-term survival of our STEMI patients<sup>[35]</sup>; the period of intensive and comprehensive exercise-based cardiac rehabilitation followed by our patients may also have contributed to their better prognosis<sup>[36]</sup>.

Low values of SDNN (lowest quartile) recorded at two weeks from the index event did not possess a predictive value for cardiac mortality in our STEMI patients, or in NSTEMI patients, or in the group of MI patients considered as a whole. In the pivotal study by Kleiger *et al.*<sup>[1]</sup>, the finding of a markedly depressed SDNN was a predictor of long-term mortality more than 5 times higher than in patients with preserved SDNN; identical results have been confirmed in the ATRAMI study<sup>[4]</sup>, and substantially similar outcomes have also been reported in other studies performed in the pre-primary-PCI era<sup>[5,29,30]</sup>, as well as in studies that included low percentage of PCI-treated patients<sup>[17]</sup>.

Among primary-PCI treated patients, Erdogan *et al.*<sup>[6]</sup> found that SDNN was lower in non-survivors

than in survivors after a mean follow-up of  $4.3 \pm 3$  years, but this HRV parameter predicted only 1 in 24 cardiac deaths, indicating that the predictive value of a depressed SDNN is low. Our results indicate that the limited derangement of HRV parameters and the low long-term mortality recorded among our patients do not allow to identify if a markedly depressed HRV (as estimated by low SDNN) could still be considered an indicator of poor survival in patients treated by primary PCI.

In the attempt to identify possible differences in secondary outcomes linked to different levels of HRV derangement among AMI patients treated by primary PCI, we studied the long-term incidence of Major Clinical Events, which is a composite parameter that has recently been used in other studies<sup>[9,16]</sup>. Other than mortality (cardiovascular and all-cause deaths), it includes also non-fatal events, such as new AMI, new coronary revascularization, episodes of heart failure, episodes of stroke.

Amongst our cases, patients with more depressed SDNN did not show any significant difference of MCE-free outcomes in comparison to patients with preserved parameters, after a median follow-up period of 25 mo (a period that is in range with most of the previous studies)<sup>[10]</sup>. This is quite a different finding in comparison to other recent small scale studies, that confirmed that abnormal HRV retains some (although low) negative predictive value on long-term prognosis also in primary-PCI treated AMI patients<sup>[9,16]</sup>.

Almost all our patients had been submitted to revascularization of the coronary culprit lesion during the initial phases of their AMI, and a substantial percentage of them had also received revascularization of other critically stenosed coronary arteries, before transferral to CR and recording of 24-h Holter. These facts, together with the pharmacological treatment with beta-blockers and ACE-inhibitors or AT-II-antagonists in use at the time of Holter recording, could have reduced both the autonomic derangement during the subacute phase of the MI and the risk of adverse events in the long-term follow-up.

### Limitations of the study

Criteria of exclusion from this study included presence of atrial fibrillation or flutter, a rhythm induced by the pacemaker, or inadequate Holter recordings. Although such patients may have had significant autonomic dysfunction, HRV could not be measured in them. Consequently it is not known if a depressed HRV could have had any long-term impact on their prognosis.

The degrees of autonomic derangement presented by our patients, that may have been conditioned by the kind of complications suffered during the initial phase of their disease, may possibly not be generalized to the other complicated or uncomplicated STEMI patients.

HRV was performed only in time domain; no analysis was available in the frequency domain. However, it is

already known that time-domain HRV indices measured over a 24-h period are well correlated with frequency domain indices in coronary artery disease patients<sup>[34]</sup>. Among time-domain parameters, SDNN was identified as having the same high predictive value as the frequency-domain LF amplitude in post-AMI patients<sup>[16]</sup>.

### Conclusions

In conclusion, in our group of patients with a recent complicated MI, abnormal autonomic parameters (evidenced by low HRV) have been found with a prevalence that was similar for STEMI and NSTEMI cases, and substantially unchanged in comparison to what reported in the pre-primary-PCI era.

Long-term outcomes in PCI-treated STEMI patients were more favorable than in old cohorts of patients. They did not correlate with the level of depression of HRV parameters recorded in the subacute phase of the disease, both in STEMI and in NSTEMI patients. Traditional HRV parameters seem to have lost their prognostic significance in the present era of immediate coronary reperfusion.

## COMMENTS

### Background

After an acute myocardial infarction (AMI), overactivation of the sympathetic component and relative suppression of the parasympathetic component of the autonomic nervous system occur, leading to a marked imbalance of cardiac autonomic regulation. Such sympatho-vagal imbalance is usually considered to be linked to increased short and long-term mortality. Clinically, cardiac autonomic modulation can be evaluated observing the fluctuations of instantaneous heart rate (intervals between normal RR complexes) during variable periods of time (often 24 h). The most simple and widely used parameter for evaluation of heart rate variability (HRV) is the SDNN (standard deviation of all normal RR intervals), that gives an overall estimate of cardiac autonomic control. In the last 30 years, various studies confirmed that depressed values of SDNN indicate poor prognosis after an AMI. Unfortunately, most of these studies on the prognostic value of depressed HRV in post-AMI patients have been conducted before the primary-PCI era: So, their results may not be easily applied to present day patients, in which early reperfusion (that may lead to salvage of cardiac muscle and preservation of better heart function), multiple pharmacological therapies and cardiac rehabilitation may impact on autonomic balance, quality of life and long-term survival.

### Research frontiers

A few small-scale studies have been conducted so far on AMI patients treated by primary PCI, investigating if depressed HRV maintains a correlation with long-term prognosis. Such studies did not reach clear conclusions. With the present work, the authors aimed at contributing and clarifying if parameters of HRV (in particular SDNN) could still be considered reliable prognostic indicators in primary-PCI-treated AMI patients.

### Innovations and breakthroughs

While in the past depressed HRV had been identified as a reliable marker of poor prognosis after an AMI, this paper demonstrates that nowadays in AMI patients treated by early revascularization HRV has lost its prognostic significance. In addition, the paper is the first to report HRV parameters separately for patients with ST-elevation and Non-ST-elevation myocardial infarction.

### Applications

The evaluation of simple HRV parameters does not seem to hold any more prognostic significance in AMI patients treated by early revascularization. Further

studies are needed in these patients to identify reliable long-term prognostic indicators.

### Terminology

HRV refers to the evaluation of the oscillations in the intervals between consecutive heart beats. They are determined by cyclic variations of sympathetic and parasympathetic autonomic influences on cardiac pace-maker cells, modulated by central and peripheral mechanisms (respiratory and vasomotor centres, fluctuations in arterial pressure, humoral factors). After an AMI, HRV usually presents various degrees of depression, linked to a marked increase of the sympathetic activity (probably due to abnormal geometry of the beating heart and consequent distortion of autonomic nervous endings). The most simple method of evaluating HRV is by statistical analysis of the time intervals between consecutive normal RR beats ("time domain" method); the standard deviation of these intervals (SDNN) has been used in our study. SDNN reflects all the cyclic components responsible for variability in the period of recording; for this reason, it has been used in various studies for assessment of risk after AMI.

### Peer-review

The authors analysed the potential prognosis of HRV in patients treated with primary PCI.

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## Observational Study

# One-year outcome of percutaneous mitral valve repair in patients with severe symptomatic mitral valve regurgitation

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**Institutional review board statement:** The study was reviewed and approved by the Ruhr-University Bochum Institutional Review Board.

**Informed consent statement:** All patients provided oral and written informed consent with respect to the intervention. However, due to the retrospective nature of the study, there was no written consent of patients prior to study enrolment. The study was approved by the Ruhr-University Bochum Institutional Review Board. All patient data were anonymized.

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## Abstract

### AIM

To investigate one-year outcomes after percutaneous mitral valve repair with MitraClip® in patients with severe mitral regurgitation (MR).

### METHODS

Our study investigated consecutive patients with symptomatic severe MR who underwent MitraClip® implantation at the University Hospital Bergmannsheil from 2012 to 2014. The primary study end-point was all-cause mortality. Secondary end-points were degree of MR and functional status after percutaneous mitral valve repair.

### RESULTS

The study population consisted of 46 consecutive patients (mean logistic EuroSCORE 32% ± 21%). The degree of MR decreased significantly (severe MR before MitraClip® 100% vs after MitraClip® 13%;  $P < 0.001$ ), and the NYHA functional classes improved (NYHA III/IV before MitraClip® 98% vs after MitraClip® 35%;  $P < 0.001$ ). The mortality rates 30 d and one year after percutaneous mitral valve repair were 4.3% and 19.5%,

respectively. During the follow-up of  $473 \pm 274$  d, 11 patients died (90% due to cardiovascular death). A pre-procedural plasma B-type natriuretic peptide level  $> 817$  pg/mL was associated with all-cause mortality (hazard ratio, 6.074; 95%CI: 1.257-29.239;  $P = 0.012$ ).

### CONCLUSION

Percutaneous mitral valve repair with MitraClip® has positive effects on hemodynamics and symptoms. Despite the study patients' multiple comorbidities and extremely high operative risk, one-year outcomes after MitraClip® are favorable. Elevated B-type natriuretic peptide levels indicate poorer mid-term survival.

**Key words:** Severe mitral regurgitation; Percutaneous mitral valve repair; MitraClip®; One-year outcome

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**Core tip:** Percutaneous mitral valve repair with the MitraClip® device has positive effects on hemodynamics and symptoms. Despite the multiple comorbidities and extremely high operative risk of the study patients, mid-term outcomes after MitraClip® implantation are favorable. Elevated B-type natriuretic peptide ( $> 817$  pg/mL) levels are indicative of poorer long-term survival.

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## INTRODUCTION

Severe mitral regurgitation (MR) is a common valvular heart disease that has an unfavorable prognosis<sup>[1]</sup>. When possible, mitral valve repair is considered the optimal surgical treatment<sup>[1]</sup>.

In the last few years, percutaneous mitral valve repair has developed into an alternative technique for patients with severe MR, with more than 20000 procedures worldwide<sup>[2,3]</sup>. However, the Everest II study is the only randomized trial that has compared percutaneous repair with heart surgery, and it mainly included patients with degenerative MR who did not have an elevated operative risk<sup>[2]</sup>. By contrast, the current European Society of Cardiology guidelines recommend applying MitraClip® only in symptomatic high-risk patients with severe functional MR (level of evidence IIb)<sup>[1]</sup>.

In recent years, some registry studies<sup>[4-6]</sup> and several smaller studies<sup>[7-11]</sup> concerning MitraClip® have been published. However, relatively little is known about the long-term results of percutaneous mitral valve repair. Therefore, the aim of this study was to assess the one-

year outcome after percutaneous mitral valve repair with MitraClip®.

## MATERIALS AND METHODS

We performed a retrospective study to evaluate the effects of percutaneous mitral valve repair using MitraClip® (Abbott Vascular, Menlo Park, California, United States) on symptoms, hemodynamics and outcomes. The primary study endpoint was all-cause mortality. The secondary endpoints were functional status and degree of MR after percutaneous mitral valve repair.

This study included consecutive patients with symptomatic severe MR who underwent MitraClip® implantation from May 2012 to December 2014 at the University Hospital Bergmannsheil. The risk of mitral valve surgery was estimated using the logistic EuroSCORE I<sup>[12]</sup> and the logistic EuroSCORE II<sup>[13]</sup>. All patient cases were discussed by the cardiology team. The decision to perform percutaneous mitral valve repair was based on: (1) a high EuroSCORE I ( $> 20\%$ ); and (2) serious comorbidities with a considerable risk for heart surgery [for example, porcelain aorta, left ventricular ejection fraction (LVEF)  $< 30\%$ , previous chest radiation and severe chronic obstructive pulmonary disease]. The contraindications were active endocarditis, intracardiac thrombus, limited life expectancy ( $< 1$  year) and unsuitable mitral valve morphology, according to the EVEREST criteria<sup>[2]</sup>.

Written informed consent was given by all patients to receive percutaneous mitral valve repair with the MitraClip®. The study was reviewed and approved by the Ruhr-University Bochum Institutional Review Board.

### Pre-procedural investigations

The pre-procedural examinations of study patients comprised an anamnesis, assessment of functional capacity (NYHA class), laboratory measurements, transthoracic and transesophageal echocardiography and coronary angiography. The diagnosis of coronary artery disease was made in patients with a coronary artery stenosis  $> 50\%$  in the pre-procedural coronary angiography, previous myocardial infarction, coronary artery bypass grafting, or percutaneous coronary intervention.

We measured plasma B-type natriuretic peptide levels on the same day as clinical and echocardiographical examinations. By using a chemiluminescent immunoassay kit (Biosite Triage, San Diego, CA, United States) we analyzed the levels of plasma B-type natriuretic peptide.

All patients underwent transthoracic and transesophageal echocardiography (Vivid 7 or Vivid 9, General Electrics, Horton, Norway) according to the guidelines of the American Society of Echocardiography<sup>[14]</sup>. Using the modified Devereux formula left ventricular myocardial mass was calculated. The Simpson method (using 4- and 2-chamber views) was applied to measure LVEF<sup>[14]</sup>.

According to the American Society of Echocardiography, MR and tricuspid regurgitation was graded as mild, moderate or severe<sup>[15]</sup>. In addition, MR was classified as degenerative, functional or mixed<sup>[15]</sup>. According to the current recommendations, systolic pulmonary pressure and tricuspid annular plane systolic excursion were measured<sup>[16]</sup>.

### **Percutaneous mitral valve repair**

Percutaneous mitral valve repair with the MitraClip® device was executed under general anesthesia without hemodynamic support using a femoral vein. The transeptal puncture and positioning of the device were performed under transesophageal echocardiography and fluoroscopic guidance. After positioning a clip, the remaining MR and mean transmitral gradient were assessed. If the reduction in MR was unsatisfactory, a second clip was positioned. A maximum mean transmitral gradient of 5 mmHg was accepted. Before and after implantation, left atrial pressure was measured invasively. The procedure and MitraClip® system have been previously described in detail<sup>[2,3]</sup>.

Patients were treated with aspirin for 6 mo and with clopidogrel for 30 d<sup>[2]</sup>. When clinically indicated (mainly due to atrial fibrillation), patients also received oral anticoagulation.

### **Postprocedural investigations**

The procedural and in-hospital difficulties were reported according to current recommendations<sup>[17]</sup>. Within 48 h after the MitraClip® procedure, a transthoracic echocardiography was performed.

Follow-up examinations of all surviving study patients were conducted  $3 \pm 2$  mo after the MitraClip® implantation and comprised an assessment of functional capacity (NYHA class) and a transthoracic echocardiography. Any changes in MR, left atrial volume and diameter and left ventricular geometry and function were documented. The follow-up of patients was at least 12 mo and death, myocardial infarction, stroke and hospitalization due to heart failure were documented. During routine ambulatory visits follow-up information was obtained. In case of patients' death, we contacted their physicians to get information about reasons of death.

### **Statistical analysis**

Numerical values were expressed as mean  $\pm$  SD. For the comparison of continuous variables we used unpaired *t* tests or Mann-Whitney *U* test, where appropriate. In order to compare categorical variables we performed  $\chi^2$  analysis. To examine continuous variables before and after MitraClip® implantation, we applied paired Student's *t* test (for normally distributed variables) or Wilcoxon test (for non-normally distributed variables). For categorical variables, we used McNemar's test to measure changes before and after MitraClip® implantation. Univariate Cox proportional hazards model was performed to assess predictors of all-cause death. For

this, all the parameters in Tables 1 and 2 were included in the analysis.

In order to determine cut-off values for plasma B-type natriuretic peptide (BNP), receiver operating characteristic (ROC) curves were performed. The Kaplan-Meier method was used for analysis of all-cause mortality. A comparison of survival between different groups of patients was assumed with log-rank tests. A *P* value  $< 0.05$  was considered to be statistically significant. All probability values reported were two-sided. A statistical review of the study was performed by a biomedical statistician. The analyses were done using SPSS software (version 20.0; SPSS Inc., Chicago, IL, United States).

## **RESULTS**

A total of 48 consecutive patients with native MR who underwent percutaneous mitral valve repair with the MitraClip® device were enrolled between May 2012 and December 2014. During the procedures, no patients died and no cases of stroke or myocardial infarction occurred. In one patient, positioning of the MitraClip® was not possible, and the procedure was thus abandoned. In another patient, leaflet detachment occurred after implantation of the clip. One day after the unsuccessful procedure, this patient received surgical mitral valve repair. Therefore, these two patients were not included in the analysis. The final study cohort consisted of 46 patients. Clip embolization, acute conversion to open surgery, pericardial tamponade, need for resuscitation, need for dialysis, respiratory failure and major bleeding did not occur after MitraClip® implantation.

### **Study cohort and procedure**

The mean age of the study patients (21 women, 25 men) was  $76.5 \pm 9.4$  years, and the mean logistic EuroSCORE I was  $32\% \pm 21\%$ . Plasma BNP was measured in 36 of the 46 patients. The baseline characteristics of the patients are provided in Table 1.

The mean procedure time was  $143 \pm 34$  min (door-to-door time, including general anesthesia). One clip was implanted in 31 patients (67%), and two clips were implanted in 15 patients (33%). Immediately after the percutaneous mitral valve repair, transesophageal echocardiography revealed remaining severe MR in 2 patients (4%). There were no cases of post-procedural mitral stenosis (the transmitral gradient was  $\leq 5$  mmHg in all patients). The invasive hemodynamic measurements demonstrated a significant decrease in mean left atrial pressure (left atrial pressure before procedure  $27 \pm 10$  mmHg vs left atrial pressure after procedure  $23 \pm 10$  mmHg, *P* = 0.018).

### **Clinical follow-up**

The mean duration of hospitalization after MitraClip® procedure was  $11 \pm 8$  d. Within 30 d after the MitraClip® implantation, 2 patients suffered from death due to heart failure. Follow-up examinations were done in

**Table 1 Clinical characteristics, laboratory values and echocardiography results**

	Total (n = 46)	Survivors (n = 35)	Non-survivors (n = 11)	P value
Age (yr)	76.5 ± 9.4	76.4 ± 9.5	76.9 ± 9.6	0.871
Women, n (%)	21 (46)	16 (46)	5 (45)	0.988
Body mass index (kg/m <sup>2</sup> )	26.8 ± 4.3	26.8 ± 4.5	26.6 ± 3.7	0.928
NYHA class				0.818
NYHA class II, n (%)	1 (2)	1 (3)	0 (0)	
NYHA class III, n (%)	27 (59)	20 (57)	7 (64)	
NYHA class IV, n (%)	18 (39)	14 (40)	4 (36)	
Hypertension, n (%)	31 (69)	23 (66)	8 (80)	0.389
Diabetes mellitus, n (%)	21 (47)	17 (49)	4 (40)	0.632
Coronary artery disease, n (%)	27 (60)	22 (63)	5 (50)	0.464
Previous coronary artery bypass grafting, n (%)	15 (34)	12 (35)	3 (30)	0.756
Previous heart valve surgery, n (%)	6 (13)	5 (14)	1 (10)	0.725
Previous stroke, n (%)	5 (11)	5 (14)	0 (0)	0.205
Atrial fibrillation/flutter, n (%)	33 (73)	25 (71)	8 (80)	0.589
Implanted PM/ICD/CRT-device, n (%)	15 (34)	9 (26)	6 (60)	0.067
Chronic obstructive pulmonary disease, n (%)	14 (31)	12 (34)	2 (20)	0.389
Peripheral artery disease, n (%)	6 (13)	4 (11)	2 (18)	0.482
Logistic EuroSCORE I (%)	31.8 ± 21.1	32.1 ± 21.4	30.9 ± 21.2	0.870
Logistic EuroSCORE II (%)	11.9 ± 9.5	12.0 ± 9.5	11.6 ± 9.98	0.885
Laboratory parameters				
Creatinine (mg/dL)	1.4 ± 0.5	1.4 ± 0.5	1.28 ± 0.39	0.476
Hemoglobin (g/dL)	12.1 ± 1.7	12.3 ± 1.6	11.4 ± 2.0	0.256
Plasma BNP (pg/mL) (n = 36)	1022 ± 897	793 ± 611	1710 ± 1264	0.006
Echocardiography				
Mitral regurgitation etiology				
Organic, n (%)	17 (37)	14 (40)	3 (27)	0.446
Functional, n (%)	21 (46)	16 (46)	5 (45)	0.988
Mixed, n (%)	8 (17)	5 (14)	3 (27)	0.322
Left atrial diameter (mm)	51 ± 6	51 ± 6	50 ± 5	0.793
Left atrial volume (mL)	115 ± 43	110 ± 42	134 ± 45	0.118
LV end-diastolic diameter (mm)	55 ± 10	55 ± 10	57 ± 10	0.498
LV end-systolic diameter (mm)	42 ± 12	41 ± 11	45 ± 12	0.313
LV end-diastolic volume (mL)	159 ± 70	152 ± 62	181 ± 93	0.258
LV end-systolic volume (mL)	96 ± 63	88 ± 55	121 ± 82	0.151
LV ejection fraction (%)	42 ± 14	44 ± 14	37 ± 14	0.203
MAPSE (mm)	12 ± 3	13 ± 3	11 ± 3	0.163
TAPSE (mm)	17 ± 5	17 ± 4	18 ± 6	0.527
Tricuspid regurgitation (moderate/severe), n (%)	31 (67)	21 (60)	10 (91)	0.070
sPAP (mmHg)	44 ± 12	44 ± 12	43 ± 14	0.844

NYHA: New York Heart Association; PM/ICD/CRT: Pacemaker, implantable cardioverter defibrillator, Cardiac Resynchronization Therapy; BNP: B-type natriuretic peptide; LV: Left ventricular; sPAP: Systolic pulmonary artery pressure.

the remaining 44 patients (the mean follow-up was 95 d after the percutaneous mitral valve repair).

Prior to the procedure, 98% of our study population was considered NYHA functional class III or IV. After the percutaneous mitral valve repairs, the NYHA functional classes and degree of MR improved significantly (both *P* < 0.001) (Figure 1). Additionally, the left atrial diameter, left atrial volume and systolic pulmonary artery pressure decreased. By contrast, the left ventricular dimensions and LVEF remained unchanged (Table 2). In our study, there were no differences in clinical course after mitral valve repair between patients with organic and with functional MR.

### Mortality and morbidity

The all-cause mortality rate 30 d after percutaneous mitral valve repair was 4.3% (*n* = 2), and this rate increased to 19.5% (*n* = 9) at one year. In the first year after the MitraClip® implantation, no cases of

myocardial infarction occurred, but 2 patients suffered from ischemic stroke. One of these patients had atrial fibrillation and received aspirin and coumarin at the time of stroke. This patient died within the first year. The other patient was in sinus rhythm and received monotherapy with aspirin. Hospitalization due to heart failure occurred in 16 patients (35% of study patients), and of these patients, 7 died within the first year after MitraClip® implantation.

During the follow-up of 473 ± 274 d, the primary endpoint (all-cause mortality) was attained in 11 patients (24%). Reasons for death included heart failure (*n* = 7), myocardial infarction (*n* = 1), unknown causes (*n* = 2) and malignancy (*n* = 1). Kaplan-Meier curves were created for the analysis of all-cause mortality (Figure 2A).

### Predictors of outcome

In the univariate Cox analysis, only plasma BNP was

**Table 2** New York Heart Association class and hemodynamics before and after MitraClip implantation (*n* = 44)

	Before MitraClip	After MitraClip	<i>P</i> value
NYHA class III and IV, <i>n</i> (%)	43 (98)	16 (35)	< 0.001
Mitral regurgitation (severe)	44 (100)	6 (14)	< 0.001
Left atrial diameter (mm)	50 ± 6	49 ± 7	0.039
Left atrial volume (mL)	114 ± 43	102 ± 42	0.008
LV end-diastolic diameter (mm)	55 ± 10	54 ± 11	0.308
LV end-systolic diameter (mm)	42 ± 12	41 ± 12	0.367
LV end-diastolic volume (mL)	158 ± 69	159 ± 75	0.866
LV end-systolic volume (mL)	95 ± 63	95 ± 61	0.993
LV ejection fraction (%)	42 ± 15	44 ± 13	0.216
Severe tricuspid regurgitation, <i>n</i> (%)	12 (27)	9 (20)	0.763
sPAP (mmHg)	44 ± 13	27 ± 10	0.027

LV: Left ventricular; sPAP: Systolic pulmonary artery pressure.

significantly associated to the primary study endpoint. Patients who died after percutaneous mitral valve repair had significantly higher pre-procedural BNP levels compared to patients who survived (Table 1). The ability of BNP to predict all cause-mortality was assessed using ROC curve analysis. Using a cut-off point of BNP > 817 pg/mL, the sensitivity was 78% and the specificity was 70% [area under the ROC curve (AUC) = 0.778, (95%CI: 0.621-0.936; *P* < 0.001)]. A pre-procedural plasma BNP level > 817 pg/mL was associated with all-cause mortality (HR = 6.074; 95%CI: 1.257-29.239; *P* = 0.012) (Figure 2B).

## DISCUSSION

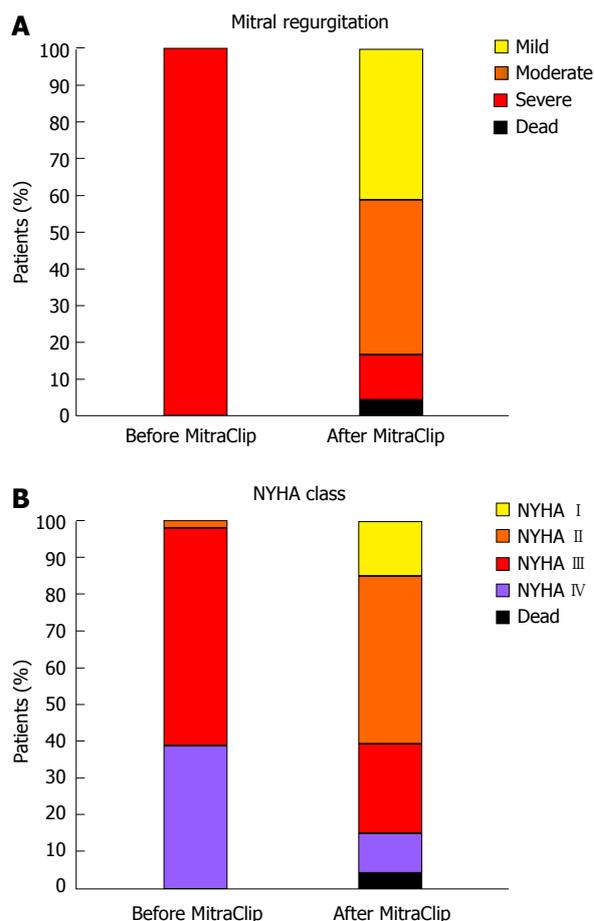
The main result of this study was an improvement in hemodynamics (Figure 1A and Table 2) and symptoms (Figure 1B) in patients with severe symptomatic MR after receiving percutaneous mitral valve repair with the MitraClip® system. However, the relatively high one-year mortality rate (19.5%) observed in the present study must be mentioned (Figure 2A). Preexisting comorbidities of these selected patients who had a very high mean logistic EuroSCORE I of 31.8% (Table 1) is the most likely explanation. Several previous studies reported comparable mortality rates after MitraClip® implantation<sup>[3-11]</sup>.

Additionally, our study suggests that pre-procedural plasma BNP is an independent predictor of all-cause mortality after percutaneous mitral valve repair (Figure 2B).

### Symptoms and hemodynamics

Since the first description of percutaneous mitral valve repair with the MitraClip® device, this technique has now widely used. Today, it is a recognized treatment for high-risk patients with severe and symptomatic MR<sup>[1]</sup>.

Several studies demonstrate symptomatic benefits of percutaneous mitral valve repair in terms of changes in NYHA functional class<sup>[3-11,18,19]</sup>. Vakil *et al*<sup>[18]</sup> found that three-quarters of patients were in NYHA class I or

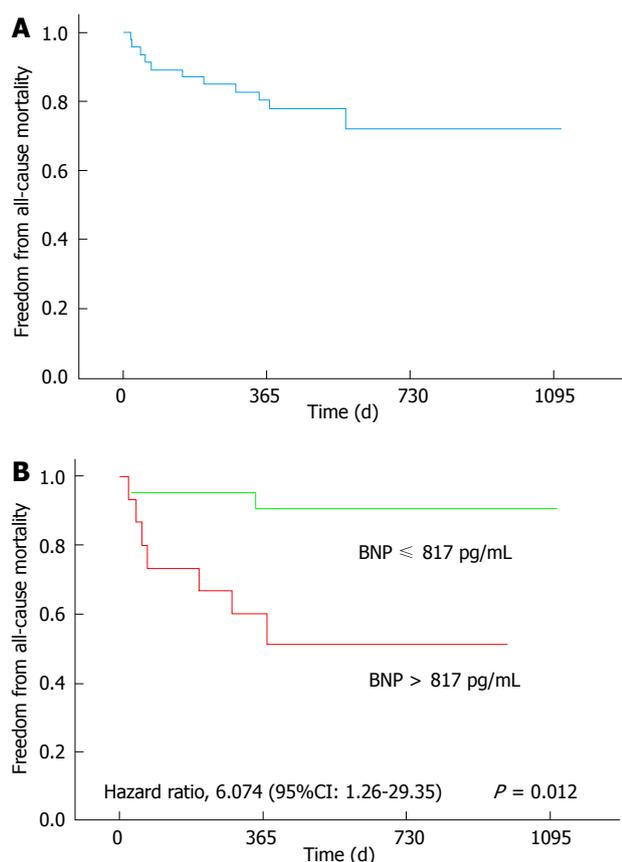


**Figure 1** Changes in mitral regurgitation and New York Heart Association functional class. A: Degree of mitral regurgitation before and after percutaneous mitral valve repair with the MitraClip® system in all study patients (*n* = 46); B: NYHA functional classes before and after percutaneous mitral valve repair with the MitraClip® system in all study patients (*n* = 46). NYHA: New York Heart Association functional class.

II after MitraClip® implantation. Our study confirmed a significant enhancement in NYHA class after MitraClip® implantation (Figure 1B and Table 2).

Other than the fact that percutaneous mitral valve repair is beneficial for treating the symptoms of valvular heart failure, some studies have additionally demonstrated favorable effects of repair on reverse cardiac remodeling<sup>[2,8,10,19]</sup>.

Taramasso *et al*<sup>[19]</sup> revealed an enhancement in LVEF after MitraClip® implantation in patients with heart failure. By contrast, Feldman *et al*<sup>[2]</sup> reported a reduction in left ventricular volumes and LVEF after MitraClip®. These different findings may be explained by the fact that patients with functional and degenerative MR have different types of reverse remodeling. In patients with degenerative MR, end-systolic volume remains stable, whereas left ventricular end-diastolic volume decreases. In contrast, in patients with functional MR, a significant decrease in left ventricular end-diastolic and end-systolic volume is observed<sup>[20]</sup>. Therefore, LVEF decreases slightly in degenerative MR<sup>[2]</sup> and remains constant or increased in functional MR<sup>[19,20]</sup>.



**Figure 2 All-cause mortality and B-type natriuretic peptide.** A: Kaplan-Meier estimates of freedom from all-cause mortality; B: Kaplan-Meier estimates of freedom from all-cause mortality according to low pre-procedural BNP levels (BNP ≤ 817 pg/mL) and high pre-procedural BNP levels (BNP > 817 pg/mL). BNP: B-type natriuretic peptide.

In our study, the proportion of patients with functional and degenerative MR was approximately equal (Table 1). There were no differences in clinical course after mitral valve repair between patients with organic and functional MR. Potentially due to the relatively small number of patients, we observed that the LVEF, the left ventricular end-systolic and end-diastolic volumes remained nearly constant (Table 2).

Our study demonstrated a clear reduction in the severity of MR (Figure 1A), a reduction in left atrial volume and size and a decline in systolic pulmonary artery pressure (Table 2).

### 30-d and one-year outcomes

The all-cause mortality rate 30 d after percutaneous mitral valve repair was 4.3%, and this rate was 19.5% at one year. During the follow-up of  $473 \pm 274$  d, 11 patients (24%) died. Cardiovascular mortality accounted for the majority of the deaths at follow-up (90%). Patients' various cardiac and non-cardiac diseases may explain the relatively high long-term mortality. Similar one-year mortality rates have been reported in several other studies<sup>[3-11]</sup>. However, it should be emphasized that the patients in our study had an extremely high operative risk (mean logistic EuroSCORE I > 31%).

Thus, the risk profile of our patient cohort was less favorable than those of most other studies<sup>[3-11]</sup>. Our study suggests that even patients with an extremely high operative risk can be successfully treated with the MitraClip® system.

### BNP and outcome

Plasma BNP levels have a prognostic impact in patients undergoing surgical mitral surgery<sup>[21]</sup>. In patients undergoing percutaneous mitral valve repair with the MitraClip® device, Taramasso *et al.*<sup>[19]</sup> found that pre-procedural pro-BNP levels (pro-BNP level ≥ 1600 pg/mL) were an independent predictor of mortality. Furthermore, Neuss *et al.*<sup>[22]</sup> demonstrated that among patients with end-stage heart failure and NT-proBNP values > 10000 pg/mL, the mortality rate was extremely high, despite a successful percutaneous mitral valve repair with MitraClip®. Our results are in line with these studies. Although pre-procedural measurements of plasma BNP were performed in only 36 of the 46 patients, we found that BNP levels > 817 pg/mL were related with a considerably higher long-term mortality rate (Figure 2B). Notably, plasma BNP was the only independent predictor of long-term mortality. On the other hand, our study suggests that patients with plasma BNP levels ≤ 817 pg/mL have favorable long-term results after MitraClip® implantation (Figure 2B).

### Limitations

The main limitation of our study is the relatively small number of patients and the fact that this study was conducted only at one center. However, the percutaneous repair of the mitral valve is a relatively new technique. There are still few long-term results of MitraClip® implantation. Another important limitation is the absence of a control group in our study. A comparison with conservatively treated patients, or patients undergoing heart surgery would give a more rigorous investigation of the effects of percutaneous mitral valve repair. As our study examined relatively few patients, the associations found in this paper must still be considered preliminary.

## COMMENTS

### Background

Mitral regurgitation (MR) is the most common heart valve disease and the second most common reason for heart valve surgery. When feasible, mitral valve repair is considered the optimal surgical treatment. However, a considerable portion of patients with severe MR cannot receive surgical treatment because of their co-morbidities and high surgical risks. In the last few years, percutaneous mitral valve repair has become an alternative technique for patients with severe MR.

### Research frontiers

In the last few years, percutaneous mitral valve repair has become an alternative technique for patients with severe MR, with more than 20000 procedures worldwide. However, the Everest II study is the only randomized trial that has compared percutaneous repair with heart surgery, and it mainly included patients with degenerative MR and without an elevated operative risk. By contrast, the

current European Society of Cardiology guidelines recommend applying the MitraClip® only in symptomatic high-risk patients with severe functional MR (level of evidence IIb). In recent years, some registry studies and several smaller studies concerning MitraClip® have been published. However, relatively little is known about the mid- and long-term results of percutaneous mitral valve repair.

### Innovations and breakthroughs

The aim of the present study was to assess the mid-term outcomes after percutaneous mitral valve repair with MitraClip®. The study demonstrates that percutaneous mitral valve repair with MitraClip® had positive effects on hemodynamics and symptoms. Despite the multiple comorbidities and extremely high operative risk of the study patients, the mid-term outcome after MitraClip® was favorable. Elevated BNP levels were indicative of a poorer long-term survival.

### Applications

The data in this study suggest that patients with an extremely high risk can also be successfully treated with the MitraClip® system. In addition, pre-procedural plasma BNP levels > 817 pg/mL were associated with significantly higher long-term mortality. On the other hand, the study suggests that patients with plasma BNP levels ≤ 817 pg/mL had favorable long-term results after MitraClip®.

### Terminology

MR is a valvular heart disease that is characterized by an abnormal systolic blood flow into the left atrium and a volume overload of the left ventricle. The reasons for this condition include defects of the valve (usually referred to as degenerative mitral valve regurgitation) or heart failure with dilatation of the ventricle (usually called functional mitral valve regurgitation). Mitral valve repair is the standard therapy. Percutaneous mitral valve repair has emerged as an alternative technique.

### Peer-review

Good article, well written, interesting for the reader, with a useful "take home message".

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## Observational Study

**How far cardio metabolic and psychological factors affect salt sensitivity in normotensive adult population?**

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**Abstract****AIM**

To evaluate the prevalence of salt sensitivity and the impact of cardiometabolic and psychological characteristics on salt sensitivity in normotensive population.

**METHODS**

Of all participants, anthropometric measurements and fasting venous blood samples were collected, and study questionnaires were completed. Salt Sensitivity was defined based on the difference in mean arterial pressure with infusion of 2 L of normal saline followed by a low sodium diet and administration of three doses

of oral furosemide the day after.

## RESULTS

Of 131 participants, 56 (42.7%) were diagnosed with salt sensitivity. Crude and age and sex adjusted regression analysis showed that low-density lipoprotein cholesterol and depression were positively associated with salt sensitivity (OR = 1.02, 95%CI: 1.01-1.04 and OR = 1.15, 95%CI: 1.00-1.34, respectively).

## CONCLUSION

The high prevalence of salt sensitivity and its significant relation with prevalent risk factors necessitates considering its reduction actions at the population level and the need for further research.

**Key words:** Salt sensitivity; Cardiovascular disease risk factors

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**Core tip:** Mean blood pressure can be reduced following a decrease in sodium intake in both hypertensive and normotensive individuals. Normotensive individuals with salt sensitivity trait are more likely to develop hypertension and other health problems. A relatively high prevalence of salt sensitivity has been indicated among Iranian adults. Low-density lipoprotein cholesterol was found to have strong positive association with salt sensitivity. Depressive individuals were more salt sensitive.

Sadeghi M, Roohafza H, Pourmoghaddas M, Behnamfar O, Pourmoghaddas Z, Heidari E, Mahjoor Z, Mousavi M, Bahonar A, Sarrafzadegan N. How far cardio metabolic and psychological factors affect salt sensitivity in normotensive adult population? *World J Cardiol* 2017; 9(1): 47-54 Available from: URL: <http://www.wjgnet.com/1949-8462/full/v9/i1/47.htm> DOI: <http://dx.doi.org/10.4330/wjc.v9.i1.47>

## INTRODUCTION

Hypertension is a prevalent well-documented risk factor for cardiovascular disease and premature mortality and therefore is an important public health issue<sup>[1]</sup>. Essential hypertension is a common disorder in areas with average daily sodium intake of over 100 meq/d (2.3 g sodium), however, is rarely seen with average daily sodium intake of less than 50 meq/d (1.2 g sodium)<sup>[2,3]</sup>.

It has been demonstrated in multiple studies that mean blood pressure (BP) can be reduced following a decrease in sodium intake in both hypertensive and normotensive individuals<sup>[4,5]</sup>. Based on these reports, a minimum level of dietary sodium independent of other risk factors is required for development of hypertension<sup>[6,7]</sup>.

There is an important clinical benefit to identify

and target individuals who are more sensitive to alterations in dietary sodium intake by implementing dietary sodium reduction interventions. BP variations in response to changes in dietary sodium intake are known as Salt Sensitivity. This responsiveness of BP, however, may vary significantly from individual to individual<sup>[8,9]</sup>. Normotensive individuals with this trait of salt sensitivity are said to be more likely to develop hypertension and other health problems including Cardiovascular, Respiratory, and renal disorders independent of hypertension later in life<sup>[10,11]</sup>.

Although incompletely understood, multiple mechanisms for sodium sensitivity have been demonstrated, from impaired renal sodium excretion, abnormalities in signaling and vascular tone, to the role of genetics in sodium regulation<sup>[12,13]</sup>.

In spite of the fact that the protocols and methods of salt sensitivity definition vary in different studies, there is a general accordance in the main observations. Salt sensitivity appears to be a reproducible phenomenon with different measurement techniques<sup>[14]</sup>.

Salt sensitivity is a practical clinical concept in spite of all the difficulties in measurement and identifying the sensitive individuals. This fact that is evident by positive outcomes of the recommended dietary approaches for the prevention and treatment of hypertension (HTN) (DASH diet)<sup>[15]</sup> There are certain traits and disorders that are markedly associated with salt sensitivity including African American ethnicity, obesity, chronic kidney disease, and cardiovascular risk factors<sup>[9,16]</sup>.

Previous studies conducted in the Eastern Mediterranean region (EMR) demonstrate a substantially high incidence rate of almost all cardiovascular diseases particularly HTN and increased rate of mortality even in treated subjects<sup>[17-20]</sup>. These findings along with the increasing trend of salt intake at the population level<sup>[21]</sup>, beside the lack of evidence of salt sensitivity of BP in Iran and in the region, highlight the importance of conducting this study. Therefore, we aimed to evaluate the prevalence of salt sensitivity in a normotensive Iranian adult population and to investigate the impact of cardiometabolic risk factors and psychological characteristics, on salt sensitivity.

## MATERIALS AND METHODS

### Participants and studied variables

The study was conducted by the hypertension research center affiliated to Cardiovascular Research Institute (a WHO collaborating center in the EMR) from July to October 2014. In order to find potential volunteers from community, we used a wide range of materials from flyers and brochures to posters. A total of 140 healthy participants volunteered to take part in this cross-sectional study. Eligibility requirements included willingness to participate in the study, age 18 years and older, normal BP defined as systolic BP below 140 mmHg and diastolic BP below 90 mmHg based on 3 screening visits of 1 wk apart. The exclusion criteria was

history of hypertension; history of special diet including low salt diets; history of taking antihypertensive medications and diuretics for any reason, oral contraceptives and nonsteroidal anti-inflammatory drugs; any history of myocardial infarction, heart failure, cerebrovascular accidents and renal failure. Written informed consents were obtained from each participant and the study protocol was approved by the ethical committee of Cardiovascular Research Institute.

A questionnaire was used at the baseline observation by trained staff to collect information on demographic characteristics as well as family history of hypertension, coronary artery disease, and lifestyle habits including regular physical activity, dietary pattern and smoking status. The Hospital Anxiety and Depression Scale questionnaire was also used to determine the score of anxiety and depression. This scale consists of seven items for anxiety and seven items for depression, with scores ranging from 0 to 21. The higher scores demonstrate more intensity in anxiety or depression level. Scores higher than 7, in both domains indicate that participants are likely to be depressed or suffer from anxiety<sup>[22,23]</sup>.

Anthropometric measurements of weight, height, waist and hip circumferences were obtained during baseline examination with the individual in minimal clothing. The WHO STEPS Surveillance Manual (The WHO STEP wise Approach to Chronic Disease Risk Factor Surveillance) was used for measuring waist and hip circumference<sup>[24]</sup>. Body mass index (BMI) was calculated as weight (in kilograms) over height squared (in meters).

Venous blood samples after fasting for at least 8 h were taken for measurement of fasting blood sugar (FBS), serum blood urea nitrogen (BUN), creatinine (Cr), uric acid (UA), sodium (Na), potassium (K) levels, and lipid profile including low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglycerides (TG), and total cholesterol (TC). Plasma measurements were assessed using commercially available kits (Parsazmoun). BP was measured by trained staff for each participant using an automated mercury sphygmomanometer with the individual in sitting position and 5 min of rest. All the participants were asked to avoid consumption of alcohol, tea, or coffee, physical exercise or smoking for at least one hour prior to admission. Mean arterial pressure (MAP) was calculated as  $[(2 \times \text{diastolic}) + \text{systolic}]/3$  and reported for each measurement.

We considered the following definitions for cardiovascular risk factors: Current smoking of at least one cigarette per day; lack of regular physical activity (less than 30 min a day, five days a week); raised blood glucose (FBS > 126 mg/dL); elevated blood cholesterol [TC > 200 mg/dL, TG > 150 mg/dL, LDL > 130 mg/dL, HDL below 40 mg/dL (male) and less than 50 mg/dL (female)]; and being overweight or obese (BMI > 25 kg/m<sup>2</sup>, waist circumference > 92 cm in males and > 88 cm in females)<sup>[25]</sup>.

### Study design

The study was conducted in two days. On the first day of the study, individuals were admitted at 8 AM and were put on a low calorie and low sodium diet (10 mmol/d). At this time, venous blood samples were obtained, anthropometric measurements were calculated, and the questionnaires were filled out from participants by trained staff. Two hours after the admission, three measurements of BP were obtained with five minutes intervals and the mean of them was recorded as the baseline BP.

After obtaining the baseline BP, 2 L of normal saline was administered intravenously over 4 h (500 mL/h). Two hours after normal saline infusion, BP was obtained and post-saline MAP was calculated. Then participants were discharged and were asked to return back to the clinic the next morning.

To ensure compliance to the study protocol, individuals were required to eat pre-packaged foods that were prepared according to the protocol including low-carbohydrate, low-fat, and low-sodium diet (10 mmol/d) and were instructed to avoid any foods that were not provided by the study staff. Participants were also followed up over the night by telephone to evaluate any potential side effects and to ensure their adherence to the study dietary protocol.

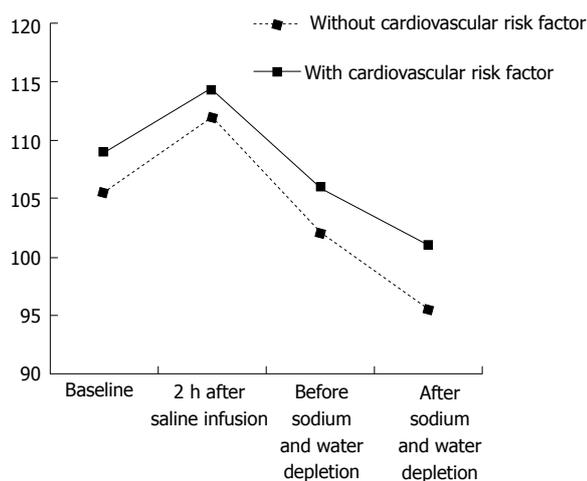
On the following day, participants were admitted again at 8 AM and BPs were obtained. Sodium and volume depletion was then induced by a low sodium diet (10 mmol/d) and administration of three doses of oral furosemide (40 mg each dose, at 10 AM, 2 PM and 6 PM). Two hours after completion of the last dose of furosemide, BP was measured according to the study protocol. The MAP after sodium and volume depletion was compared with the post-saline MAP.

Individuals who demonstrated a decrease in MAP  $\geq$  10 mmHg were defined as "salt sensitive". Those with MAP decrease < 10 mmHg were categorized as "salt insensitive" including both the salt resistant ( $\Delta$ MAP < 6 mmHg) and intermediate ( $\Delta$ MAP 6-10 mmHg) with respect to sodium sensitivity.

### Statistical analysis

All data were analyzed by SPSS, version 15 (SPSS Inc, Chicago, IL, United States). Respectively, a *P* value  $\leq$  0.05 and *P* value  $\leq$  0.1 were considered as statistically and marginally significant for all analyses. Student's *t* test for continuous variables and  $\chi^2$  test for discrete variables were used. Man-Whitney test was applied where appropriate. Multiple Logistic Regression model was carried out to examine the association between demographic, anthropometric, psychological characteristics and laboratory studies of those with the salt sensitivity. Odds ratios (ORs) were reported with the corresponding 95%CI. Repeated measure ANOVA was used for comparing the means of systolic BP in different times.

The dependent variable was salt sensitivity. Inde-



**Figure 1** Means of systolic blood pressure mmHg (vertical axes), measurements at: (1) baseline; (2) 2 h after saline infusion; (3) before sodium and water depletion; and (4) after sodium and water depletion (horizontal axes), among individuals without or with at least one cardiovascular risk factor.

pendent variables included demographic, anthropometric, psychosocial characteristics, laboratory studies, and cardiovascular risk factors of those adjusted based on age and sex. The statistical methods of the study were reviewed by biomedical statistician.

## RESULTS

Of the total of 140 participants, 9 who failed to adhere to dietary protocol or did not complete the intervention were excluded from the study. Among the 131 individuals included in the study, 56 participants (42.7%) were diagnosed with salt sensitivity while 75 (57.3%) participants including 52 (39.7%) salt resistant and 23 (17.6%) intermediate were determined as salt insensitive group. Of participants, hundred were male and 31 were female, with a mean age of  $25.70 \pm 5.71$ . Significant differences were not statistically detected in the age or sex distribution between both groups.

Table 1 shows the baseline demographic, psychological and anthropometric characteristics of participants as well as laboratory evaluations. Lipid profile tests revealed that LDL cholesterol level was significantly higher in Salt Sensitive group compared with Salt Insensitive one ( $P = 0.038$ ). In the Salt Sensitive group, BMI, FBS, BUN, and Cr levels were higher than those in the Salt Insensitive group with a marginally significant difference ( $P = 0.057, 0.072, 0.077, 0.067$ , respectively). There wasn't any significant difference in the Depression or Anxiety Score between two groups.

Table 2 shows the Crude, and age and sex-adjusted logistic regression analysis with salt sensitivity as an outcome. As shown in Table 2, with adjusted logistic regression analysis, LDL along with Depression were found to be the only two variables of significance (OR = 1.02, 95%CI: 1.01-1.04 and OR = 1.15,

95%CI: 1.00-1.34, respectively). At last, multiple logistic regression model with variables including, WC, Depression, FBS, LDL, Cr, age and sex was performed. Finding showed that there were not statistically difference between the result of multiple logistic regression model and age and sex adjusted logistic regression analysis and depression and LDL was still significant.

Means of systolic and diastolic BP measurements in participants without any cardiovascular risk factor compared with those with at least one risk factor at the baseline observation, 2 h after saline infusion, and before and after sodium and water depletion is shown in Figure 1. It has been founded that there is significant difference between baseline, 2 h after saline infusion and before and after sodium and water depletion ( $F = 102.02, P \leq 0.001$ ). No significant interaction was observed between groups and times. ( $F = 0.99, P = 0.39$ ).

## DISCUSSION

As a whole, 131 normotensive individuals properly completed the study protocol and were included in the study analysis. This study showed a relatively high prevalence of salt sensitivity among Iranian adults as well as significant and positive association between the level of LDL cholesterol and salt sensitivity. Based on age and sex adjusted logistic regression analysis, LDL cholesterol and depression were found to have strong positive association with salt sensitivity.

Multiple studies conducted in the EMR have shown high incidence rate of hypertension and its low control level in the region<sup>[18-20]</sup>. This factor along with high average intake of sodium in the Iranian diet<sup>[21]</sup> highlight the importance of integrating salt sensitivity in risk assessment and management of hypertension in the region.

The heterogeneity and susceptibility of individual BP response to Sodium intake is the basis for development of salt sensitivity and appears to be a common, normally distributed biological concept in populations<sup>[10,26]</sup>. The salt sensitivity definition and categorizing individuals to salt sensitive or insensitive is arbitrary and several methods exist to measure salt sensitivity. It can be defined as BP variations in response to a change in dietary salt or as the difference in MAP with infusion of normal saline followed by a low sodium diet and loop diuretic administration the day after<sup>[15,16]</sup>. Our protocol, with salt loading and depletion, allowed us to maximize the follow-up and adherence to the protocol with a more practical and controllable intervention. Despite the differences in the measurement or definition methods, there has been accordance in several findings<sup>[26,27]</sup>.

Overall, 42.7% of participants in our study were diagnosed with salt sensitivity. Even though relatively high, it is still in line with previous reports. The salt sensitivity has been observed in 25%-50% of normotensives and 40%-75% of hypertensive patients

**Table 1** Baseline demographic, cardiometabolic and psychological characteristics of participants with respect to salt sensitivity

Variable	Salt insensitive <i>n</i> = 75	Salt sensitive <i>n</i> = 56	<i>P</i> value
Sex (male) (%)	55 (73.3)	45 (80.4)	0.349 <sup>1</sup>
Age (yr) (mean ± SD)	25.23 ± 4.68	26.36 ± 6.91	0.272 <sup>2</sup>
Family history of HTN (y/n) (%)	22 (29.3)	16 (28.6)	0.995 <sup>1</sup>
Family history of CAD (y/n) (%)	7 (9.3)	6 (10.7)	0.770 <sup>1</sup>
Regular physical activity (y/n) (%)	30 (40.0)	19 (33.9)	0.522 <sup>1</sup>
Current smoker (y/n) (%)	12 (16.0)	8 (14.3)	0.865 <sup>1</sup>
Weight (kg) (mean ± SD)	68.21 ± 13.05	71.16 ± 12.33	0.193 <sup>2</sup>
Body mass index (kg/m <sup>2</sup> ) (mean ± SD)	22.75 ± 2.71	23.71 ± 2.93	0.057 <sup>2</sup>
Waist circumference (cm) (mean ± SD)	81.54 ± 8.96	82.86 ± 8.41	0.404 <sup>2</sup>
Hip circumference (cm) (mean ± SD)	96.97 ± 5.90	97.38 ± 5.77	0.698 <sup>2</sup>
Waist to hip ratio (mean ± SD)	0.83 ± 0.06	0.84 ± 0.05	0.346 <sup>2</sup>
Waist to height ratio (mean ± SD)	0.47 ± 0.04	0.48 ± 0.49	0.382 <sup>2</sup>
Fasting blood sugar (mg/dL) (mean ± SD)	79.71 ± 6.16	82.64 ± 10.74	0.072 <sup>2</sup>
Total cholesterol (mg/dL) (mean ± SD)	156.54 ± 28.70	164.66 ± 26.64	0.109 <sup>2</sup>
High-density lipoprotein cholesterol (mg/dL) (mean ± SD)	46.23 ± 11.90	44.09 ± 12.23	0.327 <sup>2</sup>
Low-density lipoprotein cholesterol (mg/dL) (mean ± SD)	82.56 ± 21.27	90.05 ± 17.49	0.038 <sup>2</sup>
Triglyceride (mg/dL) (mean ± SD)	136.75 ± 97.26	145.32 ± 75.93	0.594 <sup>2</sup>
Uric acid (mg/dL) (mean ± SD)	6.91 ± 6.57	6.42 ± 1.56	0.597 <sup>2</sup>
Sodium (mg/dL) (mean ± SD)	140.30 ± 2.42	140.46 ± 2.39	0.699 <sup>2</sup>
Potassium (mg/dL) (mean ± SD)	4.38 ± 0.53	4.34 ± 0.34	0.662 <sup>2</sup>
Blood urea nitrogen (mg/dL) (mean ± SD)	12.56 ± 3.72	13.73 ± 3.63	0.077 <sup>2</sup>
Creatinine (mg/dL) (mean ± SD)	0.92 ± 0.12	0.96 ± 0.10	0.067 <sup>2</sup>
Depression score (mean ± SD)	4.00 ± 2.66	3.25 ± 2.15	0.095 <sup>3</sup>
Anxiety score (mean ± SD)	3.73 ± 3.18	3.08 ± 3.25	0.161 <sup>3</sup>

<sup>1</sup>*P* value obtained from  $\chi^2$ ; <sup>2</sup>*P* value obtained from t-test; <sup>3</sup>*P* value obtained from Man-Whitney. HTN: Hypertension; CAD: Coronary artery disease.

**Table 2** Crude, age and sex-adjusted logistic regression analysis with salt sensitivity as an outcome

Variable	Crude OR (95%CI)	<i>P</i> value	Adjusted OR (95%CI)	<i>P</i> value
Total cholesterol (mg/dL)	1.01 (1.00-1.02)	0.11	1.01 (1.00-1.03)	0.12
Triglyceride (mg/dL)	1.01 (1.00-1.01)	0.59	1.00 (1.00-1.01)	0.87
High-density lipoprotein cholesterol (mg/dL)	0.99 (0.96-1.02)	0.33	0.99 (0.96-1.02)	0.45
Low-density lipoprotein cholesterol (mg/dL)	1.02 (1.01-1.04)	0.04	1.02 (1.01-1.04)	0.04
Fasting blood sugar (mg/dL)	1.04 (1.00-1.09)	0.06	1.04 (0.99-1.09)	0.14
Sodium (mg/dL)	1.06 (0.97-1.04)	0.35	1.03(0.98-1.05)	0.37
Potassium (mg/dL)	1.05 (0.99-1.07)	0.51	1.06(0.98-1.06)	0.41
Body mass index (kg/m <sup>2</sup> )	1.14 (1.00-1.28)	0.06	1.12 (0.97-1.28)	0.13
Waist circumference (cm)	1.02 (0.98-1.06)	0.40	1.02 (0.97-1.06)	0.49
Waist to hip ratio	1.19 (0.83-1.69)	0.34	1.16 (0.76-1.79)	0.48
Regular physical activity (y/n)	0.79 (0.38-1.64)	0.52	0.85 (0.39-1.82)	0.66
Smoking (y/n)	1.07 (0.95-1.15)	0.40	1.08 (0.97-1.25)	0.47
Depression (y/n)	1.14 (0.98-1.32)	0.06	1.15 (1.00-1.34)	0.04
Family history of HTN (y/n)	1.19 (0.37-3.85)	0.77	1.28 (0.35-4.76)	0.70

HTN: Hypertension.

depending on the measurement techniques and geographic variation of studies in different ethnic populations<sup>[4,5,28]</sup>.

Several mechanisms for sodium sensitivity have been demonstrated<sup>[29]</sup>. Impaired renal sodium excretion with resultant sodium retention that leads to volume expansion has been suggested as one of the underlying mechanism<sup>[30-32]</sup>. Abnormalities in signaling and vascular tone in response to sodium intake are another possible process<sup>[13,14]</sup>. Multiple genes are shown to be associated with sodium regulation and salt sensitivity<sup>[33,34]</sup>. This genetic predisposition is thought to be responsible for several relations seen in the salt sensitive group.

The strong, positive association of LDL cholesterol level with salt sensitivity presented in Table 2 can be interpreted by the role of genetic predisposition. In a study by Hoffmann *et al.*<sup>[35]</sup>, the endothelial nitric oxide synthase (*ENOS*) gene polymorphism was shown to be associated with higher levels of LDL cholesterol and reduced levels of nitric oxide (NO) production that can be responsible for the increased BP sensitivity to salt. Several previous studies have also revealed that the alpha-adducin gene polymorphisms may increase the LDL cholesterol levels and are probably responsible for salt sensitivity of BP<sup>[33,36,37]</sup>.

In the present study, depression was found to

be a potential predictive variable for salt sensitivity. The mechanism by which depression is related to salt sensitivity is not clearly understood and further studies are required. However, this association can be explained by the role of stress as a predisposing factor to depression in susceptibility of BP to salt. Previous studies have demonstrated the contribution of the stress and sympathetic nervous system to salt sensitivity<sup>[10,38,39]</sup>. One mechanism might be the impaired stress-induced renin-angiotensin-aldosterone system regulation<sup>[40]</sup>.

Depression and elevated LDL cholesterol level are reported to be highly prevalent among the Iranian population<sup>[41]</sup>. The fact that makes the importance of these two factors in salt sensitivity was even more significant among Iranian population.

Our findings showed that in the crude model, BMI, FBS, BUN and Cr levels were related to salt sensitivity with a marginally significant difference. The association between BMI and salt sensitivity has been noted in previous studies<sup>[39,42]</sup>. This relation may be explained by the higher sodium renal tubular reabsorption in obese individuals or due to drinking more soft drinks while eating salty products. Multiple previous studies have identified strong association between the plasma glucose level as a metabolic risk factor with salt sensitivity of BP independent of BMI, physical activity and hypertension<sup>[43]</sup>. Reduced renal function, which can be monitored with the level of BUN and Cr, has been also shown in previous observations to be associated with salt sensitivity<sup>[31]</sup>.

The prevalence of salt sensitivity is increased among older individuals with a family history of hypertension<sup>[11,29]</sup>, however, our results failed to show an association between higher age or positive family history of HTN and salt sensitivity. Multiple Factors such as including only normotensive participants, and relatively small sample size of the study can be considered as the reason for these inconclusive observations or differences found in our study compared to others.

The limitations of our study include relatively small sample size, the measurement method used for defining salt sensitivity, and exclusion of hypertensive individuals from the study. Even though all these factors were intentionally incorporated into the study design to enhance the practicality, feasibility and efficacy of the study, they ought to be considered as the limitations of the study.

According to our knowledge, this study is the first to investigate and report the prevalence and characteristics of salt sensitivity in our country and the EMR. The important clinical and public health implications of our study necessitate the need for more studies with larger sample size and to consider hypertensive patients too.

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## COMMENTS

### Background

Blood pressure (BP) can be reduced following a decrease in sodium intake in both hypertensive and normotensive individuals. There is an important clinical benefit to identify and target individuals who are more sensitive to alterations in dietary sodium intake by implementing dietary sodium reduction interventions. Normotensive individuals more likely develop hypertension and other health problems including cardiovascular, respiratory, and renal disorders independent of hypertension later in life.

### Research frontiers

Increasing trend of salt intake at the population level beside the lack of evidence of salt sensitivity of BP in Iran and in the region, highlight the importance of conducting this study.

### Innovations and breakthroughs

This study evaluates the prevalence of salt sensitivity in a normotensive Iranian adult population and to investigate the impact of cardiometabolic risk factors and psychological characteristics, on salt sensitivity. According to our knowledge, this study is the first to investigate and report the prevalence and characteristics of salt sensitivity in our country and the Eastern Mediterranean Region.

### Applications

Salt sensitivity is a practical clinical concept in spite of all the difficulties in measurement and identifying the sensitive individuals.

### Terminology

Salt sensitivity is a measure of how your BP responds to salt intake. People are either salt-sensitive or salt-resistant. Salt sensitive individuals are more likely to have high BP than those who are resistant to salt; Normotensive having or denoting a normal BP.

### Peer-review

This is an interesting manuscript about the relations of salt sensitivity to cardiometabolic risk factors and psychological characteristics.

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## Simultaneous ramp right heart catheterization and echocardiography in a ReliantHeart left ventricular assist device

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### Abstract

Many clinicians caring for patients with continuous flow left ventricular assist devices (CF-LVAD) use ramp right heart catheterization (RHC) studies to optimize pump speed and also to troubleshoot CF-LVAD malfunction. An investigational device, the ReliantHeart Heart Assist 5 (Houston, TX), provides the added benefit of an ultrasonic flow probe on the outflow graft that directly measures flow through the CF-LVAD. We performed a simultaneous ramp RHC and echocardiogram on a patient who received the above CF-LVAD to optimize pump parameters and investigate elevated flow through the CF-LVAD as measured by the flow probe. We found that the patient's hemodynamics were optimized at their baseline pump speed, and that the measured cardiac output *via* the Fick principle was lower than that measured by the flow probe. Right heart catheterization may be useful to investigate discrepancies between flow measured by a CF-LVAD and a patient's clinical presentation, particularly in investigational devices where little clinical experience exists. More data is needed to elucidate the correlation between the flow measured by an ultrasonic probe and cardiac output as measured by RHC.

**Key words:** Left ventricular assist devices; Right heart catheterization; Ramp study; Flow estimation

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**Core tip:** Commercially available left ventricular assist

devices estimate flow through the device, but a new investigational device with an ultrasonic flow probe directly measures flow. Despite a reported accuracy in the flow probe's measurement of flow, we found that this value was inaccurate in a patient whose flows were discrepant to the patient's clinical status by performing echocardiography and right heart catheterization. Care should be taken to verify technical advances in mechanical circulatory support, and both imaging and hemodynamic evaluations can help clinicians make more informed decisions.

Banerjee D, Dutt D, Duclos S, Sallam K, Wheeler M, Ha R. Simultaneous ramp right heart catheterization and echocardiography in a ReliantHeart left ventricular assist device. *World J Cardiol* 2017; 9(1): 55-59 Available from: URL: <http://www.wjgnet.com/1949-8462/full/v9/i1/55.htm> DOI: <http://dx.doi.org/10.4330/wjc.v9.i1.55>

## INTRODUCTION

To optimize the function of continuous left ventricular assist devices (CF-LVAD) after implantation, we and others<sup>[1]</sup> routinely use ramp right heart catheterization (RHC) protocols. These studies may provide added data beyond ramp echocardiogram protocols<sup>[2]</sup>, since a ramp RHC can simultaneously measure right and left sided filling pressures (central venous pressure and pulmonary capillary wedge pressure, respectively). While use of echocardiography has proven useful for optimization of HeartMate II (Pleasanton, CA) CF-LVAD pump speed, this has not proven helpful for other CF-LVADs<sup>[3]</sup>. As new CF-LVADs are developed and implanted, ramp RHC studies can be particularly helpful in defining optimal pump speed, since there is little clinical experience to turn to for guidance.

An investigational CF-LVAD, the ReliantHeart Heart Assist 5 (Houston, TX), incorporates an ultrasonic flow probe around the outflow graft that directly measures flow with a high reported accuracy<sup>[4]</sup>. There is no initial calibration with echo of RHC required, nor is there calibration based on blood viscosity (hematocrit) or patient's heart rhythm.

Here we provide the initial report of a combined ramp RHC and ramp echocardiogram in a patient after ReliantHeart implantation, and provide a comparison of measured flow through the CF-LVAD to cardiac output measured by right heart catheterization.

A 50-year-old man underwent placement of a ReliantHeart LVAD as a bridge to cardiac transplantation at our hospital. In the intensive care unit his flow through the CF-LVAD as measured by the flow probe ranged between 5 and 6 L/min, with cardiac output measured *via* the Fick principle in the 7-8 L/min range, and cardiac output by thermodilution in the 7-8 L/min range as well. The flow through the CF-LVAD as measured by

the flow probe increased to a range of 8-9 L/min on post-operative day 8, just prior to transfer out of the intensive care unit. Serum lactate dehydrogenase (LDH) levels were normal, and there were no signs of hemolysis in laboratory studies. The elevated measured flows with concomitant elevation in power consumption to 7-8 W raised a concern for pump malfunction, and we performed simultaneous ramp RHC and ramp echocardiography for further evaluation.

## CASE REPORT

The patient was brought to the catheterization laboratory in the post-absorptive state. A Swan-Ganz catheter was placed *via* the right internal jugular vein *via* the Seldinger technique, and two pressure transducers were attached to the catheter to measure central venous pressure and pulmonary capillary wedge pressure simultaneously. We changed the speed by 400 revolutions per minute (rpm) and waited two minutes at each setting before measuring intracardiac pressures and cardiac output (CO) *via* an assumed Fick determination ( $CO = VO_{2\max} / (\text{oxygen concentration of arterial blood} - \text{oxygen concentration of mixed venous blood})$ ).  $VO_{2\max}$  was assumed at 125 mL O<sub>2</sub>/BSA. At each setting, we also performed transthoracic echocardiography, measuring left ventricular end diastolic dimension, septal positioning, frequency of aortic valve opening, and the degree of mitral regurgitation.

Table 1 displays the measured changes in hemodynamic parameters with changes in RPM.

The baseline speed was 9100 RPM. We changed speed by 400 RPM increments to determine the best hemodynamics (normal biventricular filling pressures with normal cardiac output), as well as optimal aortic valve opening (aortic valve opening frequency of at least 1:3 cardiac cycles).

Biventricular filling pressures declined with an increase in pump speed, while cardiac output increased. The "v-wave" in the PCWP tracing was present at lower speeds (Figure 1A), but was reduced at 9100 RPM (Figure 1B). The flow measured through the CF-LVAD was consistently higher than the measured cardiac output by the Fick principle.

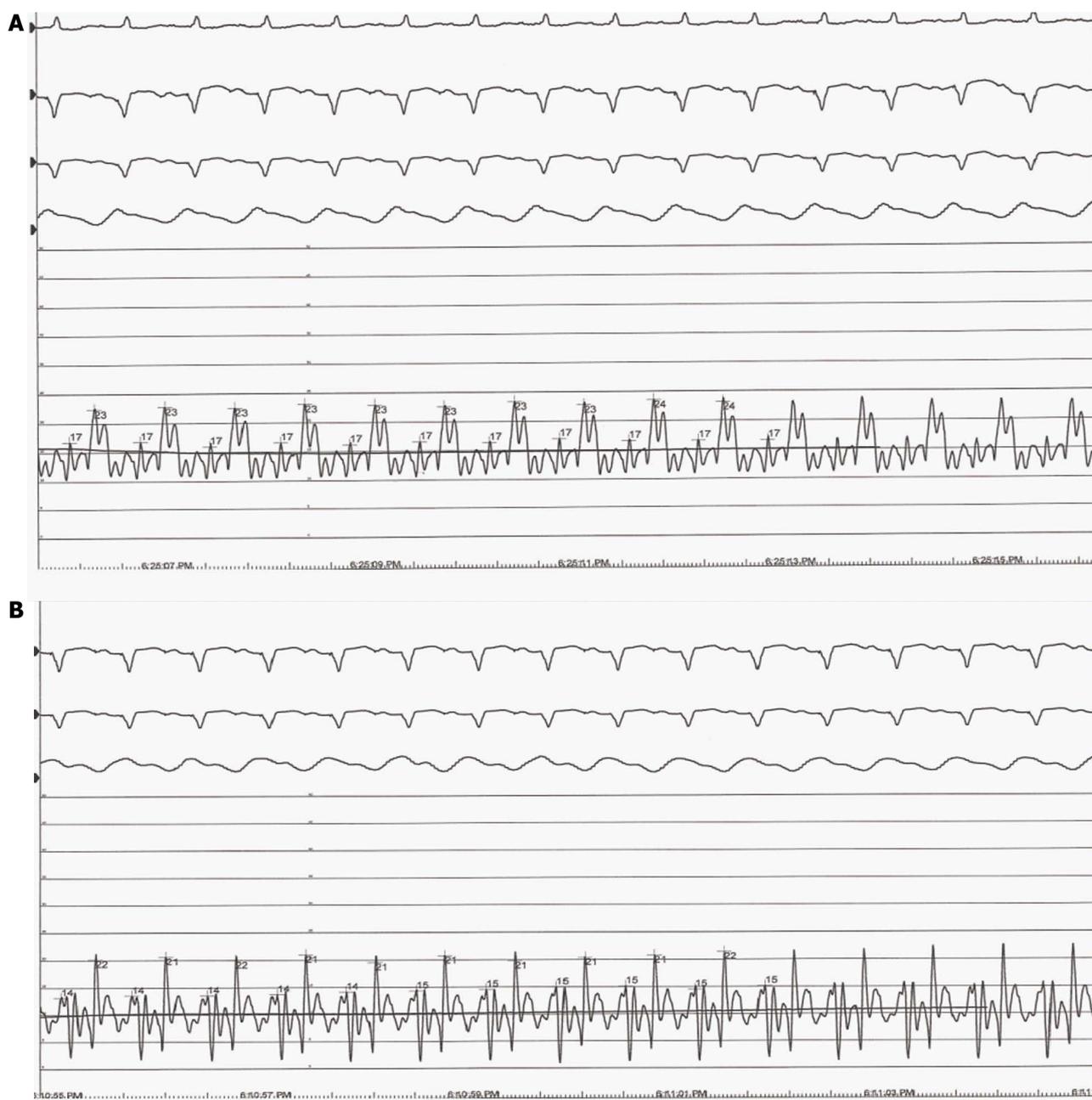
Echocardiography revealed that at 8300 RPM the aortic valve opened with every cardiac cycle, at 8700 RPM the valve opened 1:2 cardiac cycles, and the valve remained closed at 9100 RPM. At baseline RPM the left ventricular end diastolic dimension (LVIDd) was 8.0 cm and the interventricular septum (IVS) bowed mildly toward the LV. As pump speed increased, the degree of mitral regurgitation decreased, the LVIDd decreased further to 7.8 cm but the IVS shifted even more toward the LV. At lower speeds the IVS was midline, and at 8300 RPM the LVIDd was 8.3 cm. There was no evidence of aortic insufficiency or intracardiac shunting.

As a result, given acceptable hemodynamics at 8700 RPM and intermittent aortic valve opening with optimal

**Table 1** Changes in hemodynamic parameters with changes in speed of the ReliantHeart continuous flow left ventricular assist devices

RPM	RAP (mmHg)	RVP	PAP	PCWP	CO (L/min)	CI (L/min per meters square)	Flow (L/min)	Power (W)
8300	11		44/20/28	15	6.3	2.2	7.3	6.4
8700	10		40/18/25	14	6.4	2.5	7.9	7.1
9100 baseline	7	30/15	33/15/21	10	6.5	2.8	8.4	7.8
9500	6		35/15/22	10	6.7	2.9	8.7	8.6

RPM: Revolutions per minute; RAP: Right atrial pressure; RVP: Right ventricular pressure; PAP: Pulmonary arterial pressure; PCWP: Pulmonary capillary wedge pressure; CO: Cardiac output; CI: Cardiac index.



**Figure 1** This figure shows the effect of increasing pump speed on the pulmonary capillary wedge pressure tracing. In 8700 RPM (A), the PCWP is measured at 14 mmHg with a pronounced “v” wave. At 9100 RPM (B), the “V-wave” disappears, and the PCWP has decreased to 10 mmHg. Flow and Power refer to flow measured by the LVAD and power consumed by the LVAD, respectively. LVAD: Left ventricular assist devices.

position of the IVS, the speed was changed to 8700 RPM at the conclusion of the study.

## DISCUSSION

We here report, to our knowledge, the first combined ramp RHC and ramp echocardiogram procedure in a patient receiving the ReliantHeart investigational CF-LVAD. This study reinforces the importance of incorporating simultaneous hemodynamic and echocardiographic data into defining the optimal pump speed for a patient with a CF-LVAD.

Our group commonly performs both ramp RHC and ramp echocardiography in patients for speed optimization post CF-LVAD placement, in the post-operative setting, as well as annually, and with clinical and laboratory data concerning for possible pump thrombosis. Published results corroborate the finding of our clinical practice. Ramp RHC in particular can demonstrate inadequate unloading of the left ventricle in patients who seem well compensated by clinical examination, or those with significant right ventricular dysfunction.

Ramp RHC can also be used to troubleshoot abnormal CF-LVAD parameters that are discrepant from clinical evaluation. In other CF-LVADs, high pump flows may signify pump thrombus or septic physiology. In this case, because an ultrasonic flow probe measured high flow, we worried the patient could indeed be in high flow state concerning for sepsis, intra-cardiac shunt or aortic regurgitation. On invasive hemodynamic assessment, we found the patient was adequately unloaded by the CF-LVAD (normal filling pressures and cardiac output) at the baseline RPM. After increasing the RPM, the loss of the V-wave on the PCWP tracing, coupled with aortic valve closure by echocardiogram, argued against the presence of a high cardiac output state, as these suggest further unloading by the CF-LVAD.

Interestingly, the flows measured by the flow probe at the time of the study were higher than the total cardiac output, suggesting a degree of inaccuracy in the flow probe measurement. We would have expected the measured flow through the CF-LVAD to be lower than the total cardiac output as measured by the Fick principle, as the total cardiac output should account for both flow through the native heart and flow through the CF-LVAD. That relationship was seen earlier in the patient's hospital course, but was lost by the time the patient left the intensive care unit.

We do not have extensive data detailing the correlation between flow as measured by the ultrasonic flow probe of this investigational device and measured cardiac output *via* the Fick principle. We did note that the device's power consumption also increased after implant to 8 W, although this was within the manufacturer specifications. This is an investigational device, and expected pump parameters still need to be described. In any case, early high pump powers are not necessarily indicative of future adverse events<sup>[5]</sup>, and our patient had stable serum LDH values and no other evidence of pump thrombus.

One potential explanation for the unexpectedly high flows as measured by the flow probe is pressure drift,

a slow change in the sensor that can shift its calibration and lead to inaccurate readings<sup>[6]</sup>. This drift has been seen in implantable left atrial pressure sensors over time. In addition, intraoperative placement of the flow probe is important. If the graft is not contacting the flow probe, then the measured flow may not be accurate. Shift of the flow probe over time could also lead to a shift in measured flow. Clinicians should use corroborative techniques (such as RHC) to confirm abnormal changes in CF-LVAD flows before acting on that data, both for CF-LVADs that estimate flows and those that directly measure flows.

One limitation of our study was the use of an assumed Fick calculation. We felt that was mitigated somewhat by the concomitant thermodilution data in the intensive care unit, which closely correlated with the Fick cardiac output. Simultaneous measurement of Fick and thermodilution cardiac outputs in the catheterization laboratory, as well as the use of metabolic cart to calculate peak oxygen consumption would more directly address this limitation.

In summary, we report here the utility of combined ramp RHC and ramp echocardiography to optimize speed in a patient receiving an investigational CF-LVAD, and troubleshoot abnormal parameters reported by that CF-LVAD. More data is needed to elucidate the correlation between the flow measured by the ultrasonic probe and cardiac output as measured by RHC.

## COMMENTS

### Case characteristics

A 59-year-old man with a severe nonischemic cardiomyopathy presented with elevated left ventricular assist device flows as measured by an ultrasonic flow probe despite normal clinical status.

### Clinical diagnosis

Inaccurate flow estimation by ultrasonic flow probe.

### Differential diagnosis

Left ventricular assist devices (LVAD) pump thrombus, LVAD outflow graft malposition, infection.

### Laboratory diagnosis

All laboratory studies were within normal limits.

### Imaging diagnosis

Echocardiogram revealed normal LVAD function with appropriate decompression of the left ventricle as speed increased.

### Related reports

Pressure drift has been noted in other pressure sensors, such as left atrial and pulmonary artery pressure monitors.

### Term explanation

Ultrasonic.

### Experience and lessons

Ultrasonic flow probes may provide inaccurate measures of flow through left ventricular assist devices, and more data is needed to elucidate the correlation

between the flow measured by the ultrasonic probe and cardiac output as measured by right heart catheterization.

### Peer-review

The paper is well written.

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## Longitudinal deformation of a third generation zotarolimus eluting stent: "The concertina returns!"

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### Abstract

In the current case series we describe two cases of longitudinal stent deformation in ostial lesions treated with a new generation zotarolimus eluting stent and review current literature on longitudinal stent deformation. Historically not a common occurrence, longitudinal deformation occurred mainly in Promus Element everolimus eluting stents, which had only two rather than the commonly used 3 links between stent rings. Longitudinal deformation commonly occurs secondary to compression of the proximal edge of the stent by either the guide catheters, or intravascular balloons and imaging catheters. The degree of deformation however, depends on the longitudinal strength and design of the stent.

**Key words:** Coronary angioplasty; Longitudinal stent deformation; Coronary stents; Procedural complications

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**Core tip:** In the current case series we describe two cases of longitudinal stent deformation in ostial lesions treated with a new generation zotarolimus eluting stent and review current literature on longitudinal stent deformation.

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## INTRODUCTION

Over the last decade there has been remarkable progress in coronary stent design and materials. Early generation stents were stainless steel followed by the use of cobalt chromium and platinum chromium alloys, enabling stents to be thinner and more flexible, hence improving deliverability and conformability. In addition, thin stent struts have been associated with improved outcomes in drug eluting stents<sup>[1-3]</sup>. With the reduction in strut thickness, innovative designs have enabled maintenance of radial strength, however, longitudinal stent strength may have been compromised.

A recently observed complication includes longitudinal stent deformation, defined as the distortion or shortening of a stent in the longitudinal axis following successful stent deployment<sup>[4]</sup>. Longitudinal stent strength is dependent on the architectural composition - number, orientation, shape, thickness and material of the crest (or ring) and links. For example, the reduction in number of links between cells may enhance deliverability (by allowing more lateral bending) but as a consequence may compromise longitudinal strength. Longitudinal deformation can result in protrusion of struts into lumen. Extensive malapposition of struts may result in disruption of blood flow and increased risk of stent thrombosis<sup>[5,6]</sup>. In addition, longitudinal deformation of drug eluting stents may result in uneven drug delivery that can result in higher rates of in-stent restenosis<sup>[7]</sup>.

In the current case series and review we describe two cases of longitudinal deformation with the new Resolute Onyx (Medtronic Inc., United States) zotarolimus eluting stents (ZES) and review the literature on longitudinal deformation. This new generation ZES has a novel design, manufactured from a single strand of core wire (platinum iridium) shaped into a continuous sinusoidal waveform. The strut thickness is 81  $\mu\text{m}$ , rendering it extremely trackable and conformable. Every 4<sup>th</sup> crown is laser fused to provide uniform longitudinal strength across the length of the stent.

## CASE REPORT

### Case 1

A 78-year-old male with diabetes mellitus, hypertension, hypercholesterolemia, and chronic renal failure presented with stable angina. Elective coronary angiography demonstrated significant lesions in the ostial and mid segments of a tortuous right coronary artery (RCA) (Figure 1A). The Judkins Right 4 catheter

did not provide sufficient support therefore a 3 dimensional (3D) right coronary (Williams) guide catheter was used to intubate the RCA. This provided improved, yet suboptimal support, therefore a buddy wire was used to facilitate the implantation of a ZES (Resolute Onyx 2.75 mm  $\times$  38 mm, Medtronic) in the mid segment. Subsequently, the ostial-proximal lesion was pre-dilated, stented with a Resolute Onyx 3.0 mm  $\times$  22 mm ZES and post-dilated with a 3.0 mm non-compliant (NC) balloon (Figure 1B). Following stent deployment and removal of the buddy wire, significant longitudinal deformation was noted (Figure 1C), which was treated with non-compliant balloon dilatation and third ZES insertion (Resolute Onyx 3.0 mm  $\times$  18 mm) all the way to the ostium (Figure 1D).

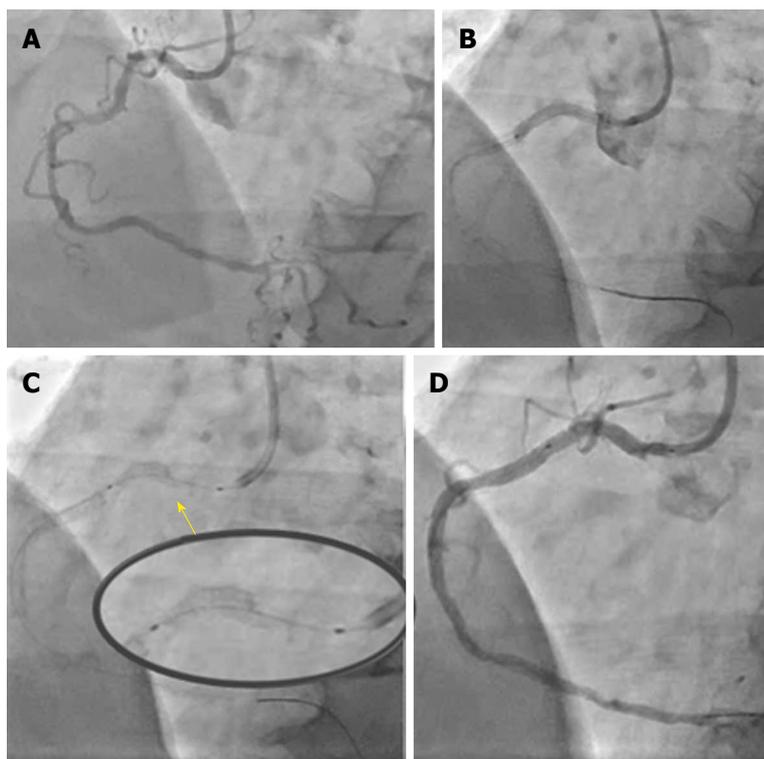
### Case 2

A 85-year-old male with end stage renal failure and severely impaired left ventricular systolic function presented with rapidly conducted atrial fibrillation and raised troponin (6000, upper normal limits 30) with inferolateral ST depression on electrocardiogram. On coronary angiography, he had severe three-vessel and left main disease. After being turned down for surgery, his proximal tight RCA lesion was stented with a Resolute Onyx 4.5 mm  $\times$  12 mm and post-dilated with a 5 mm non-compliant balloon. In view of the heavily calcified ostial/distal left main stem (LMS) and proximal left anterior descending (LAD) disease (Figure 2A) and bursting non-compliant balloons, decision was made to rotablate the lesions first with 1.5 mm burr. Subsequently a 3.0 mm non-compliant balloon was used to pre-dilate all lesions successfully. The proximal LAD was stented with a Resolute Onyx 3.0 mm  $\times$  26 mm stent. The whole length of the LMS into the proximal LAD was stented with a 3.5 mm  $\times$  34 mm Resolute Onyx covering the LMS ostium (Figure 2B and C). The LMS segment of the stent was post-dilated with a 4.5 mm NC balloon. Immediately after and despite taking care in removing the trapped LCx wire, there was longitudinal deformation of the stent, which no longer covered the LMS ostium (Figure 2D). After ballooning the deformed stent with a 4.5 mm non-compliant balloon the ostium was covered with another 4.0 mm  $\times$  8 mm stent and post-dilated with 4.5 mm NC balloon with an excellent final result (Figure 2E).

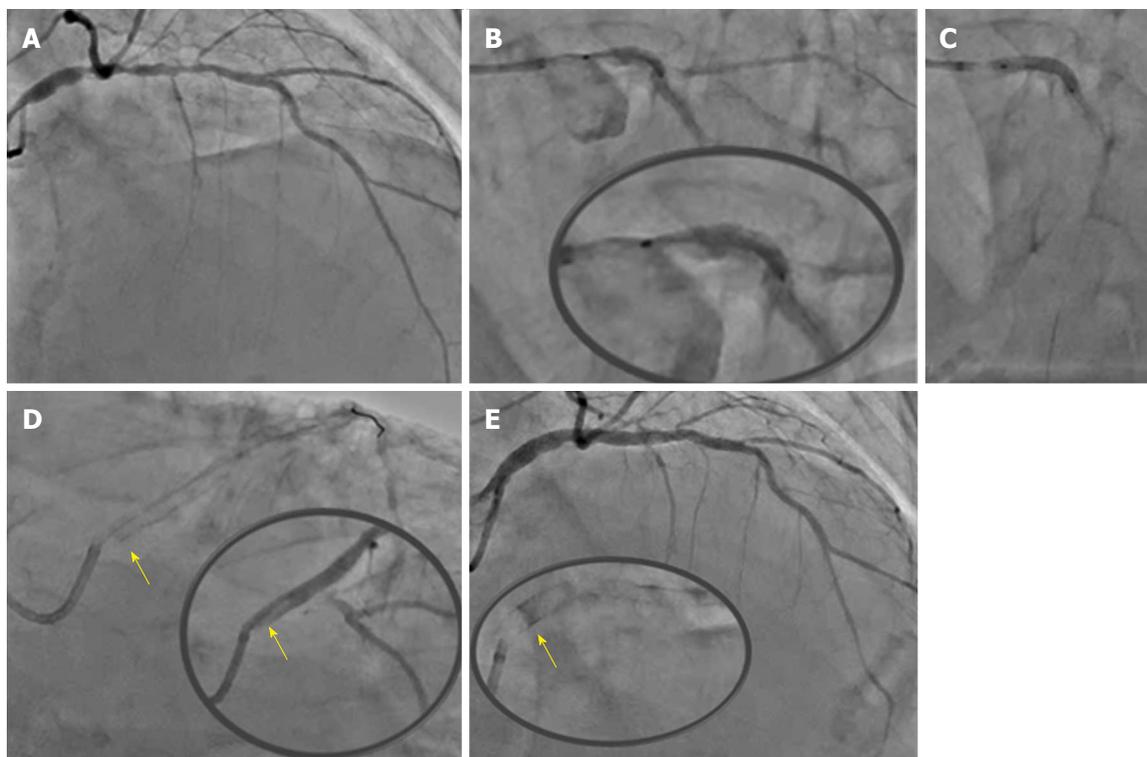
## DISCUSSION

To our knowledge this case series demonstrates the first reported cases of longitudinal deformation in patients treated with the new Resolute Onyx stent platform.

Traditionally, longitudinal strength was not considered standard characteristics for stent performance. However, recent evidence has highlighted possible complications since longitudinal deformation was first reported by Hanratty *et al*<sup>[8]</sup>, describing 3 cases where longitudinal compression of a previously deployed stent resulted in



**Figure 1** Longitudinal deformation of a stent implanted at the ostium of the right coronary artery. A: Initial angiogram showing severe calcific lesions in proximal and mid right coronary artery; B: Proximal lesion stented all the way to cover the ostium with a Resolute Onyx 3.0 mm × 22 mm stent; C: Longitudinal deformation of proximal stent treated with 3.0 non-compliant balloon and another 3.0 mm × 18 mm Resolute Onyx stent; D: Final angiographic result.



**Figure 2** Longitudinal deformation of an ostial left main stem stent. A: Initial angiogram showing significant calcific ostial and distal left main lesions with further significant proximal LAD calcific disease; B: After 1.5 burr rotablation, LMS into proximal LAD was stented with a 3.5 mm × 34 mm Resolute Onyx (B) to 14atm covering the LMS ostium (C). The LMS segment of the stent was post-dilated with a 4.5 NC balloon and the jailed LCx wire removed; D: Longitudinal deformation of the ostial LMS stent (yellow arrow pointing at the proximal deformed edge of the stent); E: Final angiographic result after covering the ostial LMS with a 4.0 mm × 8 mm Resolute Onyx stent. LAD: Left anterior descending; LMS: Left main stem.

**Table 1** Design characteristics of commonly used stents

Stents	Xience V	Xience PRIME/ Xience Xpedition	Promus Element	Promus Premier	SYNERGY	Resolute Onyx
Stent platform	Vision: CoCr	Multilink-9: CoCr	PtCr	PtCr	PtCr	PtIr core Co alloy outer
Strut thickness	81 µm	81 µm	81 µm	81 µm	74 µm	81 µm (up to 4.0 mm) 91 µm (4.5 and 5.0 mm)
Connectors	3 links	3 links	2 links	2 links (4 between the 3 proximal hoops)	2 links	Every 4 <sup>th</sup> crown laser fused (in the 2.75, 3.0 mm platforms every 5 <sup>th</sup> crown fused)
Drug eluting Polymer	Everolimus Primer layer PBMA Drug matrix layer A semicrystalline random copolymer: PvDF-HFP	Everolimus Bioabsorbable PLGA	Zotarolimus Biocompatible BioLinX polymer			
Manufacturer	Abbott vascular, Santa Clara, CA, United States	Abbott vascular, Santa Clara, CA, United States	Boston Scientific, Natick, MA, United States	Boston Scientific, Natick, MA, United States	Boston Scientific, Natick, MA, United States	Medtronic CardioVascular Ltd, MN, United States

CoCr: Cobalt–chromium; PBMA: Poly(n-butyl methacrylate); PLGA: Poly(d,l-lactide-co-glycolide); PtCr: Platinum–chromium; PtIr: Platinum-iridium; PvDF-HFP: Poly(vinylidene fluoride-co-hexa fluoropropylene).

stent deformation. Two were identified angiographically and one with the aid of intravascular imaging. It was first documented with the Promus Element (Boston Scientific) stent which was related to guide catheter compression of stents deployed in an ostial location<sup>[8]</sup>. However, Hanratty *et al.*<sup>[8]</sup> have observed this phenomenon in other drug eluting stents. A retrospective analysis of 4455 interventional cases over a four-year period showed stent deformation occurred in 0.2% of patients affecting 0.097% of stents deployed<sup>[7]</sup>. In 6 cases, Promus Element was involved, and there was 1 case each involving Endeavor (Medtronic), Biomatrix (Biosensors Interventional Technologies), and TAXUS Liberté (Boston Scientific) stents. The rate of stent deformation varied from 0% in several other stent types to 0.86% in the case of the Promus Element stent. In the same series, there was one case of late stent thrombosis attributable to longitudinal stent deformation<sup>[7]</sup>. In the DUTCH-PEERS study 906 patients were assigned to receive third generation zotarolimus-eluting stents (Resolute Integrity, Medtronic) and 905 to receive everolimus-eluting stents (Promus Element, Boston Scientific)<sup>[9]</sup>. Longitudinal stent deformation was seen only in the everolimus-eluting stent group [nine (1.0%) of 905 vs 0 of 906,  $P = 0.002$ ; nine of 1591 (0.6%) everolimus-eluting stents implanted became deformed], but was not associated with any adverse events.

Despite drug eluting stents having improved remarkably the safety and efficacy of revascularization procedures, stent design is a continuously developing field that aims to balance numerous performance attributes such as stent flexibility, shortening on expansion, trackability, scaffolding, radiopacity, longitudinal strength, radial strength and recoil. An experimental evaluation of longitudinal strength of four commercially available stent design families demonstrated that a 50 g force

resulted in longitudinal compression of 1.25–5.30 mm (4.46%–18.93%, compared with the nominal expanded stent length). The Promus Element stent platform had an average longitudinal compression of 13.20 mm (47.07%), demonstrating marked lower resistance to longitudinal compression (Table 1)<sup>[10]</sup>. Newer stent platforms with ultrathin struts (down to 60 µm) have shown non-inferiority to established everolimus platforms<sup>[11]</sup> but their longitudinal strength has yet to be assessed on the bench.

In our series both cases of longitudinal deformation occurred in the hands of very experienced operators implanting the scaffold at an ostial location. Potential reasons behind the deformation could include guide catheter compression of the proximal edge of the ostial stent post removal of jailed wires (case 1 or 2) or aggressive post-dilatation of the stent with a significantly larger NC balloon causing longitudinal shortening (case 2). It is unclear whether laser fusion provides less support compared to traditional links and further evidence is required prior to drawing any conclusions.

In conclusion, longitudinal stent deformation can occur even with new generation ZES and identification is important as, if left untreated, it may associate with a risk of future stent thrombosis, restenosis, and challenges in rewiring and retreating these lesions in the future.

## COMMENTS

### Case characteristics

The authors presented two cases, one with stable angina and one presenting with a non ST elevation myocardial infarction, requiring treatment of ostial lesions with new generation drug eluting stents.

### Treatment

Both cases were treated with the third generation zotarolimus eluting stent

Resolut Onyx, and in both cases longitudinal deformation of the stents was observed. This was managed with further ballooning and stenting.

### Experiences and lessons

Longitudinal stent deformation can occur even with new generation ZES and identification is important.

### Peer-review

This manuscript reports two cases of longitudinal deformation of a 22-mm and 34-mm third generation zotarolimus eluting stent. The issue brought up by the authors is interesting and the cases well documented.

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## Interventional treatment of the left subclavian in 2 patients with coronary steal syndrome

Julia Heid, Britta Vogel, Arnt Kristen, Wanda Kloos, Benedikt Kohler, Hugo A Katus, Grigorios Korosoglou

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### Abstract

In patients with history of coronary artery disease angina pectoris is usually attributed to the progression of atherosclerotic lesions. However, in patients with previous coronary artery bypass graft operation (CABG) using internal mammary artery grafts, great vessel disease should also be considered. Herein we present two patients with history of CABG whose symptoms were suspicious for coronary ischemia. During cardiac catheterization reverse blood flow was observed from the left artery disease to the left internal mammary artery (LIMA) graft in both cases. After angioplasty and stent implantation of the left subclavian artery antegrade flow was restored in the LIMA grafts and both patients had complete resolution of symptoms.

**Key words:** Coronary steal syndrome; Coronary artery bypass graft; Left subclavian artery; Reverse blood flow; Cardiac catheterization

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**Core tip:** Both coronary and peripheral artery diseases are comorbidities with increasing morbidity and mortality. In patients with history of coronary artery disease and previous coronary revascularization, angina pectoris is usually attributed to the progression of atherosclerotic lesions. However, in patients who previously underwent coronary artery bypass graft operation (CABG) using internal mammary artery grafts, subclavian artery disease should also be considered. Herein we present 2 patients who previously underwent CABG with symptoms of myocardial ischemia due to subclavian artery stenosis.

Heid J, Vogel B, Kristen A, Kloos W, Kohler B, Katus HA, Korosoglou G. Interventional treatment of the left subclavian in 2 patients with coronary steal syndrome. *World J Cardiol* 2017; 9(1): 65-70 Available from: URL: <http://www.wjgnet.com>

## INTRODUCTION

Coronary and peripheral artery disease (CAD and PAD) are both comorbidities which exhibit a high prevalence and increasing morbidity and mortality in the western world<sup>[1]</sup>. Especially PAD is estimated to affect over 200 million people worldwide, and around 30% of primary care individuals over 70 years old<sup>[2,3]</sup>. Patients with symptomatic PAD exhibit a life expectancy of 80% at 5 years of follow-up, whereas 20% of such patients experience non-fatal cardiovascular complications<sup>[4,5]</sup>. Interestingly, PAD patients have significantly less chance of receiving appropriate risk factor modification (*e.g.*, statin therapy) and antithrombotic treatment compared to patients with CAD<sup>[1]</sup>. In addition, the prevalence of unrecognised PAD is extremely high (68%) in patients referred for coronary angiography for suspected CAD, especially in individuals with low socioeconomic status<sup>[6]</sup>.

In patients with history of CAD and previous coronary revascularization, angina pectoris is usually attributed to the progression of atherosclerotic lesions. However, in patients who previously underwent coronary artery bypass graft operation (CABG) using internal mammary artery grafts, great vessel disease, for example of the subclavian artery, should also be considered. In this regard, the coronary subclavian steal syndrome is a rare complication after CABG when the left internal mammary artery (LIMA) graft is used. This disease is characterized by retrograde flow from the LIMA graft to the distal post-stenotic part of the subclavian artery during muscle work and increased oxygen and blood demand of the arm in order to maintain adequate perfusion of the left hand. As a result, patients with such a condition may develop typical symptoms of myocardial ischemia despite patency of the grafted vessels.

## CASE REPORT

Herein we present a mini series of two patients (Patient A, Patient B) with suspected progress of the known multi-vessel CAD. Both patients had history of previous CABG including a LIMA graft to the left artery disease (LAD). Baseline characteristics of our patients are provided in Table 1.

Patient A was referred to our department for an elective coronary angiography due to typical angina symptoms (CCS class III) during exertion since 4 wk. He had a history of multi vessel disease with prior CABG 14 years ago.

The initial coronary angiography revealed a 75% ostial stenosis of the left main coronary artery. Despite the presence of significant left main stenosis, reverse blood flow was observed from the LAD to the LIMA

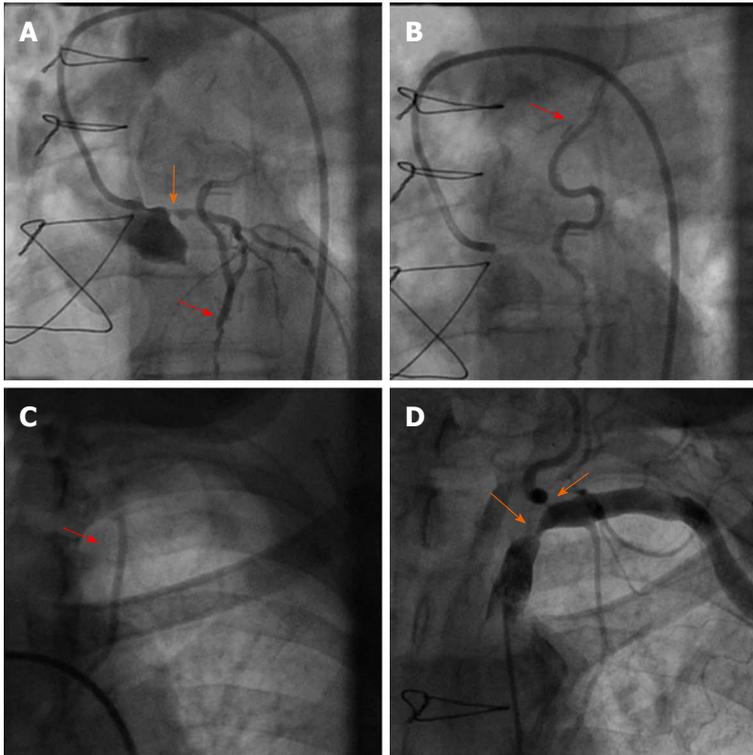
**Table 1** Baseline characteristics of our 2 patients: Typical angina symptoms indicate Canadian Cardiovascular Society

	Patient A	Patient B
Sex	Male	Male
Age (yr)	75	78
Cardiovascular risk factors	Arterial hypertension Hyperlipidemia Obesity	Arterial hypertension Hyperlipidemia Previous smoker
CAD CABG	Known 3-vessel-disease 14 yr ago LIMA graft to the LAD Venous grafts to the right coronary (RCA) and the LCX	Known 2-vessel disease 9 yr ago LIMA graft to the LAD Venous graft to the first marginal branch
Left ventricular function	Mildly impaired	Mildly impaired
PAD history	Previous recanalization of left (2009) and right (2010) superficial femoral artery	Surgical endarterectomy of the left internal carotid artery 2013 High grade lesions in the left vertebral artery and left subclavian artery (accidental finding in a computed tomography performed one year earlier)
Initial symptoms	Typical angina symptoms (CCS III)	Presyncope and atypical angina
Baseline medication	Aspirin β-blocker Angiotensin converting enzyme inhibitor Statin	Aspirin β-blocker Angiotensin converting enzyme inhibitor Statin Calcium antagonist Diuretics

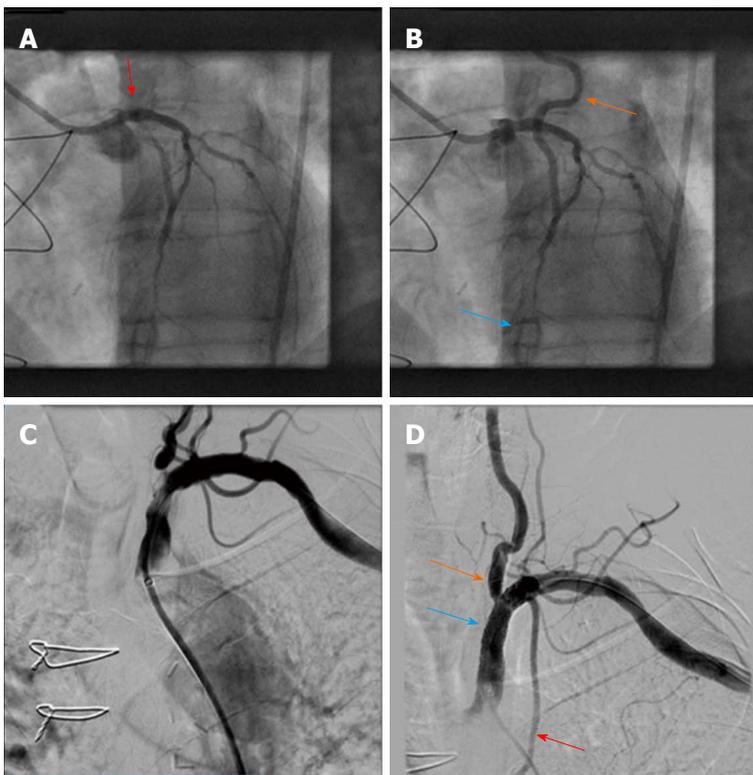
LIMA: Left internal mammary artery; LCX: Left circumflex artery; LAD: Left anterior descending; CAD: Coronary artery disease; CABG: Coronary artery bypass graft operation.

graft. Thus, contrast opacification could be followed up to the insertion of the graft at the subclavian artery (Figure 1). Both the 2 vein grafts to the left circumflex and the right coronary artery were patent. In addition, angiography of the subclavian artery revealed high grade lesions in the subclavian and the origin of the left vertebral artery (Figure 1). Hereby, con-current retrograde flow from the LAD was observed during contrast agent injection.

Due to typical angina and significant left main disease, PCI of left main artery and stent placement (Promus Element 4.0 mm × 20 mm, Boston Scientific) was performed in patient A with a good angiographic result (Figure 2). However, retrograde flow from the LAD to the LIMA graft remained after percutaneous coronary intervention (PCI), and sparse flow was seen in the distal LAD despite successful left main PCI (orange and blue arrows in Figure 2, respectively). After 4 wk the patient was scheduled for PCI of his left subclavian artery due to suspected LIMA steal syndrome. Interestingly, at that time he reported on persistence of CCS class III anginal symptoms. Angioplasty could be performed successfully, followed by bifurcation stent



**Figure 1** Reverse blood flow was observed from the left artery disease to the left internal mammary artery graft. During coronary angiography (red arrows in A and B) despite 75% stenosis of the left main coronary artery (orange arrow in A), contrast injection could be followed up to the insertion of the graft in the subclavian artery (red arrow in C). Angiography of the subclavian artery revealed high grade lesions in the subclavian and left vertebral artery (orange arrows in D).

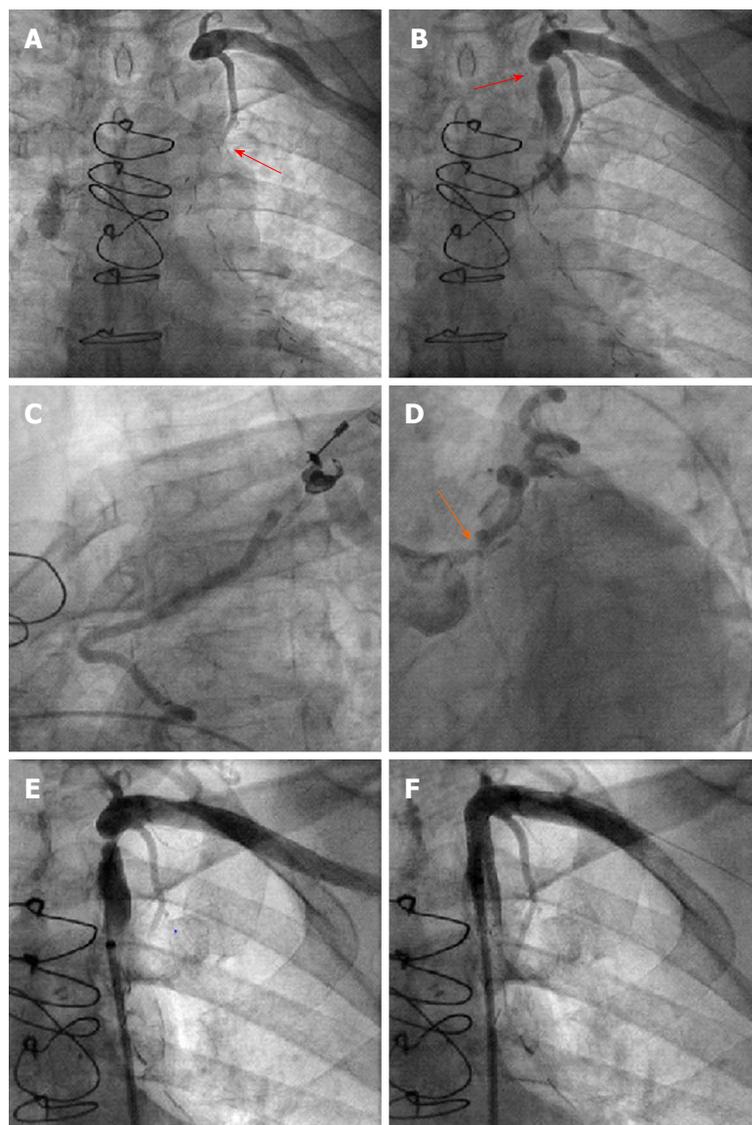


**Figure 2** Percutaneous coronary intervention of left main artery and stent placement. It was performed with a good angiographic result (red arrow in A) However, retrograde flow from the left artery disease LAD to the LIMA graft remained after PCI, and sparse flow was seen in the distal LAD (orange and blue arrows in B, respectively). DSA confirmed the presence of high grades stenosis of the left subclavian and vertebral artery (C). After angioplasty and bifurcation stent implantation a good angiographic result can be appreciated (orange and blue arrows in D) with normal opacification of the LIMA graft (red arrow in D). PCI: Percutaneous coronary intervention; LAD: Left artery disease; LIMA: Left internal mammary artery; DSA: Digital subtraction angiography.

implantation of the stenotic subclavian and vertebral arteries (balloon expandable Visi-Pro 8.0 mm × 27 mm, Covidien for the subclavian and Taxus Element 4.5 mm × 12 mm, Boston Scientific for the vertebral artery) and final kissing balloon inflation. Subsequently, a good angiographic result was observed with restored antegrade flow indicated in the LIMA graft (Figure 2).

For patient B, the initial cause for admission to our

hospital was a presyncopal episode and atypical angina. Cardiac catheterization was performed due to the high risk profile of the patient, including known multi-vessel disease and CABG 9 years ago. After selection of a left radial access for coronary angiography and wire insertion into the subclavian artery, we proceeded with selective contrast injection into the LIMA graft to the LAD. Surprisingly, contrast opacification was not possible



**Figure 3** After selective contrast injection into the left internal mammary artery graft no contrast opacification. It was shown in the left artery disease (red arrow in A). Subsequently, a high grade stenosis of the left subclavian artery was observed (red arrow in B). During coronary angiography retrograde flow from the left artery disease up to the origin of the LIMA graft could be demonstrated (C), despite left main stenosis (orange arrow in D). After angioplasty and stent placement (E) antegrade flow could be re-established in the subclavian artery (F). LIMA: Left internal mammary artery.

despite selective contrast injection into the presumably patent vessel (Figure 3). Subsequently, angiography of the left subclavian artery was performed, confirming high grade stenosis of the left subclavian artery (Figure 3), which was already accidentally diagnosed one year earlier during a computed tomography scan. Consistently an interarm blood pressure difference of 20 mmHg (left < right) could be measured with this patient. The subclavian stenosis was located proximally to the origin of the LIMA graft, thus possibly causing a coronary steal syndrome. Coronary angiography confirmed this diagnosis demonstrating retrograde flow from the LAD up to the insertion of the LIMA graft into the subclavian artery (Figure 3) despite the presence of significant left main disease (Figure 3). On the following day, stress echocardiography was performed, demonstrating an inducible hypokinesia in the anterior LV-wall by arm exertion (“hand grip method”), compatible with inducible ischemia in the LAD territory. Subsequently, balloon angioplasty and stent placement of the left subclavian artery was performed using an Armada 6.0 mm × 20 mm balloon and an 8.0 mm × 27

mm VisiPro-Stent with good angiographic result (Figure 3). Importantly, antegrade flow could be reestablished in the subclavian artery after interventional treatment (Figure 3).

Both patients were discharged the day after the procedure. During clinical follow-up patient A showed complete resolution of his angina symptoms, whereas repeated stress echocardiography showed no signs of inducible ischemia in patient B.

## DISCUSSION

Subclavian artery stenosis is a relatively frequent disease, which is more commonly described in patients with diabetes mellitus and was shown to be predictive of poor cardiovascular outcomes<sup>[7]</sup>. Known PAD accompanied by an interarm blood pressure difference greater than 10% has been suggested as a specific, but unfortunately less sensitive indicator for a subclavian stenosis<sup>[8]</sup>. The presence of subclavian artery stenosis in patients with previous CABG, who have received a LIMA graft can lead to angina symptoms independent

of atherosclerosis progression in native coronary arteries and bypass grafts. Although several cases of subclavian artery causing a so-called LIMA steal syndrome have been reported in the literature, this syndrome is still considered as relatively uncommon in patients after myocardial revascularization. However, in light of the greater number of LIMA grafts currently used and their long life expectancy its incidence may be higher than expected. In a retrospective study including 226 patients scheduled for CABG, 6 (3%) patients had significant left subclavian artery stenosis, which was successfully treated by angioplasty and stent placement in all cases before bypass surgery<sup>[9]</sup>. In our case the presence of subclavian artery stenosis was not investigated prior to CABG in our 2 cases. However, due to the long time duration between CABG and angina symptoms of the patient (A: 14 years, B: 9 years) it is more likely that subclavian stenosis developed after CABG. Thus, pre-CABG angiography would probably not have been helpful in our cases.

In the past years, significant technical developments have occurred with endovascular therapy, which offer several distinct advantages over open surgical revascularization techniques in selected lesions<sup>[10]</sup>. Although no head-to-head trials comparing interventional vs surgical treatment of the proximal subclavian artery stenosis are present so far, the effectiveness of percutaneous revascularization seems to be at least equivalent to surgery and that PCI and stent placement may be associated with fewer procedure-related serious complications<sup>[11]</sup>. In our patients subclavian (in both patients) and vertebral artery stenosis (in patient B) could be successfully treated by balloon angioplasty and stent placement. This caused restoration of the antegrade flow into the LIMA graft, resulting in resolution of anginal symptoms with patient A and restoration of the inducible wall motion abnormality by echocardiography in patient B. In patient A treatment of the subclavian artery stenosis may have been enough to restore antegrade perfusion of the LAD territory *via* the anatomically patent LIMA graft, without requiring PCI of the left main. However, PCI of the left main had already been performed in the initial session during diagnostic coronary angiography. Due to the fact that symptoms remained, we decided to perform stenting of the subclavian artery stenosis in a second session.

In patients with previous myocardial revascularization apart from CAD, great vessel disease resulting to coronary steal syndromes needs to be considered as a rare but important alternative diagnosis. In such cases, interventional treatment by angioplasty and stent placement may lead to complete resolution of symptoms and possible prevention of ischemic complications.

## COMMENTS

### Case characteristics

A 75- and 78-year-old male patient, both with known coronary artery disease, peripheral artery disease and prior coronary artery bypass graft who presented

with symptoms of myocardial ischemia.

### Clinical diagnosis

Peripheral artery disease with subclavian artery stenosis causing coronary steal syndrome.

### Differential diagnosis

Progression of coronary artery disease.

### Laboratory diagnosis

All labs were within normal limits.

### Imaging diagnosis

Peripheral artery disease was diagnosed in both patients by digital subtraction angiography.

### Pathological diagnosis

Coronary steal syndrome due to subclavian artery disease.

### Treatment

Percutaneous balloon angioplasty and stent placement in the left subclavian artery.

### Related reports

Coronary steal syndrome is a pathologic entity, which has been previously reported quite rarely so far in the current literature. This disease can sometimes be confused with coronary artery disease due to typical symptoms of myocardial ischemia in such patients.

### Term explanation

Coronary steal syndrome is a relatively rare condition, where subclavian artery stenosis causes myocardial ischemia due to reduced blood flow to the left internal mammary artery coronary graft after coronary artery bypass graft operation.

### Experiences and lessons

In patients with previous myocardial revascularization apart from coronary artery disease, great vessel disease resulting to coronary steal syndromes needs to be considered as a rare but important alternative diagnosis.

### Peer-review

The authors present 2 rare case reports of coronary subclavian steal syndrome after coronary artery bypass graft. The authors have demonstrated that interventional treatment may lead to complete resolution of symptoms and possible prevention of ischemic complications. This manuscript is nicely structured and well written.

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## Optical coherence tomography to identify the cause of an arrhythmic storm: A case report

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**Author contributions:** All authors contributed to the acquisition of data, writing, and revision of this manuscript.

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### Abstract

A 56-year-old man experienced an aborted sudden death followed by an arrhythmic storm. Angiography revealed a non-severe lesion on the left circumflex artery that was treated medically but an arrhythmic storm recurred. A repeat angiogram was comparable but optical coherence tomography imaging revealed a ruptured plaque with intraluminal thrombosis. Percutaneous coronary intervention was performed and no arrhythmia recurred.

**Key words:** Optical coherence tomography; Arrhythmic storm; Sudden death

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**Core tip:** A 56-year-old man presented to a community hospital after an aborted sudden death. After initial resuscitation, he presented an arrhythmic storm with multiple episodes of ventricular fibrillation refractory to intravenous amiodarone. Coronary angiogram showed a nonobstructive intermediate lesion in the mid left circumflex artery. Because of repeated ventricular fibrillation episodes, an optical coherence tomography (OCT) was performed and revealed a ruptured thin-cap fibroatheroma with an intraluminal thrombosis at the level of the intermediate lesion. This case suggests that performing OCT to detect vulnerable culprit lesion of less than severe angiographic severity when an ischemic event is likely, such as an aborted sudden death or arrhythmic storm, may be of diagnostic value and alter therapeutic decisions.

Couture EL, Bérubé S, Daneault B. Optical coherence tomography to identify the cause of an arrhythmic storm: A case report. *World J Cardiol* 2017; 9(1): 71-75 Available from: URL: <http://www.wjgnet.com/1949-8462/full/v9/i1/71.htm> DOI: <http://dx.doi.org/10.4330/wjc.v9.i1.71>

## INTRODUCTION

Triggers for arrhythmic storms are found in a minority of them. Careful assessment is required as some causes are reversible such as myocardial ischemia. We report the first case of an arrhythmic storm where the trigger was revealed by optical coherence tomography.

## CASE REPORT

A 56-year-old man known for smoking presented to a community hospital after an aborted sudden death. A witness immediately began cardiopulmonary resuscitation and the patient received 7 shocks from an automated external defibrillator prior to emergency arrival. Repeated electrocardiograms and a head CT-scan were normal. Five ventricular fibrillation (VF) episodes recurred and were treated with defibrillation and intravenous amiodarone. Given the refractory arrhythmia, the patient was transferred to our center to exclude myocardial ischemia.

Angiogram showed an intermediate lesion (50% stenosis) on the left circumflex artery (LCX) with a TIMI grade 3 flow (Figure 1A and B). The LCX lesion was therefore not judged as the culprit and he was admitted to the intensive care unit (ICU) with a plan to perform cardiovascular magnetic resonance after therapeutic hypothermia. Initial ICU laboratories revealed a hs-TnT of 732 ng/mL as well as normal electrolytes. A transthoracic echocardiogram demonstrated diffuse hypokinesis with a left ventricular ejection fraction of 35%. Within 24 h, 10 episodes of VF recurred and were treated with defibrillation and intravenous xylocaine. Between VF episodes, electrocardiogram transiently revealed inferior and posterior ST-elevation. Emergent angiogram was repeated and was unchanged from the day prior (Figure 1C). Optical coherence tomography (OCT) imaging study was performed in the LCX. OCT revealed a ruptured thin-cap lipid-rich plaque with intraluminal thrombosis (Figure 2). Minimal lumen area was 2.9 mm<sup>2</sup>. Because of the unstable characteristics of the plaque and clinical presentation, percutaneous coronary intervention (PCI) with a drug-eluting stent was performed (Figure 3B). Adequate stent expansion and strut apposition was confirmed by OCT (Figure 3A and C). After PCI, no arrhythmia recurred and the patient was discharged home 8 d after admission without neurological deficits and without an implantable cardioverter-defibrillator. Ten months later, he is asymptomatic with no recurrent cardiovascular event.

## DISCUSSION

Although coronary artery disease and especially acute coronary occlusion represent the most common cause of sudden cardiac arrest (SCD), diagnosis and treatment of the underlying mechanism remains a challenge<sup>[1]</sup>. In this case, because of the initial normal ECGs and the coronary angiogram showing a non-obstructive

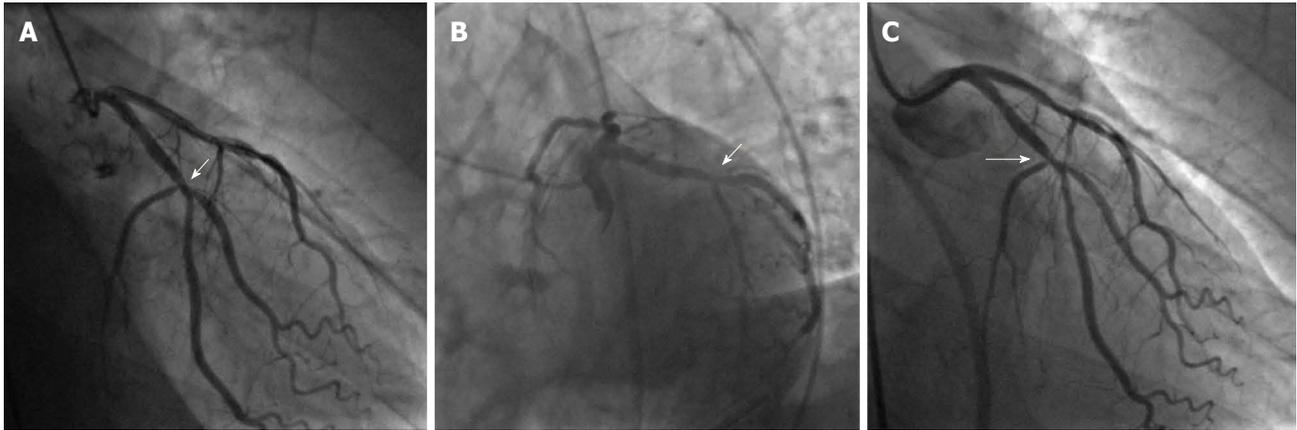
lesion, it was judged that this lesion did not cause active resting ischemia and therefore, was not the cause of the arrhythmia. Subsequent VF recurrences and transient ST-elevation in leads corresponding to the LCX prompted a repeat angiogram and the use of intravascular imaging. The unstable plaque characteristics revealed by OCT lead us to treat the lesion with PCI and the subsequent evolution proved that the arrhythmia's trigger had been effectively treated.

This case is interesting for a multitude of factors. It highlights the limitation of post-resuscitation ECG for the selection of patients who could benefit from immediate coronary angiography. When initial post-resuscitation ECGs do not demonstrate ST-segment elevation or presumably new left bundle branch block, it remains controversial to proceed to immediate coronary angiography. However, as demonstrated recently in SCD survivors, a culprit lesion (defined as > 90% coronary stenosis) was found in 19% of patients presenting with no ECG signs indicating myocardial ischemia<sup>[2]</sup>. In this case, transient ST-elevation was only documented once despite continuous ECG monitoring and 22 VF episodes.

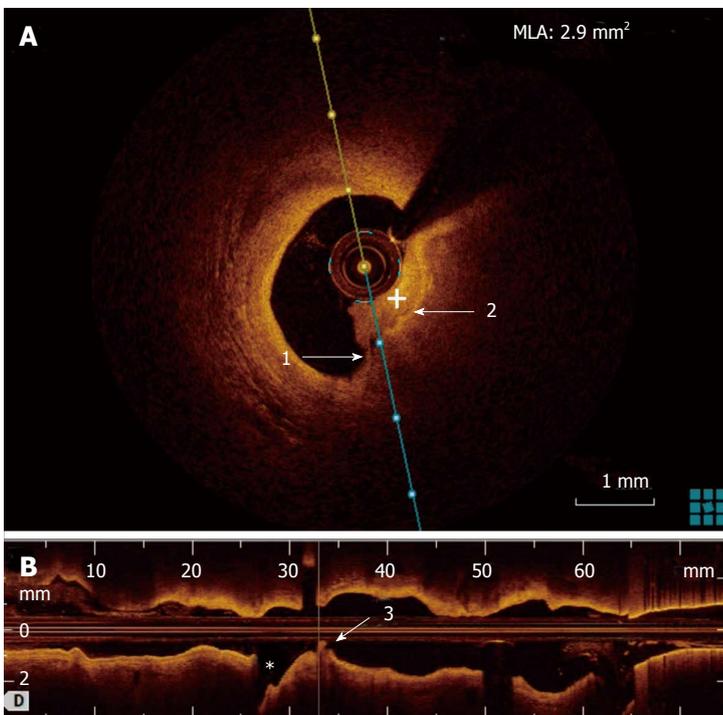
It also suggests that immediate angiography may have a central role in the management algorithm of SCD. Among initial survivors of SCD caused by VF or pulseless VT, it has been suggested that early coronary angiography was associated with higher rate of survival to discharge and favorable neurological outcome<sup>[3]</sup>. These observations are however retrospective and need to be validated in adequate trials.

Another important aspect of this case is the normal flow found in the culprit artery. In the PAMI trials, 16% of patients had TIMI 3 flow before PCI indicating spontaneous reperfusion<sup>[4]</sup>. Therefore, plaque rupture must be seen as a dynamic event as flow could be transiently occluded by thrombus with spontaneous fibrinolysis or by transient vasospasm. In this case, we supposed the arrhythmic storm was caused by multiple transient occlusive coronary spasms triggered by the plaque rupture. This phenomenon increases the difficulty in identifying ischemic causes of SCD and culprit lesion when ECGs are normal. This case demonstrated the additive value of OCT to further stratify intermediate non-obstructive lesion when an ischemic event is likely. Intravascular ultrasound (IVUS) also has been reported to reveal culprit lesion in SCD<sup>[5]</sup>. In a study of 12 survivors of SCD and high probability of coronary artery disease who underwent cardiac catheterization, 4 of them showed non-obstructive lesion a (< 50% stenosis and TIMI 3 flow) but all had intraluminal thrombosis revealed by intravascular ultrasound. However, none of the previous reports were accompanied by a such an arrhythmic storm<sup>[5,6]</sup>. Moreover, to rule out plaque rupture in survivors of SCD with non-obstructive intermediate lesion, OCT own a potential advantage over IVUS given its higher spatial resolution. Other modality such as near infrared spectroscopy could be of value in the future<sup>[7,8]</sup>.

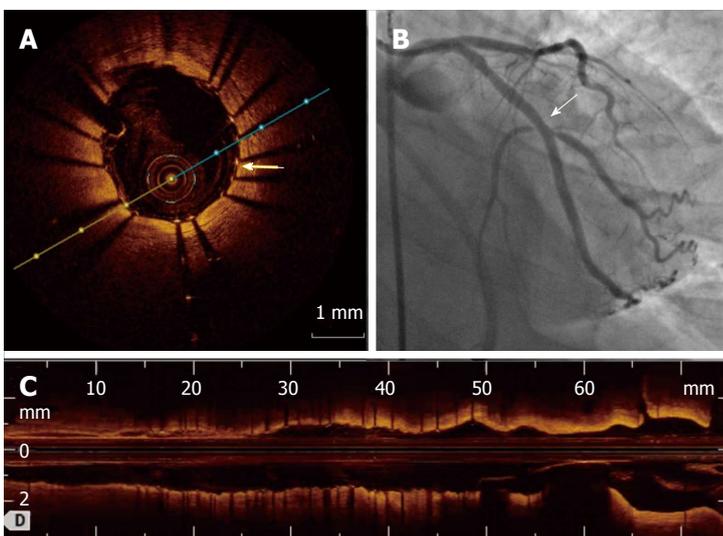
The optimal treatment of unstable plaque with



**Figure 1 Angiography images at presentation.** A, B: First angiogram. Arrows show a 50% lesion on the left circumflex artery with a TIMI grade 3 flow in the RAO/caudal view (A) and LAO/caudal view (B). After documentation of transmural ischemia and recurrence of the arrhythmic storm, the second angiogram revealed the same non-occlusive and intermediate lesion highlighted by the arrow in RAO/caudal view (C). RAO: Right anterior oblique; LAO: Left anterior oblique.



**Figure 2 Optical coherence tomography performed during the repeated angiogram.** A: OCT showing cross-section lumen reconstruction at the level of the plaque rupture. An intraluminal non-occlusive thrombus (+) is visualized. Arrow 1 shows rupture thin-cap fibroatheroma as visualized by the loss of continuity of the normal intima show by Arrow 2; B: OCT longitudinal lumen reconstruction at the mid left circumflex artery level. Arrow 3 highlights both plaque rupture and intraluminal thrombus be just before the bifurcation with the first marginal (asterisk). OCT: Optical coherence tomography.



**Figure 3 Angiogram and optical coherence tomography images after percutaneous coronary intervention.** A, C: OCT confirming stent expansion and apposition in the cross-sectional (A) and longitudinal (C) lumen reconstruction. Arrow in A highlights good strut apposition to the vessel wall and B is final angiogram. The arrow in B highlights the level of the previous stenosis and the percutaneous coronary intervention success. OCT: Optical coherence tomography.

adequate residual lumen area is however uncertain. Prior reports suggest that medical management could be adequate in these circumstances<sup>[9]</sup>. However, in our case, PCI clearly was of additional value to medical therapy. With the evolution of drug eluting stents and especially bioresorbable vascular scaffold, these technologies may impact the treatment of vulnerable lesions in the future. Large trials will be needed to evaluate the optimal diagnostic modalities and treatments for these unstable lesions.

In conclusion, this case suggests that performing OCT to detect vulnerable culprit lesion of less than severe angiographic severity when an ischemic event is likely, such as an aborted sudden death or arrhythmic storm, may be of diagnostic value and alter therapeutic decisions.

## COMMENTS

### Case characteristics

A 56-year-old man known for smoking presented to a community hospital after an aborted sudden death.

### Clinical diagnosis

Arrhythmic storm (ventricular fibrillation) episodes refractory to intravenous amiodarone.

### Differential diagnosis

Ischemic secondary to acute coronary syndrome, electrolytes abnormalities, primary cardiomyopathy.

### Laboratory diagnosis

Electrolytes were all normal at intensive care unit arrival, but hs-TnT was elevated.

### Imaging diagnosis

Coronary angiogram showed a nonobstructive intermediate lesion in the mid left circumflex artery. Optical coherence tomography (OCT) revealed ruptured thin-cap fibroatheroma with an intraluminal thrombus at the level of an angiographic intermediate lesion in the mid left circumflex artery.

### Pathological diagnosis

Acute coronary syndrome with a plaque rupture.

### Treatment

Percutaneous coronary intervention with a drug-eluting stent.

### Related reports

Very few cases of sudden death caused by a plaque rupture only detected with intravascular imaging have been described but never with a so dramatic presentation as in this case.

### Term explanation

OCT is an intravascular imaging modality that uses light to capture micrometer-resolution, three-dimensional images from within optical scattering media (e.g., coronary artery). Spatial resolution is between 2-10  $\mu\text{m}$  and its penetration varied between 1-10 mm.

### Experiences and lessons

This case suggests that performing optical coherence tomography to detect vulnerable culprit lesion of less than severe angiographic severity when an ischemic event is likely, such as an aborted sudden death or arrhythmic storm, may be of diagnostic value and alter therapeutic decisions.

## Peer-review

The paper is well written.

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## PCSK9 inhibitors: A new era of lipid lowering therapy

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### Abstract

Hyperlipidemia is a well-established risk factor for developing cardiovascular disease (CVD). The recent

American College of Cardiology and American Heart Association guidelines on lipid management emphasize treatment of individuals at increased risk for developing CVD events with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) at doses proven to reduce CVD events. However, there are limited options for patients who are either intolerant to statin therapy, develop CVD despite being on maximally tolerated statin therapy, or have severe hypercholesterolemia. Recently the Food and Drug Administration approved two novel medications for low-density lipoprotein (LDL)-cholesterol reduction: Evolocumab and Alirocumab. These agents target and inactivate proprotein convertase subtilisin-kexin type 9 (PCSK9), a hepatic protease that attaches and internalizes LDL receptors into lysosomes hence promoting their destruction. By preventing LDL receptor destruction, LDL-C levels can be lowered 50%-60% above that achieved by statin therapy alone. This review explores PCSK-9 biology and the mechanisms available to alter it; clinical trials targeting PCSK9 activity, and the current state of clinically available inhibitors of PCSK9.

**Key words:** Hyperlipidemia; Statins; Proprotein convertase subtilisin-kexin type 9

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**Core tip:** Hyperlipidemia is a well-established risk factor for developing cardiovascular disease (CVD). However, there are limited options for patients who are either intolerant to statin therapy, develop CVD despite being on maximally tolerated statin therapy, or have severe hypercholesterolemia. The Food and Drug Administration has approved two novel medications for low-density lipoprotein (LDL)-cholesterol reduction in this patient population: Evolocumab and Alirocumab. These agents target and inactivate proprotein convertase subtilisin-kexin type 9 (PCSK9), a hepatic protease that attaches and internalizes LDL receptors into lysosomes hence promoting their destruction. By preventing LDL receptor destruction, LDL-C levels can be lowered 50%-60% above that achieved by statin therapy alone. PCSK9 inhibitors are

an exciting agent for reducing LDL-C and have ushered in a new era of lipid lowering therapy.

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## INTRODUCTION

Hyperlipidemia is a well-established risk factor for developing cardiovascular disease (CVD)<sup>[1]</sup>. Multiple double blind placebo controlled trials have shown that treatment with HMG CoA Reductase inhibitors (statins) lowers low-density lipoprotein (LDL)-C levels and reduces CVD events in individuals with CVD or those at high risk for developing it<sup>[2,3]</sup>. However, CVD events continue to occur in some patients on statins, despite receiving maximal tolerated therapy. Other patients develop side effects from statins that limit their use. Hence, newer modalities of treatment to lower LDL-C are needed in clinical practice. Recently the Food and Drug Administration (FDA) approved two medications which target a novel pathway to reduce LDL-C. They are monoclonal antibodies that inactivate proprotein convertase subtilisin-kexin type 9 (PCSK9). This review will explore the biology of PCSK 9, clinical trials targeting PCSK9 activity, and the current state of clinically available inhibitors of PCSK9.

## LDL-CHOLESTEROL METABOLISM

LDL-C has been the target of therapy for improving outcomes in patients at high risk for developing CVD and has been considered a surrogate endpoint for clinical events by the FDA<sup>[1]</sup>. Reviewing LDL cholesterol metabolism is therefore important in understanding therapeutic approaches to treat hyperlipidemia.

The lipid cycle begins with the release of immature very low-density lipoprotein (VLDL) or nascent VLDL from the liver. Nascent VLDL contains apolipoprotein-B100 (apoB-100), apolipoprotein E (apoE), apolipoprotein C1 (apoC1), cholesteryl esters, cholesterol, and triglycerides. While circulating in blood, high-density lipoprotein (HDL) donates apolipoprotein C-II (apoC-II) to nascent VLDL that leads to its maturation. Mature VLDL interacts with lipoprotein lipase (LPL) in the capillary beds of adipose tissues, cardiac muscle and skeletal muscle cells, which leads to extraction of triglycerides from VLDL for storage or energy production in these tissues. VLDL combines with HDL again and an interchange occurs where apoC-II is transferred back to HDL along with phospholipids and triglycerides in exchange for cholesteryl esters *via* cholesteryl-ester-transfer protein (CETP). This exchange and removal of triglycerides leads to conversion of VLDL to intermediate-density lipoprotein (IDL)<sup>[4]</sup>. Half of IDLs are recognized and endocytosed by liver cells due to

apoB-100 and apoE. The remaining IDL lose apoE, and with an increased concentration of cholesterol compared to triglyceride, transform into low-density lipoproteins (LDL). LDL particles thus formed contain apoB-100, which acts as a ligand for binding to LDL receptors (LDLR). Once LDL binds to LDLR, LDL/LDLR complex is internalized by endocytosis into clathrin coated vesicles. In the cytosol, LDL and LDLR separate with recycling of LDLR to the cell surface. LDLR recycling is a continuous process and each receptor recycles up to 150 times after which they are endocytosed and metabolized<sup>[5]</sup>. Statins act by inhibiting 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, which is involved in intracellular production of cholesterol. This lowers the levels of intracellular cholesterol leading to increased expression of LDLR on cell surfaces causing a reduction in serum LDL-cholesterol<sup>[6]</sup>.

Seidah and colleagues discovered that proprotein convertase subtilisin/kexin type 9 (PCSK9) regulates LDLR degradation and could potentially be a target for modulating LDLR expression and consequently LDL-C levels<sup>[7,8]</sup>. PCSK9 is a hepatic protease that attaches to and internalizes LDLR into lysosomes hence promoting their destruction<sup>[9]</sup>. Clinical studies have shown that PCSK9 gain of function mutation is associated with familial hypercholesterolemia and premature CVD<sup>[10,11]</sup>. Conversely, individuals with loss of function mutations in PCSK9 have been observed to have lower lifetime levels of LDL-C and lower prevalence of CVD<sup>[12,13]</sup>.

Since the discovery of PCSK9, results from preclinical mice studies demonstrated that sterol regulatory element binding protein-2 (SREBP-2) plays a key role in regulating cholesterol metabolism. Low level of intracellular cholesterol activates SREBP-2 and leads to LDLR gene expression. This increases LDLR concentration thus enhancing LDL clearance from circulation<sup>[8,14]</sup>. At the same time SREBP-2 also induces the expression of PCSK9, which promotes LDLR degradation. Thus, the coordinated interplay of SREBP-2 induced transcription of both LDLR and PCSK9 regulates circulating LDL levels<sup>[15,16]</sup>. These discoveries resulted in the exploration and development of therapeutic agents to lower LDL levels by targeting PCSK9 activity.

## FUNCTIONAL MECHANICS OF PCSK9

Hepatocytes are the predominant site for PCSK9 production, with other sites being intestines and kidneys<sup>[17,18]</sup>. PCSK9 reduces the number of LDLR in hepatocytes by promoting their metabolism and subsequent degradation<sup>[14]</sup>. PCSK9 has been shown to act both intracellularly (playing a role as a chaperone) as well as a secreted factor promoting LDLR internalization from the hepatocellular surface. Under normal circumstances, the LDL/LDLR complex is endocytosed by endosomes. The acidic pH of the endosome reduces the affinity of LDL for LDLR with rearrangement of the LDLR's extracellular domain into a hairpin structure, aiding in its recycling

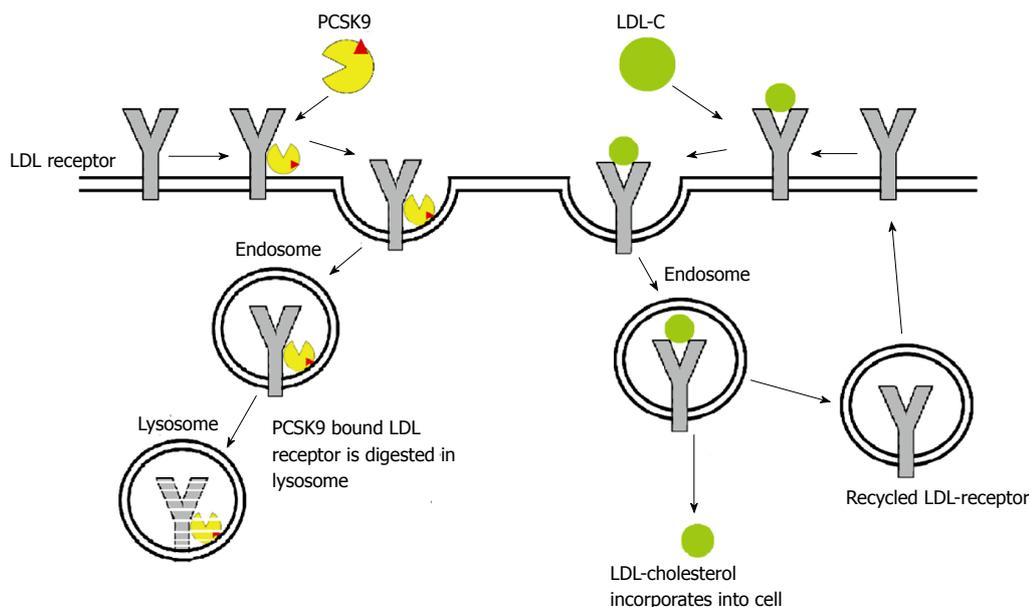


Figure 1 Mechanism and role of PCSK9 in low-density lipoprotein-cholesterol metabolism. LDL: Low-density lipoprotein.

back to plasma membrane. PCSK9 binding inhibits this change and locks the LDLR in an open conformation which prevents its recycling. The LDLR is then routed to lysosomes for degradation (Figure 1)<sup>[19,20]</sup>. The secreted form of PCSK9 circulates in the bloodstream and can be inactivated by cleavage from proprotein convertase. At a molecular level, the secretion of prodomain and catalytically inactive PCSK9 promotes regular degradation of LDLR implying that PCSK9 acts as a chaperone protein rather than an active catalytic enzyme<sup>[21,22]</sup>.

As described above, hepatic expression of PCSK9 and LDLR are closely regulated by SREBP-2 and intracellular levels of cholesterol<sup>[23,24]</sup>. Lipid lowering therapy with statins<sup>[25-27]</sup>, ezetimibe<sup>[28]</sup> and bile acid binding resins<sup>[29]</sup> cause induction of SREBP-2 and hence co-induces both PCSK9 and LDLR. The slight increase in PCSK9 activity seen with statins does not negate their therapeutic effectiveness.

## OTHER FUNCTIONS AND LOCATIONS OF PCSK9

Apart from hepatocytes, PCSK9 is also expressed in intestine, central nervous system, and mesenchymal cells of the kidney. *In vitro* studies on human intestinal epithelium have reported recombinant PCSK9 to enhance cholesterol uptake in the human intestinal epithelial cells (Caco-2/15 cell line) *via* the up regulation of the protein expression of NPC1L1 and CD36 (involved in cholesterol absorption in intestinal cells) along with an increased expression of cholesterol transporters<sup>[30,31]</sup> and reduced cholesterol synthesis (by reducing HMG-CoA reductase activity)<sup>[32]</sup>. PCSK9 has been shown to have a role in the metabolism of triglycerides and their accumulation in visceral adipose tissue<sup>[33]</sup>. It also promotes chylomicron secretion and helps regulate enterocyte cholesterol

balance<sup>[32]</sup>. Studies have evaluated PCSK9 and their association with increased susceptibility to hepatitis C viral infection. Labonté *et al.*<sup>[34]</sup> demonstrated a reduced expression of CD81 (CD81 is a co-receptor for Hepatitis C virus infection) by PCSK9 leading to protection against infection by hepatitis C. Therefore, PCSK9 inhibitors (Alirocumab) could increase CD81 expression resulting in greater infectivity. However, *in vitro* and *in vivo* studies in mice showed that PCSK9 did not reduce CD81 expression and had no effect on HCV infectivity. Hence, the literature remains inconclusive about this potential effect of PCSK9 inhibition<sup>[34]</sup>. Mbikay *et al.*<sup>[35]</sup> demonstrated that PCSK9 inhibition in mouse pancreatic islet  $\beta$  cells led to hypoinsulinemia, hyperglycemia and glucose-intolerance. Additionally the islet cells exhibited signs of malformation, apoptosis and inflammation. Current clinical data has failed to show this as a complication with PCSK9 inhibition.

## PCSK9 INHIBITION STRATEGIES

Preclinical studies demonstrate that statin-induced LDL reduction occurs through increased LDLR expression on hepatocytes along with increased LDL turnover, which leads to its enhanced clearance from the circulation. However, statins also induce PCSK9 expression, which dampens the effective LDL clearing by promoting LDLR degradation<sup>[23]</sup>. Since PCSK9 is expressed both intracellularly and in the circulation, multiple potential targets exist for its inhibition. Various modalities to inhibit PCSK9 have been studied including: (1) inhibition of production by gene silencing through antisense oligonucleotides<sup>[36]</sup> or small interfering RNA<sup>[37]</sup>; (2) prevention of PCSK9 binding to LDLR using monoclonal antibodies<sup>[38]</sup>, epidermal growth factor-like repeat A (EGF-A), mimetic peptides<sup>[39]</sup> or adnectins; and (3) inhibition of PCSK autocatalytic sites.

### Gene silencing via antisense oligonucleotides or small interfering RNA

This approach targets intracellular PCSK9 activity by utilizing antisense oligonucleotide to reduce intracellular expression of PCSK9. Preclinical trials on hyperlipidemic mice evaluating two such compounds were promising with a reduction in LDL by 38% at six weeks of therapy while doubling LDLR expression in the liver<sup>[38]</sup>. However, the phase I trials evaluating two of these agents were terminated prematurely and further development of the drug (BMS-84442) was not continued (NCT01082562). Two additional drugs: SPC5001 and SPC4061 showed successful reduction in LDL by 50% during preclinical testing in primates<sup>[40]</sup>. However, the first phase I trial in healthy human subjects and individuals with familial hypercholesterolemia were terminated early (NCT01350960)<sup>[41,42]</sup>. SPC5001 was seen to cause mild to moderate injection site reactions and renal tubular toxicity<sup>[43]</sup>. Further development of SPC4061 was discontinued for undisclosed reasons.

Similarly, small interfering RNA (siRNA) administration has been shown to significantly reduce plasma PCSK9 and LDL levels in cynomolgus monkeys<sup>[37,38,43]</sup>. ALN-PCS is a siRNA, which was tested by delivery through second-generation lipid nanoparticles. In a study by Fitzgerald *et al.*<sup>[44]</sup>, ALN-PCS demonstrated a dose dependent reduction in PCSK9 and LDL levels with a reduction of up to 70% in PCSK9 levels and 40% in LDL levels at doses of 0.4 mg/kg. This was the first study to demonstrate intracellular PCSK9 inhibition translated into reduction of circulating LDL levels.

### Monoclonal antibodies

Utilization of monoclonal antibodies has been the most effective approach thus far in inhibiting PCSK9 and reducing LDL levels. Currently, at least six monoclonal antibodies (mAb) have been or are being developed and tested: Alirocumab (formerly called SAR236553/REGN727), Evolocumab (formerly called AMG145), RG7652<sup>[45]</sup>, LGT209 (NCT01979601, NCT01859455), 1B20<sup>[46]</sup> and Bococizumab (formerly called RN316/PF-04950615). Alirocumab and Evolocumab have recently been approved by the FDA. The major clinical studies leading up to their approval are outlined later in this paper.

Bococizumab is a unique mAb, which utilizes pH sensitive binding to PCSK9 and was developed for a longer serum half-life and duration of action on LDL reduction<sup>[47]</sup>. In phase I studies, single intravenous or subcutaneous dosages significantly reduced LDL in patients with hypercholesterolemia, both with and without concomitant atorvastatin therapy<sup>[48]</sup>. In a phase II trial by Gumbiner *et al.*<sup>[48]</sup>, patients on statin therapy not at target LDL-C were enrolled and observed a 60% reduction in LDL-C after 12 wk of therapy. Five phase III trials are ongoing for Bococizumab including SPIRE-HF (evaluating the efficacy of this agent in heterozygous familial hypercholesterolemia NCT01968980); SPIRE-HR (NCT01968954) and SPIRE-LDL (NCT01968967) trials are comparing Bococizumab

to statin therapy in patients with high atherosclerotic cardiovascular risk with a follow up period of up to 12 wk. SPIRE-1 (NCT01975376) and 2 (NCT01975389) have a follow up period of up to 5 years collecting data on safety and efficacy of this drug<sup>[49]</sup>. Recently, the preliminary results of a study of Bococizumab delivery using an auto-injector device (SPIRE-AI) reported successfully meeting co-primary endpoints of percent change from baseline in fasting LDL-C at week 12 and the delivery system success rate, defined as the percent of patients whose attempts to operate the pre-filled pen. SPIRE-AI is a 12-wk, double-blind, placebo-controlled, randomized, parallel-group, multicenter, phase III clinical trial in 299 patients with hyperlipidemia or mixed dyslipidemia receiving statin therapy and whose LDL-C  $\geq 70$  mg/dL and assessed the efficacy, safety, tolerability and subcutaneous administration of Bococizumab 150 mg and 75 mg with a pre-filled pen<sup>[50]</sup>.

Along similar lines, adnectins (also known as monobody) and small peptide inhibitors have been investigated for LDL reduction in phase I clinical trials. The results in healthy patients and those with hypercholesterolemia demonstrated a maximal dose related reduction of LDL-C by up to 48%<sup>[51]</sup>. The advantage of developing adnectins is that they are smaller than mAb, making them cheaper and easier to produce. Their pharmacokinetics have been shown to be favorable with a rapid onset of action in preclinical models, further trials are awaited to see the development of this agent<sup>[52]</sup>.

### Inhibition of autocatalytic site

This mechanism as a therapeutic target was first proposed after discovering a loss of function mutation in the autocatalytic cleavage site of PCSK9<sup>[53,54]</sup>. This approach is still under preclinical investigational phase.

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## FDA APPROVAL STATUS OF PCSK9 INHIBITORS

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The FDA approved Alirocumab (Praluent) in July 2015 for adult patients with heterozygous familial hypercholesterolemia or in patients with clinically significant atherosclerotic CVD requiring additional LDL lowering after being on diet control and maximally tolerated statin therapy. Evolocumab (Repatha) was also approved in August, 2015 for use in adult patients with heterozygous familial hypercholesterolemia, homozygous familial hypercholesterolemia, or clinical atherosclerotic CVD requiring additional lowering of LDL cholesterol after being on a controlled diet and maximally-tolerated statin therapy.

### Alirocumab (status: FDA approved)

Alirocumab has been studied in three phase I trials. In two of these trials, healthy volunteers were administered Alirocumab intravenously ( $n = 40$ ) or subcutaneously ( $n = 32$ ) which reduced LDL-C in a dose-dependent fashion with a reduction of up to 65% at maximal doses<sup>[55]</sup>. The

third trial evaluated patients with non-familial hypercholesterolemia on atorvastatin and LDL > 100 mg/dL or with LDL > 130 mg/dL being managed by diet alone. Alirocumab reduced LDL-C up to 65% in patients on statins and up to 60% in patients being managed on diet alone. It was observed that Alirocumab remained effective for a longer period of time in patients not on statins<sup>[55]</sup>.

Three phase II trials<sup>[56-58]</sup> evaluated the efficacy of Alirocumab in patients with familial hypercholesterolemia. Stein *et al.*<sup>[58]</sup> evaluated 77 patients on statin therapy with LDL-C greater than 100 mg/dL and found that Alirocumab reduced LDL-C in a dose-dependent manner by up to 43% with a maximum dosage of 300 mg every 4 wk. However, the reduction was even greater (up to 70%) at a dosage regimen of 150 mg every 2 wk. Additionally, these patients had a significant reduction in apoB levels and non-high density lipoprotein cholesterol and also had increases in HDL. McKenney *et al.*<sup>[56]</sup>, in their study of 183 patients confirmed a dose dependent reduction of LDL-C with the most efficacious regimen being 150 mg every 2 wk (with LDL reduction up to 70%). Interestingly, different doses of atorvastatin did not make a significant difference in LDL-C reduction. These results were further corroborated by Roth *et al.*<sup>[57]</sup> in their study of 92 patients with LDL-C > 100 mg/dL. They showed that there was significant and comparable LDL reduction irrespective of the dosage of atorvastatin (10 mg vs 80 mg) when added to Alirocumab 150 mg every 2 wk<sup>[57]</sup>.

The phase III randomized, double-blinded ODYSSEY trials were designed to evaluate Alirocumab for long-term safety, efficacy and adverse events (Table 1) and include CHOICE I, CHOICE II, OLE, LONG TERM, COMBO I, COMBO II, FH I, FH II, HIGH FH, MONO, ALTERNATIVE, OPTIONS I and OPTIONS II. The dosage of Alirocumab administered was 150 mg every 2 wk in ODYSSEY LONG TERM and HIGH FH trials and 75 mg (titrated up to 150 mg to reach pre-specified LDL goals) in ODYSSEY ALTERNATIVE, OPTIONS I, OPTIONS II and COMBO I trials.

CHOICE I study evaluated Alirocumab vs placebo in 803 patients with poorly controlled hypercholesterolemia. Alirocumab reduced LDL by 52% in statin-naïve patients and by 59% in patients on maximally tolerated statins as compared to placebo ( $P < 0.001$ )<sup>[59]</sup>. Similarly, COMBO I and II trials evaluated 316 patients and 720 patients respectively with LDL > 70 mg/dL and high cardiovascular risk on maximally tolerated statin therapy. COMBO I showed Alirocumab reduced LDL-C up to 50% (vs 2% with placebo) after 24 wk of treatment. COMBO II compared ezetimibe to Alirocumab in patients on background statin therapy and found a 50% LDL reduction with Alirocumab vs 20% reduction with ezetimibe at 24 wk<sup>[60]</sup>. OPTIONS I trial<sup>[61]</sup> published in August 2015, randomized 355 patients with hypercholesterolemia and LDL > 70 and found the addition of Alirocumab to atorvastatin had the greatest reduction in LDL as compared to addition of ezetimibe, doubling atorvastatin

dose or switching to rosuvastatin. Atorvastatin at 20 mg and 40 mg/d regimens reduced LDL by 44% and 54% with addition of Alirocumab respectively vs 21% and 23% with addition of ezetimibe respectively vs 5% and 5% with doubling atorvastatin dose respectively compared to 21% with switching to rosuvastatin 40 mg/d. In the OPTIONS II trial, rosuvastatin was studied using a similar protocol and showed that the addition of Alirocumab had the most significant reduction in LDL-C after 24 wk of therapy as opposed to addition of ezetimibe or doubling the dose of rosuvastatin<sup>[62,63]</sup>. Another study evaluating the efficacy of Alirocumab as monotherapy (MONO study)<sup>[64]</sup> compared to ezetimibe in patients with hypercholesterolemia and moderate cardiovascular risk to monotherapy with Alirocumab and found that Alirocumab reduced LDL-C 47% vs 16% by ezetimibe after 24 wk of therapy ( $P < 0.0001$ ).

CHOICE II study evaluated Alirocumab in patients intolerant to statin therapy. Two hundred and thirty one patients with a history of statin intolerance were shown to have a 56% reduction in LDL with Alirocumab (vs placebo;  $P < 0.001$ )<sup>[59]</sup>. Another study evaluating Alirocumab in patients intolerant to statin therapy is the ODYSSEY ALTERNATIVE trial. Three hundred and fourteen patients completed this randomized controlled trial, which compared Alirocumab 75 mg every 2 wk ( $n = 126$ ) to ezetimibe 10 mg/d ( $n = 125$ ) and atorvastatin 20 mg/d ( $n = 63$ ) for 24 wk. At 24 wk, the data showed a 45% reduction in LDL with Alirocumab as opposed to 15% reduction in LDL with ezetimibe. This trial demonstrated fewer skeletal muscle adverse events in the Alirocumab group as compared to atorvastatin arm [32.5% vs 46% respectively, HR = 0.61 (0.38-0.99;  $P = 0.042$ )], with no significant difference when compared to the ezetimibe group (41%) [HR 0.71 (0.47 to 1.06;  $P = 0.09$ )]<sup>[65]</sup>.

Alirocumab has also been shown to be effective in lowering LDL-C in patients with familial hypercholesterolemia. The FH I and FH II studies evaluated a total of 735 patients ( $n = 486$  and 249 respectively) with heterozygous familial hypercholesterolemia inadequately controlled on lipid lowering therapy and found Alirocumab to reduce LDL levels 48.8% (vs a 9.1% increase in placebo: FH I study) and 48.7% (vs 2.8% increase in LDL with placebo: FH II study) from baseline<sup>[66]</sup>. ODYSSEY HIGH FH trial reported 105 patients with familial hypercholesterolemia on maximally tolerated statin therapy and LDL > 160 demonstrating a 46% reduction of LDL (vs 7% with placebo) at 24 wk ( $P < 0.001$ )<sup>[67]</sup>. OLE trial (NCT01954394) is currently ongoing with results anticipated by June 2017. This trial is recruiting patients with heterozygous familial hypercholesterolemia who have completed one of the other studies and evaluating for safety parameters including adverse events, laboratory data and vital signs.

ODYSSEY LONG TERM trial was recently published and is a 78-wk follow-up of 2341 patients with hypercholesterolemia and LDL > 70 mg/dL on maximally tolerated statins. The patients receiving 150 mg Alirocumab every 2 wk were shown to have a 62% reduction

Table 1 Summary of phase III ODYSSEY trials with Alirocumab

Name of trial	Ref. Allocation and blinding	No. of patients	Inclusion criteria	Study arms (with dosing)	Primary end point	Results
LONG TERM (NCT01507831)	Seidah <i>et al</i> <sup>[7]</sup> ; Randomized double blinded trial	2341	Either 1 or 2 below and who aren't adequately controlled with their LLT: (1) Patients with heFH with or without CHD or CHD risk equivalents OR (2) Patients with HCL with CHD or CHD risk equivalents	Alirocumab (SC) ( <i>n</i> = 1553) vs Placebo (SC) ( <i>n</i> = 788) both with background LLT	Percentage change in calculated LDL cholesterol level from baseline to week 24	-61.0% change with Alirocumab vs +0.8% change with placebo (CI: -64.3 to -59.4; <i>P</i> < 0.001)
FH I (NCT01623115)	Kastelein <i>et al</i> <sup>[66]</sup> ; Randomized double blinded	486	Patients with heterozygous familial hypercholesterolemia who are not adequately controlled with their lipid-modifying therapy	Alirocumab (SC) vs Placebo (SC) both with background LLT	Percent change in calculated LDL-C at week 24	-48.8% for Alirocumab compared with 9.1% for placebo ( <i>P</i> < 0.0001)
FH II (NCT01709500)	Kastelein <i>et al</i> <sup>[66]</sup> ; Randomized double blinded	249	Patients with heFH who are not adequately controlled with their LLT	Alirocumab (SC) vs Placebo (SC) both with background LLT	Percent change in LDL-C to week 24	-48.7% for Alirocumab compared with 2.8% for placebo ( <i>P</i> < 0.0001)
HIGH FH (NCT01617655)	Kastelein <i>et al</i> <sup>[67]</sup> ; Randomized double blinded	107	Patients with heterozygous familial hypercholesterolemia who are not adequately controlled with their lipid-modifying therapy with LDL > 160	Alirocumab (SC) ( <i>n</i> = 72) vs Placebo (SC) ( <i>n</i> = 35) both with background LLT	Percent change in calculated LDL-C at week 24	Percent decrease from baseline was 45.7% vs 6.6%, difference 39.1, <i>P</i> < 0.0001 Absolute difference in values of LDL-C at 24 wk 107 mg/dL vs 182 mg/dL
COMBO I (NCT01644175)	Colhoun <i>et al</i> <sup>[60]</sup> ; Randomized double blinded	316	Patients with hypercholesterolemia and establ CHD or CHD risk equivalents; not controlled with a maximally tolerated LLT, both at stable dose for at least 4 to 6 wk prior to screening	Alirocumab (SC) ( <i>n</i> = 205) vs Placebo (SC) ( <i>n</i> = 106)	Percent change in calculated LDL-C at week 24	-48.2% with Alirocumab (CI: -52.0% to -44.4%) and -2.3% with placebo (CI: -7.6% to 3.1%) for Alirocumab and placebo, respectively, an estimated mean difference of -45.9% (CI: -52.5% to -39.3%) ( <i>P</i> < 0.0001)
COMBO II (NCT01644188)	Moriarty <i>et al</i> <sup>[65]</sup> ; Randomized double blind	720	Patients with hypercholesterolemia and established CHD or CHD risk equivalents who are not adequately controlled with a maximally tolerated daily dose of statin at stable dose for at least 4 wk prior to the screening visit	Alirocumab (SC) + placebo (for ezetimibe) orally + background statin therapy ( <i>n</i> = 467) vs Placebo (SC) + ezetimibe orally + Background statin therapy ( <i>n</i> = 240)	Percent change in calculated LDL-C at week 24	Reductions in LDL-C from baseline were 50.6% ± 1.4% for Alirocumab vs 20.7% ± 1.9% for ezetimibe (difference 29.8% ± 2.3%; <i>P</i> < 0.0001)
OPTIONS I (NCT01730053)	Robinson <i>et al</i> <sup>[63]</sup> ; Randomized double-blinded	355	Patients with prior CV disease + LDL-C ≥ 70 mg/dL, or CV risk factors + LDL-C ≥ 100 mg/dL	Alirocumab with atorvastatin 20 mg vs Ezetimibe with atorvastatin 20 mg vs Atorvastatin 40 mg Alirocumab with atorvastatin 40 mg vs ezetimibe with atorvastatin 40 mg vs atorvastatin 80 mg vs rosuvastatin 20 mg	Percent change in calculated LDL-C to week 24	Percent reduction from baseline 44.1% (Alirocumab) vs 20.5% (ezetimibe) vs 5.0% (atorvastatin 40); <i>P</i> < 0.0001  Percent reduction from baseline 54% (Alirocumab) vs 22.6% (Ezetimibe) vs 4.8% (Atorvastatin 80) vs 21.4% (rosuvastatin 40); <i>P</i> < 0.0001

OPTIONS II	Robinson <i>et al</i> <sup>[63]</sup> ; Randomized double-blinded	305	Patients with prior CV disease + LDL-C $\geq$ 70 mg/dL, or CV risk factors + LDL-C $\geq$ 100 mg/dL	Alirocumab with rosuvastatin 10 mg vs ezetimibe with rosuvastatin 10 vs rosuvastatin 20 Alirocumab with rosuvastatin 20 mg vs ezetimibe with rosuvastatin 20 vs Rosuvastatin 40	Percent change in calculated LDL-C to wk 24	Percent reduction from baseline 50.6% (Alirocumab) vs 14.4% (ezetimibe) vs 16.3% (rosuvastatin 20); $P < 0.0001$
ALTERNATIVE (NCT01709513)	Moriarty <i>et al</i> <sup>[65]</sup> ; Randomized double-blinded	314	Primary heFH with moderate, high or very high CV risk and history of statin intolerance	Alirocumab + oral placebo vs ezetimibe (10 mg/d) + sc placebo vs atorvastatin (20 mg/d) + sc placebo	Percent change in calculated LDL-C to week 24 in intention to treat group	Percent reduction from baseline 45% (Alirocumab) vs 14.6% (Ezetimibe) with a mean difference of -30.4%; $P < 0.0001$
CHOICE I (NCT01926782)	Stroes <i>et al</i> <sup>[78]</sup> ; Randomized, double-blinded	803	Patients not having adequate control of their hypercholesterolemia based on their individual level of CVD risk	Alirocumab at q4 week regimen vs Placebo	Percent change in LDL from baseline to week 24 for Alirocumab q4w vs placebo in patients with hypercholesterolemia at moderate, high, or very high CVD risk with concomitant statin therapy ( $n = 547$ ) Percent change in LDL from baseline to week 24 for Alirocumab q4w vs placebo in patients with hypercholesterolemia not on concomitant statin therapy ( $n = 256$ )	LDL was reduced by 58.7% with Alirocumab in patients on maximally tolerated statins ( $P < 0.001$ ) LDL was reduced by 52.4% with Alirocumab in statin naïve patients vs placebo ( $P < 0.001$ )
CHOICE II (NCT02023879)	Stroes <i>et al</i> <sup>[78]</sup> ; Randomized, double-blinded	231	Patients with primary hypercholesterolemia (heFH or non-FH) not adequately controlled with their non statin lipid modifying therapy or diet and statin intolerance	Alirocumab (SC) vs placebo (SC)	The percent change in LDL-C from baseline to week 24	Alirocumab reduced LDL-C by 56.4% ( $P < 0.0001$ ) vs placebo
LONG TERM (NCT01507831)	Robinson <i>et al</i> <sup>[62]</sup> ; Randomized, double-blinded	2341	Either A or B below and who are not adequately controlled with their LLT: (1) Patients with heFH with or without established CHD or CHD risk equivalents OR (2) Patients with hypercholesterolemia together with established CHD or CHD risk equivalents	Alirocumab (SC) 150 mg every 2 wk vs placebo (SC) every 2 wk	Percentage change in calculated LDL cholesterol level from baseline to week 24, analyzed with the use of an intention-to-treat approach	150 mg Alirocumab every 2 wk had a 62% reduction in LDL as opposed to a 1% increase in LDL with placebo at 24 wk

SC: Subcutaneous; LLT: Lipid lowering therapy; heFH: Heterozygous familial hypercholesterolemia; CHD: Coronary heart disease; HCL: Hypercholesterolemia; MACE: Major adverse cardiovascular events; MI: Myocardial infarction; UA: Unstable angina; HR: Hazards ratio; CI: Confidence interval.

in LDL as opposed to a 1% increase in LDL with placebo at 24 wk. These results persisted at 78 wk. In a post-

hoc analysis, the reduction in LDL was also associated with reduction in the combined end-point of death from coronary artery disease, nonfatal myocardial infarction, fatal or nonfatal ischemic stroke or unstable angina requiring hospitalization (1.7% with Alirocumab vs 3.3% with placebo; HR = 0.52; 95%CI: 0.31-0.9;  $P = 0.02$ )<sup>[68]</sup>. The ODYSSEY Outcomes trial (NCT01663402) is ongoing is closed to recruitment, and will assess the effects of Alirocumab on CVD events in 18000 patients on maximally tolerated statin therapy. Results of this trial are expected in February 2018.

### **Evolocumab (status: FDA approved)**

Evolocumab has been studied in two phase I studies. Dias *et al*<sup>[69]</sup> evaluated healthy volunteers in phase I a and showed a short-term dose-dependent reduction in LDL by up to 65% and after 6 to 8 wk of therapy by up to 75% with a maximally administered dose of 420 mg subcutaneously/intravenously. Phase I b trial similarly demonstrated up to 75% reduction in LDL as compared to placebo over 1 to 4 wk in healthy volunteers.

Four phase II trials were subsequently performed that continued to show the benefits of Evolocumab with a dose-dependent reduction of LDL (maximal dosing up to 420 mg) when added to maximally tolerated statin therapy in patients with hypercholesterolemia (including familial hypercholesterolemia)<sup>[70-72]</sup>. In LAPLACE-TIMI57 trial<sup>[70]</sup>, Evolocumab was tested at varying doses ranging from 70 to 140 mg every 2 wk or 280 to 420 mg every 4 wk in 631 patients on stable statin therapy and LDL more than 85 mg/dL. LDL reduction up to 65% was observed with the every two-week regimen as compared to approximately 50% LDL reduction with the every 4-wk regimen. Evolocumab has also been studied as monotherapy in 160 patients with hypercholesterolemia and intolerance to statins in the GAUSS trial<sup>[73]</sup>. At doses of 420 mg every 4 wk, it was shown to reduce LDL by 40% to 50%. Furthermore, addition of ezetimibe reduced LDL by up to 65%. Subsequently, the MENDEL trial<sup>[71]</sup> showed a similar efficacy in LDL-C lowering when Evolocumab was used as monotherapy in 406 patients with hypercholesterolemia. Based on these trials, the optimal frequency of Evolocumab therapy was determined to be twice monthly to achieve a 50% to 60% reduction in LDL in combination with statins. However, when used as a monotherapy therapy, a frequency of once every 4 wk would be acceptable. Stein *et al*<sup>[74]</sup> evaluated 8 patients with homozygous familial hypercholesterolemia, and found Evolocumab (at 420 mg every 2 wk) to reduce LDL by approximately 25% vs 20% when used every 4 wk.

Evolocumab has further been evaluated in PROFICIO (Program to reduce LDL-C and cardiovascular outcomes following inhibition of PCSK9 in different populations) phase III trials (Table 2). The PROFICIO program includes 14 trials where Evolocumab is being evaluated in patients with hyperlipidemia in combination with statins (LAPLACE-2 and YUKAWA-2); hyperlipidemic

patients intolerant to statins (GAUSS-2 and GAUSS-3); standalone in hyperlipidemia (MENDEL-2); heterozygous familial hypercholesterolemia (RUTHERFORD-2 and TAUSSIG); homozygous familial hypercholesterolemia (TESLA and TAUSSIG); with primary hyperlipidemia or mixed cholesterol disorder (THOMAS-1 and THOMAS-2: Device trials). Also, long-term safety and efficacy data is being evaluated by the five following studies: DESCARTES; FOURIER; OSLER-2 trial; GLAGOV trial and TAUSSIG study.

In LAPLACE-2 study 1896 patients with fasting LDL  $\geq 150$  (when not on statins) or LDL  $\geq 100$  (on non-intensive regimen of statins) or LDL  $\geq 70$  (on intensive statin therapy) were randomized to a daily moderate or high-intensity statin regimen and after 4 wk, further randomized to receive Evolocumab, ezetimibe or placebo. Evolocumab was shown to reduce LDL levels by 66% to 75% (on every 2 wk regimen) and by 63% to 75% (on once monthly regimen) when compared to placebo in moderate- and high intensity statin groups. In moderate and high intensity statin groups, Evolocumab led to significant reduction in absolute LDL values in both regimens of Evolocumab (every 2 wk and monthly). Adverse events reported were comparable in all groups<sup>[75]</sup>. YUKAWA-2 study showed a similar reduction in LDL in 404 Japanese patients when Evolocumab regimens (140 mg once every 2 wk and 420 mg once a month) were compared to placebo on 2 regimens of low-dose background statin therapy (5 mg/d and 20 mg/d atorvastatin). Interestingly, the reduction in LDL appeared to be similar irrespective of statin dosage (in combination with Evolocumab) and showed a 67% to 76% LDL reduction at 12 wk<sup>[76]</sup>. MENDEL-2 trial compared the efficacy of Evolocumab with ezetimibe and placebo in 614 patients with LDL between 100 mg/dL and 190 mg/dL and low risk on Framingham scale ( $\leq 10\%$ ). Evolocumab was shown to reduce LDL by up to 57% more than placebo and 40% more than ezetimibe after 12 wk of therapy<sup>[77]</sup>.

GAUSS-2 trial evaluated 307 patients with statin intolerance and compared the 2 regimens of Evolocumab (140 mg once every 2 wk and 420 mg once a month) to daily oral or subcutaneous placebo (both placebo groups on ezetimibe). At 12 wk, Evolocumab group showed a reduction in LDL by 56% vs 39% in the other groups (placebo + ezetimibe arm)<sup>[78]</sup>. Along similar lines, GAUSS-3 trial evaluated the efficacy of Evolocumab in 218 statin intolerant patients compared to ezetimibe. The initial phase of the study included administration of atorvastatin (20 mg) for 10 wk and placebo randomized in a 1:1 fashion, followed by a 2-wk washout period and crossover to alternate therapy for another 10 wk. The patients who experienced muscle related adverse effects while on statin therapy and not on placebo were further enrolled in the second phase of the study, which was a 24 wk double blinded randomized controlled trial to compare Evolocumab (420 mg/mo divided in 3 doses) with ezetimibe (10 mg/d). At 24 wk, LDL-C was

**Table 2 Summary of important phase III PROFICIO (Program to Reduce LDL-C and Cardiovascular Outcomes Following Inhibition of PCSK9 In Different Populations) trials with Evolocumab**

Name of trial	Ref. Allocation and blinding	No. of patients	Inclusion criteria	Study arms (with dosing)	Primary end point	Results
LAPLACE-2 (NCT01763866)	Robinson <i>et al</i> <sup>[75]</sup> ; Randomized double blinded trial	1896	Individuals with LDL > 150 mg/dL (not on statin); or LDL > 100 mg/dL (on non-intensive statin); or LDL ≥ 80 mg/dL (with intensive statin therapy)	Initially randomized to daily moderate or high intensity atorvastatin for 4 wk. Patients were again randomized to Evolocumab (sc) <i>vs</i> ezetimibe <i>vs</i> placebo	Percentage change in calculated LDL cholesterol level from baseline to week 12	Evolocumab q2w and qmonthly: 63% to 75% reduction in LDL <i>vs</i> placebo Ezetimibe 19% to 32% reduction in LDL <i>vs</i> placebo
YUKAWA-2 (NCT01953328)	Kiyosue <i>et al</i> <sup>[76]</sup> ; Randomized double blinded	404	Japanese patients with LDL > 70 on stable dose statins for > 4 wk and high cardiovascular risk	Initially randomized to daily atorvastatin of 5 mg or 20 mg for 4 wk. They were further randomized to Evolocumab (sc) at q2 week and qmonthly <i>vs</i> placebo	Percent change in calculated LDL-C from baseline at week 12	-67.0% to -76% reduction with Evolocumab compared to placebo ( <i>P</i> < 0.0001)
GAUSS-2 (NCT01763905)	Stroes <i>et al</i> <sup>[78]</sup> ; Randomized double blinded	307	Patients with LDL not at goal according to their cardiovascular risk and not on statin or low dose statin due to history of statin intolerance (> 2 statins) with stable LLT > 4 wk	Evolocumab (SC) at q2 week and qmonthly dosing <i>vs</i> Placebo (SC) + Ezetimibe (10 mg/d) daily	Percent change in LDL-C from baseline at the mean of weeks 10 and 12 and at week 12 Change from baseline LDL at week 12	-55.3% to -56.1% for Evolocumab compared with -16.6% to -19.2% for ezetimibe ( <i>P</i> < 0.0001) -103.6 to -105.4 (Evolocumab) <i>vs</i> -33 to -39 (mg/dL)
MENDEL-2 (NCT01763827)	Koren <i>et al</i> <sup>[77]</sup> ; Randomized double-blinded	614	NCEP ATP III Framingham risk score of < 10% Fasting LDL-C ≥ 100 mg/dL and < 190 mg/dL	Oral placebo to SC placebo; ezetimibe to SC placebo and oral placebo to SC Evolocumab at dosing regimens of 140 mg biweekly and 420 mg monthly	Percent change from baseline in LDL-C level averaged at weeks 10 and 12 Percent change from baseline in LDL-C level at week 12	Percent LDL change from baseline averaged at weeks 10 and 12 in the: Once per 2 wk arm: -56.9% (with Evolocumab) <i>vs</i> -17.5 (with ezetimibe) <i>vs</i> -0.4% (placebo) For monthly arm: -58.8% (with evolocumab) <i>vs</i> -19.1 (with ezetimibe) <i>vs</i> -1.4% (placebo) Percent LDL change from baseline averaged at weeks 12: Once per 2 wk arm: -57% (with Evolocumab) <i>vs</i> -17.8 (with ezetimibe) <i>vs</i> 0.1% (placebo) For monthly arm: -56.1% (with Evolocumab) <i>vs</i> -18.6 (with ezetimibe) <i>vs</i> -1.3% (placebo)
RUTHERFORD-2 (NCT01763918)	Raal <i>et al</i> <sup>[72]</sup> ; Randomized double blinded	329	Patients with heterozygous familial hypercholesterolemia who are on stable LLT for 4 wk and LDL > 100 mg/dL	Evolocumab (SC) at 140 mg q2 weeks <i>vs</i> placebo SC q2w AND Evolocumab SC qmonthly <i>vs</i> Placebo (SC)	Percent change from baseline in LDL-C level averaged at weeks 10 and 12 Percent change from baseline in LDL-C level at week 12	Percent LDL change from baseline averaged at weeks 12 in the: Once per 2 wk arm: -61.2% (with Evolocumab) <i>vs</i> -1.1% (with placebo) For monthly arm: -63.3% (with evolocumab) <i>vs</i> 2.3% (with placebo) Percent LDL change from baseline averaged at weeks 10 and 12 in the: Once per 2 wk arm: -61.3% (with Evolocumab) <i>vs</i> -2% (with placebo) For monthly arm: -55.7% (with Evolocumab) <i>vs</i> 5.5% (with placebo)

TESLA (NCT01588496)	Raal <i>et al</i> <sup>[82]</sup> ; Randomized double-blinded	50	Homozygous familial hypercholesterolemia, on stable lipid-regulating therapy for at least 4 wk, LDL cholesterol $\geq$ 130 mg/dL (3.4 mmol/L); Triglyceride $\leq$ 400 mg/dL (4.5 mmol/L); Body weight of $\geq$ 40 kg at screening, and not receiving lipoprotein apheresis	Evolocumab (SC) 420 mg every 4 wk vs placebo (SC)	Percentage change in ultracentrifugation LDL cholesterol from baseline at week 12 compared with placebo, analyzed by intention-to-treat Percent change from baseline in LDL-C at week 52	Evolocumab significantly reduced ultracentrifugation LDL cholesterol at 12 wk by 30.9% (95%CI: -43.9% to -18.0%; $P < 0.0001$ ) vs placebo
DESCARTES (NCT01516879)	Blom <i>et al</i> <sup>[80]</sup> ; Randomized, double-blinded	901	Fasting LDL $\geq$ 75 mg/dL and meeting the following on background LLT: (1) $<$ 100 mg/dL for subjects with diagnosed CHD or CHD risk equivalent; (2) $<$ 130 mg/dL for subjects without diagnosed CHD or CHD risk equivalent; (3) on maximal background LLT defined as atorvastatin 80 mg PO QD and ezetimibe 10 mg PO QD Fasting triglycerides $\leq$ 400 mg/dL	Evolocumab (SC) 420 mg every 4 wk with diet alone vs placebo with diet Evolocumab (SC) 420 mg every 4 wk with diet + atorvastatin 10 mg/d vs placebo with diet and atorvastatin 10 mg/d Evolocumab (SC) 420 mg every 4 wk + atorvastatin 80 mg/d vs placebo + atorvastatin 80 mg/d Evolocumab (SC) 420 mg every 4 wk + atorvastatin 80 mg/d + ezetimibe 10 mg/d vs placebo + atorvastatin 80 mg/d + ezetimibe 10 mg/d	Addition of Evolocumab resulted in LDL reduction by: (1) 51% to 60% in diet alone group; (2) 59% to 64% in patients on 10 mg atorvastatin (3) 51% to 62% in patients on 80 mg atorvastatin (4) 43% to 54% in patients with atorvastatin 80 mg/d and ezetimibe 10 mg/d ( $P < 0.001$ for all)	

SC: Subcutaneous; LLT: Lipid lowering therapy; heFH: Heterozygous familial hypercholesterolemia; CHD: Coronary heart disease; HCL: Hypercholesterolemia; MACE: Major adverse Cardiovascular Events; MI: Myocardial infarction; UA: Unstable angina; HR: Hazards ratio; CI: Confidence interval.

reduced by 53% with Evolocumab compared to 17% with ezetimibe. Muscle-related side effects were reported in 21% patients on Evolocumab compared to 29% with ezetimibe with stoppage of drug administration due to muscle symptoms in 1% of patients in Evolocumab and 7% of patients on ezetimibe<sup>[79]</sup>.

DESCARTES trial<sup>[80]</sup> evaluated 901 patients with hyperlipidemia, comparing Evolocumab (420 mg once a month subcutaneous) plus background lipid lowering therapy vs placebo plus background lipid lowering therapy for a period of 52 wk. Background lipid lowering therapy included: Diet alone, low intensity atorvastatin (10 mg), high intensity atorvastatin (80 mg) or atorvastatin 80 mg/d. All patients had fasting LDL-C  $>$  75 mg/dL on background lipid lowering therapy. Addition of Evolocumab resulted in LDL reduction by 51% to 60% in diet alone group, 59% to 64% in patients on 10 mg atorvastatin, 51% to 62% in patients on 80 mg atorvastatin and 43% to 54% in patients with atorvastatin 80 mg/d and ezetimibe 10 mg/d ( $P < 0.001$  for all).

Evolocumab has also been shown to be efficacious in patients with heterozygous and homozygous familial hypercholesterolemia. In the RUTHERFORD-2 trial, 329 patients with heterozygous familial hypercholesterolemia were randomized to receive Evolocumab (140 and 420 mg respectively) or placebo at two weekly and monthly regimens. Evolocumab showed a significant reduction

in LDL with both regimens: 140 mg every 2 wk led to 59.2% reduction (CI: 53.4% to 65.1%) and 420 mg once a month led to LDL reduction by 61.3% (CI: 53.6% to 69%) as compared to placebo after 12 wk ( $P < 0.001$  for all)<sup>[81]</sup>. The TESLA trial examined 50 patients with homozygous familial hypercholesterolemia on stable lipid lowering therapy and evaluated monthly Evolocumab (420 mg) vs placebo therapy for 12 wk. Addition of Evolocumab led to a significant reduction in LDL-C by up to 31% (CI: -44% to -18%;  $P < 0.0001$ )<sup>[82]</sup>.

In the Open-Label Study of Long-Term Evaluation Against LDL-C (OSLER) 1 and 2 trials 4465 patients were enrolled who had completed 1 of the phase 2 or phase 3 studies of Evolocumab (MENDEL-1, LAPLACE TIMI 57, GAUSS-1, RUTHERFORD-1, YUKAWA-1, MENDEL-2, LAPLACE-2, GAUSS-2, RUTHERFORD-2, DESCARTES, THOMAS-1 or THOMAS-2) and randomized to receive either Evolocumab (420 mg/mo in OSLER-1 and 140 mg every 2 wk or 420 mg once a month in OSLER-2 trial) plus standard therapy ( $n = 2976$ ) or standard therapy ( $n = 1489$ ). The median follow-up was 11.1 mo. This study showed a 61% reduction in LDL-C with Evolocumab compared to standard therapy (95%CI: 59% to 63%;  $P < 0.001$ ). Overall adverse events were in 69% of patients in Evolocumab group compared to 65% in standard therapy group. Of note, the neurocognitive adverse events were low, but were more frequent in Evolocumab group and appeared

to be unrelated to LDL level at the time of treatment. Composite adverse cardiovascular events (all-cause death, coronary events including myocardial infarction, unstable angina requiring hospitalization, or coronary revascularization, cerebrovascular events including stroke or transient ischemic attack, and heart failure requiring hospitalization) were significantly lower in patients with Evolocumab compared to standard therapy (HR = 0.47; 95%CI: 0.28 to 0.78;  $P = 0.003$ )<sup>[83,84]</sup>.

The TAUSSIG trial (NCT01624142) is evaluating Evolocumab therapy in 300 patients with severe familial hypercholesterolemia to determine its efficacy and side effect profile. The results of this study are anticipated by March 2020. Preliminary results reported by Stein *et al.*<sup>[74]</sup> on 8 patients with LDLR-negative or LDLR defective homozygous familial hypercholesterolemia on stable drug therapy when treated with Evolocumab at 420 mg monthly for  $\geq 12$  wk, followed by 420 mg every 2 wk for another 12 wk showed LDL reduction by 14% to 16% at 12 wk with 2 wk and 4 wk dosing regimens respectively with no serious adverse events reported<sup>[75]</sup>. Finally, the preliminary results of GLAGOV study (NCT01813422) evaluating 950 patients with coronary artery disease on lipid lowering therapy undergoing cardiac catheterization for changes in percentage atheroma volume after 78 wk of Evolocumab therapy met primary and secondary endpoints and final results are to be reported in American Heart Association (AHA) conference in November, 2016.

## PHARMACOKINETICS AND PHARMACODYNAMICS

The pharmacokinetic and pharmacodynamics parameters of PCSK9 inhibitors are described below<sup>[85,86]</sup>.

### **Alirocumab**

The time taken to reach maximum serum concentration is 3-7 d with similar serum concentration - time profiles between abdomen, upper arm or thigh as the sites of injection. Steady state concentrations are reached at an average of 3 to 4 doses. The volume of distribution following intravenous administration is 0.04 to 0.05 L/kg. The median half-life ( $t_{1/2}$ ) observed was between 17 to 20 d at 75 or 150 mg dosing every 2 wk. Alirocumab is eliminated in two phases depending upon its plasma concentration. The predominant mode of elimination at lower concentrations is *via* saturation of the targets (PCSK9) bound to the antibodies; however, at higher concentrations it is primarily through proteolytic pathways<sup>[81]</sup>. There have been no metabolism studies conducted since it has been previously demonstrated that reticuloendothelial system is responsible for metabolizing antibodies to small peptides and amino acids<sup>[87]</sup>. The maximum reduction in free plasma PCSK9 levels and LDL was observed within 3 and 15 d respectively, after drug administration with no difference noted between different sites. No dose adjustment is needed for patients with mild or moderately impaired renal or hepatic function.

No data are available in patients with severe renal and hepatic impairment.

### **Evolocumab**

The pharmacokinetic and pharmacodynamics properties of Evolocumab<sup>[83]</sup> demonstrate non-linear pharmacokinetics in absorption at doses below 140 mg; however, between doses of 140 to 420 mg linear pharmacokinetics is observed. The time to reach maximum concentration is 3 to 4 d after a single dose. After a single 420 mg dosage, its volume of distribution has been estimated to be 3.3 L  $\pm$  0.5 L. A steady state in serum is observed after about 12 wk of dosing. The  $t_{1/2}$  of Evolocumab is between 11 to 17 d. The maximum reduction of LDL after therapy was similar after dosing of 140 mg every 2 wk or 420 mg once a month with effect within 14 d. Clinical studies have not revealed a difference in pharmacokinetics of Evolocumab in mild or moderate renal and hepatic impairment. However, subjects with severe renal and hepatic impairment have not been studied.

## ADVERSE EFFECTS AND CONTRAINDICATIONS

The following side effects have been reported by data gathered from over 7000 patients ( $n = 2476$  for Alirocumab and  $n = 5416$  for Evolocumab) evaluated in the clinical trials mentioned above. Major side effects observed for Alirocumab and Evolocumab are described below.

### **Alirocumab**

Alirocumab is contraindicated in patients who develop serious hypersensitivity reactions like hypersensitivity vasculitis or allergic reactions requiring hospitalization with its usage. The most common adverse effects observed with Alirocumab include nasopharyngitis (11.3% vs 11.1% in placebo), injection site reactions (erythema, itchiness, swelling, pain or tenderness) (7.2% vs 5.1% in placebo), influenza (5.7% vs 4.6% in placebo), urinary tract infection (4.8% vs 4.6% in placebo), diarrhea (4.7% vs 4.4% in placebo), bronchitis (4.3% vs 3.8% in placebo), myalgia (4.2% vs 3.4% in placebo), muscle spasms (3.1% vs 2.4% in placebo), sinusitis (3% vs 2.7% in placebo), cough (2.5% vs 2.3% in placebo), contusion (2.1% vs 1.3% in placebo) and musculoskeletal pain (2.1% vs 1.6% in placebo). The most common adverse events that lead to drug discontinuation were allergic reactions (0.6% for Alirocumab vs 0.2% for placebo) and elevated liver enzymes (0.3% in Alirocumab vs < 0.1% in placebo).

### **Evolocumab**

Contraindications for Evolocumab are similar to Alirocumab. The overall incidence of adverse effects with Evolocumab 140 mg every 2 wk as compared to placebo were 43.6% vs 41% respectively. The most common adverse effects were nasopharyngitis (5.9% vs 4.8% in placebo), upper respiratory tract infection (3.2% vs 2.7%

in placebo), back pain (3% vs 2.7% in placebo) and nausea (2.1% vs 1.8% in placebo). Of note the most common adverse events leading to drug discontinuation include myalgia, nausea and dizziness. Other serious adverse events noted were cardiac disorders in 2.4% individuals including palpitations (0.6% vs 0.3% in placebo), angina pectoris (0.3% vs 0.2% in placebo), and ventricular extra systoles (0.3% vs 0.1% in placebo).

In addition, data from trials evaluating Evolocumab and Alirocumab have shown a higher incidence of cognitive adverse events in patients treated with PCSK9 inhibitors (0.9% vs 0.3% for Evolocumab compared to standard care<sup>[83]</sup> and 1.2% vs 0.5% for Alirocumab compared to placebo<sup>[69]</sup>). It has been suggested that responder and ascertainment bias might have played a role in reporting of adverse cognitive events in the OSLER trial since the adverse events were not related to the degree of LDL-C lowering with no clustering in the LDL-C < 25 mg/dL group relative to the 25-50 mg/dL or > 50 mg/dL groups<sup>[88]</sup>. However, patients in ODYSSEY LONG TERM trial were blinded to treatment and followed for nearly 18 mo. Also, the neurocognitive adverse events were measured subjectively and not verified by neurocognitive testing. A dedicated study evaluating neurocognitive adverse events with PCSK9 inhibitors is underway: Evaluating PCSK9 Binding anti-Body Influence on Cognitive Health in High Cardiovascular Risk Subjects (EBBINGHAUS) (NCT02207634). It is enrolling individuals without dementia or mild cognitive impairment at baseline randomized in a double-blind, placebo-controlled fashion to evaluate Evolocumab on background statin therapy vs statin therapy alone. The primary outcome being measured is Spatial Working Memory test; an assessment of executive function and the results are expected in September 2017.

Another potential and significant complication with drugs that are monoclonal antibodies is the development of anti-drug antibodies that may interfere with clinical efficacy and increase adverse events<sup>[89]</sup>. This complication has not been reported in the trials to date using PCSK9 inhibitors.

## CLINICAL USE OF PCSK9 INHIBITORS

The 2013 American College of Cardiology/American Heart Association recommendations on cholesterol management centered on identifying patients who would have a reduction in CVD events with statin treatment. The focus shifted from treating to a specific LDL-C level, to treating at risk individuals with a treatment (statin) proven to reduce future CVD events. Subsequently, the IMPROVE-IT trial demonstrated that addition of ezetimibe to simvastatin lowers LDL-C more than that achieved by simvastatin alone and that this reduction in LDL-C was associated with a greater reduction in CVD events compared with simvastatin alone<sup>[86,90]</sup>. This study raises the issue of LDL-C treatment targets with a lower level of LDL-C corresponding to a lower risk of CVD events. The introduction of PCSK9 inhibitors will necessitate re-evaluation of existing cholesterol treatment recom-

mendations.

PCSK9 inhibitors are especially beneficial in the treatment of familial hypercholesterolemic patients who are intolerant to statins or have an elevated LDL-C level despite being on maximally tolerated statin therapy. Intuitively, addition of a PCSK9 inhibitor to low dose statin therapy will be more effective in lowering LDL and avoiding the side effects of statins, since low dose and high dose statin regimens have yielded similar efficacy when combined with PCSK9 inhibitors.

Several potential barriers exist that may impede the widespread use of these medicines. First, statins have a proven effectiveness that has been demonstrated in multiple long-term studies. Statins have been shown to reduce cardiovascular mortality by 30% and incidence of stroke by 20% in multiple long-term studies<sup>[91,92]</sup>. PCSK9 inhibitors are effective in reducing LDL-C levels but currently lack data demonstrating their use reduces CVD events. Trials evaluating the effect of PCSK9 inhibitors on long-term CVD events, however, are currently underway: FOURIER (Further cardiovascular outcomes research with PCSK9 inhibition in subjects with elevated risk;  $n = 22500$ ) for Evolocumab (NCT01764633) and ODYSSEY-OUTCOMES (ODYSSEY outcomes: Evaluation of cardiovascular outcomes after an acute coronary syndrome during treatment with alirocumab SAR236553) (NCT01663402) for Alirocumab. However, their data will not be available until December 2017 (for Alirocumab) and February 2018 (for Evolocumab).

Another potential barrier to widespread use of PCSK9 inhibitors is their cost. The Institute for Clinical and Economic Review (ICER) reported that the number needed to treat for 5 years to avoid one major adverse cardiovascular event (NNT5) is 28. However, a list price of \$ 14350 per year generates a cost-effectiveness ratio which far exceeds the accepted threshold of \$ 100000/quality-adjusted life-years<sup>[93]</sup>. To achieve cost-effectiveness at this threshold would require a price reduction by 60% to 65% of the current price. At the conclusion of their report, the ICER suggested a reduction by 85% to an annual cost of \$2177 might be required to avoid excessive cost burdens to the health care system<sup>[94]</sup>. It should be noted that since there are limited data on clinical adverse cardiovascular events, cost effectiveness data might change once results from ongoing CVD endpoint studies are available.

PCSK9 therapy is a welcome treatment option for statin intolerant patients who require treatment of their hyperlipidemia. It will be important that busy practitioners do not under-prescribe statins nor be dissuaded from attempting to find a dose of and statin agent that is tolerated by the patient because PCSK9 inhibitors are available. Despite these obstacles, PCSK9 inhibitors are an exciting agent for reducing LDL-C hyperlipidemia and have ushered in a new era of lipid lowering therapy.

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## Assessment of stable coronary artery disease by cardiovascular magnetic resonance imaging: Current and emerging techniques

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### Abstract

Coronary artery disease (CAD) is a leading cause of death and disability worldwide. Cardiovascular magnetic

resonance (CMR) is established in clinical practice guidelines with a growing evidence base supporting its use to aid the diagnosis and management of patients with suspected or established CAD. CMR is a multi-parametric imaging modality that yields high spatial resolution images that can be acquired in any plane for the assessment of global and regional cardiac function, myocardial perfusion and viability, tissue characterisation and coronary artery anatomy, all within a single study protocol and without exposure to ionising radiation. Advances in technology and acquisition techniques continue to progress the utility of CMR across a wide spectrum of cardiovascular disease, and the publication of large scale clinical trials continues to strengthen the role of CMR in daily cardiology practice. This article aims to review current practice and explore the future directions of multi-parametric CMR imaging in the investigation of stable CAD.

**Key words:** Cardiovascular magnetic resonance; Coronary heart disease; Myocardial perfusion; Viability; Prognosis

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**Core tip:** Coronary artery disease (CAD) is a leading cause of death worldwide. Cardiovascular magnetic resonance (CMR) is established in clinical practice guidelines with a growing evidence base supporting its use to aid diagnosis and management of patients with suspected or established CAD. CMR is a multi-parametric imaging modality that yields high spatial resolution images that can be acquired in any plane for assessment of global and regional cardiac function, myocardial perfusion and viability, tissue characterisation and coronary artery anatomy, all within a single study protocol and without exposure to ionising radiation.

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## INTRODUCTION

Coronary artery disease (CAD) is a leading cause of death and disability worldwide<sup>[1]</sup>. Despite major advances in the treatment of CAD resulting in significantly decreased mortality rates, CAD remains the single most common cause of death in the European Union, leading to 19% of deaths in men and 20% of deaths in women<sup>[2]</sup>; in the United States, CAD causes 1 in every 7 deaths, accounting for 370213 deaths in 2013<sup>[3]</sup>. The economic health burden of CAD is substantial with an estimated cost of CAD management at €60 billion in the European Union<sup>[4]</sup>, and \$182 billion in the United States<sup>[3]</sup>. Cardiovascular medicine benefits from a myriad of diagnostic methods that can guide intervention and clinical decision-making. Invasive coronary X-ray angiography delineates coronary anatomy in patients presenting with stable chest pain, however there is a low yield of obstructive CAD in those referred, and there are associated risks, albeit low, from major complications and ionising radiation<sup>[5]</sup>. Furthermore unless measurement of fractional flow reserve (FFR) is performed, routine coronary angiography does not give information on ischaemia burden, which according to current guidelines, is required to guide revascularisation decisions. Non-invasive functional imaging modalities such as single-photon emission computed tomography (SPECT), dobutamine stress echocardiography (DSE), cardiovascular magnetic resonance (CMR) or positron emission tomography (PET) are used to diagnose CAD, guide clinical decision making and confer prognostic information and consequently are well established for these roles in clinical practice guidelines<sup>[6,7]</sup>.

CMR is a unique multi-parametric imaging modality producing high spatial resolution images that can be acquired in any plane for the assessment of global and regional cardiac function, myocardial perfusion and viability, tissue characterisation and proximal coronary artery anatomy, all within a single study and without exposure to ionising radiation (Figure 1). Historically, long scanning times, limited scanner availability and narrow bore sizes restricted the use of CMR, but these issues have been largely resolved, such that CMR has become a first line investigation for suspected stable angina in many centres in the United Kingdom and Europe. Consequently CMR is part of international clinical practice guidelines for the assessment of known and unknown stable CAD and for the identification of those who may benefit from revascularisation<sup>[6-9]</sup>. This review aims to focus on the current utility of CMR for the diagnosis of suspected stable CAD and potential future developments and applications of CMR in this role.

## CMR IN STABLE CAD

A CMR protocol for the investigation of stable CAD will typically take between 30-60 min and involves the acquisition of cine images in multiple planes for the assessment of left ventricular function and volumes, stress and rest myocardial perfusion imaging and late gadolinium enhancement (LGE) imaging for the assessment of myocardial viability and scar quantification (Figure 2).

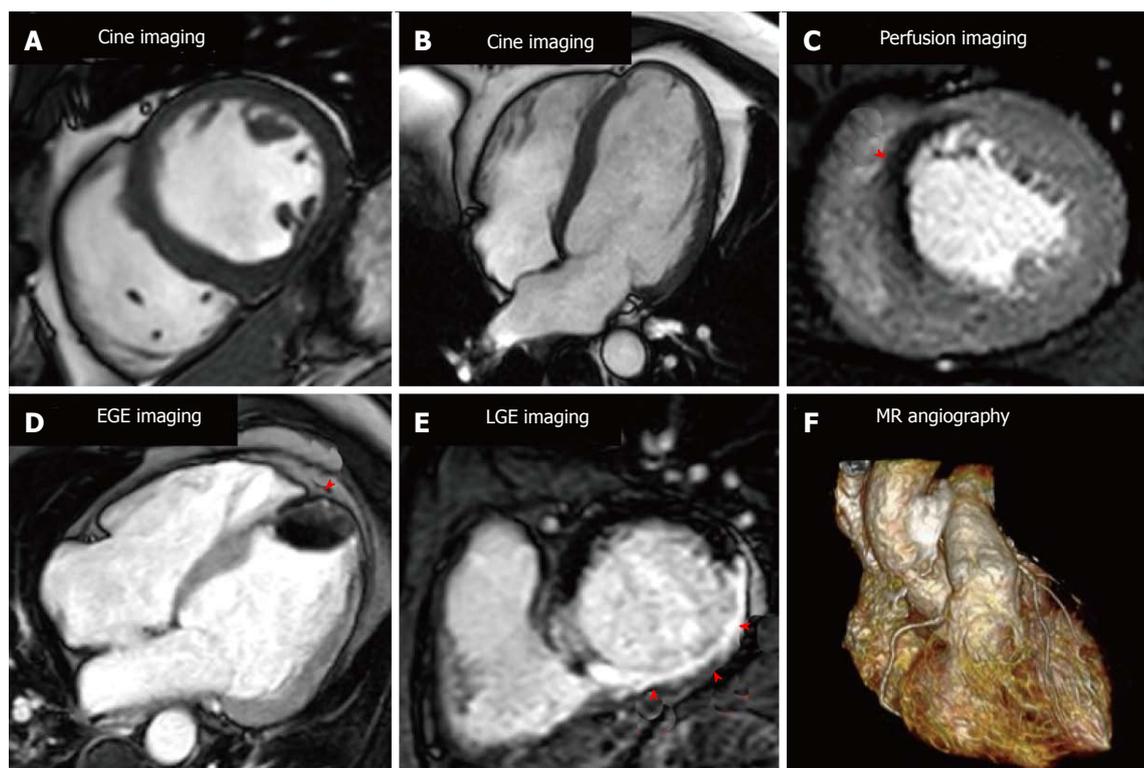
CMR is the reference standard non-invasive technique for the measurement of left ventricular (LV) and right ventricular (RV) volumes, and ejection fraction, with high intra- and inter-observer reproducibility<sup>[10,11]</sup>. Steady state free precession cine imaging is typically performed for the assessment of LV function to enable visual assessment of global and regional myocardial function in a similar manner to echocardiography; however there are no limitations due to poor acoustic windows or large body habitus degrading image quality. CMR volumetric analysis is performed by acquiring a stack of contiguous breath held cine images from the base of the heart to the apex; the endocardial and epicardial borders are subsequently contoured giving mass, volumes and function. Thus CMR provides a true 3D analysis of LV and RV function unlike 2D echocardiography that relies on geometric assumptions for volumetric calculations. Furthermore specific myocardial tagging pulse sequences can be performed that enable more detailed assessment of intra-myocardial mechanics beyond ejection fraction, including torsion, twist, strain and strain rates<sup>[12]</sup>. Additionally, feature tracking is a novel post-processing method of quantitatively assessing strain and strain rate using standard cine images without having to acquire further imaging sequences as is the case with standard CMR tissue tagging<sup>[12,13]</sup>.

## DIAGNOSIS OF CAD

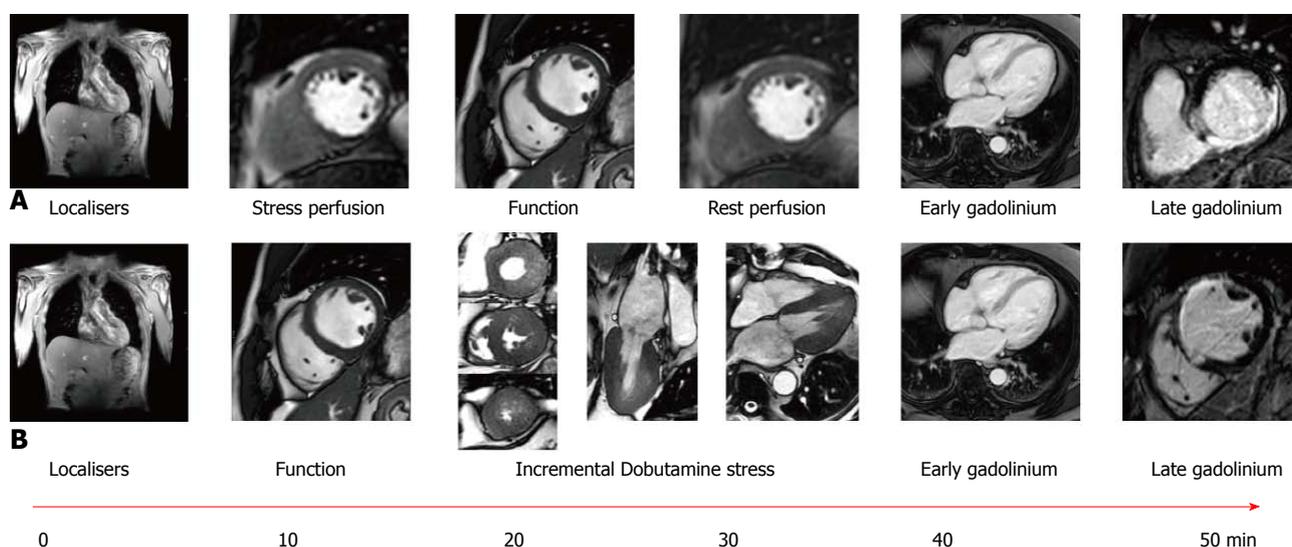
Ischaemia detection by CMR is performed using either vasodilator or inotropic stress. Ischaemia detection by CMR is recommended as a first line strategy for investigating suspected angina in patients with an intermediate pre-test likelihood of CAD in both the current European Society of Cardiology (ESC) and National Institute for Health and Care Excellence (NICE) guidelines (Table 1)<sup>[6,14]</sup>, whilst the United States guidelines are more conservative and give a grade IIa recommendation for stress perfusion CMR in patients with uninterpretable ECGs or unable to exercise<sup>[7]</sup>.

## STRESS PERFUSION CMR

Stress perfusion CMR requires the induction of hyperaemia by a vasodilating agent, and then observation of the passage of a gadolinium based contrast agent (GBCA) through the myocardium to identify perfusion defects. Typically the vasodilating agent used is adenosine though regadenoson and less commonly dipyridamole and nicorandil are also



**Figure 1 Cardiovascular magnetic resonance imaging techniques.** A and B show short axis and 4 chamber cine images respectively for anatomical and functional assessment; C shows stress perfusion with a septal perfusion defect (arrow); D shows early gadolinium enhancement imaging with a large apical thrombus (arrow); E is late gadolinium enhanced imaging with a transmural inferior infarction (arrows); F is 3D whole heart magnetic resonance angiography. LGE: Late gadolinium enhancement; EGE: Early gadolinium enhancement.



**Figure 2 Cardiovascular magnetic resonance multi-parametric protocols for the investigation of suspected coronary artery disease.** A shows a typical multi-parametric cardiovascular magnetic resonance protocol for the investigation of stable coronary artery disease with adenosine stress perfusion; and B with incremental dose dobutamine stress.

used. Adenosine produces vasodilatation in most vascular beds, including the coronary circulation, *via* A2A and A2B receptors<sup>[15]</sup>. Adenosine is given as an intravenous infusion typically at a rate of 140 mcg/kg per minute, though this can be increased if there is no haemodynamic response; the main side effects of adenosine are transient heart block, and bronchospasm can be caused in those with reversible

airways disease<sup>[15]</sup>. Regadenoson is a new selective A2A adenosine receptor agonist that is given *via* an intravenous bolus, has less respiratory side effects than adenosine, and has recently been approved by both the FDA and in Europe for this indication<sup>[16,17]</sup>. The coronary micro-vasculature can dilate up to 4 or 5 times from the resting state to ensure adequate tissue perfusion for example during exercise.

**Table 1** European Society of Cardiology and American College of Cardiology Foundation/American Heart Association Recommendations for cardiovascular magnetic resonance in stable coronary artery disease

ESC guidelines	
Suspected/stable coronary artery disease <sup>[6]</sup>	
In patients with suspected stable coronary artery disease and pretest probability of 15%-85% stress imaging is preferred as the initial test option if local expertise and availability permit	Class I
An imaging stress test is recommended in patients with resting ECG abnormalities, which prevent accurate interpretation of ECG changes during stress	Class I
CMR should be considered in symptomatic patients with prior revascularisation (PCI or CABG)	Class II a
Risk stratification is recommended based on clinical assessment and the results of the stress test initially employed for making a diagnosis of stable coronary artery disease	Class I
CMR is recommended in the presence of recurrent or new symptoms once instability has been ruled out	Class I
In symptomatic patients with revascularised stable coronary artery disease, CMR is indicated rather than stress ECG	Class I
CMR is recommended for risk stratification in patients with known stable coronary artery disease and a deterioration in symptoms if the site and extent of ischemia would influence clinical decision making	Class I
Recommendations for imaging to determine ischemia to plan revascularisation <sup>[6,144]</sup>	
An imaging stress test should be considered to assess the functional severity of intermediate lesions on coronary arteriography	Class II a
To achieve a prognostic benefit by revascularisation in patients with coronary artery disease, ischemia has to be documented by non-invasive imaging	Class I
Following MI with multivessel disease, or in whom revascularisation of other vessels is considered, CMR for ischaemia and viability is indicated before or after discharge	Class I
Heart failure <sup>[8]</sup>	
CMR should be considered in patients with HF thought to have CAD, and who are considered suitable for coronary revascularization, to determine whether there is reversible myocardial ischaemia and viable myocardium	Class II a
AHA guidelines	
Diagnosis and management of stable coronary artery disease <sup>[7]</sup>	
CMR can be used for patients with an intermediate (10%-90%) to high (> 90%) pretest probability of obstructive IHD who have an uninterpretable ECG and at least moderate physical functioning or no disabling comorbidity	Class II a
CMR is reasonable for patients with an intermediate to high pretest probability of IHD who are incapable of at least moderate physical functioning or have disabling comorbidity	Class II a
Pharmacological stress CMR is reasonable for risk assessment in patients with SIHD who are unable to exercise to an adequate workload regardless of interpretability of ECG	Class II a
CMR is reasonable in patients with known SIHD who have new or worsening symptoms (not unstable) and who are incapable of at least moderate physical functioning or have disabling comorbidity	Class II a

ESC: European Society of Cardiology; CMR: Cardiovascular magnetic resonance; ECG: Electrocardiogram; CABG: Coronary artery bypass graft; PCI: Percutaneous coronary intervention; AHA: American Heart Association; IHD: Ischemic heart disease; SIHD: Stable ischemic heart disease.

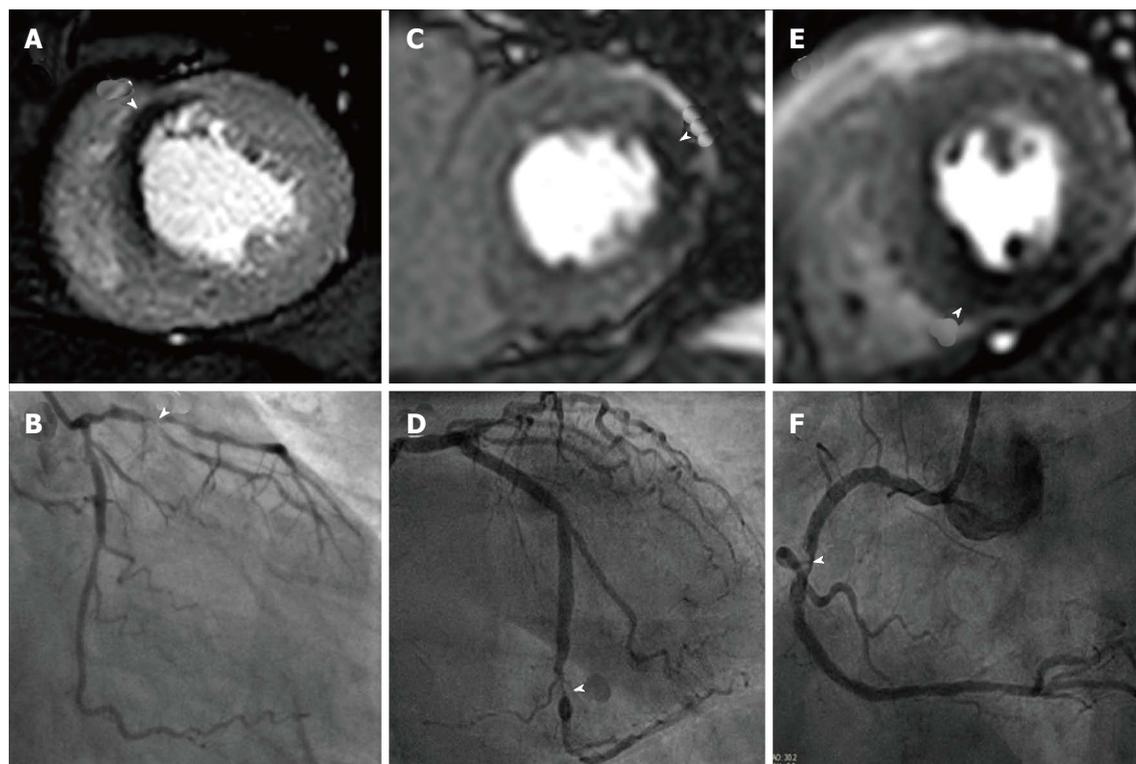
However the microvasculature distal to a stenosed coronary artery is already near-maximally vasodilated at rest and consequently when hyperaemia is provoked a coronary steal effect is caused. GBCAs increase the signal intensity in T1 weighted images and the passage of GBCAs through the myocardium causes healthy myocardium to become brighter while regions of hypoperfusion ("ischaemia") remain dark (Figure 3).

The diagnostic accuracy of stress perfusion CMR for the detection of CAD is well validated. A meta-analysis of 37 studies demonstrated a combined sensitivity of 89% (95%CI: 88%-91%) and specificity of 76% (95%CI: 73%-78%) for perfusion CMR for the diagnosis of CAD<sup>[18]</sup>. The CE-MARC study ( $n = 752$ ), the largest prospective randomised single-centre trial of CMR in this context showed superiority of perfusion CMR over SPECT, with a higher sensitivity (87% vs 67%,  $P < 0.0001$ ) and negative predictive value (91% vs 79%,  $P < 0.0001$ ) but similar specificity (83% vs 83%  $P = 0.916$ ) and positive predictive values (77% vs 71%,  $P = 0.061$ )<sup>[19,20]</sup>. Furthermore in a pre-specified gender sub analysis of CE-MARC, CMR showed similar sensitivity for CAD detection in both males and females, whilst SPECT had significantly lower sensitivity in females compared to males<sup>[21]</sup>.

The multi-centre, multi-vendor MR-IMPACT II trial

( $n = 515$ ) also confirmed CMR's superior sensitivity compared to SPECT (67% vs 59%,  $P = 0.024$ ) but with a lower specificity (61% vs 72%,  $P = 0.038$ )<sup>[22]</sup>; however unlike CE-MARC only the stress/rest perfusion component of the CMR protocol was analysed. CE-MARC included analysis of LGE for scar detection, cine imaging for regional ventricular function and magnetic resonance angiography (MRA) for coronary artery anatomy, and a subsequent sub-analysis of CE-MARC demonstrated the additive diagnostic accuracy of the summation of these components of the multi-parametric protocol<sup>[23]</sup>.

Stress perfusion CMR has also been validated against FFR in a recent meta-analysis with a pooled sensitivity and specificity of 0.90 (95%CI: 0.86-0.93) and 0.87 (95%CI: 0.82-0.90) at the patient level and 0.89 (95%CI: 0.83-0.92) and 0.86 (95%CI: 0.77-0.92) at the coronary artery and territory levels<sup>[24]</sup>. Furthermore CMR stress perfusion had comparable sensitivity and specificity to cardiac CT and PET in a recent meta-analysis of non-invasive imaging modalities, and was superior to both SPECT and DSE when using FFR as the reference standard<sup>[25]</sup>. Most trials thus far have excluded patients with arrhythmia amid concerns regarding ECG gating, however the diagnostic accuracy of stress perfusion CMR remains high in suspected CAD patients with AF or



**Figure 3 Cardiovascular magnetic resonance perfusion techniques.** A is a high spatial resolution *k-t* BLAST stress perfusion CMR study at 3.0T showing an antero-septal perfusion defect with corresponding left anterior descending lesion in B; C shows a transmural lateral perfusion defect at standard resolution at 1.5T with corresponding circumflex lesion in D; E shows a transmural inferior perfusion defect at standard resolution at 1.5T with corresponding right coronary artery lesion in F. BLAST: Broad-use linear acquisition speed-up technique; CMR: Cardiovascular magnetic resonance.

frequent ectopy (sensitivity 80%, specificity 74%)<sup>[26]</sup>.

### 1.5T VS 3.0T FIELD STRENGTH

Although 1.5T remains the standard field strength used in clinical CMR, imaging at a higher field strength of 3.0T offers increased signal to noise and contrast to noise ratios thereby giving improved spatial and temporal enhancement<sup>[27]</sup>. Consequently the diagnostic accuracy of perfusion imaging at 3.0T may be improved, and in a small direct comparison of CMR perfusion at 1.5T, 3.0T ( $n = 61$ ) showed greater diagnostic accuracy in both single vessel (AUC: 0.89 vs 0.70;  $P < 0.05$ ) and multi-vessel disease (AUC: 0.95 vs 0.82,  $P < 0.05$ )<sup>[28]</sup>. Furthermore, 3.0T has been compared to 1.5T using FFR as reference standard, corroborating its superior diagnostic accuracy<sup>[29,30]</sup>. The higher 3.0T field strength does however pose challenges with greater field inhomogeneity, susceptibility artefacts and higher local energy deposition. Also, many implants deemed "MR compatible" at 1.5T cannot be scanned at 3.0T<sup>[31]</sup>. These issues are however being overcome with improved technology and the use of multi-transmit radiofrequency CMR techniques improving field homogeneity<sup>[32]</sup>.

### IMPROVING PERFUSION IMAGING

Currently typical CMR perfusion imaging acquires 3 short axis slices of the left ventricle with an in-plane spatial

resolution of 2-3 mm. Developments in CMR technology however now allow faster scan speeds; these novel acquisition techniques allow accelerated data acquisition based on spatio-temporal undersampling (*k-t* SENSE or *k-t* BLAST and highly constrained back projection HYPR, compressed sensing and others)<sup>[33]</sup>. These faster data acquisition techniques have been applied to achieve in-plane spatial resolution  $< 2$  mm or full-coverage of the LV using 3D whole-heart perfusion imaging. High spatial-resolution imaging offers benefits by significantly reducing dark rim artefacts, as these are directly proportional to voxel size<sup>[34]</sup>. Moreover there is improved ability to detect sub-endocardial ischaemia which is critical in multi-vessel disease where there is a lack of reference healthy myocardium for comparison<sup>[35,36]</sup>. High spatial-resolution perfusion CMR has been validated at both 1.5T and 3.0T against quantitative coronary angiography (QCA) with improved diagnostic accuracy at both field strengths compared to standard resolution perfusion imaging<sup>[27,36,37]</sup>. Furthermore validation against FFR gave sensitivity and specificity to detect stenoses at a threshold of FFR  $< 0.75$  of 0.82 and 0.94 ( $P < 0.0001$ ) respectively, and an area under the curve of 0.92 ( $P < 0.0001$ )<sup>[38]</sup>.

Conventional stress perfusion CMR is typically acquired in 3 short-axis slices, and thus unlike SPECT does not truly calculate global ischaemia burden. Accelerated acquisition techniques can also be employed to achieve full LV coverage using a 3D whole-heart single shot acquisition.

Such 3D acquisitions can overcome the assumptions made about “missing” myocardium between the slices from conventional 2D multi-slice perfusion imaging. Two studies have validated the feasibility and diagnostic accuracy of 3D stress perfusion CMR against FFR; at 1.5T 3D perfusion demonstrated a sensitivity, specificity and diagnostic accuracy of 90%, 82% and 87% respectively and 91%, 90% and 91% respectively at 3.0T<sup>[39,40]</sup>. Furthermore in a recent multicentre trial of 3D stress perfusion at 3.0T, sensitivity and specificity were 84.7% and 90.8% relative to the FFR reference<sup>[41]</sup>. The main motivation for 3D perfusion is to give a more accurate quantification of total myocardial ischaemia burden; evidence from SPECT suggests a prognostic benefit for revascularisation in those with an ischaemia burden > 10%, with an ischaemia burden of 10% conferring a risk of approximately 5% for death or MI per year<sup>[42,43]</sup>. Ischaemia burden as measured by 3D stress perfusion CMR has been compared to SPECT and showed good correlation ( $r_s = 0.70$ ,  $P < 0.001$ )<sup>[44]</sup>. Intriguingly a recent pilot study compared ischaemia burden by high-resolution perfusion (using 3 short axis slices) and 3D perfusion imaging (providing whole heart coverage) suggesting that there was also a good correlation between the techniques ( $r = 0.72$ ;  $P = 0.001$ ), and that therefore the two methods are potentially interchangeable<sup>[45]</sup>.

## QUANTITATIVE PERFUSION

CMR stress perfusion studies are normally reported in a qualitative manner; however this can prove challenging in diffuse or multi-vessel disease where there is no healthy reference myocardium to use as a visual comparator. These situations can introduce subjectivity into the analysis and consequently quantitative measurement techniques have been developed to provide an objective assessment of myocardial blood flow. A number of different methods of quantitative analysis have been assessed with the Fermi deconvolution method showing most accuracy when compared to microspheres in an explanted porcine model at 1.5T and mice at 3.0T<sup>[46,47]</sup>, and when compared to SPECT and with QCA<sup>[48]</sup>. When compared to angiography with FFR, an MPR threshold of 1.58 detected a stenosis with an FFR < 0.75 with a sensitivity of 0.80, specificity of 0.89 ( $P < 0.0001$ ), and area under the curve of 0.89 ( $P < 0.0001$ )<sup>[38]</sup>. Myocardial perfusion reserve derived from quantitative CMR perfusion has also shown good correlation to PET imaging, the imaging modality that is widely regarded as the reference standard non-invasive measure of myocardial blood flow<sup>[49,50]</sup>. Currently, time consuming post-processing has limited quantitative perfusion methods to a research tool, but automated methods are being developed that may potentially overcome this<sup>[51]</sup>.

## DOBUTAMINE STRESS CMR

GBCAs have an excellent safety profile<sup>[52]</sup>, but in patients with poor renal clearance (*e.g.*, on dialysis) there is

a risk of nephrogenic systemic fibrosis<sup>[53]</sup>. In those patients unable to have GBCAs inotropic stress CMR is an alternative. Inotropic stress CMR is typically performed with dobutamine in a similar manner to DSE with inducible regional wall motion abnormalities identified in territories supplied by a stenosed coronary artery at peak stress. Unlike DSE however, DSMR's accuracy is not limited by body habitus or in those with poor acoustic windows and in a single centre study DSMR was shown to have significantly greater diagnostic performance to DSE in this context<sup>[54]</sup>. However echocardiography in this study was performed without harmonic imaging and contrast agents, so that the performance of DSE is likely to be underreported compared with contemporaneous methods. DSMR has a comparable safety profile to DSE with an event rate of 0.1% for sustained VT and 0.4% for non-sustained VT, and 1.6% for atrial fibrillation; patients thus require close monitoring during scanning and resuscitation equipment needs to be available<sup>[55]</sup>. DSMR has been shown to have high diagnostic accuracy for the detection of CAD with one meta-analysis of 14 trials showing a pooled sensitivity of 0.83 (95%CI: 0.79-0.88) and specificity of 0.86 (95%CI: 0.81-0.91)<sup>[56]</sup>; furthermore a single centre trial of DSMR vs perfusion CMR showed similar diagnostic accuracy<sup>[57]</sup>. First-pass perfusion can be performed additionally at peak dobutamine stress to provide incremental diagnostic accuracy<sup>[58]</sup>, and can be a useful adjunct in challenging patient groups such as those with pre-existing wall motion abnormalities or dyssynchrony from left bundle branch block<sup>[59]</sup>.

Exercise is commonly used rather than pharmacological agents as the stressor in echocardiography, and gives useful prognostic information such as workload in metabolic equivalent (METs) in addition to ischaemia testing<sup>[60,61]</sup>. CMR is limited in this respect due to the need for supine scanning and consistent positioning within the scanner. Recent studies however have assessed the feasibility of exercise stress CMR and showed comparable accuracy to echocardiography, though it has yet to reach mainstream clinical use<sup>[62,63]</sup>. Promising developments are “steppers” and cycle ergometers that can attach directly to the MRI scanner, and thereby eliminate the need to transfer the patient from the exercise equipment into the scanner<sup>[64,65]</sup>.

## Prognosis from stress CMR

Both perfusion CMR and DSMR provide excellent prognostic information, and this has recently been shown in two large meta-analyses. One meta-analysis of 14 studies including 12178 patients showed that a negative stress CMR was associated with a 1.03% annualised event rate, comparable to the normal population<sup>[66]</sup>. A further meta-analysis of 19 studies including 11636 patients showed a similar annualised event rate of 0.8% for a negative stress CMR over a mean follow up of 32 mo<sup>[67]</sup>. In a large prospective study of 1229 patients undergoing adenosine stress with a mean follow-up period of  $4.2 \pm 2.1$  years, patients with reversible perfusion deficits had a 3-fold

increased risk of major adverse cardiovascular events, with significantly more cardiac deaths ( $P < 0.0001$ ) and nonfatal myocardial infarctions ( $P < 0.001$ )<sup>[68]</sup>. Similarly the data from DSMR mirrors the results of first-pass perfusion CMR with a negative study conferring an equally low annual event rate of 1.3%<sup>[66,69]</sup>. Recently the five-year outcome data from CE-MARC were published with prognostic data for both CMR and SPECT in the same patient population. The analysis showed that although an abnormal result from both tests was a strong indicator of future major adverse cardiovascular events (MACE), CMR was superior at predicting time to MACE in this population<sup>[70]</sup>. Furthermore CMR remained the only independent predictor of outcome after adjustment for major cardiovascular risk factors, stratification for initial patient treatment and coronary angiographic findings<sup>[70]</sup>. These findings likely reflect CMR's overall greater diagnostic accuracy, combined with CMR's higher spatial resolution enabling greater identification of subendocardial scar compared to SPECT<sup>[71]</sup>; a feature known to confer prognostic significance beyond ejection fraction, and clinical or angiographic features<sup>[72]</sup>.

## EARLY AND LATE GADOLINIUM ENHANCEMENT IMAGING

GBCAs have a large molecular weight and cannot penetrate an intact cell membrane; consequently GBCAs are constrained to the extracellular space. In healthy myocardium the extracellular space is limited and contrast enters and clears rapidly. The extracellular space in infarcted myocardium however is substantially increased compared to normal myocardium and is less vascular. Thus in chronic myocardial infarction scar tissue composed of a matrix of collagen fibres has significantly increased extracellular space, leading to GBCA accumulation (slow washout), whilst in acute infarction GBCAs passively diffuse across disrupted myocardial cell membranes and into the intracellular space (greater volume of distribution)<sup>[73]</sup>. Thus both acute and chronic myocardial infarction retain more GBCAs. Imaged with T1 sensitive acquisition methods, this results in a higher signal.

Early gadolinium enhancement imaging is performed immediately following contrast administration; this allows mainly the visualisation of ventricular thrombi that appear "dark/black" due to a lack of contrast uptake as they are non-vascular (Figure 4). CMR has been shown to be superior to both trans-thoracic echocardiography and trans-oesophageal echocardiography for the identification of ventricular thrombi<sup>[74,75]</sup>. LGE imaging is performed between 10-20 min after contrast administration, an appropriate inversion time is set to null the normal myocardium and the areas where gadolinium is retained enhances (Figure 4). Typically a stack of short axis slices, a 4-chamber view and VLA are acquired. Alternatively, 3D LGE CMR imaging enables whole heart quantification of scar burden to be acquired in a shorter time period (although with a reduction in image quality), which may

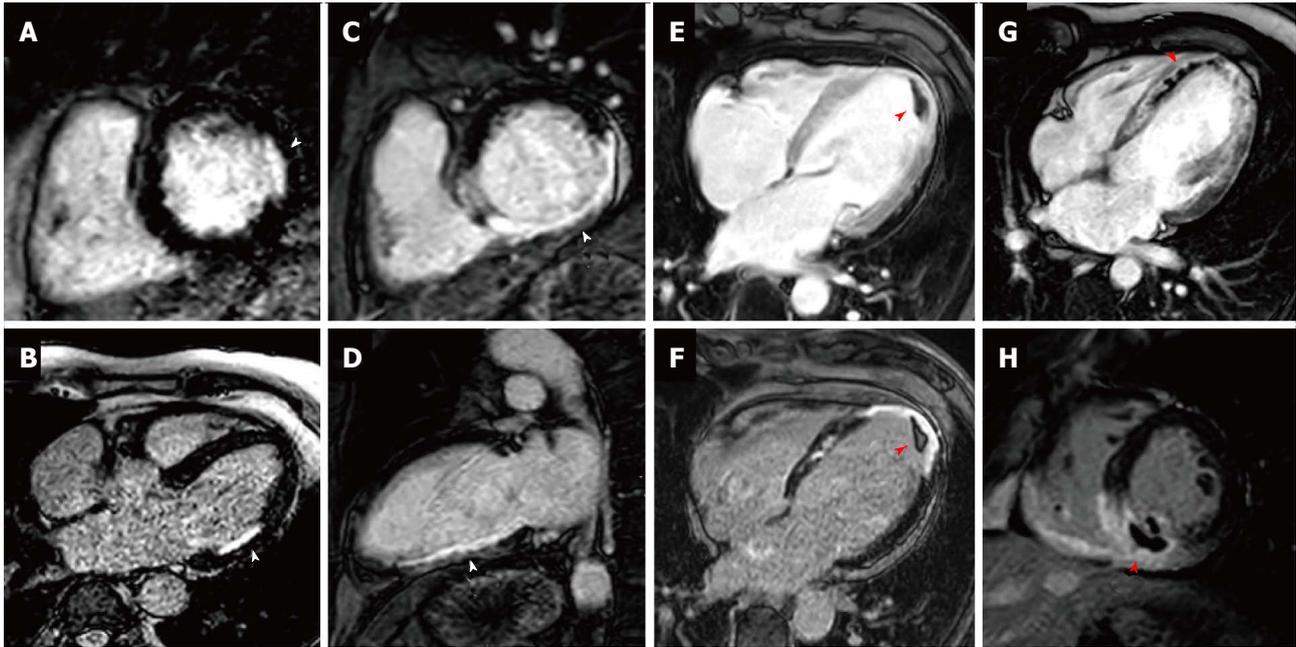
provide an alternative for patients that struggle to breath-hold<sup>[76,77]</sup>.

## VIABILITY ASSESSMENT

CMR viability assessment using LGE enables the accurate detection, and extent and trans-murality of previous myocardial infarction to be determined, and identifies regions with potential to recover function following revascularisation. Hibernating myocardium is dysfunctional myocardium that has been down-regulated through a process of chronic/repetitive ischaemia and which has the potential for functional recovery when blood flow is restored. LGE imaging detects replacement of normal viable myocytes by focal necrosis or fibrosis with high spatial resolution, and has excellent correlation to histopathology<sup>[73]</sup>. Furthermore the degree of transmural extent of hyper-enhancement on LGE imaging has a direct association to the potential for functional recovery following revascularisation; Kim *et al*<sup>[78]</sup> demonstrated that segments with less than 25% hyper-enhancement were most likely to attain functional recovery whilst segments with over 75% hyper-enhancement were unlikely to improve, notably this was irrespective of whether the region was initially hypokinetic, dyskinetic or akinetic. A meta-analysis of 331 patients using 50% trans-murality of hyper-enhancement reported a sensitivity of 95% (95%CI: 93%-97%) and specificity of 51% (40%-62%) for predicting functional recovery<sup>[79]</sup>.

CMR viability assessment is not however limited to just LGE imaging; whilst LGE identifies the transmural extent of scarring, the use of low-dose dobutamine (LDD) identifies the contractile reserve. Myocardium is considered viable if there is a 2 mm or more increase in systolic wall thickening within a segment following administration of LDD (5-10 mcg/kg per minute)<sup>[80]</sup>. While scar burden on LGE has been shown to be most sensitive method for assessment for functional recovery compared to LDD and diastolic wall thickness<sup>[81]</sup>, LDD CMR offers higher specificity and PPV for prediction of functional recovery (91% and 93%, respectively)<sup>[79]</sup>. Consequently a stepwise approach utilising LGE first followed by LDD if the trans-mural extent of LGE in the territory of the diseased coronary is between 1%-50% has been proposed<sup>[82]</sup>. Recently both tissue tagging and feature tracking have been used to give quantitative viability assessment with LDD and have been suggested as possible methods to reduce reliance on operator experience in what is currently a qualitative method of assessment<sup>[83-85]</sup>.

LGE imaging has a grade A recommendation to determine myocardial viability prior to revascularisation in the ACCF/AHA/SCMR appropriate use guidelines<sup>[86]</sup>, though viability assessment by LGE is currently not recommended for this indication in ESC or US practice guidelines for management of stable CAD or coronary revascularisation<sup>[6,7,9,87]</sup>. The utility of viability assessment has been questioned recently following the results of the STICH trial and the subsequently published viability sub-study that showed no mortality benefit from re-



**Figure 4** Early and late gadolinium enhancement. A and B show a lateral sub-endocardial infarction on short axis and 4 chamber LGE respectively; C and D show a full thickness inferior infarction on LGE imaging on short axis and VLA respectively; E and F show EGE and LGE imaging respectively of a full thickness apical infarction with an apical thrombus appearing black (highlighted by red arrow); G shows an extensive acute antero-apical infarction with a core of microvascular obstruction visible within the hyperenhancement on EGE (red arrow); H shows an acute inferior wall infarction with MVO and extension into the right ventricle on LGE (red arrow) imaging. LGE: Late gadolinium enhancement; EGE: Early gadolinium enhancement; MVO: Mitral orifice.

vascularisation following viability assessment<sup>[88,89]</sup>. This is contrary to prior observational data in large meta-analyses including over 3000 patients with viability; revascularisation was associated with 79.6% reduction in annual mortality ( $P < 0.0001$ ) compared with medical treatment<sup>[90,91]</sup> and presence of dysfunctional viable myocardium by LGE-CMR without revascularisation is an independent predictor of mortality in patients with ischemic LV dysfunction<sup>[92]</sup>. Questions have been asked however whether the STICH sub-study results would have been different if CMR had been used rather than SPECT, and consequently in Europe the third highest indication for CMR remains the assessment of viability<sup>[93]</sup>.

## SCAR BEYOND VIABILITY ASSESSMENT

In addition to identifying viable myocardium, the presence and extent of LGE provides valuable prognostic information, and the extent of scar burden by LGE is readily quantified and reproducible on CMR<sup>[94]</sup>. Impairment of left ventricular ejection fraction is well recognized as an independent risk factor in those with coronary artery disease<sup>[8,95]</sup>; LGE can provide additive prognostication in these patients and a recent study of 1560 patients established that the presence of scar by LGE irrespective of LVEF identified those at risk of increased mortality<sup>[96]</sup>. Furthermore a meta-analysis showed that the presence of LGE increases the risk of death by 4.77% and MACE by 3.9% and that each gram of scar measured by LGE increased the hazards of death and MACE by 4% and 5%, respectively<sup>[97]</sup>. Additionally the identification of previously unrecognized MI by LGE confers a significantly increased

risk of both mortality and MACE<sup>[72,98]</sup>.

The extent of scar burden by LGE in patients with ischaemic heart disease has also been identified in a number of studies to be an independent predictor of ventricular arrhythmias in patients with internal cardiac defibrillators (ICD)<sup>[99-101]</sup>, and a recent meta-analysis of 1105 patients with ICDs determined that the extent of LGE was predictive of ventricular arrhythmia whilst LVEF was not<sup>[102]</sup>. Additionally in a high risk cohort of patients with a mean LVEF of 35% being considered for ICD implantation, LGE demonstrated that significant scarring ( $> 5\%$  LV) in patients with LVEF  $> 30\%$ , conferred a risk similar to those with LVEF  $\leq 30\%$ <sup>[103]</sup>. Equally, in patients with LVEF  $\leq 30\%$ , minimal or no scar burden established a lower risk cohort similar to those with LVEF  $> 30\%$ <sup>[103]</sup>. Other studies have identified the presence of a "grey zone" on LGE imaging, a heterogeneous region of viable and non-viable myocardium at the infarct periphery, as predictive of VT<sup>[104,105]</sup>.

LGE and quantification of scar burden has also been used to predict responsiveness to cardiac resynchronization therapy (CRT)<sup>[106]</sup>, and identification of scarring in the pacing region of the LV lead has been associated with non-response to device therapy<sup>[107,108]</sup>. In a similar method to imaging the coronary artery anatomy, coronary venous anatomy can be reliably demonstrated using GBCAs, which can potentially aid planning of device implantation<sup>[109]</sup>. The combination of coronary venous imaging, assessment of ventricular function and LGE may be a useful adjunct in the management of patients with ischaemic cardiomyopathy being considered for CRT, as well as risk stratifying those being considered for

defibrillator therapy.

## COST EFFECTIVENESS

The economic burden of CAD is enormous with £6.8 billion spent in 2012 in the United Kingdom; in the United States over 15 million people have CAD costing the US economy \$108.9 billion/year<sup>[110,111]</sup>. Cost effectiveness analyses help to inform optimal management pathways in order to maximise health care benefit within the constraints of limited resources. In the United States a low yield has been reported at diagnostic angiography with just over 40% of patients referred having obstructive CAD<sup>[5]</sup>. CMR can act as a potential gatekeeper to invasive coronary angiography in order to reduce downstream costs as well as reduce risk from unnecessary invasive assessments.

Health economic analyses based on the CE-MARC dataset identified that despite the higher initial cost of CMR to SPECT, the superior diagnostic accuracy of CMR lead to an overall greater cost effectiveness in models of the United Kingdom, German and Swiss healthcare systems<sup>[112-114]</sup>. A study of 1158 German patients being investigated for suspected CAD were randomised to either DSMR prior to angiography or direct to angiography; DSMR prior to invasive angiography led to a saving of 12466€ of hospital costs per life year, furthermore this cost saving was maintained through a median period of 7.9 years follow-up<sup>[115]</sup>.

In a cost analysis comparing CMR and X-ray angiography vs angiography and FFR to determine the need for revascularisation, CMR and angiography was more cost-effective below a CAD prevalence of 62%, 65%, 83% and 82% for the Swiss, German, United Kingdom, and the United States health care systems, respectively<sup>[116]</sup>. These studies confirm that as well as the established high diagnostic accuracy, CMR is also a financially advantageous investigative strategy in patients with CAD.

## RECENTLY PUBLISHED AND FUTURE STUDIES

Studies thus far have predominantly focused on the diagnostic accuracy of CMR; forthcoming multi-centre clinical effectiveness trials are however focused on evaluating clinical pathways to improve patient outcomes. The recently published CE-MARC 2 trial is a prospective, multi-centre, 3-arm parallel group, randomised controlled trial comparing multi-parametric CMR vs UK NICE CG95 guidance<sup>[14]</sup> vs AHA/ACCF SPECT appropriate-use criteria<sup>[117]</sup> to investigate patients with suspected CAD (pre-test likelihood 10%-90%) requiring further investigation<sup>[118,119]</sup>. The primary outcome measure was FFR defined unnecessary angiography (FFR > 0.8) with the important safety secondary outcome measure of MACE at 1 and 3 years. CE-MARC 2 showed overall that CMR guided care resulted in significantly reduced rates of

unnecessary angiography at 12 mo compared to routine guideline directed care<sup>[119]</sup>.

Contemporary registry data from the United States suggests roughly 12%-26% of elective PCI are deemed inappropriate with considerable variation in practice between sites<sup>[120,121]</sup>. Both FAME and DEFER showed improved outcomes using FFR guided revascularisation based on ischaemia detection, compared to reliance on visual assessment at angiography<sup>[122,123]</sup>. These trials would suggest that a better way of selecting patients prior to invasive revascularisation procedures is required. CMR offers a non-invasive ischaemia assessment and the MR-INFORM trial aims to establish if perfusion CMR could act as a non-invasive surrogate to FFR to determine the need for revascularisation in patients with stable CAD<sup>[124]</sup>. MR-INFORM is a multi-centre, non-inferiority study comparing adenosine perfusion CMR vs angiography with FFR measurement to guide revascularisation decisions in patients with stable angina and moderate to high probability of CAD; the primary endpoint is the occurrence of MACE at one year. The trial has completed recruitment and is expected to report in 2017.

The prognostic benefit of revascularisation in stable coronary artery disease is a topic of debate; both the COURAGE trial and BARI-2D failed to show any prognostic benefit of revascularisation over optimal medical therapy (OMT) in patients with stable CAD<sup>[125,126]</sup>. Determination of extent of ischaemia in both these 2 trials was however limited; in COURAGE only 33% of patients had moderate/severe ischaemia and moreover around 40% had < 5% ischaemia<sup>[127]</sup>. In both trials however those with a higher residual ischaemia burden had a worse prognosis<sup>[127-129]</sup>. The ISCHEMIA trial aims to test the hypothesis that a routine invasive strategy with early cardiac catheterisation and revascularisation plus OMT is superior to a conservative management strategy of OMT for patients with moderate or severe ischemia<sup>[42]</sup>. The trial aims to recruit over 8000 patients worldwide with ischaemia determined by non-invasive imaging (CMR, stress echocardiography, SPECT) with a primary endpoint of time to cardiovascular death or non-fatal myocardial infarction.

### Coronary artery evaluation

Coronary MRA (CMRA) allows the non-invasive anatomical assessment of coronary arteries; currently clinical indications are limited to the detection of aberrant origin of coronary arteries, coronary ectasia and/or aneurysms (class I indication) and evaluation of bypass grafts (class II indication)<sup>[130,131]</sup>. CMRA for diagnosis of CAD is not presently part of routine clinical practice. The initial multi-centre experience using CMRA in this context showed interpretable image quality in 84% of proximal and middle coronary artery segments, though with a specificity of 42%; CMRA did however exclude triple-vessel disease and left main coronary artery stenosis with a negative predictive value of 100%<sup>[132]</sup>. Progress in CMRA techniques have improved significantly however, and a recent multi-centre study showed that CMRA at 1.5T detects significant

CAD with a sensitivity of 88% and specificity of 72% and a negative predictive value of 88%<sup>[133]</sup>. Furthermore one study showed in a direct comparison between CMRA and CT coronary angiography (CTCA) there was no significant difference between coronary imaging at 3.0T and 64-slice CTCA for the detection of CAD with a sensitivity of 87% vs 90% ( $P = 0.16$ ) and specificity of 77% vs 83% ( $P = 0.06$ ) respectively<sup>[134]</sup>.

Currently CMRA techniques are time consuming and there are questions over the incremental diagnostic merit they provide in addition to established perfusion protocols; the CE-MARC study found no additional diagnostic benefit by including CMRA into a full multi-parametric protocol vs the perfusion/LV function/LGE combination (overall accuracy 84.6% vs 84.2% ( $P = 0.5316$ ))<sup>[23]</sup>. Moreover there was no significant improvement in diagnostic accuracy when CMRA was added to perfusion imaging at 1.5T and compared to FFR as the reference standard<sup>[135]</sup>.

## FUTURE DIRECTIONS

### *T1 mapping*

Native T1, T1 mapping, and extra cellular volume fraction quantification are novel methods for CMR tissue characterisation. These techniques are currently research tools that have shown promise for diagnosis and prognostication in acute coronary syndromes and other rare disease processes (*e.g.*, Amyloid and Fabry's disease), presently however they do not have an established role in the diagnosis or management of stable ischaemic heart disease<sup>[136,137]</sup>. Post myocardial infarction however a role for these imaging "biomarkers" is being established in predicting both prognosis and adverse LV remodelling<sup>[138,139]</sup>.

### *Blood oxygen level dependent*

CMR uses the paramagnetic properties of deoxyhaemoglobin as an endogenous contrast agent; increasing deoxyhaemoglobin content leads to a reduction of signal intensity on T2 or T2\* weighted images<sup>[140]</sup>. The magnitude of the BOLD effect depends on the static magnetic field strength, with an exponential increase at 3.0T from 1.5T; consequently most studies have used 3.0T. Thus far BOLD has shown good correlation with QCA and conventional CMR perfusion imaging, but studies are generally small and single centre, limiting its clinical validation<sup>[141,142]</sup>.

Finally hyperpolarised CMR is making the transition from animal studies to human applications. Hyperpolarisation methods artificially increase the number of molecules in one orientation resulting in a significant increase in MR signal; combined with <sup>13</sup>C enriched metabolic tracers enable real time imaging of *in vivo* substrate metabolism, coronary angiography and quantitative perfusion imaging<sup>[143]</sup>. The results of human hyperpolarisation studies are eagerly awaited.

## CONCLUSION

Over the last decade the evidence base for the diag-

nostic accuracy of CMR for the investigation of stable coronary artery disease has been confirmed through the publication of large-scale clinical trials and meta-analyses, and CMR is now firmly established in clinical practice guidelines. CMR enables assessment of cardiac dimensions, function, ischaemia, scar burden and tissue viability in a single study without exposure to ionising radiation. CMR also offers prognostic information with a normal stress CMR associated with a < 1% risk of death or MI at 2 years, whilst the presence of LGE confers added prognostication above and beyond simple LV ejection fraction. New technical developments continue apace and ongoing large clinical trials will further clarify the role of CMR in routine clinical practice and guide the future development of international guidelines.

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## Cardiovascular magnetic resonance imaging assessment of outcomes in acute myocardial infarction

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### Abstract

Cardiovascular magnetic resonance (CMR) imaging

uniquely characterizes myocardial and microvascular injury in acute myocardial infarction (AMI), providing powerful surrogate markers of outcomes. The last 10 years have seen an exponential increase in AMI studies utilizing CMR based endpoints. This article provides a contemporary, comprehensive review of the powerful role of CMR imaging in the assessment of outcomes in AMI. The theory, assessment techniques, chronology, importance in predicting left ventricular function and remodelling, and prognostic value of each CMR surrogate marker is described in detail. Major studies illustrating the importance of the markers are summarized, providing an up to date review of the literature base in CMR imaging in AMI.

**Key words:** Myocardial infarction; Infarct; Cardiovascular magnetic resonance; Left ventricular remodelling; Prognosis

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**Core tip:** Cardiovascular magnetic resonance (CMR) imaging uniquely characterizes myocardial and microvascular injury in acute myocardial infarction (AMI). Contrast-enhanced CMR offers robust, validated and reproducible surrogate markers, providing an accurate representation of pathophysiology, assessment of myocardial function and injury, and predictive value for medium to long-term LV function, remodelling and prognosis following primary percutaneous coronary intervention for STEMI. These qualities significantly increase the statistical power of studies using CMR endpoints and has resulted in an exponential increase in AMI studies utilizing CMR based endpoints. An understanding of the role of CMR in the assessment of outcomes in AMI is of key importance not only to interventional and imaging cardiologists, but to the cardiology community as a whole.

Khan JN, McCann GP. Cardiovascular magnetic resonance imaging assessment of outcomes in acute myocardial infarction. *World J Cardiol* 2017; 9(2): 109-133 Available from: URL: <http://www.wjgnet.com>

## INTRODUCTION

Cardiovascular magnetic resonance (CMR) imaging uniquely characterises myocardial and microvascular injury in acute myocardial infarction (AMI), providing powerful surrogate markers of outcomes. The last 10 years have seen an exponential increase in studies utilising CMR based endpoints in patients with AMI undergoing primary percutaneous intervention. This article provides a contemporary, comprehensive review of the powerful role of CMR imaging in the assessment of outcomes in AMI. The theory, assessment techniques, chronology, importance in predicting left ventricular function and remodelling, and prognostic value of each CMR surrogate marker is described in detail. Major studies illustrating the importance of the markers are summarised, providing an up to date review of the literature base in CMR imaging in AMI.

## MARKERS OF OUTCOMES FOLLOWING PRIMARY PERCUTANEOUS CORONARY INTERVENTION IN AMI

Prognostic studies using clinical outcomes, in particular mortality require large sample sizes. Surrogate biomarkers of outcome are directly measured alternative endpoints used as a substitute for biological processes and clinical outcomes<sup>[1,2]</sup>. CMR imaging uniquely characterises myocardial and microvascular injury in AMI due to its accuracy, reliability and validity (Figure 1)<sup>[2-4]</sup>. This significantly increases the statistical power of studies, allowing sample size requirements to be reduced. CMR data are strong surrogate markers of outcome following primary percutaneous coronary intervention (PPCI) in acute ST-segment elevation MI.

## LV EJECTION FRACTION AND VOLUMES IN AMI

### Background

In the medium-term following STEMI, LV end-diastolic volume (LVEDV) increases, LV end-systolic volume (LVESV) decreases<sup>[5-7]</sup> and there can be compensatory hypertrophy of remote myocardium<sup>[8,9]</sup> in order to preserve stroke volume and ejection fraction (LVEF). Adverse remodelling results from an inability of the heart to maintain geometry post MI in the context of large infarcts and increased wall stresses<sup>[10,11]</sup>. An increase in LVEDVI > 20%<sup>[12,13]</sup> and increase in LVESVI > 15%<sup>[14]</sup> at follow-up are the most commonly used criteria for adverse remodelling.

### CMR assessment of LV volumes and ejection fraction

CMR is the gold standard modality for the assessment of ventricular function and volumes. It has higher spatial

resolution than single-photon emission computed tomography (SPECT) (approximately 1.8 mm × 1.8 mm × 8 mm vs 10 mm × 10 mm × 10 mm)<sup>[15]</sup>, and suffers from little subjectivity or reliance on patient body habitus<sup>[16]</sup>.

Volumes and mass are assessed on analysis of a 3D cine stack of short-axis biventricular contiguous slices. Modern cine sequences use breath-hold, electrocardiographic-gated, segmented steady-state free precession (SSFP) to produce high spatial resolution images with excellent myocardium-blood contrast. Regional systolic function can alternatively be assessed using wall motion scoring<sup>[17]</sup>.

CMR studies have demonstrated that recovery of LVEF occurs relatively early post STEMI. Ripa showed that improvement in LVEF and systolic wall thickening occurred by 1 mo, with no further change at 6 mo<sup>[5]</sup>. The majority of improvement in LVEF occurred between day 2 and 1 wk in the study by Mather<sup>[18]</sup>, with a final increase by 3 mo. Beek showed that 55% of segments with initially impaired systolic wall thickness improved at 13-wk<sup>[19]</sup>. Ganame *et al*<sup>[20]</sup> and Dall'Armellina *et al*<sup>[21]</sup> however showed that LVEF underwent no significant change by 6 and 12 mo post PPCI respectively. This may be because their subjects sustained less myocardial damage, represented by relatively preserved LVEF and thus lower potential for improvement<sup>[21]</sup>.

Volumetric changes occur more slowly. Ripa *et al*<sup>[5]</sup> showed a continued increase in LVEDV and reduction in LVESV until 6 mo. Engblom *et al*<sup>[7]</sup> demonstrated similar sequelae to 12-mo. Ganame showed progressive significant changes in LVEDV and LVESV and resulting LV sphericity at all timepoints to 12 mo<sup>[20]</sup>. These studies have important implications for optimising timing of follow-up CMR studies assessing remodelling.

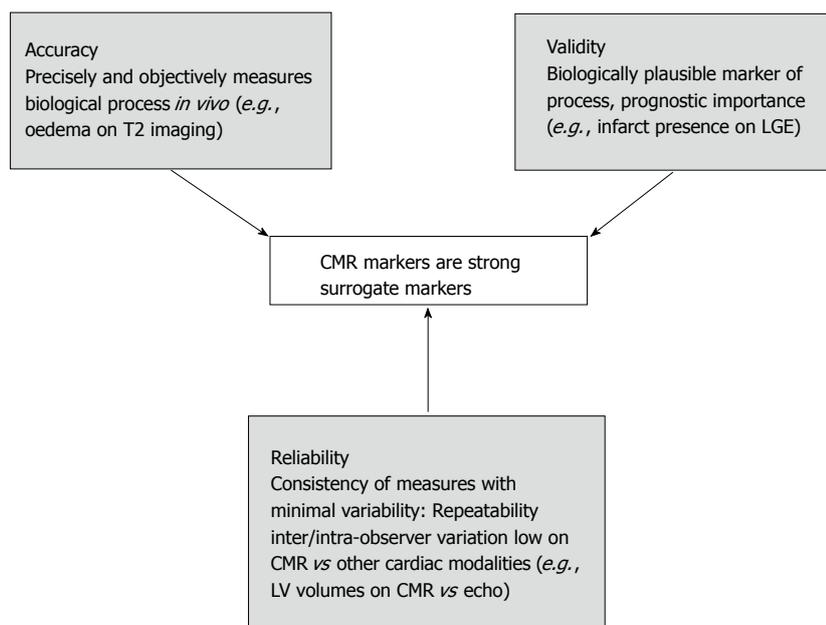
The degree of impairment of LVEF and changes in volume depend on a number of CMR-based markers including infarct size (IS)<sup>[22]</sup>, microvascular obstruction (MVO)<sup>[23,24]</sup>, intramyocardial haemorrhage (IMH)<sup>[25]</sup> and myocardial salvage [non-infarcted proportion of ischaemic area at risk (AAR)]<sup>[26,27]</sup>. Anterior STEMI results in larger IS and lower LVEF due to the greater ischaemic AAR<sup>[28]</sup>.

### Prognostic importance of LVEF and volumes in AMI

Norris *et al*<sup>[29]</sup> and White *et al*<sup>[30]</sup> first illustrated the prognostic importance of LVEF (strongest independent predictor of survival at 3.5 years) and LVESV (only independent predictor of long-term mortality at 6 years) respectively, using invasive ventriculography. Burns first demonstrated the prognostic importance of LVEF and LV volumes and their strong correlation with each other, using radionuclide analysis<sup>[31]</sup>.

A large evidence base has emerged for the prognostic impact of impaired systolic function based on reduced CMR-derived LVEF (Table 1).

In addition to LVEF-based global systolic function, Bodi demonstrated that the number of dysfunctional segments on CMR at 1-wk post STEMI was an independent predictor of combined MACE at a median follow-up of 553 d<sup>[38]</sup>. The evidence base for the prognostic importance of LV volumes is largely historical, based on large echocardiographic



**Figure 1 Cardiovascular magnetic resonance markers are ideal surrogate biomarkers for the assessment of revascularisation in acute myocardial infarction<sup>[2-4]</sup>.** CMR: Cardiovascular magnetic resonance; AMI: Acute myocardial infarction; LGE: Late gadolinium enhancement.

**Table 1 Cardiovascular magnetic resonance studies illustrating the prognostic importance of left ventricular ejection fraction in acute myocardial infarction**

Ref.	Year	n	CMR time	Main findings	Follow-up
El Aidi <i>et al</i> <sup>[32]</sup>	2014	25497	N/A	Meta analysis of prognostic value of CMR surrogate markers. LVEF was only IP for MACE (HR 1.05 per -5%)	N/A
Husser <i>et al</i> <sup>[33]</sup>	2012	304	7 d	LVEF was IP for MACE (HR 0.95 for each +1% LVEF)	140 wk
Eitel <i>et al</i> <sup>[34]</sup>	2011	208	3 d	LVEF was IP for MACE (HR 0.95 for each +1% LVEF)	18.5 mo
Amabile <i>et al</i> <sup>[35]</sup>	2010	114	6 d	LVEF was IP for MACE (HR 0.96 for each +1% LVEF)	12 mo
de Waha <i>et al</i> <sup>[36]</sup>	2010	438	3 d	LVEF was IP for MACE (OR 1.63) and all-cause mortality (OR 2.51)	19 mo
Cochet <i>et al</i> <sup>[37]</sup>	2009	127	3-7 d	LVEF of < 40% was IP for MACE (OR 1.20)	12 mo
Hombach <i>et al</i> <sup>[6]</sup>	2005	110	6 d	LVEF was IP for 9 mo MACE (P = 0.006)	225 d

CMR time: Mean/median time of CMR post acute STEMI; MACE: Major adverse cardiovascular events; IP: Independent predictor; LVEF: Left ventricular ejection fraction; CMR: Cardiovascular magnetic resonance; N/A: Not available.

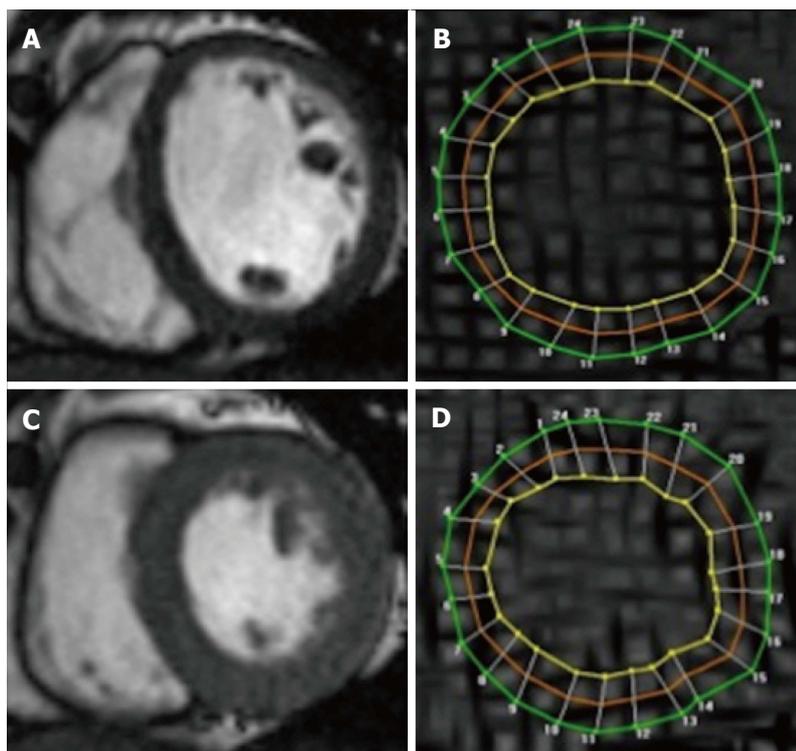
**Table 2 Studies illustrating the prognostic importance of left ventricular volumes and adverse left ventricular remodelling in acute myocardial infarction**

Ref.	Year	n	Modality	Main findings	Follow-up
Ahn <i>et al</i> <sup>[13]</sup>	2013	135	Echo	Adverse LV remodelling (> 20% inc. LVEDV) at 6 mo was IP 3 yr MACE. MACE rate approximately 25% in patients with adverse LV remodelling vs approximately 6% in non-remodelled patients	981 d
Hombach <i>et al</i> <sup>[6]</sup>	2005	110	CMR	Baseline LVEDV was IP for MACE (P = 0.038)	225 d
St John Sutton <i>et al</i> <sup>[39]</sup>	2003	512	Echo	Percentage change in LV area (surrogate for LV volume) between baseline echo and follow-up at 12 mo was IP for ventricular ectopy and VT	24 mo
Bolognese <i>et al</i> <sup>[12]</sup>	2002	284	Echo	Baseline LVESV was IP for cardiac death and MACE. Components of MACE higher in patients with adverse remodelling (> 20% inc. LVEDV: Mortality 14% vs 5%, MACE 18% vs 10%)	5 yr
Otterstad <i>et al</i> <sup>[40]</sup>	2001	712	Echo	Increase in LVESV between acute scan at 7 d and echo at 3 mo strongest IP for MACE	24 mo
St John Sutton <i>et al</i> <sup>[41]</sup>	1994	512	Echo	LV end-diastolic area (RR 1.1) and LV end-systolic area (RR 1.1) on baseline echo, and %change in LV area at 12 mo echo (RR 1.55) were strongest IPs for MACE	12 mo
White <i>et al</i> <sup>[30]</sup>	1987	605	LV gram	LVESV of LV gram at 4 wk was strongest IP of long-term mortality (P < 0.0001)	78 mo

MACE: Major adverse cardiovascular events; IP: Independent predictor; LVEDV: Left ventricular end-diastolic volume; LVESV: Left ventricular end-systolic volume; Modality: Modality of LV volume assessment (CMR: Cardiovascular MRI; Echo: Echocardiography; LV gram: LV contrast angiography).

and radionuclide studies, demonstrating the negative prognostic impact of ventricular dilatation and remodelling as summarised in Table 2.

Negative LV remodelling has demonstrated prognostic importance in two studies, based on the cut-off of LVEDVI dilation of > 20% at 6-mo follow-up<sup>[12,13]</sup>.



**Figure 2 Cardiovascular magnetic resonance assessment of strain using tissue tagging.** Cine SSFP images in end-diastole (A) and end-systole (C), with corresponding Spatial Modulation of Motion (SPAMM) tagged images (B and D). Grid lines (tags) are visible and contours drawn at 3 myocardial levels [green (epicardial), red (mid myocardial), yellow (endocardial)] allow tracking of myocardial motion and strain (circumferential), here using Harmonic Phase Analysis.

Recently, left ventricular global performance index has been proposed as a CMR marker of cardiac performance, incorporating LVEF, LV volumes and mass. It has been assessed in one study in STEMI and correlated strongly with IS, MSI, MVO and IMH extent, and had incremental prognostic value to LVEF in predicting 12-mo MACE<sup>[42]</sup>. Further work is needed to investigate its prognostic value in STEMI.

## MYOCARDIAL STRAIN IN AMI

CMR-measured myocardial strain (tissue deformity) is the gold standard non-invasive measure of systolic and diastolic myocardial function<sup>[43]</sup>. Circumferential strain (Ecc) describes shortening of fibres (contraction) in a short-axis plane tangential to the epicardium; longitudinal strain (E<sub>ll</sub>) describes shortening in the long axis, and radial strain (Err) describes lengthening (thickening) of fibres towards the centre of the ventricle. Torsion is wringing of the ventricle caused by clockwise rotation at the base, and anticlockwise at the apex.

Strain offers greater accuracy in detecting myocardial dysfunction compared with global (LVEF) and regional (visual wall-motion scoring, segmental wall thickening)<sup>[44]</sup> measures.

### CMR assessment of myocardial strain

In 1989, Axel *et al*<sup>[45]</sup> developed a T1 spoiled gradient echo sequence, creating "tags" formed by saturation of thin myocardial lines running in perpendicular directions in-plane to form a myocardial grid. These lines act as tissue markers, tracking myocardial deformation as shown in Figure 2. Peak systolic strain and peak diastolic strain

rate (relaxation rate of strain) provide very sensitive measures of systolic and diastolic function respectively. Its accuracy has been validated on comparison with sonomicrometry<sup>[46,47]</sup>. Harmonic Phase Analysis (HARP) is currently the most widely used CMR strain method<sup>[48]</sup>.

Feature tracking (FT) has been introduced as an alternative method to tagging for assessing strain on CMR. FT tracks anatomical features of interest along contour lines on routinely acquired SSFP cine images analogous to echocardiographic Speckle Tracking, obviating the need for additional tagging sequences<sup>[49]</sup>. FT-derived strain has been compared to tagging in acute STEMI and shown greater feasibility, accuracy and observer agreement<sup>[50]</sup> and remains an exciting prospect.

### CMR LV strain as a predictor of LV function and remodelling in AMI

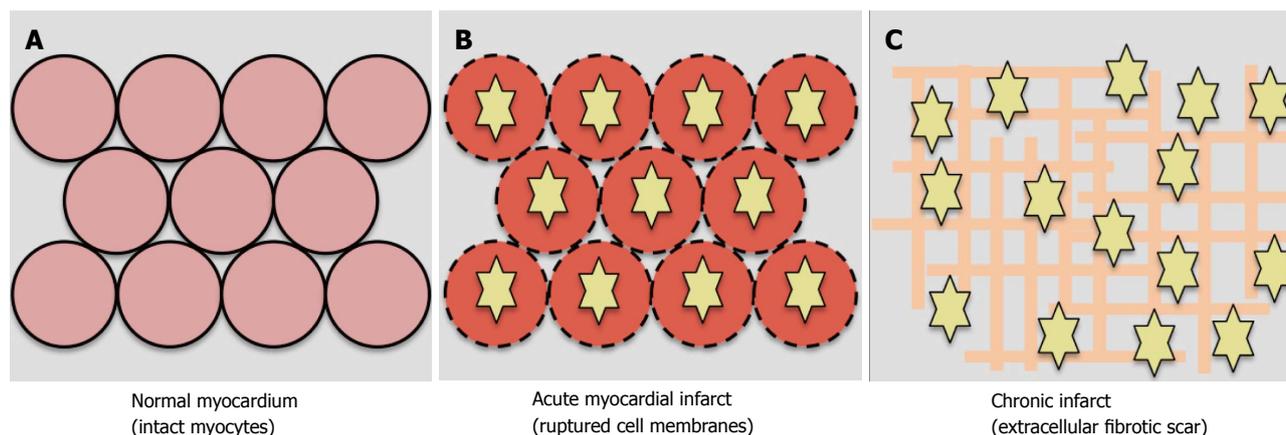
Strain could improve our understanding of the mechanics underlying LV dysfunction associated with prognostic CMR surrogate markers of myocardial damage in STEMI (e.g., MVO, IMH, oedema).

Systolic function is also in remote (non-infarcted) segments, and LV mechanics outside of the infarct zone are also affected during infarction and contribute to remodelling<sup>[44,51,52]</sup>. MVO had the highest predictive value for persistent dysfunction on circumferential strain at 7-mo post STEMI and may result in systolic dysfunction due to direct mechanical effects (myocardial stiffness)<sup>[53]</sup>. Baseline segmental circumferential strain was the strongest predictor of segmental functional recovery at 3-mo in a model containing infarct transmuralty and MVO<sup>[54]</sup>. FT-derived global circumferential strain assessed acutely post PPCI was recently shown to correlated strongly with

**Table 3** Studies illustrating the prognostic importance of left ventricular strain in acute myocardial infarction

Ref.	Year	n	Modality	Main findings	Follow-up
Ersbøll <i>et al.</i> <sup>[56]</sup>	2014	1048	TTE	(E-prime divided by peak early diastolic strain rate) strongest IP of MACE and death	29 mo
Ersbøll <i>et al.</i> <sup>[57]</sup>	2013	849	TTE	GLS was IP of MACE	30 mo
Hung <i>et al.</i> <sup>[58]</sup>	2010	610	TTE	GLS and strain-rate, and GCS and strain-rate IPs for MACE in model with WMS, LVEF	25 mo
Antoni <i>et al.</i> <sup>[59]</sup>	2010	659	TTE	GLS (HR 1.2) was IP of mortality. LVEF, wall-motion score and Tissue Doppler mitral valve inflow not	21 mo

TTE: Transthoracic echocardiography; GLS: Global longitudinal strain; MACE: Major adverse cardiovascular events; IP: Independent predictor; HR: Hazard ratio; LVEF: Left ventricular ejection fraction.



**Figure 3** Mechanism of late gadolinium enhancement. Gadolinium is extracellular. A: In normal myocardium, gadolinium washes out approximately 10 min post administration and there is no late gadolinium enhancement (LGE); B: In acute infarct, gadolinium (yellow stars) enters ruptured cell membranes and causes LGE; C: In chronic infarct, LGE results from increased extracellular space due to fibrotic scar deposition.

acute IS on late gadolinium enhancement (LGE) imaging ( $r = 0.75$ ) and final LVEF at 6 mo ( $r = -0.71$ ). Global circumferential strain was a stronger predictor of functional recovery (LVEF > 50%) at 6 mo than global longitudinal strain, age, diabetes and baseline LVEF, and was of similar predictive value to acute IS [AUC 0.86 (Ecc) vs 0.92 (IS)]<sup>[55]</sup>.

### Prognostic importance of LV strain in AMI

The evidence base for the prognostic importance of LV strain post STEMI is currently based on echocardiographic studies demonstrating that global longitudinal predicts medium and long-term using Speckle Tracking analysis as summarised in Table 3.

## INFARCT SIZE IN AMI

### Background

The "ischaemic cascade" is the sequence of pathophysiological effects developing immediately following coronary occlusion. Aerobic respiration loses efficiency resulting in cellular oedema. With increasing ischaemic time, cell membranes rupture. Following healing, necrotic cells are replaced by extracellular collagen deposition (scar). The acute and chronic phases are characterised by increased myocardial extracellular volume<sup>[60-62]</sup>.

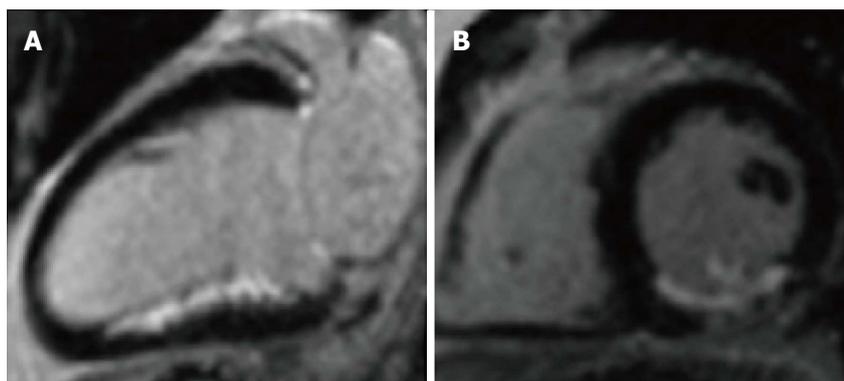
### CMR assessment of IS in AMI

Gadolinium contrast agents are large extracellular

molecules (Figure 3). Infarct can be visualised on T1-weighted imaging approximately 10 min after intravenous contrast administration, known as LGE imaging.

In acute infarct, LGE results from gadolinium entering ruptured cell membranes. In chronic infarction, LGE results from increased extracellular space due to collagen deposition and prolonged washout due to reduced capillary density within myocardium<sup>[60,63]</sup>. Gadolinium shortens T1, causing infarcted myocardium to appear bright, and normal myocardium to appear black (Figure 4)<sup>[63,64]</sup>. Normal myocardium is progressively nulled using the appropriate inversion time to provide optimal contrast between infarct and normal myocardium.

Typically, a high spatial resolution of approximately 1.4 mm × 1.6 mm × 6-8 mm is achieved<sup>[15]</sup>. IS is typically expressed as a percentage of total LV mass. Delineation of infarct can be performed visually (manual quantification)<sup>[6,9,22]</sup>, however most groups use semi-automated methods to reduce observer variability. These include enhancing myocardium exceeding a pre-defined signal intensity (SI) threshold, typically > 2-6 standard deviations above that of remote (non-infarcted) myocardium<sup>[2,65]</sup>. Currently, the semi-automated full-width at half-maximum (FWHM) method is commonly used<sup>[66-70]</sup>, defining infarct as myocardium with SI > 50% of the peak SI in the infarct core. Amado demonstrated that FWHM had the highest interobserver agreement and closest correlation with TTC-stained infarct in a dog model of acute infarction ( $r^2 = 0.94$ ), compared with standard



**Figure 4** Late gadolinium enhancement of acute infarct. Infarct appears white (enhanced) in the inferior wall, with unaffected myocardium black (nulled). A: 2-chamber long-axis view; B: Short-axis view, mid ventricular level. The posteromedial papillary muscle is also infarcted in the short-axis view.

**Table 4** Temporal changes in cardiovascular magnetic resonance-derived infarct size in acute myocardial infarction

Ref.	Year	n	CMR times post STEMI	Relative LGE IS reduction	LGE method	Main findings
Carrick <i>et al</i> <sup>[74]</sup>	2016	30	8 h → 3 d → 10 d → 7 mo	26%	Automated	Significant decrease d3 to d10 (20% ± 13% to 14% ± 10% LV mass). No change at 7 mo
Dall'Armellina <i>et al</i> <sup>[21]</sup>	2011	30	2 d → 6 mo	22%	> 2SD	IS reduced at times from 27% ± 15% LV mass 24 h post PPCI, to 21% ± 11% at 6 mo
Mather <i>et al</i> <sup>[18]</sup>	2011	48	2 d → 1 wk → 30 d → 3 mo	37%	> 2SD	27% IS drop between d2 and d7 post PPCI, no change at 3 mo
Ganame <i>et al</i> <sup>[20]</sup>	2011	58	3 d → 4 mo → 12 mo	45%	Manual	33% decrease IS d3 and 4 mo then no further decrease at 12 mo
Ibrahim <i>et al</i> <sup>[9]</sup>	2010	17	1 d → 1 wk → 1 mo → 6 mo	37%	Manual	34% reduction in IS from d2 to 1 wk, then no further change at 1 and 6 mo
Engblom <i>et al</i> <sup>[7]</sup>	2009	22	1 d → 1 wk → 12 mo	40%	Automated	28% reduction in IS between d1 and 1 wk
Ripa <i>et al</i> <sup>[5]</sup>	2007	58	2 d → 1 mo → 6 mo	30%	Manual	14% % reduction in IS from d2 to 1 mo
Hombach <i>et al</i> <sup>[6]</sup>	2005	110	6 d → 9 mo	28%	Manual	28% reduction in IS from d6 to 9 mo

LGE method: SD: Standard deviations; Total LGE IS Overest: Relative overestimation of final IS (last timepoint) on acute CMR; CMR: Cardiovascular magnetic resonance; LGE: Late gadolinium enhancement; IS: Infarct size; PPCI: Primary percutaneous coronary intervention.

deviation methods<sup>[66]</sup>. This may be because FWHM is less prone to IS overestimation in the presence of oedema, and partial volume effects giving rise to intermediate signal intensities<sup>[18,71]</sup>. Comparing techniques in STEMI patients showed that FWHM quantification had the lowest intraobserver and interobserver variability, and greatest agreement with LVEF<sup>[72]</sup>.

CMR measurement of IS on LGE is well validated<sup>[63,64]</sup>. Kim demonstrated that IS in dog myocardium on *ex-vivo* CMR corresponded closely with IS derived from tetrazolium (TTC) staining ( $r = 0.99$ )<sup>[15,64]</sup>. LGE has higher sensitivity for infarct detection compared with SPECT. In an experimental model of MI, CMR LGE detected 92% of all segments with subendocardial infarction (< 50% transmural) compared with only 28% with SPECT<sup>[15]</sup>. In patients with MI, SPECT only detects approximately 50% of the infarcts seen on LGE. The superior sensitivity is due to the increased spatial resolution and reproducibility of CMR<sup>[60]</sup>.

Since gadolinium is distributed throughout the extracellular space, gadolinium contrast agents are not specific to necrosis. Acutely, the area of LGE detects not only necrotic cells but also the increased (oedematous) interstitium surrounding viable cells, and thus can over-

estimate true IS. Studies of IS chronology in humans corroborate this (Table 4). Indeed, severely dysfunctional segments with minimal myocardial salvage early post STEMI can show significant functional improvement at follow-up<sup>[73]</sup>.

The majority of IS reduction occurs relatively early post STEMI, particularly by 1 wk. Indeed IS assessed at 1 wk has been shown to closely correlate with final IS<sup>[7,9,18]</sup>. Overestimation of necrosis by LGE-derived IS early post STEMI is due to a combination of oedema, infarct resorption and partial volume effects. Oedema results in an overestimation of LGE IS due to increased extracellular water content and thus volume of distribution of contrast agent<sup>[66,75]</sup>.

Infarct resorption results from the healing process where collagenous scar tissue is produced to provide stability and tensile strength to necrotic myocardium<sup>[7,11]</sup>. This was confirmed in a canine model where a 3.4-fold decrease in infarct volume was seen between day 3 and 8-wk post infarct on *ex-vivo* LGE and TTC-stained slices<sup>[64]</sup>. The degree of infarct resorption has been shown to be proportional to initial IS ( $r = 0.65$ ) and presence of LV remodelling ( $r = 0.41$ )<sup>[10]</sup>. The greater degree of infarct resorption relative to total myocardial

**Table 5 Cardiovascular magnetic resonance studies illustrating importance of segmental late gadolinium enhancement extent and functional recovery in acute myocardial infarction**

Ref.	Year	n	LGE method	Cutoff (LGE)	Main findings	Time of CMR 1	Time of CMR 2
Khan <i>et al</i> <sup>[85]</sup>	2016		FWHM	50% SEE	SEE strong predictor of segmental functional improvement (AUC 0.840) and normalisation (AUC 0.887)	2 d	9 mo
Wong <i>et al</i> <sup>[54]</sup>	2014	45	FWHM	50% SEE	Inverse relationship between TEE and likelihood of functional recovery on WMS at 24 wk (area under curve 0.68)	8 d	13 wk
Natale <i>et al</i> <sup>[86]</sup>	2011	46	2SD	50% TEE	Inverse relationship TEE and likelihood of functional recovery on SWT (93% sens, 75% spec)	5 d	20 wk
Engblom <i>et al</i> <sup>[7]</sup>	2008	22	Manual	50% TEE	Inverse relationship between TEE and functional recovery on WMS	7 d	24 wk
Shapiro <i>et al</i> <sup>[87]</sup>	2007	17	Manual	50% SEE	Inverse relationship between TEE and likelihood of functional recovery on WMS at 26 wk. Odds-ratio of functional recovery 0.2 with each SEE quartile	6 d	26 wk
Kitagawa <i>et al</i> <sup>[88]</sup>	2007	18	2SD	50% TEE	Inverse relationship between TEE and functional recovery. 31% segments > 50% TEE still improved	5 d	39 wk
Janssen <i>et al</i> <sup>[89]</sup>	2006	67	Manual	50% TEE	Inverse relationship between TEE and functional recovery on WMS at 12w (51%-75%: 39% segments improved, 76%+: 21% improved)	4 d	12 wk
Motoyasu <i>et al</i> <sup>[90]</sup>	2004	23	2SD	50% TEE	Inverse relationship between SEE and functional recovery on SWT	25 d	24 wk
Beek <i>et al</i> <sup>[19]</sup>	2003	30	6SD	50% SEE	Inverse relationship between SEE and functional recovery on WMS	7 d	13 wk

WMS: Wall motion scoring; SWT: Systolic wall thickening; TEE: Transmural extent of enhancement; SEE: Segmental extent of enhancement; SD: Standard deviations.

**Table 6 Cardiovascular magnetic resonance studies illustrating importance of infarct size on left ventricular function and remodelling in acute myocardial infarction**

Ref.	Year	n	LGE method	Main findings	Time post STEMI of predictive CMR	Follow-up
Ahn <i>et al</i> <sup>[13]</sup>	2013	135	Manual	IS strongest IP of LVR in model with LVEF and MI location	7 d	6 mo (echocardiogram)
Husser <i>et al</i> <sup>[33]</sup>	2012	304	> 2SD	IS IP of LVR in model incl. LVEF, IS, LV vols, MVO	6 d	189 d
Monmeneu <i>et al</i> <sup>[91]</sup>	2012	118	> 2SD	No. segments > 50% transmural IP for LVR	6 d	6 mo
Ezekowicz <i>et al</i> <sup>[92]</sup>	2010	64	Manual	IS strongest IP of LVEF in model with MVO, troponins	7 d	3 mo
Ganame <i>et al</i> <sup>[25]</sup>	2009	98	Manual	IS strongest IP of LVR (>> MVO, AAR, Troponin-I)	2 d	6 mo
Bodi <i>et al</i> <sup>[93]</sup>	2009	214	> 2SD	Extent of transmural necrosis (no. segments > 50% TEE) strongest IP for LV recovery (+ > 5% LVEF)	7 d	6 mo
Wu <i>et al</i> <sup>[94]</sup>	2008	122	Manual	IS extent only IP for LVEF and LVR	2 d	4 mo
Hombach <i>et al</i> <sup>[6]</sup>	2005	110	Manual	IS extent IP of LVR in model with MVO, % transmural	6 d	225 d

IS: Infarct size; IP: Independent predictor; LVR: LV remodelling; LVEDVI: Left-ventricular end-diastolic volume index; LVEDVI: Left-ventricular end-systolic volume index; LVEF: Left ventricular ejection fraction; MVO: Microvascular obstruction; SD: Standard deviation.

mass and volume results in an inability to maintain LV geometry in light of mechanical stresses post STEMI, resulting in adverse LV remodelling and sphericity<sup>[10,76]</sup>.

Factors known to affect IS include AAR extent<sup>[77-79]</sup>; collateral flow to the AAR<sup>[79,80]</sup>; MVO<sup>[81]</sup>; time to reperfusion<sup>[82]</sup> and hyperglycaemia<sup>[83]</sup>.

### CMR IS as a predictor of LV function and remodelling in AMI

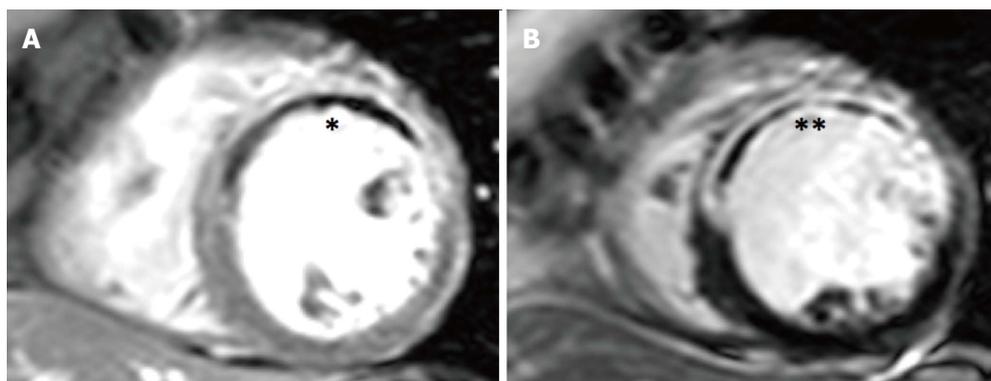
**Segmental function:** Kim illustrated in stable patients awaiting revascularisation, that LGE transmural strongly predicted recovery of systolic function in dysfunctional segments. Only 2% of segments with > 75% transmural improved after revascularisation<sup>[84]</sup>. Segmental extent of LGE has also been shown to negatively predict functional

recovery in dysfunctional segments following PPCI for acute STEMI, as summarised in Table 5.

**Global function:** IS is a powerful independent predictor of global LV function and adverse LV remodelling in the medium to long-term post STEMI as summarised in Table 6.

### Prognostic importance of CMR-derived IS in AMI

The goal of STEMI management is early reperfusion in order to minimise IS and thus maximise myocardial salvage<sup>[95]</sup>. There is a strong evidence base for the prognostic importance of CMR-derived IS post STEMI, as summarised in Table 7. IS strongly predicts medium to long-term clinical outcomes.



**Figure 5** Early and late microvascular obstruction on cardiovascular magnetic resonance. A: Early gadolinium imaging at 1-min post contrast with hyperperfusion in anteroseptal, anterior and anterolateral segments, consistent with early MVO (E-MVO, \*); B: Corresponding late gadolinium image showing transmural infarction with a hypointense late MVO core (L-MVO, \*\*) co-localising with E-MVO. MVO: Microvascular obstruction.

**Table 7** Cardiovascular magnetic resonance studies illustrating the prognostic importance of infarct in acute myocardial infarction

Ref.	Year	n	LGE method	Main findings	CMR timepoint	Follow-up
Husser <i>et al</i> <sup>[96]</sup>	2013	250	> 2SD	Extent of transmural infarction (no. of segments > 50% transmural) only IP for MACE at 6 mo	7 d	163 wk
Izquierdo <i>et al</i> <sup>[97]</sup>	2013	440	> 2SD	IS was IP for AACEs (arrhythmic cardiac events: Sudden death, VT, VF, ICD shock) in model including LVEF, hypertension	7 d	123 wk
Eitel <i>et al</i> <sup>[34]</sup>	2011	208	> 5SD	IS was IP of MACE at 19 mo in model including MVO, LVEF, MSI, Killip, TIMI post-PPCI	3 d	18.5 mo
Miszalski-Jamka <i>et al</i> <sup>[98]</sup>	2010	77	Manual	LV transmural index IP (HR 1.03) and IS (HR 1.03) IPs for MACE in a model containing RVEF and RV IS	“3-5 d”	1150 d
Larose <i>et al</i> <sup>[67]</sup>	2010	103	FWHM	IS strongest IP for MACE (HR 1.36) in model containing LVEF, CK. LGE > 23% had HR 6.1 for MACE	4.5 h	2 yr
Bodi <i>et al</i> <sup>[38]</sup>	2009	214	> 2SD	Extent of transmural infarction (no. of segments > 50% transmural) IP for MACE (HR 1.35 if > 5 segs)	7 d	553 d
Wu <i>et al</i> <sup>[99]</sup>	2008	122	Manual	IS only IP of 2 yr MACE in model containing LVEF, LVESVI	2 d	538 d

LGE: Late gadolinium enhancement; FWHM: Full-width half-maximum; SD: Standard deviations; MACE: Major adverse cardiovascular events; LVEF: Left ventricular ejection fraction; PPCI: Primary percutaneous coronary intervention; LGE method (LGE quantification method): SD: Standard deviations; FWHM: Full-width half-maximum.

## MVO IN AMI

### Background

Despite prompt IRA recanalization, perfusion of the microcirculatory bed does not always ensue. Histopathological studies have demonstrated that the infarct core (endocardial) perishes first as necrosis spreads transmurally towards the epicardium. This is known as the “wavefront theory”<sup>[100]</sup>. At the infarct core, necrosis occurs rapidly with myocardial and capillary endothelial cells perishing simultaneously. Capillaries can become obstructed by cellular debris, resulting in non-perfusion of the infarct core, despite IRA patency<sup>[101]</sup>. This is known as MVO and can be indicated at angiography, as “no reflow”<sup>[101]</sup>.

### CMR assessment of MVO in AMI

Three CMR methods demonstrate MVO (Figure 5). MVO extent is typically expressed as a percentage of LV mass: (1) Qualitative first-pass rest perfusion. A modified version involves quantification of myocardial blood flow (SI-time curve) and time to 50% of maximal SI<sup>[102,103]</sup>; (2) Hypoperfusion on inversion recovery images between 1-3

min post contrast. A fixed inversion time of approximately 440 ms nulls MVO and retains intermediate signal in normal myocardium. This is known as “early MVO (E-MVO)”<sup>[28,104]</sup>; and (3) Hypointensity within infarct core on LGE due to absence contrast perfusion, known as “late MVO (L-MVO)”. L-MVO occurs in upto 60% of patients on CMR within the first week post STEMI<sup>[5,6,18,20]</sup>. This is the preferred method of MVO demonstration in contemporary clinical practice and research.

L-MVO extent is maximal at 48 h post infarct<sup>[8,18]</sup>, and then decreases. It exists for at least 1 wk, and for up to 1 mo<sup>[8,18]</sup> and then resolves in the medium-term in humans (Table 8). Animal models corroborate these findings<sup>[105,106]</sup>.

The extent of MVO on CMR has been shown to correlate with IS<sup>[82,94,107,108]</sup>, oedema, IMH, TIMI-flow pre PCI<sup>[35,109]</sup> and time to reperfusion<sup>[35,82,110]</sup>.

### CMR MVO as a predictor of LV function and remodelling in AMI

L-MVO is a strong independent predictor of medium-term LV function and adverse remodelling (Table 9). It

**Table 8 Temporal changes in cardiovascular magnetic resonance late microvascular obstruction in acute myocardial infarction**

Ref.	Year	<i>n</i>	CMR timepoints	LGE method	Main findings
Carrick <i>et al</i> <sup>[74]</sup>	2016	30	8 h → 3 d → 10 d → 7 mo	Auto	L-MVO in 20%, peaked early at 8 h and stable at d3. Decreased by d10, absent at 7 mo
Mather <i>et al</i> <sup>[18]</sup>	2011	48	2 d → 1 wk → 30 d → 3 mo	> 2SD	L-MVO in 60%, peak at d2. Decrease at subsequent points. L-MVO absent at 3 mo
Ganame <i>et al</i> <sup>[20]</sup>	2011	58	3 d → 4 mo → 12 mo	Manual	L-MVO in 64%. L-MVO absent at 4 mo
Ripa <i>et al</i> <sup>[5]</sup>	2007	58	2 d → 6 mo	Manual	L-MVO in 42%. L-MVO absent at 6 mo
Hombach <i>et al</i> <sup>[6]</sup>	2005	110	6 d → 9 mo	Manual	46% had L-MVO (2.8% LV mass, 16% of IS) on acute CMR. L-MVO absent at 6 mo

MVO: Microvascular obstruction; LGE method: SD: Standard deviations; IS: Infarct size; LV: Left ventricle; CMR: Cardiovascular magnetic resonance.

**Table 9 Cardiovascular magnetic resonance studies illustrating the importance of late microvascular obstruction on left ventricular function and remodelling in acute myocardial infarction**

Ref.	Year	<i>n</i>	LGE method	Main findings	Time post STEMI of predictive CMR	Follow-up
Kidambi <i>et al</i> <sup>[115]</sup>	2013	39	> 2SD	L-MVO only IP of impaired infarct strain. Model with IS, TIMI flow, diabetes, transmural	3 d	3 mo
Wong <i>et al</i> <sup>[103]</sup>	2012	40	Manual	L-MVO extent only IP for LVEF at 3 mo in model including E-MVO, IS and myocardial blood flow on perfusion	3 d	3 mo
Ezekowitz <i>et al</i> <sup>[92]</sup>	2010	64	Manual	L-MVO extent was IP of LVEF in model with IS and NT-proBNP	7 d	4 mo
Weir <i>et al</i> <sup>[112]</sup>	2010	100	Manual	L-MVO extent was only IP of LVR in model with TIMI post PCI, E-MVO, IS	4 d	6 mo
Ganame <i>et al</i> <sup>[25]</sup>	2009	98	Manual	L-MVO extent was IP of LVR in model with IS, troponin-I, TTR	2 d	6 mo
Nijveldt <i>et al</i> <sup>[111]</sup>	2008	60	Manual	L-MVO presence strongest IP of LVEF change and LVR in model with TTR, IS, LVEF, E-MVO	5 d	4 mo
Hombach <i>et al</i> <sup>[6]</sup>	2005	110	Manual	L-MVO extent IP for LVR in model with baseline IS, infarct transmural	6 d	225 d

MVO: Microvascular obstruction; IS: Infarct size; IP: Independent predictor; TTR: Time to revascularisation; LVR: Left ventricular remodelling; LVEF: Left ventricular ejection fraction; LVEDVI: Left-ventricular end diastolic volume index; LVESVI: Left-ventricular end systolic volume index.

is likely that this is because L-MVO reflects more severe microvascular and myocardial damage than E-MVO<sup>[28,36]</sup>. In most studies demonstrating the independent predictive value of L-MVO on LV function and remodelling, E-MVO was not a predictor<sup>[103,111,112]</sup>. L-MVO was a predictor independent of baseline IS<sup>[6,20,92,111-113]</sup>. Monocyte recruitment, crucial in cellular debris removal and scar formation, is impaired in areas of L-MVO in rat myocardium and may contribute to the adverse remodelling<sup>[114]</sup>.

### Prognostic importance of CMR MVO in AMI

An increasing evidence base demonstrates the strong medium-term prognostic value of L-MVO following STEMI, independent of IS and LVEF<sup>[6,36,37,116]</sup> (Table 10). The 2 studies featuring both L-MVO and E-MVO showed that L-MVO was a stronger prognostic indicator<sup>[36,37]</sup>. Regenfus *et al*<sup>[117]</sup> demonstrated that L-MVO was the strongest IP of long-term combined MACE at 6 years follow-up in a model including CMR-assessed LVEF and IS (HR 3.9), providing incremental prognostic value over traditional CMR markers of myocardial damage. A meta-analysis<sup>[118]</sup> (8 studies, *n* = 1025) demonstrated that L-MVO presence was the strongest independent predictor of medium-term combined MACE (HR 3.7) and

cardiovascular death (HR 13.2) at 2 years independent of IS and LV volumes.

The strong adverse prognostic value of L-MVO may be due to its negative effects on LV function, wall thickness and stiffness, and remodelling, and subsequent risk of heart failure and arrhythmias<sup>[6,20,92,111-113]</sup>.

## IMH IN AMI

### Background

IMH is a reperfusion injury occurring when restored blood flow into damaged capillaries extravasates erythrocytes into myocardium<sup>[121,122]</sup>. CMR-derived IMH was first described in reperfused canine myocardium on *ex-vivo* T2-weighted spin-echo (T2w-TSE) imaging with excellent agreement with histology (*r* = 0.96 for IMH extent)<sup>[123]</sup>.

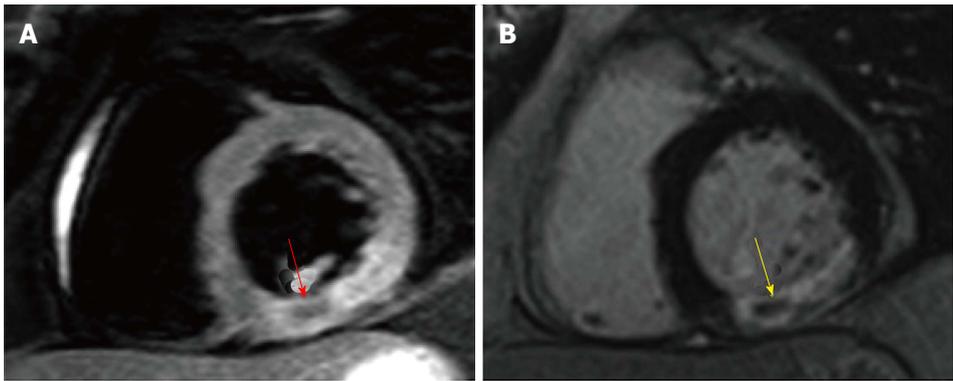
### CMR assessment of IMH in AMI

Paramagnetic haemoglobin breakdown products shorten T2 relaxation times<sup>[123,124]</sup>. IMH is seen as hypointense zones within hyperintense oedematous myocardium on T2w-TSE sequences. It shows good histological correlation in canine myocardium (*ex-vivo* MRI, *r* = 0.96)<sup>[123]</sup> and in an human autopsy case series (*in-vivo* MRI, *r* = 0.97)<sup>[124]</sup>.

**Table 10 Cardiovascular magnetic resonance studies illustrating the prognostic importance of late microvascular obstruction in acute myocardial infarction**

Ref.	Year	n	LGE method	Main findings	Time of prognostic CMR post STEMI	Follow-up
Regenfus <i>et al</i> <sup>[117]</sup>	2015	249	Manual	L-MVO extent strongest IP for MACE in model including IS, LVEF, TIMI pre and post PPCI and no. diseased vessels	3.7 d	72 mo
Eitel <i>et al</i> <sup>[119]</sup>	2014	738	> 5SD	Largest multicentre study of L-MVO in PPCI. L-MVO > 1.4% LVM and TIMI risk score only IPs of combined MACE. Adding L-MVO to model with clinical predictors, LVEF and IS increased c-statistic	7 d	6 mo
de Waha <i>et al</i> <sup>[120]</sup>	2012	438	Manual	L-MVO extent IP for combined MACE in model including IS, LV volumes (only other IP was LVEF). L-MVO/IS strongest IP in model including L-MVO extent, LVEF, IS, LV volumes	3 d	19 mo
de Waha <i>et al</i> <sup>[36]</sup>	2010	438	Manual	Presence and extent of L-MVO were strongest IPs for MACE and mortality in models with IS, LVEF, ST-res, TIMI-flow post PCI. E-MVO was not an IP	3 d	19 mo
Cochet <i>et al</i> <sup>[37]</sup>	2009	184	Manual	L-MVO strongest IP for MACE, in models including GRACE score, IS, LVEF. L-MVO stronger IP than E-MVO (OR 8.7 vs 2.5)	“3-7 d”	12 mo
Bruder <i>et al</i> <sup>[116]</sup>	2008	143	Manual	Only extent of L-MVO > 0.5% LV mass was IP for MACE; model included IS, LVEF, age, DM, sex	4.5 d	12 mo
Hombach <i>et al</i> <sup>[6]</sup>	2005	110	Manual	L-MVO IP for MACE ( <i>P</i> = 0.04) in model including LV end-diastolic volume and LVEF	6 d	268 d

MVO: Microvascular obstruction; LVEF: Left ventricular ejection fraction; IS: Infarct size; PCI: Percutaneous coronary intervention; MACE: Major adverse cardiovascular events; IP: Independent predictor.



**Figure 6 Intramyocardial haemorrhage on cardiovascular magnetic resonance.** A: T2-weighted spin-echo image with hypointensity corresponding with IMH within the hyperintense oedematous region in the inferior wall (red arrow); B: Corresponding LGE image showing co-localisation of IMH and L-MVO (yellow arrow). IMH: Intramyocardial haemorrhage; LGE: Late gadolinium enhancement; MVO: Microvascular obstruction.

IMH occurs exclusively in areas of L-MVO (*r*<sup>2</sup> for co-localisation approximately 0.9) (Figure 6)<sup>[25,33,125,126]</sup>.

Newer sequences based on direct quantification of T2 and T2\*<sup>[74,126-129]</sup> allow IMH to be quantified without the limitations of T2w-TSE imaging. Initial studies have been promising and shown that these sequences are reproducible and appear more sensitive and accurate than T2w-TSE for IMH detection<sup>[126,130,131]</sup>. O’Regan *et al*<sup>[126]</sup> showed that T2\* had 100% sensitivity for IMH detection compared to 90% for T2w-TSE, where the “gold standard” was co-localisation with L-MVO. In canines, T2\* in haemorrhagic infarcts closely correlates with iron levels on spectrometry, and T2\*-detected IMH co-localises with iron deposition on Perl’s staining<sup>[132]</sup> and extravasated erythrocytes on Haematoxylin-Eosin staining<sup>[128]</sup>. In pigs, regions of IMH on T2\* imaging showed vessel degeneration and iron deposition<sup>[8]</sup>.

There is a paucity of data on temporal changes in CMR-detected IMH. Mather *et al*<sup>[18]</sup> showed that IMH on

T2w-TSE was present in 33% of patients, with maximal extent at 48 h post PPCI and progressively resolution by 3 mo. Carrick *et al*<sup>[74]</sup> recently demonstrated that the incidence and extent of IMH on T2\* increased between 8 h and 3 d post PPCI. Its extent was significantly lower at 10 d and was seen in only 13% of patients at 7 mo. The authors also found that MVO was present in all patients with IMH, and its extent peaked earlier at 8 h suggesting that IMH is an ensuing reperfusion injury in regions of MVO.

**CMR IMH as a predictor of LV function and remodelling in AMI**

There is a small evidence base demonstrating that IMH is a strong univariate predictor of medium-term impaired LV function and remodelling, however multivariate analysis reveals mixed results, with some studies suggesting no incremental predictive value of IMH over MVO and IS (Table 11).

**Table 11 Cardiovascular magnetic resonance studies illustrating the importance of intramyocardial haemorrhage on left ventricular function and remodelling in acute myocardial infarction**

Ref.	Year	n	IMH CMR method	Main findings	CMR time post MI	Mean/median F/U CMR
Carrick <i>et al</i> <sup>[74]</sup>	2016	245	T2*	IMH strongest IP for LVR. IMH associated with lower LVEF and greater volumes	3 d	7 mo
Kidambi <i>et al</i> <sup>[115]</sup>	2013	39	T2w-TSE and T2*	IMH associated with attenuation of follow-up infarct strain	3 d	3 mo
Husser <i>et al</i> <sup>[33]</sup>	2012	304	T2w-TSE	IMH strongest IP for LVR in model with LVEF, IS, LV vol, L-MVO	6 d	189 d
Mather <i>et al</i> <sup>[131]</sup>	2011	48	T2w-TSE and T2*	IMH strongest IP of LVR in model with IS, LVEF, LVESV, E-MVO, MSI	2 d	3 mo
Beek <i>et al</i> <sup>[24]</sup>	2010	45	T2w-TSE	IMH was a univariate predictor of LVEF. However no prognostic significance beyond baseline LVEF and MVO in predicting final LVEF	5 d	4 mo
Bekkers <i>et al</i> <sup>[121]</sup>	2010	90	T2w-TSE	Acute MSI and LVEF increase at follow-up lowest if IMH present. But IMH no prognostic significance beyond MVO in predicting LVEF	5 d	103 d
O'Regan <i>et al</i> <sup>[126]</sup>	2010	50	T2*	IMH presence univariate predictor of LVEF and LV volumes. However only IS independently predicted LVEF	3 d	N/A
Ganame <i>et al</i> <sup>[25]</sup>	2009	98	T2w-TSE	IMH extent strongest IP of LVR in model with IS, E-MVO, Troponin-I, AAR, TTR, IS	2 d	4 mo

IS: Infarct size; IP: Independent predictor; LVR: Left ventricular remodelling; MVO: Microvascular obstruction; LVEF: Left ventricular ejection fraction; LVESVI: Left ventricular end systolic volume index; T2w-TSE: T2-weighted turbo spin-echo; AAR: Area at risk; MSI: Myocardial salvage index; N/A: Not applicable.

### Prognostic importance of CMR IMH in AMI

Multivariate analyses including IMH as a prognostic indicator also show mixed results. Amabile *et al*<sup>[133]</sup> demonstrated that IMH on T2w-TSE at 4 d post STEMI was the strongest independent predictor of MACE at 1-year (HR 2.8) in a model including LVEF, ST-resolution and L-MVO. Husser *et al*<sup>[33]</sup> showed that only LVEF and IMH extent on T2w-TSE independently predicted MACE at 140 wk follow-up in a model containing LV volumes, AAR, IS and L-MVO. However IMH and MVO extent showed strong correlation ( $r = 0.95$ ) and adding T2w imaging to a model containing LGE and cine imaging did not improve the predictive power for MACE, supporting a strong concordance of IMH and MVO. Eitel *et al*<sup>[125]</sup> demonstrated that IMH presence on T2w-TSE and LVEF < 53% were the only CMR independent predictors of MACE at 6 mo in a model with lone MVO. Carrick *et al*<sup>[74]</sup> recently demonstrated that IMH on T2\* mapping was the strongest independent predictor of cardiac death and heart failure hospitalisation at 830 d follow-up. In their multivariate model, L-MVO was not a predictor suggesting that IMH reflects extreme microvascular injury.

## ISCHAEMIC AAR AND MYOCARDIAL SALVAGE IN AMI

### Background

Oedema is seen in acute cardiac inflammation. In STEMI, it signifies reversible myocardial injury in the ischaemic cascade. The area of oedematous myocardium defines the ischaemic AAR supplied by the occluded IRA<sup>[61,134]</sup>.

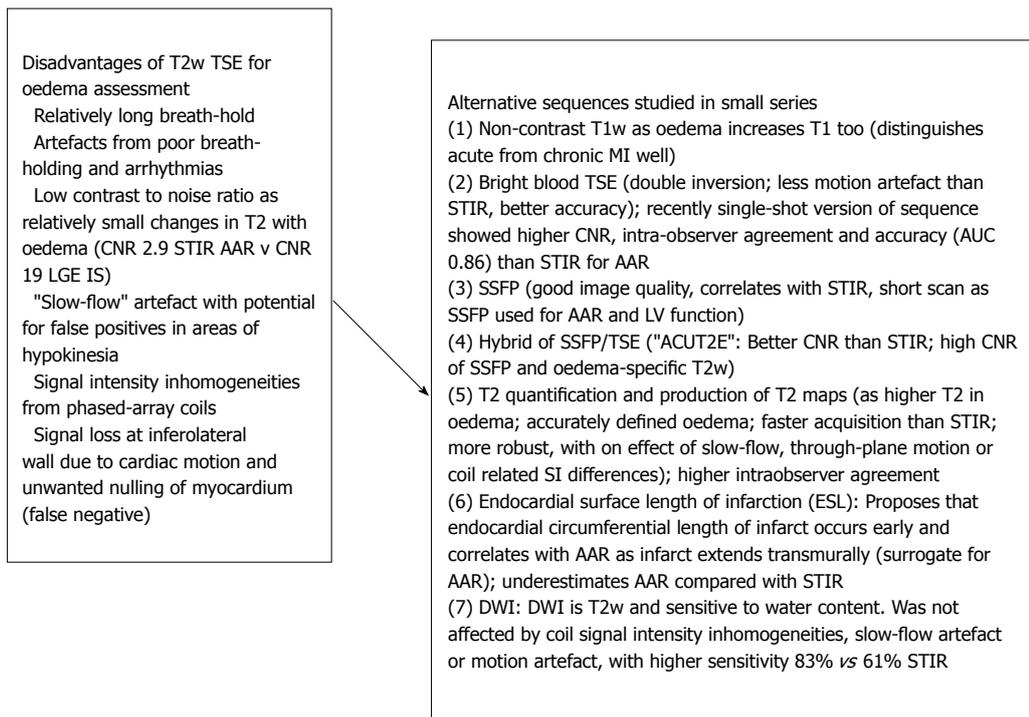
### CMR assessment of AAR and MSI in AMI

The T2 (transverse) relaxation time is increased by

regional water content<sup>[135]</sup>. T2w-TSE sequences illustrate oedema as hyperintensity<sup>[134]</sup> and are currently the mainstay of CMR oedema imaging. Most commonly used is the black-blood T2-weighted short-tau inversion-recovery sequence (T2w-STIR). This uses two initial inversion pulses to null moving blood. This is followed by a third inversion pulse, which nulls tissues with short T1 times (fat) to provide high contrast between blood (nulled) and myocardium<sup>[134,136]</sup>. T2w imaging of myocardial oedema is well-validated in animal studies assessing myocardial water volume on histological assessment<sup>[137]</sup> and fluorescent microspheres<sup>[77]</sup>. T2w oedema assessment is well-validated with SPECT<sup>[138-140]</sup> and angiographic markers of AAR (BARI<sup>[141]</sup>, APPROACHp<sup>[142]</sup> scoring). AAR on T2w can be assessed accurately for upto 1-wk post-PPCI unlike SPECT, which requires radionuclide administration during coronary occlusion and has higher spatial resolution and thus ability to detect subendocardial injury<sup>[138]</sup>.

However T2w-TSE imaging has inherent disadvantages that can compromise image quality and oedema detection. Upto 30% of datasets are non-analysable in studies<sup>[24,143,144]</sup>. New T2w sequences have been studied, with encouraging results (Figure 7).

The aim of prompt reperfusion is to limit IS by minimizing the conversion of reversibly injured myocardial cells (AAR) into necrotic, infarcted tissue (IS)<sup>[95,156]</sup>. Anterior STEMI typically results in larger IS due to the larger coronary bed supplied by the left anterior descending artery<sup>[14,80,82]</sup>. Hence a more accurate assessment of revascularisation strategies can be provided by adjusting IS for the AAR. The resulting myocardial salvage index (MSI) defines the proportion of reversibly injured tissue (AAR) that does not progress to infarction (IS, Equation 1, Figure 8). MSI is expressed as percentage of the initial AAR [0% is no salvage, 100% is complete salvage (aborted



**Figure 7 Alternative sequences to dark-blood T2-weighted turbo spin-echo for visualising oedema.** Left: Inherent disadvantages of T2w-TSE<sup>[134,144-147]</sup>; Right: Sequences compared with T2w-TSE: (1)<sup>[145]</sup>, (2)<sup>[141,142,144,148]</sup>, (3)<sup>[149,150]</sup>, (4)<sup>[144]</sup>, (5)<sup>[151,152]</sup>, (6)<sup>[153,154]</sup>, (7)<sup>[155]</sup>. T2w-TSE: T2-weighted turbo spin-echo; DWI: Diffusion-weighted imaging; AAR: Area at risk.

STEMI)]<sup>[157]</sup>.

Equation 1: Myocardial salvage index (MSI, %) = 100 × [(AAR-IS)/(AAR)].

Desch showed excellent intraobserver and inter-observer agreement for MSI assessment using T2w-STIR and LGE (coefficients of variation approximately 5.0%) and excellent test-retest reproducibility in a study of 20 acute STEMI patients<sup>[158]</sup>.

Other determinants of AAR include TTR<sup>[91,130,159-162]</sup>, extent of collateralised IRA territory flow<sup>[5,80,159,163]</sup>, TIMI-flow pre PPCI, LAD IRA and diabetes<sup>[91]</sup>.

Studies of the chronology of oedema suggest that it occurs very early in the ischaemic cascade. Abdel-Aty confirmed the presence of transmural oedema in canines on *in-vivo* T2w imaging at 28 min post LAD occlusion at which point LGE and troponin release were absent, indicating reversible injury<sup>[164]</sup>. Fernández-Jiménez *et al.*<sup>[165]</sup> however recently demonstrated a bimodal pattern of AAR extent in pigs with T2-mapping CMR and histological water quantification. They showed peak values at 2 h thought to be a direct result of reperfusion, followed by a return to baseline at 2 d and then progressive increase towards peak values at 7 d, with the latter peak felt due to water replacement of cleared cellular debris. Studies of temporal changes in AAR and MSI in humans are summarised in Table 12. Correct timing of oedema imaging is crucial in accurate calculation of AAR and MSI.

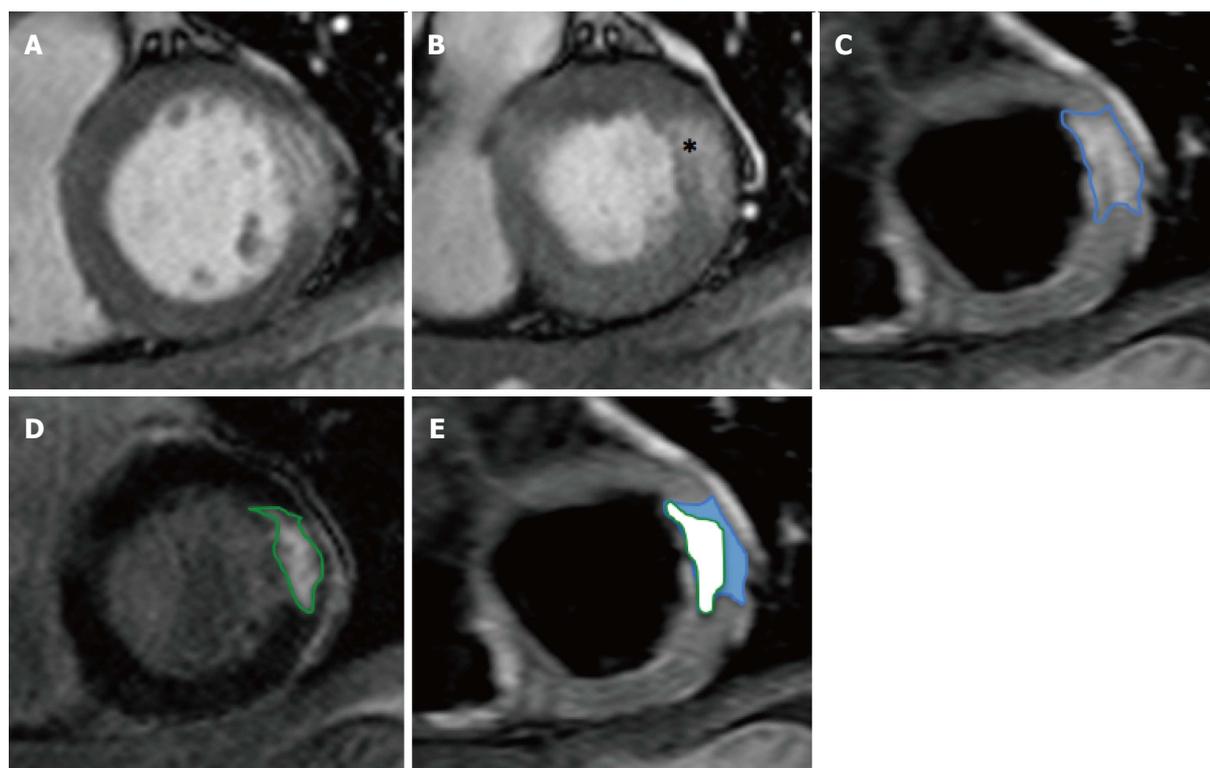
The near-resolution of oedema by 6 mo<sup>[5,18,21,91,138]</sup> allows distinction between acute and chronic infarcts when combined with LGE imaging.

### CMR MSI as a predictor of LV function and remodelling in AMI

Myocardial salvage is a strong univariate predictor of medium-term LV function<sup>[14,166,167]</sup> and adverse LV remodelling post STEMI<sup>[14,27,91,161]</sup>. Multivariate analysis demonstrates mixed results. MSI independently predicted LV remodelling in the work of Mather<sup>[131]</sup> (Table 13). However MSI was not a predictor once IS was added into multivariate models in studies by Monmeneu<sup>[91]</sup> and Masci<sup>[14]</sup>. This, in conjunction with the correlation between MSI and IS, and AAR and IS<sup>[26]</sup> questions whether MSI and IS are truly independent of each other in predicting LV remodelling and prognosis post STEMI. It could be argued that since MSI adjusts IS for the extent of AAR, it may have less inherent variability than IS. Since up to 30% of AAR datasets have been deemed non-diagnostic in previous studies<sup>[24,143,144]</sup>, this may impact on the robustness of MSI quantification whereas IS datasets are exceptionally rarely excluded based on image quality. It is not clear currently whether IS or MSI is the better measure of revascularisation success post PPCI.

### Prognostic importance of CMR MSI in AMI

Historically, the prognostic value of MSI was demonstrated using SPECT. Ndrepa first showed that MSI was the strongest independent predictor of 6-mo mortality<sup>[168]</sup>. MSI was an independent prognostic indicator in the medium term post STEMI in two studies. Although both studies were from the same patient cohort, they have both been



**Figure 8** Calculation of salvaged myocardium. A: SSFP end-diastolic cine image; B: SSFP end-systolic cine image showing hypokinetic basal anterolateral segment (\*); C: T2w-STIR image showing oedema (AAR) in anterolateral wall consistent with circumflex artery occlusion; D: Corresponding LGE image with near-transmural infarction; E: Calculation of salvaged myocardium in blue. SSFP: Steady-state free precession; T2w-STIR: T2-weighted short-tau inversion-recovery sequence; LGE: Late gadolinium enhancement.

**Table 12** Temporal changes in cardiovascular magnetic resonance-derived area at risk and myocardial salvage index in acute myocardial infarction

Ref.	Year	n	CMR timepoints post STEMI	AAR, IS method	Main findings
Mather <i>et al</i> <sup>[18]</sup>	2011	48	2 d → 1 wk → 30 d → 3 mo	> 2SD STIR, > 2SD LGE	AAR reduction at successive timepoints, 1-3 mo (-75%). No change MSI at d2 or 1 wk as IS and AAR decreased proportionally
Dall'Armellina <i>et al</i> <sup>[21]</sup>	2011	30	2 d → 1 wk → 2 wk → 6 mo	> 2SD T2p-BB, > 2SD LGE	100% had oedema at d2. AAR stable over 1st week (37% vs 39% LVM). Decreased by 2 wk and nearly resolved at 6 mo
Carlsson <i>et al</i> <sup>[38]</sup>	2009	16	1 d → 1 wk → 6 wk → 6 mo	Manual STIR, and LGE	AAR at all timepoints. AAR stable in 1st week, correlated with 1 wk SPECT. Decrease by 1 mo (10% LVM), nearly gone by 6 mo
Ripa <i>et al</i> <sup>[5]</sup>	2007	58	2 d → 1 mo → 6 mo	Manual STIR and LGE	All had oedema at d2. AAR decreased at all time points. No data on MSI in this study

AAR: Area at risk; MSI: Myocardial salvage index; AAR, LGE method: SD: Standard deviations; STIR: T2-weighted short-tau inversion recovery imaging; T2p-SS-BB: T2-prepared single-shot bright-blood; 3T: 3.0 tesla field strength; IS: Infarct size.

included in Table 14 due to their differing primary findings.

## T1, T2 AND T2\* QUANTIFICATION AND MAPPING IN AMI

The current mainstay of LGE and T2w techniques for the detection of infarct and oedema rely on semi-quantitative threshold-based quantification methods using arbitrary SI cut-offs compared to user-defined regions of interest, automated algorithms or are based on manual planimetry. There is currently no consensus on the optimal quantification method for IS or AAR using these

sequences. This can lead to subjectivity and dependence upon optimal nulling of normal myocardium and thus potential for error. In addition, commonly used T2w-TSE sequences suffer from non-diagnostic image quality in upto 30% of patients<sup>[24,143,144]</sup>.

T1, T2 and T2\* quantification present an exciting and complementary approach to LGE and T2w imaging. Developed by Messroghli *et al*<sup>[169]</sup> in 2003, their use in MI research has accelerated over the last 5 years. They allow not only the location and extent of infarction, oedema, MVO and IMH to be determined from subsequent parametric myocardial maps, but also the severity of these pathologies to be assessed through the magnitude

**Table 13 Cardiovascular magnetic resonance studies showing the importance of myocardial salvage index on left ventricular function and remodelling in acute myocardial infarction**

Ref.	Year	n	AAR, IS method	Main findings	CMR timepoint post STEMI	Follow-up
Mather <i>et al</i> <sup>[131]</sup>	2011	48	> 2SD STIR, > 2SD LGE	MSI was IP for LVR (OR 0.95) in model including LV volumes, LVEF, IS, IMH, MVO	2 d	3 mo
Monmeneu <i>et al</i> <sup>[91]</sup>	2012	118	> 2SD STIR, > 2SD LGE	MSI univariate predictor of LVR and final LVEF. However not IP of LVR in model with LVESVI, IS, no. transmural segs	6 d	6 mo
Masci <i>et al</i> <sup>[14]</sup>	2011	260	> 2SD STIR, > 5SD LGE	MSI strong univariate predictor of LVR and final LVEF. However not IP in model including IS, MVO	1 wk	4 mo
Masci <i>et al</i> <sup>[26]</sup>	2010	137	> 2SD STIR, > 5SD LGE	MSI strongest IP for LVR However IS and MSI (r = -0.72) and IS and AAR (r = 0.85) correlated	1 wk	4 mo

IS: Infarct size; IP: Independent predictor; LVR: Left ventricular remodelling; MVO: Microvascular obstruction; LVEF: Left ventricular ejection fraction; LVESVI: Left-ventricular end systolic volume index; STIR: T2-weighted short-tau inversion-recovery; LGE: Late gadolinium enhancement.

**Table 14 Cardiovascular magnetic resonance studies illustrating the prognostic importance of myocardial salvage index in acute myocardial infarction**

Ref.	Year	n	AAR, IS method	Main findings	CMR timepoint post STEMI	Follow-up
Eitel <i>et al</i> <sup>[24]</sup>	2011	208	> 2SD -STIR, > 5SD LGE	MSI was only CMR-based IP of mortality in model with age, IS, MVO, LVEF, TIMI- post PPCI, diabetes, age (IS not IP). MSI not IP of MACE (only IS, LVEF, age were)	3 d	19 mo
Eitel <i>et al</i> <sup>[161]</sup>	2010	208	> 2SD STIR, > 5SD LGE	MSI was only IP for MACE and mortality in model including LVEF, MVO, IS, ST-resolution and TIMI-grade post PCI	3 d	6 mo

IS: Infarct size; PCI: Percutaneous coronary intervention; MACE: Major adverse cardiovascular events; IP: Independent predictor; MVO: Microvascular obstruction; LVEF: Left ventricular ejection fraction.

of values obtained<sup>[170,171]</sup>. These methods are not reliant on reference regions of interest and do not suffer from T2w-TSE artefacts.

**T1 mapping (longitudinal relaxation)**

T1 relaxation curves allow calculation of the T1 time (time taken for recovery of 63% of longitudinal magnetization). The currently used curve-fitting sequences used include MOLLI (Modified Look-Locker Inversion Recovery), ShMOLLI (Shortened MOLLI), SASHA (SATuration recovery single-SHot Acquisition) and SAPHIRE (SATuration Pulse Prepared Heart rate independent Inversion REcovery)<sup>[172]</sup>. Infarcted and oedematous myocardium demonstrate prolonged pre-contrast T1 values and reduced post-contrast T1 values compared with normal myocardium, allowing infarct visualisation and quantification<sup>[169,170,173,174]</sup>. Messroghli showed that this technique had high test-retest reproducibility<sup>[175]</sup>, was stable within the range of heart rates commonly seen in clinical practice and showed comparable sensitivity for IS quantification compared with LGE<sup>[169,173,176]</sup>. T1 values within the infarct core were recently shown to demonstrate a strong inverse correlation with L-MVO extent, incidence of LV remodelling and all-cause mortality at 2.5 years<sup>[177]</sup>.

**T2 mapping (transverse relaxation)**

T2w images are generated using a T2-SSFP sequence with log-transformed curve-fitting T2 quantification, with

different T2 preparation (TE) times. T2 mapping has shown excellent reproducibility and no effect of slow-flow, through-plane movement, SI loss, or effects of coil SI inhomogeneities<sup>[151,178]</sup>. T2 mapping accurately assessed oedema in 96% of patients (good image quality in 100%), whereas T2w-STIR detected oedema in only 67% of patients (15% non-diagnostic 15%)<sup>[151]</sup>. High observer agreement and close agreement between T1 (r<sup>2</sup> = 0.94) and T2 maps (r<sup>2</sup> = 0.96), and fluorescent microspheres for AAR detection was seen in canine myocardium<sup>[179]</sup>.

**T2\* mapping (transverse relaxation in presence of field inhomogeneities)**

T2\* mapping allows visualisation and quantification of IMH due to the presence of paramagnetic haemoglobin breakdown products. A cut-off value of < 20 ms has been used to define the presence of IMH<sup>[180]</sup>. Although the evidence base for T2\* mapping in assessing IMH is currently limited, O'Regan demonstrated that it has greater sensitivity than T2w-STIR imaging (100% vs 90%) for IMH. Kali showed good correlation between *in-vivo* T2\* and histological assessment of IMH and iron levels in canine myocardium<sup>[127,128]</sup>. T2\* mapping may improve the specificity of IMH detected on CMR<sup>[131]</sup>.

T1, T2 and T2\* surrogate markers hold promise for improving the accuracy of detection of infarct, oedema and IMH respectively, and further improving statistical power of STEMI studies. However, due to the importance

**Table 15 Cardiovascular magnetic resonance studies illustrating the prognostic importance of right ventricular infarction in acute myocardial infarction**

Ref.	Year	n	RV LGE analysis method	Main findings	CMR timepoint post STEMI	Follow-up
Jensen <i>et al</i> <sup>[184]</sup>	2010	50	Manual	RVI only IP of MACE in model with age, sex, LVEF, LV IS	3 d	32 mo
Miszalski-Jamka <i>et al</i> <sup>[98]</sup>	2010	99	Manual	RVEF (HR 1.46) and RVI extent (HR 1.50) IP for MACE	“3-5 d”	1150 d
Grothoff <i>et al</i> <sup>[187]</sup>	2012	450	Manual	RVI was IP of MACE (HR 6.70)	“1-4 d”	20 mo

MACE: Major adverse cardiovascular events; IP: Independent predictor; HR: Hazard ratio; RV: Right ventricle; LVEF: Left ventricular ejection fraction; LGE: Late gadolinium enhancement; IS: Infarct size; RVI: Right ventricular infarction.

**Table 16 Key studies illustrating the independent predictive value of cardiovascular magnetic resonance markers for left ventricular remodelling**

CMR marker	Ref.	Year	n	CMR quantification	Main findings	Acute CMR time	Follow-up CMR time
IS	Husser <i>et al</i> <sup>[33]</sup>	2012	304	2SD	IS extent IP for LVR in model with LVEF, IS, LV volumes, MVO	6 d	189 d
IS	Monmeneu <i>et al</i> <sup>[91]</sup>	2012	118	2SD	Number of segments > 50% transmural IP for LVR	6 d	6 mo
IS	Wu <i>et al</i> <sup>[94]</sup>	2008	122	Manual	IS extent at 2 d only IP for LVEF and LVR	2 d	4 mo
IS	Hombach <i>et al</i> <sup>[6]</sup>	2005	110	Manual	IS extent at 6 d was an IP for LVR in model with MVO, % transmural	6 d	225 d
L-MVO	Weir <i>et al</i> <sup>[112]</sup>	2010	100	Manual	L-MVO extent was only IP of LVR in model with TIMI post PCI, E-MVO, IS	4 d	6 mo
L-MVO	Hombach <i>et al</i> <sup>[6]</sup>	2005	110	Manual	L-MVO extent IP of LVR in model with baseline IS, infarct transmural	6 d	225 d
IMH	Carrick <i>et al</i> <sup>[74]</sup>	2016	245	T2*	IMH strongest IP of LVR in model with patient/angio characteristics, LVEDVI	3 d	7 mo
IMH	Husser <i>et al</i> <sup>[33]</sup>	2012	304	T2w-TSE	IMH strongest IP for LVR in model with LVEF, IS, LV volumes, L-MVO	6 d	189 d
MSI	Monmeneu <i>et al</i> <sup>[91]</sup>	2012	118	2SD LGR/STIR	MSI univariate but not IP of LVR in model with IS, LVESVI, segments > 50%	6 d	6 mo
MSI	Masci <i>et al</i> <sup>[14]</sup>	2011	260	2SD STIR, 5SD LGE	MSI univariate predictor of LVR and final LVEF. However not IP of either	1 wk	4 mo
MSI	Masci <i>et al</i> <sup>[26]</sup>	2010	137	> SD STIR, 5SD LGE	MSI strongest IP for LVR. However IS and MSI and IS and AAR correlated	1 wk	4 mo
T1	Carrick <i>et al</i> <sup>[177]</sup>	2016	300	T1 map, 2SD STIR, 5SD LGE	Infarct core native T1 inverse relationship with LVR (OR 0.91 per -10 ms T1)	2 d	6 mo

Criteria: Individual studies with  $n \geq 100$  and follow-up CMR  $\geq 3$  mo post-PPCI. IS: Infarct size; L-MVO: Late microvascular obstruction; IMH: Intramyocardial haemorrhage; MSI: Myocardial salvage index; SD: Standard deviations; STIR: T2-weighted short-tau inversion recovery; LGE: Late gadolinium enhancement; IP: Independent predictor; LV: Left ventricular; LVEF: Left ventricular ejection fraction; AAR: Area at risk; LVEDVI: Left ventricular end-diastolic volume; CMR: Cardiovascular magnetic resonance.

of protocol standardisation, these techniques are rarely used in multicentre studies at present.

## RIGHT VENTRICULAR INVOLVEMENT IN AMI

### CMR assessment of right ventricular infarction in AMI

CMR is the gold standard imaging modality for the assessment of right ventricular (RV) volumes, function, oedema<sup>[181]</sup> and infarction (RVI)<sup>[182]</sup>. CMR identifies RVI with greater sensitivity than echocardiography, ECG (V4<sub>R</sub> ST-segment elevation) and clinical examination<sup>[183,184]</sup> and demonstrates RV L-MVO<sup>[185,186]</sup>. There is good interobserver and intraobserver agreement for the identification of RV oedema ( $\kappa = 0.62$ ,  $\kappa = 0.62$ , respectively) and very good agreement for RVI ( $\kappa = 0.70$ ,  $\kappa = 0.70$ , respectively)<sup>[181]</sup>.

The high MSI in RVI often  $> 90\%$ <sup>[187,188]</sup> is thought to be due the relatively low RV nutrient needs, direct endocardial oxygen diffusion and good collateral blood supply<sup>[188,189]</sup>.

### Prognostic importance of CMR-derived right ventricular infarction in AMI

RVI confers adverse short-term prognosis, with a large meta-analysis ( $n = 7136$ ) demonstrating that RVI on ECG, echocardiography or radionuclide imaging predicted 30-d mortality and in-hospital MACE<sup>[190]</sup>. Shah demonstrated the prognostic importance of right ventricular infarction on imaging, where RVEF  $< 38\%$  on radionuclide ventriculography post STEMI was a strong independent predictor of 1-year mortality<sup>[191]</sup>. Right ventricular infarction is a strong independent predictor of medium to long-term prognosis in a small number of CMR

**Table 17 Key studies illustrating the independent predictive value of cardiovascular magnetic resonance markers for prognosis**

CMR marker	Ref.	Year	n	CMR quantification	Main findings	Acute CMR time	Follow-up
IS	Husser <i>et al</i> <sup>[96]</sup>	2013	250	> 2SD	Extent of transmural infarction was only IP for MACE	7 d	163 wk
IS	Izquierdo <i>et al</i> <sup>[97]</sup>	2013	440	> 2SD	IS was IP for arrhythmic cardiac events in model including LVEF, hypertension	7 d	123 wk
IS	Eitel <i>et al</i> <sup>[34]</sup>	2011	208	> 5SD	IS was IP of MACE in model with MVO, LVEF, MSI, Killip, TIMI flow post-PPCI	3 d	18.5 mo
IS	Larose <i>et al</i> <sup>[67]</sup>	2010	103	FWHM	IS strongest IP for MACE in model with LVEF, CK. LGE > 23% for MACE	4.5 h	2 yr
IS	Bodi <i>et al</i> <sup>[38]</sup>	2009	214	> 2SD	Extent of transmural infarction (no. of segments > 50% transmural) IP for MACE	7 d	553 d
IS	Wu <i>et al</i> <sup>[99]</sup>	2008	122	Manual	IS only IP of 2 yr MACE in model containing LVEF, LVESVI (HR 1.06)	2 d	538 d
L-MVO	Regenfus <i>et al</i> <sup>[117]</sup>	2015	249	Manual	MVO extent strongest IP for MACE in model with IS, LVEF, TIMI and no. vessels	3.7 d	72 mo
L-MVO	Eitel <i>et al</i> <sup>[119]</sup>	2014	738	> 5SD	L-MVO > 1.4% LVM IP of MACE in model with LVEDVI, LVEF, clinical markers	7 d	6 mo
L-MVO	de Waha <i>et al</i> <sup>[120]</sup>	2012	438	Manual	L-MVO extent IP for MACE in model with IS, LV volumes. L-MVO/IS strongest IP	3 d	19 mo
L-MVO	de Waha <i>et al</i> <sup>[36]</sup>	2010	438	Manual	L-MVO strongest IP of MACE/mortality in model with IS, LVEF, STR, TIMI post	3 d	19 mo
L-MVO	Cochet <i>et al</i> <sup>[37]</sup>	2009	184	Manual	L-MVO strongest IP for MACE in model with GRACE, IS, LVEF. E-MVO weaker IP	“3-7 d”	12 mo
L-MVO	Bruder <i>et al</i> <sup>[116]</sup>	2008	143	Manual	L-MVO extent > 0.5% LV mass IP for MACE in model with IS, LVEF, age, DM, sex	4.5 d	12 mo
L-MVO	Hombach <i>et al</i> <sup>[6]</sup>	2005	110	Manual	L-MVO IP for MACE (P = 0.04) in model with LV end-diastolic volume and LVEF	6 d	268 d
IMH	Carrick <i>et al</i> <sup>[74]</sup>	2016	245	T2*	IMH strongest IP of CV death and HF. Multivariate model, L-MVO not predictor	3 d	830 d
IMH	Amabile <i>et al</i> <sup>[133]</sup>	2012	114	T2w-TSE	IMH presence was strongest predictor of MACE in model with MVO, LVEF, STR	4 d	12 mo
IMH	Husser <i>et al</i> <sup>[33]</sup>	2012	304	T2w-TSE	IMH IP for MACE in model with AAR, IS, L-MVO. T2w. No inc. value with LGE	6 d	140 wk
IMH	Eitel <i>et al</i> <sup>[125]</sup>	2011	346	T2w-TSE	IMH IP of MACE in model with L-MVO. T2w inc. value with LGE and cine	3 d	6 mo
MSI	Eitel <i>et al</i> <sup>[34]</sup>	2011	208	> 2SD/> 5SD	MSI only CMR IP of mortality in model with age, IS, MVO, LVEF, TIMI post, IS	3 d	19 mo
MSI	Eitel <i>et al</i> <sup>[161]</sup>	2010	208	> 2SD/> 5SD	MSI only IP for MACE/mortality in model with LVEF, MVO, IS, STR, TIMI post	3 d	6 mo
T1	Carrick <i>et al</i> <sup>[177]</sup>	2016	300	T1 map, > 2SD STIR, > 5SD	Infarct core T1 inverse association with risk of mortality and heart failure hospitalisation, in model with LVEF, infarct T2, IMH. Similar prognostic as L-MVO	2 d	2.5 yr

Criteria: Individual studies with  $n \geq 100$  and follow-up CMR  $\geq 6$  mo follow-up. IS: Infarct size; L-MVO: Late microvascular obstruction; IMH: Intramyocardial haemorrhage; MSI: Myocardial salvage index; SD: Standard deviations; STIR: T2-weighted short-tau inversion recovery; LGE: Late gadolinium enhancement; IP: Independent predictor; LV: Left ventricular; LVEF: Left ventricular ejection fraction; AAR: Area at risk; LVEDVI: Left ventricular end-diastolic volume; CK: Creatine kinase; T2w-TSE: T2-weighted turbo spin echo; MACE: Major adverse cardiovascular events; CV: Cardiovascular.

studies (Table 15).

### WHEN IS THE OPTIMAL TIME TO PERFORM CMR ASSESSMENT IN MI?

In acute STEMI, IS, AAR and MSI are best imaged at 7 d post PPCI due to overestimation of necrosis on LGE, and IS at 7 d best predicts final IS, LV remodelling and function and prognosis<sup>[5-7,9,18,20,21]</sup>. Human studies suggest that AAR is stable during the first week<sup>[21,138]</sup>. Although Fernández-Jiménez *et al*<sup>[165]</sup> demonstrated a bimodal AAR peak in pigs, their drop in AAR extent on T2w CMR at 2 d post-reperfusion may be due to a high incidence of IMH in pigs and peak IMH extent at 2 d<sup>[74]</sup>.

Indeed the drop in AAR extent on the gold standard of histological water analysis in their study at 2 d was much less pronounced, and at 7 d AAR extent had returned to stable peak levels. In addition, studies demonstrating close agreement between T2w-derived AAR and the reference non-invasive modality of SPECT<sup>[138,139]</sup> were undertaken at 7 d post STEMI. MVO and IMH extent peak at 48 h then decrease<sup>[18]</sup> but are present at 7 d<sup>[9,18]</sup>. Although undertaking CMR at 7-d may potentially underestimate MVO and IMH extent<sup>[9,18,74]</sup>, this may be minimised by expressing MVO and IMH extent as a proportion of IS rather than LV mass, to correct for the corresponding reduction in IS. Thus, acutely post STEMI for the assessment of IS, MSI, MVO and IMH, imaging at 7 d may provide the best compromise in relation to their

temporal changes<sup>[5-7,9,18,20,21]</sup> for accurate quantification and prediction of LV function, remodelling and prognosis. This needs to be balanced with contemporary clinical practice where patients are typically discharged at 3-4 d post-PPCI, and the risk of early attrition. Using final IS at follow-up as a primary outcome risks underestimating potential differences in treatment strategies due to greater infarct resorption with the larger infarcts.

Data on the chronology of IS suggests that infarct resorption is essentially complete by 3 mo post MI<sup>[9,18,20,74]</sup>. However a key objective of follow-up CMR is to assess LV geometry and remodelling and hence must allow the relatively slower adaptations of ventricular volumes (approximately 12 mo), compared with changes in IS and LVEF to complete. LVEF shows no significant change after 1-mo post STEMI. Follow-up CMR at 3 and 6-mo may fail to provide an accurate assessment of LV volumes and remodelling. The evidence base suggests that in order to allow completion of the trio of IS, LVEF and LV volumetric changes, follow-up CMR should be performed at 12-mo post STEMI<sup>[5,7,18,20,21]</sup>. When correlating CMR and clinical outcomes, the longer timepoint of 12-mo also permits more reliable clinical follow-up.

Standardisation of LGE, AAR and IMH sequences and quantification methods is equally important in light of newer T1, T2 and T2\*-mapping sequences and inherent image quality issues associated with T2w-TSE.

## CONCLUSION

Contrast-enhanced CMR offers robust, validated and reproducible surrogate markers, providing an accurate representation of pathophysiology, assessment of myocardial function and injury, and predictive value for medium to long-term LV function, remodelling and prognosis following PPCI for STEMI. Tables 16 and 17 summarise the key prospective studies illustrating the independent predictive value of CMR markers for LV remodelling (studies where  $n > 100$ , follow-up CMR  $\geq 3$  mo post PPCI) and prognosis (studies where  $n > 100$ ,  $\geq 6$  mo follow-up) respectively.

In the acute phase, CMR can be performed accurately for up to 7 d post PPCI. CMR delivers no radiation to the patient and this makes it ideal for serial studies. The multimodal nature of CMR allows a multiparametric study of cardiac function, structure and volumes within a single study, which can be undertaken within approximately 45 min in the majority of patients. It is likely that CMR will become the mainstay of cardiac imaging, providing an important role in risk stratification and treatment post STEMI. Focus needs to be continued in translating findings on the prognostic importance of surrogate markers to development of therapeutic targets post STEMI.

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## Aerobic vs anaerobic exercise training effects on the cardiovascular system

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### Abstract

Physical exercise is one of the most effective methods to help prevent cardiovascular (CV) disease and to promote CV health. Aerobic and anaerobic exercises are two types of exercise that differ based on the intensity, interval and types of muscle fibers incorporated. In this article, we aim to further elaborate on these two categories of physical exercise and to help decipher which provides the most effective means of promoting CV health.

**Key words:** Cardiovascular; Exercise; Training; Aerobic; Anaerobic

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**Core tip:** As the association between physical inactivity and the increased risk of cardiovascular morbidity solidified, further data and studies supported the advantages of exercise on physical well-being. Anaerobic and aerobic exercise have a favorable effect on lipid metabolism, anaerobic exercises have been shown to have a positive influence on the lipid profile.

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### INTRODUCTION

More than 250000 yearly deaths in the United States are

attributed to cardiovascular (CV) disease resulting from a lack of physical activity. On the other hand, physical inactivity is estimated to cause 30% of ischemic heart disease<sup>[1]</sup>. The association between physical inactivity and CV disease gained a foothold in the medical community in 1996, when the American Heart Association (AHA) published information advocating the benefit of physical exercise in regards to improvements in hemodynamic, hormonal, metabolic, neurological and respiratory function<sup>[2]</sup>. As the association between physical inactivity and the increased risk of CV morbidity solidified, further data and studies supported the advantages of exercise on physical well-being. The 2010 recommendations by the World Health Organization (WHO) provided activity recommendations based on three different age groups: Ages 5-17, 18-64, and > 64 years of age. In the age group of 5-17 years, individuals should accrue at least 60 min of moderate activity daily. Those in the group of 18-64 years should perform at least 150 min of moderate activity or at least 75 min of vigorous activity throughout the week. Finally, individuals above the age of 65 years are recommended similar length and intensity exercise programs as the prior group, but with a focus on activities to help enhance balance and to prevent falls<sup>[3]</sup>.

The inherent advantages of physical exercise stem from an increase in the cardiac output and an enhancement of the innate ability of muscles to extract and to utilize oxygen from the blood. This benefit is further compounded by the benefit physical exercise has on high-density lipoprotein cholesterol (HDL-C)<sup>[4]</sup>, adipose tissue distribution<sup>[5]</sup>, increased insulin sensitivity<sup>[6]</sup>, improved cognitive function<sup>[7]</sup>, enhanced response to psychosocial stressors<sup>[8]</sup>, as well as determent of depression<sup>[9]</sup>. With the benefit of physical exercise well established, the question remains which type of exercise provides the most effective and efficient means to help deter CV disease.

A recent meta-analysis published showed a decrease in the risk of all CV outcomes and diabetes mellitus incidence with increasing levels of physical activities<sup>[10]</sup>. Another meta-analysis suggested that high level of leisure time physical activity had a beneficial effect on CV health by reducing the overall risk of incident CHD and stroke among men and women by 20% to 30%, while moderate level of occupational physical activity might reduce 10% to 20% risk of CVD<sup>[11]</sup>.

Furthermore, cardiac rehabilitation, which is physical exercise based, is a promising field which showed a favorable outcome among patients with heart failure and post-CVD events<sup>[12,13]</sup>.

## AEROBIC EXERCISE

The American College of Sports Medicine (ACSM) defines aerobic exercise as any activity that uses large muscle groups, can be maintained continuously and is rhythmic in nature<sup>[10]</sup>. As the name implies, muscle groups activated by this type of exercise rely on aerobic metabolism to extract energy in the form of adenosine triphosphate (ATP) from amino acids, carbohydrates and fatty acids.

Examples of aerobic exercise include cycling, dancing, hiking, jogging/long distance running, swimming and walking. These activities can best be accessed *via* the aerobic capacity, which is defined by the ACSM as the product of the capacity of the cardiorespiratory system to supply oxygen and the capacity of the skeletal muscles to utilize oxygen<sup>[14]</sup>. The criterion measure for aerobic capacity is the peak oxygen consumption (VO<sub>2</sub>), which can be measured either through graded exercise ergometry or treadmill protocols with an oxygen consumption analyzer or *via* mathematical formulas. The value of peak VO<sub>2</sub> can be appreciated by a study performed by Vaitkevicius *et al*<sup>[15]</sup>, in which the VO<sub>2max</sub> was calculated along with other dimensions, to conclude that higher physical conditioning status was directly correlated with reduced arterial stiffness.

Various studies have been published that prove the advantages of aerobic exercise in reversing and preventing CV disease. In 2002, Wisløff *et al*<sup>[16]</sup> were the first to show the benefit of aerobic training in the myocardium after an ischemic event. Their study was performed on adult female Sprague-Dawley rats, which were placed into groups categorized based on induced myocardial infarctions (MI) with and without exercise and controls with and without exercise. Their results showed a 15% reduction in the left ventricle (LV) hypertrophy post-infarction, as well as 12% and 20% decreases in myocyte length and width, respectively, with aerobic exercise. Furthermore, a 60% improvement was noted in myocardial contractility in subjects with a MI who were assigned to the training group, suggesting enhanced myocardial Ca<sup>2+</sup> sensitivity. They were able to conclude the beneficial effects of aerobic training on cardiac remodeling and myocardial contractility<sup>[16]</sup>.

The effect of aerobic exercise were confirmed in human subjects when Wisløff *et al*<sup>[17]</sup> published another study five years later, which incorporated human subjects with post-MI heart failure. Subjects were enrolled in aerobic interval training (AIT), moderate continuous training (MCT) or a control group. The AIT group showed a 46% increase in peak VO<sub>2</sub>, which correlated with a 60% increase in the maximal rate of Ca<sup>2+</sup> reuptake in the sarcoplasmic reticulum in the skeletal muscles. Additionally, cardiac remodeling was evident in humans, much like the rat subjects in the previous study, as LV diameters declined and LV volumes increased in both the diastolic and systolic phases. Moreover, systolic function was noted to increase by 35% in the AIT group<sup>[17]</sup>, thereby further strengthening the advantages of aerobic exercise.

Furthermore, aerobic exercise has been shown to have a positive impact on other dimensions of CV health. Several studies have shown that aerobic exercise improves the lipid profile, particularly increasing the HDL-C<sup>[18]</sup>. In an Australian study, aerobic exercise led to a small but statistically significant reduction in total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C) and triglycerides (TG) ranging in a span of 0.08 mmol/L to 0.10 mmol/L. They also showed an increase in HDL-C with their aerobic exercise program of about 0.05 mmol/

L<sup>[19]</sup>. Similar results have been documented in children and adolescents, as well<sup>[20]</sup>. In a meta-analysis conducted by Kelley *et al*<sup>[21]</sup>, it was concluded that aerobic exercises contributed to a statistically significant 9% increase in HDL-C and an 11% decline in TG, but no statistically significant changes in TC and LDL-C.

A positive correlation between biochemical signal markers, such as endothelin-I (ET-1) and aerobic exercise was recently speculated by several studies. Vascular endothelial cells produce ET-1, which functions as a vasoconstrictor<sup>[22]</sup> and promoter of atherosclerosis<sup>[23]</sup>. Maeda *et al*<sup>[24]</sup> were able to demonstrate a statistically significant positive linear correlation of increasing age with rising levels of ET-1. They were also able to exhibit a visible reduction in ET-1 levels after a 3 mo aerobic exercise regimen<sup>[24]</sup>.

While aerobic exercise appears to have some beneficial effects, its contribution is limited on frequency and quantity. A very recent publication by a Danish group was able to represent what they called a "U shaped association" between aerobic exercise and mortality. Their research quantified 1 to 2.4 h of exercise over 2 to 3 times per week as the optimal quantity and frequency standard of aerobic exercise to promote improved health. Interestingly, they quantified any amount above that standard as being indifferent to the mortality risk, as that of sedentary individuals<sup>[25]</sup>.

## ANAEROBIC EXERCISE

Anaerobic exercise has been defined by the ACSM as intense physical activity of very short duration, fueled by the energy sources within the contracting muscles and independent of the use of inhaled oxygen as an energy source<sup>[14]</sup>. Without the use of oxygen, our cells revert to the formation of ATP *via* glycolysis and fermentation. This process produces significantly less ATP than its aerobic counterpart and leads to the build-up of lactic acid. Exercises typically thought of as anaerobic consist of fast twitch muscles and include sprinting, high-intensity interval training (HIIT), power-lifting, *etc.* Sustained anaerobic metabolism, in other words, anaerobic exercise, causes a sustained increase in lactate and metabolic acidosis and this transition point is referred to anaerobic threshold (AT)<sup>[26]</sup>. AT can be directly measured *via* frequent blood samples measuring the blood lactate level during a graded-exercise regimen. Once the blood lactate values are plotted, the point at which the curve makes a sudden sharp incline represents the AT. Other methods include portal lactate analyzers and mathematical formulas involving heart rate (HR).

Similar to aerobic exercise, anaerobic exercise may exert a potentially beneficial influence on the CV system. In a Turkish study completed by Akseki Temür *et al*<sup>[27]</sup>, the effects of anaerobic exercise were evaluated with a member of the natriuretic peptide family, known as C-type natriuretic peptide (CNP). CNP is synthesized by the endothelium and offers a protective effect through its effects on the vascular tone of blood vessels,

as well as exerting antifibrotic and antiproliferative properties. It produces a hyperpolarization effect on the smooth muscle layer of blood vessels, which causes vasodilatation<sup>[28]</sup>. CNP has also been reported to exert its nonproliferative effects on cardiac fibroblasts to help prevent cardiac aging through LV fibrosis *via* the cyclic guanosine monophosphate (cGMP) pathway<sup>[29]</sup>. In this study, twelve healthy young male subjects were divided into two groups based on their previous history of exercise. Once categorized into groups, the subjects were asked to participate in a thirty second high intensity exercise program, which encompassed the anaerobic exercise factor. Blood samples were obtained from the subjects before exercise and then one minute, five minutes and thirty minutes after exercise and were tested for the levels of aminoterminal proCNP (NT-proCNP), a biologically inactive peptide of CNP. The results showed a statistically significant increase of NT-proCNP level in the five minute mark post-exercise in the physically active group after anaerobic exercise.

Similar to aerobic exercise and their favorable effect on lipid metabolism, anaerobic exercises have been shown to have a positive influence on the lipid profile. A small European study composed of 16 obese subjects was able to show the increased benefits of an aerobic workout followed by anaerobic training, as compared to aerobic training alone. Subjects who underwent core training with both aerobic and anaerobic exercises showed a larger reduction in non-esterified fatty acids. The same group was also found to have the greatest reduction in their body mass index (BMI)<sup>[30]</sup>.

There are speculations about disadvantages of such an exercise program. One such shortcoming was brought to light by an Iranian study published by Manshouri *et al*<sup>[31]</sup>, which concluded that anaerobic training led to a significant reduction in human growth hormone (HGH). It has long been theorized that long-standing HGH deficiencies can attribute to CV morbidity and mortality through the development of premature atherosclerosis. HGH deficiency has been shown to result in higher BMI and TG, lower concentrations of HDL-C, as well as the development of hypertension (HTN)<sup>[32]</sup>. Furthermore, cardiac structure is affected in HGH deficient subjects, as manifested by reduced LV posterior wall thickness, smaller LV mass index and compromised LV ejection fraction (LVEF)<sup>[33]</sup>. The exact mechanism of action for such changes remains to be determined.

## CONCLUSION

With the high incidence of CV disease worldwide, it is an irrefutable notion that exercise helps deter CV morbidity and mortality. Both aerobic and anaerobic exercises have unique and collective positive correlations towards improved CV health. Despite all the research, further studies are still warranted to delve further into the impact that both aerobic and anaerobic exercise may have on human physiology to unequivocally determine if there is superiority of one type of exercise over

another.

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## Left atrial appendage occlusion: A better alternative to anticoagulation?

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### Abstract

Non-valvular atrial fibrillation is associated with a significantly increased risk of embolic stroke due to blood clot forming predominantly in the left atrial appendage

(LAA). Preventive measures to avoid embolic events are permanent administration of anticoagulants or surgical closure of the LAA. Various clinical trials provide evidence about safety, effectiveness and therapeutic success of LAA occlusion using various cardiac occluder devices. The use of such implants for interventional closure of the LAA is likely to become a valuable alternative for stroke prevention, especially in patients with contraindication for oral anticoagulation as safety, clinical benefit and cost-effectiveness of LAA occlusion has recently been demonstrated.

**Key words:** Left atrial appendage; Thrombus; Occlude; Stroke

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**Core tip:** Non-valvular atrial fibrillation is associated with increased risk of embolic stroke. To date, risk-based anticoagulation is the cornerstone to avoid this. However, several patients have got absolute or relative contraindication to this and thus are undertreated. For these patient population the implantation of a local left atrial appendage occluder might be an alternative.

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### INTRODUCTION

The left atrial appendage (LAA) is an external protrusion of the left atrium located next to the pulmonary trunk<sup>[1,2]</sup>. Compelling evidence points to the LAA as the primary origin of thrombus formation particular in the presence of non-valvular atrial fibrillation (AF); since the major risk of non-valvular AF to suffer from ischemic stroke,

the LAA has drawn much attention in the context of stroke prevention<sup>[3-5]</sup> considering missing awareness and unrecognized AF prior to strokes<sup>[6]</sup>. Thus, the current approach for stroke prevention in patients with non-valvular AF of risk-adjusted prevention *via* oral anticoagulants (OAC) or antiplatelet agents<sup>[7,8]</sup> may be challenged by elective LAA occlusion in selective patients<sup>[3,4,9-12]</sup>. In the past, physical LAA closure required either surgical excision or exclusion by suture or stapler<sup>[10,13]</sup>. With the introduction of cardiac occluder devices open surgery is not required any more and redundant for this purpose<sup>[14-16]</sup>. This review summarizes current knowledge of LAA occlusion as an emerging alternative to chronic OAC therapy for non-valvular AF patients at risk for embolic strokes.

## ANATOMY OF THE LAA

The function of the LAA is not fully understood but it has been linked to secretion of the hormone "atrial natriuretic factor" (ANF) and, hence, could be involved in the regulation and homeostatic control of water, salt and fat<sup>[17,18]</sup>. Regardless, the anatomy of the LAA is highly diverse and was classified into four different morphological types; "chicken wing" was the most frequently identified type (48%) followed by "cactus" (30%), "windsock" (19%), and "cauliflower" (3%)<sup>[19]</sup>. The "chicken wing" type has a dominant lobe, which may have secondary lobes or twigs, and is bent in the proximal or middle part or even folds back on itself at some distance from the orifice. The "cactus" type has a dominant central lobe with secondary lobes extending in both superior and inferior directions, whereas the primary structure of the "windsock" type is a dominant lobe with variation in the location and number of secondary or even tertiary lobes. Lastly, the "cauliflower" type has a short overall length with more complex internal characteristics, lacks a dominant lobe but has variable number of lobes and a more irregular shape of the LAA orifice. Previous studies indicate that the "chicken wing" type poses the lowest risk for embolism in contrast to the "cauliflower" type, which, notably, exhibits the highest degree of structural complexity<sup>[20]</sup>. However, due to the complex anatomy of the LAA, it is difficult to correctly assess length, branches and courses, as well as thrombus formation by transesophageal echocardiography (TEE) and it was demonstrated that the outcome of this visualization is dependent on the selection of the imaging plane<sup>[21]</sup>.

## LIMITATIONS OF ORAL ANTICOAGULANT THERAPY

The current gold standard for stroke prevention in patients with non-valvular AF is the oral administration of anticoagulants to reduce the risk of thrombus formation and prevent any embolic events<sup>[7,8]</sup>. Chronic anticoagulation is carried out by traditional and novel

oral anticoagulants (NOACs) also called directly acting oral anticoagulants (DOACs). Traditional anticoagulants include heparins and coumarins (vitamin K antagonists) of which warfarin is the most common. NOACs are inhibitors of coagulation factors such as factors IIa (*e.g.*, dabigatran) or factor Xa (*e.g.*, rivaroxaban, apixaban and edoxaban)<sup>[22-25]</sup>. However, chronic OAC therapy is not recommended if contraindications are present or potential interference with other therapies. Moreover, difficulties to adjust treatment, dietary restriction, low compliance or even refusal of the patient to follow treatment protocol are considered contraindication for OAC<sup>[10,22-26]</sup>. Therefore, alternative strategies for stroke prevention in patients with AF are required.

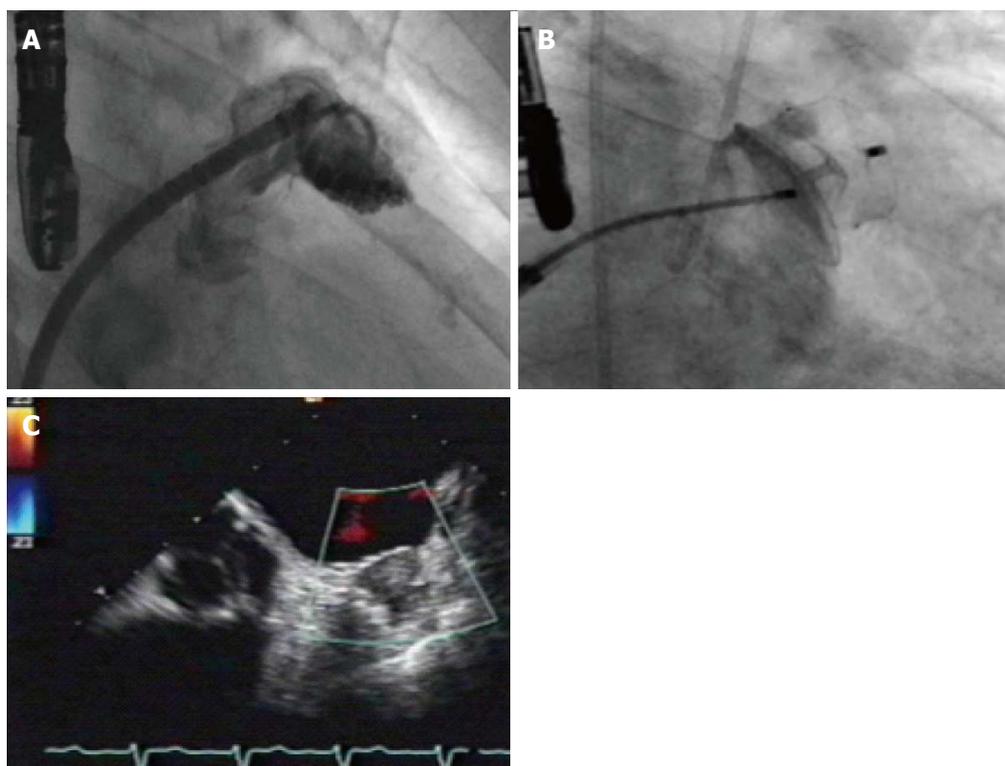
## APPROACHES FOR CLOSURE OF THE LAA

There are two fundamental approaches beyond anticoagulation to avoid emboli in patients with non-valvular AF, *e.g.*, surgical excision of the LAA or exclusion by suture line, stapler or cardiac plug<sup>[10,13]</sup>. Before introduction of cardiac occluder for LAA closure, surgical excision was the superior method while LAA closure requires either suture line<sup>[10,13]</sup>. However, a surgical excision is not risk free and may cause bleeding<sup>[27]</sup>. Nonetheless, surgical excision is still an option mostly in conjunction with other cardiac surgery<sup>[10,27]</sup>. In recent years, an alternative approach for LAA closure was established by sealing the orifice of the LAA with an occluder. Such a LAA occlusion was performed 2001 for the very first time using the PLAATO system which has been taken off market<sup>[28,29]</sup>. The current generation of occluders are the Amplatzer™ Cardiac Plug (ACP), Amplatzer Amulet™ from St. Jude Medical and the Watchman™ device from Boston Scientific<sup>[29,30]</sup>. In addition, a small number of novel devices have been mentioned and applied in the last few years such as the WaveCrest™ device and the Lariat™ device<sup>[31,32]</sup> (Table 1). The ACP-originally used for closure of atrial septal defects<sup>[33]</sup> - consists of a self-expanding flexible nitinol mesh with a distal lobe filled with polyester and is equipped with fixation barbs to adhere of the LAA. The distal lobe is connected *via* a small waist to a proximal disc sealing the orifice of the LAA<sup>[34]</sup>. Similar to the ACP, the Watchman™ device consists of a self-expanding nitinol mesh with fixation barbs and a polyester coating covering the surface facing the left atrium<sup>[35]</sup>.

Implantation of both Watchman™ device and ACP can be performed under local anesthesia and is introduced *via* catheter through the femoral vein by transseptal passage<sup>[33,36-39]</sup>. TEE guiding or intracardiac echocardiography (ICE) during implantation procedure is used to rule out intracardiac thrombus and to facilitate transseptal puncture. After transseptal puncture heparin is administered to achieve an active clotting time of > 250 s. The LAA is fluoroscopically illustrated in at least 2 standard angulations (RAO 30°, RAO 30°/10° caudal) and sized by

**Table 1 Different endocardial left atrial appendage occlusion devices<sup>[3,11]</sup>**

Device name	Company	Design
PLAATO	Appriva Medical Inc.	Single-lobe occluder; nitinol cage; ePTFE membrane hooks
WATCHMAN	Boston Scientific	Single-lobe occluder; nitinol frame; PET membrane; hooks
ACP	St. Jude Medical	Lobe and disc (polyester mesh); nitinol mesh structure; stabilizing wires
Amulet	St. Jude Medical	Lobe and disk (polyester mesh in both); nitinol mesh structure; stabilizing wires
WaveCrest	Coherex Medical	Single-lobe occluder; nitinol frame, polyurethane foam and ePTFE membrane; retractable anchors
Occlutech LAA	Occlutech	Single-lobe occluder; nitinol wire mesh; stabilizing loops; nanomaterial covering
Sideris Patch	Custom Medical Devices	Frameless detachable latex balloon covered with polyurethane
Lambre	Lifetech	Lobe and disk; nitinol; PET membrane; distal barbs anchors
Pfm	PFM Medical	Dual disk (distal anchor, variable middle connector, proximal disk); nitinol frame
Ultrasept	Cardia	Lobe and disk; nitinol frame; Ivalon covering; distal anchors



**Figure 1** Measurement of left atrial appendage (A), implantation of an Amulet device (B) and postinterventional transesophageal echocardiogram revealing good sealing without any leak (C).

TEE measurements and cine angiography. Device size will be chosen according to manufacturer's recommendations 20% larger than the landing zone (measured from left circumflex coronary artery to the ridge delineating the LAA from the left upper pulmonary vein). Optimally, the device should not protrude more than 5 mm beyond the LAA ostium and should cover the entire ostium with no or minimal (less than 5 mm by colour Doppler) residual flow and a compression grade of 8%-30%. After device releasing and sheath removal the puncture site is dealt with a Z-suture or with a pressure band. Periprocedural anticoagulation is managed by heparin or bivalirudin<sup>[14,28,33]</sup> (Figure 1). The implanted device becomes initially coated by fibrin and subsequently covered by endothelial cells forming an endocardial lining, which consequently excludes the LAA from circulating blood<sup>[40]</sup>. In order to allow the process of endothelialization patients have to take warfarin after the intervention for at least 45

d. Warfarin is then replaced by clopidogrel and aspirin for half a year, while aspirin administration is continued life-long<sup>[15]</sup>. According to newer data a dual antiplatelet therapy is more efficacious than the use of anticoagulants<sup>[37,41,42]</sup>. In addition to the general risks of catheter-based interventions including air or blood embolism, an incomplete closure of the orifice, pericardial perforation, dislodgement of the implant or the formation of blood clots on the surface of the device leading to prolonged OAC treatment may occur<sup>[14,28,33,43]</sup>. Finally, since ANF is secreted in the LAA, the LAA closure could interfere with thirst regulation and water retention in the patient, but this theoretical concept has been scarcely investigated so far<sup>[17,18]</sup>.

## STATUS QUO OF LAA OCCLUSION

For several years great effort has been devoted to the use of cardiac plugs in the prevention of AF-related

strokes. A number of studies have been published about the PLAATO system including a five-year follow-up study<sup>[28,44]</sup>. In addition to the PLAATO system, the ACP system which has been used for closure of atrial septal defects for more than 20 years and its features, design and applicability are very well studied and has been reported to be successful for LAA closure<sup>[33,34]</sup>. It is worth mentioning that a large randomized clinical trial to study the ACP for LAA occlusion was recently halted, probably due to the approval of a competitive product (*i.e.*, Watchman device) by the United States Food and Drug Administration (FDA)<sup>[45]</sup>. The successful use of the Watchman device for LAA occlusion has been shown in two large, prospective randomized clinical trials—the PROTECT-AF and the PREVAIL study—in which this implant was compared to chronic OAC therapy using warfarin<sup>[14,15]</sup>. Over five years, the PROTECT-AF study examined about 800 patients, of which 463 had received a Watchman™ device and 244 were left on warfarin<sup>[14]</sup> and demonstrated that the implant is non-inferior to OAC therapy in patients with non-valvular AF being eligible for OAC. In comparison to the OAC treatment group, the incidence of an embolic event was reduced by approximately 30% in the implant group; the overall mortality showed a reduction of the same magnitude. While the per-protocol analysis was in favor of LAA occlusion, the intention-to-treat results were neutral. Furthermore, the safety data also favored warfarin over LAA occlusion, but this was explained by the learning curve phenomenon. The highest risk from LAA occlusion arises from complications associated with the one-time interventional treatment, while the risks from chronic OAC therapy accumulates during time especially with increasing age of the patient. Recently, a 45-mo follow-up of the PROTECT-AF study demonstrated that LAA occlusion is not only as efficient as warfarin treatment but even superior in term of stroke and cardiovascular mortality<sup>[46]</sup>. Further, the safety data showed a considerable reduction in the risk for complications during intervention, likely due to increasing experience of the surgeons. However, the FDA criticized the patient selection and raised questions about the safety of LAA occlusion<sup>[47]</sup>. To address these limitations, a confirmatory randomized trial (PRE-VAIL) comparing LAA occlusion with the Watchman device to warfarin, which mandated inclusion of new operators, slight modifications in inclusion criteria, and elimination of clopidogrel 7 d before implant. In PREVAIL more than 400 patients were randomized to either warfarin ( $n = 138$ ) or occluder device ( $n = 269$ )<sup>[15]</sup>. This study showed that LAA occlusion achieved non-inferiority in stroke prevention compared to warfarin; the difference between both groups was low and not significant. Most importantly, the number of early safety events (*e.g.*, pericardial effusions) was significantly reduced compared to the PROTECT-AF study and, hence, satisfied the predefined goal. Therefore, the PREVAIL study addressed the concerns rose by the FDA and demonstrated the safety of this intervention for LAA occlusion<sup>[15]</sup>. As a result of this study the Watchman

™ device was approved by the FDA in 2015<sup>[48]</sup>. Results from the real-world EWOLUTION registry consisting of 1021 patients being implanted with the Watchman device revealed a procedural success rate of 98.5%<sup>[49]</sup>. During 30-d follow-up 28 subjects experienced serious adverse events with an overall 30-d mortality rate of 0.7%. Serious procedure related complication rates, defined as stroke, pericardial effusion, device embolism and death, were present in 8.7% in PROTECT-AF, 4.1% in CAP registry, 4.2% in PREVAIL and 2.7% in EWOLUTION. However, the average CHADS2 score of 2.8 and CHA2DS2-VASc score of 4.5 in EWOLUTION indicate a relatively higher risk of stroke than either the PROTECT AF (average CHADS2 of 2.2 and CHA2DS2-VASc of 3.4) or PREVAIL (CHADS2 score of 2.6 and CHA2DS2-VASc of 4.0) studies. In addition, 40% of EWOLUTION subjects had a HAS-BLED score of  $\geq 3$ , compared with only 20% of PROTECT AF subjects and 30% of PREVAIL subjects (Table 2). Similar results were obtained in a registry with the ACP device<sup>[50]</sup> and a large meta-analysis<sup>[51]</sup> including 2406 patients from the PROTECT AF, PREVAIL, CAP I and CAP II registries with a mean follow-up of 2.69 years. Patients receiving LAA occlusion with the Watchman device had significantly fewer hemorrhagic strokes [0.15 vs 0.96 events/100 patient-years (PY); hazard ratio (HR): 0.22;  $P < 0.004$ ], cardiovascular/unexplained death (1.1 vs 2.3 events/100 PY; HR: 0.48;  $P < 0.006$ ), and nonprocedural bleeding (6.0% vs 11.3%; HR: 0.51;  $P < 0.006$ ) compared with warfarin. All-cause stroke or systemic embolism was similar between both strategies (1.75 vs 1.87 events/100 PY; HR: 1.02; 95%CI: 0.62 to 1.7;  $P = 0.94$ ). There were more ischemic strokes in the device group (1.6 vs 0.9 and 0.2 vs 1.0 events/100 PY; HR: 1.95 and 0.22, respectively;  $P = 0.05$  and 0.004, respectively)<sup>[51]</sup>.

## COST-EFFECTIVENESS

An analysis of Panikker *et al.*<sup>[16]</sup> on 110 patients being suitable and unsuitable for long-term OAC and outcome analysis from the PROTECT-AF trial and registry study compared warfarin, dabigatran, rivaroxaban, apixaban, aspirin and no treatment using a network meta-analysis. They revealed that stroke and bleeding rates were significantly lower than PROTECT-AF results. Additionally, LAA occlusion achieved cost parity between 4.9 years vs dabigatran 110 mg and 8.4 years vs warfarin and at 10 years, occlusion was cost-saving against all therapies. Similarly, another analysis evaluated the cost effectiveness in patients suffering from AF and absolute contraindication for OAC<sup>[52]</sup>. For this purpose the ASAP study evaluating the Watchman device, the ACTIVE-A trial evaluating aspirin and clopidogrel and the AVERROES trial evaluating apixaban were compared in a cost-effectiveness analysis. At 5 years, LAA occlusion was cost effective compared with aspirin with an incremental cost-effectiveness ratio of 16971 Euro. As compared with apixaban, it was also cost-effective at 7 years with an incremental cost-effectiveness ratio of 9040 Euro. Apart

**Table 2** Summary of data for left atrial appendage occlusion

	PROTECT-AF <sup>[46]</sup>	CAP <sup>[43]</sup>	ASAP <sup>[42]</sup>	EWOLUTION <sup>[49]</sup>	ACP <sup>[50]</sup>
Patients (n)	463	460	150	1021	1047
Follow-up	4 yr	16 mo	14 mo	30 d	13 mo
CHADS-score	2.2	2.4	2.8	2.8	n.a.
CHA2DS2-Vasc score	n.a.	n.a.	4.4	4.5	4.5
Procedural success	88.00%	95.00%	94.70%	98.50%	97.30%
Procedural stroke	1.30%	0	0.70%	n.a.	0.90%
Pericardial effusion	4.80%	2.20%	1.30%	0.50%	1.20%
Device embolization	0.60%	0	1.30%	0.20%	n.a.
Major bleeding	3.50%	n.a.	n.a.	1.60%	1.50%
Long-term stroke	2.30%	1.50%	0.70%	0.30%	2.30%

AF: Atrial fibrillation; n.a.: Not applicable.

**Table 3** Different aspects of left atrial appendage occlusion

Pro	Contra
Non-inferiority to oral anticoagulation	Evaluation of other atherothrombotic sources
Alternative in patients with contraindication for anticoagulation	Unknown hemodynamic impact
Cost-effective	Postprocedural medical treatment not well defined
Reduced cumulative bleeding events during follow-up	No comparison between different devices
Good results in real-world registries	Undefined impact of residual leaks

from the population having an absolute contraindication for OAC similar analysis were performed for patient being eligible for OAC, where LAA occlusion was cost-effective at 7 years and novel oral anticoagulation was cost-effective at 16 years. However, LAA occlusion was superior to novel oral anticoagulation by year 5 and to warfarin by year 10 with respect to cost-effectiveness and cost saving for stroke prevention<sup>[53]</sup>.

## FUTURE CONSIDERATIONS

In 2012, the European Society of Cardiology (ESC) released a focused update of the guidelines for the management of AF<sup>[8]</sup>. Interestingly, the ESC also commented on LAA occlusion for prevention of stroke (class II b recommendation, level of evidence B). Due to insufficient amount of data demonstrating efficacy and safety, the ESC did not recommend an LAA occlusion at this point as a routinely alternative therapy to replace chronic OAC therapy in order to reduce AF-related stroke risk, but recommended to consider this approach for patients with an increased for stroke and contraindications for OAC treatment<sup>[8]</sup>. However, the references cited as evidence for the recommendation are the PROTECT AF study and the CAP registry. Importantly, neither of these studies included patients who had contraindications to long-term anticoagulation, and both enrolled a majority of patients with relatively low estimated stroke risk. A growing body of evidence suggests that LAA occlusion with the Watchman™ device is an important alternative for OAC therapy using warfarin, yet, a perspective randomized study comparing LAA occlusion to the NOAC is still missing and therefore a final conclusion about the general applicability of LAA occlusion using the Watchman implant

cannot be drawn at this point<sup>[49,50,54]</sup>. Additionally, there are not enough data analyzing different patient cohorts (e.g., sex, age, race, renal insufficiency) as there are data revealing a direct correlation between elevated adiponectin levels and the degree of left atrial blood stasis in men but not in women, and there are more extensive left atrial remodeling and deterioration in LAA function in women than in men<sup>[55-57]</sup>. There are some subanalyses revealing higher bleeding events in patients older than 75 years after LAA Occluder implantations compared to younger ones (4.4% vs 1.4%), as well as in males as compared to females (3.0% vs 1.8%)<sup>[58]</sup>. In accordance with the latest recommendations from the ESC, LAA occlusion should definitely be considered if complications with OAC therapy arise or a high bleeding risk exist, regardless if the patient is treated with traditional or novel anticoagulants. This therapeutic approach is even more justified if the patient undergoing chronic OAC therapy suffers a stroke. Under this circumstance and under the light of recent studies about the safety and efficacy of LAA occlusion, this interventional treatment could be a better choice and advisable for this with a CHA2DS2Vasc Score  $\geq 2$  (Table 3). Summing up the current data, LAA occlusion is a very promising treatment to prevent AF-related strokes due to its safety, cost-effectiveness and therapeutic success.

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## Clinical cardiac regenerative studies in children

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### Abstract

Although the incidence of pediatric heart failure is low, the mortality is relatively high, with severe clinical sym-

ptoms requiring repeated hospitalization or intensive care treatment in the surviving patients. Cardiac biopsy specimens have revealed a higher number of resident human cardiac progenitor cells, with greater proliferation and differentiation capacity, in the neonatal period as compared with adults, demonstrating the regeneration potential of the young heart, with rising interest in cardiac regeneration therapy in critically ill pediatric patients. We review here the available literature data, searching the MEDLINE, Google Scholar and EMBASE database for completed, and [www.clinicaltrials.gov](http://www.clinicaltrials.gov) homepage for ongoing studies involving pediatric cardiac regeneration reports. Because of difficulties conducting randomized blinded clinical trials in pediatric patients, mostly case reports or cohort studies with a limited number of individuals have been published in the field of pediatric regenerative cardiology. The majority of pediatric autologous cell transplantations into the cardiac tissue have been performed in critically ill children with severe or terminal heart failure. Congenital heart disease, myocarditis, and idiopathic hypertrophic or dilated cardiomyopathy leading to congestive heart failure are some possible areas of interest for pediatric cardiac regeneration therapy. Autologous bone marrow mononuclear cells, progenitor cells, or cardiospheres have been applied either intracoronary or percutaneously intramyocardially in severely ill children, leading to a reported clinical benefit of cell-based cardiac therapies. In conclusion, compassionate use of autologous stem cell administration has led to at least short-term improvement in heart function and clinical stability in the majority of the critically ill pediatric patients.

**Key words:** Congenital heart disease; Heart failure; Cardiac regeneration; Cell-based therapy; Hospitalization; Children

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**Core tip:** This review summarizes the available literature data involving pediatric cardiac regeneration reports.

Due to lack of randomized blinded clinical trials in pediatric cardiology patients, mostly case reports with limited number of individuals have been published in the pediatric regenerative cardiology. The majority of pediatric autologous cell transplantations into the cardiac tissue have been performed in children with severe or terminal heart failure, and led to the conclusion, that compassionate use of autologous stem cell administration may lead to at least short-term improvement in heart function and clinical stability in the majority of the critically ill pediatric patients.

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## INTRODUCTION

### **Epidemiology of heart failure in children**

The overall prevalence of pediatric heart failure is largely unknown because of the non-unique definition and classification of this disease. According to statistical estimations and pediatric registries, 2.5 million children annually are born with congenital heart disease (CHD) worldwide, and among these children, 15%-25% eventually develop heart failure<sup>[1-4]</sup>.

The incidence of pediatric dilated cardiomyopathy with consequent heart failure is low, calculated as 0.57-2.6 per 100000 children under age 18 years<sup>[5,6]</sup>. In this group, approximately two thirds of cases are idiopathic, and the remaining involve postmyocarditis syndrome or musculoskeletal diseases<sup>[7]</sup>. Dilated cardiomyopathy dominates myocardial disease-related heart failure, followed by hypertrophic cardiomyopathy, with restrictive cardiomyopathy identified least frequently<sup>[8]</sup>. The median age of the patients with dilated cardiomyopathy is approximately 1.8 years when the initial diagnosis is made<sup>[8]</sup>.

The mortality of pediatric heart failure is high, and approximately one third of patients die in the first year following diagnosis<sup>[9,10]</sup>. The surviving children develop progressive heart failure requiring intensive medical care and heart transplantation<sup>[7]</sup>. For those surviving at least 2 years after the diagnosis, mortality and the need for heart transplantation are somewhat lower (13.6%)<sup>[6]</sup>. Approximately 18 of every 100000 children are hospitalized annually because of heart failure, with 0.87 new cases per 100000 children per year<sup>[11]</sup>. The hospital mortality of these pediatric patients is 7%, and numbers are much higher compared to the adult population (4%)<sup>[11,12]</sup>. After the first hospitalization, only 21% of pediatric patients remain free from serious adverse events (rehospitalization, death, or heart transplantation)<sup>[13]</sup>. The lack of sufficient numbers of young donor organs and the relatively high post-transplantation mortality limit the incidence and success of pediatric

heart transplantation.

In addition, the cost of hospital treatment for pediatric heart failure is usually extremely high, exceeding 135000 USD per patient. Underlying CHD involving a single ventricle, for example, expands the costs of in-hospital treatment for heart failure to over 200000 USD<sup>[14]</sup>.

The medical therapy for pediatric heart failure includes the whole armamentarium used in adults; however, the benefit cannot be clearly demonstrated for all interventions in children<sup>[15]</sup>. Some established methods for adult cardiology, such as diverse regenerative therapies or left ventricular assist devices, are rarely available for young patients because of incompatibilities of implant size in growing children. Medical treatment might be insufficient because, as noted, many children end up requiring heart transplantation<sup>[16]</sup>.

### **Spontaneous cardiac regeneration capacity in children**

Newborn mice can regenerate the cardiac apex after resection but only if the resection occurs within the first 7 d after birth<sup>[17]</sup>. Lineage tracing investigations have revealed that cell cycle entry of pre-existing cardiomyocytes in mice is responsible for this regeneration. Gene expression analysis indicates that neonatal cardiomyocytes maintain proliferation capacity only up to 7 d post-birth, this regeneration property is then lost<sup>[17]</sup>. Mishra *et al.*<sup>[18]</sup> investigated the prevalence and proliferation capacity of different stem cell-like cells acquired from cardiac biopsy specimens of children undergoing open heart surgery. They showed that plenty of resident human cardiac progenitor cells (hCPCs, a subpopulation of cardiospheres, CDCs) can be found in the neonatal period but that the number of these cells decreases rapidly with advancing age, from 8.9% to 3.2% in the right atrium and from 0.4% to 0.1% in the right ventricle. In addition, c-kit<sup>+</sup> hCPCs were three times more frequently found in neonates than in children over age 2 years. The proliferation and differentiation potential of the hCPCs was also greater in neonates, as shown by the higher expression levels of c-kit and Ki67, as well as the expression of NKX2, NOTCH1, and NUMB, the genes responsible for proliferation and differentiation. Furthermore, heart tissue samples of children with CHD contained an increased number of c-kit<sup>+</sup> hCPCs and CD133<sup>+</sup> cells, and these cells expressed cardiac lineage and endothelial transcription factors during differentiation under *in vitro* conditions<sup>[19]</sup>. CDCs are a rich source of secreted regenerative substances, such as cytokines and growth factors, *e.g.*, vascular endothelial growth factor, hepatocyte growth factor, or insulin-like growth factor, and exert anti-apoptotic and proangiogenic effects in the myocardium<sup>[20,21]</sup>. CDCs found in infant hearts have higher telomerase activity compared with those of adults.

Together, these data suggest that the regenerative capacity of the heart in children is much greater than that of adults. Additional evidence comes from clinical observations that the younger heart can exhibit morphological changes after volume unloading by surgical correction of CHD<sup>[22]</sup>. Additionally, pressure overload from

**Table 1 Pediatric cardiac diseases treated with cells**

Cell-based cardiac regenerative treatment	Ongoing studies
Dilated cardiomyopathy (Dil. CMP) Idiopathic dilated CMP Cytostatics-induced dilated CMP Postmyocarditis dilated CMP Ischemic heart failure (myocardial infarction) Anomalous origin of the left coronary arteries Takayasu arteritis Congenital heart disease DORV after surgical correction Pulmonary atresia with ventricular septal defect HLHS	Dilated cardiomyopathy (Dil. CMP)           Hypoplastic left heart syndrome (HLHS)

CMP: Cardiomyopathy; DORV: Double outlet right ventricle; HLHS: Hypoplastic left heart syndrome.

a single right ventricle leads to an increase in the number of cardiac stem cells ( $0.41\% \pm 0.24\%$ ) compared to dilated cardiomyopathy ( $0.15\% \pm 0.09\%$ )<sup>[23]</sup>.

### Clinical pediatric cardiac regeneration studies

To establish standardized therapy and guidelines for treatment of diseases, randomized double-blinded clinical studies delivering evidence-based medicine are necessary. In contrast with the huge number of adult clinical trials, in pediatric cardiology, especially for cardiac regenerative therapy, large randomized trials are lacking. In addition to the understandable ethical reasons, other factors also preclude such trials: The relative rarity of heart failure with a limited number of pediatric patients in the stable clinical condition necessary for randomization, a divergence in terminology, proprietary and often incompatible informatics platforms, and variability in data standards in growing children<sup>[24]</sup>. In 2012, the United States Food and Drug Administration Safety and Innovation Act intensified pediatric product development, also enhancing the number of pediatric clinical trials. In Europe, the Pediatric Regulation and Pediatric Therapeutics programs have strengthened the applications of new medicines in evidence-based pediatric clinical studies. In contrast with the very sparse pediatric regenerative cardiology studies, pediatric cancer and HIV/AIDS treatment networks have already been successfully established and developed with standardized data validity and consistency<sup>[24]</sup>. We review here the available literature data, searching the Medline, Google Scholar and Embase database for completed, and www.clinicaltrials.gov homepage for ongoing studies involving pediatric cardiac regeneration reports.

## DISCUSSION

### Cardiac diseases for pediatric cardiac regeneration

In most cases, cardiac cell-based therapy has been applied in children with severe heart failure caused by diverse diseases, predominantly idiopathic dilated cardiomyopathy, post-myocarditis, or chemotherapy-induced dilated cardiomyopathy (Table 1 and Figure 1).

Severe heart failure has been described also with post-myocardial infarction in cases of an anomalous origin of the left coronary artery from the pulmonary artery or Takayasu's arteritis, treated with different kinds of reparative cells. Other congenital diseases such as double outlet right ventricle, pulmonary atresia with ventricular septal defect, or hypoplastic left heart syndrome (HLHS) causing severely depressed heart function, have been considered for treatment with non-committed cells. Table 2 lists the pediatric diseases for which cardiac cell-based regenerative studies might be considered.

For the reasons described, to date, only two randomized clinical cardiac regenerative trials with a low number of included children have been conducted. Both have revealed benefits of cardiac cell-based therapy<sup>[25-29]</sup>. In addition to these currently finished trials, case reports or pilot trial results have been published, mainly based on an indication of compassionate use in severely ill pediatric patients. The majority of children receiving cardiac cell-based therapy were in a critical or terminal status of cardiac decompensation, as evidenced by the fact that some of the children had to undergo heart transplants afterwards<sup>[22]</sup>.

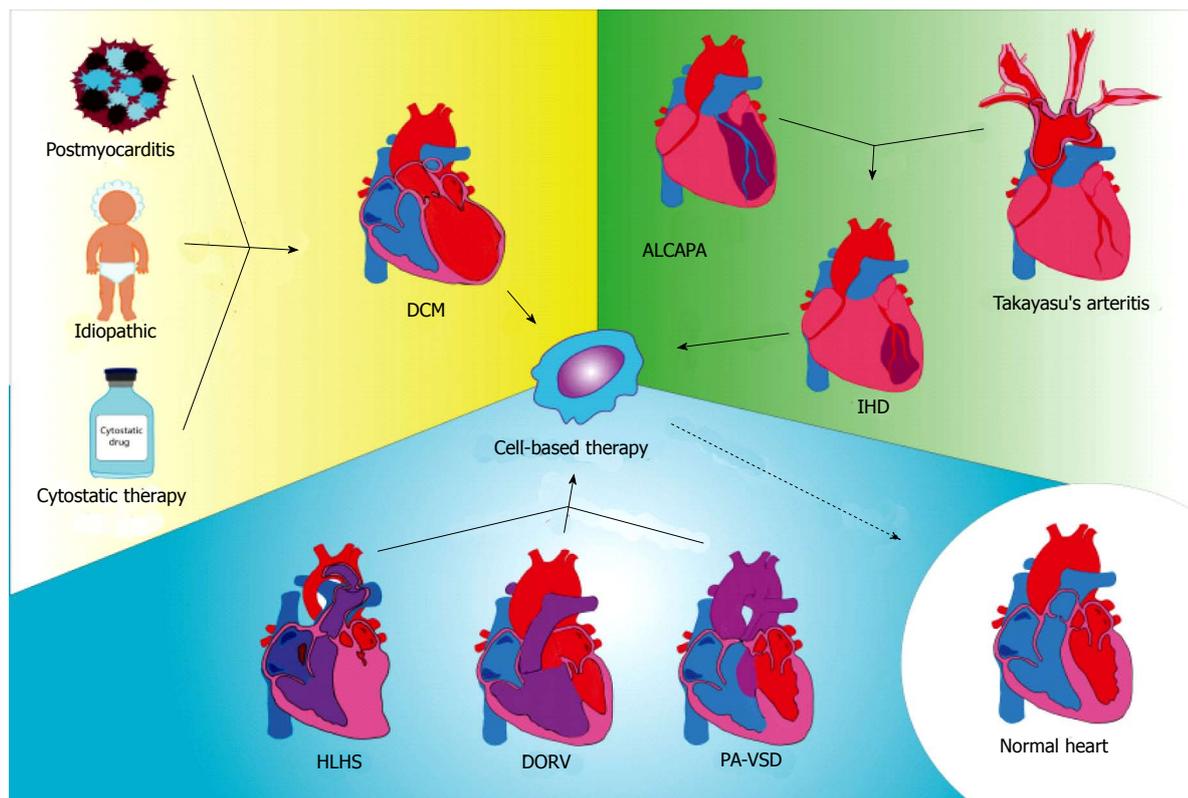
### Cell types and delivery modes

Different types of cells have been used for cardiac regenerative cell therapy in children, such as bone marrow-derived mononuclear cells, cells from leukocyte apheresis, and mesenchymal stem cells. In all cases, autologous cells were used.

Most of the children received the reparative cells *via* intracoronary injections. To ensure retention of the injected cells, echocardiography-guided transcatheter intramyocardial delivery was also used, or a transapical delivery mode was applied<sup>[30]</sup>.

### Clinical studies

The evidence for pediatric cardiac regeneration is mostly anecdotal, deriving from case reports or cohort studies including very limited number of patients (max. nine treated children in Rupp *et al.*<sup>[31]</sup>). In addition, the only comparative study, published by Ishigami *et al.*<sup>[32]</sup> allocated



**Figure 1 Schematic display of cardiac cell-based regeneration therapies in pediatric population.** DCM: Dilated cardiomyopathy; ALCAPA: Anomalous left coronary artery from the pulmonary artery; IHD: Ischemic heart disease; HLHS: Hypoplastic left heart syndrome; DORV: Double outlet right ventricle; PA-VSD: Pulmonary atresia with ventricular septal defect.

14 children with HLHS to receive either autologous CDCs ( $n = 7$ ) or standard therapy ( $n = 7$ ) without randomization. Because of these significant limitations of the available literature, a usual review or meta-analysis of cardiac regenerative studies in children is not reasonable. Thus, this review summarizes the published cases and their conclusions.

Autologous stem cell administration has led to at least short-term improvement in heart function and clinical stability in the majority of patients. Because of the lack of randomization and control groups, an unambiguous interpretation of the results is not possible. At the least, the outcomes indicate a compassionate use of cell-based cardiac regeneration in critically ill patients.

Rupp *et al.*<sup>[33,34]</sup> reported two cases of bone marrow-origin progenitor cell intracoronary injection, one involving a 2-year-old boy with dilated cardiomyopathy and the other an 11-mo-old infant with HLHS; both of them were in a critical clinical condition of heart failure. The bone marrow progenitor cells were injected into the left anterior descending and left circumflex coronary arteries in the first case and into the dominant right coronary artery in the second case, using a stop-flow technique. The cardiac cell therapy led to an increase in the left ventricular ejection fraction from 24% to 45% at 6 mo of follow-up in the first case, and to reverse remodeling and marked improvement in clinical status in the second case.

In further work, Rupp *et al.*<sup>[34]</sup> published a somewhat larger cohort study of nine pediatric patients receiving

intracoronary injections of autologous bone marrow mononuclear cells (BM-MNCs). The reasons for terminal heart failure in these children were anthracycline-induced dilated cardiomyopathy; post-myocarditis, idiopathic, or congenital cardiomyopathy; CHD with poor ventricular function, such as hypoplastic left heart or double outlet right ventricle; and pulmonary atresia with ventricular septal defect after surgical corrections. Three of the nine patients received a heart transplant and one patient died after cell treatment. The surviving children showed an improvement in clinical status during the 24 to 52 mo of follow-up.

De Lezo *et al.*<sup>[35]</sup> presented a case of a 5-mo-old infant with severe heart failure due to extensive myocardial infarction because of an anomalous origin of the left coronary artery. After surgical re-implantation of the left coronary artery to the aorta, the artery was occluded, then stented, then dilated after stent occlusion. Because of the critical clinical situation, during the second percutaneous procedure, autologous bone marrow-origin mononuclear cells were injected into the left main branch, which led to a gradual improvement in clinical status and allowed the discharge of the patient.

After mobilizing stem cells from the bone marrow with granulocyte colony-stimulating factor (G-CSF), Olguntürk *et al.*<sup>[36]</sup> selected peripheral blood-origin stem cells and performed intracoronary injections of these cells into both the left and right coronary arteries in two patients both with dilated cardiomyopathy and severe

**Table 2** Published clinical studies with pediatric cell-based cardiac regeneration

Ref.	Study type	Diagnosis	No. of children	Mean age of children (m)	Sex	Type of stem cell	Cell application	FUP	Main results
Lacis <i>et al</i> <sup>[30]</sup>	Case report	Dil. CMP	1	3.5 mo	F	BM-MNC	IM	4 mo	LV EF from 20% to 41%
Rupp <i>et al</i> <sup>[31]</sup>	Case report	Dil. CMP	9	4 mo-16 yr	NA	BM-MNCs	IC	1-52 mo	3 patients HTX, 1 patient died, others improved
Ishigami <i>et al</i> <sup>[32]</sup> (TICAP study)	Controlled study	HLHS	7 treated and 7 controls	< 6 yr	NA	CDCs	IC	18 mo	Increase in RV EF from 46.9% to 52.1% in treated patients
Rupp <i>et al</i> <sup>[33]</sup>	Case report	HLHS	1	11 mo	M	BMC	IC	14 mo	RV EF from 22% to 44%
Rupp <i>et al</i> <sup>[34]</sup>	Case report	Dil. CMP	1	2 year	M	BMC	IC	6 mo	EF from 24% to 45%, BNP and NYHA decreased
De Lezo <i>et al</i> <sup>[35]</sup>	Case Report	Post-AMI	1	7 mo	NA	BM-MNCs	IC	14 mo	LV EF from 20% to 43%
Olguntürk <i>et al</i> <sup>[36]</sup>	Case report	Dil. CMP	2	6 and 9 yr	M, F	PBSC after G-CSF treatment	IC	8 wk, and 6 mo	1 <sup>st</sup> patient LV EF from: 16% to 39%; 2 <sup>nd</sup> patient LV EF from 34% to 54%
Limsuwan <i>et al</i> <sup>[37]</sup>	Case report	HF post-AMI	1	9 yr	F	BMC after G-CSF treatment	IC	3 mo	LV EF from 30% to 47%
Zeinaloo <i>et al</i> <sup>[38]</sup>	Case report	Dil. CMP	1	11 yr	M	BM-MSC	IC	1 yr	LV EF from 20% to 42%
Rivas <i>et al</i> <sup>[39]</sup>	Case report	Dil. CMP	2	3 and 4 mo	M	PBSC after G-CSF treatment	IC	4 mo	EF from < 30% to > 40%
Bergmane <i>et al</i> <sup>[40]</sup>	Case report	Dil. CMP	7	4 mo-17 yr	NA	BMC	IM	1 yr	6 patients controlled, LV EF from 33.5% to 54%
Burkhardt <i>et al</i> <sup>[41]</sup>	Case report	HLHS	1	3 m	NA	Umbilical cord blood derived cells	IM	3 mo	EF increased to 45%

BMC: Bone marrow cells; CDC: Cardiosphere-derived cells; BNP: Brain natriuretic peptide; HTX: Heart transplantation; NYHA: New York Heart Association Classification; G-CSF: Granulocyte-colony stimulating factor; CMP: Cardiomyopathy; LV: Left ventricle; EF: Ejection fraction; BM-MNC: Bone marrow mononuclear cell; PBSC: Peripheral blood stem cell; RV: Right ventricle; IC: Intracoronary; IM: Intramyocardial; FUP: Follow-up; NA: Data not available; HLHS: Hypoplastic left heart syndrome; F: Female; M: Male.

congestive heart failure. At the 4-mo follow-up, both children showed impressive improvement, and one of them could be removed from the heart transplantation list.

Similarly, Limsuwan *et al*<sup>[37]</sup> applied the first daily injections of G-CSF, followed by bone marrow aspiration and selection of CD133<sup>+</sup>/CD34<sup>+</sup> cells in an 8.5-year-old girl who had had an acute extensive anterior myocardial infarction related to Takayasu arteritis one year earlier. The selected stem cells were injected into the left anterior descending artery with the stop-flow technique. The 3-mo follow-up showed an increase in ejection fraction from 30% to 47.8% by cardiac magnetic resonance imaging.

Zeinaloo *et al*<sup>[38]</sup> selected autologous bone marrow mesenchymal stem cells in an 11-year-old boy with a diagnosis of dilated cardiomyopathy and injected them into the left and right coronary arteries. The one-year clinical check-up revealed an improvement of the left ventricular ejection fraction from 20% to 42%.

Lacis *et al*<sup>[30]</sup> treated a 3-mo-old child, who was in critical clinical condition with dilated cardiomyopathy, with autologous BM-MNCs *via* echocardiography-guided transcutaneous transapical intramyocardial injections. The ejection fraction increased from 20% to 41% at the

4-mo follow-up, and the child's clinical well-being was obvious.

Rivas *et al*<sup>[39]</sup> treated two children who both had dilated cardiomyopathy and were ages 3 and 4 mo, respectively, by administering peripheral blood progenitor cells, mobilized by G-CSF treatment. One month later, both children presented improvement, but one child developed progression later. This article described a temporary effect of the cell-based cardiac regenerative therapy.

Ishigami *et al*<sup>[32]</sup> published a nonrandomized prospective cohort study comparing data for seven patients treated with intracoronary injection of cardiosphere-derived cells and seven controls treated with standard therapy. All children had HLHS with planned stage 2 or 3 surgical palliation, which allowed the collection of autologous tissue for selection of CDCs in the treated group. The intracoronary injection of CDCs proved to be safe, and the right ventricle ejection fraction increased and remained constant at the 18 mo follow-up.

Bergmane *et al*<sup>[40]</sup> treated seven children with dilated cardiomyopathy with autologous bone marrow cells administered transcutaneously and intramyocardially by subxyphoid needle puncture under echocardiographic guidance. Six of the seven patients showed dramatically

**Table 3** On-going registered clinical studies

Clinical trials. gov ID	Diagnosis	Intervention	Study design	No. of patients to enroll	Age eligible	Status
NCT01504594	Dilated CMP	Intracoronary autologous stem cell infusion	Single Group Assignment	10	1 to 16	Suspended
NCT02256501	CMP	Intracoronary	Randomized	32	1 to 16	Recruiting
NCT02398604	HLHS	intramyocardial injection of allogeneic mesenchymal cells during the Bi-Directional Cavopulmonary Anastomosis	Randomized	30	to 28 d	Study is not yet open
NCT01883076	HLHS	injections of autologous umbilical cord blood cells into the right ventricle of HLHS children undergoing a scheduled Glenn surgical procedure.	Safety Study	10	< 18 mo	Recruiting
NCT01829750	HLHS	efficacy of intracoronary infusion of cardiac progenitor cells in patients with univentricular heart disease	Randomized	34	< 20 yr	Recruiting

HLHS: Hypoplastic left heart syndrome; CMP: Cardiomyopathy.

increased left ventricular ejection fraction at one year after the treatment, paralleled by a decrease in N-terminal proBNP and improved clinical status.

Burkhardt *et al.*<sup>[41]</sup> injected autologous umbilical cord blood-derived cells directly into the right ventricle during a second palliative operation of a child with HLHS. Three months later, the ejection fraction had increased to 45% with a marked decrease in plasma pro-BNP. Ongoing registered clinical studies are listed in Table 3.

## CONCLUSION

Cell-based cardiac regeneration therapy in pediatric patients has led to at least transient improvement of heart function and improvement of heart failure symptoms in a limited number of pediatric patients included in mostly non-randomized studies or case reports.

The majority of pediatric autologous cell transplantations into the cardiac tissue have been performed in critically ill children with severe or terminal heart failure, indicating that at the moment, this treatment strategy is a supplement after standard therapies have been exhausted. Whether specific age groups or those with structural heart diseases may benefit more than others has to be elucidated.

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## Retrospective Cohort Study

**Optimal timing of same-admission orthotopic heart transplantation after left ventricular assist device implantation**

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**Author contributions:** All authors contributed substantially to the study; Gulati G, Ouyang D and Banerjee D designed the research; Gulati G and Ouyang D contributed equally to this work, performed the analysis, interpreted the results, and drafted the manuscript; Ha R and Banerjee D provided clinical advice and supervised the report.

**Institutional review board statement:** The study used de-identified, publicly available data, which does not require evaluation by the Institutional Review Board (IRB).

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**Data sharing statement:** The statistical methods and original anonymous dataset are available on request from the corresponding author at [dipanjan@stanford.edu](mailto:dipanjan@stanford.edu).

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**Abstract****AIM**

To investigate the impact of timing of same-admission orthotopic heart transplant (OHT) after left ventricular assist device (LVAD) implantation on in-hospital mortality and post-transplant length of stay.

**METHODS**

Using data from the Nationwide Inpatient Sample from 1998 to 2011, we identified patients 18 years of age or older who underwent implantation of a LVAD and for whom the procedure date was available. We calculated in-hospital mortality for those patients who underwent OHT during the same admission as a function of time from LVAD to OHT, adjusting for age, sex, race, household income, and number of comorbid diagnoses. Finally, we analyzed the effect of time to OHT after LVAD implantation on the length of hospital stay post-transplant.

**RESULTS**

Two thousand and two hundred patients underwent implantation of a LVAD in this cohort. One hundred and sixty-four (7.5%) patients also underwent OHT during

the same admission, which occurred on average 32 d (IQR 7.75–66 d) after LVAD implantation. Of patients who underwent OHT, patients who underwent transplantation within 7 d of LVAD implantation (“early”) experienced increased in-hospital mortality (26.8% *vs* 12.2%,  $P = 0.0483$ ) compared to patients who underwent transplant after 8 d (“late”). There was no statistically significant difference in age, sex, race, household income, or number of comorbid diagnoses between the early and late groups. Post-transplant length of stay after LVAD implantation was also not significantly different between patients who underwent early *vs* late OHT.

### CONCLUSION

In this cohort of patients who received LVADs, the rate of in-hospital mortality after OHT was lower for patients who underwent late OHT (at least 8 d after LVAD implantation) compared to patients who underwent early OHT. Delayed timing of OHT after LVAD implantation did not correlate with longer hospital stays post-transplant.

**Key words:** Mechanical circulatory support; Orthotopic heart transplant; Bridge to transplant; Left ventricular assist device outcomes

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**Core tip:** The optimal timing of same-admission orthotopic heart transplantation (OHT) after the implantation of a left ventricular assist device (LVAD) is unknown. The need for clinical stability and time to recover from surgery is counterbalanced by the risk of LVAD complications and formation of adhesions and scarring, particularly when OHT is considered early after LVAD implantation. We reviewed adult patients in the Nationwide Inpatient Sample who underwent same-admission OHT after LVAD between 1998 and 2011. Compared to early transplantation after LVAD, OHT after 8 d of LVAD implantation was associated with decreased mortality risk without increased post-transplant length of stay.

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### INTRODUCTION

Heart failure (HF) affects an estimated 5.8 million people in the United States and contributes to over 300000 deaths every year<sup>[1,2]</sup>. It is the most common cause of hospital admission and readmission in people greater than 65 years of age, annually accounting for over 2.4 million hospitalizations<sup>[2,3]</sup> and \$39 billion in healthcare costs<sup>[1,4]</sup>. Although most patients respond favorably to standard medical treatment, a considerable number of

patients progress to end-stage HF refractory to medical therapy<sup>[5]</sup>. Currently, orthotopic heart transplant (OHT) is the gold standard therapy for these patients<sup>[6-8]</sup>, but the number of donor hearts available for transplantation is far fewer than the number of patients on the transplant list. For this reason, left ventricular assist devices (LVADs), a class of electromechanical devices used for cardiac circulatory support, are increasingly being used to bridge patients to cardiac transplantation<sup>[5]</sup>.

The REMATCH trial in 2001 showed significant mortality reductions in patients placed on a pulsatile-flow LVAD compared to standard medical treatment<sup>[9]</sup>. Several subsequent studies since have confirmed the survival benefit of both the older pulsatile and newer continuous-flow LVADs<sup>[10-13]</sup>. Although LVADs have substantially reduced mortality in end-stage HF patients, the absolute mortality rates still remain high. A large portion of this mortality is attributable to complications and other occurrences during the patient’s stay in the hospital<sup>[14]</sup>. In-hospital mortality rates as high as 27% have been reported in patients after LVAD surgery<sup>[15-18]</sup>.

As the rate of LVAD implantation in the United States continues to increase<sup>[19-22]</sup>, effective recommendations for the in-hospital management of LVAD implantation are needed. Although the majority of cardiac transplants performed after LVAD implantation occur after a patient has been discharged from hospital, there is an important cohort of patients who cannot be discharged from hospital post-LVAD implant due to severe right ventricular failure, arrhythmias refractory to oral therapy, and infectious complications. Patients bridged to OHT with a LVAD achieve similar survival rates as patients who undergo direct heart transplant<sup>[14]</sup>, but there is little data to guide clinicians on the optimal timing of same-admission OHT after LVAD implantation. Though patients receiving LVADs may be considered for OHT while still inpatients, some have argued that performing OHT early after LVAD placement poses an increased risk of morbidity and mortality to patients.

Past studies on the appropriate use and outcomes of LVADs have been mostly limited to institutional experience and case series of select populations. While such descriptive investigations are useful, they are often limited by small sample size and variation between institutions and comparison groups. We used the Nationwide Inpatient Sample (NIS), the largest national database of hospitalizations in the United States with data from over 36 million hospitalizations, to assess the optimal timing of OHT after LVAD implantation. The NIS dataset complements the UNOS database and INTERMACS dataset with additional information on patient comorbidities, additional same-hospitalization procedures, hospital and center characteristics, and markers of patient’s socioeconomic status including insurance provider and regional income quartiles. In addition, the NIS dataset contains data on both LVAD and inpatient OHT, which are not simultaneously available in the UNOS or INTERMACS databases.

We analyzed a patient cohort who had OHT performed

during the same admission after LVAD implantation. We hypothesized that early OHT after LVAD implantation would be associated with higher mortality than late OHT, and that the hospital length of stay (LOS) after early OHT would be less than LOS after late OHT.

## MATERIALS AND METHODS

### Data source

The NIS, from the Healthcare Cost and Utilization Project sponsored by the Agency for Healthcare Research and Quality is the largest database of all-payer inpatient discharge information, sampling approximately 20% of all non-federal United States hospitals and including approximately 9 million hospital admissions each year. It contains discharge data from over 5000 hospitals located across 45 states, of which approximately 1200 hospitals are sampled each year to create a stratified sample of United States hospitals. Each NIS entry includes all diagnosis and procedure codes of activity during the patient's hospitalization at the time of discharge, as well as patient demographics, hospital characteristics, and short-term complications of the hospitalization.

### Study design and cohorts

This was a retrospective cross-sectional study using the NIS between 1998 and 2011. We identified all hospitalizations from 1998 to 2011 of patients 18 years of age or older who underwent LVAD implantation and for whom the hospital day of each procedure was available. Procedures during the hospitalization in addition to LVAD placement, including OHT, extracorporeal membrane oxygenation, intubation, hemodialysis, invasive hemodynamic monitoring, and surgical revision were identified by associated ICD9 codes (Supplementary Table 1). Additionally, hospital mortality and perioperative morbidity such as post-operative infections, cardiopulmonary complications, and hemorrhagic complications requiring endoscopy were identified.

### Statistical analysis

The statistical methods of this study were reviewed by Dr. David Ouyang from the Stanford University Department of Medicine. Python 2.7 (Python Software Foundation, [www.python.org](http://www.python.org)) and R 2.13 (R Foundation, [www.r-project.org](http://www.r-project.org)) were used for statistical analysis. *P*-values for numerical and count data were calculated by two-sided *t*-tests and  $\chi^2$  tests, respectively, with significance thresholds of 0.05. The multivariate linear model evaluating post-LVAD OHT mortality was performed using a generalized linear model with input variable selection by Bayesian Information Criteria (BIC). The dependent variable was in-hospital mortality. Independent variables of age, gender, median income, race, number of comorbidities, LVAD era, and timing of OHT were evaluated in the model.

## RESULTS

### Baseline patient characteristics

We identified 2200 patients greater than 18 years of

age between 1998 and 2011 who underwent LVAD implantation and for whom hospital day of procedure was listed (66.4% of all LVAD patients in the NIS database 1998-2011). Comparison of baseline characteristics between this study sample and all LVAD patients in the NIS 1998-2011 database confirmed that our study sample is representative of the entire patient population. The two groups were well matched based on age, sex, household income, prevalence of comorbidities, length of stay, and number of comorbidities, however there were more patients without documented race in the overall group (Supplementary Table 2). The mean age of all patients was 53.4 years (SD = 13.7, range = 18-92 years). Baseline patient demographics, patient comorbidities, and hospital characteristics were well matched between LVAD patients with and without same-admission OHT (Table 1). Most LVAD implantations were performed in large (87.8%), urban (99.1%), teaching hospitals (92.4%). The most common comorbidities were diabetes (17.8%), disorders of lipid metabolism (14.1%), hypertension (13.7%), history of or current use of tobacco (6.5%), and BMI  $\geq$  30 kg/m<sup>2</sup> (4.4%). The mean day of LVAD implantation was 9.4 d (SD = 12.5 d) into the hospitalization. The overall in-hospital mortality rate was 26.8%, with respiratory failure, cardiac dysrhythmias, right HF, and renal failure among the most frequent in-hospital complications immediately following LVAD implantation (Table 2).

Our dataset includes patients from both the pulsatile-flow era (1998-2005) and the continuous-flow era (2006-2011) of mechanical support (Table 3). Comparing the two eras, there was significantly less mortality in the continuous-flow era compared to the pulsatile-flow era (20.4% vs 43.0%; *P* < 0.001) even as patients were older (55.4 years vs 53.2 years; *P* < 0.001) and suffering more comorbid diagnoses (13.5 vs 10.6; *P* < 0.001). During the continuous-flow era, fewer patients received OHT during the same admission as LVAD implantation (3.8% vs 17.3%; *P* < 0.001), and mechanical support was more frequently initiated in large (88.8% vs 85.1%; *P* = 0.002), teaching (94.4% vs 87.1%; *P* < 0.001) institutions. Median household income quartile and race distribution also were different between the two eras, although there was no difference in gender ratio of patients.

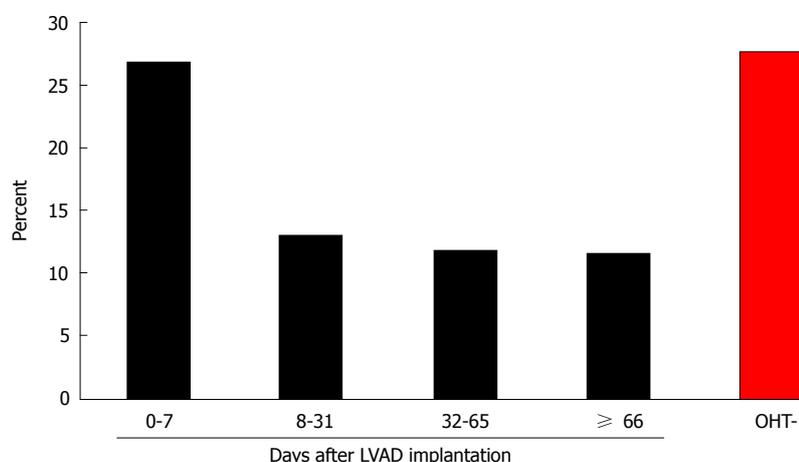
### Timing of post-LVAD OHT

Of the patients who underwent LVAD implantation, 164 (7.5%) also underwent OHT during the same admission. OHT occurred a median of 32 d (IQR 7.75-66 d) after LVAD implantation. Patients who underwent OHT at least 8 d after LVAD implantation experienced significantly lower mortality compared to patients who underwent OHT earlier (26.8% vs 12.2%; *P* = 0.048; Table 1 and Figure 1). Baseline patient demographics, patient comorbidities, and hospital characteristics were similar between the early and late OHT groups. LVAD patients who underwent late OHT also had lower mortality compared to LVAD patients who were not transplanted (12.2% vs 27.0%; *P* < 0.001). However, LVAD patients who underwent early

**Table 1** Baseline demographics for patients who waited 0-7 d, 8-31 d, 32-65 d, and  $\geq 66$  d for an orthotopic heart transplant after left ventricular assist device implantation

	0-7 d (n = 41)	8-31 d (n = 38)	32-65 d (n = 42)	$\geq 66$ d (n = 43)	No OHT (n = 2036)
Length of stay, mean $\pm$ SD	39.3 $\pm$ 33.2	48.9 $\pm$ 25.6	85.8 $\pm$ 40.1	151.2 $\pm$ 52.6	37.1 $\pm$ 34.6
Length of stay after OHT, mean $\pm$ SD	23.8 $\pm$ 21.4	21.7 $\pm$ 15.8	27.6 $\pm$ 37.1	27.1 $\pm$ 22.8	NA
Mortality, n (%)	11 (26.8)	5 (13.2)	5 (11.9)	5 (11.6)	564 (27.3)
Age, mean $\pm$ SD	50.6 $\pm$ 12.6	48.6 $\pm$ 12.7	47.4 $\pm$ 15.3	46.3 $\pm$ 13.1	55.4 $\pm$ 13.2
Sex, n (%)					
Male	33 (80.5)	32 (84.2)	35 (83.3)	34 (79.1)	1525 (74.9)
Female	8 (19.5)	6 (15.8)	7 (16.7)	9 (20.9)	511 (25.1)
Race, n (%)					
White	25 (61.0)	19 (50.0)	23 (54.8)	22 (51.2)	1185 (58.2)
Black	3 (7.3)	5 (13.2)	8 (19.0)	6 (14.0)	330 (16.2)
Hispanic	3 (7.3)	7 (18.4)	2 (4.8)	5 (11.6)	125 (6.1)
Asian/Pacific Islander	2 (4.9)	0 (0.0)	1 (2.4)	4 (9.3)	44 (2.2)
Native American	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (0.2)
Other or unknown	8 (19.5)	7 (18.4)	8 (19.0)	6 (14.0)	347 (17.0)
Median household income, n (%)					
\$1-24999	4 (9.8)	8 (21.1)	8 (19.0)	8 (18.6)	447 (22.0)
\$25000-34999	10 (24.4)	10 (26.3)	10 (23.8)	7 (16.3)	454 (22.3)
\$35000-44999	12 (29.3)	8 (21.1)	10 (23.8)	13 (30.2)	509 (25.0)
\$45000 or more	129 (29.3)	12 (31.6)	14 (33.3)	14 (32.6)	579 (28.4)
Unknown	3 (7.3)	0 (0.0)	0 (0.0)	1 (2.3)	47 (2.3)
Comorbidities					
Diabetes	8 (19.5)	5 (13.2)	4 (9.5)	2 (4.7)	373 (18.3)
Hyperlipidemia	5 (12.2)	2 (5.3)	3 (7.1)	3 (7.0)	297 (14.6)
Hypertension	5 (12.2)	1 (2.6)	2 (4.8)	2 (4.7)	291 (14.3)
History of smoking	5 (12.2)	2 (5.3)	0 (0.0)	0 (0.0)	137 (6.7)
BMI $\geq 30$ kg/m <sup>2</sup>	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	96 (4.7)
No. of comorbid diagnoses, mean $\pm$ SD	11.9 $\pm$ 3.1	12.3 $\pm$ 3.0	12.5 $\pm$ 3.2	12.5 $\pm$ 3.2	12.8 $\pm$ 2.9
Location of hospital, n (%)					
Rural	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	17 (0.8)
Urban	41 (100.0)	38 (100.0)	42 (100.0)	43 (100.0)	2017 (99.1)
Unknown	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)
Size of hospital, n (%)					
Small	4 (9.8)	0 (0.0)	0 (0.0)	2 (4.7)	32 (1.6)
Medium	7 (17.0)	6 (15.8)	5 (11.9)	0 (0.0)	211 (10.4)
Large	30 (73.2)	32 (84.2)	37 (88.1)	41 (95.3)	1791 (88.0)
Unknown	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)
Teaching status of hospital, n (%)					
Nonteaching	1 (2.4)	1 (2.6)	2 (4.8)	1 (2.3)	160 (7.9)
Teaching	40 (97.6)	37 (97.4)	40 (95.2)	42 (97.7)	1874 (92.0)
Unknown	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)

SD: Standard deviation; BMI: Body mass index; LVAD: Left ventricular assist device; OHT: Orthotopic heart transplant.



**Figure 1** Percent in-hospital mortality by quartiles of wait time for orthotopic heart transplant after left ventricular assist device implantation and no orthotopic heart transplant after left ventricular assist device implantation. Percent mortality for each quartile was calculated as number of deaths per quartile by total number of patients per quartile. LVAD: Left ventricular assist device; OHT: Orthotopic heart transplant.

transplant did not experience a similar mortality benefit (26.8% vs 27.0%;  $P = 0.946$ ). The reduced mortality

trend with delayed OHT post-LVAD was observed in both the pulsatile-flow (13.8% vs 36.4%;  $P = 0.081$ )

**Table 2 Complications in hospitalized patients with or without same admission orthotopic heart transplant after left ventricular assist device**

	Early OHT (n = 41)	Late OHT (n = 123)	OHT- (n = 2036)	Total (n = 2200)
Acute renal failure	24 (58.5)	64 (52.0)	963 (47.3)	1051 (47.8)
Reoperation	28 (68.3)	87 (70.7)	803 (39.4)	918 (41.7)
Bleeding requiring transfusion	7 (17.1)	30 (24.4)	780 (38.3)	817 (37.1)
Acute respiratory failure	8 (19.5)	37 (30.1)	518 (25.4)	563 (25.6)
Sepsis	2 (4.9)	17 (13.8)	233 (11.4)	252 (11.5)
Postoperative cardiac complication	7 (17.1)	15 (12.2)	234 (11.5)	256 (11.6)
Acute liver failure	3 (7.3)	9 (7.3)	224 (11.0)	236 (10.7)
Device failure	0 (0.0)	4 (3.3)	62 (3.0)	66 (3.0)
Stroke	1 (2.4)	1 (0.8)	53 (2.6)	55 (2.5)

All pairwise comparisons of early *vs* late OHT were not statistically significant ( $P > 0.05$ ). OHT: Orthotopic heart transplant.

**Table 3 Baseline demographics of all left ventricular assist device patients, left ventricular assist device patients from 1998-2005 (pulsatile-flow era), and left ventricular assist device patients from 2006-2011 (continuous-flow era)**

	All LVADs (n = 2200)	1998-2005 (n = 589)	2006-2011 (n = 1611)	P-value <sup>a</sup>
Mortality, n (%)	590 (26.5)	253 (43.0)	329 (20.4)	< 0.001
Same admission OHT, n (%)	164 (7.5)	102 (17.3)	62 (3.8)	< 0.001
Early same admission OHT, n (%)	41 (25.0)	22 (21.6)	19 (30.6)	0.373
Early same admission OHT mortality, n (%)	11 (26.8)	8 (36.4)	3 (15.8)	0.319
Length of stay after early OHT, mean $\pm$ SD	23.8 $\pm$ 21.4	30.9 $\pm$ 26.0	17.6 $\pm$ 14.3	0.054
Late same admission OHT, n (%)	123 (75.0)	80 (78.4)	43 (69.4)	0.849
Late same admission OHT mortality, n (%)	15 (12.2)	11 (13.8)	4 (9.3)	0.774
Length of stay after late OHT, mean $\pm$ SD	25.6 $\pm$ 26.9	26.1 $\pm$ 22.9	25.4 $\pm$ 29.0	0.883
Length of stay, mean $\pm$ SD	40.5 $\pm$ 38.9	44.7 $\pm$ 48.6	39.0 $\pm$ 34.6	0.008
Age, mean $\pm$ SD	53.4 $\pm$ 13.7	53.2 $\pm$ 13.4	55.4 $\pm$ 13.4	< 0.001
Sex, n (%)				
Male	1659 (75.4)	433 (73.5)	1226 (76.1)	0.23
Female	541 (24.6)	156 (26.5)	385 (23.9)	
Race, n (%)				< 0.001
White	1274 (57.9)	327 (55.5)	947 (58.8)	
Black	352 (16.0)	62 (10.5)	290 (18.0)	
Hispanic	142 (6.5)	28 (4.8)	114 (7.1)	
Asian/Pacific Islander	51 (2.3)	13 (2.2)	38 (2.4)	
Native American	5 (0.2)	1 (0.2)	4 (0.2)	
Other or unknown	376 (17.1)	143 (24.3)	148 (9.2)	
Median household income, n (%)				< 0.001
\$1-24999	475 (21.6)	88 (14.9)	387 (24.0)	
\$25000-34999	491 (22.3)	126 (21.4)	365 (22.7)	
\$35000-44999	552 (25.1)	141 (23.9)	411 (25.5)	
\$45000 or more	631 (28.7)	214 (36.3)	417 (25.9)	
Unknown	51 (2.3)	20 (3.4)	31 (2.4)	
Comorbidities				
Diabetes	391 (17.8)	91 (15.4)	300 (18.6)	0.097
Hyperlipidemia	310 (14.1)	61 (10.4)	249 (15.5)	0.003
Hypertension	309 (14.0)	88 (14.9)	221 (13.7)	0.508
History of smoking	131 (6.0)	29 (4.9)	102 (6.3)	0.257
BMI $\geq$ 30 kg/m <sup>2</sup>	96 (4.4)	12 (2.0)	84 (5.2)	0.002
No. of comorbid diagnosis, mean $\pm$ SD	12.7 $\pm$ 2.9	10.6 $\pm$ 2.9	13.5 $\pm$ 2.5	< 0.001
Location of hospital, n (%)				0.73
Rural	17 (0.8)	5 (0.8)	12 (0.7)	
Urban	2181 (99.1)	583 (99.0)	1598 (99.2)	
Unknown	2 (0.1)	1 (0.2)	1 (0.1)	
Size of hospital, n (%)				0.002
Small	38 (1.7)	20 (3.4)	18 (1.1)	
Medium	229 (10.4)	67 (11.4)	162 (10.1)	
Large	1931 (87.8)	501 (85.1)	1430 (88.8)	
Unknown	2 (0.1)	1 (0.2)	1 (0.1)	
Teaching status of hospital, n (%)				< 0.001
Nonteaching	165 (7.5)	75 (12.7)	90 (5.6)	
Teaching	2033 (92.4)	513 (87.1)	1520 (94.4)	
Unknown	2 (0.1)	1 (0.2)	1 (0.1)	

<sup>a</sup>Pairwise *t*-test or  $\chi^2$  test for patients before 2006 and patients 2006 and afterwards. SD: Standard deviation; BMI: Body mass index; LVAD: Left ventricular assist device; OHT: Orthotopic heart transplant.

**Table 4** A generalized multivariate linear model to evaluate post-left ventricular assist device orthotopic heart transplant mortality (positive estimates reflect positive association with increased mortality)

	Regression coefficient	Standard error	P-value
Age	0.003	0.002	0.158
Female sex	0.071	0.075	0.342
Caucasian race	-0.01	0.027	0.695
Median household income	0.013	0.027	0.638
Number of comorbidities	0.006	0.010	0.518
Years 1998-2005	0.096	0.060	0.113
Early OHT	0.2	0.067	0.004 <sup>a</sup>

<sup>a</sup>P-value < 0.05. OHT: Orthotopic heart transplant.

and continuous-flow eras (9.3% vs 15.8%;  $P = 0.672$ ), although due to small sample numbers in each subgroup, the differences were not statistically significant (Table 2). Multivariate linear model also confirmed the strong association between early OHT after LVAD and in-hospital mortality, independent of patient age, LVAD era, comorbidities, and demographics (Table 4).

Comparing the quartiles of post-LVAD OHT transplant times, there was no statistically significant difference in post-transplant length of stay ( $23.8 \pm 21.4$  d for the first quartile,  $21.7 \pm 15.8$  d for the second quartile,  $27.6 \pm 37.1$  d for the third quartile,  $27.1 \pm 22.8$  d for the fourth quartile;  $P = 0.6571$  comparing first quartile to other quartiles; Table 1). However, as expected, patients who waited longer after LVAD implantation for OHT had longer overall hospital stays ( $39.3 \pm 33.2$  d for the first quartile,  $48.87 \pm 25.6$  d for the second quartile,  $85.8 \pm 40.1$  d for the third quartile,  $151.2 \pm 52.6$  d for the fourth quartile;  $P < 0.001$  comparing first quartile to other quartiles; Table 1).

## DISCUSSION

Our study addresses the difficult question of timing of same-admission OHT after LVAD implantation. Using the inpatient data on procedure timing from the NIS 1998-2011, we show that mortality risk significantly decreases in patients who undergo OHT at least 8 d after LVAD implantation. We also report that post-transplant length of stay is independent of the timing of OHT after LVAD.

For patients who receive an LVAD for bridge to transplant therapy (BTT), the optimal timing of post-LVAD OHT is controversial. The need for clinical stability and time to recover from major surgery is counterbalanced by the risk of LVAD complications and the formation of adhesions and scarring, particularly when OHT is considered early after LVAD implantation.

The high failure rate of the early, pulsatile-flow LVADs had in part led to the initial 1999 UNOS allocation algorithm giving LVAD patients 30 d of IA status on the transplant list. The elective nature of the 30-d IA status allows for optimization of management prior to transplant and suggests the time period immediately post-mechanical support is often not the optimal time for transplant. Our data showing that delaying post-

LVAD transplant can lead to superior outcomes is consistent with the excellent long term outcomes of BTT mechanical support, pushing some groups to question the justification of elective IA status<sup>[23]</sup>.

Our study, using a large national database, solidifies and extends previous findings that early transplantation after initiation of BTT mechanical support is associated with worse outcomes. In the pulsatile-flow era of LVAD, John *et al*<sup>[24]</sup> (2010) had shown that cardiac transplants done less than 6 wk after LVAD confer higher mortality risk in patients, and Gammie *et al*<sup>[25]</sup> (2003) and Ashton *et al*<sup>[26]</sup> (1996) have similarly reported optimal timing to be 2 wk after LVAD implantation. With the advantage of procedural timing data of patients who underwent same admission LVAD implantation and transplant, we add to those findings by showing there is an increased mortality associated with early same-admission transplant after LVAD in the continuous flow era.

During the study period between 1998 and 2011, there was a significant increase in the number of LVAD implantations, but patient characteristics of this population - including timing of LVAD, usage of invasive hemodynamic monitoring, and timing of post-LVAD OHT - has remained relatively unchanged. Our sample patient population is representative of LVAD patients studied in other databases with regards to age, gender, race, and other demographic characteristics and also mortality trends between the pulsatile and continuous-flow eras. Without randomized control trials to better characterize the optimal management and timing of transplant after LVAD, our study describes representative clinical practice and trends in outcomes associated with changing practice patterns.

Our study has a few limitations. First, the NIS is a deidentified administrative database dependent on the appropriate coding of individual ICD-9-CM codes. Studies using such databases are susceptible to errors related to coding such as undercoding complications or variation in the application of diagnostic codes. This database also lacks many details available in registries, and unmeasured confounders cannot be excluded. Additionally, the NIS only captures events during the hospitalization, so complications and adverse events after discharge are not recorded. This limitation is counterbalanced by the larger sample size relative to other studies and the absence of reporting bias as compared to studies relying upon the

institutional experiences from a few specialized centers. Additionally, patients who undergo LVAD implantation have long hospital stays that capture most, if not all, of the acute complications causing morbidity and mortality. Finally, the ability of the NIS to capture detailed LVAD implantation and OHT data provided advantages in answering our central question over either the INTERMACS or UNOS databases, which capture largely LVAD or transplant data, respectively.

It is important to note that our cohort only assessed outcomes of OHT after LVAD placement in hospitalized patients. This represents a minority of patients (7.5%) in practice, as most institutions prefer to wait 2-3 mo after LVAD implantation to list patients for cardiac transplantation. Nevertheless, there will continue to be patients in the future who receive same-admission OHT after LVAD implantation, and our study provides meaningful guidelines on the timing of such OHT.

In conclusion, our analysis suggests that delayed same-admission OHT after LVAD implantation decreases mortality risk without increasing post-transplant length of stay, and, therefore, may be the preferred option in such a clinical setting. This new understanding of the optimal timing of same-admission OHT after LVAD implantation can greatly improve patient outcomes, although prospective data will be needed to enhance the validity of our findings.

## COMMENTS

### Background

Heart failure (HF) affects an estimated 5.8 million people in the United States and contributes to over 300,000 deaths every year. Although most patients respond favorably to standard medical treatment, a considerable number of patients progress to end-stage HF refractory to medical therapy. Orthotopic heart transplant (OHT) is currently the gold standard therapy for these patients, but the number of donor hearts available for transplantation is far fewer than the number of patients on the transplant list. For this reason, left ventricular assist devices (LVADs), a class of electromechanical devices used for cardiac circulatory support, are increasingly being used to bridge patients to OHT. The optimal timing of when patients with LVADs should be bridged to OHT is an important consideration for patient care and has yet to be characterized.

### Research frontiers

As the rate of LVAD implantation in the United States continues to increase, effective recommendations on the in-hospital management of LVAD implantation are needed. The optimal timing of when to bridge patients with LVADs to OHT remains controversial and is an active area of research.

### Innovations and breakthroughs

Few groups have studied the impact of timing of same-admission OHT after LVAD on patient outcomes. Past studies on the appropriate use and outcomes of LVADs have been mostly limited to institutional experience and case series of select populations. The authors used the Nationwide Inpatient Sample (NIS), the largest national database of hospitalizations in the United States with data from over 36 million hospitalizations, to assess the optimal timing of OHT after LVAD implantation. It has been suggested that performing OHT early after LVAD placement confers an increased risk to patient. The study corroborates these claims and concludes that early OHT after LVAD placement (less than 8 d) is associated with increased in-hospital mortality. Therefore, depending on the clinical scenario, it might be reasonable for physicians to defer OHT immediately after LVAD placement.

### Applications

This study offers recommendations for cardiologists and cardiac surgeons on the optimal timing of same-admission OHT after LVAD implantation. It also summarizes the demographics and characteristics of LVAD and post-LVAD OHT patients in the United States.

### Terminology

Left ventricular assist device (LVAD): A class of electromechanical devices that help the left ventricle pump blood to the rest of the body; Orthotopic heart transplant (OHT): A procedure in which the patient's heart is removed and replaced with a donor heart.

### Peer-review

Very interesting and clinically relevant question with novel use of the NIS database. Overall well written with interesting findings.

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## Clinical Trials Study

**Consumption of energy beverage is associated with attenuation of arterial endothelial flow-mediated dilatation**

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**Abstract****AIM**

To investigate whether consumption of an energy drink will acutely impair endothelial function in young healthy adults.

**METHODS**

Energy drinks are being consumed more and more worldwide, and have been associated with some deaths in adolescents and young adults, especially when consumed while exercising. After fasting and not smoking for at least 8 h prior, eleven medical students (9 males) received an electrocardiogram, blood pressure and pulse check, and underwent baseline testing (BL) of endothelial function using the technique of endothelium-dependent flow mediated dilatation (FMD) with high-resolution ultrasound

(according to recommended guidelines of the University of Wisconsin Atherosclerosis Imaging Research Program Core Laboratory). The subjects then drank an energy beverage (EB), a 24-oz can of Monster Energy, and the above was repeated at 90 min after consumption. The relative FMD (%) was calculated as the ratio between the average post-cuff release and the baseline diameter. Each image was checked for quality control, and each artery diameter was measured from the media to media points by two experts, 3 measurements at the QRS complex, repeated on 3 separate beats, and then all were averaged.

## RESULTS

Subjects characteristics averages (given with standard deviations) include: Age  $24.5 \pm 1.5$  years, sex 9 male and 2 female, weight  $71.0 \pm 9.1$  kg, height  $176.4 \pm 6.0$  cm, BMI  $22.8 \pm 2.7$  kg/m<sup>2</sup>. The hemodynamics were as follows, BL *vs* EB group respectively (mean  $\pm$  SD): Heart rate  $65.2 \pm 11.3$  *vs*  $68.2 \pm 11.8$  beats per minute, systolic blood pressure  $114.0 \pm 10.4$  mmHg *vs*  $114.1 \pm 10.4$  mmHg, diastolic blood pressure  $68.8 \pm 9.3$  mmHg *vs*  $70.6 \pm 7.1$  mmHg; all were not significantly different. However after drinking the EB, a significantly attenuated peak FMD response was measured (mean  $\pm$  SD): BL group  $5.9\% \pm 4.6\%$  *vs* EB group  $1.9\% \pm 2.1\%$ ;  $P = 0.03$ ). Given the increased consumption of energy beverages associated with exercise in young adults, more research is needed.

## CONCLUSION

Energy beverage consumption has a negative impact on arterial endothelial function in young healthy adults.

**Key words:** Energy drinks; Endothelial function; Exercise; Flow mediated dilatation; Blood pressure

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**Core tip:** Energy drinks are being consumed worldwide, and are gaining in popularity, especially amongst youth. We studied the acute effects that one energy drink has on endothelial function, a measure of vascular health. We found that consumption of a single 24-oz can of Monster Energy resulted in attenuation of brachial artery endothelium-dependent flow mediated dilatation in 11 healthy volunteers.

Higgins JP, Yang B, Herrin NE, Yarlaga S, Le GT, Ortiz BL, Ali A, Infanger SC. Consumption of energy beverage is associated with attenuation of arterial endothelial flow-mediated dilatation. *World J Cardiol* 2017; 9(2): 162-166 Available from: URL: <http://www.wjgnet.com/1949-8462/full/v9/i2/162.htm> DOI: <http://dx.doi.org/10.4330/wjc.v9.i2.162>

## INTRODUCTION

Energy beverages are being consumed increasingly

worldwide, and have been associated with deaths in adolescents and young adults, especially when consumed while exercising<sup>[1]</sup>.

What effect these energy drinks have on endothelial cells could help explain its effect on the cardiovascular system. These cells are part of the inner lining of blood vessels and have metabolic and also synthetic functions<sup>[2]</sup>. When endothelial cells are functioning abnormally or "endothelial dysfunction", it is associated with poor vascular reactivity, pro-thrombosis, pro-adhesion, pro-inflammation, and growth promotion<sup>[1,3]</sup>.

Several recent reviews on cardiovascular complications associated with energy drink consumption suggest that the impact on endothelial function could be a factor in subsequent cardiac events<sup>[1,4]</sup>. Some of their ingredients individually or in combination may be associated with reduced endothelial function<sup>[5-7]</sup>.

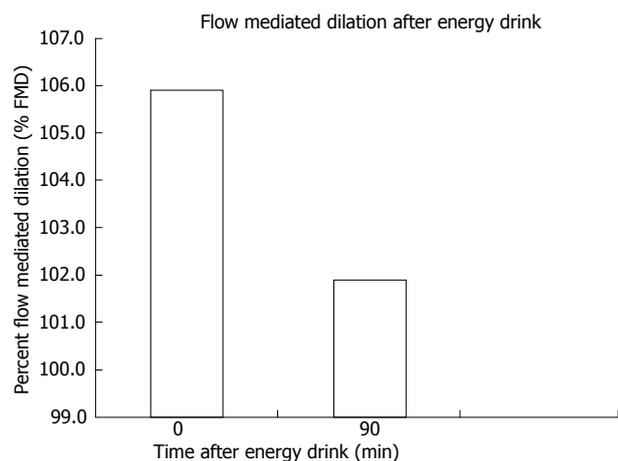
Mechanistically, endothelial dysfunction, where the endothelium's ability in regulating vascular resistance is impaired, may be related to reduced coronary blood flow<sup>[6,8]</sup>. Following exposure to stress such as exposure to cold, mental arithmetic, anger, exercise, cigarette smoking, cocaine, excess food or alcohol, the impaired ability to dilate the coronary arteries could result in supply-demand imbalance or coronary spasm, potentially leading to myocardial ischemia, coronary vasospasm, thrombosis and/or cardiac arrhythmia<sup>[6,9]</sup>. Importantly, this acute endothelial dysfunction could lead to ischemia, which in turn could lead to serious arrhythmia, coronary vasospasm, and myocardial infarction<sup>[1,6,10]</sup>.

This study describes the acute changes of normal endothelial function after consumption of a single can of a popular energy drink<sup>[11]</sup>.

## MATERIALS AND METHODS

After fasting from caffeine for at least 24 h and food for at least 8 h prior, eleven healthy non-smoker medical students (9 males), average age 24.5 years (range 23-27 years), average BMI 22.8, received an electrocardiogram (ECG), blood pressure and pulse check, and underwent baseline testing (BL) of endothelial function using the technique of endothelium-dependent flow-mediated dilatation (FMD) with high-resolution ultrasound according to recommended guidelines of the University of Wisconsin Atherosclerosis Imaging Research Program Core Laboratory by a single registered vascular ultrasonographer who was certified by the University of Wisconsin Atherosclerosis Imaging Research Program Core Laboratory<sup>[12]</sup>.

After resting supine for 10-min in a temperature-controlled room, a blood pressure cuff was placed on the widest part of proximal right forearm approximately 1 cm distal to the antecubital fossa. Using a 10 MHz resolution linear array vascular ultrasound transducer with a Philips iE33 ultrasound machine, the brachial artery was located above the elbow and scanned in longitudinal sections. After recording baseline B-mode digital images of the brachial artery and spectral Doppler images of



**Figure 1** Flow mediated dilation at baseline (0 min) and after energy drink (90 min). Consumption of the EB resulted in a significantly attenuated peak FMD response (mean  $\pm$  SD): BL group 5.9%  $\pm$  4.6% vs EB group 1.9%  $\pm$  2.1%;  $P = 0.03$ . FMD: Flow mediated dilatation; BL: Baseline testing; EB: Energy beverage.

flow, the forearm cuff was inflated to 250 mmHg for 5 min to induce reactive hyperemia. Immediately after deflation, spectral Doppler images are obtained to verify hyperemia. FMD of the brachial artery was measured 60 and 90 s after cuff deflation. The relative FMD (%) was calculated as the ratio between the largest post-cuff release and the baseline diameter. Each image was checked for quality control, and each artery diameter was measured from the media to media points by two experts, 3 measurements at the QRS complex, repeated on 3 separate beats, and then averaged.

The subjects then drank an energy beverage (EB), a 24-oz can of Monster Energy Drink<sup>®</sup> in approximately 1 min. The contents of this can include 54 g Sucrose, glucose, sucralose, maltodextrin, Sodium 360 mg Sodium Citrate Sodium Chloride, Caffeine 240 mg, Taurine 2000 mg, Niacin 40 mg 200% RDA Niacinamide, Pyridoxine 4 mg 200% RDA, Cyanocobalamin (B12) 12 mcg 200% RDA, Riboflavin (B2) 3.4 mg 200% RDA, Ginseng Extract 400 mg, Glucuronolactone, Inositol (B8), Guarana Extract, and L-Carnitine all listed as a part of a 5000 mg "Energy Blend", and Sodium Benzoate.

The subjects had FMD repeated at 90 min after consumption of the EB. The subjects were in the supine position for all ECGs and FMD measurements.

### Statistical analysis

Statistical analyses were performed by John P Higgins and the statistical methods of this study were reviewed by Benjamin Yang using Microsoft Excel 2010 and the Data Analysis ToolPak. We used the *t*-test: Paired Two Sample for Means, and significance was defined as a *P*-value of 0.05 or less.

## RESULTS

Subjects characteristics averages (given with standard deviations) include: Age 24.5  $\pm$  1.5 years, sex 9 male

and 2 female, weight 71.0  $\pm$  9.1 kg, height 176.4  $\pm$  6.0 cm, BMI 22.8  $\pm$  2.7 kg/m<sup>2</sup>.

The hemodynamics were as follows, BL vs EB group respectively (mean  $\pm$  SD): Heart rate 65.2  $\pm$  11.3 vs 68.2  $\pm$  11.8 beats per minute, systolic blood pressure 114.0  $\pm$  10.4 mmHg vs 114.1  $\pm$  10.4 mmHg, Diastolic blood pressure 68.8  $\pm$  9.3 mmHg vs 70.6  $\pm$  7.1 mmHg; all were not significantly different.

With drinking the energy beverage, a significantly attenuated peak FMD response was found (mean  $\pm$  SD): BL group 5.9%  $\pm$  4.6% vs EB group 1.9%  $\pm$  2.1%;  $P = 0.03$  (Figure 1).

## DISCUSSION

There are few studies exploring the effects on endothelial function following consumption of energy drinks.

In one study, fifty healthy volunteers (34 male, aged 22  $\pm$  2 years) consumed either a 250-mL sugar-free energy drink or 250 mL carbonated water (control)<sup>[13]</sup>. They found that an hour after consumption of an energy drink, there was an acute decreased in endothelial function and increased platelet aggregation<sup>[7,13]</sup>.

Another study involving 25 healthy young adults (13 male, aged 22.5  $\pm$  0.6 years) who consumed either 355-mL Red Bull or 355-ml tap water noted that 2 h later, while blood pressure, heart rate and cardiac output were significantly increased, there was no reduction in endothelial function *via* finger skin microcirculation<sup>[14]</sup>.

A 47-year-old healthy Caucasian male was noted to have a progressive attenuation of peak flow-mediated dilatation at 45 and 90 min following consumption of a 24-oz can of Monster Energy Drink<sup>®</sup><sup>[7]</sup>.

Energy drinks likely increase myocardial oxygen demand, and this may be increased under stress. For example, one study has noted that the combination of Red Bull and mental stress results in greater increases in heart rate and blood pressure, *i.e.*, a greater cardiovascular load<sup>[15]</sup>.

While our study has noted a change in endothelial function after consumption of energy drinks, which is consistent with some of the previous studies, it still however conflicts with other studies. A possible explanation for these contrasting results on endothelial function, blood pressure, and heart rate in response to energy drinks include difference in methods of assessing endothelial function, difference in methods of monitoring blood pressure, difference in types of energy drinks consumed, difference in study participant profiles, and varying environmental stimuli<sup>[15,16]</sup>. Further investigations should take in account these differences, and also investigate how energy drink consumption in stress conditions affect endothelial function, as it would help simulate conditions in which energy drinks are used in real-life.

Weaknesses of our study include the fact that human measurement was performed on the arterial segments, which may be less accurate than automated detection methods. However one study analyzing variability and

reproducibility of FMD found that the mean absolute difference in %FMD from baseline FMD assessment was 1.04% and 0.99% for short-term (48 h) and medium-term (3 mo) repeat measurements, respectively<sup>[17]</sup>. Potential improvements in the future include a water load as a control, and having FMD baseline measurements performed on one day, followed by the FMD measurements with energy beverage consumption on the next day. In addition, this was a small sample, and such medical student volunteers may be healthier than the normal population.

Consumption of energy drinks may lead to an acute attenuation of endothelial function. Given the popularity of energy drinks, especially among youth, the combination of their consumption and exercise/extreme sports, and the rise in emergency room visits associated with their consumption, it is important that the specific physiological effects they are having be elucidated. Due to the potential endothelial dysfunction that may occur with energy drinks and the potential morbidity when consumed with exercise, further research is needed to explore these mechanisms and significance of their effects.

## COMMENTS

### Background

Energy drinks are being consumed more and more worldwide, and have been associated with deaths in adolescents and young adults, especially when consumed while exercising. Adverse cardiovascular events can be caused by abnormal endothelial cell function or "endothelial dysfunction". Endothelial cells form the inner lining of blood vessels and have metabolic as well as synthetic functions, which allow them to carry out multiple important tasks such as regulating vascular resistance. Mechanistically, reduced coronary blood flow may be a symptom of endothelial dysfunction, and is associated with poor vascular reactivity, pro-thrombosis, pro-adhesion, pro-inflammation, and growth promotion.

### Research frontiers

There is a paucity of studies describing the effects on endothelial function following consumption of energy drinks. Several recent reviews on cardiovascular complications associated with energy drink consumption suggest that effects on endothelial function may play a role in subsequent cardiac events. Some of their ingredients individually or in combination may be associated with reduced endothelial function.

### Innovations and breakthroughs

The current study describes the acute changes of normal endothelial function following consumption of a single can of a popular energy drink. While the study has noted a change in endothelial function after consumption of energy drinks, which is consistent with some of the previous studies, it still however conflicts with other studies. A possible explanation into these contrasting results on endothelial function, blood pressure, and heart rate in response to energy drinks include a difference in study methods and energy drink types. Further investigations should take in account these differences, and also investigate how energy drink consumption in stress conditions affect endothelial function, as it would help simulate conditions in which energy drinks are used in real-life.

### Applications

Consumption of energy drinks may lead to an acute attenuation of endothelial function. Given the popularity of energy drinks, especially among youth, the combination of their consumption and exercise/extreme sports, and the rise in emergency room visits associated with their consumption, it is important that

the specific physiological effects they are having be elucidated. Further, due to the possibility that endothelial dysfunction may play a role in morbidity with concomitant energy drink intake and exercise, more research is recommended to clarify the mechanisms of and significance of these effects.

### Terminology

Energy drinks are also known as energy beverages. Popular brand names include Monster Energy Drink® and Red Bull Energy Drink® that contain high caffeine content, along with other ingredients. Flow-mediated dilatation is a non-invasive technique using high-resolution ultrasound to assess a vessel's endothelium-dependent (nitric oxide release) vasomotor function.

### Peer-review

In this study, Dr. Higgins and his colleagues have done a very interesting investigation even though the report is very brief. They show a significant result that one kind of the "energy beverage" is associated with endothelial dysfunction. The study is well designed and outcome is enough to warn the lovers of those drinks.

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## Observational Study

**Critical analysis of ineffective post implantation implantable cardioverter-defibrillator-testing**

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**Author contributions:** All the authors contributed to the manuscript.**Institutional review board statement:** Data were assessed for quality assurance. Retrospective analysis of these data is accepted without the approval of a review board in our institution.**Informed consent statement:** Patient's agreement with retrospective analysis of their data is included in the initial agreement on admission to the hospital. There is no informed consent statement for this retrospective analysis of patients file.**Conflict-of-interest statement:** No conflicts of interests of any of the authors have to be declared.**Data sharing statement:** No additional data are available.**Open-Access:** This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>**Manuscript source:** Invited manuscript**Correspondence to:** Markus Roos, MSc, MD, Heart Center, Salzburger Leite, 97616 Bad Neustadt a.d. Saale, Germany. [roosmarkus@bluewin.ch](mailto:roosmarkus@bluewin.ch)  
**Telephone:** +49-9771-662602  
**Fax:** +49-9771-65982602**Received:** August 8, 2016**Peer-review started:** August 8, 2016**First decision:** September 12, 2016**Revised:** October 30, 2016**Accepted:** November 27, 2016**Article in press:** November 29, 2016**Published online:** February 26, 2017**Abstract****AIM**

To test of the implantable-cardioverter-defibrillator is done at the time of implantation. We investigate if any testing should be performed.

**METHODS**

All consecutive patients between January 2006 and December 2008 undergoing implantable cardioverter-defibrillator (ICD) implantation/replacement (a total of 634 patients) were included in the retrospective study.

**RESULTS**

Sixteen patients (2.5%) were not tested (9 with LA/LV-thrombus, 7 due to operator's decision). Analyzed were 618 patients [76% men, 66.4 ± 11 years, 24% secondary prevention (SP), 46% with left ventricular ejection fraction (LVEF) < 20%, 56% had coronary artery disease (CAD)] undergoing defibrillation safety testing (SMT) with an energy of 21 ± 2.3 J. In 22/618 patients (3.6%) induced ventricular fibrillation (VF) could not be terminated with maximum energy of the ICD. Six of those (27%) had successful SMT after system modification or shock lead repositioning, 14 patients (64%) received a subcutaneous electrode array. Younger age ( $P = 0.0003$ ), non-CAD ( $P = 0.007$ ) and VF as index event for SP ( $P = 0.05$ ) were associated with a higher incidence of ineffective SMT. LVEF < 20% and incomplete revascularisation in patients with CAD had no impact on SMT.

**CONCLUSION**

Defibrillation testing is well-tolerated. An ineffective SMT occurred in 4% and two third of those needed implantation of a subcutaneous electrode array to pass

a SMT > 10 J.

**Key words:** Implantable cardioverter defibrillator; Implantable cardioverter-defibrillator; Sudden cardiac death; Defibrillation test; Safety margin test; Ventricular fibrillation; Subcutaneous electrode array

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**Core tip:** The implantable cardioverter defibrillator is crucial for primary and secondary prevention of severe life-threatening ventricular tachyarrhythmia. However the importance concerning intra-operative defibrillation testing and clinical relevance of inadequate testing of implantable cardioverter-defibrillator (ICD) devices remains still under debate. In this study, we analyzed our single-center data of patients undergoing ICD implantation or replacement to determine the number of failed internal defibrillation testing at the time of ICD implantation and the consequences for management. We critically reflect the progressive trend to omit defibrillation testing at the time of ICD placement.

Roos M, Geller JC, Ohlow MA. Critical analysis of ineffective post implantation implantable cardioverter-defibrillator-testing. *World J Cardiol* 2017; 9(2): 167-173 Available from: URL: <http://www.wjgnet.com/1949-8462/full/v9/i2/167.htm> DOI: <http://dx.doi.org/10.4330/wjc.v9.i2.167>

## INTRODUCTION

The implantable cardioverter defibrillator (ICD) is widely accepted for primary<sup>[1,2]</sup> and secondary prevention<sup>[3,4]</sup> of severe life-threatening ventricular tachyarrhythmia. The Heart Rhythm Society updated appropriate use criteria for ICD therapy<sup>[5]</sup>, however the importance concerning intra-operative defibrillation testing and clinical relevance of inadequate testing of ICD devices remains still under debate<sup>[6-10]</sup>.

One limitation of recent observational studies is a bias against testing in patients with more severe illness who are felt to be at increased risk for complications during intra-operative defibrillation testing<sup>[11-14]</sup>. Although severely impaired left ventricular function predicts higher intra-operative defibrillation threshold<sup>[8,15,16]</sup>, patient with lower left ventricular ejection fraction (LVEF) are less likely<sup>[11-14]</sup> or even excluded<sup>[17]</sup> to undergo intra-operative defibrillation testing. Furthermore, severe, non revascularized coronary artery disease (CAD) is described as an absolute or relative contraindication for intra-operative defibrillation testing<sup>[15,18,19]</sup> and were less likely to undergo such testing in recent studies<sup>[12,14,16,19]</sup> although these patients would probably benefit most from an adequate defibrillation threshold.

We analyzed all consecutive patients between January 2006 and December 2008 undergoing ICD im-

plantation or replacement to determine the number of failed internal defibrillation testing at the time of ICD implantation and the consequences for management. Our study extends the existing literature by also including patients excluded in previous studies. We critically reflect the progressive trend to omit defibrillation testing at the time of ICD placement<sup>[9,10,14]</sup>.

## MATERIALS AND METHODS

All consecutive patients undergoing initial ICD implantation or generator replacement from January 2006 to December 2008 were analyzed in this retrospective, single-center analysis.

Devices of all 4 important international companies were implanted. They were implanted in the catheter laboratory by 5 experienced cardiologists. In all patients, adequate ventricular sensing (> 9 mV) and pacing threshold (< 1 V) was confirmed. In the absence of absolute contraindications [e.g., left atrial appendage (LAA) or left ventricular (LV) thrombus], intra-operative ICD testing was routinely performed to confirm correct sensing, processing, shock delivery and termination of T-wave shock-induced VF. Our protocol for intra-operative ICD testing required at least one induction of VF with successful first shock terminating VF at a safety margin of at least 10 Joule (J) below the maximum output of the implanted device. If the first shock was not successful, a second shock at the maximum output of the device was delivered. In case this shock was still not successful, external defibrillation with a 360 J biphasic shock was performed. Patients with the need of a second shock at the maximum output or external defibrillation in order to terminate VF were considered as ineffective safety margin testing (SMT) and were included in our study. Further management of these patients included intra-operative right ventricular lead reposition or ICD-system modification such as addition or subtraction of the superior vena cava (SVC) shock coil and polarity reversal, respectively. In case the SMT was still ineffective, the implantation of a subcutaneous electrode array, considered to be the most effective method for reducing defibrillation threshold<sup>[20]</sup>, was planned.

Clinical characteristics, the consecutive management of pts with ineffective SMT and follow up data were explored by reviewing the medical records. Biplane left ventricular ejection fraction (LVEF) was derived by echocardiography and all measurements were done or supervised independently by an experienced cardiologist specialized in echocardiography. According to our center's standard practice, all patients underwent coronary angiography prior to ICD placement, ascertaining a definite coronary status. The implanted subcutaneous electrode array was solely a Medtronic 6996SQ.

### Statistical analysis

Descriptive data were reported as frequencies, means and standard deviations or median and interquartile

range, respectively. Two-sided *t*-tests for independent samples were used for continuous variables.  $\chi^2$  analysis was used to compare categorical variables and one-way analysis of variance (ANOVA) was used to compare continuous variables. All statistics were computed with SPSS software (SPSS Inc, Chicago, Illinois). All probability values are 2-sided, with values of  $< 0.05$  considered significant.

## RESULTS

### **Patient characteristics**

From 634 analyzed patients, 16 (2.5%) had no intra-operative defibrillation testing (9 patients (1.4%) due to LV- or LAA-thrombus and 7 (1.1%) due to decision of the operator (mainly atrial fibrillation with ineffective oral anticoagulation). Included in this retrospective analysis were 618 consecutive patients who received defibrillation testing after transvenous ICD implantation or ICD replacement. The population is described in Table 1. LVEF was  $\leq 20\%$  in 284 patients (46%). The indications for ICD placement included primary (76%) as well as secondary prevention (24%). The index arrhythmia for secondary prevention was sustained ventricular tachycardia (VT) in 72% and ventricular fibrillation (VF) in 28%, respectively. Patients with coronary artery disease (CAD) were further divided in those completely revascularized (56%) and those with residual significant stenoses  $> 70\%$  or a central occluded main vessel, respectively (29% and 15%, respectively). Further on we distinguished whether one (36%) or more than one main vessel (8%) was not completely revascularized. Patients with the diagnosis of a non-ischemic cardiomyopathy were subdivided whether they suffered from post myocarditis dilated cardiomyopathy (DCM) or from other types of cardiomyopathy (e.g., ARVD, LV non-compaction, HOCM, primary channelopathy).

### **Results of intra-operative defibrillation testing**

Effective defibrillation SMT was performed in 596 patients (96.4%) with a mean energy of  $20.8 \pm 2.3$  J. In 22 patients (3.6%) induced VF could only be terminated with the maximum energy of the implanted device or with an external defibrillation (Table 1). There were no severe complications (death, major or minor strokes or cardiogenic shock) in any of the 618 SMT performed.

In 22 patients (3.6%) a  $> 10$  J SMT could not be achieved intra-operatively with the initial ICD configuration. The patients with ineffective SMT were younger ( $P = 0.003$ ), and in univariate analysis they were less likely to have CAD as underlying diagnosis ( $P = 0.007$ ) or VT as the index arrhythmia ( $P = 0.05$ ) for secondary ICD indication (Table 1).

Variables without impact on the efficiency of SMT in univariate analysis included whether or not patients had a LVEF  $< 20\%$ , had a secondary preventive indication for ICD, were incompletely revascularized, had more than one main coronary vessel significantly diseased and were

taking amiodarone, respectively (Table 1).

### **Management of patients with ineffective initial SMT**

The characteristics of the patients with ineffective SMT are depicted in Table 2. One or more of the following system modifications were initiated: Reprogramming the defibrillation polarity in 21 and deactivation of the SVC shock coil in 19 patients as well as repositioning the right ventricular lead in 12 patients. Six patients (27%) passed subsequent SMT, 16 patients had still ineffective SMT and were planned for a subcutaneous electrode array. Two patients refused further procedures and in the remaining 14 patients an adequate SMT  $> 10$  J was documented post implantation of a subcutaneous electrode array.

### **Tachyarrhythmia events during follow up**

The mean follow up was 23.6 (+21) mo for patients with initially effective SMT and 15.8 (+21) mo for those with initially ineffective SMT. Antiarrhythmic medication was equally balanced between both groups (Table 3). In general, there were significantly more events in patients with CAD (19.6%) compared to patients with non CAD (12.1%)  $P = 0.02$ . There was a trend towards more events in patients with secondary prophylactic ICD indication ( $P = 0.08$ ). No death or resuscitation occurred during the follow-up period, and 124/530 patients (23.4%) with initial effective SMT and 2/22 patients (9.1%) with initially ineffective SMT ( $P = 0.02$ ) experienced tachyarrhythmia events (Table 3).

## DISCUSSION

We analyzed a very large population undergoing intra-operative ICD defibrillation testing<sup>[6]</sup>, including a significant group of patients (284 patients, 46% of total) with an LVEF  $< 20\%$ , a patient group that was unlikely undergoing intra-operative ICD testing<sup>[11-14,16]</sup> or was even excluded from former studies<sup>[17]</sup>.

Our data show several important findings: (1) Ineffective SMT occurred in roughly 4% of ICD implantations. Despite ICD-System reprogramming as well as RV shock lead repositioning, two thirds of those required implantation of a subcutaneous electrode array to pass a SMT  $> 10$  J; (2) SMT can be performed safely and without major complications, even in patients with an LVEF  $< 20\%$ . There was no impact on the efficacy of SMT compared to patients with an LVEF  $> 20\%$ ; (3) Severe coronary 2 or 3 vessel disease with residual significantly stenosed/occluded main vessels showed no impact on safety and efficacy of SMT; and (4) The percentage of patients who are unsuitable for intra-operative defibrillation testing is small (2.5% of our study population).

### **Ineffective intra-operative safety margin testing**

Despite advancements during the last years in ICD systems and lead technology resulting in enhanced defibrillation efficacy, 4% in our patient population failed to

**Table 1 Baseline characteristics**

	All	Effective SMT	Ineffective SMT	P-value
Number, n (%)	618	596 (96.3)	22 (3.7)	
Sex				
Male, n	470	452	18	
Female, n	148	144	4	
Age (years)				
Mean (± SD)	66.4 (± 11)	66.7 (± 10.6)	54.6 (± 16.5)	P = 0.0003
Median (IQR)	69 (60-74)	69 (62-74)	54 (41-69)	
LVEF (%)				
Mean (± SD)	31 (± 12.4)	31 (± 12.5)	26.9 (± 9.0)	P = n.s.
Median (IQR)	30 (22-35)	30 (23-35)	30 (20-35)	
LVEF > 30%, n (%)	248 (40.1)	240 (36.9)	8 (3.2)	
LVEF < 30%, n (%)	370 (59.9)	356 (56.1)	14 (3.8)	P = n.s. (> 30% vs < 30%)
LVEF > 20%, n (%)	334 (54.0)	320 (49.8)	14 (4.2)	
LVEF < 20%, n (%)	284 (46)	276 (43.2)	8 (2.8)	P = n.s. (> 20% vs < 20%)
BMI (kg/m <sup>2</sup> )				
Mean (± SD)	28.4 (± 4.7)	28 (± 4.7)	29 (± 4.0)	P = n.s.
Median (IQR)	28 (17-28)	28 (25-31)	29 (25.5-33)	
Indikation				
Primary prevention, n (%)	468 (76)	452 (72.6)	16 (3.4)	
Secondary prevention, n (%)	150 (24)	144 (20)	6 (4.0)	P = n.s. (pp vs sp)
Type of arrhythmia for secondary prevention, n (%)				
Sustained VT	108 (72)	106 (70.1)	2 (1.9)	
VF	42 (28)	38 (18.1)	4 (9.5)	P = 0.05 (VT vs VF)
SMT-Energy (J)				
Mean (± SD)	21 (± 2.3)	20.8 (± 2.3)	30.9 (± 2.0)	
Median (IQR)	20 (20-22)	20 (20-20)	30 (30-30)	
Diagnosis				
Non CAD, n (%)	270	254 (94.1)	16 (5.9)	
DCM (myocarditis), n (%)	232 (85)	218 (79)	14 (6.0)	
Other CM (non myocarditis), n (%)	38 (15)	36 (9.8)	2 (5.2)	
CAD, n (%)	348	342 (98.3)	6 (1.7)	P = 0.007 (nonCAD vs CAD)
Complete revascularized, n (%)	196 (56)	192 (54)	4 (2.0)	
Not complete revascularized, n (%)	152 (44)	150 (42.7)	2 (1.3)	P = n.s. (complete vs in-complete revascularized)
One vessel disease	124 (81.6)	122 (80.0)	2 (1.6)	
> One vessel disease	28 (18.4)	28 (18.4)	0 (0)	P = n.s. (one vessel vs > one)
Stenosed	100 (65.8)	100 (65.8)	0 (0)	
Occluded	52 (34.2)	50 (30.4)	2 (3.8)	P = n.s. (stenosed vs occluded)
Medication				
Amiodaron medication, n (%)	124 (20)	118 (15.2)	6 (4.8)	
No amiodaron, n (%)	494 (80)	478 (76.8)	16 (3.2)	P = n.s. (amio vs no amio)

SMT: Safety margin test; n: Number; SD: Standard deviation; IQR: Interquartile range; LVEF: Left ventricular ejection fraction; BMI: Body mass index; pp: Primary prevention; sp: Secondary prevention; VT: Ventricular tachycardia; VF: Ventricular fibrillation; CAD: Coronary artery disease; DCM: Dilated cardiomyopathy; CM: Cardiomyopathy; amio: Amiodarone; n.s.: Not significant; n/a: Not applicable.

achieve the conventional SMT > 10 J. This in line with similar findings of 6%-7% insufficient SMT in older retrospective studies<sup>[11,16]</sup> using less sophisticated ICD-systems, suggesting that an adequate defibrillation threshold is not only dependent on the implanted ICD-system. Russo *et al.*<sup>[16]</sup> found that simply changing to a high output ICD-system to pass an initially insufficient SMT was not enough in 48% of patients. This further highlights the fact that an SMT < 10 J exhibits a more complex problem than just deliver higher shock energy<sup>[9]</sup> and that individual measures have to be taken to reach an acceptable SMT > 10 J. According to our data and in line with previous findings, VF as the index arrhythmia for ICD implantation, the diagnose of a non-ischemic cardiomyopathy and younger age were associated with a higher incidence of ineffective SMT. However, none of these predictors helped to identify the 22 patients of our study who failed to pass

a SMT > 10 J (Table 2). In line with previous findings<sup>[12,16]</sup>, our study revealed that still two third of patients after ICD system modification and RV lead replacement required further measures to reach a subsequent SMT > 10 J. In our study, we implanted a subcutaneous electrode array, a measure that is considered to be the most effective for reducing defibrillation threshold<sup>[15]</sup>. Inconsistent evidence exists regarding long term outcome of patients who do not meet an intra-operative SMT > 10 J<sup>[6,7,18]</sup> or where not tested at all<sup>[9,10]</sup>.

On the other side, the HRS/EHRA/APHS/SOLACE expert consensus statement on ICD programming and testing<sup>[21]</sup> states with a Class IIa recommendation, "that it is reasonable to omit defibrillation testing in patients undergoing initial left pectoral transvenous ICD implantation procedures where appropriate sensing, pacing and impedance values with fluoroscopically

**Table 2** Characteristics of patients with failed intra-operative safety margin test

<i>n</i>	Age at time of implantation (years)	Sex (m/f)	Indication for ICD implantation	LVEF (%)	Primary vs secondary ICD indication	Further management after failed initial SMT
1	46	m	LAD stenosed	30	pp	Subcutaneous array
2	45	w	oCM	15	pp	PDT OK
3	74	w	oCM	36	pp	Subcutaneous array
4	41	m	cmpl revasc	39	pp	Subcutaneous array
5	54	w	DCM	10	pp	Subcutaneous array
6	25	m	oCM	20	sp	Subcutaneous array
7	68	m	DCM	35	sp	Subcutaneous array
8	69	m	RCA occluded	31	sp	PDT OK
9	73	m	oCM	30	pp	PDT OK
10	37	m	TGV surgery	30	pp	Subcutaneous array
11	69	m	DCM	20	pp	none
12	46	m	LAD stenosed	30	pp	Subcutaneous array
13	45	w	DCM	15	pp	PDT OK
14	74	w	DCM	36	pp	Subcutaneous array
15	41	m	cmpl revasc	39	pp	Subcutaneous array
16	54	w	DCM	10	pp	Subcutaneous array
17	25	m	DCM	20	sp	Subcutaneous array
18	68	m	DCM	35	sp	Subcutaneous array
19	69	m	RCA occluded	31	sp	PDT OK
20	73	m	DCM	30	pp	PDT OK
21	37	m	vs D surgery	30	pp	Subcutaneous array
22	69	m	DCM	20	pp	None

m: Male; w: Women; ICD: Internal cardioverter defibrillator; LAD: Left anterior descendent coronary artery; oCM: Other cardiomyopathy; cplm revasc: Complete revascularized; RCA: Right coronary artery; TGV: Transposition of the great vessels; VSD: Ventricular septum defect.

**Table 3** Follow up

	All	Effective SMT	Ineffective SMT	<i>P</i> -value
FU, <i>n</i> (%)	552 (89.3)	530 (96)	22 (100)	
FU duration (mo)	Mean (± SD)	21.1 (± 21)	15.8 (± 21)	<i>P</i> = n.s.
Antiarrhythmica, <i>n</i> (%)				
	Amiodarone	122 (23.0)	6 (27)	<i>P</i> = n.s.
	Sotalex	2 (0.4)	0 (0)	<i>P</i> = n.s.
	β-blocker	485 (91.5)	20 (91)	<i>P</i> = n.s.
Events during FU, <i>n</i> (%)				
	Inadequate therapy	124 (23.4)	2 (9.1)	<i>P</i> = 0.02
	ATP	4 (0.8)	2 (9.1)	<i>P</i> = n.s.
	Shock delivery	58 (10.9)	0 (0)	
	ATP and shock delivery	36 (6.8)	0 (0)	
	VT ablation	20 (3.8)	0 (0)	
		6 (1.1)	0 (0)	

FU: Follow up; ATP: Anti tachycardia pacing; n.s.: Not significant.

well-positioned RV leads". Furthermore, with a class IIa recommendation the expert consensus state "that defibrillation testing is reasonable in patients undergoing a right pectoral transvenous ICD implantation or ICD pulse generator changes".

For the arguments mentioned above we recommend that a decision to perform intraoperative testing during ICD placement without absolute contraindication should be taken case-by-case. Our data suggest that the intraoperative testing should be considered for patients who are younger, patients with non-CAD as underlying disease and VF as the index arrhythmia for secondary ICD indication. Furthermore patients with HCM, special conditions such as severe obesity, amiodarone use and right pectoral implants as well as pre-existing

RIATA (SJM) leads should be considered to be tested intraoperatively.

#### **Rationale for intra-operative defibrillation testing**

Up to 65% of implantation procedures are performed without any induction test<sup>[6,14]</sup>. Patients less likely to be tested were sicker and therefore more likely to have adverse outcomes, including death<sup>[6,11,13,16]</sup>. The strength of our study is that intra-operative testing was done in 97.5% of all consecutive patients. In contrast to former studies<sup>[11-13,16]</sup> we could show that testing the ICD at the time of placement is safe and effective, even if sicker patients (*e.g.*, LVEF < 20% and severe, non revascularized coronary 2 or 3 vessel disease) were included. Newer ICD systems with advancements in

defibrillator and lead technology and resulting enhanced defibrillation efficacy may be one reason for this finding. Nevertheless, 22 patients (4%) of our study population had an ineffective intra-operative SMT and would have been missed without consequently passing all patients without a clear contraindication through an intra-operative defibrillation test. Even if only a small fraction of patients could potentially benefit from a SMT at ICD-implantation, it poses a forensic issue to prove at least once device efficacy in adequate sensing, computing and termination of VF. In our study, 14/22 patients needed the implantation of a subcutaneous electrode array to achieve adequate DFTs. Although several reasons imply that long term survival may not necessarily be affected whether or not defibrillation testing is done<sup>[6,9,10,18]</sup>, one study suggested that not having a defibrillation test was an independent risk factor of SCD even if sicker patients were the ones not tested<sup>[11]</sup>. However, no study so far was sufficiently powered to establish equivalence or superiority of a strategy of no testing vs SMT at the time of ICD placement as Strickberger *et al.*<sup>[22]</sup> calculated a sample size of approximately 29000 patients that would need to be randomized in a mortality study to achieve definite conclusions on this question with an adequate statistical power.

Two recently published randomised studies showed that defibrillation testing at the time of ICD implantation does not appear to predict total mortality<sup>[9,10]</sup>. But still it remain legal and regulatory considerations: The labelling on all ICD's recommend an assessment of defibrillation efficacy at implant not least to document the defibrillation behaviour with new drugs and the integrity of new ICD systems coming to the market.

For the reasons mentioned above and underlined with the finding of our study, we conclude that defibrillation testing remains an important part of ICD placement and the decision to perform or omit testing should be taken case-by-case.

In conclusion, in the absence of sufficiently powered studies evaluating long term outcome of patients with an ineffective intra-operative defibrillation testing, our findings underline that routine SMT still remains an important part of ICD placement. An ineffective SMT occurs in about 4% of patients, and even after ICD system modification and RV shock lead repositioning three quarter of those need implantation of a subcutaneous electrode array to pass a SMT > 10 J.

## COMMENTS

### Background

The implantable cardioverter defibrillator (ICD) is widely accepted for primary and secondary prevention of severe life-threatening ventricular tachyarrhythmia. However the importance concerning defibrillation testing at the time of implantation and clinical relevance of inadequate testing of ICD devices still remains under debate.

### Research frontiers

Defibrillation testing was done at the time of implantation in randomized trial investigating the efficacy of ICD therapy. They critically reflect the progressive

trend to omit defibrillation testing at the time of ICD placement.

### Innovations and breakthroughs

Two recently published randomised studies showed that ICD implantation without defibrillation testing is non-inferior to implantation with testing. Although one of these studies included 2500 patients, it is still underpowered to address the question of future shock efficacy or reduction of arrhythmogenic death. The authors' study present a large cohort of patients undergoing ICD-implantation and showed that in 4% of the patients the ICD did not terminate induced VT during intraoperative testing. Furthermore their data suggested that intraoperative testing of the ICD is a well-tolerated procedure.

### Applications

The data of their study showed that intraoperative ICD-testing lead in a not negligible percentage of patients to a system modification or even a subcutaneous array implantation to prove correct detection and termination of induced ventricular fibrillation at the time of ICD-implantation.

### Terminology

ICD are routinely implanted since 30 years to prevent sudden cardiac death. The detection of a life-threatening ventricular arrhythmia leads to a biphasic high energy 30-40 J impulse between the RV-coil and the subscapular located aggregate to terminate the arrhythmia. Testing the correct detection and termination of induced ventricular fibrillation at the time of ICD implantation is included as a recommendation in product labels.

### Peer-review

This is a well-written paper.

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## Observational Study

**Association between high cystatin C levels and carotid atherosclerosis**

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**Institutional review board statement:** This study was reviewed and approved by the Human Ethics Committee of Juntendo University.

**Informed consent statement:** The participants' clinical data were retrospectively retrieved from an institutional database. All of the examinations included in this study were performed as a routine part of the program, and none were aimed at specifically collecting data for the current study. The study protocol was approved by the institutional ethics committee. So, we did not obtain informed consent from every participant.

**Conflict-of-interest statement:** None of the authors of this paper has a financial or personal relationship with other people or organizations that could inappropriately influence or bias the content of the paper.

**Data sharing statement:** The technical appendix, statistical code, and dataset are available from the corresponding author at [tykobaya@juntendo.ac.jp](mailto:tykobaya@juntendo.ac.jp). Consent was not obtained but the presented data are anonymized and risk of identification is low.

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**Abstract****AIM**

To investigate the association between carotid atherosclerosis and cystatin C (CysC) and to determine the optimal CysC cut-off value.

**METHODS**

One hundred twenty-eight subjects were included in this study. Atherosclerosis was defined as a maximum carotid plaque thickness (MCPT) of greater than 2 mm. A receiver operating characteristic curve analysis was used to determine the diagnostic value of serum CysC for atherosclerosis. The subjects were divided into two groups according to the CysC cut-off value. We screened

for diabetes, hypertension, dyslipidemia, smoking status, alcohol consumption, and exercise behavior. The association between atherosclerosis and CysC levels was assessed using multivariate analysis.

## RESULTS

The subjects were then divided into two groups according to the CysC cut-off value (0.73 mg/L). The median age of the high CysC group was 72 years (85% males), whereas that of the low CysC group was 61 years (63% males). The CysC levels were significantly correlated with Cr and estimated glomerular filtration rate (eGFR) values. Body-mass index, visceral fat area, hypertension, diabetes mellitus, and MCPT were significantly higher in the high CysC group than in the low CysC group. Furthermore, the eGFR was significantly lower in the high CysC group. Regarding lifestyle habits, only the exercise level was lower in the high CysC group than in the low CysC group. Multivariate analysis, adjusted for age and sex, revealed that high CysC levels were significantly associated with an MCPT of  $\geq 2$  mm (odds ratio: 2.92; 95%CI: 1.13-7.99).

## CONCLUSION

Higher CysC levels were associated with an MCPT of  $\geq 2$  mm. The CysC cut-off value of 0.73 mg/L appears to aid in the diagnosis of atherosclerosis.

**Key words:** Cystatin C; Atherosclerosis; Carotid plaque; Maximum carotid plaque thickness; Visceral fat

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**Core tip:** Atherosclerosis is a leading worldwide cause of morbidity and mortality. The association between cystatin C (CysC) and atherosclerotic disorders remains controversial, and the cut-off value of CysC for atherosclerosis is unknown. Our study revealed that the optimal CysC cut-off point was 0.73 mg/L by receiver operating characteristic curve analysis. Higher CysC levels were significantly and independently correlated with an maximum carotid plaque thickness of  $\geq 2$  mm in multivariate analysis. Our data indicate that CysC could be a useful laboratory tool for predicting atherosclerosis during health checkups.

Kobayashi T, Yokokawa H, Fujibayashi K, Haniu T, Hisaoka T, Fukuda H, Naito T. Association between high cystatin C levels and carotid atherosclerosis. *World J Cardiol* 2017; 9(2): 174-181 Available from: URL: <http://www.wjgnet.com/1949-8462/full/v9/i2/174.htm> DOI: <http://dx.doi.org/10.4330/wjc.v9.i2.174>

## INTRODUCTION

Atherosclerosis is a leading worldwide cause of morbidity and mortality<sup>[1,2]</sup>. The incidence of cardiovascular diseases (CVDs), including cerebrovascular, peripheral arterial, and coronary artery disease, is increasing and

accounts for approximately one-fourth of all deaths in World Health Organization member states<sup>[3]</sup>. More than 17 million people die annually from CVDs, and, by 2030, more than 23 million CVD-related deaths are expected to occur worldwide. In Japan, the age-standardized fraction of mortality from CVDs is approximately 30%.

The ankle-brachial index, pulse-wave velocity, flow-mediated dilation, and ultrasonic evaluation have been introduced as methods for assessing the structural and functional effects of atherosclerosis<sup>[4-6]</sup>. Carotid atherosclerosis, estimated by intima-media thickness (IMT), is a sensitive surrogate marker for CVD and can now be non-invasively measured by B-mode ultrasonography<sup>[7,8]</sup>. IMT is a marker for systemic subclinical atherosclerosis and a strong predictor of incident myocardial infarction and ischemic stroke<sup>[9,10]</sup>. Carotid plaque may be an even more powerful predictor of vascular outcomes than IMT<sup>[11,12]</sup>. Maximum carotid plaque thickness (MCPT), widely used for assessing atherosclerotic change, is associated with an increased risk of vascular morbidity<sup>[13]</sup>.

High plasma adiponectin independently predicted death and major adverse cardiovascular events in a large community-based population<sup>[14]</sup>. High-sensitivity C-reactive protein serum levels were reported to be significantly related to the severity of coronary atherosclerosis<sup>[15]</sup>. In addition to these markers, serum cystatin C (CysC) has recently been proposed as a more reliable biomarker for atherosclerosis and chronic renal disease. Furthermore, high CysC levels are indicated as a useful marker for identifying an elevated risk of CVD and a higher total mortality among patients assessed as being at low risk by both creatinine (Cr) and estimated glomerular filtration rate (eGFR) values<sup>[16,17]</sup>. A previous study revealed that atherosclerotic changes associated with inflammation could be one mechanism by which CysC is associated with CVD<sup>[16]</sup>. However, the association between CysC and atherosclerotic disorders remains controversial, the cut-off values of CysC for atherosclerosis are unknown, and previous reports on this association as well as the association between CysC and MCPT are limited<sup>[18-20]</sup>. A diagnostic CysC cut-off value has not been determined. In this study, we examined the association between CysC levels and atherosclerotic changes in Japanese subjects.

## MATERIALS AND METHODS

### Subjects

The present cross-sectional study included 133 Japanese subjects who underwent an inpatient medical health checkup at Juntendo University Hospital, Tokyo from October 2010 to January 2013. Among these subjects, five were excluded because of missing laboratory data. Thus, 128 subjects [98 men and 30 women; median age, 70 years (age range, 39-87 years)] were included.

The subjects were asked to complete a self-administered questionnaire about their sociodemographic characteristics, past medical history (diabetes, hypertension, and dyslipidemia), and lifestyle behaviors (alcohol

consumption, current smoking status, and daily exercise activity).

The body weight, height, and waist circumference of the patients were measured, and the body-mass index [BMI (kg/m<sup>2</sup>)] was calculated. Systolic and diastolic blood pressure were measured in a sitting position after a 15-min rest using a standard mercury sphygmomanometer. Venous blood samples were collected following overnight fasting. Plasma glucose concentrations, hemoglobin A1c (HbA1c), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), triglyceride (TG), Cr, and CysC levels were also measured. Low-density lipoprotein cholesterol was estimated using the Friedewald equation [TC-HDL-C-(TG/5)]. For the assessment of visceral fat accumulation, abdominal fat areas were measured from abdominal CT scans taken at the umbilical level while in the supine position and during late expiration, according to the Japanese Guidelines for Obesity Treatment<sup>[21]</sup>.

The following parameters were calculated: eGFR was calculated using the Japanese GFR inference formula, which was developed by the Japanese Society of Nephrology<sup>[22]</sup>:  $eGFR \text{ (mL/min per } 1.73 \text{ m}^2) = 194 \times \text{serum Cr (mg/dL)} - 1.094 \times \text{age (years)} - 0.287 (\times 0.739 \text{ if female})$ .

HbA1c was calculated as the National Glycohemoglobin Standardization Program (NGSP) value (%), which was developed by the Japan Diabetes Society<sup>[23]</sup>:  $\text{HbA1c} = \text{NGSP} (\%) \times 1.02 + 0.25$ .

Lifestyle-related diseases were defined using several criteria: (1) diabetes mellitus was defined as an HbA1c level of  $\geq 6.5\%$ , a fasting plasma glucose level of  $\geq 126 \text{ mg/dL}$ , or current antidiabetic therapy<sup>[24]</sup>; (2) hypertension was defined by a systolic blood pressure of  $\geq 140 \text{ mmHg}$ , a diastolic blood pressure of  $\geq 90 \text{ mmHg}$ , or current antihypertensive therapy<sup>[25]</sup>; and (3) dyslipidemia was defined as a fasting TG level of  $\geq 150 \text{ mg/dL}$ , a low-density lipoprotein cholesterol level of  $\geq 140 \text{ mg/dL}$ , or an HDL-C level of  $< 40 \text{ mg/dL}$ <sup>[26]</sup>. Three unhealthy lifestyle behaviors were evaluated in this study: Drinking alcohol more than once a week, current smoking, and no regular physical activity.

A detailed protocol for measuring carotid artery atherosclerosis has been published<sup>[27]</sup>. Carotid plaque and IMT were measured using high-resolution B-mode ultrasonography to estimate atherosclerosis in the carotid artery. Eight technicians who were trained by a supervisor physician and who were certified in the protocol assessed carotid plaque and the mean IMT of the common carotid artery. A plaque was defined as a maximum IMT of  $> 1.0 \text{ mm}$ . MCPT was measured at the peak plaque prominence in any of the carotid artery segments. Atherosclerosis was defined on the basis of the severity of carotid atherosclerosis by MCPT at a cut-off level of 2 mm. As previously reported, an MCPT of  $\geq 2 \text{ mm}$  is defined as an atherosclerotic change<sup>[13]</sup>.

### Statistical analysis

The results were expressed as medians of the test

parameters. The Youden index, a point on the receiver operating characteristic (ROC) curve, was used to determine the diagnostic values of serum CysC levels that were indicative of atherosclerosis.

In a second analysis, the subjects were divided into two groups according to CysC levels above and below the cut-off value. Their demographic characteristics were then compared using the *t* test for continuous variables and the chi-square test for categorical variables. Multiple logistic regression analysis with adjustments for age and sex was conducted to determine the correlations between an MCPT of  $\geq 2 \text{ mm}$  and metabolic variables including CysC level. Our study included only 128 subjects, of whom 52 had arteriosclerosis. Because there is a limit to the number of adjusted variables, we combined several metabolic related variables in one item. Variables that were significantly associated with an MCPT of  $\geq 2 \text{ mm}$  were then investigated with multiple logistic regression analysis.

Statistical test results were considered significant when the *P* value was  $< 0.05$ . All calculations were performed using JMP Pro, version 11 (SAS Institute, Cary, NC, United States). The study protocol was approved by the Human Ethics Committee of Juntendo University. The participants' clinical data were retrospectively retrieved from an institutional database. All of the examinations included in this study were performed as a routine part of the program, and none were aimed at specifically collecting data for the current study. The study protocol was approved by the institutional ethics committee, so it was not necessary to obtain informed consent from the participants. A biostatistician reviewed the study.

## RESULTS

The subject characteristics are shown in Table 1. The median age was 70 years (77% males). Twenty-three (18%) subjects smoked, 78 (61%) were alcohol consumers, and 90 (70%) did not exercise regularly. The median visceral fat area was 125.2 cm<sup>2</sup>. Sixty-one (48%) subjects were diagnosed with hypertension, 72 (56%) with dyslipidemia, and 29 (23%) with diabetes mellitus. The ROC analysis conducted to determine the cut-off value of CysC revealed a significantly higher risk of atherosclerosis at 0.73 mg/L (Figure 1) (sensitivity: 82.7%, specificity: 52.6%).

The subjects were then divided into two groups according to the CysC cut-off value (0.73 mg/L). The subjects' characteristics according to the CysC level are shown in Table 2. The median age of the high CysC group was 72 years (85% males), whereas that of the low CysC group was 61 years (63% males). The CysC levels were significantly correlated with Cr and eGFR values. BMI, visceral fat area, hypertension, diabetes mellitus, and MCPT were significantly higher in the high CysC group than in the low CysC group. Furthermore, the eGFR was significantly lower in the high CysC group. Regarding lifestyle habits, only the exercise level was

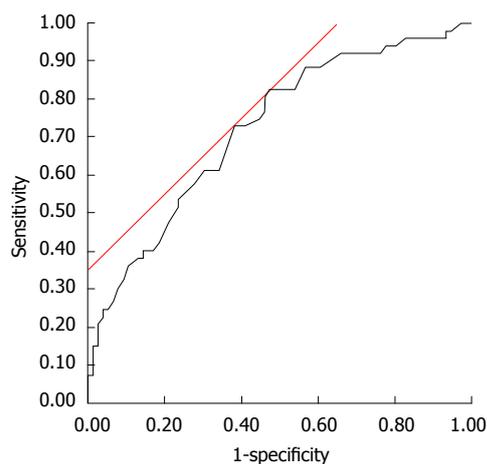
**Table 1** Baseline characteristics of the study population

Variables	Median (min, max) or n (%)
Age (yr)	70 (39, 87)
Sex (male)	98 (77)
Body-mass index (kg/m <sup>2</sup> )	24.2 (15.1, 38)
Lifestyle-related items	
Current smokers	23 (18)
Alcohol consumers	78 (61)
No exercise habits	90 (70)
Visceral fat area (cm <sup>2</sup> )	125.2 (22.9, 281.7)
Clinical history	
Ischemic heart disease, n (%)	6 (5)
Blood pressure	
Systolic blood pressure (mmHg)	122 (92, 156)
Diastolic blood pressure (mmHg)	68 (50, 86)
Diagnosed hypertension	61 (48)
Lipid metabolism	
Total cholesterol (mg/dL)	194.5 (115, 727)
High-density lipoprotein cholesterol (mg/dL)	54 (30, 96)
Low-density lipoprotein cholesterol (mg/dL)	111 (41, 205)
Triglycerides (mg/dL)	99.5 (37, 593)
Diagnosed dyslipidemia	72 (56)
Glucose metabolism	
Fasting plasma glucose (mg/dL)	93.5 (74, 226)
Hemoglobin A1c (%)	5.3 (4.5, 8.3)
Diagnosed diabetes mellitus	29 (23)
Kidney function	
Creatinine (mg/dL)	0.75 (0.38, 1.36)
Estimated glomerular filtration rate (mL/min per 1.73 m <sup>2</sup> )	78.4 (38.9, 122.6)
Cystatin C (mg/L)	0.78 (0.49, 1.45)
Carotid ultrasonography	
Right common carotid artery plaque thickness (mm)	0 (0, 3.6)
Right carotid bulb-internal carotid artery plaque thickness (mm)	1.5 (0, 5.5)
Left common carotid artery plaque thickness (mm)	0 (0, 2.8)
Left carotid bulb-internal carotid artery plaque thickness (mm)	1.5 (0, 4.2)
Right common carotid artery maximum intima-media thickness (mm)	1.0 (0.6, 1.9)
Left common carotid artery maximum intima-media thickness (mm)	1.0 (0.7, 2.3)

lower in the high CysC group than in the low CysC group. In addition, sensitivity, specificity, positive predictive value, and negative predictive value as calculated from the data in Table 2 were 83%, 53%, 54% and 82%, respectively.

Next, we compared differences in demographics and clinical variables between subjects with MCPTs of  $\geq 2$  mm or  $< 2$  mm (Table 3). Age, visceral fat area, hypertension, diabetes mellitus, Cr, eGFR, and CysC were significantly higher in the MCPT of  $\geq 2$  mm group than the  $< 2$  mm group. Furthermore, the eGFR was significantly lower in the MCPT of  $\geq 2$  mm group. The two groups did not differ with regard to lifestyle habits.

The factors associated with an MCPT of  $\geq 2$  mm are shown in Table 4. Multivariate analysis, adjusted for age and sex, revealed that high CysC levels were significantly associated with an MCPT of  $\geq 2$  mm (odds ratio: 2.92; 95%CI: 1.13-7.99).



**Figure 1** Receiver operating characteristic curve for predictive value of serum cystatin C levels. The receiver operating characteristic curve for the predictive value of serum CysC levels in detecting a MCPT of  $> 2$  mm in 128 subjects had an area under the curve of 0.724. A serum CysC level of  $\geq 0.73$  mg/L indicated an MCPT of  $> 2$  mm with 82.7% sensitivity and 52.6% specificity. CysC: Cystatin C; MCPT: Maximum carotid plaque thickness.

## DISCUSSION

In this study, multivariate analysis revealed that higher CysC levels were significantly associated with carotid atherosclerosis, as defined by an MCPT of  $\geq 2$  mm, in middle-aged and elderly Japanese subjects. The cut-off CysC value (0.73 mg/L) could aid in the diagnosis of atherosclerosis. To our knowledge, this is the first report demonstrating an association between CysC and carotid atherosclerosis as assessed by MCPT. The CysC cut-off level potentially has promising clinical value in the diagnosis of atherosclerosis.

Our results revealed a significant association between high CysC levels and an MCPT of  $\geq 2$  mm. A meta-analysis previously revealed that CysC is strongly and independently correlated with the risk of subsequent cardiovascular disease<sup>[28]</sup>. Although several studies have revealed an association between high CysC levels and atherosclerosis, their results differed from ours because of the different targets and indicators used. A previous study, which analyzed 637 Japanese subjects without chronic kidney disease, revealed that CysC was positively correlated with the cardio-ankle vascular index in women<sup>[19]</sup>. In a study of 60 Japanese hypertensive patients, serum CysC levels were positively correlated with carotid IMT<sup>[29]</sup>. In data collected *via* 64-slice CT coronary angiography, a high CysC level was found to be significantly correlated with early-stage coronary atherosclerotic plaques in 405 Japanese patients without established chronic kidney dysfunction<sup>[18]</sup>. Our results are in agreement with the previous hypothesis that CysC level is a reliable marker for atherosclerosis.

There are several possible explanations for the association between CysC and atherosclerotic change. First, inflammation may be associated with both CysC and atherosclerosis. The Cardiovascular Health Study<sup>[30]</sup>, which

**Table 2** Subject characteristics associated with cystatin C levels

Variables	Median (min, max) or <i>n</i> (%)		<i>P</i> value
	Higher cystatin C ( $\geq 0.73$ ) ( <i>n</i> = 79)	Lower cystatin C ( $< 0.73$ ) ( <i>n</i> = 49)	
Age (yr)	72 (46, 87)	61 (39, 80)	$< 0.01^1$
Sex (male)	67 (85)	31 (63)	$< 0.01^2$
Body-mass index (kg/m <sup>2</sup> )	24.9 (17.0, 38.0)	23.5 (15.1, 30.2)	$< 0.01^1$
Visceral fat area (cm <sup>2</sup> )	142.7 (48.3, 281.7)	103.7 (22.9, 249.2)	$< 0.01^1$
Lifestyle habits			
Current smokers	14 (23)	9 (19)	0.88 <sup>2</sup>
Alcohol consumers	47 (59)	31 (63)	0.67 <sup>2</sup>
No exercise habits	28 (35)	10 (20)	0.07 <sup>2</sup>
Diagnosed hypertension	48 (61)	13 (27)	$< 0.01^2$
Diagnosed dyslipidemia	45 (57)	27 (55)	0.84 <sup>2</sup>
Diagnosed diabetes mellitus	24 (30)	5 (10)	$< 0.01^2$
Kidney function			
Creatinine (mg/dL)	0.81 (0.45, 1.36)	0.62 (0.38, 0.97)	$< 0.01^1$
Estimated glomerular filtration rate (mL/min per 1.73 m <sup>2</sup> )	70.6 (38.9, 110.2)	88.7 (59.7, 122.6)	$< 0.01^1$
Carotid ultrasonography			
Maximum carotid plaque thickness $\geq 2$ mm	43 (54)	9 (18)	$< 0.01^2$

<sup>1</sup>Student *t* test was used for estimating the significance; <sup>2</sup> $\chi^2$  test.

**Table 3** Subject characteristics associated with maximum carotid plaque thickness

Variables	Median (min, max) or <i>n</i> (%)		<i>P</i> value
	MCPT $\geq 2$ mm ( <i>n</i> = 52)	MCPT $< 2$ mm ( <i>n</i> = 76)	
Age (yr)	72 (51, 87)	66 (39, 83)	$< 0.01^1$
Sex (male)	42 (81)	56 (74)	$< 0.35^2$
Body-mass index (kg/m <sup>2</sup> )	24.1 (17.0, 38.0)	24.3 (15.1, 31.7)	$< 0.35^1$
Visceral fat area (cm <sup>2</sup> )	138.9 (30.5, 281.7)	115.8 (22.9, 249.2)	$< 0.10^1$
Lifestyle habits			
Current smokers	9 (17)	14 (18)	0.85 <sup>2</sup>
Alcohol consumers	28 (54)	50 (66)	0.17 <sup>2</sup>
No exercise habits	18 (35)	20 (26)	0.31 <sup>2</sup>
Diagnosed hypertension	32 (62)	29 (38)	$< 0.01^2$
Diagnosed dyslipidemia	29 (56)	43 (57)	0.93 <sup>2</sup>
Diagnosed diabetes mellitus	18 (35)	11 (14)	$< 0.01^2$
Kidney function			
Creatinine (mg/dL)	0.80 (0.45, 1.36)	0.75 (0.38, 1.17)	$< 0.03^1$
Estimated glomerular filtration rate (mL/min per 1.73 m <sup>2</sup> )	73.3 (38.9, 111.9)	80.2 (47.9, 122.6)	$< 0.02^1$
Cystatin C (mg/L)	0.83 (0.55, 1.45)	0.72 (0.49, 1.22)	$< 0.01^1$

<sup>1</sup>Student *t* test was used for estimating the significance; <sup>2</sup> $\chi^2$  test.

analyzed 4637 ambulatory elderly patients, revealed a significant linear association between CysC and C-reactive protein but not Cr or eGFR<sup>[31]</sup>. It is well known that inflammation plays a role in atherogenesis, atherosclerotic plaque progression, and acute coronary syndrome. Second, CysC plays an important role in maintaining atherosclerotic plaque stability. A previous study<sup>[32]</sup> analyzed 31 plaques removed by endarterectomy, demonstrating with immunohistochemistry that CysC in human carotid plaques localized with collagen and elastin. An imbalance between cysteine proteases and CysC in arterial wall remodeling occurs in vascular diseases, such as atherosclerosis and abdominal aortic aneurysm<sup>[33]</sup>.

Imaging assessments, such as ultrasound and CT, are often performed for assessing arteriosclerotic vascular disease. However, not all institutions can practice such assessments because of the lack of sonographers or

appropriate devices. Therefore, it is potentially important that atherosclerosis can be evaluated using a blood test, such as for CysC levels. A diagnostic CysC cut-off value has not been previously determined. Our study revealed that the CysC cut-off value of 0.73 mg/L could contribute to the diagnosis of atherosclerosis.

Our study had a few limitations. First, the subjects were selected from a single institution, the sample size was small, and  $> 70\%$  of our subjects were healthy men. Selection bias may have affected the analysis, as the investigated cohort did not accurately represent the Japanese population. Thus, future large-scale cohort studies are required. Second, lifestyle habits were evaluated using a self-administered questionnaire, and the subjects may have stated that they had a healthier lifestyle than they actually did. Further evaluations of lifestyle habits based on a validated questionnaire are

**Table 4** Univariate and multivariate logistic regression analysis for variables associated with an maximum carotid plaque thickness of  $\geq 2$  mm

Variables	Univariate		Multivariate <sup>1</sup>	
	Odds ratio	95%CI	Odds ratio	95%CI
Cystatin C	5.31	2.27-12.39	2.92	1.13-7.99
Diabetes mellitus	3.13	1.33-7.37	1.82	0.70-4.86
Hypertension	2.59	1.26-5.36	1.56	0.69-3.53
Dyslipidemia	0.97	0.48-1.97		
Current smoking	0.91	0.36-2.30		
Alcohol consumers	0.61	0.29-1.25		
Exercise habits	0.67	0.31-1.45		
Visceral fat area $\geq 100$ cm <sup>2</sup>	1.31	0.62-2.78		
$\Delta$ AICc <sup>2</sup>			158	
<sup>3</sup> R <sup>2</sup>			0.16	

<sup>1</sup>Adjusted for age and sex; <sup>2</sup>Akaike's Information Criterion; <sup>3</sup>Coefficient of determination.

necessary. Third, causal inferences cannot be made because of the cross-sectional nature of the study design. A prospective study is required for determining whether higher CysC levels are associated with the development of atherosclerosis-related diseases or death.

In conclusion, higher CysC levels were correlated with carotid atherosclerosis as defined by an MCPT of  $\geq 2$  mm among middle-aged and elderly Japanese subjects. Higher CysC levels have a low specificity but a high sensitivity and can therefore help exclude atherosclerosis. The CysC cut-off value of 0.73 mg/L appears to aid in the diagnosis of atherosclerosis. Our data indicate that CysC could be a useful laboratory tool for predicting atherosclerosis during health checkups.

## ACKNOWLEDGMENTS

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## COMMENTS

### Background

Atherosclerosis is a leading worldwide cause of morbidity and mortality. Carotid plaque may be a powerful predictor of vascular outcomes. Maximum carotid plaque thickness (MCPT), widely used for assessing atherosclerotic change, is associated with an increased risk of vascular morbidity.

### Research frontiers

Serum cystatin C (CysC) has recently been proposed as a reliable biomarker for atherosclerosis and chronic renal disease. However, the association between CysC and atherosclerotic disorders remains controversial, the cut-off values of CysC for atherosclerosis are unknown, and previous reports on this association as well as the association between CysC and MCPT are limited. A diagnostic CysC cut-off value has not been determined.

### Innovations and breakthroughs

Higher CysC levels were associated with an MCPT of  $\geq 2$  mm. The CysC cut-off value of 0.73 mg/L appears to aid in the diagnosis of atherosclerosis.

### Applications

It may be difficult for an institution to practice imaging assessment because of the lack of sonographers or appropriate devices. Therefore, it is potentially

important that atherosclerosis can be evaluated using a blood test, such as CysC levels. The CysC cut-off value of 0.73 mg/L could contribute to the diagnosis of atherosclerosis.

### Terminology

CysC is a 13-kD protease inhibitor which is produced by all nucleated cells. It is mainly used as a biomarker of kidney function. Recently, it has been studied for its role in predicting new-onset or deteriorating cardiovascular disease.

### Peer-review

This is a well-written article investigating the association between CysC and carotid atherosclerosis.

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## Ivabradine in the treatment of systolic heart failure - A systematic review and meta-analysis

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### Abstract

#### AIM

To perform a systematic-review and meta-analysis to compare outcomes of ivabradine combined with beta-blocker to beta-blocker alone in heart failure with reduced ejection fraction (HFrEF).

#### METHODS

We searched PubMed, Cochrane, EMBASE, CINAHL and Web of Science for trials comparing ivabradine + beta-blocker to beta-blocker alone in HFrEF. We performed a systematic-review and meta-analysis of published literature. Primary end-point was combined end point of cardiac death and hospitalization for heart failure.

#### RESULTS

Six studies with 17671 patients were included. Mean follow-up was  $8.7 \pm 7.9$  mo. Combined end-point of heart failure readmission and cardiovascular death was better in ivabradine + beta-blocker group compared to beta-blocker alone (RR: 0.93, 95%CI: 0.79-1.09,  $P = 0.354$ ). Mean difference (MD) in heart rate was higher in the ivabradine + beta-blocker group (MD: 6.14, 95%CI: 3.80-8.48,  $P < 0.001$ ). There was no difference in all cause mortality (RR: 0.98, 95%CI: 0.89-1.07,  $P = 0.609$ ), cardiovascular mortality (RR: 0.99, 95%CI: 0.86-1.15,  $P = 0.908$ ) or heart failure hospitalization (RR: 0.87, 95%CI: 0.68-1.11,  $P = 0.271$ ).

#### CONCLUSION

From the available clinical trials, ivabradine + beta-blocker resulted in a significantly greater reduction in HR

coupled with improvement in combined end-point of heart failure readmission and cardiovascular death but with no improvement in all cause or cardiovascular mortality. Given the limited evidence, further randomized controlled trials are essential before widespread clinical application of ivabradine + beta-blocker is advocated for HFrEF.

**Key words:** Ivabradine; Heart failure

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**Core tip:** Ivabradine was recently given a class IIa indication in the 2016 focused update on systolic heart failure in the ACC/AHA/HFSA guidelines. But it is unclear whether ivabradine offers any additional benefit over and above that offered by beta blockers. Our analysis showed lower heart rate and combined end point of cardiac death and heart failure hospitalization at follow-up with ivabradine combined with beta blocker compared to beta blocker alone. Combined therapy did not improve cardiovascular mortality, all cause mortality or heart failure hospitalization. Further studies are essential before widespread use of combination therapy with ivabradine can be recommended.

Anantha Narayanan M, Reddy YNV, Baskaran J, Deshmukh A, Benditt DG, Raveendran G. Ivabradine in the treatment of systolic heart failure - A systematic review and meta-analysis. *World J Cardiol* 2017; 9(2): 182-190 Available from: URL: <http://www.wjgnet.com/1949-8462/full/v9/i2/182.htm> DOI: <http://dx.doi.org/10.4330/wjc.v9.i2.182>

## INTRODUCTION

Chronic congestive heart failure affects nearly 2%-3% of population and is associated with a one-year mortality of 6.4% in a recent study<sup>[1]</sup>. Standard pharmacological treatment for heart failure with reduced ejection fraction (HFrEF) includes beta-blockade which unequivocally decreases cardiovascular and heart failure related morbidity and mortality, in addition to promoting beneficial reverse remodeling<sup>[2,3]</sup>.

Elevated resting heart rates has been shown to be an independent predictor of mortality in heart failure, presumably acting through increased myocardial oxygen demand, and also serves as a marker of severity of underlying neurohormonal activation and cardiovascular disease<sup>[4-6]</sup>. In regard to the former, in patients with left ventricular dysfunction associated with ischemic cardiomyopathy, heart rates > 70 beats per minute (bpm) are associated with a 34% increase in cardiovascular mortality and 53% increase in hospitalization when compared to heart rates below 70 bpm<sup>[7]</sup>. Benefits derived from beta-blockers seem to be derived partly from their heart rate lowering properties<sup>[8]</sup>. However, their negative inotropic properties can have undesirable actions on

myocardial contractility<sup>[9]</sup>.

Ivabradine is a novel drug that inhibits the pacemaker current I(f) thereby slowing heart rates without exhibiting negative inotropic effect on the myocardium<sup>[10]</sup> or altering ventricular action potential<sup>[11]</sup>. In SHIFT<sup>[12]</sup>, ivabradine improved the composite end point of hospitalization and cardiovascular death in patients with HFrEF in sinus rhythm with heart rates  $\geq 70$ <sup>[12,13]</sup>. The 2016 American College of Cardiology/American Heart Association/Heart Failure Society of America (ACC/AHA/HFSA) Focused Update on the Management of Heart Failure<sup>[14]</sup> and the European Society of Cardiology (ESC) guidelines<sup>[15]</sup> have given a Class IIa (level of evidence B) recommendation for ivabradine use for patients with chronic HFrEF who are on guideline directed medical therapy [includes a maximum tolerated dose of beta-blocker, ACEi and mineralocorticoid receptor antagonist (MRA)] and who are in sinus rhythm with resting heart rates above 70 bpm (> 75 bpm in the European Society). It should be noted that in the SHIFT trial<sup>[12]</sup>, only 26% of the patient population were on target beta-blocker dosage. Thus the utility of ivabradine in the modern era, particularly with the recent approval of sacubitril with its dramatic improvement in mortality and heart failure outcomes<sup>[16]</sup> remains uncertain. To consolidate the available evidence regarding ivabradine in HFrEF, we performed a systematic review and meta-analysis including all the available clinical trials to date to evaluate the benefit of ivabradine therapy in combination with beta-blocker compared to beta-blocker alone in chronic HFrEF.

## MATERIALS AND METHODS

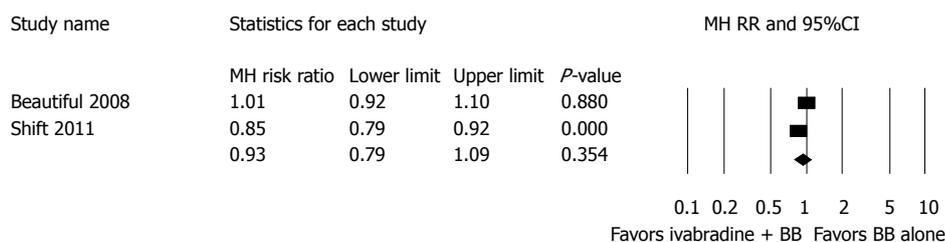
### Data search

An electronic database search was performed with the following search terms "ivabradine", "heart failure with reduced ejection fraction", "resting heart rates" and "systolic heart failure" in PubMed, EMBASE, Cochrane, CINAHL and Web of Science for studies published between January-1960 and August-2016 comparing the addition of ivabradine to beta-blocker vs beta-blocker only therapy. Supplementary appendix-1 shows PubMed search strategy.

The systematic review and meta-analysis was performed per PRISMA guidelines as shown in the Supplementary checklist<sup>[17]</sup> and Supplementary Figure 1 shows the PRISMA flowchart. We also reviewed relevant editorials, review articles and reference sections of included studies. We excluded conference abstracts with unpublished data as mentioned in the Cochrane guidelines for meta-analysis. An expert biostatistician has reviewed the paper for statistical accuracy.

### Inclusion criteria

Studies selected met the following criteria: Randomized controlled trials (RCTs), retrospective or prospective observational cohorts; included HFrEF of < 40%; compared two groups, one with ivabradine and beta-blocker and the other with beta-blocker alone; included adult patients;



**Figure 1** Comparison of Mantel-Haenszel risk ratio for combined end points of cardiovascular death and hospitalization for heart failure between ivabradine + beta-blocker vs beta-blocker alone. MH RR: Mantel-Haenszel risk ratio; BB: Beta blockers.

published in English language.

### Study definitions

We defined all cause mortality as death from any cause at follow-up. Cardiovascular mortality was defined as death from any cardiac cause including heart failure, myocardial infarction, arrhythmia, sudden cardiac death or stroke.

### Data extraction

Table 1 shows extracted patient demographics including mean age, sample size, co-morbidities, mortality data and risk estimates. Authors Mahesh Anantha Narayanan and Yogesh N Reddy reviewed the studies independently. A consensus was achieved by a third reviewer when the first two reviewers could not resolve any disagreement. We sought help from an experienced librarian when articles were not available online.

### Outcomes

The primary outcome was combined end-point of heart failure and cardiovascular death. Secondary outcomes included mean reduction in heart rate at follow up compared to baseline, all cause mortality, cardiovascular mortality, six-minute walking distance (6MWD) and ejection fraction (EF) at follow up.

### Statistical analysis

We used comprehensive meta-analysis (CMA) version 3.3.07 for statistical analysis. Categorical events were pooled using the random effects model, with pooled effect size represented by Mantel-Haenszel (MH) risk ratio (RR) with a 95% confidence interval (CI) limit. MH RR is a technique that generates an estimate of association between exposure and outcome after adjusting for confounding. Difference in Means (MD) was used for reporting outcomes with continuous variables. The combined ivabradine and beta-blocker group was the experimental group and so any MH RR (with 95%CI) that is less than 1 favors this cohort. Funnel-plots were used for assessing bias visually. Cochrane's Q-statistics were used to determine heterogeneity.  $I^2$  values of > 50%, 25%-50% and 0%-25% were considered to be high, moderate and low heterogeneity, respectively. We used an exclusion sensitivity analysis to analyze heterogeneity when required. P value of < 0.05 was considered statistically significant. A meta-regression

was performed when necessary to analyze the impact of moderator variables on outcomes of interest.

## RESULTS

### Characteristics of the included studies

A total of 696 studies were obtained using the initial search strategy as shown in Supplementary Figure 1. Initially 7 studies<sup>[12,18-23]</sup> met our inclusion criteria. We excluded the SHIFT sub group study as the sub group was not independent of the main SHIFT study population. Finally, we included 6 studies<sup>[12,18-21,23]</sup> with a total of 17671 patients. Mean follow-up was  $8.7 \pm 7.9$  mo. A total of 8845 patients received ivabradine with beta-blocker and 8826 patients received only beta-blocker. Table 1 shows characteristics of the included studies and Supplementary Table 1 summarizes the results of analyses comparing ivabradine and beta-blocker vs beta-blocker alone in patients with chronic HFrEF.

### Combined end point of cardiovascular death and hospitalization for worsening heart failure

A total of two studies reported combined end-point of cardiovascular death and hospitalization at follow up between the combined ivabradine + beta-blocker and the beta-blocker only group (Figure 1). MH RR was lower in the combined therapy group when compared to beta-blocker only group (MH RR: 0.93, 95%CI: 0.79-1.09,  $P = 0.354$ ). Heterogeneity was high ( $I^2 = 87%$ ) among the included studies.

### Heart rates at follow up

Change in heart rates at follow up from baseline was reported in all included studies. Difference in means (MD) for reduction in heart rate from baseline was greater in the ivabradine + beta-blocker group when compared to beta-blocker alone difference in means (MD): 6.14, 95%CI: 3.80-8.48,  $P < 0.001$  (Figure 2). Funnel-plot showed low risk of bias as shown in Supplementary Figure 2A and heterogeneity was high ( $I^2 = 95$ ). A sensitivity analysis performed with exclusion of the study<sup>[18]</sup> with the maximum strength did not alter the results of the analysis (MD: 6.24, 95%CI: 2.71-9.78;  $P = 0.001$ ). Analysis of only RCTs still showed that mean reduction in heart rates from baseline was greater in the combined ivabradine and beta-blocker group when compared to beta-blocker alone (MD: 6.88, 95%CI:

Table 1 Patient demographics

Ref.	Type of study	Total No. of patients	Age mean or median in years		Ivabradine + beta blocker alone (n)	Ivabradine + beta blocker (n)	Beta blocker alone (n)	Follow up time (mean/median) months	Mean baseline HR	NYHA class III - IV %		Coronary artery disease n (%)	Mean baseline ejection fraction	Atrial fibrillation		Beta blockers	
			Ivabradine + beta blocker	Beta blocker alone						Ivabradine + beta blocker	Beta blocker alone			Ivabradine + beta blocker	Beta blocker alone		
ETHIC-AHF <sup>[23]</sup> 2016	RCT	71	66 (15)	68 (12)	33	38	38	4	88	93	97	5 (10)	30%	NA	NA	88	97
Bagriy <i>et al.</i> <sup>[21]</sup> 2015	Prospective non-randomized	69	63 (12)	62 (11)	33	36	36	5	83	59	58	39 (57)	37%	NA	NA	100	100
CARVIVA HF <sup>[20]</sup> 2011	RCT	80	67 (9)	67 (10)	42	38	38	3	78	50	42	NA	27%	NA	NA	55	57
Amosova <i>et al.</i> <sup>[9]</sup> 2011	Retrospective cohort	29	59 (5)	59 (6)	17	12	12	2	75	NA	NA	29 (100)	39%	NA	NA	100	100
BEAUTIFUL <sup>[8]</sup> 2011	RCT	10917	65 (9)	65 (8)	5479	5438	5438	19	72	24	23	9645 (88)	32%	NA	NA	87	87
SHIFT <sup>[12]</sup> 2010	RCT	6505	61 (11)	60 (12)	3241	3264	3264	23	80	52	52	3666 (56)	29%	8%	8%	89	90

HR: Heart rate; RCT: Randomized controlled trial.

4.17-9.59;  $P < 0.001$  for RCTs) (Figure 3).

**All cause mortality**

Three studies that reported all cause mortality at follow-up were analyzed (Figure 4). There was no difference in all cause mortality between the combined group and the beta-blocker alone group (MH RR: 0.98, 95%CI: 0.89-1.07,  $P = 0.609$ ). Heterogeneity was low ( $I^2 = 17%$ ). When we excluded the study with maximum weight<sup>[12]</sup>, results remained unaltered (MH RR: 1.04, 95%CI: 0.89-1.07,  $P = 0.609$ ). A meta-regression of follow up time on all cause mortality was insignificant (Supplementary Figure 2B).

**Cardiovascular mortality**

Two studies reporting adverse events at follow-up were analyzed (Figure 5). There was no difference in cardiovascular mortality between the combined group and the beta-blocker alone group (MH RR: 0.99, 95%CI: 0.86-1.15,  $P = 0.908$ ). Heterogeneity was high ( $I^2 = 66%$ ).

**Hospitalization for heart failure**

Two studies reported hospitalization for heart failure (Figure 6). There was no difference in heart failure hospitalization between the combined group and the beta-blocker alone group (MH RR: 0.87, 95%CI: 0.68-1.11,  $P = 0.271$ ). Heterogeneity was high ( $I^2 = 89%$ ).

**6MWD**

Two studies reported 6MWD at follow up when compared to baseline between the combined therapy group with ivabradine plus beta-blocker and the beta-blocker alone group (Figure 7). 6MWD improved significantly from baseline in the combined therapy group (MD: 46.47, 95%CI: 14.678-3,  $P = 0.004$ ). Heterogeneity was low ( $I^2 = 0%$ ).

**Ejection fraction**

Three studies reported ejection fraction at follow up (Figure 8). Improvement in ejection fraction was better in the combined therapy group with ivabradine plus beta-

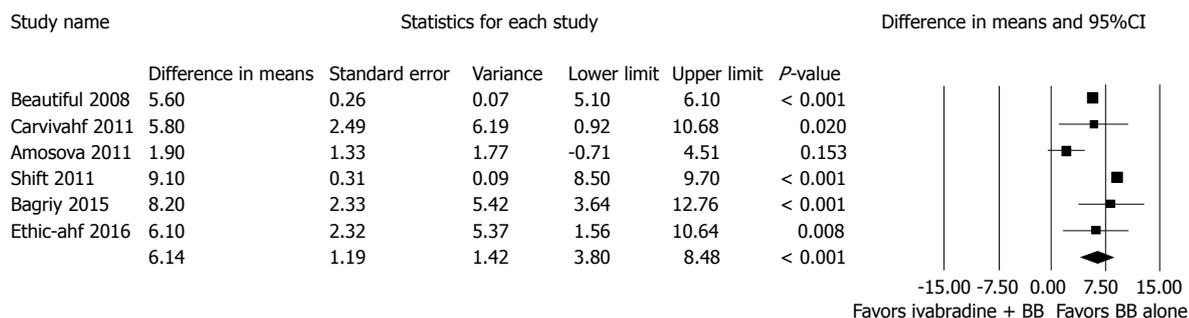


Figure 2 Comparison of mean change in heart rates from baseline between ivabradine + beta-blocker vs beta-blocker alone. BB: Beta blockers.

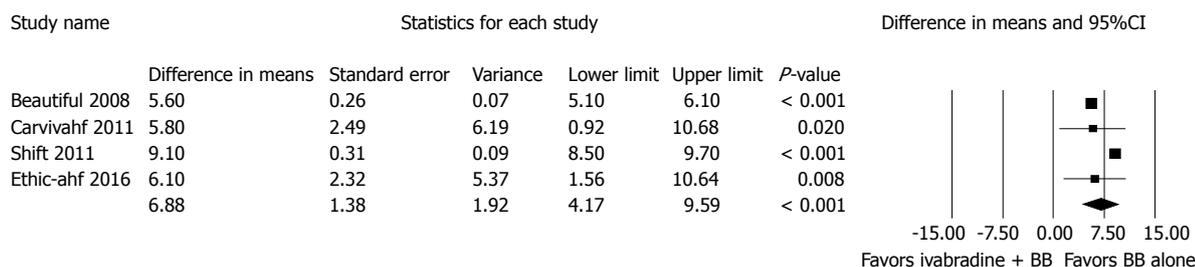


Figure 3 Comparison of mean change in heart rates from baseline between ivabradine + beta-blocker vs beta-blocker alone including only randomized controlled trials. BB: Beta blockers.

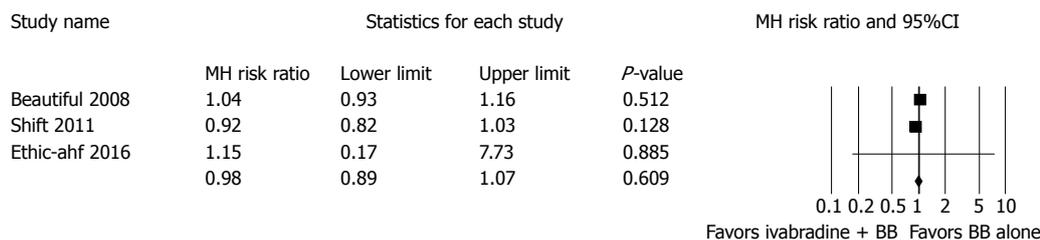


Figure 4 Comparison of Mantel-Haenszel risk ratio for all cause mortality between ivabradine + beta-blocker vs beta-blocker alone. BB: Beta blockers.

blocker when compared to the beta-blocker alone group (MD: 3.27, 95%CI: 0.42-6.13,  $P = 0.025$ ). Heterogeneity was moderate ( $I^2 = 45\%$ ).

## DISCUSSION

In this meta-analysis, ivabradine combined with beta-blockers resulted in a greater reduction of heart rates at follow up when compared to beta-blocker only group. Also, combined therapy was associated with significantly lower composite end-point of cardiovascular death or hospitalization for worsening heart failure. On the other hand, in the relatively short follow-up offered by the included studies, there was no improvement in secondary outcomes including isolated cardiovascular or all cause mortality or individual outcome of heart failure hospitalization. However surrogate markers such as 6MWD and ejection fraction appeared to improve in the ivabradine plus beta-blocker group vs beta-blocker alone. The importance of an improvement in EF with more bradycardia is difficult to determine since at

slower heart rates more complete emptying can occur and may manifest as an improvement in EF without a true increase in LV intrinsic contractility or end systolic elastance.

Ivabradine was approved by the United States Food and Drug Administration for treatment of HFrEF in 2015. It is a very specific inhibitor of hyperpolarization activated cyclic nucleotide gated channels, which decreases the diastolic  $I(f)$  current and reduces sinus rate<sup>[24]</sup>. Ivabradine has no effect on the atrio ventricular node itself<sup>[24]</sup>. In addition, it has been shown that  $I(f)$  channels may increase in chronic heart failure in ventricular myocytes, and this could be arrhythmogenic<sup>[25]</sup>, therefore inhibition of these channels by ivabradine could be beneficial in patients with HFrEF. Ivabradine has use dependency<sup>[26]</sup> and thus the reduction in heart rate is proportional to the baseline heart rate in individuals. Given all these characteristics and its effect of lowering heart rate without inducing the negative inotropic effect of beta-blockers, ivabradine was expected to not only be better tolerated than beta-blockers in HFrEF, but also to be

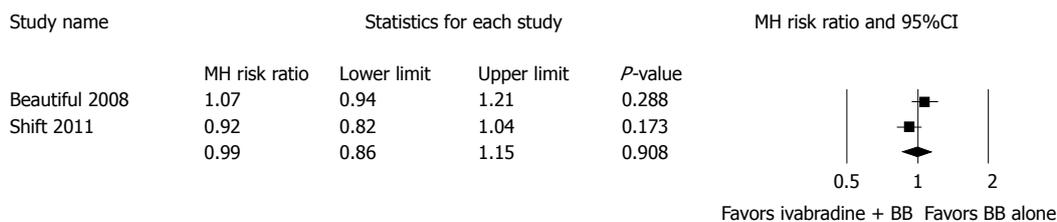


Figure 5 Comparison of Mantel-Haenszel risk ratio for cardiovascular mortality between ivabradine + beta-blocker vs beta-blocker alone. BB: Beta blockers.

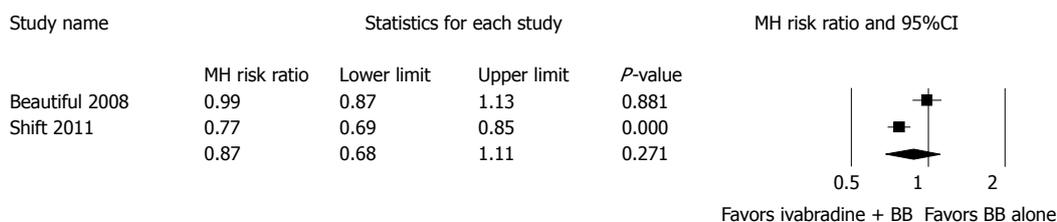


Figure 6 Comparison of Mantel-Haenszel risk ratio for heart failure hospitalization between ivabradine + beta-blocker vs beta-blocker alone. BB: Beta blockers.

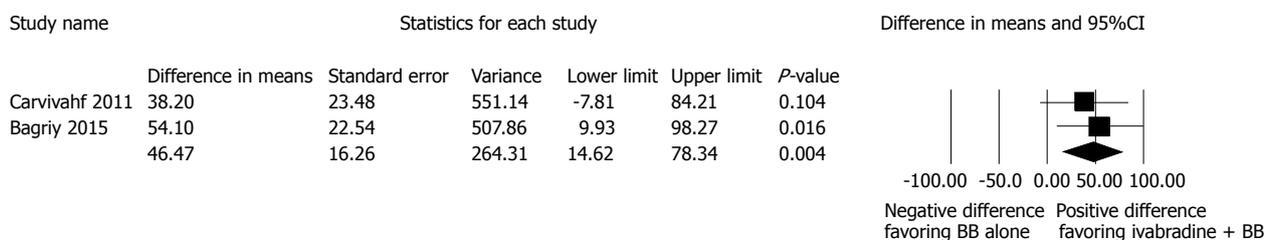


Figure 7 Comparison of difference in means of 6-min walking distance between ivabradine + beta-blocker vs beta-blocker alone. BB: Beta blockers.

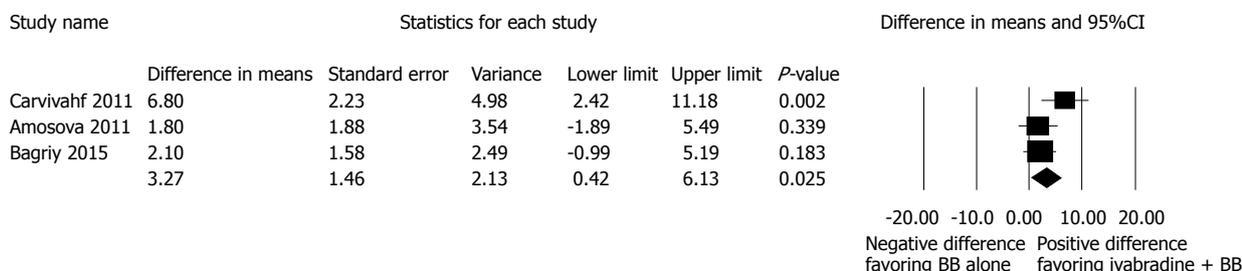


Figure 8 Comparison of difference in means of ejection fraction between ivabradine + beta-blocker vs beta-blocker alone. BB: Beta blockers.

beneficial by minimizing the adverse cardiac structural changes associated with tachycardia<sup>[12]</sup>.

**Summary of existing trials**

In the BEAUTIFUL trial<sup>[18]</sup>, a double blind RCT, 10917 patients with coronary disease and HFrEF and an EF < 40% were randomized to either ivabradine or placebo. Both groups were on optimal conventional heart failure medications with 87% of the patient population in both groups on beta-blockers; though there was no mention of whether the subjects were on maximal tolerated beta-blocker doses. The BEAUTIFUL study<sup>[18]</sup> reported that 84% of population was in NYHA Class II or III. Four percent of subjects were lost during follow-up. At 24 mo follow up, ivabradine group had a greater improvement in Heart rate with a MD (difference in means) of 5.6

bpm when compared to the placebo group. However, although mortality benefit with heart rate reduction has been shown in multiple studies, BEAUTIFUL<sup>[18]</sup> failed to show any benefit in terms of combined cardiovascular end-point of cardiovascular death, hospital admission for myocardial infarction or new onset worsening heart failure. Also there was no improvement in individual secondary outcomes including all cause mortality, cardiac mortality, hospitalization or worsening heart failure in both the groups.

In the sub-group with heart rates of 70 bpm or more<sup>[18]</sup>, the MD in change from baseline was 6.9 bpm at 24 mo in the ivabradine arm. Although there was no difference between the groups in their primary end-points, there was a statistically significant reduction in secondary outcomes including number of follow

up hospital admissions for myocardial infarction and coronary revascularization. A borderline reduction in the composite end-point was noted in the ivabradine group when 14% of patients with activity limiting angina were analyzed separately, both in the overall group and in the sub group of HR > 70 bpm.

The SHIFT trial<sup>[12]</sup> is the next largest ivabradine RCT, and randomized 6505 patients with stable chronic ischemic and non-ischemic HFrEF of < 35% to receive either ivabradine or placebo in conjunction with optimal medical therapy for heart failure. SHIFT reported that 89% of patient population were being treated with beta-blockers at the beginning of the trial. All patients were in NYHA Class II-IV with almost 99% patient population in class II and III. The study mentioned that only 26% of the patient population was receiving optimal target dose of beta-blocker, and the most common reason for not being able to achieve the target dose was hypotension (almost 45% population in both groups). The results showed that the ivabradine group had a lower incidence of combined end-point of cardiovascular death or hospitalization for worsening of heart failure though all cause-mortality was not different between the groups. The sub-group carvedilol only study<sup>[22]</sup> still retained the benefit for combined end-point in the ivabradine plus carvedilol but cardiovascular mortality was not different between ivabradine plus carvedilol and the carvedilol only group.

In a pooled analysis of the SHIFT<sup>[12]</sup>, and the BEAUTIFUL<sup>[18]</sup> trials<sup>[27]</sup>, ivabradine achieved highest heart rate control in patients with a baseline HR of > 75 bpm when compared to patients with HR < 60 bpm; this finding is consistent with the use-dependence property of the drug. The lower heart rate at follow up in the ivabradine sub-group was associated with the lowest mortality (17.4% in < 60 bpm vs 32.4% in > 75 bpm). When the investigators did a statistical adjustment for heart rate and other prognostic factors, the benefit of ivabradine was eliminated. Consequently, it may be that ivabradine improved the combined end-point mainly by heart rate reduction, although other possible mechanisms including I(f) blockade in ventricular myocardium in chronic HFrEF cannot be eliminated. In SHIFT<sup>[12]</sup>, the MD in heart rate from baseline in the ivabradine group was greater than in BEAUTIFUL<sup>[18]</sup>; the relatively lower heart rate reduction achieved in BEAUTIFUL could be a possible explanation for absence of improvement in combined end-point of cardiovascular death or hospitalization for heart failure in the latter.

It should be noted in SHIFT<sup>[12]</sup> that patients on < 50% of the target beta-blocker dosage achieved more benefit at the combined end-point when combined with ivabradine, as compared to the overall group. One possible explanation could be patients with < 50% of target beta-blocker dosage have a higher HR and these patients tend to achieve higher benefit with ivabradine therapy than patients with a lower HR (secondary to the use-dependence property of ivabradine).

In ETHIC-AHF, a smaller recent RCT published by

Hidalgo *et al*<sup>[23]</sup>, 71 patients with acute heart failure and with EF of < 40%, sinus rhythm and HR > 70 bpm were randomized to ivabradine plus beta-blockers and beta-blockers alone. HR at 1-mo and at 4-mo follow-up were lower in the ivabradine group but the difference did not translate into improved clinical outcomes which showed no difference between the two groups in hospitalization rates for heart failure or death at follow-up.

The European Medical Agency set 75 bpm as HR cut-off<sup>[15]</sup> while the ACC/AHA guidelines<sup>[14]</sup> recommended 70 bpm as cut off for use of ivabradine in chronic HFrEF. Though the combined end-point of heart failure hospitalization or cardiac mortality was reduced along with improvement in ejection fraction and 6MWD, there was no reduction in all cause mortality, cardiovascular mortality or heart failure hospitalization alone in the current study. Also, in SHIFT<sup>[12]</sup>, the benefit was higher in patients on < 50% target dose of beta-blocker, limiting its generalizability and suggesting, that there may be only a sub group that might benefit from ivabradine therapy. Therefore, before further evidence becomes available, it is essential to follow the current guidelines and up-titrate the dosage of beta-blockers before initiating ivabradine therapy for HFrEF. Further randomized trials with long term follow-up will determine if the short-term benefit in composite end-point translates to long term mortality benefit.

### Limitations

The limitations of our meta-analysis are similar to any meta-analysis, including all limitations and biases associated with the original studies. We did not have access to patient level data and so we were not able to include outcomes of interest not reported in some articles. The meta-analysis included four RCTs and two sub-groups from RCTs along with two non-randomized trials and could be a source of bias. To diminish the bias, we analyzed RCTs separately which did not alter the outcomes. We could not adjust for confounding variables that were not adjusted for in the primary studies. The optimal dosage of beta-blockers tolerated was not reported in some trials and thus we could not analyze the correlation between baseline beta-blocker dose and ivabradine dependent outcomes. Thus, it still remains unclear if ivabradine would maintain its efficacy in patients who are on maximal tolerated doses of beta-blockers. Unavoidably, publication bias is a limitation of any meta-analysis.

In summary, the results of our systematic review and meta-analysis of the published literature supports use of ivabradine in patients with chronic HFrEF in sinus rhythm and with HR of > 70 bpm per guidelines, however the strength of evidence supporting this recommendation is weak. This approach is associated with demonstrable benefit in terms of composite end-point of cardiovascular mortality or hospitalization for heart failure. There was an improvement in ejection fraction and 6MWD at follow up but this was not reported in the majority of the published trials. More evidence is needed before ivabradine can be recommended more broadly to patients with HFrEF. The

current evidence supporting its approval is limited.

## ACKNOWLEDGMENTS

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## COMMENTS

### Background

Ivabradine is a novel heart rate reducing agent by selectively inhibiting the cardiac pacemaker current if thereby slowing heart rates without exhibiting negative inotropic effect on the myocardium. It was approved by the United States Food and Drug Administration for treatment of heart failure with reduced ejection fraction (HFrEF) in 2015.

### Research frontiers

The 2016 American College of Cardiology/American Heart Association/Heart Failure Society of America (ACC/AHA/HFSA) Focused Update on the Management of Heart Failure and the European Society of Cardiology (ESC) guidelines have given a Class IIa (level of evidence B) recommendation for ivabradine use for patients with chronic HFrEF who are on guideline directed medical therapy. It is unclear, however, whether ivabradine offers any additional benefit when combined with beta-adrenergic blockade.

### Innovations and breakthroughs

Two large RCTs (BEAUTIFUL and SHIFT) and some small RCTs compared the efficacy of ivabradine with beta blockers combined with beta blocker alone in people with chronic systolic heart failure. Both BEAUTIFUL and SHIFT failed to show mortality benefit but target beta blocker dosage achieved in these studies was lower, creating bias and suggesting there may be only a sub group that might benefit from ivabradine therapy.

### Applications

The systematic review and meta-analysis supports use of ivabradine in patients with chronic HFrEF in sinus rhythm and with HR of > 70 bpm per the updated guidelines. Further randomized controlled trials are essential before ivabradine can be recommended more broadly to patients with HFrEF and the current evidence supporting its approval is limited.

### Peer-review

A useful and interesting paper that should be published after authors make some changes to ensure the article is clearer, easy to read and not too technical statistically.

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## Dysphagia after arteria lusoria dextra surgery: Anatomical considerations before redo-surgery

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**Author contributions:** Mayer J drafted the initial and further case report; Kroll J as experienced pediatric cardiovascular surgeon performed both operations and contributed important, detailed information for the surgical and anatomical discussion; Grohmann J was one of the leading cardiologists in charge during the entire duration of treatment and played an important role in developing and reviewing the final manuscript; all authors were involved in the patient management as an interdisciplinary team, critically reviewed the manuscript and approved the final manuscript as submitted.

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### Abstract

Aberrant right subclavian artery (arteria lusoria) is the most common congenital root anomaly, remaining asymptomatic in most cases. Nevertheless, some of the 20%-40% of those affected present tracheo-esophageal symptoms. We report on a 6-year-old previously healthy girl presenting with progressive dysphagia over 4 wk. Diagnostics including barium swallow, echocardiography and magnetic resonance angiography (MRA) revealed a retro-esophageal compression by an aberrant right subclavian artery. Despite the successful, uneventful transposition of this arteria lusoria to the right common carotid *via* right-sided thoracotomy, the girl was suffering from persisting dysphagia. Another barium swallow showed the persistent compression of the esophagus on the level where the arteria lusoria had originated. As MRA showed no evidence of a significant re-obstruction by the transected vascular stump, we suspected a persisting ligamentum arteriosum. After a second surgical intervention *via* left-sided thoracotomy consisting of transecting the obviously persisting ligamentum and shortening the remaining arterial stump of the aberrant right subclavian artery, the patient recovered fully. In this case report we discuss the potential relevance of a persisting ligamentum arteriosum for patients with left

aortic arch suffering from dysphagia lusoria and rational means of diagnosing, as well as the surgical options to prevent re-do surgery.

**Key words:** Arteria lusoria dextra; Persisting ligamentum arteriosum; Dysphagia; Retroesophageal compression; Redo-surgery

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**Core tip:** We present a pediatric case of dysphagia caused by the common congenital root anomaly of an aberrant right subclavian artery. However, persisting symptoms after primary treatment *via* right-sided thoracotomy required redo-surgery *via* left-sided thoracotomy with transection of a persisting ligamentum arteriosum and shortening of the remaining lusorian arteries' stump. Based on this experience, we want to emphasize the potential co-existence of a compressing ligamentum arteriosum even in patients with left aortic arch.

Mayer J, van der Werf-Grohmann N, Kroll J, Spiekerkoetter U, Stiller B, Grohmann J. Dysphagia after arteria lusoria dextra surgery: Anatomical considerations before redo-surgery. *World J Cardiol* 2017; 9(2): 191-195 Available from: URL: <http://www.wjgnet.com/1949-8462/full/v9/i2/191.htm> DOI: <http://dx.doi.org/10.4330/wjc.v9.i2.191>

## INTRODUCTION

Aberrant right subclavian artery is the most common congenital root anomaly in general population with a prevalence ranging from 0.5% to 1.8%<sup>[1]</sup>. The arteria lusoria was first described in 1794 by David Bayford<sup>[2]</sup>, it results from an atypical obliteration of the 4th aortic arch, whereby the right subclavian artery is formed by the persistent right dorsal aorta in connection with the 7<sup>th</sup> intersegmental artery. The resulting aberrant right subclavian artery has an atypical origin from the descending aorta and reveals a retro-esophageal course to supply the right arm with blood<sup>[1,3]</sup>.

The aberrant right subclavian artery usually remains asymptomatic<sup>[4]</sup>. Nevertheless 20%-40% of patients have tracheo-esophageal symptoms, with dysphagia being the most frequent symptom in 90% of patients with clinical symptoms<sup>[1,5]</sup>. Respiratory symptoms like cough, dyspnea, stridor, increased respiratory infections or thoracic pain are more frequent in children than in adults<sup>[6]</sup>.

Surgical treatment should be restricted to seriously symptomatic patients and is usually performed *via* right-sided thoracotomy. This operative intervention consists of mobilization and transection of the aberrant right subclavian artery from the descending aorta, and re-implantation into the right common carotid artery<sup>[7]</sup>.

## CASE REPORT

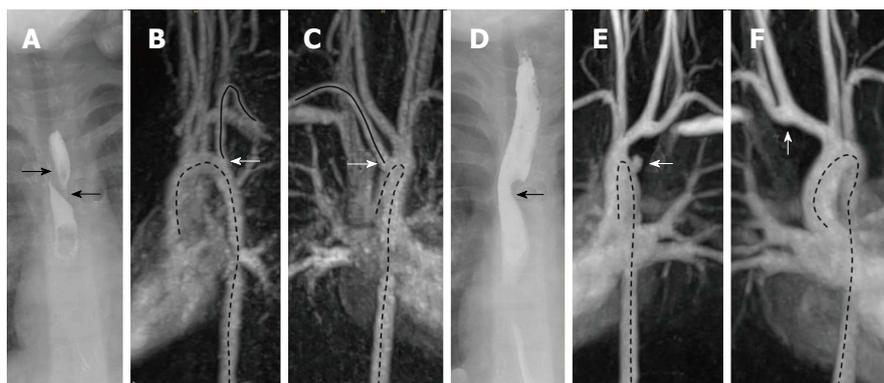
A 6-year-old girl presented with recurrent and progressive dysphagia over 4 wk. At first contact, she had lost 8 kg over 4 wk, showed severe difficulty swallowing solid foods and also suffered from recurrent thoracic pain. She underwent a barium swallow for differential diagnosis purposes which demonstrated a severe compression of the esophagus in its intermediate third, highly suspicious of vascular compression (Figure 1A). Subsequent echocardiography led to the presumptive diagnosis of an aberrant right subclavian artery with its origin in the descending aorta and a retro-esophageal course to the right side. The authors also diagnosed a truncus bicaroticus. Subsequent MRA confirmed the diagnosis of an isolated arteria lusoria (Figure 1B and C), which was considered as the proven cause for the girl's dysphagia.

Because her dysphagia had worsened so rapidly (she could only swallow liquids), her discomfort and significant weight loss, the decision for an operative intervention was made. *Via* right-sided thoracotomy over the 4<sup>th</sup> intercostal space (ICS), the aberrant right subclavian artery was mobilized, transected behind the esophagus and transposed to the right common carotid by an end-to-side-anastomosis. There were no perioperative complications. Upon her discharge on day 12 after surgery, the patient was free of symptoms such as dysphagia or thoracic pain.

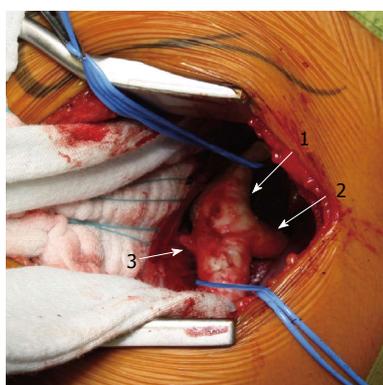
During follow-up a few weeks later, she returned suffering again from dysphagia, hypersalivation, dry cough and sore throat. Analgesics had not relieved her symptoms.

As the girl kept presenting with recurrent thoracic pain and mild symptoms of dysphagia accompanied by intermittent symptom-free periods and the lack of significant findings in clinical and diagnostic examinations, a somatoform disorder was suspected as the origin of her symptoms.

Sixteen months after corrective surgery and following a symptom-free 7-mo interval, the patient presented again with severe dysphagia (no solid food) but no thoracic pain as described before. Another barium swallow was performed (Figure 1D) which showed persistent compression of the esophagus on the level where the arteria lusoria had originated. Subsequent MRA displayed the vascular stump with a maximum length of 10 mm and diameter of 4-5 mm (Figure 1E). There were no further changes compared to the images taken 12 mo earlier. The region of the vascular anastomosis showed no abnormalities (Figure 1F). Finally, the suspicion of two factors causing the ongoing compression of the esophagus and the recurrent symptoms arose: First, compression by the persisting stump of the aberrant right subclavian artery and second, an incomplete vascular ring due to a persisting ligamentum arteriosum, which was not transected.



**Figure 1** Fluoroscopy and magnetic resonance angiography at initial presentation and at follow-up. A-C: Fluoroscopy and MRA at initial presentation; A: The arrows mark the outer boundary of the esophagus. There is a filling defect in between which runs from right side superior to left side inferior due to compression of the vessel; B and C: The arrow marks the right sided subclavian artery which originates distally to the left supraaortic vessels. The course of the artery is shown by the uninterrupted line. The dotted lines mark the course of the thoracic aorta; D-F: Fluoroscopy and MRA at follow up; D: The arrow marks a filling defect of the esophagus; E: The arrow marks the vascular stump. The dotted lines mark the course of the thoracic aorta; F: The arrow marks the anastomosis. The dotted line represents the course of the aorta. MRA: Magnetic resonance angiography.



**Figure 2** Operative findings in redo-surgery: Surgical approach over the 3<sup>rd</sup> intercostal space via left-sided thoracotomy: A structure consistent with the ligamentum arteriosum can be presented leading to the descending aorta distal the left subclavian's origin. 1: Aorta descendens; 2: Left subclavian artery; 3: Ligamentum arteriosum.

Therefore, redo-surgery was performed, this time over the 3<sup>rd</sup> ICS via left-sided thoracotomy (Figure 2) and consisted of shortening the remaining lusorians' stump and transecting the ligamentum arteriosum. The patient experienced an uneventful and complete recovery.

The barium swallow she underwent 6 wk after reoperation demonstrated no more signs of esophageal compression. At all subsequent clinical follow-ups over 6 mo after surgery, she had no more dysphagia and had regained weight.

## DISCUSSION

We report on a 6-year-old girl presenting with dysphagia attributed to an aberrant right subclavian artery that unexpectedly caused persisting symptoms after corrective surgery via right-sided thoracotomy.

As the aberrant right subclavian artery often remains asymptomatic<sup>[3]</sup>, surgical repair is restricted to highly-symptomatic patients, and it is usually very successful.

Nevertheless, a small percentage of these patients return complaining of recurrent respiratory or swallowing problems<sup>[8]</sup>.

There is a potential anatomical explanation for ongoing postoperative symptoms like dysphagia: Compared to a left-sided aortic arch, the right-sided aortic arch combined with an aberrant left subclavian artery maintains a persisting ligamentum arteriosum. In contrast, in those with a left-sided aortic arch and an aberrant right subclavian artery, a left-sided ligamentum arteriosum is much rarer but it remains a potential anatomical finding. Such a ligamentum arteriosum - a fibrous relict of the ductus arteriosus - leads from the proximal descending aorta to the left pulmonary artery. In the presence of a coexisting aberrant right subclavian artery, an incomplete vascular ring can form that compresses the esophagus<sup>[9]</sup>.

We thus maintain that, to ensure optimum recovery after a surgical intervention for arteria lusoria, it is essential to be fully aware of the patient's cardiothoracic anatomy beforehand, especially the existence of a persisting ligamentum arteriosum. In selecting the diagnostic tools, we suggest an age-dependent approach. In fetuses, newborns and infants presenting the incidental finding of an arteria lusoria, echocardiography has great potential to validate the cardiovascular system in detail, especially a vascular ring with a fibrous ductus arteriosus. Echocardiography remains highly informative even in symptomatic infants and children. Barium swallow and MRA are additional key diagnostic tools in this age group. In case of older children and adolescents, the first-line modality should be MRA. At that age, echocardiography becomes secondary because it precludes a thorough evaluation of the patient's anatomy.

Another key factor for surgical success is the choice of surgical access. Regarding the preferred approach to the aberrant right subclavian artery in children, van Son *et al.*<sup>[10]</sup> found that this vessel originates from the posteromedial side of the distal aortic arch. Therefore,

a strong argument for currently-mandated right-sided thoracotomy in children is the vessel's optimal mobilization, transection and reconnection.

However, assessing a ligamentum arteriosum is limited in this access path, thus in case of a left aortic arch with left-sided ligamentum arteriosum, the recommended surgical access to reach this usually fibrous strand is *via* left-sided thoracotomy.

In summary, we suggest considering a median thoracotomy to address both contrary structural conditions and to effectively treat a right arteria lusoria in combination with a left ligamentum arteriosum at the same time. *Via* this median access, the course of the aberrant right subclavian artery can be corrected, and the surgeon is able to explore and transect a persisting ligamentum arteriosum.

In conclusion, we suggest that our patient continued to suffer dysphagia after initial surgery of the aberrant right subclavian artery due to the persisting pathology of a ligamentum arteriosum causing further esophageal compression. Since this experience, our recommendation for other patients with a left-sided aortic arch and right arteria lusoria is first to focus on obtaining a detailed preoperative visualization of the individual's anatomy by means of diagnostic imaging, especially to watch out for a ligamentum arteriosum. In case of a potential ligamentum arteriosum, we favor a median thoracotomy because of its optimal provision of intraoperative anatomical overview and accessibility to both the aberrant artery and ligamentum arteriosum.

## ACKNOWLEDGMENTS

We are grateful to Carole Cürten for language editing.

## COMMENTS

### Case characteristics

This is a rare pediatric case about a 6-year-old girl with an aberrant right subclavian artery unexpectedly presenting with persisting severe dysphagia after initial corrective surgery *via* right-sided thoracotomy.

### Clinical diagnosis

Apart from mild symptoms such as hypersalivation and a dry cough, there were no other significant anomalies in clinical examination.

### Differential diagnosis

Ingested foreign bodies, esophageal infection or neoplasia, disorders in esophageal innervations or secondary to cardiovascular compression or thyroid disease.

### Laboratory diagnosis

The authors' laboratory tests revealed no pathology.

### Imaging diagnosis

The initial diagnosis of an aberrant right subclavian artery was confirmed *via* barium swallow, subsequent echocardiography and magnetic resonance angiography (MRA), whereas during the persistent dysphagia after her first intervention, only the barium swallow demonstrated a dorsal esophageal compression that led us to suspect an incomplete vascular ring due to a persisting ligamentum arteriosum.

## Pathological diagnosis

Persisting esophageal compression after arteria lusoria dextra surgery caused by an incomplete vascular ring due to a persisting ligamentum arteriosum.

## Treatment

Redo-surgery *via* left-sided thoracotomy entailing the transection of a persisting ligamentum arteriosum and shortening of the remaining lusorian arteries' stump.

## Related reports

Although arteria lusoria is the most common embryologic abnormality of the aortic arch and its potential esophageal compression can result in dysphagia, a case of persisting symptoms after corrective surgery because of a co-existing ligamentum arteriosum in patients with left aortic arch has never been reported in the literature so far.

## Term explanation

Magnetic resonance angiography (MRA) is a type of magnetic resonance imaging scan to evaluate blood vessels and helps to identify vascular abnormalities by using a powerful magnetic field and pulses of radio wave energy.

## Experiences and lessons

Based on this experience, the authors wish to emphasize the potential co-existence of a compressing ligamentum arteriosum even in patients with left aortic arch; furthermore, the authors would like to inspire discussion about an age-dependent approach regarding which diagnostic tools are employed for pre-operative planning, as well as what constitutes the optimal surgical approach.

## Peer-review

This is a rare case report about a pediatric case of dysphagia attributed to an aberrant right subclavian artery that unexpectedly caused persisting symptoms after corrective surgery *via* right-sided thoracotomy. The authors suggest considering a median thoracotomy to address both contrary structural conditions and to effectively treat a right arteria lusoria in combination with a left ligamentum arteriosum at the same time. This manuscript is nicely structured and well written.

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## Very late transcatheter heart valve thrombosis

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**Author contributions:** All authors contributed to the acquisition of data, writing, and revision of this manuscript.

**Institutional review board statement:** This case report was exempt from the Institutional Review Board standards at Centre de recherche du centre hospitalier universitaire de Sherbrooke.

**Informed consent statement:** The patient involved in this study gave her written informed consent authorizing use and disclosure of her protected health information.

**Conflict-of-interest statement:** Dr. Masson is a proctor/consultant for Edwards Lifesciences Inc. All other authors have no conflicts of interests to declare.

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### Abstract

We describe a case of very late transcatheter heart valve (THV) thrombosis of a first-generation SAPIEN prosthesis (Edwards Lifesciences, Irvine, CA) implanted in a 64-year-old woman with severe symptomatic aortic stenosis. More than 54 mo after implantation, she presented with severe symptomatic prosthesis dysfunction (stenosis) which was successfully treated with oral anticoagulation. To our knowledge, this is the tardiest case of THV thrombosis ever reported. This case should increase clinical awareness for THV thrombosis even beyond the first two-year period following implantation.

**Key words:** Valve thrombosis; Transcatheter heart valve; Transcatheter aortic valve replacement

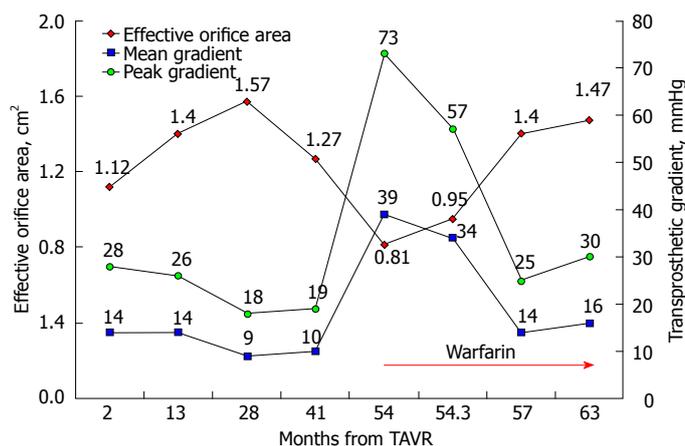
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**Core tip:** We describe the tardiest case of transcatheter aortic valve replacement (TAVR) thrombosis ever reported. A 64-year-old woman with severe symptomatic aortic stenosis underwent TAVR with a first-generation SAPIEN prosthesis. More than four years (> 54 mo) following implantation, she presented with a severe symptomatic prosthesis dysfunction (stenosis) which was successfully treated with oral anticoagulation.

Couture EL, Lepage S, Masson JB, Daneault B. Very late transcatheter heart valve thrombosis. *World J Cardiol* 2017; 9(2): 196-199 Available from: URL: <http://www.wjgnet.com/1949-8462/full/v9/i2/196.htm> DOI: <http://dx.doi.org/10.4330/wjc.v9.i2.196>

### INTRODUCTION

We describe a case of very late transcatheter heart valve (THV) thrombosis of a first-generation SAPIEN prosthesis (Edwards Lifesciences, Irvine, CA) implanted in a 64-year-old woman with severe symptomatic



**Figure 1** Transprosthetic gradients and effective orifice area following transcatheter aortic valve replacement (2 to 54 mo), at the time transcatheter heart valve thrombosis (54 mo) and following anticoagulation therapy (54 to 63 mo). TAVR: Transcatheter aortic valve replacement; THV: Transcatheter heart valve.

aortic stenosis. More than 54 mo after implantation, she presented with severe symptomatic prosthesis dysfunction (stenosis) which was successfully treated with oral anticoagulation. To our knowledge, this is the tardiest case of THV thrombosis ever reported. This case should increase clinical awareness for THV thrombosis even beyond the first two-year period following implantation.

## CASE REPORT

A 64-year-old woman with severe symptomatic aortic stenosis and porcelain aorta underwent transcatheter aortic valve replacement (TAVR) using a first-generation balloon-expandable Edwards SAPIEN (Edwards Lifesciences, Irvine, CA) 23 mm THV in January 2011. The patient was discharged home with aspirin and clopidogrel for three months followed by low dose aspirin.

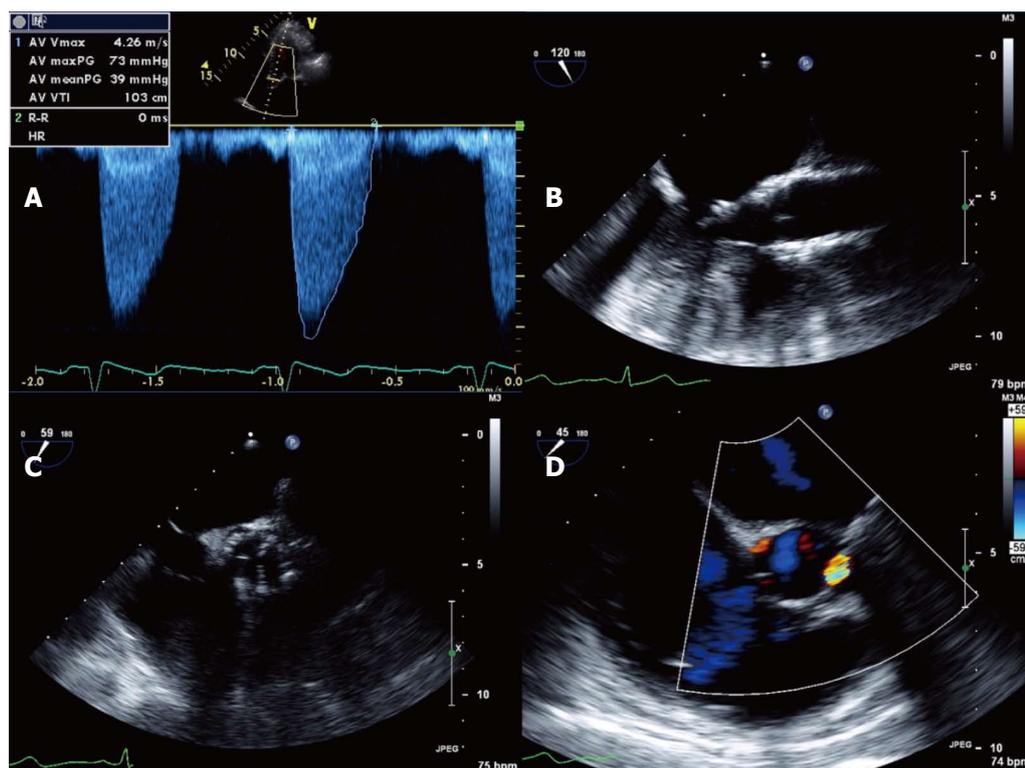
More than 54 mo following TAVR, she presented with progressive dyspnea, angina and dizziness on moderate exertion. Transthoracic echocardiogram (TTE) revealed a severe THV dysfunction with an aortic valve area (AVA) of 0.81 cm<sup>2</sup>, peak and mean trans prosthetic gradients (TPG) of 76 and 39 mmHg respectively and a preserved left ventricular ejection fraction (Figure 1). Transesophageal echocardiogram (TEE) did not demonstrate abnormal leaflet function neither THV thrombosis (Figure 2) but revealed a moderate paravalvular leak (PVL) (Figure 2D) already known from the immediate post-TAVR TEE. THV thrombosis was suspected given the absence of other explanatory findings and the abrupt progression of TPG. Therefore, anticoagulation with warfarin and unfractionated heparin was empirically started. A coronary angiogram and a cardiovascular magnetic resonance (CMR) were also performed. Angiogram revealed a severe, non-thrombotic, left main mid-shaft stenosis and percutaneous coronary intervention (PCI) with a drug-eluting stent was performed. CMR revealed an aortic regurgitation fraction of 23% consistent with the moderate PVL previously seen on the TEE. No evidence of THV thrombosis other than elevated peak velocity was detected on CMR. Nine days after initiation of anticoagulation, a repeat TTE showed mild improvement

in TPG (Figure 1). The patient was discharged home with aspirin, clopidogrel and warfarin for three months, followed by clopidogrel and warfarin. Angina was relieved immediately after PCI, but dyspnea on exertion improved over weeks. After three months, symptoms had resolved completely and TPG returned to their baseline values. They remained unchanged after nine months under chronic anticoagulation (Figure 1).

## DISCUSSION

In two series, less than 30 cases of THV thrombosis have been reported with a median presentation time of 6 mo (range, 3-735 d) with only two cases occurring beyond one year<sup>[1,2]</sup>. A case of a Direct Flow Medical THV thrombosis three years following TAVR has also been reported recently<sup>[3]</sup>. To our knowledge, never a THV thrombosis has been described so late after implant (> 54 mo) as in this case. THV thrombosis is a new entity that needs to be recognized not only by TAVR specialists. Even though estimated incidence is low (0.61%), consequences can be catastrophic if appropriate therapy is not initiated promptly<sup>[1]</sup>. Only reported cases treated with anticoagulation had favorable outcome. Therefore, a sudden increase in TPG should trigger further investigation or therapies to exclude THV thrombosis. Valve hemodynamic deterioration (VHD), defined by an increase in mean TPG of more than 10 mmHg over time, was observed more frequently in patients with smaller THV (23 mm) and those not receiving oral anticoagulation<sup>[4]</sup>. Most of these patients did not have a progressive deterioration after the first year. VHD does not seem to be part of a continuum towards THV thrombosis and this later remains unpredictable. However, the pathophysiology of VHD may include some degree of sub-clinical leaflet thrombosis.

In our case, TEE evaluation was not diagnostic. In a series of 3 pathology-proven THV thrombosis, TEE was also negative in each cases<sup>[2]</sup>. However, Makkar *et al*<sup>[5]</sup> showed that 4D-CT and TEE had a diagnostic concordance of 100% in 10 patients presenting reduced leaflets motion following TAVR. Whether 4D-CT is the optimal imaging modality remains to be proven. CMR was chosen over CT scan to assess PVL severity but



**Figure 2** Transesophageal echocardiogram. It shows transprosthetic gradients compatible with severe aortic stenosis (A); Absence of obvious mass or valve thrombosis on Transesophageal echocardiogram (B, C) but moderate paravalvular leak (D).

also failed to identify the THV thrombosis. Therefore, negative imaging should not preclude an anticoagulation trial when the diagnostic is highly suspected.

Reports have revealed subclinical leaflet thrombosis detected by TEE and 4D CT scan early after THV implantation<sup>[5]</sup>. Most of these cases were seen in patients who did not receive anticoagulation. The clinical significance of these findings remains unknown at this point. Studies are ongoing to evaluate the optimal antiplatelet/anticoagulant therapy after TAVR. The ARTE (clopidogrel; NCT01559298) and REAC-TAVI (ticagrelor vs clopidogrel; NCT02224066) trials are evaluating different antiplatelet strategies and the GALILEO (rivaroxaban; NCT02556203) and ATLANTIS (apixaban; NCT02664649) studies are looking at the effect of non-vitamin K oral anticoagulant following TAVR. Similarly, the POPular-TAVI trial (NCT02247128) is evaluating the effect of adding clopidogrel for 3 mo following implantation in patients with and without ongoing vitamin-K oral anticoagulation treatment.

This case is also particular because of the concurrent left main stenosis. Although thrombus migration in the left main could be considered an explanation, the angiographic appearance was more in favor of disease progression of a previous non-significant lesion seen on the pre-TAVR angiogram. Moderate PVL could be associated with a different flow pattern over the leaflets and in the left main that could lead to THV thrombosis as well as accelerated progression of atherosclerosis although this relationship is speculative.

This case should increase clinical awareness for THV thrombosis even beyond the first two-year period following implantation. Risk predictors for THV thrombosis and optimal antiplatelet/anticoagulant therapy post TAVR are still unknown and warrants clinical trials.

## COMMENTS

### Case characteristics

More than 54 mo following transcatheter aortic valve replacement, a 64-year-old woman presented with progressive dyspnea, angina and dizziness on moderate exertion.

### Clinical diagnosis

Prosthesis dysfunction.

### Differential diagnosis

Transcatheter heart valve (THV) degeneration; THV thrombosis; THV endocarditis.

### Imaging diagnosis

Transesophageal echocardiogram (TEE) revealed a prosthesis dysfunction with a severe stenosis. TEE failed to reveal THV thrombosis as well as vegetations.

### Treatment

Empiric treatment with unfractionated intravenous heparin followed by long-term anticoagulation with warfarin.

### Related reports

Less than 30 cases of THV thrombosis have been reported with a median presentation time of 6 mo (range, 3-735 d) with only two cases occurring beyond one year.

**Experiences and lessons**

This case should increase clinical awareness for THV thrombosis even beyond the first two-year period following implantation. Even if TEE does not reveal THV thrombosis.

**Peer-review**

The paper is well written.

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## Angiotensin receptor blocker drugs and inhibition of adrenal beta-arrestin-1-dependent aldosterone production: Implications for heart failure therapy

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### Abstract

Aldosterone mediates many of the physiological and pathophysiological/cardio-toxic effects of angiotensin II (AngII). Its synthesis and secretion from the zona glomerulosa cells of the adrenal cortex, elevated in chronic heart failure (HF), is induced by AngII type 1 receptors (AT<sub>1</sub>Rs). The AT<sub>1</sub>R is a G protein-coupled receptor, mainly coupling to G<sub>q/11</sub> proteins. However, it can also signal through β-arrestin-1 (βarr1) or -2 (βarr2), both of which mediate G protein-independent signaling. Over the past decade, a second, G<sub>q/11</sub> protein-independent but βarr1-dependent signaling pathway emanating from the adrenocortical AT<sub>1</sub>R and leading to aldosterone production has become appreciated. Thus, it became apparent that AT<sub>1</sub>R antagonists that block both pathways equally well are warranted for fully effective aldosterone suppression in HF. This spurred the comparison of all of the currently marketed angiotensin receptor blockers (ARBs, AT<sub>1</sub>R antagonists or sartans) at blocking activation of the two signaling modes (G protein-, and βarr1-dependent) at the AngII-activated AT<sub>1</sub>R and hence, at suppression of aldosterone *in vitro* and *in vivo*. Although all agents are very potent inhibitors of G protein activation at the AT<sub>1</sub>R, candesartan and valsartan were uncovered to be the most potent ARBs at blocking βarr activation by AngII and at suppressing aldosterone *in vitro* and *in vivo* in post-myocardial infarction HF animals. In contrast, irbesartan and losartan are virtually G protein-“biased” blockers at the human AT<sub>1</sub>R, with very low efficacy for βarr inhibition and aldosterone suppression. Therefore, candesartan and valsartan (and other, structurally similar compounds) may be the most preferred ARB agents for HF pharmacotherapy, as well as for treatment of other conditions characterized by elevated aldosterone.

**Key words:** Adrenal cortex; Adrenocortical zona glomerulosa cell; Aldosterone; Angiotensin receptor blocker; Angiotensin II type 1 receptor; β-arrestin-1; Heart failure;

## Suppression efficacy

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**Core tip:** The angiotensin II type 1 receptor (AT<sub>1</sub>R) endogenously expressed in adrenocortical cells was known for decades to induce aldosterone production *via* a well-defined G<sub>q</sub> protein-mediated signaling pathway. Over the past decade, a number of studies have elucidated another,  $\beta$ -arrestin-1 ( $\beta$ arr1)-dependent signaling cascade, which proceeds in parallel to, and independently of the G<sub>q</sub>-mediated one, and also results in aldosterone synthesis and secretion from the adrenal cortex. Importantly, although all of the Food and Drug Administration-approved angiotensin receptor blocker (ARB) drugs (AT<sub>1</sub>R antagonists) are very effective at blocking the G<sub>q</sub>-mediated pathway, as expected, since they were designed to do so (*i.e.*, to block the G protein signaling of the AT<sub>1</sub>R), they seem to display varying efficacies at blocking this new,  $\beta$ arr1-dependent pathway, which translates into significant variation at aldosterone suppression efficacies. In that context, candesartan and valsartan appear the most effective agents at blocking also the  $\beta$ arr1 pathway emanating from the adrenocortical AT<sub>1</sub>R, and thus, these two agents may be the best aldosterone suppressors within the ARB drug class.

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## INTRODUCTION

Aldosterone is a mineralocorticoid hormone with several cardio-toxic actions, whose plasma levels are extremely high in chronic heart failure (HF) negatively affecting progression of the disease<sup>[1]</sup>. Amongst its main actions on the failing myocardium is overall promotion of adverse remodeling *via* maladaptive hypertrophy, chamber dilatation, collagen deposition and fibrosis, increased inflammation and reactive oxygen species production, *etc.* The net result of all of these effects is acceleration of cardiac functional decline<sup>[2-4]</sup>. The main source of circulating aldosterone is the adrenocortical zona glomerulosa (AZG) cells, which synthesize and secrete it in response to high serum K<sup>+</sup> levels (hyperkalemia), since its main action on the kidneys is K<sup>+</sup> excretion (along with Na<sup>+</sup> and water reabsorption)<sup>[5]</sup>. Another powerful physiological stimulus for aldosterone secretion from AZG cells is the octapeptide hormone angiotensin II (AngII), which activates its type 1 receptors (AT<sub>1</sub>Rs), endogenously expressed in AZG cells<sup>[5,6]</sup>.

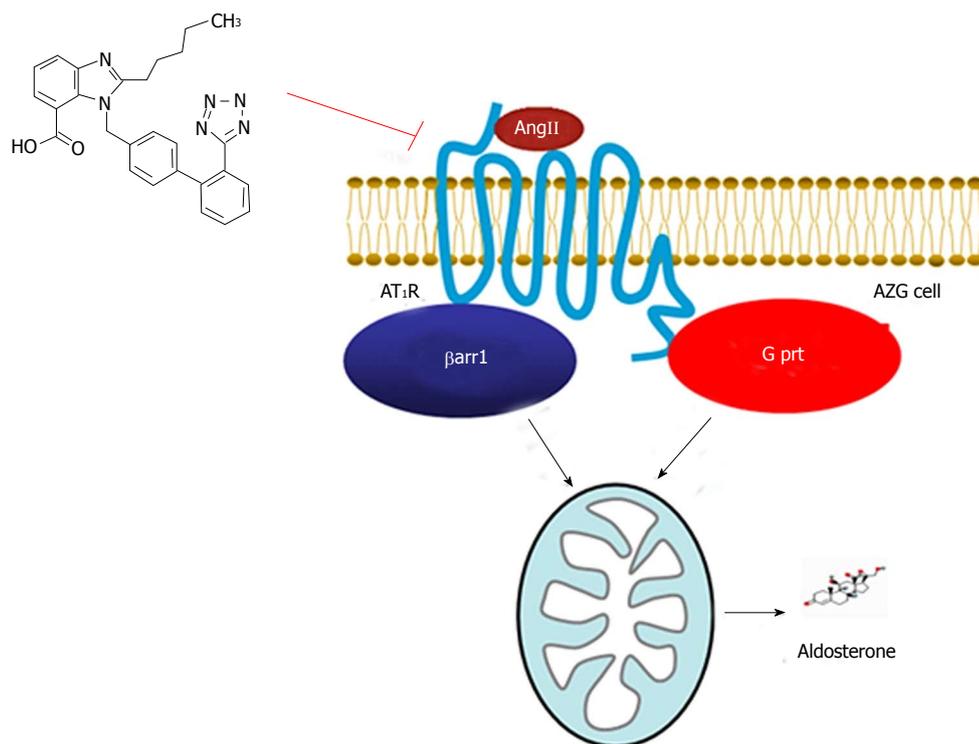
The AT<sub>1</sub>R is a 7-transmembrane-spanning or G pro-

tein-coupled receptor (GPCR); upon agonist activation, it couples primarily to the G<sub>q/11</sub> family of G proteins<sup>[6]</sup>. Nowadays however, it is known to signal also through other types of G proteins, like G<sub>i/o</sub> and G<sub>s</sub>, as well as through G protein-independent pathways mediated by the universal GPCR adapter proteins  $\beta$ -arrestin-1 ( $\beta$ arr1) and  $\beta$ arr2 (also known as arrestin-2 and -3, respectively)<sup>[7-9]</sup>. The  $\beta$ arrs bind agonist-activated and GPCR-kinase (GRK)-phosphorylated GPCRs to uncouple them from G proteins (receptor desensitization) and to target them to clathrin-coated vesicles for internalization (receptor endocytosis). At the same time, they initiate their own, "second wave" of signal transduction independently of G proteins<sup>[10-13]</sup>.

## ANGII-DEPENDENT ALDOSTERONE PRODUCTION: THE SUM OF TWO SIGNALING MODALITIES

The G<sub>q/11</sub> protein-dependent signaling pathway elicited by the AngII-activated AT<sub>1</sub>R that culminates in aldosterone synthesis and secretion in AZG cells has been well characterized (Figure 1)<sup>[14]</sup>. More specifically, diacylglycerol (DAG) and inositol trisphosphate (IP<sub>3</sub>), the two second messengers produced by this pathway, ultimately lead to: (1) aldosterone secretion, *via* elevated intracellular free Ca<sup>2+</sup> concentration, which directly stimulates exocytosis and hormonal (in the context of AZG cells, aldosterone) secretion; and (2) aldosterone synthesis, *via* extracellular signal-regulated kinase (ERK) MAPK activation, which, in turn, stimulate aldosterone biosynthesis in AZG cells by transcriptionally upregulating the StAR (steroidogenic acute regulatory) protein<sup>[14]</sup>. This protein mediates the mitochondrial uptake of the precursor of all adrenal steroids cholesterol and is the rate-limiting enzyme of aldosterone biosynthesis in AZG cells<sup>[14]</sup>.

In the chronic HF setting, adrenal GRK2 is up-regulated and, along with  $\beta$ arr1, hyperphosphorylates and severely desensitizes the sympatho-inhibitory  $\alpha_2$ -adrenergic receptors (ARs) of chromaffin cells in the adrenal medulla<sup>[15-21]</sup>. The result of this is chronic elevation of adrenal catecholamine secretion, which significantly contributes to the heightened sympathetic nervous system outflow and increased norepinephrine and epinephrine levels that further damage the failing heart<sup>[22-26]</sup>. Since aldosterone is also increased in HF and its production is stimulated by the AT<sub>1</sub>Rs of the adrenal cortex<sup>[1]</sup>, which are also GRK2 and  $\beta$ arr1 substrates, it was theorized that the upregulated (in HF) adrenal GRK2 could lead to excessive interaction of  $\beta$ arr1 also with the AT<sub>1</sub>R in the adrenal cortex, thereby modulating aldosterone secretion in the chronic HF setting, as well. Indeed, this was found to be the case<sup>[27]</sup>. *Via* a combination of *in vitro* experiments in the human AZG cell line H295R and *in vivo* experiments in experimental rats developing HF following an acute, surgically induced myocardial infarction (MI), we were



**Figure 1 Angiotensin II type 1 receptor and aldosterone production.** Schematic representation of the parallel G prt- and  $\beta$ arr1-mediated, AngII-bound AT1R signaling cascades that converge on mitochondrial aldosterone synthesis in adrenocortical zona glomerulosa (AZG) cells. The structure of the proposed AT1R antagonist (2-pentyl-1-((4-[2-(2H-1,2,3,4-tetrazol-5-yl)phenyl]phenyl)methyl)-1H-1,3-benzodiazole-7-carboxylic acid)<sup>[40]</sup>, discussed in the text, capable of suppressing both pathways equally well, is also shown (upper left corner). See text for details. G prt: G $\alpha$  protein;  $\beta$ arr1:  $\beta$ -arrestin1; AngII: Angiotensin II; AT1R: AngII type 1 receptor.

able to show that adrenal  $\beta$ arr1 actually promotes AngII-dependent aldosterone synthesis and secretion by also mediating AT1R signaling to ERK-dependent StAR upregulation independently of G proteins (Figure 1)<sup>[27,28]</sup>. This finding was somewhat surprising, given that  $\beta$ arr1 would normally be expected to reduce AngII-dependent aldosterone production thanks to desensitizing the AT1R (terminating its G protein-dependent signaling, see above). Nevertheless, it was discovered that, after abolishing the G $\alpha$ -dependent signaling by the AT1R in AZG cells, AT1R-bound  $\beta$ arr1 initiated its own signaling to aldosterone synthesis by recruiting a DAG-kinase to the activated receptor<sup>[29]</sup>, which converted the second messenger lipid DAG to phosphatidic acid (PA)<sup>[27]</sup>. PA can directly activate the small (monomeric) G protein Ras at the plasma membrane, which then initiates the cascade that results in ERK phosphorylation and activation<sup>[30]</sup>. Thus, AT1R-activated  $\beta$ arr1 elicits a "second (delayed) wave" of signaling leading to sustained ERK activation in AZG cells in its own right (*i.e.*, independently of G proteins), which, as discussed above, promotes aldosterone production *via* StAR upregulation<sup>[27]</sup>. Importantly, since StAR regulates synthesis not only of aldosterone but of all adrenal steroids throughout the three anatomical zones of the adrenal cortex<sup>[14]</sup>, adrenal  $\beta$ arr1 may also affect the synthesis of glucocorticoids and of androgens in the adrenal cortex.

Notably, adrenal  $\beta$ arr1 may not only stimulate the

AT1R-dependent aldosterone synthesis *via* its "second wave" of signaling to ERK-dependent StAR upregulation but also facilitate the acute AT1R-dependent aldosterone secretion at the plasma membrane of AZG cells and in parallel to the G protein-mediated signaling by the receptor (Figure 1). Recent evidence in transfected heterologous systems suggests such a role in the "first wave" of GPCR signaling for the  $\beta$ arrs<sup>[31,32]</sup> and a very intriguing study, done specifically in the adrenal medulla, suggested an acute stimulation of catecholamine secretion and of Ca<sup>2+</sup>-dependent exocytosis by AT1R-activated  $\beta$ arr1 (but interestingly not by  $\beta$ arr2) in adrenal chromaffin cells, thanks to its direct interaction with the plasma membrane Ca<sup>2+</sup> channel short transient receptor potential channel-3 (TRPC3)<sup>[33]</sup>. Thus, it is quite plausible that AT1R-bound  $\beta$ arr1 can directly stimulate TRPC3-dependent Ca<sup>2+</sup> currents and hence, exocytosis, also in AZG cells, thereby acutely stimulating AngII-dependent aldosterone secretion within seconds of agonist binding (and in parallel to the G $\alpha$ -mediated signaling by the AT1R). This interesting possibility of another signaling mechanism by which  $\beta$ arr1 can induce aldosterone production in AZG cells is definitely worthy of investigation in future studies.

Most importantly, adrenal  $\beta$ arr1-dependent aldosterone production has been documented to occur also *in vivo*, both under physiological (in normal, healthy animals) and pathophysiological (in the post-MI HF setting) conditions<sup>[27,28]</sup>. Specifically, adrenal-targeted

$\beta$ arr1 overexpression increased aldosterone serum levels *in vivo* in normal rats<sup>[27]</sup>, and caused severe hyperaldosteronism also in post-MI rats on top of the circulating aldosterone elevation normally occurring due to the MI injury<sup>[28]</sup>. Importantly, in the latter animals, adrenal-specific  $\beta$ arr1 blockade *in vivo* with a  $\beta$ arr1 C-terminal fragment during post-MI HF progression helped stall the decline of cardiac function and even reversed several aspects/markers of adverse cardiac remodeling courtesy of normalization of circulating aldosterone levels<sup>[28]</sup>. What's more, aldosterone levels remarkably show no increase in  $\beta$ arr1-knockout mice post-MI, which further highlights the importance of adrenal  $\beta$ arr1 in regulation of circulating aldosterone levels<sup>[34]</sup>. Together, these *in vivo* studies strongly suggest adrenal  $\beta$ arr1, in conjunction with GRK2, as an attractive therapeutic target for diseases associated with, and aggravated by hyperaldosteronism, such as post-MI HF<sup>[9,25]</sup>. Adding to its importance as a therapeutic target is also the fact that aldosterone can produce effects independently of its mineralocorticoid receptor (MR) (the so-called "non-genomic" actions of aldosterone)<sup>[4]</sup>. Obviously, these effects cannot be countered by MR antagonist drugs (*e.g.*, eplerenone, finerenone, spironolactone) and thus, suppression of aldosterone production at its source, *i.e.*, the adrenal cortex, *via* adrenal  $\beta$ arr1 blockade would be much more preferable from the therapeutic standpoint.

## WHICH ARB DRUG WINS THE ALDOSTERONE SUPPRESSION "CONTEST"?

The realization that AngII-dependent aldosterone production from the adrenal cortex proceeds through two independent signaling modalities, *i.e.*, G $\alpha$  protein- and  $\beta$ arr1-dependent (Figure 1), signaled that complete blockade of both of these modalities is needed to attain full suppression of adrenal aldosterone production and effectively lower circulating aldosterone levels in HF and in other diseases. This, coupled with the fact that some AT $_1$ R antagonist drugs (angiotensin receptor blockers, ARBs, or sartans) appear ineffective at lowering aldosterone in HF, despite their full capacity to block AT $_1$ R-G protein coupling<sup>[35-38]</sup>, prompted us to test the relative efficacy of the currently available ARBs at inhibiting the  $\beta$ arr1-dependent aldosterone production by the AT $_1$ R in an effort to identify the most effective agent(s). Indeed, the prototypic agent of this class, losartan, was found totally ineffective at preventing adrenal  $\beta$ arr1-dependent aldosterone production and combatting hyperaldosteronism post-MI due to very weak antagonism of  $\beta$ arr1 activation by the AT $_1$ R<sup>[28]</sup>. Interestingly however, the active metabolite of losartan EXP1374 was found quite effective at blocking AT $_1$ R-dependent aldosterone production and  $\beta$ arr1 activation<sup>[39,40]</sup>.

Upon subsequent head-to-head testing of all the

currently Food and Drug Administration (FDA)-approved ARB drugs, it was found that, although all ARBs (including losartan) are potent inhibitors of G protein activation by the AT $_1$ R, their potencies at preventing  $\beta$ arr1 activation by the human AT $_1$ R *in vitro* varied enormously<sup>[40]</sup>. Specifically, candesartan and valsartan appeared the most potent blockers of  $\beta$ arr1 activation and the most efficacious aldosterone suppressors *in vitro* and *in vivo*<sup>[39,40]</sup>. At the opposite end of the spectrum and in addition to losartan, was irbesartan, which was found to be a very weak  $\beta$ arr1 inhibitor and hence, a very ineffective aldosterone suppressor both *in vitro* and *in vivo*, despite its excellent G protein-blocking ability<sup>[39,40]</sup>. The rest of the class fell more or less in the middle of the  $\beta$ arr1 inhibition and AT $_1$ R-dependent aldosterone suppression scales, *i.e.*, their potency values were lower than candesartan's and valsartan's but much higher than losartan's and irbesartan's<sup>[39,40]</sup>. Importantly, their effects on cardiac function of in post-MI HF animals *in vivo* were in complete concordance with their effects on circulating aldosterone levels; candesartan and valsartan induced significant improvements in cardiac function and remodeling post-MI, whereas irbesartan and losartan were not able to alter the course of progression of post-MI animals to full-blown HF<sup>[39]</sup>.

## IMPLICATIONS FOR HF PHARMACOTHERAPY

It is widely recognized nowadays that the members of the ARB drug class display significant variation in their pharmacological and clinical properties, which has significant repercussion for their use in HF pharmacotherapy<sup>[41]</sup>. In fact, certain agents have already been shown to afford larger improvements in morbidity and mortality of chronic HF than others<sup>[42-45]</sup>. Part of the reason for these differences among these agents that belong to the same pharmacological class and share the same mechanism of action (AT $_1$ R antagonism) may be differences in their efficacies at combating the hyperaldosteronism that accompanies and burdens chronic HF<sup>[1]</sup>. In other words, agents that suppress aldosterone effectively are bound to work better for HF therapy and, since adrenal  $\beta$ arr1 plays a pivotal role in regulation of this cardio-toxic hormone's levels, the ARBs that are most effective at blocking the AT $_1$ R- $\beta$ arr1 interaction in the adrenal cortex would be expected to be preferred agents. In that vein, our aforementioned recent findings that candesartan and valsartan are the most efficacious  $\beta$ arr1 inhibitors at the AT $_1$ R, coupled with their excellent efficacy at lowering aldosterone *in vitro* and *in vivo*, point to these two ARBs as being the most preferable agents of their class to use in HF treatment (and in other hyperaldosteronic conditions, *e.g.*, salt-sensitive hypertension). In contrast, irbesartan and losartan were found very weak  $\beta$ arr1-dependent aldosterone inhibitors, a finding that may have some bearing on the lack of therapeutic benefit of these two

agents demonstrated in HF with preserved ejection fraction (HF-PEF) and on their therapeutic inferiority to candesartan in terms of HF mortality reduction<sup>[44,45]</sup>. Of course, future trials providing data on the serum aldosterone levels of the ARB-treated HF patients are needed to confirm such a link between adrenal  $\beta$ arr1-dependent aldosterone suppression efficacy and clinical benefit for this important cardiovascular drug class.

On the other hand, failure of these agents to suppress aldosterone, otherwise referred to as "aldosterone breakthrough" or "aldosterone escape", is a clinically well-documented phenomenon<sup>[46-49]</sup> and the efficacy of each agent at inhibiting  $\beta$ arr1-dependent aldosterone production may be inversely proportional to the probability of the ARB to exhibit it. In other words, the more potent  $\beta$ arr1-dependent aldosterone suppressor an ARB is, the lower the likelihood is that the treated patient will suffer from "aldosterone breakthrough". Thus, candesartan and valsartan may be the safest ARB drugs to use in HF patients in terms of the risk of "aldosterone breakthrough". However, large trials closely monitoring the circulating aldosterone levels of treated patients are again needed in order to confirm this hypothesis.

## IMPLICATIONS FOR AT<sub>1</sub>R BLOCKER MEDICINAL CHEMISTRY

The studies on the relative potencies/efficacies of the currently FDA-approved ARBs at inhibiting AT<sub>1</sub>R- $\beta$ arr1 interaction and  $\beta$ arr1-dependent aldosterone turnover provided some interesting medicinal chemistry and pharmacological insights, as well. Specifically, as far as the ARBs that are tetrazolo-biphenyl-methyl derivatives are concerned, which is a subgroup that includes losartan (and its metabolite EXP1374), irbesartan, candesartan, valsartan, and olmesartan, it was concluded that a substitution both bulky and negatively charged attached to the one side of the methylene group of the biphenyl-methyl backbone (the other end has the tetrazolo-biphenyl group attached) is needed to confer good inhibitory potency of  $\beta$ arr1 at the AT<sub>1</sub>R and consequently, effectively suppress aldosterone<sup>[40]</sup>. Indeed, both candesartan and valsartan, as well as EXP1374, have spacious, long aliphatic chain-containing and anionic (carboxylic acid) groups attached to that end of the biphenyl-methyl backbone<sup>[40]</sup>. In contrast, both losartan and irbesartan possess neutrally charged (unionizable) groups (albeit also bulky) at that biphenyl-methyl backbone end<sup>[40]</sup>. Finally, olmesartan, which also has an anionic (carboxylic acid) substitution but of intermediate bulkiness (*i.e.*, less long aliphatic chain) compared to candesartan and valsartan on that side of its backbone, displays intermediate potency at inhibiting  $\beta$ arr1 activation and suppressing aldosterone<sup>[40]</sup>. Based on these observations, we have designed the compound 2-pentyl-1-({4-[2-(2H-1,2,3,4-tetrazol-5-yl)phenyl]phenyl}methyl)-1H-1,3-benzodiazole-7-carboxylic acid (Figure 1)<sup>[40]</sup>, which carries a bulky,

carboxyl acid group with a long aliphatic chain on the other end of the tetrazolo-biphenyl-methylene backbone, and we are currently testing both its potency at blocking  $\beta$ arr1 activation by the human AT<sub>1</sub>R and its efficacy at suppressing aldosterone secretion *in vitro* and in the post-MI HF setting *in vivo*. Our hope is that it will prove to be even more efficacious than candesartan and valsartan at suppressing aldosterone levels and thus, an even better drug for HF treatment than all currently available ARBs. Of course, the above mentioned ARB structure-activity relationship inferences have to be confirmed by crystal structure resolutions of the AT<sub>1</sub>R bound to  $\beta$ arrs. The first glimpse into the human AT<sub>1</sub>R crystal structure was recently provided and it was the first step towards that goal<sup>[50]</sup>. Unfortunately however, that crystal structure lacked the intracellular C-terminal tail of the receptor, which is exactly the AT<sub>1</sub>R region that interacts with  $\beta$ arrs<sup>[51]</sup>.

## CONCLUSION

A head-to-head comparison of the ARBs currently on the United States market identified candesartan and valsartan as the most potent  $\beta$ arr1 antagonists and the most efficacious aldosterone suppressors at the human AT<sub>1</sub>R. Conversely, irbesartan and losartan were found to be largely G protein-"biased" inhibitors, with minimal efficacy towards inhibition of AngII-dependent aldosterone production. Thus, from a therapeutic standpoint, candesartan and valsartan may be the most preferable agents of this drug class, as they provide the biggest benefit for cardiac function and patient survival in post-MI HF and have the lowest propensity to cause the "aldosterone escape" adverse effect (failure to suppress aldosterone). Future studies on this class of drugs and on the effects of  $\beta$ arrs at the adrenal AT<sub>1</sub>R will help solidify these inferences and will also provide additional important information regarding AngII/AT<sub>1</sub>R pharmacology for clinicians and medicinal chemists alike.

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## Coronary stenting: A matter of revascularization

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### Abstract

In the last few decades, the recommended treatment for

coronary artery disease has been dramatically improved by percutaneous coronary intervention (PCI) and the use of balloon catheters, bare metal stents (BMSs), and drug-eluting stents (DESs). Catheter balloons were burdened by acute vessel occlusion or target-lesion restenosis. BMSs greatly reduced those problems holding up the vessel structure, but showed high rates of in-stent re-stenosis, which is characterized by neo-intimal hyperplasia and vessel remodeling leading to a re-narrowing of the vessel diameter. This challenge was overtaken by first-generation DESs, which reduced restenosis rates to nearly 5%, but demonstrated delayed arterial healing and risk for late in-stent thrombosis, with inflammatory cells playing a pivotal role. Finally, new-generation DESs, characterized by innovations in design, metal composition, surface polymers, and anti-proliferative drugs, finally reduced the risk for stent thrombosis and greatly improved revascularization outcomes. New advances include bioresorbable stents potentially changing the future of revascularization techniques as the concept bases upon the degradation of the stent scaffold to inert particles after its function expired, thus theoretically eliminating risks linked with both stent thrombosis and re-stenosis. Talking about DESs also dictates to consider dual antiplatelet therapy (DAPT), which is a fundamental moment in view of the good outcome duration, but also deals with bleeding complications. The better management of patients undergoing PCI should include the use of DESs and a DAPT finely tailored in consideration of the potentially developing bleeding risk in accordance with the indications from last updated guidelines.

**Key words:** Drug-eluting stent; Bare metal stent; In-stent re-stenosis; Stent thrombosis; Coronary artery disease

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**Core tip:** Percutaneous coronary intervention (PCI) has made progress in leaps and bounds in the last 20 years. Complications occurring with catheter balloons and bare metal stents have been overwhelmed by drug-eluting

stents (DESs), especially the new-generation ones. They are characterized by innovations in design, metal composition, surface polymers, and anti-proliferative drugs, thus reducing the risk for stent thrombosis and greatly improving revascularization outcomes. DESs also need dual antiplatelet therapy (DAPT), but the latter implies bleeding complications, too. Patients undergoing PCI should be implanted with DESs and DAPT should be tailored on each patient considering the bleeding risk.

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## INTRODUCTION

Since the 1990s, percutaneous coronary intervention (PCI) has brought a revolution in the field of coronary artery disease (CAD). Coronary stents have been found to efficiently halt dissection flaps and restore the round lumen in order to decrease the possibility of acute occlusion of the vessel. Bare metal stents (BMSs) have been demonstrated to limit early vessel recoil and late remodeling, justifying the lower rates of re-stenosis with respect to balloon angioplasty<sup>[1]</sup> and the favorable outcomes in terms of mortality, myocardial infarction, and stent thrombosis (ST) (Figure 1)<sup>[2]</sup>. Nonetheless, they also increased the formation of the neo-intima layer leading to re-stenosis, which was partially limited by the thinning of stent struts<sup>[3,4]</sup>. Hence, the development of drug-eluting stents (DESs) was required (Figure 1). Early DESs are characterized by a metallic structure coupled with anti-proliferative drugs, usually controlled by surface polymers demonstrating a lower risk of clinical re-stenosis compared to BMSs<sup>[2]</sup> and reduced angiographic target-vessel revascularization<sup>[5]</sup>. New-generation DESs featured durable or biodegradable polymer-coated, metallic, thin scaffold releasing anti-proliferative drugs, thus improving the post-PCI vessel injury and the healing response leading to neo-intimal hyperplasia<sup>[6]</sup>. In general, DESs naturally limiting healing processes can lead to an incomplete endothelialization, which appears as a main contributor to ST resulting in acute myocardial infarction and mortality rates ranging from 20% to 40%<sup>[6]</sup>.

According to the 2014 European Society of Cardiology (ESC)/European Association for Cardio-Thoracic Surgery (EACTS) guidelines, revascularization by either PCI or coronary artery by-pass graft (CABG) is generally indicated in coronary stenoses leading to a reduced flow in order to limit myocardial ischemia, relieve symptoms, and improve the prognosis<sup>[7]</sup>. Several studies concluded that neither PCI nor CABG alone provided a definitive solution for the entire spectrum of stable CAD needing revascularization, which should be considered as a complementary to the medical therapy. We believe that

an exhaustive discussion about PCI or CABG indications would deserve appropriate focus in systematic reviews, meta-analyses or position papers. Therefore, additional speculation appears out of the scope to the present editorial<sup>[7]</sup>.

As stated by the 2014 ESC/EACTS guidelines, no indication for BMSs over new-generation DESs is stated, irrespective of patient and lesion subset<sup>[7]</sup>. Similarly, in randomized clinical trials, BMSs and DESs did not significantly differ in long-term rates of death or myocardial infarction<sup>[2,8]</sup>. DESs have been described to better prevent coronary re-stenosis<sup>[9]</sup>. New-generation DESs have been found to reduce ST rates<sup>[10-12]</sup>, being safer and more efficient than early DESs<sup>[13,14]</sup>; finally, new-generation DESs were demonstrated to decrease the rates of death and myocardial infarction<sup>[10,11,15]</sup>.

## ST AND IN-STENT RE-STENOSIS

### ST

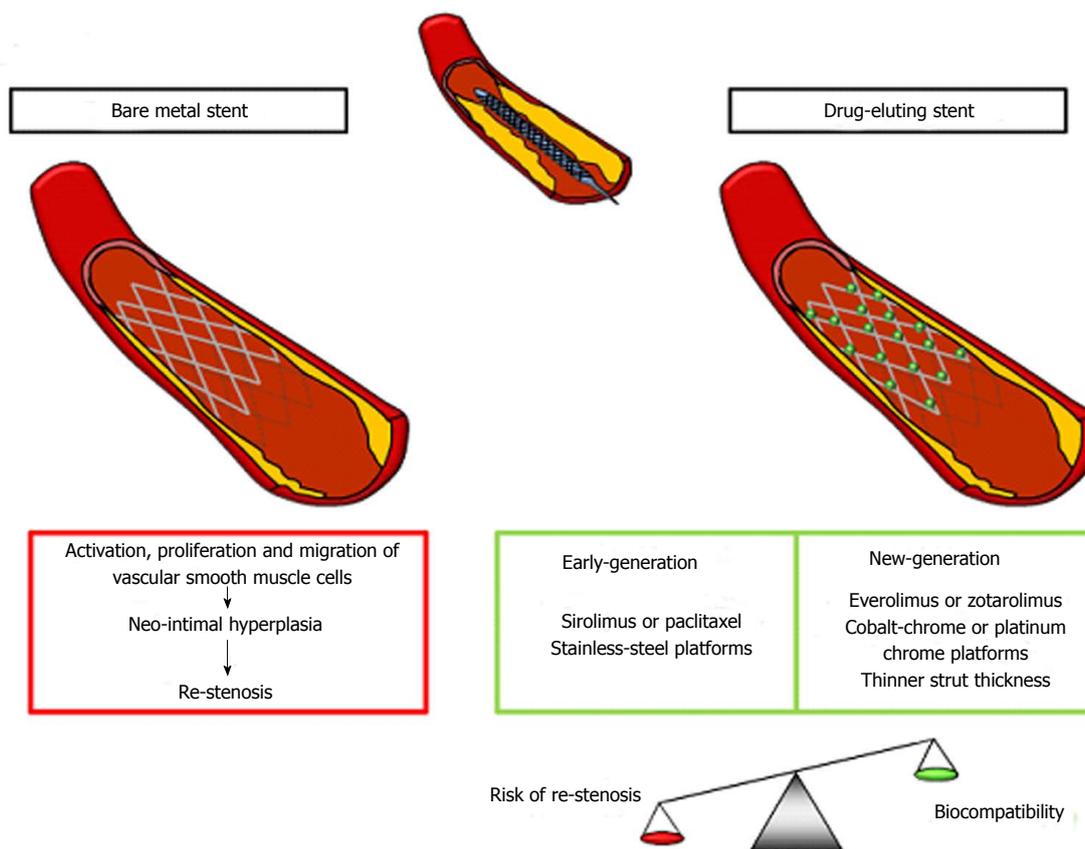
ST is a relatively rare complication (around 1% up to 3 years) characterized by angiographic or post-mortem evidence of a thrombus in a stented segment of the coronary tree<sup>[6]</sup>. The definition includes definite, probable, and possible ST according to the presence of a thrombus and the angiographic detection of an occlusion or not<sup>[16]</sup>. Moreover, ST can be divided between early (within the first 30 d from stent implantation) and late (beyond 30 d), with the former accounting for the great majority of the cases<sup>[17]</sup>. Recognized risk factors can be attributed to patient characteristics, such as diabetes, impaired left ventricular function, and premature antiplatelet disruption; stent features (BMS vs DES); and procedure-related problems, such as primary PCI, stent undersizing, and residual dissection or stenosis. The most important mean to prevent ST is represented by the prescription of an appropriate duration of a post-PCI dual antiplatelet therapy (DAPT).

### In-stent re-stenosis

Re-stenosis is defined as a re-narrowing of more than 50% of the vessel diameter when evaluated by angiography technique or as a re-narrowing of more than 75% of the reference vessel area in cross-section when measured by intravascular imaging techniques<sup>[6]</sup>. The pathophysiology starts with the vessel injury caused by BMS implantation, followed by neo-intimal hyperplasia, inflammation and remodeling of the coronary vessel<sup>[18]</sup>. Risk factors for in-stent re-stenosis can be considered as patient-dependent (such as diabetes and chronic renal disease), stent-dependent (such as BMS vs DES and early vs new-generation DESs), and procedure-related (such as small vessel, residual stenosis, longer stented segment, and bifurcation lesion)<sup>[6]</sup>.

## BMS AND DES: IS IT TIME FOR A RE-APPRAISAL?

In light of new stent design and different scaffold



**Figure 1 Bare metal stents and drug-eluting stents.** Percutaneous coronary intervention for coronary artery disease has seen important evolution in last few decades. Early bare metal stents showed a high rate of in-stent re-stenosis. Drug-eluting stents tried to overcome this complication using anti-proliferative molecules; in this sense, new-generation ones, with thinner strut thickness, showed more biocompatibility and less complications with respect to previous models.

composition, Bønaa *et al*<sup>[19]</sup> have evaluated new-generation DESs and new-generation BMSs in a randomized trial conducted in eight centers in Norway, named Norwegian Coronary Stent Trial (NORSTENT). Among more than 20000 patients undergoing PCI between 2008 and 2011, 12425 met the eligibility criteria and 9013 were randomly assigned to either DESs or BMSs. After a 5-five year follow-up period, no significant differences were found between groups for either the primary outcome (composite of death from any cause and non-fatal spontaneous myocardial infarction) or the secondary ones (death; fatal and non-fatal spontaneous and peri-procedural myocardial infarction and stroke; hospitalization for unstable angina pectoris). Interestingly, even if not considered as the primary end-point, new-generation DESs have shown better performances than BMSs in terms of rates of any revascularization (16.5% vs 19.8%, respectively,  $P < 0.001$ ), target-lesion revascularization (5.3% vs 10.3%, respectively,  $P < 0.001$ ) both for PCI and coronary artery bypass graft surgery, and definite ST (0.8% vs 1.2%,  $P = 0.0498$ ).

This trial is worth being considered not only for its results, but also because it is well-designed, correctly powered, and especially not sponsored by industry. Results are very interesting as they partly oppose to those who claimed that there is no longer a role for

BMSs in PCI because of the larger superiority of DESs; these conclusions are surely derived from studies which were underpowered, only observational or from meta-analyses pooling results<sup>[15,20,21]</sup>. Moreover, results from the NORSTENT trial are important because they are not centered on death or recurrent myocardial infarction, certainly reduced also by lifestyle modifications and appropriate drugs, but rather on reduction of need for revascularization and ST. Indeed, in the latter case, the result in absolute terms is very encouraging, but between-group difference is to be considered to the extreme limit of the statistical significance ( $P = 0.0498$ ).

As things stand at present, new-generation DESs are to be preferred in the majority of clinical situations. Recent recommendations from the American College of Cardiology/American Heart Association allow a shorter duration of DAPT to 6 mo in patients developing a high risk of bleeding<sup>[22]</sup>. If this possibility is considered, the choice of DESs with respect to BMSs becomes surely more attractive. Moreover, several trials have demonstrated that a prolonged DAPT (over 12 or 24 mo) did not add benefits in terms of major cardiovascular events, including ST, across a median 2- or 5-year follow-up period, but rather increased the frequency of bleeding complications<sup>[23,24]</sup>. These data have also been confirmed in a meta-analysis by Valgimigli *et al*<sup>[25]</sup>, who did not find any significant difference in

ischemic end-points, such as cardiac death, myocardial infarction with or without stroke, and death from any or cardiovascular causes. Indeed, in spite of the poor number of ST, prolonged DAPT duration has not been shown to provide a decrease in the definite or probable ST when compared to shorter DAPT duration. Moreover, clear evidence for prolonged DAPT for 1 year or more was found for major bleeding events and the risk of stroke<sup>[25]</sup>. Recently, Helft *et al*<sup>[26]</sup> partially confirmed the same results in the OPTimal DUAL antiplatelet therapy trial showing no reduction in adverse clinical events in the prolonged DAPT group and no apparent difference in the major bleeding rate, even if the reduced trial power has to be considered in this case; interestingly, STs were rare with no between-group differences.

Anyway, it is important to underline that BMSs might be recommended in patients with a large vessel diameter, and they show low re-stenosis rates, with poor compliance to DAPT or need for non-cardiac surgery, with reimbursement problems, and with increased risk of bleeding (such as patients with recent bleeding or under concurrent anticoagulation therapy), as indicated by Morice *et al*<sup>[27]</sup>. The latter study showed how the choice of BMSs seems to be guided mainly by the concern of bleeding or poor compliance, considering only 1 mo of DAPT for BMSs compared to 6-12 mo for DESs according to European or American guidelines, and neglecting the potential, future need for revascularization, which is accordingly an ineluctable matter to be considered in terms of costs and quality of life.

In conclusion, DESs have to be considered as the first choice in patients undergoing PCI both in stable CAD and in acute coronary syndrome as they demonstrated to reach better outcomes in terms of mortality, recurrent myocardial infarction, and revascularization. The DAPT duration is still debated depending on bleeding and ischemic risks following stent implantation both changing over time. The known rule of one-year DAPT duration cannot be applied to all patients, but rather the therapy should be tailored for each patient according to the latest guidelines. For example, those treated with new-generation DES for stable coronary disease can be administered DAPT for 6 mo or 3 mo in case of bleeding risk, while for those treated for acute coronary syndrome the choice should be at least 12 mo, which can be reduced to 6 mo in case of developing a high risk bleeding.

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## Patient selection for transcatheter aortic valve replacement: A combined clinical and multimodality imaging approach

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### Abstract

Transcatheter aortic valve replacement (TAVR) has been validated as a new therapy for patients affected by severe symptomatic aortic stenosis who are not eligible for surgical intervention because of major contraindication or high operative risk. Patient selection for TAVR should be based not only on accurate assessment of aortic stenosis morphology, but also on several clinical and functional data. Multi-Imaging modalities should be preferred for assessing the anatomy and the dimensions of the aortic valve and annulus before TAVR. Ultrasounds represent the first line tool in evaluation of this patients giving detailed anatomic description of aortic valve complex and allowing estimating with enough reliability the hemodynamic entity of valvular stenosis. Angiography should be used to assess coronary involvement and plan a revascularization strategy before the implant. Multislice computed tomography play a central role as it can give anatomical details in order to choice the best fitting prosthesis, evaluate the morphology of the access path and detect other relevant comorbidities. Cardiovascular magnetic resonance and positron emission tomography are emergent modality helpful in aortic stenosis evaluation. The aim of this review is to give an overview on

TAVR clinical and technical aspects essential for adequate selection.

**Key words:** Aortic stenosis; Doppler echocardiography; Cardiac computed tomography; Two-dimensional strain; Three dimensional echocardiography; Cardiac magnetic resonance; Transcatheter aortic valve replacement

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**Core tip:** Transcatheter aortic valve replacement (TAVR) has been validated as a new therapy for patients affected by severe symptomatic aortic stenosis who are not eligible for surgical intervention because of major contraindication or high operative risk. Patient selection for TAVR should be based not only on accurate assessment of aortic stenosis morphology, but also on several clinical and functional data. Multi-Imaging modalities are preferred for assessing the anatomy and the dimensions of the aortic valve and annulus before TAVR. The aim of this review is to give an overview on TAVR clinical and technical aspects essential for adequate selection.

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## INTRODUCTION

Transcatheter aortic valve replacement (TAVR) has been validated as a new therapy for patients affected by severe symptomatic aortic stenosis who are not eligible for surgical intervention because of major contraindication or high operative risk<sup>[1,2]</sup>. Recently this option, performed in experienced centers, using next generation devices has demonstrated to be not inferior to standard surgery also in intermediate-risk patients<sup>[3]</sup>.

The safety and efficacy of prosthesis implantation depends on a proper patient selection and procedural guidance, based on a multimodality imaging approach<sup>[4,5]</sup>. A precise measurements of annulus and aortic root allow to make a correct "sizing", that means to choose the best fitting prosthesis in native aortic seat, representing one of the most important predictor of a successful procedure<sup>[6,7]</sup>.

## CLINICAL EVALUATION

Patient selection requires a multidisciplinary team approach including interventional cardiologists, surgeons, anesthesiologists and imaging specialists in order to delineate risk profile, study the anatomy of

aortic valve, aorta and peripheral vascular structures.

First line risk evaluation is usually performed using the Logistic European System for Cardiac Operative Risk Evaluation (EuroSCORE) and/or the STS Predicted Risk of Mortality Score, defining a high risk in case of logistic EuroSCORE  $\geq 15\%$ -20% or a STS score  $\geq 10\%$ . These scores present clear limitations mostly in elderly population and have not been created for TAVR procedures but for surgery so that their suitability in percutaneous valve implantation has been questioned and a risk overestimation suspected in this context<sup>[8]</sup>.

In patient with prior cardiac surgery, including de-generation of an implanted aortic bioprosthesis (valve in valve implantation), chest radiation therapy, porcelain aorta, liver cirrhosis, pulmonary hypertension and/or right ventricular dysfunction a TAVR approach should be reasonably preferred.

On the other hand, in elderly population, frailty has been associated with worst prognosis in several pathological conditions and also after TAVR and must be considered in patient evaluation. It can be definite as a syndrome of impaired physiologic reserve with decreased resistance to stressors<sup>[9]</sup> and can be quantified using a composite of four markers: Serum albumin, dominant hand grip strength, gait speed on a 15 ft (4.57 m) walk and independence in activities in daily living. These components can be summed to derive a frailty score (ranging 0 to 12) able to identify frail patients in case of score  $\geq 5$ .

Moreover, patients with poor life expectancy (less than 1 year) or in which TAVR has not expected to significantly improve quality of life should be excluded from this selection<sup>[10]</sup>.

Relative and absolute contraindications to TAVR are listed in Table 1.

One of the main advantages of TAVR vs SAVR is the more rapid recovery from TAVR and this benefit is different according to access site and is greater for transfemoral approach. Transapical access for TAVR is an accepted approach for patients in whom vascular anatomy do not permit a transfemoral approach and if on one hand it avoids potential site complications of iliac and femoral vessels, on the other hand has some limitations including an increase in respiratory complications<sup>[11]</sup>.

## ECHOCARDIOGRAPHY

### Role of transthoracic echocardiography

Echocardiography represents the first line tool in the setting of pre- and post-interventional evaluation and planning of Transcatheter Aortic Valve Replacement procedures (Figures 1-3).

Transthoracic echocardiography (TTE) gives detailed anatomic description of aortic valve complex and allows to estimate with enough reliability the haemodynamic entity of valvular stenosis.

An adequate TTE examination in a patient presenting with aortic valve stenosis should include information

**Table 1** Contraindications for transcatheter aortic valve implantation

<b>Absolute contraindications</b>
Absence of heart team or surgery on the site
Estimated life expectancy < 1 yr
Improvement of quality of life by TAVI unlikely because of comorbidities
Severe primary associated disease of other valves with major contribution to the patient's symptoms, that can be treated only by surgery
Inadequate annulus size (< 18 mm, > 29 mm)
Thrombus in the left ventricle
Active endocarditis
Elevated risk of coronary ostium obstruction (asymmetric valve calcification, short distance between annulus and coronary ostium, small aortic sinuses)
Plaques with mobile thrombi in the ascending aorta, or arch
For transfemoral/subclavian approach: inadequate vascular access (vessel size, calcification, tortuosity)
<b>Relative contraindications</b>
Bicuspid or non-calcified valves
Untreated coronary artery disease requiring revascularization
Haemodynamic instability
LVEF < 20%
For transapical approach: severe pulmonary disease, LV apex not accessible

TAVI: Transcatheter aortic valve implantation; LVEF: Left ventricular EF.

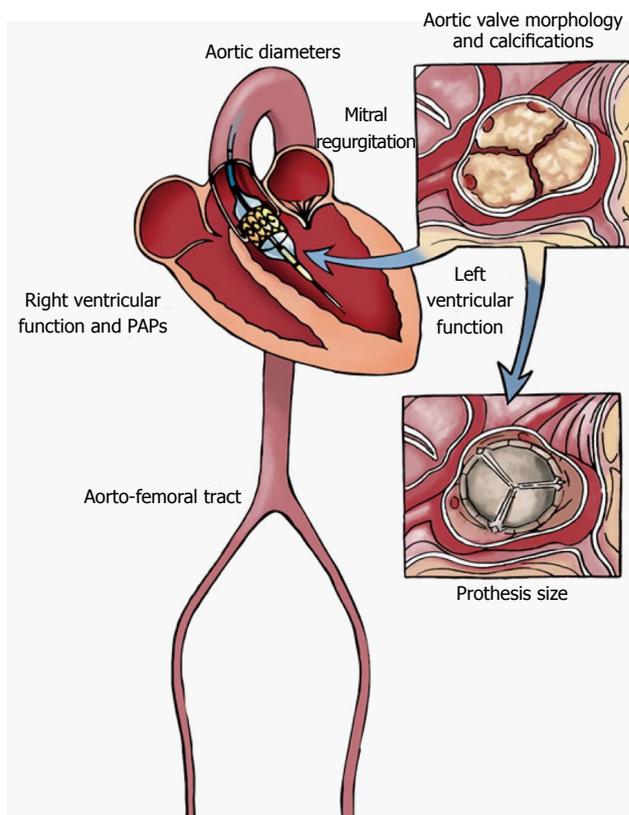
about valve anatomy (bicuspid or tricuspid valve) and severity of impairment of cusp motion. Moreover TTE provides an accurate evaluation of alterations in left and right ventricular morphology and function induced by the increase in afterload and allows to structurally and functionally investigate the other cardiac valves<sup>[12]</sup>.

Ultrasounds allow to underlie factors associated with outcome: In a longitudinal study of echo parameters in cohort A of the PARTNER trial authors showed that the TAVR and the SAVR groups had different univariate factors associated with outcome. In fact, in TAVR group, baseline low peak gradients predicted worse outcome expressing a low stroke volume status while in SAVR population the strongest determinant of mortality was mitral regurgitation<sup>[13]</sup>.

### Severity of aortic stenosis

An appropriate haemodynamic evaluation of aortic valve stenosis requires the assessment of functional aortic valve area (AVA) or indexed AVA by body surface area, derived using continuity equation, peak transvalvular gradient and velocity (Vmax), mean transvalvular pressure gradient (MPG) and Stroke Volume index (SVi). According to latest recommendations by American College of Cardiology/American Heart Association, aortic valve stenosis is considered severe when Vmax is above 4 m/s, mean pressure exceeds 40 mmHg and estimated or measured AVA is under 1 cm<sup>2</sup> (< 0.6 cm<sup>2</sup>/m<sup>2</sup> if indexed for body surface area), assuming a normal left ventricular EF (LVEF)<sup>[14]</sup>.

When performing continuity equation it should be remembered that diameter of left ventricular outflow tract (LVOT) diameter should be taken within 1 to 5 mm



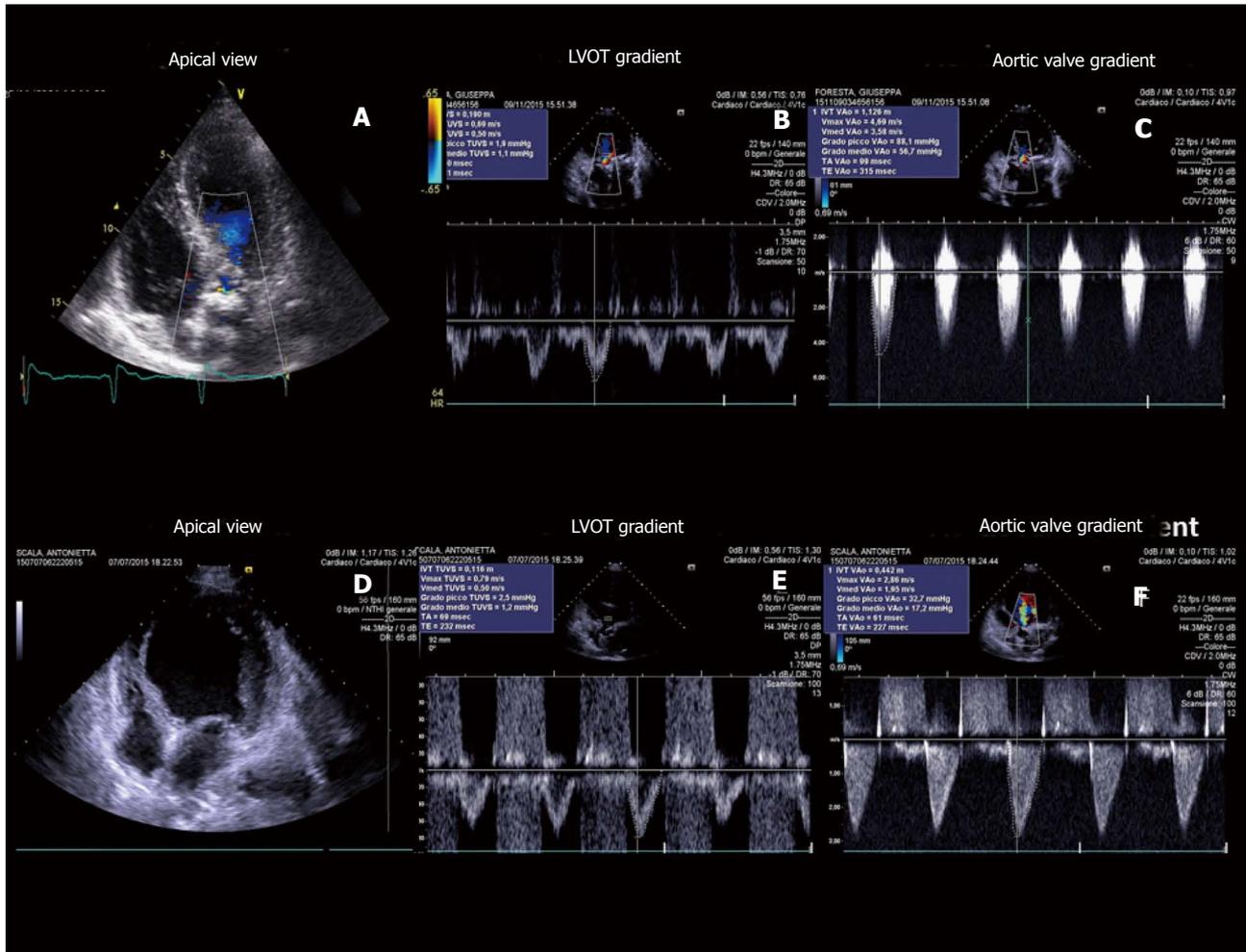
**Figure 1** Main morphologic and functional parameters to assess by Multi-Imaging approach in the setting of pre-interventional evaluation and planning of Transcatheter Aortic Valve Replacement procedures (illustrator by Germano Massenzio). PAPs: Pulmonary arterial systolic pressure.

from aortic valve annulus in order to obtain maximum diameter<sup>[15]</sup>. LVOT often is elliptical so in case of measurement of the shortest dimension the continuity equation may still under-estimate the AVA and the stroke volume.

The calculation of the valvuloarterial impedance (Zva) should be part of a routine echocardiographic examination because this parameter provide an estimate of the global hemodynamic load<sup>[16]</sup> and can be an useful parameters in the evaluation of paradoxical aortic stenosis.

In clinical practice discordance between these parameters is often encountered so that commonly a severely restricted AVA can be found concomitantly with mean and peak pressure gradients falling into the moderate or mild category. This pattern is typically observed when systolic stroke volume and consequently transvalvular flow are reduced, thus realizing a so called low-flow low-gradient (LF-LG) aortic stenosis. In this condition visual assessment of structure, calcification and mobility of aortic valve is a crucial element as it can allow suspecting the diagnosis of severe aortic stenosis regardless of Doppler values.

Two forms of LF-LG aortic stenosis have been described<sup>[17]</sup>: (1) classical LF-LG aortic stenosis defined as an AVA < 1 cm<sup>2</sup> in presence of LVEF < 50% and MPG < 40 mmHg or Vmax < 4 m/s; (2) paradoxical LF-LG aortic stenosis in presence of an AVA < 1 cm<sup>2</sup>,



**Figure 2** Transthoracic echocardiography gives detailed anatomic description of aortic valve complex and allows to estimate with enough reliability the haemodynamic entity of valvular stenosis by assessment of functional aortic valve area, derived using continuity equation. Two examples of severe aortic stenosis with normal ejection fraction and gradients (A-C), and with classical "low flow-low gradient" pattern (D-F). LVOT: Left ventricular outflow tract.

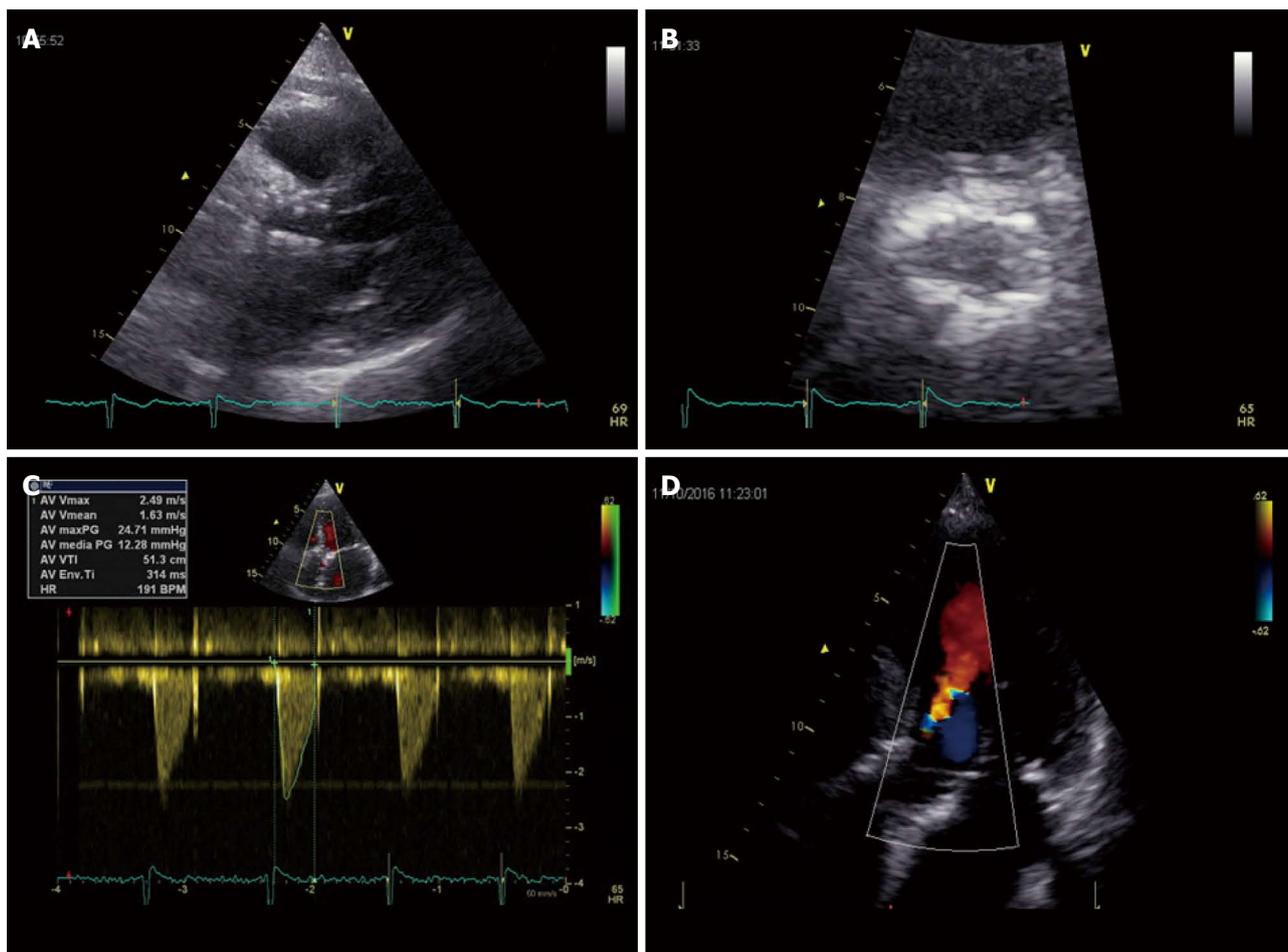
LVEF > 50%, a reduced left ventricular stroke volume (< 35 mL/m<sup>2</sup>), MPG < 40 mmHg or Vmax < 4 m/s. In this case stroke volume is low usually because of a markedly hypertrophied left ventricle with a small cavity that is unable to be filled appropriately and subsequently eject a normal stroke volume, in case of reduced volume load due to diuretic therapy<sup>[18,19]</sup> or in presence of a high valvulo-arterial impedance (ZVa > 5.5 mmHg/mL/mq)<sup>[20]</sup>. These patients seem to have a dismal prognosis, which can be improved by aortic valve replacement or TAVI, as demonstrated in a PARTNER study sub-group analysis<sup>[21]</sup>.

On the other hand, a severely reduced functional AVA associated with low transvalvular gradient may be consequent to a reduced transvalvular flow due to left ventricular dysfunction that cannot allow cusps opening, defined as "pseudo-severe" aortic stenosis. It is important to distinguish these two conditions since in this last case aortic valve intervention may not improve prognosis. In patients with reduced EF low-dose dobutamine stress echocardiography ( $\leq 20 \mu\text{g/kg}$  per minute) can be used to discriminate LF-LG severe aortic stenosis from pseudo-severe aortic stenosis as, in

the case of a severely stenotic valve, estimated AVA remains < 1 cm<sup>2</sup> and contemporarily transvalvular gradient increase<sup>[14,10]</sup>, but this variation can only be achieved in presence of a significant flow reserve (stroke volume increase > 20%).

In patients with asymptomatic severe aortic stenosis echo stress can be used, with caution and in expert centre, for unmask exercise-limiting symptoms, a drop in systolic blood pressure by > 20 mmHg, exercise increase in mean gradient  $\geq 18$  to 20 mmHg, the absence of contractile reserve (no or < 5% exercise increase in LVEF) or the presence of exercise pulmonary hypertension (> 60 mmHg) that are all strong predictors of cardiac events<sup>[22-25]</sup>.

When performing TTE evaluation of a stenotic aortic valve multiple windows should be investigated, including apical three or five chambers views and right parasternal approach, in order to obtain the best alignment of Doppler beam to transvalvular flow, thus avoiding inconsistency between estimated functional AVA and pressure gradient<sup>[26-28]</sup>. Recently in a study including 100 patients it has been shown that right parasternal window is more accurate than apical approach; in fact, when



**Figure 3** Post-implantation echocardiographic transcatheter aortic valve replacement assessment in long-axis (A) and short-axis (B) parasternal views; Normal trans-prosthesis flow gradient by Doppler analysis (C); Mild paravalvular aortic regurgitation in this apical 5-chamber view of the same patient (D).

only apical approach is used a quarter of patients was incorrectly classified, underestimating severity in two thirds of patients deemed as moderate and misjudging a third as paradoxical LF-LG<sup>[29]</sup>.

Systemic blood pressure and calibre of ascending aorta can influence severity estimation, increased left ventricular global afterload due to hypertension may cause a reduction in transvalvular flow, thus leading to stenosis underestimation<sup>[30]</sup>.

Whereas if ascending aorta diameter is smaller than 30 mm, transvalvular pressure gradient may be overestimated because of a pressure recovery phenomenon distally to the aortic valve<sup>[31]</sup>.

### **Aortic valve morphology**

Conventional 2D-TTE allows in majority of patients to determine the number and disposition of aortic valve cusps. Bicuspid aortic valve with its asymmetrical closure line tends to develop degenerative alterations earlier than normal tricuspid valves and has a markedly elliptical annulus with eccentrically disposed calcium deposition<sup>[32]</sup>.

In presence of a bicuspid aortic valve percutaneous implanted prosthesis may fail to expand completely with consequent periprosthetic regurgitation (up to 28% of

cases) and the risk of valve misplacement<sup>[33,34]</sup>. Dilation of ascending aorta, which can be a contro-indication to TAVI, is also common in bicuspid aortic valve disease, moreover TAVR could increase the risk of aortic dissection in these subjects<sup>[35]</sup>. Because of these technical conundrums PARTNER trial did not include subjects with bicuspid aortic valvular stenosis<sup>[1]</sup>. Anyway TAVR is still possible in these patients and several cases have been reported up today<sup>[36]</sup>. Phan *et al*<sup>[37]</sup> have published a meta-analysis and systematic review of literature collecting 149 patients undergone TAVR procedure there was no significant difference for patients with bicuspid aortic valves in 30-d mortality, post-procedural prosthetic haemodynamics and presence of moderate to severe perivalvular aortic regurgitation or rate of bleeding or vascular complications, indicating that TAVR can be an effective treatment also in this setting. No difference in 30-d and one year mortality between bicuspid and tricuspid stenotic valves undergoing TAVR was also found in the Poland National Registry<sup>[38]</sup>. In light of this evidence more and more centres are proposing TAVR as a valuable option for treatment patients carrying a bicuspid aortic valve, considering this condition no more an absolute but a relative contraindication to the procedure.

### **Evaluation of left ventricular function**

The presence of a left ventricle systolic dysfunction, defined as aEF < 50%, constitutes a negative prognostic marker both in symptomatic and asymptomatic severe aortic stenosis. In patients considered unsuitable for surgical aortic valve replacement enrolled in PARTNER B cohort 30-d and 1-year prognosis was not different for patients with a LVEF over 50% confronted with those with reduced LVEF<sup>[39]</sup>. Moreover in this arm of PARTNER study an increase in LVEF > 10% subsequently TAVR was found in 50% of patients considered unfit for surgery, especially for those with smaller LV chamber diameters and lower grade of mitral regurgitation before TAVR. Although LVEF improvement was not associated with improvement in survival, in those with no post-procedural increase in LVEF there was a worse prognosis at one year of follow-up.

In light of these evidences TAVR represents a valuable option in severe aortic stenosis and markedly reduced left ventricular systolic function and should be taken in consideration by the Heart Team, because in these very high risk patients for surgery TAVR may show a better outcome.

Furthermore an alteration in LV structure and function has been demonstrated in patients with severe aortic stenosis regardless a preserved LVEF and this phenomenon can be studied also with speckle tracking echocardiography, a relative new technique that provides non-Doppler evaluation of myocardial deformation as expression of systolic and diastolic dynamics<sup>[40]</sup>. In this context, in fact, a reduced GLS (global longitudinal score) has been documented with a more evident alteration in the basal LV segments and a value > -15.9% correlated with adverse prognosis<sup>[41,42]</sup>.

In patients with severe aortic stenosis undergoing TAVR, LV reverse remodelling and improvement of longitudinal myocardial function assessed by speckle tracking echocardiography have been observed together with a decrease of aorto-valvular impedance and an improvement of atrial morphology and function<sup>[43]</sup>. In fact, our group evaluated 55 patients before and 6 mo after CoreValve implantation demonstrating a significant reduction in mean transaortic gradient, LV mass, LA volume index, and an improvement of ejection fraction ( $P < 0.0001$ ). In addition, LV GLS and LA longitudinal strain significantly increased after TAVI and at the multiple logistic regression analysis, LV mass before TAVI ( $P < 0.001$ ) and peak CK MB mass after TAVI ( $P < 0.0001$ ) were powerful independent predictors of lower improvement of LV GLS. Moreover, LV mass index ( $P < 0.001$ ) and LV GLS strain ( $P < 0.001$ ) before TAVI was powerful independent predictor of LA longitudinal strain after TAVI (Figure 4).

### **Mitral regurgitation**

Haemodynamically relevant mitral regurgitation is present in a substantial amount of patients with severe valvular aortic stenosis. It may have many different underlying mechanisms, both organic and functional.

Functional mitral regurgitation may be also of ischemic nature, because of the common occurrence of coronary artery disease in these subjects. Moreover left ventricular systolic dysfunction and dilatation and concomitant aortic regurgitation may contribute to cause or aggravate mitral regurgitation<sup>[44]</sup>.

In addition high grade mitral regurgitation may result in reduced transvalvular flow and lead to incorrect classification of stenosis severity, so it has to be taken in consideration in pre-procedural TTE for a comprehensive global assessment of aortic valve disease.

Interestingly in these subset of patients improvement of mitral insufficiency is reported in around 50%, more often in the case of secondary mitral regurgitation<sup>[45,46]</sup>. This finding was consistent with the results of a recently published meta-analysis which demonstrated that MR improvement was associated with pre-procedural grade and not with causative mechanism<sup>[47]</sup>.

### **Right ventricular function and pulmonary hypertension**

Pre-procedural TTE should include a comprehensive evaluation of right ventricular dimensions and function, in addition to estimation of pulmonary arterial systolic pressure (PAPs) from tricuspid regurgitation velocity.

Registries report that after TAVR moderate or severe tricuspid regurgitation is frequent (occurring in about 15%) and in most cases it is not improved after the procedure<sup>[48]</sup>.

Pulmonary hypertension (PH) can be found in up to 25% of subjects affected by severe aortic stenosis, secondary to post-capillary increase of left ventricular filling pressure and the eventual presence of associated mitral regurgitation. PH is a predictor of worse prognosis following surgical aortic valve replacement and recently there is increasing evidence that it is a negative prognostic marker together with tricuspid regurgitation also in the setting of transcatheter aortic intervention<sup>[49]</sup>.

Evidence from TAVR registries suggests that PH (estimated PAPs over 40 mmHg on TTE) does not negatively influence success rate, amount of complications in the early phase and 30-d survival, but a negative prognostic effect is present regarding 1 year mortality, which is raised up to 22% (or higher if estimated PAPs is above 60 mmHg)<sup>[50]</sup>.

### **Role of transoesophageal echocardiography**

Transesophageal echocardiography (TEE) allows to better visualize aortic cusps, define etiology (bicuspid vs tricuspid) and directly measure aortic valve area by planimetry in doubt cases, when TTE is not conclusive. TEE can be used in association with other imaging techniques for optimal pre-procedural planning in the setting of TAVI.

### **Annulus size measurement**

Aortic valve annulus can be defined as a ring-shaped structure virtually identifiable at the level of basal attachment of aortic cusps measured in systole<sup>[46]</sup>. A correct measurement of annular size allows an appro-

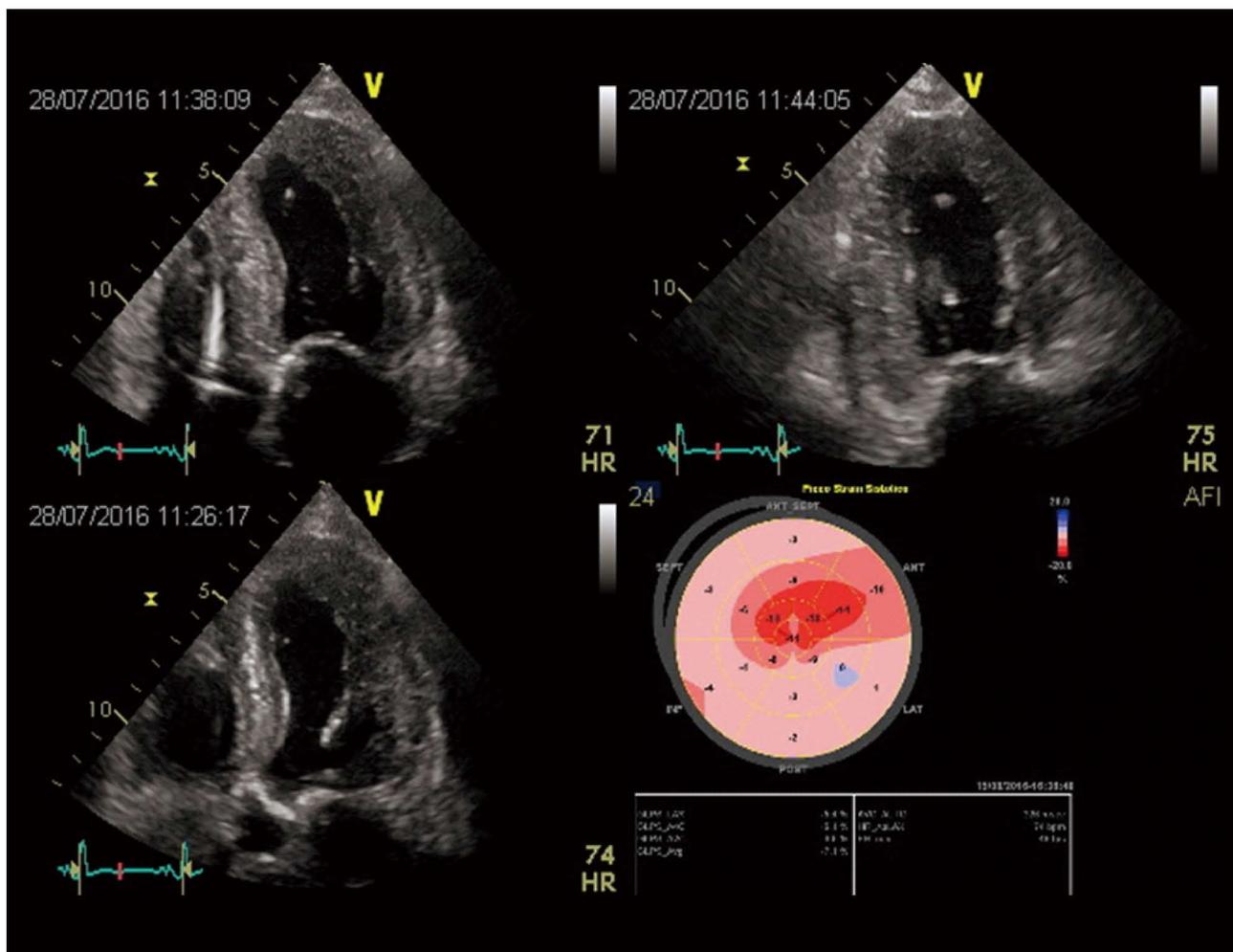


Figure 4 Two-dimensional LV strain in a patient with low flow-low gradient aortic stenosis, showing a severe and diffused impairment of myocardial deformation.

priate delivery of aortic valve prosthesis and reduce the incidence of complications<sup>[51]</sup>.

When aortic annulus is underestimated the delivery of a prosthesis too small can be followed by displacement or paraprosthetic regurgitation<sup>[4]</sup>. On the other hand prosthesis oversizing can cause insufficient expansion and valvular or paraprosthetic regurgitation or annular rupture. Optimal annular sizing aims to deliver a valve of an adequate dimension large enough to avoid paravalvular regurgitation, but not exceeding more than 20% the measured annular diameter, which increases risk of rupture.

In practice antero-posterior annular diameter is measured by TEE in mid-esophageal long axis view (120°-150°) in correspondence of basal hinge points of aortic cusps to aortic root.

Three dimensional TEE allows to visualize the real shape of LVOT, which is oval in 90% of patients<sup>[52]</sup>. 3D-TEE has proved more effective in providing optimal annular measurement and was more useful in predicting paravalvular aortic regurgitation compared to 2D-TEE<sup>[53,54]</sup> (Figure 5).

3D-TEE has been directly compared with cardiac

CT demonstrating the two imaging modalities were equally effective in predicting paraprosthetic aortic regurgitation<sup>[55]</sup>, although annulus diameter and planimetric area determined by 3D-TEE tend to result smaller than those measured by cardiac CT, except for sagittal dimensions. Considering sagittal dimensions both diagnostic techniques were equally accurate in predicting prosthetic dimensions with good post-procedural results. In conclusion before TAVI, 3D-TEE can be considered a valuable alternative to cardiac CT in pre-procedural planning, especially in patients with chronic kidney disease.

### Root anatomy

Transesophageal Echocardiography is able to evaluate the distance of coronary arterial ostia from aortic annulus and to correlate this distance with aortic cusp length, in long axis view. If cusp length is longer than coronary-annular distance there is a risk of coronary occlusion after valve delivery, when aortic valve cusps are displaced by the prosthesis expansion.

In clinical practice in order to avoid coronary occlusion, coronary-annular distance should be higher than

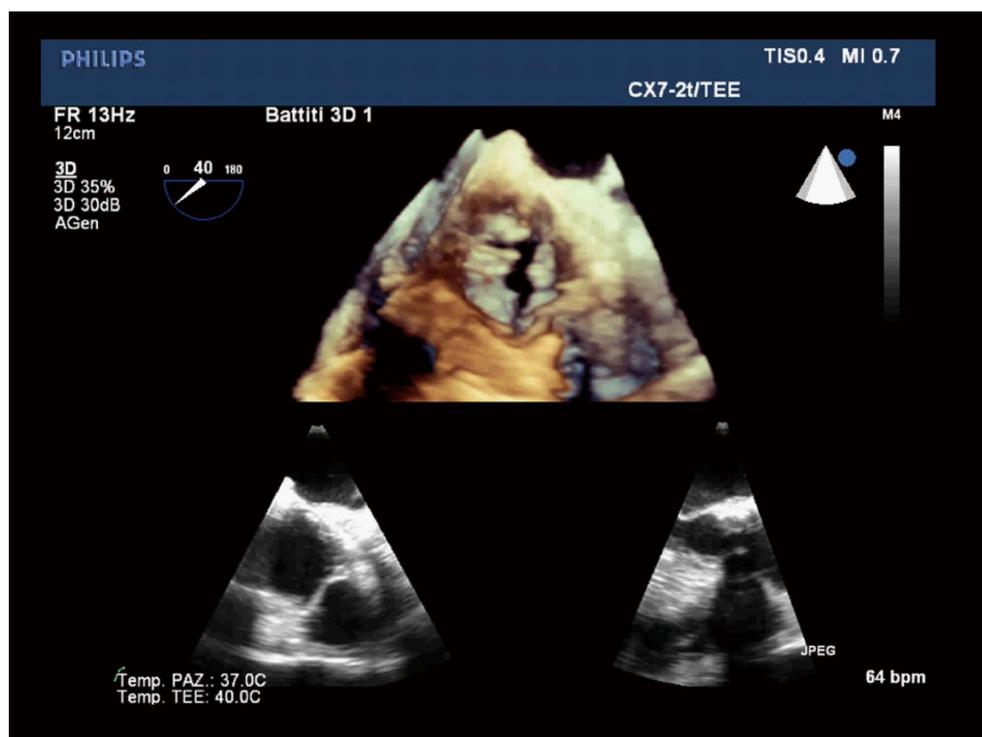


Figure 5 Three dimensional transesophageal echocardiography allows to visualize the real shape of left ventricular outflow tract, and has proved more effective in providing optimal annular measurement and was more useful in predicting paravalvular aortic regurgitation compared to 2D-transesophageal echocardiography.

10 mm<sup>[56,57]</sup>. Moreover aortic valve calcium burden should be always assessed and confronted with aortic sinus capacity. Although it is possible to measure coronary-annular distance with 2D-TEE, in the majority of patients it is necessary to use Multi Slice Computed Tomography (MSCT) or as an alternative 3D-TEE.

#### **Distribution of calcium**

TEE allows visualization of calcium deposits, which are present in almost all subjects affected by degenerative aortic stenosis, and their distribution. The presence of extensive aortic valve calcifications may cause paravalvular regurgitation due to formation of gaps between prosthetic and native valve and increase the risk of coronary ostium obstruction after TAVI delivery<sup>[58]</sup>. In addition extensively calcified sino-tubular junction may impair the expansion at the aortic end of the prosthesis eventually causing ventricular displacement of the prosthetic valve during delivery<sup>[59,60]</sup>. Great amount of calcification, particularly in subvalvular region, is also associated with increased risk of periprocedural annular rupture or sinus rupture.

#### **Characteristics of aorta and significant left ventricular septal hypertrophy**

TEE examination provides an higher spatial and temporal resolution and in pre-procedural phase allows to evaluate the ascending aorta and the descending thoracic tract in order to exclude the presence of extensive and soft atheromas which are associated with higher risk of peri-procedural ischemic stroke because they can be

mobilized and hinder the passage of delivery system<sup>[61,62]</sup>. It remains a suboptimal tool for the assessment of the distal ascending aorta and the proximal arch (TEE "blind spot" due to tracheal air shadowing) as well as for the abdominal aorta. Finally TEE may show a significant basal septal hypertrophy that may lead to prosthesis displacement in periprocedural or postprocedural phase<sup>[63,64]</sup>.

## **CORONARY ANGIOGRAPHY AND PCI**

Coronary angiography represents an essential part of patient evaluation before planning a TAVR procedure. Significant coronary artery disease is commonly found in patients with indication to TAVI, however there is no universal agreement about if and how it should be treated<sup>[61,65]</sup>. Secondary left ventricular hypertrophy may cause myocardial ischemia irrespectively of the presence of obstructive atherosclerotic lesions in major coronary arteries, in fact manifestations of angina are reported also by patients without evidence of relevant coronary artery disease (CAD) on angiographic examination<sup>[66]</sup>.

Moreover even though degenerative stenotic aortic valve disease has the same risk factors of CAD, there is substantial variability in CAD prevalence in aortic stenosis population between different studies, ranging from 34% to 75%<sup>[67,68]</sup>. A possible explanation for this inconsistency can be found in the definition adopted for significant CAD and which method is used for its diagnosis, usually angiographic examination,

which shows relevant interobserver variability. Usually angiographic cut-off for coronary obstruction is considered  $\geq 50\%$ <sup>[69-72]</sup>, but some authors use a cut off value of  $\geq 70\%$ <sup>[73-75]</sup>.

Latest recommendations about myocardial revascularization released from European Society of Cardiology suggest PTCA for patients undergoing TAVI in the presence of coronary obstructive lesions of more than 70% (class IIa, level of evidence C), despite the impact on long term survival of obstructive CAD is controversial according to different TAVI registries<sup>[76-78]</sup>. In order to definite the prognostic benefit of percutaneous revascularization of anatomically relevant CAD in patients undergoing TAVR a randomized controlled trial, the ACTIVATION study, is ongoing<sup>[79]</sup>.

In addition the burden of CAD in this setting fall in a broad spectrum going from a simple single lesion to multiple complex lesions, with different prognostic implications. Currently CAD treatment can be guided by coronary angiography and Anatomical Scoring Systems. Moreover in patients with borderline risk profile the assessment or the exclusion of coronary artery disease can induce the Heart Team to lean towards SAVR or TAVR.

### **Angiography-guided revascularization**

According to angiographic data significant obstructive CAD is found in 40%-60% of TAVR patients, evaluated through quantitative coronary angiography (QCA). Khawaja *et al*<sup>[66]</sup> in a retrospective study "Coronary artery disease in patients undergoing TAVI- why not to treat" including 271 patients evaluated through QCA, reported an incidence of obstructive CAD of 34% (defined as a 70% or more stenosis of a major coronary artery or 50% or more in left main stem or a venous graft); 26.9% of them underwent revascularization before TAVR procedure. Moreover no significant increase in mortality for patients carrying obstructive CAD was found in this study, either at 30 d or at 1 year and among them, those treated by revascularization also did not show any significant prognostic improvement.

However QCA has several pitfalls: (1) eccentric and markedly calcific plaques are difficult to assess through this technique because of calcium pools projection by X-rays; and (2) extremely tortuous epicardial coronary arteries may cause mistakes in vessel measurement and thus in stenosis evaluation<sup>[80]</sup>. Alternatively markedly calcific and contorted lesions may be more reliably evaluated through optical coherence tomography or intravascular ultrasonography, but at present the use of these techniques has not been investigated in TAVR population.

Finally according to old fashioned studies using QCA of left coronary artery in aortic valve stenosis it was demonstrated a progressive increase in coronary vessel dimensions as aortic valvular stenosis progresses, such phenomenon was reverted by SAVR, so angiographic evaluation may not reliably predict CAD extension after

TAVR procedure<sup>[81]</sup>.

### **Anatomical score system**

Anatomical scores are used to grade coronary artery disease extension in everyday clinical practice, among them the most frequently used is SYNTAX score<sup>[82]</sup>. Recently these scoring systems have been applied in small TAVR registries, taking in consideration the location and complexity of coronary lesions in order to estimate procedural risk of coronary revascularization<sup>[83,84]</sup>.

In the previously cited retrospective analysis by Khawaja *et al*<sup>[66]</sup> a SYNTAX score  $> 33$  (which defines an high risk according to SYNTAX study) had an higher rate of periprocedural complications during TAVR, whereas a SYNTAX score between 0 and 22 identified patients with a lower risk. Moreover a cut off value of 9 was a predictor of all-cause death at one month and at one year of follow-up so that revascularization may be indicated for patients with a SYNTAX score  $\geq 9$ .

Furthermore comparing surgical aortic valve replacement with TAVR in the setting of low flow-low gradient aortic stenosis, which represent an higher risk population, the extent of CAD evaluated through SYNTAX score or remaining CAD severity assessed by residual SYNTAX score after revascularization were both predictors of worse prognosis and cardiovascular death after 1 year follow-up<sup>[85]</sup>.

### **Fractional flow reserve guided revascularization**

No methods are validated to assess ischemia in patient with severe aortic stenosis and also evaluation offunctional significance of coronary artery stenosis by fractional flow reserve (FFR) is not recommended in this population. In fact the mechanism of ischemia in severe aortic stenosis is more complex and due to multiple hemodynamic factors so that aortic pressure waveform and coronary blood flow regulation is altered by left ventricular hypertrophy leading to an impaired coronary flow reserve also in absence of coronary obstruction<sup>[86]</sup>. In addition, the increased left ventricular filling pressure will rise left ventricular diastolic wall stress, this phenomenon together with reduced diastolic time may contribute to impair diastolic coronary blood flow per se.

On the other hand the administration of vasodilator drugs, necessary to asses FFR, could induce critical fall in systemic arterial pressure with potentially hemodynamic instability.

## **MULTISLICE COMPUTED TOMOGRAPHY**

Among the imaging modalities, computed tomography (CT) plays a central role in the evaluation of patients with severe aortic stenosis prior to TAVR since it allows to study anatomical details in order to choice the best fitting prosthesis, evaluate the morphology of the access path, select the best fluoroscopic projection angles and detect other relevant comorbidities (Figure 6).

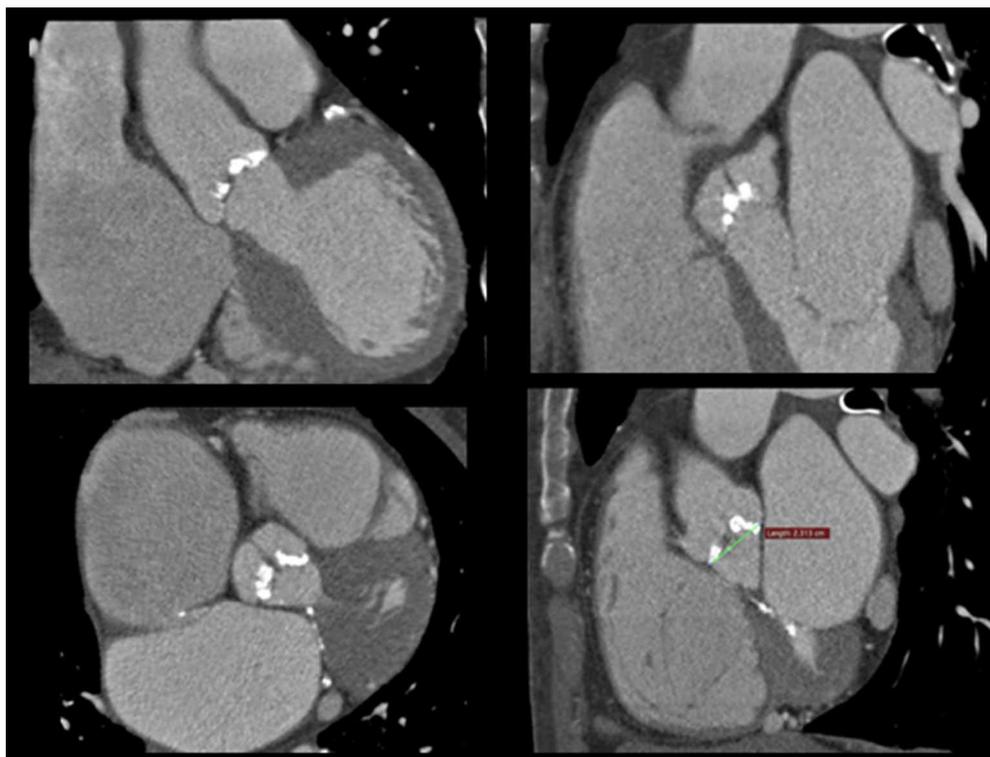


Figure 6 Multi-slice enhanced computed tomography images showing the aortic valve cusps and the first tract of the ascending aorta, with associated presence of extensive valvular calcifications.

### Measurement of aortic annulus and evaluation of aortic root

Multidetector scanners allow multiplanar reformation and 3-dimensional reconstruction of aortic root, ascending tract, arch and descending segments of aorta. Novel technological advances in CT result in higher image quality with substantially reduced scan duration, contrast volume and radiation exposure. CT provide an accurate measurement of anatomic AVA by a cross-sectional view of the aortic valve derived from left sagittal and left coronal oblique views<sup>[52]</sup>. Moreover this modality gives precise measurements diameters, expressed also as mean value between different planar reliefs, area and perimeter of aortic annulus which are essential information for a correct prosthesis choice. The annulus size is larger when measured by MSCT than by 2D transthoracic or transoesophageal echocardiography with an absolute difference  $\leq 1.52 \pm 1.1$  mm. Comparing the measurements of aortic annulus size as obtained by CT angiography and 2-dimensional transoesophageal echocardiography with direct surgical measurement in patients undergoing surgical valve replacement, CTA overestimates aortic annulus diameter in 72.2% of cases, with 46.3% > 1 TAVI valve-size (> 3 mm) overestimations, whereas TEE underestimated aortic annulus diameter in 51.1% of cases, with 16.7% > 1 valve-size underestimations<sup>[87,88]</sup>.

MSCT allows also to give precise measurements of the distance between annulus and coronary ostia and represents the gold standard for this purpose, providing a more comprehensive assessment, showing an average

annular-right coronary artery distance of  $13.6 \pm 2.8$  mm and annular-left coronary artery distance of  $13.4 \pm 3.2$  mm<sup>[89,90]</sup>. The distance between the aortic valve annular plane and the coronary ostia should be at least of  $\geq 10$ -11 mm for both type of most used prosthesis (Corevalve and Edwards). It is important also to evaluate the dimensions of ascending aorta at 45 mm above the annulus plane when the strategy foresees the implantation of a Corevalve prosthesis as this value should not exceed 40 mm for the 26-mm valve and 43 mm for the 29-mm and 31-mm.

This technique is useful to make many reconstructions with adjunctive information about calcification severity, plaque burden and prohibitive risk findings as dissections and complex atheroma of aorta<sup>[91]</sup>.

### Aortic valve calcium score

CT permits to calculate aortic valve calcium scoring. In severe aortic annular calcification the protrusion of calcium into the lumen > 4 mm can lead to an undersizing of the prosthesis valve and predict a post procedural paravalvular regurgitation<sup>[92]</sup>. Furthermore a high calcium score can help to distinguish between severe and pseudosevere aortic stenosis in patients with low left ventricle ejection fraction. Different cutoff values of calcium score in aortic stenosis have been described for men ( $\geq 2000$  AU or  $\geq 480$  AU/cm<sup>2</sup>) and women ( $\geq 1200$  AU or  $\geq 290$  AU/cm<sup>2</sup>) to identify severe AS<sup>[93]</sup>. In risk stratification, mostly in asymptomatic or paucisymptomatic patients, the aortic valve calcium load assessed by MSCT is a powerful predictor of rapid

**Table 2** Magnetic resonance sequences used for pre transcatheter aortic valve implantation evaluation<sup>[96]</sup>

Three-plane localizer	To localize aortic valve plane
Axial SSFP non ECG gated without contrast	To identify potential ascending aorta and subclavian access sites To determine size, calcification, and presence of aneurysmal dilatation of aorta
Breath held free breathing 2D ECG gated SSFP	To evaluate aortic annulus, aortic valve structure, and sinus height
Coronal aorta, LVOT and aortic root	Planimetry valve orifice area
SSFP ECG gated images: short axis stack	Calculate ejection fraction, ventricular volumes and mass
Breath held free breathing phase contrast at aortic orifice	Calculate blood flow velocity, pressure gradient, and flow volume across the aortic valve Calculate Aortic regurgitant volume
3D Navigator assisted SSFP	Coronary ostia height Aortic diameter
T2 black blood	Useful in presence of susceptibility artifacts from sternal wires or prosthetic valves

LVOT: Left ventricular outflow tract; SSFP: Steady state free procession; ECG: Electrocardiography.

stenosis progression and of cardiac events<sup>[94]</sup>.

### Detection of coronary artery disease

Invasive coronary angiography remains the gold standard diagnostic modality for the detection of significant CAD in patients with severe aortic stenosis. The role of coronary computed tomography angiography (CTA) in selection of patients for TAVR until now remains not established mainly because there are few data regarding its diagnostic accuracy in this context. In a large unselected cohort of patients with severe aortic stenosis, the identification of significant CAD has been limited by feasibility and an overall moderate accuracy (driven by the high rate of false-positive observations) so that this test cannot be used instead of invasive coronary angiography<sup>[95]</sup>. In fact, also in patients without arrhythmias, high heart rate and coronary stents up to 25% of the CTA images were found to be not fully evaluable representing coronary calcification the major confounding factor<sup>[96-98]</sup>. On the other hand, CTA has shown a good sensitivity (97%) and negative predictive value (97%) so that it can be reasonably be used as a rule-out test in some selected cases mostly in patients without prior known CAD and little calcifications<sup>[95]</sup>.

### Comorbidities detection

Computed tomography as a part of pre-TAVR diagnostic work-up is often able to detect other concomitant pathologies with important influence on outcome and sometimes questioning the indication to the procedure as in case of detection of potentially malignant diseases with poor prognosis. In fact, during CT aortography, images are acquired throughout the thorax and abdomen, and potentially significant incidental findings can be found. Until today patients candidates to TAVR tend to be elderly and it has been shown a very high overall incidence of incidental pathological findings in this population (more than 50%) and in 18.1% of cases a clinical significance has been documented<sup>[99]</sup>.

### Assessment of peripheral accesses

Appropriate approach selection is crucial for a good results of TAVR and is based on minimal aorto-femoral tract diameter detected by projection aortography or

CTA. In addition to conventional angiography (XA), CTA provides more detailed 3D images including calcification and tortuosity and allows to exclude a transfemoral access in patients with poor vessel quality or small diameter in aorto-femoral tract considering that the 18 Fr sheath requires a minimal arterial diameter of 6 mm of the aorto-femoral tract for prosthesis delivery<sup>[100,101]</sup>. It is important to know that the semi-automated CTA diameter measurement of the aortoiliac tract resulted statistically significantly smaller compared to XA-based measurements.

Patients not suitable for transfemoral TAVR should be considered for transapical implantation or conventional surgery<sup>[102]</sup>.

## MAGNETIC RESONANCE IMAGING

Cardiovascular magnetic resonance (CMR) is an emergent modality for evaluation of patients before TAVR and it is expected to gain more and more space in this setting, mostly in patients with contraindications to contrast medium. As MSCT, this technique provides precise measurements of aortic valve, annulus, aortic root, coronary ostia, definition of the thoraco-abdominal aorta and luminal caliber of the iliofemoral branches (Table 2)<sup>[103]</sup>. Moreover it is able to study LV function with the advantage of not using ionizing radiation (Figure 7).

Non contrast MR should have an important role in preoperative evaluation in selected groups of patients with aortic stenosis: (1) patients affected by severe renal function impairment with GFR < 30 mL/min/mq; (2) patients with inadequate acoustic window mostly in the context of low gradient detection and/or reduced left ventricle ejection fraction; (3) discrepancy between parameters obtained by echocardiography and symptoms; and (4) History of allergic reactions to iodinated contrast medium.

MRI technique are influenced by some limitations. In the first place multiple breath holds, claustrophobia and the presence of arrhythmias can interfere with an adequate acquisition. Aneurism clips, carotid vascular clamp, neurostimulator devices, insulin or infusion pumps, ear implant and ocular foreign bodies represent

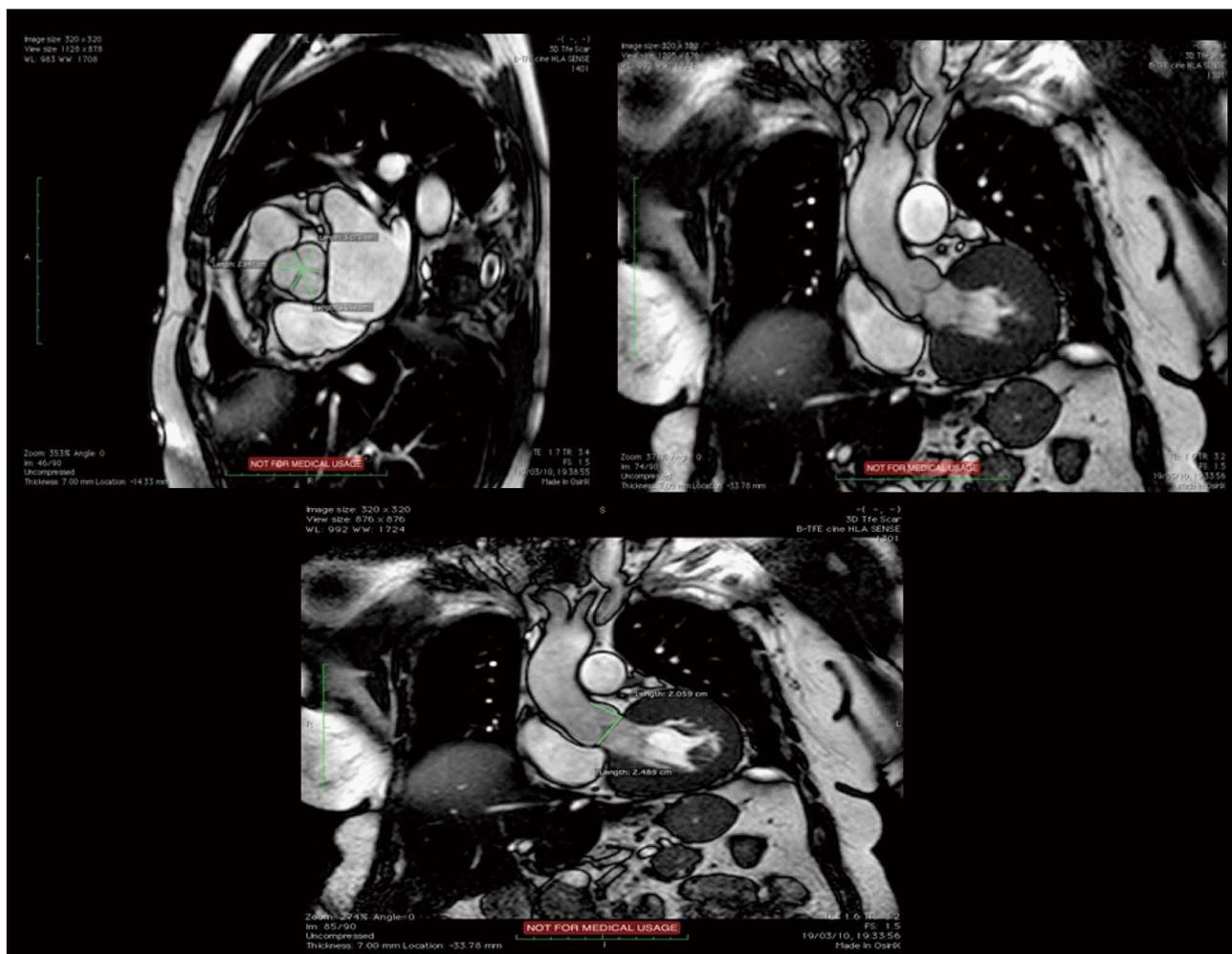


Figure 7 Balanced fast-field echo unenhanced magnetic resonance images showing the normal tricuspid aortic valve, with the typical “Mercedes-Benz Sign” and the first tract of the ascending aorta.

absolute contraindications.

### Aortic valve and root evaluation

MRI is able to provide accurate measurements of aortic annulus that in terms of capacity to predict the presence and the severity of post-implantation aortic regurgitation is similar to MSCT<sup>[104]</sup>. A good concordance between MSCT, CMR and echocardiography has been documented for aortic valve morphology definition and aortic valve area measurements<sup>[105]</sup>. In fact MRI is able to provide the planimetry of aortic valve opening area which is similar to other diagnostic modality as 3D TEE and flow-derived area calculation by catheterization using the Gorlin equation or by Doppler echocardiography using the continuity equation<sup>[106]</sup>. Although anatomic planimetry of aortic stenosis and assessment of valvular anatomy and motion is possible with MRI, this became less than optimal in patients with severe calcifications mostly in the presence of non-planar orifices. Furthermore assessment of severity of aortic stenosis can be completed by velocity-encoded cine MRI with other standard measures as peak anterograde velocity and pressure gradient but

it is necessary to know that velocities and gradients are usually underestimated if compared with Doppler echocardiography<sup>[107]</sup>.

MRI can be an alternative to 3D imaging modality for the measurement of aortic annulus (minor and major diameters, area and perimeter) having showed a good agreement with CT in this context also in presence of oval shape of the structure in which, after adequate plane orientation and 3 dimensional reconstruction, generally the coronal diameter is larger than the sagittal one<sup>[108]</sup>. As for MSCT, MRI diameters were found to be larger than those measured by 2D TEE modality.

Measurements of sinus of Valsalva diameters and definition of aortic root orientation are also possible with this approach but conversely this doesn't represent a good modality to thoracic aorta plaque burden definition as calcifications cause signal voids<sup>[103]</sup>.

The concordance with CT has been documented also for the assessment of the distance between the annulus and the ostium of the left coronary artery in relation to the length of the left coronary leaflet but at the moment more studies are needed to determine whether a strategy based on a different imaging method could

**Table 3** Multimodality imaging in pre transcatheter aortic valve replacement evaluation

Technique	Principal advantages	Disadvantages
Transthoracic echocardiography	Widespread availability First line diagnostic tool	Poor acoustic window Frequent discrepancy between different parameters
Transesophageal echocardiography 3 D reconstruction	Good spatial resolution Semi-invasive exam	Suboptimal for distal ascending aorta and arch Anatomic definition and annulus measurement
Multislice computed tomography	Multiplanar reconstruction Quantification of calcium score Evaluation of aorto-femoral tract	Potential nephrotoxicity of contrast medium Radiations exposition Controlled heart rate
Magnetic resonance imaging	Tissue characterization Multiplanar reconstruction Evaluation of aorto-femoral tract Controlled heart rate	Reduced availability Poor evaluation of calcifications Contraindicated in metallic devices wearers
Positron emission tomography	Evaluation of calcification and inflammation	Poor spatial resolution

achieve better results. A3-D SSFP free breathing stack in late diastole with a respiratory navigator allows to measure the height of coronary ostia from the annular plane.

Moreover magnetic resonance angiography can characterize aorto-ilio-femoral arteries in order to plan the more adequate access<sup>[109]</sup>.

#### Ventricular volume and function

MRI provides quantitative evaluation of left ventricle volumes and function and late gadolinium enhancement at T1-weighted sequences allows to detect myocardial fibrosis which is more often localized in mid-wall of myocardium, like in pressure-overload cardiomyopathies, and represents a predictor of poor prognosis<sup>[110]</sup>. Fibrosis represents one of the most important factors implicated in progression of hypertrophy towards heart failure and an early detection can be useful in risk profile definition mostly in asymptomatic patients or in case of borderlines parameters at conventional echocardiography evaluation. Advanced fibrosis replacement of left ventricle myocardium predicts a lack of improvement in LV systolic function after aortic valve replacement and is an independent predictor of all-cause mortality<sup>[111,112]</sup>.

#### POSITRON EMISSION TOMOGRAPHY/CT

An emergent role in pre-TAVR evaluation is attributable to positron emission tomography (PET)/CT with the advantage of combining the anatomic definition derived from CT and the functional and metabolic characterization gained from PET<sup>[15]</sup>. <sup>18</sup>F-sodium fluoride (<sup>18</sup>F-NaF) is a tracer used to detect calcification and in aortic stenosis the amount of uptake correlates with disease severity and is able to predict the progression of the disease<sup>[113-115]</sup>. On the other hand <sup>18</sup>F-fluorodeoxyglucose uptake, representing the burden of inflammation, is higher in patients with mild or moderate aortic stenosis and decrease with stenosis progression.

#### CONCLUSION

Patient selection for TAVR should be based not only on

accurate assessment of aortic stenosis morphology, but also on several clinical and functional data. The Heart Team is key in the overall risk evaluation of this population. Multi-Imaging modalities are preferred for assessing the anatomy and the dimensions of the aortic annulus before TAVI (Table 3). In any case, we should tailor our patient selection and prosthesis selection on a case-to-case basis.

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## Paroxysmal atrial fibrillation ablation: Achieving permanent pulmonary vein isolation by point-by-point radiofrequency lesions

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### Abstract

Pulmonary vein isolation by point-by-point radiofre-

quency catheter ablation constitutes the cornerstone of catheter ablation strategies for the treatment of atrial fibrillation. However, despite advances in pulmonary vein isolation ablation strategies, long-term success rates after ablation remain suboptimal, which highlights the need to develop techniques to achieve more durable lesions. Strategies proposed to improve the durability of pulmonary vein isolation can be divided into two groups: Those addressed to improving the quality of the lesion and those that optimize the detection of acute PV reconnection during the ablation procedure. This manuscript reviews the role and potential benefits of these techniques according to current clinical evidence.

**Key words:** Atrial fibrillation; Pulmonary vein isolation; Lesion durability; Contact force; Pulmonary vein reconnection

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**Core tip:** Results of pulmonary vein isolation remains suboptimal in terms of long-term outcomes. Improving lesion durability could reduce atrial fibrillation recurrence rate after pulmonary vein isolation. This manuscript reviews current techniques proposed in order to achieve more durable pulmonary vein isolation by point-by-point radiofrequency ablation. The role and potential benefits of these techniques are discussed according to current clinical evidence. Furthermore a stepwise approach to achieve permanent pulmonary vein isolation is proposed.

Pedrote A, Acosta J, Jáuregui-Garrido B, Frutos-López M, Arana-Rueda E. Paroxysmal atrial fibrillation ablation: Achieving permanent pulmonary vein isolation by point-by-point radiofrequency lesions. *World J Cardiol* 2017; 9(3): 230-240 Available from: URL: <http://www.wjgnet.com/1949-8462/full/v9/i3/230.htm> DOI: <http://dx.doi.org/10.4330/wjc.v9.i3.230>

## INTRODUCTION

Atrial fibrillation (AF) is one of the major causes of stroke, heart failure, and cardiovascular morbidity worldwide<sup>[1]</sup>. Since Haïssaguerre *et al*<sup>[2]</sup> identified the pulmonary veins (PVs) as triggers capable of initiating AF paroxysms, radiofrequency (RF) catheter ablation through pulmonary vein isolation (PVI) has been developed and now constitutes the cornerstone of catheter ablation strategies for the treatment of AF<sup>[3]</sup>. Current indications for PVI include symptomatic paroxysmal or persistent AF, in general as second-line treatment after failure of or intolerance to antiarrhythmic drug therapy, but also as first-line therapy in selected cases<sup>[4]</sup>.

According to the most recent consensus statement on catheter ablation of AF<sup>[3]</sup>, the technique for achieving PVI should target a wide area around the PVs, called the antrum, with complete electrical isolation as the endpoint of the procedure. However, despite advances in PVI ablation strategies, long-term success rates after ablation remain suboptimal, which has led to the development of new techniques to achieve more durable lesions.

## PV RECONNECTION AS THE MAIN CAUSE OF AF RECURRENCE AFTER PVI

In the majority of patients with AF recurrence, an electrical reconnection between the PV and LA can be observed<sup>[5-7]</sup>. The probability of AF recurrence during follow-up after a PVI procedure has been linked with the presence of gaps, defined as poor isolation areas between the PV and LA, due to suboptimal RF lesions<sup>[8]</sup>. A recent meta-analysis of 11 studies<sup>[9]</sup> including 683 patients showed that 85.5% of patients with AF recurrence had at least one PV reconnected, opposed to 58.6% of those without AF recurrence. Although not fully established, it has been suggested that the biological mechanism underlying PV reconnection may be related to the recovery of tissue conduction after a transient phase of reversible tissue injury with inflammation and edema<sup>[10]</sup>. Therefore, achievement of permanent PV isolation should be considered the main goal of current AF ablation approaches in order to avoid recurrences.

## PERMANENT PV ISOLATION AS THE ENDPOINT OF AF ABLATION: HOW TO ACHIEVE IT?

The reasons for long-term failure of AF ablation are largely based on a suboptimal ability to effectuate a durable transmural lesion using the contemporary ablation toolset. While electrical PVI may be achieved acutely, the combination of inadequate electrode-tissue contact, insufficient power delivery, and tissue edema

may prevent RF-induced heating of myocardium to lethal temperatures. With time, as the acute effects of RF energy resolve, the transient injury induced at the time of index ablation recovers, revealing gaps in the initial line of ablation and allowing PV triggers to excite the adjacent LA and induce AF<sup>[6,10]</sup>. Several techniques to improve the durability of PVI have been proposed, and can be divided into two groups: Those addressed to improving the quality of the lesion and those that optimize the detection of acute PV reconnection during the ablation procedure.

## TECHNIQUES TO IMPROVE LESION DURABILITY

The use of irrigated catheters for PVI was associated with a dramatic decrease in PV reconnection rate<sup>[11]</sup>. However, even when irrigated catheters are used, the recurrence rate after a single PVI procedure remains high (30%-35%)<sup>[12]</sup>. Further strategies are required in order to improve long-term durability of the lesions obtained with this type of catheters.

### Use of sheaths

Efficient catheter contact can be facilitated through the use of non-steerable and steerable sheaths that allow easy maneuverability, access, and contact to target sites. Piorkowski *et al*<sup>[13]</sup> compared the use of steerable sheaths with the use of non-steerable sheaths during AF ablations in a prospective randomized trial. Although the rate of acute PVI and total RF application time did not differ between the study groups, single procedure success was significantly higher in patients treated with a steerable sheath (76% vs 53% at 6 mo). The difference persisted at 12 mo (75.7% success) after a single AF catheter ablation procedure using steerable sheath<sup>[14]</sup>. Therefore, use of a steerable sheath may help to improve the maneuverability of the ablation catheter, catheter stability, and tissue contact. This could potentially reduce recurrence through the enhancement of lesion continuity and transmurality.

### General anesthesia

In a multicenter trial, Di Biase *et al*<sup>[15]</sup> randomized 257 consecutive patients undergoing a first AF ablation procedure to general anesthesia or conscious sedation. During follow-up (mean 17 ± 8 mo), fewer patients randomized to conscious sedation were free of atrial arrhythmias while off antiarrhythmic drugs (69% vs 88% of patients randomized to general anesthesia). In their study, all patients with recurrence had a second procedure. Interestingly, 42% of PVs in the conscious sedation arm at the repeat procedure had recovered PV conduction, compared with 19% in the general anesthesia group<sup>[15]</sup>. Better and more stable tissue-catheter contact due to controlled breathing patterns and elimination of patient movements may explain this finding.

### Contact force sensing catheters

Contact force (CF) sensing is a novel technology used to assess the degree of catheter-tissue contact through a sensor at the distal tip of the ablation catheter. Studies based on animal models have shown that catheter-tissue CF is directly correlated with lesion size, and that excessive CF (> 50 g) could even provoke steam pops<sup>[16,17]</sup>. The concept of force-time integral (FTI) has also been proposed as a major factor in RF lesion size<sup>[18]</sup>. Shah *et al*<sup>[18]</sup> calculated the FTI by measuring the area under the CF curve beyond 60 s and found a linear correlation with lesion size during RF ablation. Despite similar power and peak CF values, lesions were larger with constant contact and smaller with intermittent contact.

### CF and lesion transmuralty

Several studies have assessed the relationship between CF and lesion transmuralty by means of electrogram analysis, cardiac imaging, and histopathology. Squara *et al* assessed the CF and FTI needed to create effective transmural lesions during AF ablation by analyzing bipolar electrograms before, during, and after RF application. Based on post-ablation changes in electrogram characteristics, they identified a cutoff FTI of > 392 gs to predict transmuralty with 89% sensitivity and 93% specificity<sup>[19]</sup>. Two cardiac MRI studies have demonstrated a direct correlation of CF and FTI with lesion transmuralty. In the first study, Sohns *et al*<sup>[20]</sup> performed contrast-enhanced cardiac MRI in patients treated with AF ablation using CF catheters. They found a correlation between regions where higher FTI (> 1200 g) was maintained during ablation and those showing increased late gadolinium enhancement on MRI at 3 mo after ablation<sup>[20]</sup>. In the second study, Andreu *et al* performed cardiac MRI at 3 mo after PVI ablation to assess CF thresholds required to create permanent lesions using a dragging catheter (as opposed to a point-by-point lesion delivery) technique<sup>[21]</sup>. They reported that PV segments where MRI gaps were seen had lower maximal CF values, compared to segments without gaps, and a CF threshold of > 12 g predicted the formation of a complete PV lesion with 94% specificity and 91% positive predictive value.

Results from a recent study question the correlation between CF and chronic lesion formation. Williams *et al*<sup>[22]</sup> placed linear intercaval right atrial lesions in eight pigs using high (> 20 g) or low (< 10 g) CF, intentionally leaving a gap between segments. Voltage maps and cardiac MRI were performed before, immediately after, and 2 mo after ablation. The authors found that tissue edema was greater in the acute post-ablation setting with high CF, but there was no difference in chronic lesion size or volume by voltage mapping or cardiac MRI between high vs low CF regions at 2 mo. Their results suggest that a transmural lesion can be created whenever continuous tissue-catheter contact is achieved (independently of the CF value) and adequate power is delivered with a stable catheter position throughout the

lesion.

### CF variability according to left atrium anatomy

Obtaining adequate CF can be difficult in certain portions of the LA, and certain LA regions may require less CF to achieve transmuralty with RF ablation. This may explain the observation that PV reconnection tends to recur at specific regions in the LA. For example, Schluermann *et al*<sup>[23]</sup> reported lower CF obtained in left PVs than in right PVs and found the lowest values in the anterior segments, where the ridge between the left upper PV and the LA appendage represents an especially challenging region for obtaining appropriate CF. Consistently with these data, our group observed that when operators were blinded to CF, the lowest CF values were recorded at the anterior segments of left PVs<sup>[24]</sup> (Figure 1).

On the other hand, given the differences in LA wall thickness, the amount of CF needed to achieve transmural lesions may vary in different portions of the LA. Sotomi *et al*<sup>[25]</sup> showed that higher CF may be necessary in certain regions such as the inferior right PV and posterior-superior right PV regions (22 g CF), while other areas such as the posterior-inferior right PV region may require only 10 g CF to assure acute PVI. Knowledge of CF requirements in various regions of the LA can improve safety during ablation by allowing the operator to control RF power based on CF to prevent steam pops without compromising lesion durability.

### Impact of CF on ablation outcomes-clinical studies

Several studies (Table 1) have assessed the role of CF technology in short and long-term ablation outcomes.

The TOCCATA study was the first multicenter, prospective study to demonstrate the safety of CF-sensing catheters (Tactiath, Endosense) for ablation of cardiac arrhythmias<sup>[26]</sup>. The study included 34 patients undergoing PVI for paroxysmal AF and showed that low CF was associated with higher rates of AF recurrence<sup>[26]</sup>. Specifically, all patients treated with a CF < 10 g experienced AF recurrences, whereas 80% of the patients treated with an average CF > 20 g remained free from AF recurrence at 12 mo<sup>[26]</sup>.

In order to demonstrate the correlation between CF parameters during initial procedure and PV reconnection, the EFFICAS-I study of PVI using CF-sensing catheters assessed the incidence of isolation gaps at 3-mo follow-up (Tactiath, Endosense)<sup>[27]</sup>. Interestingly, operators were blinded to CF information during the initial procedure. Isolation gap sites correlated with lower minimum CF and FTI during the initial ablation, and the authors proposed an optimal CF target of 20 g with minimum FTI of 400 gs. These cut-off values were prospectively tested in the EFFICAS-II study, which showed that 85% of PVs treated within the proposed CF guidelines were chronically isolated, suggesting a more durable PVI<sup>[28]</sup>.

The SMART-AF trial, a prospective, multicenter, non-randomized single-arm study, examined the efficacy

**Table 1** Clinical studies on contact force monitoring and mid/long-term outcomes

Study	n	Type of study	CF catheter	Control catheter	Follow-up (mo)	Findings
Andrade <i>et al</i> <sup>[55]</sup> , 2014	75	Prospective observational	Thermocool SmarTouch	Navistar Thermocool	13.3	CF reduced dormant conduction (16% vs 52%) and improved long-term arrhythmia-free survival (88% vs 66%)
Kimura <i>et al</i> <sup>[31]</sup> , 2014	38	Randomized controlled trial	Thermocool SmarTouch	Thermocool SmarTouch (blinded operator)	6	CF reduced procedure time and additional touch-up ablation
Marijon <i>et al</i> <sup>[61]</sup> , 2014	60	Prospective observational	Thermocool SmarTouch	EZ Steer Thermocool	12	CF reduced AF recurrence at 12 mo (10.5% vs 35.9%)
Shurrab <i>et al</i> <sup>[33]</sup> , 2015	42	Observational	Thermocool SmarTouch	Navistar Thermocool	2.5	CF reduced reconnection rate at 30 min postablation
TOCCASTAR, 2015	300	Randomized controlled trial	Tacticath	Thermocool Navistar	12	No differences in arrhythmia-free survival
Pedrote <i>et al</i> <sup>[24]</sup> , 2016	50	Randomized controlled trial	Thermocool SmarTouch	Thermocool SmarTouch (blinded operator)	12	CF reduced PV gaps (20% vs 68%). No benefits in arrhythmia-free survival
Ullah <i>et al</i> <sup>[34]</sup> , 2016	117	Randomized controlled trial	Thermocool SmarTouch	Thermocool SmarTouch (blinded operator)	12	CF reduced acute reconnections (22% vs 32%). No benefits in arrhythmia-free survival

CF: Contact force.

and safety of AF ablation using a SmartTouch CF-sensing catheter<sup>[29]</sup>. Only 2.5% of the 172 patients included had severe complications, suggesting that safety was not inferior to non-CF-sensing catheters. On the other hand, CF-sensing ablation that remained within target range > 80% of the time resulted in superior 1-year ablation success (81% of patients free from AF recurrence vs 66%,  $P = 0.005$ )<sup>[29]</sup>.

The TOCCASTAR study was a prospective, multi-center, randomized clinical trial that compared AF ablation with CF (TactiCath) vs non-CF (ThermoCool Navistar) catheters in 300 patients<sup>[30]</sup>. Achieving optimal CF resulted in higher rates of acute PVI and no differences were observed in long-term success (freedom from AF or atrial tachycardia recurrence at 12 mo, excluding 3-mo blanking period).

Kimura *et al*<sup>[31]</sup> compared acute bidirectional block after PVI in 38 patients randomized to non-CF guided vs CF-guided (target CF 10-20 g) ablation using Thermocool Smart Touch catheter. This study showed that CF-guided PVI reduces procedure time and the need for additional touch-up ablation. Furthermore, a nonsignificant trend towards lower AF recurrence rate at 6 mo post-PVI was observed in the CF-guided group.

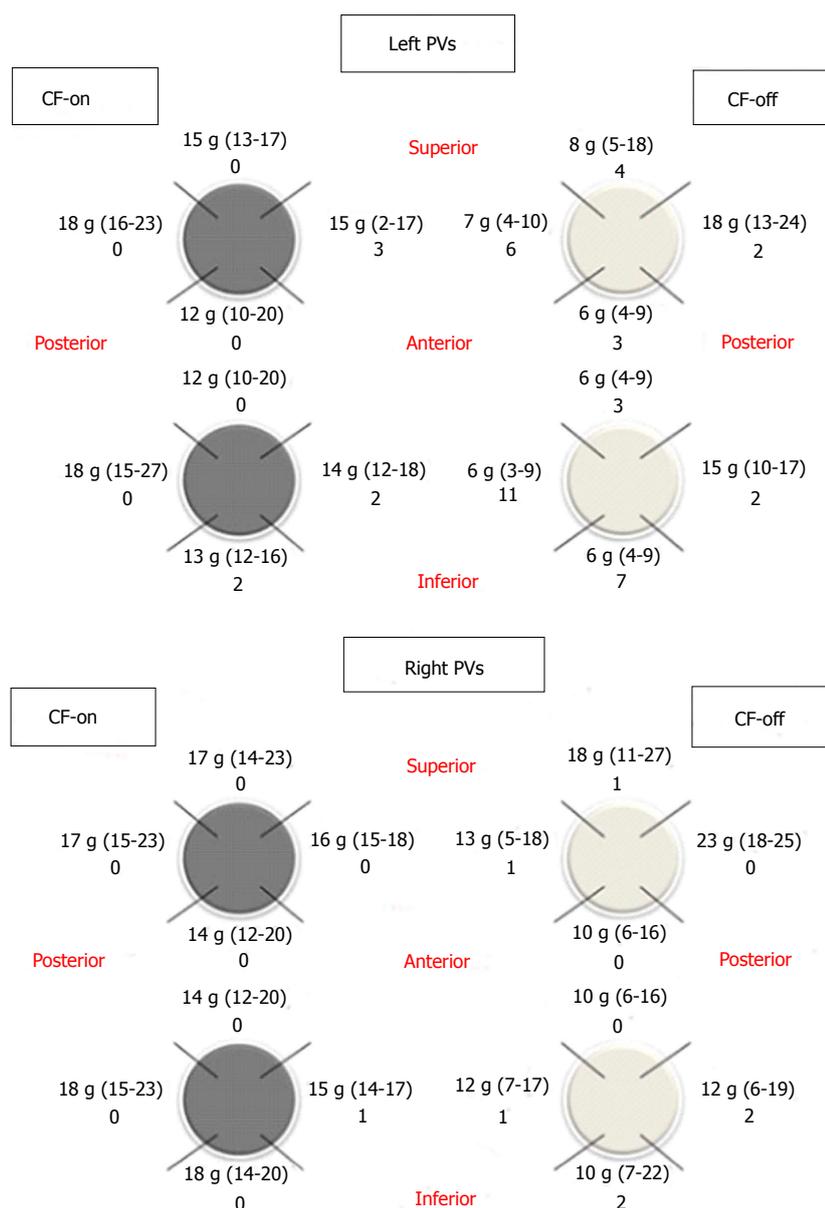
Two large meta-analyses have compared AF ablation with CF vs non-CF catheters. Afzal *et al*<sup>[32]</sup> examined data on 1148 patients in 9 studies and found that the use of CF-sensing technology reduced AF recurrence 37% overall at a median 12 mo of follow-up. Those treated with CF catheters also had reduced RF ablation duration, although no significant difference was seen in total procedure length or fluoroscopic exposure, compared to non-CF catheters. Shurrab *et al*<sup>[33]</sup> subsequently published another meta-analysis, which included 1428 patients from 11 studies (an overlap of 6 studies from the previous meta-analysis). They found a similar 38% overall reduction in AF recurrence at long-

term follow-up. However, in addition to reduced RF ablation time, overall procedure length and fluoroscopic exposure duration were significantly lower in patients treated with CF technology. This meta-analysis also demonstrated a non-significant trend toward lower complication rates in the CF group.

It should be noted that the studies mentioned above assessed the impact of CF parameters in PVI performed with a circular catheter inside the PV. The use of circular catheters allows continuous recording of the electrical signal inside the PV, which can condition the endpoint of the procedure and prevents "naïve" assessment of the potential benefit of CF monitoring. In order to test the benefits of CF monitoring in PVI with an exclusively anatomic approach (blinded to the PV catheter), our group conducted a randomized, controlled study in which 50 patients with paroxysmal atrial fibrillation were randomized into CF-on (CF > 10 g) or CF-off (CF blinded;  $n = 25$ ) groups. In the CF-on group, there was a reduction in the PV gaps at the expense of the left PVs and shortening of the procedure and radioscopy times. This confirms the benefits of operator monitoring and control of a mean CF > 10 g during PVI<sup>[24]</sup>. However, at 12 mo the AF recurrence rate was similar in both groups<sup>[24]</sup>. Consistent with these data, a larger study by Ullah *et al*<sup>[34]</sup> using the same methodology showed that access to CF data during the procedure was associated with reduced acute PV reconnection, although no benefit was observed in terms of 1-year success rate. These results suggest that CF monitoring during PVI may not impact long-term clinical outcome because it is only one of multiple factors that determine lesion durability.

### Ablation index

As has been explained, previously described endpoints (CF and FTI) do not take the power used during RF



**Figure 1 Contact force variability according to left atrium anatomy.** Contact force (CF) is expressed in grams (g; median and 25<sup>th</sup>-75<sup>th</sup> percentile) and the number of pulmonary veins segments with conduction gaps (bold) in the CF-on group (dark gray) and the CF-off group (light gray). Reproduced with permission from Pedrote *et al*<sup>[24]</sup>.

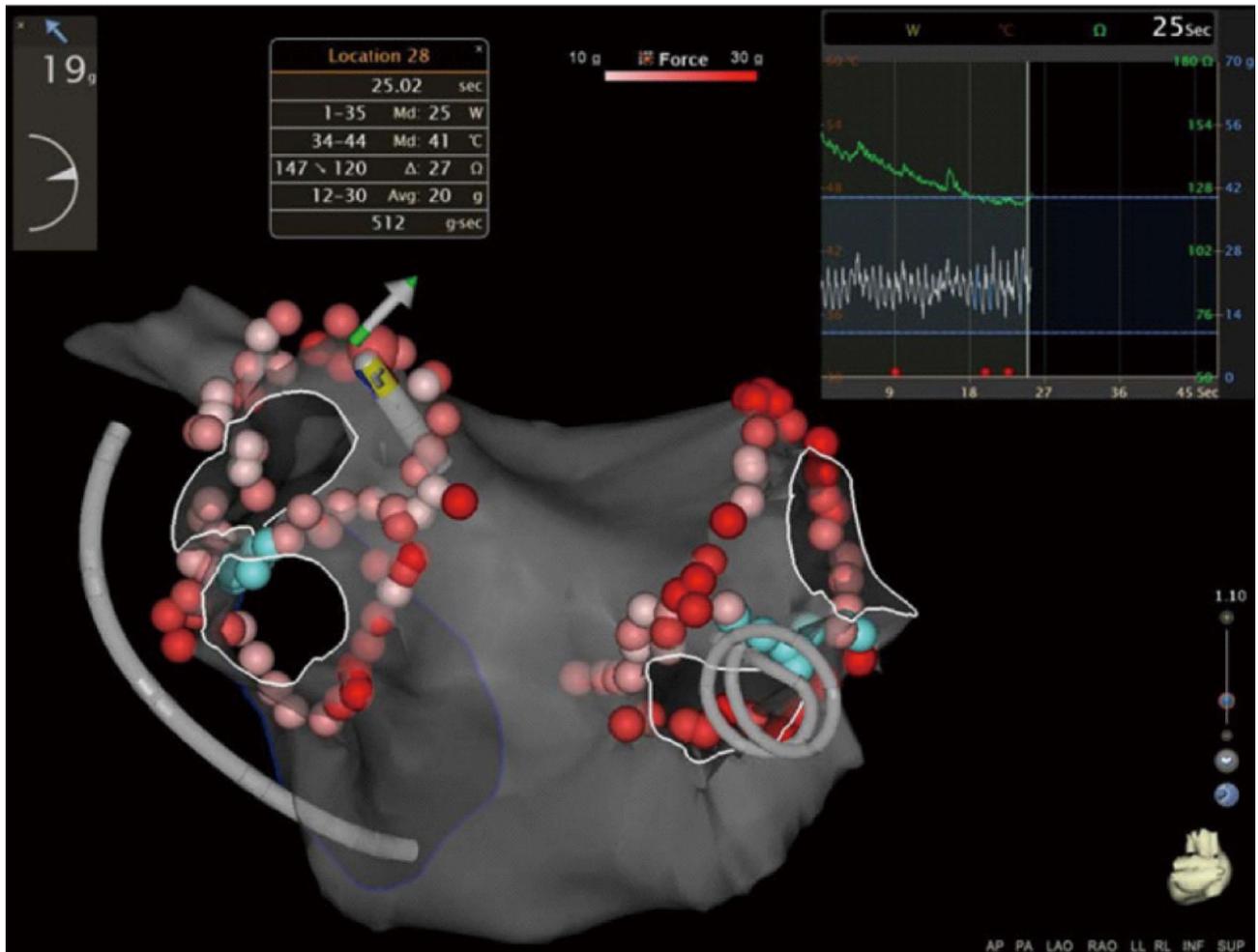
application into account. In order to resolve this limitation, the ablation index has been proposed as a marker of ablation lesion quality that incorporates CF, ablation time, and RF power in a weighted formula (the greater the impact of power over CF, the greater the impact on the initial phase of ablation). A recent study by Das *et al*<sup>[35]</sup> showed that the minimum ablation index was an independent predictor of conduction recovery after PVI. Furthermore, in this study, higher ablation index values were required to prevent reconnection of anterior/roof segments, compared to posterior/inferior segments<sup>[35]</sup>.

### Lesion contiguity

The EFFICAS-II study demonstrated that lesion contiguity is an essential component of effective PVI. The analysis

of the contiguity index revealed that even with effective use of optimized CF, 15% of PVs were reconnected after ablation due to non-contiguity between point-by-point lesions along ablation line<sup>[28]</sup>. Consistent with these data, Park *et al*<sup>[36]</sup> showed that acutely durable PVI can be achieved in CF-guided ablation when RF lesions are delivered with a mean CF > 10 g and an inter-lesion distance < 5 mm.

A novel automated technology for tagging ablation lesions (VisiTag module) allows real-time assessment of catheter stability, contact force, power, and impedance drop during radiofrequency applications (Figure 2). This technology improves lesion efficiency and reduces the number of ineffective applications<sup>[37]</sup>. Catheter stability tracking during PVI is essential in order to achieve appropriate lesion contiguity. Okumura *et al*<sup>[38]</sup> reported



**Figure 2 Automatic tagging of radiofrequency lesions.** The contact force (CF) of each application is color-coded (color bar). The manually acquired RF applications are displayed in green. The central box shows the information collected by the VisiTag™ module on each point, including average CF, time, force-time integral, temperature, power, and delta impedance. The force and impedance graphs from this RF point are shown on the right, and the real-time CF and direction dashboard are shown on the left. Reproduced with permission from Pedrote *et al.*<sup>[24]</sup>. RF: Radiofrequency.

that a strict stability setting (3-mm distance limit for at least 10 s) for VisiTag reduced acute PV reconnection, although no benefit was observed in mid-term outcomes.

## HOW TO OPTIMIZE THE DETECTION OF ACUTE PV RECONNECTION DURING THE ABLATION PROCEDURE

### **Circular mapping catheters**

Circumferential PVI guided by nonfluoroscopic electroanatomic mapping systems, without confirmation of electrical isolation with a circular mapping catheter, has been shown to be ineffective in achieving long-term arrhythmia control<sup>[39]</sup>. Additionally, a randomized study comparing PVI guided by circular mapping catheter vs PVI using only RF catheter showed that the use of circular mapping catheter is associated with better acute results and lower recurrence rates<sup>[40]</sup>. Therefore, electroanatomic mapping-guided circumferential PV ablation without use of the circular mapping catheter

has been demonstrated to be less reliable to achieve PVI and significantly less effective than circular mapping catheter-guided PVI in terms of arrhythmia-free survival.

### **Identification of dormant conduction**

The identification of dormant tissue that has been rendered unexcitable by “stunning” or edema is a significant challenge that may potentially increase risk of AF recurrence. The detection of such “dormant conduction” during the initial ablation procedure may therefore help identify PVs with the potential to reconnect after the index procedure, and targeted ablation at these sites may reduce the risk of recurrent AF. Adenosine has been shown to effectively uncover dormant conduction. Following ablation, adenosine selectively hyperpolarizes PV cells by increasing inward rectifier potassium current, thereby restoring excitability of inactivated voltage-dependent Na<sup>+</sup> (INa) and reestablishing conduction in dormant PVs<sup>[41]</sup>. Multiple studies have shown that adenosine is clinically useful in identifying PV reconnection, as well as cavotricuspid isthmus reconnection<sup>[42]</sup>. An early study reported that

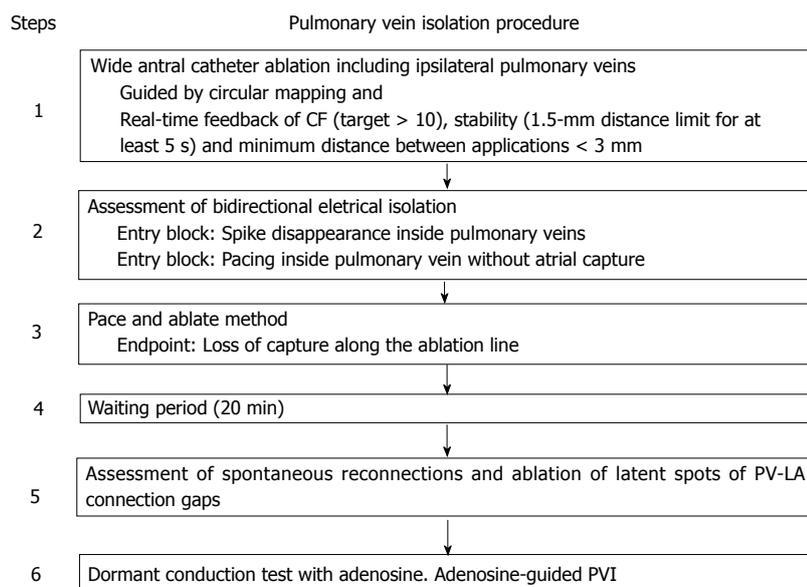


Figure 3 Stepwise approach for permanent pulmonary vein isolation. CF: Contact force; PVI: Pulmonary vein isolation.

adenosine induced reconnection in 25% of PVs immediately after successful isolation<sup>[43]</sup>. Tritto *et al.*<sup>[44]</sup> further demonstrated that delivering additional RF lesions at electrical gap sites elicited by adenosine definitively eliminated recovery of PV reconnection in all cases. Subsequent studies have shown that AF recurrence after PV isolation could be reduced by delivering additional ablation lesions to eliminate adenosine-induced dormant PV conduction<sup>[45-47]</sup>. Other studies<sup>[48,49]</sup> did not confirm the usefulness of adenosine in AF recurrence after PVI, fueling a need for randomized trials.

Two randomized trials (ADVICE and UNDER-ATP) have assessed whether elimination of dormant PV conduction after PVI is better than conventional PVI in terms of arrhythmia-free survival. The ADVICE study showed that the use of adenosine to identify and target areas of dormant conduction significantly improved long-term arrhythmia-free survival, compared to PVI alone<sup>[50]</sup>. In contrast, the UNDER-ATP trial found no significant reduction in arrhythmia-free survival by ATP-guided PVI, compared with conventional PVI<sup>[51]</sup>. The discrepancy between ADVICE and UNDER-ATP trials may be due to differences in the rate of dormant conduction, around 50% in the ADVICE trial and 28% in UNDER-ATP. This suggests that the benefit of using adenosine after PVI depends on how frequently dormant conduction is observed; which is highly affected by the ablation procedural method.

### Pace and ablate

Entrance and exit block confirmed by the absence of PV potentials and by pacing inside the PVs is a common procedural endpoint of encircling PVI. However, it has been suggested that pacing along the ablation line may identify latent spots of PV-LA antrum connection gaps not detected by circular mapping catheters. Steven *et al.*<sup>[52]</sup> showed that more RF ablation energy

was required to achieve loss of pace capture along the ablation line than for entrance block into the PVs, suggesting that reaching the endpoint of loss of capture along the ablation line may be associated with more durable lesions. Consistent with this hypothesis, a randomized study confirmed that the use of pacing to ensure an unexcitable gap along the ablation line improved success rates at 12 mo post-PVI, compared to reliance on bidirectional block alone (83% vs 52%, respectively)<sup>[53]</sup>. However, it should be noted that adenosine was not used to identify dormant conduction after PVI in this study. In contrast to these findings, two recent studies showed that although PVI followed by the pace and ablate method reduced dormant PV conduction unmasked by adenosine, there was no difference in 1-year AF recurrence, compared to adenosine-guided ablation<sup>[54,55]</sup>.

Although the available results suggest that both techniques achieve similar long-term outcomes, the potential effect on recurrence rates of combining pace and ablate with adenosine-guided PVI remains unknown. A recent study by Kogawa *et al.*<sup>[56]</sup> showed that sites with adenosine-induced dormant PV reconnection did not match the excitable gaps identified by pacing, suggesting a difference in the underlying mechanism to elucidate potential PV-antrum gaps. Thus, the authors proposed that an adenosine provocation test followed by pace and ablate method could be useful in reducing AF recurrence. Further prospective and randomized studies are required to confirm this hypothesis.

### NON-PV SOURCES OF AF RECURRENCE

It should be noted that a variable proportion of patients may have AF recurrence despite persistent PVI. This could be due to the existence of non-PV triggers<sup>[57]</sup>. Typically, these non-PV triggers are located in specific

regions such as the crista terminalis, the superior vena cava, the Eustachian ridge, the fossa ovalis, the left atrial appendage, the inferior mitral annulus and the coronary sinus. Empirical ablation of these common origins of triggers is not recommended. However, once a trigger is identified, it should be eliminated in order to achieve better outcomes<sup>[58]</sup>.

## EXPERT RECOMMENDATIONS

Based on our own experience, we propose the following step-wise approach to achieve permanent PVI (Figure 3). Our unit adopted this strategy two years ago, with good arrhythmia-free survival at 12 mo (84%), a very low complication rate (1%), and no increase in procedure time<sup>[24,59]</sup>.

## FUTURE PERSPECTIVES

The implementation of non-fluoroscopic navigation systems in the electrophysiology laboratory has improved anatomic definition of cardiac structures. However, the increased complexity of ablation procedures demands better intra-procedural anatomic definition and improved accuracy in catheter positioning. Novel non-fluoroscopic systems have been proposed for catheter guidance during PVI procedures. In animal studies, Ranjan *et al*<sup>[60]</sup> showed the feasibility of catheter tracking, electrogram recording, and RF energy delivery in a real-time MRI environment. Intra-procedural MRI allowed real-time visualization of lesion formation and tissue characterization, which could permit the assessment of lesion depth and transmural. Furthermore, their work demonstrates the utility of MRI-guided PVI to identify gaps intra-procedurally and guide catheter positioning to target them. However, this proof-of-concept has not been tested in humans. In order to use this technology in clinical settings, several technical challenges must be overcome to obtain better signals and develop more maneuverable and easily visible catheters. However, this promising technology will provide considerable benefits by delivering accurate anatomic definition and monitoring of RF lesions.

## CONCLUSION

PVI is the cornerstone of catheter-based therapies for AF. PV reconnection after PVI represents the main limitation of AF ablation techniques. Efforts should be made to develop strategies that achieve more durable lesions. Current techniques associated with better acute (and probably long-term) outcomes include antral PVI guided by circular mapping catheters, the use of CF catheters, lesion contiguity, and the assessment of dormant PV conduction by adenosine and/or pace and ablate. Finally, a subset of patients may still have AF recurrences despite persistent PVI, due to the presence of non-PV triggers. Efforts should be made in order to individualize the treatment according to each patient's

specific mechanism of recurrence (drivers, rotors, focal activity...).

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Retrospective Cohort Study

## Accuracy of gestalt perception of acute chest pain in predicting coronary artery disease

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### Abstract

#### AIM

To test accuracy and reproducibility of gestalt to predict

obstructive coronary artery disease (CAD) in patients with acute chest pain.

#### **METHODS**

We studied individuals who were consecutively admitted to our Chest Pain Unit. At admission, investigators performed a standardized interview and recorded 14 chest pain features. Based on these features, a cardiologist who was blind to other clinical characteristics made unstructured judgment of CAD probability, both numerically and categorically. As the reference standard for testing the accuracy of gestalt, angiography was required to rule-in CAD, while either angiography or non-invasive test could be used to rule-out. In order to assess reproducibility, a second cardiologist did the same procedure.

#### **RESULTS**

In a sample of 330 patients, the prevalence of obstructive CAD was 48%. Gestalt's numerical probability was associated with CAD, but the area under the curve of 0.61 (95%CI: 0.55-0.67) indicated low level of accuracy. Accordingly, categorical definition of typical chest pain had a sensitivity of 48% (95%CI: 40%-55%) and specificity of 66% (95%CI: 59%-73%), yielding a negligible positive likelihood ratio of 1.4 (95%CI: 0.65-2.0) and negative likelihood ratio of 0.79 (95%CI: 0.62-1.02). Agreement between the two cardiologists was poor in the numerical classification (95% limits of agreement = -71% to 51%) and categorical definition of typical pain (Kappa = 0.29; 95%CI: 0.21-0.37).

#### **CONCLUSION**

Clinical judgment based on a combination of chest pain features is neither accurate nor reproducible in predicting obstructive CAD in the acute setting.

**Key words:** Acute chest pain; Clinical judgment; Gestalt; Coronary artery disease; Acute coronary syndrome

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**Core tip:** In the scenario of acute chest pain, individual features of chest pain presentation are intuitively combined to form physician's impression, by a process called "gestalt". Physicians commonly assess probability of disease by unstructured clinical judgment. Although commonly used and presumed to be accurate, diagnostic assessment by gestalt of acute chest pain lacks validation. In the present manuscript, we investigated the accuracy of gestalt in the prediction of coronary artery disease (CAD). Our results indicate that clinical judgment (gestalt) of acute chest pain characteristics has low diagnostic accuracy for obstructive CAD. Thus, physicians should be cautious when relying on chest pain characteristics and investigators should redirect their focus to identify validated predictors.

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Cerqueira Junior AMS, Lopes FOA, de Sá NC, Suerdieck JG, de Souza TMB, Correia VCA, Sodré GS, da Silva AB, Alexandre FKB, Ferreira FRM, Correia LCL. Accuracy of gestalt perception of acute chest pain in predicting coronary artery disease. *World J Cardiol* 2017; 9(3): 241-247 Available from: URL: <http://www.wjgnet.com/1949-8462/full/v9/i3/241.htm> DOI: <http://dx.doi.org/10.4330/wjc.v9.i3.241>

## **INTRODUCTION**

In the scenario of acute chest pain, specific features of symptoms have either null or weak association with coronary artery disease (CAD) etiology<sup>[1-3]</sup>. However, in clinical practice, these characteristics are not analyzed separately. Individual features of chest pain presentation are intuitively combined to form the physician's impression by a process called "gestalt". Although presumed to be accurate, diagnostic assessment by gestalt of acute chest pain lacks validation<sup>[4,5]</sup>. In fact, it remains uncertain how much physicians should rely on acute chest pain characteristics to estimate pretest probability of CAD.

Our aim was to test the hypothesis that physicians' gestalt accurately estimates probability of CAD. Since gestalt accuracy depends on chest pain characteristics, and knowing that these findings have a broad and variable spectrum, we focused our analysis exclusively on clarifying the reliability of this component. In order to isolate chest pain characteristics variables, we invited an experienced cardiologist, blind to patient's demographic and clinical features, to estimate probability of CAD based on 14 symptom characteristics obtained by remote standardized interview. The accuracy of unstructured clinical judgment was tested against non-invasive or invasive tests that were used as reference standards. Additionally, a second cardiologist performed the same evaluation in order to test for reproducibility of clinical judgment.

## **MATERIALS AND METHODS**

### **Sample selection**

During a period of 24 consecutive months, all patients admitted in the Chest Pain Unit of our Hospital due to chest discomfort were included in the study, regardless of electrocardiogram or troponin results. The study was approved by an institutional review committee and all subjects gave informed consent.

### **Clinical judgment of chest pain**

Data collection was planned a priori and performed prospectively. At admission, chest pain characteristics were collected by standardized interview performed by 3 investigators (MC, NS, FL), trained to diminish bias and improve reproducibility of data collection. Fourteen standardized questions were recorded on a specific form: Precordial location (lower left side), compressive

nature, radiation to left arm, radiation to neck, severe intensity, similarity to previous infarction (if applicable), presence of vagal symptoms, worsening with body movement, worsening with palpation, worsening with arms movement, worsening with deep breath, and relief by nitrate. Characteristics were considered positive if patient's answer was clearly affirmative. Dubious answers ("maybe", "sometimes", "not sure") were taken as negative. In addition, 3 numeric variables were recorded: Intensity of chest pain from 0 to 10 (defined by the patient according to a visual scale), number of pain episodes at rest and duration of the longest episode in minutes. No additional information regarding demographic or clinical characteristics was recorded on this form.

Subsequently, a cardiology faculty member (CV, with 23 years of experience in the field of acute chest pain) assessed the forms and classified chest pain according to the 14 characteristics. This investigator did not have any contact with the patients, and was completely blind to additional information such as name, gender, age, previous history or additional tests. This method guaranteed that medical judgment was based exclusively on chest pain characteristics. In order to assess reproducibility of medical judgment, the same procedure was independently performed by a second faculty member (LLJ) in all patients and his classification was compared with the first.

Chest pain was classified in four ways: (1) typical or atypical; (2) Non-anginal, Undefined or Anginal Chest Pain; (3) definitely angina, probably angina, probably not or definitely not; and (4) numeric probability of coronary etiology from 0 to 100. No objective predefinition of these classifications was provided to the evaluators of chest pain, enabling the definition to be a result of the physician's unstructured discretion. This method guaranteed that answers reflected authentic clinical judgment.

### **Obstructive CAD**

Outcome data was collected by 3 other independent investigators (MC, FK, FF) and adjudicated by a fourth investigator (LC). Obstructive CAD was defined by a stenosis  $\geq 70\%$  on angiography. For diagnostic evaluation, patients underwent invasive coronary angiography or a non-invasive test (perfusion magnetic resonance imaging or nuclear single-photon emission computed tomography), at the discretion of the assistant cardiologist. In case of a positive non-invasive test, patients underwent angiography for confirmation. A negative non-invasive test indicated absence of obstructive CAD and no further test was required. In case of a dominant alternative diagnosis as confirmed by imaging (such as pericarditis, pulmonary embolism, aortic dissection or pneumonia), the etiology was defined as non CAD.

### **Statistical analysis**

Frequencies were compared by Pearson's  $\chi^2$  test and

means by Student's *t* test. The accuracy of clinical judgment in predicting CAD was described by point-estimate and 95%CI of sensitivity, specificity, likelihood ratios and predictive values. The accuracy of numerical estimative of CAD probability was described by the area under the ROC curve with 95%CI.

For analysis of reproducibility, the Kappa test was utilized to assess agreement between two observers regarding the different forms of categorical classification. For numeric estimation of CAD probability, the Bland-Altman analysis was used: mean absolute error between the two observers (mean of differences without the signal), mean signed difference (bias) and 95% limits of agreement.

Sample size was calculated based on an expected CAD prevalence of 50%. Thus, a sample size of 300 would provide 150 patients with and 150 patients without CAD. Considering assumptions of 70% sensitivity and specificity, 150 patients would yield a  $\pm 8\%$  precision for the 95%CI.

## **RESULTS**

### **Sample characteristics**

From 2011 to 2013, a sample of 330 patients was studied,  $59 \pm 15$  years old, 58% males, 54% presented ischemic electrocardiographic changes and 48% had positive troponin. All individuals had gestalt evaluation and reference standard performed during the same admission. Obstructive CAD was identified according to study protocol in 48% of the individuals. Baseline characteristics are depicted on Table 1.

### **Accuracy of clinical judgment**

**Typical vs atypical chest discomfort:** Chest discomfort was classified as typical in 41% of patients. Obstructive CAD was present in 56% of individuals with typical symptoms, compared with 42% of those with atypical symptoms ( $P = 0.02$ ). Among 158 individuals with obstructive CAD, the discomfort was defined as typical in 75, yielding a sensitivity of 48% (95%CI: 40%-55%). Conversely, in 172 individuals free of CAD, 113 had symptoms defined as atypical, leading to a specificity of 66% (95%CI: 59%-73%). Consequently, typical pain had a negligible positive likelihood ratio of 1.4 (95%CI: 0.65-2.0), as well as a negative likelihood ratio of 0.79 (95%CI: 0.62-1.02). The positive predictive value of typical chest pain was only 56% (95%CI: 48%-64%), while the negative predictive value was 58% (95%CI: 51%-65%), Table 2.

### **Non-anginal, undefined or anginal chest pain:**

Patients were equally distributed among the 3 classifications, 36% defined as non-anginal, 34% as undefined and 30% as anginal. Prevalence of CAD was respectively 38%, 49% and 55% ( $P = 0.04$ ). Among 158 individuals with CAD, only 66 had anginal pain, leading to a sensitivity of 42% (95%CI: 34%-50%), positive likelihood ratio of 1.35 (95%CI: 0.89-2.1) and

**Table 1 Clinical characteristic n (%)**

Variable	Description
Sample size	330
Age (yr)	59 ± 15
Male gender	192 (58)
History of coronary disease	112 (34)
Diabetes	104 (32)
Ischemia on EKG	179 (54)
Positive troponin	157 (48)
Signs of left ventricular failure	28 (8.5)
Final diagnosis	
Unstable angina	52 (16)
Myocardial infarction	142 (43)
No CAD, but undefined diagnosis	103 (31)
Gastrointestinal disorder	5 (1.5)
Osteo-muscular disorder	1 (0.3)
Pericarditis	12 (3.6)
Pulmonary embolism	2 (0.6)
Aortic dissection	2 (0.6)
Pneumonia	2 (0.6)
Other	9 (2.7)

CAD: Coronary artery disease.

positive predictive value of 56% (95%CI: 47%-65%). Conversely, in 172 individuals free of CAD, 62 had symptoms defined as non-anginal, leading to a specificity of 36% (95%CI: 29%-43%), negative likelihood ratio of 0.67 (95%CI: 0.40-1.1) and negative predictive value of 62% (95%CI: 53%-62%) (Table 2).

**Definitely angina, probably angina, probably not and definitely not:** Patients were equally distributed among the 4 categories, with 25% classified as definitely angina, 32% as probably angina, 23% as probably not and 20% as definitely not. Prevalence of CAD was similar among the first 3 groups, respectively 49%, 56% and 51%, while patients classified as definitive no-angina had a lower prevalence of 30%, which was responsible for the statistical difference among the 4 groups ( $P = 0.008$ ). Thus, the threshold of definitely not was utilized for accuracy. Among 158 individuals with CAD, 138 were not classified as definitely not, leading to sensitivity of 83% (95%CI: 77%-89%). Among the 172 patients free of disease, only 47 were definitely not, yielding 27% specificity (95%CI: 20%-34%). Thus, the negative likelihood ratio of definitely not was a negligible 0.63 (95%CI: 0.32-1.15), with a negative predictive value of 70% (95%CI: 59%-81%) (Table 2).

**Subjective estimation of CAD probability:** Probability of CAD had a mean of 59% ± 34%, with a median of 70% (interquartile range = 30%-90%). Individuals with CAD had a median probability of 80% (interquartile range = 50%-95%), compared with 60% in patients free of disease (interquartile range = 10%-90%) -  $P < 0.001$ . The diagnostic area under the ROC for numeric probability was 0.61 (95%CI: 0.55-0.67) (Figure 1).

### Reproducibility of clinical judgment

The two observers agreed in 62% of the patients regarding typical vs atypical chest pain, yielding a weak Kappa of 0.29 (95%CI: 0.21-0.37;  $P < 0.001$ ). For non-anginal, undefined or anginal chest pain, agreement was 53% (Kappa = 0.28; 95%CI: 0.20-0.36;  $P < 0.001$ ). For definitely angina, probably angina, probably not and definitely not, agreement was 42%, leading to a weak Kappa of 0.21 (95%CI: 0.14-0.28;  $P < 0.001$ ).

Regarding numeric estimation of probability, mean absolute error was 23% ± 23%, with a mean signed difference (bias) of - 9.7% ± 31%, with 95% limits of agreement from - 71% to + 51%. The Bland-Altman plot showed a diamond pattern with reasonable agreement in very low (< 20%) or very high (> 80%) ranges of probability, with increasing disagreement as probability becomes more intermediate (Figure 2).

## DISCUSSION

The present study indicates that clinical judgment (gestalt) of acute chest pain has low diagnostic accuracy for obstructive CAD. In addition, there was poor agreement between the gestalt of two physicians, indicating low precision of intuitive interpretation of chest pain features. These findings confront the common belief that physicians should take into account the typicality of symptoms when evaluating patients with acute chest pain.

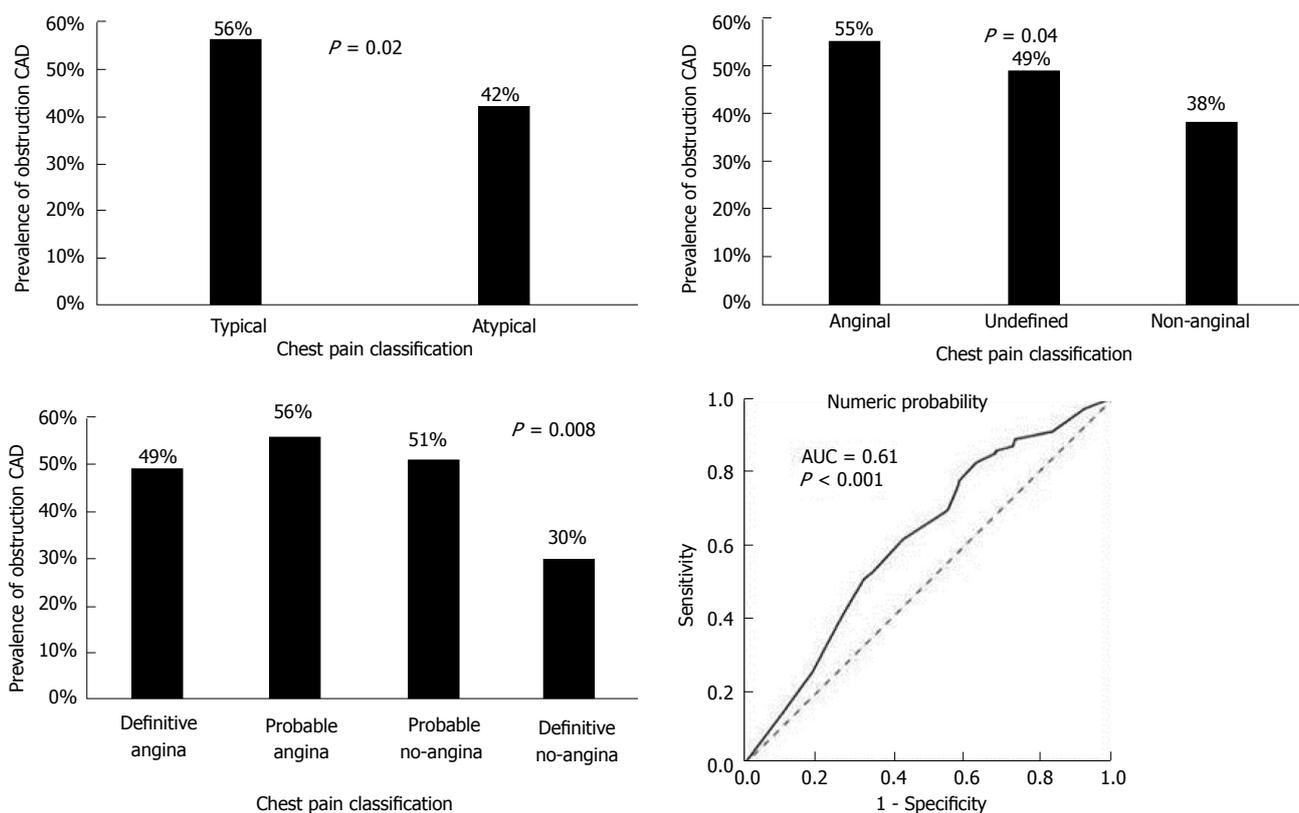
Our primary interest was to assess the role of chest pain features on clinical evaluation. Thus, our methods were designed to evaluate accuracy of clinical judgment that comes specifically from chest pain characteristics, as opposed to the entire clinical presentation. In order to do this, we blinded the physician to demographics, clinical characteristics or patient's appearance. Secondly, we tested physician's intuitive judgment that comes from the combination of all features, instead of the accuracy of specific symptom characteristics. Thus, there was not an a priori criterion for classifying chest pain, allowing the physician to use his own intuition (unstructured clinical judgment).

Physicians commonly assess probability of disease by unstructured clinical judgment. Although medical doctors normally put confidence into this type of judgment, it tends to be inaccurate. As described by Nobel Prize laureates and psychologists Kahneman and Tversky, judgment under uncertainty is vulnerable to cognitive bias, due to heuristics utilized in the process of intuitive thinking<sup>[6]</sup>. A common example of heuristics is "representativeness": If A resembles B, when A is present we think B is highly probable to be present. Oppressive chest pain resembles angina. Hence, a physician may jump to conclude that a patient with oppressive chest pain has a high probability of CAD. However, the likelihood ratio of oppressive chest pain is very low. These cognitive biases that are present in intuitive thinking explain why mechanical models are

**Table 2 Accuracy of the 3 classifications of chest pain according to medical judgment**

	Sensitivity	Specificity	Positive LR	Negative LR	Positive PV	Negative PV
Classification 1 (2-level)						
Typical ( <i>vs</i> atypical)	48% (40%-55%)	66% (59%-73%)	1.4 (0.65-2.0)	0.79 (0.62-1.02)	56% (48%-64%)	58% (51%-65%)
Classification 2 (3-level) <sup>1</sup>						
Angina ( <i>vs</i> undefined/ <i>no</i> -angina)	42% (34%-50%)	69% (62%-76%)	1.35 (0.89-2.1)		56% (47%-65%)	
No-angina ( <i>vs</i> undefined/ <i>angina</i> )	76% (69%-83%)	36% (29%-43%)		0.67 (0.40-1.1)		62% (53%-72%)
Classification 3 (4-level) <sup>1</sup>						
Definitely no-angina ( <i>vs</i> the other 3 groups)		27% (20%-34%)		0.63 (0.32-1.15)		70% (59%-81%)

Numbers in parenthesis are 95%CI. <sup>1</sup>Because only no-angina distinguished itself from the other 3 classifications, only specificity, negative LR and negative PV were calculated. LR: Likelihood ratio; PV: Predictive value.



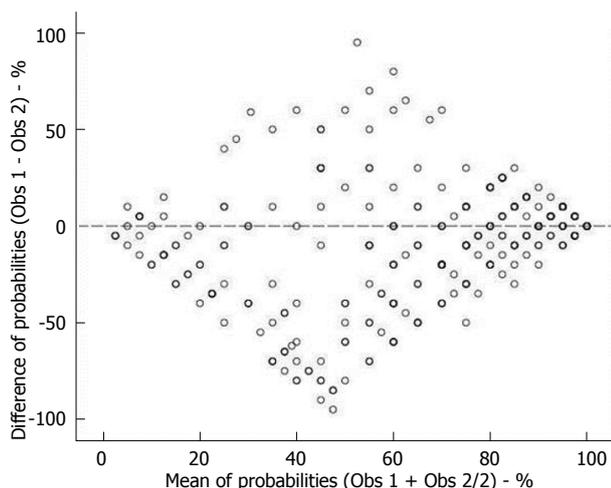
**Figure 1 Categorical and numerical accuracy of gestalt, regarding the prediction of obstructive coronary artery disease. CAD: Coronary artery disease.**

usually better predictors than medical judgment. For instance, a systematic review of several medical and non-medical situations consistently showed better predictability of probabilistic models, in comparison with specialist' decision<sup>[7]</sup>. Therefore, in order to avoid heuristics when evaluating a chest pain scenario, physicians should increase awareness of the low diagnostic value of chest pain characteristics or invest in probabilistic models able to predict obstructive disease more precisely.

The lack of reproducibility between two independent cardiologists also deserves attention. While lack of accuracy promotes diagnostic errors, lack of agreement impairs consensus regarding medical management. Thus, relying too much on chest pain characteristics does not only promote probabilistic errors, but also promote differences in clinical impressions, leading to

confusion and discordance among the medical team.

Although an experienced physician made clinical judgment, we cannot guarantee that his analysis is similar to most physicians. In fact, this would be unlikely, considering the low level of reproducibility found in our head-to-head comparisons. Nevertheless, the concept of accuracy is somewhat independent of agreement. Accuracy depends on the proportion of correct predictions. Two models can have the same proportion of correct predictions and not be related to the same patients. Indeed, we should not expect different people to have the same intuition regarding diagnosis. This rationale is the basis for testing the concept of accuracy of physician judgment by using one specific professional as a proxy of the average physician. Nevertheless, we recognize that further studies are needed to validate our findings, extending it to different populations of



**Figure 2** Bland-Altman plot of agreement between two observers regarding gestalt's numerical probability of coronary disease.

physicians and patients.

Usually, accuracy studies of acute chest pain utilize myocardial infarction as the outcome of interest. Differently, we opted to use obstructive CAD as the outcome to be predicted by clinical judgment, because it has a more objective definition than myocardial infarction. This objectiveness was important because we were evaluating physician's cognitive judgment based on clinical data, and definition of myocardial infarction as an outcome is also influenced by clinical judgment. Therefore, to avoid this redundancy, we used obstructive CAD defined by angiography or functional tests.

A sense of surprise regarding our results may arise from the traditional belief that a careful history is important. Firstly, our findings do not undermine the value of the history as a whole, because our analysis only refers to chest pain characteristics. Secondly, our data is in line with chest pain characteristics being consistently demonstrated to be inaccurate. The novelty of our study is the gestalt evaluation of these characteristics taken together. And the main application of our results prompts us to reconsider how much value we should assign to classifications such as typical or atypical chest pain, as these have little or no influence on probability of CAD. The fact that typicality of pain did not show significant differences on predicting CAD probability has important practical implications, since decision-making during the clinical management of patients can be initially guided by these subjective classifications. The overvaluing of the current categorization may be misleading, resulting in under or overdiagnosis of CAD and mismanagement of cases. Therefore, the use of probabilistic models is supposed to be a more effective way to avoid representativeness heuristics.

In conclusion, our findings indicate that physician's gestalt based on acute chest pain features lacks accuracy and reproducibility in estimating the probability of CAD. Physicians should be cautious when relying on chest pain characteristics and investigators should

redirect their focus to identify validated predictors.

## COMMENTS

### Background

Traditionally, physicians tend to strongly rely on chest pain characteristics to define whether a patient has low or high probability of having coronary artery disease, through a process called gestalt. This kind of clinical judgment, however, does not seem to have good diagnostic accuracy in predicting coronary artery disease (CAD) etiology.

### Research frontiers

Many authors have compared the accuracy of scores vs medical judgment in acute coronary syndromes. However, the study intends to clarify a current non-scientific trend of the physician community to make cardiovascular inferences directly from chest pain characteristics. This research establishes a new perspective for chest pain analysis, and reinforces the need to identify strong diagnostic clinical predictors of obstructive disease and then develop a multivariate model to help the emergency physician to assess this condition, instead of intuitive univariate diagnostic association currently applied.

### Innovations and breakthroughs

The main idea presented was the evaluation of the diagnostic accuracy of chest pain characteristics in predicting the probability of CAD. This was performed by using only pain characteristics and with no further information. The novelty of the study is the gestalt evaluation of these characteristics taken together, while previous others had analyzed the diagnostic probability of each symptom separately. Additionally, previous literature has tested medical gestalt vs probabilistic scores, while the authors have tested medical gestalt vs real diagnosis.

### Applications

The main application of the results relies on avoiding putting too much value of classifications such as typical or atypical chest pain. These classifications merely refer to chest pain characteristic and this isolated aspect has little or no influence on probability of CAD.

### Terminology

Clinical gestalt refers to the theory that physicians and healthcare professionals organize clinical perceptions into "unified wholes". This means that physicians can make clinical decisions without necessarily having complete information, posteriorly using this information to create solutions that can be generalized from one situation to another. Clinical gestalt represents an overall analysis, cultivated mainly by personal experience, history and examination.

### Peer-review

The present study essentially supports that the elements of the chest pain history are only a little bit associated with increasing accuracy of diagnosis with CAD. Furthermore, it is very interesting that there were poor agreement between the two cardiologists. The methods are sound, and the used statistics seem also sound.

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Retrospective Study

## Validity of electrocardiographic criteria for increased left ventricular mass in young patients in the general population

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### Abstract

#### AIM

To investigate validity of electrocardiographic (ECG) criteria for left ventricular hypertrophy (LVH) in young adults.

#### METHODS

Retrospectively, echocardiograms showing LVH and concomitant electrocardiograms were collected in patients 18 to 39 years old. A control group of patients without LVH was collected. Using echocardiogram as the gold standard, electrocardiograms were analyzed using common voltage criteria.

#### RESULTS

Study included 100 subjects (52% male, mean age = 28 ± 6.8 years, 96% Hispanic or African-American) with 50% LVH prevalence. Sensitivity and specificity for Sokolow-Lyon criteria were 24% (95%CI: 13.5%-38.4%) and 88% (95%CI: 74.9%-95%). For Cornell criteria, sensitivity was 32% (95%CI: 19.9%-46.8%) and specificity 98% (95%CI: 87.9%-99.8%). For R in aVL criteria, sensitivity was 12% (95%CI: 4.9%-25%) and specificity 100% (95%CI: 91.1%-100%).

#### CONCLUSION

In young adults common ECG voltage criteria have low sensitivities and high specificities similar to other age groups. Low sensitivities preclude these ECG criteria from serving as effective screening tests.

**Key words:** Electrocardiographic; Left ventricular hypertrophy criteria; Young adults

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**Core tip:** The electrocardiographic (ECG) has been used for years to diagnose left ventricular hypertrophy (LVH). However, to the best of our knowledge, there were no prior studies validating most common ECG criteria for LVH in young adults. The authors believe that this is important group of population, as athletes screening for pre participation to professional sport falls into this category. ECG is one of the proposed screening tools and we think that it should be validated for diagnosis of LVH. This study showed that common ECG criteria for LVH can be used in young adults with similar sensitivity and specificity to other age groups.

Sklyar E, Ginelli P, Barton A, Peralta R, Bella JN. Validity of electrocardiographic criteria for increased left ventricular mass in young patients in the general population. *World J Cardiol* 2017; 9(3): 248-254 Available from: URL: <http://www.wjgnet.com/1949-8462/full/v9/i3/248.htm> DOI: <http://dx.doi.org/10.4330/wjc.v9.i3.248>

## INTRODUCTION

Epidemiologic studies have demonstrated that increased left ventricular mass (LVM) is a risk factor for cardiovascular disease and death<sup>[1-4]</sup>. Left ventricular hypertrophy (LVH) has a significant prevalence in the general population with some estimates approaching 16%-20% in population based samples<sup>[5,6]</sup>, and up to 50% in those with hypertension<sup>[7-9]</sup>. As a result of the obesity epidemic, even the adolescent population has had a higher incidence of hypertension and LVH<sup>[10]</sup>, with some estimates showing LVH in nearly 30% of younger hypertensive<sup>[11]</sup>. Thus, with the high prevalence of LVH that extends even into the young population and the increased cardiovascular risk it confers, it is important to identify patients with increased LVM so that they may receive appropriate care.

Another important indication for detecting LVH, specifically in younger individuals in the general population, is in the setting of pre-participation screening prior to partaking in athletic activities. Current screening methods often involve looking for evidence of LVH on electrocardiogram (ECG) and transthoracic echocardiogram (TTE) to help identify those who may be at risk for sudden cardiac death<sup>[12]</sup>. Unfortunately, LVH is often misdiagnosed during these pre-participation screenings which can lead to unwanted outcomes<sup>[13]</sup>. Due to the immense importance of detecting increased LVM in the screening process of this younger population, a reliable screening tool is vital for this age group.

The ECG is the simplest and most commonly used

method to detect LVH, but to date there has been no study evaluating the correlation between the established ECG criteria and increased LVM detected by TTE in adults from the general population with a mean age of 18 to 39 years old. Although numerous investigations have been conducted to validate the ECG criteria for LVH in individuals of the pediatric and older populations, the data for younger adults have been limited. Thus, with the growing number of young individuals with hypertension and LVH, along with the need for effective pre-participation screening, the quick and simple electrocardiographic methods for detecting increased LVM and obtaining prognostic information need to be validated for use in the younger members of the general population. Therefore, the aim of this study is to examine this particular subset of the population in order to determine the efficacy of this potentially valuable tool for identifying patients at increased risk for cardiovascular morbidity and mortality.

## MATERIALS AND METHODS

This was a single-center, retrospective study involving ECG and TTE data conducted in the Cardiology Division of the Department of Medicine at Bronx Lebanon Hospital Center, a large teaching medical center in Bronx, New York. After receiving approval from the Institutional Review Board, the hospital's electronic database was used to collect all consecutive TTEs with the finding of LVH performed between January 2010 and July 2011 on male and female patients aged 18-39 years old who were referred or admitted to the hospital. A control group of age-matched patients without LVH on TTE was also collected in the same manner from the database. Subjects were also required to have a standard 12-lead ECG within 30 d before or after the reference TTE. Excluded were patients with ECGs showing myocardial infarction, bundle branch block, paced rhythm, pre-excitation, or any intraventricular conduction delay, as these ECG findings can interfere with voltage measurements and were not included in the original studies from which the ECG criteria for detecting increased LVM were derived<sup>[14,15]</sup>. After creating the study and control groups based on the presence or absence of increased LVM using TTE as the gold standard for diagnosis, the subjects' ECGs were analyzed using several ECG criteria for detecting LVH in order to determine their efficacy in this cohort of patients.

Study subjects had previously completed the pre-requisite two-dimensional (2-D) rest echocardiogram using a standard, commercially available ultrasound transducer and machine (M3S probe, Vivid 7, GE Medical Systems). In each patient, standard parasternal views (long and short axis) and apical views (4- and 2-chamber) were obtained. TTE images were saved digitally in raw data format for off-line analysis using GE Medical Systems' EchoPAC PC software. These TTEs

were previously read by board-certified cardiologists on the day of acquisition, and it was these interpretations that were used to extract the study population from the hospital database. In order to ensure uniformity of the echocardiographic data used in this study, all subjects' TTEs were reread by a single board-certified noninvasive cardiologist who was blinded to the study arm in which the TTE's belonged. This reader remeasured left-ventricular end-diastolic dimension (LVEDd), end-diastolic posterior wall thickness (PWTd), and end-diastolic septal wall thickness (SWTd) in the standard 2-D parasternal long axis view as detailed by the American Society of Echocardiography (ASE)<sup>[16]</sup>. These measurements were then used to calculate LVM using the ASE recommended formula for estimation of LVM from left ventricular linear dimensions<sup>[16]</sup>:  $LVM = 0.8 \times \{1.04[(LVEDd + PWTd + SWTd)^3 - (LVEDd)^3]\} + 0.6$  grams. The LVM was then indexed to body surface area (BSA) which was obtained from the original reference TTE reports. The ASE gender specific cut-off values for LVM<sup>[16]</sup> were used to classify patients as having increased LVM if the LVM indexed to BSA was greater than 88 g/m<sup>2</sup> for women and greater than 102 g/m<sup>2</sup> for men.

All subjects had previously undergone a standard 12-lead rest ECG at 25 mm/s speed, 10 mm/mV sensitivity, and 0.05 Hz to 150 Hz frequency within 30 d of the index TTE. Of the various ECG criteria for LVH including, Sokolow-Lyon voltage<sup>[14]</sup>, Sokolow-Lyon product<sup>[17]</sup>, R in aVL voltage<sup>[14]</sup>, Cornell voltage<sup>[15]</sup>, Cornell product<sup>[17]</sup>, and Gubner voltage<sup>[18]</sup>, three of the most commonly used criteria in many clinical trials<sup>[19-21]</sup>, Sokolow-Lyon voltage, Cornell voltage, and R in aVL voltage, were then selected to analyze the ECGs. For Sokolow-Lyon voltage, the amplitude of the S wave in lead V1 was added to the largest amplitude of the R wave in either lead V5 or V6, with a value greater than or equal to 35 mm meeting criteria for LVH. For Cornell voltage, the amplitude of the S wave in lead V3 was added to the amplitude of the R wave in lead aVL, with a value greater than 28 mm for men and greater than 20 mm for women signifying LVH. For R in aVL voltage, an amplitude of the R wave in lead aVL greater than or equal to 11 mm was indicative of LVH. All study ECGs were evaluated for these three criteria using manual calipers by each of two trained readers who were blinded to the study group in which the ECGs belonged. Any discrepancies in measurements between the two readers were evaluated by a board-certified electrophysiologist who made the final decision on the ECG findings.

### Statistical analysis

Data management and descriptive analysis were performed with IBM SPSS 20 (Statistical Packages for the Social Sciences). Data are presented as mean (SD) for continuous variables and proportions for categorical variables. For measurements of sensitivity and specificity, increased LVM as detected by TTE was

used as the reference standard against which the performance of the ECG criteria was compared. Mean values of continuous variables were compared by using an independent sample t-test. Linear correlations were evaluated with the Pearson's r correlation. Receiver operating characteristic (ROC) curves were constructed for each ECG criteria to evaluate test performance over a wide range of possible partition values. A two-tailed value of  $P < 0.05$  was considered statistically significant.

## RESULTS

The initial database query revealed 1107 subjects who had a TTE performed during the search period. Of these 1107 patients, 239 had LVH documented in their TTE report. Using the aforementioned inclusion and exclusion criteria, 84 subjects were then found for the increased LVM group. After left ventricular dimensions were re-measured by our expert reader, there were 50 remaining subjects with increased LVM by ASE criteria. Fifty subjects without increased LVM were found for the control group, resulting in a prevalence of increased LVM by TTE of 50%. The total study population had a mean age of  $28 \pm 6.8$  years and consisted of 52 men and 48 women, of which 96% were either Hispanic or African-American. The 1007 excluded subjects had similar demographics with a mean age of  $29 \pm 6.2$  years, 38% men, and 96% Hispanic or African-American. There were no significant differences noted in age, gender, or BSA between the increased LVM and control arms (Table 1). As expected, the increased LVM group had a mean LVM indexed to BSA of  $130.35 \pm 36.76$  g/m<sup>2</sup> which was significantly higher ( $P < 0.001$ ) than the control group's value of  $63.61$  g/m<sup>2</sup>  $\pm 11.73$  (Table 1). The increased LVM group also had significantly higher values ( $P < 0.001$ ) for SWTd, PWTd, and LVEDd as compared to the control group (Table 1).

Sensitivities and specificities for detecting increased LVM with each ECG criteria are displayed in Table 2. Sensitivity and specificity for the Sokolow-Lyon criteria were 24% (95%CI: 14%-38%) and 88% (95%CI: 75%-95%), respectively. For the Cornell voltage criteria, sensitivity was 32% (95%CI: 19%-47%) and specificity was 98% (95%CI: 88%-99%). For the R in aVL criteria, sensitivity was 12% (95%CI: 5%-25%) and specificity was 100% (95%CI: 91%-100%). Positive predictive values (PPV) and negative predictive values (NPV) are also shown in Table 2. PPVs were 67% (95%CI: 41%-86%) for Sokolow-Lyon, 94% (95%CI: 69%-99%) for Cornell, and 100% (95%CI: 52%-100%) for R in aVL. NPVs were 54% (95%CI: 42%-65%) for Sokolow-Lyon, 59% (95%CI: 48%-69%) for Cornell, and 53% (95%CI: 43%-63%) for R in aVL.

ROC curves illustrating the performance of each ECG criteria in detecting increased LVM are shown in Figures 1-3. Areas under the ROC curve were 0.560 for Sokolow-Lyon, 0.650 for Cornell, and 0.560 for R in aVL. All three ECG criteria also demonstrated good statistical correlation with increased LVM by TTE (Table 3).

**Table 1 Clinical characteristics of the study population**

Parameter	Increased LVM (n = 50)	Controls (n = 50)	P value
Age (yr)	29.7 ± 5.9	26.9 ± 7.4	0.05
Male/female	27/23	25/25	0.69
BSA (m <sup>2</sup> )	1.95 ± 0.34	1.88 ± 0.32	0.30
SWTd (cm)	1.09 ± 0.16	0.79 ± 0.08	< 0.001
LVEDd (cm)	5.70 ± 0.68	4.69 ± 0.43	< 0.001
PWTd (cm)	1.05 ± 0.11	0.76 ± 0.09	< 0.001
LVM/BSA (g/m <sup>2</sup> )	130.35 ± 36.76	63.61 ± 11.73	< 0.001

LVM: Left ventricular mass; BSA: Body surface area; SWTd: Septal wall thickness at end diastole; LVEDd: Left ventricular end-diastolic dimension; PWTd: Posterior wall thickness at end diastole.

**Table 2 Sensitivity, specificity, positive and negative predictive values for electrocardiographic criteria for left ventricular hypertrophy**

ECG criteria	Sensitivity (95%CI)	Specificity (95%CI)	PPV (95%CI)	NPV (95%CI)
Sokolow-lyon	0.24 (0.14-0.38)	0.88 (0.75-0.95)	0.67 (0.41-0.86)	0.54 (0.42-0.65)
Cornell	0.32 (0.19-0.47)	0.98 (0.88-0.99)	0.94 (0.69-0.99)	0.59 (0.48-0.69)
R in aVL	0.12 (0.05-0.25)	1 (0.91-1)	1 (0.52-1)	0.53 (0.43-0.63)

PPV: Positive predictive value; NPV: Negative predictive value.

**Table 3 Correlation between left ventricular mass index and electrocardiographic criteria for left ventricular hypertrophy**

ECG criteria	Pearson's r correlation	P value <sup>a</sup>
Sokolow-lyon	0.28	0.005
Cornell	0.51	< 0.001
R in aVL	0.26	0.01

<sup>a</sup>Correlation is significant when P < 0.05. ECG: Electrocardiographic.

## DISCUSSION

This investigation found that three frequently used ECG voltage criteria are effective in identifying increased LVM in the subset of the general population aged 18 to 39 years old. Sensitivity was highest with the Cornell criteria at 32%, as compared to 24% with the Sokolow-Lyon criteria and 12% with the R in aVL criteria. The highest specificity was found with the R in aVL criteria at 100%, while the Cornell and Sokolow-Lyon criteria had somewhat lower specificities of 98% and 88%, respectively. Although there is some minor variation among these values, all three criteria demonstrated a low sensitivity but high specificity for detecting increased LVM in this young adult population. These findings are similar to those previously published for other age groups and populations.

Prior studies examining the accuracy of these ECG criteria in older individuals of the general population encompassing mean ages from 45 to 70 years old<sup>[21-24]</sup>

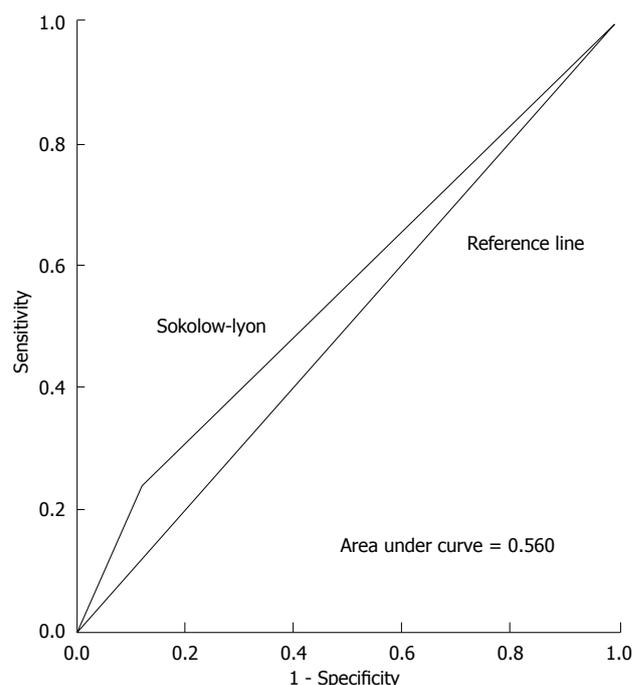


Figure 1 Receiver operating characteristic curve for Sokolow-lyon criteria.

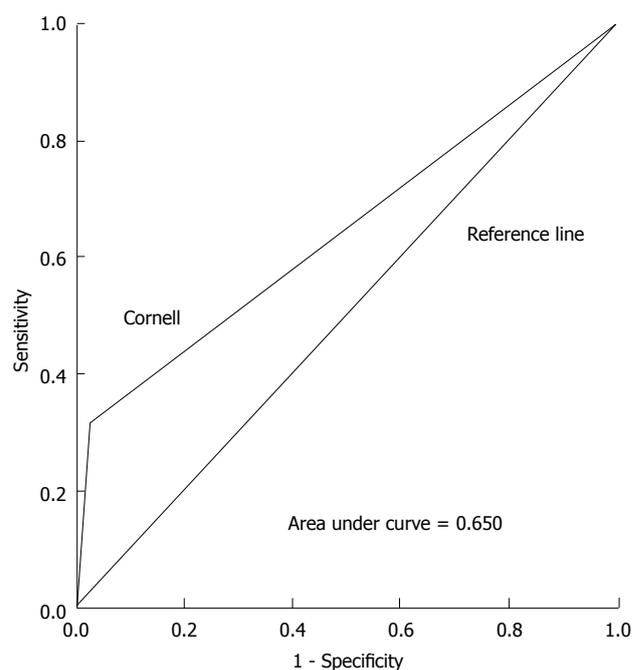


Figure 2 Receiver operating characteristic curve for Cornell criteria.

have shown similar findings with values for sensitivity ranging from 4% to 52% for the Sokolow-Lyon criteria and 2% to 41% for the Cornell criteria, and specificities ranging from 53% to 100% for the Sokolow-Lyon criteria and 89% to 100% for the Cornell criteria, as reported in a large meta-analysis<sup>[21]</sup>. In another large study in patients with mean age of 65 years old, the Sokolow-Lyon criteria had a sensitivity of 17% and

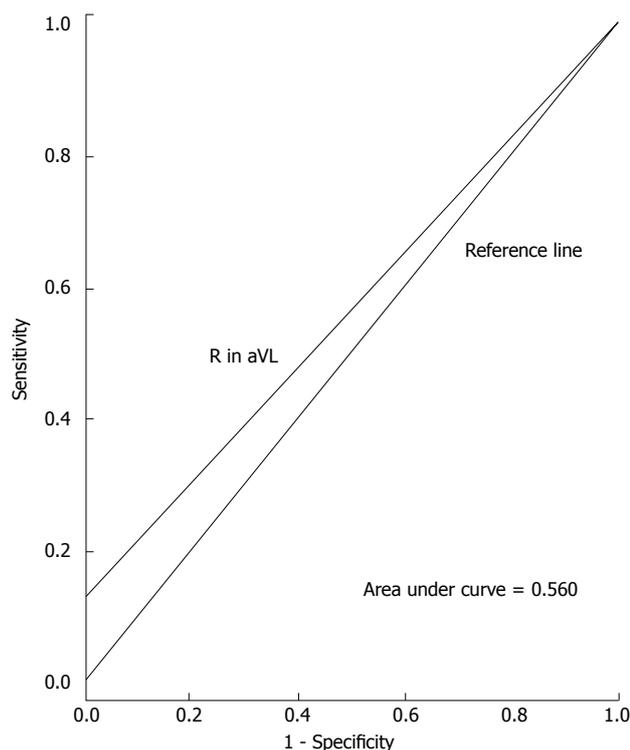


Figure 3 Receiver operating characteristic curve for r in aVL criteria.

specificity of 90%, the Cornell criteria had a sensitivity of 5.9% and a specificity of 99%, and the R in aVL criteria had a sensitivity of 8% and specificity of 94%<sup>[25]</sup>. The original Cornell criteria study<sup>[15]</sup> and a follow-up paper<sup>[26]</sup> by the same authors also found similarly low sensitivities and high specificities in the older population. Evaluation of the Sokolow-Lyon criteria in a pediatric population encompassing infants to 15 year olds also yielded a low sensitivity of 25% and high specificity of 95%<sup>[27]</sup>.

In young adults from the general population there have been no data for ECG voltage criteria until the present study was conducted and demonstrated that these commonly used criteria perform equally well as in other age groups. Prior studies involving young adults were conducted in very distinct subsets of the population. In a recent study of healthy male Air Force candidates, the Sokolow-Lyon and Cornell criteria were found to have a sensitivity of 55% and specificity of 87%<sup>[28]</sup>. Another study involving healthy young male military recruits found the Sokolow-Lyon criteria to have a sensitivity of 50% and specificity of 71%, and the Cornell criteria to have a sensitivity of 25% and specificity of 88%<sup>[29]</sup>. Other studies in the young adult population involved highly trained athletes and found poor correlation between the Sokolow-Lyon criteria and increased LVM<sup>[30,31]</sup>.

Hypertension has become more prevalent in the young adult population<sup>[10]</sup>, and has been shown to cause increased LVM and even heart failure if left untreated<sup>[32]</sup>. With proper antihypertensive therapy LVH can regress

and left ventricular dysfunction can improve<sup>[33,34]</sup>. Thus, with our findings that ECG voltage criteria are highly specific for increased LVM in young adults, it is reasonable to conclude that such a patient meeting ECG criteria for LVH may benefit from further testing, including TTE, to identify and treat increased LVM, a known and modifiable risk factor for cardiovascular disease and death<sup>[1-4]</sup>. Our results also suggest that ECG voltage criteria may not be suitable for pre-participation screening prior to partaking in athletic activities. Some screening methods often involve looking for evidence of LVH on ECG to identify those who may be at risk for sudden cardiac death<sup>[12]</sup>, but with this study demonstrating such low sensitivities for detecting increased LVM, ECG voltage criteria may not perform adequately as screening tools. This finding is in agreement with the current United States guidelines for pre-participation screening, as laid forth by the American Heart Association, which do not recommend performing an ECG as part of pre-athletic screening<sup>[35]</sup>. Despite their low sensitivities, the ECG voltage criteria showed rather high specificity for detecting increased LVM in young adults. This result brings into question the notion that the presence of ECG voltage criteria in young adults is merely a normal variant<sup>[36]</sup>. Regardless of the initial indication, if an ECG performed in a young adult meets voltage criteria for LVH, the finding should not be assumed normal until completing further investigation with an imaging modality such as TTE.

In conducting a retrospective analysis it was necessary to accept certain limitations inherent with this type of design, the most significant being the lack of randomization. In analyzing the study and control groups, however, there were no significant differences in baseline characteristics as shown in Table 1. Although this was a study of the general population, the majority of subjects were Hispanic or African-American, with few Caucasian individuals. It is likely that the ECG voltage criteria tested would also show efficacy in other races, but this cannot be concluded from this study alone. This study examined only three of the numerous ECG criteria that have been developed for detecting LVH, but this was done intentionally as those chosen are among the most commonly used and simplest to perform, with no difficult calculations or point systems.

In conclusion, three commonly used ECG voltage criteria, Sokolow-Lyon, Cornell, and R in aVL, show efficacy in detecting increased LVM in young adults of the general population and have sensitivities and specificities that are similar to those found in other age groups. Although their low sensitivities preclude these ECG criteria from serving as effective screening tests, their relatively high specificities would necessitate further evaluation if the criteria were present in a young individual. Our results provide evidence that these simple diagnostic tools can be utilized in a population subset that may benefit from the valuable prognostic information that they provide.

## COMMENTS

### Background

Electrocardiographic (ECG) is a very common test to evaluate for structural heart disease, including left ventricular hypertrophy (LVH). The ECG criteria for LVH are widely studied in older patients; its utility in young adults is unknown. ECG was proposed to be a screening test for detection of structural abnormality of the heart, however in order to be a screening test it should have high sensitivity for detection of pathology. Thus, it's important to evaluate sensitivity and specificity of ECG criteria for LVH in young adults.

### Research frontiers

ECG has been used for years to diagnose LVH. However, to the best of the authors' knowledge, there were no prior studies validating most common ECG criteria for LVH in young adults.

### Innovations and breakthroughs

The results of this study contribute to clarifying the ECG diagnostic criteria for LVH in young adults in comparison to older patients and its sensitivity and specificity.

### Applications

In young adults common ECG voltage criteria have low sensitivities and high specificities similar to other age groups. Although their low sensitivities preclude these ECG criteria from serving as effective screening tests, their relatively high specificities would necessitate further evaluation if the criteria were present in a young individual. The results provide evidence that these simple diagnostic tools can be utilized in a population subset that may benefit from the valuable prognostic information that they provide.

### Peer-review

The authors have done a good job analyzing retrospectively common electrocardiographic criteria for LVH in young adults.

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## Retrospective Study

## Pheochromocytoma and stress cardiomyopathy: Insight into pathogenesis

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### Abstract

#### AIM

To investigate the occurrence of cardiomyopathy (CMP) in a cohort of patients with histologically proven pheochromocytoma (pheo), and to determine if catecholamine excess was causative of the left ventricular (LV) dysfunction.

#### METHODS

A retrospective chart review spanning years 1998 through 2014 was undertaken and patients with a diagnosis of pheo confirmed with histopathologic examination were included. Presenting electrocardiograms and cardiac imaging studies were reviewed. Transthoracic echocardiography (TTE), ventriculography or single positron emission computed tomography imaging was evaluated and if significant abnormalities [left ventricular hypertrophy (LVH) or LV dysfunction] were noted in the pre operative period a follow up post-operative study was also analyzed. Multivariate analysis using logistic regression was used to investigate independent predictors for outcomes of interest, LV dysfunction and LVH.

#### RESULTS

We identified 18 patients with diagnosis of pheo confirmed on pathology. Mean age was  $54.3 \pm 19.3$  years and 11 (61.1%) patients were females. 50% of such patients had either resistant hypertension or labile blood pressures during hospitalization, which had raised suspicion for a pheo. Cardiac imaging studies were available for 12 (66.7%) patients at the time of inclusion into study and preceding the adrenalectomy.

7 (58.3%) patients with a TTE available for review had mild or more severe LVH while 3 (25%) patients had LV dysfunction of presumably acute onset. In a multivariate analysis, elevated catecholamine levels as assessed by urinary excretion of metabolites was not an independent predictor of development of LV systolic dysfunction or of presence of LVH on TTE. Two female patients with a preceding history of hypertension had marked LV hypertrophy and systolic anterior motion of the mitral valve. Prolongation of the QTc interval was noted in 5 (27.8%) patients but no acute arrhythmias were observed in any patient.

### CONCLUSION

This study adds to the growing body of literature on the predilection of patients with pheochromocytomas to develop non-ischemic CMP. Degree of catecholamine excess as measured by urinary secretion of metabolites did not predict the development of CMP but 2 of 3 patients developed CMP in the setting of significant acute physiologic stress. Our findings provide support to the proposed etiologic role of elevated catecholamines in TC and other stress induced forms of CMP, however, activation of a brain-neural-cardiac axis from acute stress and local release of catecholamines but not chronic catecholamine elevations are likely to be responsible in pheo related CMP.

**Key words:** Pheochromocytoma; Cardiomyopathy; Stress

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**Core tip:** A non-ischemic cardiomyopathy (CMP) may be observed in patients with pheochromocytoma and shares several features with takotsubo cardiomyopathy. Although it is believed that pheochromocytoma related CMP is due to the catecholamine excess, the exact pathogenesis is unclear. CMP in pheochromocytoma patients often follows acute stress and while clinical course maybe complicated by acute hemodynamic compromise, prognosis is good. On the basis of our findings, where 3 of 18 pheochromocytoma patients developed an acute CMP, we suggest that activation of a brain-neural-cardiac axis from acute stress and local release of catecholamines but not chronic catecholamine elevations may likely be responsible for pheo related CMP.

Agrawal S, Shirani J, Garg L, Singh A, Longo S, Longo A, Fegley M, Stone L, Razavi M, Radoianu N, Nanda S. Pheochromocytoma and stress cardiomyopathy: Insight into pathogenesis. *World J Cardiol* 2017; 9(3): 255-260 Available from: URL: <http://www.wjgnet.com/1949-8462/full/v9/i3/255.htm> DOI: <http://dx.doi.org/10.4330/wjc.v9.i3.255>

### INTRODUCTION

Pheochromocytomas (pheo) are rare tumors of chrom-

affin cells originating most frequently in the adrenal medulla<sup>[1]</sup>. Catecholamines are secreted by these tumors in varying amounts and proportions<sup>[1]</sup> accounting for the various associated clinical symptoms. Cardiovascular manifestations of this catecholamine excess are several. Hypertension (both sustained and paroxysmal), ventricular hypertrophy, myocardial infarction, and arrhythmias (supraventricular and ventricular) are reported to occur in relation to this hormonal excess<sup>[2]</sup>. Left ventricular (LV) dysfunction may develop in patients with pheo and is termed catecholamine cardiomyopathy (CC)<sup>[2]</sup>. Although thought to arise from the incident catecholamine excess, the exact mechanism of such cardiac dysfunction remains elusive<sup>[3]</sup>. "Stress" or takotsubo cardiomyopathy (TC) is a syndrome characterized by transient acute LV systolic dysfunction encompassing multiple vascular territories in the absence of flow-limiting epicardial coronary artery disease (CAD)<sup>[4,5]</sup> and is purported to be caused by myocardial stunning resulting from exaggerated adrenergic signaling<sup>[6]</sup>. A similar morphologic pattern of LV dysfunction characterized by apical akinesis with preservation of contractility of more basal LV segments and described classically as apical ballooning has been described for both TC and CC<sup>[3,7]</sup>. It is therefore plausible that a common etiologic link exists between these two entities. We sought to investigate the occurrence of cardiomyopathy (CMP) in a cohort of patients with histologically proven pheo and to determine if catecholamine excess was causative of this LV dysfunction.

### MATERIALS AND METHODS

#### Patient characteristics

A retrospective chart review spanning years 1998 through 2014 was undertaken to search for patients with a diagnosis of pheo. Medical records of patients with a probable diagnosis of pheo were perused and patients were included in this study only if such diagnosis had been confirmed with histopathologic examination. The institutional review board approved the study protocol. Data on patient demographics, clinical characteristics, radiologic imaging, laboratory investigations (specifically plasma and urine catecholamine levels); and surgical and pathologic findings were collected. Presenting electrocardiograms (ECG) and cardiac imaging study results were reviewed. Transthoracic echocardiography (TTE), ventriculography and single positron emission computed tomography (SPECT) imaging was evaluated and if significant abnormalities [LV hypertrophy (LVH) or LV dysfunction] were noted in the pre-operative period a follow up post-operative study was also analyzed if available. Two physicians unaware of the knowledge of the diagnoses independently interpreted the ECG and imaging studies. LVH on ECG was diagnosed if any of the accepted voltage criteria was judged to be satisfied<sup>[8]</sup>. Echocardiograms were obtained according to a standardized institutional protocol [parasternal, apical, subcostal and suprasternal imaging planes were

**Table 1 Patient demographics**

	<i>n</i> = 18
Age (yr)	54.33 ± 19.30
Female gender ( <i>n</i> , %)	11 (61.1)
Hypertension ( <i>n</i> , %)	12 (66.7)
Acute hypertension ( <i>n</i> , %)	6 (33.3)
DM ( <i>n</i> , %)	5 (27.8)
HLD ( <i>n</i> , %)	4 (22.2)
CAD ( <i>n</i> , %)	1 (5.6)
Migraine ( <i>n</i> , %)	2 (11.1)

DM: Diabetes mellitus; HLD: Hyperlipidemia; CAD: Coronary artery disease.

scanned using Vivid 7 machine (GE® medical systems, Waukesha, Wisconsin, United States)]. Two dimensional (2D), M-mode and Doppler modalities were utilized. LVEF was calculated using the Simpson's method of disc summation and adjudicated independently by two reviewers. Our primary outcome of interest was the incidence of LV dysfunction, which was defined as an LVEF ≤ 50%, with or without regional wall motion abnormalities. LVH was defined as an increase in LV mass indexed for body surface area per guideline recommendations of the American Society of Echocardiography<sup>[9]</sup>. Disagreements in ECG or TTE interpretation were resolved by a consensus meeting or after consultation with a third author. Plasma and urine catecholamine levels were measured by a method of liquid chromatography according to current diagnostic guidelines<sup>[10]</sup>.

### Statistical analysis

Results are expressed as numbers (frequencies) for categorical variables and mean ± standard deviation (SD) for continuous variables. Differences between groups were analyzed with the use of the Student's *t* test for continuous variables and the chi-square test for categorical variables respectively. Multivariate logistic regression analysis was used to investigate predictors for outcomes of interest. A two sided *P*-value less than 0.05 was considered statistically significant. Statistical analyses were performed using IBM SPSS, Statistics version 20.0 (IBM Corp., Armonk, New York).

## RESULTS

We identified 18 patients with pathologically confirmed pheo. The demographics, clinical presentations and comorbidities for these patients are described in Table 1. Mean age was 54.3 ± 19.3 years (range 17-83 years) and 11 (61.1%) patients were females; 9 (50%) tumors were localized to the left adrenal gland while 5 (27.8%) tumors were bilateral, extra-adrenal or metastatic (Table 2). Two (11.1%) patients presented with a recurrence and both had metastatic disease. One patient, a young male had an extra-adrenal paraganglioma in close proximity to the urinary bladder. All except for one patient who had diffuse metastatic disease

**Table 2 Tumor characteristics**

	<i>n</i> (%)
Left	9 (50)
Right	4 (22.2)
Bilateral	1 (5.6)
Extra-adrenal	2 (11.1)
Metastatic	2 (11.1)
Size (range) (c.c.)	15.63-3025
Incidental diagnosis	14 (77.8)
Open adrenalectomy	9/17 (52.9)

underwent surgical removal of pheo. Open (52.9%) and laparoscopic approaches were utilized for tumor removal. A history of hypertension was present in 12/18 (66.7%) patients of which 50% was either resistant or labile. Prior history of CAD was uncommon; one patient had known history of obstructive CAD and another was found to have non-flow limiting atherosclerosis. Two patients were admitted for acute cardiovascular events. The first was a 37-year-old woman with a large ischemic stroke in the middle cerebral artery territory. She had experienced a self-resolving episode of LV dysfunction presumed to be secondary to a viral myocarditis 5 years before this event. Bilateral adrenal cystic tumors were found on CT and she subsequently underwent successful bilateral adrenalectomy. No LV dysfunction was noted during this time or subsequently. The other patient was a 77-year-old woman who was admitted originally with complaint of chest pain accompanied by headache and nausea suspicious for an acute coronary syndrome. Coronary angiography was negative and systolic blood pressure (BP) elevation of more than 200 mmHg had initiated a search for pheo. Overall, 14 (77.8%) patients had incidentally noted adrenal masses. One of these patients had an existing diagnosis of multiple endocrine neoplasia syndrome type 2b and was undergoing serial biochemical testing to rule out hormonal production for a known history of an enlarging adrenal mass. Plasma catecholamine secretion and 24-h urine catecholamine excretion were elevated to varying degrees in most patients (Tables 3 and 4). All patients survived to discharge after adrenalectomy.

LV function was evaluated in 12 (66.7%) patients at the time of inclusion into study and preceding the adrenalectomy (Table 5) and, thus, no assessment of LVEF was available for 6 patients and these patients were excluded from statistical comparisons. Seven (58.3%) patients with a TTE available for review had mild or more severe LVH while 3 (25%) patients had LV dysfunction of presumably acute onset. LVH and LV dysfunction patients were serially compared with patients without these findings serving as controls. Clinical characteristics, catecholamine secretion, TTE and ECG findings were compared using multivariate analysis, and elevated catecholamine levels as assessed by urinary excretion of metabolites was not found to be an independent predictor of development of LV systolic dysfunction or of presence of LVH on TTE.

Two of the 3 patients with LV dysfunction had global

**Table 3 Plasma catecholamine secretion**

(n) (lab normal, pg/mL)	Mean ± SD (pg/mL)
Epi (7/18) (< 99)	873.86 ± 2074.92
NE (7/18) (< 339)	4121.43 ± 4833.55
NM (10/18) (< 111)	1506.1 ± 1856.72
Meta (9/18) (< 60)	1065.33 ± 1668.24

Epi: Epinephrine; NE: Norepinephrine; NM: Normetanephrine; Meta: Metanephrine.

**Table 4 Urine catecholamine excretion**

(n) (lab normal, ug/24 h)	Mean ± SD (ug/ 24 h)
NE (11/18) (< 140)	1099.27 ± 1233.70
Epi (11/18) (< 24)	307.73 ± 520.34
Dopa (11/18) (< 610)	377.91 ± 239.94
NM (9/18) (< 1050)	12960.67 ± 15197.26
Meta (10/18) (< 640)	22030.4 ± 40060.17
VM (6/18) (< 6.7 mg/dL)	3498.17 ± 8380.88

Epi: Epinephrine; NE: Norepinephrine; NM: Normetanephrine; Meta: Metanephrine; Dopa: Dopamine; VM: Vanillylmandelic acid.

hypokinesia. The first patient was an apparently healthy 47-year-old male who had a precipitous decline in BP after an initial malignant elevation shortly after elective endotracheal intubation and induction of anesthesia. Acute ST-segment elevation was noted on an ECG and warranted an emergent coronary angiography. No significant CAD or spasm was reported but severe diffuse hypokinesia was observed on TTE. Peak cardiac troponin I level was 6.8 ng/mL. Elevated 24-h urine catecholamine levels prompted a CT scan at which time a large left adrenal tumor was identified and subsequently excised. The second patient was a 64-year-old man who was admitted for severe anaphylactic reaction following multiple Hymenoptera stings. Clinical course was complicated by acute pulmonary edema and BP was labile. Acute severe diffuse LV hypokinesia and elevated cardiac troponins suggested an acute coronary syndrome, which was subsequently ruled out with a normal coronary angiogram. Pheo was detected and the tumor was excised. A follow up TTE (10 d) showed resolution of LV dysfunction and mild LVH. The third patient was a 67-year-old woman who was undergoing evaluation for severe systemic hypertension. No obstructive CAD was found on coronary angiography done previously when she was noted to have an abnormal ECG in the setting of dyspnea and chest pressure. A diagnosis of "classic" TC was made at that time in view of mid to distal wall segment hypokinesia consistent with "apical ballooning". An adrenal mass and elevated catecholamine levels were noted on a second presentation and a right adrenalectomy was performed for a moderate sized pheo.

Two women with preceding history of hypertension had marked LV hypertrophy. One such patient with septal and posterior wall thickness of 18 mm had systolic anterior motion of the mitral valve but no

**Table 5 Echo and electrocardiograms findings of study cohort**

	n (%)
Echo available	12
LV dysfunction	3/12 (25)
LVEF (%) (mean ± SD)	50 ± 16.88
Prior LV dysfunction	1/12 (8.3)
Asymmetric hypertrophy with mitral SAM	2/12 (16.67)
LVH	7/12 (58.3)
LVH on ECG	2/18 (11.1)
Prolonged QTc	5/18 (27.78)

QTc prolongation defined as > 440 ms in males; > 460 ms in females. LV: Left ventricle; LVH: Left ventricle hypertrophy; LVEF: LV ejection fraction; SAM: Systolic anterior motion; ECG: Electrocardiogram.

resting gradient across the LV outflow tract (LVOT). The LVH resolved post adrenalectomy in this patient. The second patient had asymmetric septal hypertrophy and a resting LVOT gradient of 23 mmHg. LVH was present on admission ECG in 11.1% patients, which resolved after tumor removal in 1 patient. Prolongation of the QTc interval (> 440 ms in males and > 460 ms in females) was noted in 5 (27.8%) patients. A univariate analysis for predictors of QTc prolongation was attempted, three of those patients were females, 4 had LVH by echo criteria and 2 had acute LV dysfunction. No acute arrhythmias were observed in any patient.

## DISCUSSION

In our study, 3 out of 18 patients with histologically proven pheochromocytoma were found to have de novo non-ischemic CMP which was defined as acute onset of systolic dysfunction with LVEF ≤ 50% in the absence of flow limiting CAD on coronary angiogram. The prevalence of this "idiopathic" pheo-related CMP was therefore 17% in the overall cohort, and 25% for patients who underwent any imaging for assessment of LV function. Previous studies have reported that the incidence of such pheo-related CMP is approximately 11%<sup>[11,12]</sup>. Overall, 7.5% of patients with TC have been found to have a pheo subsequently<sup>[13]</sup> and therefore it is recommend that pheo be excluded in patients with TC<sup>[14]</sup>. Elevation of circulating catecholamine levels in TC<sup>[6]</sup> and with pheo suggests excess catecholaminergic activity may be a shared pathogenic mechanism. Catecholamines cause myocardial toxicity by enhancing lipid mobility, calcium overloading, oxygen derived free radical production, increased sarcolemmal permeability as well as by provoking a state of oxygen supply-demand mismatch<sup>[15]</sup>. Further, recurrence of CMP in patients with unresected pheo<sup>[3]</sup> and resolution of CMP after treatment of adrenergic excess also suggest a causal relationship between catecholamine excess from pheo and CMP.

Provocation of a brain-heart-neural axis by various emotional and physical "stressors" has been theorized to result in massive releases of catecholamines locally into cardiac tissue while only a small leak occurs into

the systemic circulation<sup>[16,17]</sup>. In 2 of 3 patients that developed acute LV dysfunction in our study such events followed acute stress, suggesting that increases in catecholamine levels over and above the background elevation precipitated by “stress” may provoke acute LV dysfunction in pheo patients in a manner similar to TC. No independent predictors of LV dysfunction were found in this study including degree of adrenergic excess as assessed by urinary catecholamine excretion. In a study of 5 patients with TC like LV dysfunction, catecholamines levels were elevated in coronary sinus but not peripheral blood suggesting local norepinephrine release<sup>[18]</sup>. Endogenous release of catecholamines from myocardial sympathetic nerve terminals rather than circulating catecholamines may therefore mediate neurocardiogenic injury explaining the noted lack of higher catecholamine levels in pheo patients with acute LV dysfunction despite an attendant “acute stress”<sup>[19]</sup>. The absence of universal LV dysfunction despite the chronic adrenergic excess in all pheo patients is also intriguing. Persistent elevation of plasma catecholamine levels might induce adrenergic receptor desensitization *via* mechanisms that include receptor modulation and uncoupling from down-stream effectors<sup>[20,21]</sup>. Genetic susceptibility mediated through adrenergic receptor<sup>[22,23]</sup> and G protein coupled receptor kinase polymorphisms (GRK5)<sup>[24]</sup> may also account for differences in predisposition to cardiac dysfunction in pheo and TC related LV dysfunction despite similar catecholamine elevations.

Despite sharing a common morphology and possibly a shared etiology, pheo related CMP tends to differ from “idiopathic” TC in terms of patient demographics and clinical features. A study based on a population of 38 cases assimilated from published case reports of pheo related TC found such patients to be younger; and although the majority was still females, the sexual inequality was less skewed compared to TC patients without pheo<sup>[3]</sup>. Such patients experienced an inciting event less often but experienced more recurrent episodes (13.2% vs 3.5%).

Our study has some limitations. First, the sample size is small. However, this is related to the rare incidence of the disease process being studied. Second is the utilization of a retrospective design, again necessitated by the infrequent occurrence of the disease.

In conclusion, this study adds to the growing body of literature on the predilection of patients with pheo to develop non-ischemic CMP. In doing so it provides support for the proposed etiologic role of elevated catecholamines in TC and other stress induced forms of CMP. Degree of catecholamine excess as measured by urinary secretion of metabolites did not predict the development of CMP but 2 of 3 patients developed CMP in the setting of significant acute physiologic stress. Thereby acute stress mediated activation of a brain-neural-cardiac axis and local release of catecholamines as has been described previously but not chronic catecholamine elevations are likely to be responsible in pheo related CMP.

## COMMENTS

### Background

Pheochromocytomas are adrenal medullary tumors associated with a chronic elevation in catecholamine levels. They can rarely be associated with a non-ischemic cardiomyopathy.

### Research frontiers

Acute cardiomyopathy which may develop in patients with a pheochromocytoma is similar to “stress” or “takotsubo” cardiomyopathy in several ways including an elevated levels of catecholamines in both conditions. This suggests that the two forms of cardiac dysfunction might share a common etiologic link.

### Innovations and breakthroughs

Pheochromocytoma related cardiomyopathy developed in 3 of 18 patients. Two of these patients experienced an acute stressful event in a manner similar to classic takotsubo cardiomyopathy. The authors did not find an association between urinary excretion of catecholamines and development of cardiac dysfunction.

### Applications

The findings of this study need to be confirmed in a larger multicenter international registry.

### Terminology

Pheochromocytoma: Adrenal medulla tumors that may secrete varying amounts and combinations of catecholamines; Takotsubo cardiomyopathy: A form of acute cardiac dysfunction that develops classically after an acute stressful events and without obstruction of epicardial coronary arteries.

### Peer-review

This paper is interesting review concerning association pheochromocytoma and cardiomyopathy. Therefore, this article should be published.

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## Observational Study

**Significance of inferior wall ischemia in non-dominant right coronary artery anatomy**

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**Abstract****AIM**

To investigate the relationship of inferior wall ischemia on myocardial perfusion imaging in patients with non-dominant right coronary artery anatomy.

**METHODS**

This was a retrospective observational analysis of consecutive patients who presented to the emergency department with primary complaint of chest pain. Only patients who underwent single photon emission computed tomography (SPECT) myocardial perfusion imaging (MPI) were included. Patients who showed a reversible defect on SPECT MPI and had coronary angiography during the same hospitalization was analyzed. Patients with prior history of coronary artery disease (CAD) including history of percutaneous coronary intervention and coronary artery bypass graft surgeries were excluded. True positive and false positive results were identified on the basis of hemodynamically significant CAD on coronary angiography, in the same territory as identified on SPECT MPI. Coronary artery dominance was determined on coronary angiography. Patients were divided into group 1 and group 2. Group 1 included patients with non-dominant right coronary artery (RCA) (left dominant and codominant). Group 2 included patients with dominant RCA anatomy. Demographics, baseline characteristics and positive predictive value (PPV) were analyzed for the two

groups.

## RESULTS

The mean age of the study cohort was 57.6 years. Sixty-one point seven percent of the patients were males. The prevalence of self-reported diabetes mellitus, hypertension and dyslipidemia was 36%, 71.9% and 53.9% respectively. A comparison of baseline characteristics between the two groups showed that patients with a non-dominant RCA were more likely to be men. For inferior wall ischemia on SPECT MPI, patients in study group 2 had a significantly higher PPV, 32/42 (76.1%), compared to patients in group 1, in which only 3 out of the 29 patients (10.3%) had true positive results ( $P$  value  $< 0.001$   $Z$  test). The difference remained statistically significant even when only patients with left dominant coronary system (without co-dominant) were compared to patients with right dominant system (32/40, 76.1% in right dominant group, 3/19, 15.8% in left dominant group,  $P$  value  $< 0.001$   $Z$  test). There was no significant difference in mean hospital stay, re-hospitalization, and in-hospital mortality between the two groups.

## CONCLUSION

The positive predictive value of SPECT MPI for inferior wall ischemia is affected by coronary artery dominance. More studies are needed to explain this phenomenon.

**Key words:** Myocardial perfusion imaging; Single photon emission computed tomography; False positive results; Coronary artery dominance; Inferior wall ischemia

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**Core tip:** A positive test for ischemia on single photon emission computed tomography (SPECT), myocardial perfusion imaging (MPI) is often followed up with coronary angiography. The aim of our study was to assess the relationship of inferior wall ischemia on SPECT MPI with non-dominant right coronary artery (RCA) anatomy. We found that positive predictive value of inferior wall ischemia on SPECT MPI was significantly lower in patients with non-dominant RCA anatomy. We postulate that in non-dominant RCA anatomy flow tracer may show relatively decreased uptake in the inferior wall that might not be indicative of flow limiting stenosis.

Malik AO, Abela O, Devabhaktuni S, Malik AA, Allenback G, Ahsan CH, Malhotra S, Diep J. Significance of inferior wall ischemia in non-dominant right coronary artery anatomy. *World J Cardiol* 2017; 9(3): 261-267 Available from: URL: <http://www.wjgnet.com/1949-8462/full/v9/i3/261.htm> DOI: <http://dx.doi.org/10.4330/wjc.v9.i3.261>

## INTRODUCTION

Single photon emission computed tomography (SPECT) myocardial perfusion imaging (MPI) is most often used to assess the likelihood of obstructive coronary artery

disease (CAD), presence of ischemia in a patient with known CAD, and evaluating the extent of ischemia for prognostic value<sup>[1]</sup>. In essence SPECT MPI accomplishes this by measuring relative changes in perfusion of myocardial territories before and after augmenting coronary blood flow<sup>[1]</sup>. SPECT MPI has enjoyed widespread clinical use because of its well documented diagnostic and prognostic utility in CAD<sup>[2]</sup>.

Coronary artery dominance is determined by the artery supplying the posterior portion of interventricular (IV) septum<sup>[3]</sup>. In a right dominant system, the right coronary artery (RCA) supplies this territory and feeds the posterior descending artery, in contrast to left dominant system in which the left circumflex artery (LCX) accomplishes this role<sup>[3]</sup>. In a co-dominant system, the supply of posterior IV septum is shared by both RCA and LCX<sup>[3]</sup>. Right dominant system is the more prevalent variant occurring in approximately 70% of people, followed by left dominant and co-dominant system<sup>[4]</sup>.

The prognostic significance of coronary artery dominance in patients with CAD has been studied. Left dominant system has been shown to be an independent risk factor of morbidity and mortality in patients undergoing both surgical and percutaneous revascularization, especially in patients with ST segment elevated myocardial infarction (STEMI)<sup>[4-7]</sup>.

The effect of coronary anatomy on diagnostic accuracy of cardiac magnetic resonance imaging (CMR) has been studied<sup>[8]</sup>. However, no study to our knowledge has evaluated the effect of coronary artery dominance on diagnostic accuracy of SPECT (MPI studies). We present the first report showing the effect of coronary artery dominance on positive predictive value of SPECT MPI.

## MATERIALS AND METHODS

### Study design

The study was a single center retrospective analysis conducted at a tertiary care center.

### Inclusion and exclusion criteria

All patients who underwent rest and stress SPECT MPI from January 1<sup>st</sup> 2013 to June 30<sup>th</sup> 2014, for diagnostic purposes were included in our study. All patients who did not undergo a coronary angiogram during the same hospital stay were excluded. Furthermore, all patients who did not have evidence of reversible ischemia on SPECT MPI were excluded.

These patients presented with chest pain that were deemed to be of intermediate pre-test probability for ischemia. The images were initially read by an experienced radiologist and results verified by the cardiologist.

### Institute review board approval

The study was approved by the Institute Review Board at University Medical Center of Southern Nevada. This study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of

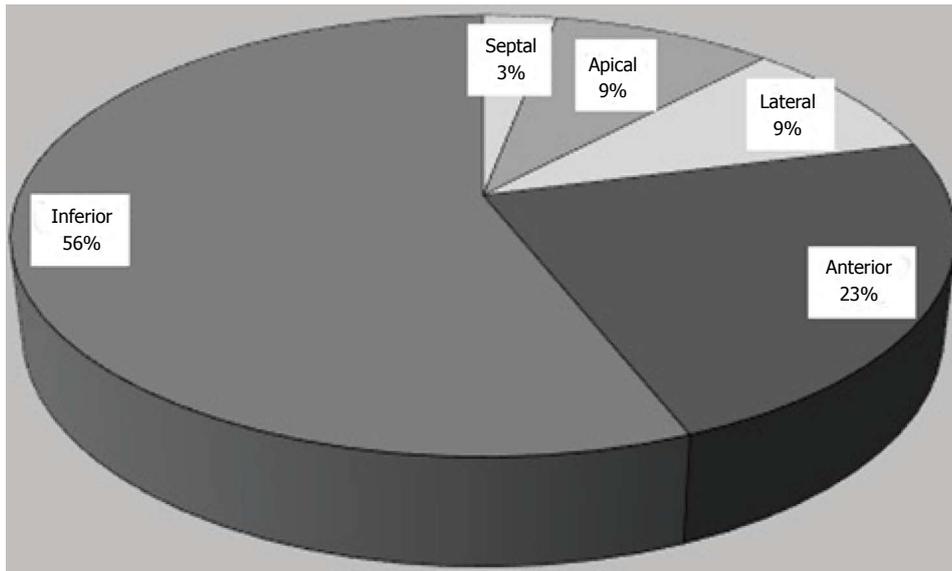


Figure 1 Defect location on single photon emission computed tomography myocardial perfusion imaging.

Helsinki and its later amendments or comparable ethical standards.

#### Coronary angiography and defining obstructive CAD

All of the patients subsequently underwent a coronary angiogram during the same hospital stay after the SPECT MPI. Patients were divided into two groups on the basis of coronary artery dominance. Group 1 included patients with a non-dominant RCA (left dominant and co-dominant). Group 2 included patients with right dominant coronary artery system.

The coronary angiogram was performed by an experienced interventional cardiologist. It was noted if there was obstructive CAD, in the same distribution as shown by the SPECT MPI the study was deemed to be true positive. Obstructive CAD was defined as maximal coronary artery stenosis of more than 70%.

#### SPECT MPI and determination of reversible ischemia

SPECT MPI was performed using standard protocols approved by the American Society of Nuclear Cardiology<sup>[9]</sup>. An experienced radiologist initially read the images and the presence of any reversible ischemia was verified by the cardiology team. Figure 1 shows representative images of SPECT MPI, showing inferior wall ischemia and normal scan respectively.

#### Study outcome

The primary study outcome was determining diagnostic accuracy of the SPECT MPI, with the coronary angiogram as gold standard. The positive predictive value of SPECT MPI was compared in both groups.

#### Statistical analysis

Data for each study variable were summarized initially for the whole cohort and then by dominant coronary artery group, using means for continuous variables

and frequencies/percentages for categorical variables. Means for the non-dominant RCA and dominant RCA groups were compared using independent-samples *t*-tests (or Mann Whitney *U* tests, for variables with non-normally distributed data). Frequencies/percentages were compared using  $\chi^2$  tests. Positive predictive values for were compared *via* *Z* tests of proportions. The significance level (alpha) was set at 0.05, and all analyses were completed *via* SPSS, version 22 (IBM).

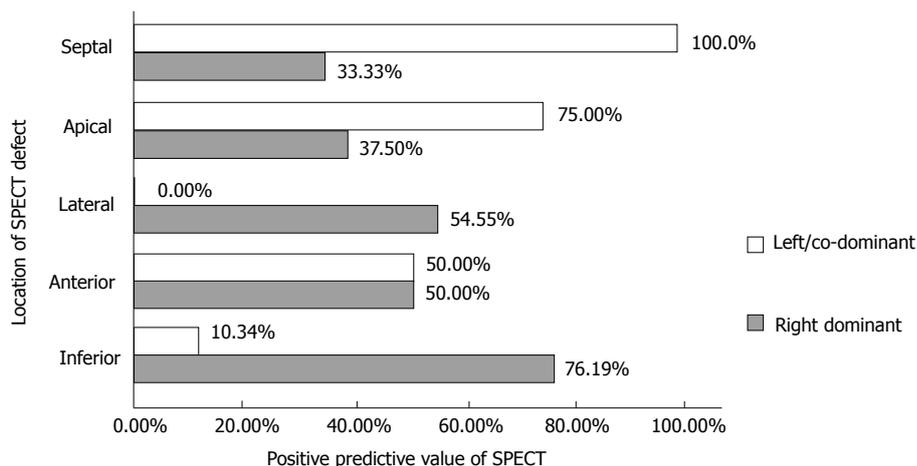
## RESULTS

The mean age of the study cohort was 57.6 years. Sixty-one point seven percent of the patients were males. The prevalence of self-reported diabetes mellitus, hypertension and dyslipidemia was 36%, 71.9% and 53.9% respectively. A comparison of baseline characteristics between the two groups showed that patients with a non-dominant RCA were more likely to be men. Table 1 shows comparison of other baseline characteristics.

The most common location for the reversible defect was seen the inferior wall (Figure 2).

The positive predictive value (PPV) was analyzed and compared between the two study groups. Sub-group analysis showed that for inferior wall ischemia on SPECT MPI, patients in study group 2 had a significantly higher PPV, 32/42 (76.1%), compared to patients in group 1, in which PPV was 10.3% (3/29) (*P* value < 0.001 *Z* test) Figure 2 illustrates the results. The difference remained statistically significant even when only patients with left dominant coronary system (without co-dominant) were compared to patients with right dominant system. (32/40, 76.1% in right dominant group, 3/19, 15.8% in left dominant group, *P* value < 0.001 *Z* test).

There was no significant difference in mean hospital stay, re-hospitalization, and in-hospital mortality between the two groups as shown in Table 2.



Significant difference between left/co-dominant and right dominant,  $P < 0.001$ .

**Figure 2** Positive predictive value of single photon emission computed tomography for patients in group 1 and group 2. SPECT: Single photon emission computed tomography.

	Dominant RCA $n = 87$	Non-dominant RCA $n = 41$	$P$ value (test)
Age	56.92 yr	59.24 yr	0.252 ( $t$ test)
Male gender	48/87 (55.17)	31/41 (75.61)	0.026 ( $\chi^2$ )
BMI	28.29	28.87	0.459 (Mann-Whitney)
PMH of DM	33/87 (37.93)	14/41 (34.15)	0.679 ( $\chi^2$ )
PMH HTN	64/87 (73.56)	27/41 (65.85)	0.369 ( $\chi^2$ )
PMH dyslipidemia	51/87 (58.62)	18/41 (43.90)	0.119 ( $\chi^2$ )
PMH of a fib	2/87 (2.30)	1/41 (2.45)	1.000 ( $\chi^2$ )
PMH of PVD	17/87 (19.54)	8/41 (19.51)	0.997 ( $\chi^2$ )
PMH of COPD	5/87 (5.75)	7/41 (17.07)	0.053 ( $\chi^2$ )
Current smoker	27/87 (31.03)	15/41 (36.59)	0.533 ( $\chi^2$ )
Drug abuse	10/87 (11.49)	7/41 (17.07)	0.386 ( $\chi^2$ )
Alcohol use	23/87 (26.45)	11/40 (27.50)	0.900 ( $\chi^2$ )
PMH of sleep apnea	3/87 (3.45)	1/41 (2.44)	1.000 ( $\chi^2$ )
PMH of CKD	9/87 (10.34)	2/41 (4.88)	0.501 ( $\chi^2$ )
ESRD on HD	4/87 (4.60)	2/41 (4.88)	1.000 ( $\chi^2$ )

RCA: Right coronary artery; BMI: Body mass index; PMH: Past medical history; DM: Diabetes mellitus; HTN: Hypertension; a fib: Atrial fibrillation; PVD: Peripheral vascular disease; COPD: Chronic obstructive pulmonary disease; CKD: Chronic kidney disease; ESRD: End stage renal disease; HD: Hemodialysis.

## DISCUSSION

Around 15 million patients seek medical attention for symptoms concerning for CAD<sup>[10]</sup>. In stable patients, not having acute coronary syndrome non-invasive testing like SPECT MPI, act as gatekeepers to coronary angiography because of risks and costs associated with coronary angiography<sup>[11,12]</sup>. Despite the use of conventional non-invasive testing such as SPECT MPI an analysis of almost 400000 coronary angiograms in patients with no prior history of CAD disease revealed no obstructive disease in more than 60% of the cases, resulting in unnecessary risks and costs<sup>[13,14]</sup>. Hence, from a public health standpoint, it is imperative that we

study the reasons for false positive diagnoses associated with non-invasive tests such as SPECT MPI.

SPECT MPI is widely used for diagnostic purposes in patients presenting with chest pain when acute coronary syndrome (ACS) has been ruled out<sup>[2]</sup>. A recent study showed that SPECT MPI is widely used for diagnostic and risk stratification purposes in the United States and patient's socio-economic status did not significantly affect the use of SPECT MPI by physicians<sup>[15]</sup>. In the developing world several studies have shown the widespread use of SPECT MPI by physicians to aid in diagnosis in management<sup>[16,17]</sup>. One such report from Iran regarding SPECT MPI referral practices showed that 72.5% (211/291) of the referrals found to be appropriate per ASNC recommendations<sup>[16]</sup>.

The utilization of SPECT MPI is often on the physician's assessment of pre-test probability. The American College of Physicians pre-test probability assessment and Duke chest pain score are two common objective tools used for this assessment<sup>[18]</sup>. In our retrospective analysis, SPECT MPI was done, on the physician's assessment of the patient's pre-test probability.

Our study shows that SPECT MPI in patients with non-dominant RCA has significantly high false positive results for inferior wall ischemia. In a study using positron emission tomography measuring absolute myocardial blood flow (MBF) in low risk normal patients' authors found baseline MBF in the inferior region was significantly ( $P < 0.0001$ ) lower than either the anterior or lateral regions<sup>[19]</sup>. However, coronary anatomy was not available in this study population. Nonetheless this finding may contribute to our observation as well. One study using stress CMR also showed a statistically significant difference in false positive rate correlating with dominance<sup>[8]</sup>. They also showed a correlation with the vessel size, postulating that the smaller vessel size that usually comes with non-dominant vessels was the factor leading to false positive readings<sup>[8]</sup>.

**Table 2 Comparison of outcomes between study groups**

	<b>Dominant RCA n = 87</b>	<b>Non-dominant RCA n = 41</b>	<b>P value (test)</b>
Mean hospital stay (d)	4.33	4.29	0.713 (Mann-Whitney)
In-hospital mortality	0/87	0/41	-
30-d re-hospitalization for chest pain	10/87 (11.49%)	2/41 (4.88%)	0.231 ( $\chi^2$ )

RCA: Right coronary artery.

Gender differences in vessel caliber and coronary artery dominance could also play a role. As shown in our results patients with non-dominant RCA were more likely to be men. This is consistent with the report by Gebhard *et al*<sup>[5]</sup> in which patients with left dominant coronary artery anatomy were more likely to be males. In contrast in a cohort of patients with STEMI, lower percentage of patients with left dominant circulation were men compared to patients with right dominant circulation<sup>[7]</sup>. This was not statistically significant. Vessel caliber was not available in either of these studies. Whether gender differences affect coronary artery, dominance is not clear at this time.

Regardless our study finding has important consequences. First, it has been shown that patients with left dominant system are at high risk in terms of cardiovascular events<sup>[6]</sup>; hence, it is important that significant CAD is promptly addressed in these patients. If the diagnostic accuracy of SPECT MPI is particularly low in this sub group of patients, then it is important that more studies are done to evaluate the negative predictive value (NPV) in this subset to reach a better understanding about role of SPECT MPI in excluding significant CAD in these patients. In our retrospective analysis patients with negative SPECT MPI imaging did not have a coronary angiogram, hence analysis of NPV was not possible.

Second, if the diagnostic accuracy of inferior wall ischemia on SPECT MPI is affected by coronary artery dominance and it has a significantly lower PPV in patients with non-dominant RCA, it would mean that many patients in this sub-group are exposed to unnecessary invasive procedures. This is in addition to utilizing the resources when it will not help the patient.

In conclusion, based on our findings we hypothesize that the flow tracer in a non-dominant RCA may show relatively decreased uptake in the inferior wall that might not be indicative of flow limiting stenosis. More multi-center studies to explore the relationship of coronary artery dominance on SPECT MPI are needed to reach a better understanding regarding positive or negative results in patients in the context of non-dominant RCA anatomy.

### Study limitations

This study was done only at a single center and the

SPECT MPI results were only read by one group of physicians. Prone imaging was not done. Also some patients could have had inferior wall abnormality and coronary computed tomography angiogram was not utilized. Coronary angiograms were not done on patients with normal SPECT MPI results. Hence we could not analyze the effect of coronary dominance on NPV. We did not strictly use objective validated models to quantify SPECT MPI defect so some measurement bias may be present.

## COMMENTS

### Background

Single photon emission computed tomography (SPECT) myocardial perfusion imaging (MPI) is most often used to assess the likelihood of obstructive coronary artery disease (CAD), presence of ischemia in a patient with known CAD, and evaluating the ex-tent of ischemia for prognostic value. SPECT MPI has enjoyed widespread clinical use because of its well documented diagnostic and prognostic utility in CAD. The authors' study aims to understand the effect of coronary artery dominance on the positive predictive value (PPV) of SPECT MPI.

### Research frontiers

The effect of coronary anatomy on diagnostic accuracy of cardiac magnetic resonance imaging (CMR) has been studied. However, no study to our knowledge has evaluated the effect of coronary artery dominance on diagnostic accuracy of SPECT MPI studies. The authors' present the first report showing the effect of coronary artery dominance on PPV of SPECT MPI.

### Innovations and breakthroughs

They studied the effect of coronary artery dominance on the PPV of SPECT MPI. The effect of coronary anatomy on diagnostic accuracy of cardiac magnetic resonance imaging (CMR) has been studied. In a study using positron emission tomography measuring absolute myocardial blood flow (MBF) in low risk normal patients' authors found baseline MBF in the inferior region was significantly lower than either the anterior or lateral regions. However, coronary anatomy was not available in this study population. They studied the effect of coronary artery dominance on the PPV of SPECT MPI.

### Applications

In stable patients, not having acute coronary syndrome non-invasive testing like SPECT MPI, act as gatekeepers to coronary angiography because of risks and costs associated with coronary angiography. Despite the use of conventional non-invasive testing such as SPECT MPI an analysis of almost 400000 coronary angiograms in patients with no prior history of CAD disease revealed no obstructive disease in more than 60% of the cases, resulting in unnecessary risks and costs. Hence, from a public health standpoint, it is imperative that the study the reasons for false positive diagnoses associated with non-invasive tests such as SPECT MPI. They show in the study that the PPV of SPECT MPI for inferior wall ischemia in stable patients not having ACS, is affected by coronary artery dominance. Although more studies are needed to explain this phenomenon, maybe this subset of patients should undergo further non-invasive testing before proceeding to invasive coronary angiography.

### Terminology

SPECT MPI: SPECT MPI is most often used to assess the likelihood of obstructive CAD, presence of ischemia in a patient with known CAD, and evaluating the ex-tent of ischemia for prognostic value. In essence SPECT MPI accomplishes this by measuring relative changes in perfusion of myocardial territories before and after augmenting coronary blood flow; coronary artery dominance: Coronary artery dominance is determined by the artery supplying the posterior portion of interventricular (IV) septum. In a right dominant system, the right coronary artery (RCA) supplies this territory and feeds the posterior descending artery, in contrast to left dominant system in which the left circumflex artery (LCX) accomplishes this role. In a co-dominant system, the supply of

posterior IV septum is shared by both RCA and LCX.

**Peer-review**

This is an interesting manuscript about the association of a positive test for inferior wall ischemia on MPI with non-dominant RCA anatomy.

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## Observational Study

**Risk of ventricular arrhythmia in patients with myocardial infarction and non-obstructive coronary arteries and normal ejection fraction**

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**Author contributions:** Bière L and Niro M contributed equally to this work, generated analysis, and interpretation of the data, and drafted the initial manuscript; Furber A and Probst V were the guarantors of the study; Pouliquen H participated in the acquisition; Gourraud JB and Prunier F revised the article critically for important intellectual content.

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**Abstract****AIM**

To assess the arrhythmic determinants and prognosis of patients presenting with myocardial infarction and non-obstructive coronary arteries (MINOCA) with normal ejection fraction (EF).

**METHODS**

This is an observational analysis of 131 MINOCA patients with normal EF. Three cardiac magnetic resonance (CMR) diagnosis classes were recognized according to the late gadolinium enhancement (LGE) pattern: Myocardial infarction (MI) ( $n = 34$ ), myocarditis ( $n = 47$ ), and "no LGE" ( $n = 50$ ). Ventricular events occurring during hospitalization were recorded and the entire population

was followed-up at 1 year.

## RESULTS

Ventricular arrhythmia was observed in 18 (13.8%) patients during hospitalization. The “no LGE” patients experienced fewer ventricular events than the MI and myocarditis patients [4.0% *vs* 26.5% and 14.9%, respectively ( $P = 0.013$ )]. There was no significant difference between the MI and myocarditis groups. On multivariate analysis, LGE transmural extent [OR = 1.52 (1.08-2.15),  $P = 0.017$ ] and ST-segment elevation [OR = 4.65 (1.61-13.40),  $P = 0.004$ ] were independent predictors of ventricular arrhythmic events, irrespective of the diagnosis class. Finally, no patient experienced sudden cardiac death or ventricular arrhythmia recurrence at 1-year.

## CONCLUSION

MINOCA patients with normal EF presented no 1-year cardiovascular events, irrespective of the CMR diagnosis class. LGE transmural extent and ST segment elevation at admission are risk markers of ventricular arrhythmia during hospitalization.

**Key words:** Ventricular tachycardia; Myocarditis; Myocardial infarction; Late gadolinium enhancement; Cardiac magnetic resonance; Myocardial infarction and non-obstructive coronary arteries

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**Core tip:** Out of 131 myocardial infarction and non-obstructive coronary arteries patients, 18 experienced a ventricular arrhythmic event during hospitalization, consisting of 17 ventricular tachycardia and one ventricular fibrillation. No patient died during the 1-year follow-up. Cardiac magnetic resonance classified the underlying diagnosis in 61.8% of the cases, as a myocarditis or a myocardial infarction. Rather than the diagnosis itself, late gadolinium enhancement and ST-segment elevation were found as valuable tools to stratify the risk for arrhythmia of these patients. These findings may be useful to select patients who might be eligible for either arrhythmia prevention or secondary prevention therapy.

Bière L, Niro M, Pouliquen H, Gourraud JB, Prunier F, Furber A, Probst V. Risk of ventricular arrhythmia in patients with myocardial infarction and non-obstructive coronary arteries and normal ejection fraction. *World J Cardiol* 2017; 9(3): 268-276 Available from: URL: <http://www.wjgnet.com/1949-8462/full/v9/i3/268.htm> DOI: <http://dx.doi.org/10.4330/wjc.v9.i3.268>

## INTRODUCTION

Sudden cardiac death is still the most common cause of death worldwide, accounting for over 50% of all deaths

from cardiovascular disease. Coronary artery disease represents approximately 80% of all cases<sup>[1]</sup>. However, 1%-12% of patients with chest pain and cardiac troponin elevation present with normal coronary arteries on angiography analysis<sup>[2]</sup>. This pathological entity is called myocardial infarction and non-obstructive coronary arteries (MINOCA) and encompasses myocarditis, transient apical ballooning syndrome, and authentic ischemic injuries<sup>[2]</sup>. Cardiac magnetic resonance (CMR) imaging is helpful for providing detailed information on myocardial tissue characteristics, and has become the gold standard for *in vivo* detection of necrosis, notably in acute myocardial infarction (MI) and myocarditis<sup>[3]</sup>.

Early-sustained ventricular arrhythmias complicate 2%-20% of acute MIs and are associated with increased hospital mortality rates<sup>[4,5]</sup>. While the arrhythmic prognosis of MI with abnormal coronary angiography is well known, there is little data concerning MINOCA, even when the arrhythmic prognosis seems to be relatively good<sup>[6,7]</sup>. As a result of the lack of data concerning this entity, there are no specific guidelines concerning hospitalization duration, follow-up, or treatment for this specific setting.

Our study sought to evaluate the risk of ventricular arrhythmias of presumed low-risk MINOCA patients at both early-stage consultation and 1-year follow-up, based on the diagnosis class established by CMR imaging.

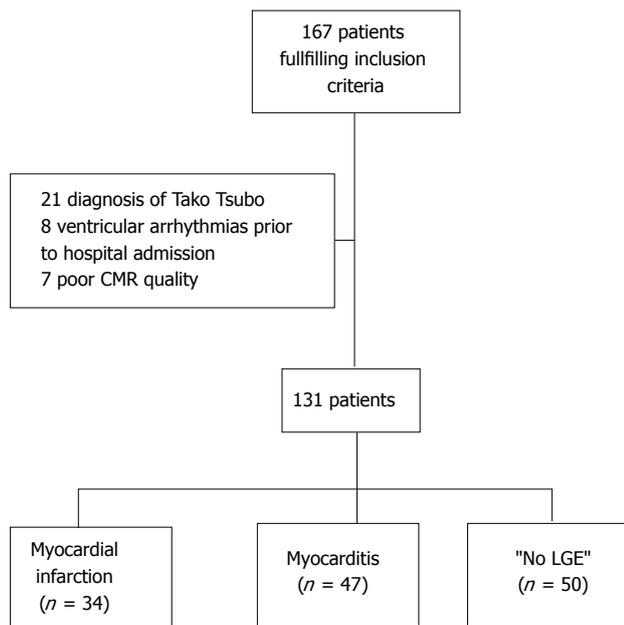
## MATERIALS AND METHODS

One hundred and sixty-seven patients were retrospectively enrolled between 2007 and 2012 in the French university hospitals of Nantes and Angers. The inclusion criteria were: (1) hospitalization for acute anginal chest pain; (2) increase in troponin rates superior to the normal range; (3) left ventricular ejection fraction (LVEF)  $\geq 45\%$ ; and (4) absence of coronary artery stenosis or thrombosis (stenosis  $< 50\%$  of the diameter of the epicardial vessel).

All patients underwent CMR and the arrhythmic evaluation included at least 48 h of electrocardiography (ECG) monitoring after admission.

In order to avoid overestimating the arrhythmic risk in this population, patients hospitalized for sustained ventricular tachycardia ( $n = 8$ ) or cardiopulmonary arrest were not included in the study. Patients presenting with Tako-Tsubo ( $n = 21$ ) were therefore also from the study due to this syndrome's specific pathophysiology. Seven more patients could not be included due to poor CMR quality so that the study was performed on 131 patients (Figure 1). The study complies with the Declaration of Helsinki and local ethics committee has approved the research protocol.

Ventricular tachycardia (VT) was defined as at least three consecutive ventricular beats with a rate  $> 100$  bpm<sup>[8]</sup>. Prolonged VT was defined as at least eight consecutive ventricular beats<sup>[9]</sup>. Ventricular fibrillation



**Figure 1** Flow chart of the study population. CMR: Cardiac magnetic resonance; LGE: Late gadolinium enhancement.

was defined as an irregular ventricular rhythm with marked variability in the QRS cycle length, morphology, and rapid amplitude, usually over 300 bpm/200 ms (cycle length: 180 ms or less)<sup>[8]</sup>.

All data concerning the initial hospitalization were recorded from the patient medical files. Repolarization abnormalities were defined as ST-segment depression  $\geq 0.1$  mV at 0.08 s from the junction (J point) (STD), asymmetrical T wave inversion  $\geq 0.1$  mV deep in two or more leads except lead aVR, and ST-segment elevation  $\geq 0.2$  mV (STE). Q waves  $> 0.3$  mV in depth or  $> 0.04$  s in duration in at least two leads, except lead aVR, were considered abnormal.

At the 1-year follow-up, the following outcomes were collected: Ventricular arrhythmia, death from any cause, cardiovascular (CV) death, and particularly sudden cardiac death. The chosen treatments were evaluated on hospital discharge and at 1 year. If necessary, the referring cardiologists or general practitioners were contacted to obtain information concerning the patients at 1-year follow-up. Data on 1-year survival was completed for every patient.

CMR was performed using 1.5T scanners (Avanto, Siemens, Erlangen, Germany) with 8-element phased-array cardiac receiver coils. The median time from presentation of MINOCA to CMR was 7 d (interquartile range: 4; 13).

LV function was determined by means of cine imaging, in multiple short-axis views covering the entire LV. The typical in-plane resolution was 1.6 mm  $\times$  1.9 mm and 7.0-mm thickness sections were used. Temporal resolution was around 35-45 ms.

Late gadolinium enhancement (LGE) was performed 10 min after administering the gadolinium-based contrast agent, at a cumulative dose of 0.2 mmol/kg,

by means of a two-dimensional segmented inversion recovery gradient-echo pulse sequence. The inversion time was set to null the signal of the viable myocardium, typically ranging from 240 to 300 ms.

A post-hoc core analysis was specifically performed for this study, using a dedicated software package (Medis 7.1, Mass, Leiden, The Netherlands). For all qualitative assessments, the recommended 17-segment system was applied, requiring the consensus of two blinded observers.

On all the short-axis cine slices, the endocardial and epicardial borders were outlined manually on the end-diastolic and end-systolic images, with the exclusion of the trabeculae and papillary muscles. The reproducibility of the LVEF and LV volumes assessments was good, the details of which are published elsewhere<sup>[10]</sup>.

The cine imaging was assessed visually by analyzing the LV wall thickening using a three-grade scale: 0 = normal, 1 = hypokinesia, 2 = akinesia. We counted the number of segments affected in order to determine the extent of hypokinesia. Furthermore, pericardial effusion was noted when considered exceeding trivial effusion<sup>[3]</sup>.

LGE was evaluated by means of visual analysis. We estimated the maximal transmural extent of LGE within each segment as a percentage of the LV using a five-grade scale: 0% = 0, 0%-25% = 1, 25%-50% = 2, 50%-75% = 3, and  $> 75\%$  = 4 (Figure 2). The number of segments with LGE defined the LGE transversal extent.

Following analysis by means of CMR, the patients were classified according to LGE pattern, as described: Subendocardial LGE was revealed in the MI group, subepicardial or medioventricular LGE in the myocarditis group, and absence of LGE in the "no LGE" group<sup>[11]</sup>.

When the extent of LGE was transmural ( $> 75\%$ ), the border zones were analyzed to more precisely determine the CMR diagnosis, for example, if the signal of LGE borders was subendocardial, myocardial infarction was diagnosed.

### Statistical analysis

Statistical analyses were performed using SPSS Version 15.0 software for Windows (SPSS Inc., Chicago, Illinois, United States). The data was presented as mean  $\pm$  standard deviation (SD) or median (25<sup>th</sup>; 75<sup>th</sup> percentiles) in cases of non-normal distribution, with categorical data expressed as frequencies and percentages. Continuous variables were compared by means of the unpaired *t* test or Wilcoxon rank-sum test, when necessary. Non-continuous variables were compared using the  $\chi^2$  test. Differences were considered significant with a *P* < 0.05. For the multivariate analysis of ventricular events during hospitalization, clinical and CMR data were tested by means of an ascending step-by-step binomial logistic regression analysis, including variables with *P* values < 0.05 in univariate analysis. The Hosmer-Lemeshow goodness-of-fit test was used to assess the applied models.

Table 1 Patient characteristics

	All patients (n = 131)	MI (n = 34)	Myocarditis (n = 47)	"No LGE" (n = 50)	P
Age, yr	48.5 ± 16.1	52.4 ± 14.2	40.5 ± 13.5 <sup>1</sup>	53.4 ± 16.9 <sup>3</sup>	< 0.001
Risk factors, n (%)					
Male gender	87 (66.4)	22 (64.7)	39 (83.0)	26 (52.0) <sup>2,3</sup>	0.005
Hypertension	39 (29.8)	13 (38.2)	8 (17.0)	18 (36.0)	0.06
Diabetes	11 (8.4)	4 (11.8)	2 (4.3)	5 (10.0)	0.42
Dyslipidemia	38 (29.0)	9 (26.5)	10 (21.3)	19 (38.0)	0.18
Current smoker	45 (34.4)	14 (41.4)	12 (25.5)	19 (38.0)	0.27
Family history of premature CHD	25 (19.1)	11 (34.2)	5 (10.6)	9 (18.0)	0.05
Time from symptom onset to admission, h	9 [2; 24]	3.5 [2; 13.5]	13 [4; 48] <sup>1</sup>	9.5 [2; 24]	0.01
Hospitalization duration, d	6 [4; 7]	5.5 [4; 7]	6 [5; 7]	5 [4; 7]	0.42
ECG monitoring duration, d	5 [4; 6]	5 [4; 6]	5 [4; 7]	4 [3; 6]	0.12
Primary ECG abnormality, n (%)	91 (69.5)	26 (76.5)	34 (72.3)	31 (62.0)	0.32
ST-segment elevation	46 (35.1)	9 (26.5)	22 (46.8)	15 (30.0)	0.10
ST-segment depression	8 (6.1)	2 (5.9)	4 (8.5)	2 (4.0)	0.65
T-wave inversion	31 (23.7)	11 (32.4)	8 (17.0)	12 (24.0)	0.27
Q wave	2 (1.5)	2 (5.9)	0	0	0.06
Atrioventricular block	1 (0.8)	0	0	1 (2.0)	0.28
Laboratory measurements					
Peak troponin, µg/L	2.1 ± 5	3.6 ± 6.1	2.9 ± 6.3	0.5 ± 0.6 <sup>2,3</sup>	0.013
Leucocytes on admission, G/L	9.3 ± 3.6	9.3 ± 3.9	9.2 ± 3.5	9.2 ± 3.4	0.99
CRP on admission, mg/L	28.2 ± 41.1	8.8 ± 18.9	39.5 ± 38.4 <sup>1</sup>	31.0 ± 50.4 <sup>2</sup>	0.004
Coronary atheroma, n (%)	45 (34.6)	15 (45.5)	14 (29.8)	16 (32.0)	0.31
β-blocker use, n (%)					
During hospitalization	91 (69.5)	27 (79.4)	31 (66.0)	33 (66.0)	0.34
At 1 yr	16 (12.2)	10 (29.4)	1 (2.1)	5 (10.0)	0.05
ACEI use, n (%)					
During hospitalization	56 (43.1)	16 (48.5)	16 (34.0)	24 (48.0)	0.29
At 1 yr	17 (13.0)	10 (29.4)	1 (2.1) <sup>1</sup>	6 (12.0)	0.042

<sup>1</sup>P significant between MI and myocarditis groups; <sup>2</sup>P significant between MI and "no LGE" groups; <sup>3</sup>P significant between myocarditis and "no LGE" groups. MI: Myocardial infarction; LGE: Late gadolinium enhancement; ACEI: Angiotensin converting enzyme inhibitor; CHD: Coronary heart disease; CRP: C-reactive protein.

## RESULTS

A total of 131 patients (87 men, median age: 48.5 ± 16 years) fulfilled our criteria. LGE was present in 81 of the 131 patients (61.8%). There were 34 (25.9%) patients classified in the MI group, 47 (35.9%) in the myocarditis group, and 50 (38.2%) in the "no LGE" group (Table 1). The myocarditis group exhibited a specific pattern of myocarditic lesions, located predominantly in the free lateral wall (42/47 cases) and in the subepicardial layers (45/47 cases). The ischemic lesions were distributed homogeneously (Figure 2).

Patients classed in the myocarditis group were younger ( $P < 0.001$ ) and more frequently male ( $P < 0.005$ ) than the others. No differences in cardiovascular risk factor were noted.

The median time between symptom onset and hospital admission was 9 h (2; 24). Patients from the MI group were admitted to the hospital more quickly than those in the myocarditis group ( $P = 0.002$ ).

The prevalence of ECG abnormalities was 69.5%, predominantly consisting of STE (35.7%) and T-wave inversion (23.1%). There were no differences in the frequency of ECG abnormalities between the groups.

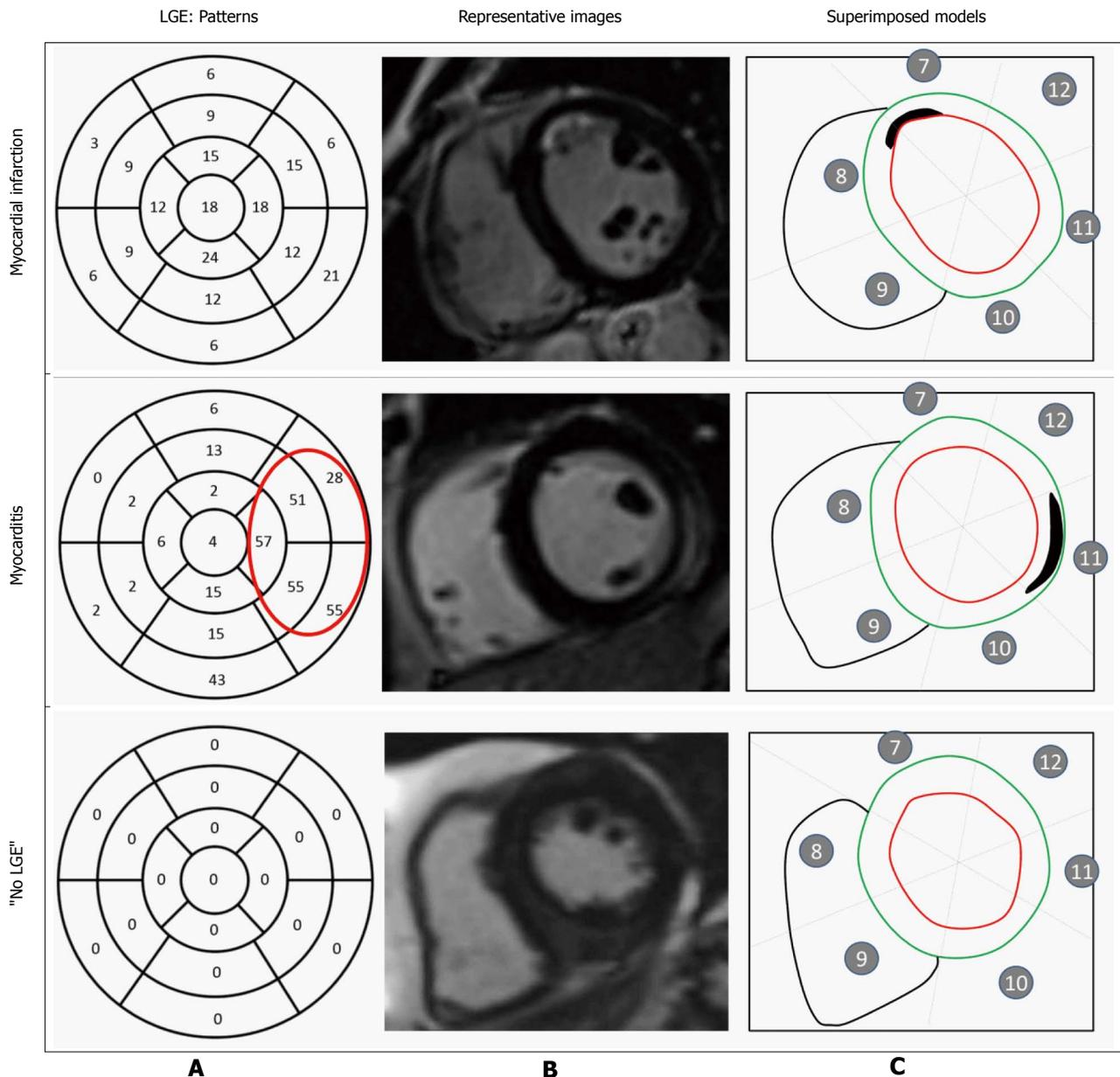
Troponin rates were lower in the "no LGE" group compared to those of the MI and myocarditis groups ( $P = 0.001$  and  $P = 0.013$ , respectively).

The MI patients presented with lower C-reactive protein (CRP) rates than the myocarditis and "no LGE" patients ( $P < 0.001$  and  $P = 0.020$ , respectively). Elevated CRP was observed in 42 (93.3%), 22 (66.7%), and 37 (82.2%) patients from the myocarditis, MI, and "no LGE" groups, respectively.

During hospitalization, 69% of patients were treated with β-blockers and 43% received angiotensin-converting enzyme inhibitors (ACEIs), with no difference observed between the different groups. At 1 year, only 13% of the patients were receiving either β-blockers or ACEIs, with a trend for higher rates of treatment seen in the MI group, though this difference was not statistically significant. Notably, no other antiarrhythmic drug than β-blockers was given at any time of the study.

The mean LVEF was 58.6% ± 8.2%. No significant differences were observed in either LVEF or LV end-diastolic volume between the groups. The "no LGE" group exhibited smaller LV end-systolic volumes than those of the MI and myocarditis patients. LV wall thickening was more often altered in the MI group. Moreover, the MI patients presented with higher rates of akinesia compared to the myocarditis and "no LGE" patients (58.8% vs 4.3% and 2.0%,  $P < 0.001$ ). Pericardial effusion was detected nonspecifically in 20 patients (15.4%) (Table 2).

During hospitalization, 18 patients experienced



**Figure 2** Pattern of late gadolinium enhancement. A: Incidence of late gadolinium enhancement (LGE) within each segment (percentage) of all patients, including those with and without LGE. In myocarditis cases, LGE was predominantly on the lateral wall. In myocardial infarction, no specific pattern of LGE could be identified; B: Representative short-axis slice images showing LGE location; C: Superimposed segmental models showing location and spatial extent of LGE (outlined).

a ventricular arrhythmic event, consisting of 17 VTs and one ventricular fibrillation (Tables 3 and 4). No differences were observed between the MI and the myocarditis groups ( $n = 9$ , 26.5% vs  $n = 6$ , 12.8%,  $P = 0.10$ ), whereas the MI patients exhibited higher rates of VT than the "no LGE" group ( $n = 2$ , 4.0%,  $P = 0.001$ ). All these events occurred in the early stages of hospitalization, with a median onset of 1 (0-1) d. One episode of ventricular fibrillation occurred in a myocarditis patient on day 3, who was successfully defibrillated. We found no differences in cardiovascular risk factor, CRP, coronary atheroma, or use of  $\beta$ -blockers and ACEIs in correlation with the ventricular events.

The transmural extent of LGE was more marked in the MI group ( $P < 0.001$ ). An LGE transmural extent  $> 50\%$  was observed in 32 patients (94.1%)

in the MI group, in contrast to 16 patients (34.0%) in the myocarditis group ( $P < 0.001$ ). LGE was more contained in the MI group, exhibiting lower transversal extents than the myocarditis group. Only eight patients (23.5%) were found to have more than two segments with LGE presence in the MI group, vs 27 (57.4%) in the myocarditis group ( $P = 0.002$ ).

Of note, the concordance among Cine and LGE data was higher in the MI group compared to the myocarditis group (88.2% vs 41.3%,  $P < 0.001$ ).

The multivariate analysis demonstrated that STE [OR = 5.72 (1.77-18.46),  $P = 0.004$ ] and LGE transmural extent [OR = 1.50 (1.02-2.20),  $P = 0.039$ ] were both independently related to ventricular events during hospitalization (Table 5). STE presented high sensitivity for the diagnosis of prolonged VT (83%), achieving a

**Table 2** Cardiac magnetic resonance parameters

	Total (n = 131)	MI (n = 34)	Myocarditis (n = 47)	"no LGE" (n = 50)	P
LVEF (%)	58.6 ± 8.2	57.1 ± 7.8	57.9 ± 8.6	60.2 ± 7.8	0.18
LVEDV (mL)	154.7 ± 37.7	158.8 ± 41	159.6 ± 28.6	147.3 ± 42.1	0.21
LVESV (mL)	64.5 ± 22.1	69.5 ± 25.5	67.1 ± 16.9	58.6 ± 22.9 <sup>2,3</sup>	0.048
LV wall thickening abnormality, n (%)	62 (47.3)	30 (88.2)	22 (46.8) <sup>1</sup>	10 (20.0) <sup>2,3</sup>	< 0.001
Hypokinetic extent, segments	1.1 ± 1.5	2 ± 1.6	1.2 ± 1.6 <sup>1</sup>	0.4 ± 1.1 <sup>2,3</sup>	< 0.001
0 segment, n (%)	69 (52.7)	4 (11.8)	25 (53.2)	40 (80.0)	
1-2 segments, n (%)	43 (32.9)	20 (58.8)	14 (29.8)	9 (18.0)	
> 2 segments, n (%)	19 (14.5)	10 (29.4)	8 (17.0)	1 (2.0)	
LGE transmural extent, segments	0.9 ± 0.8	3.6 ± 0.6	2.1 ± 0.9 <sup>1</sup>	0	< 0.001
< 50%, n (%)	83 (73.4)	2 (5.9)	31 (66.0)	0	
> 50%, n (%)	48 (36.6)	32 (94.1)	16 (34.0)	0	
LGE transversal extent, segments	1.9 ± 2.2	1.9 ± 1.3	3.5 ± 2.4	0 <sup>2,3</sup>	< 0.001
0 segment, n (%)	50 (38.2)	0	0	50 (100.0)	
1-2 segments, n (%)	46 (35.1)	26 (76.5)	20 (42.6)	0	
> 2 segments, n (%)	35 (26.7)	8 (23.5)	27 (57.4)	0	
LGE/CINE concordance, n (%)	49 (37.4)	30 (88.2)	19 (41.3) <sup>1</sup>	0	< 0.001
Pericardial effusion, n (%)	20 (15.3)	4 (11.8)	8 (17.4)	8 (16)	0.8

<sup>1</sup>P significant between MI and myocarditis groups; <sup>2</sup>P significant between MI and "no LGE" groups; <sup>3</sup>P significant between myocarditis and "no LGE" groups. MI: Myocardial infarction; LGE: Late gadolinium enhancement; LV: Left ventricle; LVEDV: Left ventricular end diastolic volume; LVESV: Left ventricular end systolic volume; LVEF: Left ventricular ejection fraction.

**Table 3** Acute event rates

	All patients (n = 131)	MI (n = 34)	Myocarditis (n = 47)	"No LGE" (n = 50)	P
Ventricular event, n (%)	18 (13.8)	9 (26.5)	7 (14.9)	2 (4.0) <sup>1</sup>	0.013
VT, n (%)	17 (13.0)	9 (26.5)	6 (12.8)	2 (4.0) <sup>1</sup>	0.011
Prolonged VT or VF, n (%)	8 (6.1)	4 (11.8)	4 (8.5)	0 <sup>1</sup>	0.06
VF, n (%)	1 (0.8)	0	1 (2.1)	0	0.41

<sup>1</sup>P significant between MI and "no LGE" groups. MI: Myocardial infarction; LGE: Late gadolinium enhancement; VF: Ventricular fibrillation; VT: Ventricular tachycardia.

specificity of 77% and negative predictive value of 92%. At 1 year, no patients presented with sudden cardiac death or recurrence of symptomatic ventricular event. One patient died of cancer.

## DISCUSSION

The key point of the study is to demonstrate that none of the patients presenting with MINOCA and normal LVEF died of cardiovascular death or sudden cardiac death following the initial phase of hospitalization. ST segment elevation and LGE extent were the best predictors of in-hospital ventricular arrhythmic events, irrespective of the etiology.

During hospitalization, 13.8% of the patients experienced a ventricular arrhythmic event, primarily consisting of VT, with one case of ventricular fibrillation. Most of these events occurred during the first 48 h following symptom onset. These results are consistent with the literature, with previous reports of similar rates of early arrhythmic outcomes among patients with MINOCA<sup>[7,12-14]</sup> or in cases of myocarditis<sup>[15]</sup>. Our study demonstrated that, in the absence of decreased LVEF, MI and myocarditis patients are affected by the same arrhythmic risks. Following the initial phase of the disease, where the risk of ventricular arrhythmia is

present, the arrhythmic risk appears very low.

The initial arrhythmic risk of myocarditis is well known and studies have shown that in patients < 35 years, myocarditis was the second most common identified cause of sudden cardiac death after coronary artery disease<sup>[16]</sup>.

Our study demonstrated that STE is an independent predictor of ventricular arrhythmia at early-stage disease, achieving a good negative predictive value of 92% for prolonged VT. Data on the prognostic role of ECG abnormalities are currently scarce. This finding was assumed to be in relation to the transient character of the ST changes in myocarditis<sup>[17]</sup>, as well as the weak relationship between STE and LGE localization<sup>[17,18]</sup>.

The adverse prognostic value of LGE-CMR in ischemic and non-ischemic cardiomyopathy has been proven in patients with reduced LVEF<sup>[19]</sup>. Conversely, Grün *et al.*<sup>[20]</sup> demonstrated a relevant cardiac mortality of 15% in 203 patients with myocarditis, which was primarily driven by the presence of LGE. Nevertheless, a large proportion of their patients presented with heart failure and decreased LVEF. In another report of fewer selected patients with suspected myocarditis, LGE was found in only 28% of cases, and LGE and LVEF were defined as predictors for a composite of cardiac death and heart failure<sup>[15]</sup>. In our study, considering the

**Table 4 Acute event characteristics**

Patient	Gender	Age (yr)	ECG	Troponin (µg/L)	LVEF (%)	Diagnosis	LGE transmural extent <sup>1</sup>	β-blocker use	ACEI use	VT	VF	CMR delay (d)	Ventricular arrhythmia length
13	Male	39	STE	0.3	51.7	MI	4	1	0	1	0	1	10 VPBs
52	Male	45	Normal	0.4	57.7	MI	3	0	0	1	0	1	10 VPBs
53	Female	30	STE	17.3	45.5	MI	4	1	1	1	0	0	30 VPBs
63	Male	51	Normal	0.3	57.8	MI	3	1	1	1	0	1	6 VPBs
64	Male	56	STE	1.6	61.2	MI	4	1	1	1	0	1	15 VPBs
75	Male	32	STE	0.8	63.2	MI	4	1	0	1	0	0	7 VPBs
92	Male	57	STD	0.4	48.1	MI	3	1	0	1	0	0	6 VPBs
128	Female	55	STD	0.6	49.8	MI	4	1	1	1	0	1	5 VPBs
97	Male	83	STD	0.2	46.5	MI	2	1	1	1	0	0	6 VPBs
3	Male	45	STE	0.1	66.9	Myocarditis	3	1	0	1	0	2	9 VPBs
37	Male	40	STE	4.8	56.1	Myocarditis	2	0	1	1	0	2	5 VPBs
44	Male	25	STE	36.6	65.7	Myocarditis	3	0	0	0	1	3	VF
94	Male	28	STE	1.4	57.1	Myocarditis	2	1	0	1	0	0	4 VPBs
76	Male	53	STE	1.4	69.6	Myocarditis	2	1	1	1	0	0	7 VPBs
104	Female	42	STE	21.2	57.1	Myocarditis	4	1	0	1	0	1	13 VPBs
131	Female	31	STD	0.6	51.7	Myocarditis	1	1	0	1	0	1	8 VPBs
80	Male	34	STE	0.4	53.1	No LGE	0	0	1	1	0	0	7 VPBs
125	Male	56	Normal	0.1	62.4	No LGE	0	1	1	1	0	4	3 VPBs

<sup>1</sup>LGE transmural extent: 0 = 0%, 1 = 0%-25%, 2 = 25%-50%, 3 = 50%-75%, and 4 > 75%. LGE: Late gadolinium enhancement; ECG: Electrocardiography; LVEF: Left ventricular ejection fraction; STD: ST-segment depression; STE: ST-segment elevation; VT: Ventricular tachycardia; VF: Ventricular fibrillation; VPBs: Ventricular premature beats; MI: Myocardial infarction; ACEI: Angiotensin-converting enzyme inhibitor.

**Table 5 Univariate and multivariate analysis for ventricular arrhythmia**

	Univariate analysis		Multivariate analysis	
	Odds ratio (95%CI)	P	Odds ratio (95%CI)	P
STE	4.65 (1.61-13.40)	0.004	5.72 (1.77-18.46)	0.004
STD	-	0.06	-	-
T-wave inversion	-	0.99	-	-
Troponin	1.10 (1.02-1.20)	0.02	-	0.27
Hypokinetic extent	-	0.09	-	-
LGE transmural extent	1.52 (1.08-2.15)	0.017	1.50 (1.02-2.20)	0.039
LVEF	-	0.31	-	-
LVEDV	-	0.3	-	-
LVESV	-	0.17	-	-
Pericardial effusion	-	0.24	-	-
Coronary atheroma	-	0.68	-	-
CMR diagnosis	-	0.12	-	-
MI or myocarditis	0.17 (0.04-0.77)	0.022	-	-

LVEDV: Left ventricular end-diastolic volume; LVESV: Left ventricular end-systolic volume; LVEF: Left ventricular ejection fraction; STD: ST-segment depression; STE: ST-segment elevation; MI: Myocardial infarction; CMR: Cardiac magnetic resonance.

excellent prognosis of the population, we have found that LGE is not useful for evaluating cardiac outcomes.

Despite this, however, the transmural extent of LGE was identified as an independent predictor for ventricular arrhythmia during the acute phase of the disease. This could therefore be of great value, if performed very early after the hospitalization, to identify at-risk patients requiring special attention and perhaps more prolonged rhythmic monitoring.

In our study, CMR imaging provided etiological diagnosis in 81 patients (61.8%), which is consistent with previous reports<sup>[21,22]</sup>. Clinical evaluations including

biopsy have demonstrated that myocarditis could be present in patients with normal CMR results in 32% to 47% of cases<sup>[20,23]</sup>. It is likely that the frequency of myocarditis was underestimated in our study, especially in the “no LGE” group, as suggested by the CRP levels that were similar to those with myocarditis. It has been suggested that global LV involvement in myocarditis may be the cause of LGE absence<sup>[24]</sup>.

The choice of medical management strategy for these patients remains controversial. There is little data, which is also conflicted, on the use of a secondary prevention treatment involving at least β-blockers in patients affected by myocarditis mimicking acute MI<sup>[25]</sup>. In our cohort, 69.5% of the patients received β-blockers during hospitalization, reflecting the management of a recent MI. Regarding the relatively-high percentage of patients who experienced ventricular arrhythmia, there is no doubt that this treatment is of interest during this period of time.

In our study, the absence of sudden cardiac death at 1 year suggests that β-blockers should not be continued over the long term, even if the β-blocker treatment had already been stopped in most of the population, with only one myocarditis patient still undergoing treatment. The need to prolong the treatment immediately after the hospital discharge is, however, a more controversial topic. LGE and ST segment elevation may represent valuable tools to stratify the risk of these patients and select those eligible for secondary prevention therapy.

The first limitation of our study was the sample size, which was too small to detect any statistical difference between the myocarditis group and the MI group. Secondly, the retrospective study design also, evidently, posed a limit. Finally, no systematic rhythm

monitoring was organized to screen the last recurrence of ventricular events after discharge. Similarly, the therapeutic management that may be chosen based on such preclinical events was left to the discretion of the referring cardiologist, and the use of  $\beta$ -blockers or ACEIs was extremely low at follow-up (12.2% and 13.0%, respectively). Nevertheless, none of our patients presented with sudden cardiac death or severe arrhythmia during follow-up. We must also admit that prognosis may differ by ethnicity but are not stressed in our study.

In conclusion, our study indicated that patients with MINOCA and normal LVEF did not present any 1-year CV events, particularly no sudden cardiac death, after hospital discharge. Most of them had even stopped treatment at 1-year follow-up.

STE on admission and LGE transmural extent appear to be good markers for identifying patients at risk of ventricular events in the early stages of disease.

## COMMENTS

### Background

About 1%-12% of patients with chest pain and cardiac troponin elevation present with normal coronary arteries on angiography analysis. While the arrhythmic prognosis of myocardial infarction with abnormal coronary angiography is well known, there is little data concerning myocardial infarction with non-obstructive coronary arteries (MINOCA). This study sought to evaluate the risk of ventricular arrhythmias of presumed low-risk MINOCA patients, based on the diagnosis class established by cardiac magnetic resonance (CMR) imaging.

### Research frontiers

Numerous patients are affected by MINOCA, and yet prognosis is expected to be favorable as soon as left-ventricular ejection fraction (LVEF) is good. Nevertheless, the mere presence of a myocardial injury/scar/fibrosis, let us empirically dare for the occurrence of ventricular arrhythmia.

### Innovations and breakthroughs

CMR was used systematically to identify MINOCA's aetiology, but also to assess myocardial injury and its extent. Continuous electrocardiography was also systematically performed to solve the question of arrhythmic risk during the first days after symptoms onset. It was continued by a one-year clinical follow-up. Nevertheless, this study does not focus on medical therapy, including the effect of  $\beta$ -blockers on ventricular arrhythmia.

### Applications

This study provides evidence on the good prognosis (including arrhythmic events) presented by patients with MINOCA and preserved LVEF. When ventricular arrhythmias occurred, they correlated with myocardial injury, as assessed by transmural late gadolinium enhancement (LGE) by CMR. Therefore, this study provides reassuring data about survival but also point out the need to stress the effect of antiarrhythmic therapies on the newly-identified risk markers that are LGE and ST segment elevation.

### Terminology

MINOCA is a recent terminology that relates to ischemic injuries, myocarditis, tako-tsubo cardiomyopathy, hypertrophic cardiomyopathy, dilated cardiomyopathy, and other causes such as pericarditis and amyloidosis.

### Peer-review

This paper is interesting, novel, and an overall well-conducted study. It provides a timely study on this field.

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## Prospective Study

## Children with transposition of the great arteries: Should they actually be born in Nigeria?

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### Abstract

#### AIM

To describe the clinical and echocardiographic features of Nigerian children with transposition of the great arteries and emphasize the need for collaboration with cardiac centres in the developed countries to be able to salvage the children.

#### METHODS

Prospective and cross sectional involving consecutive patients diagnosed with transposition of the great arteries using clinical evaluation and echocardiography at the Paediatric Department of Lagos State University

Teaching Hospital, Lagos Nigeria as part of a large study between January 2007 and December 2015.

### RESULTS

There were 51 cases of transposition of the great arteries within the study period with a male to female ratio of 2:1 and a prevalence of 1.55 per 10000 among population of children who presented to centre during the study. Its proportion amongst children with congenital heart disease was 4.9%, while it was 15.4% among those with cyanotic congenital heart disease. The mean age  $\pm$  SD of the subjects was 10.3  $\pm$  21.8 mo. Up to 70% of the patients were less than 6 mo of age at initial presentation. The most common mode of presentation was cyanosis. The most common associated intracardiac anomaly was ventricular septal defect which occurred in 56% of the patients.

### CONCLUSION

Transposition of the great arteries is as common in Nigeria as in the other parts of the world. The most common mode of presentation was cyanosis. There is an urgent need to establish paediatric cardiac centres in Nigeria if these children are to be salvaged.

**Key words:** Transposition; Cyanosis; Children; Salvage; Nigeria

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**Core tip:** Transposition of the great arteries is as common in Nigeria as in the other parts of the world. The most common mode of presentation in our subjects was cyanosis. Palliative and definitive interventions are currently not available for them in Nigeria. A lot of lives are being wasted yearly because of unavailable and inaccessible surgical care.

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### INTRODUCTION

Transposition of the great arteries (TGA) affects children of all races as documented earlier<sup>[1,2]</sup> and African children are no exception<sup>[3,4]</sup>. Advance surgical techniques to manage children with congenital heart lesions is still in infancy stage in Nigeria<sup>[5,6]</sup>. That notwithstanding, cases of TGA are seen and managed within the available limitations. There are only very few reports on TGA in Africa especially from sub-Saharan Africa. At best TGA is only mentioned as part of other congenital heart disease or as case reports. There has been no report on cohorts of children with

TGA in West Africa. This article will describe the pattern and presentation of children diagnosed with TGA and the management and outcome of such patients in a tertiary hospital in sub-Saharan Africa. This is to make data available on these group of subjects for reference purpose for future research in the region, create awareness on TGA among health professionals in the region and for advocacy on the urgent need to establish paediatric cardiac centres in Nigeria so that these children can be salvaged, especially the need for collaboration with established paediatric cardiac centres in the developed countries in order to improve the outcome of children born with TGA in the West Africa region through early diagnosis and prompt intervention.

### MATERIALS AND METHODS

This was a review of prospectively collected data of all patients less than 13 years of age diagnosed with TGA using echocardiography at the Paediatric Department of Lagos State University Teaching Hospital Lagos Nigeria between January 2007 and December 2015.

The hospital is a tertiary institution in Southwestern Nigeria and receives referral from the region. Patients with suspected cardiac lesion are referred to the department for evaluation from within the state and sub-region. A paediatric cardiologist is in charge of the cardiology unit. Patients referred to the cardiology unit of the department are evaluated with chest radiograph, electrocardiography other ancillary investigations as required including echocardiography.

One echocardiography machine was used on all the subjects throughout the study period, a GE Vivid Q echocardiography machine reference number 14502 WP SN 2084. It has facility for two dimensional, M-mode and color flow Doppler imaging. The paediatric cardiologist performed the echocardiography on all the subjects.

Definitive diagnosis is based on echocardiography which demonstrates the characteristic bifurcation of the pulmonary artery arising posteriorly from the left ventricle in the parasternal long axis view and the aorta anterior and to the right of the pulmonary artery. Other associated cardiac anomalies such as the atrial septal defect (ASD), ventricular septal defect (VSD), patent ductus arteriosus, double outlet right ventricle (DORV), pulmonary stenosis (PS) and abnormal coronary arteries were documented for all the patients. A diagnosis of TGA was made based on the combination of clinical signs and symptoms, with or without a chest radiograph features described above with the characteristic echocardiographic features<sup>[7,8]</sup>.

All the patients were followed up at the paediatric cardiology clinic. Surgical correction was required by all the subjects but this is not available in Nigeria and thus the patients were referred outside Nigeria for the correction. The patients who had surgical correction were referred back to the unit after the correction and they were followed up in the unit.

The data were imputed in a personal laptop and

**Table 1** Yearly incidence and percentage of transposition of the great arteries amongst the congenital heart disease

Year	Total patients seen	Patients with CHD (n)	Patients with TGA (n)	Prevalence of TGA amongst CHD (%)	Prevalence of TGA per 10000 children
2007	47343	87	1	1.15	0.21
2008	49387	119	8	6.72	1.62
2009	49141	90	2	2.22	0.41
2010	36400	103	14	13.59	3.84
2011	37404	153	6	3.92	1.60
2012	28475	143	4	2.79	1.40
2013	32220	180	6	3.33	1.86
2014	32800	108	7	6.48	2.13
2015	13492	140	3	2.14	2.22
Total	326662	1123	51	4.54	1.56

TGA: Transposition of the great arteries; CHD: Congenital heart disease.

analysed using Statistical Package for Social Sciences version 20. The children's age, sex, indication for echocardiograph, echocardiographic findings and outcome and were documented. Tables and charts were used to depict those variables. Means of continuous variables were compared using the Student *t* test, and proportions using  $\chi^2$  test. Level of significance set at  $P < 0.05$ .

## RESULTS

### Prevalence of TGA

Prevalence rates were based on 51 cases of TGA diagnosed between January 2007 and December 2015. A total of 326662 children were seen at the department during the study period and 1693 had echocardiography done. Of the 1693 who had echocardiography done, 1123 had congenital heart diseases (772 and 351 for acyanotic and cyanotic congenital heart defects respectively).

Table 1 shows the yearly distribution, prevalence of TGA and proportion of subjects with TGA amongst the cases of congenital heart disease. The prevalence of TGA within the study period was 1.55 per 10000 populations of children who present to the hospital. The percentage of TGA amongst children with congenital heart disease was 4.5% and 14.5% amongst those with cyanotic congenital heart disease.

### Clinical presentation

There were 51 cases of TGA within the study period. They comprised 34 males and 17 females with a male to female ratio of 2:1. The mean age of the children at initial presentation in month was  $10.3 \pm 21.8$  with a median age of 4 mo and a bimodal age of 1 and 4 mo. The mean age of the males was  $9.3 \pm 24.3$  while that of the females was  $12.2 \pm 16.8$  ( $P = 0.28$ ). The distribution of the age of the patients was the same across both sexes. The median age for the males and females was 3.5 and 5.5 mo respectively. The modal age for the males was 4 mo while that of the females was bimodal, 2 and

**Table 2** Ages at echocardiography and sex distribution of the patients

Age (mo)	Male	Female	$\chi^2$	<i>P</i>
0-6	25	11	2.0	0.36
6.1-12	4	2		
$\geq 12.1$	5	4		
Total	34	17		

$\chi^2 = 2.0$ ,  $P = 0.36$ .

6 mo. Up to 70% of the patients were less than 6 mo of age at initial presentation. The youngest patient was 14 d old while the oldest patient was 11 years old. Table 2 depicts the age distribution of the children at diagnosis.

All the children were ill at presentation. Forty-seven children were cyanosed while 4 were acyanosed at presentation. The indications for echocardiography are depicted in Table 3. In most cases there were more than one reasons/indication for echocardiography. All the study subjects had d-TGA. Other associated intracardiac anomaly are as highlighted in Table 4. The most common associated intracardiac anomaly was ventricular septal defect which occurred in 56% of the patients and this co-existed alone or in combination with other intracardiac connections.

### Treatment and outcome

The patients received anti-congestive agents and angiotensin converting enzyme inhibitors. Five patients had surgical intervention done outside the study centre. One patient had atrial switch and is doing well on follow up three years post surgery. The other four had arterial switch surgeries. One patient succumbed at the immediate post up period. Another died about two months' post surgery in a secondary centre. Another died about one-year post surgery secondary to a non-cardiac illness. The remaining patient is on followed up in the department eight-year post-surgery and is stable. The other patients who could not afford treatment succumbed while sourcing for funds to do surgery. More than 90% of the patients died at infancy, a few at about 14 mo of age. All the patients who had surgery were operated in India.

## DISCUSSION

TGA is the most common cyanotic congenital heart lesion in the newborn<sup>[9]</sup>. The Center for Disease Control (CDC) estimated that each year, 1901 babies in the United States are born with TGA or an approximate of 5 in 10000 babies born yearly with it<sup>[10]</sup>. It is present in 5%-7% of all patients with congenital heart disease<sup>[11]</sup>. There is a male predominance with a male to female ratio of 1.5:1 to 3:2<sup>[12-14]</sup>. The mortality in untreated patients is up to 50% in the first month and 90% by the end of the first year<sup>[7]</sup>. Maron *et al*<sup>[1]</sup> in the United States over four decades ago, documented that there was no racial difference in the frequency of TGA.

**Table 3** Indication for cardiac evaluation of the subjects

Indication	Frequency	% of all patients
Cyanosis	47	92
ACHD	4	7.8
Breathlessness	10	19.6
CCF	1	1.9
Stroke	1	1.9
Murmur	1	1.9
Failure to thrive	1	1.9
Suspected TGA	1	1.9
Dextro Cardia	1	1.9
Down syndrome	2	3.9

Some patients had more than one indication. ACHD: Acyanotic congenital heart disease; CCF: Congestive cardiac failure.

However, a more recent study by Botto *et al.*<sup>[2]</sup> in the same country documented a higher occurrence of TGA in whites compared to negroes. In 10% of cases of TGA association with noncardiac malformations have been documented<sup>[15]</sup>.

The aetiology is largely unknown. Associated risk factors include gestational diabetes mellitus<sup>[16,17]</sup>, maternal exposure to rodenticides and herbicides<sup>[18]</sup> and maternal use of antiepileptic<sup>[19]</sup>. Genetic mechanisms have been implicated and some genetic mutations have been implicated<sup>[20,21]</sup>.

The prevalence of TGA in this study was 1.55 per 10000 populations of children who presented to the hospital. This result is less than the CDC report of 5 in 10000 live births in the United States<sup>[12]</sup>. However the CDC report is a study on the proportions of live birth which is a different denominator compared to the present study. We have also documented the yearly prevalence of TGA. It was highest in 2010, 3.84 per 10000 children and lowest in 2007, 0.21 per 10000 children per year. Reasons why it may have been low in the first year is because the echocardiography machine was just made available and there was little awareness of its availability for evaluation of children with structural heart disease within the region. Thus there were little referral for cardiac evaluation at that time. The prevalence rate documented in this study may be a far cry from the actual prevalence rate because a lot of cases may have been missed in the neonatal period and early infancy for a number reasons. Firstly, prenatal cardiac evaluations are rarely done in Nigeria thus a sizeable number may have been missed at birth. Secondly, the clinical presentation of TGA is non-specific and thus a number of cases may have been ill and in the absence of proper evaluation with a high index of suspicion of a congenital heart disease some babies may have be managed for other morbidities and died without a cardiac evaluation. Thirdly, because of cultural practices prevalent in the region, infants who died before a proper evaluation was done may not have autopsy done to confirm a suspicion of a congenital heart disease and TGA to be specific<sup>[22]</sup>.

TGA was documented in 4.5% of all congenital

**Table 4** Associated intracardiac connections in subjects

Cardiac anomaly	Frequency	% of all TGA
ASD	19	37.3
AVCD	3	5.9
DORV	10	19.6
HLH	1	1.9
PDA	15	29.4
PFO	2	3.9
PS	6	11.8
TAPVC	1	1.9
TOF	1	1.9
TR	3	5.9
VSD	27	52.9

Most patients had more than one intracardiac connections. TGA: Transposition of the great arteries; ASD: Atrial septal defect; AVCD: Atrioventricular canal defect; DORV: Double outlet right ventricle; HLH: Hypoplastic left heart; PDA: Patent ductus arteriosus; PFO: Patent foramen ovale; TAPVC: Total anomalous pulmonary venous connections; TOF: Tetralogy of fallot; TR: Tricuspid regurgitation; VSD: Ventricular septal defect.

heart disease within the study period. Two decades ago, Jaiyesimi *et al.*<sup>[23]</sup> in UCH Ibadan documented a prevalence rate of 4.8% in cardiac lesions which is similar to findings in the present study. International rate of TGA amongst all congenital heart lesion is 5%-7%<sup>[14]</sup> and this is also similar to the value documented in the present study. We also documented a male predominance in TGA with a male to female ratio of 2:1. This is consistent with international ratio of 1.5:1-3.2:1<sup>[12-14]</sup>.

The mean age of the children with TGA was 9.3 ± 24.3. The mean age was not different in both sex. The youngest child was 2 wk and the oldest was 11 years old. Although 70% of the patients were ≤ 6 mo old there were three patients who were three, six and eleven years old and those values significantly affected the mean age and resulted in a large standard deviation. In an earlier study by Adegboye *et al.*<sup>[4]</sup> in Ibadan, southwestern Nigeria, the mean age of the children with TGA who underwent palliative surgery was 6.8 ± 2.4. The mean age recorded in Ibadan was not significantly different from that documented in this study although the subjects were fewer in the later study. In contrast, in advanced countries, diagnosis of TGA is made in neonatal period.

Patients with TGA present with central cyanosis from the first month of life with varying clinical manifestation based on the degree of mixing between the two circulations<sup>[17]</sup>. Patients with a large ventricular septal defect and or a patent ductus arteriosus (PDA) may present early with congestive cardiac failure. Long term complications are secondary to cyanosis. A definitive diagnosis of TGA is made with an echocardiogram<sup>[8]</sup>.

The most common mode of presentation in our subjects was cyanosis and some patients presented with more than one presentation. This is not an unusual finding as the signs and symptoms of TGA varies depending on the associated intracardiac lesion<sup>[8]</sup>.

Cyanosis may go unnoticed in some patients with large ventricular septal defects without right outflow. Similarly, 8% of our study subjects were not cyanosed at presentation and one had congestive cardiac failure.

Complications from cyanosis and polycythemia may occur especially in untreated cases. One of the subjects was a 3.25-year-old male who had been cyanosed from infancy, he presented to the hospital for the first time with cerebrovascular accident and cardiac evaluation revealed a TGA.

D-TGA is the common form of TGA worldwide and all our study subjects had d-TGA. Simple TGA is not compatible with extra-uterine life except there are intracardiac connections for admixture of blood<sup>[24,25]</sup>. All our subjects had intracardiac connections and not surprisingly the most common was a VSD which occurred either alone or in combination with other intracardiac lesions. ASD was the second most common closely followed by a PDA in 37.3% and 29.4% respectively. Left ventricular outflow obstruction may occur in one eighth to a third of patients with TGA. We report in this study 12.5% of cases of pulmonary stenosis and all but one of those subjects had an associated VSD while the other patient had an atrioventricular canal defect. Other complex lesions documented in this study are TOF, hypoplastic left heart, TAPVC, DORV and tricuspid atresia.

TGA is known to be associated with other congenital disorder in 10% of cases<sup>[6]</sup>. Sporadic association of TGA with trisomy 8, 18, VACTERL and CHARGE syndrome have been documented<sup>[26,27]</sup>. Two (3.9%) of our subjects had Down syndrome and the others had no dysmorphologies.

Treatment of patients with TGA is both medical and surgical. Initial palliative care is instituted to achieve optimal intercirculatory mixing and optimize the clinical condition<sup>[7,18]</sup>. Mechanical ventilation and oxygen may be needed for unstable infants, correction of metabolic acidosis and administration of prostaglandin E<sub>1</sub> to maintain arterial duct patency<sup>[7]</sup>. Balloon atrial septostomy may be done to maintain admixture of blood at atrial level. Surgery provides the definitive treatment. It may be offered within the first month of life depending on the clinical setting. The arterial switch procedure can be done. Others include the Rastelli operation and Nikaidoh's procedure<sup>[8]</sup>.

In the current study, all our patients required definitive surgical corrections which is currently not available in Nigeria. Only three (5.9%) could afford to do corrective surgery outside Nigeria. Three patients presented within the first two weeks of life and all three had a PDA with either a VSD or an ASD. They required palliative surgery but could not afford one. Almost 90% of the patients could not access the much needed surgical care and succumbed before help could be provided. This was not surprising because the case fatality rate for TGA is as high as 50% by the end of the first month and 90% at one year for untreated cases. These are largely preventable deaths if diagnosis can be made on time

and appropriate treatment instituted timely.

In conclusion, transposition of the great arteries is as common Nigeria as in the other parts of the world. The most common mode of presentation in our subjects was cyanosis. Palliative and definitive interventions are currently not available for them in Nigeria. A lot of lives are being wasted yearly because of unavailable and inaccessible surgical care. There is an urgent need to establish paediatric cardiac centres in Nigeria so that these children can be salvaged. Collaboration is needed from established paediatric cardiac centres from developing and developed world if this is to be achieved.

## ACKNOWLEDGMENTS

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## COMMENTS

### Background

Transposition of the great arteries (TGA) affects children of all races as documented earlier including African children. Prompt and advance surgical intervention needed to salvage these children is currently not available in Nigeria.

### Research frontiers

Arterial switch is one of the surgical option for correction of TGA is preferable done during the neonatal period.

### Innovations and breakthroughs

This article described pattern and presentation of children diagnosed with TGA and the management and outcome of such patients in a tertiary hospital in sub-Saharan Africa. Data on these group of subjects has been provided by this study for reference purpose.

### Applications

The data provided in this study is useful for, future research in the region on the subject, awareness creation on TGA among health professionals in the region, for advocacy on the urgent need to establish paediatric cardiac centres in Nigeria if these children can be salvaged, especially the need for collaboration with established paediatric cardiac centres in the developed countries in order to improve the outcome of children born with TGA in the West Africa region through early diagnosis and prompt intervention.

### Terminology

TGA is a congenital heart anomaly that occurs when the two main arteries of the heart, aorta and pulmonary arteries, are switched in position so that the aorta arises from the right ventricle and the pulmonary artery from the left ventricle. Other names or synonyms used to describe TGA are: Physiologically uncorrected transposition, complete transposition and atrioventricular concordance with ventriculoarterial discordance. TGA is classified based on the spatial relationship between the great arteries to each other and or the infundibular morphology. dextro-TGA (D-TGA) is when the aorta is anterior and to the right of the pulmonary artery and it is the most common form. levo-TGA (L-TGA) describes the aorta that is anterior and to the left of the pulmonary artery. Furthermore, irrespective of either the L- or D-TGA, the patients may still have a subaortic infundibulum, absence of a subpulmonary infundibulum and a fibrous continuity between the mitral and pulmonary valves. Aside the above classifications, different presentations and exceptions have been described. However, the unifying hallmark is the ventriculoarterial discordance. In TGA, the pulmonary and systemic circulations run in parallel rather than in series. Oxygenated blood flows through a closed circuit that involves the lungs and left

cardiac chambers, while deoxygenated blood also flows in a closed circuit that starts from the systemic circulation and ends in the right heart chambers. This parallel circulation is incompatible with prolonged survival, so there is usually admixture of blood through the atrial or ventricular septum and or a patent ductus arteriosus.

### Peer-review

The paper is well-written and provides an appropriate view about the current situation and future interventions.

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## Early stent thrombosis secondary to food allergic reaction: Kounis syndrome following rice pudding ingestion

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### Abstract

Kounis syndrome is the concurrence of coronary spasm, acute myocardial infarction or stent thrombosis, with allergic reactions in the setting of mast-cell and platelet activation. In this report Kounis syndrome manifesting as stent thrombosis with left ventricular thrombus formation was triggered by a food-induced allergic reaction. The allergic reaction to food was confirmed by oral rice pudding ingredients challenge test while skin tests were inconclusive. To our knowledge, this is first report of early stent thrombosis secondary to food allergic reaction in a 70-year-old man patient who was found to have left ventricular thrombus and undiagnosed hypertrophic cardiomyopathy.

**Key words:** Allergic myocardial infarction; Allergic reaction; Kounis syndrome; Stent thrombosis

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**Core tip:** Kounis syndrome highlights, the role of anaphylactic mediated acute coronary syndromes complicating stent thrombosis in the era of invasive treatment of coronary artery disease. Drugs, stings,

bites, contrast material, atopic diathesis and even food ingestion could be the culprits. Managing the complex pathophysiology of this condition is a challenging issue, especially in the emergency setting, that requires rapid treatment decisions. The role of detailed past history and of preventive anti-allergic medication in high risk patients with anaphylactic reactions should be considered in randomized studies.

Tzani G, Bonou M, Mikos N, Biliou S, Koniari I, Kounis NG, Barbetseas J. Early stent thrombosis secondary to food allergic reaction: Kounis syndrome following rice pudding ingestion. *World J Cardiol* 2017; 9(3): 283-288 Available from: URL: <http://www.wjgnet.com/1949-8462/full/v9/i3/283.htm> DOI: <http://dx.doi.org/10.4330/wjc.v9.i3.283>

## INTRODUCTION

Kounis syndrome is a variety of acute coronary syndromes triggered by the release of inflammatory mediators following an allergic insult<sup>[1]</sup>. Stent thrombosis is a rare, but serious, complication that is strongly associated with severe morbidity and mortality. Stent thrombosis associated with allergic mediated inflammatory reaction has been described as a serious manifestation of Kounis syndrome<sup>[2-4]</sup>. Several reports exist in the medical literature on patients with coronary stent implantation who developed stent thrombosis, concurrently with an allergic reaction manifesting as Kounis syndrome. Such reactions had been triggered by non anionic contrast material iopromide, flavonate-propylphenazone, non steroidal anti-inflammatory agent acemetacine, insect stings, snake bite and clopidogrel, the drug that is given itself to prevent stent thrombosis<sup>[5-10]</sup>. In the following report we describe a patient who suffered early stent thrombosis with left ventricular thrombus formation triggered by an allergic reaction following food consumption. To the best of our knowledge, this is the first case of early stent thrombosis associated with food-induced allergy reaction.

## CASE REPORT

A 70-year-old man smoker with a previous history of a transient ischemic attack, was referred to the emergency department of our hospital because of a pain to the left shoulder and arm that had started 4 d ago and was unresponsive to analgesics.

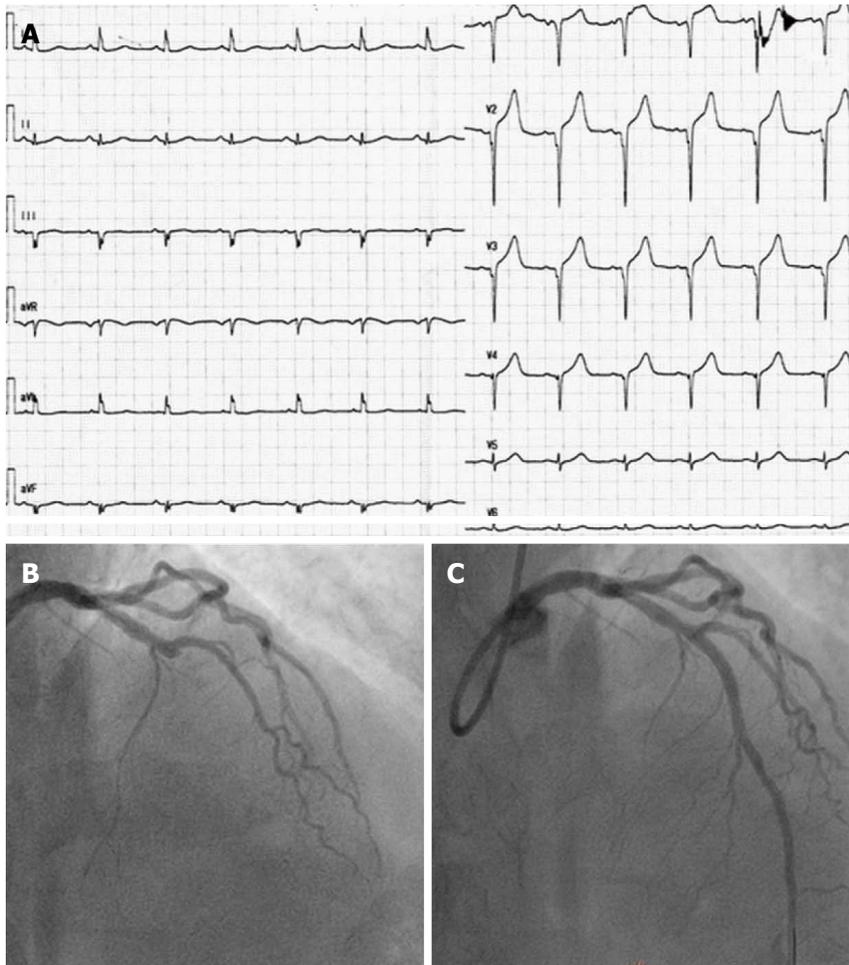
Upon admission, the electrocardiogram showed anteroseptal ST elevation myocardial infarction (Figure 1A) and transthoracic echocardiography revealed left ventricular hypertrophy, that was more pronounced at the interventricular septum, compatible with hypertrophic cardiomyopathy. Additional findings were an apical aneurysm, and moderate attenuation of systolic function. High sensitivity troponin I was elevated to

11037 ng/L. The patient was transferred to the coronary care unit and the next day coronary angiography revealed left anterior descending artery occlusion at the mid-level (Figure 1B). Subsequently, he was submitted to balloon angioplasty with placement of a drug-eluting stent (Resolute Integrity, 3 mm × 18 mm, Figure 1C). The patient remained asymptomatic and was discharged under optimal medical treatment including aspirin, clopidogrel, simvastatin, metoprolol, furosemide, lisinopril and eplerenone.

Four days later and about 20 min after taking his evening medication that was metoprolol and simvastatin and during ingestion of Greek rice pudding made of sheep milk, rice and sugar, the patient started gradually to develop lip swelling and itching followed by erythematous rash in all over his body. Within, approximately, 15 min he complained of chest pain and discomfort spreading to the left shoulder and arm. He was immediately transferred to the emergency department of our hospital. On arrival, the patient was covered in all his body with rash accompanied by itching and angioedema of the lips. The electrocardiogram showed ST elevation in V1-V4 leads (Figure 2A). Hydrocortisone and dimetindene maleate was given intravenously together with oral desloratadine and he was transferred to the catheterization laboratory, where coronary angiography revealed stent thrombosis with left anterior descending coronary artery occlusion (Figure 2B). The patient underwent thrombus aspiration that was followed by an additional stent placement (stent in stent procedure, drug eluting stent 3 mm × 16 mm, Figure 2C). However, mild chest pain remained for about 2 h and was attributed to "no reflow" phenomenon. Transthoracic echocardiography revealed, apart from hypertrophic cardiomyopathy with asymmetrical septal hypertrophy, also thrombus formation in an apical aneurysm (Figure 2E and F) necessitating heparin infusion. Contrast-echocardiography with SonoVue-Sulfur hexafluoride microbubbles revealed sessile apical thrombus (Figure 2F). Tryptase was elevated confirming an allergic reaction. The patient had an uneventful recovery and was scheduled for discharge after an allergology investigation.

### Oral food challenge test

In order to identify what had triggered the allergic reaction, skin prick tests were performed, under strict hemodynamic monitoring, for simvastatin and metoprolol that were the drugs the patient was taking after the first episode, and were inconclusive. Subsequently, it was decided to proceed to an oral food challenge test, again under strict hemodynamic monitoring, using the rice pudding ingredients that were sheep milk, rice and sugar according to the protocol described previously<sup>[11]</sup>. Following an initial amount of 0.6 g of sheep milk given slowly and 15 min after swallowing of 5 g of sheep milk the patient suddenly felt unwell, dizzy, started sweating, developed urticarial rash and complained of severe dyspnea. Soon after, he became



**Figure 1** First presentation with acute coronary syndrome. A: Electrocardiograph upon admission; B: Coronary angiography showing critical stenosis in left anterior descending; C: After implantation of resolute integrity drug-eluting stent.

disorientated and sleepy. On examination, he was pale with bronchospasm accompanied by hypoxemia (SpO<sub>2</sub> 82%), and sinus tachycardia (110/60 mmHg, 125 bpm), feeling itchy but without electrocardiographic changes. He was immediately treated with 250 mg hydrocortisone intravenously, 4 mg dimetindene maleate intravenously and 5 mg desloratadine orally with improvement in signs and symptoms. He gradually became stable and asymptomatic. Blood examinations, 10 min after onset of symptoms were performed for troponin, IgE antibodies and tryptase. Troponin was not increased, eosinophils were 70/ $\mu$ L, but IgE levels were increased to > 1000 IU/mL (normal values: 1-183 IU/mL). We did not proceed to challenge the patient with rice or sugar on ethical grounds, while the patient recalled that he was apprehended to sheep milk in the past.

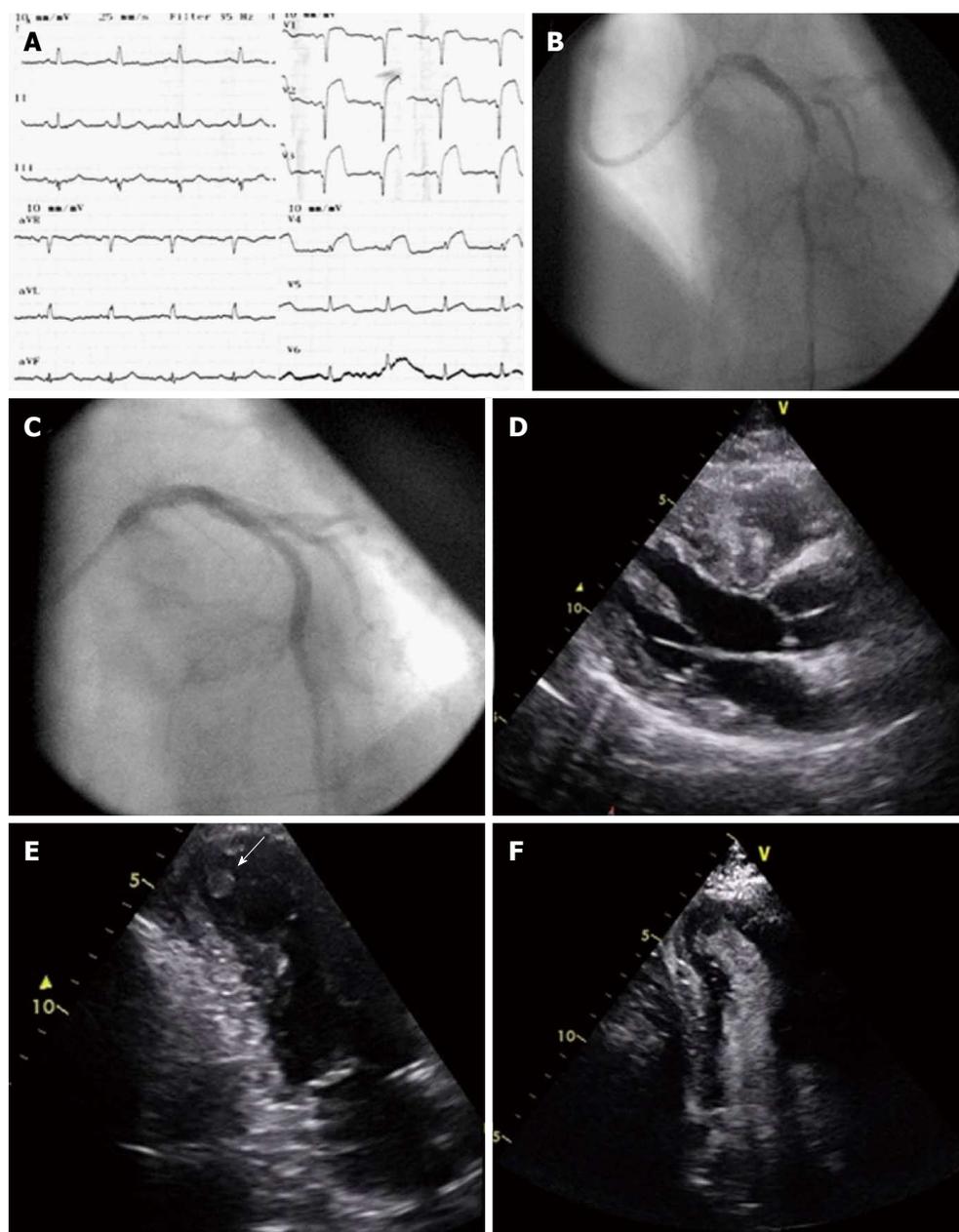
He had an uncomplicated hospital follow-up and was discharged with the advice neither to eat rice pudding nor to drink sheep's milk again.

## DISCUSSION

Acute myocardial infarction after a prolonged allergic reaction was firstly described in 1950<sup>[12]</sup>. However, a

detailed description of the allergic angina syndrome progressing to acute myocardial infarction was described in 1991 by Kounis *et al.*<sup>[13]</sup>. Three variants of Kounis syndrome have been described so far<sup>[14]</sup>: Type I that includes patients with normal coronary arteries in whom the acute release of inflammatory mediators can induce coronary artery spasm that could progress to acute myocardial infarction. Type II that includes patients with culprit and quiescent atheromatous disease in whom the acute release of inflammatory mediators may induce plaque erosion or rupture manifesting as acute myocardial infarction. The type III variant includes coronary artery stent thrombosis in the setting of allergic or hypersensitivity and anaphylactic or anaphylactoid insults. In this type, the thrombus is infiltrated by eosinophils and/or mast cells.

The patient was found to have a previously undiagnosed hypertrophic cardiomyopathy with septal hypertrophy and apical thrombus formation. Coexisting of hypertrophic cardiomyopathy with coronary spasm is not frequent and clinical characteristics in patients with both diseases have not been clarified yet. However, in a study of 36 patients with hypertrophic cardiomyopathy challenged with acetylcholine provocation test coronary



**Figure 2** Kounis syndrome following rice pudding consumption. A: Electrocardiograph upon admission; B: Coronary angiography showing stent thrombosis; C: After implantation of drug-eluting stent (stent in stent); D: Parasternal long axis view showing excessive hypertrophy of the septum; E: Thrombus in aneurysmatic apex, apical 2-chamber view; F: Contrast derived image, with thrombus in the apex, apical 2-chamber view.

vasospasm was induced in 10 (28%). The conclusion was that coronary vasospasm appears to play a significant role in the etiology of myocardial ischemia in patients with hypertrophic cardiomyopathy and smoking, as in our patient, might be a major risk factor for coexistence of coronary vasospasm<sup>[15]</sup>.

The apical thrombus formation could be attributed to pre-existing ischemic disease with aneurysmal dilatation of the apex. However, the activation of the thrombotic path during Kounis syndrome may have played an additional role. Indeed, platelet surface membrane contains, not only the well known receptors for thromboxane, adenosine diphosphate, IIb/IIIa but additional receptors for multiple exogenous agonists which contribute to platelet activation. These include

receptors for thrombin, serotonin, epinephrine collagen, platelet activating factor and histamine<sup>[16]</sup>. Additionally, a subset of platelets bear in their surface high and low affinity FC $\gamma$ RI, FC $\gamma$ RII, FC $\epsilon$ RI and FR $\epsilon$ RII IgE receptors<sup>[17]</sup> that are activated during hypersensitivity responses.

The anaphylactic reaction was confirmed during hospitalization with oral food consumption test and it was found that the patient was allergic to sheep milk. Tryptase levels were not elevated and this might be due to blood sample collection soon after the onset of symptoms, and according to tryptase kinetics these levels are found to elevate later<sup>[18]</sup>. Immunoglobulin E antibodies were highly elevated that explains the IgE-mediated allergic reaction. In a study comparing cow milk allergy with sheep and goat milk allergy, it was

found that the latter affects older children and appears at a later age. In sheep or goat milk allergic patients, the IgE antibodies recognize the caseins but not the whey proteins. Moreover, IgE specificity and affinity was high to sheep-goat milk and lower to cow milk caseins despite their marked sequence homology<sup>[19]</sup>.

Both physicians and susceptible individuals should be aware that high risk patients and patients with predisposition to allergies, especially allergy to sheep or goat milk require strict avoidance of such milk and milk derived products as reactions could be severe and life threatening. Vigorous anti-allergic medication and standardized treatment protocol is mandatory in order to prevent allergic insults and catastrophic cardiovascular adverse events.

## COMMENTS

### Case characteristics

A 70-year-old man with coronary artery disease who suffered early stent thrombosis with left ventricular thrombus formation triggered by a food-induced (sheep milk in rice pudding) allergic reaction and was found by oral food challenge test to be sensitized to sheep milk.

### Clinical diagnosis

Clinical diagnosis Kounis syndrome, complicating early stent thrombosis following Greek rice pudding consumption, in a patient with coronary artery disease and hypertrophic cardiomyopathy.

### Differential diagnosis

Acute coronary syndrome and anaphylactic shock. Both of them are the two sides of the same coin when investigating the complex pathophysiology of Kounis syndrome.

### Laboratory diagnosis

Increased cardiac enzymes, IgE antibodies and tryptase levels.

### Imaging diagnosis

Coronary angiography revealed stent thrombosis completely occluding left anterior descending artery. Echocardiography demonstrated left ventricular hypertrophy compatible with hypertrophic cardiomyopathy, an apical aneurysm and moderate attenuation of systolic function with thrombus formation in the apical aneurysm.

### Pathological diagnosis

In the acute setting of the coronary syndrome, no thrombus was kept for pathological analysis.

### Treatment

The patient underwent balloon angioplasty with placement of a drug-eluting stent in the acute setting of the stent thrombosis. In the second allergic reaction, during the allergic skin tests and the oral food challenge test, he was treated with hydrocortisone, dimetindene maleate and desloratadine with improvement in signs and symptoms of the allergic reaction.

### Related reports

To our knowledge, this is the first report of Kounis syndrome with the clinical manifestation of early stent thrombosis after food allergic reaction.

### Experience and lessons

Kounis syndrome is "a new twist on an old disease", which is frequently misdiagnosed. The early diagnosis could improve patients' outcome and prognosis, while original randomized studies could investigate the role of

preventive anti-allergic medication in high risk patients with anaphylactic reactions.

### Peer-review

This manuscript is well-written and an interesting case report with addressing type III Kounis syndrome (anaphylactic reaction) induced by food allergy.

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## Importance of a second spasm provocation test: Four cases with an initial negative spasm provocation test

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**Author contributions:** Teragawa H wrote the manuscript; Fujii Y, Uchimura Y and Ueda T collected and evaluated the data.

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### Abstract

The spasm provocation test (SPT) is an important test in the diagnosis of vasospastic angina (VSA). In many cases, this test is performed as the gold standard test, and VSA is considered not present if the SPT is negative. However, some patients continue to experience chest symptoms despite a negative SPT. In this study, we report four cases in which SPT was repeated to evaluate chest symptoms despite the negative results of the first SPT. Two men in their 70s, one woman in her 60s, and one woman in her 70s, all with chest symptoms, underwent a second SPT at 4, 3, 2, and 3 years, respectively, after the first SPT, which was negative. Three patients had positive results in the second SPT (75%). In conclusion, even when SPT is negative, the diagnosis of VSA should be made with clinical symptoms in consideration. In some cases, a second SPT may be required to confirm the diagnosis of VSA.

**Key words:** Coronary spasm; Acetylcholine; Spasm provocation test; Pressure wire

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**Core tip:** The spasm provocation test (SPT) is an important examination when diagnosing vasospastic angina (VSA). In general, if the SPT is negative, VSA is considered not present. However, we encountered four patients who underwent a second SPT although the first SPT was negative. In these patients, some show a positive second SPT result. SPT is not a perfect examination, and in the clinical setting, the diagnosis of VSA should be made with the consideration of their clinical symptoms and examinations.

Teragawa H, Fujii Y, Uchimura Y, Ueda T. Importance of a second spasm provocation test: Four cases with an initial negative spasm provocation test. *World J Cardiol* 2017; 9(3): 289-295

## INTRODUCTION

Coronary spasm is characterized by transient vasoconstriction of the epicardial coronary artery, leading to myocardial ischemia. Coronary spasm is the cause of not only typical rest angina but also exertional angina, acute myocardial infarction, and sudden cardiac death<sup>[1,2]</sup>. Therefore, the diagnosis of vasospastic angina (VSA) should be made with certainty. VSA is diagnosed by the presence of chest symptoms accompanied by transient ST deviation on the electrocardiogram (ECG)<sup>[3,4]</sup>. This can, however, be difficult in the clinical setting because angina attacks do not necessarily occur during the one day of ECG monitoring or because ST changes are not always documented by ECG even in the presence of chest symptoms. In such cases, the spasm provocation test (SPT) can be used<sup>[3-5]</sup>. In the clinical setting, SPT is the gold standard examination to diagnose VSA. However, we observed some cases in which chest symptoms continued despite a negative SPT. Here, we report four such cases in which a second SPT was performed to evaluate chest symptoms despite negative results in the first SPT.

## CASE REPORT

At our institution, SPT is performed in the afternoon. Vasodilators are stopped 2 d before SPT. For SPT, acetylcholine (ACh) is usually used as the provocation drug, with 30 and 50  $\mu\text{g}$  for the right coronary artery (RCA) and 50 and 100  $\mu\text{g}$  for the left coronary artery (LCA). If the SPT results are negative with these doses, additional doses of ACh (80  $\mu\text{g}$  for the RCA and 200  $\mu\text{g}$  for the LCA) and/or ergonovine maleate (EM; 20, 40, and 60  $\mu\text{g}$  for the LCA) are sometimes added. A positive SPT is defined as the presence of transient vasoconstriction > 90% in response to intracoronary infusions of provocative drugs on coronary angiograms. The positive result is accompanied by the usual chest symptoms and/or ischemic ST deviations in the patient's ECG<sup>[3]</sup>.

### Case 1

A man in his 70s underwent an SPT because of chest pain at rest. His coronary risk factors were smoking (30 cigarettes per day for 30 years) and hypertension. The SPT showed negative results after intracoronary infusions of ACh with 50  $\mu\text{g}$  for the RCA and 100  $\mu\text{g}$  for the LCA (Figure 1A). Thereafter, he continued to experience chest pain at rest but did not seek further help for his chest symptoms. Four years later, he felt severe chest pain at rest in the early morning, which was relieved by sublingual nitroglycerin (NTG).

Therefore, he underwent a second SPT, which was positive for the RCA with an intracoronary infusion of 30  $\mu\text{g}$  ACh. The result was accompanied by the usual chest symptoms and ECG changes, despite negative LCA results after an intracoronary infusion of NTG (Figure 1B). At that time, we used a pressure wire inserted into the distal RCA. The distal intracoronary pressure /aortic pressure (Pd/Pa) decreased from 0.99 at baseline to 0.73 after the ACh infusion. He was diagnosed with VSA and discharged with a prescription for a calcium channel blocker (CCB).

### Case 2

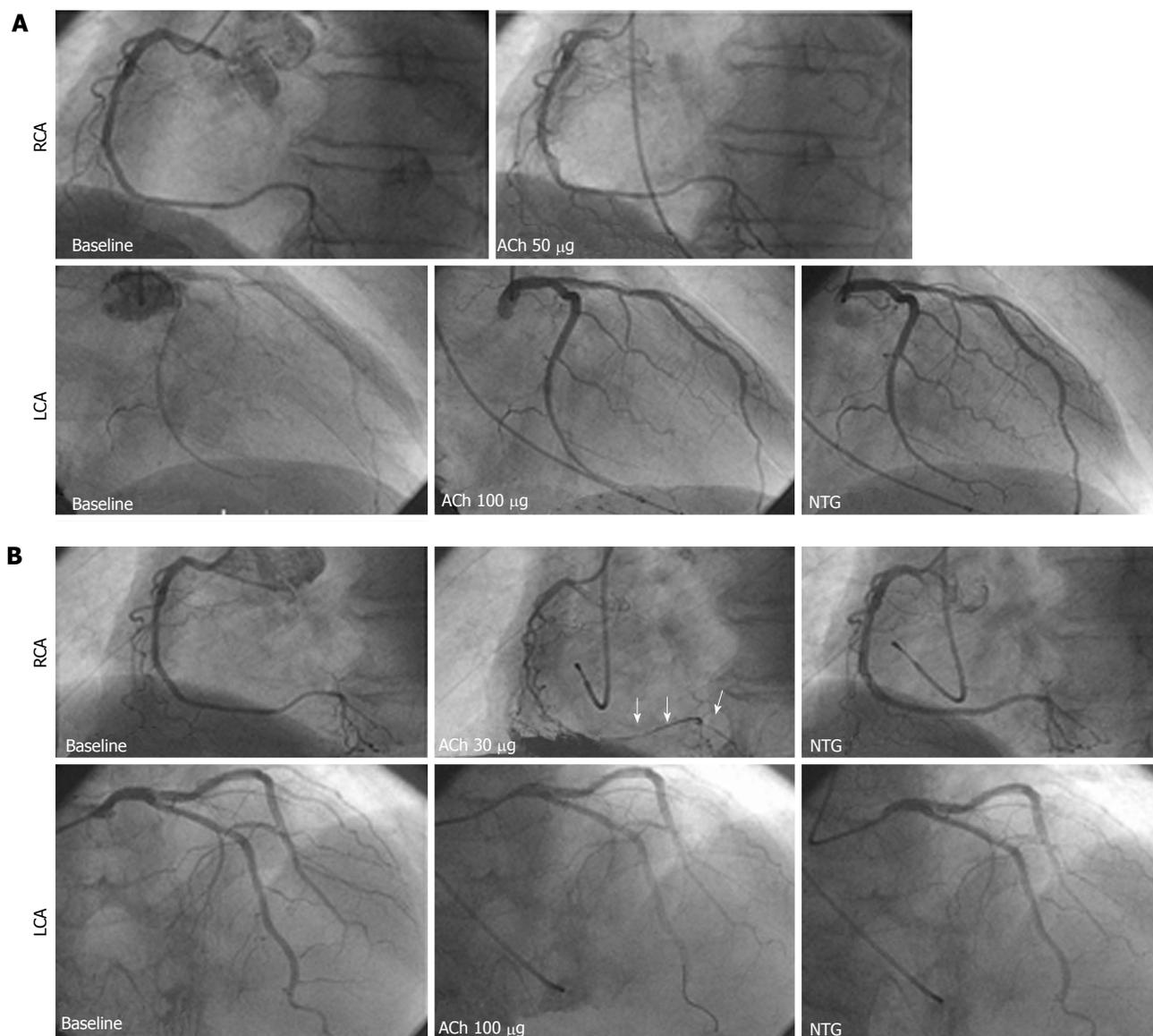
A male in his 70s underwent an SPT because of chest pain at rest, which occurred for 1-2 min and frequently 3-4 times/wk. He had no coronary risk factors. The SPT showed moderate vasoconstriction of the RCA after 50  $\mu\text{g}$  ACh and moderate vasoconstriction of the LCA after 100  $\mu\text{g}$  ACh (Figure 2A). However, he did not experience chest symptoms or ST deviation on ECG during the SPT. Hence, the SPT result was judged as negative. His chest symptoms continued thereafter, and he had severe chest pain at midnight 3 years later; therefore, he underwent a second SPT 3 years after the first SPT. The second SPT showed positive results for both the RCA after intracoronary infusions of 50  $\mu\text{g}$  ACh and the LCA after infusions of 100  $\mu\text{g}$  ACh (Figure 2B). The test was accompanied by the usual chest symptoms. The Pd/Pa decreased from 0.96 at baseline to 0.75 during the RCA spasm and from 0.93 at baseline to 0.74 during the left anterior descending coronary artery (LAD) spasm. He was diagnosed with VSA and was discharged with CCB medication.

### Case 3

A female in her 60s underwent an SPT due to 1-2-min chest pain at rest during the night. She had no coronary risk factors. The SPT showed negative RCA results after 50  $\mu\text{g}$  ACh and for the LCA after an intracoronary infusion of 100  $\mu\text{g}$  ACh (Figure 3A). Nevertheless, her symptoms continued. CCB did not help, and she underwent the second SPT 3 years after the first SPT. The second SPT showed negative RCA results after 80  $\mu\text{g}$  ACh and for the LCA after 200  $\mu\text{g}$  ACh (Figure 3B). The Pd/Pa did not change significantly, from 1.00 at baseline to 0.92 with 80  $\mu\text{g}$  ACh in the RCA and from 0.95 at baseline to 0.93 with 200  $\mu\text{g}$  ACh in the LAD. She was discharged with analgesic and anti-depressive medication.

### Case 4

A female in her 70s underwent an SPT to evaluate chest pain in the evening lasting for 1 min. Her coronary risk factors were hypertension and lipid disorder. The SPT showed negative RCA results after 50  $\mu\text{g}$  ACh and for the LCA after 100  $\mu\text{g}$  ACh (Figure 4A). Thereafter, her chest symptoms were infrequent, but she felt severe



**Figure 1** Coronary angiograms during the first and second spasm provocation test in case 1. A: The first spasm provocation test (SPT) showed negative results after intracoronary infusions of acetylcholine (ACh) with 50 µg for the right coronary artery (RCA) and 100 µg for the left coronary artery (LCA); B: The second SPT showed positive RCA results with an infusion of 30 µg ACh, accompanied by the usual chest symptoms and electrocardiogram changes, despite negative LCA results after an intracoronary infusion of nitroglycerin (NTG). Arrows indicate coronary spasm.

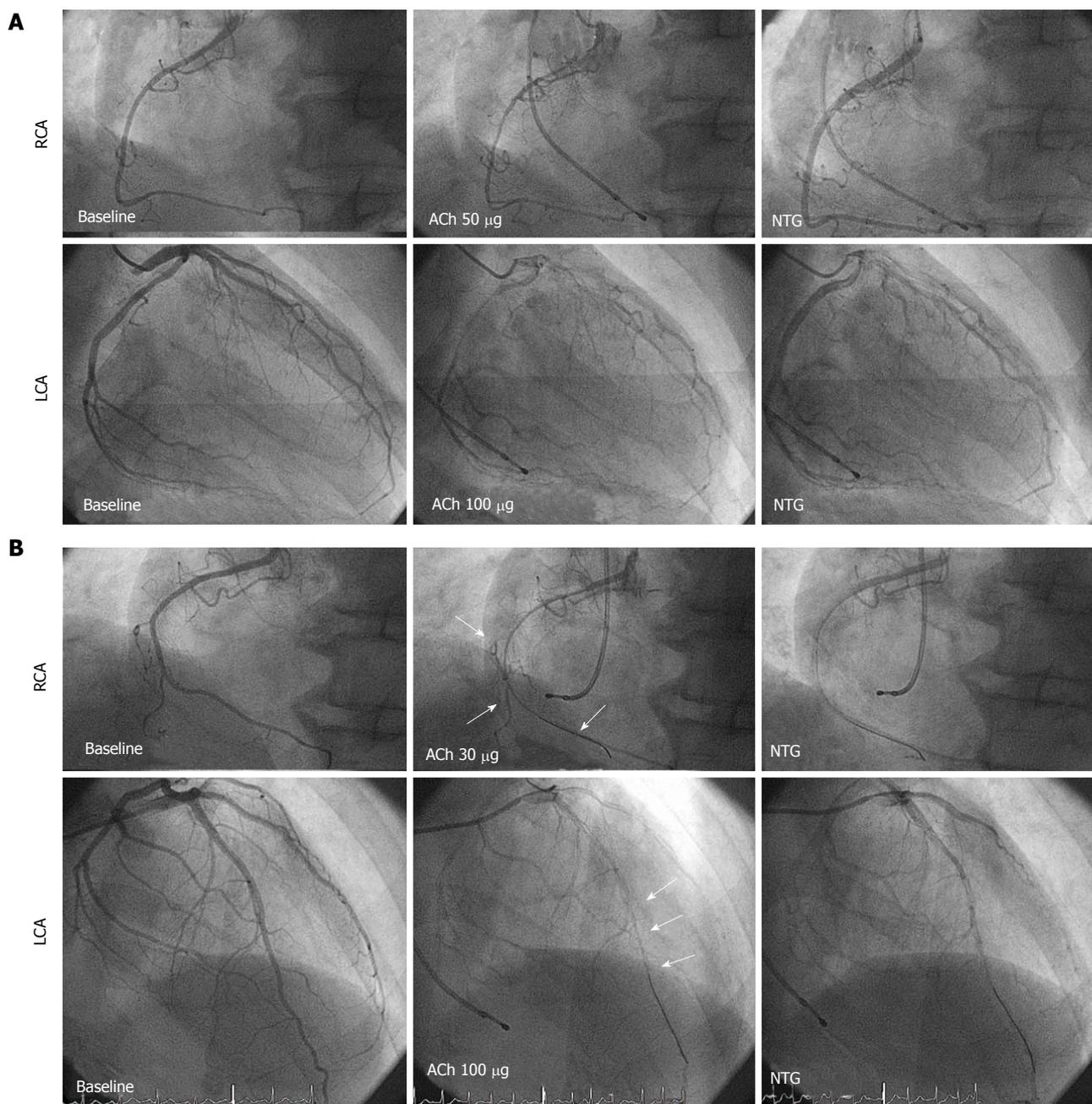
chest pain at rest 3 years later, when she presented at our institution for the second SPT. The second SPT showed negative RCA results after an intracoronary infusion of 50 µg ACh, and severe vasoconstriction at the distal LAD without chest symptoms and ECG changes after an intracoronary infusion of 100 µg ACh (Figure 4B). At the time, the Pa/Pa decreased from 0.90 at baseline to 0.73 after the ACh infusion. Based on the angiograms and pressure wire findings, she was diagnosed with VSA. She was discharged with CCB medication and has not experienced chest symptoms since.

In summary, there were three positive results from a second SPT (75%) of four cases that experienced chest symptoms and had negative results for the first SPT.

## DISCUSSION

In the present report, we present four patients who underwent a second SPT for the evaluation of chest symptoms, despite negative results from the first SPT. Of the four cases, there were three positive cases (75%). From these cases, we learned that SPT is not an absolute and final examination for diagnosing VSA.

SPT has been widely adopted as the final examination for the diagnosis of VSA. However, several factors may affect a positive SPT finding, such as VSA activity, time of day when the SPT is performed, and the duration of the withdrawal of vasodilators. VSA activity is variable, not only daily but also seasonally or yearly<sup>[3]</sup>, and this may contribute to the difference in SPT results. According to the time spent performing the SPT, it may

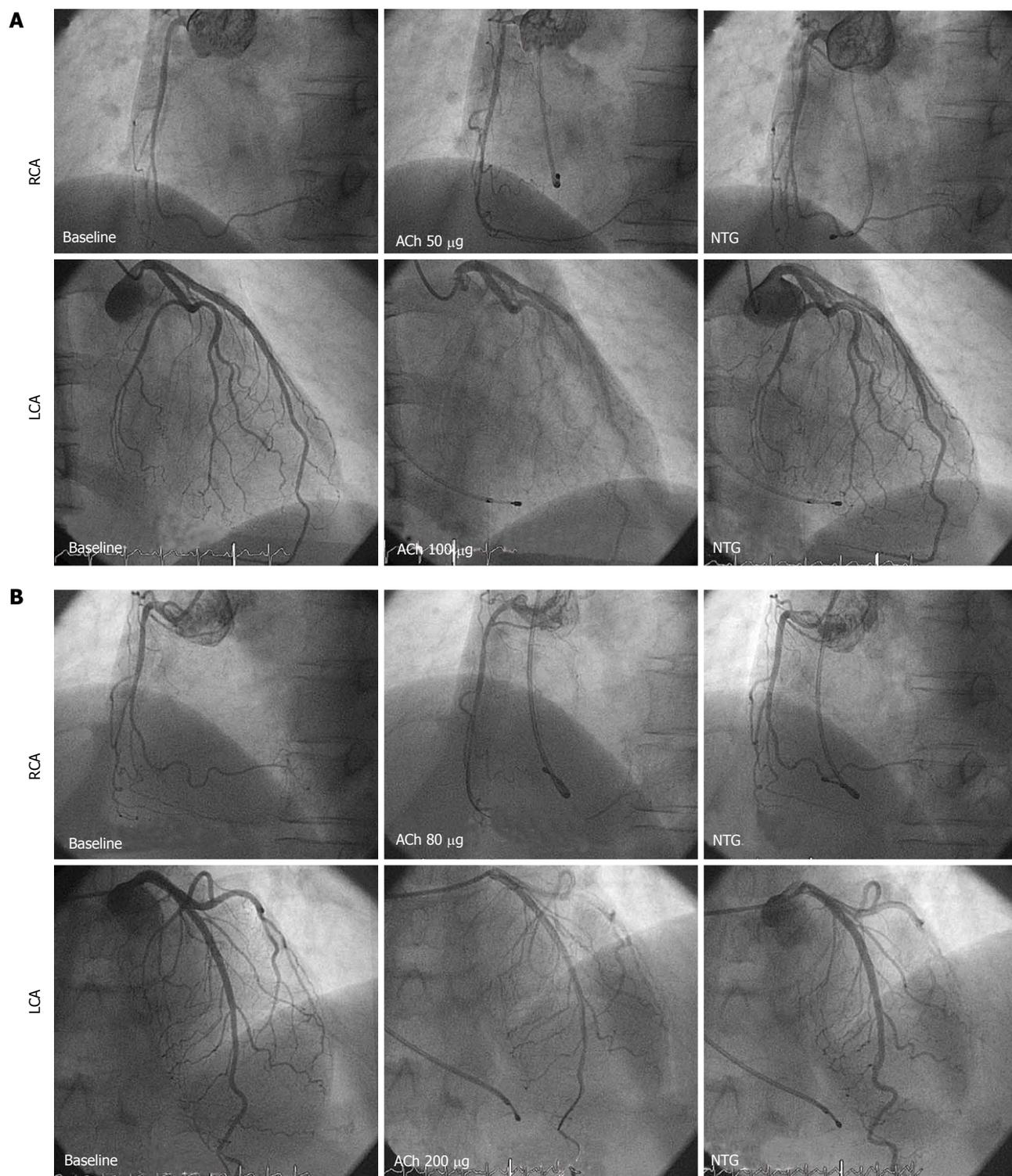


**Figure 2** Coronary angiograms during the first and second spasm provocation test in case 2. A: The first spasm provocation test (SPT) showed moderate vasoconstriction of the right coronary artery (RCA) after infusions of 50 µg acetylcholine (ACh) and moderate left coronary artery (LCA) vasoconstriction after infusions of 100 µg ACh. However, neither chest symptoms nor ST deviation of the electrocardiogram occurred during the SPT; B: The second SPT showed positive results with both the RCA after intracoronary infusions of 50 µg ACh and the LCA after infusions of 100 µg ACh, accompanied by the usual chest symptoms. Arrows indicate coronary spasms.

be ideal to perform the SPT when VSA angina attacks occur easily, particularly in the morning. However, at our institution, SPTs are performed only in the afternoon. In these four cases presented here, both the first and second SPTs were performed at the same time in the afternoon. For the withdrawal of vasodilators before SPT, vasodilators were withheld at least 48 h before SPT<sup>[3,6]</sup>; however, 2 d may be insufficient for the withdrawal of long-acting CCBs. This factor may contribute to the discrepancy of SPT results.

The SPT procedure is another important problem.

The maximal doses of 50 µg ACh for the RCA and 100 µg for the LCA, in general, are recommended<sup>[3]</sup>. However, SPT using higher ACh doses of 80 µg for the RCA and 200 µg for the LCA<sup>[7,8]</sup> and/or using a combination of ACh and EM<sup>[6,8]</sup>, have recently been recommended. The use of higher ACh doses and/or a combination of ACh and EM may decrease the number of incomplete SPTs. In case 3, we judged the results as negative after higher ACh intracoronary infusion doses for the second SPT. To deny the possibility of VSA, it may be ideal to perform the SPT using higher

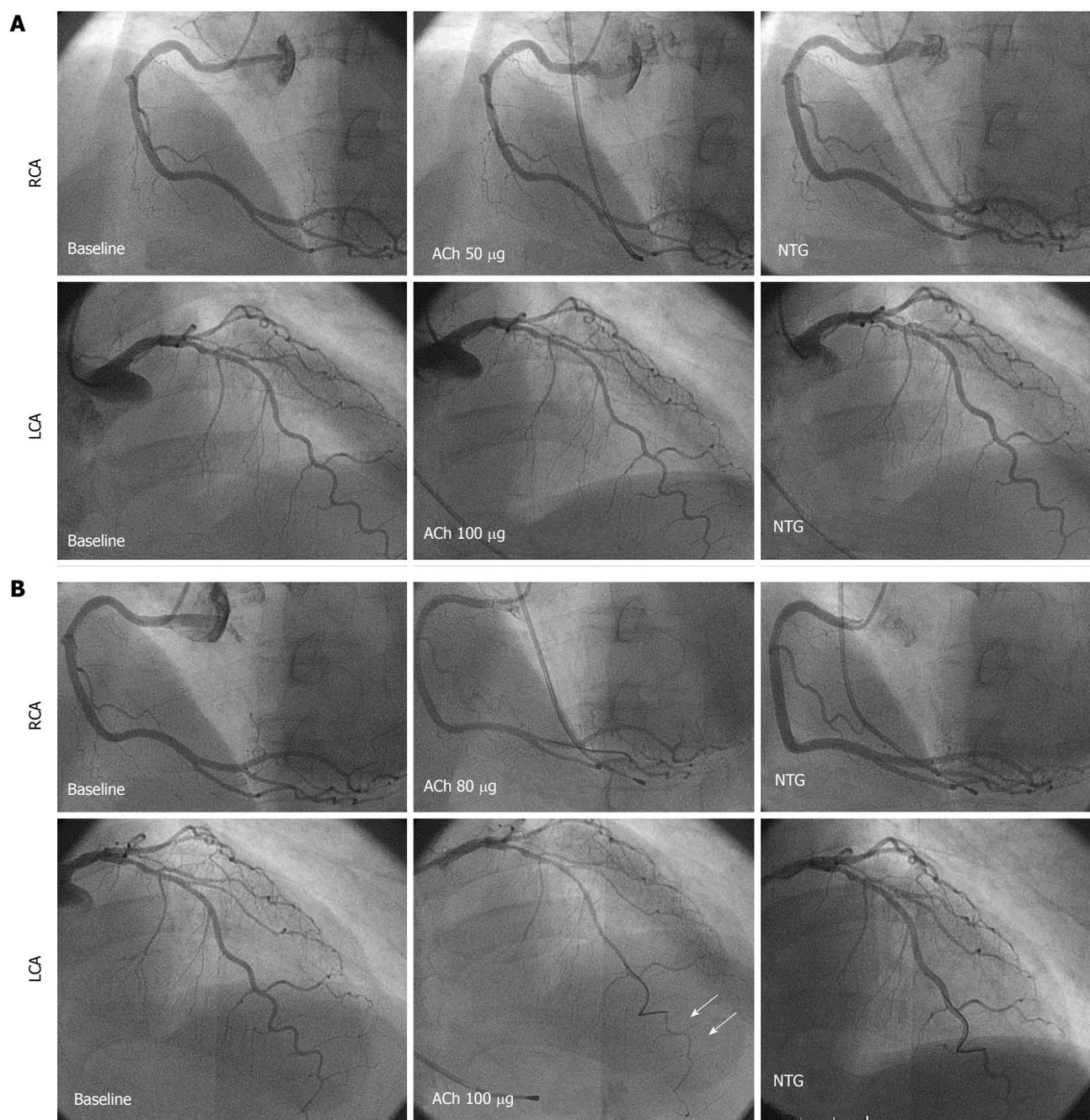


**Figure 3** Coronary angiograms during the first and second spasm provocation test in case 3. A: The first spasm provocation test (SPT) showed negative right coronary artery (RCA) results after an intracoronary infusion of 50 µg acetylcholine (ACh) and of the left coronary artery (LCA) after an intracoronary infusion of 100 µg ACh; B: The second SPT also showed negative RCA results after an intracoronary infusion of 80 µg ACh and of the LCA after an intracoronary infusion of 200 µg ACh.

concentrations of ACh. In addition, we used a pressure wire in all four cases. Using a pressure wire in SPT may be useful for diagnosing VSA<sup>[9]</sup> because the presence of myocardial ischemia can be detected promptly when the Pd/Pa is continuously monitored. Although an SPT

using a pressure wire is not always recommended in all patients, this technique may provide additional information for VSA diagnosis and may, therefore, be useful for the second SPT.

In our cases shown here, there were the gaps of 3 to



**Figure 4** Coronary angiograms during the first and second spasm provocation test in case 4. A: The first spasm provocation test (SPT) showed negative right coronary artery (RCA) results after an intracoronary infusion of 50 µg acetylcholine (ACh) and of the left coronary artery (LCA) after an intracoronary infusion of 100 µg ACh; B: The second SPT showed negative RCA results after an intracoronary infusion with 50 µg ACh, and severe vasoconstriction at the distal left anterior descending coronary artery, after an intracoronary infusion of 100 µg ACh. Arrows indicate coronary spasms.

4 years between the first and second SPT. During these periods, vascular dysfunction and/or atherosclerotic changes were newly developed. Thus, we cannot deny the possibility that coronary spasticity emerges during such periods, leading to a positive result for second SPT despite a negative result of the first SPT.

Even when the SPT is negative, the diagnosis of VSA should be with clinical symptoms in consideration. In some cases, a second SPT may be needed to confirm the diagnosis of VSA. Cardiologists should keep these concepts in mind.

## COMMENTS

### Case characteristics

There are four patients who underwent a spasm provocation test (SPT) for a second time to evaluate chest symptoms despite negative results for the first SPT.

### Clinical diagnosis

Vasospastic angina, which was diagnosed with the second SPT.

### Differential diagnosis

Microvascular angina, chest pain syndrome and gastroesophageal reflux

disease.

### Laboratory diagnosis

All labs were within normal limits.

### Imaging diagnosis

In 3 of 4 patients, the second SPT showed positive results with the angiographical coronary vasoconstriction, accompanied by usual chest symptoms and reduced intracoronary pressure measured with a pressure wire and/or ischemic changes of the electrocardiogram (ECG).

### Treatment

Vasodilators, including calcium-channel blockers, were administered in 3 patients who had positive results in the second spasm SPT, and analgesics and anti-depressive medication were administered in 1 patient with a negative result for the second SPT.

### Related reports

There are many case reports and studies of the spasm provocation test; however, this is the first report showing positive results for the second SPT despite negative results for the first SPT.

### Term explanation

Vasospastic angina (VSA) is characterized by the transient vasoconstriction of the epicardial coronary artery, leading to myocardial ischemia. It is the cause of not only rest angina but also exertional angina, acute coronary syndrome and ischemic cardiac arrest. VSA is diagnosed with chest symptoms and transient ischemic changes of the ECG, mainly at rest, but there are many cases in which the diagnosis is difficult when only based on chest symptoms and ECG monitoring. In such cases, an SPT using acetylcholine and/or ergonovine are performed and the results of the SPT are considered the final decision.

### Experience and lessons

Even when SPT is negative, the diagnosis of VSA should be made with the consideration of clinical symptoms. In some cases, a second SPT may be needed to confirm the diagnosis of VSA.

### Peer-review

This paper is interesting.

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## Pacemaker recycling: A notion whose time has come

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### Abstract

The purpose of this paper is to summarize the need, feasibility, safety, legality, and ethical perspectives of pacemaker reutilization in low- and middle-income countries (LMICs). It will also describe, in-depth, Project My Heart Your Heart (PMHYH) as a model for pacemaker reuse in LMICs. The primary source of the discussion points in this paper is a collection of 14 publications produced by the research team at the University of Michigan and its collaborative partners. The need for pacemaker reutilization in LMICs is evident. Numerous studies show that the concept of pacemaker reutilization in LMICs is feasible. Infection and device malfunction are the main concerns in regard to pacemaker reutilization, yet many studies have shown that pacemaker reuse is not associated with increased infection risk or higher mortality compared with new device implantation. Under the right circumstances, the ethical and legal bases for pacemaker reutilization are supported. PMHYH is a proof of concept pacemaker donation initiative that has allowed funeral home and crematory directors to send explanted devices to an academic center for evaluation and re-sterilization before donation to underserved patients in LMICs. The time is now to pursue large-scale studies and trials of pacemaker reuse for the betterment of society. PMHYH is leading the way in the effort and is poised to conduct a prospective randomized, non-inferiority, multicenter study to confirm the clinical efficacy and safety of pacemaker

reuse, for clinical and legal support.

**Key words:** Pacing and clinical electrophysiology; Bradyarrhythmia; Disparity; Project My Heart Your Heart; Cardiovascular disease

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**Core tip:** The purpose of this paper is to summarize the need, feasibility, safety, legality, and ethical perspectives of pacemaker reutilization in low- and middle-income countries (LMICs). It also illustrates Project My Heart Your Heart as a model for pacemaker reuse in LMICs. The primary source of the discussion points in this paper is a collection of 14 publications produced by experts at the University of Michigan and their collaborative partners.

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## INTRODUCTION

The purpose of this paper is to summarize the need for, feasibility, safety, legality, and ethical perspectives of pacemaker reutilization in low- and middle-income countries (LMICs). It will also show Project My Heart Your Heart (PMHYH) as a model for pacemaker reuse in LMICs. The source of the discussion points in this paper is a collection of 14 publications<sup>[1-14]</sup> produced by experts at the University of Michigan and their collaborative partners.

## NEED

Cardiovascular disease (CVD) comprises about 30% of all deaths in the world, more than any other singular disease or condition<sup>[15]</sup>. CVD causes twice as many deaths as the major contemporary infectious diseases-human immunodeficiency virus/acquired immune deficiency syndrome, malaria, and tuberculosis<sup>[16]</sup>. Major advances in the science of medicine, and a greater emphasis on primary prevention have improved the morbidity and mortality attributed to CVD in the industrialized world<sup>[17]</sup>. A similar improvement has not taken place in LMICs. Of the 17.5 million deaths worldwide in 2012, which were due to CVD, over 75% occurred in LMICs<sup>[15]</sup>.

The disparity in CVD care between developed nations and LMICs is especially evident in the field of heart rhythm disorders. It is estimated that 1 million individuals die every year because they cannot access bradyarrhythmia therapy<sup>[18]</sup>. Pacemaker implantation, a common treatment for bradyarrhythmia, is strikingly uncommon where it is most needed - in LMICs. In 2005, 752 pacemakers were

implanted per million individuals residing in the United States and an average of 475 per million were implanted in European countries<sup>[19]</sup>. In the same year there were only 22, 14, and 4 pacemaker implantations per million in Thailand, Peru, and Bangladesh, respectively<sup>[19]</sup>. This disparity remained unchanged in a 2009 survey showing that while 767 pacemakers were implanted per million individuals in the United States and 782 per million in France, only 30, 5, and 4 per million were placed in patients in Peru, Bangladesh, and Pakistan, respectively<sup>[20]</sup>.

The World Bank defines LMICs as any nation, whose gross per capita national product is under United States \$12736<sup>[21]</sup>. Thus, not surprisingly, a major hurdle for patients in LMICs in need of a pacemaker is its prohibitive cost. A pacemaker generally costs between \$2500 and \$3000, with leads priced as high as \$800 and \$1000<sup>[5]</sup>. Implantable cardioverter-defibrillator (ICD) generators, used to treat life threatening ventricular tachy-arrhythmias, may cost between \$20000 and \$40000, with leads priced sometimes over \$10000<sup>[5]</sup>. It is often the case that the cost of a pacemaker or an ICD far exceeds the per capita annual economic output of individuals in LMICs<sup>[19]</sup>.

Founded in 1984, Heartbeat International is a charity, which aims to distribute pacemakers and ICDs approaching the use-by-date to a dozen or more recipient implantation centers in LMICs. Device manufacturers such as Medtronic, St Jude Medical, Boston Scientific, and more recently BIOTRONIK have supported this work. Since its beginnings, Heartbeat International has distributed over 14000 near-expired devices to needy patients<sup>[18]</sup>. Nonetheless, this supply of near-expired devices cannot possibly satisfy the enormous unmet need for pacemakers and ICDs in LMICs.

In the developed world, pacemaker implantation commonly results from sinus node dysfunction<sup>[22]</sup>. In LMICs however, the most common reason patients undergo pacemaker implantation is complete heart block<sup>[23,24]</sup>. This difference is in part due to greater prevalence of infectious diseases in LMICs vs developed nations. Chagas disease, for example, is caused by an infection with *Trypanosomiasis cruzi*, and is particularly common in Latin America<sup>[25]</sup>. Seventy-two percent of pacemaker recipients in a Brazilian study by Oliveira *et al.*<sup>[26]</sup> were seropositive for *Trypanosomiasis cruzi*. Also contributing to the great need in LMICs for cardiac implantable electronic devices - pacemakers and ICDs - is coronary artery disease, owing to increased tobacco use and an increased prevalence of hypertension and diabetes worldwide<sup>[14]</sup>.

## FEASIBILITY

Pacemaker reuse is a feasible and efficacious method to reduce the health disparity between developed economies and LMICs. The concept of pacemaker reuse has been considered for decades. For example, in the early 1990s, 5% of pacemakers implanted in Sweden were reused devices<sup>[27]</sup>. However, as Sweden joined the European Union, this practice ended. Due to the high demand for devices in LMICs, lack of sufficient supply

of expired devices, and financial constraints of LMIC citizens to afford new devices, pacemaker and ICD reutilization must be re-considered.

Postmortem pacemaker donation from the funeral industry is a potential source of devices harvested for the purpose of reutilization<sup>[1]</sup>. In the United States alone 225000 pacemakers are implanted each year<sup>[19]</sup>. And while in a recent pacemaker recipient registry the mean longevity of pacemakers was  $11.2 \pm 2.6$  years, patients receiving the devices often do not live that long<sup>[28]</sup>. Brunner *et al*<sup>[29]</sup> found that only 66% of pacemaker recipients are still alive at 5 years after implantation.

According to funeral directors, 85% of the deceased with pacemakers and ICDs are buried with their device<sup>[8]</sup>. Of those devices removed prior to burial, some are donated to charity to be reused, though many, indeed the majority, are treated as waste or abandoned<sup>[30]</sup>. Pacemakers must be extracted before the deceased are cremated due to the risk of device explosion, and according to The Cremation Association of North America, the rate of cremation in the United States is projected to rise from 39% in 2010 to 59% in 2025<sup>[31]</sup>. The vast majority (over 90%) of patients with pacemakers, when surveyed, were positively inclined to advance directives to donate their devices postmortem to poor patients in LMICs<sup>[32]</sup>.

In 2008, Detroit area funeral homes rendered 50 pacemakers to World Medical Relief<sup>[12]</sup>. Eighteen of these devices met the threshold of at least 70% of battery life remaining<sup>[12]</sup>. In a 2012 study, flyers were mailed to the Michigan Funeral Directors Association regarding device collection - and of the 3176 devices returned, 21% had acceptable battery life ( $\geq 75\%$  or  $\geq 4$  years estimated longevity)<sup>[1]</sup>. Thus, funeral homes and crematories represent a useful source for pacemakers and ICDs with adequate battery life to be reused in LMICs.

An additional source of pacemakers for reutilization is devices explanted in hospitals due to changing clinical indications. A study at The University of Michigan found that 52% of pacemakers, 54% of ICDs, and 48% of cardiac resynchronization therapy defibrillators explanted for clinical indications, other than elective replacement indicator, had sufficient battery life ( $\geq 48$  mo or  $> 75\%$  battery life) and appeared to function well<sup>[11]</sup>. According to the National Cardiovascular Data Registry, between 2010 and 2012, over 63500 devices were explanted annually in the United States<sup>[11]</sup>. If the yield nationwide were similar to that of The University of Michigan, perhaps as many as 13000 pacemakers and ICDs with sufficient battery could be harvested from this pool each year for donation<sup>[11]</sup>.

While supplying pacemakers from the funeral homes, crematories, and hospitals appears viable, obtaining leads from these sources is less so. Leads are generally not reusable for at least three reasons: (1) lead extraction would add a great deal of complexity to the donation process; (2) the integrity of most extracted leads would be inadequate for repurposing; and (3) cleaning and sterilization of the leads would be fraught

with significant technical challenges<sup>[5]</sup>. Thus, a patient in a LMIC would either have to receive a donated new lead or purchase a new lead himself or herself. Both of these are plausible options, especially because the cost of the leads is much less than the pacemakers or defibrillators. This might be possible with charitable donations from companies<sup>[5]</sup>. Also, given that at government-run facilities in LMICs, patients would not be required to pay for the implantation procedure, if lead donations were to fall short of the demand, a patient and his or her family could potentially pool resources to pay for a new pacemaker or ICD lead. This is especially true given that manufacturers in India currently produce a low-cost lead priced near \$200<sup>[3]</sup>.

## SAFETY

With regards to safety, there are two prime concerns that must be considered in regard to pacemaker and ICD reutilization: Infection and device malfunction. Adequate sterilization requires removal of all organic material. This task is made difficult by the composition and geometry of the epoxy header<sup>[5]</sup>. Nonetheless, several studies have shown that pacemaker reuse does not result in higher rates of infection or mortality when compared with new pacemaker surgery. Romero *et al*<sup>[33]</sup> described four trials enrolling a total of 603 subjects, in whom reuse did not result in greater infection risk. Similarly, Nava *et al*<sup>[34]</sup> reported comparable infection rates between new and refurbished pacemakers. Panja *et al*<sup>[35]</sup> found comparable mortality and infection rates for new and used pacemakers. In a meta-analysis of studies with hard outcomes of pacemaker reuse<sup>[4]</sup>, pooled patient data ( $n = 2270$ ) from 18 trials indicated that there was no significant difference in infection rate between new and reused pacemakers. This analysis did find that in 0.68% of cases, device malfunction became apparent at the time of pacemaker surgery or shortly thereafter, which admittedly is far higher than the risk of malfunction for a new pacemaker. While the studies comprised in the analysis were heterogeneous, and some important information may not have been universally reported, none of the papers indicated that the malfunction lead to patient death.

To minimize the risk of infection and device malfunction, comprehensive protocols for device cleaning, sterilization, and functionality testing must be developed. One such sterilization process, used successfully for pacemaker reutilization in previous studies<sup>[36,37]</sup>, is shown in Figure 1. Key areas of any proposed cleaning protocol must be the treatment of set-screws and header connections<sup>[6]</sup>. In prior reports, set-screw abnormalities developed during extraction led to most malfunctions in refurbished devices<sup>[8,34]</sup>. The complex process of device handling at the funeral home and shipment to a collection center exposes the pacemakers to an additional risk of damage, which may not be grossly evident. Thus it is imperative to assess the major pacemaker functions, so that no patient experiences critical device failure<sup>[30]</sup>.

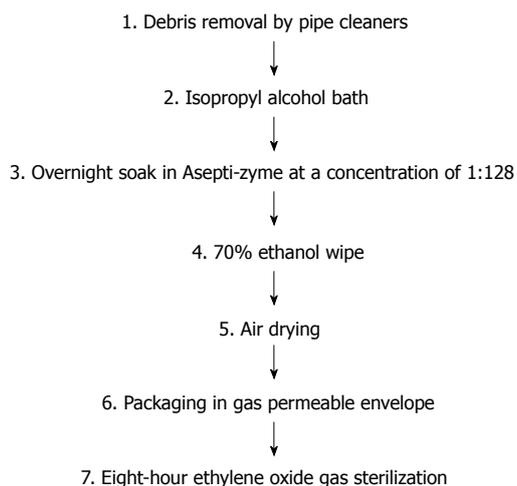


Figure 1 Pacemaker sterilization process.

Aspects of proper pacemaker interrogation are shown in Figure 2.

Anecdotal evidence of safety in pacemaker reutilization is strong. Twelve of the 50 devices donated to World Medical Relief from Detroit Metropolitan funeral homes, mentioned above, were offered to impoverished patients at the Philippine General Hospital (PGH) in Manila. The patients were screened by the local social services, which determined that these individuals were not in a position to pay the local market price for the pacemaker. There were no acute complications at the time of implantation, and a 2-mo follow-up showed that none of the pacemakers malfunctioned or became infected.

One powerful example of successful pacemaker reutilization is a patient at PGH. In a 2010 publication, Romero *et al*<sup>[2]</sup> detailed implantation of a pacemaker, which had been procured post-mortem, into a 65-year-old Filipino woman. This woman, a widow with two adult children, experienced third-degree heart block and was recommended to have a temporary pacemaker but ultimately refused a permanent pacemaker implantation due to lack of financial resources. She requested to be discharged, but returned one week later to the hospital with another syncopal episode. With her family unable to afford a new pacemaker, World Medical Relief donated a pacemaker obtained post-mortem with battery life of about 85%, and this reused pacemaker was implanted without complication. She showed no signs or symptoms of infection and her pacemaker had normal function 6-mo after the implantation.

## LEGALITY

The prime legal hurdle for pacemaker reprocessing in the United States is that the Food and Drug Administration (FDA) considers cardiac implantable electronic devices to be single-use devices (SUDs)<sup>[5]</sup>. Reuse of SUDs is highly regulated and while pacemaker reuse is technically possible, the United States FDA currently

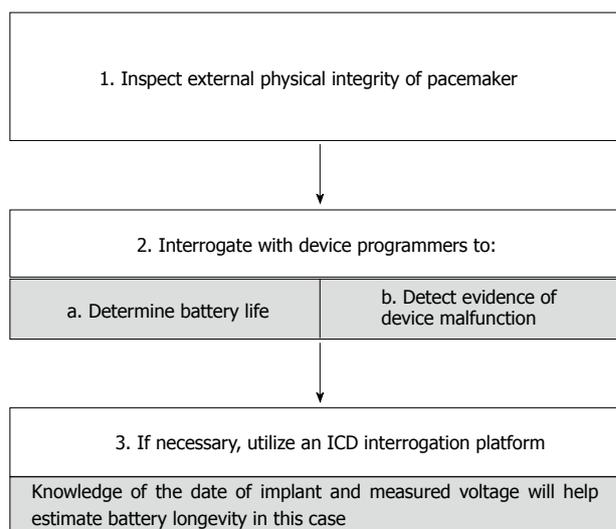


Figure 2 Aspects of pacemaker interrogation. ICD: Implantable cardioverter-defibrillator.

views it as “an objectionable practice”<sup>[38]</sup>. It is important to note that reuse of dialysis filters is commonplace in the United States and falls under stringent regulation<sup>[5]</sup>. For pacemaker reuse though, there exist other legal concerns to consider.

One is a concern among device manufacturers regarding a potential for legal action as a consequence of reused device failure. This sort of action is unlikely for two reasons. First, there are very few laws regarding SUDs in LMICs<sup>[5]</sup>. The United States is a highly litigious country, but the legal environment in countries where pacemakers would be reused is generally less susceptible to civil litigation<sup>[5]</sup>. Second, there is little tying device manufacturers to reuse of their products. Pacemakers are labeled as SUDs, warranties do not cover reuse, and none of the manufacturers sanctions pacemaker reuse. These two points notwithstanding, patients in LMICs receiving these devices must be made fully aware of the pacemaker origin, that the pacemaker no longer adheres to the original equipment manufacturer specifications, and that there may be rare risks of which we are not aware<sup>[5]</sup>.

Ownership of explanted devices, post-mortem or after an extraction due to new clinical circumstances, presents an additional legal obstacle. There are no United States federal statutes addressing the ownership of medical devices after the patient’s death or a generator replacement procedure<sup>[5]</sup>. So theoretically patients, physicians, device manufacturers, and insurers could all lay claim to explanted devices. In Sweden in the 1990s, when pacemaker reuse was frequent, ownership of an explanted device was understood to belong to the medical center, which had placed the device<sup>[5]</sup>. In Holland and Canada, devices have traditionally been property of the patients or their heirs<sup>[39]</sup>. Alternatively, the medical professional who implants pacemakers could insist that the devices be returned to him/her for analysis<sup>[5]</sup>. An agency within the United States Department of Health

and Human Services provides payment for the cost of the pacemakers and ICDs and associated implantation costs for a lion share of the elderly and the disabled, and it is conceivable that the payer might legally seek to own the product<sup>[5]</sup>. Device manufacturers may also lay claim through a contractual agreement that states the devices must be returned to the company after explantation for quality improvement<sup>[5]</sup>. Heart Rhythm Society endorses the return of devices to manufacturers for assessment and quality improvement<sup>[40]</sup>.

Ultimately, under the precept of patient autonomy, which is deeply embedded in the medical ethics, device removal from a deceased patient without express patient or next of kin authorization is probably objectionable<sup>[5]</sup>. While insurers may wish to lay claim, premiums and/or taxes paid by the patient fund these entities. Any other claims for the device would do not prevail over patient's property rights. In fact, the National Institutes of Health has embraced the notion of patient ownership<sup>[41]</sup>. An advance directive/pacemaker living will would officially outline patient wishes and authorize the funeral and crematory directors to retrieve pacemakers for donation or send them back to the manufacturer<sup>[5]</sup>.

## ETHICS

Health can be viewed through a prism of both private (individual) and societal (collective) good<sup>[13]</sup>, and as such must be considered from many ethical and moral perspectives. In considering pacemaker reuse, the first question to ask is "does donating a device not approved for use in the donor country create a double standard too great to be morally acceptable<sup>[13]</sup>?" The World Health Organization (WHO) maintains that the donated device quality should be high enough so that the donor would find it acceptable<sup>[42]</sup>. Refurbished pacemakers would certainly be deemed unacceptable by the WHO given that their use in the United States is not approved<sup>[13]</sup>.

Under egalitarian principles the ethics regarding pacemaker reuse is less clear. The most basic provision of health care to all is justified under most egalitarianism conceptions<sup>[13]</sup>. However, under egalitarian conceptions one would assert that there must be equal quality of healthcare resources available to all patients. This stance comports with the WHO and argues against pacemaker reutilization<sup>[13]</sup>.

Utilitarian theories in the health care domain emphasize the utility of being healthy<sup>[13]</sup>. Much like how food banks acquire donated food and deliver it for those in need despite the fact that some items may not be "readily marketable", pacemaker reutilization is consistent with the utilitarian concept given that the recipient benefit exceeds any harm to device donor<sup>[13]</sup>. Utilitarian theories often follow the rule of the greatest good for the greatest number of people<sup>[13]</sup>. In the context of pacemaker reutilization, the good that can be provided through device return for quality improvement must be considered and weighed against the good of reutilization. It can be argued however, that after a certain number

of devices are returned to the manufacturer, the devices remaining will provide the most benefit through pacemaker reutilization<sup>[5]</sup>.

According to the Difference Principle, proposed by Rawls<sup>[43]</sup>, inequalities should be arranged "to the greatest benefit of the least advantaged". In a 2010 WHO World Health Report<sup>[44]</sup>, authors noted that 100 million people are impoverished every year due to their inability to meet the costs of the health care they need. Whether the recipients of reutilized pacemakers are the least advantaged is debatable. However, if pacemaker reuse improves patient physical condition and well-being, it may likely be considered tolerable under the Difference Principle<sup>[13]</sup>. As with many of the other theories discussed, a thorough exploration of the benefits and detriments of pacemaker reutilization is needed for a complete reconciliation with the Difference Principle<sup>[13]</sup>.

The burdens, risks, and acceptable criteria of pacemaker reutilization must be considered as well. While the use of reprocessed pacemakers appears to be beneficial, measures need be in place to ensure that if a device malfunction or infection occurs, the implanting institution is capable of handling an emergency immediately and the patient is still able to receive a functioning device<sup>[13]</sup>. Nonmaleficence must be considered, as some patients may not be able to adhere to the recommended and important follow up with the implanting institution<sup>[5]</sup>. There is a potential of causing more harm than good with pacemaker reutilization if the patient is not able to access regular follow-up, and this risk requires careful examination<sup>[5]</sup>. Decisions on acceptable pacemaker condition, battery life, and resource distribution should be made collaboratively by all stakeholders - including members of the medical field and the lay public - to ensure equitable distribution of donated devices<sup>[13]</sup>. The risk of a "black market" for refurbished pacemakers is real and proper procedural strategies must be implemented to avoid foul play<sup>[5]</sup>. It is essential that there is a robust tracking system of the devices from the point of donation, through reprocessing, shipment, distribution to local implanting centers, and ultimately to the recipient patients. Careful patient screening for clinical and financial need can help ensure that the right resources get to the right recipient in the right place at the right time<sup>[5]</sup>.

Voltaire is often quoted "the best is the enemy of the good"<sup>[45]</sup>. In the face of no reasonable alternative, as is the case for many in the target population for pacemaker reutilization, the benefit provided through a donated refurbished device significantly outweighs the possible risks<sup>[7]</sup>. A re-sterilized pacemaker can enhance the quality of life or even preserve life with no loss of equivalent moral value; thus it is a practice that ought to be pursued<sup>[7]</sup>.

## PMHYH

PMHYH shows that pacemaker donation involving funeral homes and crematories and an academic medical center

**Table 1 Project My Heart Your Heart framework for device acquisition and performance measures**

1. ID device for potential reuse
2. Obtain signed consent from family
3. Train funeral directors in device explanation
4. Send device to center of excellence for investigation
  - a. Center does interrogation to assure adequate battery life and other performance-testing specifications
  - b. Use cutoff of  $\geq 70\%$  battery life
5. Devices that pass all quality-control measures undergo process to erase all patient identifiers
6. Sterilize and package
7. Send device to nonprofit charitable organization that specializes in delivering medical equipment for distribution to low- and middle-income countries
8. Device implanted with new unused leads

is a viable means of providing underserved patients in LMICs with much needed device therapy<sup>[6]</sup>. PMHYH was founded in 2010 by physicians within The University of Michigan Frankel Cardiovascular Center in collaboration with World Medical Relief, the Michigan Funeral Directors Association, and a company that recycles the metallic by-products of the cremation process (Implant Recycling, LLC)<sup>[14]</sup>. The goal of PMHYH is to create a blueprint for treating those with severe bradyarrhythmia in LMICs<sup>[9]</sup>.

Device acquisition is a key aspect of PMHYH. Specifically, funeral home industry is afforded access to an infrastructure of resources for obtaining consent from families of the deceased for pacemaker removal and an easy charge-free shipment of pacemaker after its removal<sup>[6]</sup>. As of 2013, PMHYH had collected over 10000 devices from funeral directors in the state of Michigan and 21% of the devices had  $\geq 75\%$  battery life or  $\geq 4$  years expected longevity<sup>[8]</sup>.

Any pacemakers acquired will be subject to stringent interrogation to inspect for evidence of damage, to ensure sufficient battery life, and to check other important performance measures. To satisfy device manufacturers, interrogation printouts, necessary for reuse, can be provided after PMHYH interrogation<sup>[5]</sup>. For manufacturers, this is certainly more information than when devices are buried with the deceased or discarded as medical waste<sup>[5]</sup>. Devices with sufficient battery life that pass interrogation will then undergo a validated cleansing and sterilization protocol.

Once sterilized, devices can be packaged and made ready for shipment. Device storage prior to shipment, interrogation, cleaning, and sterilization would all occur at a centralized center of excellence. Project MHYH estimates the cost of the entire collection, reprocessing, and distribution to be roughly \$75-\$100 per device. Assuming implanting physicians and hospitals are willing to provide their services free of charge or at an acceptably low rate, individual and corporate donations would allow the pacemakers and ICDs to be provided to patients without charge<sup>[6]</sup>.

In order for an institution to become a recipient of donated refurbished pacemaker or ICD, implanting hospitals will be required to provide some evidence of the existing infrastructure, where the implantation may take place, as well as physician and staff expertise in pacemaker and ICD implantation and related care<sup>[6]</sup>. This

may include a visit from physicians in the United States and other nations who are affiliated with PMHYH. Upon approval of the institution and arrival of the devices, local physicians will implant the refurbished devices with new leads into patients with the greatest need based on recipients' financial status and degree of conduction disease<sup>[9]</sup>. These same local physicians will then provide necessary follow-up services. This course of action taken by local physicians will aid in implantation success and patient health, and will reduce even further the risk for manufacturers of liability and potential legal action. The established relationships between PMHYH and UP-PGH in the Philippines and Indus Hospital in Karachi, Pakistan are good examples of the cross-institutional coordination necessary for pacemaker reuse and may prove valuable for future, large-scale implementation.

A web-based database would be created, allowing physicians to monitor patients with refurbished pacemakers<sup>[6]</sup>. This hopefully would restrain any inappropriate sale of refurbished pacemakers as well as provide a means (beyond routine follow-up) for communication between implanting physicians and patients in the case of device recall, or other emergent issues<sup>[6]</sup>.

A brief summary of the PMHYH model, from collection to implantation, is shown in Table 1<sup>[8]</sup>.

## CONCLUSION

Numerous studies show that the concept of pacemaker reutilization in LMICs is feasible. Most ethical concepts support pacemaker reuse. Rates of malfunction for reused devices have been found in prior studies to be no higher than that for new devices. The increased rate of malfunction found in the recent meta-analysis while concerning, is a risk believed to be acceptable for patients in dire need of bradyarrhythmia therapy in LMICs<sup>[10]</sup>. PMHYH is poised to conduct a prospective randomized, non-inferiority, multicenter study to confirm the clinical efficacy and safety of pacemaker reuse, for clinical and legal support.

There exists now a wonderful opportunity to positively affect countless lives in impoverished countries through pacemaker reutilization. A resource, which is currently not used, could enhance quality of life and extend life in LMICs and the time is now to pursue trials of pacemaker reuse for the betterment of society.

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## Coronary artery disease detection - limitations of stress testing in left ventricular dysfunction

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### Abstract

Incidental diagnosis of left ventricular systolic dysfunction

(LVD) is common in clinical practice. The prevalence of asymptomatic LVD (Ejection Fraction, EF < 50%) is 6.0% in men and 0.8% in women and is twice as common as symptomatic LVD. The timely and definitive exclusion of an ischemic etiology is central to optimizing care and reducing mortality in LVD. Advances in cardiovascular imaging provide many options for imaging of patients with left ventricular dysfunction. Clinician experience, patient endurance, imaging modality characteristics, cost and safety determine the choice of testing. In this review, we have compared the diagnostic utility of established tests - nuclear and echocardiographic stress testing with newer techniques like coronary computerized tomography and cardiac magnetic resonance imaging and highlight their inherent limitations in patients with underlying left ventricular dysfunction.

**Key words:** Coronary artery disease; Stress testing; Left ventricular dysfunction; Myocardial perfusion imaging; Dobutamine stress echocardiography

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**Core tip:** Left ventricular systolic dysfunction is common in clinical practice and may be detected in asymptomatic patients. The timely and definitive exclusion of an ischemic etiology is central to optimizing care and reducing mortality. Clinician experience, imaging modality characteristics, cost and safety determine the choice of testing. We compare the diagnostic utility of established tests like nuclear and echocardiographic stress testing with newer techniques like coronary computerized tomography and cardiac magnetic resonance imaging. Due to limitations inherent to each non-invasive modality, oftentimes cardiac catheterization remains the definitive method to exclude coronary artery disease in patients with underlying left ventricular dysfunction.

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## INTRODUCTION

Incidental diagnosis of left ventricular systolic dysfunction (LVD) is common in clinical practice. The prevalence of asymptomatic LVD (ejection fraction, EF < 50%) is 6.0% in men and 0.8% in women<sup>[1]</sup>. Asymptomatic LVD is at least twice as common as symptomatic LVD<sup>[2]</sup>. The diagnosis of LVD is usually made by demonstration of reduced systolic contractility and low EF by echocardiography. To determine whether LVD is due to coronary artery disease (CAD) is critical in the management of these patients as coronary revascularization has been shown to substantially reduce mortality in ischemic LVD. Modalities available for CAD diagnosis are either invasive coronary angiography (CA) or various non-invasive techniques such as dobutamine stress echocardiography (DSE), myocardial perfusion imaging (MPI) or single photon emission computerized tomography (SPECT), positron emission tomography (PET), cardiac magnetic resonance imaging (CMR) and coronary computerized tomography (CCT). Clinician experience, patient endurance, imaging modality characteristics, cost, safety and local availability determine the choice of testing.

ACC/AHA in 2005 recommended CA for patients with heart failure who have angina or significant ischemia; CA was felt to be reasonable in patients with chest pain that may or may not be cardiac in origin in whom coronary anatomy is not known, those with known or suspected CAD as well as patients with myocardial viability on noninvasive tests<sup>[3]</sup>. The 2013 revised guidelines finds it reasonable (class II a) to pursue either non-invasive imaging or CA in revascularization eligible patients<sup>[4]</sup>. CA is an invasive procedure with potentially serious complications such as atheroembolism, bleeding, renal failure, myocardial infarction, ventricular tachyarrhythmias, stroke and death. The low yield of CA in the setting of LVD further highlights the unfavorable risk benefit ratio. Therefore, a noninvasive method that can identify ischemic myocardial scarring or coronary luminal narrowing would be ideal in this setting. This would reduce the number of unwanted CA in patients with a truly non-ischemic cardiomyopathy. On the other hand, importantly, an ischemic etiology for cardiomyopathy can be missed when relying solely on non-invasive tests. In patients undergoing cardiac transplantation, severe CAD was found in all patients with a pretransplant diagnosis of ischemic cardiomyopathy (57 percent of a total 112 patients); unexpectedly at the time of transplant, severe CAD was also found in 9 of 38 patients previously thought to have idiopathic dilated cardiomyopathy (DCM) and 3 of 4 with presumptive alcoholic cardiomyopathy<sup>[5]</sup>.

DSE and MPI are commonly used modalities for evaluation of CAD. Both have proven to be clinically useful in large series, are widely available and provide prognostic information as well. Despite the high sen-

sitivity and specificity reported with these tests over the last 2 decades, clinicians still have to deal with ambiguous test results when evaluating systolic heart failure patients. Available literature suggests that the sensitivity and specificity of non-invasive methods ranges between 80%-95%; this implies that the etiology of cardiomyopathy may be misdiagnosed in approximately 1 out of every 10 patients. Myocardial perfusion using newer imaging modalities like CMR and PET provide physiological data similar to DSE and SPECT while CCT predominantly provides anatomical information along the lines of invasive angiography. In this review, we will focus specifically on CAD detection in patients with LVD; role of imaging in LVD associated with myocarditis or specific cardiomyopathies like tachycardia induced cardiomyopathy, peripartum cardiomyopathy and stress cardiomyopathy are beyond the scope of this review.

## LITERATURE SEARCH

We performed a search of MEDLINE, PUBMED, SCOPUS, Clinical trials.gov and The Cochrane Library from January 1975 through Dec 2015. We set no geographic or language restrictions. To increase yield, we also searched the references of all the retrieved manuscripts and review article. MeSH terms used were Coronary Artery Disease; Ventricular Dysfunction, Left; Magnetic Resonance ImagingCine; Computerized Tomogram, Echocardiography, Stress; Dobutamine; Positron-Emission Tomography; Tomography, X-Ray Computed; and Tomography, Emission-Computed, Single-Photon.

After extensive review it was noted that though modalities like DSE, SPECT, PET and magnetic resonance imaging (MRI) have been extensively studied and written about as regards to assessment of viability in patients with cardiomyopathy, recent published literature is scant specifically with diagnosis of CAD in these patients. A few recent reviews extensively discuss specific technical aspects<sup>[6,7]</sup>. We present our review highlighting the limited literature specifically pertaining to diagnostic accuracy of various cardiac imaging modalities in left ventricular (LV) systolic dysfunction.

## DISCUSSION

### SPECT

SPECT allows direct assessment of myocardial perfusion. Parameters that factor into SPECT reporting are myocardial perfusion, wall motion abnormalities and LV ejection fraction. An inducible perfusion abnormality indicates impaired perfusion reserve which in turn corresponds to epicardial coronary obstruction.

Various studies have evaluated the utility of SPECT in detection of CAD. Bulkley *et al*<sup>[8]</sup> in 1977 reported that SPECT could reliably differentiate between ischemic and idiopathic cardiomyopathy obviating the need for cardiac catheterization. A similar conclusion was made by Tauberg *et al*<sup>[9]</sup> in 1993; based on the size of perfusion

deficit, they showed that large defects have 97% predictive value for ischemic cardiomyopathy and 94% predictive value for idiopathic cardiomyopathy, and could reliably differentiate the two entities<sup>[9]</sup>. In contrast, Dunn *et al.*<sup>[10]</sup> in 1982 reported lower accuracy (80%) for SPECT in differentiating between the two entities. Moreover, only complete perfusion defects indicated CAD in this study; partial perfusion defects as well as reversible defects were seen both in CAD as well as DCM. A study by Wu *et al.*<sup>[11]</sup> in 2003 reported that SPECT was only of modest value to distinguish between ischemic and idiopathic cardiomyopathy and concluded that SPECT cannot be relied upon in an individual patient to differentiate the two entities. Overall, the existing literature points to a high sensitivity for SPECT in CAD detection (nearly 100% in some published studies) while specificity on average is only about 40%-50% in LVD patients<sup>[12-15]</sup>.

### Limitations of SPECT

Although individual studies report high diagnostic accuracy for detecting CAD, SPECT has limitations specific to prior LVD that impact reliability. Regional wall motion abnormalities may point to CAD if located in particular coronary distributions. However, in a study of 50 DCM patients, 64% had regional wall motion abnormalities<sup>[16]</sup>; other studies report the presence of regional wall motion abnormalities in 30%-50% of patients with DCM<sup>[17-19]</sup>. Thus, regional wall motion abnormalities do not automatically imply an ischemic etiology for the cardiomyopathy.

Reversible myocardial perfusion defects are traditionally considered specific for ischemia. However reversible perfusion defects can occur in dilated cardiomyopathy as well. In one study, complete perfusion defects in thallium redistribution studies appeared to imply an ischemic etiology but was seen in only a few patients<sup>[11]</sup>; the key finding in this study was that partially reversible defects occur in both DCM and ischemic cardiomyopathy when the LVD is severe (EF in the 25% range). In most instances, there is overlap of perfusion abnormalities between DCM and ischemic cardiomyopathy (even when large or reversible perfusion defects are present), thereby limiting the role of SPECT in the setting of LVD.

There are several possible reasons for the presence of perfusion defects in DCM. Structural changes in the myocardium of DCM patients like fibrosis and scarring could account for fixed perfusion defects<sup>[19]</sup>. Dilatation of ventricle and abnormal cell membrane permeability could lead to variable radioactive tracer uptake and redistribution. Stress testing induced LV geometry changes are also known to cause reversible defects in DCM<sup>[20]</sup>. Exercise induced coronary spasm<sup>[21]</sup>, mitral valve prolapse<sup>[22]</sup>, and aortic stenosis<sup>[23]</sup> have been associated with SPECT abnormalities. Clinicians should consider the role of these confounders while interpreting SPECT results.

In a given patient with LVD, DCM is likely if SPECT shows normal perfusion and global (*i.e.*, non-regional)

systolic dysfunction. However, if reversible defects are detected, especially in coronary territories, possibility of CAD remains high<sup>[24]</sup>. Another important concern in patients with severe LVD is balanced ischemia. Severe left main or triple vessel disease could cause equal reduction in tracer uptake in all major segments. As SPECT does not involve absolute quantification of tracer uptake, this matched perfusion defect in multiple territories appears as "normal" in this qualitative comparison of segments relative to each other<sup>[25]</sup>. In patients with balanced ischemia, diffuse ST depression during stress, subtle perfusion defects and transient cavity dilatation (TID) may be the only clues for underlying severe CAD.

### DSE

In contemporary clinical practice, DSE and exercise stress echocardiography play a major role in detection of CAD and risk stratification. A graded dobutamine infusion starting at 5 mg/kg per minute and increasing at 3-min intervals to 10, 20, 30 and 40 mg/kg per minute is the standard for dobutamine stress testing<sup>[26]</sup>. If LVD is known to be of ischemic etiology, presence of myocardial viability and the probability of recovery after revascularization can be reliably predicted based on demonstrating contractile reserve with low dose dobutamine stress testing. There is a paucity of literature for exercise stress echocardiography in LVD.

Geleijnse *et al.*<sup>[27]</sup> reported the sensitivity, specificity and accuracy of DSE for detection of CAD to be 80%, 84% and 81% respectively. In a study by Marcovitz *et al.*<sup>[28]</sup>, DSE had 96% sensitivity and 66% specificity for detection of CAD based on resting or inducible wall motion abnormalities. Similarly, in a study evaluating chest pain, Hennesse *et al.*<sup>[29]</sup> showed that the overall sensitivity and specificity of DSE were 82% and 65% respectively: Positive and negative predictive values were 89% and 51% respectively. In a recent meta-analysis of 32 studies, DSE had a higher sensitivity (94% vs 75%,  $P < 0.001$ ) and lower negative likelihood ratio (0.21 vs 0.47,  $P < 0.001$ ) compared to SPECT for detection of left main or triple vessel disease<sup>[30]</sup>. These studies were performed predominantly in patients with preserved cardiac function.

Few DSE studies have been specifically performed in patients with LVD. One study by Jong *et al.*<sup>[31]</sup> showed that most of the patients with DCM were found to have an abnormal regional myocardial contractile response to dobutamine. Cohen *et al.*<sup>[32]</sup> reported in a study that although dobutamine had a reasonable specificity and positive predictive value, it lacked sensitivity in diagnosis of CAD in DCM patients. Sharp *et al.*<sup>[33]</sup> reported that using the change in global wall motion score index from low to peak dose, DSE had a sensitivity of 83% and a specificity of 71% for detection of CAD. In one study, changes in left ventricular geometry as seen in patients with DCM can lead to false positive and false negative results in approximately 22% patients, hence reducing the accuracy of DSE<sup>[34]</sup>. Vigna *et al.*<sup>[35]</sup> showed that

although DSE has a specificity of 96% it has a lower sensitivity of 80% in diagnosis of CAD in patients with DCM.

### **Limitations of DSE**

Similar to SPECT, the reliability of DSE for CAD detection remains a challenge in the setting of LVD. Coronary territory specific hypokinesia, characteristic thinning and scar related hyperechoic signals would help confirm an ischemic etiology. When baseline LVD is significant with predominantly global hypokinesia, lack of response to dobutamine could mean a poor contractile reserve and not necessarily ischemia. On the other hand, some regional variability in improved contractility may be due to endothelial dysfunction, microvascular abnormalities or focal fibrosis. These factors together with increased wall stress may lead to a reduced myocardial perfusion reserve and wall motion abnormalities in the absence of CAD. Segmental wall motion abnormalities and abnormal contractile response that could be interpreted as ischemia or hibernation are common in patients with DCM despite the absence of CAD<sup>[36]</sup>. Finally, DSE is an observer and patient dependent procedure, the accuracy of which depends on the experience of the interpreter as well the acoustic windows available during stress testing.

Not much data is available comparing the accuracy of SPECT and DSE in detection of ischemia in patients with prior LVD. There are multiple studies comparing these modalities in patients with preserved cardiac function and a pooled analysis concluded that MPI was more sensitive compared to DSE (84% vs 80%) but DSE was more specific (86% vs 77%)<sup>[37]</sup>. The accuracy for both modalities is likely to be significantly lower in patients with LVD and dilated hearts.

### **CCT**

Many new techniques are clinically useful in LVD providing information about etiology, ischemia and prognosis. Prominent among them are coronary computed tomography (CT) and cardiac magnetic resonance imaging (MRI). Currently 64-slice CT is considered the minimum standard for evaluation of coronary stenosis. In a study using 64-slice CT, the accuracy, sensitivity, specificity, positive and negative predictive value were found to be 95%, 90%, 97%, 93% and 95% respectively for identifying ischemic cardiomyopathy<sup>[38]</sup>. Another new study also using 64-slice CT showed sensitivity, specificity, positive and negative predictive values of 96%, 99%, 94%, and 100% respectively for detection of > 70% coronary stenosis in patients with cardiomyopathy of unknown etiology<sup>[39]</sup>. Compared to CA, CT technology has advanced rapidly with 256- and 320-slice CT becoming available in many centers; it is likely that these newer scanners will provide better results. Thus, CCT is a non-invasive alternative to CA in patients with LVD for detection of CAD; however, CCT in its current state cannot overcome the inherent limitation of luminography, *i.e.*, ability to provide only coronary anatomic

information. Detection of atherosclerosis or stenotic lesions may not prove causality in LVD. Active research is underway to test the feasibility of ischemia detection simultaneously using myocardial perfusion CT.

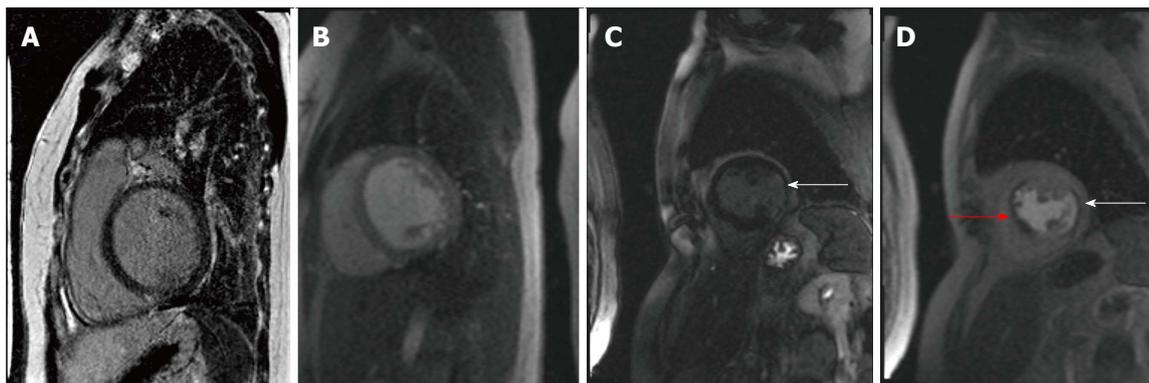
### **CMR**

In evaluation of patients with LVD, CMR has distinct advantages over other modalities. Delayed enhancement CMR is the only technique that is able to directly visualize myocardial infarction *in vivo*. Subendocardial and transmural hyperenhancement corresponding to coronary perfusion territories is observed in CAD compared to mid-myocardial and epicardial hyperenhancement that may be found in non-ischemic cardiomyopathies<sup>[40]</sup>. Delayed enhancement CMR has 40 times higher spatial resolution compared to nuclear imaging<sup>[41]</sup>; it can detect small subendocardial infarcts that are likely to be missed by nuclear imaging<sup>[42]</sup>. CMR can also help in identifying the specific etiology of DCM<sup>[40]</sup>.

CMR is now considered as an effective alternative to CA for CAD diagnosis in patients with heart failure (Figure 1, illustrative images). In one study, delayed enhancement CMR was shown to have sensitivity and specificity comparable to CA in differentiation between ischemic and non-ischemic cardiomyopathy<sup>[43]</sup>. In a recent study, it was named as a noninvasive gatekeeper to CA due to its accuracy and cost-effectiveness; delayed enhancement CMR had a sensitivity of 100%, specificity of 96%, and diagnostic accuracy of 97% for CAD detection, which were equivalent to CA<sup>[44,45]</sup>. One study clearly showed that the absence of CAD type hyperenhancement can reliably exclude myocardial infarction or severe CAD in patients with LVD and may obviate the need for CA<sup>[46]</sup>. With high sensitivity and specificity, CMR is now considered the gold standard for differentiation of ischemic and non-ischemic cardiomyopathy<sup>[47]</sup>.

### **PET**

PET imaging can help determine if CAD is the etiology of LVD based on sequential Perfusion-Metabolic scan using flow tracer N-13 Ammonia (N-13 NH<sub>3</sub>) followed by metabolic tracer F-18 2 fluorodeoxyglucose (FDG). Two techniques have traditionally been used for reading PET scans: Visual analysis and Circumferential Profile Analysis<sup>[48]</sup>. On Visual analysis it was observed that patients with DCM had a homogenous distribution of blood flow on the N-13 NH<sub>3</sub> and glucose metabolism on FDG in contrast to patients with CAD who exhibited LV segments with discrete blood flow reduction and enhanced or concordantly reduced glucose utilization. On Circumferential Profile Analysis ICMP patients had a regional reduction in N-13 NH<sub>3</sub> Myocardial uptake<sup>[49]</sup>. DCM patients with left bundle branch block demonstrate selective uptake of FDG in the septum resulting in false positive results. PET imaging has limitations, including assumption of uniformity of myocardial thickness and decreased spatial resolution. Patchy fibrosis in DCM can falsely resemble a CAD pattern. The most important



**Figure 1** Two patients underwent cardiac stress magnetic resonance imaging for evaluation of significant left ventricular dysfunction systolic dysfunction. Patient 1 with Idiopathic dilated cardiomyopathy, EF 30%: Panel A shows post gadolinium contrast images with absence of delayed enhancement in the left ventricular myocardium and Panel B shows lack of perfusion defect with adenosine stress imaging. Patient 2 with Ischemic cardiomyopathy, EF 15%: Panel C shows subendocardial delayed enhancement in the inferolateral wall (arrow) and Panel D shows stress perfusion defect in the anteroseptum (red arrow) consistent with ischemia and another matched perfusion defect caused by the inferolateral infarction (arrow).

**Table 1** Comparative analysis of the sensitivity, specificity and diagnostic accuracy for coronary artery disease detection using various imaging modalities<sup>1</sup>

Modality	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Diagnostic accuracy
SPECT	80%-100%	40%-50%	90%-95%	90%-95%	75%-80%
DSE	80%-85%	60%-80%	80%-90%	45%-60%	75%-80%
PET	85%-90%	80%-85%	85%-90%	80%-95%	80%-85%
CCT	70%-90%	85%-90%	90%-95%	90%-95%	90%-95%
CMR	95%-100%	90%-95%	90%-95%	90%-95%	95%-100%

<sup>1</sup>This data is limited as it includes both patients with and without left ventricular dysfunction. DSE: Dobutamine stress echocardiography; SPECT: Single photon emission computerized tomography; PET: Positron emission tomography; CCT: Coronary computerized tomography; CMR: Cardiac magnetic resonance imaging.

limiting factor is cost and availability. In most centers, PET is thus used for viability assessment in LVD patients to determine revascularization suitability after CA quantifies CAD burden. Combined PET-CT imaging has shown promise in low risk patients<sup>[50]</sup> and in the future may provide the combined functional and anatomic information to obviate the need for invasive CA.

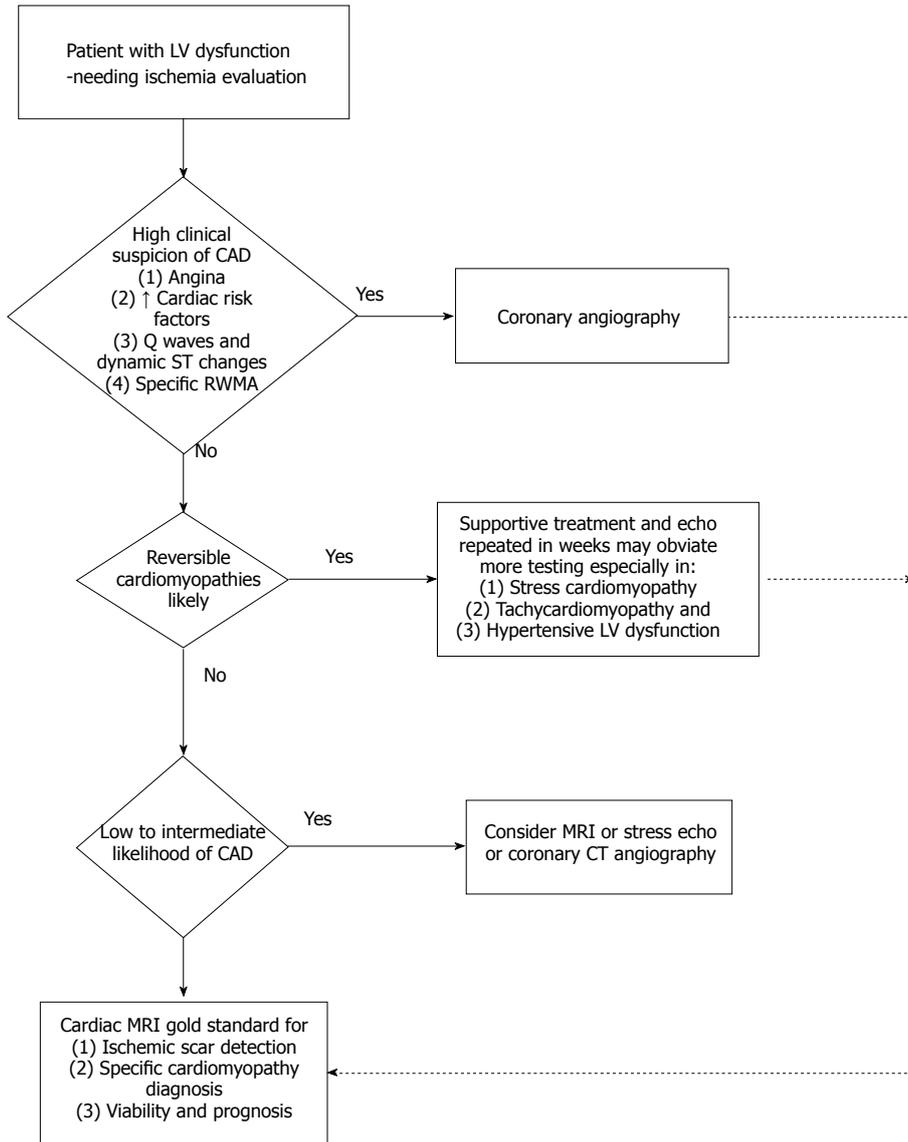
**Recommendations**

Identifying the etiology in patients with LVD is critical. The imaging modalities differ in their accuracy for CAD detection (Table 1). In patients with ischemic cardiomyopathy, adequate revascularization, especially if done early, significantly improves outcome. To achieve favorable risk-benefit ratio as well as cost effectiveness, we suggest a stepwise algorithm that incorporates patient demographics, clinical presentation and probability of CAD to determine the imaging approach for CAD detection. In patients with LVD and high index of suspicion for CAD, proceeding directly to CA would be prudent (Figure 2). When a reversible etiology such as stress cardiomyopathy or tachycardiomyopathy is likely, supportive treatment and repeat imaging in few weeks may obviate the need for invasive CA<sup>[51,52]</sup>. A sizeable proportion of patients with cardiomyopathy

of undetermined etiology have a low to intermediate probability of CAD; here various imaging modalities may serve as the gatekeeper for CA. In our opinion, the wide availability of DSE or SPECT makes these modalities reasonable in those with low likelihood of CAD. CCT is also appropriate in low to intermediate risk groups<sup>[53]</sup>. Our algorithm for evaluation of LVD patients is outlined in Figure 2. CMR, if available, would arguably be the ideal test in the setting of LVD to identify CAD scar pattern; at the same time, CMR may establish the specific etiology in several non-ischemic cardiomyopathies (Table 2). Finally, even in patients with CA proven CAD, the CMR scar pattern will help differentiate true ischemic cardiomyopathy (embolic or recanalized coronary lesions) from coincidental CAD.

**CONCLUSION**

Incidental LVD is not uncommon in clinical practice. Numerous imaging modalities are available to help establish the etiology and guide management in this population. When the suspicion of CAD is high, proceeding directly to CA would be of highest clinical value eliminating the need for noninvasive testing. In other settings where noninvasive testing would be appropriate, an algorithmic



**Figure 2** Algorithm for management of left ventricular dysfunction based on clinical presentation to optimize outcomes with cost-effective cardiac testing. LV: Left ventricular; CAD: Coronary artery disease; MRI: Magnetic resonance imaging; CT: Computerized tomography; RWMA: Regional wall motion abnormality.

**Table 2** Key advantages and limitations of various imaging modalities in detection of coronary artery disease in patients with left ventricular dysfunction

Modality	Advantages	Limitations
SPECT	Wide availability	Radiation May miss left main and triple vessel disease
DSE	Wide availability Evaluates valves and pericardium	Inter-observer variability Nonspecific response to inotrope in LVD
PET	Viability evaluation Quantifies myocardial blood flow	Radiation
CCT	Anatomic information like invasive angiogram	Radiation Iodinated contrast in renal dysfunction
CMR	Evaluates valves and pericardium Viability evaluation Determine etiology of DCM	Gadolinium in renal dysfunction

DSE: Dobutamine stress echocardiography; SPECT: Single photon emission computerized tomography; PET: Positron emission tomography; CCT: Coronary computerized tomography; CMR: Cardiac magnetic resonance imaging; LVD: Left ventricular systolic dysfunction.

imaging approach would optimize patient care.

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## Feature tracking cardiac magnetic resonance imaging: A review of a novel non-invasive cardiac imaging technique

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### Abstract

Cardiovascular disease is a leading cause of morbidity and mortality globally. Early diagnostic markers are gaining popularity for better patient care disease outcomes. There is an increasing interest in noninvasive cardiac imaging biomarkers to diagnose subclinical cardiac disease. Feature tracking cardiac magnetic resonance imaging is a novel post-processing technique that is increasingly being employed to assess global and regional myocardial function. This technique has numerous applications in structural and functional diagnostics. It has been validated in multiple studies, although there is still a long way to go for it to become routine standard of care.

**Key words:** Feature tracking cardiac magnetic resonance imaging; Feature tracking; Myocardial tagging

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**Core tip:** Feature tracking cardiac magnetic resonance imaging (FT-CMR) is novel non-invasive imaging technique that is being used commonly in assessment of different cardiac disorders. FT-CMR utilizes standard steady-state free precession sequences and is simpler, more practical and easily available. It has been validated in multiple studies. The objective of our literature review is to look at the current literature regarding validation, normal and abnormal values, advantages and limitations of FT-CMR in

research and clinical trials.

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## INTRODUCTION

Cardiovascular diseases constitute a major global public health burden. It accounts for about one third (30.9%) of patient mortality worldwide<sup>[1]</sup>. Due to increasing economic burden and shrinking resources, there is a major shift in strategy towards prevention and early detection of cardiac disease worldwide.

Among non-invasive diagnostic techniques, cardiac magnetic resonance imaging (MRI) is a gold standard. Strain imaging on cardiac magnetic resonance imaging (CMR) through myocardial tagging was in vogue since the ground-breaking work of Zerhouni in 1988. Since then many imaging sequences have been designed to measure the global and regional function of myocardium. However, most of these sequences are fraught with fading of tag lines in diastole, long the breath-hold time which are cumbersome in acutely ill and advanced cardiac failure and those with coexistent pulmonary diseases.

Strain imaging using Echocardiographic measurements obtained using tissue Doppler is limited by noise interference and angle dependency. While speckle tracking has largely overcome these issues, it is often limited by image quality CMR with feature tracking is a novel technique which uses myocardial deformation for global and segmental functional analysis. Feature tracking uses different myocardial strain patterns including longitudinal, radial and circumferential strain measurements for global and segmental functional assessment<sup>[2]</sup>. Strain on feature tracking is not dependent on loading conditions, unlike ejection fraction, and it is actually a ratio of initial and final myocardial lengths during different portions of myocardial cycle. Strain is equal to  $L - L_0/L_0$ , where L is final length and  $L_0$  is initial length.

Strain is a measure of myocardial deformation, longitudinal strain is measured in long axis while circumferential and radial strains are measured in short-axis. As cardiac magnetic resonance feature tracking (CMR-FT) is less time consuming due to no prolonged post processing times involved, it may have a better future value in quick assessment of myocardial mechanics<sup>[2]</sup>. It has been well studied in last few years and it has shown to play a great role in the diagnosis of multiple cardiac conditions as detailed below. The purpose of our literature review was to assess its integration in routine clinical care for the assessment of myocardial function to avoid unnecessary invasive diagnostic, e.g., intravascular ultrasound and cardiac catheterization.

## VALIDATION OF CMR AS NOVEL IMAGING MODALITY

Feature-tracking (FT) is a novel technology which is used to calculate strain for the assessment of cardiovascular disease, is not a validated technique at the moment, against a standard myocardial tagging analysis for any strain parameter. It needs to be validated before incorporating it into routine clinical practice. We will compare CMR-FT with other diagnostic modalities such as echocardiogram to assess its equivalence vs superiority or inferiority. Echocardiographic measurements obtained using tissue Doppler imaging are limited by noise interference and angle dependency. While speckle tracking has largely overcome these issues, it is often limited by image quality. In order to label it as standard of care, we also need to look for inter study, inter and intra observer reproducibility of CMR feature tracking (Table 1).

Taylor *et al*<sup>[3]</sup> studied 20 healthy volunteers and measured myocardial strain using FT. They found FT highly reproducible within operators and needed a short analysis time of  $3 \pm 1$  min.

Augustine *et al*<sup>[4]</sup> used feature tracking in 145 healthy individuals to measure different myocardial deformation parameters including radial, circumferential and longitudinal strain, and segmental levels based on age and gender and recorded the normal values. They found these values to be similar when compared to prior studies based on age and gender. They also used myocardial tagging in 20 of these subjects to measure these same values and compared them with those obtained by feature tracking. Feature tracking measurements of circumferential but not longitudinal or radially directed global strain showed reasonable agreement with myocardial tagging and acceptable inter-observer reproducibility. Similarly, Schuster *et al*<sup>[2]</sup> studied feature tracking measurements in 20 healthy subjects with 2 sets of measurements, one at baseline and other after 4 wk. They found that FT-CMR had reasonable intra observer reproducibility in different groups of individuals. It was most reproducible for left ventricular circumferential strain measurements while it was least reproducible for right ventricular longitudinal strain.

Use of Feature tracking was not only studied in primary cardiovascular disease patients but was also used to study left ventricular radial and circumferential strain to assess anthracycline induced cardiotoxicity. Both circumferential and radial strain detected subclinical cardiac dysfunction in this cohort. Feature tracking was compared with harmonic phase imaging analysis (HAARP). Circumferential strain was found to be a robust and reproducible index in this study while radial strain did not show much promise<sup>[5]</sup>.

To assess the reproducibility of myocardial strain, FT was compared with tagging in a small patient cohort of left bundle branch block (LBBB) and hypertensive cardiomyopathy. It concluded that peak circumferential strain and time to peak circumferential strain are not good

Table 1 Validation studies at glance

Ref.	Technique compared	Cardiac disease	Population studied (n)	Results of validation
Taylor <i>et al</i> <sup>[10]</sup>	-	Healthy individuals	55	FT is highly reproducible within operators, requiring a short analysis time
Augustine <i>et al</i> <sup>[4]</sup>	Myocardial tagging	Healthy individuals	145	FT measurements of circumferential strain showed reasonable agreement with myocardial tagging
Schuster <i>et al</i> <sup>[2]</sup>	-	Healthy individuals	20	FT showing reasonable intra-observer reproducibility in different groups of individuals
Lu <i>et al</i> <sup>[5]</sup>	HAARP	Anthracycline induced cardiomyopathy	26	Circumferential strain was found to be a robust and reproducible index of myocardial deformation
Hor <i>et al</i> <sup>[7]</sup>	HAARP	Duchenne muscular dystrophy	233	Good correlation between CMR-FT and HAARP for the mean circumferential strain values
Morton <i>et al</i> <sup>[8]</sup>	-	Healthy individuals	16	FT had good inter-study reproducibility for global strain analysis
Kempny <i>et al</i> <sup>[9]</sup>	STE and simple EBD	ToF	25	Feature tracking showed better inter observer reproducibility for circumferential or radial left ventricular and longitudinal right ventricular global strain when compared to STE
Padiyath <i>et al</i> <sup>[10]</sup>	2D echocardiography	20 patients with ToF and 20 healthy controls	40	Reasonable agreement between FT and 2D echo in measurement of global circumferential strain and global longitudinal strain for the left ventricle
Harrild <i>et al</i> <sup>[12]</sup>	Myocardial tagging	HCM	24	Closer agreement between 2 modalities in measuring time to peak strain
Orwat <i>et al</i> <sup>[13]</sup>	Trans-thoracic echocardiogram with speckle tracking	HCM	40	Trans-thoracic echocardiogram with speckle tracking. They found decent agreement between left ventricular longitudinal strain measurements between the 2 modalities while the agreement for circumferential strain not encouraging

HCM: Hypertrophic cardiomyopathy; EBD: Endocardial border delineation; STE: Speckle tracking echocardiography; ToF: Teratology of Fallot; HAARP: Harmonic phase imaging analysis; CMR-FT: Cardiac magnetic resonance feature tracking; FT: Feature tracking; 2D: 2-Dimensional.

indices in this patient population. Although it was well designed study, but due to small sample size ( $n = 20$ ) it would be far from conclusive<sup>[6]</sup>.

Another well designed study on large cohort ( $n = 233$ ) Duchene Muscular Dystrophy (DMD) patients stratified into various groups based on EF and late gadolinium enhancement (LGE) after age and gender matching. There was a good correlation between CMR-FT and HAARP for the mean circumferential strain values ( $-13.3\% \pm 3.8\%$  for CMR-FT vs  $13.6\% \pm 3.4\%$  for HAARP) with an  $r = 0.899$ <sup>[7]</sup>.

Morton *et al*<sup>[8]</sup> imaged 16 healthy individuals with CMR feature tracking 3 times in a single day and different time points to look for inter-study reproducibility. They concluded that CMR-FT had good inter-study reproducibility for global strain analysis while it was poor for segmental strain. Though, they did not find any diurnal variation in strain measurements<sup>[8]</sup>.

Kempny *et al*<sup>[9]</sup> used feature tracking for biventricular myocardial function assessment in 28 patients of repaired Teratology of Fallot (ToF) and healthy 25 controls and compared it with speckle tracking echocardiography (STE) and simple endocardial border delineation (EBD). They found close agreement between right and left ventricular global strain. Inter observer agreement for features tracking and STE was moderate for longitudinal left ventricular global strain while feature tracking showed better inter observer reproducibility for circumferential or radial left ventricular and longitudinal right ventricular global strain when compared to STE. Feature tracking

showed poor reproducibility for regional strain. The relative systolic length change of endocardial border as measured by EBD was similar to feature tracking global strain<sup>[9]</sup>. Similarly studying similar population and comparing this novel technique with 2D echocardiography, Padiyath *et al*<sup>[10]</sup> studied myocardial mechanics in 20 patients with Teratology of Fallot and 20 healthy controls using 2D STE echocardiography and FT-CMR. They found reasonable agreement between the 2 modalities in measurement of global circumferential strain and global longitudinal strain for the left ventricle ( $9.5\%$  and  $16.4\%$  inter modality variability, respectively) while right ventricular global longitudinal strain had an inter modality variability of  $25.7\%$ . Also, the global radial strain measurements had high inter modality and inter observer variability<sup>[10]</sup>. When compared with 2D echocardiography for right ventricular strain assessment, CMR-FT showed reasonable agreement with 2D echo in these assessments<sup>[11]</sup>.

In hypertrophic cardiomyopathy (HCM) patients, feature tracking was compared with myocardial tagging in 13 normal subjects and 11 patients of HCM patients, showing closer agreement between 2 modalities in measuring time to peak strain while agreement was more modest in measuring magnitude of the peak strain<sup>[12]</sup>. Orwat *et al*<sup>[13]</sup> studied feature tracking myocardial measurements in 20 healthy volunteers (10 male, mean age  $24 \pm 3$  years) and 20 patients with HCM (12 male, mean age  $47 \pm 19$  years) and compared them with trans-thoracic echocardiogram with speckle tracking. They found decent agreement between left ventricular longitudinal

strain measurements between the 2 modalities while the agreement for circumferential strain and strain rate was not encouraging. There was high reproducibility for left ventricular peak global strain measurements as compared to strain rate<sup>[13]</sup>.

Validity of FT-CMR was also studied in patients with recent or past myocardial infarction patients. Gao *et al.*<sup>[14]</sup> examined 3 healthy controls and 41 patients with either recent or past MI to assess left ventricular strain and compared with DENSE [displacement encoding with stimulated echoes in cardiac functional magnetic resonance imaging (MRI)]. He found good agreement in peak circumferential and peak radial strain values in patient population although peak radial strain measurements in healthy patients was overestimated in healthy controls when using cine CMR as compared to DENSE<sup>[14]</sup>. Also in aortic stenosis patients ( $n = 30$ ), a reasonable agreement was found in deformation measurements as measured from myocardial strain using FT as compared to tagging technique<sup>[15]</sup>. In another study, Schneeweis *et al.*<sup>[16]</sup> measured circumferential strain by using speckle tracking echocardiography (STE), FT and myocardial tagging and compared these three modalities. They found that FT and Tagging had moderate agreement in global circumferential strain analysis while agreement was poor for segmental analysis. No agreement was found between CMR (FT and MT) based global and segmental circumferential strain measurements and ST based values<sup>[16]</sup>.

Anwar *et al.*<sup>[17]</sup> studied 15 single ventricle Fontan ("Fontan" is a procedure done in pediatric patients who have 1 functional ventricle when born) patients with FT and compared it with tagging. They found moderate agreement between these 2 modalities in the assessment of circumferential strain<sup>[17]</sup>.

## REFERENCE VALUES OF FT-CMR FOR NORMAL AND DISEASED PATIENTS

Feature tracking imaging could reliably be used to assess myocardial function in patients with early dysfunction. Multiple parameter datasets are available for radial systolic strain values, circumferential strain values, circumferential strain, longitudinal endocardial systolic strain, longitudinal strain and segmental reproducibility for systolic strain measurements<sup>[18]</sup>. Similarly, Taylor *et al.*<sup>[19]</sup> studied the values for feature tracking in a cohort of 108 cardiomyopathy patients and 55 normal healthy controls. Healthy controls ( $n = 55$ , age:  $42.9 \pm 13$  years, LVEF:  $70\% \pm 5\%$ , QRS:  $88 \pm 9$  ms) and patients with cardiomyopathy ( $n = 108$ , age:  $64.7 \pm 12$  years, LVEF:  $29\% \pm 6\%$ , QRS:  $147 \pm 29$  ms) underwent FT-CMR for the assessment of the circumferential uniformity ratio estimate (CURE) and radial uniformity estimate ratio (RURE) based on myocardial strain (both CURE and RURE: 0 to 1; 1 = perfect synchrony). CURE ( $0.79 \pm 0.14$  vs  $0.97 \pm 0.02$ ) and RURE ( $0.71 \pm 0.14$  vs  $0.91 \pm 0.04$ ) were lower in patients with cardiomyopathy than in healthy controls (both  $P < 0.0001$ ). CURE [area under the receiver-operator

characteristic curve (AUC): 0.96], RURE (AUC: 0.96) and an average of these [CURE: RURE atrioventricular groove (AVG), AUC: 0.98]. They concluded that measures like CURE and RURE provide absolute differentiation between patients with cardiomyopathy and normal healthy controls with a sensitivity of 90%, specificity of 98% at a cut-off of 0.89<sup>[19]</sup>. Buss *et al.*<sup>[20]</sup> and Shang *et al.*<sup>[21]</sup> measured reference values in 110 healthy adult patients and 115 healthy pediatric patients. Their work was based on the fact that some observational studies of left ventricular function in adults suggest that global longitudinal strain correlate with EF, and is superior to EF as a predictor of outcome. Also, Kadiyala *et al.*<sup>[22]</sup> measured values of myocardial strain in 60 normal subjects and tabulated them for reference.

### Features tracking algorithm

Proto-type software is TomTec (Diogenes Medical, Germany). Different algorithms are available for strain measurement. Elnakib *et al.*<sup>[23]</sup> suggested the algorithm shown in Table 2.

### Clinical applications of feature tracking

Assessment of left ventricular function is a key application of CMR. Feature tracking imaging is a fast and rapid method that provides an objective and reliable measurement of left ventricular function. CMR-FT is a novel promising technique to diagnose structural and functional heart disease. It provides a rapid a method to diagnose these conditions without long and watchful waiting processing times<sup>[3]</sup>. In 1 study<sup>[7]</sup>, analysis of a complete data set using Feature Tracking was quicker than by tagging ( $8.8 \pm 4.7$  min vs  $15.4 \pm 4.9$  min,  $P < 0.05$ ). It does not require any extra imaging sequences and can be applied to any imaging sequence.

**Structural heart disease:** In single ventricular patients, feature tracking could help to identify ventricular dysfunction based on specific type of defect present. Moore *et al.*<sup>[24]</sup> collected the data from 25 control subjects and 30 patients with single ventricle (right or left) and used feature tracking for mechanical dyssynchrony and strain analysis in these patients. They concluded that analysis of circumferential strain is abnormal in single ventricle patients despite normal ejection fraction<sup>[24]</sup>. In patients after repair of coarctation of aorta, FT can detect early systolic dysfunction. Kutty *et al.*<sup>[25]</sup> used FT to identify abnormal strain patterns as indication of early systolic dysfunction despite normal ejection fraction in 81 patients 10-13 years after repair for coarctation of aorta. It was noted that global longitudinal strain measurements were worse in the presence of left ventricular hypertrophy<sup>[25]</sup>. FT was found to be better, fast and reliable method in quantification of wall mechanics and strain after 10 healthy subjects were examined with CMR-FT to for quantitative wall motion assessment during intermediate dose dobutamine stress CMR<sup>[26]</sup>. In addition to diagnosing early cardiac dysfunction in structural heart disease patients, FT allows quantitative elaboration of myocardial tissue and blood flow<sup>[27]</sup>. Fifteen patients with

**Table 2 Feature tracking algorithm**

Algorithm	Strain estimation algorithm
Step 1	Wall borders segmentation Segment the LV wall from cine CMR
Step 2	For each image, find the centerline of the LV wall as follows Start with the inner border of the LV wall Solve the Laplace equation between the inner and outer wall borders to find the corresponding outer points to the defined inner points in step 2(a) Pick the points located equidistant from the corresponding point-pairs Form the centerline ( <i>i.e.</i> , mid-wall border) using a closed spline fit for the selected points
Step 3	Tracking For each two successive images, solve the Laplace equation between their respective inner borders, mid-walls, and outer borders Track the co-allocated points at the inner, mid-wall, and outer edges of the first image frame (defined in step 2) throughout the cardiac cycle
Step 4	Strain estimation Estimate the circumferential strains by tracking the change in distance between tracked points on the same border ( <i>i.e.</i> , inner, mid-wall, and outer borders) Estimate the radial strains by tracking the change in distance between radially oriented tracked points

CMR: Cardiac magnetic resonance imaging; LV: Left ventricle.

ischemic cardiomyopathy were enrolled in 1 study for viability assessment *via* feature tracking measurements. FT imaging was done both at rest and during low-dose dobutamine stress. Feature tracking was found to be a reliable method for quantitative assessment of myocardial viability in patients with ischemic cardiomyopathy<sup>[28]</sup>. Feature tracking was also useful in identifying higher indexes of left ventricular dyssynchrony which were associated with ventricular tachycardia and death in patients with repaired tetralogy of Fallot<sup>[29]</sup>. This technique was also used to study the impact of transcatheter pulmonary valve placement on biventricular strain and synchrony in patients with right ventricular outflow tract conduit dysfunction which showed improved right and left ventricular global strain and left ventricular synchrony, showing the value of feature tracking in this patient population<sup>[30]</sup>. Role of feature tracking in the diagnosis of muscular dystrophy associated cardiomyopathy has been evaluated in some studies. Rosales *et al.*<sup>[31]</sup> found the role of FT in diagnosis of Limb Girdle Dystrophy associated cardiac dysfunction including cardiomyopathy with systolic dysfunction, myocardial fibrosis and diastolic dysfunction.

**Ischemic cardiomyopathy:** Usefulness of FT is not only limited to structural heart diseases, it has been studied extensively in patients with ischemic cardiomyopathy secondary to coronary artery disease. In a study by Buss *et al.*<sup>[32]</sup>, FT was used in 74 patients with first STEMI 2-4 d after reperfusion. Circumferential strain analysis provided an objective method in the assessment of infarct size<sup>[32]</sup>. They found similar utility of FTI in another study of 54 patients with first time STEMI<sup>[33]</sup>.

**Non-ischemic cardiomyopathies:** FT doesn't limit its usefulness in ischemic and structural heart disease patients, non-ischemic cardiomyopathies can also be managed early in the course if FT is used. Breuninger *et al.*<sup>[34]</sup> used FT to assess myocardial strain in 88 patients with

dilated cardiomyopathy and 30 healthy controls and found it to be reliable in analyzing global myocardial function. Steinmetz *et al.*<sup>[35]</sup> studied 26 patients with uncorrected Ebstein's anomaly and 10 healthy controls with FT to measure right and left ventricular deformation and dyssynchrony which showed RV intraventricular dyssynchrony and reduced RV global strain in patients with Ebstein's Anomaly as compared to healthy controls. Buss *et al.*<sup>[33]</sup> studied 210 patients with dilated cardiomyopathy with FT and noted that LV longitudinal strain assessment *via* FT was an independent predictor of patient survival and thus a helpful diagnostic tool for risk stratification in this patient population beyond clinical parameter and standard CMR<sup>[32]</sup>. Similarly, in hypertrophic cardiomyopathy (HCM) patients, Smith *et al.*<sup>[36]</sup> used FT to follow 30 HCM pediatric patients (14.1 ± 3.2 years) and the relationship of LGE (present in 17 of those patients) to adverse clinical outcome (defined as cardiac death non sustained Ventricular tachycardia, ventricular fibrillation and appropriate AICD discharge) over a period of 26.9 mo. They found LGE presence in these pediatric patients comparable to adult population in terms of decreased myocardial strain and adverse clinical outcome<sup>[36]</sup>. Thavendiranathan *et al.*<sup>[37]</sup> studied 30 patients with myocarditis and takotsubo cardiomyopathy with CMR and feature tracking and they found it a rapid and reliable method to diagnose myocardial injury in these conditions<sup>[37]</sup>. Petryka *et al.*<sup>[38]</sup> used FT in 137 children with known or suspected HCM, DCM or LV non compaction to measure strain and its prognostic significance. Circumferential Strain measurements in these patients were thought to be valuable in predicting adverse outcome.

**Advanced heart failure:** Cardiac resynchronization therapy (CRT) provides both morbidity and mortality benefit in advanced heart failure patients. Measurement of left ventricular mechanical dyssynchrony in these patients might provide prognostic information along with QRS duration. Onitsha *et al.*<sup>[39]</sup> studied 72 patients

to assess left ventricular dyssynchrony using CMR-FT and speckle tracking echocardiography with promising results concluding FT as a reasonable technique for patients with more marked dyssynchrony.

**Cardio-oncology:** Use of feature tracking for the diagnosis of chemotherapy-induced cardiomyopathy has been established in multiple studies<sup>[5,40]</sup>. In another study, Kowallick *et al.*<sup>[41]</sup> used this technique to measure left atrial mechanics in 10 healthy controls, 10 patients with HCM and 10 patients with heart failure with preserved LVEF (HFpEF). They concluded that FT reliably differentiated between healthy controls and patients with impaired left ventricular relaxation based on LA longitudinal strain and strain rate measurements<sup>[41]</sup>.

**Other diseases:** A small study identified the role of feature tracking in diagnosing myocardial abnormalities in patients with Churg-Strauss syndrome and Wegener's Granulomatosis and in clinical remission with normal EKG and transthoracic echocardiogram<sup>[30]</sup>. Feature tracking could also be useful in the diagnostic workup of left ventricular hypertrophy and the detection of early cardiac involvement in Anderson Fabry's disease which is an X-linked lipid storage disorder (characterized by multi organ involvement and premature death due to cardiac failure, renal failure, stroke and arrhythmias), with potential for therapy monitoring<sup>[42]</sup>. Strain measurements using feature tracking should play a major role in instituting early therapy for cardiomyopathy in patients with Duchenne Muscular Dystrophy associated cardiomyopathy and other similar cardiomyopathies where abnormal strain patterns precede the systolic dysfunction<sup>[43,44]</sup>. These measurements could also be helpful in following paroxysmal atrial fibrillation patients after ablation therapy to look for the presence and reversibility of cardiac dysfunction<sup>[29]</sup>. Bratis *et al.*<sup>[45]</sup> found FT to be helpful in differentiating between normal controls and Kawasaki Disease patients in a study of 29 KD convalescent patients and 10 healthy controls.

## FUTURE DIRECTION

Despite recent surge in the number of studies looking at this diagnostic modality, we still need large randomized trials. More studies are needed to assess the role of feature tracking in the assessment of right ventricular/right and left atrial dysfunction<sup>[11]</sup>. Further refinements are needed to overcome poor reproducibility in left ventricular segmental strain measurements and right ventricular strain measurements<sup>[27]</sup>.

## CONCLUSION

CMR-FT is a new and potentially useful noninvasive technique for measuring myocardial strain from routine cine CMR images using feature-tracking algorithms that were initially designed for echocardiographic strain analysis. FT-CMR tracks tissue voxel motion using standard steady-state

free precession sequences and is simpler, more practical and easily available and less time consuming than other CMR-based strain techniques for global and segmental myocardial function analysis. It needs to be further studied and validated for routine use in current clinical practice.

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## Basic Study

## Dissection of Z-disc myopalladin gene network involved in the development of restrictive cardiomyopathy using system genetics approach

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## Abstract

### AIM

To investigate the regulation of Myopalladin (*Mypn*) and identify its gene network involved in restrictive cardiomyopathy (RCM).

### METHODS

Gene expression values were measured in the heart of a large family of BXD recombinant inbred (RI) mice derived from C57BL/6J and DBA/2J. The proteomics data were collected from *Mypn* knock-in and knock-out mice. Expression quantitative trait locus (eQTL) mapping methods and gene enrichment analysis were used to identify *Mypn* regulation, gene pathway and co-expression networks.

### RESULTS

A wide range of variation was found in expression of *Mypn* among BXD strains. We identified upstream genetic loci at chromosome 1 and 5 that modulate the expression of *Mypn*. Candidate genes within these loci include *Ncoa2*, *Vcpip1*, *Sgk3*, and *Lgi2*. We also identified 15 sarcomeric genes interacting with *Mypn* and constructed the gene network. Two novel members of this network (*Syme1* and *Myom1*) have been confirmed at the protein level. Several members in this network are already known to relate to cardiomyopathy with some novel genes candidates that could be involved in RCM.

### CONCLUSION

Using systematic genetics approach, we constructed *Mypn* co-expression networks that define the biological process categories within which similarly regulated genes function. Through this strategy we have found several novel genes that interact with *Mypn* that may play an important role in the development of RCM.

**Key words:** System genetics; Myopalladin; System proteomics; Cardiomyopathy; Mutation

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**Core tip:** Myopalladin (*Mypn*) is one of genes associated with many types of familial cardiomyopathies including dilated, hypertrophic and restrictive cardiomyopathy (RCM). Using systematic genetics approach, we constructed *Mypn* co-expression networks of similarly regulated genes that function within defined biological

processes. Several novel *Mypn*-interacting genes with potential important role in the development of RCM were discovered.

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## INTRODUCTION

Cardiomyopathies are heterogeneous diseases of heart muscle with unknown etiologies in 60%-70% of cases<sup>[1]</sup>. Outcomes such as heart failure, transplant or death in children and adults due to lack of definite effective treatment make cardiomyopathies one of the most devastating diseases<sup>[2]</sup>. Familial restrictive cardiomyopathy (RCM), a rare form of cardiomyopathy, is characterized by diastolic dysfunction with restrictive physiology due to fibrosis and stiffness of the myocardium. Familial RCM has high incidence of sudden cardiac death, particularly in children with 2-year survival of 50% which drops up to 25% in 5-year survival period<sup>[3]</sup>. History of familial RCM is documented in 30% of cases with possible presence of dilated or hypertrophic cardiomyopathies (DCM and HCM, respectively)<sup>[4]</sup>. Only a few genes, troponins (*cTnI* and *cTnT*), myosin-binding protein C (*MyBP-C*) - myosin heavy chain (*MYH7*), myosin light chain2 and 3 (*MYL2*, *MYL3*), desmin (*DES*) and myopalladin (*MYPN*), have been reported to be associated with familial RCM.

The *MYPN* gene, located at chromosome 10q21.3, encodes a 147-kDa protein containing five immunoglobulin (Ig) domains<sup>[5]</sup>. *MYPN* localizes to the Z-discs and nucleus in striated muscle and functions in sarcomere assembly and regulation of gene expression. To date, twenty-three monoallelic heterozygous mutations in *MYPN* associated with DCM, HCM and RCM have been reported<sup>[6-8]</sup>. Clinical presentation of cardiomyopathy and heart failure typically exhibits in adulthood. Interestingly, different phenotypes were observed in family members and unrelated individuals carrying the same mutation. For instance, teenage siblings carrying the heterozygous c.1585C>T (p.Q529X-MYPN) nonsense mutation exhibited signs of overlapping phenotypes of DCM, HCM and RCM. The c.1585C>T mutation escapes a nonsense-mediated mRNA decay and produces a truncated 65-kDa MYPN protein, acting as a "poison peptide"<sup>[7,9]</sup>. The phenotype of knock-in mutant mice carrying heterozygous *Mypn*-Q526X mutation (KI), equivalent to human MYPN-Q529X, resembles RCM<sup>[9]</sup>. On the other hand, the homozygous mutants with biallelic *Mypn*-Q526X acted as the *Mypn*-null model due to ablation/knock-out (KO) of *Mypn* protein as a result of nonsense-mediated mRNA decay.

Over the last decade, it has become clear that genes do not work in isolation but in a complex combination with other genes and the environment. Thus, it is critical to identify gene networks rather than individual gene for complex traits or many diseases, including cardiomyopathies. We hypothesized that *Myfn* as a cardiomyopathy causal gene interacts with many other genes in a gene network to cause cardiomyopathy symptoms. The purpose of this investigation is to define novel cardiomyopathy causative genes through *Myfn* network using combined approaches of systems genetics and proteomics. To explore the *Myfn* gene network, we used BXD mice, a recombinant inbred (RI) strains derived from C57BL/6J strain (B6) and DBA/2J (D2) mouse cross. The *Myfn* gene is highly expressed and highly variable in the myocardium of BXD RI mouse strains. We identified an upstream modulator of *Myfn* and defined both pathway and gene network. Proteomics studies in *Myfn* KI and KO mice defined potential mechanisms through which Q526X-*Myfn* mutation induced RCM and familial cardiomyopathies in general.

## MATERIALS AND METHODS

### Animal care and use statement

BXD and *Myfn* KI and KO mice described earlier were used<sup>[9-11]</sup>. Mice were maintained in micro-isolator cages at 25 °C under a 14/10 h light/dark cycle with free access to water and food. PCR analysis of tail genomic DNA was used for genotyping of knock-in and knock-out mice. Genotyping of BXD mice was generated using GigaMUGA genotyping array that typed approximately 150000 SNPs. All animal studies were approved by institutional IACUC of the University of Tennessee Health Science Center (UTHSC).

### Tissue harvest, RNA extraction and microarray

The animals were sacrificed under isoflurane anesthesia. Cardiac perfusion were performed after an overnight fast. Hearts were taken immediately after perfusion, and then frozen in liquid nitrogen no more than a minute after sacrifice. The pieces of tissue were taken from frozen heart (most of them from ventricles) randomly. The hearts were harvested from 40 strains of the BXD family (BXD43 - BXD103) and both parental strains (C57BL/6 and DBA/2). Five animals per strain were used for this study.

RNA was extracted using QIAGEN RNA extraction kits (<https://www.qiagen.com>) as per the manufacturer's instructions. In order to reduce the inhomogeneous nature of tissues due to the presence of different segments of the heart, the individual RNA sample from 5 mice at same strain were pooled evenly (by microgram of RNA) into a single RNA sample. The pooled RNA samples were then purified using RNeasy kit. The Agilent 2100 Bioanalyzer was used to evaluate RNA integrity and quality. The RNA integrity values had to be greater than 1.8 to pass quality control. The RIN of most samples were greater than 2. The Affymetrix Mouse Gene 2.0 ST arrays were used for

gene expression measurement and were run in a single batch.

### Data processing

Raw microarray data were normalized using the Robust Multichip Array (RMA) method. The expression data were then re-normalized using a modified z-score described previously<sup>[12-15]</sup>. We calculated the log base 2 of normalized values above, computed Z scores for each array, multiplied the Z scores by 2, and added an offset of 8 units to each value. The reason for this transformation is to produce a set of Z-like scores for each array that have a mean of 8 and standard deviation of 2. The advantage of this modified Z score is that a two-fold difference in expression corresponds approximately to a 1-unit change.

### Expression QTL mapping

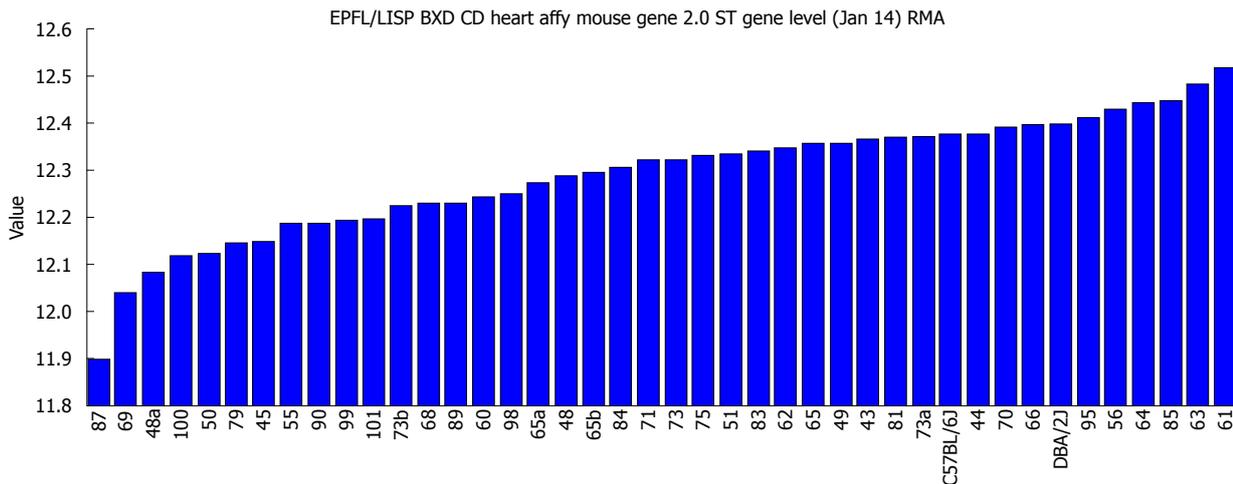
Expression QTL (eQTL) mapping was performed at gene and exon levels through the WebQTL module on GeneNetwork as published previously<sup>[12-14]</sup>. This methodology uses regression analysis to determine the association between variability in a trait vs variability in alleles at markers across the genome. Simple interval mapping was performed to identify potential eQTLs that regulate *Myfn* expression levels and estimate the significance at each location consistent to known genotype data for those sites. Composite interval mapping was also performed to control for genetic variance associated with major eQTLs as well as any potentially masked secondary eQTLs. A quantitative measure of confidence of linkage between the observed phenotype, known genetic markers and expression level of *Myfn* was provided by creating a likelihood ratio statistic (LRS). Then, we established genome-wide significance for each eQTL using a permutation test that compared the LRS of our novel site with the LRS values for 1000-10000 genetic permutations<sup>[16]</sup>.

### Identification of upstream candidate genes

To identify upstream gene of *Myfn*, we determined the 1.5-LOD location of the significant eQTL of *Myfn*. All genes in this eQTL region were used for candidate gene analysis. The following criteria were used to identify the most likely candidates: (1) the gene is highly expressed in the heart; (2) the gene is significant ( $P < 0.05$ ) correlated with *Myfn* expression in the heart; and (3) the gene has non-synonymous SNP, missense SNP or indel in coding regions of the gene, or the gene has significant *cis*-eQTL<sup>[14]</sup>.

### Genetic correlation and partial correlation analysis

We calculated Pearson product-moment correlations between expression of *Myfn* and expression of all other probe sets across the genome and produced sets of genetically correlated genes. After that, in order to identify biologically relevant correlates of *Myfn*, we also performed partial correlation analyses to remove linkage disequilibrium by controlling for *cis*-regulated



**Figure 1** Rank-ordered expression of *Mypn* in the heart across the 40 BXD strains and their parental strains. The X-axis denotes the strain name while the Y-axis denotes the mean expression given in a LOG2 scale.

genes near *Mypn*<sup>[14]</sup>. Both genetic correlation and partial correlation can be computed using the tools on GeneNetwork.

#### Gene set enrichment analysis

The genes that have both significant genetic correlation and partial correlation with *Mypn* were selected for gene set enrichment analysis. After removing Riken clones, intergenic sequences, predicted genes, and probes not associated with functional mouse genes, the remaining list of correlates with mean expression levels above baseline in the heart were uploaded to Webgestalt (<http://bioinfo.vanderbilt.edu/webgestalt/>) for gene enrichment analysis<sup>[17]</sup>. The *P* values generated from the hypergeometric test were automatically adjusted to account for multiple comparisons using the Benjamini and Hochberg correction<sup>[18]</sup>. The categories with an adjusted *P* value (adjp) of < 0.05 indicated that the set of submitted genes are significantly over-represented in that categories.

#### Gene network construction

The gene network was constructed and visualized using Cytoscape utility through "Gene-set Cohesion Analysis Tool (GCAT)" (<http://binf1.memphis.edu/gcat/index.py>). The nodes in the network represent genes and the edge between two nodes represent cosine score of Latent Semantic Indexing (LSI) that determines the functional coherence of gene sets is larger than 0.6. The significance of the functional cohesion is evaluated by the observed number of gene relationships above a cosine threshold of 0.6 in the LSI model. The literature *P*-value (LP) is calculated using Fisher's exact test by comparing the cohesion of the given gene set to a random one<sup>[19]</sup>.

#### Protein isolation and 2D-DIGE analysis in *Mypn* KO and KI mice

To investigate genetic and proteomics correlations and

to discover possible posttranslational alterations at the onset of restrictive phenotype, 3-mo-old wild-type (WT), mutant heterozygous *Mypn*<sup>WT/Q526X</sup> (KI) and homozygous *Mypn*<sup>Q526X</sup> (KO) male littermate mice were used<sup>[9]</sup>. The total protein from left ventricular (LV) myocardium was isolated, aliquoted, snap-frozen in liquid nitrogen and kept at 80 °C until further analysis. Two-dimensional gel electrophoresis (2D-DIGE) including protein labeling, 2D-electrophoreses, gel analysis and identification of proteins of interests using tandem mass spectrometry (MS) were performed by Applied Biomics (Hayward, CA) using established protocols as described previously<sup>[20]</sup>.

#### MALDI-TOF (MS) and TOF/TOF (tandem MS/MS)

Tandem MS/MS were performed on a 5800 mass spectrometer (AB Sciex) as described previously<sup>[20]</sup>. Candidates with either protein score CI% or Ion CI% greater than 95 were considered significant.

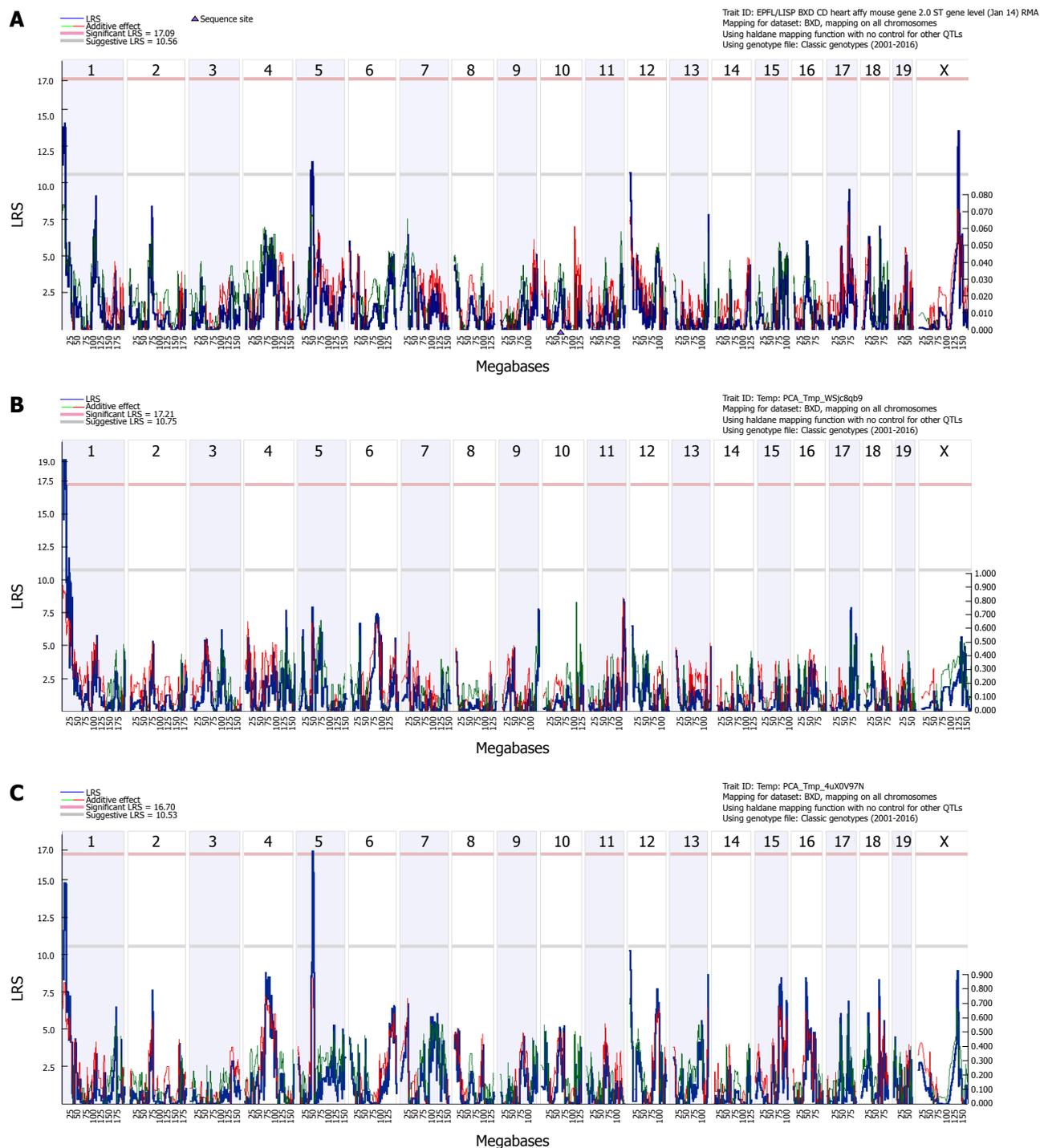
## RESULTS

#### *Mypn* expression levels in heart of BXD mice

*Mypn* which is highly expressed in the heart shows broad variability in expression among the BXD strains. The average expression of *Mypn* in all BXD strains was  $12.29 \pm 0.02$  (log<sub>2</sub> scale, mean  $\pm$  SEM). The highest expression levels of 12.52 was found in BXD61 strain and the lowest of 11.89 was found in BXD87 strain (Figure 1), a difference more than 1.5 fold.

#### eQTL mapping and candidate regulator of *Mypn*

By performing simple interval mapping for *Mypn* at the transcript level, we found four suggestive eQTLs that are located on chromosome (Chr) 1, 5, 12 and X, respectively (Figure 2A). Simple interval mapping at exon level showed the expression of exons 6, 12 and 17 map to the same locus on Chr 1; and the expression of exons 7, 14, 18 and 19 map to the same locus at Chr 5. Principal component analyses were then performed



**Figure 2 Genetic mapping of *Mypn* expression in the heart of BXD mice.** The interval mapping at the transcript level identified 4 suggestive eQTLs at chromosome 1, 5, 12, and X respectively (A). The interval mapping for the first principal component of exon 6, 12, and 17 showed a significant eQTL (genome-wide  $P < 0.05$ ) at Chr 1 (B). The interval mapping for the first principal component of exons 7, 14, 18, and 19 showed a suggestive eQTL at Chr 1 and a significant eQTL (genome-wide  $P < 0.05$ ) at Chr 5 (Figure 2C). The left Y-axis provides LRS score in blue and right Y-axis provides the additive effect in green. The red and green lines show the effect of the D or B allele on trait values, respectively. The upper X-axis shows location by chromosome and the lower X-axis shows location in megabases. The two horizontal lines across the plot make the threshold for genome-wide significant ( $P < 0.05$ , red or upper line) and suggestive ( $P < 0.63$ , grey or lower line) thresholds. eQTL: Expression quantitative trait locus; LRS: Likelihood ratio statistic.

to identify the main factor contributing to the variable expression of those exons. The first principal component (PC1) captured 67% of the expression variance for exons 6, 12 and 17. Simple interval mapping for this PC1 identified a significant eQTL with LRS of 19 (genome-wide  $P < 0.05$ ) at Chr 1 whose location is the same as

for gene level (Figure 2B). The first principal component captured 49% of the expression variance for exons 7, 14, 18 and 19. Simple interval mapping for this PC1 identified a suggestive eQTL with LRS of 14.7 at Chr 1 and a significant eQTL with LRS of 17.2 (genome-wide  $P < 0.05$ ) at Chr 5 whose locations are the same as for

**Table 1** The disease enrichment analysis

Disease	Gene No.	Adjusted value
Cardiovascular diseases	59	4.38E-05
Heart diseases	50	0.0002
Vascular diseases	49	0.0003
Cardiovascular abnormalities	27	0.0003
Bradycardia	9	0.0067
congenital long QT syndrome	6	0.0094
Metaplasia	26	0.0094
Cerebrovascular disorders	25	0.0094
Arrhythmias, cardiac	19	0.0094
Syncope	12	0.0094
Romano-ward syndrome	6	0.0094
Neovascularization, pathologic	24	0.0094
Atrial fibrillation	14	0.0094
Glycogen storage disease	8	0.0097
Myocardial ischemia	34	0.0097
Glycogen storage disease, type IV	5	0.0181
Heart murmurs	4	0.0207
Congenital abnormalities	61	0.0207
Adhesion	64	0.0207
Heart defects, congenital	17	0.0207
Ventricular dysfunction	14	0.0207
Atrioventricular block nitrous oxide system	8	0.0264
Heart block	11	0.0315
Parkinson disease	18	0.0450
Mesothelioma	10	0.0450
Coronary artery disease	31	0.0450
Stress	50	0.0450
Coronary disease	31	0.0450
Jervell-lange nielsen syndrome	4	0.0450

gene level (Figure 2C). The first principal component for any other exons did not show any significant eQTLs by performing simple interval mapping. Composite interval mapping at both gene and exon levels revealed no other loci that modulate *Mypn* expression levels; so, *Mypn* expression in heart is regulated by two trans-eQTLs. The 1.5 LOD intervals of trans-eQTLs are located from 3 to 13.2 Mb of Chr 1 and 47 to 53 Mb of Chr 5 respectively.

There are more than 70 genes/probesets in eQTL 1.5 LOD interval at Chr 1 and there are 22 genes/probesets whose expression is significantly correlated with *Mypn* expression ( $P < 0.05$ ). After further filtering by expression value, sequence polymorphism, and eQTL type, there are only 3 genes that match the criteria for candidate genes. They are nuclear receptor coactivator 2 (*Ncoa2*), valosin containing protein (*Vcpi1*), and serum (*Sgk3*). *Ncoa2* and *Vcpi1* have nonsynonymous SNP between B6 and D2, while *Sgk3* is *cis*-regulated. All three genes are highly expressed in the heart and considered as candidate genes that regulate *Mypn* expression.

There are more than 30 genes/probesets in eQTL 1.5 LOD interval on Chr 5. The expression of four of them is significantly correlated with *Mypn* expression ( $P < 0.05$ ), but only leucine-rich repeat LGI family member 2 (*Lgi2*) is *cis*-regulated and is highly expressed in the heart. Accordingly, this gene is considered as the candidate gene at Chr 5 locus that regulates *Mypn* expression.

### Gene function enrichment

The expression of 2843 transcripts/probesets has been

found to correlate significantly with that of *Mypn* ( $P < 0.05$ ). There are 1704 transcripts/probesets left after partial correction analysis. Among them, 1593 transcripts have unique Entrez gene IDs and were submitted for enrichment analysis. The most significant enrichments in the biological function category are "cellular process" (1026 genes,  $\text{adjp} = 0.000000000001$ ) and "development process" (369 genes,  $\text{adjp} = 0.000000036$ ) including "anatomical structure development" (321 genes,  $\text{adjp} = 0.0000009$ ), "muscle structure development" (64 genes,  $\text{adjp} = 0.0000084$ ) and "muscle cell differentiation" (47 genes,  $\text{adjp} = 0.0000031$ ). The most relevant enrichments in the molecular function category are "cytoskeletal protein binding" (63 genes,  $\text{adjp} < 0.006$ ), "SH3 domain binding" (19 genes,  $\text{adjp} < 0.01$ ), "growth factor binding" (19 genes,  $\text{adjp} < 0.003$ ), and "Protein serine/threonine kinase activity" (47 genes,  $\text{adjp} < 0.01$ ). The most significant enrichments in the cellular component category that is relative to muscle function are "contractile fiber" (24 genes,  $\text{adjp} < 0.009$ ), "myofibril" (21 genes,  $\text{adjp} < 0.03$ ), "sarcomere" (19 genes,  $\text{adjp} < 0.03$ ), "Z disc" (13 genes,  $\text{adjp} < 0.05$ ), "Phosphorylase kinase complex" (3 genes,  $\text{adjp} < 0.02$ ), and "AMP-activated protein kinase complex" (4 genes,  $\text{adjp} < 0.02$ ).

The disease enrichment analysis showed that those genes are significantly involved in 29 diseases ( $\text{adjp} < 0.05$ , Table 1). Almost all of diseases shown in Table 1 are cardiovascular related diseases, including cardiac arrhythmias, ventricular dysfunction and cardiovascular abnormalities. Diseases such myocardial ischemia, Romano-Ward syndrome, congenital heart defects, congenital long QT syndrome, atrial fibrillation (AF), atrioventricular block, nitrous oxide system (NOS) and coronary disease are the novel diseases that could be an interest.

The gene pathway analysis showed that those genes are significantly enriched in 10 pathways. Table 2 demonstrates top seven pathways, including "Insulin signaling pathway", "Hypertrophic cardiomyopathy", "Arrhythmogenic right ventricular cardiomyopathy", "ECM-receptor interactions", and "Focal adhesion" that are known mechanisms involved in the development of cardiomyopathy.

### Genetic network

The strength of correlation among genes with which *Mypn* is involved can be evaluated by co-expression network. In order to identify known biological relations among co-expressed genes, we selected genes that statistically significantly enriched in sarcomere (19 genes,  $\text{adjp} < 0.03$ ), and uploaded them to GCAT (<http://binf1.memphis.edu/gcat/index.py>) for the functional coherence analysis and gene network construction. Three genes out of these 19 are not found in the database or have no functional relationship with other genes. The remaining 16 genes showed significant functional cohesion with literature  $P$  value of  $1.15e-10$  (Figure 3). Multiple resources including Chilibot, GeneCard, and PubMed were used to determine whether members of the *Mypn* co-expression network had been previously associated

**Table 2 The significantly enriched gene pathways**

Pathway name	No. Gene	Adjusted value
Insulin signaling pathway	28	9.47E-06
Endocytosis	33	0.0003
Hypertrophic cardiomyopathy	15	0.0171
Arrhythmogenic right ventricular cardiomyopathy	13	0.0385
Extracellular matrix-receptor interaction	14	0.0445
Focal adhesion	24	0.0462
Prostate cancer	14	0.0462
Tryptophan metabolism	9	0.0462
Pathways in cancer	35	0.0462
MAPK signaling pathway	30	0.0462

MAPK: Mitogen-activated protein kinase.

with cardiomyopathy. In addition to *Mypn*, another 6 genes in this network (*Ldb3*, *Des*, *Actn2*, *Fhod3*, *Tpm2*, *Syne1*) are already known to relate to cardiomyopathy. Furthermore, 6 genes (*Myo18b*, *Fhod3*, *Myom1*, *Bmp10*, *Myl4*, *Obscn*, *Pdim5*) in the network have missense SNP that could change their protein function.

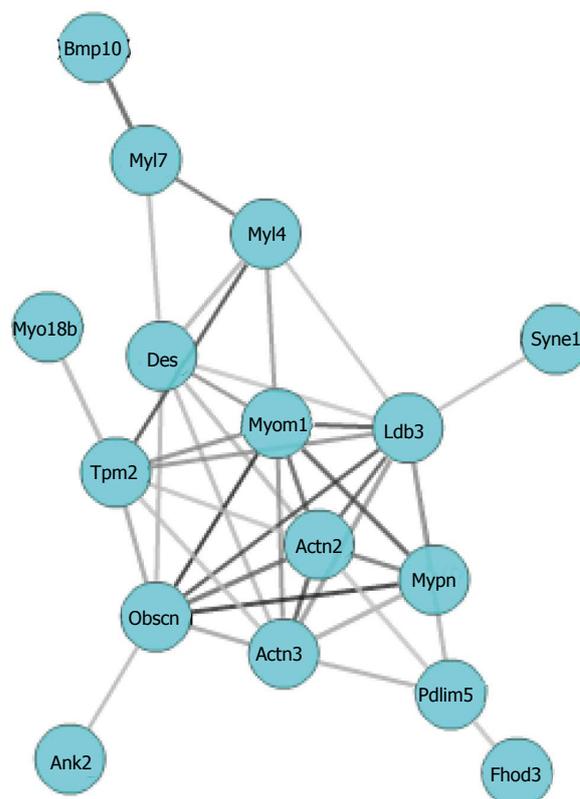
**Myocardial proteomics in *Mypn*-KI and *Mypn*-KO mouse hearts**

In order to confirm if the selected transcriptional networks are reproduced on a protein level, the proteomic profile of the myocardium from KI and KO *Mypn* mice were compared to the myocardial protein profile from WT littermates (*n* = 3). In 2D-DIGE analysis, about 2100 matched spots on each 2D gel were detected by DeCyder software, among of which a relative abundance of 65 polypeptides were altered between WT vs KI (Figure 4A), WT vs KO (Figure 4B) and KI vs KO (Figure 4C). Out of these 65 peptides, 27 are significantly changed ( $\geq 1.5$  fold and  $P \leq 0.05$ ) between WT and both of KO and KI mice. Table 3 demonstrates differential protein profiling in mutant mice vs control WT littermates and strong association of these 27 proteins with RCM phenotype. For example, proteins involved in regulation of focal adhesion, sarcomere, actin-cytoskeleton, microtubule organization and Ca-signaling are upregulated in KI mice compared to control WT mice, while KO hearts display downregulation of these proteins compared to WT.

Out of these 27 proteins, 12 were also significantly correlated with *Mypn* in mouse hearts at the transcriptional level (Table 4). Further, two of them (*Syne1* and *Myom1*, Tables 3 and 4, asterisks) have the closest connection with *Mypn* representing as potential members of *Mypn* gene network described above.

**DISCUSSION**

Cardiomyopathies are devastating heart muscle diseases with lack of definite, effective treatment, ultimately resulting in heart failure, transplant or death in children and adults<sup>[2]</sup>. Clinically, cardiomyopathies are heterogeneous diseases and classified into 5 distinctive groups characterized by changes in chamber size, thickness of myocardial walls,



**Figure 3 *Mypn* gene network graph created using Gene-set Cohesion Analysis Tool described in the methods. Gene symbols are located at nodes in circles and lines interconnecting the nodes are based on literature correlation.**

and function<sup>[1]</sup>. Although many studies have identified disease-causative mutations in all forms of cardiomyopathy, etiology remains unknown in 60%-70% of cases<sup>[21,22]</sup>. Most of genetic studies consider individual genes and mutations rather than co-regulated genes networks. The systems genetics approach is a powerful tool in identifying candidate genes and constructing genetic networks that regulate complex traits and phenotypes of mono- and poly-genetic diseases<sup>[12]</sup>. Thus, we used the system biology methodology in BXD RI strains and genetically engineered KI and KO *Mypn* mice to reveal the gene network that is co-regulated with *Mypn*, a gene that contributes to the development of cardiomyopathies.

The MYPN protein, a nodal messenger molecule, transmits stretch-signaling from Z-discs to the nucleus in cardiac myocytes<sup>[5]</sup>. It has been reported that mutations in *Mypn* cause autosomal dominant cardiomyopathies in humans with variable penetrance<sup>[6-8]</sup>. Murine models used in this study are well-characterized model of human RCM, which carries a Q526X-*Mypn* mutation<sup>[9]</sup>. Characteristic features of RCM phenotype in heterozygous mutant (KI) model include diastolic dysfunction with abnormal relaxation or impaired ventricular filling during diastole without systolic dysfunction due to "poison (mutant) peptide" effect. Homozygous mutants considered as a *Mypn*-null (KO) models due to ablation of *Mypn* gene did not manifest RCM phenotypes. Upon this functional knowledge, we sought to

**Table 3** Differentially expressed proteins identified by MALDI MS-MS

No.	Protein code	Gene ID	KI/WT	KO/WT	KO/KI	Pathways
1	PKP1	18772	1.76	-1.13	-1.99	Focal adhesion, apoptosis
2	HRC	15464	1.62	1.06	-1.53	Calcium signaling
4	PYGB	53313	1.61	1.16	-1.39	Glucagon signaling, insulin signaling
5	MSN <sup>1</sup>	17698	-2.68	4.71	12.57	Cell shape, actin-cytoskeleton
6	VINC	22330	-4.18	4.96	20.64	Cell-cell adhesion, cell shape, actin cytoskeleton
8	SYNE1 <sup>1</sup>	64009	-3.59	5.82	20.82	Nucleus-cytoskeleton connection
14	ADAM10	11487	1.71	-1.18	-2.02	Inflammation, amyloidosis
17	TNPO3	320938	-1.11	1.51	1.67	Nucleus-cytoskeleton connection
18	CAPN8	170725	2.15	-1.02	-2.19	Inflammation
19	CGNL1	68178	1.58	-1.03	-1.63	Focal adhesion
20	VIM	22352	1.43	1.40	-1.02	Cell division, fibrosis
23	MYH6	17888	1.02	-3.41	-3.49	Sarcomere, actin-cytoskeleton
24	NRAP	18175	-1.03	1.79	1.84	Focal adhesion, actin cytoskeleton
28	ANXA3	20480	1.23	-1.80	-2.23	Prostaglandin synthesis and regulation
29	LATS2	23805	-1.58	-1.51	1.04	Hippo signaling pathway, DNA damage
32	SPTB1	20741	1.56	-1.01	-1.59	Actin-cytoskeleton
33	GCC2	11426	1.04	-3.78	-3.92	Vesicle-mediated transport, retrograde transport at the <i>trans</i> -Golgi-network
37	ACADS	12306	-2.01	1.12	2.24	Mitochondrial fatty acid beta-oxidation
39	FHL2	14200	1.05	-2.25	-2.37	Focal adhesion, Wnt, calcineurin signaling
39	MYO2	59006	1.05	-2.25	-2.37	Cytoskeleton, calcineurin signaling, myofibrillogenesis
47	FGF9	14180	2.93	5.90	2.01	Fibrosis
53	DST	13518	2.23	1.01	-2.21	Focal adhesion, actin cytoskeleton
59	FEZ2	56069	1.89	-1.11	-2.12	N/A
59	CSRP3	13009	1.89	-1.11	-2.12	Stress sensing, myogenesis
62	MYOM1	319565	-1.37	1.58	2.15	Striated muscle contraction
63	MYOM2	17930			+++	Sarcomere
65	EZR/MSN	17698			+++	Cell surface organization, adhesion, microtubule

<sup>1</sup>Genes with statistically significant correlation with that of *Myfn* in mouse hearts. KI: Knock-in *Myfn* mouse; KO: Knock-out *Myfn* mouse; WT: Wild type littermates; -: Proteins downregulated compared to WT; +++: Proteins with differentially phosphorylated proteins in KI vs KO; N/A: Not applicable.

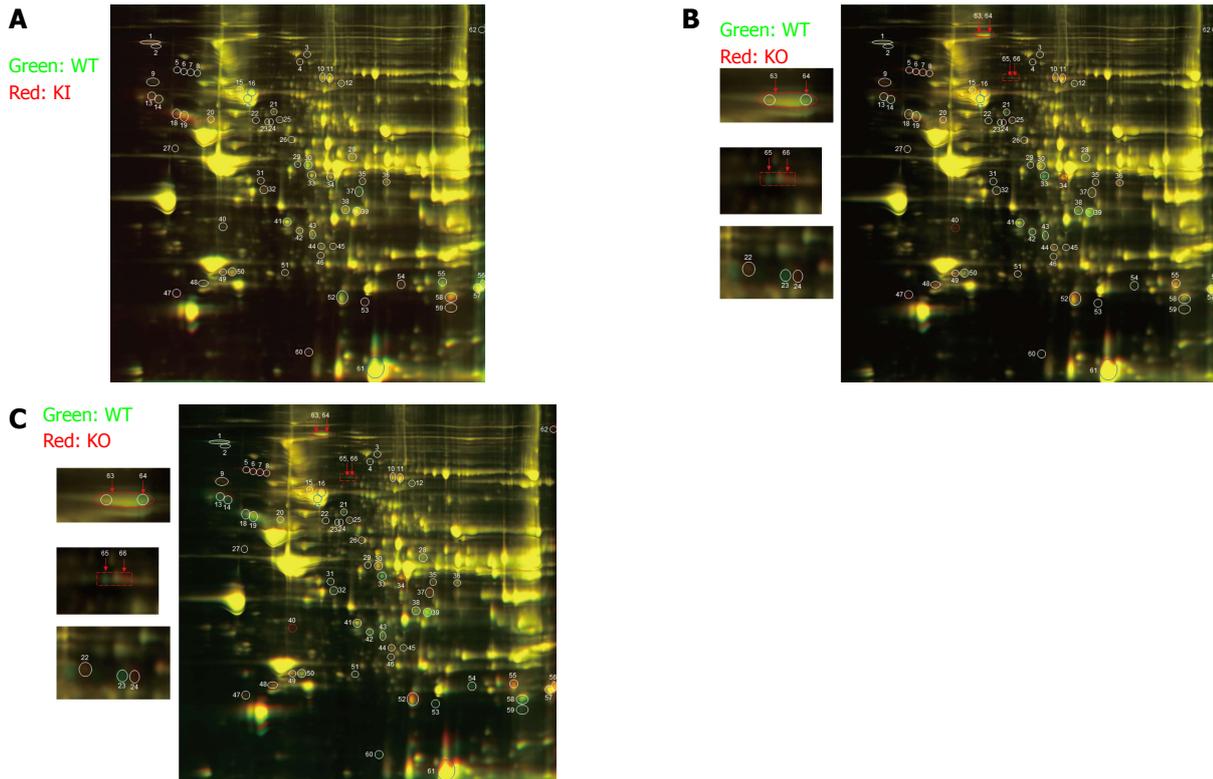
expand identifying loci that regulate expressions of *Myfn* and other genes whose expression levels are co-regulated along with *Myfn*. We have identified two loci of interest that regulate *Myfn* expression in the heart. The first locus located at proximal Chr 1 is associated with *Myfn* exon 6, 12 and 17 (Figure 5). Three genes at this locus, *Ncoa2* (nuclear receptor coactivator 2, also known as *Grip1*), *Vcpip1* (valosin containing protein interacting protein 1), and *Sgk3* (serum/glucocorticoid regulated kinase family member 3), match criteria of candidate genes. Interestingly, *Ncoa2* is shown to be required in regulation of muscle-specific gene expression for expression of *MYOG* (OMIM169980), *CDKN1A* (OMIM116899) and *MEF2C* (OMIM600662) in both proliferating and confluent myoblasts<sup>[23]</sup>. Second locus located at the middle of Chr 5 is associated with *Myfn* exons 7, 14, 18 and 19. Only one gene, *Lgi2* (leucine-rich repeat LGI family, member 2), at this locus matches the criteria of candidate genes.

To reveal the possible mechanisms by which *Myfn* variants affect individuals with RCM, we further performed gene enrichment analysis for genes that significantly co-vary with *Myfn* in the heart. The gene ontology analysis found multiple significant biological processes for *Myfn* and its correlated genes. It includes "cytoskeletal protein binding", "SH3 binding domains", "growth factor binding", "muscle structure development", and "muscle cell differentiation". For example, genes such as *Des*, *Plec*, *Fln*, *Actn2*, *Actn3*, *Tpm2*, *Obscn* and *Ank2* from "cytoskeletal protein binding" are known cytoskeletal

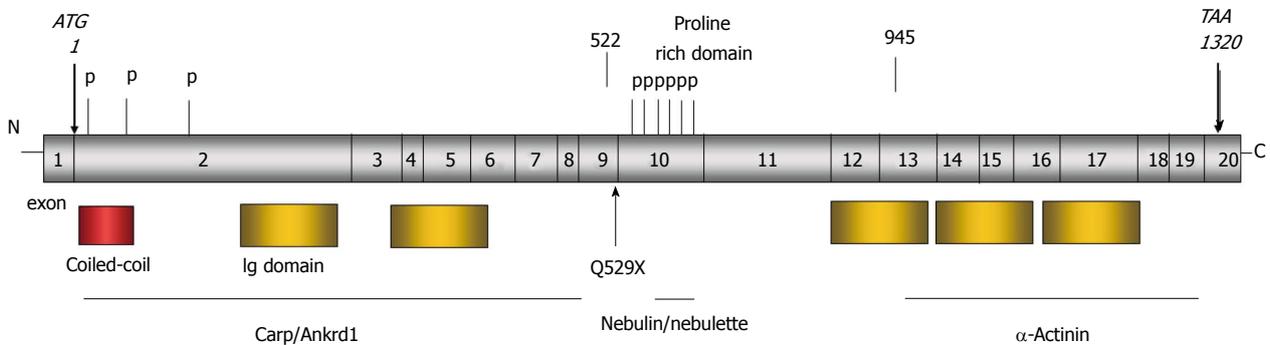
genes associated with cardiomyopathies. Interestingly, many genes from those categories could be candidates for further investigation as possible disease-causative genes for RCM. As shown in Figure 5, *Myfn* has several phosphorylation sites in the N-terminal Carp/Ankrd1 binding domain. The rod domain of *Myfn* responsive for the SH3-nebulin/nebulette binding has also several phosphorylation sites at the proline rich domain. Related to this, we found 47 genes involved in the "protein serine/threonine kinase activity", suggesting possibly novel biological processes in which *Myfn* may be involved.

The gene ontology analysis also revealed several significant cellular component categories. They are especially enriched at "contractile fiber", "myofibril", "sarcomere", and "Z-disc". All these cytoskeletal genes encode a protein network team with distinct function of each that play key roles in the orchestrated contractile function of myocytes. We discovered posttranslational changes in *Myom2* and *MSN/moesin* (Table 3) directing our attention to the genes from "phosphorylase kinase complex" and "AMP-activated protein kinase complex". These findings support the idea that *Myfn* mutations may alter phosphorylation of other cytoskeletal proteins.

The disease enrichment analysis showed that those genes are considerably involved in 29 diseases. Almost all of those 29 diseases are cardiovascular related, which support the involvement of *Myfn* and its networked genes in the development and progression of cardiovascular diseases including RCM.



**Figure 4** Two-dimensional gel electrophoresis of heart lysates from 12-wk-old mice. Comparative proteomics analysis revealed 10 non-redundant proteins in KI (heterozygote mutant) vs WT controls (A), 8 non-redundant proteins in KO (homozygote mutant) vs WT mouse hearts (B); 19 non-redundant protein changes in KO vs KI (C). Arrows indicate differential phosphorylation of proteins in WT vs KO and KI vs KO mice hearts (B and C, respectively).



**Figure 5** Structure of *Mypn* gene and functional domain of the protein. The N-terminal domain containing two immunoglobulin (Ig) and coiled-coil domains binds to cardiac ankyrin repeat protein (Carp/Ankrd1), the negative regulator of muscle gene expression. The rod domain contains proline rich domain with phosphorylation residues and binds to the SH3-domain of nebulin/nebulette at the Z-discs. The C-terminal domain containing 3 Ig domains binds to  $\alpha$ -actinin at the Z-discs.

The KEGG database was queried to identify pathways correlated to *Mypn* expression. We identified 10 significant pathways, most of which are involved in known mechanisms of cardiomyopathy including for instance insulin signaling, HCM, focal adhesion and MARK signaling. We found novel pathways as well, such as ARVC and EMC-receptor interactions that can be of high importance during development of cardiomyopathy.

Further, we used 16 genes that are significantly enriched in the sarcomere to create a gene network. All genes from the "sarcomere" network are highly expressed in the heart and significantly correlated with *Mypn* expression. We found well-known cardiomyopathy-associated genes

such as *Ldb3*, *Des*, *Actn2*, *Fhod3*, *Tpm2*, and *Syne1* in this network. Other genes in the network including *Myo18b*, *Fhod3*, *Myom1*, *Bmp10*, *Myl4*, *Obscn*, and *Pdlim5* are likely to be modifier genes interacting with *Mypn* to induce cardiomyopathy, especially genes that have missense SNPs. For example, the Z-discs *Myo18b* (OMIM607295), a potential *Mypn*-partner gene with nonsynonymous SNPs at exons 7, 18, 22, may alter *Mypn* protein function and lead to similar phenotypes. A human homozygous p.S2302X nonsense mutation in MYO18B was reported as causative for Klippel-Feil syndrome with nemaline myopathy and facial dysmorphism<sup>[24]</sup>. We also found that nonsynonymous SNP at exon 2 in *Myl4* (a fetal-specific myosin light chain

**Table 4** Genes whose gene expression has significant correlation with *Myfn* and gene product have significant change comparing with KI or KO mice

Protein code	Corr <i>P</i> value	KI/WT	KO/WT	KO/KI
CGNL1	0.0024	1.58	-1.03	-1.63
PKP1	0.0082	1.76	-1.13	-1.99
SYNE1 <sup>1</sup>	0.0114	-3.59	5.82	20.82
PYGB	0.0157	1.61	1.16	-1.39
MSN	0.0194	-2.68	4.71	12.57
ANXA3	0.0319	1.23	-1.8	-2.23
MYOM1 <sup>1</sup>	0.0335	-1.37	1.58	2.15
ACADS	0.035	-2.01	1.12	2.24
GCC2	0.0375	1.04	-3.78	-3.92
FEZ2	0.0399	1.89	-1.11	-2.12
LATS2	0.0431	-1.58	-1.51	1.04

<sup>1</sup>Genes with statistically significant correlation with that of *Myfn* in mouse hearts. KI: Knock-in *Myfn* mouse; KO: Knock-out *Myfn* mouse; WT: Wild type littermates; -. Proteins downregulated compared to WT.

4 highly expressed in atrial myocardium) to be connected with *Myfn*. To support our finding, a heterozygous p.G11L mutation in *MYL4* (OMIM160770) in a family with early-onset AF was recently reported<sup>[25]</sup>. Another mutation, p.E17K in *MYL4* causes disruption of F-actin-Z-disc complex, consequently disturbing the mechano-electrical integration and calcium signaling in cardiomyocytes leading to atrial myopathy with AF. Given our findings, we highlight possible implication of *Myfn* gene network in arrhythmia disorders involving primary atrial-specific or overlapping ventricular/atrial inherited myopathies.

Two novel genes (*Syne1* and *Myom1*) in this gene network have been found to interact with *Myfn* at the protein level in *Myfn*-KO and KI mice hearts. Both genes are highly expressed the heart and have highly significant correlation with *Myfn* at the transcriptional level. Human *SYNE1* (OMIM608441) encodes the nesprin, a giant 8797-amino acid protein. The N-terminus of nesprin is localized to the sarcomeres of cardiac and skeletal muscle, while the C-terminus is localized to the nuclear envelope participating in a complex that links the nucleoskeleton to the cytoskeleton (LINC)<sup>[26]</sup>. Mutations in *SYNE1* are associated with Emery-Dreifuss muscular dystrophy and DCM<sup>[27]</sup>. Common features of MYPN and SYNE1 proteins are that both are involved in a force transmission between cytoskeleton and the nucleus. This further highlights importance of *Myfn*-*Syne1* interactions in transducing the mechanical signal into transcriptional response.

Here we report that *Myom1*, encoding protein Myomesin1/Skelemin, is a novel candidate gene for RCM due to its strong genetic correlations to known RCM networked genes. *Myom1* is *cis*-regulated gene and has non-synonymous SNPs in coding areas with strong downstream effects on cardiomyopathy phenotypes. *Myom1* is found to be significantly altered on a protein level in *Myfn* mouse disease models. Common features of MYOM1 and MYPN proteins are that both contain Ig-domains that play critical structural roles during muscle force-generation<sup>[28]</sup>. Like MYPN, MYOM1 is also detected in

the nucleus and cytoskeleton, suggesting that it may play a role in gene expression and stretch-induced signaling<sup>[29]</sup>. The only missense mutation, p.V1490I, that affects dimerization and elastic properties of MYOM1 was reported in a family with inherited HCM<sup>[30]</sup>. Important functions of MYOM1 in regulating titin, a giant molecular spring which is responsible for the passive elasticity of muscle further underscore such a possibilities<sup>[31]</sup>. We also hypothesize that posttranslational phosphorylation of MYOM1 may contribute to the development of RCM in *Myfn* mouse models.

In summary, we have discovered two genetic loci that modulate the expression of *Myfn*. We have found *Myfn* co-varies with a different sets of genes and enriched in pathways involved in the development of cardiomyopathy. Finally, we constructed a sarcomeric *Myfn* gene network containing 16 genes. Moreover, expression changes in *SYNE1* and *MYOM1* were confirmed on a protein level in RCM model *in vivo*. We emphasize that systems genetic and genomics analysis in patients may define novel candidate genes and mechanisms of cardiomyopathies.

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## COMMENTS

### Background

Genetic differences mediate individual differences in susceptibility to cardiomyopathies and severity of disease symptoms. *Myfn* gene mutations are associated with familial restrictive cardiomyopathy (RCM). Mutant mice carrying human mutations recapitulate the RCM phenotype.

### Research frontiers

Most of genetic studies consider individual genes and mutations rather than associated networks of co-regulated genes. Systems genetics and proteomics approaches have proven to be a powerful tool for identifying candidate genes and constructing genetic and protein networks that regulate complex traits and phenotypes of mono- and polygenetic diseases.

### Innovations and breakthroughs

This study is the first constructing the *Myfn*-gene network and discovering novel RCM-causative genes using systems genetics and proteomics approaches.

### Applications

The study will provide bases for discovering novel genes that are associated with the development of cardiac muscle diseases.

### Terminology

Cardiomyopathies are diseases of heart muscle that ultimately result in heart failure, transplant or death in children and adults.

### Peer-review

Very great study, methodology is well.

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## Retrospective Cohort Study

**Blood conservation pediatric cardiac surgery in all ages and complexity levels**

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**Abstract****AIM**

To demonstrate the feasibility of blood conservation methods and practice across all ages and risk categories in congenital cardiac surgery.

**METHODS**

We retrospectively analyzed a collected database of 356 patients who underwent cardiac surgery using cardiopulmonary bypass (CPB) from 2010-2015. The patients were grouped into blood conservation ( $n = 138$ ) and non-conservation ( $n = 218$ ) groups and sub-grouped based on their ages and procedural complexity scores.

**RESULTS**

There were no statistical differences in gender, weight, pre-operative and pre-CPB hematocrit levels in both groups. Despite equivalent hematocrit levels during and after CPB for both groups, there was significantly less operative homologous blood utilized in blood conservation group across all ages and complexity levels.

**CONCLUSION**

Blood conservation surgery can be performed in con-

genital patients needing cardiac surgery in all age groups and complexity categories. The above findings in addition to attendant risks and side effects of blood transfusion and the rising cost of safer blood products justify blood conservation in congenital cardiac surgery.

**Key words:** Congenital heart disease; Cardiac surgery; Blood conservation

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**Core tip:** We evaluated the feasibility of blood conservation pediatric cardiac surgery for all age groups and complexity levels in this retrospective study. We reviewed 356 patients who underwent cardiac surgery from 2010-2015. The patients were grouped into historical non-conservation (NC = 218) and blood conservation (BC = 138) cohorts. The blood conservation was performed by miniaturizing bypass circuit, changing the trigger point for transfusion and adapting protocols and guidelines accepted and implemented by the group. We demonstrated that the blood conservation practice can be performed safely in all ages and complexity levels by reducing cardiopulmonary bypass prime volume and institutional commitment to guidelines and practice of blood conservation cardiac surgery.

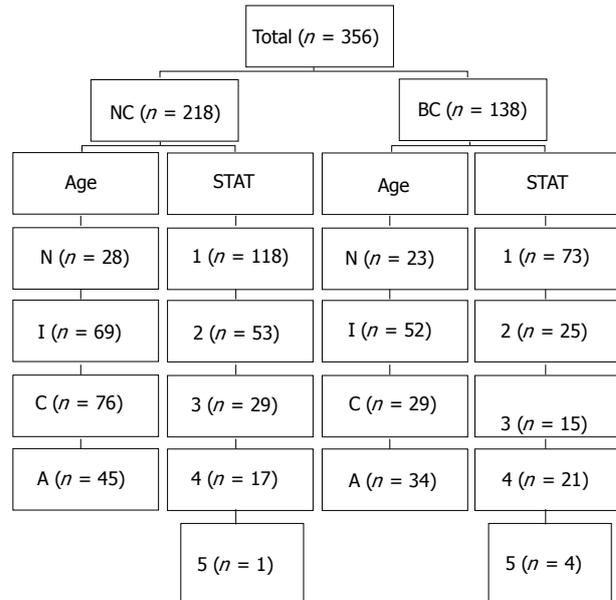
Karimi M, Sullivan JM, Linthicum C, Mathew A. Blood conservation pediatric cardiac surgery in all ages and complexity levels. *World J Cardiol* 2017; 9(4): 332-338 Available from: URL: <http://www.wjgnet.com/1949-8462/full/v9/i4/332.htm> DOI: <http://dx.doi.org/10.4330/wjc.v9.i4.332>

## INTRODUCTION

There are accumulating evidences of the association of red blood cell (RBC) transfusion with adverse outcomes in both adult and pediatric patients undergoing cardiac surgery<sup>[1-5]</sup>. The increasing costs associated with blood transfusion and the need for preservation of limited blood supplies have mandated that RBC transfusion to be included as a quality indicator in cardiac surgery<sup>[6]</sup>.

There are many blood conservation strategies available for children undergoing cardiac surgery depending on age and type of surgery. The main goal of blood conservation is to minimize exposure to allogeneic transfusion while maximizing the use of autologous red cells. Although, the effects and costs of all these methods have not yet been completely assessed, many of these strategies have been implemented in clinical practice collectively with great efficacy.

The purpose of this single-center study is to demonstrate the feasibility of blood conservation cardiac surgery practice across different age groups and complexity scores in congenital cardiac surgery.



**Figure 1** Histogram of demographics in age and STAT categories for blood conservation and non-conservation cohorts. BC: Blood conservation; NC: Non-conservation; STAT: Society of Thoracic Surgeons-European Association for Cardio-Thoracic Surgery Congenital Heart Surgery Mortality Scores; N: Neonate; I: Infant; C: Child; A: Adolescent.

## MATERIALS AND METHODS

Retrospective analysis of 356 patients who underwent open heart surgery from 2010 to 2015 was investigated. The patients were categorized into blood conservation (BC) and non-conservation (NC) groups and subcategorized by their different age categories and the Society of Thoracic Surgeons-European Association for Cardio-Thoracic Surgery Congenital Heart Surgery Mortality scores (STAT Complexity Scores) (Figure 1). The NC group (n = 218) underwent surgical procedures between 2010 and 2014 using conventional cardiopulmonary bypass (CPB) without utilizing intra-operative blood conservation methods or protocols. The BC group (n = 138) underwent surgical procedures between 2014 and 2015 by incorporating blood conservation equipment, techniques, and intra-operative guidelines for homologous RBC transfusion.

The patients were analyzed for the amount of intraoperative RBC usage based on by their age categories and STAT complexity scores. There were no changes in clinical personnel as far as anesthesia, perfusion, intensive care, or cardiology care givers for both groups. A comprehensive database including demographics and intra-operative data was created for all the patients in the cohort using electronic and paper medical records. All the data collection was complete for the primary outcome of total intraoperative RBC usage in eligible patients undergoing cardiac surgery. The subjects requiring extracorporeal membrane oxygenator before or after surgery were excluded from the study groups. The institutional review board has exempted patients' consent and approved the study.

**Table 1 Perfusion technique and equipment**

Equipment and technique	NC	BC
Integrated arterial filter with oxygenator	N	Y
Retrograde arterial priming	N	Y
Modified ultrafiltration	Y/N <sup>1</sup>	Y
In-line blood gas analyzer	N/Y <sup>1</sup>	Y
Point of care blood micro sampling	Y	Y
Cerebral saturation	Y	Y
Mixed venous saturation	Y	Y
Pediatric cell salvage	N	Y

<sup>1</sup>Some did and some did not. BC: Blood conservation; NC: Non-conservation; Y: Yes; N: No.

Intraoperative data included CPB and aortic cross-clamp (CC) times, hematocrit levels, and amount of homologous RBC transfusion. Preoperative hematocrit was measured by the preoperative work up in the core laboratory. Pre-bypass hematocrit was defined as the patient hematocrit measure by the blood gas analyzer prior to CPB. On bypass hematocrit was defined as hematocrit immediately after initiation of CPB. Post-bypass hematocrit was defined as the hematocrit prior to leaving the operating room suite. Intraoperative RBC transfusion was defined as the total amount of homologous RBC that the patient received from the time of arrival to the operating room until leaving the operating room, including prime volume for the CPB circuit. All the patients received irradiated and leukocyte depleted RBC based on the institutional blood bank protocol.

A strategic protocol by the surgeons, anesthesiology, and perfusion staff was formulated and agreed upon to achieve a reduction in hemodilution and trigger points for RBC transfusion. The formulation of the plan was divided into equipment and technique.

**Equipment**

The Terumo System One Heart Lung Machine (Terumo Cardiovascular, Ann Arbor, MI) was modified and positioned close to the operating table to reduce tubing lengths. Four different arterio-venous loops were customized specific to the weight of the patient. The Terumo FX05 (weight < 12 kg), FX15 (weight 12-75 kg), and FX25 (weight > 75 kg) oxygenators with integrated arterial filter were utilized for the CPB runs. The Terumo Capiox CP50 was configured for the administration of cold cardioplegia and modified ultrafiltration (MUF). The Hemocor HPH 400TS (Minntech Corporation, Minneapolis, MN) was used to remove excess fluid from the circuit. The Haemonetics Cell Saver 5 (Haemonetics Corporation, Braintree, MA) has allowed for successful return of shed blood during and after surgery. Continuous arterial and venous blood gas monitoring (CDI 500 Terumo Cardiovascular, Ann Arbor, MI), and cerebral saturation monitoring (Somanetics INVOS 5100 C system, Somanetics Corporation, Troy, MI) provided additional hemodynamic information regarding adequacy of patient oxygenation and perfusion in order to tailor the need for blood transfusion. Utilization of point of care testing with

i-STAT<sup>®</sup> (Abbott Point of Care, Princeton, NJ) and the Hemochron Signature Elite (ITC, Edison, NJ) allowed us for micro sampling of 0.5 mL of patient blood throughout the operative management. The differences in perfusion equipment for the two eras are depicted in Table 1.

**Perfusion technique**

The anesthesiology staff made every effort to minimize the amount of intravenous crystalloid infusion at the induction and throughout the operation to minimize hemodilution. Our current practice allows the primary perfusion staff to customize the patient circuitry with four available tubing packs and three oxygenators. These selections provided optimal circuit configuration based on patient size in order to decrease hemodilution while working safely within Food and Drug Administration (FDA) product specifications. The differences in priming volume between the two groups are demonstrated in Table 2. The circuit is positioned closed to the operating bed while avoiding crowdedness around the surgeon and assistant. Incorporating vacuum assisted drainage has made it possible to increase the height of the oxygenator to the level of the patient decreasing the arterial and venous tubing length and significantly reducing hemodilution. Retrograde arterial and venous priming have been instrumental in displacing the crystalloid priming volume of the circuit with the patients’ own blood reducing hemodilution effect at the initial stage of CPB.

We also aggressively ultrafiltrated the added crystalloid volume to the circuit to maintain an even fluid balance throughout the case. In addition, we performed arteriovenous MUF on all patients at the conclusion of the CPB. We routinely ultrafiltrated the remainder of the volume in the circuit and checked the hematocrit to ensure it was greater than or equal to the patient’s most recent hematocrit before reinfusion. This whole blood containing clotting factors and the cell saver processed blood are given to the patient prior to leaving the operating room or taken to the intensive care unit for postoperative transfusion as needed.

**Statistical analysis**

Standard descriptive statistics were used for patient demographic information. Values were calculated as mean ± SD. Continuous variables were compared between blood conservation and non-conservation groups using independent sample *t*-tests, for each of the 4 age groups (neonate, infant, child, and adolescent) and 5 STAT categories. *P* value < 0.05 was considered to be statistically significant. SPSS software (IBM, Armonk, New York) was used for statistical analysis.

**RESULTS**

There were a total of 356 patients with 218 patients in NC and 138 in BC arms. The breakdown of the patients in the ages and STAT categories for both groups are depicted in Figure 1. There were in general no statistically

Table 2 Cardiopulmonary bypass circuit prime volume			
Body weight (kg)	NC (mL)	BC (mL)	Reduction (%)
Neonate-12	400	160	60
12-35	600	445	26
35-55	800	520	35
55-75	1000	765	24
> 75	1000	880	12

BC: Blood conservation; NC: Non-conservation.

discernible differences in gender, weight, preoperative hematocrit, or pre-bypass hematocrit levels between the two groups across all ages and STAT categories. There was a trend toward longer bypass and cross clamp times in neonates, infants, and patients with STAT scores of 3 and 4 in NC cohort than BC counterpart, but did not consistently reach statistical significance (Tables 3 and 4). The neonates in NC group had higher post-bypass hematocrit ( $P = 0.001$ ) despite comparable on-bypass hematocrit due to usage of larger volume of RBC ( $P > 0.001$ ). The infants in BC group were younger ( $P = 0.001$ ) and had shorter CBP and CC times and much less RBC transfusion ( $P < 0.001$ ) despite comparable on-bypass hematocrits. The children in BC group had shorter bypass time ( $P = 0.04$ ) but comparable CC time, on-bypass, and post-bypass hematocrit, but statistically less RBC usage ( $P = 0.002$ ). Interestingly, the adolescence patients had higher on-bypass and post-bypass hematocrit ( $P < 0.001$ ) despite less RBC usage ( $P = 0.02$ ) signifying the efficacy of our circuit and protocol to conserve blood (Table 3). Overall, there was significantly less homologous RBC utilization across all age groups in BC than NC cohorts (Figure 2).

The data was also further analyzed looking at the differences in complexity of the procedures based on STAT mortality scores (1, least complex - 5, more complex) (Table 4). Patients in BC STAT 1 complexity level had higher post-bypass hematocrit ( $P = 0.02$ ) with comparable on-bypass hematocrit despite less RBC usage ( $P < 0.001$ ). Patients in BC STAT 2 group were younger ( $P = 0.001$ ) and had shorter bypass time ( $P = 0.03$ ), which was also evident in BC STAT 3 category ( $P = 0.02$ ). The BC STAT 1-4 categories in general had equivalent on-bypass hematocrit with less intraoperative RBC transfusion, which were all statistically significant. The STAT 5 groups could not be compared due to lack of sufficient subjects and power in NC group. Overall, there was significantly less homologous RBC utilization in BC group than NC group across all STAT complexity scores (Figure 3).

## DISCUSSION

Blood conservation in pediatric cardiac surgery has been a panacea and quest of cardiac surgeon due to societal and institutional push for quality care. Despite its challenges, blood conservation cardiac surgery has been practiced in all stages of cardiac surgery in adult

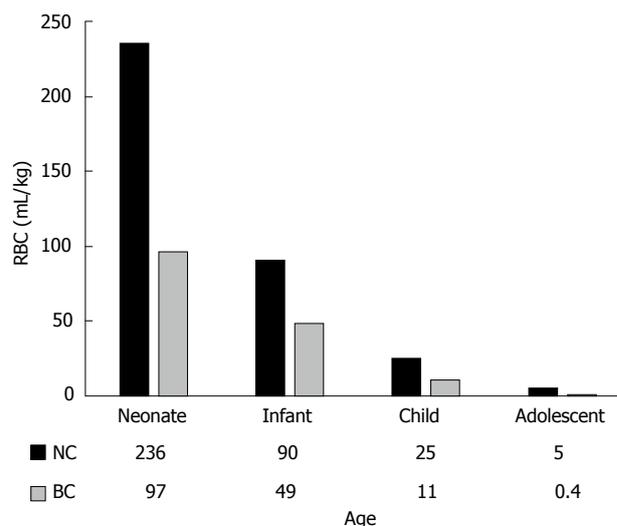


Figure 2 Bar graph for red blood cell usage in age categories for blood conservation and non-conservation cohorts. RBC: Red blood cell; BC: Blood conservation; NC: Non-conservation.

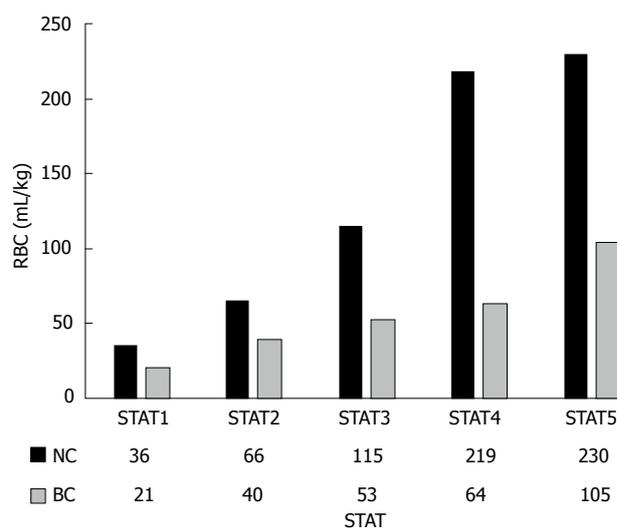


Figure 3 Bar Graph for red blood cell usage in STAT categories for blood conservation and non-conservation cohorts. RBC: Red blood cell; STAT: Society of Thoracic Surgeons-European Association for Cardio-Thoracic Surgery Congenital Heart Surgery Mortality Scores; BC: Blood conservation; NC: Non-conservation.

and pediatric in certain circumstances with a great success<sup>[7,8]</sup>. There is a great variability in practice of blood transfusion for a given diagnostic code and complexity and pediatric population is no exception to the rule<sup>[9]</sup>. By far, pediatric patients undergoing cardiac surgery are exposed to more blood transfusion intra and post-operatively with no consensus or scientific evidence to what would be the optimal hematocrit level across different diagnosis and physiologic status<sup>[10-15]</sup>.

In this retrospective study we have looked at the effectiveness of intra-operative blood conservation practice as compared to the historical non-conservation cohort. We have adapted novel techniques in CPB by miniaturizing and customizing the circuit to the patient's weight and using parameters such as mixed venous saturation,

**Table 3 Intraoperative variables in age categories for blood conservation and non-conservation cohorts**

Operative variables	NC	BC	P	NC	BC	P	NC	BC	P	NC	BC	P
	neonate n = 28 (12%)	neonate n = 23 (16%)		infant n = 69 (32%)	infant n = 52 (38%)		child n = 76 (35%)	child n = 29 (21%)		adolescent n = 45 (21%)	adolescent n = 34 (25%)	
Average age (d)	10 ± 9	12 ± 10	0.08	187 ± 109	139 ± 86	0.001	1638 ± 806	1730 ± 1012	0.44	6280 ± 1977	6671 ± 3103	0.78
Weight (kg)	3 ± 0.7	3 ± 1	0.94	6 ± 2	6 ± 2	0.3	19 ± 9	20 ± 9	0.49	60 ± 20	57 ± 17	0.19
% Male	60%	52%	0.35	45%	35%	0.59	45%	52%	0.83	69%	47%	0.07
Bypass (min)	161 ± 74	136 ± 53	0.15	124 ± 66	85 ± 39	< 0.001	83 ± 48	71 ± 45	0.04	116 ± 63	106 ± 59	0.54
Cross clamp (min)	75 ± 47	75 ± 39	0.99	74 ± 45	45 ± 30	< 0.001	37 ± 38	30 ± 32	0.16	46 ± 53	57 ± 46	0.3
Pre-operative Hct (%)	32 ± 2	37 ± 5	0.11	30 ± 5	32 ± 7	0.19	31 ± 4	31 ± 5	0.63	32 ± 7	34 ± 4	0.26
Pre-bypass Hct (%)	36 ± 7	35 ± 6	0.19	30 ± 6	31 ± 7	0.89	33 ± 5	31 ± 5	0.1	34 ± 5	33 ± 3	0.54
On-bypass Hct (%)	25 ± 3	23 ± 3	0.07	25 ± 3	23 ± 3	0.09	24 ± 3	23 ± 3	0.1	25 ± 3	28 ± 3	< 0.001
Post-bypass Hct (%)	47 ± 4	34 ± 5	0.001	35 ± 5	34 ± 4	0.3	31 ± 5	32 ± 4	0.75	28 ± 3	34 ± 4	< 0.001
Operative RBC (mL/kg)	236 ± 220	97 ± 34	0.01	90 ± 58	49 ± 24	< 0.001	25 ± 26	11 ± 10	0.01	5 ± 13	0.4 ± 2	0.02
RBC exposure (unit)	2 ± 0.5	1.0 ± 0.2	< 0.001	1.6 ± 0.7	0.8 ± 0.3	< 0.001	1.2 ± 0.9	0.6 ± 0.6	0.002	0.9 ± 2	0.04 ± 0.2	0.02

BC: Blood conservation; NC: Non-conservation; RBC: Red blood cell; Hct: Hematocrit.

**Table 4 Intraoperative variables in STAT categories for blood conservation and non-conservation cohorts**

Operative variables	NC	BC	P	NC	BC	P	NC	BC	P	NC	BC	P
	STAT 1 n = 118 (54%)	STAT 1 n = 73 (53%)		STAT 2 n = 53 (24%)	STAT 2 n = 25 (18%)		STAT 3 n = 29 (13%)	STAT 3 n = 15 (11%)		STAT 4 n = 17 (8%)	STAT 4 n = 21 (15%)	
Average age (d)	2419 ± 2667	3088 ± 3498	0.12	1500 ± 1947	1012 ± 2176	0.001	899 ± 1762	619 ± 1659	0.62	1724 ± 3559	1447 ± 2817	0.81
Weight (kg)	27 ± 26	29 ± 24	0.53	17 ± 18	15 ± 23	0.58	11 ± 13	9 ± 12	0.65	16 ± 25	14 ± 21	0.81
% Male	58%	42%	0.07	47%	56%	0.63	45%	40%	0.76	47%	38%	0.74
Bypass (min)	82 ± 37	74 ± 39	0.2	127 ± 68	94 ± 47	0.03	185 ± 73	131 ± 73	0.02	155 ± 66	132 ± 49	0.22
Cross clamp (min)	42 ± 29	38 ± 31	0.35	59 ± 55	43 ± 43	0.21	87 ± 64	81 ± 45	0.77	81 ± 58	71 ± 37	0.52
Pre-operative Hct (%)	31 ± 4	31 ± 4	0.77	29 ± 5	36 ± 8	0.09	34 ± 11	34 ± 6	0.95	37 ± 8	37 ± 7	0.7
Pre-bypass Hct (%)	31 ± 4	30 ± 4	0.62	35 ± 8	33 ± 7	0.39	35 ± 7	32 ± 6	0.14	35 ± 7	35 ± 6	0.7
On-bypass Hct (%)	24 ± 3	25 ± 4	0.07	25 ± 4	25 ± 4	0.45	25 ± 4	23 ± 3	0.04	25 ± 3	24 ± 4	0.37
Post-bypass Hct (%)	31 ± 4	33 ± 3	0.02	35 ± 5	36 ± 4	0.63	38 ± 5	32 ± 3	0.02	39 ± 12	34 ± 5	0.39
Operative RBC (mL/kg)	36 ± 50	21 ± 30	0.02	66 ± 65	40 ± 39	0.03	115 ± 78	53 ± 31	0.03	219 ± 301	64 ± 47	0.05
RBC exposure (unit)	0.9 ± 0.7	0.5 ± 0.6	< 0.001	1.7 ± 1	0.7 ± 0.4	< 0.001	2.2 ± 2.2	0.8 ± 0.5	< 0.001	2.0 ± 0.9	0.7 ± 0.4	< 0.001

BC: Blood conservation; NC: Non-conservation; RBC: Red blood cell; Hct: Hematocrit; STAT: Society of Thoracic Surgeon and European Association for Cardio-Thoracic Surgery Mortality Score.

regional cerebral saturations, and serum lactic acid levels to tailor our decision about RBC transfusion. The bypass circuit was primed with the patients' own blood by performing retrograde arterial and venous priming once the aortic and venous cannulas were in place for majority of the operative procedures. We also performed aggressive hemofiltration during the bypass run and performed arteriovenous MUF after termination of CPB to remove excessive intravascular volume. Pediatric cell saver also was used throughout the operation and the salvaged blood was infused before leaving the operating room or immediately after arrival to the PICU. The efficacies of these conservation measures and practices have been reported by others as the result of greater emphasis that has recently been placed in performing blood conservation cardiac surgery in pediatric population<sup>[16-19]</sup>.

Our general trigger point for RBC transfusion was hematocrit of less than 21% for older age and low complexity category patients with biventricular physiology, and less than 25% for neonates, high complexity, and

cyanotic univentricular patients. This protocol was followed as long other critical parameters of adequate systemic and cerebral perfusion remained within acceptable range. There were no patients in the blood conservation group whom experienced adverse neurologic events or other complications as the result of these changes in philosophy of RBC transfusion trigger points. We consistently maintained mixed venous saturation at greater than 60% and regional cerebral saturation at greater than the baseline level by increasing flow and cerebral vasodilation using pH-stat during cooling. The trend in serum lactate level after CPB was also used to determine the need for blood transfusion prior to leaving the operating room. Implementation of intraoperative transfusion algorithms in pediatric cardiac operations has also been shown to significantly reduce perioperative blood product use and morbidity<sup>[20]</sup>. Similarly, a comprehensive intraoperative blood-sparing approach that resulted in no transfusion in 25% of children undergoing cardiac operations compared with children who received a transfusion during the

surgery demonstrated a shorter length of postoperative mechanical ventilation and a shorter PICU stay<sup>[21]</sup>. This has also been demonstrated that blood conservation in pediatric cardiac surgery was associated with a decrease in post-operative inotropic needs, days on ventilator, and length of stay in patients with biventricular physiology<sup>[22]</sup>.

Historically, hemodilution during CPB was introduced to decrease homologous blood use and has been thought to improve microcirculatory flow<sup>[23,24]</sup>. Hemodilution also potentially could reduce perfusion pressure, which increases the risk of an adverse neurologic outcome after CPB, increases cerebral blood flow and thereby increases the microembolic load to the brain, and reduces the oxygen carrying capacity of blood which might critically limit oxygen delivery to neurons and other cells<sup>[25]</sup>. Intraoperative implementation of hemodilution restriction prior to CPB to maintain the hematocrit close to preoperative hematocrit is paramount to a successful blood conservation cardiac surgery practice. By limiting crystalloid infusion during and after anesthesia induction, we significantly reduced the additional hemodilution that the patient will invariably face upon initiation of CPB. Having higher hematocrit prior to CPB will allow for retrograde priming of the bypass circuit and higher hematocrit during and after bypass. This was consistently achieved with our protocol and circuit modification throughout the operation despite lower RBC utilization signifying the efficacy of our conservation strategies across all ages and complexity levels.

This study carries some of the known limitations of a retrospective study design. It precludes accurate assessment of practice pattern and trigger points for RBC transfusion in the non-conservation group. There were also differences in surgeons as well as perfusion techniques and equipment that collectively could affect the variability in RBC transfusion trigger point and practices. Also, because of the lack of electronic charting and the absence of specific intraoperative measurements (*i.e.*, cerebral and somatic saturation, serum lactic acid level) for non-conservation cohorts, we could not perform any statistical comparison for some variables between the two groups.

This study has shown that blood conservation in pediatric cardiac surgery is reproducible across different ages and complexity categories. Miniaturization of the CPB circuit, contemporary techniques and equipment, and institutional commitments and protocols were paramount in establishing a successful blood conservation program. Future improvements in perfusion technology and blood conservation protocols in association with additional prospective randomized trials will further capitalize our understanding of the benefit of blood conservation in pediatric cardiac surgery.

surgical patients are at high risk of receiving blood transfusion as the result of cardiopulmonary bypass. Blood conservation surgery practice has been encouraged to reduced or eliminate related risks.

### Research frontiers

The principle author has demonstrated previously that blood conservation in pediatric cardiac operations is associated with fewer ventilator days, lower inotropic scores, and shorter lengths of stay in patients with biventricular physiology. This study has expanded the safety and applicability of blood conservation cardiac surgery practice to all ages and complexity levels in patients with biventricular and univentricular hearts.

### Innovations and breakthroughs

Blood conservation cardiac surgery has been a quest of surgeons for a long time due to associated risks inherent to homologous blood transfusion. There are sporadic successful reports of blood conservation surgery in pediatric population with no concrete methodology or guidelines accepted by most practices to adapt and implement it in their practices. In most part, there are no accepted guidelines in what would be a safe hematocrit range during circulatory support in order to avoid cerebral and end organ ischemic injuries. This single-intuition retrospective study is the only study that has demonstrated blood conservation pediatric cardiac surgery can safely be performed in all ages and complexity categories in a wide spectrum of structural congenital cardiac defects.

### Peer-review

The authors present their experience with implementing a blood conservation strategy for pediatric cardiac surgery at their institution. Overall, the manuscript is best categorized as a quality improvement evaluation.

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## COMMENTS

### Background

Transfusion of homologous red blood cell has been associated with increase in morbidity in pediatric patients undergoing cardiac surgery. Pediatric cardiac

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Retrospective Cohort Study

## Bilateral *vs* unilateral internal mammary revascularization in patients with left ventricular dysfunction

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**Institutional review board statement:** Our retrospective study of patients' files was approved by the Commission Nationale Informatique et Libertés (CNIL), in keeping with French law for single-center usual care observational studies.

**Informed consent statement:** All study participants, or their legal guardian, provided informed written consent prior to study enrolment.

**Conflict-of-interest statement:** None of the authors have any conflict of interest regarding the content of this article.

**Data sharing statement:** Consent was not obtained but the presented data are anonymized and risk of identification is low.

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### Abstract

#### AIM

To investigate the survival benefit of bilateral internal mammary artery (BIMA) grafts in patients with left ventricular dysfunction.

#### METHODS

Between 1996 and 2009, we performed elective, isolated, primary, multiple cardiac arterial bypass grafting in 430 consecutive patients with left ventricular ejection fraction  $\leq 40\%$ . The early and long-term results were compared between 167 patients undergoing BIMA grafting and 263 patients using left internal mammary artery (LIMA)-saphenous venous grafting (SVG).

#### RESULTS

The mean age of the overall population was  $60.1 \pm 15$  years. In-hospital mortality was not different between the two groups (7.8% *vs* 10.3%,  $P = 0.49$ ). Early postoperative morbidity included myocardial infarction (4.2% *vs* 3.8%,  $P = 0.80$ ), stroke (1.2% *vs* 3.8%,  $P = 0.14$ ), and mediastinitis (5.3% *vs* 2.3%,  $P = 0.11$ ). At 8-year follow-up, Kaplan-Meier-estimated survival (74.2% *vs* 58.9%,  $P = 0.02$ ) and Kaplan-Meier-estimated event-

free survival (all cause deaths, myocardial infarction, stroke, target vessel revascularization, heart failure) (61.7% and 41.1%,  $P < 0.01$ ) were significantly higher in the BIMA group compared with the LIMA-SVG group in univariate analysis. The propensity score matching analysis confirmed that BIMA grafting is a safe revascularization procedure but there was no long term survival ( $P = 0.40$ ) and event-free survival ( $P = 0.13$ ) in comparison with LIMA-SVG use.

### CONCLUSION

Our longitudinal analysis suggests that BIMA grafting can be performed with acceptable perioperative mortality in patients with left ventricular dysfunction.

**Key words:** Bilateral internal mammary artery grafting; Heart failure; Coronary artery disease

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**Core tip:** This study reports a daily practice observation of patients with multivessel coronary artery disease and left ventricular (LV) dysfunction undergoing surgical revascularization. We evaluate the periprocedural safety of bilateral internal mammary artery grafting (BIMA) in this high risk population and its long-term survival benefit compared with the left internal mammary artery grafting (LIMA) to left anterior descending artery with additional saphenous venous grafting (SVG). Our longitudinal analysis suggests that BIMA grafting can be performed with acceptable perioperative mortality in patients with LV dysfunction but there was no survival difference in our follow up in comparison with LIMA-SVG use.

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## INTRODUCTION

Coronary artery disease is an important contributor to the rise in the prevalence of heart failure and its associated morbidity and mortality<sup>[1,2]</sup>. Severe left ventricular (LV) dysfunction caused by extensive coronary artery disease usually carries a poor prognosis, although surgical revascularization is thought to be the most effective treatment strategy<sup>[2-4]</sup>. Myocardial revascularization in patients with severe LV dysfunction preserves the remaining myocardium, prevents further myocardial damage, and induces the recovery of systolic function in ischemic LV myocardial segments. However, although advances in surgical techniques and myocardial protection have improved outcomes, cardiac arterial bypass grafting (CABG) in patients with LV impairment is still associated

with high perioperative risk and the long-term survival remains unsatisfactory overall.

The use of a single internal mammary artery rather than vein graft to the left anterior descending coronary artery has become the standard operation, largely due to excellent long-term graft patency into the first and second postoperative decade<sup>[5]</sup>. The superior outcome associated with left internal mammary artery (LIMA) grafting has quickly encouraged the use of bilateral internal mammary artery (BIMA)<sup>[6,7]</sup>. However, the widespread adoption of BIMA grafting is hindered because it might be associated with increased early morbidity.

We report here our experience in patients with multivessel coronary artery disease and LV dysfunction undergoing surgical revascularization. We evaluate the periprocedural safety of BIMA grafting in this high risk population and its long-term survival benefit compared with the conventional standard-of-care CABG using the LIMA to left anterior descending artery with additional saphenous venous grafting (SVG).

## MATERIALS AND METHODS

### Patients

From April 1996 to December 2009, 4210 patients underwent isolated CABG at our university center. From this group, we identified 430 patients with left ventricular ejection fraction (LVEF) of  $\leq 40\%$  who underwent primary isolated multivessel CABG with a least 2 grafts. Among them, 167 procedures were performed using BIMA grafting  $\pm$  SVG and 263 procedures were performed with LIMA and SVG. Exclusion criteria were patients older than 80 years, surgical myocardial revascularization of only one coronary artery, concomitant repair/replacement of valve, cardiac rupture, ventricular aneurysm or ascending aortic aneurysm.

Coronary artery disease was defined as a reduction of the vessel diameter by  $\geq 70\%$  in 1 view on coronary angiography. The presence of stenosis  $\geq 70\%$  in the left anterior descending, circumflex, or right coronary system was used as the criterion for single, double, or triple-vessel disease.

The preoperative measurement of LV chamber size at end-diastole and end-systole as well as the assessment of mitral regurgitation were performed by transthoracic two-dimensional echocardiographic images in the parasternal long-axis view (including M-mode) and by apical four-chamber view. LVEF was measured using Simpson's method with two views. LV chamber dilatation was defined by LV diastolic diameter  $> 54$  mm and  $> 60$  mm in women and men respectively<sup>[8]</sup>. Mitral regurgitation was quantified according to the prevailing guidelines at the time of the study and was taken into account as reported by the expert cardiologist who performed the examination. Before myocardial revascularization, the heart team, including cardiologists and surgeons, systematically identified the target vessels according to myocardial viability. Revascularization was considered complete if every significant target vessel was grafted.

### Surgical technique

Our selection of patients for LIMA-SVG and BIMA grafting was not random but was influenced by the heart team decision and was decided from the *in situ* graft size. CABG was performed using standard on-pump or off-pump bypass techniques at the discretion of the operating surgeon. Myocardial preservation during cardiopulmonary bypass involves normothermic, intermittent, antegrade and retrograde blood cardioplegia.

The LIMA was harvested as a pedicle and grafted exclusively to the left coronary system. The right internal mammary artery (RIMA) was mostly harvested as a pedicle and grafted to the left coronary system or the right coronary artery, and in a minority of cases, used as a free graft. A free RIMA was used when the length of the conduit was too short, or if the distal anastomotic site was unreachable with a pedicled RIMA. The composite graft included an end-to-side anastomosis of the free RIMA onto an *in situ* LIMA. The right gastroepiploic artery or radial artery was not used as a third arterial conduit in our study.

### Definitions of terms and data collection

The in-hospital course was studied in terms of procedural characteristics, vital status, renal status, peri- and post-operative red blood cell transfusions, infectious complications, myocardial infarction, cerebrovascular events, mesenteric ischemia, emergency repeat coronary and/or peripheral revascularization procedures and arrhythmias.

Patients did not undergo systematic control angiography during the follow-up period. Perioperative myocardial infarction (*i.e.*, within 7 d after intervention) was defined as a creatine kinase-MB  $\geq 5$  times the upper limit of normal, with new Q waves in 2 contiguous leads on the postoperative electrocardiogram or the new development of bundle branch block. In the case of elevated creatine kinase levels at baseline, myocardial infarction was defined as an increase of  $> 50\%$  over baseline values after intervention. After this postoperative period, myocardial infarction was defined as the presence of new pathologic Q waves or the new development of left bundle branch block with increased cardiac marker levels (*i.e.*, creatine kinase-MB  $\geq 3$  times the upper limit of normal). Cardiovascular death included death resulting from an acute myocardial infarction, sudden cardiac death, hospitalization for heart failure, stroke, pulmonary embolism or digestive ischemia.

Event free survival is a composite end point of all cause deaths, myocardial infarction, stroke, target vessel revascularization and first hospitalization for heart failure.

Follow up was obtained through comprehensive questionnaires and by telephone with the patient's personal physician. If subsequent hospitalization, death, or other events had occurred, the patient's physician or appropriate hospital record department were interviewed to document the events.

This study was conducted according the principles

of the Helsinki declaration. The retrospective study of patients' files was approved by the Commission Nationale Informatique et Libertés (CNIL), in keeping with French law for single-center usual care observational studies.

### Statistical analysis

Continuous variables are presented as means  $\pm$  standard deviation (SD), categorical variables as frequencies (percentages). Comparison of patients characteristics between groups were carried out using Student's *t* tests, Wilcoxon tests or Pearson's  $\chi^2$  tests as required. Kaplan-Meier survival curves were compared using the log-rank test.

The associations between mortality and age, sex, risk factors, previous history, clinical presentation and LV ejection fraction were performed using Cox regression models. Assumptions of log-linearity, absence of interaction between surgical strategy and adjustment covariate mentioned above, absence of collinearity and proportionality of hazards were thoroughly verified. Cox proportionality assumption was verified using interaction between time and each covariate. A propensity score was developed to control the selection bias potentially related to surgery strategy. Propensity scores were constructed using logistic model with surgery strategy as predicted event and independent covariates which were selected a priori on the basis of their known or suspected association with both surgery strategies and mortality and cardiovascular events. A value of  $P < 0.05$  was used to determine the statistical significance of all tests.

## RESULTS

The patients' baseline and operative characteristics are presented in Tables 1 and 2.

From April 1996 to December 2009, we identified 430 patients with LVEF  $\leq 0.4$  who underwent isolated CABG including patients with LVEF  $\leq 30\%$  in 34% of cases.

Patients who received LIMA-SVG grafting were significantly older than BIMA group ( $64 \pm 9$  years vs  $58.5 \pm 10$  years,  $P = 0.01$ ), with more frequent dyslipidemia ( $59.6\%$  vs  $69.6\%$ ,  $P = 0.04$ ) and trend for a more frequent peripheral artery disease ( $42.2\%$  vs  $33.1\%$ ,  $P = 0.07$ ).

Patients who received BIMA grafting were significantly younger than LIMA-SVG ( $58.5 \pm 10$  years vs  $64 \pm 9$  years,  $P = 0.01$ ) with less frequent dyslipidemia ( $59.6\%$  vs  $69.6\%$ ,  $P = 0.04$ ). Although acute coronary syndrome and ambulatory myocardial infarction were the most common clinical presentations in both groups, NYHA class 3 and 4 in the preoperative period was more frequent in group 2 ( $P = 0.03$ ).

The analysis of echocardiographic parameters showed that mean LVEF, LV chamber dilatation and the presence of mitral insufficiency  $\geq 2$  were not significantly different between two groups.

The number of grafts per patient was similar in both

**Table 1 Clinical and demographic characteristics of the study groups**

Characteristics [n (%)]	Unmatched groups			Propensity score-matched groups		
	BIMA (n = 167)	LIMA-SVG (n = 263)	P	BIMA (n = 130)	LIMA-SVG (n = 130)	P
Age (yr)	58.5 ± 10.3	64.3 ± 9.0	0.01	60.6 ± 9.9	60.5 ± 10.0	0.95
Female sex	20 (12.0)	30 (11.5)	0.88	16 (12.3)	19 (14.6)	0.71
Hypertension	87 (52.4)	163 (61.5)	0.07	70 (53.8)	73 (56.2)	0.80
Diabetes mellitus	66 (39.5)	97 (36.9)	0.61	53 (40.8)	54 (41.5)	0.90
Hypercholesterolemia <sup>1</sup>	99 (59.6)	183 (69.6)	0.04	79 (60.8)	82 (63.1)	0.79
History of smoking	116 (69.5)	173 (65.8)	0.53	84 (64.6)	83 (63.8)	0.89
Body mass index (kg/m <sup>2</sup> )	27.6 ± 4.4	27.4 ± 4.3	0.85	27.6 ± 4.5	27.3 ± 4.3	0.56
Other comorbid conditions	16 (9.6)	31 (11.8)	0.53	12 (9.2)	9 (6.9)	0.65
Chronic renal insufficiency COPD <sup>2</sup>	28 (16.8)	53 (20.5)	0.38	24 (18.5)	23 (17.7)	0.87
Peripheral artery disease	55 (33.1)	111 (42.2)	0.07	44 (33.8)	45 (34.6)	0.89
Prior ischemic cardiopathy	83 (49.7)	154 (58.5)	0.11	68 (52.3)	67 (51.5)	0.90
Previous PCI	48 (28.7)	70 (26.6)	0.66	36 (28.5)	38 (29.2)	0.89
EuroSCORE logistic <sup>3</sup> (%)	7.5 ± 6.9	8.0 ± 6.0	0.21	7.5 ± 7.1	8.0 ± 6.1	0.90
Symptoms						
Stable angina pectoris	50 (30.1)	70 (26.6)	0.90	36 (28.5)	36 (27.7)	0.90
Acute coronary syndrome	71 (42.5)	117 (44.5)	0.86	58 (44.6)	55 (42.3)	0.90
ambulatory Q wave MI	22 (13.2)	40 (15.2)	0.95	18 (13.8)	21 (16.2)	0.85
silent ischemia	33 (13.8)	36 (13.7)	0.98	17 (13.1)	18 (13.8)	0.90
NYHA class 3-4	47 (28.1)	112 (42.8)	0.03	45 (34.6)	46 (35.4)	0.99
Angiographic parameters: Three coronary arteries narrowed (≥ 70%)	112 (67.1)	165 (62.7)	0.35	83 (63.8)	85 (65.4)	0.90
Mitral insufficiency grade ≥ 2	24 (14.6)	46 (18.0)	0.19	22 (16.9)	24 (18.5)	0.80
Left ventricular chamber dilatation	55 (32.9)	100 (38.0)	0.29	45 (34.6)	47 (36.1)	0.42
Ejection fraction (%)	35.2 ± 5.9	33.5 ± 5.8	0.58	34.5 ± 6.0	34.6 ± 5.6	0.80

<sup>1</sup>Previously documented diagnosis of dyslipidemia or new diagnosis for a total cholesterol > 200 mg/dL; <sup>2</sup>Creatinine clearance < 40 mL/min; <sup>3</sup>EuroSCORE: European System for Cardiac Operative Risk Evaluation score. BIMA: Bilateral internal mammary artery; LIMA: Left internal mammary artery; SVG: Saphenous vein graft; COPD: Chronic obstructive pulmonary disease; PCI: Percutaneous coronary intervention; MI: Myocardial infarction; NYHA: New York Heart Association.

**Table 2 Procedural characteristics of the study groups**

Characteristics [n (%)]	BIMA group (n = 167)	LIMA-SVG group (n = 263)	P
On-pump surgery	164 (98.8)	245 (93.1)	0.80
Mean number of grafts per patient	2.5 ± 0.6	2.5 ± 0.7	0.91
Complete coronary revascularization	117 (70.1)	175 (66.5)	0.50
Extracorporeal circulation time (min)	79.5 (65.2-100)	80.0 (64-100)	0.86
Median (IQR)			
Length of stay in ICU (d)	3.1 (2-4)	3.2 (2-5)	0.11
Median (IQR)			
Length of stay in hospital (d)	8.2 (7-11)	9.3 (6-12)	0.12
Median (IQR)			
Ventilation time < 24 h	160 (95.8)	210 (79.9)	< 0.01
IABP	12 (7.2)	24 (9.1)	0.80
Vasopressors or inotropic drugs (> 24 h)	45 (27.3)	107 (41.1)	< 0.01
Transfusion (red blood cell units ≥ 3)	53 (31.7)	123 (46.7)	< 0.01

BIMA: Bilateral internal mammary artery; LIMA: Left internal mammary artery; SVG: Saphenous vein graft; ICU: Intensive care unit; IABP: Intra-aortic balloon counterpulsation.

groups, most surgeries were performed on-pump, and complete revascularization was obtained in 70% of group 1 compared with 66.5% of group 2 (*P* = 0.50).

In group 1, the LIMA was harvested almost exclusively as a pedicle and grafted onto the left coronary system. The LIMA was grafted onto the circumflex as a free graft in 4 patients. A sequential anastomosis technique for the left anterior descending artery and diagonal branch was used in 30 patients. The RIMA graft was anastomosed to the left coronary system in 141 (82%) patients and the

right coronary artery in 31 (18%) patients. The RIMA was harvested as a pedicle in most cases and was grafted onto the circumflex artery as a free graft or on an *in situ* LIMA in 39 patients (23% of cases).

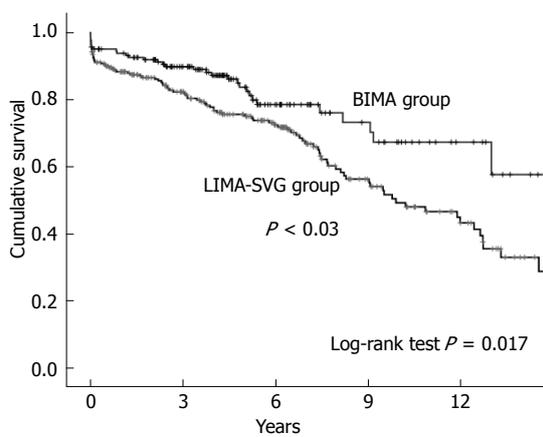
**Early results**

The older age of patients and worse initial clinical status in LIMA group influenced the post-operative period with longer ventilation time, higher vasopressor use and transfusion.

**Table 3** In-hospital course

Characteristics [n (%)]	BIMA group (n = 167)	LIMA-SVG group (n = 263)	P
All-cause mortality	13 (7.8)	27 (10.3)	0.49
Cardiovascular mortality	8 (4.8)	23 (8.7)	0.10
Myocardial infarction	7 (4.2)	10 (3.8)	0.80
Redo CABG	2 (1.2)	2 (0.8)	0.64
Stroke	2 (1.2)	10 (3.8)	0.14
Mesenteric ischemia	3 (1.8)	5 (1.9)	0.94
Mediastinitis	9 (5.3)	6 (2.3)	0.11
Cardiac rehabilitation	79 (47.3)	104 (39.5)	0.40
1-yr follow up LVEF	44.2% ± 10.1%	41.3% ± 10.2%	0.81

BIMA: Bilateral internal mammary artery; LIMA: Left internal mammary artery; SVG: Saphenous vein graft; CABG: Coronary artery bypass graft; LVEF: Left ventricular ejection fraction.



Patients at risk:	0	3	6	9	12
BIMA group	167	106	49	24	10
LIMA-SVG group	263	168	109	49	26

**Figure 1** Kaplan-Meier estimated overall survival in unmatched cohorts. BIMA: Bilateral internal mammary artery; LIMA: Left internal mammary artery; SVG: Saphenous venous graft.

The overall in-hospital mortality rate in our study was 9.5%, and cardiovascular mortality represented 75% of deaths. The analysis of in-hospital course showed that all-cause mortality (7.8% vs 10.3%,  $P = 0.49$ ) and early postoperative morbidity including myocardial infarction (4.2% vs 3.8%,  $P = 0.80$ ), stroke (1.2% vs 3.8%,  $P = 0.14$ ), and digestive ischemia (1.8% vs 1.9%,  $P = 0.94$ ) were not significantly different between two groups (Table 3).

Mediastinitis requiring sternal re-opening and antibiotics occurred in 15 patients without significant difference between two groups group (5.3% vs 2.3%,  $P = 0.11$ ). Among patients who experienced mediastinitis, 8 (53.3%) patients were diabetic and 7 (43%) were obese.

**Long-term results**

The long-term follow-up (mean follow up: 6.2 ± 3.8 years; median follow up: 5.6 years) revealed 135 deaths, including 75 cardiovascular deaths.

The evidence-based medical postoperative treatment didn't significantly differ between LIMA-SVG group and BIMA group: Statin therapy (88.3% vs 94.7%,  $P = 0.4$ ),

beta blockers (77.1% vs 82.0%,  $P = 0.4$ ), angiotensin-converting enzyme inhibitor (84.3% vs 88.6%,  $P = 0.6$ ) and aspirin (90.5% vs 94.7%,  $P = 0.7$ ). During the follow up, 18 patients received an implantable cardiac defibrillator without significant difference between two groups.

At 1-year follow-up, LVEF value was obtained in 93.0% of cases, and mean LVEF in the overall population was 43.1% ± 6.2%. In comparison with the preoperative LVEF estimation, 1-year LVEF was improved in 72.5% of cases (in LIMA-SVG and BIMA groups: 71.3% and 74.9%, respectively,  $P = 0.32$ ) and unchanged or worsened in 27.5% of cases. A LVEF of > 50% was achieved in 49.1% of cases.

Figure 1 show Kaplan-Meier estimated overall survival in unmatched cohorts. The Kaplan-Meier 8-year estimated overall survival for patients in the BIMA group compared with patients in the LIMA-SVG group were 74.2% and 58.9%, respectively ( $P = 0.02$ ) but this significant difference became insignificant after multivariate adjustment hazard ratio (HR) [95% confidence interval (CI)] 1.02 (0.68-1.56),  $P = 0.8$ .

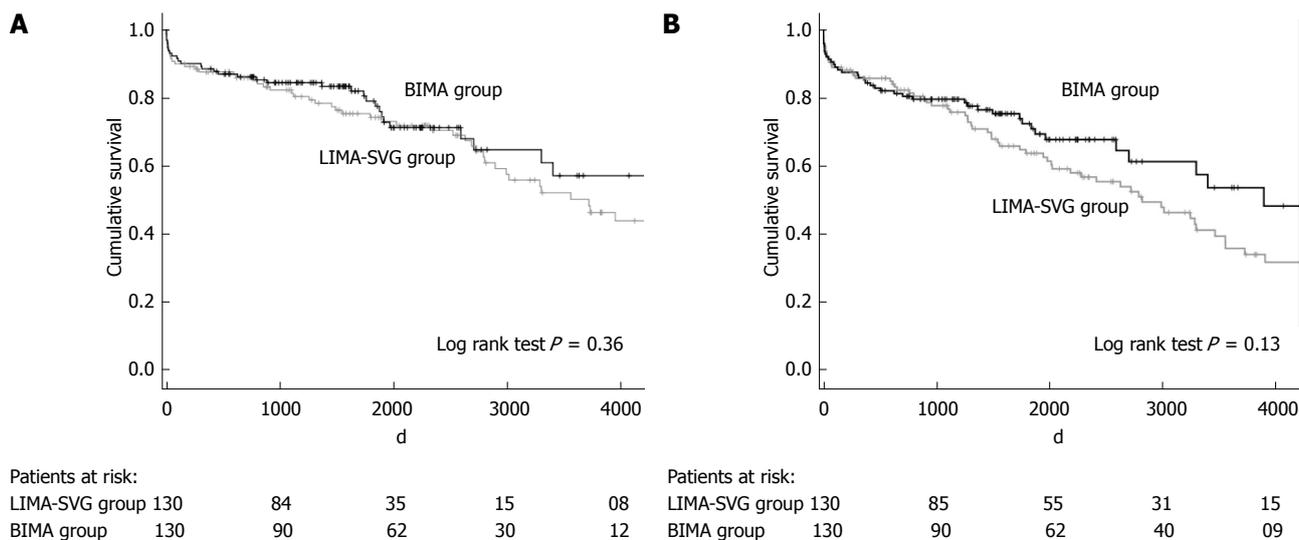
We performed 1:1 propensity score matching to select patients receiving BIMA or LIMA SVG group with comparable preoperative characteristics (Figure 2).

The propensity score matching analysis revealed that BIMA grafting is a safe revascularization procedure without on long term survival ( $P = 0.40$ ) or event free survival ( $P = 0.13$ ) difference in comparison with LIMA-SVG use.

**DISCUSSION**

We present a large, single-center observational study of surgical coronary revascularization in patients with reduced LVEF, which represent a sizeable proportion of all procedures performed at our hospital during this period (11% of cases).

Our analysis of the overall postoperative course is consistent with large contemporary reports on the topic, which indicate an in-hospital mortality ranging from about 4% to greater than 20% according to the comorbid conditions and the degree of LV dysfunction<sup>[4,9,10]</sup>.



**Figure 2** Kaplan-Meier estimated overall survival curves. A: Event-free survival; B: Comparing BIMA and LIMA-SVG in a propensity score-matched cohorts. BIMA: Bilateral internal mammary artery; LIMA: Left internal mammary artery; SVG: Saphenous vein graft.

One of the most interesting points of our study is to confirm that BIMA grafting does not modify the postoperative mortality in patients with LV impairment compared to LIMA-SVG grafting. Furthermore, although BIMA grafting appears to be the technically more challenging of the two techniques, the duration of surgical procedures did not differ between the two groups. This similarity may explain the relatively good postoperative outcome. The safety of BIMA grafting was also demonstrated by relatively low rates of periprocedural stroke, myocardial infarction and mesenteric ischemia, with no significant differences from the control group.

Sternal deep wound infection is a major complication after cardiac surgery with high in-hospital mortality (30% in our study). This complication concerned 3.5% of our overall population without significant difference between both surgical revascularization strategies. Among patients who experienced mediastinitis in our report, diabetes and obese patients represent well known high-risk subgroups (54% and 43% respectively)<sup>[11,12]</sup>. There is now good evidence in the contemporary literature that the use of both internal mammary arteries doesn't significantly increase the rate of sternal deep wound complication, especially with the skeletonized technique<sup>[13,14]</sup>. Moreover, high-risk subgroups as diabetic patients have the most to gain from this technique thereby preserving collaterals and sternal blood supply<sup>[14,15]</sup>. Galbut *et al*<sup>[16]</sup> also confirms that BIMA grafting doesn't significantly increase the rate of sternal wound infection whatever the preoperative LV function.

Late survival, although reduced when compared with patients with no decrease in LVEF, remains relatively high with estimated 5- and 8-year overall survival rates of 77% and 64%, respectively, in our study. This prognosis is largely influenced by the reduction of ischemia and the preservation of the remaining myocardium leading to the improvement of postoperative LVEF. In our study, we noted that LVEF was improved by surgical

revascularization in 72.5% of cases at 1 year follow-up, and LVEF was > 50% in 49.1% of cases. This benefit on LVEF is especially shown in patients with ischemic but viable myocardium who subsequently underwent revascularization<sup>[17,18]</sup>. However, the lack of interaction between myocardial viability status and benefit from CABG in the Stich trial indicates that assessment of myocardial viability alone should not be the deciding factor in selecting the best therapy for these patients<sup>[8]</sup>. Other structural predictive parameters such as LV volumes and ischemic mitral regurgitation should be taken into account for intervention planning.

Long-term survival after CABG is presumed to be directly correlated with late patency of the selected conduits and grafts. The internal mammary artery upregulates eNOS and therefore has higher concentration of NO than other conduits, which not only explain its improved patency but also likely has a significant impact on vascular endothelium and resistance to atherosclerosis in the grafted coronaries or in the coronaries that were not bypassed<sup>[19]</sup>.

However, the benefit of arterial conduits seems to concern internal mammary artery conduits in a majority of cases. Ruttman *et al*<sup>[20]</sup> demonstrated the superiority of the internal mammary artery graft over the radial artery as a second graft, and the benefit of all-arterial revascularization using additional radial artery is still debated.

Several large studies recently added to the growing literature that confirms the superiority of BIMA grafting over LIMA use, particularly in terms of improved long-term mortality with no significant increase in perioperative complications<sup>[7,13,21]</sup>. Recently, Locker *et al*<sup>[7]</sup> showed that multi-artery grafting compared with LIMA-SVG improved long-term survival in almost all comorbid conditions, including impaired LV function.

In our analysis, the difference between the BIMA group and the LIMA-SVG group concerning long-term

survival and event-free survival was significant in a univariate analysis. The older age of patients in LIMA-SVG group and the difference in baseline characteristics between the two groups may explain in part these results. However, the propensity score matching analysis revealed that BIMA grafting is a safe revascularization procedure but no significant difference on long term survival in comparison with LIMA-SVG was noted. These results reflect possibly the small size of two groups after propensity score matching analysis and therefore a type II error. It also suggests that the difference between these surgical strategies remains small in patients with low to moderate LVEF ( $\leq 40\%$ ) despite a long term follow up.

Galbut *et al.*<sup>[16]</sup> recently confirmed also that the benefit of BIMA grafting on long term survival concerned especially patients with normal LV function and moderate LV dysfunction (LVEF from 30% to 50%). However, this revascularization strategy should be considered with more caution in patients with low LV dysfunction.

It seems that the advantage of BIMA grafting compared with LIMA-SVG grafting in patients with reduced ejection fraction increases over time and the real benefit depends on survival probability determined by age and comorbidities. Comorbid factors, especially postoperative atrial fibrillation also increase the risk of long-term mortality and should be given important consideration when evaluating the benefits of the surgical revascularization strategy<sup>[22]</sup>. Therefore, further stratified analyses with larger number of patients and a follow up of one or two decades should be encouraged to identify the exact benefit from BIMA grafting in this situation.

### Limitations

Our study was a non-randomised, retrospective, and observational study with inherent bias.

There was a definite patient selection bias, demonstrated by a younger population in BIMA group that led to overestimate the benefits of this procedure in univariate analyses. The cut-off value of ejection fraction  $\leq 40\%$  has also influenced the results of our study. Further stratified analysis with larger number of patients should identify the exact benefit of BIMA grafting according to different level of LV dysfunction. Other variables not included in the multivariate models, however, may also influence the results of surgical revascularization as the quality of coronary vessels requiring bypass grafting and the location of both grafts. Likewise, we cannot exclude that the degree of viability or extent of fibrosis/necrosis might have led to the preferred choice of one or the other operative technique.

Medications including beta blockers, statins or ACE inhibitors at the time of discharge but also LV remodelling<sup>[23]</sup> and mitral regurgitation<sup>[24]</sup> might have affected the long term results. However, multiple adjustments using many factors could not be performed because of limited number of events.

Patients with severe coronary artery disease and markedly reduced LVEF represent a high-risk group

that can undergo CABG safely. Our longitudinal analysis suggests that BIMA grafting can be performed with acceptable perioperative mortality in patients with LV dysfunction but there was no survival difference in our follow up in comparison with LIMA-SVG use. Further studies, assessing the long-term impact hybrid approaches using BIMA and elective PCI using drug eluting stents will determine whether these new approaches constitute a true improvement in the field of myocardial revascularization<sup>[25]</sup>.

## COMMENTS

### Background

Patients with severe coronary artery disease and markedly reduced left ventricular ejection fraction represent a high-risk group that can undergo cardiac arterial bypass grafting (CABG) safely. The excellent outcome associated with left internal mammary artery (LIMA) grafting has quickly encouraged the use of bilateral internal mammary artery (BIMA). However, the widespread adoption of BIMA grafting is hindered because it might be associated with increased early morbidity. The aim of this study was to review the authors' institutional experience over 13 years with 430 patients with left ventricular (LV) dysfunction who underwent surgical revascularization.

### Research frontiers

To our knowledge, this is the largest single center observational report on patients with LV dysfunction who underwent myocardial surgical revascularization.

### Innovations and breakthroughs

This longitudinal analysis demonstrates that BIMA grafting can be performed with acceptable perioperative mortality in patients with LV dysfunction but there was no survival difference in our follow up in comparison with LIMA-SVG use.

### Applications

Appropriate patient selection.

### Terminology

BIMA grafting (bilateral internal mammary artery grafting) and LIMA-SVG (left internal mammary artery with saphenous venous) grafting: Two surgical strategies used to revascularize heart with impaired function.

### Peer-review

The manuscript is well written and addresses interesting and important facts regarding the revascularisation in left ventricular dysfunction.

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## Retrospective Study

**QT prolongation is associated with increased mortality in end stage liver disease**

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**Informed consent statement:** Patients were not required to give informed consent to the study because the analysis used clinical data without storage of patient identifiers that were obtained after each patient agreed to treatment by written consent. Waiver of informed consent was also obtained because the research involved no more than minimal risk and met criteria specified by federal regulations.

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## Abstract

### AIM

To determine the prevalence of QT prolongation in a large series of end stage liver disease (ESLD) patients and its association to clinical variables and mortality.

### METHODS

The QT interval was measured and corrected for heart rate for each patient, with a prolonged QT cutoff defined as QT > 450 ms for males and QT > 470 ms for females.

Multiple clinical variables were evaluated including sex, age, serum sodium, international normalized ratio, creatinine, total bilirubin, beta-blocker use, Model for End-Stage Liver Disease (MELD), MELD-Na, and etiology of liver disease.

### RESULTS

Among 406 ESLD patients analyzed, 207 (51.0%) had QT prolongation. The only clinical variable associated with QT prolongation was male gender (OR = 3.04, 95%CI: 2.01-4.60,  $P < 0.001$ ). During the study period, 187 patients (46.1%) died. QT prolongation was a significant independent predictor of mortality (OR = 1.69, 95%CI: 1.03-2.77,  $P = 0.039$ ). In addition, mortality was also associated with viral etiology of ESLD, elevated MELD score and its components ( $P < 0.05$  for all). No significant reversibility in the QT interval was seen after liver transplantation.

### CONCLUSION

QT prolongation was commonly encountered in an ESLD population, especially in males, and served as a strong independent marker for increased mortality in ESLD patients.

**Key words:** Cirrhosis; Electrophysiology; Arrhythmias; QT prolongation; Mortality; Liver transplantation

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**Core tip:** We performed a case-control retrospective study in a large cohort of patients with end stage liver disease (ESLD) to determine the prevalence of QT prolongation and its association to clinical variables and mortality. Our results showed a high prevalence of QT prolongation in ESLD patients (51%), especially in males, and QT prolongation was a significant independent predictor of mortality. Based on our findings, we recommend close monitoring of the QT interval in ESLD patients with increased attention to any modifiable causes for QT prolongation.

Kim SM, George B, Alcivar-Franco D, Campbell CL, Charnigo R, Delisle B, Hundley J, Darrat Y, Morales G, Elayi SC, Bailey AL. QT prolongation is associated with increased mortality in end stage liver disease. *World J Cardiol* 2017; 9(4): 347-354 Available from: URL: <http://www.wjgnet.com/1949-8462/full/v9/i4/347.htm> DOI: <http://dx.doi.org/10.4330/wjc.v9.i4.347>

## INTRODUCTION

The QT interval on an electrocardiogram (ECG) is a measure of ventricular depolarization and repolarization. Prolongation of the QT interval is associated with ventricular arrhythmias as well as sudden cardiac death in both congenital and acquired conditions. Multiple factors are thought to be responsible for the prolongation

of the QT interval in both congenital and acquired conditions, including electrolyte abnormalities, ventricular channelopathies, myocardial ischemia, medications, alcohol toxicity, and autonomic imbalance with sympathetic nervous system hyperactivity<sup>[1-11]</sup>. Recent studies have shown that end stage liver disease (ESLD) is associated with several electrophysiological changes; specifically, an increased prevalence of QT prolongation is seen in this population<sup>[12-30]</sup>. While the exact mechanism for QT prolongation is unknown, both improvement in liver function and liver transplantation have been associated with significant shortening in the QT interval in studies with small sample sizes<sup>[25-31]</sup>. Likewise, previous studies demonstrate reduction in the QT interval for cirrhotic patients who receive beta-adrenergic blockade in both the acute and chronic settings<sup>[32-34]</sup>. Thus, this may be a modifiable condition and amenable to therapy. Although some studies suggest a prolonged QT interval is related to severity of liver disease, etiology of liver disease, and increased mortality, conflicting results exist regarding these important clinical questions<sup>[14,19,24-30,35,36]</sup>.

We aimed to determine the prevalence and variables associated with QT prolongation in ESLD patients. Furthermore, we assessed whether QT prolongation was associated with increased mortality in these patients.

## MATERIALS AND METHODS

The research study was conducted in accordance to the ethical guidelines of the 1975 Declaration of Helsinki as reflected by approval by the institutional review board. After institutional review board approval was obtained, we performed a case-control retrospective study estimating the prevalence of QT prolongation in a cohort of cirrhotic patients with ESLD being evaluated for liver transplant. We then quantified the associations of QT prolongation with multiple clinical variables including etiology of liver disease, sex, age, Model for End-Stage Liver Disease (MELD) score, MELD-Na (MELD with incorporation of serum sodium) score, sodium level, international normalized ratio (INR), creatinine, total bilirubin, beta-blocker use, liver transplantation, and mortality. Variables were collected from the most recent labs collected (within 90 d of baseline ECG) as part of routine outpatient care. We utilized the Organ Transplant Tracking Record (OTTR) database and hospital records to identify our cohort and track their survival.

Patients included men and women above age of 18 with ESLD who were undergoing a liver transplant evaluation for any indication and had ECGs available for visual analysis. For patients who did not undergo a liver transplant, the most recent ECGs were used as baseline. For transplanted patients, the ECG prior to transplant was used as the baseline ECG while the average QT interval from the post-transplant ECGs was used to determine the effects of transplant on QT prolongation. This was done to eliminate artifacts due to the unstable or immediate post transplantation recovery period when the

patients' ECGs are vulnerable to medication changes or electrolyte imbalances. Patients without an interpretable ECG, or with conduction abnormalities, recent myocardial infarction (within the last 30 d by history), or pacemaker use, were excluded from the study.

### QT determination

For all 12 lead ECGs, the QT interval based on Bazett's principle (QT<sub>c</sub>) was obtained automatically using a computerized ECG machine (General Electronics MAC 5500 HD) to avoid interobserver variability. With Bazett's principle, the QT interval is measured from the beginning of the QRS complex to the termination of the T-wave and divided by the square root of the R-R interval in seconds<sup>[37]</sup>. A QT<sub>c</sub> > 450 ms for males and a QT<sub>c</sub> > 470 ms for females was considered abnormal or prolonged, as defined by European regulatory guidelines<sup>[38]</sup> and Goldenburg *et al.*<sup>[39]</sup> to account for gender differences. Patients with QT<sub>c</sub> prolongation were subdivided into three categories for analytic purposes: mild (451-470 ms in males; 471-490 ms in females), moderate (471-490 ms in males; 491-510 ms in females), and severe (> 490 ms in males; > 510 ms in females).

### Statistical analysis

Patients with ( $n = 207$ ) and without QT<sub>c</sub> prolongation ( $n = 199$ ) were compared on various clinical characteristics by *T* tests (for continuous variables and after log transformation for INR, creatinine, and bilirubin) and Fisher's exact tests (for dichotomous variables). Logistic regressions with QT<sub>c</sub> prolongation as the outcome were performed to identify significant unadjusted and adjusted associations with clinical characteristics identified in the next sentence. The first of three multivariate models included beta blocker use, etiology (viral, ethanol, non-alcohol steatohepatitis), MELD components (sodium, log INR, log creatinine, and log bilirubin), gender, and age as predictors; the second and third multivariate models replaced MELD components by total MELD score and total MELD-Na score respectively. Four logistic regressions with mortality as the outcome were also performed. The first related mortality to degree (mild, moderate, severe) of QT<sub>c</sub> prolongation. The second through fourth analyses related mortality to QT<sub>c</sub> prolongation and the aforementioned clinical characteristics, in parallel with the three multivariate models for QT<sub>c</sub> prolongation. A paired signed rank test was used to examine the change in QT<sub>c</sub> before and after surgery in a subset of patients ( $n = 74$ ) receiving liver transplantations. Approximately 25% of the patients did not have routine outpatient labs within the 90 d of their baseline ECG. Therefore, the analyses involving the MELD components and MELD totals were performed using multiple imputation. Microsoft Excel, SAS, and R were used for data analysis and visualization. Statistical significance was declared when  $P < 0.05$ .

## RESULTS

### Patient characteristics

The OTTR database revealed that 729 patients were

evaluated for a liver transplant at the University of Kentucky over a recent 12-year period. Of the 729 patients, 406 met the inclusion criteria for this study. In addition, approximately 25% of the patients (102 out of 406) did not have routine outpatient labs within the 90 d of their baseline ECG. The effective sample size for comparison of QT interval pre- and post-transplantation was 74. The estimated prevalence of QT prolongation was 51.0% (207 out of 406).

Table 1 shows that the 207 patients with QT prolongation (QT<sub>c</sub> by Bazett's  $\geq 450$  for males and  $\geq 470$  ms for females) were generally similar to the 199 patients without QT prolongation based on clinical variables. However, males with QT prolongation had higher creatinine, MELD, and MELD-NA scores than males without QT prolongation. Beta-blocker use was more common in females without QT prolongation.

In logistic regression analysis with QT<sub>c</sub> prolongation as an outcome variable, there was a significant association with male sex [estimated odds ratio (OR) 3.04, 95%CI: 2.01-4.60,  $P < 0.001$ ]. The association persisted in all three multivariate models, with adjusted OR between 3.05 and 3.09 ( $P < 0.001$  in all cases); there were no other significant predictors of QT<sub>c</sub> prolongation in these models.

Of the 406 patients, 187 (46.1%) died during the study period. Any level (mild, moderate, or severe) of QT<sub>c</sub> prolongation was associated with significantly increased mortality (Table 2). However, the risk of mortality did not exhibit an increasing pattern with respect to the level of prolongation.

Figure 1 shows that QT<sub>c</sub> prolongation is a significant predictor of mortality (OR 1.69, 95%CI: 1.03-2.77,  $P = 0.039$ ) in a multivariate model which adjusts for the components of MELD and other clinical variables. This model also reveals significant associations with mortality for viral etiology, ethanol etiology, combined viral and ethanol etiology, INR, creatinine, and bilirubin. Figure 2 depicts findings for an additional multivariate model in which MELD replaces its components, while Figure 3 pertains to a model with MELD-Na. In all the models, QT<sub>c</sub> prolongation and the aforementioned etiologies remain significant predictors of mortality.

Effective sample size for comparison of QT<sub>c</sub> interval pre- and post-transplantation was 74. Median pre-transplant QT<sub>c</sub> was 457 with interquartile range of 435-472 ms. Median post-transplant QT<sub>c</sub> was 450 with interquartile range of 429-468. Our study showed no significant change in the QT<sub>c</sub> interval after liver transplantation ( $P = 0.24$ ).

## DISCUSSION

Electrophysiologic cardiac abnormalities are well documented in patients with ESLD. As noted in our study, QT prolongation is a common finding within this population. Although the exact mechanism for QT prolongation in ESLD remains to be established, previous studies have suggested QT prolongation in ESLD may be multifactorial

**Table 1 Patient characteristics n (%)**

Variable	QTc prolongation			No QTc prolongation		
	All (n = 207)	Male (n = 150)	Female (n = 57)	All (n = 199)	Male (n = 92)	Female (n = 107)
Beta-blocker use <sup>1</sup>	161 (77.8)	122 (81.3)	39 (68.4)	153 (77.7)	66 (71.7)	87 (82.9) <sup>3</sup>
Viral etiology	80 (38.7)	65 (43.3)	15 (26.3)	69 (34.7)	42 (45.7)	27 (25.2)
Ethanol etiology	90 (43.5)	78 (52.0)	12 (21.1)	68 (34.2)	46 (50.0)	22 (20.6)
Non-alcohol steatohepatitis etiology	47 (22.7)	28 (18.7)	19 (33.3)	57 (28.6)	13 (14.1)	44 (41.1)
Viral and ethanol etiology	35 (16.9)	32 (21.3)	3 (5.3)	24 (12.1)	17 (18.5)	7 (6.5)
Sodium <sup>2</sup>	135.6 + 6.2	135.4 + 6.4	136.3 + 5.3	136.2 + 5.6	135.4 + 5.6	136.9 + 5.6
INR <sup>2</sup> (logarithm)	0.39 + 0.32	0.39 + 0.32	0.37 + 0.31	0.35 + 0.34	0.31 + 0.26	0.39 + 0.39
Creatinine <sup>2</sup> (logarithm)	0.39 + 0.51	0.43 + 0.50	0.30 + 0.53	0.30 + 0.43	0.29 + 0.40 <sup>3</sup>	0.31 + 0.46
Bilirubin <sup>2</sup> (logarithm)	1.19 + 1.05	1.18 + 1.07	1.20 + 0.99	1.06 + 0.96	0.90 + 0.86	1.20 + 1.03
MELD-NA <sup>2</sup>	21.0 + 9.5	21.6 + 9.5	19.5 + 9.3	19.3 + 9.1	18.6 + 7.7 <sup>3</sup>	19.8 + 10.2
MELD <sup>2</sup>	19.0 + 9.6	19.4 + 9.7	18.0 + 9.3	17.3 + 9.0	16.0 + 7.2 <sup>3</sup>	18.3 + 10.1
Age	56.1 + 9.1	56.2 + 8.8	56.0 + 9.7	56.7 + 9.0	56.3 + 9.3	57.0 + 8.7

Entries are number (percent) or mean + SD. <sup>1</sup>Excluded for two subjects; <sup>2</sup>Excluded for 102 subjects; <sup>3</sup>Significantly different (*P* < 0.05) *vs* patients of same gender with QTc prolongation.

**Table 2 Estimated odds ratios for mortality based on levels of QTc prolongation**

	OR	P	95%CI
Mild QTc prolongation <i>vs</i> none	1.67	0.045	1.01-2.76
Moderate QTc prolongation <i>vs</i> none	2.11	0.013	1.17-3.81
Severe QTc prolongation <i>vs</i> none	1.83	0.044	1.02-3.31

Mild QTc prolongation: 451-470 ms in males and 471-490 ms in females; Moderate QTc prolongation: 471-490 ms in males and 491-510 ms in females; Severe QTc prolongation: > 490 ms in males and > 510 ms in females.

and related to abnormalities in potassium channels involved in repolarization, high plasma concentrations of bile salts, and autonomic dysfunction<sup>[12-19,40]</sup>.

In our study, the majority of patients (51.0%) demonstrated QT prolongation when calculated using Bazett’s formula. Of the 406 patients evaluated, 187 (46.1%) died between years 2000 to 2013, confirming the high mortality in ESLD. An increase in mortality was seen at all levels of prolonged QT. Moreover, some etiologies and MELD components, as well as total MELD and MELD-Na scores, were predictive of mortality. These findings suggest worse outcomes in patients with viral hepatitis or combined viral and ethanol etiology, and they further validate the utility of MELD, MELD-Na, and its components for predicting survival in ESLD<sup>[41,42]</sup>. Importantly, QT prolongation predicts mortality above and beyond the aforementioned factors.

A number of studies have evaluated the association between QT prolongation and severity of ESLD as measured by Child-Pugh scores<sup>[14,19,24,25,28,36]</sup>. The majority of such studies have shown an increase in QT prolongation in association with higher Child-Pugh scores with the exception of studies done by Carey *et al.*<sup>[27]</sup> and Adigun *et al.*<sup>[30]</sup>. Due to the interobserver variability and use of subjective parameters in Child-Pugh classifications, MELD and MELD-Na scores are now widely viewed as superior indices for predicting mortality and allocating

transplants<sup>[41,42]</sup>. In our study, no significant associations were seen between QT prolongation and these superior indices of ESLD, in accord with the smaller studies by Zurick *et al.*<sup>[29]</sup> and Day *et al.*<sup>[35]</sup>.

Our study is unique in that we used validated thresholds for QT prolongation. While other studies used a cutoff of 440 msec, our study uses gender specific cutoffs as suggested by Goldenberg *et al.*<sup>[39]</sup>, to account for gender differences in QT prolongation that are typically longer for females<sup>[7,38,39,43]</sup>. Given our use of higher thresholds (> 450 ms for males and > 470 for females), which allowed higher selectivity for more severe QT prolongation, we may have underestimated the prevalence of QT prolongation while overestimating its association with other variables. Although Adigun *et al.*<sup>[30]</sup> demonstrated that a physiologic gender difference in the QTc interval is abolished in cirrhosis and that gender hormone concentrations have no effect on the QTc interval, our study reports a much higher prevalence of QT prolongation among males. When QTc prolongation was a dependent variable in our logistic regression models, both unadjusted and adjusted results showed statistically significant associations between QTc prolongation and male sex, while no other variables considered were significantly associated with QTc prolongation. A potential limitation to our study and explanation for these findings may be the use of gender specific thresholds and the corresponding assumption that gender differences in QT interval exist among ESLD patients. In particular, the higher cutoff for females may tend to understate QT prolongation prevalence within that gender.

Due to their utility and wide use in portal hypertension, the effects of acute and chronic beta-blockers on QT prolongation have been evaluated, with results showing a reduced QT interval<sup>[32-34]</sup>. In addition, partial or full reversal of QT prolongation following liver transplantation has also been noted<sup>[14,26-31]</sup>. Contrary to these findings, in our study, QTc prolongation was not significantly influenced by etiology, age, beta-blocker use, or transplantation. Although beta-blocker use had a trend towards lower

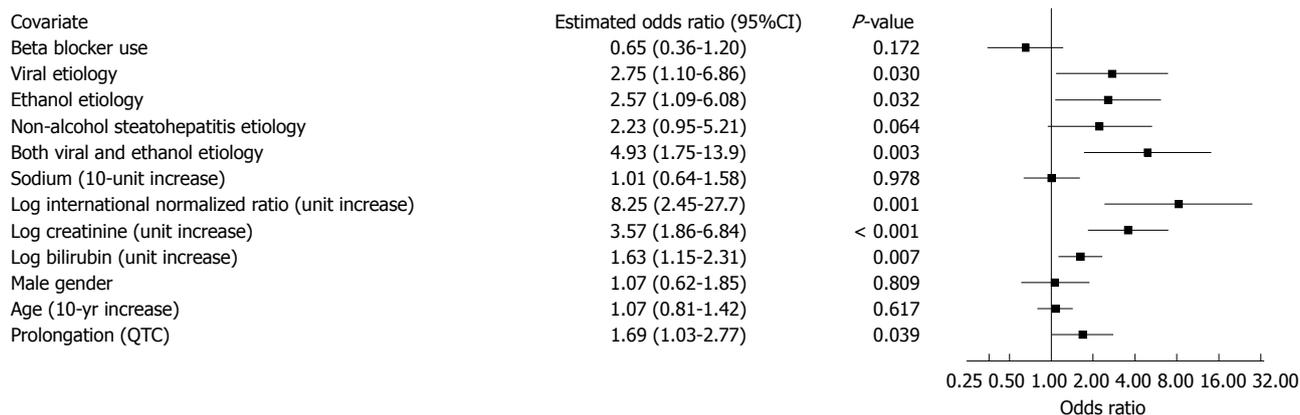


Figure 1 Association of mortality with Model for End-Stage Liver Disease components and clinical variables.

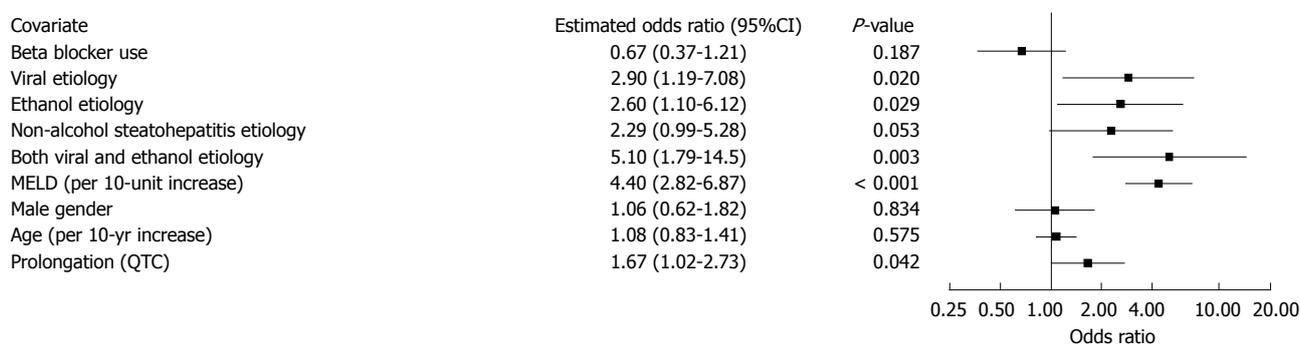


Figure 2 Association of mortality with total Model for End-Stage Liver Disease score and clinical variables.

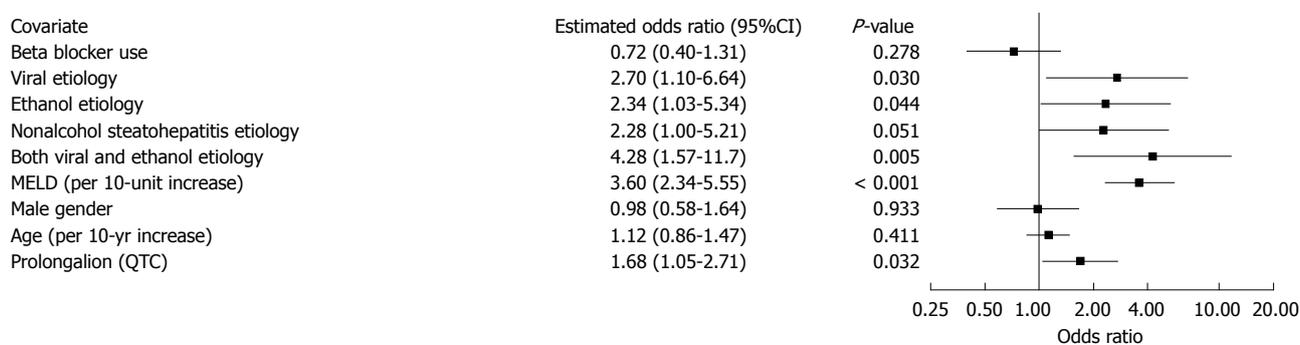


Figure 3 Association of mortality with total Model for End-Stage Liver Disease with incorporation of serum sodium score and clinical variables.

mortality, this did not meet statistical significance. The lack of reversibility in the QT interval following liver transplantation in our study may be due to our small effective sample size.

Several additional limitations need to be considered in our present investigation. As a retrospective study, our results have the potential for unintentional selection bias. Patients from our study were mostly Caucasian residing in rural areas from the state of Kentucky, which may not generalize geographically to the entire country. Our preoperative and postoperative ECGs were obtained during unspecified hospital or clinic visits, exposing our study to sampling bias related to factors such as electrolyte imbalance or concomitant use of QT

prolonging drugs. As noted above, MELD variables were unavailable from 102 out of 406 patients (25%) due to lack of outpatient labs within 90 d of their baseline ECG. Although MELD scores are frequently calculated for cirrhotics as part of their routine assessment, acute biochemical changes are often observed during inpatient hospitalizations, while labs performed outside 90 d of the baseline ECG may not accurately reflect the 90-d mortality rate assessed by MELD score in association to the observed ECG changes. Despite unavailable MELD scores on 102 patients, our analyses re-confirmed what is already well established in current literature that higher MELD scores are associated with higher mortality in ESLD patients. When the MELD components and

total score were evaluated in relation to the presence of QT prolongation, our results did show that males with QT prolongation had higher creatinine, MELD, and MELD-NA scores than males without QT prolongation (Table 1). Although males with worse MELD scores (*i.e.*, sicker patients) may have had a higher prevalence of QT prolongation, the retrospective nature of this study does not establish a cause and effect relationship, and the findings do not directly impact the main conclusion of our study where QT prolongation was an independent risk factor for mortality in ESLD.

When examining the severity of QT prolongation and its association with mortality, we defined mild, moderate, and severe levels of prolongation to categorize our patients. However, this categorization may not yield the best discriminatory power. Although the vast majority of heart rates in our study were within an acceptable range, calculation of QT intervals using Bazett's formula is thought to be less accurate with particularly low or high heart rates<sup>[44]</sup>. Furthermore, our study relies on the implicit assumptions of accurate data gathering and correct QT interval readings from our ECG machine, which may be prone to systematic error; however, the ECG machine does eliminate interobserver variability. Finally, although QT prolongation has been associated with increased mortality secondary to ventricular arrhythmias, our study did not differentiate specific causes of death.

Our study showed that QT prolongation was common, especially for male patients, in ESLD. Although an association between mortality and QT<sub>c</sub> prolongation was evident, a greater degree of QT<sub>c</sub> prolongation did not clearly portend worse outcomes. Finally, while QT<sub>c</sub> interval may be an independent risk factor for mortality in ESLD patients, the exact mechanism for the increase in mortality remains to be established. Based on our findings, it is reasonable to recommend close monitoring of the QT interval in ESLD patients with attention to any modifiable causes for QT prolongation, such as electrolyte imbalances or medications.

## COMMENTS

### Background

The QT interval on an electrocardiogram (ECG) is a measure of ventricular depolarization and repolarization. Prolongation of the QT interval is associated with ventricular arrhythmias as well as sudden cardiac death in both congenital and acquired conditions. Multiple factors are thought to be responsible for the prolongation of the QT interval in both congenital and acquired conditions, including electrolyte abnormalities, ventricular channelopathies, myocardial ischemia, medications, alcohol toxicity, and autonomic imbalance with sympathetic nervous system hyperactivity.

### Research frontiers

Recent studies have shown that end stage liver disease (ESLD) is associated with several electrophysiological changes; specifically, an increased prevalence of QT prolongation is seen in this population. While the exact mechanism for QT prolongation is unknown, improvement in liver function, beta-blocker use, and liver transplantation have been associated with shortening in the QT interval in studies with small sample sizes. Although some studies suggest a prolonged QT interval is related to severity of liver disease, etiology of liver disease, and

increased mortality, conflicting results exist regarding this important clinical question.

### Innovations and breakthroughs

The authors aimed to determine the prevalence of QT prolongation in a large series of ESLD patients and its association to clinical variables and mortality. The QT interval was measured and corrected for heart rate (QT<sub>c</sub>) for each patient, with prolongation defined as QT<sub>c</sub> > 450 ms for males and QT<sub>c</sub> > 470 ms for females. Multiple clinical variables were evaluated including sex, age, serum sodium, international normalized ratio, creatinine, total bilirubin, beta-blocker use, Model for End-Stage Liver Disease (MELD), MELD-Na, and etiology of liver disease. Among 406 ESLD patients analyzed, 207 (51.0%) had QT prolongation. The only clinical variable associated with QT prolongation was male gender (OR = 3.04, 95%CI: 2.01-4.60, *P* < 0.001). During the study period, 187 patients (46.1%) died. QT prolongation was a significant independent predictor of mortality (OR = 1.69, 95%CI: 1.03-2.77, *P* = 0.039). In addition, mortality was also associated with viral etiology of ESLD, elevated MELD score and its components (*P* < 0.05 for all). No significant reversibility in the QT<sub>c</sub> interval was seen after liver transplantation.

### Applications

QT<sub>c</sub> interval may be an independent risk factor for mortality in ESLD patients and thus the authors recommend close monitoring of the QT interval in ESLD patients and increased attention to any modifiable causes for QT prolongation such as electrolyte imbalances or medications.

### Terminology

ESLD: End stage liver disease; MELD: Model for End-Stage Liver Disease; MELD-Na: Model for End-Stage Liver Disease score with serum sodium; OTTR: Organ Transplant Tracking Record; QT<sub>c</sub>: QT interval corrected for heart rate.

### Peer-review

This is an interesting and important finding, as QT measurement is not formally considered in liver transplant clinics. The results of this study are interesting and relevant.

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Retrospective Study

## Determinants of percutaneous coronary intervention success in repeat chronic total occlusion procedures following an initial failed attempt

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### Abstract

#### AIM

To investigate the rates and determinants of success of repeat percutaneous coronary intervention (PCI) following an initial failed attempt at recanalising the chronic total occlusions (CTO) percutaneously.

#### METHODS

In 445 consecutive first attempt CTO-PCI procedures in our institution, procedural failure occurred in 149 (33.5%). Sixty-four re-PCI procedures were performed in 58 patients (39%) all had a single CTO. Procedural and outcome data in the re-PCI population was entered into the institutional database. A retrospective analysis of clinical, angiographic and procedural data was performed.

#### RESULTS

Procedural success was achieved in 41 (64%) procedures. Univariate analysis of clinical and angiographic characteristics showed that re-PCI success was associated with intravascular ultrasound (IVUS) guidance (19.5% vs 0%,  $P = 0.042$ ), while failure was associated with severe

calcification (30.4% *vs* 9.7%,  $P = 0.047$ ) and a JCTO score  $> 3$  (56.5% *vs* 17.1%  $P = 0.003$ ). Following multiple regression analysis the degree of lesion complexity (J-CTO score  $> 3$ ), IVUS use, involvement of an experienced CTO operator and LAD CTO location were significant predictors of successful re-PCI. Overall the complication rate was low, with the only MACCE two periprocedural MI's neither of which required intervention.

### CONCLUSION

Re-PCI substantially increases the overall success rate of CTO revascularization. Predictors of re-PCI success included the use of IVUS, the involvement of an experienced CTO operator in the repeat attempt and the location of the CTO.

**Key words:** Repeat percutaneous coronary intervention; Chronic total occlusion

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**Core tip:** Failed percutaneous recanalization of chronic total occlusions (CTO) constitutes a clinical conundrum. While percutaneous treatment is often abandoned in favour of medical therapy, CTO-percutaneous coronary intervention (PCI) expertise and alternative techniques may contribute to improve procedural success. This study shows that with careful pre-procedural planning reattempt PCI in CTO's is both safe and efficacious.

Cuevas C, Ryan N, Quirós A, Del Angel JG, Gonzalo N, Salinas P, Jiménez-Quevedo P, Nombela-Franco L, Nuñez-Gil I, Fernandez-Ortiz A, Macaya C, Escaned J. Determinants of percutaneous coronary intervention success in repeat chronic total occlusion procedures following an initial failed attempt. *World J Cardiol* 2017; 9(4): 355-362 Available from: URL: <http://www.wjgnet.com/1949-8462/full/v9/i4/355.htm> DOI: <http://dx.doi.org/10.4330/wjc.v9.i4.355>

## INTRODUCTION

Revascularization of chronic total occlusions (CTO) is a well accepted technique, albeit one of the most challenging procedures in interventional cardiology with the presence of a CTO a strong predictor against percutaneous recanalisation<sup>[1,2]</sup>. There is growing evidence that CTO recanalization confers benefit to patients<sup>[3-11]</sup>, however the success rate of CTO percutaneous coronary intervention (PCI) is significantly lower than in non-CTO lesions, ranging from 51% to  $> 80\%$  in different series<sup>[3,8,12,13]</sup>. Several attempts have been made to rate procedural difficulty in CTOs, with the JCTO score<sup>[14]</sup>, the most commonly used score, identifying prior CTO failure as one of the five key determinants of PCI success. The introduction of novel techniques including parallel wiring, CART/reverse CART, hybrid procedures and bilateral injections have increased the success of the procedure<sup>[15-17]</sup>, with several studies promoting the use of intravascular ultrasound (IVUS)

in guiding wiring of the true lumen and optimizing CTO-PCI outcomes<sup>[17-19]</sup>. Despite the potential benefits of CTO recanalization a significant proportion of patients are managed medically rather than reattempting CTO-PCI<sup>[5]</sup>, perhaps because, when compared to initial attempts at CTO-PCI, the predictors of and success rates in re-PCI are largely unknown. The purpose of this study was to evaluate the success rate of re-PCI, as well as to identify predictors of success.

## MATERIALS AND METHODS

Between January 2008 and September 2012, 445 patients had first time native vessel CTO PCI procedures in our institution. In 149 patients the initial procedure was unsuccessful with re-PCI planned in 58 patients (39%) who underwent 64 further procedures, four patients had two re-PCI attempts while one patient had three re-PCI attempts (Figure 1). Procedural and outcomes data in this re-PCI population was entered into the institutional database.

Data was collected in relation to factors that may affect procedural success, including fluoroscopy time, use of stiffer polymer coated CTO guide-wires and *ad-hoc* PCIs. Re-PCI data collected including change of strategy, IVUS guidance and involvement of an experienced operator. The patients were divided into subgroups according to procedural outcome (successful/failure) for analysis. Post-procedural data including evidence of periprocedural MI, renal impairment and death was obtained from the institutional database.

CTO was defined as a TIMI (thrombolysis in myocardial infarction) grade 0 flow in the target segment, with a duration  $> 3$  mo, determined based on clinical symptoms or prior angiography when available<sup>[12]</sup>. Angiographic success was defined as a residual stenosis  $< 30\%$  with TIMI grade flow  $\geq 2$ . The EuroCTO club definition of an operator with a success rate of at least 80% in CTO PCI was used to identify experienced operators<sup>[1]</sup>, all other operators were considered non-experienced operators. IVUS guidance included two techniques (IVUS-guided wiring of the CTO stump, and IVUS-guided penetration from the subintimal space). The lesion complexity was classified using the J-CTO score with lesions scored as 0-5 dependent on the presence of one or more of the following features: Blunt stump, length  $> 20$  mm, severe calcification,  $> 45^\circ$  tortuosity and previous failed attempt<sup>[14]</sup>.

### Statistical analysis

Categorical and continuous variables are expressed as counts (%) and mean  $\pm$  SD, respectively. The angiographic, clinical and procedural factors were analyzed as possible determinants of success in a new attempt at recanalization and were compared between patient groups.

Categorical variables were compared with the Fisher's exact test and continuous variables were compared with a *t* test. All indices with a *P*-value  $< 0.1$  in the

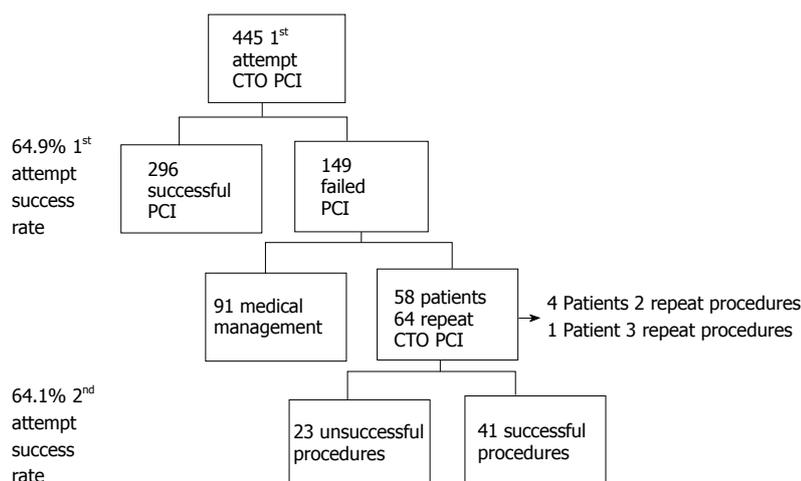


Table 1 Baseline patient characteristics

Patient demographics	Overall (n = 58)	Success (n = 40)	Failure (n = 18)	P value
Age, yr	59.2 ± 11.6	59.2 ± 11.6	60.2 ± 11.7	0.78
Male	50 (86.2%)	33 (82.5%)	17 (94.4%)	0.41
Obesity	20 (34.4%)	14 (35%)	6 (33.3%)	1
Hypertension	39 (67.2%)	24 (60%)	15 (83.3%)	0.15
Dyslipidaemia	41 (70.6%)	27 (67.5%)	14 (77.8%)	0.63
Diabetes	23 (39.6%)	15 (37.5%)	8 (44.4%)	0.84
Smoking	38 (65.5%)	26 (65%)	12 (66.7%)	1
Previous MI	22 (37.9%)	15 (37.5%)	7 (38.9%)	1
Previous PCI	27 (46.6%)	17 (42.5%)	10 (55.6%)	0.52
Previous CABG	2 (3.4%)	1 (2.5%)	1 (5.6%)	0.52
LVEF < 45%	22 (37.9%)	15 (37.5%)	7 (38.9%)	1
CKD IV	3 (5.2%)	3 (7.5%)	0 (0%)	0.55

MI: Myocardial infarction; PCI: Percutaneous coronary intervention; CABG: Coronary artery bypass grafting; LVEF: Left ventricular ejection fraction; CKD: Chronic kidney disease.

univariate analysis were included in a multiple logistic regression analysis and the final model was selected by Akaike's Information Criterion<sup>[20]</sup>. Fitting a classical logistic regression model with this dataset leads to a non-identifiable problem, as some variables induce a separation. In order to obtain stable logistic regression coefficients, we use Bayesian inference<sup>[21]</sup>. The computations required to estimate the coefficients of the model are implemented in the arm package for applied regression and multilevel modelling in R v.3.2.2 software.

## RESULTS

The success rate for CTO re-PCI was 64.1%. The baseline clinical characteristics of the patients are shown in Table 1. The mean age was 59.5 ± 11.5 years, and 86.2% were male. There were no significant differences between the successful and failed re-PCI groups. Baseline angiographic and procedural characteristics are shown in Tables 2 and 3. The left anterior descending artery (LAD) and the right coronary artery (RCA) were the most commonly affected vessel in the successful and failed groups respectively. Of the individual components of the JCTO score only calcification was significant with

more severely calcified lesions in the failed group (30.4% vs 9.7%,  $P < 0.047$ ). The successful group had a lower average J-CTO score ( $2.73 \pm 0.84$  vs  $3.2 \pm 0.99$ ,  $P < 0.010$ ), with fewer lesions with a J-CTO score  $\geq 4$ .

Inability to cross the lesion with a guidewire is the most common reason for failure in CTO-PCI. We analyzed factors associated with the initial failed attempt that may reflect the effort invested in the initial attempt and therefore could have an indirectly proportional relationship with success in re-PCI. These included fluoroscopy time, use of dedicated guidewires and a planned initial attempt vs *ad-hoc* CTO-PCI. There were no significant differences in any of these variables. In the patients who underwent a reattempt 30% of the initial failed procedures were *ad-hoc* CTO PCI attempts at the time of diagnostic angiography. The group who underwent initial *ad-hoc* PCI had a higher success rate than those who underwent an initial planned attempt (89% vs 48.8%,  $P = 1$ ) however this did not reach statistical significance.

All IVUS guided procedures were successful ( $P = 0.020$ ). There were no significant differences observed with the use of individual pieces of equipment such as guide catheters, guidewire type or microcatheters; or

**Table 2** Angiographic characteristics

Angiographic characteristics	Overall (n = 64)	Success (n = 41)	Failure (n = 23)	P value
CTO Site				0.0045
LAD	27 (42.2%)	21 (51.5%)	6 (26.1%)	
RCA	31 (48.4%)	16 (39.0%)	15 (65.2%)	
LCx	6 (9.4%)	4 (9.7%)	2 (8.7%)	
Blunt stump	19 (29.7%)	10 (24.3%)	9 (39.1%)	0.34
Tortuous vessel	23 (35.9%)	12 (29.2%)	11 (47.8%)	0.225
Calcified lesion	11 (17.2%)	4 (9.7%)	7 (30.4%)	0.047
Lesion length > 20 mm	49 (93.8%)	30 (73.1%)	19 (82.6%)	0.58
J-CTO Score	2.9 ± 0.92	2.73 ± 0.84	3.2 ± 0.99	0.0063
J-CTO 1	4 (6.25%)	3 (7.3%)	1 (21.4%)	1
J-CTO 2	18 (28.1%)	12 (29.3%)	6 (26.1%)	1
J-CTO 3	22 (34.4%)	19 (46.3%)	3 (39.1%)	0.015
J-CTO 4	20 (31.2%)	7 (17.1%)	13 (56.5%)	0.0028
Rentrop class 3	43 (67.2%)	26 (48.8%)	17 (73.9%)	0.56
Segment				
Distal	4 (6.2%)	2 (4.9%)	2 (8.7%)	0.61
Mid	27 (42.2%)	16 (39.0%)	11 (47.8%)	0.67
Proximal	33 (51.6%)	23 (56.1%)	10 (43.5%)	0.47
Segment length	26.95 ± 12.2	25.4 ± 10.3	29.7 ± 14.9	0.23
Presence of proximal disease	15 (23.4%)	9 (21.9%)	6 (26.1%)	0.95

LAD: Left anterior descending; LCx: Left circumflex; RCA: Right coronary artery; CTO: Chronic total occlusions; J-CTO: Japanese chronic total occlusion.

**Table 3** Procedural characteristics

Procedural characteristics	Overall (n = 64)	Success (n = 41)	Failure (n = 23)	P value
Planned initial attempt	45 (70.3%)	29 (70.7%)	16 (69.6%)	1
Retrograde approach	9 (14.1%)	6 (14.6%)	3 (13.0%)	1
Contralateral injection	36 (56.3%)	22 (53.6%)	14 (60.9%)	0.76
Parallel wire	16 (25%)	10 (24.3%)	6 (26.1%)	1
Intravascular ultrasound	8 (12.5%)	8 (19.5%)	0 (0%)	0.042
Rotablator	5 (7.8%)	5 (12.2%)	0 (0%)	0.15
Change of operator	39 (60.9%)	27 (65.9%)	12 (52.2%)	0.41
Experienced operator	36 (56.3%)	27 (65.9%)	9 (39.1%)	0.065
Change in guide catheter	11 (17.2%)	7 (17.1%)	4 (17.4%)	1
Change of wire	38 (59.4%)	23 (56.1%)	15 (65.2%)	0.65
Microcatheter use	46 (71.9%)	28 (68.3%)	18 (78.3%)	0.57
Procedure time	127.8 ± 44.3	129.1 ± 51.3	125.3 ± 32.8	0.71
Fluoroscopy time	45.44 ± 21	43.3 ± 21.5	49.2 ± 20.0	0.27
Contrast (mL)	337.5 ± 127.5	355.5 ± 127.2	305.4 ± 124.3	0.13

implementation of new strategies such as retrograde access, contralateral injection or parallel wiring.

Multiple logistic regression analysis identified the degree of lesion complexity (J-CTO score ≤ 3 and >3), IVUS use, involvement of an experienced CTO operator in the repeat PCI attempt, and LAD location of the CTO as independent predictors of procedural success/failure (Table 4). A model for predicting probability of procedural success was developed with logistic regression analysis that combined these angiographic and technical variables (Figures 2 and 3). As seen in Figures 2 and 3, IVUS use in combination with an experienced CTO operator increases the probability of success particularly when the J-CTO score is > 3.

Overall, the complication rate was low with 2 peri-procedural MI's one occurring in a successful procedure and one in a failed procedure, both were characterized by minimal elevation in cardiac enzymes post procedure and

neither required further intervention. There were no deaths in the population and no contrast induced nephropathy.

## DISCUSSION

The main conclusion of our study is that re-PCI in CTO after a failed attempt is associated with a good success rate. Adequate pre procedural evaluation and planning is crucial. In complex lesions factors such as IVUS-guidance and experienced CTO operators increase the chances of success. Less complex lesions, particularly those in the LAD, may be attempted by non-experienced CTO operators with a good success rate.

In our study population, the success rate for CTO-re-PCI was 64.1%, this compares favorably with the Japanese CTO registry where re-PCI attempts had a procedural success rate of 68.5%<sup>[11]</sup>. Involvement of experienced operators and used of IVUS is associated

Table 4 Predictors of procedural success/failure					
Variable	Coefficient (b)	SD (b)	95%CI	P (b ≠ 0   data)	P value
J-CTO ≤ 3	0.26	0.52	-2.04	0.69	0.31
J-CTO > 3	-1.67	0.67	-3.34	0.99	0.01
LAD	0.9	0.6	-2.36	0.93	0.07
IVUS use	2.96	1.58	-6.2	0.97	0.03
Experienced operator	0.78	0.58	-2.28	0.91	0.09

LAD: Left anterior descending, J-CTO: Japanese chronic total occlusion; IVUS: Intravascular ultrasound.

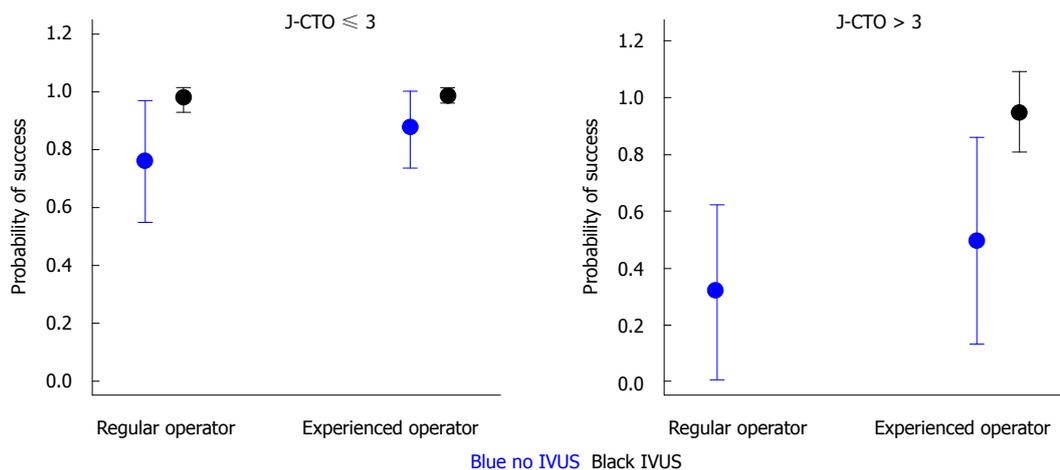


Figure 2 Mean probability of success with 95%CI dependent on angiographic and procedural variables in left anterior descending chronic total occlusion. LAD: Left anterior descending; JCTO: Japanese chronic total occlusion; IVUS: Intravascular ultrasound.

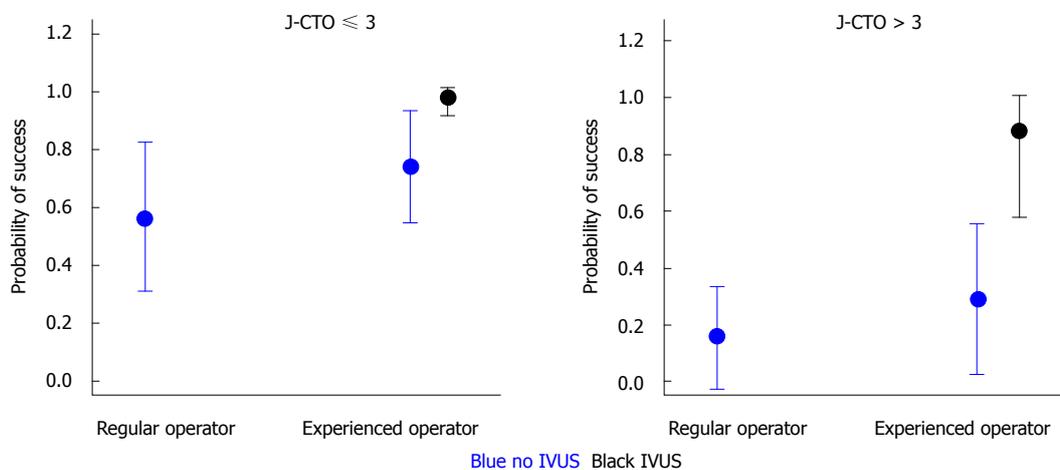


Figure 3 Mean probability of success with 95%CI dependent on angiographic and procedural variables in non left anterior descending chronic total occlusion. LAD: Left anterior descending; JCTO: Japanese chronic total occlusion; IVUS: Intravascular ultrasound.

with improved success, particularly in CTOs in the LAD location. Compared to the Japanese CTO data where success rates in re-PCI cases were significantly lower than initial attempts (68.5% vs 86.6% respectively), in our group, we found a similar overall success rate in the re-PCI group (64.1% vs 66.5%). This is likely explained by a less aggressive initial approach to CTO-PCI in our population during the study period. Patients who underwent initial *ad-hoc* PCI had a higher re-PCI success rates than those who underwent an initial planned

attempt (89% vs 48.8%,  $P = 1$ ), probably reflecting a less dedicated attempt, with difficulties easily overcome in a second, more aggressive procedure. The success rate in re-PCI contributes to a significant increase in per patient success of PCI in this complex anatomical scenario.

There have been several attempts to rate CTO procedural difficulty. The J-CTO score, the most popular of the CTO procedural difficulty scores, was developed by Morino *et al*<sup>[14]</sup> in their large multicenter registry to

classify the difficulty of antegrade lesion crossing, and identified prior CTO failure as a one of the five key determinants of PCI success. In our population, we found only one of the traditional predictors of procedural difficulty in initial attempt CTO-PCI, severe calcification to be significantly associated with procedural success re-PCI. Nombela-Franco *et al.*<sup>[22]</sup> validated the predictive value of the J-CTO score in successful antegrade crossing of the lesion within thirty minutes however they failed to show an ability to predict procedural success. Although not validated for predicting success the J-CTO score remains a useful tool in stratifying lesion complexity with significantly more patients with a J-CTO score > 4 in the failed group. Similar to data from Thompson *et al.*<sup>[23]</sup> showing a significantly higher PCI success rate with experienced operators (75.2% vs 58.9%;  $P < 0.001$ ), we found an experienced operator an important predictor of success in re-PCI attempts.

Data from the EuroCTO club puts IVUS use at 1.5% amongst its members in 2010. This is likely due to economic constraints and differs from Japan and the US where imaging techniques play a much larger role in CTO revascularization<sup>[24]</sup>. In our population, IVUS was used in 20% of all successful re-PCIs, in 6 (15%) cases a second wire was introduced into the true lumen *via* IVUS guidance after visualizing the first wire in false lumen and in 2 (5%) cases IVUS was used for ostial wiring. Furthermore, in these cases IVUS aided vessel sizing prior to stent implantation suggesting IVUS can be used to enhance the safety of CTO-PCI and optimize final results.

The CTO PCI reattempt rate remains relatively low, approximately 38% in this study, perhaps due to lack of large randomized clinical trials demonstrating benefit with CTO revascularisation. A large meta-analysis from Joyal *et al.*<sup>[25]</sup> in 2010 comparing successful to failed CTO recanalization showed a 44% reduction in mortality, 78% reduction in subsequent CABG and a 55% reduction in residual angina in successfully recanalised CTO's. However there was significant heterogeneity amongst the clinical outcomes and successful recanalization did not impact on MI or MACE. Other studies have shown successful percutaneous coronary intervention in a chronic total occlusion (CTO-PCI) to be beneficial in terms of recurrent myocardial, infarction, all-cause death, recurrent angina pectoris, subsequent CABG and cumulative survival rate compared to conservative management after failed PCI attempts however these are small heterogeneous populations<sup>[3-8]</sup>. In the context of acute myocardial infarctions it has been shown that the presence of a CTO increases long term mortality<sup>[9]</sup>, with CTO an independent predictor of mortality in STEMI with cardiogenic shock<sup>[10]</sup>. The high success rate, low procedural complication and in-hospital MACE rates observed in this study suggest that after failed attempt a reattempt a CTO-PCI should be considered.

Finally, combination of the angiographic and procedural factors identified by multiple regression analysis as predictive of success or failure (degree of lesion complexity,

IVUS use and an experienced CTO operator) yielded anticipated success rates ranging from 16% to 99%. It was observed that the implementation of procedural factors such as IVUS-guidance and experienced CTO operators are crucial when it comes to complex lesions (J-CTO score > 3), increasing in the probability of success from 16% to 99%. In comparison in less complex lesions (J-CTO score < 3), technical factors play a lesser role and these lesions even when attempted by non-experienced operators using IVUS have a high probability of success. These factors should be considered when planning a CTO-PCI strategy.

### Limitations

There are a number of limitations to our study. First, it is a descriptive and retrospective study designed only to look at the angiographic success rates and immediate in hospital outcomes of reattempt PCI. Long-term clinical and angiographic outcomes require evaluation in large-scale prospective clinical trials. Second, the angiographic characteristics of the CTOs were evaluated retrospectively. Third, this is a small sample from a single centre therefore one must be cautious when interpreting these results.

In conclusion, our findings suggest that re-PCI increased substantially the overall success rate of CTO revascularization. Predictors of re-PCI success included the use of IVUS, the involvement of an experienced CTO operator in the repeat attempt and the location of the CTO. The high success rate, low procedural complication and in-hospital MACE rates observed in this study suggest that after failed attempt a carefully planned reattempt at CTO-PCI should be considered.

## COMMENTS

### Background

Failed percutaneous recanalization of chronic total occlusions (CTO) constitutes a clinical conundrum. While percutaneous treatment is often abandoned in favour of medical therapy, CTO PCI expertise and alternative techniques may contribute to improve procedural success. There is growing evidence that CTO recanalization confers benefit to patients, however the success rate of CTO PCI is significantly lower than in non-CTO lesions, ranging from 51% to > 80% in different series. In this study the authors evaluated the success rates and predictors of success in reattempt PCI in CTO's.

### Research frontiers

Recanalising CTO's with viable myocardium appears to be beneficial to patients. Few prior studies have evaluated the benefit of reattempting PCI after an initial failed attempt.

### Innovations and breakthrough

Re-PCI in CTO after a failed attempt is associated with a good success rate. Adequate pre procedural evaluation and planning is crucial. In complex lesions factors such as IVUS-guidance and experienced CTO operators increase the chances of success. Less complex lesions, particularly those in the LAD, may be attempted by non-experienced CTO operators with a good success rate.

### Applications

The results of this study can assist operators in adequate pre-procedural planning in CTO's.

## Terminology

CTO: Chronic total occlusion an artery that has been occluded for longer than three months. IVUS: Intra-vascular ultrasound a technique that can be used to assist in visualizing the stump of a CTO, identifying wire position periprocedurally and optimizing stenting. PCI: Percutaneous coronary intervention a transcatheter technique used to revascularise a coronary territory.

## Peer-review

This study has value as it emphasizes the need for pre-procedural evaluation of lesion complexity and therefore complex lesions must be faced by experienced operators through an IVUS guided CTO-PCI approach.

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## Observational Study

**Speckle tracking echocardiography to assess regional ventricular function in patients with apical hypertrophic cardiomyopathy**

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**Informed consent statement:** The patient involved in this study gave their written informed consent authorizing use and disclosure of their protected health information.

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**Abstract****AIM**

To explore regional systolic strain of midwall and endocardial segments using speckle tracking echocardiography in patients with apical hypertrophic cardiomyopathy (HCM).

**METHODS**

We prospectively assessed 20 patients (mean age 53 ± 16 years, range: 18-81 years, 10 were male), with apical HCM. We measured global longitudinal peak systolic strain (GLPSS) in the midwall and endocardium of the left ventricle.

**RESULTS**

The diastolic thickness of the 4 apical segments was 16.25 ± 2.75 mm. All patients had a normal global systolic

function with a fractional shortening of  $50\% \pm 8\%$ . In spite of supernormal left ventricular (LV) systolic function, midwall GLPSS was decreased in all patients, more in the apical ( $-7.3\% \pm -8.8\%$ ) than in basal segments ( $-15.5\% \pm -6.93\%$ ), while endocardial GLPPS was significantly greater and reached normal values (apical:  $-22.8\% \pm -7.8\%$ , basal:  $-17.9\% \pm -7.5\%$ ).

### CONCLUSION

This study shows that two-dimensional strain was decreased mainly confined to the mesocardium, while endocardium myocardial deformation was preserved in HCM and allowed to identify subclinical LV dysfunction. This transmural heterogeneity in systolic strain had not been previously described in HCM and could be explained by the distribution of myofibrillar disarray in deep myocardial areas. The clinical application of this novel finding may help further understanding of the pathophysiology of HCM.

**Key words:** Apical hypertrophic cardiomyopathy; Two-dimensional strain; Speckle tracking; Endocardium; Mid-wall; Regional myocardial systolic function

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**Core tip:** In this study we prospectively assessed 20 patients with apical hypertrophic cardiomyopathy (HCM) in which we used speckle tracking echocardiography for measuring global longitudinal peak systolic strain in the midwall and endocardium of the left ventricle. We showed that two-dimensional strain was decreased mainly confined to the mesocardium, while endocardial deformation was preserved. This finding allowed to identify subclinical left ventricular systolic dysfunction. This transmural heterogeneity in systolic strain had not been previously described in HCM and could be explained by the distribution of myofibrillar disarray in deep myocardial areas. The clinical application of this novel finding may help further understanding of the pathophysiology of HCM.

Saccheri MC, Cianciulli TF, Morita LA, Méndez RJ, Beck MA, Guerra JE, Cozzarin A, Puente LJ, Balletti LR, Lax JA. Speckle tracking echocardiography to assess regional ventricular function in patients with apical hypertrophic cardiomyopathy. *World J Cardiol* 2017; 9(4): 363-370 Available from: URL: <http://www.wjgnet.com/1949-8462/full/v9/i4/363.htm> DOI: <http://dx.doi.org/10.4330/wjc.v9.i4.363>

## INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is a genetic disease transmitted with an autosomal dominant pattern, whereby the direct relatives of affected subjects carry 50% chances of having the disease<sup>[1]</sup>. Its prevalence in the general population is 0.2% and it is frequent cause of sudden cardiac death in patients younger than age 30,

including athletes. The annual mortality rate is 1%, but may be as high as 6% during childhood and adolescence; of note, sudden death may be the first symptom of disease<sup>[2]</sup>. It is a heterogeneous disease in its clinical as well as genetic aspects, characterized by the presence of primary left ventricular hypertrophy (LVH), with variable clinical expression and outcome<sup>[3]</sup>, and caused by genetic mutations that lead to abnormal sarcomeric proteins<sup>[4]</sup>.

In patients with complete phenotypic expression, characteristic findings are: Hypertrophy, myofibrillar disarray, interstitial fibrosis and microvascular dysfunction, all of which contribute to the progression to heart failure, ventricular arrhythmias and sudden death. Recent studies with MRI have shown that many patients with HCM have multiple areas of myocardial fibrosis, even with normal LV ejection fraction<sup>[5]</sup>.

Epicardial coronary arteries in patients with HCM are usually normal, but coronary flow reserve is diminished due to narrowing of the small intramyocardial arteries<sup>[6]</sup>. This microvascular ischemia is one of the factors resulting in LV diastolic dysfunction, which in turn is the main functional consequence of this disease.

Although patients with HCM have a normal ejection fraction, studies with Doppler tissue imaging have documented a regional systolic dysfunction in the longitudinal fibers of the LV<sup>[7-10]</sup>.

Regional LV function may be assessed non-invasively by measuring strain or systolic deformation. Initially, strain calculated with colour tissue Doppler proved to be a useful and sensitive tool to detect early systolic function abnormalities in patients with HCM<sup>[11]</sup>. However, its clinical application proved to be hindered by the complexity of data collection and limited reproducibility.

Recently, a method derived from the two-dimensional (2-D) echocardiogram, called "speckle tracking" of 2-D strain, has been developed to measure systolic strain<sup>[12]</sup>. The goal of this study was to assess the abnormalities of global and regional systolic LV function using 2-D strain in patients with apical HCM.

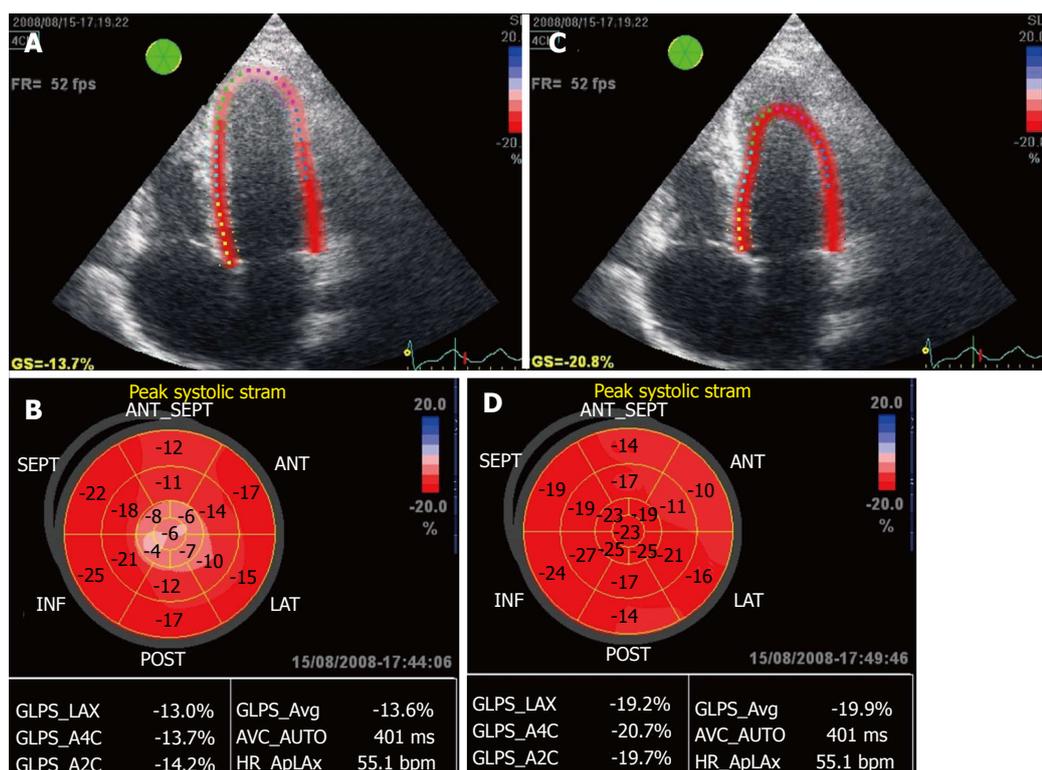
## MATERIALS AND METHODS

### Population

The study has a cross-sectional design and included 20 patients with apical HCM who were being followed at our tertiary referral center. Using a retrospective methodology, 2-D strain was measured in 340 myocardial segments.

The diagnostic criteria for apical HCM included demonstration of asymmetric left ventricular hypertrophy (LVH), confined predominantly to the LV apex with an apical wall thickness  $> 15$  mm, a ratio of maximal apical to posterior wall thickness  $> 1.5$ <sup>[13]</sup>, and a "spade shape" deformity of the left ventricle with apical cavity obliteration in end-systole based on 2-D echocardiography.

Inclusion criteria were: HCM with apical involvement, non-dilated LV, normal global and regional systolic LV function, normal blood pressure, sinus rhythm, absence of comorbidities and without history of hypertension.



**Figure 1** Apical 4-chamber view of a patient with apical hypertrophic cardiomyopathy. A: Midwall parametric image; B: Midwall bull's eye with a mean global longitudinal peak systolic strain (GLPS\_Avg) of -13.6%; C: Endocardial parametric image; D: Endocardial bull's eye with a GLPS\_Avg of -19.9%. Red: Normal strain; Pink: Reduced strain; Light pink: Severely reduced strain.

Noninvasive evaluation of global and regional systolic LV function was done by calculation of LV ejection fraction and visual judgement of segmental function from 2-D echocardiographic images.

Exclusion criteria were obesity, poor echocardiographic window, concomitant diseases that could cause ventricular hypertrophy or abnormal systolic or diastolic function (hypertension, diabetes, coronary heart disease, valve disease, cardiomyopathy, pericardial disease, congenital heart disease or systemic disease).

The study was approved by the Education and Research Committee and the Ethics Committee of the "Dr. Cosme Argerich" Hospital. All patients signed the informed consent form, including the authorization to use the data collected for future studies.

### Echocardiographic measurements

Standard echocardiographic examinations were performed in all patients using a Vivid Seven digital ultrasound system (GE Medical System, Hotern, Norway). Cardiac cycles were stored in digital, cine-loop format for off-line analysis performed by two independent observers (TFC and JAL) with a dedicated software package (EchoPAC PC, version 108.1.5).

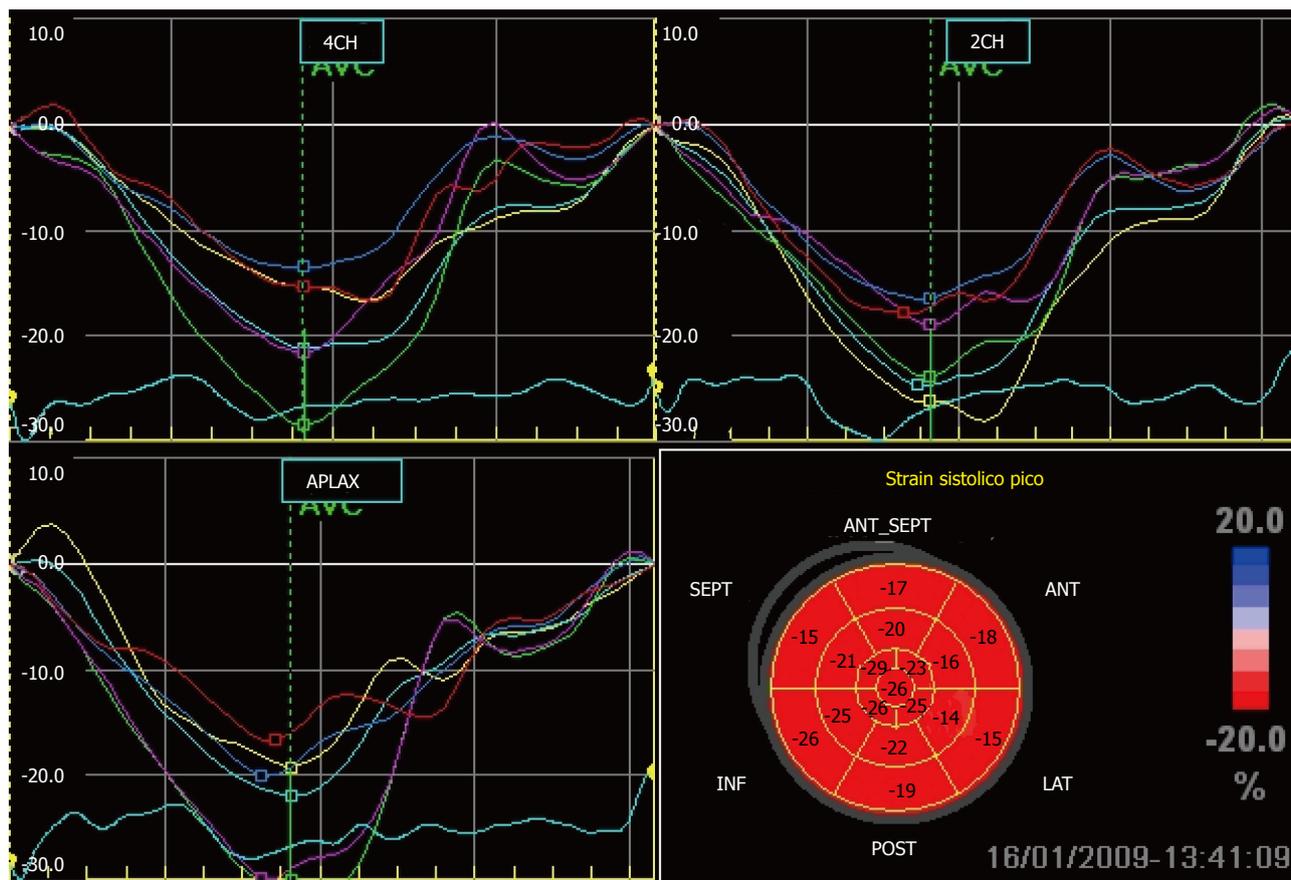
Both parasternal long- and short-axis views were analyzed. The M-mode echo was derived from the parasternal short-axis at the papillary muscle level, and the following measurements were obtained according to the American and European Societies of Echocardiography<sup>[14]</sup>:

LV end-diastolic diameter (EDD), LV end-systolic diameter (ESD), interventricular septum and posterior LV wall thickness, and end-systolic left atrial diameter. Ejection fraction was measured by Simpson method. Continuous Doppler from the apical 5-chamber view was used to rule out the presence of a dynamic subaortic gradient.

### Measurement of 2-D strain

2-D strain is a novel non-Doppler-based method to evaluate strain from standard 2-D acquisitions<sup>[15]</sup>. By tracing the endocardial contour on an end-systolic frame, the software will automatically track the contour on subsequent frames. Adequate tracking can be verified in real-time and corrected by adjusting the region of interest (ROI) or manually correcting the contour to ensure optimal tracking. A minimum frame rate of 30 Hz was required for reliable operation of this program and frame rates of 30 to 80 Hz were used for routine gray scale imaging. 2-D longitudinal strains were assessed in 2 orthogonal apical views (4- 3 and 2-chambers, 17 segments) starting from the septal, posterior and the inferior atrioventricular wall junction, respectively. The 2-D strain software adequately tracked > 85% of the attempted segments.

The ROI was reduced and shifted to the meso-cardium to obtain the parametric image, which allowed quantifying strain in each of the 17 segments of the LV as a "bull's eye" (Figure 1A and B), the mean value of peak global systolic strain and strain in the 3 apical views. Later, the ROI was shifted to the endocardium to obtain



**Figure 2** Curves of global longitudinal peak systolic strain from each apical view in a normal subject. Note that in most segments, peak strain occurs during aortic closure. 4CH: Apical 4-chamber; 2CH: Apical 2-chamber; APLAX: Apical long-axis (apical 3-chamber).

the endocardial strain of the 17 segments represented as a bull's eye (Figure 1C and D).

In the present study we only used global longitudinal peak systolic strain (GLPSS), which was plotted as a negative curve with a peak close to the aortic closure (Figure 2). These GLPSS curves represent the maximum myocardial longitudinal shortening during contraction in each of the 17 segments. In a normal subject (Figure 3) GLPSS varies between -15% and -20%<sup>[15]</sup>.

**Reproducibility**

The first 10 studies were analyzed blindly by a second operator who measured longitudinal 2-D strain in 170 myocardial segments. Intraobserver variability was calculated from the mean of the differences obtained in the 170 segments. Interobserver variability was calculated as the absolute difference divided by the mean of the 2 observations for all segments measured<sup>[16]</sup>.

**Statistical analysis**

Quantitative data with a normal distribution were expressed as the mean ± SD and data without a Gaussian distribution were expressed as medians (interquartile interval).

For the comparison of quantitative variables with a normal distribution we used the Student's *t* test for paired data; for variables without a normal distribution

we used the *Wilcoxon or Signed Rank Test*.

All *P* values < 0.05 were considered statistically significant. Statistical analyses were performed with Statistix 7.0 software for Windows.

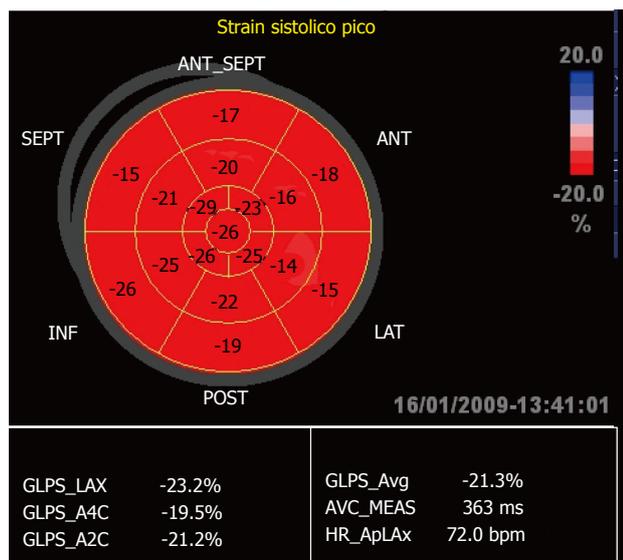
**RESULTS**

The clinical and echocardiographic characteristics of patients with apical HCM are summarized in Table 1. No patient was receiving medication at the time of inclusion in this study.

All patients exhibited apical hypertrophy, (the diastolic thickness of the 4 apical segments is described in Table 1). All patients had a normal ejection fraction (69% ± 5%).

A total of 20 patients with apical HCM were assessed and 340 myocardial segments were analyzed; midwall longitudinal peak systolic strain (LPSS) was measured and compared to endocardial LPSS (Table 2 and Figure 4). We confirmed that, in spite of a supernormal systolic LV function, midwall GLPSS exhibited a diminished percent of strain, which was more marked in the apical than in basal segments. By contrast, endocardial GLPSS was significantly higher and reached normal values.

Midwall GLPSS in the basal segments (Table 3) was lower than the endocardial GLPSS, but without significant differences (-15.5% ± -6.93% vs -17.9% ± -7.5%, *P*



**Figure 3** Bull's eye image of the same normal subject shown in Figure 2, showing percent strain value in the 17 segments analyzed. Mean value of the peak overall systolic strain is also reported (GLPS\_Avg: -21.8%) as well as that of each of the 3 apical views (GLPS\_LAX: -20.1%, GLPS\_A4C: -23.3% and GLPS\_A2C: -22%).

= NS). Midwall GLPSS was significantly decreased in the medial segments (-12.4% ± -7.3% vs -19.7% ± -7.6%, *P* < 0.001), with a 52% increase in endocardium strain. But the largest difference between midwall and endocardial strain was found in the apical segments, with a 168% increase in endocardial strain (-7.3% ± -8.8% vs -22.8% ± -7.8%, *P* < 0.001). The increase of the GLPSS from basal to apex segments can be seen in the dotted line (Figure 4).

Using 2D-based method for myocardial velocity strain (XStrain) that allows analyse the endocardial and epicardial border, this transmural gradient between the midwall and endocardial of global longitudinal peak systolic strain were seen in normal subjects, but without significant differences.

**Reproducibility**

In our laboratory, intraobserver and interobserver variability of 2-D strain was low and varied between 3.6% and 5.3% and 7% and 11.8% respectively.

**DISCUSSION**

To our knowledge, this is the first study to show that in a selected population of patients with apical HCM and normal LV ejection fraction, the regional systolic strain is decreased in the mesocardium, with a compensatory effect in the endocardium. The clinical application of this new finding may help to further understanding the pathophysiology of apical HCM.

Mutations of genes that code for contractile proteins of the sarcomere are responsible for the structural and functional changes seen in patients with HCM, and cause ventricular hypertrophy, myofibrillar disarray and interstitial fibrosis. In spite of the hyperdynamic systolic

**Table 1** Demographic and echocardiographic variables

No. of patients	20
Age (yr)	53 ± 16
Women, n (%)	10 (50)
RV (mm)	15 ± 5
LVDD (mm)	48 ± 5
LVSD (mm)	24 ± 5
EF (%)	69 ± 5
LA (mm)	44 ± 7
Antero-apical (mm)	16 ± 2
Infero-apical (mm)	15 ± 3
Lateral-apical (mm)	17 ± 3
Septal-apical (mm)	17 ± 3
Apex/LVPW ratio	2.1 ± 0.4

Values are expressed as number (%) of patients or mean ± SD. RV: Right ventricle; LVDD: Left ventricular diastolic diameter; LVSD: Left ventricular systolic diameter; LA: Left atrial diameter; LVPW: Left ventricular posterior wall thickness in diastole.

**Table 2** Midwall and endocardial long peak systolic strain

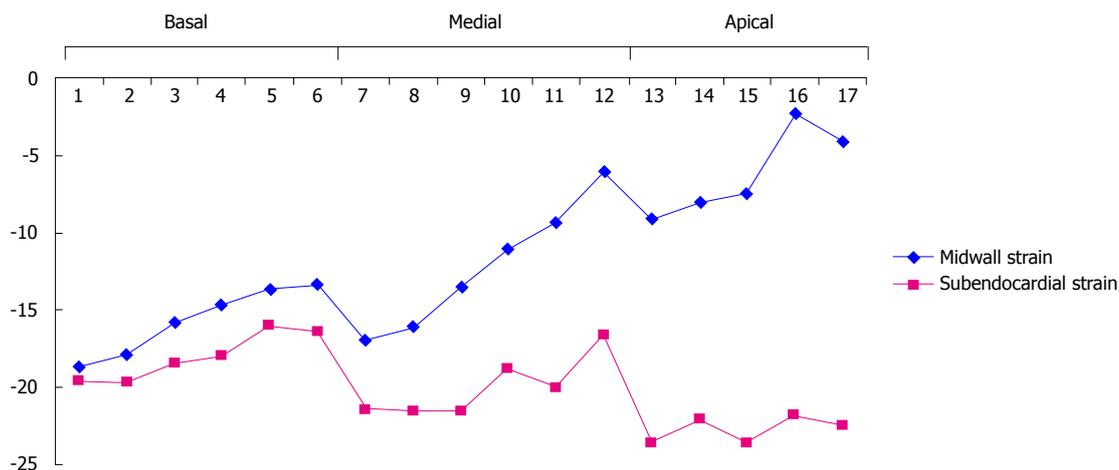
Segments	Midwall LPSS (%)	Endocardial LPSS (%)	<i>P</i> value
Mean GLPSS	-13 (-14/-8.8)	-19.4 (-23.9/-16.2)	< 0.001
Antero-basal	-14.5 (-18/-8)	-16 (-19.5/-12.3)	NS
Lateral-basal	-12 (-14/-10)	-15 (-18.7/-12)	NS
Postero-basal	-15 (-20/-9)	-17 (-19.7/-14.2)	NS
Infero-basal	-19 (-22.7/-13.7)	-21 (-22/-17.2)	NS
Postero-basal septum	-16 (-23.5/-14)	-18 (-22.7/-13.2)	NS
Antero-basal septum	-17.5 (-21/-8.25)	-18 (-25.2/-14)	NS
Antero-medial	-11.5 (-15/-7.2)	-19 (-23.5/-12)	< 0.001
Lateral-medial	-7.5 (-8.7/-2.5)	-18 (-20.7/-10.5)	< 0.001
Postero-medial	-10.5 (-13.7/-7.2)	-17.5 (-23/-15)	< 0.001
Infero-medial	-16 (-20.7/-12.5)	-20.5 (-22.7/-18.2)	< 0.001
Postero-medial septum	-18 (-22.5/-11.5)	-20 (-29/-15)	< 0.001
Antero-medial septum	-16.5 (-18.7/-9.2)	-23.5 (-27.7/-16.2)	< 0.001
Antero-apical	-8 (-16/-1.5)	-21.5 (-29.7/-16.2)	< 0.001
Lateral-apical	-2 (-8/-2.5)	-22.5 (-28.7/-15)	< 0.001
Infero-apical	-8 (-18.2/-0.25)	-22.5 (-28.7/-18)	< 0.001
Septal-apical	-9 (-17.2/-5.2)	-23.5 (-31.5/-16.2)	< 0.001
Apex	-8 (-16/-1.5)	-21.5 (-29.7/-10.2)	< 0.001

Values are expressed as medians and their respective interquartile intervals. LPSS: Longitudinal peak systolic strain; NS: No significance.

function seen by echo, midwall 2-D strain detected a decrease in myocardial strain in all of our patients.

All patients had hypertrophy of the LV apex with normal apical wall motion, but they exhibited a decreased midwall 2-D strain, predominantly in the apex. One might postulate that this finding expresses myofibrillar disarray with microvascular ischemia, which contributes to increased myocardial fibrosis in those segments with greater hypertrophy.

In patients with HCM, Popović *et al*<sup>[17]</sup> have shown that 2-D strain was lower in patients whose MRI showed myocardial fibrosis than in patients without fibrosis, but they did not analyze whether longitudinal strain had



**Figure 4** The dotted line shows the mean global longitudinal peak systolic strain in the 20 patients. Midwall strain is shown in blue and endocardial strain is shown in red. In both lines, each point illustrates the strain value in each of the 17 segments (Basal segments: segments 1-6; Medial segments: segments 7-12; Apical segments: segments 13-17).

Segments	Mesocardial GLPSS (%)	Endocardial GLPSS (%)	Media of increment	CI	Increase of GLPSS	P value
Basal	-15.5 ± -6.93	-17.9 ± -7.5	-2.4	-3/-1.3	18%	NS
Medial	-12.4 ± -7.3	-19.7 ± -7.6	-7.2	-8.4/-6	52%	< 0.001
Apical	-7.3 ± -8.8	-22.8 ± -7.8	-15.5	-17/-13	168%	< 0.001

Values are expressed as mean ± standard deviation. GLPSS: Global longitudinal peak systolic strain; CI: Confidence intervals; NS: No significance.

transmural heterogeneity, as shown in our study.

The normal LV contracts longitudinally in systole and also radially. The array of myocardial fibers in the ventricular wall is quite unique; endocardial and subepicardial fibers align longitudinally, in a spiral shape, and midwall fibers are aligned circumferentially. This latter group is responsible for the radial contraction in the minor axis of the LV (similar to the movement of the bellows of an accordion), while the former cause longitudinal contraction similar to the movement of a piston. This fiber orientation is so efficient that a 15%-20% reduction in the myocyte's length can result in a 40%-60% radial wall thickening, thus allowing the LV to achieve an ejection fraction of 60%.

In patients with apical HCM, longitudinal midwall strain allowed to identify subclinical global systolic dysfunction, with a lower intra and interobserver variability than for strain derived from colour tissue Doppler<sup>[18]</sup>.

In our study of 20 patients with apical HCM, we analyzed 340 myocardial segments with midwall LPSS and compared it to endocardial LPSS. We confirmed that although systolic ventricular function was supernormal, midwall GLPSS exhibited a decrease in the percent of strain, more evident in apical than in medial segments, whereas endocardial GLPSS was significantly greater, and reached normal values<sup>[19]</sup>. These findings indicate that in spite of the apical ventricular hypertrophy with excellent ejection fraction parameters, there is subclinical abnormality in midwall strain, while endocardial function

is preserved. An explanation for this phenomenon could be that myofiber disarray<sup>[5,20]</sup> and interstitial fibrosis<sup>[21-23]</sup> are mostly located in the mid third of the ventricular wall. This particular distribution of histological abnormalities in apical HCM also explains why endomyocardial biopsy is not useful in the diagnosis of HCM, since the biotome does not reach the myocardium with fiber disarray and interstitial fibrosis<sup>[24]</sup>.

**Study limitations**

One limitation of this study is that we only measured longitudinal strain. It is possible that measurement of radial and circumferential strain will add useful information to the data obtained in this work. 2-D strain is a sensitive method to measure myocardial strain, but it is very much dependent on echo image quality, and in patients with necrotic scars strain may be measured in 80% of segments analyzed<sup>[12]</sup>. Such limitation is not applicable to our population, since the presence of LVH helped in obtaining a good quality image.

Another limitation is that the ROI of speckle tracking method cannot be diminished more than 10 mm. The most patients did not exhibit hypertrophy of the basal segments; hence, further midwall strain overlapped with endocardial strain, which might explain the smaller difference between them.

In conclusion, this study shows that 2-D strain assessed by "speckle tracking" is a sensitive method to detect subclinical systolic LV dysfunction. When

midwall and endocardial strain values were compared, we confirmed that the decrease in strain was confined to the midwall, while endocardial myocardial function was preserved. This transmural heterogeneity of systolic deformity in apical HCM has not been previously described. A possible explanation could be that myofibrillar disarray and interstitial fibrosis are distributed in deeper areas of the myocardium. The clinical application of this new finding may help in the pathophysiological interpretation of HCM.

Future studies, with more subjects, will allow assessing whether patients with greater change in midwall strain may be at higher risk for ventricular arrhythmias, sudden death or progression to heart failure due to systolic dysfunction. Additionally, the method could help in evaluating the benefit of conventional treatment and new therapeutic strategies.

## ACKNOWLEDGMENTS

We would like to thank Ing. Ariel Desseno (General Electric) for his technical assistance.

## COMMENTS

### Background

Hypertrophic cardiomyopathy (HCM) is associated with normal left ventricular (LV) ejection fraction and impaired LV strain, but there are no studies so far comparing midwall and endocardial strain.

### Research frontiers

The diagnostic criteria for apical HCM included demonstration of asymmetric left ventricular hypertrophy (LVH), confined predominantly to the LV apex with an apical wall thickness > 15 mm, a ratio of maximal apical to posterior wall thickness > 1.5, and a "spade shape" deformity of the left ventricle with apical cavity obliteration in end-systole based on 2-D echocardiography.

### Innovations and breakthroughs

This study shows that two-dimensional strain assessed by "speckle tracking" is a sensitive method to detect subclinical systolic LV dysfunction. When midwall and endocardial strain values were compared, the authors confirmed that the decrease in strain was confined to the midwall, while endocardial myocardial function was preserved. This transmural heterogeneity of systolic deformity in apical HCM has not been previously described. A possible explanation could be that myofibrillar disarray and interstitial fibrosis are distributed in deeper areas of the myocardium. The clinical application of this new finding may help in the pathophysiological interpretation of HCM.

### Applications

Two-dimensional strain is a novel non-Doppler-based method to evaluate strain from standard two-dimensional acquisitions. By tracing the endocardial contour on an end-systolic frame, the software will automatically track the contour on subsequent frames. Two-dimensional longitudinal strains were assessed in 2 orthogonal apical views (4- 3 and 2-chambers, 17 segments). The region of interest (ROI) was reduced and shifted to the mesocardium to obtain the parametric image, which allowed quantifying strain in each of the 17 segments of the LV. Later, the ROI was shifted to the endocardium to obtain the endocardial strain of the 17 segments.

### Peer-review

The study by Saccheri *et al* reports the data obtained by speckle tracking echocardiography in patients with apical hypertrophic cardiomyopathy. The authors show that two-dimensional strain is able to identify subclinical systolic

left ventricular dysfunction in this patient population. The manuscript is interesting and well written.

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**P- Reviewer:** De Ponti R, Kettering K, Vermeersch P  
**S- Editor:** Song XX **L- Editor:** A **E- Editor:** Lu YJ



## Observational Study

**Inter-ethnic marriages and severity of coronary artery disease: A multicenter study of Arabian Gulf States**

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## Abstract

### AIM

To assess the association of inter-ethnic vs intra-ethnic marriage with severity of coronary artery disease (CAD) in men undergoing angiography.

### METHODS

We conducted a prospective multicenter, multi-ethnic, cross sectional observational study at five hospitals in Saudi Arabia and the United Arab Emirates, in which we used logistic regression analysis with and without adjustment for baseline differences.

### RESULTS

Data were collected for 1068 enrolled patients undergoing coronary angiography for clinical indications during the period of April 1<sup>st</sup>, 2013 to March 30<sup>th</sup>, 2014. Ethnicities of spouses were available only for male patients. Of those enrolled, 687 were married men and constituted the cohort for the present analysis. Intra-ethnic marriages were reported in 70% and inter-ethnic marriages in 30%. After adjusting for baseline differences, inter-ethnic marriage was associated with lower odds of having significant CAD [adjusted odds ratio 0.52 (95%CI: 0.33, 0.81)] or multi-vessel disease (MVD) [adjusted odds ratio 0.57 (95%CI: 0.37, 0.86)]. The adjusted association with left main disease showed a similar trend, but was not statistically significant [adjusted odds ratio 0.74 (95%CI: 0.41, 1.32)]. The association between inter-ethnic marriage and the presence of significant CAD and MVD was not modified by number of concurrent wives (*P* interaction > 0.05 for both).

### CONCLUSION

Among married men undergoing coronary angiography, inter-ethnic, as compared to intra-ethnic, marriage is associated with lower odds of significant CAD and MVD.

**Key words:** Arabian Gulf; Inter-ethnic marriage; Coronary artery disease; Cardiac epidemiology; Coronary angiography

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**Core tip:** One thousand and sixty-eight enrolled patients underwent coronary angiography for clinical indications. Ethnicities of spouses were available for only male patients. Of the 771 males, 687 were married. Seventy percent of them were in intra-ethnic marriages and 30% in inter-ethnic marriages. After adjusting for baseline differences, inter-ethnic marriage was associated with lower odds of having significant coronary artery disease (CAD) or multi-vessel disease (MVD). The adjusted association with left main disease showed a similar trend, but was not statistically significant. The association between inter-ethnic marriage and the presence of significant CAD and MVD was not modified by number of concurrent wives.

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## INTRODUCTION

Coronary artery disease (CAD) is a major cause of death throughout the world. The high prevalence and mortality have led to great importance in understanding the risk factors associated with CAD<sup>[1-3]</sup>. Traditional risk factors comprise the majority of the increase for cardiovascular events<sup>[4]</sup>. Additional factors such as physiological, psychological, emotional, social, and stress, both acute and chronic, have been studied<sup>[5-23]</sup>. The interactions between risk factors also have great consequences<sup>[24]</sup>. Studies investigating the association between marital status and CAD have predominantly been performed in developed countries, and none examined the role of spousal ethnicities and CAD<sup>[25-32]</sup>. Selecting a spouse is often influenced by social norms, and cultural practices typically prefer marriages between persons of the same ethnic background. However, inter-ethnic marriages are increasingly common as societal attitudes and demographic patterns change. Studies from Western societies demonstrated that such marriages are associated with increased stress and lower relationship quality<sup>[33-35]</sup>. Due to these findings, we examined the relationship between inter-ethnic marriages and severity of CAD in two Gulf States.

## MATERIALS AND METHODS

### Study population and data collection

The details regarding the design, methods, and end-points of this multicenter, observational study came from the Polygamy and Risk of Coronary Artery Disease

in Men Undergoing Angiography<sup>[36]</sup>. In the current study the data were collected prospectively from five hospitals in two Gulf Regions (the Kingdom of Saudi Arabia and the United Arab Emirates), during the period of April 1<sup>st</sup>, 2013 to March 30<sup>th</sup>, 2014. The study was approved by King Faisal Specialist Hospital and Research Center Institutional Review Board, and an invitation letter was given to all participants who affirmed verbal consent prior to their enrollment. For each patient undergoing coronary angiography for clinical indication, two separate data forms, one general and one angiographic, were filled out by the research assistant and assigned cardiologist, respectively. Both forms were completed before the patients were discharged from hospital. All data forms were reviewed by the assigned cardiologist then sent online to the principle investigator, who also checked the forms prior to submission for analysis. All patients undergoing coronary angiography were recruited for the study. There was no exclusion criteria.

#### **Contents of personal data form**

Demographic data: Age, ethnic background; Physiologic status: Hypertension, diabetes, dyslipidemia, BMI; Life style: Smoking history; Past medical history: CAD, percutaneous coronary intervention, coronary artery bypass surgery, cerebral vascular disease, peripheral arterial disease, congestive heart failure, atrial fibrillation, chronic kidney disease. Socioeconomic data: Occupation (unemployed, private sector, government sector, self-employed), living in rural or urban area, highest level of education completed (illiterate, secondary school, university, masters, PhD), monthly income (< 1300, 1300 to 2600, 2600 to 5300, 5300 to 7900, 7900 to 10600, > 10600 USD); Number of wives: Single or multiple concurrent wives; Ethnicity of spouse (Arabic Gulf region, Arabs non-Gulf region, non-Arabic).

#### **Contents of angiographic data form**

Reason for coronary angiography: Elective or urgent/emergent; Number of vessels involved (severity); Treatment: Medical or revascularization.

#### **Definitions**

Significant CAD was defined as  $\geq 70\%$  luminal stenosis in a major epicardial vessel or  $\geq 50\%$  stenosis in the left main coronary artery. Multi-vessel disease (MVD) was defined as having more than one significant CAD; Inter-ethnic marriage was defined as Arab men from the Gulf region marrying Arab women from a non-Gulf region or non-Arab women; Intra-ethnic marriage was defined as Arab men from the Gulf region marrying Arab women from the same region.

#### **Statistical analysis**

Standard summary statistics were used to describe the cohort. Continuous variables are presented as mean  $\pm$  SD and were compared across multiple groups using the analysis of variance test. Categorical variables are

presented as percentages and compared using the  $\chi^2$  test. The associations between inter-ethnic or intra-ethnic marriage and CAD, MVD and left main disease (LMD) were assessed using logistic regression models and quantified with odds ratios. Adjusted regression models included the following explanatory variables: Age, community setting (urban vs rural), employment, income level, education level, number of concurrent wives, and additional variables that differed by ethnicity of spouse in univariate comparisons ( $P < 0.1$ ). All statistical tests were two-tailed and significance was defined as  $P < 0.05$ . No adjustments for multiple comparisons were made.

## **RESULTS**

### **Overall characteristics of patients and coronary angiogram findings**

A detailed description can be found in Polygamy and Risk of Coronary Artery Disease in Men Undergoing Angiography<sup>[36]</sup>.

### **Patients characteristics stratified by ethnicity of spouse**

We enrolled 1068 patients in the current study. Ethnicities of spouses were available for only male patients, so the analysis excludes female patients. Of the 771 males, 685 were married; however, spouse ethnicity was not available for two of these men. Married men were categorized according to number of wives: The majority had one wife (68%), while some had a history of two wives (19%), three wives (10%) or four wives (3%). Most were in intra-ethnic marriages 481 (70%), as opposed to inter-ethnic marriages 204 (30%), Table 1. The majority of inter-ethnic marriages were between Gulf nationals and non-Gulf Arab women (65%). Men in inter-ethnic marriages were more likely to have a history of hypertension and CABG, to live in rural communities, and to be in polygamous marriages. In univariate analyses, there was a significant association between inter-ethnic marriage and presence of LMD therefore the rate of CABG was higher in these subjects when compared with those in intra-ethnic marriages, who had undergone more PCI (Table 1). In multivariate logistic regressions adjusting for baseline differences, inter-ethnic marriage was associated with lower odds of having significant CAD [adjusted odds ratio 0.52 (95%CI: 0.33, 0.81)] or MVD [adjusted odds ratio 0.57 (95%CI: 0.37, 0.86)]. The adjusted association with LMD showed a similar trend, but was not statistically significant [adjusted odds ratio 0.74 (95%CI: 0.41, 1.32)] (Figure 1). The association between inter-ethnic marriage and the presence of significant CAD or MVD was not modified by number of concurrent wives ( $P$  interaction  $> 0.05$  for both) (Figure 2).

## **DISCUSSION**

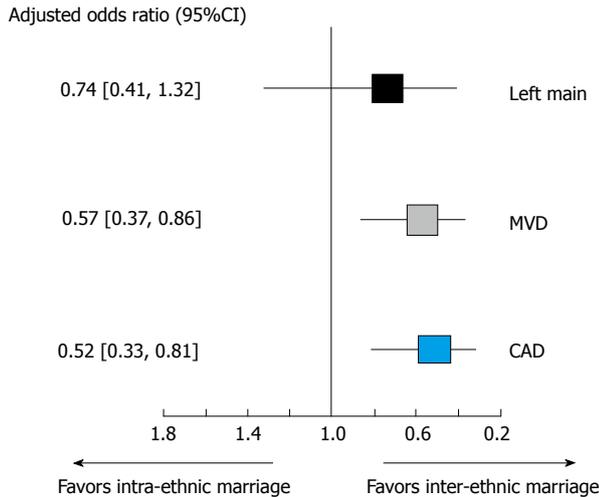
Previous literature from non-Gulf regions demonstrated that inter-ethnic marriages were found to have lower income and education level and poor level of family

**Table 1 Overall patient characteristic stratified by ethnicity of spouse**

	All (n = 685)	Intra-ethnic (n = 481)	Inter-ethnic (n = 204)	P value
Age (yr)	59 ± 12	58 ± 13	60 ± 12	0.0879
BMI (kg/m <sup>2</sup> )	28 ± 6	28 ± 6	27 ± 5	0.4009
Rural, n (%)	27	25	34	0.0148
DM, n (%)	56	57	54	0.5226
Hypertension, n (%)	57	54	64	0.0209
Smoking, n (%)	54	53	57	0.1428
Dyslipidemia, n (%)	66	65	68	0.4734
Past history, n (%)				
CAD	45	45	45	0.9468
PCI	24	23	26	0.3263
CABG	6	5	9	0.0329
Atrial fibrillation	5	4	5	0.3990
CHF	13	13	11	0.5102
CVA	4	4	5	0.4388
CKD	14	14	13	0.7020
Depression	8	8	8	0.8363
PAD	2	2	3	0.1453
Ethnicity, n (%)				0.3597
Arabic gulf region	87	87	88	
Arabic non-gulf	6	7	4	
Non Arabic	7	6	8	
No. of wives, n (%)				< 0.0001
1	68	81	38	
2	19	13	32	
3	10	5	22	
4	3	1	8	
Monthly income, n (%)				0.1760
\$ < 1300	50	50	52	
\$ 1300-2600	29	30	27	
\$ 2600-5300	13	14	10	
\$ 5300 to 7900	4	4	5	
\$ 7900 to 10600	2	1	3	
\$ > 10600	2	1	3	
Job category, n (%)				0.6824
Jobless	21	21	23	
Private sector	18	18	16	
Government sector	43	42	45	
Self employs	18	19	16	
Education level, n (%)				0.0403
Illiterate	42	42	40	
Secondary school	38	37	40	
Post graduate	16	18	12	
Master	3	2	7	
PhD	1	1	1	
Indication for CAG, n (%)				0.1483
Elective	48	48	47	
NSTEMI	46	44	50	
STEMI	6	8	3	
Findings on CAG, n (%)				< 0.001
No CAD	28	29	27	
Single vessel	24	25	21	
Double vessel	26	29	19	
Triple vessel	22	17	34	
Multi-vessel	48	46	53	0.1020
Left main	12	10	17	0.0175
Intervention, n (%)				< 0.0001
Medical therapy	36	33	43	
PCI	47	54	31	
CABG	17	13	26	

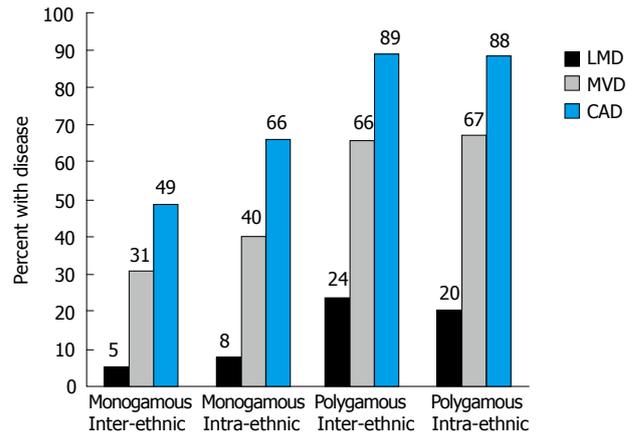
DM: Diabetes mellitus; CAD: Coronary artery disease; CHF: Congestive heart failure; CVA: Cerebrovascular accident; CKD: Chronic kidney disease; PAD: Peripheral arterial disease; \$: United States dollars; PhD: A doctor of philosophy; STEMI: ST segment elevation myocardial infarction; NSTEMI: Non-ST-segment elevation acute coronary syndromes; CAG: Coronary angiography; PCI: Percutaneous coronary intervention; CABG: Coronary artery bypass grafting.

acceptance and support when compared to intra-ethnic marriages. In addition, inter-ethnic couples reported lower



**Figure 1** Adjusted association between type of marriage (inter-ethnic vs intra ethnic) and presence of any coronary artery disease, multi-vessel disease and left main disease. CAD: Coronary artery disease; MVD: Multi-vessel disease.

relationship satisfaction, and increased conflict within the relationship over such issues as money and spending time together. These factors are associated with increased stress and lower relationship quality<sup>[33-35]</sup>. Furthermore, it is known that acute and chronic stress is associated with the development of CAD<sup>[17,18]</sup>. However, the impact of inter-ethnic marriage on the severity of CAD is unknown. Our study is the first to analyze the association between inter-ethnic vs intra-ethnic marriage and severity of CAD among men using coronary angiography, the gold standard for identifying CAD. After adjusting for baseline characteristics, we observed that inter-ethnic marriage was associated with lower odds of having significant CAD or MVD. The adjusted association with LMD showed a similar trend, but was not statistically significant. Studies from western societies reported an increase in stress within inter-ethnic marriages; however, our study found lower odds of CAD in inter-ethnic vs intra-ethnic marriage, which may suggest lower levels of stress in these marriages. A number of factors may contribute to our results. First, in the current study, 80% of the patients reported income levels of 32000 USD or less annually. Although there is family and societal pressure to marry within the same region, the overall cost of getting married and maintaining the relationship within the Gulf region is high, which may impact men from this region leading them to select a spouse from elsewhere. The high cost of marriage in the Gulf is associated with complex family interactions, which possibly creates unrealistic expectations when anticipating a marital lifestyle. This may be a source of significant stress in and of itself. Second, almost 80% of the patients in our study had low level of education. In the Gulf region, there are increased opportunities for educated men to marry, which may necessitate less educated men to select a spouse from outside the region. Additionally, the conservative social and cultural practices in the Gulf region may play a role in stress levels when compared to non-Gulf regions. Men from Gulf region who marry women



**Figure 2** The proportion of patients with any coronary artery disease, multi-vessel disease or left main disease stratified by type of marriage (inter- or intra-ethnic and polygamous vs monogamous). CAD: Coronary artery disease; MVD: Multi-vessel disease; LMD: Left main disease.

from outside the region may be more health conscious than men who marry women from inside the Gulf. Classically, women from the Gulf region tend to prepare dishes rich in fat, which are atherogenic, whereas wives from elsewhere may favor dishes that are more healthy, notably those from the Arab Mediterranean region<sup>[37-39]</sup>. Non-Gulf wives may encourage their husbands to be healthy and maintain fitness, as their literacy and health awareness may be superior to that of Gulf-native women.

**Strengths of this study**

This study is the first to look at the association between inter-ethnic vs intra-ethnic marriages and severity of CAD using coronary angiography in men from Arabian Gulf States.

**Contributions of the study**

The study provides additional knowledge on the risks associated with inter-ethnic vs intra-ethnic marriages. This information will be useful for personalizing care and preventing CAD. Not only will it provide patients information concerning social risk factors, it will also help providers identify and treat adults who are at increased risk of CAD. Further studies are required to confirm our findings and to investigate the mechanism underlying these findings in order to identify possible interventions to reduce these risks. In future studies, assessment of the local culture, social and medical practices, and attitudes toward inter-ethnic marriage should be performed.

**Study limitations**

Limitations of the study include a small sample size and the lack of documentation of the length of marriages prior to cardiac catheterization; this interval may influence the findings. Our study population was selected to undergo coronary angiography if clinically indicated, and as such, cannot be generalized to all married men in the Gulf region. Additionally, 42% of the patients were illiterate and 80% reported income levels of 32000 USD or less

annually; indicating that the results may not be applicable to those with higher incomes or higher levels of education. We did not look at unmeasured confounding variables such as dietary habits, physical activity, inflammatory or stress markers, or additional variables that may have played a role.

## ACKNOWLEDGMENTS

We would like to sincerely thank all patients who agreed to participate in this study.

## COMMENTS

### Background

Selecting a spouse is often influenced by social norms, and societies typically prefer marriages of the same ethnic background. However, inter-ethnic marriages are increasingly common as societal attitudes and demographic patterns change. Studies from Western societies have demonstrated that inter-ethnic marriages are associated with increased stress and lower relationship quality. The majority of these studies examine the association between marital status and coronary artery disease (CAD), but none have examined the role of spousal ethnicity and CAD.

### Research frontiers

It is unknown whether such marriages have an impact on the severity of CAD.

### Innovations and breakthroughs

This study is the first to look at the association between inter-ethnic vs intra-ethnic marriages and severity of CAD using coronary angiography in men from Arabian Gulf States.

### Applications

The data in this study suggest that among married men undergoing coronary angiography, inter-ethnic marriage is associated with lower odds of significant CAD and multi-vessel disease (MVD). Further studies are required to confirm these findings and to investigate the mechanism underlying these findings in order to identify possible interventions to reduce these risks. In future studies, assessment of the local culture, social and medical practices, and attitudes toward inter-ethnic marriage should be performed.

### Terminology

Significant coronary artery disease (CAD) was defined as  $\geq 70\%$  luminal stenosis in a major epicardial vessel or  $\geq 50\%$  stenosis in the left main coronary artery. MVD was defined as having more than one significant CAD. Inter-ethnic marriage was defined as Arab men from the Gulf region marrying Arab women from a non-Gulf region or non-Arab women. Intra-ethnic marriage was defined as Arab men from the Gulf region marrying Arab women from the same region.

### Peer-review

The data is interesting.

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## Contrast use in relation to the arterial access site for percutaneous coronary intervention: A comprehensive meta-analysis of randomized trials

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### Abstract

#### AIM

To compare the amount of contrast used during percutaneous coronary intervention (PCI) *via trans*-radial access (TRA) *vs trans*-femoral access (TFA).

#### METHODS

Scientific databases and websites were searched for: randomizedcontrolledtrials (RCTs). Data were extracted by two independent reviewers and was summarized as the weighted mean difference (WMD) of contrast used with a 95%CI using a random-effects model.

#### RESULTS

The meta-analysis included 13 RCTs with a total of 3165 patients. There was no difference between the two strategies in the amount of contrast used (WMD = - 0.65 mL, 95%CI: -10.94-9.46 mL;  $P = 0.901$ ).

#### CONCLUSION

This meta-analysis shows that in patients undergoing PCI, the amount of contrast volume used was not different between TRA and TFA.

**Key words:** Femoral; Contrast; Percutaneous coronary interventions; Radial

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**Core tip:** Adaptation of radial access for percutaneous coronary interventions in patients with chronic kidney disease is slower because of concern about contrast-induced nephropathy from the greater contrast load. Data from individual studies vary; therefore we performed a comprehensive meta-analysis of randomized controlled trials comparing the amount of contrast used between radial access and femoral access.

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## INTRODUCTION

Trans-radial access (TRA) for percutaneous coronary interventions (PCIs) results in a lower risk for bleeding and vascular complications than trans-femoral access (TFA)<sup>[1-5]</sup>. However, CathPCI registry data suggest that adaptation of TRA-PCI in patients with lower glomerular filtration rates (GFRs) is lower compared to patients with higher GFRs; one wonders if this could be the result of concern over the larger amount of contrast used in TRA compared to TFA<sup>[6]</sup>. Data from individual studies have been variable: Some show larger contrast volume is used with TRA<sup>[2,7]</sup>, others show equal amounts used in both strategies<sup>[5,8]</sup>, and yet others show less contrast used with TRA<sup>[3,9]</sup>. Therefore, we performed an updated comprehensive meta-analysis of randomized controlled trials (RCTs) comparing the amounts of contrast used in TRA and TFA during PCI.

## MATERIALS AND METHODS

This meta-analysis was performed according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines for systematic reviews and meta-analyses<sup>[10]</sup>. We performed a systematic search of PubMed, Embase, and the Cochrane Library and cross-referenced relevant articles using various combinations of keywords such as "radial", "femoral", "cardiac catheterization", and "coronary intervention" for eligible published studies. Data were collected by two independent investigators, and disagreements were resolved by consensus. Trials were included if they enrolled patients undergoing PCI and randomly assigned them to TRA or TFA. We recorded mean contrast volume used. We also contacted corresponding authors for those articles not reporting

contrast volume or reporting the median contrast used. We were able to obtain the mean contrast used for only one additional trial<sup>[11]</sup>.

We summarized the data as the weighted mean difference (WMD) of contrast used with a 95%CI using Comprehensive Meta-Analysis (CMA) system version 3 (Comprehensive Meta-Analysis; Biostat Inc., Englewood, NJ, United States). A random-effects model was used to analyze data. The presence of heterogeneity across trials was evaluated using the Cochran Q test and the Higgins  $I^2$  test<sup>[12]</sup>. The measure of  $I^2$  can be interpreted as the percentage of variability resulting from heterogeneity between studies rather than sampling error<sup>[12]</sup>. Finally, an additional sensitivity analysis was performed where one study at a time was excluded, and the impact on the summary results of removing each was evaluated.

## RESULTS

Among 26 identified RCTs, only 15 trials reported the amount of contrast used. However, data for the mean contrast used was available for only 13 RCTs, which used 3165 patients, and these were used for final analysis<sup>[4,5,7,11,13-20]</sup>. Figure 1 shows the search flow diagram. The bias assessment for each RCT is shown in Figure 2.

The characteristics of the individual trials included in the meta-analysis are shown in Table 1. Most studies were single-center studies with broad spectra of patient populations, including patients with stable angina, acute coronary syndrome, or ST-elevation myocardial infarction. The majority of the procedures were performed by radial experts.

There was no difference in the amount of contrast used during either TRA or TFA (WMD = - 0.65 mL, 95%CI: -10.94 to 9.46 mL;  $P = 0.901$ ; Figure 3). We found significant between-trial heterogeneity ( $Q = 260.8$ ,  $df = 12$ ;  $P < 0.001$ ;  $I^2 = 95.4$ ). However, during sensitivity analysis, removal of any single study did not affect summary results (Figure 4).

## DISCUSSION

In this study, we compared a broad spectrum of 3165 patients enrolled in 13 RCTs in terms of the contrast volume used during TRA or TFA during PCI. Overall, there was no difference in contrast volume use between the two access strategies. However, most trials were single-centered, and the majority of procedures were performed by radial experts.

Acute kidney injury (AKI) is a well-recognized complication of PCI that is associated with greater risk of in-hospital mortality and poor long-term outcomes<sup>[21]</sup>. The two major causes of post-PCI AKI are contrast-induced nephropathy (CIN) and renal atheroembolus<sup>[22,23]</sup>. The reported incidence of CIN post-PCI varies widely depending on numerous clinical, demographic, and procedural

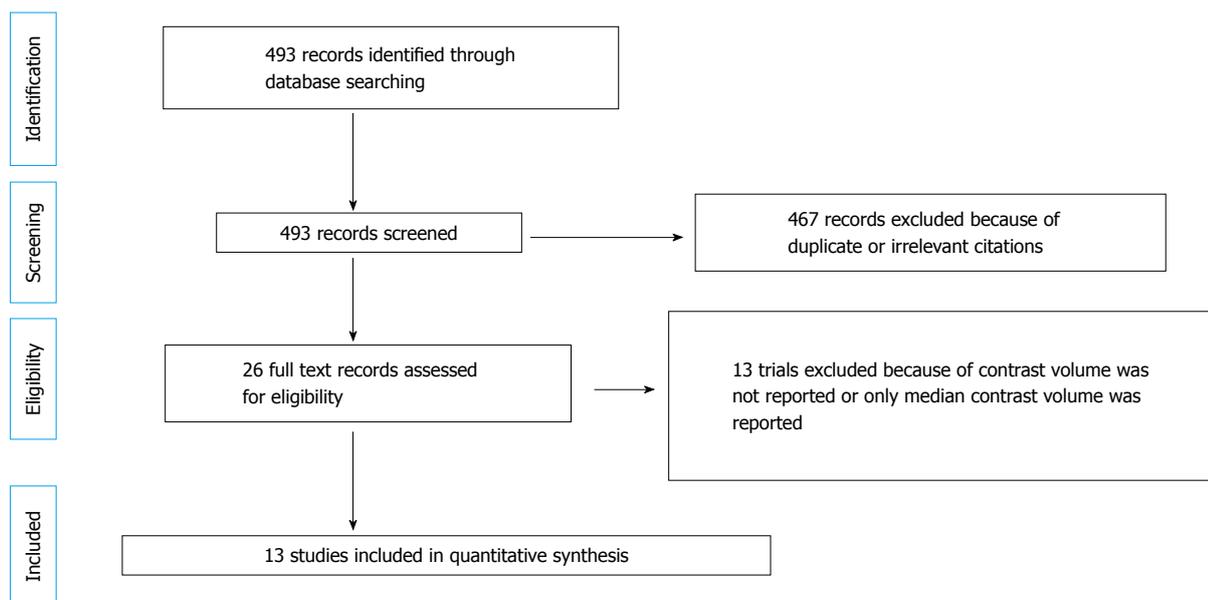


Figure 1 Flow diagram for study selection.

Mann	?	-	-	?	?	?
Saito	?	?	-	-	?	?
Reddy	+	?	-	?	+	+
Brasselet	?	-	-	?	?	+
Achenbach	?	-	-	?	+	+
Sentas	?	-	?	?	+	+
Chodor 2009	-	-	?	?	+	+
Vazquez	+	?	-	?	+	?
Chodor 2011	-	-	-	?	+	+
Wang	+	?	-	+	+	+
Bernat	+	?	-	+	+	+
Michael	+	+	-	?	+	+
Koftowski	+	?	-	?	+	+
	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting

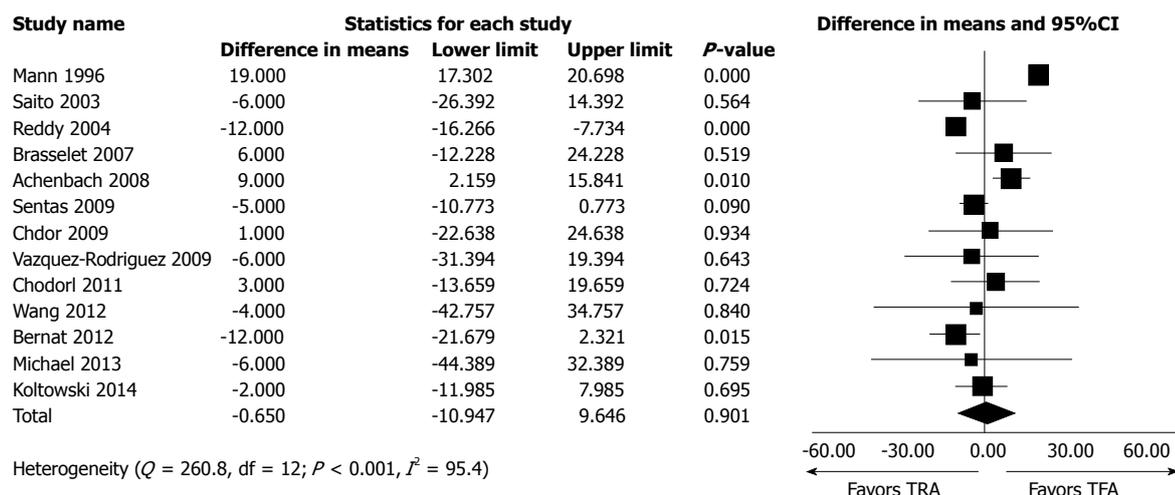
+ Low risk of bias  
 - High risk of bias  
 ? Unclear risk of bias

Figure 2 Risk of bias of included randomized controlled trials.

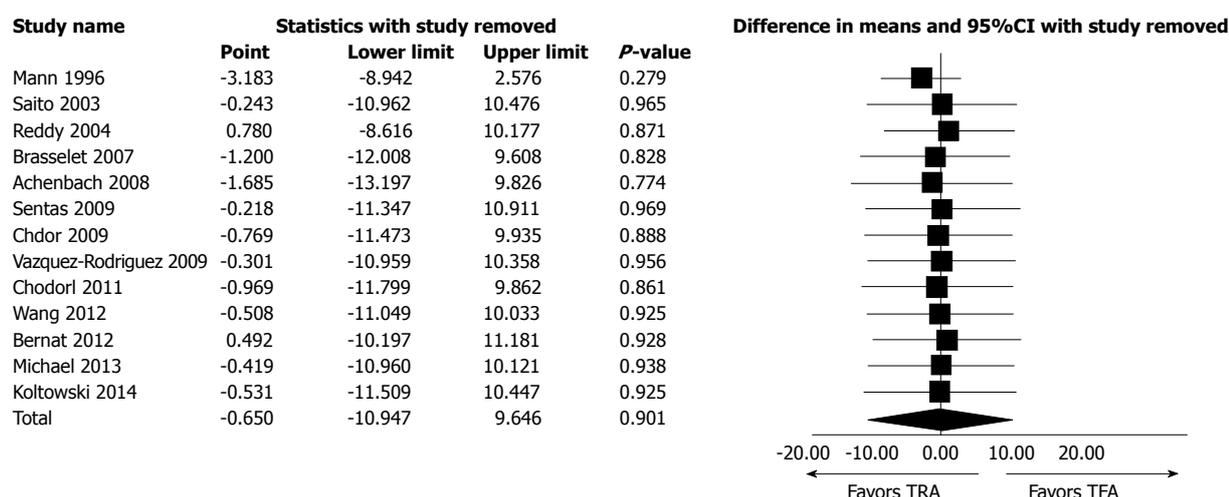
factors<sup>[22]</sup>. Among these, contrast volume is a well-established, dose-dependent, and potentially modifiable risk factor for CIN<sup>[22]</sup>. Although there have been reports of greater contrast use with TRA and concerns about possible subsequent CIN from this more extensive dye load<sup>[2,7,24]</sup>, our meta-analysis shows that the volume of contrast used is not higher among patients undergoing PCI with TRA compared to TFA.

In contrast, a report from the British Columbia Cardiac and Renal Registries that included 69214 patients after coronary catheterization and PCI showed that chronic kidney disease (CKD) onset within 6 mo was significantly lower with TRA compared to TFA (0.5% vs 2.2%,  $P < 0.001$ ) even after adjusting for baseline variables<sup>[9]</sup>. Similarly, another propensity-matched study showed that TRA, compared to TFA, was associated with a lower risk of AKI<sup>[25]</sup>. Finally, a recent meta-analysis of observational studies (adjusted by propensity score matching) showed that TRA, compared to TFA, was associated with lower risk of AKI<sup>[26]</sup>. The primary mechanism by which TRA was associated with a lower risk of kidney injury is thought to be through a reduced likelihood of renal atheroembolization because it offers the additional advantage of avoiding passage through potential atheromatous aortae and renal vessels<sup>[9,23]</sup>. The other mechanism by which TRA leads to less kidney injury is through a reduced risk of bleeding and the subsequent need for a blood transfusion. Post procedure bleeding and blood transfusion are independently associated with the development of AKI<sup>[27,28]</sup>.

The potential benefits of TRA in CRD patients is in paradox to the CathPCI registry data, which show a slow adaption of TRA-PCI in patients with lower GFRs compared to patients with higher GFRs<sup>[6]</sup>. It is not clear if this is a result of misconceptions about potential increases in contrast use with radial access<sup>[24]</sup> or due to



**Figure 3** Forest plot showing weighted mean difference of contrast use. The size of the square represents the weight that the corresponding study exerts in the meta-analysis. The larger the square, the more the study contributes to the overall estimate. Diamonds indicate the overall summary estimate for the analysis, its width representing the 95%CI. TRA: *Trans*-radial access; TFA: *Trans*-femoral access.



**Figure 4** Forest plot showing weighted mean difference of contrast use with sensitivity analysis evaluating the impact on overall summary results of removing each study. TRA: *Trans*-radial access; TFA: *Trans*-femoral access.

pressure from nephrologists who routinely recommend against using TRA in patient with CKD<sup>[29]</sup>. Even the Fistula First Initiative Coalition, sponsored by the Centers for Medicare and Medicaid Services, discourages use of the radial artery for access of the arterial vasculature in patients at risk for, or with known Stage 4 or 5 CKD<sup>[30]</sup>. This needs further investigation to assure we are not withholding beneficial intervention in these patient populations because of the theoretical possibility that dialysis access will be lost in the future.

This meta-analysis has several limitations. First, as with all meta-analyses, it is subject to various biases because data were combined from many studies with varying protocols. Second, most of the studies were single-centered, and the majority of procedures were performed by radial experts. Furthermore, in a majority of the trials, patients with coronary artery bypass grafts (CABG) were excluded. Therefore, the generalizability

of this study may be limited, particularly to operators less-skilled in radial access and to patients with CABG. Finally, apart from the AKI-MATRIX sub-study, none of the randomized studies comparing TRA and TFA has ever systematically explored the issue of renal complications<sup>[31]</sup>. Therefore, we were not able perform the meta-analysis using AKI as one of the outcomes.

In conclusion, this meta-analysis of RCTs showed that in patients undergoing PCI, the amount of contrast volume used was not different between the TRA and TFA arms.

## COMMENTS

### Background

Trans-radial access (TRA) for percutaneous coronary interventions (PCIs) results in lower bleeding and vascular complications than trans-femoral access (TFA). A recent randomized controlled trial (RCT) and several updated meta-

**Table 1 Characteristics of included trials**

Ref.	Year	TRA (n)	TFA (n)	Mean contrast volume (mL)		TRA operator experience	Patient population
				TRA	TFA		
Mann <i>et al</i> <sup>[13]</sup>	1996	73	75	138	119	NR	ACS
Saito <i>et al</i> <sup>[14]</sup>	2003	77	72	180	186	Experienced	AMI
Reddy <i>et al</i> <sup>[15]</sup>	2004	25	50	123	135	Low	Elective PCI
Brasselet <i>et al</i> <sup>[4]</sup>	2007	57	57	97	91	Intermediate-experienced	ACS
Achenbach <i>et al</i> <sup>[5]</sup>	2008	152	155	88	79	Experienced	ACS, Elective PCI
Sentas <i>et al</i> <sup>[16]</sup>	2009	335	335	84	89	Experienced	ACS, Elective PCI
Chodór <i>et al</i> <sup>[17]</sup>	2009	50	50	198	197	Experienced	STEMI
Vazquez-rodriguez <i>et al</i> <sup>[18]</sup>	2009	217	222	275	281	Experienced	AMI
Chodór <i>et al</i> <sup>[19]</sup>	2011	49	59	165	162	Experienced	STEMI
Wang <i>et al</i> <sup>[20]</sup>	2012	60	59	160	164	Experienced	STEMI
Bernat <i>et al</i> <sup>[3]</sup>	2012	348	359	170	182	Experienced	STEMI
Michael <i>et al</i> <sup>[7]</sup>	2013	63	63	171	142	Experienced	NSTEMI or elective PCI with previous CABG
Koltowski <i>et al</i> <sup>[11]</sup>	2014	52	51	63	65	Experienced	STEMI

ACS: Acute coronary syndrome; AMI: Acute myocardial infarction; CABG: Coronary artery bypass graft; NSTEMI: Non-ST-elevation myocardial infarction; PCI: Percutaneous coronary intervention; STEMI: ST-elevation myocardial infarction; TRA: *Trans*-radial access; TFA: *Trans*-femoral access.

analyses of RCTs have also shown that TRA also improves mortality compared to TFA in patients with acute coronary syndrome.

**Research frontiers**

Despite the proven benefits of TRA for PCI, its adaptation for patients with chronic kidney disease has been slow because of concern about contrast-induced nephropathy from greater contrast use. Data from individual studies have been variable: Some show larger contrast volumes with TRA, but others show equal amounts of contrast use in both strategies.

**Innovations and breakthroughs**

In this study, the authors investigated the amounts of contrast used in TRA compared to TFA during PCI. This is the most comprehensive meta-analysis of RCTs in this field.

**Applications**

This study shows that the amount of contrast used does not differ between TRA-PCI and TFA-PCI. Therefore, TRA-PCI should not be avoided in patients with chronic kidney disease solely because of concern for increased contrast use.

**Peer-review**

The authors investigated the dose of contrast volume in patients who underwent trans-radial percutaneous coronary intervention (PCI) or trans-femoral PCI, using the meta-analysis method. They showed no difference in contrast medium between the two arms. This meta-analysis seems to be interesting.

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## Three-dimensional optical coherence tomography reconstruction of bifurcation stenting using the Szabo anchor-wire technique

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### Abstract

Ostial lesions present unique challenges for percutaneous coronary intervention (PCI). These lesions are often more calcified, fibrotic, rigid, and more prone to elastic recoil. Intervention on these lesions is associated with higher procedural complications and higher rates of restenosis. Ostial lesions require precise stent placement in the ostium with the absence of side branch compromise. Accurate stent placement in the ostium without side branch compromise is difficult to accomplish with angiography alone. The Szabo technique uses two coronary guidewires for the correct placement in the aorto-ostial or bifurcation lesion. One guidewire is passed through the final cell of the stent strut and acts as the anchor wire. It helps to prevent migration of the stent beyond the ostium and facilitates the precise stenting at the ostium. This technique has several advantages including less reliance on angiography, lower rates of stent malposition and lower rates of incomplete stent coverage. Potential disadvantages include stent distortion and dislodgement from stent manipulation. We describe two cases of successful PCI to bifurcation lesions using the Szabo technique and confirmation of correct placement in the ostium with optical coherence tomography.

**Key words:** Cardiac catheterization; Bifurcation lesion; Percutaneous coronary intervention; Optical coherence tomography; Ostial stenosis

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**Core tip:** Percutaneous intervention of ostial and bifurcation lesions is associated with higher rates of restenosis and procedural complications. Vessel anatomy, histology, and the variable angle of takeoff of ostial lesions contribute to the challenging nature of intervention. Lesion histology demonstrates greater calcification, rigidity, eccentricity as well as thicker muscular and

elastic tissue, which contribute to greater elastic recoil. The Szabo two-wire technique provides accurate and complete stent positioning within the ostium, with less dependence on angiography. Intravascular imaging such as with intravascular ultrasound and optical coherence tomography (OCT) can confirm proper stent positioning. We describe two cases of successful percutaneous coronary intervention to bifurcation lesions using the Szabo technique and confirmation of correct placement in the ostium with OCT.

Yu K, Hundal H, Zynda T, Seto A. Three-dimensional optical coherence tomography reconstruction of bifurcation stenting using the Szabo anchor-wire technique. *World J Cardiol* 2017; 9(4): 384-390 Available from: URL: <http://www.wjgnet.com/1949-8462/full/v9/i4/384.htm> DOI: <http://dx.doi.org/10.4330/wjc.v9.i4.384>

## INTRODUCTION

The Szabo or anchor-wire technique utilizes two coronary guidewires for the precise placement of stents in aorto-ostial or bifurcation lesions. One guidewire is placed in the main artery, while the second wire is placed in the side branch or aorta and threaded through the most proximal strut of the stent<sup>[1,2]</sup>. Gutiérrez-Chico *et al.*<sup>[3]</sup> evaluated it in a retrospective study in 2010 that showed reduction in incidence of angiographic malpositioning in bifurcation and aorto-ostial lesions without increasing complications. Others have concluded that the technique is imprecise with stent protrusion into the proximal main vessel after evaluation with intravascular ultrasound (IVUS) or stent dislodgement<sup>[4,5]</sup>. We present two such cases of evaluation of stent placement by the Szabo technique using optical coherence tomography (OCT).

## CASE REPORT

### Case 1

A 27-year-old female with CREST syndrome, limited scleroderma, interstitial lung disease, mild pulmonary hypertension, and chronic kidney disease (CKD) from scleroderma renal crises presented with intermittent atypical chest pain. It was midsternal, not worsened with exercise or relieved with rest, but relieved with nitroglycerin. During one episode of chest pain, she had an elevated troponin to 5.0 ng/mL. She was initially managed conservatively due to her CKD and equivocal nuclear stress test findings. She continued to have daily angina that was responsive to nifedipine so a coronary angiography was performed.

Her angiogram revealed a severe stenosis of the proximal left anterior descending (LAD) distal to the bifurcation of a high diagonal vessel (Figure 1) with associated collaterals from the right coronary artery and slow flow. The right coronary artery and left circumflex were normal. The patient had chest pain during the angiogram. Nitroglycerin relieved her symptoms and

improved the angiographic flow of the LAD, but the stenosis distal to the takeoff of the diagonal was persistent.

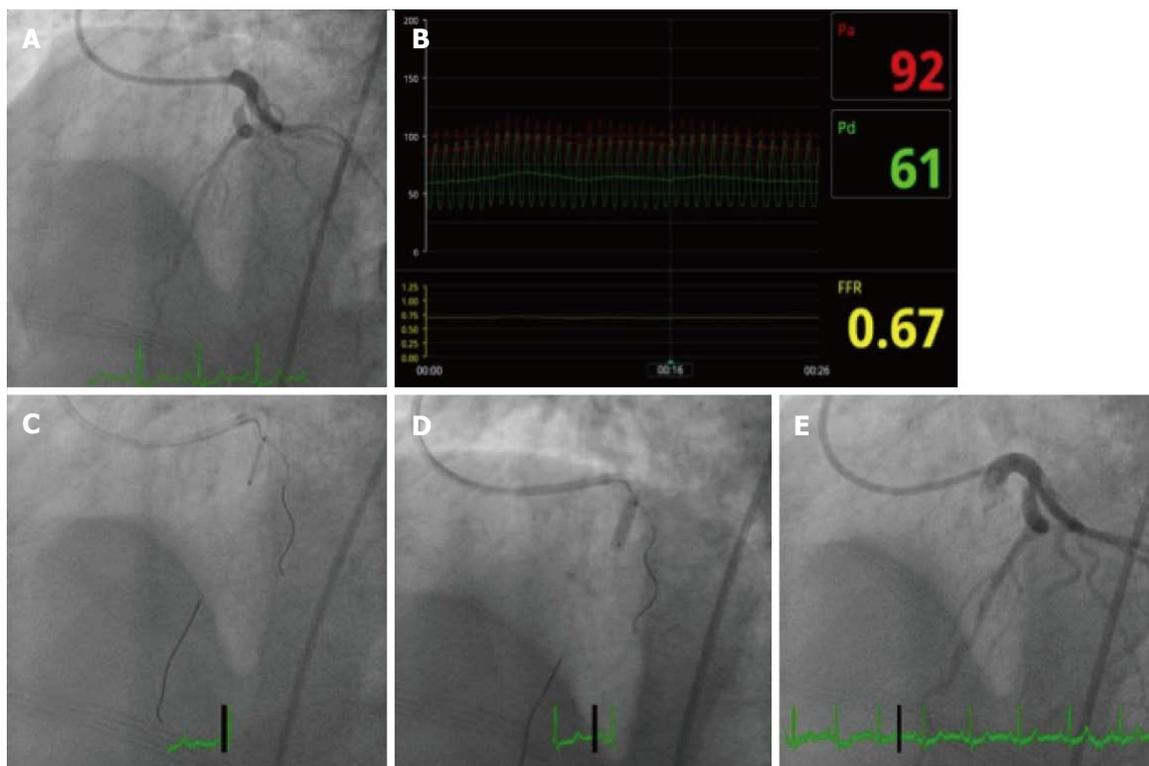
Using an XB 3.5 guide catheter, a pressure wire (PressureWire Aeris, St. Jude Medical, St. Paul, MN, United States), was advanced across the LAD lesion and the resting Pd/Pa ratio was found to be ischemic at 0.67. A HiTorque Whisper MS wire (Abbott Vascular, Temecula, CA, United States) was advanced past the lesion in the LAD and the PressureWire was removed. A second wire, PT 2 (Boston Scientific, Natick, MA), was advanced into the high diagonal. The LAD lesion was pre-dilated with a 2.0 mm × 12 mm compliant balloon. Coronary stent placement was performed using the Szabo technique with a 3.0 mm × 15 mm drug eluting stent. Post-dilation was performed with a 3.0 mm × 8 mm non-compliant balloon. Intravascular imaging with OCT was performed from the LAD, and showed stent malapposition and insufficient expansion of the distal portion of the stent, but also demonstrated optimal stent positioning with only a single stent strut visible beyond the ostium of the main branch of the LAD. Repeat OCT from the diagonal artery showed no stent struts encroaching on the diagonal artery. Other notable OCT findings were the absence of atherosclerotic disease and the presence of intimal medial hypertrophy in the proximal LAD rather than atherosclerosis. Following OCT images, the stent was post-dilated with a 4-0 noncompliant balloon with excellent results (Figure 2).

### Case 2

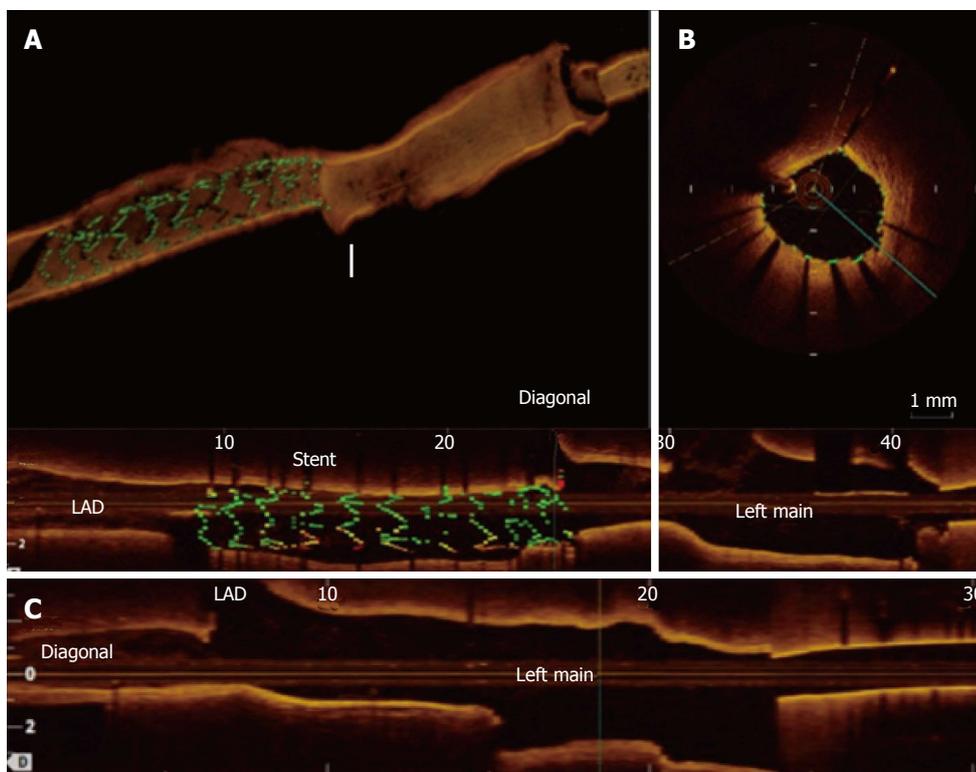
A 65-year-old man with atypical chest pain underwent stress echocardiography, which demonstrated ischemia in the LAD territory. Angiography showed separate ostia of the LAD and left circumflex artery (LCx) and proximal moderate to severe LAD stenosis (Figure 3). Percutaneous coronary intervention (PCI) using the anchor wire technique was performed. An IL 3.5 guide catheter was used to engage the LAD. A Balanced Middleweight 0(Abbott).014" coronary guidewire was placed across the lesion. A Whisper MS wire (Abbott) was backloaded through the proximal stent strut and across the LCx artery. A Vision 3.5 × 23 bare metal stent (Abbott) was deployed in the proximal LAD, anchored by the LCx wire. OCT of the LAD revealed adequate stent apposition. OCT of the LCx did not show any protrusion of stents into the branch vessel (Figure 4).

## DISCUSSION

Precise stent placement in ostial and bifurcation lesions can be technically challenging. Proper stent placement is essential as a stent placed too proximally may obstruct side branches or make future interventions difficult by preventing guiding catheter engagement. A stent placed too distally results in the use of additional stents leading to stent overlap and an increased risk of stent restenosis and adverse outcomes. Angiography alone has inherent limitations in visualizing bifurcation and ostial lesions of due to foreshortening, vessel overlap,

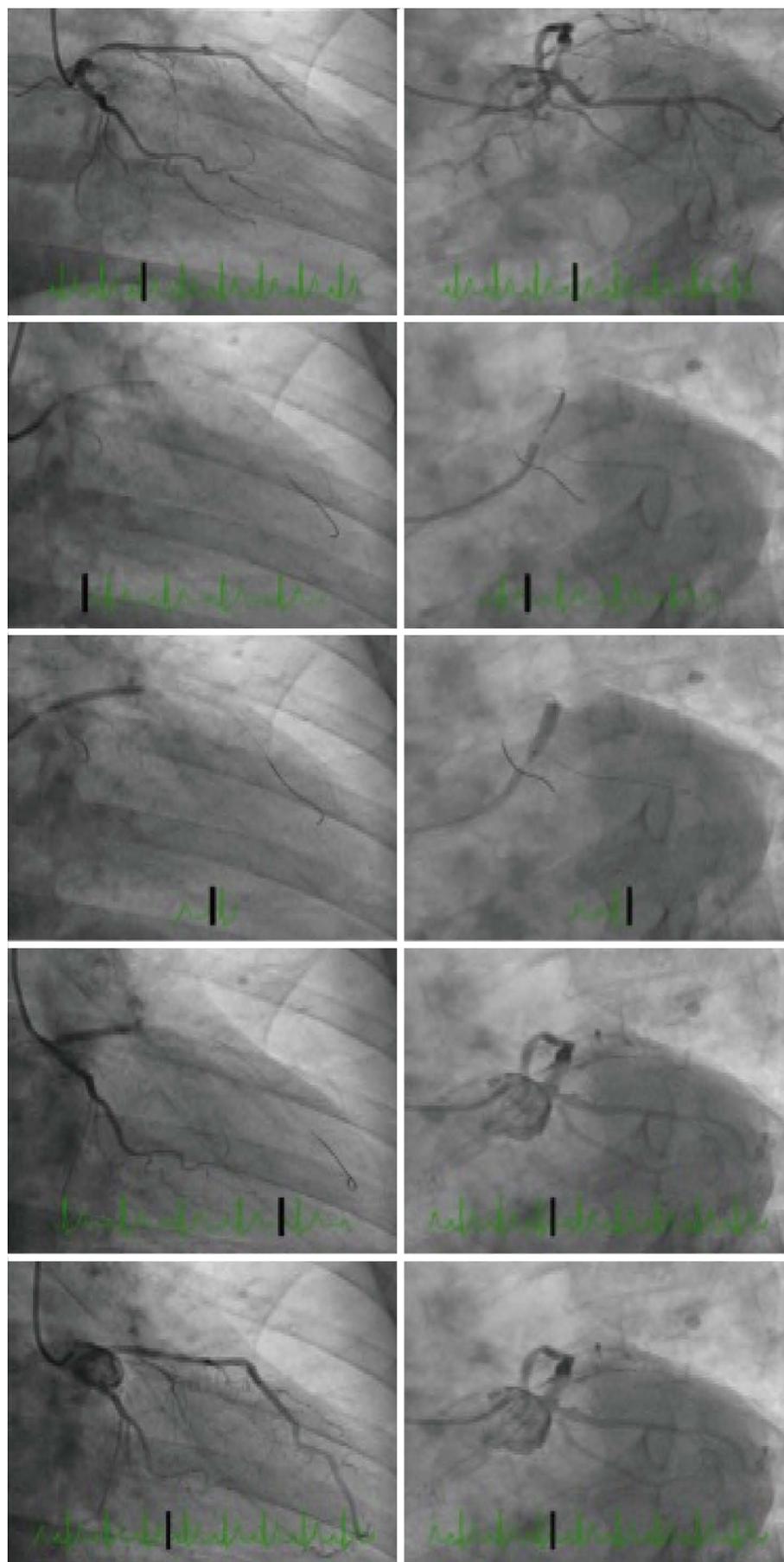


**Figure 1** Angiographic findings for case 1. A: Diagnostic angiogram; B: Fractional flow reserve of left anterior descending artery; C: Stent positioning using Szabo technique; D: Inflation of stent balloon; E: Final angiogram after stent deployment.

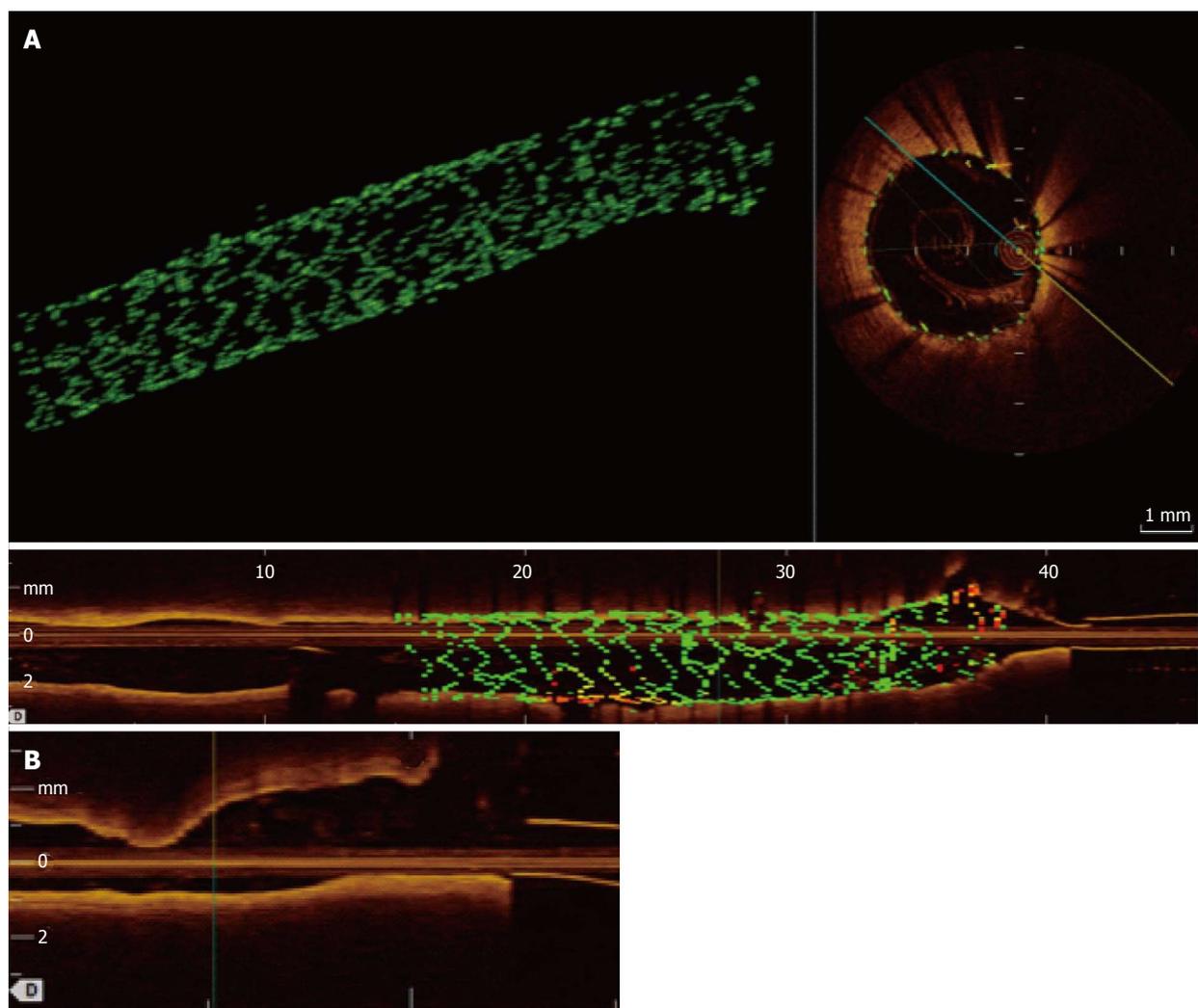


**Figure 2** Optical coherence tomography images for case 1. A: Three-dimensional reconstruction of OCT; B: Cross-sectional OCT image through stent (top right); two-dimensional view of LAD that shows the proximal stent terminating just at the bifurcation with part of one stent strut protruding into the bifurcation; C: OCT of high diagonal does not show protrusion of stent struts into the main vessel; OCT: Optical coherence tomography; LAD: Left anterior descending.

and poor resolution. Intravascular imaging with OCT or IVUS are essential in such cases.



**Figure 3** Angiographic images for case 2. Coronary angiography showed separate ostia of the LAD and left circumflex artery (LCx) and proximal moderate to severe LAD stenosis. RAO caudal (left) and LAO caudal (right) images with diagnostic images (top), Szabo technique (center three panels) and final images (bottom). LAD: Left anterior descending; LCx: Left circumflex artery.



**Figure 4** Optical coherence tomography images for case 2. A: Three-dimensional OCT of LAD shows excellent stent apposition; B: OCT of left circumflex does not show protrusion of stent struts. LAD: Left anterior descending; OCT: Optical coherence tomography.

Several different interventional techniques have been developed to treat ostial or bifurcation lesions. Many operators attempt to optimize placement with careful fluoroscopic views, but this is associated with a significant risk of geographic miss and restenosis. PCI with a single stent approach extending across the side branch can be reasonable when there is no significant disease in the side branch and the side branch is comparably small. Side branch wiring without anchoring the stent strut can be used to mark the bifurcation but has limited accuracy. Bifurcation stenting with a two-stent strategy would have been inappropriate for these Medina 0, 1, 0 lesions because there was no disease in the side branch and five-year outcome data from the Nordic bifurcation study confirmed an absence of benefit and an increase in complications with an empiric two-stent strategy<sup>[6]</sup>.

We performed PCI using an anchor wire technique in both cases because the side branches were comparably large and without disease. With the anchor wire technique, both the main and side branch vessel are wired. The stent is loaded onto the main branch wire and the

back end of the side branch wire (aka anchor wire) is carefully inserted through the final cell of the stent. This can be done by partially flaring the back of the stent using a partial inflation of the balloon while the stent cover is still in place. The stent is then manually re-crimped onto the balloon and advanced gently over both wires. The stent is pushed across the lesion, until the anchor wire prevents further forward motion. The stent is then deployed, the anchor wire removed, and the stent post-dilated. The advantages of this technique are decreased dependence on angiographic localization and avoidance of proximal protrusion or side branch compromise (Figure 5).

The Szabo technique has been evaluated by angiography and intravascular ultrasonography<sup>[7]</sup>. A series of 26 patients using the Szabo technique demonstrated a success rate of only 88% by angiography with a few cases of stent dislodgment and deformation<sup>[4]</sup>. In a series of 41 patients, PCI at the ostial lesion by the Szabo technique showed success rate 97.6% by IVUS<sup>[8]</sup>. In our experience, there are several ways to minimize complications. First, this technique is probably safest for

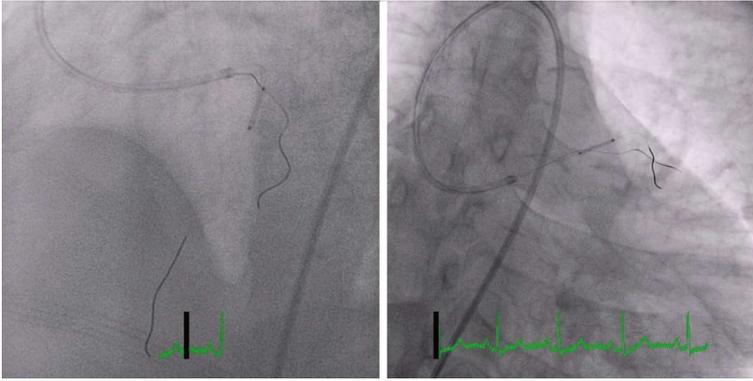


Figure 5 Angiographic images illustrate the position of the stent and the side branch anchor during this technique.

aorto-ostial lesions where the stent does not need to traverse any part of the coronary artery before reaching the lesion. Second, the side branch wire should be stiff to allow for resistance to stent advancement and should not have a polymer coating that may be stripped off as the wire is removed through the stent struts. Third, balloon expansion when backloading the wire onto the stent should be minimized or even avoided as any stent deformation may interfere with stent advancement and recovery. Lastly, testing the advancement of the stent into the main branch without the anchor wire will ensure that the stent will advance smoothly and reduce the risk of stent dislodgement upon attempted withdrawal.

While the Szabo technique has been evaluated by angiography and intravascular ultrasonography, it has not been studied with OCT. OCT has a resolution of 10-15  $\mu$ m and provides excellent images of a stented vessel, especially the adequacy of stent apposition and positioning. OCT of the non-stented vessel can also provide excellent visualization of stent struts, which may be deformed or protruding into the side-branch. This technology provides more definitive evidence of successful stent placement as compared to angiography alone as individual stent struts are easily imaged with OCT. Advances in image processing capabilities have enabled three-dimensional OCT reconstruction of the artery and the stent position within the artery. This allows for even finer evaluation of individual stent struts for deformation, malapposition, or side-branch encroachment.

These two cases demonstrate that the anchor wire method can provide complete ostial coverage and optimal placement for ostial lesions as documented by OCT. Prospective evaluation of the anchor wire technique combined with three-dimensional OCT may further elucidate factors that can contribute to suboptimal long-term outcomes and adverse events.

## COMMENTS

### Case characteristics

A woman with CREST syndrome and a man with risk factors for coronary artery disease present with chest pain.

### Clinical diagnosis

The woman from case 1 developed elevated troponin and the man from case 2

had a positive stress echocardiogram.

### Differential diagnosis

Gastroesophageal reflux disease, coronary vasospasm, musculoskeletal chest pain.

### Laboratory diagnosis

The woman with CREST syndrome developed a troponin of 5 ng/mL and had a chronically elevated BUN/Cr due to chronic kidney disease.

### Imaging diagnosis

The woman from case 1 had a severe stenosis of the proximal left anterior descending artery (LAD) distal to the bifurcation of a high diagonal vessel, and the man from case 2 had separate ostia of the LAD and left circumflex artery (LCx) and proximal moderate to severe LAD stenosis.

### Pathological diagnosis

Optical coherence tomography of the woman with CREST syndrome showed intimal medial hypertrophy, and the man from case 2 had atherosclerotic coronary artery disease.

### Treatment

After percutaneous coronary intervention, both patients were treated with dual antiplatelet therapy.

### Related reports

There are different interventional techniques to treat ostial and bifurcation lesions. The accuracy of the Szabo technique has been evaluated by both angiography and intravascular ultrasonography.

### Term explanation

An ostial lesion begins within 3-5 mm of the origin of a major epicardial artery. The Szabo technique uses two coronary guidewires for the correct placement in the aorto-ostial or bifurcation lesion.

### Experiences and lessons

Precise stent placement in ostial and bifurcation lesions can be technically challenging, but the anchor wire method can be used to provide complete ostial coverage and optimal placement.

### Peer-review

It is a fine case presentation with new stenting technique. The manuscript is well-written and deserves publication.

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## Conservative management of aortic root rupture complicated with cardiac tamponade following transcatheter aortic valve implantation

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### Abstract

Aortic root rupture and cardiac tamponade during

transcatheter aortic valve implantation is a frightening complication with high mortality rate. A conservative management of this complication could represent an initial strategy, especially in high-risk patients, to avoid emergent cardiac surgery. This conservative management includes: Immediate detection of pericardial effusion by echocardiography, a fast instauration of pericardial drainage, auto-transfusion and anticoagulation reversal. We describe two cases of patients who suffered this complication and were treated successfully with this initial approach.

**Key words:** Aortic valve stenosis; Catheters; Heart valve prosthesis; Prosthesis implantation; Cardiac tamponade

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**Core tip:** Aortic root rupture during transcatheter aortic valve implantation is a rare but severe complication with high mortality rate. We described two cases of aortic root rupture where we realized a conservative management with rapid anticoagulation reversal and pericardial drainage with blood auto-transfusion. These cases highlight the utility of rapid identification of aortic root hematoma and pericardial effusion by transesophageal echocardiography. Immediate detection of this complication allows to stabilize the patient avoiding further urgent interventions.

Vannini L, Andrea R, Sabaté M. Conservative management of aortic root rupture complicated with cardiac tamponade following transcatheter aortic valve implantation. *World J Cardiol* 2017; 9(4): 391-395 Available from: URL: <http://www.wjgnet.com/1949-8462/full/v9/i4/391.htm> DOI: <http://dx.doi.org/10.4330/wjc.v9.i4.391>

### INTRODUCTION

Transcatheter aortic valve implantation (TAVI) is gaining ground for the treatment of severe aortic stenosis (AS)

in patients with high risk of surgery or contraindications. However, it is a technical and complex procedure with intra and periprocedural risks of complications that could eventually need emergent cardiac surgery (ECS). Among the potential complications, aortic root rupture with subsequent cardiac tamponade is one of the most feared. No data are available about the best management of cardiac tamponade secondary to aortic root rupture during TAVI. Nevertheless, it is well known that ECS, especially in patients with cardiac tamponade, entails a high mortality rate<sup>[1]</sup>. Pericardiocentesis followed by conservative management of cardiac tamponade secondary to aortic root rupture during TAVI could be an initially effective approach to this complication if the prosthetic valve function is preserved.

We herein present two cases of conservative management of cardiac tamponade following aortic root rupture during TAVI.

## CASE REPORT

### Case 1

An 89-year-old lady with symptomatic severe AS was scheduled for a TAVI. Transthoracic echocardiography (TTE) showed a severe AS (mean gradient: 48 mmHg; aortic valve area of 0.5 cm<sup>2</sup>, with preserved ejection fraction, 55%). Computed tomography scanner (CT-scan) showed severe calcification of the valve and the following measurements: Minimum/maximum annulus transverse diameter of 23 mm/26 mm, aortic root perimeter of 83 mm and aortic root area of 5 cm<sup>2</sup>. She was rejected for surgical aortic valve replacement because of high surgical risk related to advanced age (Charlson score: 6; Barthel Score: 100; Logistic Euroscore: 13.57%).

General anaesthesia and mechanical ventilation support were used to allow trans-esophageal echocardiography (TEE) guidance. TEE showed an aortic annulus diameter of 22-mm (Figure 1A and B). Anticoagulation with unfractionated heparin adjusted for body weight was administered before the implantation. Aortic valve pre-dilatation under fast ventricular pacing was performed without complications and a 26-mm Edwards Sapien XT valve (Edwards Lifesciences, Irvine, California) was implanted.

Immediately after implantation, the patient presented sudden hypotension and TEE showed an expanding aortic root hematoma (Figure 1C and D); with progressively formation of pericardial effusion with signs of cardiac tamponade (Figure 1C, E and F). Percutaneous pericardiocentesis was performed, draining 200 mL of blood that were re-infused. Volume replacement and coagulation reversal with protamine were also performed with initial patient stabilization.

ECS was dismissed because of the high surgical risk and a conservative management was decided. During the first 72 h the patient persisted with hemodynamic instability controlled with volume load (fluid and blood) and repeated pericardial drainages to maintain a mean arterial pressure > 60 mmHg. Finally, the weaning from

mechanical ventilation was successfully performed and the patient could be transferred to the conventional ward and discharged one month after the procedure.

At one-year follow-up the patient was almost fully independent for basic activities of daily living (Barthel Score: 95).

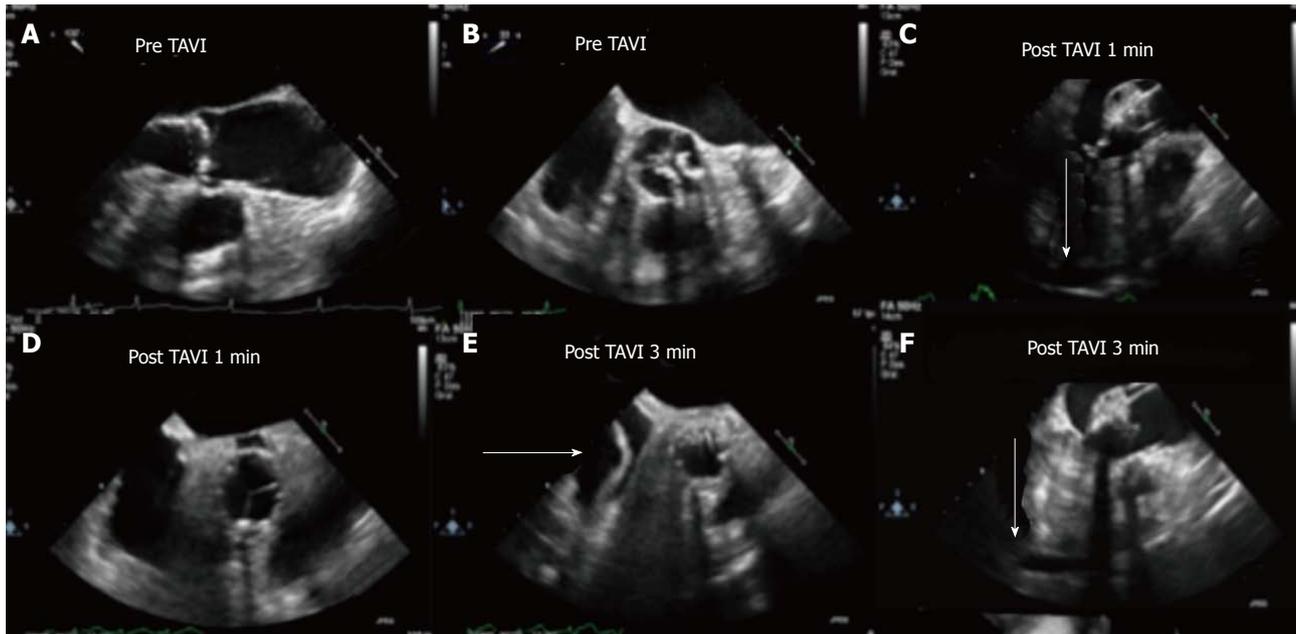
### Case 2

An 81-year-old woman with hypertension, renal impairment with glomerular filtration rate < 30 mL/min and severe AS (TTE mean gradient: 55 mmHg; aortic valve area of 0.78 cm<sup>2</sup>) with preserved ejection fraction (65%) was referred to TAVI. The patient had refused surgical treatment, after a complete evaluation by the Heart Team a TAVI procedure was proposed and finally accepted. TEE showed a severe calcified AS (mean-maximum transvalvular gradient were 58/100 mmHg, respectively) with an aortic annulus diameter of 22 mm. CT-scan measures (minimum/maximum annulus transverse diameters 22 mm and 27 mm, respectively; aortic root perimeter of 80 mm with an area of 4.7 cm<sup>2</sup>) and TEE lead to the selection of a 26 mm Edwards Sapien XT valve (Edwards Lifesciences, Irvine, California). Anticoagulation was reached with unfractionated heparin adjusted for body weight. Aortic valve predilatation under fast ventricular pacing was performed without complications; and the 26 mm valve was implanted. TEE immediately after TAVI showed a minimal paravalvular leak with normofunctional prosthetic valve.

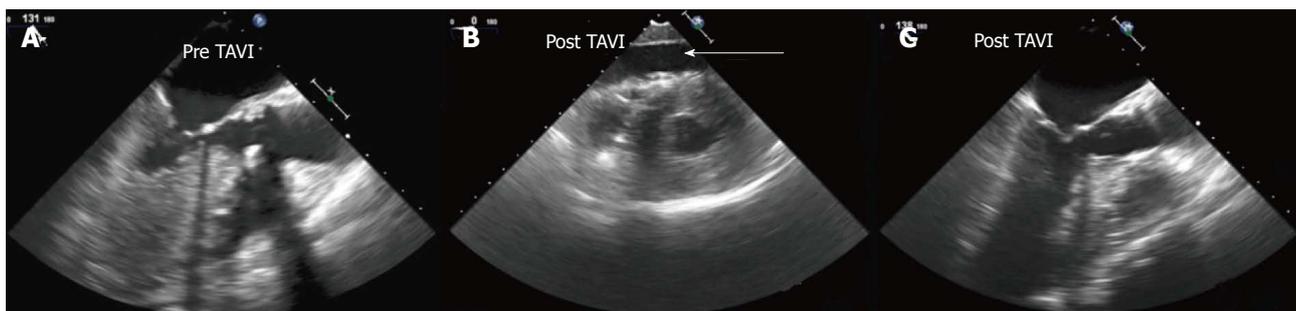
However, one minute later, the patient presented sudden hypotension, and pericardial effusion and signs of cardiac tamponade appeared evident on TEE without signs of aortic root hematoma or dissection (Figure 2). Percutaneous pericardiocentesis was performed draining 300 mL of blood that were reinfused into the patient and coagulation was reversed with protamine. The patient was hemodynamically stabilized and was transferred to the acute cardiac care unit.

Pericardial drainage was performed every eight hours during two days to maintain mean arterial pressure > 60 mmHg. After successful weaning from the ventilator, the patient was dismissed from the coronary intensive care unit and was finally discharged home at day 19 after TAVI procedure.

At one month follow-up, the patient presented new onset symptoms of heart failure. A TEE showed a severe aortic regurgitation with three different jets: One main central jet (apparently secondary to valve geometry alteration with an eccentric closure of valves) and two perivalvular leaks, with minimal pericardial effusion. The patient did not respond to optimal medical treatment and persisted in functional class NYHA IV. Finally, the heart team decided a surgical approach for TAVI replacement. A biologic valve prosthesis Mitroflow 19 mm (Sorin Group Inc.) was successfully implanted and aortic root rupture was confirmed. However, the patient suffered from several postoperatively complications including septic shock that resulted in death 1 mo after second procedure.



**Figure 1 Aortic root rupture and aortic root hematoma (Case 1).** A and B: Aortic valve assessment before TAVI, TEE mid esophageal long axis view (A) and short axis view (B); C and D: Aortic valve assessment post TAVI 1 min; E and F: Aortic valve assessment post-TAVI 3 min. We can observe the development of the aortic root hematoma and the pericardial effusion (arrowhead). TAVI: Transcatheter aortic valve implantation; TEE: Trans-esophageal echocardiography.



**Figure 2 Aortic root rupture and cardiac tamponade (Case 2).** A: Aortic valve assessment before TAVI, TEE mid esophageal long axis view; B: Aortic valve assessment after TAVI, TEE transgastric mid-ventricular short axis. Severe pericardial effusion is evidenced (arrow); C: Aortic valve assessment after TAVI, TEE mid esophageal long axis view. No signs of aortic root hematoma were observed in this case. TAVI: Transcatheter aortic valve implantation; TEE: Trans-esophageal echocardiography.

## DISCUSSION

An initially conservative management of aortic root rupture and cardiac tamponade during TAVI procedures may represent an appropriate approach in this high-risk population. Although uncontained aortic root rupture affects only to 0.5%-1% of the patients treated with a TAVI intervention, a contained rupture could occur in up to 5% of procedures<sup>[1]</sup>. Otherwise, as mentioned above, it is well known the increased risk of mortality of ECS in patients with cardiac tamponade<sup>[2]</sup>. Data on the need of ECS after TAVI is scarce, but it has been reported an incidence of about 1%<sup>[2]</sup>. In this regard, 30-d mortality rate in TAVI patients who need ECS may exceed 50%<sup>[2]</sup>. This is especially true in patients complicated with cardiac tamponade or annulus rupture in whom mortality rate may range between 60% and 100%<sup>[2-4]</sup>.

There are several issues to be taken into account

during the conservative management of this complication. First, it is mandatory to immediately identify the root rupture during the procedure. In this regard, intraoperative TEE is useful as aortic root hematoma could represent the first sign of aortic root rupture and may precede the development of hemodynamic instability and pericardial effusion. Aortic root hematoma was identified only in the first case. In the second case, the evidence of pericardial effusion on TEE allowed the diagnosis that was confirmed during valve-replacement surgery. Secondly, the rapid reversal of coagulation with protamine sulfate may help avoid progression of the hematoma. Finally a rapid percutaneous pericardial drainage and blood auto-transfusion connecting a drainage catheter directly into a central line is mandatory to stabilize hemodynamics of the patient.

Although it is well known that patients who need ECS present poor prognosis<sup>[2-5]</sup>, except for tamponade

secondary to right ventricular tears<sup>[6]</sup>, it is not clear whether the patient with cardiac tamponade secondary to aortic root rupture could benefit from an invasive management.

Several mechanisms could be involved in the development of this complication. The extensive calcification of left ventricular outflow tract (LVOT), the mismatches between the aortic root and the prosthesis (TAVI oversizing) and the ellipsoid geometry of aortic root have been proposed as potential predictors of this ominous complication<sup>[1,7,8]</sup>.

In the above-mentioned cases, the aortic annulus measured with CT-scan revealed an ellipsoid geometry (26 mm × 23 mm and 26 mm × 22 mm), with an eccentricity indexes of 0.12 and 0.15, respectively that did not exceed the normal value described in previous series<sup>[7]</sup>. The combination of ellipsoid geometry and the presence of severe and extensive calcification could be the cause of aortic root injury. Oversizing was calculated in 6% and 13% in our first and second case, respectively. A significant area-oversizing threshold > 20% was associated with aortic rupture<sup>[7]</sup>. However, it is plausible that an oversizing that exceeds 10% may still entail a higher risk of aortic root rupture.

An extensive study of the aortic root area with measurement of the perimeter, diameter, geometry and annulus-LVOT calcification with CT-scan, may help avoid excessive prosthesis oversizing and identify geometry incompatibility between prosthesis and landing zone because of its irregular geometry.

This initial conservative management could stabilize both patients and as a matter of fact, they were successfully discharged home. In the second case, however, further alteration of valve geometry caused severe prosthetic dysfunction and a surgical procedure was required. Eventually, the patient suffered from postoperatively complications and finally died. Nevertheless, the initial conservative management could allow further surgery in a more stable condition with higher chances of survival.

In conclusion, the risk of aortic root rupture during TAVI is difficult to predict despite an extensive study by TEE and CT-scan. Immediate detection of this complication during the TAVI procedure may allow rapid instauration of measures (anticoagulation reversal and pericardial drainage with auto-transfusion) that lead to stabilize the patient and avoid further ECS. Further investigation is needed to predict, avoid and manage the aortic root rupture in TAVI patients.

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## COMMENTS

### Case characteristics

The authors describe two cases of post-transcatheter aortic valve implantation (TAVI) cardiac tamponade with successful initial conservative management.

### Clinical diagnosis

Sudden hypotension and hypoperfusion.

### Differential diagnosis

Acute bleeding (retroperitoneal, TAVI-access site bleeding), heart-block, prosthetic-valve dysfunction.

### Laboratory diagnosis

Transesophageal echocardiography and invasive hemodynamics are the main diagnostic tools.

### Imaging diagnosis

Transesophageal echocardiography confirmed cardiac tamponade in both cases. In the case 1 showed an aortic root hematoma and pericardial effusion, in the case 2 did not identify signs of aortic root injury but identified progressive pericardial effusion.

### Treatment

Immediate anticoagulation reversal and pericardial drainage with autotransfusion that lead to stabilize the patient may avoid further emergency cardiac surgery.

### Related reports

Uncontained aortic root rupture is a rare post-TAVI complication (0.5%-1%) but with high mortality rate. TAVI patients who need emergency cardiac surgery with cardiac tamponade or aortic root rupture present a mortality rate between 60% and 100%. The data among conservative management are scarce.

### Term explanation

The aortic root is a complex structure that connects the heart to the systemic circulation, it is composed of distinct parts extremely sensitive to injury during TAVI: Valve leaflets (with the commissure and leaflet attachment), inter leaflet triangle, the sino tubular junction and the ventriculo-aortic junction.

### Experiences and lessons

Immediate detection of cardiac tamponade during TAVI procedure may allow rapid instauration of measures (anticoagulation reversal and pericardial drainage with auto-transfusion) that lead to stabilize the patient and that can avoid further interventions. Transesophageal echocardiography is the main diagnostic tool.

### Peer-review

The case report was well written, and may give rise to an interesting discussion on the described problem.

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## Sleep, health behaviors, and behavioral interventions: Reducing the risk of cardiovascular disease in adults

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diet, smoking, and sleep, play a major role in preventing the development and progression of cardiovascular disease (CVD). Among these behaviors, sleep may play a pivotal role, yet it has been studied somewhat less than other behaviors and there have been few well-designed sleep intervention studies targeting CVD. Furthermore, despite the fact that these behaviors are often inter-related, interventions tend to focus on changing one health behavior rather than concurrently intervening on multiple behaviors. Psychological constructs from depression to positive affect may also have a major effect on these health behaviors and ultimately on CVD. In this review, we summarize the existing literature on the impact of sleep and other cardiac health behaviors on CVD onset and prognosis. We also describe interventions that may promote these behaviors, from established interventions such as motivational interviewing and cognitive behavioral therapy, to more novel approaches focused on mindfulness and other positive psychological constructs. Finally, we outline population-health-level care management approaches for patients with psychiatric conditions (*e.g.*, depression) that may impact cardiac health, and discuss their potential utility in improving mental health, promoting health behaviors, and reducing CVD-related risk. Much work is still needed to better understand how sleep and other health behaviors may uniquely contribute to CVD risk, and additional high-quality studies of interventions designed to modify cardiac health behaviors are required to improve cardiovascular health in individuals and the population at large.

**Key words:** Sleep; Diet; Physical activity; Cardiovascular disease; Care management

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**Core tip:** This manuscript discusses the link between modifiable health behaviors; including sleep, diet, activity, and their relationship to adult risk for cardiovascular disease. Despite knowing that these behaviors are

### Abstract

Numerous health behaviors, including physical activity,

often interrelated, interventions to date have primarily focused on changing one health behavior *vs* intervening on multiple behaviors simultaneously. Population health level care management approaches are outlined to aide providers in counseling their patients.

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## INTRODUCTION

Recent guidelines for adequate sleep duration from the American Academy of Sleep Medicine and Sleep Research Society state that a typical adult needs at least 7 h of sleep each night to maintain optimal health<sup>[1,2]</sup>. Population-based studies estimate that one in three adults in the United States report sleeping fewer than 7 h per night<sup>[3,4]</sup>. This statistic is alarming as research has shown that individuals with insufficient sleep are at a significantly greater risk for many chronic diseases, including cardiovascular disease (CVD)<sup>[5-8]</sup>, which is responsible for one in four deaths in the United States<sup>[9]</sup>. Additional health behaviors beyond sleep, including poor diet, low levels of physical activity, and prolonged sedentary time, are also major risk factors for the development of CVD<sup>[6]</sup>. This review will discuss the current literature linking these modifiable health behaviors to an increased risk of CVD, and the evidence-based interventions that can modify them, in order to guide future intervention targets and strategies aimed at reducing CVD risk in adults.

## IMPORTANCE OF SLEEP IN REDUCING CVD RISK

In recent literature, both insufficient sleep duration (most often defined as fewer than 7 h) and long sleep duration (more than 9 h) have been associated with poor health outcomes and increased mortality risk<sup>[6,10]</sup>. In one such large, population-based study, individuals who reported fewer than 6 h of sleep had a 15% higher incidence of CVD compared to those who reported sleeping between 7-8 h<sup>[8]</sup>.

Many biomarkers related to CVD risk have been examined in relation to insufficient sleep duration. The relationship between short sleep duration and hypertension is well documented, extending from experimental studies to longitudinal epidemiological studies and intervention studies<sup>[11-13]</sup>. Short sleep duration (collected *via* self-report questionnaire) has been associated with higher blood pressure in cross-sectional studies and greater overall incidence of hypertension in population studies. Studies tend to vary in their definition

of short sleep duration, but overall conclude that 5 or fewer hours of sleep each night is related to the worst blood pressure outcomes. These poor blood pressure outcomes are reported to be most common in women and adults who are less than 65 years old. Racial/ethnic differences have been found showing that relationships between short sleep duration (fewer than six hours per night) and hypertension are strongest in non-Hispanic whites, blacks, and Hispanics/Latinos populations<sup>[5]</sup>.

Insufficient sleep has also been associated with other conditions linked with CVD, such as obesity and type 2 diabetes mellitus (T2DM). Short sleep duration has been strongly linked to an increased risk of obesity across all populations<sup>[14]</sup>, and, conversely, for each additional hour of sleep an individual's body mass index (BMI) decreases by 0.35 units<sup>[14]</sup>. Racial/ethnic differences have been found, with the strongest relationship of very short sleep (less than five hours per night) and obesity in individuals who identify as African American/black<sup>[5]</sup>. Further research has shown that women who reported sleeping less than 6 h per night over the course of 16 years gained significantly more weight compared to women that slept at least 7 h<sup>[15]</sup>. Individuals with short sleep duration (fewer than 6 h per night) have also been shown to have an increased risk of T2DM<sup>[16,17]</sup>. It remains unclear whether this increased risk is mediated by obesity or if there are other mechanisms, including glucose metabolism, that may explain the increased risk of T2DM.

There is less data on the connection between short sleep duration and other biological markers of health<sup>[6]</sup>. Regarding inflammatory markers, when sleep is experimentally restricted to fewer than four hours per night, increases in C-reactive protein and interleukin-1 receptor have resulted<sup>[18,19]</sup>. Studies examining the effects of short sleep duration and insulin resistance are also rare. Self-report of fewer than 6 h of sleep per night has been associated with increased insulin and hemoglobin A1C (HbA1c), but this result was attenuated when BMI was added to the model<sup>[20]</sup>. Studies of sleep restriction (fewer than 6 h in bed) have found an increase in insulin resistance<sup>[21,22]</sup>; however, these studies were limited to healthy, young males. Therefore, the relevance of these associations to the general population remain unclear.

### **Importance of other health behaviors in reducing CVD risk**

Dietary intake, physical activity, and sedentary time have also been associated with CVD risk in adults. The effects of numerous dietary components on CVD risk have been examined<sup>[23]</sup>. For example, adherence to a Mediterranean diet, consisting of a high intake of fruits and vegetables, fish, olive oils, and dairy, has been associated with a lower risk of CVD events including myocardial infarction and stroke as well as lower cardiovascular mortality<sup>[24]</sup>. A similar dietary eating pattern, the DASH eating plan, consisting of fruits and vegetables, low-fat dairy, whole grains, poultry, fish, and nuts, has also been found to lower incidence of adverse cardiovascular events<sup>[25]</sup>. Specific dietary components have also been associated

with a reduced risk of CVD. Diets high in polyunsaturated fatty acids and low in sodium have are linked to fewer cardiovascular events<sup>[23]</sup>. Increasing physical activity levels, at any intensity level, has been shown to lower CVD risk. Individuals with higher daily overall physical activity (measured *via* accelerometer) and moderate-vigorous physical activity have been shown to have lower CVD mortality<sup>[26]</sup>. Although reducing sedentary time appears important to overall health, sedentary time has generally not been associated with CVD mortality<sup>[26]</sup>.

## POTENTIAL RELATIONSHIPS BETWEEN MULTIPLE HEALTH BEHAVIORS IN REDUCING CVD RISK

Despite the strong evidence of increased CVD risk associated with each of the above behaviors on poor health outcomes, an important issue in this line of research is detangling the effects of these health behaviors from one another, as they tend to be strongly correlated within individuals. Due to this, it can be difficult to discern which health behaviors independently contribute to improved health outcomes. For example, there is limited data regarding how sleep combines with the other behaviors. Additional evidence is needed to define how these behaviors may cluster or pattern together resulting in an increased risk of disease; such knowledge can help to inform future public health intervention guidelines and policy in this area. Intervention and policy strategies to date have focused on changing individual behaviors, with very few strategies attempting to target multiple lifestyle behaviors simultaneously<sup>[27]</sup>. A study in over 500000 United Kingdom adults aged 37-63 years found that individuals with CVD were more likely to report low levels of physical activity, more than 3 h of TV viewing per day, and fewer than 7 h of sleep per night, compared to individuals without CVD<sup>[27]</sup>. The clustering of these behaviors was termed a “unhealthy phenotype” and individuals with this unhealthy phenotype had poorer disease outcomes.

Multiple health behavior interventions have been shown to have improved health outcomes, such as blood pressure, cholesterol, and glucose, when changes to both diet and activity are changed simultaneously<sup>[28]</sup>. However, there is very limited evidence to date that these types of interventions directly impact CVD events or mortality<sup>[28]</sup>.

## STANDARD HEALTH BEHAVIOR INTERVENTIONS AND THEIR IMPACT IN CVD RISK POPULATIONS

### **Cognitive-behavioral therapy**

Cognitive-behavioral therapy (CBT) is an evidence-based intervention for improving cardiac health behaviors and outcomes. It is a short-term skills-based psychotherapy that teaches cognitive (*e.g.*, cognitive restructuring,

probability estimation) and behavioral strategies (*e.g.*, behavioral exposures, behavioral activation) to reduce emotional distress, improve well-being, and promote healthy behavioral choices. Originally developed for treating emotional problems, CBT is often most useful for improving health behaviors among patients with or at risk for chronic medical conditions who may be more motivated for change, and psychiatric symptoms among individuals with mental health disorders who have the greatest room for symptom improvement. For example, in a study of CBT for improving sleep in healthy college students, only those with poor sleep at baseline showed significant improvement (Trockel *et al.*, 2011). Thus, much of the work on CBT and cardiac risk factors has been aimed at improving sleep and other health behaviors and psychiatric symptoms in patients with insomnia, mental health problems, or those with or at risk for CVD. Table 1 shows representative studies examining the effects of standard health behavior interventions on health outcomes.

CBT is useful for improving sleep and other health behaviors in patients with or at risk for CVD. A recent review of CBT for insomnia (CBT-I) in CVD patients found that there is limited but promising evidence for CBT-I to improve sleep characteristics (*e.g.*, sleep efficiency and quality), CVD biomarkers, symptom burden, functional impairment, and quality of life<sup>[29,30]</sup>. CBT has also been shown to improve health behaviors including diet (*e.g.*, reduced sugar, increased fruits/vegetables), physical activity, and smoking cessation in some studies of healthy adults and those with or at risk for CVD<sup>[31-35]</sup>.

In line with the original aim of CBT, much of the research on CBT and cardiac health has focused on the efficacy of CBT in improving psychosocial problems in CVD patients given that these problems have a significant negative impact on cardiac morbidity and mortality<sup>[36,37]</sup>. The results of several randomized clinical trials (RCT) support the efficacy of CBT in improving depression, anxiety, and quality of life in CVD patients, patients suffering an acute coronary syndrome (ACS), heart surgery patients, and heart failure patients<sup>[38-44]</sup>. A systematic review and meta-analysis of psychological interventions for depression in CVD found that CBT had the strongest effects<sup>[45]</sup>, and the American Heart Association specifically recommends CBT for treating depression in CVD patients<sup>[46]</sup>. CBT is also associated with improved psychosocial outcomes among individuals at risk for CVD including those with type 2 diabetes, hypertension, and overweight and obesity<sup>[31,34,47]</sup>.

Evidence for direct effects of CBT on physical health outcomes is less consistent. A Cochrane review of 64 RCTs found that psychological interventions produced small-moderate improvements in depression and anxiety and a small effect on cardiac mortality in CVD patients, but no effect on total death or cardiac events<sup>[44]</sup>. Another systematic review found improvements in depression symptoms but no effect on all-cause mortality, cardiac mortality, or cardiac events<sup>[43]</sup>. In the Enhancing Recovery in Coronary Heart Disease Patients trial, a randomized trial of 2481 post-ACS patients, CBT was asso-

**Table 1** Representative studies examining the effects of cognitive behavioral therapy and motivational interviewing on health-related outcomes

Ref.	Population	Intervention	Outcome
Tsiros <i>et al</i> <sup>[33]</sup> , 2008	<i>n</i> = 47 adolescents with overweight or obesity	CBT <i>vs</i> no-treatment	Greater improvements in weight, BMI, body fat, sugar intake (soft drinks) in CBT group at 20-wk follow-up
Welschen <i>et al</i> <sup>[34]</sup> , 2013	<i>n</i> = 154 diabetes patients	CBT <i>vs</i> managed care	Greater improvement in physical activity, quality of life, and depression in CBT group at 6-mo follow-up; no group differences at 12-mo follow-up
Freedland <i>et al</i> <sup>[39]</sup> , 2009	<i>n</i> = 123 CABG patients with depression	CBT <i>vs</i> supportive stress management	Greater depression remission in CBT than supportive stress management group at 3-mo and 9-mo follow-up
Berkman <i>et al</i> <sup>[48]</sup> , 2003	<i>n</i> = 2481 MI patients	CBT <i>vs</i> usual care	Greater improvement in depression and social support in CBT group at 6-mo follow-up; no group differences in survival at 29-mo follow-up
Woollard <i>et al</i> <sup>[55]</sup> , 1995	<i>n</i> = 166 patients with hypertension	MI low dose <i>vs</i> MI high dose <i>vs</i> usual care	Greater improvements in alcohol and salt intake in low-MI <i>vs</i> usual care; greater improvements in weight and blood pressure in high-MI <i>vs</i> usual care at 18-wk follow-up
Ma <i>et al</i> <sup>[59]</sup> , 2014	<i>n</i> = 120 Chinese patients with hypertension	MI <i>vs</i> usual care	Greater improvements in treatment adherence and blood pressure in MI group
Ogedegbe <i>et al</i> <sup>[60]</sup> , 2008	<i>n</i> = 190 African American patients with hypertension	MI <i>vs</i> usual care	Greater improvements in medication adherence and blood pressure in the MI group at 12-mo follow-up
Cain <i>et al</i> <sup>[68]</sup> , 2011	<i>n</i> = 104 adolescents	MI and sleep education <i>vs</i> no intervention	Greater improvements in sleep knowledge and out-of-bed time in MI group; improvements in sleep and daytime functioning in both groups

BMI: Body mass index; CABG: Coronary artery bypass graft; CBT: Cognitive behavioral therapy; MI: Motivational interviewing.

ciated with improvements in depression symptoms, but did not affect survival or cardiac events at 6-mo follow-up<sup>[48]</sup>. It is possible that longer-term follow-up is needed to identify physical health benefits of CBT, which may take time to develop and require continued use of CBT skills<sup>[49,50]</sup>.

Recent studies have explored telephone-based and web-based CBT interventions for improving psychosocial outcomes in patients with CVD. These studies have shown mixed but promising results. For example, a RCT of telephone-delivered CBT for post-ACS patients with depression found greater improvements in depression symptoms following CBT as compared to usual care, with effects maintained up to one year later<sup>[42]</sup>. A pilot study of web-based CBT for heart failure patients also found improvements in depression symptoms though there were no significant between-group differences<sup>[51]</sup>. In a study of post-transplant patients, however, telephone-delivered CBT was not found to be acceptable, and while patients who did participate showed significant reductions in anxiety and depression symptoms, most (67%) continued to show elevated scores<sup>[52]</sup>. Given that there is evidence of potential feasibility and efficacy, and mobile health interventions have the potential to improve access to mental health care for CVD patients<sup>[53]</sup>, further controlled studies should explore virtual CBT interventions

### **MI based interventions and their impact in CVD risk population**

An even more traditional approach to health behavior change is motivational interviewing (MI). Over 30 years of research have established MI, a patient-centered method for identifying and enhancing intrinsic motivation, as an effective and straightforward technique for promoting behavioral change<sup>[54,55]</sup>. MI is effective and can

be delivered remotely by different avenues with good fidelity<sup>[56,57]</sup>. MI interventions have led to improved health behaviors in patients with cardiac risk factors, including increased physical activity in patients with diabetes<sup>[58]</sup> and hypertension<sup>[59]</sup>. Additional studies have demonstrated improved medication adherence and significant reductions in systolic blood pressure in patients with hypertension<sup>[60-62]</sup>. Furthermore, a Cochrane review of MI for smoking cessation showed a modest but significant increase in quitting compared to usual care<sup>[63]</sup>. There are several ongoing trials assessing the potential of different MI-based interventions to improve other health behaviors and cardiac risk factors, including improving statin adherence in patients with hypercholesterolemia<sup>[64]</sup>, optimizing risk factors in patients undergoing cardiovascular procedures<sup>[65]</sup>, and comparing group-based to individual MI interventions in patients at high risk for CVD<sup>[66]</sup>. Although few interventions have used MI to modify sleep behaviors<sup>[67,68]</sup>, MI may be well-suited to address sleep in a manner similar to that used for other health behaviors. Further, despite MIs extensive use in research studies and clinical care, the effects of solely MI-based interventions for activity promotion in patients with T2D<sup>[58]</sup> and other major cardiac risk factors may not be significant enough to prevent CVD or major cardiac events, raising the possibility that additional interventions may be necessary in these patients.

## **NOVEL INTERVENTIONS TO TARGET HEALTH BEHAVIORS AND CARDIAC OUTCOMES**

### **Mindfulness and mind-body interventions**

Mindfulness and other mind-body interventions have

received increased attention for improving cardiac health behaviors and outcomes. Mind-body interventions encompass a range of techniques that aim to unite the body and mind to promote well-being, such as progressive muscle relaxation, meditation, yoga, and tai chi. Mindfulness is a specific approach that involves paying attention to present moment experiences with an attitude of openness, non-judgment, and curiosity<sup>[69]</sup>. A large body of research supports the efficacy of mind-body interventions, particularly mindfulness-based interventions that incorporate elements of CBT (*e.g.*, mindfulness-based stress reduction, mindfulness-based cognitive therapy) for improving a range of physical and mental health outcomes (*e.g.*, Hofmann *et al.*<sup>[70]</sup>, 2010).

Mindfulness-based interventions may improve cardiac health behaviors. Recent systematic reviews have concluded that mindfulness interventions promote smoking cessation<sup>[71]</sup> and healthy eating<sup>[72]</sup>. Evidence for improvements in sleep are somewhat limited, with a systematic review finding few randomized controlled trials and no significant between-group differences in sleep outcomes, but a significant correlation between amount of mindfulness meditation practice and improved sleep<sup>[73]</sup>. Subsequent RCTs, however, have found significant effects of mindfulness training on insomnia<sup>[74]</sup>. There has been less research using mindfulness-based interventions to promote physical activity, though there is some evidence to suggest that mindfulness training can increase physical activity in healthy young adults<sup>[75]</sup> and CVD patients<sup>[76]</sup>, and that the ability to be mindful during daily life in general (*i.e.*, trait mindfulness) might increase physical activity levels by making activity seem more satisfying<sup>[77]</sup>.

Mindfulness-based interventions have also been associated with improved health outcomes in patients with and at risk for CVD. Research suggests that mindfulness training can promote weight loss among patients with obesity<sup>[78]</sup>; improve disease management and HbA1c levels among patients with diabetes<sup>[79]</sup>; and improve coping and blood pressure in patients with hypertension<sup>[80]</sup>. A systematic review among individuals with CVD or other risk factors (*e.g.*, hypertension and diabetes patients) found significant improvements in stress, depression, anxiety, and quality of life following mindfulness interventions; however, similar to studies of CBT, effects on physical health outcomes were less consistent<sup>[49]</sup>. Among CVD patients specifically, a systematic review of 11 RCTs of mind-body practices found significant improvements in depression, anxiety, and QoL, though these studies were found to be of overall low quality<sup>[81]</sup>. Mindfulness-based interventions have also been integrated into cardiac rehabilitation programs<sup>[82]</sup>, and several studies suggest that meditation, tai chi, and yoga may be useful for improving health outcomes in heart failure patients<sup>[83-85]</sup>. Indeed, a systematic review of 29 trials (9 RCTs) found that tai chi is associated with reduced blood pressure and exercise capacity in patients with CVD and risk factors<sup>[86]</sup>. Further research on mind-body interventions for CVD risk

behaviors and outcomes is needed, though providers should be aware that existing mind-body approaches may be useful for cardiovascular outcomes.

### **Positive psychological interventions for health behavior and cardiac outcome improvement**

There has been increasing interest in the use of positive psychology (PP) interventions that aim to boost positive emotional experiences and cognitive processes through the use of simple tasks focusing on positive psychological constructs, such as optimism and positive affect. These positive constructs have been shown to correlate with improved adherence to cardiac health behaviors, such as physical activity<sup>[87,88]</sup>, diet<sup>[89,90]</sup>, and medication adherence<sup>[91]</sup>. They have further been associated with improved rates of heart disease and cardiac mortality<sup>[92-94]</sup>. Specific PP exercises found effective in medically healthy persons include recalling and discussing positive events, identifying and deliberately using personal strengths, and planning and performing acts of kindness<sup>[95,96]</sup>.

PP interventions are simple for patients and do not require extensive provider training, raising the attractive possibility of a cost-effective and efficient means of improving mood and cardiac health behaviors. Despite this, there has been limited study of PP-based interventions to promote health behaviors, improve sleep, or reduce cardiac events or mortality. PP interventions have been applied in studies of T2D<sup>[97]</sup> and immunodeficiency virus<sup>[98]</sup>, and a meta analysis has shown that their successful implementation leads to improvements in psychological outcomes<sup>[99]</sup>. Positive psychology interventions focused on gratitude have also promoted improvement in sleep hours and quality in patients with neuromuscular disease<sup>[100]</sup>.

Among patients with existing CVD, there is a small literature on PP interventions<sup>[101-103]</sup>, generally finding that such interventions are well-accepted and have beneficial effects on both positive and negative psychological states<sup>[101-106]</sup>. Additionally, randomized controlled trials of positive affect interventions have shown increased medication adherence in hypertensive patients<sup>[104]</sup> and improved physical activity in patients post-percutaneous coronary intervention<sup>[105]</sup>. Furthermore, combining PP with established health behavior interventions could provide additional benefit, building on the literature showing that PP exercises lead to increases in self-efficacy, confidence, and interpersonal connectedness<sup>[106-108]</sup> and findings that these same characteristics can improve engagement in health behavior interventions<sup>[109,110]</sup>.

### **Management of mental health conditions/care management**

Additional novel approaches to modifying health behaviors *via* mental health-related interventions may include care management programs for patients with psychiatric conditions. Depression and other psychiatric syndromes are common in patients with, or at risk for,

CVD<sup>[111,112]</sup>, and they can be identified *via* systematic screening in clinical cardiology settings<sup>[113]</sup>. Patients with depression and related conditions are at substantially elevated risk for nonadherence, including nonadherence to cardiac health behaviors<sup>[114-116]</sup>. Given the high prevalence and substantial impact of these psychiatric conditions, utilizing population-based interventions to efficiently manage these conditions is a promising approach to improving psychiatric symptoms, health behavior adherence, and overall cardiac risk in the greatest number of patients. For example, “collaborative care” interventions utilize a non-physician care manager (often a nurse) to assess and longitudinally monitor psychiatric conditions for patients in inpatient and outpatient medical settings<sup>[117,118]</sup>. The care manager can also provide psychotherapeutic interventions and support to patients, and receives psychiatric medication recommendations when indicated from a team psychiatrist. These medication recommendations are conveyed to primary care physicians, who then prescribe all medications. This allows a large number of patients to receive ongoing and expert management of psychiatric care, while maintaining such care within their existing medical home.

Collaborative care interventions have been found to be effective in improving psychiatric symptoms in over 90 prior trials<sup>[117]</sup>. This includes several prior trials in patients with CVD or cardiac risk factors (*e.g.*, diabetes)<sup>[118-124]</sup>, with beneficial effects on depression and/or anxiety symptoms. They have not typically included specific interventions to improve sleep or other health behaviors, and they have had more mixed effects on adherence, with some trials finding improvement in adherence to health behaviors (*e.g.*, diet, exercise, and medication adherence)<sup>[120,125]</sup>, while others have not measured effects on adherence or found no significant change. Effects on cardiovascular outcomes have similarly been mixed, though an analysis of the large IMPACT trial of collaborative care found that the intervention was associated with lower risk of cardiovascular events among those participants with no CVD at the outset of the trial<sup>[126]</sup>.

One promising approach to improving behavioral and cardiovascular outcomes is a “blended” collaborative care management approach that utilizes a nurse care manager to address depression, health behaviors, and medical targets (*e.g.*, blood pressure) in patients with medical illness. The TEAMCare randomized trial tested such an approach in patients with diabetes or coronary artery disease, and found that such an intervention led to improved medical outcomes, including hemoglobin A1c and blood pressure, using this combined psychiatric, behavioral, and medical approach<sup>[127]</sup>. The COMPASS project then implemented this intervention in 172 real-world clinics among 3609 patients<sup>[128,129]</sup>. Overall 40% had depression remission or response, one-quarter met criteria for control of blood glucose, and nearly 60% met criteria for blood pressure control, impressive findings for real-world implementation in a

complex population.

## CONCLUSION

The importance of sleep as a health behavior to lower the risk of CVD in adults has not been widely studied. With recent guidelines shedding light on the importance of adults maintaining adequate sleep (defined as at least seven hours) for optimal health and the growing number of Americans not meeting this recommendation, future research needs to include sleep when assessing CVD risk factors and intervention targets. Research to date has primarily focused on other health behaviors including diet, physical activity, and sedentary time. Many of these interventions have focused on one health behavior, rather than changing multiple behaviors, despite the fact that these behaviors tend to be inter-related. The same theories and intervention strategies used to change individual health behaviors, including CBT, MI, mindfulness and mind-body interventions, and PP-based interventions, could be adapted to promote all relevant health behaviors as we have outlined in this review. Further, moving toward blended collaborative care models may be a promising approach to improve health behaviors in those with psychiatric conditions. Such interventions that focus on psychological status, health behaviors, and medical targets may indeed hold substantial promise to modify sleep and other health behaviors to reduce cardiac risk.

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## Heart failure after myocardial infarction in the era of primary percutaneous coronary intervention: Mechanisms, incidence and identification of patients at risk

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### Abstract

Myocardial infarction (MI) remains the most common cause of heart failure (HF) worldwide. For almost 50 years HF has been recognised as a determinant of

adverse prognosis after MI, but efforts to promote myocardial repair have failed to translate into clinical therapies. Primary percutaneous coronary intervention (PPCI) has driven improved early survival after MI, but its impact on the incidence of downstream HF is debated. The effects of PPCI are confounded by the changing epidemiology of MI and HF, with an ageing patient demographic, an increasing proportion of non-ST-elevation myocardial infarction, and the recognition of HF with preserved ejection fraction. Herein we review the mechanisms of HF after MI and discuss contemporary data on its incidence and outcomes. We review current and emerging strategies for early detection of patients at risk of HF after MI, with a view to identification of patient cohorts for novel therapeutic agents.

**Key words:** Angioplasty; Heart failure; Myocardial infarction; Percutaneous coronary intervention; ST-elevation myocardial infarction

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**Core tip:** Heart failure (HF) is a major cause of late morbidity and mortality after myocardial infarction. Several approaches exist for early identification of patients at risk of HF, including clinical and angiographic scoring, cardiac imaging, and invasive coronary physiology, but these are currently poorly integrated. Here we provide an overview of the incidence, mechanisms, and outcomes of HF following myocardial infarction in the era of primary percutaneous coronary intervention, and discuss HF risk-stratification for the individual patient. Looking ahead, accurate and early prediction of HF will allow targeting of novel therapeutic agents to high-risk patients before ventricular remodelling and clinical HF have become established.

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in the era of primary percutaneous coronary intervention: Mechanisms, incidence and identification of patients at risk. *World J Cardiol* 2017; 9(5): 407-415 Available from: URL: <http://www.wjgnet.com/1949-8462/full/v9/i5/407.htm> DOI: <http://dx.doi.org/10.4330/wjc.v9.i5.407>

## INTRODUCTION

Primary percutaneous coronary intervention (PPCI) has revolutionised the management and outcome of acute myocardial infarction (MI)<sup>[1,2]</sup>. It is the reperfusion strategy of choice throughout the developed world, with 90000 procedures performed annually in the United States alone<sup>[3,4]</sup>. Contemporary PPCI in the United Kingdom is characterised by door-to-balloon times of < 60 min, radial access, second generation drug-eluting stents and tailored use of antiplatelet and antithrombotic agents<sup>[5,6]</sup>. The introduction of PPCI and adjunctive therapies have driven a reduction in inpatient mortality following acute MI from 20% in the late 1980s to approximately 5%-7% in contemporary series<sup>[7,8]</sup>.

Despite this success, coronary artery disease remains the commonest cause of heart failure (HF)<sup>[9]</sup>. HF after MI is the major driver of late morbidity, mortality and healthcare cost. The effect of PPCI on the incidence of HF is debated, with studies confounded by the changing definitions and epidemiology of both MI and HF. Targeted therapies to prevent HF after MI have lagged behind advances in reperfusion, with Entresto (valsartan/sacubitril) the only novel pharmacotherapy for HF to enter the mainstream market in over a decade. Despite the evident burden of HF, many MI trials have predominantly focused on thrombosis, bleeding and composite endpoints [e.g., major adverse cardiac events (MACE)] rather than HF events specifically.

In this review we outline the challenge of HF following MI in contemporary practice. We provide an overview of the mechanisms and definitions of HF after MI, and the data on temporal trends in HF incidence from the pre-thrombolysis era through to the modern day. We review current and emerging strategies to identify patients at risk of HF, including coronary physiology, cardiac magnetic resonance and hybrid imaging, and suggest how improved mechanistic understanding of HF can be used to inform the next generation of clinical trials for these patients.

## DEFINING HF AFTER MI

HF is defined as "a clinical syndrome resulting from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill or eject blood"<sup>[10]</sup>. This has been translated into several validated diagnostic criteria (e.g., the Framingham criteria<sup>[11]</sup> and the European Society of Cardiology criteria<sup>[12]</sup>), but the primary definition of HF as a clinical syndrome has led to differing clinical, imaging and biomarker definitions

coexisting in clinical practice and research. Unlike MI, there is no "universal definition" and consequently, the diagnosis of HF is often heterogeneous between studies and over time<sup>[13]</sup>.

Early studies of HF following MI used clinical criteria such as the Killip and New York Heart Association classifications<sup>[14,15]</sup>. While crude, Killip class has retained prognostic value in more recent cohorts such as the GRACE registry: Patients in Killip class I had an in-hospital mortality of 3%, rising to 20% for those in class III<sup>[16]</sup>. In the PPCI population, higher Killip class at presentation is an independent predictor of in-hospital and 6-mo mortality<sup>[17]</sup>. Clinical HF scores were refined by the development of echocardiography, which led to objective measurement of ejection fraction and ventricular volumes as an intrinsic part of a HF diagnosis<sup>[18]</sup>.

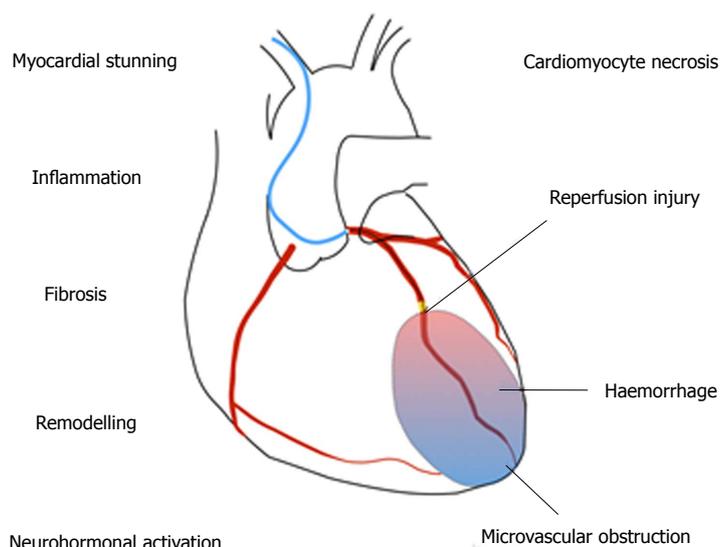
The timing of HF following MI is important clinically, mechanistically and for research. Three key time periods need to be distinguished: HF at the index MI presentation, during the course of the first admission, and after discharge. The timing of HF is often not well-defined by research studies, making comparison between studies challenging. From a statistical perspective, older studies failed to treat HF as a time-dependent, evolving covariate whose incidence was modifiable by the up-front treatment, meaning that late-onset HF after MI is less well characterised than HF at presentation<sup>[19]</sup>.

## PATHOPHYSIOLOGY OF HF AFTER MI

Several overlapping mechanisms contribute to HF after MI (Figure 1). HF during the index MI occurs due to a combination of myocardial stunning, myocyte necrosis, decompensation of pre-existing HF or acute mitral regurgitation due to papillary muscle dysfunction. HF during the hospitalisation may also be due to any of the above, compounded by fluid or contrast overload, renal dysfunction, or complications such as ventricular septal defect or cardiac tamponade. Late HF reflects the consequences of cardiomyocyte death and scar formation occurring alongside ventricular remodelling.

The cellular pathophysiology of MI has been clearly defined in animal models. Within 30 min of ischaemia, cardiomyocyte structural changes and oedema develop, leading to progressive cell death from three hours. Acute contractile dysfunction occurs due to oxidative stress and calcium overload, which is reversible if flow is restored<sup>[20]</sup>. Reperfusion itself causes a second wave of injury, by production of reactive oxygen species. Despite successful epicardial reperfusion, embolization of thrombotic debris, plugging by inflammatory cells and release of vasoactive mediators from damaged endothelium leads to ongoing microvascular dysfunction in up to 50% of patients<sup>[21]</sup>.

Myocardial injury leads to activation of a stereotyped inflammatory cascade, comprised of early neutrophil ingress followed by monocyte-macrophage infiltration.



**Figure 1** Mechanisms of heart failure after myocardial infarction.

Between days 3-5 following MI there is a transition from inflammation to repair, with activation of fibroblasts and progressive scar deposition<sup>[22]</sup>. Over time there is compensatory activation of the renin-angiotensin and sympathetic nervous systems and pathological remodelling, with changes to the ventricular geometry, wall thinning, ischaemic mitral regurgitation and further cardiomyocyte loss. The precise contribution of the different pathophysiological components (*e.g.*, microvascular dysfunction, inflammation) to injury is likely to be heterogeneous, and understanding mechanistic pathways in specific patient subgroups will be key to identifying novel therapeutic strategies<sup>[23]</sup>.

## TEMPORAL TRENDS IN HF AFTER MI

HF after MI was first described as an adverse prognostic feature by Killip in the 1960s<sup>[14]</sup>. HF was associated with large infarcts and multivessel disease, and the presence of impaired ventricular function was linked to worsening mortality<sup>[24,25]</sup>. Prior to thrombolysis, the incidence of in-hospital HF after ST-elevation myocardial infarction (STEMI) was approximately 40%<sup>[15]</sup>. This appeared to reduce after the introduction of thrombolysis, with HF present in approximately 3% of patients at presentation and 17% during admission<sup>[26]</sup>. Successful reperfusion was associated with improved LV function and long-term survival<sup>[27]</sup>. HF during admission remained an adverse prognostic feature, with 1-year mortality rates approximately 5 fold higher in those with HF<sup>[28]</sup>.

More recent studies have suggested a further reduction in HF rates with use of primary PCI. In an Italian cohort of 2089 MI patients treated exclusively by PPCI between 1995 and 2005, 17% presented in HF, but only a further 1% developed new onset HF during the hospital admission<sup>[29]</sup>. Similarly, in an analysis from the HORIZONS-AMI cohort of 3602 patients recruited between 2005-2007 treated with PPCI, 8.0% of patients

were in Killip class II-IV at presentation. At 30 d, only 4.6% of patients had developed a clinical HF syndrome (defined by NYHA/Killip class), rising to 5.1% at 2 years<sup>[30]</sup>.

These studies are not directly comparable, and reflect selected trial cohorts with a short duration of follow-up and differing methods of HF ascertainment. Several dedicated time trend analyses have now been performed. In Olmsted County, 1537 patients with an index MI between 1979 and 1994 were identified, spanning the introduction of thrombolysis in the late 1980s<sup>[31]</sup>. Over the study period the 5-year incidence of HF decreased from 40% to 33%. In a later study of 2596 MI patients between 1990 and 2010, there was increasing use of PPCI and a reduced risk of both early (0-7 d; HR = 0.67, 95%CI: 0.54-0.85) and late (8 d-5 years; HR = 0.63, 95%CI: 0.45-0.88) HF over time<sup>[32]</sup>. In patients with HF, mortality was higher for those with delayed vs early onset HF<sup>[33]</sup>.

A reduction in post-MI HF has also been seen in other studies. In a sample of 2.8 million MI hospitalisations (in Medicare beneficiaries) between 1998-2010, there was a reduction in the incidence of subsequent HF hospitalisation from 16 to 14 per 100 person-years<sup>[34]</sup>. In a Danish cohort, the incidence of HF at 90 d post-MI reduced from 24% to 20% alongside a an increase in PCI from 2.5% to 38% between 1997 and 2010<sup>[35]</sup>. Similarly, in Western Australia there was a reduction in the prevalence of HF at 90 d from 28% to 17% between 1996 and 2007<sup>[36]</sup>. Finally, in the SWEDEHEART registry of 19851 patients admitted with an MI between 1996 and 2008, there was a reduction in the incidence of clinical HF (albeit measured during the index hospitalization) from 46% to 28% alongside increasing use of PPCI<sup>[37]</sup>.

In contrast, data from Framingham Heart Study shows an increase in HF over time<sup>[38,39]</sup>. In 676 patients who developed a first MI between 1970 and 1999, both the 30-d and 5-year incidence of HF increased. At

Infarct size/characterisation		Salvage/repair
Age Male sex Killip class Pain to balloon time	Patient	Age Killip class Pain to balloon time
LAD culprit artery TIMI flow pre/post PCI MBG	Angiography	Pre-PCI TIMI flow Collateral flow
IMR CFR	Coronary physiology	IMR $\Delta$ CFR
Cardiac function/volumes WMSI	Echocardiography	MVO $\Delta$ Cardiac function $\Delta$ Cardiac volumes - remodelling
MVO Infarct haemorrhage Cardiac function/volumes	Cardiac MRI	
Inflammation	PET	Required
CK/Tnl and BNP	Biomarkers	Required

**Figure 2 Heart failure after myocardial infarction - strategies for prediction of infarct size and salvage.** BNP: B-type natriuretic peptide; CFR: Coronary flow reserve; CK: Creatine kinase; IMR: Index of microcirculatory resistance; LAD: Left anterior descending; MBG: Myocardial blush grade; MVO: Microvascular occlusion; PET: Positron emission tomography; PCI: Percutaneous coronary intervention; TIMI flow: Thrombolysis In Myocardial Infarction flow score; Tnl: Troponin I; WMSI: Wall motion score index.

5 years, the incidence of HF was 28% in 1970-1979 and 32% in 1990-1999, which remained significant after multivariate adjustment, with a risk ratio of 1.74 (95%CI: 1.07-2.84) for HF in 1990-1999 compared with 1970-1979<sup>[39]</sup>. Similarly, the Worcester Heart Attack Study showed an increasing incidence of HF between 1975 and 2001, and in the Alberta Elderly MI cohort, there was a 25% increase in the incidence of in-hospital HF between 1994-2000, from 31% to 39%<sup>[40,41]</sup>.

In the face of conflicting data from a relatively small number of studies, it remains difficult to draw firm conclusions on the impact of PPCI on the incidence of HF. There are key differences between studies in the definition of HF and MI, the validation of these diagnoses, the timing of ascertainment and the duration of follow-up. While the majority appear to suggest that PPCI is associated with reduced HF incidence, for many the duration of follow-up is short. Some studies have not differentiated between incident and prevalent cases. Reconciling these differences will require further studies with long term follow-up. If increasing survival from MI is leading to a rise in HF, this may only be seen in updated analyses, as interventionalists take on increasingly frail and elderly patients who previously were not surviving<sup>[42]</sup>.

## RISK STRATIFICATION FOR HF AFTER MI

Given the ongoing contribution of HF to morbidity and mortality after MI, early risk stratification and preventative therapeutic strategies are required. Although a number of clinical, angiographic, physiological, imaging and biomarker approaches to HF risk stratification following MI have been proposed (Figure 2), few are in routine clinical use. In addition to prognostication,

emerging hybrid imaging and coronary physiology approaches are shedding light on the mechanisms driving HF in different patient subgroups, and might also be used as early surrogate endpoints for trials. Given the historical failure of generic approaches targeting processes such as inflammation, it seems likely that tailored therapies for specific patient groups will be required.

### Clinical evaluation

Infarct size is the major determinant of downstream HF and prognosis<sup>[43]</sup>. Predictors of HF on admission are related to underlying LV function (*e.g.*, prior MI), markers of coronary artery disease severity (*e.g.*, diabetes mellitus) and features of an extensive infarct (*e.g.*, anterior location, increasing duration from symptom onset to reperfusion)<sup>[29]</sup>. Clinical predictors of late HF are of greater use for risk stratification. In the HORIZONS-AMI cohort, predictors of new-onset HF at 2 years were a history of MI (OR = 1.81, 95%CI: 1.22-2.67), ejection fraction (per 10% decrease OR = 1.35, 95%CI: 1.21-1.5), female sex (OR = 1.34, 95%CI: 1.1-1.51) and insulin-treated diabetes (OR = 1.68, 95%CI: 0.96-2.65)<sup>[30]</sup>. Similarly, in the CARE and VALIANT studies of MI survivors, predictors of late HF were age, diabetes, renal insufficiency, LVEF post-MI, and Killip class at index MI  $\geq 2$ <sup>[44,45]</sup>. A dedicated scoring system for prediction of late HF which integrated these parameters would be of value. Although not designed for HF events, the GRACE score, originally developed for ACS risk stratification, has recently been shown to predict late HF events after both STEMI and NSTEMI<sup>[46]</sup>.

### Coronary angiography and haemodynamics

Coronary angiography provides a number of patient-

specific markers for risk stratification, albeit often for MACE rather than HF specifically (Figure 2). The presence of multivessel disease and lack of normal flow in the infarct related artery are key adverse prognostic features after PPCI<sup>[47,48]</sup>. TIMI flow in the infarct related artery pre and post-procedure predicts outcome, with post-procedural  $\leq$  TIMI 2 flow associated with a HR of 3.8 (95%CI: 2.5-5.7) for 1-year mortality<sup>[49]</sup>. Impaired microvascular perfusion, assessed angiographically using the TIMI myocardial blush grade, also predicts 1-year mortality, which rises from 1.4% in patients with normal blush to 6.2% in patients with absent blush<sup>[50]</sup>. Patients with no-reflow have a higher incidence of arrhythmia, remodelling, HF and mortality<sup>[21]</sup>.

Recent attempts to categorise no-reflow have focused on the upstream causes, including distal embolisation of thrombus, new thrombus formation mid-procedure, and intraprocedural stent thrombosis, collectively badged as intraprocedural thrombotic events (IPTE). The incidence of IPTE was 12.2% in a recent STEMI cohort, with each IPTE component independently associated with 30-d death and MACE<sup>[51]</sup>. Beyond angiography, invasive hemodynamic measurement in the cath lab can provide further risk stratification: Measurement of LV end-diastolic pressure is an independent predictor of mortality at 2 years, even after adjustment for baseline LV function<sup>[52]</sup>.

### Coronary physiology

Invasive coronary physiology provides a highly sensitive readout of microcirculatory function, and has demonstrated significant value in prediction of myocardial recovery after MI. The index of microcirculatory resistance (IMR) is the ratio of distal coronary pressure to the inverse of the mean transit time during maximal hyperaemia. Measured after PPCI, IMR is a predictor of ejection fraction and infarct volume at 3 mo post-MI<sup>[53]</sup>. An IMR > 40 is associated with increased risk of death or rehospitalisation for HF (HR = 2.1,  $P = 0.034$ )<sup>[54]</sup>. IMR is now being used as a surrogate endpoint in ongoing trials of aspiration thrombectomy and intracoronary GpIIb/IIIa agents<sup>[55]</sup>. Hyperaemic microvascular resistance (HMR), another specific read-out of microcirculatory function, is also predictive of CMR-defined microvascular occlusion (MVO), and impaired local blood flow as measured by PET<sup>[56]</sup>.

Invasive measurement of coronary flow reserve (CFR), zero-flow pressure (Pzf), and fractional flow reserve (FFR) may also have a role in risk stratification following PPCI. CFR is the ratio of ratio of hyperaemic to resting coronary flow and incorporates both the epicardial and microvascular circulations. In 44 patients undergoing PPCI, the change in CFR between presentation and day 1 post-PPCI was predictive of the degree of myocardial salvage and ejection fraction at 6 mo<sup>[57]</sup>. Pzf, derived from pressure-velocity loop analysis, is the distal coronary pressure at which the flow in a coronary artery would theoretically cease and represents extra-vascular compression of the microcirculation by oedema

or haemorrhage. Pzf correlates with HMR, and also predicts residual scar at 6 mo post-MI with an AUC of 0.94<sup>[56,58]</sup>. FFR, the ratio of myocardial blood flow at maximal hyperaemia in comparison to normal proximal myocardial flow, is also predictive of adverse outcome, with an FFR of  $\leq 0.8$  associated with an HR of 3.24 for MACE<sup>[58]</sup>. The utility of coronary physiology in day-to-day practice, and the optimal index for HF risk stratification remains to be established.

### Imaging

Complimentary imaging modalities are providing increasingly detailed phenotyping of myocardial injury, function and healing. Standard echocardiographic indices including ejection fraction, LV volumes, wall motion score index, E/E' ratio and right ventricular function provide prognostic information after MI<sup>[59]</sup>. More recently, longitudinal and circumferential strain rate have been shown to be predictive of death or hospital admission for HF, with longitudinal strain rate adding significant incremental value in the prediction of all-cause mortality beyond clinical variables, LVEF, and wall motion score index<sup>[60]</sup>.

Cardiac MRI offers a broad armamentarium for tissue and functional characterisation, including quantification of the area at risk, infarct size, salvage index, microvascular obstruction, haemorrhage, heterogeneity and scar. Several indices are independently predictive of late outcome, including CMR-determined infarct size, myocardial salvage index and extent of microvascular obstruction<sup>[61-63]</sup>. In a study of 249 patients, CMR measurement of MVO was the strongest predictor of MACE over a 6-year follow-up<sup>[64,65]</sup>. CMR characterisation of infarct core characteristics, including identification of infarct haemorrhage (by T2W and T2\*) or native T1 signal, are recently-described predictors of adverse remodelling and clinical outcome<sup>[66-68]</sup>.

Combining metabolic imaging by <sup>18</sup>F-fludeoxyglucose (<sup>18</sup>F-FDG) with MRI has the potential to provide further characterisation of myocardial injury and repair. <sup>18</sup>F-FDG accumulates in monocyte-macrophages and other highly metabolically active tissues<sup>[69]</sup>. In a study of 49 patients hybrid <sup>18</sup>F-FDG PET-MRI was performed at a median 5 d following MI. The intensity of <sup>18</sup>F-FDG signal correlated with infarct size and predicted cardiac function at 6-9 mo follow-up. Interestingly, FDG signal remained an independent predictor after multivariate analysis, providing the first clue that imaging of inflammatory response can be used to risk stratify patients<sup>[70]</sup>. Recently, PET imaging of CXCR4, a receptor expressed on leucocytes and haematopoietic stem cells was demonstrated in human patients after MI. This type of approach holds great potential for understanding the biological heterogeneity in the healing response *in vivo*<sup>[71]</sup>.

### Biomarkers

Cardiac biomarkers such as troponin and BNP have established core use for the diagnosis of MI and HF,

and also demonstrate prognostic value for long-term outcome<sup>[72]</sup>. A recent study shows that combining serial measurement of traditional biomarkers (*e.g.*, NT-proBNP, hs-cTnT, aspartate transferase, alanine transaminase, lactate dehydrogenase and high-sensitivity C-reactive protein) gives an area under the curve of 0.85 for prediction of LV remodelling<sup>[73]</sup>. Looking forward, the field needs biomarkers which define specific biological groups at risk of HF who can be targeted with novel therapeutic agents. These might include biomarkers of inflammation, persistent fibrosis or matrix remodelling. There are data which highlight the potential value of measuring the inflammatory cascade for risk stratification: For example, the ratio of neutrophil:lymphocyte count predicts mortality after NSTEMI and STEMI, which may reflect the functional transition from inflammation to repair<sup>[74,75]</sup>.

There are a number of emerging potential biomarkers for future HF, including tenascin-C, myeloperoxidase, cytokines, matrix metalloproteinases and growth factors<sup>[76]</sup>. Tenascin-C is an extracellular matrix glycoprotein which is not normally expressed in the heart, but is upregulated following MI, or in myocarditis. In patients with acute MI, peak tenascin-C level measured at day 5 is independently predictive of LV remodelling, HF and MACE, and provides additive value to TIMI score and BNP<sup>[77,78]</sup>. Copeptin, the C-terminal portion of proavopressin, was the strongest marker of HF after MI from the OPTIMAAL study: A doubling of copeptin was related to a 1.83 fold (1.26-2.64) increased risk of mortality ( $P < 0.0001$ )<sup>[79,80]</sup>. Galectin-3 has shown some promise as a marker of matrix and fibrosis, but has not been found to be an independent predictor of LV remodelling<sup>[81]</sup>.

## CONCLUSION

HF remains a major challenge after MI. Despite the difficulties of interpreting incidence over time, HF indisputably drives much of the late mortality after successful revascularisation and therapeutic interventions to prevent HF in patients at high risk would be hugely valuable. Trials would be facilitated by consensus definitions for HF events and imaging endpoints (*e.g.*, oedema, myocardial salvage and remodelling). Given the long follow-up required for HF events, use of surrogate markers of HF risk (*e.g.*, IMR) could be used for early translational studies. To date, despite an attractive window of opportunity to target myocardial healing, therapies in this field have failed to translate. In part this may reflect divergent mechanisms of HF in different patients, with varying contributions from microcirculatory dysfunction, inflammation, haemorrhage, oedema and remodelling. Coronary physiology and CMR imaging can be used to identify discrete subsets of patients, for example those with MVO, for targeted therapies. For risk stratification, the optimal combination of predictive modalities needs to be defined. Looking ahead, there are three key questions: What is the risk of downstream HF, what mechanisms can be identified, and what therapies

can we trial?

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## Transcervical access, reversal of flow and mesh-covered stents: New options in the armamentarium of carotid artery stenting

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### Abstract

In the last 25 years, the very existence of carotid artery stenting (CAS) has been threatened on a number of occasions. The initial disappointing results that even lead to the discontinuation of an early randomized controlled trial have improved considerably with time. Novel devices, advanced stent and equipment technology, alternative types of access and several types of filters/emboli protecting devices have been reported to reduce stroke/death rates during/after CAS and improve CAS outcomes. The present review will provide a description of the various technology advances in the field that aim to reduce stroke and death rates associated with CAS. Transcervical access, reversal of flow and mesh-covered stents are currently the most promising tools in the armamentarium of CAS.

**Key words:** Carotid artery stenting; Stroke; Carotid artery stenosis; Filters

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**Core tip:** Carotid artery stenting (CAS) has improved considerably in the last few years. This comprehensive review provides the various technology advances in the field that aim to reduce stroke and death rates after CAS. These include transcervical access, reversal of flow and mesh-covered stents.

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## INTRODUCTION

During its evolution, carotid artery stenting (CAS) has often gone through some difficult times. One of the first randomized controlled trials comparing CAS with carotid endarterectomy (CEA), the Leicester trial, had to be stopped prematurely after randomizing less than 20 patients<sup>[1]</sup>. All 10 patients that were randomized to CEA proceeded without complications. On the other hand, 5 of the 7 patients who were randomized to CAS suffered a stroke ( $P = 0.0034$ ), three of which were disabling at 30 d<sup>[1]</sup>.

Fortunately, CAS outcomes have improved considerably since then and continue to improve constantly. Technological advances such as proximal/distal embolic protection devices (EPDs), flow reversal, transcervical/transradial access and double layer mesh stent technology are adjuncts that have been developed to improve CAS outcomes. The current article presents an overview of these technological advances.

## EPDS

Proximal and distal EPDs are commonly utilized with CAS with the aim of preventing atherosclerotic debris from embolizing to the brain. Catheter manipulation within the aorta and supra-aortic arteries causes plaque embolization. Up to 90% of CAS procedures can be complicated by embolic events and EPDs may capture these embolized particles<sup>[2]</sup>. Although some studies report good outcomes for various distal EPDs (also known as filtering devices)<sup>[3-5]</sup>, others studies argue that distal filters may not be able to prevent all perioperative emboli<sup>[6-9]</sup>. The pore size of most available filter devices is  $> 80 \mu\text{m}$ <sup>[3]</sup>, but many emboli are  $< 80 \mu\text{m}$  in size<sup>[10,11]</sup>. Furthermore, due to the rigidity of many filter devices and a required minimal distal landing zone depending on the length of the basket of the filter device, the vessel wall apposition may not be optimal (especially in tortuous vessel segments) and could therefore allow cerebral embolization<sup>[12]</sup>. These studies have supported that, compared with distal EPDs, proximal EPDs reduce the perioperative microembolic signals detected by transcranial Doppler and the number of new ischemic lesions<sup>[6-9]</sup>.

A study from Milan, Italy compared the rate of cerebral microembolization during CAS with a proximal EPD [Mo.Ma system (Invatec, Roncadelle, Brescia, Italy);  $n = 26$ ] vs distal protection with a filter [FilterWire EZ (Boston Scientific Corporation, Santa Clara, California);  $n = 27$ ] in patients with high-risk, lipid-rich plaques<sup>[7]</sup>. Compared with use of the FilterWire EZ, the Mo.Ma system significantly reduced mean microembolic signal counts during lesion crossing (mean: 18 vs 2, respectively;  $P < 0.0001$ ), stent crossing (mean: 23 vs 0, respectively;  $P < 0.0001$ ), stent deployment (mean: 30 vs 0, respectively;  $P < 0.0001$ ), stent dilation (mean: 16 vs 0, respectively;  $P < 0.0001$ ) and total microembolic signals (mean: 93 vs 16, respectively;  $P$

$< 0.0001$ )<sup>[7]</sup>.

The Mo.Ma proximal EPD is a safe and effective neuro-protection system during CAS that achieves very low periprocedural stroke rates. A registry of 1300 patients undergoing CAS using the Mo.Ma device reported very low major adverse cardiac or cerebrovascular events including 5 deaths (0.38%), 6 major strokes (0.46%), 5 minor strokes (0.38%) and 0 myocardial infarctions (MIs)<sup>[13]</sup>. The incidence of postprocedural events did not increase even in the presence of theoretical anatomical contraindications to proximal endovascular occlusion (*e.g.*, contralateral carotid occlusion). The excellent results reported for the Mo.Ma device suggest that it is a promising technique for the achievement of low stroke rates after CAS.

A prospective randomized study, the Prevention of Cerebral Embolization by Proximal Balloon Occlusion Compared to Filter Protection During Carotid Artery Stenting study, compared the embolic load of filter-protected ( $n = 31$ ) vs proximal balloon-protected CAS ( $n = 31$ )<sup>[9]</sup>. Proximal balloon occlusion lead to a considerable reduction in the percentage of new cerebral ischemic lesions (45.2% vs 87.1%, for proximal balloon occlusion vs filter protection, respectively;  $P = 0.001$ ). Proximal balloon occlusion reduced both the number [median (range): 2 (0-13) vs 0 (0-4);  $P = 0.0001$ ] and the volume [0.47 (0-2.4)  $\text{cm}^3$  vs 0 (0-0.84)  $\text{cm}^3$ ;  $P = 0.0001$ ] of new cerebral ischemic lesions. Furthermore, contralateral hemisphere lesions were detected in 29.0% vs 6.5% of patients receiving a filter vs balloon occlusion, respectively ( $P = 0.047$ ). Finally, the 30-d major adverse cardiovascular and cerebral events rate was 3.2% for filter protection vs 0% for balloon occlusion, respectively ( $P = \text{not significant}$ )<sup>[9]</sup>.

A meta-analysis ( $n = 8$  studies; 357 patients) evaluated and compared the results of filter cerebral protection vs proximal balloon occlusion in preventing embolization during CAS as evaluated by diffusion-weighted magnetic resonance imaging (DW-MRI)<sup>[14]</sup>. The incidence of new ischemic lesions after CAS/patient detected by DW-MRI (effect size: -0.43; 95%CI: -0.84 to -0.02;  $I^2 = 70.08$ ;  $Q = 23.40$ ) and the incidence of contralateral site lesions (effect size: -0.50; 95%CI: -0.72 to -0.27;  $I^2 = 0.00$ ;  $Q = 3.80$ ) were both significantly lower in the proximal balloon occlusion group<sup>[14]</sup>. The results of this meta-analysis support the superiority of proximal balloon occlusion as compared with filter cerebral protection with respect to the degree of CAS-related brain embolization<sup>[14]</sup>.

Others, however, have supported that proximal EPDs have similar results with distal filter EPD<sup>[15]</sup>. The lack of difference in proximal occlusion vs distal filter EPD results was also verified in a meta-analysis<sup>[16]</sup>. This meta-analysis included 7 studies ( $n = 392$  patients; 193 with proximal occlusion; 199 with distal filters). The use of proximal occlusion vs distal filter did not reduce the risk of new cerebral lesions (OR = 0.65; 95%CI: 0.28-1.52;  $P = 0.32$ ) or the risk of death/cerebrovascular event (OR = 0.59; 95%CI: 0.22-1.60;  $P = 0.30$ )<sup>[16]</sup>. A more

recent meta-analysis verified the equipoise in clinical outcomes between proximal balloon occlusion and distal filter protection<sup>[17]</sup>. This meta-analysis ( $n = 18$  studies; 12281 patients) did not demonstrate any significant difference between the two modalities in terms of the risk of stroke or mortality, nor was there any difference in the incidence of new cerebral lesions on DW-MRI or contralateral DW-MRI lesions. The conclusion reached was that both proximal and distal EPDs provide similar levels of protection from periprocedural stroke and 30-d mortality<sup>[17]</sup>. Finally, a national cardiovascular data registry analysis from the United States compared stroke/death rates between proximal EPDs and distal filter EPDs in 10,246 consecutive elective CAS procedures. Both EPDs were associated with similar 30-d adverse event rates (2.7% vs 4.0%, after proximal vs distal filter EPDs, respectively;  $P = 0.22$ )<sup>[18]</sup>.

## TRANSCERVICAL ACCESS WITH FLOW-REVERSAL

The first description of flow reversal as a cerebral protection device was in 2000<sup>[19]</sup>. Although initially CAS with flow reversal was performed *via* the transfemoral approach<sup>[19]</sup>, a subsequent modification was the use of transcervical approach for CAS with flow reversal<sup>[20]</sup>. This technique is described in detail elsewhere<sup>[20]</sup>. Several independent studies have published very low 30-d stroke/death/MI rates and low incidence of complications for transcervical CAS with flow reversal<sup>[21-25]</sup>. It was recently demonstrated that transcervical CAS with flow reversal demonstrates embolization rates comparable with CEA<sup>[26]</sup>. Transcervical CAS with flow reversal thus seems a promising method for the reduction of strokes associated with CAS<sup>[27]</sup>.

Elderly patients (> 70 years) have inferior outcomes with transfemoral CAS compared with CEA<sup>[28]</sup>. The poor outcome of transfemoral CAS in this age group may be explained by the anatomic characteristics of the aortic trunk and supra-aortic vessels as well as by a high prevalence of aortic arch atheromatosis<sup>[21]</sup>. Transcervical CAS with flow reversal for cerebral protection avoids these unfavorable characteristics. An early study reported a 2.2% 30-d combined stroke/death/MI rates in 219 patients > 70 years of age (55.7% asymptomatic; 44.3% symptomatic)<sup>[21]</sup>. Symptomatic patients had a 5.1% combined stroke/death/MI rates whereas asymptomatic patients had a 0% rate<sup>[21]</sup>. Thus, transcervical CAS with flow reversal may be the preferred option for this age group.

Not long ago, the Reverse Flow Used During CAS Procedure (ROADSTER) multicenter trial reported its results from the evaluation of the safety and efficacy of the ENROUTE Transcarotid NPS (Silk Road Medical Inc, Sunnyvale, Calif), a novel transcarotid neuroprotection system that provides direct surgical common carotid access and cerebral embolic protection *via* high-rate flow reversal during CAS<sup>[29]</sup>. This study reported an

overall stroke rate of 1.4%, which is the lowest reported for any prospective multicenter clinical trial of CAS. The stroke/death rates (2.8%) and the stroke/death/MI rates (3.5%) reported were also similarly low<sup>[29]</sup>.

Direct percutaneous carotid access is an alternative access that has been described for CAS. This access can be used in individuals with difficult anatomies, high-risk patients and certain emergent situations that warrant easy and rapid access to the CCA<sup>[30]</sup>. A systematic review ( $n = 12$  studies; 739 CAS procedures) showed that direct CAS with transcervical access (filter protected or unprotected;  $n = 250$  patients) and CAS with transcervical access under reversed flow (with arteriovenous shunt in most cases;  $n = 489$  patients) are both associated with a low incidence of stroke and complications<sup>[31]</sup>. The incidence of stroke, MI and death was 1.1%, 0.14% and 0.41%, respectively. The incidence of stroke was 1.2% (3 of 250) in direct CAS with transcervical access and 1.02% (5 of 489) in CAS under reversed flow ( $P =$  not significant). Transient ischemic attack occurred in 20 patients (2.7%)<sup>[31]</sup>.

## HEAD-TO-HEAD COMPARISON/ COMBINATION OF STRATEGIES

Several studies have compared/combined the various proposed adjuncts to improve CAS outcomes in an attempt to identify those measures that would help improve CAS results to a greater extent. A study from Argentina compared transradial vs transfemoral CAS<sup>[32]</sup>. A total of 775 consecutive patients undergoing CAS during 16 years were included (101 transradial vs 674 transfemoral). The primary combined end-point was in-hospital major adverse cardiac and cerebral events, whereas secondary end-points included angiographic outcome after the procedure and cross-over rate to another puncture site. Angiographic success was achieved in all 775 patients. There was a significant difference in cross-over rate (4.9% vs 0%, for the transradial vs the transfemoral approach, respectively;  $P < 0.05$ ), but not in the incidence of in-hospital major adverse cardiac and cerebral events (2% vs 3.6%, for the transradial vs transfemoral approach, respectively;  $P =$  not significant)<sup>[32]</sup>. It was concluded that both approaches are safe and efficacious. These results verified the results of an earlier study<sup>[33]</sup>.

An earlier study from Atlanta, Georgia, United States compared revascularization outcomes after CEA ( $n = 226$ ) vs CAS with a distal filter EPD ( $n = 216$ ) vs CAS with a proximal flow reversal system ( $n = 53$ )<sup>[34]</sup>. The 3 groups did not differ in the overall composite end-point of death, cerebrovascular accident and MI (4% vs 5.1% vs 0%, respectively;  $P = 0.1$ ) or any individual major adverse event<sup>[34]</sup>. Overall, patients undergoing CAS with EPD had a greater incidence of minor cerebrovascular accidents than CEA patients (6 vs 1, or 3.4% vs 0.5%, respectively;  $P = 0.031$ ). This was driven by the increased risk for a cerebrovascular accident for

asymptomatic patients. Of note, patients undergoing CAS with flow reversal ( $n = 53$ ) had zero adverse events (minor/major stroke, MI or death)<sup>[34]</sup>.

A study from Japan evaluated the effectiveness of the combined use of distal filter protection device [FilterWire EZ (Boston Scientific, Natick, MA)] and the Mo.Ma Ultra (Medtronic, Minneapolis, MN)<sup>[35]</sup>. The Mo.Ma Ultra is an EPD for interrupting the antegrade blood flow to the internal carotid artery. This study demonstrated that the combined use of a distal filter protection device and Mo.Ma Ultra could provide a more reliable embolic protection in CAS<sup>[35]</sup>.

A study from Italy reported the outcomes of 214 patients undergoing CAS *via* a transradial ( $n = 154$ ) or a transbrachial ( $n = 60$ ) approach with either the Mo.Ma proximal protection ( $n = 61$ ) or the distal filter protection ( $n = 163$ )<sup>[36]</sup>. As a result of technical difficulties in catheterizing the target vessel, crossover to a femoral approach was required in 11 of 153 (7.1%) filter patients, but only in 1 of the 61 (1.6%) Mo.Ma patients. On the other hand, 5 Mo.Ma patients developed acute intolerance to proximal occlusion (4 were subsequently shifted to filter protection). One patient undergoing CAS *via* the transradial approach was shifted to filter because the Mo.Ma system was too short. Overall, CAS was technically successful in 55 of the 60 (90%) Mo.Ma patients and in 142 of the 154 (93%) filter patients. The 30-d major adverse cardiovascular/cerebrovascular events rate did not differ significantly between the 2 groups (0% for Mo.Ma patients vs 2.8% for filter patient;  $P = 0.18$ ). There was similarly no difference in radiation exposure between the 2 groups. Major vascular complications occurred in 1 of the 61 (1.6%) Mo.Ma patients and in 3 of the 153 (1.96%) filter patients, respectively ( $P = 0.18$ ). All these complications occurred during the early learning phase of the transbrachial approach. After a mean follow-up of  $8.1 \pm 7.5$  mo, chronic radial artery occlusion was detected by Doppler ultrasound in 2 of the 30 (6.6%) Mo.Ma patients and by clinical assessment in 4 of 124 (3.2%) filter patients ( $P = 0.25$ ). The conclusion reached was that CAS with proximal protection *via* a transradial or a transbrachial approach is a safe, feasible and effective technique with low rate of vascular complications<sup>[36]</sup>.

A study from Japan compared the effectiveness of the embolization prevention mechanism of 2 types of EPDs - a distal protection balloon ( $n = 82$  patients) and a distal protection filter ( $n = 82$  patients)<sup>[37]</sup>. Positive findings on postoperative diffusion-weighted imaging were found in more patients with distal protection balloon compared with the distal protection filter (34 vs 22 patients, or 41.4% vs 26.8%, respectively). Furthermore, in the distal protection balloon group there were more strokes than in the distal protection filter group (2 minor and 2 major strokes vs 0 strokes, respectively)<sup>[37]</sup>. A combination of flow reversal and distal filter may be more effective than either modality alone<sup>[38]</sup>.

Controversial results were reported in a small study from Brazil<sup>[39]</sup>. This study compared flow reversal vs filter protection in 40 patients undergoing CAS using a femoral approach. Compared with flow reversal ( $n = 21$ ), filter protection ( $n = 19$ ) resulted in a reduction in the incidence (15.8% vs 47.6%, respectively;  $P = 0.03$ ), number (0.73 vs 2.6, respectively;  $P = 0.05$ ) and size (0.81 mm vs 2.23 mm, respectively;  $P = 0.05$ ) of new ischemic brain lesions<sup>[39]</sup>. Flow reversal was associated with a tendency toward increased incidence of ipsilateral ischemic lesions more than those who had filter protection (70% vs 0.0%, respectively;  $P = 0.07$ ). In addition, flow reversal showed a greater tendency toward increased incidence of ipsilateral lesions than bilateral (70% vs 30%, respectively;  $P = 0.07$ )<sup>[39]</sup>. As the authors mentioned, this trial was the first to show better results using filter protection than a proximal protective technique during CAS. The authors attributed these good results to their considerable operator experience with CAS, the general anesthesia (which minimized the risk of movement accidents) and to the filter protection device profile<sup>[39]</sup>.

## ADVANCES WITH STENT DESIGN

Several important advances in stent design have also lead to improved CAS outcomes. For instance, the Inspire MD technology (Tel Aviv, Israel) includes a bare-metal stent (Inspire MD C-Guard stent) covered by a micron level mesh (MicroNet). Preliminary results appear encouraging<sup>[40]</sup>. A prospective multicenter study, the C-Guard CARotid Embolic protection using microNET trial evaluated the feasibility of the C-Guard carotid embolic protective stent system<sup>[41]</sup>. This is a novel thin-strut nitinol stent combined with a polyethylene terephthalate mesh covering. This study reported a 0% 30-d major adverse cardiac or cerebrovascular events rate in 30 patients<sup>[41]</sup>. Another stent that has demonstrated promising results is the double-layer CASPER-RX stent<sup>[42]</sup>. Finally, the Roadsaver Micromesh stent is a novel nitinol double-layer micromesh stent. Preliminary results from high-volume centres showing a low incidence of embolic events and new ipsilateral ischemic brain lesions are encouraging<sup>[43,44]</sup>.

During CAS, debris is often trapped in stent interstices. When flow is restored following CAS, the trapped debris may prolapse through the stent struts and result in delayed cerebral embolization<sup>[45]</sup>. Three companies (Roadsaver™ Micromesh Carotid Stent, Terumo, Japan; C-Guard™ MicroNet-Covered Embolic Prevention Stent System, InspireMD, Boston, MA, United States; and Scaffold Stent, W.L. Gore and Associates, Flagstaff, AZ, United States) are evaluating membrane or mesh covered carotid stents with smaller interstices to prevent such delayed strokes<sup>[45]</sup>.

The advances in carotid stent material and the new types of stents introduced in the market are beyond the scope of this review and are more extensively described elsewhere<sup>[46]</sup>.

## CONCLUSION

The battle for CAS is not lost<sup>[47]</sup>. The long-term results of the Carotid Revascularization Endarterectomy vs Stenting Trial did not show a significant difference in periprocedural stroke, MI or death and subsequent ipsilateral stroke between symptomatic and asymptomatic patients undergoing CAS or CEA<sup>[48]</sup>. Similarly, the Asymptomatic Carotid Trial demonstrated non-inferiority for CAS compared with CEA for asymptomatic patients with respect to the primary composite end-point of 30-d death, stroke or MI and ipsilateral stroke within 1 year<sup>[49]</sup>. New devices, membrane- and mesh-covered stents, alternative approaches and a combination of EPDs are tools in the armamentarium of CAS to improve its results. There is more to see in the future and we will all be awaiting the results of new trials incorporating the advances in CAS technology.

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## Empirical anticoagulation for patients in sinus rhythm at high risk of ischaemic stroke: A review of current literature

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### Abstract

Ischaemic stroke is one of the commonest causes of morbidity and mortality worldwide and around a fifth of events can be attributed to a cardioembolic source. This is typically due to atrial fibrillation (AF), the most common sustained cardiac arrhythmia. However, AF can, at times, be difficult to detect due to a relative lack of symptoms and the fact that it can be paroxysmal in nature. Studies have shown that diagnosis of AF improves as the length of cardiac monitoring increases. However, prolonged cardiac monitoring is not a cost-effective way of diagnosing AF. Therefore, an alternative approach may be to empirically anticoagulate individuals who are at high risk of stroke. This article summarises current evidence surrounding stroke risk prediction, the use of anticoagulation in the secondary prevention of stroke and its use in the primary prevention of stroke in high risk groups with the aim of determining whether empirical anticoagulation is a safe and effective strategy.

**Key words:** Anticoagulation; Ischaemic stroke; Atrial fibrillation; CHA<sub>2</sub>DS<sub>2</sub>-VASc; CHADS<sub>2</sub>; Heart failure; Coronary artery disease; Peripheral arterial disease

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**Core tip:** This is a contemporary review exploring issues related to the risk of stroke and use of anticoagulation in patients who are in sinus rhythm (SR). It examines the prediction of stroke in patients without known atrial fibrillation (AF), the identification of AF in patients following stroke and the use of anticoagulation in post-stroke patients seemingly in SR or those at high-risk of stroke. The main findings are: (1) prolonged cardiac monitoring increases the rate of AF diagnosis but is not cost-effective; (2) current risk stratification schemes such as CHA<sub>2</sub>DS<sub>2</sub>-VASc can identify those in sinus rhythm who are at risk of stroke; and (3) further research is required to determine whether individuals at high-risk of stroke would benefit from anticoagulation.

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## INTRODUCTION

Ischaemic stroke is a leading cause of morbidity and mortality worldwide<sup>[1]</sup> and, following a first event, around a quarter of patients will go on to have a recurrent stroke<sup>[2,3]</sup>. Atrial fibrillation (AF), a common cause of stroke, is the most common sustained cardiac arrhythmia with an estimated prevalence approximately 3% in adults aged 20 years or older<sup>[4]</sup>, a figure that is expected to double over the next 50 years<sup>[5]</sup>. This arrhythmia carries a five-fold risk of stroke and patients who experience an AF-related stroke often suffer the most severe forms of the condition<sup>[6]</sup>.

Risk scores such as CHADS-2 and, more recently, CHA<sub>2</sub>DS<sub>2</sub>VASc have been developed in order to identify those patients with AF and an increased risk of stroke who would potentially benefit from anticoagulation. However, these risk scores are currently used only in patients with a confirmed diagnosis of AF, a condition which is underdiagnosed due to the fact it can be asymptomatic and paroxysmal. Therefore, given that 45% of all AF-related strokes occur in patients with previously undetected AF<sup>[7]</sup>, many more patients could potentially benefit from empirical anticoagulation therapy and there may be a role for using these risk scores in patients without known AF but with risk factors for developing stroke.

In view of the fact that AF can be difficult to detect, a number of studies have attempted to determine whether it is appropriate to give empirical anticoagulation to patients in sinus rhythm (SR) with risk factors for stroke. This article aims to summarise these studies and determine whether there are clinically relevant scenarios where anticoagulating patients in SR may be appropriate to reduce their risk of stroke.

## LITERATURE SEARCH AND METHOD

A Medline and Embase search was performed in August 2016 using the following terms: CHADS-2, CHA<sub>2</sub>DS<sub>2</sub>VASc, anticoagulation, vitamin K antagonist, warfarin, Coumadin, novel oral anticoagulant, direct oral anticoagulant, apixaban, eliquis, dabigatran, pradaxa, rivaroxaban, xarelto, edoxaban, lixiana, sinus rhythm, non-atrial fibrillation, normal heart rhythm, "without atrial fibrillation", stroke, cerebrovascular accident, cerebrovascular event, transient ischaemic attack (TIA), mini-stroke, heart failure, cardiac failure, left ventricular failure, left ventricular impairment, left ventricular dysfunction, impaired ventricle, coronary artery disease,

coronary heart disease, myocardial ischaemia, myocardial infarction, acute coronary syndrome, peripheral arterial disease and peripheral vascular disease.

## STROKE RISK PREDICTION IN A GENERAL POPULATION WITHOUT AF

In patients without known AF, risk assessment tools currently focus on overall cardiovascular risk rather than determining their specific risk of stroke. However, could risk scores such as CHADS-2 and CHA<sub>2</sub>DS<sub>2</sub>VASc be used within this patient group to determine their cerebrovascular event risk?

An analysis of the Chin-Shan Community Cohort Study tested a number of risk stratification schemes which are currently used to predict thromboembolic risk in AF, including CHADS-2 and CHA<sub>2</sub>DS<sub>2</sub>VASc, in a Chinese population without known AF<sup>[8]</sup>. This showed a modest predictive value of these risk stratification schemes in predicting stroke in non-AF patients with a C-statistic value ranging from 0.658 to 0.728, values which were broadly similar to those seen in an exploratory analysis of patients with AF within the same community.

Similar results were found in a meta-analysis performed by Santos *et al* who examined the use of the CHADS-2 score at predicting cerebrovascular events<sup>[9]</sup>. They found that CHADS-2 was able to identify patients at risk of stroke, regardless of whether AF was present or not.

More recently, Saliba *et al*<sup>[10]</sup> assessed the performance of CHADS-2 and CHA<sub>2</sub>DS<sub>2</sub>VASc within a large Israeli population over a three year follow-up period. In individuals without AF, the C-statistic values were 0.718 and 0.714 for CHADS-2 and CHA<sub>2</sub>DS<sub>2</sub>VASc respectively and in individuals with AF, the C-statistic values were 0.606 and 0.610 respectively. The authors concluded that these risk tools had a relatively high performance at predicting thromboembolism in patients without AF.

In all of these studies, the results suggest that current risk stratification schemes used in AF patients to predict thromboembolism could also be used in patients without AF as a screening tool to predict their risk of stroke. It remains unclear, however, as to whether anticoagulating these patients is a superior strategy to giving antiplatelet therapy.

## SECONDARY PREVENTION OF ISCHAEMIC STROKE/TIA

Around a fifth of ischaemic strokes are cardioembolic in origin<sup>[11]</sup> and these patients typically receive oral anticoagulants to reduce their risk of future events. However, around a third of ischaemic strokes are termed cryptogenic<sup>[12]</sup>, or without an attributable cause despite extensive work-up. The majority of these cases are likely to have an embolic mechanism and a significant proportion are likely to be related to undiagnosed AF.

**Table 1** Randomised control trials which show an increased yield of atrial fibrillation detection with extended cardiac monitoring

Ref.	Design	No. of patients	Inclusion/exclusion criteria	Type of monitoring	Outcome	Comments
Higgins <i>et al</i> <sup>[14]</sup> (2013)	RCT	100	Inclusion: Ischaemic stroke within 7 d; Exclusion: History of AF	7-d event recorder <i>vs</i> 24-h ECG (control)	Detection of AF: Sustained (> 20 s) and non-sustained (minimum 6 beats)	Sustained AF detected in 18% (control 2%); Non-sustained AF in 44% (control 4%)
Gladstone <i>et al</i> <sup>[15]</sup> (2014)	RCT	572	Inclusion: Cryptogenic stroke, Age ≥ 55 yr; Exclusion: History of AF	30-d triggered event recorder <i>vs</i> 24-h ECG (control)	Detection of AF (> 30 s)	AF detected in 16.1% (control 3.2%)
Sanna <i>et al</i> <sup>[16]</sup> (2014)	RCT	441	Inclusion: Cryptogenic stroke, Age ≥ 40 yr; Exclusion: History of AF	Insertable cardiac monitor <i>vs</i> Standard care (control)	Detection of AF (> 30 s)	At 6 mo, AF detected in 8.9% (control 1.4%) At 12 mo, AF detected in 12.4% (control 2.0%)
Brachmann <i>et al</i> <sup>[17]</sup> (2016)			Exclusion: History of AF (including 24-h ECG)			At 36 mo, AF detected in 30% (control 3.0%)

AF: Atrial fibrillation; RCT: Randomized controlled trial.

Ziegler *et al*<sup>[13]</sup> analysed data from patients at risk of thromboembolism (stroke/TIA) who had implantable cardiac devices capable of recording atrial arrhythmias. They identified newly detected episodes of atrial fibrillation/tachycardia in 28% of patients over a 1-year follow-up period.

Multiple studies have shown that the yield of detecting AF increases as the length of ambulatory monitoring increases (Table 1)<sup>[14-17]</sup>. A systematic review and meta-analysis performed by Dussault *et al* assessed the relationship between the duration of ECG monitoring and the incidence of AF detection in patients who had suffered a cerebrovascular event, using data from 31 studies<sup>[18]</sup>. They found that extending monitoring from 24 h to 30 d improved AF detection from 4.38% to 15.2% and if this monitoring was extended out to 180 d, detection rates increased to 29.15%.

Studies have also shown that in patients with implantable electronic devices, asymptomatic episodes of AF can be associated with an increased risk of thromboembolic events<sup>[19-25]</sup>, with a hazard ratio ranging from 2.2 to 9.4<sup>[26]</sup>. The length of each episode that is required to increase overall stroke risk varies in these studies, from a minimum of 5 min in the Ancillary MOde Selection Trial<sup>[19]</sup> to a maximum of 24 h in the Italian AT500 Registry<sup>[20]</sup>. At present, the episode duration and burden of asymptomatic AF that best predict future thromboembolic events are still matters of debate and need to be addressed by future studies.

A more recent systematic review performed by the Canadian Agency for Drugs and Technologies in Health examined not only the clinical effectiveness of cardiac monitoring in patients who had recently experienced a stroke or TIA, but also the cost effectiveness<sup>[27]</sup>. They showed that there was a substantial increase in the detection of AF when monitoring was performed for more than 24 h. Monitoring beyond 30 d increased this detection further although these improvements were modest. From an economic point of view, they

concluded that in patients who were admitted with a cerebrovascular event and did not receive in-patient continuous cardiac monitoring, 7 d cardiac monitoring was likely to identify significantly more cases of AF compared with current 24 h monitoring, with an acceptable increase in cost [CAN\$ 50000-80000/QALY (£ 28000-46000/QALY) gained]. Cost-effectiveness could be improved further by targeting stroke survivors who were relatively healthy and in whom there was a higher suspicion of underlying AF. However, they also concluded that extending monitoring beyond 7 d was unlikely to be cost-effective [ > CAN\$ 85000/QALY (>£ 49000/QALY) gained].

Current guidance continues to recommend long-term cardiac monitoring in patients who have a stroke with an undiagnosed cause with the AHA/ACC/HRS specifying at least 30 d. In view of the fact that this may not be cost-effective, would it be more appropriate to use current risk stratification schemes to identify those patients who may be at risk of further cerebrovascular events?

A trial by Ntaios *et al*<sup>[28]</sup> examined whether CHADS<sub>2</sub> and CHA<sub>2</sub>DS<sub>2</sub>VASc scores could be used to predict long-term outcomes in non-AF stroke patients. They divided patients into low, intermediate or high risk sub-groups, dependent upon their pre-stroke CHADS<sub>2</sub> and CHA<sub>2</sub>DS<sub>2</sub>VASc score. In both the CHADS<sub>2</sub> and CHA<sub>2</sub>DS<sub>2</sub>VASc sub-groups, they found that there were significant differences in stroke recurrence, cardiovascular events and 5-year mortality. They also demonstrated that compared with the low-risk sub-group, patients in the high-risk sub-group had a higher risk of stroke recurrence [CHADS<sub>2</sub>, hazard ratio (HR): 1.71; CHA<sub>2</sub>DS<sub>2</sub>VASc, HR: 2.93]. These results suggest that current clinical risk scores can be used to predict future events in patients who have had a stroke or TIA.

To improve the accuracy of these risks scores in post-stroke patients further, modification of certain variables may be helpful. Thijs *et al*<sup>[29]</sup> assessed

patients who had suffered a cryptogenic stroke or TIA and had an insertable cardiac monitor to determine whether there were specific factors which could predict the development of AF in this population. Following multivariate analysis, they found that increasing age [HR per decade 1.9 (1.3-2.8),  $P = 0.0009$ ] and PR interval prolongation [HR per 10 ms: 1.3 (1.2-1.4),  $P < 0.0001$ ] were independently associated with an increased incidence of AF. Therefore, in non-AF stroke/TIA patients, the addition of PR interval duration and placing further emphasis on age may help improve the accuracy of current risk scores.

Nevertheless, despite the fact that CHADS-2 and CHA<sub>2</sub>DS<sub>2</sub>-VASc may help to predict future events in non-AF stroke/TIA patients, more evidence is required to determine whether those within an intermediate or high-risk group should be offered anticoagulation.

## PRIMARY PREVENTION OF ISCHAEMIC STROKE/TIA IN SPECIFIC GROUPS

### Heart failure

It has long been established that heart failure (HF) is associated with an increased risk of thromboembolism and in particular, stroke. A systematic review performed by Witt *et al* analysed stroke rates in heart failure patients and found the risk of stroke to be 1.8% in the first year of HF diagnosis, rising to 4.7% at 5 years<sup>[30]</sup>. Multiple studies have attempted to clarify whether HF patients in SR would benefit from anticoagulant therapy. Initial trials suffered from poor recruitment and underpowered results and so it is not surprising that they failed to demonstrate an overall benefit of anticoagulation in this population<sup>[31-33]</sup>. One of these studies, the Warfarin and Antiplatelet Therapy in Chronic Heart Failure (WATCH) trial, did however show a significant reduction in non-fatal ischaemic strokes in patients on warfarin compared with aspirin or clopidogrel ( $P < 0.01$ )<sup>[33]</sup>. This was at the expense of a higher rate of major bleeding events.

More recently, the Warfarin vs Aspirin in Reduced Cardiac Ejection Fraction (WARCEF) trial compared warfarin and aspirin in patients with HF in SR, using the primary endpoints of ischaemic stroke, intracerebral haemorrhage or death from any cause<sup>[34]</sup>. Although there was no overall difference in the combined primary endpoints between the two treatments ( $P = 0.4$ ), warfarin was associated with a significant reduction in the rate of ischaemic stroke (2.5% vs 4.7%,  $P = 0.005$ ) without a significant difference in the rate of intracerebral or intracranial haemorrhage ( $P = 0.82$ ). Once again, the rate of major bleeding was higher (warfarin 5.8% vs aspirin 2.7%,  $P < 0.001$ ).

One limitation of the WARCEF study was the time in therapeutic range (TTR) among patients in the warfarin group which was relatively low at 63% (high-quality warfarin treatment is defined as a TTR > 70%<sup>[35]</sup>). Low TTRs are strongly associated with adverse outcomes

such as major haemorrhage and thromboembolic events<sup>[35]</sup>. The higher bleeding risk with warfarin may, in part, be related to this low TTR. One solution to this could be use of direct oral anticoagulants (DOACs) which, in the absence of compliance issues, provide a much more consistent level of therapeutic anticoagulation. DOACs have already been shown to be non-inferior, and in some cases, superior to warfarin with respect to stroke and major bleeding risk reduction<sup>[36-39]</sup>. Further research exploring the use of DOACs in HF patients is needed to determine whether they can reduce thromboembolic risk without significantly increasing bleeding risk.

In terms of estimating stroke risk within HF patients without AF, current clinical risk scores have been assessed. A recent prospective cohort study investigated whether CHA<sub>2</sub>DS<sub>2</sub>-VASc could be used to predict the risk of ischaemic stroke in HF patients without AF<sup>[40]</sup>. It performed moderately at predicting ischaemic stroke at 1- and 5-year follow-up (C-statistics 0.67 and 0.69 respectively) and performed well at identifying those at low risk of ischaemic stroke with a negative predictive value of 92%. Additionally, the authors found that those with a CHA<sub>2</sub>DS<sub>2</sub>-VASc score of  $\geq 2$  had a stroke risk of > 1% per year. To put this into context, patients with AF are typically offered anticoagulation once their annual stroke risk exceeds 1%. This would suggest that the CHA<sub>2</sub>DS<sub>2</sub>-VASc score may have a use in identifying those HF patients without AF who are at risk of stroke. Whether these patients would gain benefit from anticoagulation remains to be seen and clinical trials are needed to clarify this.

### Coronary artery disease

Coronary artery disease (CAD) has been identified as an independent risk factor for stroke<sup>[41]</sup> and co-existent vascular disease, such as coronary or peripheral artery disease, is present in around 40% of stroke patients<sup>[42]</sup>. Studies have previously examined the addition of warfarin to antiplatelet therapy in patients with acute coronary syndrome (ACS). These were performed in an era before the widespread use of dual antiplatelet therapy. A meta-analysis of the studies found that the addition of warfarin led to reduction in major adverse cardiovascular events {MACE: death, non-fatal MI, non-fatal ischaemic stroke; [OR = 0.73 (0.63-0.84),  $P < 0.0001$ ]} but this was at the expense of an increased risk of major bleeding [OR 2.32 (1.63-3.29),  $P < 0.00001$ ]<sup>[43]</sup>. As a result, anticoagulation is not routinely given to patients following ACS. However, a proportion of these patients will be at significant risk of thromboembolic events and if a clinical risk score could accurately identify this sub-group, they might well benefit from anticoagulation.

A prospective registry study by Mitchell *et al*<sup>[44]</sup> assessed the accuracy of CHADS-2 and CHA<sub>2</sub>DS<sub>2</sub>-VASc at predicting cerebrovascular events in non-AF patients who had suffered an ACS. They found that the incidence of stroke increased with increases in each risk score and

that a CHADS-2 score  $\geq 3$  or a CHA<sub>2</sub>DS<sub>2</sub>VASc score  $\geq 4$  was associated with an annual stroke incidence of  $\geq 1\%$ . Both CHADS-2 and CHA<sub>2</sub>DS<sub>2</sub>VASc performed moderately at predicting ischaemic stroke [C-Statistics (0.68 and 0.71 respectively)].

Similar results were found in a prospective cohort study which assessed the accuracy of CHADS-2 at predicting cerebrovascular events in non-AF patients who had stable CAD<sup>[45]</sup>. Those with a CHADS-2 score of 2-3 had a 2.7 times higher rate of stroke and those with a CHADS-2 score of 4-6 had a 4.6 times higher rate of stroke. They concluded that stable CAD patients with a CHADS-2 score of 5-6 had a comparable stroke rate to AF patients with a CHADS-2 score of 2-3, the level at which anticoagulation is felt to be beneficial.

In both of these studies, cerebrovascular events occurred despite antiplatelet therapy. They indicate that in patients with CAD, high CHADS-2 or CHA<sub>2</sub>DS<sub>2</sub>VASc scores can predict those at risk of stroke or TIA. These patients may therefore benefit from the addition of anticoagulation and further studies are required to clarify this.

### Peripheral arterial disease

The presence of peripheral arterial disease (PAD) is a significant predictor of stroke and in one study was found to be present in 14.4% of major ischaemic strokes and 8.9% of minor ischaemic strokes<sup>[46]</sup>. Warfarin has also been evaluated for the use in this patient group. A meta-analysis which assessed the use of anticoagulation in PAD patients provided inconclusive results<sup>[47]</sup> and led to the development of the Warfarin Antiplatelet Vascular Evaluation (WAVE) Trial<sup>[48]</sup>. This compared oral anticoagulation plus antiplatelet therapy vs antiplatelet therapy alone. They found no significant difference in MACE events (relative risk: 0.92; 95%CI: 0.73-1.16;  $P = 0.48$ ). However, those receiving combination therapy had a significantly higher rate of major bleeding rate (4.0%), compared with in those receiving antiplatelet monotherapy (1.2%). There is some evidence that patients undergoing vein graft bypass surgery gain benefit from warfarin monotherapy<sup>[49]</sup> and this is the only sub-group of PAD patients in which anticoagulation is currently indicated.

To date, there is only one trial which has examined the use of clinical risk scores to predict thromboembolic events in patients with PAD. Yang *et al*<sup>[50]</sup> assessed the accuracy of CHADS-2 and CHA<sub>2</sub>DS<sub>2</sub>VASc in predicting 5-year cumulative ischaemic stroke risk in PAD patients. They found that each increase in the risk scores led to an increased stroke risk, and both scores performed well at predicting 5-year cerebrovascular events (C-statistics 0.92 for CHADS-2, 0.862 for CHA<sub>2</sub>DS<sub>2</sub>VASc). In multivariate analysis, each increment of the CHADS-2 or CHA<sub>2</sub>DS<sub>2</sub>VASc score was associated with around a three-fold increase in stroke risk.

As with CAD, current risk scores appear to be able to identify those PAD patients who are at high-risk of cerebrovascular events and this sub-group may also

benefit from anticoagulation therapy. More clinical evidence is required to confirm this.

## CONCLUSION

Cerebrovascular disease remains one of the leading causes of death throughout the world. Those that survive are commonly left with serious long-term disability and are at an increased risk of recurrent events. AF is a common cause of stroke/TIA but because the arrhythmia can be paroxysmal and asymptomatic, it remains a challenge to detect. Long-term ambulatory monitoring has not been shown to be a cost-effective way of diagnosing the arrhythmia. Additionally, the duration of AF which represents an increased risk of thromboembolism is still to be determined.

An alternative strategy is to use current risk stratification schemes such as CHADS-2 or CHA<sub>2</sub>DS<sub>2</sub>VASc. There is evidence to suggest that these scores can identify those at significant risk of thromboembolic events, not only in the general population but more specifically in those that have suffered a cerebrovascular event or have co-existent HF, CAD or PAD.

At present, it remains unclear as to the most appropriate way of treating these high-risk patients once they have been identified. With the dawn of DOACs, which can provide a more steady-state of anticoagulation and potentially have a better bleeding profile, there are now therapeutic options which may benefit high-risk groups. Future trials should use risk scores to identify high-risk groups in a variety of clinical settings to determine whether anticoagulation therapy can reduce the burden of cerebrovascular disease.

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## Antitachycardia pacing programming in implantable cardioverter defibrillator: A systematic review

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### Abstract

Implantable cardioverter defibrillator (ICD) programming

involves several parameters. In recent years antitachycardia pacing (ATP) has gained an increasing importance in the treatment of ventricular arrhythmias, whether slow or fast. It reduces the number of unnecessary and inappropriate shocks and improves both patient's quality of life and device longevity. There is no clear indication regarding the type of ATP to be used, except for the treatment of fast ventricular tachycardias (188 bpm-250 bpm) where it has been shown a greater efficacy and safety of burst compared to ramp; 8 impulses in each sequence of ATP appears to be the best programming option in this setting. Beyond ATP use, excellent clinical results were obtained with programming standardization following these principles: extended detection time in ventricular fibrillation (VF) zone; supraventricular discrimination criteria up to 200 bpm; first shock in VF zone at the maximum energy in order to reduce the risk of multiple shocks. The MADIT-RIT trial and some observational registries have also recently demonstrated that programming with a widespread use of ATP, higher cut-off rates or delayed intervention reduces the number of inappropriate and unnecessary therapies and improves the survival of patients during mid-term follow-up.

**Key words:** Implantable cardioverter defibrillator programming; Antitachycardia pacing; Ventricular tachycardia; Electrical antitachycardia therapy

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**Core tip:** Antitachycardia pacing (ATP) has a great importance in the treatment of ventricular arrhythmias, whether slow or fast. It reduces the number of unnecessary shocks and it improves both patient's quality of life and device longevity. Beyond ATP use, excellent clinical results were obtained with programming standardization following these principles: Extended detection in ventricular fibrillation (VF) zone; supraventricular discrimination criteria up to 200 bpm; first shock in VF zone at the maximum energy in order to reduce the risk of

multiple shocks. The MADIT-RIT trial and some registries have also recently demonstrated that programming with a widespread use of ATP, higher cut-off rates or delayed intervention reduces the number of inappropriate therapies and improves the survival of patients during medium term follow-up.

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## INTRODUCTION

The efficacy of implantable cardioverter-defibrillator (ICD) in reducing sudden death and total mortality is well documented<sup>[1]</sup>, initially in secondary prevention<sup>[2-4]</sup>, more recently also in primary prevention<sup>[5,6]</sup>. In particular, two big trials, MADIT II<sup>[5]</sup> and SCD-HeFT<sup>[6]</sup>, helped to define high risk patients after a myocardial infarction (MI) or with heart failure (HF) associated with reduced left ventricle ejection fraction.

These studies showed that the overall survival rate was higher in patients with ICD compared with those who received conventional medical therapy<sup>[5,6]</sup>.

In the last decade, ICD implants have grown exponentially<sup>[7]</sup>, leading manufacturers to heavily invest in this field to improve therapies and develop sophisticated algorithms with high sensitivity and specificity for arrhythmias discrimination. Once detected, the ICD can treat ventricular arrhythmias with high-energy shocks or antitachycardia pacing (ATP).

Although ICDs are usually well accepted by most patients, there are several clinical reports of anxiety and depression after implantation<sup>[8,9]</sup>. Quality of life can, in fact, be negatively influenced when receiving painful shocks, especially if multiple<sup>[10]</sup>. The main benefit of ATP therapy, from the patient's point of view, is to avoid painful shocks; actually, ATP is rarely noticed by patients and therefore well tolerated. Moreover, battery life of the device is extended if the high-energy shock therapy is avoided. Even more important, it has also been demonstrated that shock therapy is associated with a higher risk of mortality compared to ATP sequences only<sup>[11]</sup>.

With the increase in ICD indications, the choice of an optimal device programming, both for discrimination and therapy, is becoming increasingly important. A critical analysis of the most important clinical studies in this field is crucial in order to achieve an effective and safe therapy that improves patient's outcome without adversely affecting quality of life.

## WHAT IS ATP?

ATP consists of one or more trains of pacing stimuli

(usually 8 impulses for each train) conventionally expressed as a percentage of the tachycardia cycle length for a given RR interval, from the onset of the preceding R wave. Pace stimulation delivered at very short coupling intervals (*i.e.*, < 84%) is more likely to enter a reentrant circuit but also accelerate the arrhythmia. Unlike shock therapy, the locations of the ICD generator and shocking coils do not affect ATP efficacy. ATP is usually delivered from the right ventricular apex (RVA), but efficacy is similar also when pacing from outflow tract. ATP from RVA is less effective in terminating ventricular tachycardia (VT) with a basal exit site<sup>[1]</sup>.

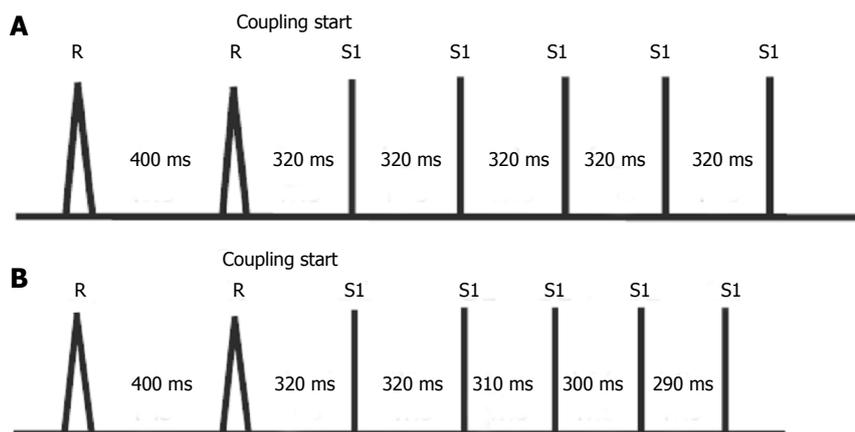
The rationale for ATP efficacy relies on the fact that monomorphic VT can be interrupted with appropriately timed pacing stimuli delivered into the excitable gap of a reentrant circuit. The chance of arrhythmia interruption depends on several factors: The conduction time from pacing stimulus site to the reentrant circuit; the duration of the excitable gap; the presence of anatomic/functional barriers; the state of the sympathetic nervous system. For example, beta-blockers drugs increase the duration of excitable gap, thus increasing ATP efficacy<sup>[10]</sup>.

VT with spontaneous RR interval variability are more likely to be ATP responsive, while those with greater variation in QRS morphology are less responsive. This is the reason why polymorphic VT and ventricular fibrillation (VF), usually lacking an organized reentry, are rarely interrupted by pacing.

ICDs allow delivering different ATP therapy types, in particular the two most important are: (1) burst with impulse trains at constant coupling in a programmable number; and (2) ramp with autodecremental coupling (Figure 1).

## WHEN SHOULD WE PROGRAM ATP?

Schaumann *et al.*<sup>[12]</sup>, in 1998, evaluated whether ATP could be safely used even in those patients in whom ATP testing on induced VT was not performed. All devices were programmed with the same ATP scheme in the VT zone (< 200 bpm): 3 ramps from 8 to 10 impulses, with 8 ms decrease and 81% coupling. The study enrolled 200 patients divided in two groups: The first included subjects in whom efficacy of ATP was demonstrated on sustained VT induced in the electrophysiology laboratory (Tested group); in the second group ATP was programmed empirically (Empirical group). During the follow-up period (20 ± 11 mo) ATP therapy proved to be highly effective in both groups. In particular, success rate was 95% in the T group and 90% of the E group. Moreover, this study provided a strong response to one of the most frequent criticisms to pacing therapy, the risk of tachycardia acceleration. Acceleration after ATP occurred only in 2% in group T and 5% in group E. The conclusions of the study were, therefore, that the success rate of ATP therapy was not dependent on efficacy testing and ATP was recommended for VT



**Figure 1** Examples of antitachycardia pacing patterns. A: Burst with 5 impulses and coupling at 80%; B: Ramp with 5 impulses, coupling at 80% and with a 10 ms decrease.

treatment in any patient with ICD.

During the 90s other studies were published about the efficacy and the safety of the ATP therapy. These studies reported that ATP sequences successfully interrupted 78%-94% of slow VT (< 188 bpm), with an acceleration rate between 2% and 4%<sup>[13-15]</sup>. Based on these results the ATP was conventionally programmed only for slower VT, presumably hemodynamically well tolerated.

Fast VTs (from 188 to 250 bpm) were, instead, still treated like VF, with high energy shocks. Faster VTs have a shorter excitable gap that is more difficult to be penetrated and interrupted by a pacing stimulus.

Nevertheless, in 2001, Wathen *et al.*<sup>[16]</sup> with the PainFREE Rx I trial showed, for the first time, that ATP therapy was also effective for fast VT (FVT). This trial, however, had many limitations: Only patients with coronary artery disease were included; it was nonrandomized; ICDs were programmed with a short detection interval (12 of 16 beats), which could imply that many treated arrhythmias were non-sustained VTs, destined to run out on their own.

In 2004, the same authors published a prospective, single-blinded trial, the PainFREE Rx II<sup>[17]</sup>, which exceeded the limits of the first study. This trial enrolled 637 ICD patients randomized to ATP ( $n = 315$ ) or shock therapy ( $n = 322$ ) to evaluate episode duration between the two arms (primary endpoint). Baseline clinical variables were similar between the 2 groups, in particular age (average, 67 years), ejection fraction (average, 32%), sex (male 77%), coronary artery disease (85%), syncope (35%). Both groups received similar pharmacological therapies. Primary prevention indication for ICD involved 44% of patients. Fast VT was defined as a zone between 240 and 320 ms (188-250 bpm); faster rates were considered as VF. In the first group the initial therapy in the FVT zone was ATP (8 impulses burst at 88% of arrhythmia cycle length), while in the second group shock was directly delivered at the defibrillation threshold (DFT) + 10 J. The detection for FVT, as well as for VF, was 18 of 24 beats. The

first important result was that the FVTs represented 76% of all ventricular arrhythmias. In the ATP group the bursts resulted effective in 77% of the FVTs; when it failed, shocks were effectively delivered to interrupt the arrhythmia. There was no significant difference between percentage (and number) of patients who had fast VT in either the ATP or shock arms (15% vs 16% respectively). In addition, after accounting for 2 patients in the ATP arm who together had 131 episodes, numbers of fast VT in the ATP and shock arms were similar (151 vs 144, respectively). Moreover, there was no significant difference in episode duration between the shock and ATP arms (10 s vs 9.7 s, respectively). Not all patients with fast VT episodes received shock therapy in the shock arm (only 67% of episodes being shocked) and 30% of fast VT episodes self-terminated after detection. In comparison, only 20% of patients in the ATP arm received shocks. The acceleration was rare, with 2% incidence in the ATP arm and 1% the shock arm. Syncopal events were also low and comparable between the two groups. It is interesting to note that the success rate of the first shock (92%) was identical in both groups, even if delivered after an ineffective ATP. In conclusion, this study showed that ATP therapy was safe and effective compared to shocks also for the treatment of FVT, with a 70% relative reduction of shocks in the ATP group.

After these studies, scientific community started to consider ICDs as stimulation devices with a defibrillation backup, only as a security option, with a consequent improvement in patient's quality of life. It is noteworthy that these trials used bursts coupled to 88% of arrhythmia cycle: This was a "little aggressive" therapy, so the risk of arrhythmias acceleration was low<sup>[18]</sup>.

In order to avoid significant delays in the delivery of shock therapy (in case of ATP failure) algorithms of ATP sequences during or before capacitor charging were soon implemented in the VF zone for most manufacturers; this strategy has been subsequently clinically validated as safe and effective<sup>[11]</sup>.

## WHICH PATTERN OF ATP SHOULD BE PREFERRED?

The importance of the ATP therapy in the context of ICD programming is well documented, but we should understand if there is a specific pacing pattern to prefer, especially in relation to the type of ventricular arrhythmia.

Several studies comparing the efficacy of two different types of ATP pattern (burst and ramp) on induced VTs did not show significant differences in the percentage of success: Gills *et al.*<sup>[19]</sup> reported 76% efficacy for burst and 68% for ramp in a study with 21 patients enrolled; Calkins *et al.*<sup>[20]</sup> reported a success rate of 70% for burst and 72% for ramp (44 patients); Kantoch *et al.*<sup>[21]</sup> reported a 69% success for burst and 72% for ramp in 31 patients. The rate of acceleration was low and did not change significantly between the two patterns.

Burst vs Ramp were evaluated also in the setting of spontaneous VTs: Gills *et al.*<sup>[19]</sup> found, in this case, a success rate of 96% for burst and 93% for ramp; Ardashev *et al.*<sup>[22]</sup> reported 61% efficacy for burst and 76% for ramp with 54 patients enrolled. The latter study, therefore, was the only indicating a significant difference in efficacy between the two techniques ( $P < 0.01$ ), in favor of the ramp.

Overall, from the analysis of several studies, there was not a clear difference in the efficacy of burst and ramp for treatment of non-FVT, in ischemic and non-ischemic cardiomyopathies. The choice of the pattern was, therefore, left to the clinician's experience and to an empirical case-by-case approach<sup>[18]</sup>. An important exception is represented by patients with arrhythmogenic right ventricular dysplasia: The success rate of ramp fell down to 25%, with an acceleration rate of 24%, while the burst resulted in a better outcome<sup>[22]</sup>.

Different considerations have to be made for FVT in which burst seems to be better. The PITAGORA ICD<sup>[23]</sup> trial was a randomized Italian study that aimed to compare two ATP strategies (burst and ramp) in terms of efficacy, arrhythmia acceleration and syncope on FVT episodes. Two hundred and six patients were randomized into two groups, with two different therapies: 88% coupling-8 impulses burst vs 91% coupling-8 impulses ramp with 10 ms decrement. The FVT zone was programmed between 188 and 250 bpm, with a detection of 18 of 24 beats. The study demonstrated that burst was significantly more effective than ramp (75% vs 54%;  $P = 0.015$ ) to interrupt FVT episodes. Regarding safety, burst was associated with a lower percentage of acceleration compared to ramp (2% vs 7%), although this difference was not statistically significant. The overall incidence of syncope was 1%. The adopted strategy, with ATP as the first therapy and prolonged detections (18 of 24 compared to 12 of 16), allowed the end of the arrhythmic episode before shock delivery in 81% of the cases<sup>[23]</sup>.

In 2010, the results of the trial ADVANCED-D<sup>[24]</sup> were

published. This study aimed to compare 8 impulses burst with 15 impulses burst on FVT. Nine hundred and twenty-five patients were enrolled and randomized into two groups treated with the two different sequences of ATP. The window of FVT remained between 188 and 250 bpm and detection 18 of 24 beats. No significant difference was detected between the two sequences, 8 pulses burst terminated 64% of episodes compared to 70% of 15 pulses burst. Moreover, there were not significant differences also regarding syncope or rate of acceleration. The sequence of 15 pulses was more effective only in patients with no history of HF ( $P = 0.014$ ) and with left ventricular ejection fraction  $> 40\%$  ( $P = 0.016$ ). The conclusion of the study was that an ATP sequence of 15 pulses can be considered effective, but also safe, in FVT comparable with a sequence of 8 pulses.

## ATP IN BIVENTRICULAR ICD

Thanks to the coronary sinus lead which stimulates the left ventricle, cardiac resynchronization therapy devices equipped with a cardioverter defibrillator (CRTD) offer the potential for alternative sites for ATP. The possibility to deliver therapy from either the left ventricular lead (LV-ATP) or the left and the right ones simultaneously (BiV-ATP) may theoretically increase the rate of success compared to right ventricular stimulation (RV-ATP). Several studies reported an increased efficacy of BiV-ATP configuration compared to the RV-ATP for termination of VT events both slow and fast<sup>[25]</sup>. However, the ADVANCED CRT-D<sup>[26]</sup> trial demonstrated a significant superiority of BiV-ATP only in ischemic patients with FVTs. Moreover, few papers compared LV-ATP with the other configurations. In this context, a study by Haghjoo *et al.*<sup>[27]</sup> compared efficacy and safety of the three ATP therapy sites (RV, LV and BiV) for VT treatment in patients with a CRTD device. The study enrolled 89 patients (with ischemic and non-ischemic etiologies) divided into 3 groups with 3 different pacing sites during ATP. The mean follow-up was 38 mo with 259 detected VT episodes in 46 patients. The results showed: (1) greater efficacy of BiV-ATP compared to both LV-ATP and RV-ATP for the treatment of FVT (188-250 bpm); (2) higher success rate and lower acceleration rate of both LV-ATP and BiV-ATP compared to RV-ATP for slower VTs ( $< 188$  bpm)<sup>[27]</sup>. Therefore, left ventricular lead allows further possibilities to increase the success of ATP; in patients with CRTD it is recommended to set either biventricular or left ventricular ATP therapy for the slowest therapy zone ( $< 188$  bpm), while biventricular ATP should be programmed for faster arrhythmias.

## THE STANDARDIZATION OF THE ICD PROGRAMMING

The therapeutic programming of an ICD involves several

parameters. It is worthwhile to understand if a strategic standardized choice can be as effective and safe as a patient-tailored programming, which is inevitably time-consuming for the physician. Indeed, the customization of the ICD setting is useful only if it provides improvements in clinical outcomes or in patient's quality of life; otherwise both the simplification and the standardization of the therapy can be convenient and minimize the risk of random errors.

In this framework, EMPIRIC trial<sup>[10]</sup> randomized 900 patients with ICDs (48% implanted for primary prevention, 52% for secondary prevention) to a standardized (EMPIRIC group) or a physician-tailored (TAILORED group) VT/VF programming and followed them for 1 year. The EMPIRIC programming (Table 1) was created by taking into account some key strategies to safely reduce the number of shocks for VT/VF and supraventricular tachycardias (SVTs) and to avoid untreated slow VT: (1) three attempts of ATP for VT < 200 bpm. In particular, 2 burst of 8 intervals coupled at 88% with 20 ms decrement and 1 ramp of 8 intervals coupled at the 81% with 10 ms decrement; (2) a sequence of ATP for FVT between 200 bpm and 250 bpm. In particular, 1 burst of 8 intervals coupled at the 88% (as in the PainFREE Rx II); (3) long detection time (18 out of 24) in VF and FVT (as in the PainFREE Rx II, PITAGORA ICD e ADVANCED-D trials); (4) first shock at the maximum energy in VF and FVT zones to reduce the risk of multiple shocks; and (5) discrimination criteria for SVT in the VF zone.

The results of the study reported no significant differences in the number of deaths, syncope events and arrhythmias acceleration between the two groups of patients. Moreover, the rate of hospitalization was significantly lower ( $P = 0.001$ ) in the EMPIRIC group<sup>[10]</sup>. The overall ATP efficacy was 92%; consequently, a significant reduction of VT shocks was reported in the EMPIRIC group compared to the TAILORED group ( $P < 0.001$ ). It is interesting to observe that the EMPIRIC group had a threshold for the VT zone of 150 bpm, value which is lower than the average in the TAILORED group (171 bpm). Nevertheless, the study did not show an increase of the SVTs inappropriately treated, thanks to the discrimination algorithms. To conclude, EMPIRIC study entails that a simplified and standardized programming is possible, without reducing efficacy and safety of the therapy.

The PREPARE study<sup>[1]</sup> analyzed a different standardized setting with the aim of reducing shocks occurrence, syncopes and untreated symptomatic VT in patients with ICDs for primary prevention<sup>[28]</sup>. The PREPARE programming was developed on the basis of some key strategies: (1) to detect only fast tachycardias (> 182 bpm); (2) to discriminate only sustained tachycardias (discrimination set to 30 of 40 in the FVT and FV zones); (3) to deliver ATP as the first therapy for FVT; (4) to always deliver the high-energy shock (at least 30 J); and (5) to use discrimination criteria for SVT up to 200 bpm.

The PREPARE programming (Table 2) provided a lower mortality ( $P = 0.01$ ) compared to a control cohort of patients from the EMPIRIC<sup>[10]</sup> the MIRACLE ICD (Multicenter InSync Implantable Cardioverter Defibrillators Trial) studies. The extension of the detection duration (30 out of 40 beats), fast rate cutoffs for the therapy (182 bpm), the use of SVT discrimination criteria reduced the number of shocked episodes. Moreover, at 12 mo follow up the incidence of syncopal events was 1.6% and mortality 4.9%. This study demonstrated how a strategically chosen tachycardia detection and conservative therapy options, can make the device more acceptable by the patient without negatively affecting its efficacy and safety.

In 2012 a large randomized multicenter study, Multicenter Automatic Defibrillator Implantation Trial-Reduce Inappropriate Therapy (MADIT-RIT)<sup>[29]</sup>, was published in the New England Journal of Medicine. The aim of this study was to test two ICD programming strategies in patients with an ICD implanted for primary prevention. In particular, the first strategy was characterized by therapies only for high heart rates (> 200 bpm) while the second was to increase of the detection delay duration before the initiation of therapies, with values variable in relation to the heart rate (60 s delay for rates between 170 bpm and 199 bpm, 12 s delay for rates between 200 bpm and 249 bpm, 2.5 s delays for higher rates). As explained by the authors, the MADIT-RIT study was based on the hypothesis that these two strategies would have reduced the number of patients receiving appropriate and inappropriate shocks and ATPs, compared to a conventional programming, without increasing mortality and morbidity. The study involved 98 centers in the United States, Canada, Europe, Israel and Japan, enrolling a total of 1500 patients with either ischemic or non-ischemic heart disease and indicated for implantation of an ICD or a CRTD in primary prevention. Patients with atrial fibrillation were excluded. The first episode of inappropriate therapy represented the primary endpoint of the study: This outcome was evaluated by comparing each treatment group with the control group. The rates of both syncope and mortality (for any cause) were secondary endpoints. A significant reduction in the risk of any inappropriate therapy was observed in the two groups with "unconventional" programming in a follow-up of 1.4 years: The results showed a 79% relative risk reduction for patients with "High-Rate Therapy" and a 76% risk reduction for those with "Delayed Therapy" (HR of "High-Rate therapy" vs conventional therapy: 0.21, 95%CI,  $P < 0.001$ ; HR of "Delayed Therapy" vs conventional therapy: 0.24, 95%CI,  $P < 0.001$ ). Another significant result of the MADIT-RIT regarded one of the secondary endpoints of the study. The "High-Rate Therapy" programming reduced the risk of death from any cause (HR = 0.45,  $P = 0.01$ ) by a factor of 55% compared to conventional therapy. The group with "Delayed Therapy" showed a 44% reduction of the mortality risk, but it did not reach statistical significance compared to the conventional therapy group (HR = 0.56,

**Table 1** EMPRIC programming

Detection	Threshold (bpm)	Beats to detect	Therapies
VF	250	18 out of 24	30 J × 6
FVT	200	18 out of 24	1 × burst, 30 J × 5
VT	150	16	2 × burst, 1 × ramp, 30 J × 3

Burst: 8 impulses coupled at the 88% with 20 ms decrement; Ramp: 8 intervals coupled at the 81% with 10 ms decrement. VF: Ventricular fibrillation; FVT: Fast ventricular tachycardia; VT: Ventricular tachycardia.

$P = 0.06$ ). Concerning syncopal episodes, no difference among the three groups was observed.

Recently, the OBSERVational registry on long-term outcome of ICD patients<sup>[30]</sup> confirmed, in a “real world setting”, the results of MADIT-RIT trial. OBSERVO-ICD was a multicenter, retrospective, registry enrolling (from 2010 to 2012) all consecutive patients undergoing ICD implantation in 5 Italian centers. The aim of the study was to test whether a too aggressive ICD programming could be associated with electrical storms (ES). A total of 1319 patients were enrolled, both primary and secondary prevention. During follow up (median 39 mo) 4.7% of patients experienced at least 1 ES episode. Patients with ES presented with significantly lower VF detection zone ( $P = 0.002$ ), more frequently had ATP therapies during capacitor charging programmed off ( $P = 0.001$ ), and less frequently had delayed therapies for VT zone ( $P = 0.042$ ) and VF zone ( $P = 0.036$ ). Patients with ES had a significantly higher incidence of death and HF-related death compared to patients with no VTs and patients with unclustered VTs/VFs ( $P = 0.025$  and  $P = 0.001$ , respectively). In conclusion, patients with less aggressive ICD programming (higher VF detection rates, higher detection times, ATP therapies during capacitor charging turned on) had a decreased likelihood of ES and lower risk of death.

## CONCLUSIONS AND “TAKE HOME MESSAGES”

ATP is a safe, effective and painless therapy for VTs with large clinical evidence supporting its routine use in primary and secondary ICD patients<sup>[31,32]</sup>.

ATP therapy is effective in interrupting VTs, both slow and fast, with a consequent reduction of unnecessary shocks and an improvement of clinical outcome, patients’ quality of life and device longevity<sup>[12,16,17,31]</sup>.

In a recent expert consensus document on ICD programming, from the most important world leading arrhythmological societies<sup>[32]</sup>, it was stated that “in all patients with structural heart disease... that ATP therapy be active for all ventricular tachyarrhythmia detection zones to include arrhythmias up to 230 bpm, to reduce total shocks except when ATP is documented to be ineffective or proarrhythmic”.

In patient with inherited cardiac channelopathies

**Table 2** PREPARE programming

Detection	Threshold (bpm)	Beats to detect	Therapies
VF	250	18 out of 24	30 J/35 J × 6
FVT	182	18 out of 24	1 × Burst, 30 J/35 J × 6
VT	167	32	Off

Burst: 8 impulses coupled at the 88%. VF: Ventricular fibrillation; FVT: Fast ventricular tachycardia; VT: Ventricular tachycardia.

(Brugada syndrome, Long and Short QT syndrome, catecholaminergic polymorphic VT, early repolarization syndromes) the index clinical arrhythmia is polymorphic VT or VF: These arrhythmias usually lack an organized reentry and are rarely interrupted by pacing, so ATP should not be routinely programmed<sup>[31,32]</sup>.

As concerns the type of ATP to be used, clear conclusions cannot be drawn, except for the treatment of fast TV (188 bpm–250 bpm) for which greater efficacy and safety of burst was showed compared to ramp<sup>[23,31,32]</sup>. So, as a first choice, it is indicated to program burst in preference to ramp. Ramp should be reserved for patients in whom burst fails and ramp is proven to be effective. A “little aggressive” burst programming (several studies used impulses coupled at the 88%) seems to be related to lower rates of arrhythmia acceleration<sup>[18]</sup>. Moreover, the optimal number of impulses in each sequence of ATP has been proved to be minimum 8<sup>[24,32]</sup>.

In patients with biventricular devices the lead placed in the coronary sinus offers further opportunities for a successful ATP therapy, due to biventricular pacing (ATP-BiV) or left ventricular only pacing (LV-ATP)<sup>[25-27]</sup>.

In the last years, a great effort has been devoted to standardize the ICD programming, particularly in the primary prevention. Two studies provided excellent results in this field: EMPERIC<sup>[10]</sup> and PREPARE<sup>[1]</sup>. The fundamental principles of these programming strategies were: (1) prolonged detection for the VF zone (18 out of 24 and 30 out of 40); (2) delayed detection time in any window; (3) SVT discrimination criteria up to 200 bpm; (4) ATP as first therapy for FVT; and (5) first shock at maximum energy in the VF zone to reduce the risk of multiple shocks.

The MADIT-RIT<sup>[29]</sup> trial and the OBSERVO-ICD registry<sup>[30]</sup> have recently confirmed this programming philosophy, showing that higher cut-off rates, more prolonged detections and ATP during capacitor charging reduce the number of inappropriate and unnecessary therapies compared to a more “conventional” programming. This reduction translates in a better clinical outcome in terms of morbidity and even mortality. The results of these studies add new chapters in the development of the ICD therapy, especially in primary prevention patients.

More studies are needed, instead, in a secondary prevention setting to design effective ATP strategies. Secondary prevention patients can represent an

opportunity to a more “tailored” approach compared to primary prevention, on the basis of the knowledge of arrhythmia history (ECG morphology, cycle length, arrhythmia mechanism, patient’s tolerance, hemodynamic impact)<sup>[31]</sup>. In patients with prior known VTs the device must be programmed to cover all clinical arrhythmias; slower monomorphic and better tolerated VTs should be treated with at least 2-3 sequences of ATP and at least 8 impulses. A second burst of ATP increases efficacy from 64% to 83% in FVT range, although programming > 2 bursts usually does not add further benefit<sup>[31,32]</sup>.

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## Retrospective Cohort Study

# Clinical characteristics and outcomes of octogenarians presenting with ST elevation myocardial infarction in the Australian population

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## Abstract

### AIM

To investigate the characteristics and outcomes of octogenarians who presented with ST-elevation myocardial infarction (STEMI) compared to non-octogenarians and to investigate the outcomes of octogenarians that received primary percutaneous coronary intervention (PCI) compared to those managed conservatively.

### METHODS

We performed a single center retrospective case controlled study. All octogenarians who presented with STEMI to a tertiary referring hospital between 2007 and 2012 were included. The subsequent non-octogenarian patient who presented with a STEMI following the octogenarian patient was assigned to the control group in a 1:1 manner. The outcomes measured were peri-procedural cardiac arrest, death on table, cerebrovascular accidents (CVA), in-hospital and 30-d mortality.

### RESULTS

A total of 146 patients were analyzed. The octogenarian group had a higher percentage of females, higher overall comorbidities, higher Charlson Comorbidity Index score, worse renal function and were more likely to require residential care and home help. The octogenarian group were also less likely to have PCI attempted and had a longer symptom onset to PCI

time. Mortality rate was high amongst octogenarians who presented with STEMI. However, those managed conservatively had a higher in-hospital and 30-d mortality rate

### CONCLUSION

Octogenarians who presented with STEMI that were managed conservatively had a higher mortality rate compared to those who had primary PCI. Therefore, we propose that revascularization may be beneficial to patients in this age group.

**Key words:** Coronary disease; Acute coronary syndrome; Myocardial infarction; Percutaneous coronary intervention; Aged 80 and over

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**Core tip:** The octogenarian group represents a complex population with multiple comorbidities. Percutaneous coronary intervention in this group is challenging and is associated with a high rate of failure and complications. This study shows that the mortality rate amongst octogenarians presenting with ST elevation myocardial infarction is high. However, there may be a mortality benefit in those treated with percutaneous coronary intervention, compared to those managed conservatively.

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## INTRODUCTION

Advanced age is associated with increased risk of acute coronary syndrome (ACS) and cardiovascular comorbidities<sup>[1]</sup>. The octogenarian population (age  $\geq$  80 years) is a fast growing segment of the population worldwide, and represent a high risk group for procedural complications during percutaneous coronary intervention (PCI) particularly in the settings of ST-segment elevation myocardial infarction (STEMI)<sup>[2]</sup>. These patients are underrepresented in randomized clinical trials evaluating primary PCI for STEMI and a high mortality has been reported<sup>[3,4]</sup>. These patients are typically treated less aggressively than are younger patients, due partly to the increased risk of adverse events and PCI related complications, and partly to a lack of standard management guidelines. Evidence based management of octogenarian patients with STEMI thus remains suboptimal despite the high mortality<sup>[2]</sup>. The overseas observational trials have suggested that despite the recommendations being

that age should not influence the decision of reperfusion strategy in STEMI patients, older age remains one of the strong predictors of not receiving it. There is paucity of Australia data on outcomes of octogenarian who present with STEMI. In this context, the aim of our study was to assess the clinical characteristics and outcomes of octogenarians presenting with STEMI, as compared with non-octogenarian patients (age < 80 years), as well as the outcomes of octogenarians who received primary PCI, compared to those that were managed conservatively.

## MATERIALS AND METHODS

This study is a single center retrospective case controlled study including all octogenarians who presented with STEMI between 2007 and 2012 in a tertiary Australian hospital. The subsequent non-octogenarian patient who presented with STEMI following an octogenarian STEMI was assigned to the control group in 1:1 manner. Detailed data on baseline and procedural characteristics and patient comorbidities were obtained through electronic medical records, and compared between octogenarian and non-octogenarian STEMI patients. The charlson comorbidity index (CCI) was calculated based on the patient's comorbidities. CCI predicts long-term survival according to a patient's medical condition<sup>[5]</sup>. STEMI was defined as persistent angina for 20 min in conjunction with either: (1) an ST-segment elevation at the J point of 0.25 mV in men aged < 40 years or 0.2 mV in men aged > 40 years or 0.15 mV in women in the precordial leads V2 to V3, and 0.1 mV in all other leads; or (2) the presence of a new left bundle branch block<sup>[6]</sup>. PCI success was defined as TIMI 2 or 3 flow post intervention. Left ventricular ejection fraction (EF) was derived either from the echocardiogram performed following the presentation or coronary angiogram during the index admission. Outcomes compared between the two groups included peri-procedural cardiac arrest, death on table, cerebrovascular accident (CVA), in-hospital and 30-d mortality. CVA was defined a clinical evidence of neurological deficit leading to a documented diagnosis of transient ischaemic attack or stroke. Subgroups of octogenarian STEMI patients who received PCI vs who did not (conservatively managed) were also compared for baseline and clinical characteristics. In-hospital and 30-d mortality was compared between all subgroups and independent predictors calculated.

All data were analyzed using IBM SPSS v22 and presented as percentages or mean value  $\pm$  standard deviation (SD). Independent *t* test was used to compare continuous while  $\chi^2$  and Fisher's exact tests were performed for categorical data. Logistic regression and multivariate analysis were performed to identify independent predictors. A two tailed *P* value of < 0.05 was considered statistically significant. The statistical methods of this study were reviewed by our biostatistics expert Dr. Asrar Ul-Haq, MBBS.

**Table 1** Baseline characteristics, procedural data, and outcomes of octogenarians as compared to non-octogenarians (controls)

	Octogenarians (n = 73)	Controls (n = 73)	P
Age	85.2 ± 4.1	67.1 ± 5.3	< 0.005
Females	56	29	< 0.005
Residential care	23	2.7	< 0.005
LLC	11	0	< 0.005
HLC	12	2.7	< 0.005
Home help	25	0	< 0.005
Medical comorbidities			
Diabetes	38	19	< 0.05
eGFR	48.7 ± 19.9	68.1 ± 20.3	< 0.005
PVD	30	12	< 0.05
Prior IHD	36	20	0.06
EF	53.6 ± 14.1	50.8 ± 13.1	0.4
Charlsons	3.2 ± 2.3	1.7 ± 2.2	< 0.005
Presentation and procedural characteristics			
Location of MI			
Anterior	51	49	0.8
Inferior	42	47	0.5
Lateral	4.1	4.1	1.0
PCI attempt	47	84	< 0.005
PCI success (TIMI 2-3)	91	99	0.1
Symptoms onset to PCI < 6 h	16	45	< 0.005
Outcomes			
Peri-procedural cardiac arrest	5	3	0.1
Death on table	1.8	0.9	0.2
Stroke	1.4	0	0.3
Inhospital mortality	28	7	< 0.005
30-d mortality	45	12	< 0.005

Data are means ± SD or n (%). LLC: Low level care; HLC: High level care; PVD: Peripheral vascular disease; EF: Ejection fraction; PCI: Percutaneous coronary intervention; MI: Myocardial infarction.

## RESULTS

### Octogenarians vs non-octogenarians

A total of 146 patients were analysed (octogenarians = 73; non-octogenarians = 73). The mean age was 85.2 ± 4.1 years in the octogenarian group and 67.1 ± 5.3 years in the control group (Table 1). The octogenarian group had a higher percentage of females (56% vs 29%, *P* < 0.005), higher overall comorbidities, a higher CCI score (3.2 ± 2.3 vs 1.7 ± 2.2, *P* < 0.001), were more likely to require residential care (23% vs 2.7%, *P* < 0.001) as well as home help (25% vs 0%, *P* < 0.001), and had worse renal function (eGFR 48.7 ± 19.9 vs 68.1 ± 20.3 mL/min per 1.73 m<sup>2</sup>, *P* < 0.001).

Octogenarians were less likely to have PCI attempted compared to the non-octogenarians (47% vs 84%, *P* < 0.001). The rate of symptom onset-to-PCI of < 6 h was significantly lower in octogenarians (16% vs 45%, *P* < 0.001). The rate of PCI success was high in both groups (91% vs 99%, *P* = 0.1). Reasons PCI was not attempted in non-octogenarians include: No culprit found (3), embolic event (1), recent CVA (1), known or new triple vessel disease/complex anatomy (2), other comorbidities (5); and in octogenarians: No culprit found (9), embolic event (2), recent CVA (4), known or

**Table 2** Baseline characteristics and outcomes of octogenarians who received percutaneous coronary intervention compared to conservatively managed octogenarians (no-percutaneous coronary intervention)

	PCI (n = 34)	No-PCI (n = 39)	P
Age	84 ± 3.4	86 ± 4.3	< 0.05
Females	44	67	0.06
Residential care	3	41	< 0.005
LLC	3	18	< 0.005
HLC	0	23	< 0.005
Home help	18	35	0.2
Medical comorbidities			
Diabetes	32	44	0.3
eGFR	54 ± 23	44 ± 16	< 0.05
PVD	21	38	0.1
Prior IHD	35	36	1
EF	54 ± 13	53 ± 16	0.2
Charlsons	2.52 ± 2	3.8 ± 2	< 0.05
Presentation			
Location of MI			
Anterior	41	59	0.2
Inferior	50	36	0.2
Lateral	6	3	0.6
Outcomes			
Inhospital mortality	18	37	0.1
30-d mortality	29	59	< 0.05

Data are means ± SD or n (%). LLC: Low level care; HLC: High level care; PVD: Peripheral vascular disease; EF: Ejection fraction; PCI: Percutaneous coronary intervention; MI: Myocardial infarction.

new triple vessel disease/complex anatomy (13), other comorbidities (11). Octogenarians had a significantly higher overall in-hospital mortality (28% vs 7%, *P* < 0.005) and 30-d mortality (45% vs 12%, *P* < 0.001).

The independent predictors of 30-d mortality in octogenarians included age (OR 1.20/year of advancing age, *P* < 0.01), place of residence (OR = 4.4, *P* < 0.01 for nursing home), conservative management (No intervention - OR 2.77, *P* < 0.05), and declining renal function (OR = 0.9, *P* < 0.05).

### PCI vs conservatively managed octogenarians

The 39 (53%) octogenarians who did not receive PCI were older (86 ± 4.3 years vs 84 ± 3.4 years, *P* < 0.05) and were more likely to be in residential care (41% vs 3%, *P* < 0.001), had higher CCI score (3.8 ± 2 vs 2.52 ± 2, *P* < 0.05) and worse renal function (eGFR 44 ± 16 mL/min vs 54 ± 23 mL/min per 1.73 m<sup>2</sup>). Type of myocardial infarction was not different as compared to octogenarians who received PCI (Table 2).

Mortality rate was high among octogenarians who presented with STEMI. However, those who were managed conservatively had a higher in-hospital and 30-d mortality (37% vs 18%, *P* = 0.1; and 59% vs 29%, *P* < 0.05 respectively).

Independent predictors of intervention in octogenarians included younger age (OR = 0.86, *P* < 0.05), place of residence (OR = 0.1, *P* < 0.05 for nursing home), lower CCI (OR = 0.7, *P* < 0.05), and renal

function (OR = 1.03,  $P < 0.05$ ).

## DISCUSSION

### **High mortality**

Our study demonstrated that mortality rate amongst octogenarians presenting with STEMI is high in Australian population despite the offered treatment, although much worse when treated conservatively. This appears to be associated with higher overall comorbidities, higher CCI score, worse renal function, and need for residential care or home help (which maybe the indirect measure of overall comorbidities and physical state). These findings are consistent with overseas studies looking at similar age groups<sup>[7-9]</sup>. Some factors reported to affect the mortality in these studies include heart failure, multiple co-morbidities, cachexia, cognitive state, history of intra-cranial bleeding and pre-hospital physical activity status<sup>[10,11]</sup>. Furthermore, it has been shown that the elderly are less likely to receive evidence based medical treatment such as aspirin, clopidogrel, beta-blockers, statins or glycoprotein IIb/IIIa inhibitors<sup>[7,8]</sup>. This may be due to concerns with regards to potential side effects in this age group. Previous studies have also shown that the elderly is associated with a higher rate of PCI failure. However, this is not reflected in our study, likely because the candidates for treatment were carefully selected.

### **Underuse of invasive treatment**

Our study suggested that despite having a higher mortality rate, octogenarians are less likely to have PCI attempted as compared to non-octogenarians. Frailty, co-morbidities and time delays have been shown to contribute to the underuse of invasive therapies. In our study, the proportion of those who received PCI in less than 6 h was significantly lower in the octogenarian group. This might reflect difficulty in decision-making with regards to reperfusion strategy. Atypical clinical presentation is also more common in the elderly and could contribute to time delay as well as the higher prevalence of cardiac failure. In addition, female gender was more prevalent in the octogenarian group. Previous studies have shown that female gender is associated with lower use of invasive therapies, especially in the elderly<sup>[12]</sup>.

### **Invasive treatment appears beneficial**

Another major finding of our study is that despite a relatively poor prognosis, octogenarians who received primary PCI had a significantly lower 30-d mortality. This however maybe related to the selection bias, a limitation of observational study design. Patients managed conservatively in our study were older, more likely to be in residential care, had a higher CCI score and worse renal function, and this represents a group with higher risk profile. The most common reasons PCI was not performed in the elderly were triple vessel disease/complex anatomy, other co-

existing comorbidities and the absence of a clear culprit lesion. There was no significant difference in in-hospital mortality between those managed who received intervention and those managed conservatively. Other factors affecting 30-d mortality included age, place of residence and declining renal function, highlighting the complexity of this patient population.

### **Limitations**

Our study is not randomized, and therefore limited by selection bias. However, it is an "all comers" registry which reflects "real world" data on management and outcomes of elderly patients who presents with STEMI. A randomised trial in this particular group is not viable. Propensity score matching would be the next best option and requires larger studies. Furthermore, we did not evaluate long term mortality and re-infarction rates, which may provide incremental information and a better picture of the utility of invasive management in this group.

In conclusion, this study is the first Australian report on the outcomes of octogenarians who present with ST-elevation myocardial infarction. This group represents a complex population with multiple medical comorbidities and PCI is challenging, associated with high failure and complication rates. Consequently, mortality is high in this group. However, the detrimental prognosis of conservatively managed octogenarians and relative mortality benefit associated with PCI suggests that revascularization therapy may benefit this age group.

## COMMENTS

### **Background**

The elderly have an increased risk of acute coronary syndrome. However, there are more likely to be managed conservatively compared to the younger cohort. This is due to concerns regarding procedural complications and success. The elderly is also under-represented in major clinical trials evaluating primary percutaneous coronary intervention (PCI). Recognizing this there have been recent overseas studies evaluating the elderly and primary PCI.

### **Research frontiers**

This study is the first to evaluate the characteristics and outcome of octogenarians who presents with ST-elevation myocardial infarction (STEMI) in an Australian setting. The authors also evaluated the outcomes of octogenarians who received primary PCI compared to those that were managed conservatively.

### **Innovations and breakthroughs**

This paper showed that despite poor prognosis among octogenarians who presents with STEMI, primary PCI may offer some benefit, with significantly lower 30 d mortality in the group that received it.

### **Applications**

Primary PCI should be considered in octogenarians who presents with STEMI. The patient's co-morbidities, quality of life and life expectancy should be taken into account when making this decision.

### **Terminology**

Primary PCI consists of urgent balloon angioplasty (with or without stenting), without the previous administration of fibrinolytic therapy or platelet glycoprotein IIb/IIIa inhibitors, to open the infarct-related artery during an acute myocardial infarction with ST-segment elevation.

**Peer-review**

This is an interesting and well-written article dealing with care on octogenaries after acute myocardial infarction. The authors have found worse clinical characteristics in octogenaries in comparison with non octogenaries, as well as lower referral for interventional procedures.

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## Retrospective Study

**Jailing polymer jacketed guide-wires during bifurcation coronary interventions is associated with procedural myocardial infarction**

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**Informed consent statement:** The institutional Review Board of the University of Alabama at Birmingham waived the need for informed consent since this was a retrospective study using de-identified data only.

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**Abstract****AIM**

To study the relationship of jailed polymer jacketed guide wires (PGW) with procedural myocardial infarction (PMI) after bifurcation coronary interventions.

**METHODS**

Consecutive bifurcation interventions performed from January 2010 to October 2014 were included in the study. Chart review was performed to obtain demographic, clinical and procedural data. PMI was defined as Creatine Kinase MB > 3 × upper reference limit of normal. Multivariate logistic regression was used to ascertain relationship of PGW use with PMI.

**RESULTS**

Two hundred and ninety-three patients (age 63.5 ± 12.3 years; 33.8% diabetic) were included in the study. Eighty point two percent ( $n = 235$ ) were true bifurcation lesions use of PGW was associated with PMI on univariate analysis (OR = 4.1;  $P = 0.002$ ). This association remained significant after adjusting for other possible risk factors (OR = 3.5;  $P = 0.02$ ).

## CONCLUSION

Our results suggest that PGW use for side branch protection may be associated with PMI. Randomized studies are needed to validate these findings.

**Key words:** Coronary bifurcation lesions; Percutaneous coronary intervention; Procedural myocardial infarction; Jailed guidewire; Polymer shearing

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**Core tip:** This is a retrospective study aiming to investigate the relationship of jailed polymer jacketed guide wires (PGW) with procedural myocardial infarction (PMI) after a bifurcation coronary intervention. There is concern that this causes polymer shearing and distal micro-embolization. Our data suggests that jailed PGW are strongly associated with PMI, even after adjusting for pertinent risk factors. Thus caution should be exercised in routinely jailing PGW until further definitive data are available.

Chatterjee A, White JS, Hashim T, Leesar MA. Jailing polymer jacketed guide-wires during bifurcation coronary interventions is associated with procedural myocardial infarction. *World J Cardiol* 2017; 9(5): 442-447 Available from: URL: <http://www.wjgnet.com/1949-8462/full/v9/i5/442.htm> DOI: <http://dx.doi.org/10.4330/wjc.v9.i5.442>

## INTRODUCTION

Coronary bifurcation lesions (CBL) are a challenging subset of day to day coronary interventions with a higher adverse event profile as compared to non-bifurcation lesions<sup>[1]</sup>. In the past decade, multiple studies have investigated the optimum approach to bifurcation lesions *vis-à-vis* simple (provisional side branch stenting only) vs complex (mandatory main and side branch stenting) approaches<sup>[2-4]</sup>. These have led to a widespread consensus that the simple approach should be preferred in majority of CBLs as the complex strategy showed higher incidence of adverse cardiac events, mainly myocardial infarction<sup>[5]</sup>.

In the simple approach, a coronary guidewire is frequently inserted into the side-branch (SB) as a strategy to prevent occlusion. This is considered to be an important step as side branch compromise is associated with higher incidence of myocardial infarction and death<sup>[6,7]</sup>. Stent deployment in the main vessel (MV) "jails" this guidewire which then has to be pulled from underneath the stent struts. Polymer jacketed guidewires (PGW) have the advantage of maximum lubricity which allows them to be easily withdrawn from a jailed position. However there are concerns over wire damage and shearing of the polymer jacket<sup>[8]</sup> and hence these are not universally recommended for

jailing<sup>[9]</sup>. In addition, studies of pathological specimens have revealed evidence of embolized polymer in the myocardium<sup>[10,11]</sup>. Guidewires with no or minimal polymer coatings are felt to be safer but run a risk of wire fracture during attempts at withdrawal<sup>[12]</sup>. In a pilot study using scanning electron microscopy (SEM) at our institution, it was established that polymer shearing is a real phenomenon and that the amount of polymer sheared is weakly correlated with biomarker release post procedure<sup>[13]</sup>. These studies have posed a question regarding an incremental risk of myonecrosis and possibly procedural myocardial infarction (PMI) with jailing of PGW and polymer shearing.

To try and answer this question, we performed a retrospective analysis of consecutive CBL interventions at our institution to determine if there is any association between type of guidewire jailed and PMI.

## MATERIALS AND METHODS

All coronary interventions performed between January 2010 and October 2014 at our institution were reviewed to identify CBL interventions. Inclusion criteria were: CBL requiring percutaneous coronary intervention (PCI), MV diameter  $\geq 2.5$  mm and side branch diameter  $\geq 2$  mm. Criteria for exclusion were PCI for chronic total occlusions, cases where dual antiplatelet therapy was started after PCI and unavailability of biomarker levels at least 12 h after PCI. The Institutional Review Board of the University of Alabama at Birmingham approved the study. Chart review was performed to extract demographic and clinical parameters. Patients were divided into two groups based on occurrence of PMI as defined below.

### Angiographic definitions

Angiograms were reviewed and quantitative measurements made using the CAAS system. A CBL was defined as a lesion located at a major coronary bifurcation point. Lesions were classified according to the Medina classification with a score of "1" or "0" being given to the proximal MV, distal MV and the SB components if they had  $\geq 50\%$  diameter stenosis. Lesions were also classified as true bifurcation lesions (Medina type 1,1,1; 1,0,1 or 0,1,1) vs non-true bifurcation lesions (Medina type 1,0,0; 0,1,0 or 0,0,1).

### Definition of procedural myocardial infarction

PMI was defined as creatine kinase (CK) MB  $> 3 \times 99^{\text{th}}$  percentile of upper limit of normal post procedure if the pre-procedure levels were normal or a  $> 20\%$  increase if pre-procedure levels were abnormal but stable or down-trending. If there were any unrelated cause for biomarker elevation, *e.g.*, acute stent thrombosis, no reflow, SB occlusion,  $<$  TIMI 3 flow in MV or SB, shock or hypotension in the immediate 24 h post PCI, acute kidney injury, stroke, bleeding requiring transfusion, pulmonary embolism, access complication causing limb

**Table 1** Demographic and clinical characteristics of the study population

	No PMI (n = 270)	PMI (n = 23)	P value
Age (yr)	63.6 ± 12.1	62.9 ± 14.4	0.80
Male sex	68.1%	60.9%	0.49
Smoking	55.6%	52.2%	0.86
Diabetes mellitus	33.0%	43.5%	0.36
Hypertension	78.1%	65.2%	0.33
Hyperlipidemia	73.7%	78.3%	0.87
Acute coronary syndrome	45.6%	52.2%	0.66

PMI: Procedural myocardial infarction.

ischemia or sustained arrhythmia these cases were classified as not having PMI. This was done to focus only on cases without a clear explanation for cause of PMI.

### Statistical analysis

Continuous variables are represented as mean ± SD and compared using the Welch's *t* test as the sample sizes are unequal. Categorical variables were compared using the Fisher's exact test. Statistical analyses were carried out using SPSS v 22.0 (SPSS, Chicago, Illinois). Multivariate logistic regression was used to ascertain relationship of the following variables with PMI: Age, Diabetes Mellitus, severe lesion calcification, true bifurcation lesion, use of newer antiplatelet agent (Ticagrelor and Prasugrel), Bivalirudin use, upstream Glycoprotein IIb/IIIa use, use of preplanned two stent technique, SB protection with any guidewire and SB protection with PGW.

## RESULTS

A total of 293 consecutive patients undergoing CBL interventions were included in the study. Seven point eight percent (*n* = 23) patients were classified as having had a PMI. Demographic and clinical characteristics of the patients broken down into two groups depending on whether or not PMI occurs are shown in Table 1. There were no statistically significant differences between the two groups. Table 2 shows the angiographic and procedural characteristics of patients with and without PMI. The most common bifurcation lesions included were left anterior descending/diagonal and left circumflex/marginal branch respectively. Proportion of true bifurcation lesions was higher and Bivalirudin use lower in the PMI group but these differences did not reach statistical significance. Seventy-four point four percent of total patients had a wire placed in the side branch and jailed with no difference amongst the two groups. However a jailed PGW was much more common in the PMI group (43.4% vs 15.9%, *P* = 0.003). There were no instances of wire entrapment or wire rupture in either group. The most common PGW jailed was a Hi Torque Whisper (Abbot Vascular, Abbott Park, IL, United States) while non PGW jailed were Runthrough NS

**Table 2** Angiographic and procedural characteristics

	No PMI (n = 270)	PMI (n = 23)	P value
Vessels involved			0.68
LM bifurcation	15.9%	21.7%	
LAD/Diagonal	40.0%	47.8%	
LCX/OM	34.8%	21.7%	
RPDA/RPLA	8.8%	4.3%	
RCA/RV marginal	0.003%	0%	
Severe calcification	57.4%	65.2%	0.52
True bifurcation (Medina 1,1,1; 1,0,1; 0,1,1)	79.3%	91.3%	0.27
Main vessel diameter (mm)	3.3 ± 0.5	3.3 ± 0.4	0.4
Side branch diameter (mm)	2.6 ± 0.5	2.6 ± 0.4	0.94
Antiplatelet therapy			0.97
Plavix	73.7%	69.6%	
Prasugrel	7.0%	8.7%	
Ticagrelor	19.3%	21.7%	
Anticoagulant			0.08
Heparin	45.2%	65.2%	
Bivalirudin	54.8%	34.8%	
Upstream GpIIb/IIIa use	11.5%	13.0%	0.74
Planned 2 stent approach	28.1%	39.1%	0.34
Final kissing balloon angioplasty	45.9%	56.5%	0.39
SB protected	73.3%	87%	0.21
PGW jailed	15.9%	43.4%	0.003

PMI: Procedural myocardial infarction; PGW: Polymer jacketed guide wires.

(Terumo Interventional Systems, Somerset, NJ, United States), Cougar LS (Medtronic, Minneapolis, MN, United States) and HT Balance Middle Weight (BMW, Abbot Vascular, Abbott Park, IL, United States).

Univariate logistic regression analysis did not reveal any significant association of PMI with age, Diabetes, lesion calcification, use of newer antiplatelet agents, use of Bivalirudin, upstream use of Gp IIb/IIIa use, SB protection, pre-planned use of complex 2 stent strategy or Medina classification as true bifurcation lesion. The use of jailed PGW was strongly associated with PMI with an odds ratio of 4.1 (95%CI: 1.7-9.9; *P* = 0.002). Performing multivariate logistic regression to adjust for all the aforementioned factors still showed a strong association between jailing of PGW and PMI (Figure 1, Odds ratio 3.5; 95%CI: 1.2-9.9; *P* = 0.02).

## DISCUSSION

SB protection is of considerable importance during CBL interventions. Occlusion of a SB > 1.0 mm has been associated with a 14% risk of MI<sup>[6]</sup>. In a large series of 2227 CBL interventions, Hahn *et al*<sup>[7]</sup> reported a SB occlusion rate of 8.4% and this increased the rate of major adverse cardiovascular events. The only protective factor found to prevent SB occlusion was the presence of a jailed guide-wire. Similar findings were reported in the Nordic study illustrating the importance of the jailed SB wire<sup>[14]</sup>. The jailed guide wire provides a physical impediment to closure of the SB ostium and also facilitates re-wiring of the vessel by making the angle between the MV and the SB wider<sup>[15]</sup>. Thus jailing

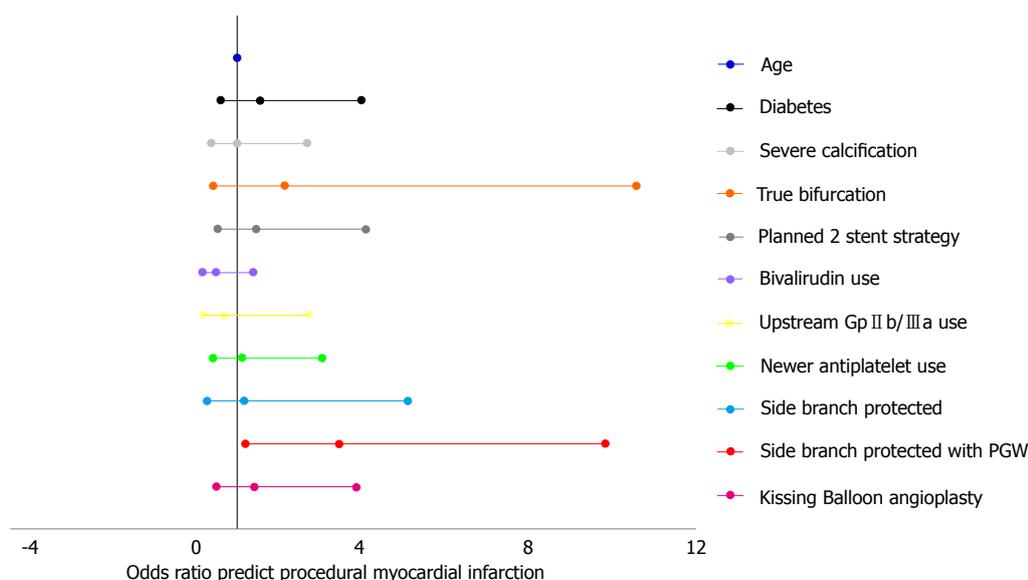


Figure 1 Multi-variate Odds ratios for various factors in predicting procedural myocardial infarction. PGW: Polymer jacketed guide wires.

a wire in the SB during MV stenting is a widely accepted practice for CBL interventions. However there is less consensus on the type of guide-wire to jail.

All coronary guide-wires have some degree of polymer coating on them with varying degrees of polymer cover or jacket. Based on the latter, guide-wires are broadly classified into three categories: (1) Wires with no polymer jacket - minimum lubricity, *e.g.*, HT BMW, Prowater and HT Floppy II; (2) Wires with intermediate polymer jacket - lack polymer jacket at the very distal end only; medium lubricity, *e.g.*, HT BMW Universal, Runthrough NS, Cougar LS; and (3) Wires with full polymer jacket - polymer jacket throughout the length of the wire; maximum lubricity; *e.g.*, HT Whisper, HT Pilot, HT Fielder XT.

PGW (3<sup>rd</sup> category) offer the attractive quality of lubricity and are easily withdrawn from underneath stent struts. However the interventional community has been wary of these as the initial reports of wire rupture were consistently with hydrophilic PGW<sup>[8]</sup>. Since then multiple reports of non hydrophilic wires being entrapped have been published as well<sup>[16-19]</sup>. With the lesser degree of lubricity of a non PGW, greater force may be required to extract the wire and hence risk deep intubation of the guide catheter and injury to the vessel as well.

Some reports have also raised the possibility of shearing of the polymer jacket during extraction of the jailed PGW<sup>[20]</sup>. Grundeken *et al*<sup>[11]</sup> examined the possibility of distal polymer embolization in two ways - they examined the aspirate from patients undergoing aspiration thrombectomy and reported that 45% samples had polymer material in them. Also, examination of autopsy specimens from patients who had undergone PCI showed intramyocardial polymer in 10% subjects. The amount of polymer detected increased as the polymer jacket increased with the maximum embolization noted in cases using HT Whisper

wires. This study is especially concerning because polymer embolization occurred even without jailing the guide-wire. It is notable that distal embolization of athero-emboli is considered an important contributor in the etiology of PMI<sup>[21]</sup> - hence embolization of non-degradable polymer is a plausible hypothetical cause for PMI as well.

To try and quantify the extent of polymer shearing and embolization, we have previously performed a small study examining jailed HT Whisper and Runthrough NS wires with SEM<sup>[13]</sup>. This revealed polymer shearing in both types of wires but up to 5 fold higher in the HT Whisper, a PGW. Amount of polymer shearing was also weakly correlated with the level of CK MB post procedure. Pan *et al*<sup>[22]</sup> randomized 235 patients who underwent CBL interventions with the jailed wire technique to use of PGW or non PGW and examined the jailed wires using an optical microscope. They reported more structural damage to non PGW although no wire fracture was noted. It should be noted though that the study used magnification up to 6.3X only, which is insufficient to detect shearing of polymer and also used wires with no polymer cover as the comparison group, the use of which has gone down in comparison to wires with intermediate polymer cover. Also, the rate of PMI was not different in the two groups.

In this respect, our study is the second study to investigate the relationship of type of wire jailed to PMI. Our results show a strong association of jailed PGW to PMI which are contrary to the results of Pan *et al*<sup>[22]</sup>. One reason may be that there are varied reasons why patient have elevated cardiac biomarkers post PCI. Some of these may be no reflow phenomenon, distal athero-embolization, occlusion of SB, coronary perforation, development of cardiogenic (or other types of) shock, access complications causing limb ischemia, arrhythmias, bleeding causing hemodynamic instability,

*etc.* These, at least by our current knowledge of PMI are more likely to be contributors than polymer embolization from jailed PGW. Hence we meticulously excluded all cases which may have had any confounding factor causing a biomarker elevation and categorized these cases as having no PMI. This further strengthens our belief in the credibility of our results.

### Limitations

Our study has all the limitations of a retrospective analysis and the inherent biases. However we have attempted to correct these biases by careful data acquisition, exclusion of cases with potential confounding factors and a multivariate logistic regression analysis. We also note that the definition of PMI used is inconsistent with the 3<sup>rd</sup> universal definition of MI consensus document<sup>[23]</sup> which defines PMI as  $> 5 \times$  ULN of cardiac Troponin (cTn) along with symptoms, electrocardiographic, imaging or angiographic evidence of ischemia. Multiple studies have been done that question the relevance of the  $5 \times$  ULN of cTn criterion as a  $> 3 \times$  ULN of CK-MB cut-off is better correlated with mortality<sup>[24]</sup> and evidence of new myocardial injury as detected by cardiac MRI<sup>[25]</sup>. In fact, a cut off of  $3 \times$  ULN of CK-MB is equivalent to a cut-offs of  $20 \times$  cTn for mortality and  $40 \times$  cTn for MRI proven new myocardial injury. Hence while the updated definition is valid in conjunction with clinical evidence of ischemia, CK MB may be a better choice for isolated biomarker analyses.

In conclusion, our study shows that jailed PGW may be associated with a threefold higher risk of PMI. Given the retrospective design, this finding should be treated as hypothesis generating and hopefully will trigger prospective analysis to confirm or refute this association. The etiology for this risk is believed to be polymer shearing and micro-embolization which has been proven by multiple small but rigorously conducted studies<sup>[11,13]</sup>. We believe that much has to be learned about the potential role of polymer shearing and embolization in myonecrosis post CBL intervention. There is also a need to determine if the wires with intermediate polymer cover may be the best middle path compromise in the argument of lubricity vs fracture and polymer shearing.

## COMMENTS

### Background

Polymer jacketed guide wires (PGW) are frequently used for side branch protection during bifurcation coronary interventions. Their lubricity is an attractive property for this use as it makes them easy to retract from underneath stent struts. However, microscopic shearing of polymer from jailed guide wires has been reported and may be a potential cause of procedural myocardial infarction (PMI) as this may cause distal micro-embolization. Hence, the authors performed a retrospective analysis of bifurcation interventions at this institution to ascertain relationship of PGW use with PMI.

### Research frontiers

PMI has important prognostic implications in patients undergoing percutaneous coronary intervention. Thus it is important to understand if any procedural factors such as use of PGW have any effect on PMI.

### Innovations and breakthroughs

This is only the second study to ascertain if there is a relationship between use of jailed PGW and PMI. In their data there is a strong association of these which translates to a three fold higher risk of PMI if a PGW is jailed.

### Applications

These results should caution interventional cardiologists from adopting PGW as their go to wire for jailing until prospective data comparing different types of wires are available. Randomized studies are needed to compare newer generation non polymer jacketed, intermediate polymer jacketed and full polymer jacketed coronary guide wires.

### Terminology

PGW: Polymer jacketed guide wires; PMI: Procedural myocardial infarction.

### Peer-review

This is an interesting manuscript about the relation of jailing PGW to PMI. The authors demonstrated that jailed PGW might be associated with PMI. This manuscript is nicely structured and well written.

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## Observational Study

**Markers of inflammation and cardiovascular disease in recently diagnosed celiac disease patients**

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**Abstract****AIM**

To evaluate novel risk factors and biomarkers of cardiovascular disease in celiac disease (CD) patients compared with healthy controls.

**METHODS**

Twenty adult patients with recent diagnosis of CD and 20 sex, age and body mass index-matched healthy controls were recruited during a period of 12 mo. Indicators of carbohydrate metabolism, hematological parameters and high sensitive C reactive protein were determined. Moreover, lipoprotein metabolism was also explored through evaluation of the lipid profile and

the activity of cholesteryl ester transfer protein and lipoprotein associated phospholipase A2, which is also considered a specific marker of vascular inflammation. The protocol was approved by the Ethic Committee from School of Pharmacy and Biochemistry, University of Buenos Aires and from Buenos Aires Italian Hospital, Buenos Aires, Argentina.

## RESULTS

Regarding the indicators of insulin resistance, CD patients showed higher plasma insulin levels [7.2 (5.0-11.3) mU/L *vs* 4.6 (2.6-6.7) mU/L,  $P < 0.05$ ], increased Homeostasis Model Assessment-Insulin Resistance [1.45 (1.04-2.24) *vs* 1.00 (0.51-1.45),  $P < 0.05$ ] and lower Quantitative Sensitive Check index [0.33 (0.28-0.40) *vs* 0.42 (0.34-0.65),  $P < 0.05$ ] indexes. Folic acid concentration [5.4 (4.4-7.9) ng/mL *vs* 12.2 (8.0-14.2) ng/mL,  $P < 0.01$ ] resulted to be lower and High-sensitivity C reactive protein levels higher ( $4.21 \pm 6.47$  mg/L *vs*  $0.98 \pm 1.13$  mg/L,  $P < 0.01$ ) in the patient group. With respect to the lipoprotein profile, CD patients showed lower high density lipoprotein-cholesterol (HDL-C) ( $45 \pm 15$  mg/dL *vs*  $57 \pm 17$  mg/dL,  $P < 0.05$ ) and apo A-I ( $130 \pm 31$  mg/dL *vs*  $155 \pm 29$  mg/dL,  $P < 0.05$ ) levels, as well as higher total cholesterol/HDL-C [4.19 (3.11-5.00) *vs* 3.52 (2.84-4.08),  $P < 0.05$ ] and apo B/apo A-I (0.75  $\pm$  0.25 *vs* 0.55  $\pm$  0.16,  $P < 0.05$ ) ratios in comparison with control subjects. No statistically significant differences were detected in lipoprotein-associated lipid transfer protein and enzymes.

## CONCLUSION

The presence and interaction of the detected alterations in patients with CD, would constitute a risk factor for the development of atherosclerotic cardiovascular disease.

**Key words:** Inflammation; Cardiovascular disease; High density lipoprotein-cholesterol; Lipoproteins; Celiac disease

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**Core tip:** Given that data about the presence of metabolic alterations and atherogenic risk factors in celiac disease are scarce and contradictory, we aimed to investigate carbohydrate metabolism, lipoprotein profile and inflammatory status in patients with celiac disease (CD). Patients presented higher insulin levels, Homeostasis Model Assessment-Insulin Resistance index, apo B/apo A-I ratio and High-sensitivity C reactive protein concentration, as well as lower Quantitative Sensitive Check index index, high density lipoprotein-cholesterol and apo A-I levels in comparison with sex and aged-matched healthy controls. Persistence of these alterations through long periods of time in a chronic pathologic condition, as it is the case with CD, would constitute a high risk of developing atherosclerotic cardiovascular disease.

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## INTRODUCTION

Celiac disease (CD) is a multisystemic disease which mainly affects the digestive system, though not exclusively. Its main trait is chronic and diffuse inflammation of the mucosa of the small intestine and it can present a wide variety of clinical symptoms<sup>[1]</sup>. Thus far, the only available therapy for CD consists of the implementation of a gluten free diet (GFD), whose efficacy depends on strict adherence.

It is remarkable that most cases of CD lack typical gastrointestinal symptoms and are, instead, very frequently associated with presentations known as atypical or extra-intestinal. Thus, its diagnosis represents one of the main challenges for health professionals<sup>[2]</sup>.

Commonly, CD has been associated with certain physiopathological conditions (type 1 diabetes, Hashimoto thyroiditis, *etc.*) which are not directly related to gluten ingestion<sup>[3]</sup>. Among these conditions, it is worth noting that the evidence linking CD and atherosclerotic cardiovascular disease (CVD) is scarce. It is well known that CD patients do not show classical CVD risk factors. In fact, hypertension and hypercholesterolemia are less frequent in CD patients than in the general population<sup>[4]</sup>. However, previous studies have failed to show lower CVD risk in CD patients than in healthy subjects<sup>[4,5]</sup>. Furthermore, an important study carried out in Sweden in approximately 14000 hospitalized CD patients showed higher risk of acute myocardial infarction, chest angina, cardiac insufficiency, brain hemorrhage and ischemic stroke when compared to sex and age-paired healthy controls<sup>[6]</sup>.

These facts suggest that CD would be associated with novel atherogenic risk factors or even with other non-identified risk factors. In fact, inflammation and anemia, among other signs that characterize CD, could represent a link between this pathology and CVD<sup>[7,8]</sup>.

Atherosclerosis is presently understood as a chronic inflammatory disease in which endothelial dysfunction and biomarkers of inflammation are present since the early stages of the pathology<sup>[9]</sup>. So far, the inflammatory process typical of CD has not been described in relation to increased risk of CVD.

The aim of the present study was to evaluate novel risk factors and biomarkers of CVD in CD patients in comparison to sex, age and body mass index (BMI)-matched healthy controls. In addition, the metabolic differences between patients with typical and atypical presentations of the disease were also analyzed.

## MATERIALS AND METHODS

### Subjects

Twenty patients with CD were consecutively recruited from the service of gastroenterology, Buenos Aires Italian Hospital, during a period of 12 mo. The inclusion criteria were adult age and recent diagnosis of CD (< 3 mo) based on histopathological findings and serological markers (anti-gliadin IgG and IgA and anti-transglutaminase IgA). Patients were not treated and they had not still started a GFD. All individuals presenting any other intestinal inflammatory disease, IgA deficiency, malignant diseases, chronic infections, pregnancy, thyroid, renal or hepatic alterations, history of CVD, smoking, alcohol consumption > 40 g/d, and treatment with drugs known to affect lipid and/or carbohydrate metabolism were excluded. Patients were classified according to the presence of gastrointestinal (typical presentation) or extra-digestive symptoms (atypical presentation)<sup>[2]</sup>. Gastrointestinal manifestations analyzed were: Diarrhea, abdominal distention, weight loss, and malabsorption syndrome. Extra-digestive alterations considered were: Anemia, mouth ulcers, osteoporosis, and modifications of liver function tests. Employing these criteria, 11 out of the 20 CD patients showed gastrointestinal symptomatology and 9 showed only extradiigestive symptoms. The group of CD patients was compared with a sex, age and BMI-matched group of healthy volunteers ( $n = 20$ ). Weight, height and waist circumference were registered in all subjects and an exhaustive anamnesis was performed. All participants in the study signed an informed consent. The protocol was approved by the Ethical Committees from School of Pharmacy and Biochemistry, University of Buenos Aires and from Buenos Aires Italian Hospital. Buenos Aires, Argentina.

### Study protocol and samples

Blood samples were obtained from the antecubital vein after 12 h of fasting. Serum and EDTA plasma (final EDTA concentration 1 mg/mL) were prepared from venous blood collected into sterile, evacuated tubes. The former was centrifuged at 1500 g for 15 min at 4 °C. Serum was isolated and stored at 4 °C and -70 °C.

### Determination of general biochemical parameters

Plasma concentrations of glucose, urea, uric acid, total bilirubin, folic acid and vitamin B12, as well as aspartate aminotransferase (ASAT), alanin aminotransferase and alkaline phosphatase activities, and hemogram were determined by standardized methods. Insulin levels were measured by radioimmunoassay (Diagnostics Products Corp., Los Angeles CA, United States). Homeostasis Model Assessment-Insulin Resistance (HOMA-IR) was calculated using the formula  $[\text{glucose (mmol/L)} \times \text{insulin (uU/mL)}] / 22.5$  and Quantitative Sensitive Check index (QUICKI) using the formula  $1 / [\ln \text{Glucose (mmol/L)} + \ln \text{Insulin (mU/L)}]$ <sup>[10,11]</sup>. High-sensitivity

C reactive protein (hsCRP) levels were determined by immunoturbidimetry (Roche, Mannheim, Germany) in a Hitachi 917 autoanalyzer (Tokyo, Japan).

### Determination of the lipid, lipoprotein and apolipoprotein profile

Plasma levels of total cholesterol (TC) and triglycerides were quantified by standardized methods (Roche, Mannheim, Germany) in a Hitachi 917 autoanalyzer (Tokyo, Japan). High density lipoproteins (HDL) were isolated from the supernatant obtained after selective precipitation of apolipoprotein (apo) B-containing lipoproteins using 0.44 mmol/L phosphotungstic acid in presence of magnesium ions<sup>[12]</sup>. Cholesterol (C) of low density lipoprotein (LDL) was estimated as the difference between TC and the cholesterol contained in the supernatant obtained after selective precipitation of LDL with 10 g/L polyvinil sulfate in poliethilenglicol (600 Da; 2.5 w/v; pH = 6.7)<sup>[13]</sup>. Non HDL-C was calculated as the difference between TC and HDL-C. Very low density lipoprotein cholesterol (VLDL-C) was calculated as the difference between the supernatants of the LDL-C and HDL-C precipitations. Apo B and apo A-I levels were quantified by immunoturbidimetry (Roche, Mannheim, Germany) in a Hitachi 917 autoanalyzer (Tokyo, Japan). Results were expressed as mg/dL. The following ratios were calculated: TG/HDL-C, TC/HDL-C and apo B/apo A-I.

### Determination of cholesteryl ester transfer protein activity

Cholesteryl ester transfer protein (CETP) activity was evaluated in serum samples following the radiometric method previously described with minor modifications<sup>[14]</sup>. Briefly, the capacity of the serum to promote the transfer of tritiated esterified cholesterol (EC) from the biosynthetically marked HDL3 subfraction (<sup>3</sup>H-EC-HDL3) (NEN Life science products, Boston, United States) to apo B containing lipoproteins present in the serum. Serum samples were incubated with <sup>3</sup>H-CE-HDL3 (50 μmol/L cholesterol) with iodoacetate (1.5 mmol/L) in TBS buffer (pH = 7.4) during 3 h at 37 °C. After incubation, apo B-containing lipoproteins were separated from HDL by selective precipitation with phosphotungstic acid (0.44 mmol/L) in the presence of magnesium ions. Radioactivity was measured in the reaction cocktail and in the supernatant containing the HDL subfraction in a liquid scintillation counter (Packard 210 TR, Packard Instruments, Meridians, CT, United States). Results were expressed as the percentage of tritiated EC transferred from HDL3 to apo B-containing lipoproteins, per ml, per hour. All samples were processed in the same assay.

### Determination of lipoprotein associated phospholipase A2 activity

Lipoprotein associated phospholipase A2 activity (Lp-PLA2) was evaluated employing the radiometric assay described by Blank *et al.*<sup>[15]</sup> with minor modifications.

**Table 1** Clinical and biochemical characteristics from patients with celiac disease and control subjects

	Patients with celiac disease (n = 20)	Control subjects (n = 20)	P
Age (yr)	50 (25-58)	47 (28-60)	ns
Men/woman	5/15	5/15	ns
BMI (kg/m <sup>2</sup> )	22.8 (20.4-26.2)	23.0 (21.0-24.7)	ns
Glucose (mg/dL)	87 ± 11	86 ± 12	ns
Insulin (mU/L)	7.2 (5.0-11.3)	4.6 (2.6-6.7)	< 0.05
HOMA-IR	1.45 (1.04-2.24)	1.00 (0.51-1.45)	< 0.05
QUICKI	0.33 (0.28-0.40)	0.42 (0.34-0.65)	< 0.05
Urea (mg/dL)	27 (21-34)	35 (34-39)	< 0.01
Creatinine (mg/dL)	0.74 (0.63-0.88)	0.80 (0.75-1.10)	< 0.05
Uric acid (mg/dL)	5.0 ± 1.2	4.3 ± 1.6	ns
Bilirubin (mg/dL)	0.7 (0.5-0.8)	0.6 (0.6-0.8)	ns
ASAT (U/L)	26 (20-35)	14 (12-20)	< 0.01
ALAT (U/L)	22 (17-39)	18 (16-22)	ns
ALP (U/L)	80 (59-102)	124 (67-219)	ns

BMI: Body mass index; HOMA-IR: Homeostasis Model Assessment insulin resistance; QUICKI: Quantitative insulin sensitivity check index; ASAT: Aspartate-amine transferase; ALAT: Alanine-amine transferase; ALP: Alkaline phosphatase; ns: Non significant. Data are shown as mean ± SD or median (interquartile range) according to data distribution.

The extraction of the marked acetate was performed using chloroform and the radioactivity of the aqueous phase was measured in a liquid scintillation counter (Packard 210 TR, Packard Instruments, Meridians, CT, United States). The radioactivity of the reaction buffer was also measured. Results were expressed as µmol of acetate liberated, per millilitre, per hour. All samples were processed in the same assay.

### Statistical analysis

The sample size was calculated based on previous studies carried out in our laboratory. The outcome variables chosen to perform the sample size calculation for this study were HDL-C, CETP and Lp-PLA2. Having defined a 0.8 power, an effect size of 1.0 and a significance level of 0.05, the number of patients to be included in the present study was at least 17. Data distribution was analyzed with the Shapiro-Wilks test and data was expressed as mean ± SD, if distribution was found to be parametric, or as median (interquartile range) if distribution was non-parametric. To assess differences between groups, both parametric and non-parametric methods were employed. Correlation analyses were performed using Spearman or Pearson tests depending on variable distribution. When partial correlations, linear regressions or adjusted group differences were performed, all non-parametric variables were normalized prior to be included in the analysis. Statistical significance was defined as  $P < 0.05$ . A statistical review of the study was performed by a biomedical statistician. For the statistical analysis, the programs Infostat (Universidad Nacional de Cordoba, Argentina) and SPSS 19.0 (IBM, Chicago, United States) were used.

**Table 2** Hematological parameters from patients with celiac disease and control subjects

	Patients with celiac disease (n = 20)	Control subjects (n = 20)	P
Erythrocytes (10 <sup>6</sup> /mL)	4.40 ± 0.48	4.58 ± 0.27	ns
Hematocrite (%)	38.5 ± 4.0	40.1 ± 2.6	ns
Hemoglobin (g/dL)	13.0 ± 1.4	13.3 ± 0.9	ns
Serum iron (µg/dL)	73 ± 35	105 ± 61	ns
Ferritin (ng/mL)	33 (13-110)	92 (43-117)	ns
Transferrin (mg/dL)	261 ± 62	293 ± 59	ns
Transferrin Sat. (%)	25 ± 14	29 ± 14	ns
Vitamin B12 (pg/mL)	337 (251-482)	315 (265-393)	ns
Folic acid (ng/mL)	5.4 (4.4-7.9)	12.2 (8.0-14.2)	< 0.01

ns: Non significant; Sat.: Saturation. Data are shown as mean ± SD or median (interquartile range) according to data distribution.

## RESULTS

As expected, CD patients and control subjects did not show any difference in age, sex distribution and BMI (Table 1). Nevertheless, CD patients had significantly higher insulin levels and HOMA-IR, as well as lower QUICKI (Table 1). Both urea and creatinine concentrations were lower in the patient group, though individual results were comprised within the reference values. Additionally, ASAT activity was significantly increased in patients compared to controls.

The evaluation of hematological parameters showed no significant decrease in hemoglobin concentration in patients. Furthermore, only one woman met the criteria for anemia diagnosis (hemoglobin < 12 g/dL for women and < 13 g/dL for men). Similarly, there were no differences in total iron content, transferrin saturation or concentrations of ferritin, transferrin and vitamin B12. Only folic acid concentration was found to be significantly lower in patients (Table 2). Employing the reference values established by the World Health Organization<sup>[16,17]</sup>, the prevalence of folic acid deficiency resulted to be 10% (< 4 ng/dL), of iron deficiency 15% (ferritin < 15 ng/dL) and of low vitamin B12 7.5% (< 203 pg/mL).

Regarding the lipid and lipoprotein profile, no differences were detected in TG, TC, LDL-C and apo B levels. However, statistically significant decreases in HDL-C and apo A-I concentrations were observed (Table 3). Furthermore, both parameters showed a strong positive correlation between them ( $r = 0.78$ ;  $P < 0.0001$ ). TC/HDL-C and apo B/apo A-I ratios, both of which possess high predictive value for CVD, were significantly higher in patients, whilst TG/HDL-C showed no difference between groups. On the other hand, CETP activity was similar in patients and controls (145% ± 32%/mL.h vs 132% ± 33%/mL.h,  $P > 0.05$ ) and exhibited direct correlations with TG levels ( $r = 0.52$ ;  $P < 0.005$ ) and apo B/apo A-I ratio ( $r = 0.48$ ;  $P < 0.005$ ), and negative ones with HDL-C ( $r = -0.58$ ;  $P < 0.0001$ ) and apo A-I ( $r = -0.40$ ;  $P < 0.005$ ).

**Table 3** Lipid, lipoprotein and apolipoprotein profile from patients with celiac disease and control subjects

	Patients with celiac disease (n = 20)	Control subjects (n = 20)	P
TG (mg/dL)	81 (65-119)	78 (60-114)	ns
TC (mg/dL)	185 ± 37	194 ± 39	ns
VLDL-C (mg/dL)	18 ± 8	17 ± 7	ns
LDL-C (mg/dL)	139 (89-149)	107 (95-147)	ns
HDL-C (mg/dL)	45 ± 15	57 ± 17	< 0.05
Non-HDL-C (mg/dL)	153 (105-167)	137 (112-167)	ns
Apo A-I (mg/dL)	130 ± 31	155 ± 29	< 0.05
Apo B (mg/dL)	93.6 ± 23.8	83.5 ± 20.7	ns
TG/HDL-C	2.09 (1.13-2.98)	1.29 (1.06-1.93)	ns
TC/HDL-C	4.19 (3.11-5.00)	3.52 (2.84-4.08)	< 0.05
ApoB/apo A-I	0.75 ± 0.25	0.55 ± 0.16	< 0.01

TG: Triglycerides; TC: Total cholesterol; VLDL: Very low density lipoprotein; LDL: Low density lipoprotein; HDL: High density lipoprotein; apo: Apolipoprotein; ns: Non significant. Data are shown as mean ± SD or median (interquartile range) according to data distribution.

Evaluation of inflammation markers showed an increase in hsCRP levels in CD patients (Figure 1), which also correlated with apo B/apo A-I ratio ( $r = 0.42$ ;  $P < 0.01$ ). Even though white blood cell count (WBC) showed no differences between the two groups ( $6.11 \pm 1.31 \cdot 10^3/\text{mL}$  vs  $6.17 \pm 1.15 \cdot 10^3/\text{mL}$ ), it was directly associated with several parameters of the lipid profile ( $r/p$ ; TG,  $0.33 < 0.05$ ; HDL-C,  $-0.34 < 0.05$ ; apo B,  $0.42 < 0.05$ ; TG/HDL-C,  $0.37 < 0.05$ ; TC/HDL-C,  $0.44 < 0.01$ ; and apo B/apo A-I,  $0.51$ ;  $< 0.005$ ). Lastly, Lp-PLA2 activity was similar between patients and controls ( $7.20 \pm 1.28 \mu\text{mol/mL.h}$  vs  $7.91 \pm 2.02 \mu\text{mol/mL.h}$ ) and was positively associated with LDL-C, main carrier of the enzyme in circulation ( $r = 0.50$ ;  $P < 0.005$ ).

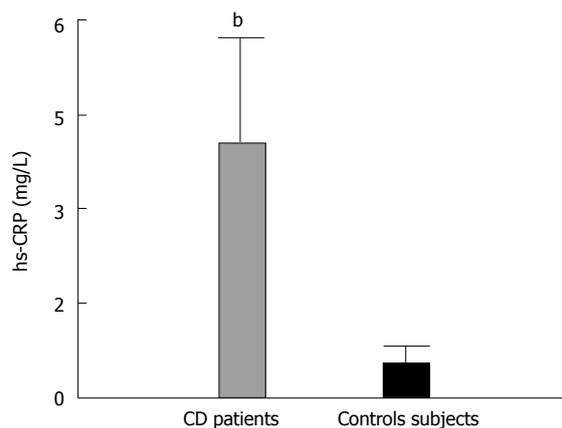
Moreover, folic acid level was significantly associated with several parameters of the lipid profile ( $r/p$ ; HDL-C,  $0.52 < 0.05$ ; apo A-I,  $0.45 < 0.01$ ; TG/HDL-C,  $-0.36 < 0.05$ ; and apo B/apo A-I,  $-0.34 < 0.05$ ) and with hsCRP concentration ( $r = -0.42$ ;  $P < 0.05$ ).

When comparing patients according to the clinical features, no differences were detected between patients with typical and atypical presentation of the disease in any of the parameters analyzed (data not shown).

## DISCUSSION

Patients with CD showed a slight alteration in carbohydrate metabolism, decreased folic acid levels, a more atherogenic lipoprotein profile and an increase in the inflammatory marker hsCRP, with no difference evidenced between typical and atypical presentation of the disease. Likely, in both groups, the severity of duodenal lesion would not be a determining factor in the metabolic alterations nor in the increase of hsCRP observed in this study.

Unlike other pathologies characterized by the presence of systemic inflammation, such as lupus erythematosus and rheumatoid arthritis, in which patients



**Figure 1** Levels of high sensitive C-reactive protein in patients with celiac disease (n = 20) and control subjects (n = 20). <sup>b</sup> $P < 0.01$ . hsCRP: High sensitive C reactive protein; CD: Celiac disease.

show higher CVD morbidity and mortality<sup>[18,19]</sup>, available evidence for CD appears less solid and more controversial. Even though some studies have described an increase in CVD risk compared with the general population<sup>[20-22]</sup>, this has not been the case in other reports<sup>[4,23]</sup>. A group of CD patients, retrospectively studied in comparison with data from general population<sup>[24]</sup>, showed less CVD risk employing the Framingham score. Nevertheless, assessment of cardiac functionality, specifically of the left ventricle<sup>[25]</sup>, and the study of the presence of subclinical atherosclerosis, analyzed through aortic stiffness, aortic strain, and aortic distensibility<sup>[26,27]</sup>, evidenced a clear association between CD and CVD. Moreover, a previous study showed higher carotid intima media thickness (an established marker of generalized atherosclerosis that correlates with the extent of coronary artery disease and predicts future cardiovascular events) in CD patients compared to healthy controls and similar to that of patients with type 1 diabetes<sup>[28]</sup>. Lastly, it is worth noting that a recent meta-analysis<sup>[29]</sup>, based on ten studies performed in CD patients, showed a slight increase in the risk of stroke, acute myocardial infarction, and cardiovascular death, though only in the first case this increase reached statistical significance. As evidenced by the bibliography, the subject remains highly controversial.

In CD patients, a systemic pro-inflammatory status was evidenced through an increase in plasma hsCRP levels. According to the guides of the American Heart Association<sup>[30]</sup>, values above 3 mg/dL, such as those observed in the group of the CD patients studied, would be indicative of high CVD risk. Even though Lp-PLA2 activity, considered a specific marker of vascular inflammation<sup>[31]</sup>, showed no differences between patients and controls, there is solid evidence about the increase of other inflammation markers in CD. In this regard, a previous study reported an increase in tumor necrosis factor (TNF)- $\alpha$ -producing innate lymphoid cells in the intestinal mucosa of untreated CD patients in comparison with treated patients and healthy controls<sup>[32]</sup>.

Moreover, an increase in TNF- $\alpha$  and interleukin (IL)-6 levels has been reported in the epithelium and the lamina propria of the intestinal mucosa of untreated CD patients<sup>[33,34]</sup>. Additionally, higher levels of IL-6 have been observed in the plasma of untreated CD patients compared to treated ones and healthy controls<sup>[35,36]</sup>.

Regarding markers of carbohydrate metabolism, even though insulin levels and HOMA-IR were increased and QUICKI diminished, the analysis of the individual values did not allow the diagnosis of insulin resistance in any of the patients included in the present study. In fact, the results obtained were below the values reported for patients with metabolic syndrome or type 2 diabetes, though above those reported for the general population<sup>[37-40]</sup>. Nevertheless, even the presence of a subtle alteration in carbohydrate metabolism in untreated CD patients would possess great clinical impact. Actually, GFD, the only available treatment for CD, contains higher caloric density than similar diets based on gluten containing foods, and its implementation could, as a result, increase the risk of developing obesity, and, consequently, metabolic syndrome and diabetes<sup>[41-43]</sup>. Therefore, assessment of fasting glucose and insulin in patients diagnosed with CD before and during the introduction of GFD should be performed. However, the subject is still controversial. Kabbani *et al.*<sup>[44]</sup> reported lower prevalence of metabolic syndrome and type 2 diabetes in patients under GFD treatment, regardless of treatment duration. Moreover, experiments carried out in C57BL/6 mice fed on a hyper fat diet with and without gluten showed that GFD reduced insulin resistance, adiposity and inflammation<sup>[45]</sup>, although it is necessary to consider that these mice did not present CD. In the present study, the finding of significantly higher insulin levels and HOMA-IR and lower QUICKI than in controls suggests the presence of a slightly altered carbohydrate metabolism, which could be related to the pro-inflammatory status described in CD patients and evidenced in our study by higher hsCRP levels. It has been previously proposed that inflammation could be a causative agent for alterations in carbohydrate metabolism through the action of cytokines such as TNF- $\alpha$ , IL-6 and IL-1 $\beta$ , among others<sup>[46,47]</sup>.

Studying lipoprotein profile in CD patients appears interesting, since there is evidence for both a decrease in cholesterol absorption and an increase in its synthesis<sup>[48-50]</sup>. In the current study, patients showed TC and LDL-C levels similar to controls. These findings are in disagreement with the decrease in both parameters previously reported for CD patients<sup>[5,51,52]</sup>. Patients evaluated in this study also presented lower HDL-C levels. There is prior evidence showing a 12% prevalence of CD in patients with low HDL-C concentration<sup>[53]</sup>, much higher than that reported for the general population, which implies a causal relationship between the presence of CD and the decrease in HDL-C. Unlike in the case of patients with insulin resistance<sup>[54,55]</sup>, this decrease was not found to be associated with higher CETP activity. Therefore,

this alteration could result from a lower synthesis and secretion of apo A-I<sup>[56]</sup>. Furthermore, longitudinal studies described an increase in HDL-C and apo A-I values after initiation of treatment with GFD<sup>[51]</sup>. In addition, CD patients presented an increase in TC/HDL-C and apo B/apo A-I ratios<sup>[57]</sup>, which reflect an imbalance between proatherogenic and antiatherogenic lipid factors. Another possibility that could explain HDL-C decrease is that HDL particles from CD patients would possess less capability to promote cholesterol efflux from cells. In fact, apo A-I has not only got a structural role in HDL particles, but it is also involved in multiple antiatherogenic functions including cholesterol efflux promotion<sup>[58]</sup>. Due to the decrease in intestinal apo A-I synthesis, the number of circulating HDL particles would be diminished and, in turn, each particle would be depleted in this apolipoprotein. As a matter of fact, in other inflammatory pathologies such as rheumatoid arthritis, alterations in HDL functionality have been associated with higher risk of CVD<sup>[59]</sup>. Study of HDL functions in affected patients could provide important evidence linking CD and CVD risk.

Regarding hematological parameters, only folic acid was decreased in CD patients. This finding is consistent with previous reports that show a decrease in folic acid levels as a consequence of impaired intestinal absorption, resulting from the damage to the intestinal epithelium caused by the inflammatory process<sup>[60]</sup>. This folic acid deficiency persists, in many cases, even after the initiation of treatment with GFD<sup>[61]</sup>. It is worth noting that a decrease in folic acid levels may lead to an increase in homocysteine concentration. One of the main homocysteine clearance pathways consists of its re-methylation and recycling to methionine, a process catalyzed by the methionine synthase (MTR) enzyme, which links the folate cycle with homocysteine metabolism<sup>[62]</sup>. In fact, different studies showed higher homocysteine levels in CD patients<sup>[26,63,64]</sup>. Importantly, this increment was independently associated with increased risk and severity of coronary artery disease<sup>[65]</sup>. Moreover, high homocysteine levels were also identified as independent predictors of a suboptimal response to antiplatelet therapy with acetyl salicylic acid, thus favouring thrombotic complications in patients with coronary artery disease<sup>[66]</sup>. In addition, in a meta-analysis of randomized controlled trials, Liu *et al.*<sup>[67]</sup> demonstrated that folic acid supplementation could improve the endothelial dysfunction observed in patients with coronary artery disease. Nevertheless, studies on homocysteine-lowering interventions with vitamin B6, folic acid (vitamin B9) or vitamin B12, administered alone or in combination with the purpose of preventing cardiovascular events, failed to consistently demonstrate their efficacy<sup>[68]</sup>. Therefore, consideration of increased homocysteine levels as a risk factor for CVD is still a controversial topic<sup>[69]</sup>.

In the present study, newly diagnosed CD patients, who were not following a GFD, presented higher insulin

levels, HOMA-IR index, apo B/apo A-I ratio and hsCRP concentration, as well as lower QUICKI index, HDL-C and apo A-I levels in comparison with sex and aged-matched healthy controls.

### Limitations

The main limitation of the present study is that, due to its cross-sectional design, it only provides a “snapshot” of the outcome and the characteristics associated with it, at a specific point in time. Then, only associations that may exist and are therefore useful in generating hypotheses for future research may be established. Another limitation is the sample size, which may be attributed to the fact that this study only included newly diagnosed CD patients, but that hampered the search for a possible correlation between intestinal inflammation factors and the risk of atherosclerosis.

### Conclusions

According to the results reported in the current study, untreated CD patients would present modifications in carbohydrate and lipoprotein metabolism and a pro-inflammatory status. Even though the magnitude of the alterations here described is not major, their presence and interaction through long periods of time in a chronic pathologic condition, as it is the case with CD, would constitute a high risk of developing atherosclerotic CVD.

## COMMENTS

### Background

Celiac disease (CD) is a multisystemic disease which main trait is chronic and diffuse inflammation of the mucosa of the small intestine. The only available therapy for CD consists of the implementation of a gluten free diet (GFD). It is well known that CD patients do not show classical cardiovascular disease (CVD) risk factors suggesting that CD would be associated with novel atherogenic risk factors or even with other non-identified risk factors such as inflammatory markers.

### Research frontiers

The role of novel atherogenic risk factors or inflammatory markers for CVD in CD patients has been poorly studied. The research hotspot is to assess which factors or markers for cardiovascular disease are found in CD patients in order to be able to prevent or treat them.

### Innovations and breakthroughs

It is well known that CD patients do not show classical CVD risk factors. Therefore in these patients, detection of novel atherogenic risk factors would be crucial to reduce the risk of CVD.

### Applications

The detection of CVD risk factors in CD patients is an important tool for the implementation of an adequate treatment.

### Terminology

CD is a disease which mainly affects the digestive system. Its main trait is chronic and diffuse inflammation of the mucosa of the small intestine and it can present a wide variety of clinical symptoms. It is remarkable that most cases of CD lack typical gastrointestinal symptoms and are, instead, very frequently associated with presentations known as atypical or extra-intestinal. Thus, its diagnosis represents one of the main challenges for health professionals

### Peer-review

This is an interesting study showing that patients with CD do have an atherogenic lipoprotein profile that may dispose them to develop CVD.

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## Prospective Study

**Combined assessment of myocardial damage and electrical disturbance in chronic heart failure**

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**Author contributions:** In this study, Kadowaki S helped design the study, obtained and analyzed data, and drafted the manuscript; Watanabe T and Kubota I contributed to discussions about study design and data analyses; Kadowaki S, Otaki Y, Narumi T, Honda Y, Takahashi H, Arimoto T, Shishido T and Miyamoto T were involved with data collection, and assisted with data analysis; all authors read and approved the final manuscript.

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**Abstract****AIM**

To investigate feasibility of combined assessment of biochemical and electrophysiological myocardial impairment markers risk-stratifying patients with chronic heart failure (CHF).

**METHODS**

Serum levels of heart-type fatty acid binding protein (H-FABP) as a marker of ongoing myocardial damage and QRS duration on electrocardiogram were measured at admission in 322 consecutive patients with CHF. A prolonged QRS duration was defined as 120 ms or longer. The cut-off value for H-FABP level (4.5 ng/mL) was determined from a previous study. Patients were prospectively followed during a median follow up period of 534 d. The primary endpoint was cardiac deaths and rehospitalization for worsening CHF.

**RESULTS**

There were 117 primary events, including 27 cardiac deaths and 90 rehospitalizations. Patients were stratified into four groups according to H-FABP level and QRS duration ( $\geq 120$  ms). Multivariate analysis demonstrated that high H-FABP levels [hazard ratio (HR) = 1.745,  $P = 0.021$ ] and QRS prolongation (HR

1.612,  $P = 0.0258$ ) were independent predictors of cardiac events. Kaplan-Meier analysis demonstrated that the combination of high H-FABP levels and QRS prolongation could be used to reliably stratify patients at high risk for cardiac events (log rank test  $P < 0.0001$ ).

### CONCLUSION

Combined assessment of myocardial damage and electrical disturbance can be used to risk-stratify patients with CHF.

**Key words:** QRS prolongation; Heart-type fatty acid binding protein; Heart failure; Prognosis

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**Core tip:** This was a prospective single center study with 322 consecutive patients with chronic heart failure (CHF) seeking to evaluate the feasibility of combined assessment of biochemical and electrophysiological markers of myocardial impairment for risk-stratifying patients with CHF. QRS prolongation and high heart-type fatty acid binding protein levels are independently associated with cardiac events in patients with CHF.

Kadowaki S, Watanabe T, Otaki Y, Narumi T, Honda Y, Takahashi H, Arimoto T, Shishido T, Miyamoto T, Kubota I. Combined assessment of myocardial damage and electrical disturbance in chronic heart failure. *World J Cardiol* 2017; 9(5): 457-465 Available from: URL: <http://www.wjgnet.com/1949-8462/full/v9/i5/457.htm> DOI: <http://dx.doi.org/10.4330/wjc.v9.i5.457>

## INTRODUCTION

Chronic heart failure (CHF) is a major health problem with high mortality despite advance in medical therapy<sup>[1-3]</sup>. Various pathophysiological changes are reportedly associated with initiation and progression in CHF<sup>[4]</sup>. The role of biomarkers continues to increase in importance to evaluate and risk-stratify CHF patients<sup>[5]</sup>.

Heart-type fatty acid binding protein (H-FABP) is a small molecule protein (14-15 kDa), abundant in cytoplasm of cardiomyocytes and easily leaks to the circulation from damaged myocardium<sup>[6-8]</sup>. H-FABP is a potential myocardial damage marker. We and others reported that elevated serum H-FABP levels can predict poor outcomes in patients with CHF<sup>[9,10]</sup>. Progression of CHF is associated with persistent loss of cardiomyocytes, which can be clinically detected as a continuous increase in serum H-FABP levels<sup>[11]</sup>.

Electrocardiography (ECG) is routinely performed and is useful for evaluating the etiology of heart failure. Several electrocardiographic parameters were reported to predict poor outcome in HF patients<sup>[12-14]</sup>. QRS prolongation indicated electrical disturbance and is associated with left ventricular dyssynchrony and poor cardiac prognosis in patients with CHF<sup>[15-17]</sup>. Not

surprisingly, due to the complex pathogenesis of CHF, a single biomarker cannot be used to predict the absolute risk of future cardiac events. Therefore, the purpose of the present study was to investigate whether a combined measurement of a myocardial damage marker and electrical disturbance can be used to risk-stratify CHF patients.

## MATERIALS AND METHODS

### Study population

We prospectively studied 322 patients with CHF, who were admitted to our hospital for the diagnosis or treatment of CHF. The diagnosis of CHF was made by two cardiologists who used the generally accepted Framingham criteria, including a history of dyspnea and symptomatic exercise intolerance, signs of pulmonary congestion, peripheral edema, and radiologic or echocardiographic evidence of left ventricular enlargement or dysfunction. Demographic and clinical data including age, gender, New York Heart Association (NYHA) functional class, and medications at discharge were obtained from hospital medical records and interviews with patients. The diagnoses of hypertension, diabetes mellitus and hyperlipidemia were ascertained from the medical records or current or previous medical therapy. Glomerular filtration rate (GFR) was estimated using the modification of diet in renal disease equation with the Japanese coefficient, as previously reported<sup>[18]</sup>. The exclusion criteria for the present study were acute coronary syndrome, bundle branch block, pace maker implantation, a serum creatinine concentration  $> 2.0$  mg/dL, and implantation of a heart valve prosthesis.

### Electrocardiographic and echocardiographic studies

Standard 12-lead ECG was performed at admission. QRS duration was measured by averaging of all heartbeats all leads. A normal QRS duration was defined as less than 120 ms and a prolonged QRS as 120 ms or longer. Transthoracic echocardiography was performed by physicians who were blinded to the biochemical data.

### Assay of H-FABP and brain natriuretic peptide concentrations

Venous blood samples were obtained at admission for measurements of serum H-FABP levels. These samples were immediately centrifuged at 2500 G for 15 min at 4 °C. The clarified serum samples were frozen, stored at -70 °C, and thawed just before assay. H-FABP concentration was measured using a two-step sandwich enzyme-linked immunosorbent assay kit (MARKIT-M HFABP, Dainippon Pharmaceutical Co Ltd, Tokyo, Japan) as previously reported<sup>[19,20]</sup>. The cut-off value for H-FABP concentration (4.5 ng/mL) was determined from a previous study<sup>[21]</sup>. The same blood samples were used for measurement of plasma brain natriuretic peptide (BNP) concentrations. The samples were transferred to chilled tubes containing of ethylene diamine tetraacetic acid disodium salt (4.5 mg) and aprotinin (500 U/mL),

and immediately centrifuged at 1000 G for 15 min at 4 °C. The clarified plasma samples were frozen, stored at -70 °C and thawed just before assay. BNP concentrations were measured using a commercially available specific radioimmunoassay for human BNP (Shiono RIA BNP assay kit, Shionogi Co Ltd, Tokyo, Japan). The analytical ranges, and intra- and inter-assay coefficients of variation for the H-FABP and BNP assays were, 1.1-250 ng/mL, 3% and 3.5%, and 4.0-2000 pg/mL, 10.9% and 10.6%, respectively.

### End points and follow-up

Patients were prospectively followed for a median period of 534 d (range 203-1014). Patients were followed in our hospital outpatient clinic every month. The other patients were followed by telephone twice a year until 2555 d after discharge. The end points were cardiac death, defined as death due to progressive heart failure, myocardial infarction or sudden cardiac death, and progressive heart failure requiring rehospitalization. Sudden cardiac death was defined as death without definite premonitory symptoms or signs, and was established by the attending physician. The study was approved by the Institutional Ethics Committee, and all patients gave written informed consent prior to participating. The study was performed in accordance with the Helsinki Declaration.

### Statistical analysis

Results are presented as the mean values  $\pm$  SD for continuous variables and as percentages of the total number of patients for categorical variables. The independent samples *t* test and  $\chi^2$  test or linear regression analysis were used for comparison of continuous and categorical variables, respectively. A Cox proportional hazard analysis was performed to assess the independent predictors for cardiac events in the entire population. Statistical significance was defined as  $P < 0.05$ . Variables identified as significant by univariate analysis were entered into the multivariate analysis. The cardiac event-free curve was computed according to the Kaplan-Meier method, and comparison of cardiac event-free survival between subgroups was performed using the log-rank test. Receiver operating characteristic (ROC) curve analysis, as well as area under the curve (AUC) was used as measures of the predictive accuracy of traditional prognostic factors for cardiac events. In addition, the net reclassification improvement (NRI) and integrated discrimination improvement (IDI) were calculated in order to quantify the improvement for the corrected reclassification and sensitivity after inclusion of high H-FABP levels and QRS prolongation in the model. Statistical analyses were performed using a standard software package (JMP version 8; SAS Institute Inc., Cary, NC, United States) or R 3.0.2 with additional packages (Rcmdr, Epi, pROC and PredictABEL).

## RESULTS

### Patient characteristics

Table 1 shows that clinical characteristics of the study patients. The mean age of the patients was  $69 \pm 13$  years. There were 175 patients in NYHA functional class II, 105 in NYHA class III, and 42 in NYHA class IV. Diabetes mellitus, dyslipidemia, and hypertension were identified in 117 (36%), 87 (26%), and 217 (67%) of the CHF patients, respectively. The etiology of heart failure was dilated cardiomyopathy in 80 (25%) patients, hypertensive heart disease in 14 (4%), hypertrophic cardiomyopathy in 21 (7%), ischemic heart disease in 65 (20%), valvular heart disease in 80 (25%), arrhythmia in 24 (7%), and other etiologies in 38 (12%) patients. The median H-FABP and BNP levels were 4.7 (3.3-7.6) ng/mL and 397 (135-853) pg/mL, respectively. The mean QRS duration was  $107 \pm 20$  ms and 61 patients (19%) showed QRS prolongation. Simple linear regression analysis showed that QRS duration was not correlated with H-FABP level ( $r = 0.091$ ,  $P = 0.1019$ ) or BNP level ( $r = 0.066$ ,  $P = 0.2356$ ) as shown in Figure 1.

### Clinical outcomes

During the follow-up period, there were 117 primary events, including 27 cardiac deaths and 90 re-admissions for worsening CHF. Among 27 cardiac deaths, there were 21 deaths from worsening CHF, 2 fatal acute myocardial infarction, and 4 sudden cardiac deaths. The patients with cardiac events were older and had a more severe NYHA functional class compared to those who did not (Table 1). Furthermore, higher BNP and H-FABP levels, and a higher prevalence of QRS prolongation were observed in patients who experienced cardiac events, compared with those who did not. Patients who experienced cardiac events also had a lower estimated GFR (eGFR) compared with those who did not. There was no difference in gender, prevalence of atrial fibrillation, hypertension, diabetes mellitus or hyperlipidemia between CHF patients with and without cardiac events. Patients who experienced cardiac events took loop diuretics more frequently than patients who were event-free.

### Independent predictors of cardiac events

To investigate the risk factors for cardiac events, Cox proportional hazards regression analyses were performed (Table 2). In the univariate analysis, high H-FABP levels and QRS prolongation were significantly associated with cardiac events. Further, age, NYHA functional class, BNP levels, and eGFR were significantly associated with cardiac events. In the multivariate analysis, NYHA functional class, eGFR, high serum H-FABP levels, and prolonged QRS duration were independently associated with cardiac events.

**Table 1 Comparison of the clinical characteristics of patients with and without cardiac events**

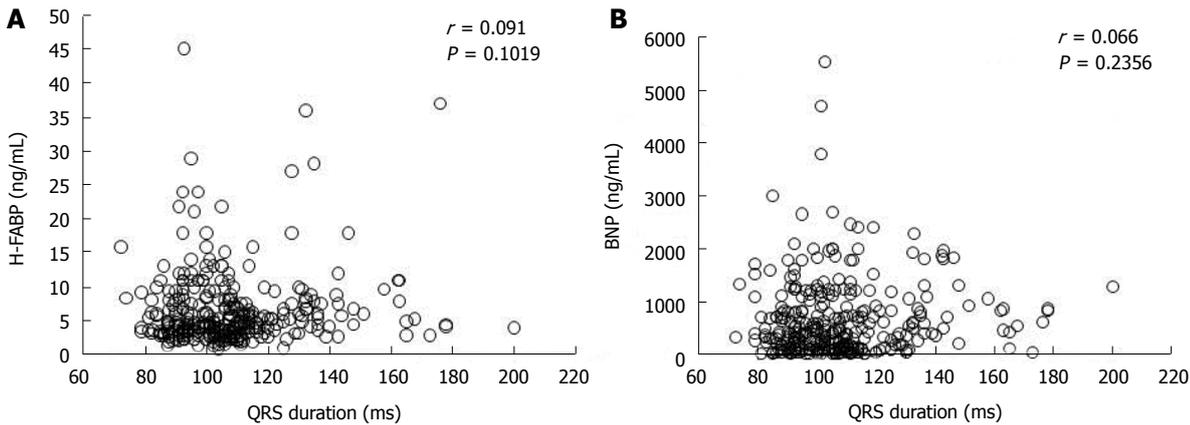
	All patients (n = 322)	Event-free (n = 205)	Cardiac event (n = 117)	P value
Age, yr	69 ± 13	67 ± 14	72 ± 11	0.0041
Female, n (%)	140 (43)	92 (45)	48 (41)	0.5024
NYHA functional class, II/III/IV	175/105/42	125/53/27	50/52/15	0.002
Etiology, n (%)				0.5273
Dilated cardiomyopathy	80 (25)	56 (27)	24 (21)	
Hypertensive heart disease	14 (4)	10 (5)	4 (3)	
Hypertrophic cardiomyopathy	21 (7)	15 (7)	6 (5)	
Ischemic heart disease	65 (20)	36 (18)	29 (25)	
Valvular heart disease	80 (25)	52 (25)	28 (24)	
Arrhythmia	24 (7)	14 (7)	10 (8)	
Others	38 (12)	22 (11)	16 (14)	
Atrial fibrillation, n (%)	109 (34)	64 (31)	45 (38)	0.1866
Diabetes mellitus, n (%)	117 (36)	71 (35)	44 (38)	0.5923
Dyslipidemia, n (%)	87 (26)	56 (26)	31 (27)	0.8732
Hypertension, n (%)	217 (67)	137 (67)	80 (68)	0.7758
Blood biomarkers				
BNP, pg/mL (IQR)	397 (135-853)	314 (101-710)	625 (280-1147)	0.0326
H-FABP, ng/mL (IQR)	4.7 (3.3-7.6)	4.0 (2.9-6.3)	6.0 (4.2-10.0)	< 0.0001
eGFR, mL/min per 1.73 m <sup>2</sup>	65 ± 22	69 ± 23	58 ± 19	< 0.0001
Echocardiographic data				
LV end-diastolic diameter, mm	55 ± 10	54 ± 9	55 ± 12	0.6018
LV ejection fraction, %	49 ± 18	50 ± 18	47 ± 18	0.1472
Electrocardiogram				
Heart rate, beat/min	77 ± 22	78 ± 21	74 ± 19	0.0841
QRS duration, ms	107 ± 20	106 ± 18	109 ± 22	0.0989
QRS prolongation, n (%)	61 (19)	28 (17)	33 (28)	0.0014
Medications, n (%)				
ACE inhibitors and/or ARBs, n (%)	213 (66)	138 (67)	75 (64)	0.5577
β-blockers, n (%)	170 (53)	106 (52)	64 (55)	0.6048
Ca channel blockers, n (%)	66 (21)	41 (21)	25 (20)	0.77
Diuretics, n (%)	202 (63)	111 (54)	91 (78)	< 0.0001
Statins, n (%)	83 (26)	54 (26)	29 (25)	0.759

Data are presented as mean ± SD or % unless otherwise indicated. ACE: Angiotensin-converting enzyme; ARB: Angiotensin receptor blocker; BNP: Brain natriuretic peptide; eGFR: Estimated glomerular filtration rate; H-FABP: Heart-type fatty acid-binding protein; LV: Left ventricular; NYHA: New York Heart Association.

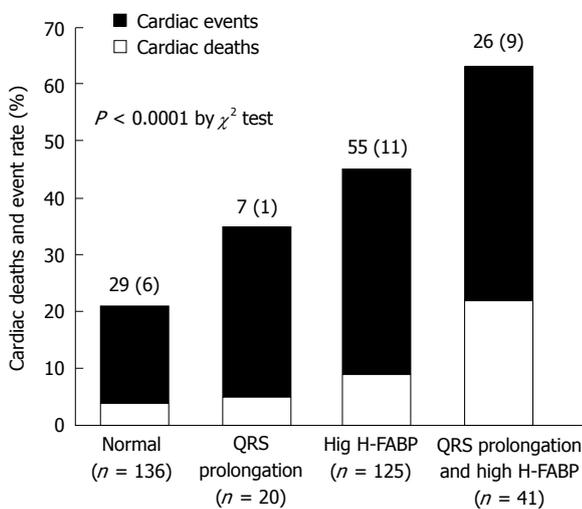
**Table 2 Univariate and multivariate analyses for cardiovascular events**

	HR	95%CI	P value
Univariate analysis			
Age, per 10-yr increase	1.297	1.105-1.524	0.0016
Female gender	0.829	0.573-1.199	0.3183
NYHA functional class II and III vs IV	1.960	1.381-2.747	0.0003
Atrial fibrillation	1.256	0.865-1.824	0.2304
Diabetes mellitus	1.103	0.758-1.605	0.6062
Dyslipidemia	0.958	0.635-1.447	0.8417
Hypertension	0.986	0.667-1.457	0.9459
BNP, per 1SD increase	1.166	1.019-1.334	0.0249
eGFR, per 1SD increase	0.589	0.467-0.733	< 0.0001
LV end-diastolic diameter, per 1SD increase	1.062	0.877-1.280	0.5272
LV ejection fraction, per 1SD increase	0.881	0.734-1.074	0.1998
Heart rate, per 1SD increase	0.869	0.724-1.062	0.1724
High H-FABP (> 4.5 ng/mL)	2.994	1.996-4.504	< 0.0001
QRS prolongation (≥ 120 ms)	1.897	1.264-2.832	0.0019
Multivariate analysis			
Age, per 10-yr increase	1.093	0.921-1.298	0.3055
NYHA functional class II and III vs IV	1.55	1.055-2.309	0.0262
BNP, per 1SD increase	0.948	0.811-1.151	0.7003
eGFR, per 1SD increase	0.733	0.571-0.938	0.0144
High H-FABP (> 4.5 ng/mL)	1.745	1.088-2.793	0.0210
QRS prolongation (≥ 120 ms)	1.612	1.060-2.451	0.0258

HR: Hazard ratio; SD: Standard deviation; BNP: Brain natriuretic peptide; eGFR: Estimated glomerular filtration rate; NYHA: New York Heart Association.



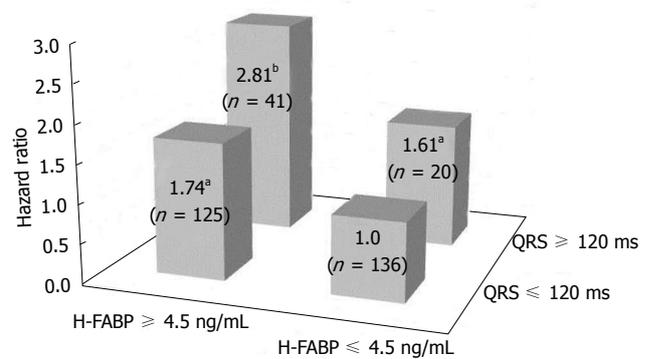
**Figure 1** Relationship between QRS duration and heart-type fatty acid binding protein levels (A) and brain natriuretic protein levels (B). BNP: Brain natriuretic peptide; H-FABP: Heart-type fatty acid-binding protein.



**Figure 2** Cardiac mortality and all cardiac events among the four groups based on heart-type fatty acid-binding protein level and QRS duration. Normal group ( $n = 136$ ), H-FABP  $\leq 4.5$  ng/mL and QRS duration  $< 120$  ms; QRS prolongation group ( $n = 20$ ), H-FABP  $\leq 4.5$  ng/mL and QRS duration  $\geq 120$  ms; high H-FABP group ( $n = 125$ ), H-FABP  $> 4.5$  ng/mL and QRS duration  $< 120$  ms; and high H-FABP + QRS prolongation group ( $n = 41$ ), H-FABP  $> 4.5$  ng/mL and QRS duration  $\geq 120$  ms. H-FABP: Heart-type fatty acid-binding protein.

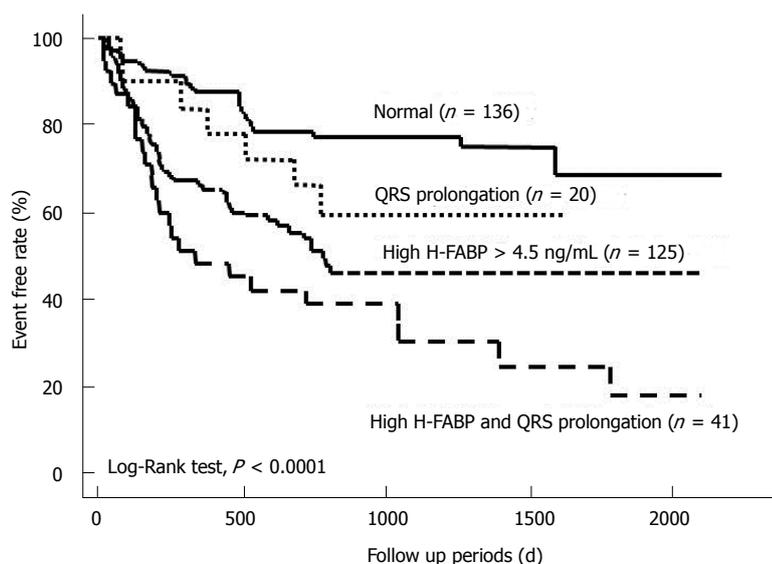
**A combined assessment of QRS duration and H-FABP level**

Simple linear analysis demonstrated that QRS duration was not correlated with H-FABP or BNP levels in patients with CHF (Figure 1). The patients were divided into four groups based on QRS prolongation and H-FABP cutoff values as shown in Figure 2: (1) normal group ( $n = 136$ ), H-FABP  $\leq 4.5$  ng/mL, QRS duration  $< 120$  ms; (2) QRS prolongation group ( $n = 20$ ), H-FABP  $\leq 4.5$  ng/mL, QRS  $\geq 120$  ms; (3) high H-FABP group ( $n = 125$ ), H-FABP  $> 4.5$  ng/mL, QRS duration  $< 120$  ms; and (4) high H-FABP + QRS prolongation group ( $n = 41$ ), H-FABP  $> 4.5$  ng/mL, QRS duration  $\geq 120$  ms. High serum H-FABP + QRS prolongation group showed the highest rates of cardiac deaths and cardiac events ( $P < 0.001$ ). Multivariate Cox hazard analysis revealed that after



**Figure 3** Hazard ratios relative to the normal group after adjustment for age, New York Heart Association functional class, brain natriuretic peptide level and estimated glomerular filtration rate. <sup>a</sup> $P < 0.05$ , <sup>b</sup> $P < 0.01$  vs normal group. H-FABP: Heart-type fatty acid-binding protein.

adjustment for age, NYHA functional class, BNP levels and eGFR, the QRS prolongation, high H-FABP, and high H-FABP + QRS prolongation groups had 1.61-fold ( $P < 0.05$ ), 1.74-fold ( $P < 0.05$ ), and 2.81-fold higher risks of cardiac events ( $P < 0.01$ ), respectively, compared with the normal group (Figure 3). The characteristics of these four groups are presented in Table 3. The QRS prolongation group had lower BNP levels than the high H-FABP and high H-FABP + QRS prolongation groups. The QRS prolongation group also had the lowest left ventricular (LV) ejection fraction and largest LV end-diastolic diameter among 4 groups. Kaplan-Meier analysis demonstrated that the high H-FABP + QRS prolongation group had a significantly higher rate of cardiac events than the other groups (Figure 4). In order to examine whether model fit and discrimination improved with the addition of high H-FABP levels and QRS prolongation to the traditional prognostic factors of age, BNP level, NYHA functional class and eGFR, the differences in area under the ROC curves, and the improvement in NRI and IDI were evaluated for two models: With (group 2) or without (group 1) a high H-FABP level and QRS prolongation. The area under the ROC curve for predicted cardiac events was significantly



**Figure 4** Kaplan-Meier analysis of the cardiac event-free curve in patients with chronic heart failure, who were stratified into four groups based on QRS duration and heart-type fatty acid-binding protein level. H-FABP: Heart-type fatty acid-binding protein.

**Table 3** Clinical characteristics of the 4 subgroups of chronic heart failure patients

	Normal (n = 136)	QRS prolongation (n = 20)	High H-FABP (n = 125)	High H-FABP and QRS prolongation (n = 41)
Age, yr	65 ± 13	59 ± 11	74 ± 11 <sup>a,b</sup>	71 ± 13 <sup>b</sup>
Female, n (%)	58 (42)	10 (50)	55 (45)	17 (41)
NYHA functional class, II/III/IV	97/30/9	3/4/2013	51/54/20	14/18/9 <sup>e</sup>
Etiology, n (%)				
Dilated cardiomyopathy	33 (24)	8 (40)	24 (19)	15 (37)
Hypertensive heart disease	8 (6)	1 (5)	5 (4)	1 (2)
Hypertrophic cardiomyopathy	11 (8)	3 (15)	6 (5)	0 (0)
Ischemic heart disease	21 (15)	3 (15)	31 (24)	10 (24)
Valvular heart disease	40 (30)	3 (15)	29 (24)	8 (20)
Arrhythmia	12 (9)	0 (0)	8 (7)	4 (10)
Others	11 (8)	2 (10)	22 (17)	3 (7)
Atrial fibrillation, n (%)	48 (35)	7 (35)	41 (33)	13 (32)
Diabetes mellitus, n (%)	46 (33)	6 (28)	46 (37)	17 (41)
Dyslipidemia, n (%)	39 (28)	4 (20)	32 (26)	12 (29)
Hypertension, n (%)	92 (67)	11 (55)	89 (72)	25 (61)
Blood biomarkers				
BNP, pg/mL (IQR)	347 (69-453)	389 (213-855)	700 (311-1257) <sup>a</sup>	628 (328-1075) <sup>a</sup>
H-FABP, ng/mL (IQR)	3.2 (2.4-3.9)	3.6 (2.8-4.2)	7.6 (5.7-11.0) <sup>a,b</sup>	7.6 (5.7-9.8) <sup>a,b</sup>
eGFR, mL/min per 1.73 m <sup>2</sup>	75 ± 20	71 ± 26	57 ± 20 <sup>a</sup>	52 ± 17 <sup>a,d</sup>
Echocardiographic data				
LV end-diastolic diameter, mm	52 ± 10	65 ± 9 <sup>a,d</sup>	54 ± 9 <sup>b</sup>	60 ± 10 <sup>a,c</sup>
LV ejection fraction, %	55 ± 18	35 ± 15 <sup>a</sup>	49 ± 17 <sup>b</sup>	38 ± 14 <sup>a,d</sup>
Electrocardiogram				
Heart rate, beat/min	78 ± 19	72 ± 13	79 ± 22	72 ± 20
QRS duration, ms	100 ± 10	143 ± 23 <sup>a,d</sup>	100 ± 10	138 ± 14 <sup>a,d</sup>
Medications, n (%)				
ACE inhibitors and/or ARBs, n (%)	86 (62)	13 (65)	85 (69)	29 (71)
β-blockers, n (%)	65 (47)	15 (75)	64 (52)	26 (63)
Ca channel blockers, n (%)	36 (26)	0 (0)	24 (20)	6 (15)
Diuretics, n (%)	72 (52)	14 (70)	82 (67)	34 (83) <sup>e</sup>
Statins, n (%)	40 (29)	5 (25)	28 (23)	10 (24)

<sup>a</sup>P < 0.01 vs normal; <sup>b</sup>P < 0.01 vs QRS prolongation; and <sup>c</sup>P < 0.05 and <sup>d</sup>P < 0.01 vs High H-FABP by analysis of variance with the Scheffe post hoc test. <sup>e</sup>P < 0.01 by  $\chi^2$  test. Normal group (n = 136): H-FABP ≤ 4.5 ng/mL and QRS duration < 120 ms; QRS prolongation group (n = 20): H-FABP ≤ 4.5 ng/mL and QRS duration ≥ 120 ms; High H-FABP group (n = 123): H-FABP > 4.5 ng/mL and QRS duration < 120 ms; and High H-FABP and QRS prolongation group (n = 41): H-FABP > 4.5 ng/mL and QRS duration ≥ 120 ms. ACE: Angiotensin-converting enzyme; ARB: Angiotensin receptor blocker; BNP: Brain natriuretic peptide; eGFR: Estimated glomerular filtration rate; H-FABP: Heart-type fatty acid-binding protein; LV: Left ventricular; NYHA: New York Heart Association.

**Table 4** Statistics for model fit and improvement with the addition of high heart-type fatty acid-binding protein and QRS prolongation predicted on the prediction of cardiac events

	Group 1	Group 2	P value
AUC of ROC curve	0.668	0.706	0.029
NRI (95%CI)	Ref	0.223 (0.073-0.372)	0.003
IDI (95%CI)	Ref	0.036 (0.015-0.056)	0.016

AUC: Area under the curve; CI: Confidence interval; IDI: Integrated discrimination improvement; NRI: Net reclassification improvement; ROC: Receiver operator characteristics. Group 1: Age + BNP + NYHA + eGFR; Group 2: Group 1 + H-FABP > 4.5 ng/mL + QRS duration  $\geq$  120 ms. BNP: Brain natriuretic peptide; eGFR: Estimated glomerular filtration rate; H-FABP: Heart-type fatty acid-binding protein; NYHA: New York Heart Association.

greater for group 2 than group 1 (Table 4). Further, the group 2 model improved the NRI and IDI values for predicting cardiac events compared with the group 1 model.

## DISCUSSION

In the present study, we demonstrated that QRS prolongation as a marker of electrical disturbance, and high H-FABP levels as a marker of ongoing myocardial damage are significantly related to cardiac events in CHF patients. The inclusion of high H-FABP level and QRS prolongation with BNP level, NYHA functional class and eGFR in the model for predicting cardiac events improved the NRI and IDI values, indicating effective reclassification and discrimination. Therefore, a combined measurement of H-FABP levels and QRS duration is a promising strategy for risk stratification for future cardiac events in CHF patients.

There are several markers of myocardial damage, including troponin T, troponin I and H-FABP<sup>[9,22]</sup>. Since H-FABP is a small cytosolic protein, it is readily released into the circulation when cardiomyocytes are injured. The mechanism by which serum levels of H-FABP are increased in CHF has been reported to be related to cardiomyocyte necrosis, apoptosis, chronic inflammation and microcirculatory disorder<sup>[8,23]</sup>. In this study, elevated levels of H-FABP were significantly associated with cardiac events, which are consistent with previous reports<sup>[19,24]</sup>.

QRS duration reflects LV conduction disturbance, LV systolic dysfunction and LV dilation<sup>[25]</sup>. In this study, the QRS prolongation group had the lowest LV ejection fraction and the greatest LV end-diastolic diameter compared with the other groups. Since left bundle branch block is an unfavorable prognostic marker in CHF patients<sup>[26,27]</sup>, patients with bundle branch block were excluded from the present study. Therefore, QRS prolongation is an independent risk factor for cardiac events in patients with CHF, irrespective of bundle branch block. Recently, it was reported that cardiac resynchronization therapy (CRT) can improve the cardiac prognosis in patients with QRS prolongation<sup>[28,29]</sup> and

measurement of QRS duration has attracted widespread interest.

The present study showed that there was no correlation between QRS duration and H-FABP or BNP levels in patients with CHF. These results suggest that H-FABP and BNP levels and QRS duration reflect different pathophysiological backgrounds. In the multivariate analysis, high H-FABP levels and QRS prolongation were independent predictors of cardiac events. In addition, multivariate Cox hazard analysis revealed that the combination of elevated H-FABP levels and QRS prolongation was associated with the highest increase in risk for cardiac events (2.81-fold) compared with the normal group.

Taniguchi *et al.*<sup>[30]</sup> reported that the combined measurement of BNP levels and QRS duration can be used to predict cardiac events in heart failure patients. We recently determined that the AUC for prediction of cardiac events in heart failure was greater for H-FABP level than for BNP level<sup>[10]</sup>. Both the sensitivity and the specificity for predicting cardiac events were significantly greater for H-FABP level than for BNP level, indicating that H-FABP level is superior to BNP level for predicting cardiac events in CHF patients<sup>[10]</sup>. In this study, BNP level was not associated with cardiac events in the multivariate analysis. A weak correlation between H-FABP levels and BNP levels was observed (data not shown), which was consistent with the results from a previous study<sup>[10]</sup>. H-FABP and BNP reflect different pathophysiological backgrounds as markers of left ventricular overload. Combined assessment of H-FABP as a biochemical marker of myocardial damage and QRS prolongation as an electrophysiological marker of myocardial impairment is a potentially useful method for risk-stratification in CHF patients.

This study has several limitations. The effect of changes in QRS duration and H-FABP level between the time of hospitalization and discharge were not evaluated. However, it was reported that QRS duration in patients with CHF did not change significantly over two years<sup>[31]</sup>. On the other hand, although H-FABP level is usually decreased at discharge, persistently elevated H-FABP levels were reported to be associated with adverse outcomes in patients with CHF<sup>[32]</sup>. Therefore, further research is needed to elucidate whether the combined assessment of H-FABP level at discharge and QRS prolongation can be used to more precisely predict the cardiac prognosis of patients with CHF.

In conclusion, the combined assessment of markers of ongoing myocardial damage and electrical disturbance can be used to risk-stratify patients with CHF.

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## COMMENTS

### Background

Despite advancing medical therapy, chronic heart failure (CHF) is a major health problem with high morbidity and mortality. It is important to risk-stratify patients with CHF.

### Research frontiers

Prolonged QRS duration reflects intraventricular conduction disturbance caused by left ventricular fibrosis and cardiac myocyte loss, and is associated with cardiac prognosis in patients with CHF. However, there are CHF patients with narrow QRS duration showing poor prognosis. Biochemical myocardial damage markers are also useful for predicting prognosis in addition to electrophysiological myocardial impairment markers in CHF patients.

### Innovations and breakthroughs

The combined assessment of markers of ongoing myocardial damage and electrical disturbance can risk-stratify patients with CHF.

### Applications

It may be difficult to predict prognosis of CHF patients using a single biomarker precisely. The combined assessment of commonly used biomarkers is easily applicable to clinical practice.

### Terminology

Since heart-type fatty acid binding protein (H-FABP) is a low molecular weight protein and abundant in the cytosolic fraction of cardiomyocytes, it is rapidly released into the circulation from damaged myocardium. Therefore, H-FABP is a potential marker of ongoing myocardial damage.

### Peer-review

The manuscript was very easy to follow and well written.

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## Cough induced syncope: A hint to cardiac tamponade diagnosis

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lung adenocarcinoma who presented with shortness of breath and frequent episodes of cough-induced syncope. A large pericardial effusion was found on echocardiogram suggestive of cardiac tamponade. Pericardiocentesis was done which improved the dyspnea and eventually resolved the syncope. There are only two other cases reported in the literature with cough-induced syncope in the setting of pericardial effusion or cardiac tamponade. Our clinical vignette also highlights the importance of pulsus paradoxus identification in patients with cough induced syncope to rule out cardiac tamponade since this is the most sensitive physical finding for its diagnosis.

**Key words:** Cardiac tamponade; Cough-induced syncope; Pericardial effusion

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**Core tip:** Cough-induced syncope should be a hint towards the consideration of either pericardial effusion or cardiac tamponade. Aside from the medical history and the diagnostic imaging modalities to include echocardiogram and chest computed tomography, clinical evaluation to explore pulsus paradoxus is imperative which has a high sensitivity in the diagnosis of cardiac tamponade. Timely diagnosis of cardiac tamponade because of these clues translate into prompt intervention to prevent the deleterious complications associated with it.

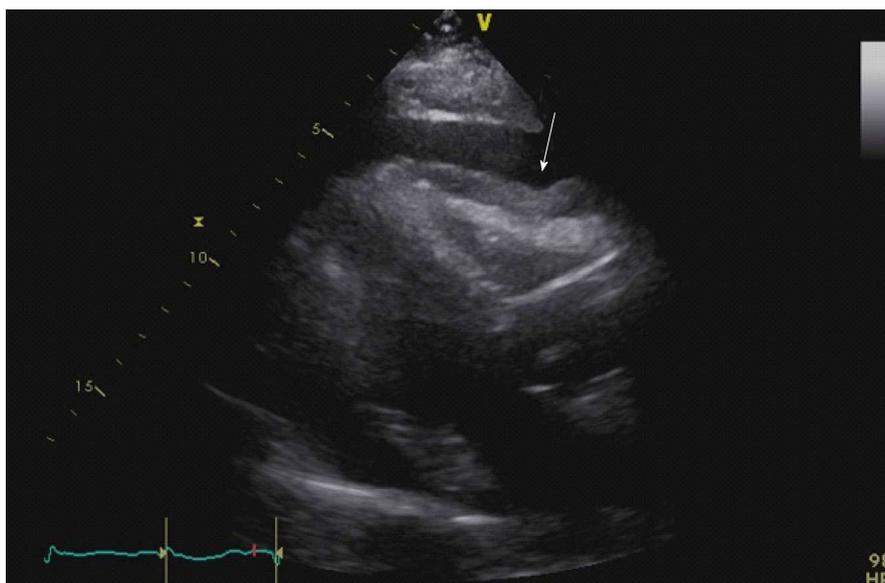
Ramirez R, Lasam G. Cough induced syncope: A hint to cardiac tamponade diagnosis. *World J Cardiol* 2017; 9(5): 466-469 Available from: URL: <http://www.wjgnet.com/1949-8462/full/v9/i5/466.htm> DOI: <http://dx.doi.org/10.4330/wjc.v9.i5.466>

### Abstract

We report a case of a 75-year-old male with history of

### INTRODUCTION

Cough-induced syncope is a validated rare phenomenon



**Figure 1** Transthoracic echocardiogram showing a large pericardial effusion with right ventricular diastolic indentation and collapse suggestive of tamponade.

which denotes cough as the etiology of the syncope and has been linked with chronic obstructive disease and constrictive pericarditis. It is very rare to have cough-induced syncope in a case of pericardial effusion or cardiac tamponade with only two other reported cases in the literature. Therefore, we describe a case of cough-induced syncope in an elderly gentleman with cardiac tamponade, elaborating further the pathophysiology behind this rare occurrence.

## CASE REPORT

A 75 years old male with known history of stage 4 adenocarcinoma of the lung with recent right lung biopsy, chronic obstructive pulmonary disease, hypertension, diabetes mellitus, hyperlipidemia and peripheral vascular disease presented with symptoms of increased shortness of breath for several days before hospitalization accompanied by cough with subsequent syncopal episodes. He had three syncopal episodes, two of them witnessed and were associated with coughing spells, lasting for 30 s to 1 min with complete recovery thereafter. No seizure-like activity was noted during the syncopal event. Prior to this presentation, he had never had a syncopal episode. The patient's syncope was not associated with other precipitants including laughter and micturition. On admission to the hospital, he was hypertensive with a blood pressure of 151/88 mmHg and with a pulse rate of 100. General appearance was apparent for occasional cough with no signs of cyanosis nor worsening shortness of breath. Further examination revealed mild diminished breath sounds at the bases. Cardiac evaluation showed sinus tachycardia with a soft 2/6 systolic murmur at the apex and a pulsus paradoxus of 16 mmHg but no note of muffled heart sounds, distended neck veins or peripheral edema.

Neuroexamination was intact and nonfocal. Pericardial effusion was considered immediately on admission because of his medical history, his symptoms, and the pulsus paradoxus which was confirmed later on by imaging studies. Hemogram revealed mild anemia (12.5 g/dL) and leukocytosis (12.8/nL). Electrocardiogram demonstrated sinus tachycardia (103 bpm) with intraventricular conduction delay but no low voltage complexes. No evident electrical alternans appreciated. Carotid ultrasound was done during his hospitalization which demonstrated no evidence of hemodynamically significant stenosis of the carotid system bilaterally and with normal antegrade flow of the vertebral arteries. Chest radiograph showed right pleural effusion. Chest computed tomography confirmed worsening bilateral pleural effusion as well as pericardial effusion but with no pulmonary embolus. Transthoracic echocardiography revealed a large pericardial effusion with right ventricular diastolic indentation and collapse suggestive of tamponade (Figure 1) which was also evident on the M-mode (Figure 2). Mitral valve inflow E wave velocity showed greater than 25% respiratory variation also suggestive of tamponade physiology (Figure 3). The cardiothoracic surgery team was involved to move forward with a pericardial window. Pericardiocentesis was done and drained 600 mL of hemorrhagic fluid. Subsequently, thoracentesis was performed and drained 500 mL of serosanguineous pleural fluid. Pericardial and pleural fluid cytology revealed adenocarcinoma. After drainage of both pericardial and pleural effusion, his dyspnea improved significantly and subsequently his cough-induced syncope resolved.

## DISCUSSION

Cough-induced syncope is a well-recognized but uncom-

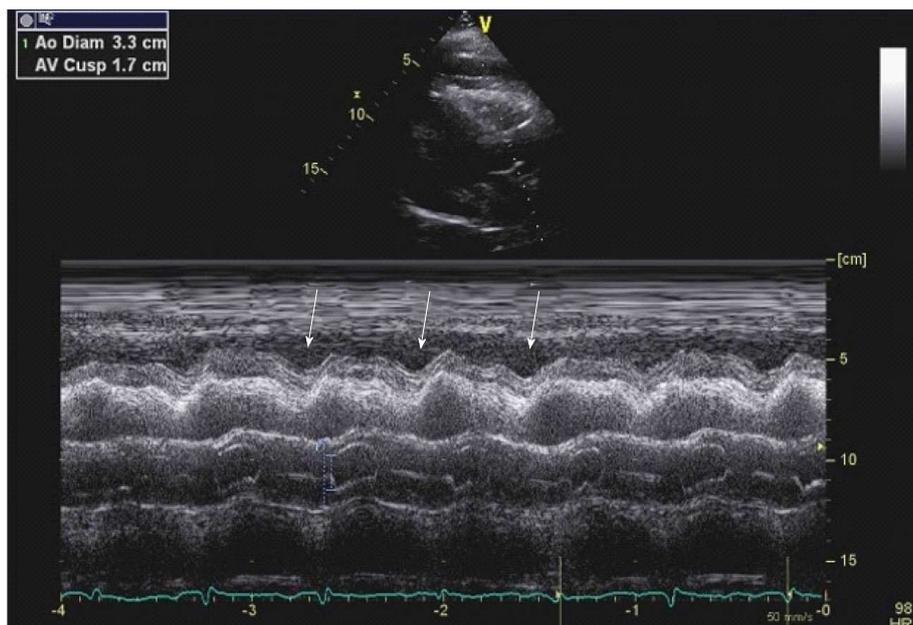


Figure 2 M-mode showing right ventricular diastolic indentation.

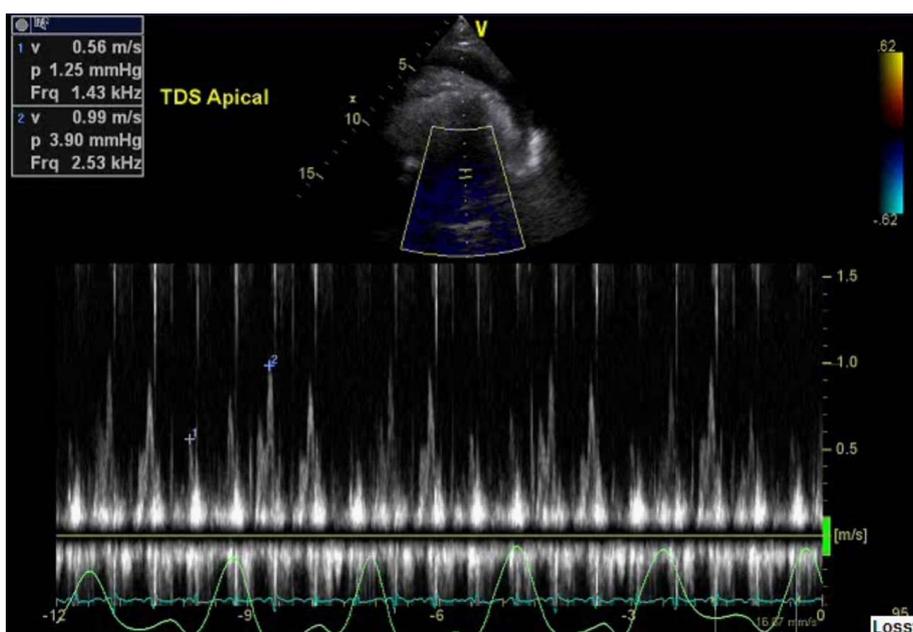


Figure 3 Transthoracic echocardiogram showing a mitral valve inflow E wave velocity greater than 25% respiratory variation suggestive of tamponade physiology.

mon phenomenon in which the cough is the main culprit of the syncope<sup>[1]</sup>. It is associated with chronic obstructive pulmonary disease and constrictive pericarditis<sup>[2]</sup>, although it is very rare to have cough induced syncope in a case of pericardial effusion or cardiac tamponade<sup>[3]</sup>. The proposed pathophysiology is multifactorial wherein there is a more exaggerated drop in blood pressure in response to cough compared to patients with other causes of syncope<sup>[4]</sup>. Also, the cough increases intrathoracic pressure, which decreases blood return to the heart and cardiac output, which is already reduced by the cardiac tamponade or moderate/large pericardial

effusion. This phenomenon has been reported with even small pericardial effusions<sup>[5]</sup>. The combination of these events leads to cerebral hypoperfusion resulting to syncope. In subacute cardiac tamponade, these events occur over days to weeks and is usually associated with neoplastic, uremic or idiopathic pericarditis; it may be asymptomatic early in the course, but once intracardiac pressures reach a critical value, the patients develop symptoms of increased filling pressures and limited cardiac output and syncopal events<sup>[6]</sup>. There are two reported cases in the literature of moderate pericardial effusion associated with cough-induced syncope which

also presented with pulsus paradoxus with a drop of > 15 mmHg systolic blood pressure but no evidence of echocardiographic criteria for tamponade<sup>[1,3]</sup>. Pulsus paradoxus greater than 10 mmHg with a pericardial effusion increases the likelihood of tamponade (likelihood ratio, 3.3; 95%CI: 1.8-6.3), while a pulsus paradoxus of 10 mmHg or less lowers the likelihood (likelihood ratio, 0.03; 95%CI: 0.01-0.24)<sup>[7]</sup>. Sensitivity of pulsus paradoxus for tamponade exceeds 80% and is higher than any other single physical finding although its specificity is only 70%<sup>[8]</sup>. Echocardiogram's sensitivity is not significantly superior than clinical examination with reported sensitivity of the echocardiographic findings of right atrial collapse ranging from 50% to 100% and specificity ranging from 33% to 100%. Its sensitivity in identifying right ventricular collapse ranges from 48% to 100% whereas specificity ranges from 72% to 100%<sup>[9,10]</sup>. In one of the reported cases of cough induced syncope, the pericardial effusion was from metastatic non-small cell carcinoma, while the other case was secondary to suspected viral pericarditis in which pericardiocentesis of both cases afforded complete resolution of cough-syncope syndrome cycle<sup>[1,3]</sup>.

It is important to consider either pericardial effusion or cardiac tamponade in any case of cough-induced syncope. Pulsus paradoxus has a high sensitivity in the diagnosis of cardiac tamponade and should therefore be checked in every patient with cough-induced syncope, consequently, can provide early diagnosis and intervention.

## COMMENTS

### Case characteristics

This is an interesting clinical vignette on syncope that was precipitated by cough which may serve as a clue to consider the diagnosis of pericardial effusion or cardiac tamponade.

### Clinical diagnosis

The patient presented with progressive shortness of breath accompanied by cough with subsequent syncopal episodes, noted clinically to have pulsus paradoxus, and was found out to have a pericardial effusion with tamponade physiology on echocardiogram.

### Differential diagnosis

Cerebrovascular accident, vasovagal syncope, seizure.

### Laboratory diagnosis

Pericardial and pleural fluid cytology revealed adenocarcinoma.

### Imaging diagnosis

Chest computed tomography showed both pericardial effusion and bilateral pleural effusion but with no pulmonary embolus while transthoracic echo-

cardiography revealed a large pericardial effusion with tamponade.

### Treatment

Surgical drainage of the pericardial and pleural fluid afforded significant improvement of dyspnea and resolution of cough-induced syncope.

### Related reports

Cough-induced syncope is a very rare occurrence that has been associated with evolving pericardial effusion or cardiac tamponade with only two similar cases reported in the literature.

### Term explanation

Pulsus paradoxus is a drop in systolic blood pressure of more than 10 mmHg during inspiration which is a sign of cardiac tamponade or pericarditis.

### Experiences and lessons

Pericardial effusion or cardiac tamponade should be considered in patients with cough-induced syncope especially if accompanied by pulsus paradoxus which has a high sensitivity in such case.

### Peer-review

The report has clinical interest.

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## Cardiac damage in athlete's heart: When the "supernormal" heart fails!

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### Abstract

Intense exercise may cause heart remodeling to compensate increases in blood pressure or volume by increasing muscle mass. Cardiac changes do not involve only the left ventricle, but all heart chambers. Physiological cardiac modeling in athletes is associated with normal or enhanced cardiac function, but recent studies have documented decrements in left ventricular function during intense exercise and the release of cardiac markers of necrosis in athlete's blood of uncertain significance. Furthermore, cardiac remodeling may predispose athletes to heart disease and result in electrical remodeling, responsible for arrhythmias. Athlete's heart is a physiological condition and does not require a specific treatment. In some conditions, it is important to differentiate the physiological adaptations from pathological conditions, such as hypertrophic cardiomyopathy, arrhythmogenic dysplasia of the right ventricle, and non-compaction myocardium, for the greater risk of sudden cardiac death of these conditions. Moreover, some drugs and performance-enhancing drugs can cause structural alterations and arrhythmias, therefore, their use should be excluded.

**Key words:** Athlete's heart; Cardiac damage; Fibrosis; Intense exercise; Arrhythmogenic dysplasia of the right ventricle; Atrial fibrillation; Doping; Anabolic-androgenic steroids; Hypertrophic cardiomyopathy

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**Core tip:** Athlete's heart is a physiological condition that in some cases can simulate pathological disease,

sometimes due to the use of doping drugs. Furthermore, exercise can induce atrial dilation and arrhythmias. Our objective is to analyze the current literature and to review the most important changes in the heart of athletes, from the different molecular pathways to the structural anomalies.

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## INTRODUCTION

High-intensity exercise training leads to morphological, functional, and electrical remodeling of the heart, which are included in the "athlete's heart", characterized by increased left ventricular mass (LVM), cavity dimensions and wall thickness<sup>[1]</sup>. Athletes with left ventricular (LV) hypertrophy generally have normal cardiac function and normal systolic and diastolic function<sup>[2]</sup>. Athletes exhibit an improvement in myocardial diastolic indices and supernormal LV diastolic function<sup>[3]</sup>. Recent studies have documented decrements, especially in right ventricular (RV) function, during intense endurance exercise<sup>[4,5]</sup>. Actual evidence suggests that there may be some overlap between physiological and pathological conditions, such that a modest amount of fibrosis may be present in cardiac remodeling associated with lifelong endurance training and then acts as a substrate for arrhythmias<sup>[6]</sup>.

Our objective is to describe the mechanisms of cardiac remodeling in athletes and to delineate the most important differences, from the molecular mechanisms to the structural changes, between athlete's heart and pathological conditions, taking into account the most important cardiomyopathy, arrhythmias and the abuse of performance-enhancing drugs.

## PHYSIOLOGICAL VS PATHOLOGICAL CARDIAC HYPERTROPHY: FROM PHYSICAL PRINCIPLES TO MOLECULAR MECHANISMS

Cardiac hypertrophy is an adaptive response to the increased cardiac loading that normalizes wall stress, according to Laplace relationship (Figure 1). Unfortunately, long-term maladaptive remodeling of reactive hypertrophy in various cardiovascular diseases (*e.g.*, valvular heart disease, myocardial ischemia, coronary artery disease, hypertension, and cardiomyopathy) is associated with gradual ventricular dilation, due to loss of myocytes and cardiac fibrosis<sup>[7]</sup>. Physiological hypertrophy, such as athlete's heart, is typically not associated with myocyte

death, although recent studies have shown myocardial damage during intense exercise and RV inflammation and fibrosis in long term endurance athletes<sup>[4,8]</sup>. The shift from compensated pathological hypertrophy to failure of myocardium includes cellular and molecular events, such as myocyte death, with three different mechanisms: Apoptosis, necrosis and autophagic cell death<sup>[9,10]</sup>. Cardiomyocyte replacement and myocardial fibrosis are representative of all types of pathological hypertrophy and proceed along with functional decompensation. To explain fibrosis and necrosis in athlete's heart, interesting is the "ischemic core" hypothesis: Hypertrophic cardiomyocyte becomes ischemic when his surface exceeds the distance across which oxygen can diffuse down its concentration gradient from adjacent capillaries, with contractile depression and cellular death<sup>[11]</sup>. Physiological hypertrophy is associated with a normal or increased number of myocardial capillaries, due to the activation of VEGF pathway<sup>[9]</sup>. Akt is a serine/threonine protein kinase responsible for the cellular growth in multiple cell types, which can be activated by exercise. Recent data suggest that Akt pathway might be implicated both in physiological and pathological cardiac growth. In animal models, myocardial expression of Akt pathway caused reversible hypertrophy after 2 wk of strenuous exercise, but an irreversible cardiomyopathy with decreased capillary density and fibrosis after 6 wk of intense training. It seems that myocardial angiogenesis is more intense in the acute phase of heart hypertrophy but insufficient in the advanced phase: Excessive "physiological" hypertrophy might be associated with poor angiogenesis and consequently with heart failure<sup>[12]</sup>.

Autocrine and paracrine triggers are released in response to hemodynamic overload, and definite substances are preferentially released for pathological or physiological stimuli. Insulin like growth factor 1 (IGF1) is released in the course of postnatal development and during exercise training and is increased in swim-trained rats and in veteran athletes compared with controls<sup>[13]</sup>, whereas elevated levels of angiotensin II (Ang II), catecholamine and endothelin-1 (ET-1) were observed in pathological hypertrophy and in heart failure subjects<sup>[14]</sup>. IGF1 promotes the PI3K-Akt molecular pathway to induce physiological cardiac hypertrophy, whilst the mitogen activated protein kinase (MAPK) pathway and calcineurin system are activated by Ang II and ET-1 in pathological hypertrophy (Table 1)<sup>[15]</sup>.

In conclusion, familial hypertrophic cardiomyopathy<sup>[16]</sup> is associated with sarcomeric protein mutations, such as cardiac troponin I or T,  $\beta$ -MHC,  $\alpha$ -MHC, myosin light chain,  $\alpha$ -tropomyosin, titin, and actin, with loss of contractile filaments and proteins of sarcomeric skeleton<sup>[17]</sup>.

## CARDIOMYOCYTE DAMAGE DURING INTENSE EXERCISE

After intense exercise, acute increases in troponin (cTn) and B-type natriuretic peptide have been detected in

**Table 1 Differences in between physiological and pathological hypertrophy**

Physiological hypertrophy	Pathological hypertrophy
Angiogenesis, release of VEGF	Perivascular fibrosis and inflammation
Activation of IGF-1 pathway (IGF-1- > PI3K- > Akt)	Activation of Angiotensin II, Catecholamine and Endotelin-1
No fibrosis	MAPK and Calcineurin pathway
Normal gene expression	Fibrosis, myocyte necrosis and apoptosis
Proportional chamber enlargement	Cardiac dysfunction

The table summarizes the differences in the cellular and molecular pattern between physiological and pathological hypertrophy. VEGF: Vascular endothelial growth factor; IGF-1: Insulin like growth factor; PI3K: Phosphoinositide 3-kinase; MAPK: Mitogen-activated protein kinase.

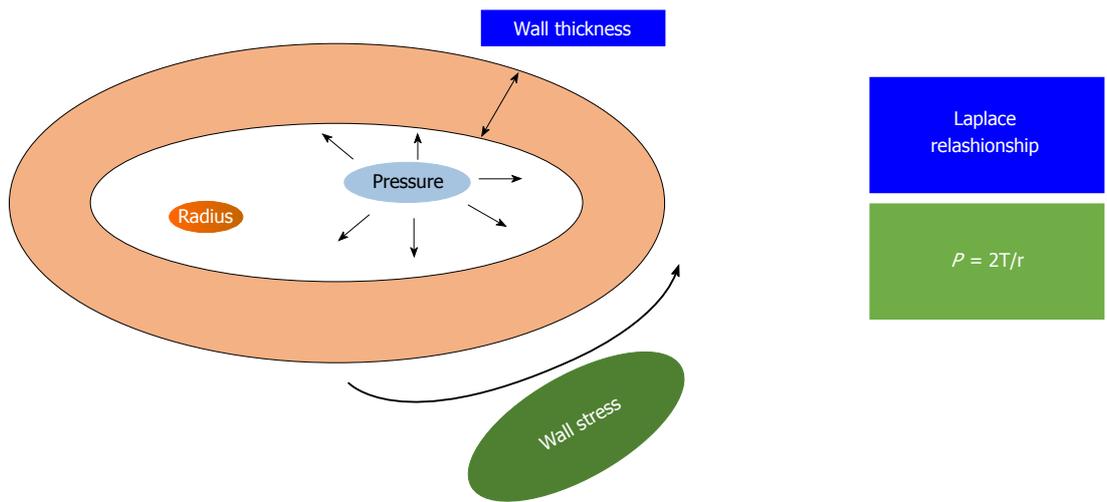


Figure 1 The figure shows the Laplace relationship: The pressure (P) generated in a sphere is directly proportional to the wall tension (T) and inversely related to the radius of the sphere (r).

athletes<sup>[18]</sup>. These are specific markers of myocyte injury and strain, but do not indicate a permanent injury. Potential mechanisms have been showed to elucidate cTn elevation after intense exercise, but actually, the elevation of cTn levels in healthy individuals cannot be explained by any of these theories<sup>[18]</sup>. It is possible that exercise induces an increase in myocardial sarcolemma permeability, due to mechanical stress on the cardiomyocytes and to increased production of oxidative radicals or altered acid base balance exercise, with passive diffusion of cTn from the intra- to extra-cellular compartment<sup>[18]</sup>. Cellular stretching might cause transient disruption of the myocardial plasma membrane and then, the release of cTn<sup>[19]</sup>. Furthermore, it can stimulate integrins, mediating the transport of entire cTn molecules out of viable cardiomyocytes<sup>[20]</sup>. Increased levels of cTn are more common in cycling or triathlon and depend on the exercise intensity<sup>[21]</sup>.

Case reports have shown myocardial fibrosis and late gadolinium enhancement, associated with cTn elevation post-exercise, in a small number of veteran athletes, but the pathogenesis of these cases remains unclear<sup>[18]</sup>.

## EXERCISE-INDUCED MYOCARDIAL FIBROSIS

Despite the widely recognized benefits of regular physical

activity, high-level exercise training may be associated with increased arrhythmia risk and even with sudden cardiac death<sup>[22]</sup>.

The athlete's heart is a benign condition, representing a normal adaptation to chronic exercise, in which loss of myocytes and abnormal deposition of collagen do not usually occur<sup>[15]</sup>. Pathological hypertrophy is associated with apoptosis and necrosis; in this case, the loss of myocytes is replaced with excessive collagen deposition. Excessive collagen deposition increases the stiffness of the ventricles, with consequent impaired contraction and relaxation, electrical conduction system fibrosis and reduced capillary density, leading to myocardial ischemia and the transition from hypertrophy to failure<sup>[15]</sup>. Interestingly, recent studies have shown myocardial inflammation and fibrosis in animal models of long term, intensive exercise. Chen *et al*<sup>[23]</sup> forced rats to swim strenuously and found histological evidence of localized myocyte damage, myocardial necrosis and inflammatory infiltrates. Benito *et al*<sup>[24]</sup> instituted an intensive treadmill running protocol in rats and demonstrated an increase in atrial and ventricular inflammation and fibrosis and a greater risk of ventricular arrhythmias in the "marathon rats". Fibrosis and inflammatory infiltrates have been identified in well-trained athletes who underwent cardiac biopsy for high probability of identifying a cardiac pathology<sup>[25]</sup>. Histology offers the tangible evidence of fibrosis, but inflammatory infiltrates and fibrosis are

non-specific and their etiology can be supposed only by other clinical factors. Furthermore, cardiac biopsy is an invasive procedure with significant risks and it is not applicable in the absence of high suspicion of heart disease. An accurate, non-invasive surrogate tool for detecting fibrosis is cardiac magnetic resonance (CMR) imaging with gadolinium contrast. Gadolinium-based extracellular paramagnetic contrast agents concentrate in areas of fibrosis and thus can be used to characterize injured myocardium. Using gradient-echo inversion recovery imaging, fibrosis appears as bright signal, with a prolonged wash-out time for gadolinium [delayed gadolinium enhancement (DGE)], contrasting with the normal myocardium, which looks black<sup>[6]</sup>. Several studies have identified the presence of DGE in the heart of extensively trained veteran athletes. In most cases, the patches of DGE were very small and sited in the septum and in RV insertion points, regions subjected to local stretching during exercise<sup>[6]</sup>. More recently, La Gerche *et al.*<sup>[4]</sup> have shown myocardial fibrosis by CMR and a reduction in RV systolic function in athletes with long-term exercise, suggesting that the heart has a limited capacity to tolerate the overload exercise. The patches of cardiac fibrosis may be the substrate for ventricular tachycardia and sudden death, in predisposed individuals<sup>[4]</sup>. Some authors have recently suggested a new entity, the so called Phidippides cardiomyopathy: Long term strenuous exercise can induce cardiac dilation and also activates resident macrophages, pericytes, and fibroblasts, resulting in the deposition of collagen and fibrosis<sup>[26,27]</sup>. CMR can also specifically detect intra-myocardial fibrofatty infiltration of the RV wall, typical of the arrhythmogenic right ventricular cardiomyopathy (ARVC), which often leads to ventricular arrhythmias and usually appears in young adulthood and affected asymptomatic or minimally symptomatic individuals<sup>[27]</sup>. In conclusion, it is possible that the RV is more susceptible to fatigue than the left ventricle after prolonged exercise. It needs more studies to identify a probable effect of exercise "dose" and their implication in the development of heart failure.

## IS CARDIAC REMODELING IN ATHLETES ALWAYS BENIGN?

Cardiac adaptations to exercise not involve only the left ventricle, but all the heart chambers. Often these changes are absolutely physiological, but in some cases, they can predispose to pathological conditions, such as arrhythmias. Below, we report the main morpho-functional changes of the different cardiac structures in athletes and their implications in the pathogenesis of cardiovascular diseases.

## ATHLETE'S ATRIA FUNCTION AND DYSFUNCTION

Atrial abnormalities can be present in athletes, such as

a mild increase in atrial volume and diameter, and may be considered a physiological adaptation to exercise<sup>[28]</sup>. The pathophysiological mechanisms are not well defined. Studies in animal models have shown that, in rats, prolonged and vigorous exercise resulted in eccentric hypertrophy and diastolic dysfunction with atrial dilatation and fibrosis, especially in the atria and the right ventricle, and increased fibrotic mRNA compared with controls<sup>[24]</sup>. A recent meta-analysis of 7189 adult elite athletes have shown that exercise causes an increase in left atrium (LA) dimensions, compared with controls, evaluating both diameter and volume, corrected for body surface area. The endurance athletes reported the largest average LA diameters<sup>[29]</sup>. Since pre-adolescence, the long-term endurance exercise results in considerable bi-atrial remodeling and enlargement compared with sedentary subjects of the same age, with a preserved cardiac function<sup>[30,31]</sup>. LA enlargement could be considered part of athlete's heart, considering that the LA pressure rises during ventricular diastole more than in sedentary subjects, to maintain adequate filling whereas LV stiffness or pressure are increased<sup>[32]</sup>. On the other hand, there is evidence that the endurance exercise increases the risk of developing atrial fibrillation (AF) and atrial flutter in the middle age, in subjects without any clinical or echocardiographic signs of cardio-pulmonary pathologies or hypertension<sup>[33]</sup>. The mechanisms responsible for these arrhythmias might be: The major incidence of atrial ectopic beats in this population, as a consequence of physical activity; the influence of autonomic nervous systems, and in particular the vagal system, responsible for the "vagal AF"<sup>[34]</sup>; the atria dilatation, fibrosis, and inflammation induced by high exercise training and the atrial remodeling<sup>[33]</sup> (Table 2). In mice, exercise can induce TNF $\alpha$ -dependent activation of both NF- $\kappa$ B and p38MAPK, increasing inflammation and AF susceptibility<sup>[35]</sup>.

Moreover, AF might be closely connected with oxidative cellular changes and redox imbalance in the atrium. The oxidative species, generated from cardiomyocytes in stress conditions such as strenuous exercise, can increase inflammation and activate downstream molecular pathways, promoting morphological and electrical modeling. Recently, Mont *et al.*<sup>[36]</sup> have shown that loss of Nrf2, a gene with antioxidant function in the atria, could be associated with atrial hypertrophy and AF, suggesting that the preservation of the redox state is essential for the atrium health.

Finally, in athletes AF appears as some symptomatic and paroxysmal episodes that could become more frequent and progress to persistent AF. The GIRAFA study has showed that the crisis appears in the night or after the meal, related to an increased vagal tone<sup>[36]</sup>.

Data about right atrial (RA) function in top level athletes are lacking. Previously, our group has delineated the upper limits of RV and RA dimensions in highly-trained athletes and showed that right heart dimensions were greater in elite endurance-trained athletes than in age- and ex-matched strength athletes and controls<sup>[37]</sup>. Then, D'Ascenzi *et al.*<sup>[38]</sup> investigated the RA function and dimension in 100

**Table 2 Pathological mechanisms of atrial fibrillation in long-term athletes**

Pathological mechanism
Atrial ectopic beats
Vagal nervous system
Atrial fibrosis
Atrial dilatation
Myocardial injury
Inflammation
Redox imbalance

The table shows the most important mechanisms involved in atrial fibrillation exercise related.

top level athletes by standard echocardiography and 2D speckle tracking echocardiography and showed that RA area, volume, volume index, and inferior vena cava were significantly greater in athletes than in controls and the peak atrial longitudinal strain and peak atrial contraction strain values were lower in athletes than in controls. This strain reduction should not represent a real dysfunction, but only a physiological phenomenon, and can be included in the "athlete's heart"<sup>[38]</sup>.

## LV CHANGES IN EXERCISE RELATED AND PATHOLOGICAL CONDITIONS

In some highly-trained athletes, the LV wall thickness may be increased, mimicking a hypertrophic cardiomyopathy (HCM). The thickening is usually mild, but in some cases, it may be significant and creates difficulties to differentiate athlete's heart and hypertrophic cardiomyopathy, especially in the ambiguous "gray zone", when the wall thickness is of 13 to 15 mm (12 to 13 mm in women)<sup>[39]</sup>. This differential diagnosis is important, since most cases of sudden death in athletes are probably due to HCM<sup>[40]</sup>. Echocardiography plays an important role in the differential diagnosis: HCM is probable with LV end-diastolic cavity < 45 mm, evidence of pathogenic sarcomere mutation, family history of HCM, abnormal LV diastolic function, left atrial dilatation, and late gadolinium enhancement on contrast-enhanced CMR imaging. Usually athlete's heart is characterized by LV cavity enlargement (> 55 mm), peak VO<sub>2</sub> > 110% of expected, and thickness or mass decreases with short periods of detraining<sup>[41,42]</sup>. Pelliccia *et al.*<sup>[43]</sup> have shown that LV wall thickness ≥ 13 mm is mostly present in elite rowers and cyclists, and the upper limit appeared to be 16 mm (Figure 2).

Other conditions that can cause cardiac hypertrophy include valve disease, hypertension and non-compaction myocardium. Despite the prevalence of hypertension is approximately 50% lower in athletes compared with the general population, it is also the most common cardiovascular condition in athletes. The pharmacological therapy can be difficult for the competition regulations and potential adverse effects<sup>[44]</sup>. It is important to

diagnose this condition, because it is associated with an increased risk of developing heart failure. Recently, an elevated prevalence of LV noncompaction (LVNC) has been reported in athletes, phenotypically characterized by a more thick endocardial noncompact layer, increased trabeculations and deep recesses<sup>[45]</sup>. Caselli *et al.*<sup>[46]</sup>, in a recent study, have shown that in a large population of athletes, only a small subgroup presented LVNC. The increased trabeculations may represent a LV variant of athlete's heart without any clinical significance<sup>[46]</sup>.

Figure 3 summarizes the different characteristics of physiological remodeling and pathological condition of LV.

## EXERCISE-RELATED RIGHT VENTRICLE REMODELING

Strenuous and prolonged exercise can cause RV dysfunction, usually transient, with evidence of increased biomarkers of cardiac damage. On the other hand, repeated bouts of exercise can lead to RV structural remodeling and arrhythmias and can lead to a syndrome similar to familial ARVC, without an identifiable genetic predisposition<sup>[47,48]</sup>. ARVC is present in 4% to 22% of athletes with sudden cardiac death<sup>[49,50]</sup>. As mentioned above, the RV function may be more interested by intense endurance training, therefore the diagnostic criteria for ARVC should be nonspecific in athletes with electrocardiographic anomalies and biventricular dilation.

Marcus *et al.*<sup>[51]</sup> in a multi-center study of 108 probands with ARVD/C showed that 34% were athletes. Vigorous or long term athletic exercise might facilitate the phenotypic expression of ARVC due to the repetitive stretch of the RV with an underlying genetic desmosomal protein anomaly<sup>[51]</sup>.

Signs of RV dysfunction seem to include: Syncope; Q waves in precordial leads; augmented QRS duration; three abnormal signal averaged electrocardiography parameters; delayed gadolinium enhancement; RV ejection fraction < 45% or wall motion anomalies at CMRI; > 1000 ventricular extra-systoles (or > 500 non-RV outflow tract) per 24 h; ventricular tachyarrhythmia or abnormal blood pressure response during exercise (Table 3)<sup>[52,53]</sup>. RV cavity size is not significantly larger in ARVC patients compared with athletes, whereas RV outflow tract is larger in ARVC subjects than in athletes<sup>[53]</sup>. The thickened and high reflective moderator band, commonly considered typical of ARVC, are present also in athletes and could be due to RV dilatation<sup>[53]</sup> (Figure 4). Further studies regarding the differential diagnosis between ARVC and physiological remodeling in athletes are needed to create useful clinical diagnostic algorithms.

## PERFORMANCE-ENHANCING DRUGS AND CARDIAC DAMAGE

Some banned athletic performance-enhancing drugs

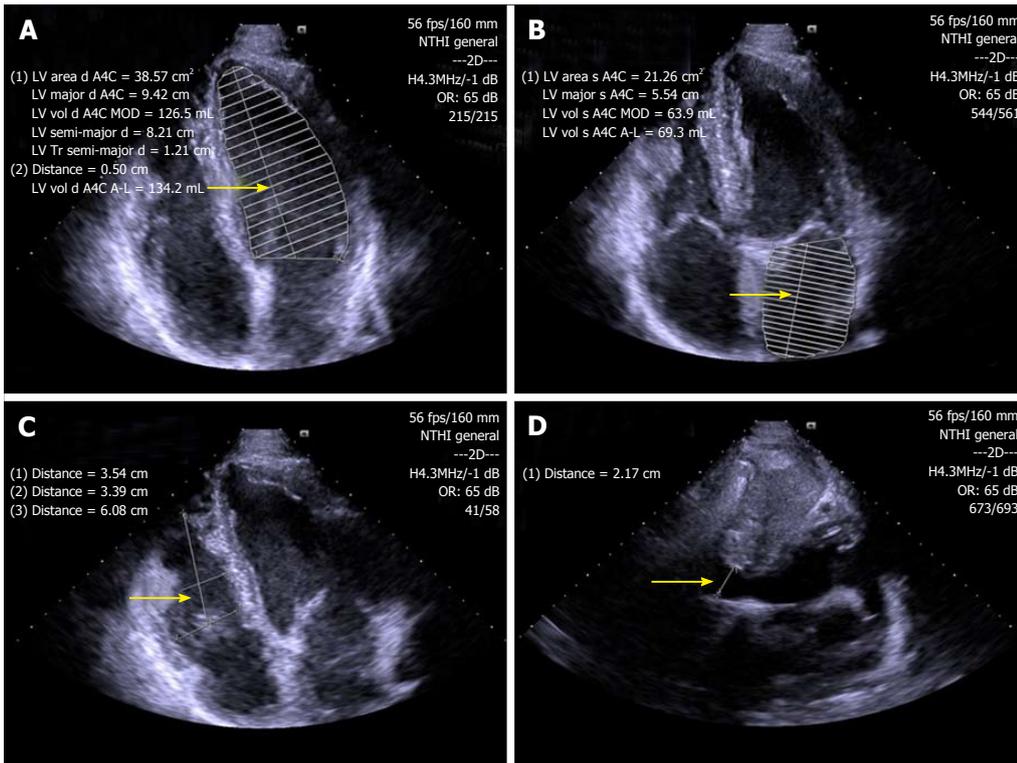


Figure 2 Standard B-mode echocardiography of endurance athlete showing enlargement of left ventricular (A), left atrial (B) and right ventricular (C) chambers, as well as inferior vena cava dilatation (D) (arrows). LV: Left ventricular.

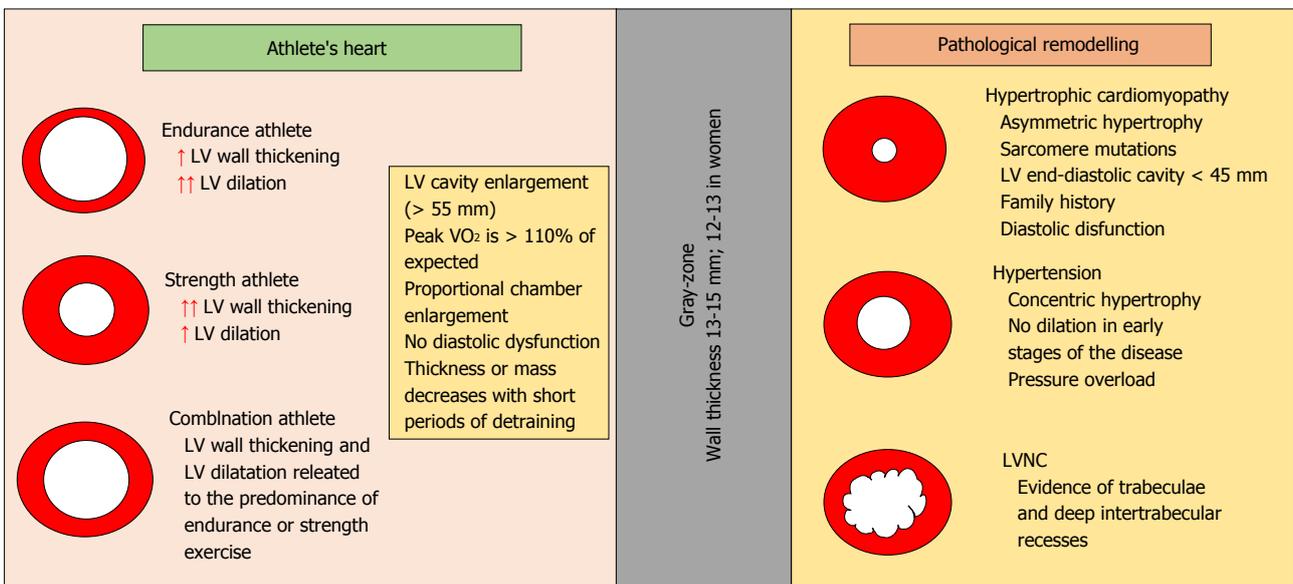


Figure 3 Different characteristics of physiological remodeling and pathological condition of the left ventricle. LV: Left ventricular; LVNC: LV noncompaction.

might have cardiac toxic effects, such as anabolic-androgenic steroids (AASs) and growth hormone (GH).

Healthy athletes abusing AASs may exhibit LV hypertrophy with both systolic and diastolic myocardial dysfunction and focal areas of DGE at CMR, with non-ischemic distribution<sup>[54]</sup> (Figure 5). AASs have direct toxicity on myocardial structures, with increased collagen deposition, fibrosis, and intimal hyperplasia of the intra-

mural coronary vessels with chronic ischemic damage and microcirculation alterations. Moreover, testosterone might inhibit the extra-neuronal uptake of neuroamine and consequently result in vasospasm due to an abnormal vascular response to norepinephrine<sup>[55]</sup>. Post-mortem studies of athletes who used AASs have found infiltration of eosinophils into myocardial cells, as well as destruction of myofibrils. Endothelial dysfunction was

**Table 3** Indicators of right ventricle pathology

Episodes of syncope
> 1000 ventricular extra-systoles (or > 500 non-RV outflow tract) per 24 h; ventricular tachyarrhythmias; Q waves in precordial leads; augmented QRS duration
≥ 3 abnormal signal averaged electrocardiography parameters
Delayed gadolinium enhancement; RV ejection fraction < 45%, or wall motion abnormalities at CMRI; impaired RV strain imaging
Attenuated blood pressure response during exercise
Dilatation of RV outflow tract

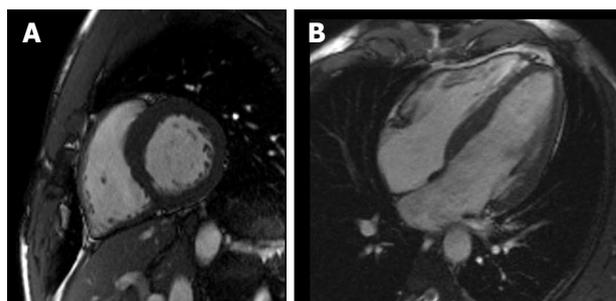
The table shows the indicators of right ventricle pathology (ARVC *vs* athlete's heart). CMRI: Cardiac magnetic resonance imaging; RV: Right ventricle; ARVC: Arrhythmogenic right ventricular cardiomyopathy.

also observed<sup>[56]</sup>.

GH abuse has tainted many sports, including baseball, cycling, and track and field, for promoting an increase in muscle mass, though its effects on physical performance are not completely supported by the literature<sup>[57]</sup>. GH promotes cellular growth by stimulating protein synthesis, inhibiting catabolism, and inducing IGF-1 production. At the molecular level, GH binds its receptor and induces subsequent expression of growth-promoting molecules<sup>[58]</sup>. GH, both in excess or in deficient states, is related to increased cardiovascular mortality. The excess, like in acromegaly or in doping, results in cardiac hypertrophy and an increase in collagen, fibrosis, and cellular infiltration. *In vivo* studies on healthy mice demonstrated that increased GH levels induce significant LV hypertrophy and an increase in concentric anterior and posterior wall thicknesses, LV diastolic diameters and volumes, and cardiac output<sup>[59]</sup>. Unfortunately, the majority of conclusions about GH abuse and its cardiac effects result from data regarding acromegaly and not from direct data, which are lacking.

Also, erythropoietin (EPO), which increases hematocrit levels and thus improves aerobics capacity, may lead to cardiac dysfunction, increasing blood viscosity and cardiac afterload, and predisposes to hypertension and thromboembolism. Experimental studies have shown hypertension, cardiac hypertrophy and fibrosis after administration of high doses of EPO<sup>[60]</sup>.

Thyroxine is used, generally, by athletes to promote weight loss. Thyroid hormones (TH) play an important role in cardiac growth and might cause cardiac hypertrophy and also heart failure if they are in excess. High levels of TH might result in elevated heart rate, decreased total peripheral resistance, widened pulse pressure, blood volume expansion, increased LVM and cardiac output, with improved contractile function and hemodynamic parameters in the short term. Long-standing hyperthyroidism can lead to dilatation of cardiac chambers and heart failure. Interestingly, the diminished cardiac function is often reversible when euthyroidism is re-established<sup>[61]</sup>. Weltman *et al*<sup>[61]</sup> showed that hyperthyroid rodents had important cardiac hypertrophy and adverse cardiac remodeling with chamber dilatation, LV systolic and diastolic dysfunction, decreased relative



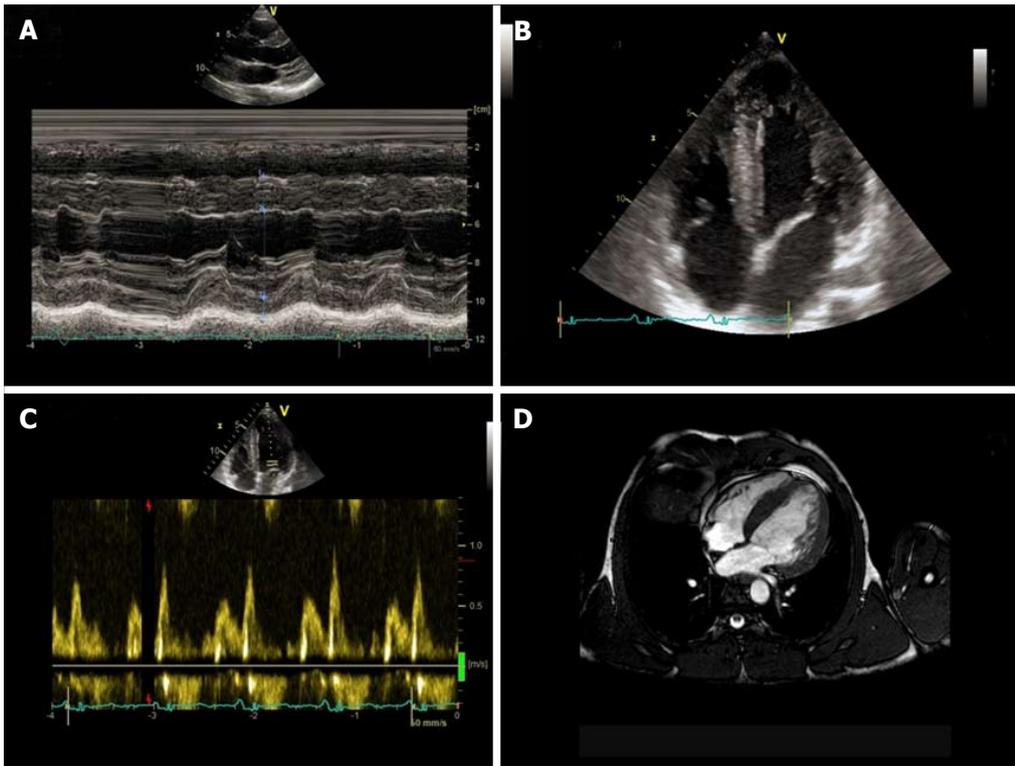
**Figure 4** Cardiac magnetic resonance depicting in short-axis (A) and long-axis (B) view balanced biventricular enlargement in endurance athlete.

wall thickness, and fibrosis<sup>[61]</sup>. Few data in the literature are about the cardiac consequences of the prolonged use of thyroxine treatment. Thyroxine treatment, in high doses which suppress serum thyrotropin to below normal, has been associated with LV hypertrophy (in the absence of significant changes in heart rate, stroke volume, blood pressure, and LV systolic function), but untreated thyrotoxicosis resulted in more pronounced cardiovascular changes than thyroxine treatment<sup>[62]</sup>. Further studies are necessary to evaluate the cardiovascular risk in patients treated with thyroxine.

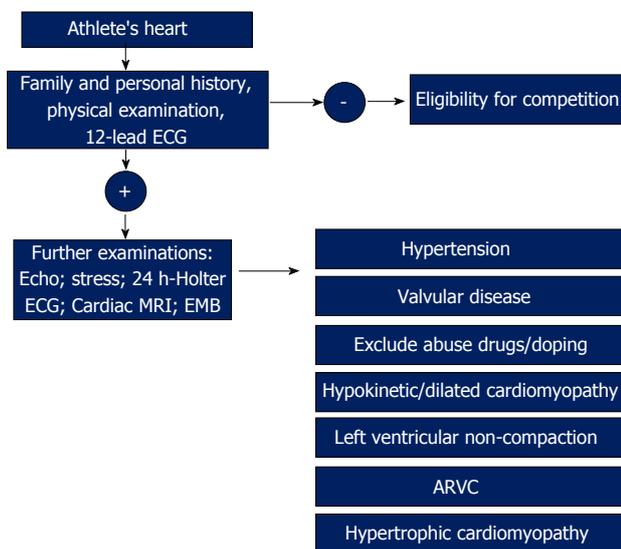
Many other drugs are responsible for heart failure in athletes, such as corticotrophin, beta 2 agonists, amphetamines and cocaine. Often athletes use combinations of different banned drugs, resulting in additive effects on cardiac remodeling. Cardiac alterations may lead to arrhythmias, heart failure and sudden death. It is important to exclude the abuse of these drugs, when athletes with heart dysfunction come to our attention. Figure 6 shows a flow chart to differentiate athlete's heart from pathological conditions.

## ENERGY DRINK CONSUMPTION AND HEMODYNAMIC EFFECTS

A growing number of case reports of cardiovascular adverse events associated with energy drinks (EDs) are present in the literature. The use of EDs is more common in young students and in athletes. The consumption of EDs negatively affects the hemodynamic system. Important changes in arterial pressure and heart rate may occur with the ingestion of only one can (355 mL drink volume). Furthermore, it seems that EDs may diminish cerebral blood velocity, increasing breathing frequency<sup>[63]</sup>. Caffeine and sugar appear to be the ingredients underlying hemodynamic impact of EDs. Taurine and vitamin B complex play a minor role<sup>[64]</sup>. Genetic polymorphisms in cytochrome P-450 enzymes and variations of adenosine receptors play a role in the different responses to the caffeine<sup>[65]</sup>. Caffeine improves athletic performance in rowing<sup>[66]</sup>, swimming<sup>[67,68]</sup>, soccer<sup>[69]</sup> and hockey<sup>[70]</sup>. On the other hand, EDs can cause many cardiovascular adverse



**Figure 5 Non-invasive evaluation of power athlete abusing of steroids.** Standard M-mode (A) and 4-chamber view B-mode (B) echocardiography, evidencing severe left ventricular hypertrophy, with diastolic dysfunction (C) underlined by Doppler transmittal flow pattern. Cardiac magnetic resonance confirmed severe left ventricular hypertrophy (D).



**Figure 6 The management of athlete's heart.** The figure shows an algorithm to distinguish athlete's heart from pathological conditions. ARVC: Arrhythmogenic right ventricular cardiomyopathy; ECG: Electrocardiograph; MRI: Magnetic resonance imaging.

effects (Table 4), such as hypertension, palpitations, ischemic stroke, epileptic seizure<sup>[71]</sup> and myocardial ischemia, with no additional trigger<sup>[72]</sup>. The possible mechanism is related to the caffeine interaction with the G-protein coupled receptors on the cardiomyocytes that leads to an increase in intracellular cyclic-AMP and calcium concentrations with chronotropic and inotropic

**Table 4 Adverse effects of energy drinks**

Adverse effect
Hypertension
Palpitations/arrhythmias (atrial fibrillation)
QTc prolongation
Myocardial ischemia
Ischemic stroke/Transient ischemic attack
Epileptic seizure
Anxiety, insomnia, irritability
Psychosis/Mania

The table shows the most common adverse effect of consumption of energy drinks.

effects<sup>[73]</sup>. Large studies regarding EDs and their effects on the cardiovascular system are necessary, especially for the widespread consumption of these substances in recent years.

## CONCLUSION

The exact clinical significance and prognostic value of cardiac injury and fibrosis in athletes are unknown. Physiological remodeling is characterized by specific molecular activation and gene expression. More large studies are needed to gain a better understanding of these conditions and the pathological changes in the heart structure in athletes and to investigate the cardiac effects of performing-enhanced drugs and EDs in this population.

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## Assessment of aortic valve disease - a clinician oriented review

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### Abstract

Aortic valve disease [aortic stenosis (AS) and aortic regurgitation (AR)] represents an important global health

problem; when severe, aortic valve disease carries poor prognosis. For AS, aortic valve replacement, either surgical or interventional, may provide definite treatment in carefully selected patients. For AR, valve surgery (either replacement or - in selected cases - aortic valve repair) remains the gold standard of care. To properly identify those patients who are candidates for surgery, the clinician has to carefully assess the severity of valve disease with an understanding of the potential pitfalls involved in these assessments. This review focuses on the practical issues concerning the evaluation of patients with AS and AR from a general cardiologist's perspective. The most important issues regarding the documentation of the severity of AS and AR are summarized. More specific issues, such as the role of stress echocardiography, other imaging techniques and details regarding the treatment options (medical, surgical, or interventional), are mentioned briefly.

**Key words:** Echocardiography; Aortic stenosis; Aortic regurgitation; Treatment; Evaluation

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**Core tip:** Aortic stenosis (AS) and aortic regurgitation (AR) represent important health problems world-wide. This review focuses on the practical issues concerning the evaluation of patients with AS and AR from a general cardiologist's perspective. The most important issues regarding the documentation of the severity of AS and AR are summarized, and potential pitfalls are highlighted. More specific issues, such as the role of stress echocardiography, other imaging techniques and details regarding the treatment options (medical, surgical, or interventional), are mentioned briefly.

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## INTRODUCTION

Aortic valve disease [aortic stenosis (AS) and aortic regurgitation (AR)] represents an important global health problem. The data on the exact prevalence of AS and AR in the general population are lacking, but studies performed in Western populations estimate that 3% to 4% of the adult population suffers from moderate or severe aortic valve disease. The prevalence of AS and AR increases with age; it is estimated that 1% of persons aged < 55 years and 6% of persons aged > 75 years suffer from moderate or severe AS/AR<sup>[1,2]</sup>.

This review focuses on the practical issues concerning the evaluation of patients with AS and AR from a general cardiologist's perspective. The most important issues regarding the documentation of the severity of AS and AR using echocardiography are summarized. More specific issues, such as the role of stress echocardiography, other imaging techniques and details regarding the treatment options (medical, surgical, or interventional), are mentioned briefly. For more detailed information on these topics, the reader is referred to several recent excellent reviews, mostly regarding AS<sup>[3-11]</sup>.

## AS

AS is defined as a narrowing of the surface area of the aortic orifice [aortic valve area (AVA)] below the normal value (approximately 3 cm<sup>2</sup>). AS becomes significant [*i.e.*, determines a significant increase in left ventricular (LV) afterload] only after the AVA decreases by more than half. In general, the accepted criteria for the definition of severe AS is an AVA ≤ 1 cm<sup>2</sup> (or ≤ 0.6 cm<sup>2</sup>/m<sup>2</sup> of body surface area). These cut-off values have been used in clinical studies but are patient-dependent and do not completely overlap with other indices that are also used to define severe AS (*e.g.*, transaortic pressure gradients - see below).

### Etiology

In Western countries, AS has the following two major causes: Degenerative (calcific) and congenital. Calcific AS is predominant in the elderly population, shares common pathological features and is commonly associated with atherosclerosis. Congenital AS [> 90% represented by bicuspid aortic valve (BAV)] manifests clinically 10 to 20 years earlier than calcific AS. Contemporary data from 932 isolated aortic valves excised from adults aged 26 to 91 years between 1993 and 2004 suggest that 54% of these cases were congenital in origin<sup>[12]</sup>.

AS is a slowly progressive disease. Almost 50 years ago, Ross and Braunwald highlighted that the appearance of symptoms marks a sharp decline in survival with nearly universal death within 5 years<sup>[13]</sup>. The types of symptoms are important, as follows: The mean survival after the

appearance of angina was 5 years, 3 years after syncope and 2 years after the appearance of heart failure. When these data were published, the predominant etiology was rheumatic heart disease, and the mean patient age was 63 years old<sup>[14]</sup>. Thus, the contemporary application of these data is limited. Recent data suggest that the presence of AS is associated with a 68% increased risk of coronary events, a 27% increased risk of cerebrovascular events, and a 36% increased risk of mortality<sup>[15]</sup>. The data from the PARTNER study in elderly patients with severe calcific AS suggest an annual mortality of 50% with conservative treatment<sup>[16]</sup>.

### Evaluation of AS

The evaluation of patients with AS must define the following 2 issues: (1) identification of patients with severe AS; and (2) in patients with severe AS, identification of patients whose prognosis will be improved by aortic valve replacement (AVR) (surgical or interventional).

**Identifying patients with severe AS:** The clinical (presence of symptoms, grade ≥ 4/6 ejection murmur, and "tardus et parvus" peripheral pulse), electrocardiographical (left ventricular hypertrophy) or radiological (valve calcification) criteria for severity have high sensitivity but low specificity in identifying patients with severe AS. Therefore, objective assessment of AS severity is needed.

Historically, invasive direct measurement of transaortic pressure gradients was performed, and the aortic valve area was calculated using the Gorlin formula. This practice was abandoned because of the following important drawbacks: (1) invasively measured pressure gradients (mean transaortic pressure gradient and the difference between peak aortic pressure and peak LV systolic pressure) do not overlap with the Doppler estimation of transaortic pressure gradients. This is because Doppler echocardiography measures instantaneous velocities and through the use of Bernoulli equation estimates instantaneous pressure gradients, whereas peak LV pressure occurs before peak aortic pressure (the invasively measured peak-to-peak transaortic pressure difference is not instantaneous); and (2) the risk of atherosclerotic cerebral embolism during the transaortic passage of the pressure catheter may reach 20%<sup>[17]</sup>. Thus, today, objective assessment of AS severity almost completely relies on proper performance and interpretation of Doppler echocardiography.

The currently used criteria for the definition of severe AS by echocardiography are listed in Table 1<sup>[18]</sup>. These criteria have advantages and disadvantages.

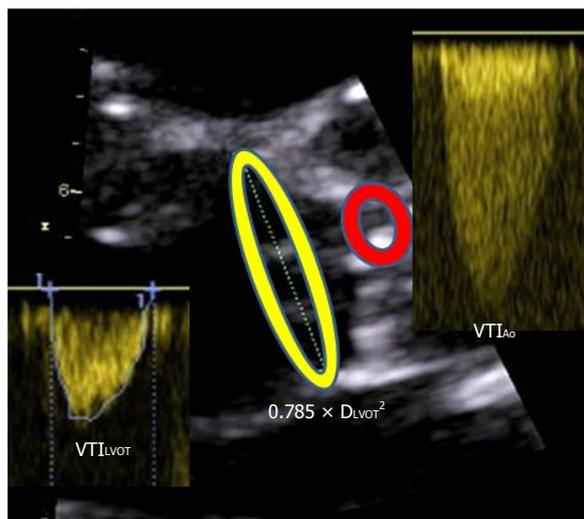
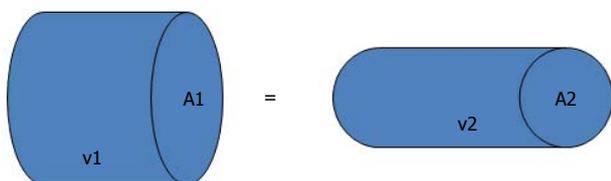
It is of critical importance that the echocardiographic evaluation of AS is based on correctly performed measurements, using an integrative approach, because the echocardiographic criteria for the definition of severe AS are not interchangeable, and the criteria based on pressure gradients and velocities are highly dependent on blood flow.

The most robust and reproducible estimation of AVA

**Table 1 Echocardiographic criteria for the definition of severe aortic stenosis: Advantages and disadvantages<sup>[18]</sup>**

Criteria	Severe AS	Advantages	Disadvantages
Aortic surface area	$\leq 1.0 \text{ cm}^2$	Measures effective AVA. However, this may also constitute a disadvantage because it does not measure anatomical AVA Less flow-dependent compared with other measurements	Very sensitive to measurement errors
Indexed AVA to body surface area	$\leq 0.6 \text{ cm}^2/\text{m}^2$	Useful for extreme heights/weights	Very sensitive to measurement errors
Mean transaortic pressure gradient	$\geq 40 \text{ mmHg}$		Flow-dependent Requires correct alignment of Doppler signal with the flow direction
Peak transaortic flow velocity	$\geq 4.0 \text{ m/s}$	Measures instantaneous velocity Best predictor of adverse events	Flow-dependent Requires correct alignment of Doppler signal with the flow direction
Ratio between peak transaortic flow velocity and peak LVOT velocity	$\leq 1/4$	Good reproducibility (compared with AVA calculation)	Limited data on prognostic utility

AS: Aortic stenosis; AVA: Aortic valve area; LVOT: Left ventricular outflow tract.



$$A_{LVOT} \times VTI_{LVOT} = AVA \times VTI_{Ao} \rightarrow AVA = A_{LVOT} \times VTI_{LVOT}/VTI_{Ao}$$

where  $A_{LVOT} = (\pi \times D_{LVOT}^2)/4 = 0.785 \times D_{LVOT}^2$

**Figure 1 Relationship between flow, area and velocity.** Calculation of the aortic valve area (AVA) based on the continuity equation. Flow (mL) equals the cross-sectional area (cm<sup>2</sup>) of the vessel multiplied by the mean flow velocity through that cross-sectional area during a period of time [measured as velocity-time-integral, VTI (cm)]. The flow is constant throughout the length of the vessel without ramifications. Thus, at the aortic valve level, the flow below the valve (in the left ventricular outflow tract, LVOT) equals flow through the aortic valve. Therefore, the AVA equals the LVOT area multiplied by the mean flow velocity through the LVOT area during ejection [LVOT velocity-time-integral, VTI<sub>LVOT</sub> (cm)] divided by the transaortic mean flow velocity during ejection [transaortic velocity-time-integral, VTI<sub>Ao</sub> (cm)]. The LVOT area, given the theoretical circular shape of the LVOT, is calculated by measuring its internal diameter [D<sub>LVOT</sub> (cm)]. A: Area; V: Velocity; D<sub>LVOT</sub>: Left ventricular outflow tract diameter; VTI: Velocity-time-integral.

is based on the continuity equation (Figure 1).

To calculate the AVA, it is essential to perform correct

measurements, especially for the left ventricular ejection tract diameter (D<sub>LVOT</sub>) and velocities.

Any error in the measurements of D<sub>LVOT</sub> will be squared when calculating AVA using the continuity equation. Thus, for a correct measurement of D<sub>LVOT</sub>, the following technical requirements are suggested: (1) use of the “zoom” function on the echocardiograph to focus and enlarge the LVOT; (2) decrease the grey-scale gain towards the minimum; (3) D<sub>LVOT</sub> measurement is performed from the inner anterior edge to the inner posterior edge of the LVOT in mid-systole (“inner-edge to inner-edge”), which is immediately under the aortic valve. The maximal visualized D<sub>LVOT</sub> is considered, using an echocardiographic section that passes through the center of the LVOT and is not excentric because an excentric slice will underestimate the true maximal diameter. The measured D<sub>LVOT</sub> should be compatible with the patient’s height and weight. A D<sub>LVOT</sub> < 16 mm is extremely rarely seen in adults and should raise suspicion of measurement errors<sup>[19]</sup>.

It is important to realize that the true shape of the LVOT is not circular but oval; thus, echocardiographically determined AVA will always be an estimation and not a true measurement.

The correct measurement of transaortic velocities and gradients requires the use of the following multiple echo windows: Modified apical 5 chamber view towards the axilla; apical long axis view; 4<sup>th</sup> right intercostal space; and suprasternal window. Given these views, the following precautions should be applied: (1) the full envelope of the Doppler signal should be measured to avoid noise and/or aliasing; (2) measurements should not be made on post-extrasystolic beats; (3) correct measurement of the LVOT velocity-time-integral (VTI<sub>LVOT</sub>) should be made. The sample area should be placed immediately under the aortic valve in the middle of the LVOT where the velocity is maximal. In this location, the signal should record the clear click of the aortic valve closure without the click of the aortic valve opening; and (4) for the correct assessment of AVA using the simplified Bernoulli equation (automatically given by the echocardiograph), the measured VTI<sub>LVOT</sub> should be < 1.5 m/s. When the

$VTI_{LVOT}$  is  $\geq 1.5$  m/s (e.g., increased LVOT flow due to severe AR, etc.), the simplified Bernoulli equation cannot be used because it will overestimate the transaortic pressure gradient and AS severity based on the continuity equation and calculated AVA.

In conclusion, a correct and complete echocardiographic assessment of AS severity should report on the overall context of the cardiac pathology, LV volumes and LVEF, stroke volume (based on Doppler, not volumetric measurements), grade of calcification of the aortic valve (is it compatible with the measured severity?), associated abnormalities, estimation of pulmonary pressures, dimensions of right heart chamber, and estimation of right ventricular function.

The echocardiographic criteria for the definition of severe AS are not interchangeable. For example, a recent study on the correlation between mean transaortic pressure gradient and AVA in patients with AS and normal LVEF proved that for a mean pressure gradient of 40 mmHg, the corresponding AVA was  $0.8 \text{ cm}^2$  and not  $1 \text{ cm}^2$  as is the standard definition of severe AS<sup>[20]</sup>. Similarly, it is important to understand that a simple documentation of an AVA  $\leq 0.8 \text{ cm}^2$  does not prove the presence of severe AS because AVA is calculated using pressure gradients that are highly dependent on flow. Thus, when the transaortic flow is low, any valve (including normal ones) will appear "stenotic" because the orifice will not be fully opened. It has been proven that at transaortic flow rates  $< 125 \text{ mL/s}$  (corresponding to a cardiac output of approximately 3 L/min) the effective orifice area of any aortic valve, from mild anatomic AS to severe anatomic AS, will be  $\leq 1 \text{ cm}^2$ . Similarly, the mean transaortic pressure gradient will be  $\leq 40 \text{ mmHg}$  for any AS severity (from mild to severe, based on anatomical AVA) when the transaortic flow is  $< 175 \text{ mL/min}$ <sup>[21]</sup>.

Thus, the major problem in assessing AS severity rests with low-flow states. The prevalence of "low-flow, low-gradient" severe AS is approximately 25% of all severe AS cases. A low flow state is defined as an indexed stroke volume  $< 35 \text{ mL/m}^2$  of the body surface area. A low-flow/low-gradient state can appear in patients with both reduced LVEF due to myocardial systolic dysfunction or preserved LVEF due to small LV cavity size<sup>[22]</sup>. These 2 conditions will be detailed below.

**Low-flow, low-gradient, low-LVEF, severe AS:** Low-flow, low-gradient, low-LVEF, severe AS ("classical" low-flow, low-gradient severe AS) was described for the first time by Carabello *et al*<sup>[23]</sup> in 1980. It is defined as severe AS in the presence of systolic LV dysfunction (LV ejection fraction  $< 40\%$ ) with a mean transaortic pressure gradient  $< 40 \text{ mmHg}$  if estimated by echocardiography or  $< 30 \text{ mmHg}$  if measured invasively.

When the calculated AVA is  $\leq 1 \text{ cm}^2$  in low flow states, one should differentiate whether this is primarily due to the low flow (pseudo severe AS, where the anatomical AVA is  $> 1 \text{ cm}^2$ ) or if there is true severe AS (AVA remains fixed and  $\leq 1 \text{ cm}^2$  regardless of flow). Dobutamine stress echocardiography (DSE) is typically

performed to differentiate between the two conditions because it evaluates the response of AVA to increased transaortic flow. Figure 2 exemplifies the role of DSE in diagnosing low-flow, low-gradient, low-EF severe AS<sup>[24]</sup>.

Thus, when the calculated AVA is  $\leq 1 \text{ cm}^2$ , the mean transaortic pressure gradient is  $< 40 \text{ mmHg}$  and the LVEF is  $< 40\%$ , the DSE will help define the following parameters: (1) the severity of AS; and (2) the presence or absence of LV flow/contractile reserve, which is defined as an increase in LV stroke volume  $> 20\%$  compared with baseline at maximal dobutamine dose. Thus, the following 2 responses to dobutamine and 3 conditions associated with AS are seen when using DSE.

Low-flow, low-gradient, low-EF severe AS is diagnosed when there is increased flow/contractile reserve with a subsequent increase in transaortic pressure gradient to  $> 40 \text{ mmHg}$  while AVA remains  $\leq 1 \text{ cm}^2$ . AVR is indicated in these patients.

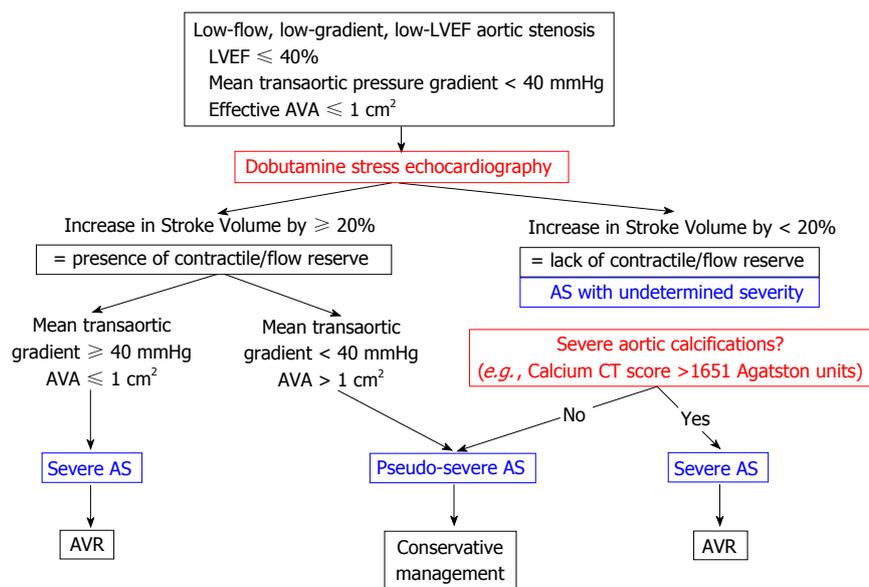
Pseudo-severe AS is diagnosed when there is flow (contractile) reserve, but the AVA increases in parallel with the flow to  $> 1 \text{ cm}^2$ . AVR is not indicated in these patients.

AS with undetermined severity is defined by the lack of flow/contractile reserve<sup>[25]</sup>. Even in this situation, identifying severe AS is important because the prognosis without AVR is grim, although surgical mortality is high. Identifying low-flow, low-gradient, severe AS without flow (contractile) reserve is based on the following: (1) statistical data - approximately 95% of low-flow, low-gradient, low-EF AS with undetermined severity have truly severe AS; and (2) objective data - evidence of severe aortic valve calcification (using echocardiogram, plain radiology or computed tomography) is highly specific for severe AS<sup>[26]</sup>. In this situation, a calcium score of  $\geq 1651$  Agatston units on computed tomography has an 82% sensitivity, 80% specificity, 88% negative predictive value and 70% positive predictive value for severe AS<sup>[27]</sup>. Of note, for the same hemodynamic severity of AS, women have lower aortic calcium load compared with men, so the thresholds should probably be lower in women compared with men<sup>[28]</sup>.

#### **Low-flow, low-gradient severe AS with preserved LVEF:**

Approximately 10% of patients with anatomically severe AS have low-flow/low-gradient characteristics despite preserved LVEF ("paradoxical" low-flow, low-gradient severe AS). This form of severe AS was first described by Hachicha *et al*<sup>[29]</sup> in 2007 and is characterized by the following features: (1) concentrically remodeled LV with preserved LVEF, severe diastolic dysfunction, impaired LV filling and low cardiac output (stroke volume  $< 35 \text{ mL/m}^2$ ); and (2) increased LV afterload generated by the AS and increased peripheral vascular resistance due to the rigid arterial system and frequent severe arterial hypertension in these patients.

Estimation of the global afterload faced by the LV (defined as the ventriculo-arterial impedance, Zva) is important because it is an independent negative prognostic factor and correlates with the appearance of symptoms



**Figure 2** The role of dobutamine stress echocardiography in diagnosing low-flow, low-gradient/low-ejection fraction severe<sup>[24]</sup>. LVEF: Left ventricular ejection fraction; CT: Computed tomography; AVR: Aortic valve replacement; AVA: Aortic valve area; AS: Aortic stenosis.

in these patients<sup>[30]</sup>. Zva is calculated according to the following formula:

$$Zva = [\text{Systolic blood pressure (mmHg)} + \text{mean transaortic pressure gradient (mmHg)}] / [\text{indexed stroke volume (mL/m}^2)].$$

Taking into account the transaortic flow and pressure gradients, severe AS with preserved LVEF has been recently classified into the following 4 forms<sup>[31]</sup>: (1) normal flow, low-gradient (NFLG) - representing approximately 1/4 of patients; (2) normal flow, high-gradient: Representing approximately 2/3 of patients; (3) low-flow, low-gradient (LFLG) - also known as "paradoxical" low-flow/low-gradient - representing 10% of patients; and (4) low-flow, high-gradient - representing the remaining 10% of patients.

The principle of this classification scheme can be extended to all forms of AS, regardless of LVEF<sup>[11]</sup>.

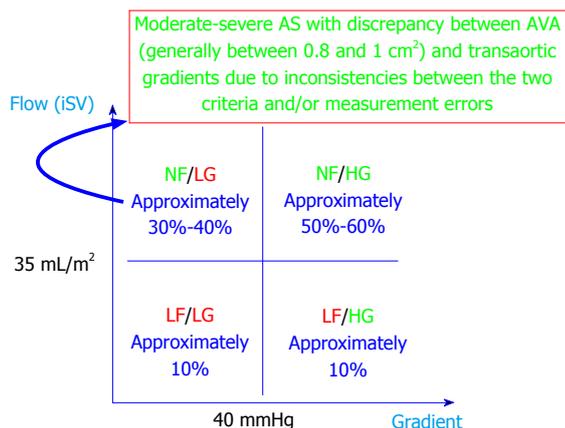
This classification has prognostic importance in patients with severe AS with preserved LVEF. The best prognosis [major adverse cardiovascular event (MACE) rate, 35% at 3 years] is carried by NFLG, and the most severe prognosis (MACE rate, 90% at 3 years) is carried by LFLG severe AS with preserved LVEF. The "high-gradient" forms have similar prognoses because they are intermediate forms between NFLG and LFLG<sup>[31]</sup>. However, this classification is limited by the fact that the existence of NFLG severe anatomical AS is counterintuitive. Indeed, the prognosis of these patients is similar to that for patients with moderate AS and is better than that for any other form of severe AS<sup>[32]</sup>. Thus, it is highly likely that what is known as NFLG severe AS with preserved LVEF is in fact moderate AS where the discrepancy between calculated AVA (which usually rests between 0.8 and 1 cm<sup>2</sup> in these cases) and transaortic gradients is a consequence of the inconsistency of the criteria used to define severe AS (see above) and/or measurement errors (Figure 3).

Thus, when one is faced with a discrepancy between the calculated AVA and measured gradients, the following elements should be taken into account: (1) measurement errors, especially of the  $D_{LVOT}$  diameter and  $VT_{LVOT}$  (underestimating flow); (2) extremes in body surface areas (very small or large individuals) - always use indexed measurements; and (3) inconsistency between the cut-off values used to define severe AS: An AVA of 1 cm<sup>2</sup> corresponds better to a transaortic pressure gradient of 30-35 mmHg and not 40 mmHg (see comments above for NFLG "severe" AS with preserved LVEF).

To establish a diagnosis of LFLG severe AS with preserved LVEF the following 3 criteria are recommended. First, confirmation of low-flow states by and indexed stroke volume < 35 mL/m<sup>2</sup>. Second, confirmation of increased global LV afterload (ventriculo-arterial impedance) by  $Zva \geq 4.5$  mmHg/mL per square meter. Third, confirmation of concentric LV remodeling by the following: (1) relative wall thickness (RWT)  $\geq 0.45$ . RWT is calculated using the following formula:  $RWT = (IVS + LVPW)/LVEDD$ , where IVS is the end-diastolic ventricular septal thickness; LVPW is the end-diastolic LV posterior wall thickness; and LVEDD is the end-diastolic LV diameter; (2) end-diastolic LV diameter < 47 mm; and (3) indexed end-diastolic LV volume < 55 mL/m<sup>2</sup>.

#### Identification of patients with severe AS who are candidates for aortic valve replacement:

After establishing the diagnosis of severe AS, the next step is to identify those patients who will benefit from AVR. The European Society of Cardiology/European Association for Cardio-Thoracic Surgery (ESC/EACTS) and the American Heart Association/American College of Cardiology (AHA/ACC) guidelines establish clear indications for AVR in patients with *symptomatic* severe AS (class I for normal flow/normal LVEF and for patients



**Figure 3** Classification of severe aortic stenosis with preserved left ventricular ejection fraction based on flow and transaortic pressure gradients<sup>[29]</sup>. iSV: Indexed stroke volume; NF: Normal flow; LF: Low flow; HG: High gradient; LG: Low gradient; AVA: Aortic valve area; AS: Aortic stenosis.

with normal flow/low LVEF and class IIa for patients with low-flow/low-gradient/low LVEF with true severe AS) and asymptomatic severe AS with LV systolic dysfunction or symptoms unmasked at stress tests (Table 2)<sup>[33,34]</sup>.

Establishing the presence or absence of symptoms can be difficult because many older patients (the majority of patients with AS) deny the presence of symptoms due to lifestyle adaptations to lower functional needs. Also, older patients refer symptoms that can be vague (e.g., fatigue), related to AS or to other comorbidities related with advanced age but not caused by AS. In these patients, unmasking the presence of symptoms (by treadmill or bicycle stress test) and/or LV systolic dysfunction (by stress echocardiography) establishes the indication for AVR<sup>[35]</sup>. The prognosis of patients with asymptomatic severe AS by positive stress test is identical to that for patients with symptomatic severe AS<sup>[36,37]</sup>.

The indication for AVR in patients with asymptomatic severe AS with preserved LVEF is highly controversial<sup>[38,39]</sup>. For a detailed discussion and extensive review of the literature on this highly important topic, the reader is referred to the excellent article by Génèreux *et al*<sup>[10]</sup>. The 1- and 5-year mortality rates for asymptomatic severe AS with preserved LVEF are 3% and 26.4%, respectively; also, 46% of initially asymptomatic patients develop symptoms during the next 5 years, and 20% develop heart failure<sup>[40]</sup>. Among patients with asymptomatic severe AS with preserved LVEF, those with very severe AS (defined as having a maximal transaortic velocity of  $\geq 5.5$  m/s) have twice the rate of MACE compared with that of patients with severe AS and a maximal transaortic velocity of 4 to 5 m/s (96% vs 39% at 4 years)<sup>[41]</sup>. Almost all patients (97%) with severe AS and a maximal velocity of  $\geq 5$  m/s suffered a MACE within 6 years of follow-up<sup>[41]</sup>. A recent registry study on patients with asymptomatic very severe AS, which compared 102 patients who had surgical AVR with 95 patients who were treated conservatively, showed that surgical AVR was

associated with an 86% reduction in mortality compared with the conservatively managed group after 6 years of follow-up (2% vs 32%; HR = 0.14, 95%CI: 0.03-0.6,  $P = 0.008$ )<sup>[42]</sup>. Based on these non-randomized, single-center data, current guidelines provide a class IIa ("is reasonable"; "should be considered") for AVR in patients with asymptomatic very severe AS with preserved LVEF (defined as having a maximal velocity of  $\geq 5.5$  m/s in the ESC/EACTS guidelines or  $\geq 5$  m/s in the AHA/ACC guidelines) only if the estimated perioperative mortality in that center is low<sup>[32,34]</sup>. Current guidelines also give a class IIa indication for AVR in patients with severe low-flow AS with preserved LVEF if the symptoms are judged to be secondary to AS only.

Observational and retrospective data suggest that several risk factors for MACE and poor prognosis may be useful to take into account in these cases (Table 3). However, it should be noted that the sensitivity and specificity of these parameters for the identification of patients with a good post-operative prognosis are only approximately 80%. Thus, implementation of these parameters to wide clinical practice cannot be recommended at present but can they can be useful for individual decision making in patients proposed for AVR. Among these parameters, the most widely studied are the prognostic role of aortic valvular calcifications and the hemodynamic response at stress echocardiography.

Eighty percent of patients with asymptomatic severe AS with preserved LVEF who have moderate or severe valvular calcifications develop MACE within the next 4 years, compared with only 20% of patients without moderate or severe calcifications<sup>[26,43]</sup>.

The response of transaortic pressure gradient to exercise has also been suggested to have prognostic importance. Thus, MACE event rate is highest (100% at 2 years) in patients with high resting transaortic pressure gradient ( $> 35$  mmHg) that increases by  $> 20$  mmHg during exercise, intermediate in patients where the transaortic pressure gradient increases by  $< 20\%$  during exercise (50% at 2 years for patients with high resting transaortic pressure gradient, and 20% at 2 years for patients with low transaortic pressure gradient), and lowest (10% at 2 years) in patients with low transaortic pressure gradient ( $\leq 35$  mmHg) that increases by  $< 20\%$  during exercise<sup>[44]</sup>.

Another study that evaluated 105 patients with asymptomatic severe AS with preserved LVEF showed that the inducibility of pulmonary hypertension during exercise (defined as an echocardiographically estimated systolic pulmonary arterial pressure  $\geq 60$  mmHg) was associated with twice the risk of MACE within 3 years of follow-up compared with patients with asymptomatic severe AS with preserved LVEF who did not develop pulmonary hypertension during exercise (22% vs 55%,  $P = 0.014$ )<sup>[45]</sup>. However, the incidence of MACE in both of these groups was very high. In addition, a recent meta-analysis of 4 observational studies with a total of 2486 patients reporting on the utility of AVR (21%

**Table 2** Indication for aortic valve replacement according to European Society of Cardiology/European Association for Cardio-Thoracic Surgery and American Heart Association/American College of Cardiology guidelines<sup>[33,34]</sup>

Criteria	Level of recommendation		Differences between guidelines
	ESC/EACTS	AHA/ACC	
Severe AS with any symptoms clearly due to AS, based on history or unmasked by stress test	I	I	"High-gradient" in AHA/ACC guidelines
Asymptomatic severe AS with LVEF < 50%	I	I	
Severe AS and another indication for surgery (CABG, thoracic aorta, another valve)	I	I	
Asymptomatic severe AS where the systolic blood pressure does not increase by > 20 mmHg or drops compared with baseline during the treadmill test	II a	II a	AHA/ACC guidelines acknowledge the presence of fatigability during stress test as an indication for AVR
Moderate AS and another indication for surgery (CABG, thoracic aorta, another valve)	II a	II a	
Low-flow/low-gradient/low-LVEF severe AS with proof of contractile reserve presence	II a	II a	
Symptomatic low-flow/low-gradient/preserved LVEF severe AS after careful confirmation of severity	II a	II a	
Truly asymptomatic severe AS (no symptoms during treadmill test, no risk criteria) with preserved LVEF if the surgical risk is deemed low and the following criteria are also satisfied: Very severe AS (maximal velocity $\geq$ 5.5 m/s); Severe valvular calcification and increased maximal velocity by $\geq$ 0.3 m/s per year	II a	II a for velocity $\geq$ 5 m/s (see text)  II b for maximal velocity increase by $\geq$ 0.3 m/s per year	AHA/ACC guideline: Velocity $\geq$ 5 m/s or mean gradient $\geq$ 60 mmHg AND severe calcifications; velocity 4 to 4.9 m/s or mean gradient 40 to 59 mmHg AND severe valvular calcification AND stress test demonstrating reduced tolerance or drop in blood pressure
Truly asymptomatic severe AS (no symptoms during treadmill test, no risk criteria) with preserved LVEF if the surgical risk is deemed low and 1 or more of the following criteria are also satisfied: Severely increased BNP/Nt-ProBNP levels at serial determinations and without an alternative explanation; increased transaortic pressure gradient at stress echocardiography by > 20 mmHg; excessive LV hypertrophy without an alternative explanation	II b	-	This indication is not covered in the AHA/ACC guidelines
Low-flow/low-gradient/low-LVEF severe AS without contractile/flow reserve	II b	-	This indication is not covered in the AHA/ACC guidelines

Class I : It is indicated, it is recommended; Class II a: Should be considered, it is reasonable; Class II b: May be considered; Class III: It is not indicated, it is contraindicated; ESC: European Society of Cardiology; EACTS: European Association for Cardio-Thoracic Surgery; AHA/ACC: American Heart Association/American College of Cardiology; AS: Aortic stenosis; LVEF: Left ventricular ejection fraction; CABG: Coronary artery bypass graft.

**Table 3** Suggested high-risk criteria in asymptomatic severe aortic stenosis

Test	High risk criteria
Electrocardiogram	Presence of LV hypertrophy with secondary ST segment deviation ("LV strain")
Blood tests	Highly increased BNP/Nt-ProBNP levels
Stress test	Unmasked symptoms: Fatigability/dyspnea at < 75 W, syncope/near syncope; angina Lack of increase in systolic blood pressure by > 20 mmHg (or decrease) with exercise Inducible myocardial ischemia (ST segment depression $\geq$ 2 mm) Severe ventricular arrhythmias (sustained VT, polymorphic VT, VF)
Conventional Doppler echocardiography	Very severe AS (AVA $\leq$ 0.6 cm <sup>2</sup> ; maximal velocity $\geq$ 5 m/s) LVEF < 50% Severe LV hypertrophy ( $\geq$ 15 mm)? Reduced LV longitudinal strain Zva $\geq$ 4.5 mmHg/mL per square meters Lack of contractile reserve
Dobutamine stress echocardiography (in low-flow, low-gradient, low LVEF)	
Exercise echocardiography (ergometric bicycle)	Increase in transvalvular pressure gradient by > 20 mmHg during exercise
- any severe AS	Inducible pulmonary hypertension during exercise (systolic pulmonary pressure $\geq$ 60 mmHg)
Documentation of valvular calcification	Presence of severe valvular calcifications: Qualitatively (radiology, conventional echocardiography); quantitatively (computed tomography): Calcium score $\geq$ 1651 Agatston units (lower in women vs men)

LVEF: Left ventricular ejection fraction; AS: Aortic stenosis; AVA: Aortic valve area.

of patients) vs watchful waiting (until development of symptoms for a class I indication of AVR) (79% of patients) found that patients who were treated

medically had a 3.5-fold increase in mortality compared with those who underwent AVR, suggesting the benefit of early AVR in this population<sup>[10]</sup>. However, in these

observational studies, patients who were medically treated were older and sicker, and up to 50% of them developed a class I indication for AVR during follow-up but were refused for various reasons - suggesting they were too sick to undergo either surgical or interventional AVR<sup>[40]</sup>. Thus, there is urgent need for a randomized trial to directly compare the two strategies<sup>[46]</sup>.

Although the ESC/EACTS guidelines for valvular heart disease suggest the use of natriuretic peptide levels (Nt-ProBNP) for decisions regarding the need for AVR in patients with asymptomatic severe AS with preserved LVEF<sup>[33]</sup>, a recent study found that the discriminating value of Nt-ProBNP in identifying patients who need AVR is suboptimal (area under the curve, AUC 0.73)<sup>[47]</sup>. Further research is needed to establish the use of natriuretic peptides in these patients.

### **Aortic valve replacement**

In patients proposed for AVR, estimation of operative risk is essential. Currently, two risk scores are widely used. The EuroSCORE II (<http://www.euroscore.org/calc.html>) includes 12 predictors identified from a retrospective population of 14799 patients who underwent different cardiovascular surgical interventions (mainly coronary artery bypass graft) in Europe, in 1995. The STS score (Society of Thoracic Surgeons, <http://riskcalc.sts.org>) includes 24 predictors identified from a population of 64292 patients who underwent surgical intervention only for AS in the United States between 2002 and 2006. The STS score is widely used in the United States for evaluating surgical risk for AS.

Both the EuroSCORE II and the STS score are quite precise in identifying patients with low surgical risk, but they tend to overestimate the risk of patients with high surgical risk (EuroSCORE II more than STS). For example, a patient with a logistic EuroSCORE II > 20 has an estimated surgical mortality of 39%, which is much higher than the real-world mortality of 11%<sup>[43]</sup>. Importantly, both the EuroSCORE II and the STS score can be used in practice in surgical institutions where the operative mortality lies within 1 standard deviation from the mean calculated mortality for the respective surgical procedure. None of the scores include frailty, which is a major limitation. The AHA/ACC guidelines recommend that the overall surgical risk should be divided into 4 groups (low, intermediate, high, and prohibitive) based on the overall assessment of surgical risk (STS score), patient frailty (Katz score)<sup>[48]</sup>, presence of major comorbidities (e.g., severe LV systolic dysfunction, fixed pulmonary hypertension, severe chronic renal failure, respiratory failure, cerebral dysfunction, cancer, and liver cirrhosis), and anticipated difficulties for surgical intervention (e.g., porcelain aorta, thoracic deformities, previous radiotherapy, internal mammary artery crossing the mid-line, and arterial bypass grafts that adhere to the posterior thoracic wall)<sup>[34]</sup>. The ESC/EACTS guidelines do not have similar recommendations<sup>[33]</sup>.

Importantly, the overall decision regarding the relative risks vs benefits for AVR and the most appropriate

type of AVR in individual patients should be made by a multidisciplinary heart team, consisting of a general cardiologist, an interventional cardiologist, a cardiac and vascular surgeon, imaging specialists (echocardiography, computed tomography), and an intensive care specialist with expertise in cardiac anesthesia.

Currently, the most effective treatment for AS is AVR. Simple valvuloplasty has no role in the treatment of severe AS except as a short-term palliation or as a bridge to more definite treatments (e.g., patients with very severe AS who also have abdominal surgical emergencies). Surgical AVR remains the main treatment option, and either a mechanical valve (in younger patients or patients with other indications for long-term anticoagulant therapy) or a bioprosthesis (in older patients due to durability issues or patients with contraindications to life-long anticoagulant therapy) can be used<sup>[49]</sup>. For a detailed discussion regarding the choice of surgical prosthesis, the reader is referred to recent reviews<sup>[50,51]</sup>. The newer alternative of percutaneous transcatheter AVR (TAVR) is given a class I indication for patients who have an indication for AVR but are not candidates for surgery (e.g., porcelain aorta, severe frailty) and a class IIa indication for patients with high surgical risk scores<sup>[33,34,52]</sup>. The morbidity and mortality associated with TAVR have significantly decreased recently as the technique has matured and experience increased; thus, TAVR is currently being investigated for possible expansion to lower risk patients with an indication for a bioprosthesis because recent trials have suggested that TAVR compared favorably to SAVR in these groups<sup>[53]</sup>. For a detailed discussion regarding the selection of TAVR candidates, the reader is referred to excellent recent reviews<sup>[7,8]</sup>.

## **AR**

AR is defined as the presence of diastolic incompetence of the aortic valve with the subsequent regurgitation of blood back from the aorta into the LV. The generally accepted criteria for the definition of severe AR is a regurgitant volume > 60 mL/cardiac cycle or an effective regurgitant orifice area (EROA) > 0.3 cm<sup>2</sup>. However, these parameters are very difficult to measure; therefore, numerous alternative parameters are used to define AR severity. One should be careful when using these parameters because the cut-off values are not interchangeable, and their sensitivity and specificity are suboptimal. Similarly to any other valvular heart disease, the echocardiographic assessment has to use an integrative, complete and correct approach.

### **Etiology**

The prevalence of AR is much lower compared with that for AS, and thus, far fewer studies are available for AR diagnosis and management. AR can be acute or chronic. Acute AR appears primarily as a result of aortic dissection or infective endocarditis. The heart cannot adapt by compensatory dilatation; as a result, the clinical picture is

dominated by signs of low cardiac output (due to reduced effective circulating volume) and pulmonary edema (due to high LV filling pressures secondary to large regurgitant volume). The classical signs of severe chronic AR (diastolic murmur, peripheral signs due to wide pulse pressure) are absent in severe acute AR because the diastolic pressure gradient between the aorta and the LV quickly equalizes. For the same reason, some echocardiographic signs of severe AR may be absent (such as the Doppler signal aliasing in the LVOT); in these situations, documenting diastolic reversal flow in the descending aorta prevents missing the diagnosis of severe AR. The presence of severe acute AR should be considered in the differential diagnosis of any patient presenting with acute severe heart failure or cardiogenic shock in the absence of obvious causes (such as myocardial infarction)<sup>[54]</sup>.

Chronic AR is mostly due to BAV or aortic root dilatation. Degenerative aortic valve disease is also important, whereas other etiologies are rare. Patients remain asymptomatic for a long time, but irreversible LV dysfunction may appear before symptom onset.

Bicuspid aortic valve (BAV) is the most frequent congenital heart disease in humans (prevalence: 2% of the general population)<sup>[55]</sup>. Congenital abnormalities of the aortic valve, of which > 90% are represented by BAV, are at the base of > 50% of so-called "calcific" severe AS in adults with an indication for AVR<sup>[12]</sup>. BAV is probably a disease of the entire aortic root characterized by fragmentation of elastin fibers, alteration of the media and increased collagen deposition in the ascending aorta<sup>[56]</sup>. These alterations are frequently seen in patients with ascending aortic dilatation and increased risk for aortic dissection.

BAV is characterized by fusion of one of the aortic commissures, which results in two functional aortic cusps of different dimensions. The terminology used to classify BAV may be confusing. Depending on the commissure that is fused, the orientation of the abnormal orifice can be anterior-posterior (by fusion of the right with the left coronary cusps - encountered in 56% of cases) or right-left (by fusion of the non-coronary with the right coronary cusp - encountered in 44% of cases). Less than 2% of cases are characterized by fusion of the non-coronary with the left coronary cusp. Thus, the morphology of the BAV can be described by the orientation of the opening orifice (anterior-posterior, AP/right-left, RL)<sup>[57]</sup> or by the cusps that fuse (right - left coronary, RL/right coronary - non-coronary, RN)<sup>[58]</sup>.

Recently, in a study that used 4-dimension flow magnetic resonance imaging, Mahadevia *et al*<sup>[58]</sup> suggested that the type of BAV determines the pattern of dilatation of the ascending aorta through the direction of the systolic transaortic jet and subsequent differential pressures on the various regions of the ascending aortic walls. Thus, BAV type AP/RL is associated with an eccentric systolic jet and increased parietal pressures on the anterior and right ascending aortic wall and is frequently (87%) associated with dilatation of the root or the entire ascending thoracic aorta. Conversely, BAV type RL/RN determines increased

parietal pressures on the right and posterior ascending aortic wall and is rarely associated with aortic dilatation. The role of hemodynamic vs genetic factors in stratifying the risk associated with BAV and aortic root disease is unclear<sup>[59]</sup>.

### Evaluation of AR

The evaluation of AR severity follows the same principles as that for the other valvular heart disease and is primarily based on echocardiography. For AR, the following goals are to be achieved by the echocardiographic evaluation: (1) identification of patients with severe AR; (2) identification of patients with an indication for AVR (surgical); and (3) identification of patients with dilated ascending aorta (with or without aortic bicuspid valves).

**Identifying patients with severe AR:** The most important echocardiographic criteria for identification of severe AR are listed in Table 4. For AR patients, the impact of different flow states (normal vs low) has not been investigated and is not applicable for routine clinical practice. Studies that validated the echocardiographic criteria for AR severity have used angiography as the comparator<sup>[60,61]</sup>. Only one study has prospectively evaluated the role of echocardiographic AR severity criteria in relation to the long-term prognosis of patients with severe, asymptomatic AR<sup>[62]</sup>.

**Identifying patients who are candidates for AVR:** SAVR remains the gold-standard treatment for AR. In a few experienced centers, surgical aortic valve reconstruction may be an alternative for patients with favorable anatomy (*e.g.*, dilated aortic root, prolapsed aortic cusp)<sup>[63,64]</sup>. TAVR has a very limited role in treating AR and has only been used anecdotally in these patients<sup>[65]</sup>.

Unlike AS, the current recommendations for AR evaluation and management are based on far fewer data. Additionally, most of the data on the prognosis of AR come from studies published more than 2 decades ago, which used outdated evaluation techniques.

Severe acute AR is a surgical emergency. The current indications for surgery for chronic severe AR are summarized in Table 5<sup>[33,34]</sup>. Regarding patients with dilatation of the ascending aorta, there are considerable differences between different guidelines, and a summary is provided in Table 6<sup>[33,34,66]</sup>. This summary does not cover patients with connective tissue disorders (*e.g.*, Marfan syndrome). In these patients, a recent AHA/ACC statement tried to clarify the differences between the 2 guidelines published in 2014 by the AHA/ACC (the "2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease"), and in 2010 by other collaborating societies (the "2010 ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM Guidelines for the Diagnosis and Management of Patients With Thoracic Aortic Disease")<sup>[67]</sup>.

The indications for surgery in AR are based on only a few small-medium sized prospective studies all of which were observational and published before 2000. Bonow *et al*<sup>[68]</sup> evaluated the long-term prognosis (mean follow-up, 8

**Table 4** Criteria for the diagnosis of severe aortic regurgitation

	Mild AR	Moderate AR	Severe AR
Ratio between the AR jet diameter and the LVOT diameter	< 25%	25%-64%	≥ 65%
Vena contracta (mm)	< 3	3-5.9	≥ 6
Regurgitant volume (mL/beat)	< 30	30-59	≥ 60
Regurgitant fraction	< 30%	30%-49%	≥ 50%
EROA (cm <sup>2</sup> )	< 0.1	0.1-0.29	≥ 0.3
Diastolic backflow in the descending thoracic and/or abdominal aorta	Minimal	Less than holodiastolic	Holodiastolic (especially for backflow documented in the abdominal aorta)
Angiographic	1+	2+	3-4+
LV dilatation	No	No	Yes (mandatory for chronic severe AR)

AR: Aortic regurgitation; LVOT: Left ventricular outflow tract; EROA: Effective regurgitant orifice area.

years) of 104 patients with severe AR and preserved LVEF recruited between 1973 and 1988. In these patients, the independent prognostic factors were age, the initial end-systolic LV diameter, and modification in time of the LVEF. In this study, patients with an end-systolic LV diameter > 50 mm and an end-diastolic LV diameter > 70 mm had a > 10%/year risk for death, development of symptoms or development of LV systolic dysfunction. The LV diameters were measured using simple, M-mode echocardiography, which has major limitations and is completely outdated today.

A second prospective observational study evaluated the prognosis of 104 patients with severe AR recruited beginning in 1979 and followed-up for an average of 7.3 years<sup>[69]</sup>. In this study, the most powerful prognostic factor was the rate of decline of LVEF (normalized to wall stress). Tornos *et al*<sup>[70]</sup> evaluated 101 patients with asymptomatic severe AR and normal LVEF, and followed-up these patients for up to 10 years. The rate of AVR was 12% at 5 years and 24% at 10 years. The independent prognostic factors required for AVR were an end-systolic LV diameter > 50 mm and an LVEF < 60% (determined by radionuclide cardiac scan); patients who needed AVR more frequently had progressive LV systolic dysfunction. Dujardin *et al*<sup>[71]</sup> evaluated 246 patients with severe AR included between 1985 and 1994, and followed-up these patients for an average of 10 years. The incidence of MACE during this period was very high (83%) as follows: 34% deceased; 47% developed heart failure and 62% received AVR<sup>[71]</sup>. In this study, the following were the independent predictors of survival: Age, New York Heart Association functional class, presence of co-morbidities, presence of atrial fibrillation, end-systolic LV indexed diameter > 25 mm/m<sup>2</sup>, and the LVEF. In a retrospective cohort study of 166 patients with asymptomatic severe AR and severe systolic dysfunction (LVEF < 35%), Kamath *et al*<sup>[72]</sup> showed that those who underwent surgery had much better prognosis compared with that of patients treated medically (HR = 0.59, 95%CI: 0.42-0.98, *P* = 0.04).

Importantly, AR severity in these studies was determined by angiographic and not echocardiographic criteria. Only one study evaluated the utility of echocardiographic indices in AR severity by identifying patients who will

need surgery. Detaint *et al*<sup>[62]</sup> evaluated 251 patients with asymptomatic severe AR with preserved LVEF (> 50%) recruited between 1991 and 2003 (a relatively contemporary population in comparison with previous studies). The independent prognostic factors required for AVR were severe AR as determined by quantitative echocardiographic indices and an end-systolic LV indexed volume > 45 mL/m<sup>2</sup> (as measured by the Simpson bi-plane method). Patients with severe AR and an end-systolic LV indexed volume > 45 mL/m<sup>2</sup> had an 87% risk of MACE at 10 years compared with only 40% of patients with severe AR and an end-systolic LV volume < 45 mL/m<sup>2</sup>. This study also showed that quantitative echocardiographic indices of AR severity had superior prognostic value compared with that of qualitative echocardiographic indices<sup>[62]</sup>.

These studies also suggested that patients with severe AR may have severe prognosis even before the appearance of symptoms or LV dysfunction. The mortality of patients with asymptomatic severe AR with preserved LVEF may reach 35% at 10 years<sup>[62,71]</sup>. However, there is insufficient prognostic data that can be used to identify patients at risk. The role of stress echocardiography in stratifying the risk of patients with severe AR has been much less studied compared with for patients with AS, but it may be used to evaluate the presence of contractile reserve<sup>[73]</sup>.

The role of myocardial deformation imaging in the selection of patients who may need AVR is also under investigation. A study of 64 patients with moderate or severe AR (regardless of symptoms and LVEF) showed that patients for whom AVR was eventually performed (*n* = 29) had lower values of LV strain, LVEF and higher LV volumes compared with patients who did not need surgery. However, the reported cut-off values for identifying patients who will need surgery had sensitivities and specificities that make them poorly applicable in clinical practice (area under the curve < 0.77)<sup>[74]</sup>.

B-type natriuretic peptide (BNP) levels may also play a role in predicting outcomes in patients with severe AR. Pizarro *et al*<sup>[75]</sup> studied 294 patients with severe asymptomatic AR and LVEF > 55%, and found that a BNP level > 130 pg/mL had 77% sensitivity and 94% specificity for predicting LV dysfunction symptoms

**Table 5** Indications for aortic valve replacement in chronic aortic regurgitation<sup>[33,34]</sup>

Criteria	Class of indication		Differences between guidelines
	ESC/EACTS	AHA/ACC	
Symptomatic severe AR (any LVEF)	I	I	
Asymptomatic severe AR with depressed LV function (LVEF < 50%)	I	I	
Severe AR in patients with another indication for cardiac surgery (e.g., CABG, thoracic aorta, another valve)	I	I	
Asymptomatic severe AR with normal LVEF (> 50%) but with severe LV dilatation	II a	II a	Definition of severe LV dilatation: ESC/EACTS guideline: End-diastolic LV diameter > 70 mm, or end-systolic LV diameter > 50 mm (or > 25 mm/m <sup>2</sup> ); AHA/ACC guidelines: End-systolic LV diameter > 50 mm
Moderate AR in patients with another indication for cardiac surgery (e.g., coronary bypass, thoracic aorta, another valve)	-	II a	This indication is not covered in the ESC/EACTS guidelines
Severe AR with normal LVEF (> 50%) but with progressive LV dilatation (end-diastolic LV diameter > 65 mm) if the surgical risk is low	-	II b	This indication is not covered in the ESC/EACTS guidelines

Class I : It is indicated, it is recommended; Class II a: Should be considered, it is reasonable; Class II b: May be considered; it is contraindicated; ESC/EACTS: European Society of Cardiology/European Association for Cardio-Thoracic Surgery; AHA/ACC: American Heart Association/American College of Cardiology; AR: Aortic regurgitation; LVEF: Left ventricular ejection fraction; CABG: Coronary artery bypass graft.

**Table 6** Indication for surgery in patients with bicuspid aortic valve and aortic root disease<sup>[33,34,66,67]</sup>

Class of indication	Guideline		Differences between guidelines
	ESC/ EACTS 2012	AHA/ACC 2016 Consensus on AHA/ACC 2014, and ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM 2010 Guidelines	
I	-	Asymptomatic bicuspid aortic valve with dilatation of Valsalva sinuses or the ascending thoracic aortic diameter > 55 mm	No class I indications in the 2012 ESC/EACTS guidelines
II a	Bicuspid aortic valve with an ascending thoracic aortic diameter > 50 mm if the patient also has at least one of the followings: Family history of aortic dissection; documented increase in the aortic diameter > 2 mm/yr (assessed using the same imaging method, at the same level, and with comparative images available); arterial hypertension; coarctation of the aorta	Bicuspid aortic valve AND dilatation of the Valsalva sinuses or of the ascending thoracic aorta (> 50 mm) AND at least one of the following Family history of aortic dissection Documented increase in aortic diameter > 5 mm/yr OR low surgical risk in an expert center	
	-	Replacement of the ascending aorta if the patient also has an indication for surgery for AS/AR, and the ascending aortic/Valsalva sinus diameter is > 45 mm	Not covered by the 2012 ESC guidelines

Class I : It is indicated, it is recommended; Class II a: Should be considered, it is reasonable; Class II b: May be considered; ESC: European Society of Cardiology; EACTS: European Association for Cardio-Thoracic Surgery; AHA/ACC: American Heart Association/American College of Cardiology; ACCF: American College of Cardiology Foundation; AHA: American Heart Association Task Force on Practice Guidelines; AATS: American Association for Thoracic Surgery; ACR: American College of Radiology; ASA: American Stroke Association; SCA: Society of Cardiovascular Anesthesiologists; SCAI: Society for Cardiovascular Angiography and Interventions; SIR: Society of Interventional Radiology; STS: Society of Thoracic Surgeons; SVM: Society for Vascular Medicine, North American Society for Cardiovascular Imaging; AR: Aortic regurgitation; AS: Aortic stenosis.

or death after  $38 \pm 9$  mo of follow-up. BNP level had additive prognostic value to echocardiographic prognostic indices<sup>[75]</sup>. Further studies are needed to establish the role of BNP levels for indication of surgery in patients with AR.

A recent study of 159 patients with moderate or severe AR without a formal indication for surgery according to current guidelines (LVEF > 50%, end-diastolic LV diameter  $\leq$  70 mm, end-systolic LV diameter  $\leq$  70 mm or  $\leq$  25 mm/m<sup>2</sup>) showed that 31% of these patients needed AVR within  $30 \pm 21$  mo of follow-up. The independent prognostic factors for early surgery were as follows: Global longitudinal LV strain, right ventricular longitudinal

strain, and tricuspid annular peak systolic excursion (TAPSE); the combination of these 3 factors had a higher discriminating power compared with each one taken individually ( $\chi^2 = 64.4$ ,  $P < 0.001$ )<sup>[76]</sup>. However, the individual variability of these indices was high, and their utility for clinical practice must be validated in prospective clinical studies. This study confirmed that patients with significant AR without an initial formal indication but who eventually needed AVR, developed progressive LV dilatation and LVEF decline during follow-up, despite similar degrees of LV dilatation and LVEF at baseline, when compared to patients who did not need AVR during follow-up<sup>[76]</sup>.

Cardiac magnetic resonance imaging (CMRI) is highly accurate in quantifying cardiac chamber volumes, aortic regurgitant volume and EROA. CMRI is recommended for patients with suboptimal echocardiography for whom the exact determination of AR severity is important and has therapeutic consequences (class II a indication, according to ACC/AHA guidelines)<sup>[34]</sup>.

A recent study of 113 patients with moderate and severe AR (as determined by echocardiography) followed-up for up to 9 years suggested that a regurgitant fraction > 33% as determined by CMRI had a high positive predictive value (93%) in identifying patients who will need AVR. Additionally, an end-diastolic LV volume > 246 mL was also useful in identifying these patients (positive predictive value for AVR, 88%)<sup>[77]</sup>. However, contrary to previous data, in this study, the CMRI-measured LVEF was not useful in identifying patients with asymptomatic severe AR who needed AVR. More studies are needed to establish the exact role of all these parameters in selecting patients with asymptomatic severe AR who will need AVR.

## CONCLUSION

AS and AR represent important health problems worldwide; when severe, they carry poor prognoses. For AS, both SAVR and TAVR may provide definite treatment in carefully selected patients. For AR, valve surgery (either SAVR or - in selected cases - aortic valve repair) remains the gold standard of care. To properly identify those patients who are candidates for surgery, the clinician has to carefully assess the severity of valve disease with an understanding of the potential pitfalls involved in these assessments. Thus, evaluation of aortic valve disease requires "a global view and a global understanding"<sup>[4]</sup>.

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## Atrial tachyarrhythmia in adult congenital heart disease

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### Abstract

The adult congenital heart disease (ACHD) population continues to grow and most cardiologists, emergency room physicians and family doctors will intermittently come into contact with these patients. Oftentimes this may be in the setting of a presentation with atrial tachyarrhythmia; one of the commonest late complications of ACHD and problem with potentially serious implications. Providing appropriate initial care and ongoing management of atrial tachyarrhythmia in ACHD patients requires a degree of specialist knowledge and an awareness of certain key issues. In ACHD, atrial tachyarrhythmia is usually related to the abnormal anatomy of the underlying heart defect and often occurs as a result of surgical scar or a consequence of residual hemodynamic or electrical disturbances. Arrhythmias significantly increase mortality and morbidity in ACHD and are the most frequent reason for ACHD hospitalization. Intra-atrial reentrant tachycardia and atrial fibrillation are the most prevalent type of arrhythmia in this patient group. In hemodynamically unstable patients, urgent cardioversion is required. Acute management of the stable patient includes anticoagulation, rate control, and electrical or pharmacological cardioversion. In ACHD, rhythm control is the preferred management strategy and can often be achieved. However, in the long-term, medication side-effects can prove problematic. Electrophysiology studies and catheter ablation are important treatments modalities and in certain cases, surgical or percutaneous treatment of the underlying cardiac defect has a role. ACHD patients, especially those with complex CHD, are at increased risk of thromboembolic events and anticoagulation is usually required. Female ACHD patients of child bearing age may wish to pursue pregnancies. The risk of atrial arrhythmias is increased during pregnancy and management of atrial tachyarrhythmia during pregnancy needs specific consideration.

**Key words:** Congenital heart disease; Arrhythmia; Adult; Ablation

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**Core tip:** This review highlights the importance of atrial tachyarrhythmia in adult congenital heart disease (ACHD) patients. It discusses causative mechanisms of arrhythmia, treatment of arrhythmia in the acute setting and on a long-term basis, including: Medications, catheter ablation, and anticoagulation. We include specific comments on the treatment of arrhythmias in ACHD patients who are pregnant.

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## INTRODUCTION

With an estimated incidence of 9 per 1000 live births, congenital heart disease (CHD) is the most frequent major birth defect<sup>[1]</sup>. Improved diagnosis and management have led to recent rapid growth in numbers of adult survivors, particularly in the subset of patients with complex heart lesions<sup>[2]</sup>. Individuals with adult congenital heart disease (ACHD) often have residual cardiac lesions that promote abnormal hemodynamics and electrical disturbance. Electrical abnormalities are exacerbated by surgical scar, prosthetic patches and diffuse myocardial fibrosis and increasingly as these patients age, by the additional burden of traditional cardiovascular risk factors<sup>[3,4]</sup>. It is perhaps not surprising that arrhythmia is one of the most important problems faced by ACHD patients and has become the leading cause of ACHD hospitalization<sup>[5]</sup>. In this population, atrial arrhythmia is far more common than ventricular and is associated with substantial morbidity and mortality.

Atrial arrhythmia in ACHD occurs with a prevalence 3 times greater than that seen in the general population<sup>[6]</sup>. The risk increases with age<sup>[7]</sup> and varies according to underlying congenital cardiac anomaly (Table 1<sup>[8-16]</sup>). The prevalence is greatest in those with complex defects where it is estimated at > 50% by the age of 65 years<sup>[6]</sup>. Atrial arrhythmias in ACHD can herald adverse or declining intra-cardiac hemodynamics and their occurrence is a risk factor for other significant clinical events<sup>[6,17]</sup>. Prompt diagnosis and appropriate management may help avoid important complications, the risks of which are higher in specific ACHD subgroups. In patients with simple lesions<sup>[18]</sup>, atrial arrhythmia can be managed in a similar manner to arrhythmia in patients with structurally normal hearts. However, for patients with lesions of moderate or high complexity<sup>[18]</sup>, involvement of an ACHD specialist and/or electrophysiologist with subspecialty expertise is recommended<sup>[17,18]</sup>. Most ACHD patients with arrhythmia

will initially present locally, to general cardiologists, family physicians and emergency doctors and given population demographics, it is increasingly likely these care providers will encounter such patients. This review is intended to raise awareness of atrial arrhythmia as a complication of ACHD and of the necessary caveats to deliver care safely. It focuses on issues seen frequently in our day-to-day clinical practice and of importance to primary care providers. For a more comprehensive analysis and further reading we suggest the 2014 PACES/HRS Expert Consensus Statement on the Recognition and Management of Arrhythmias in Adult Congenital Heart disease<sup>[17]</sup>.

## CLINICAL IMPLICATIONS OF ATRIAL TACHYARRHYTHMIA IN ACHD

Given the retrospective and observational nature of most studies, teasing out "cause and effect" for the clinical implications of atrial arrhythmia in ACHD is challenging. However, it is certain that ACHD patients who develop atrial arrhythmia are at increased risk of other adverse clinical events. In their large ( $n > 38000$ ) analysis of Quebec's ACHD patients, Bouchardy *et al*<sup>[6]</sup> found patients with a history of atrial arrhythmia experienced a 50% increase in mortality, a 100% increase in stroke or heart failure and a 300% increase in the risk of cardiac interventions, as compared those with no history of atrial arrhythmia. These findings from a large and heterogeneous ACHD population are borne out by those from smaller studies of diagnosis-specific cohorts. Two large multi-center studies identified atrial arrhythmia as a powerful predictor of mortality and/or ventricular tachycardia in patients with tetralogy of Fallot (TOF)<sup>[19,20]</sup>. In a single-centre study of 321 Fontan patients "clinically relevant arrhythmia" was the strongest predictor of outcome, increasing the risk of death or transplant 6-fold<sup>[21]</sup>. In our own cohort of Mustard patients, patients who had experienced an atrial arrhythmia had worse subaortic right ventricular (RV) function and more tricuspid regurgitation than those who had not<sup>[22]</sup>.

## TYPES OF ATRIAL TACHYARRHYTHMIA IN ACHD AND THEIR MECHANISMS

Any type of atrial tachyarrhythmia can occur in ACHD patients. However, by nature of their underlying heart defects and previous surgeries, some subtypes are more frequently encountered than others. Intra-atrial reentry tachycardia (IART) is the sub-type encountered most frequently at the current time<sup>[23]</sup>. This may change as the ACHD patient population ages and increases in the incidence of atrial fibrillation have been already noted<sup>[24-26]</sup>. Atrioventricular nodal reentry, typical atrial flutter and focal atrial tachycardias<sup>[17,27]</sup> are also seen and atrial arrhythmia mediated by accessory pathway(s) is a particular idiosyncrasy of patients with Ebstein anomaly of the tricuspid valve<sup>[27]</sup>.

**Table 1 Summary of studies describing the prevalence of arrhythmia in adult congenital heart disease**

Ref.	Diagnosis	No. of patients in study	Duration of follow-up (yr)	Prevalence of atrial arrhythmia (%)
[8]	Fontan	94	11	41
[9]	Fontan	334	9	16
[10]	TGA: Mustard or Senning	86 Mustard	8	48
[11]	TGA: Mustard or Senning	60 Mustard	Mustard 16	Mustard 28.8
		62 Senning	Senning 11	Senning 11.9
[12]	TGA: Arterial switch	374	19	2
[13]	Ebstein anomaly	285	20	36
[14]	Tetralogy of Fallot	242	16	12
[15]	Repaired AVSD	300	11	14
[16]	Repaired ASD	213	4	14

TGA: Transposition of great arteries; AVSD: Atrio-ventricular septal defect; ASD: Atrial septal defect.

### ***Intra-atrial reentry tachycardia and atrial flutter***

Macro reentry circuits within the atria of people without CHD usually produce typical isthmus-dependent atrial flutter, which can also occur in patients with ACHD. However, the scarred, dilated and thickened atria of ACHD patients produce additional barriers to conduction and promote macro reentry pathways independent of the tricuspid valve-inferior vena cava isthmus with low voltage electrocardiogram (ECG) signals and without the typical saw-toothed p-wave appearance of flutter waves. We refer to this type of arrhythmia as IART. With atrial rates ranging from 150-200 per minute, IART is usually slower than typical flutter and has a stable cycle length and p wave morphology<sup>[27]</sup>. Although both IART and atrial flutter can occur in ACHD and may coexist in individual patients<sup>[28,29]</sup> in our experience IART is the more frequently encountered and so we use this term preferentially when discussing atrial macro reentry in ACHD patients.

IART is the most common arrhythmia in adults with an atrial redirection procedure (Mustard or Senning operation) for transposition of the great arteries (TGA) and also in those with a Fontan circulation<sup>[23]</sup>. IART is also prevalent in patients with repaired TOF and reported to be an important cause of morbidity<sup>[25,30]</sup>. While the occurrence of atrial arrhythmia in ACHD increases with time<sup>[6]</sup> and subaortic ventricular dysfunction is a generalized risk factor<sup>[11]</sup>, more specific risk factors for IART have been identified in some subgroups. In patients with TGA and an atrial redirection procedure identified IART risk factors include: A Mustard procedure<sup>[31]</sup>, the occurrence of perioperative bradyarrhythmia, need for reoperation and loss of sinus rhythm during follow-up<sup>[26]</sup>. Older age at operation, history of an atrial septectomy, and an atriopulmonary connection have been identified as risk factors for IART in the Fontan population<sup>[10,32]</sup>.

The propagation route for an IART circuit differs depending on the anatomic defect and type of surgical repair<sup>[33]</sup>. The pathway is often restricted to right atrial tissue, modified by regions of fibrosis from previous suture lines, patches, and baffles which act in combination with natural conduction barriers like crista terminalis, valve orifices, and the superior and inferior caval orifices to

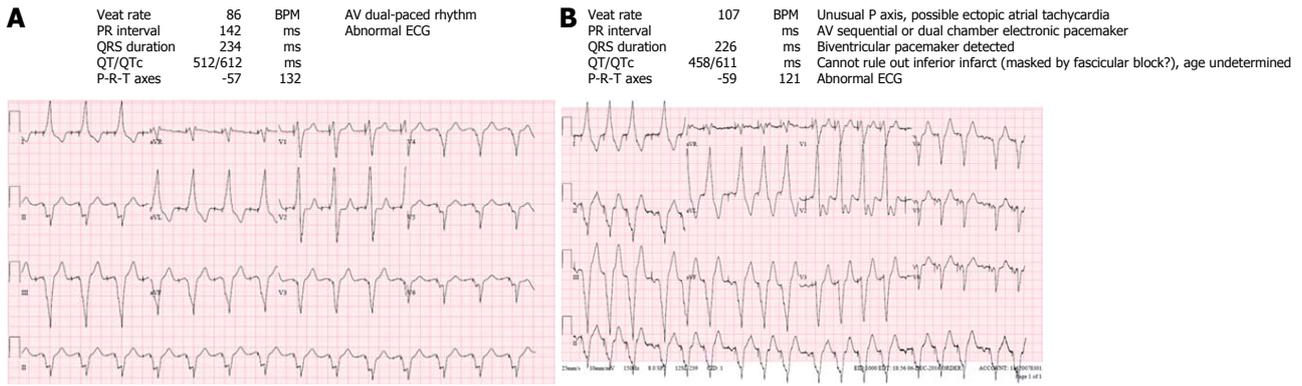
channel the wave front along a macroreentrant loop<sup>[34,35]</sup>. If a tricuspid valve is present, the isthmus between the valve ring and the inferior vena cava is often involved in such circuits, but in the absence of tricuspid valve or if there is a deformed valve, the circuit path is less predictable and can usually only be identified by electrophysiological mapping<sup>[36]</sup>. Multiple IART pathways can be present in the same patient<sup>[37]</sup>.

In the setting of a healthy AV node A:V conduction may occur 1:1. If so, the resultant fast ventricular rhythm can produce hypotension, syncope, or possibly cardiac arrest in ACHD patients who often have abnormal baseline hemodynamics or impaired ventricular function<sup>[36]</sup>. Rapid conduction is of particular concern in patients with atrial baffles (Mustard and Senning) who are unable to augment sub-aortic RV filling rates and stroke volume during tachycardia<sup>[38,39]</sup> and also in patients with a single ventricle physiology. The clinical picture of instability combined with tachycardia sometimes give rise to erroneous interpretation of the rhythm as being of ventricular origin. We see this mistake made most frequently in patients with TOF, since they usually have a baseline broad RBBB which persists during atrial tachycardia.

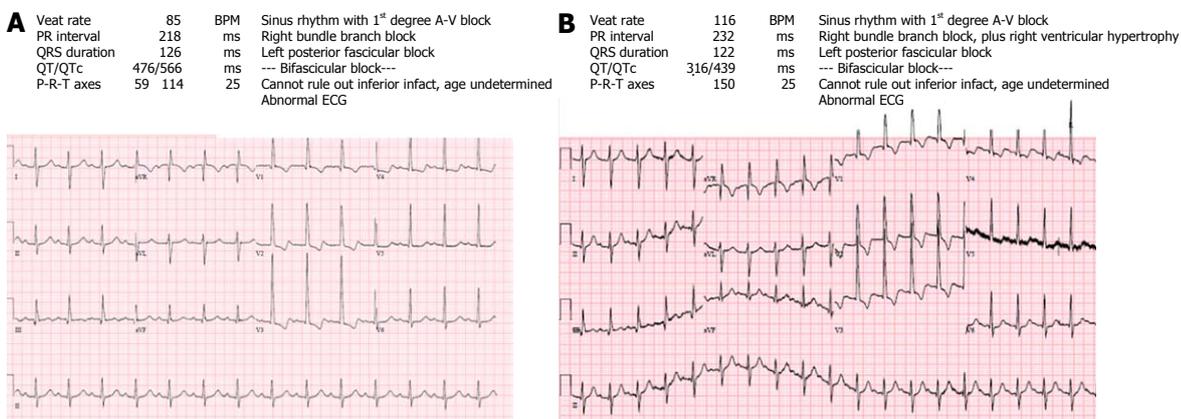
Conversely, in patients who remain clinically stable, IART with 2:1 or 3:1 conduction can easily be misinterpreted as sinus rhythm on the surface ECG of a patient with ACHD. This is not infrequently encountered in patients with a Fontan circulation or atrial redirection procedure for TGA. These patients often experience IART with a ventricular rate only slightly above their baseline rate and may have fractionated, difficult to see p-waves. Reviewing previous ECGs is often key to establishing the correct diagnosis. Hidden p-waves may be uncovered by vagal maneuvers or intravenous adenosine infusion, which can be useful when used with caution if still uncertain<sup>[36]</sup>. A high degree of clinical suspicion is required when interpreting the ECG in an adult CHD patient who presents with palpitations, especially if that patient has a Fontan or Mustard/Senning circulation (Figures 1 and 2).

### ***Atrial fibrillation***

Atrial fibrillation is the result of multiple micro reentry circuits and in ACHD is less prevalent than IART. A single-



**Figure 1** Electrocardiograms from a patient with an interatrial lateral tunnel Fontan for double inlet left ventricle. Patient has an epicardial DDI pacemaker for management of postoperative complete heart block. A: Atrio-ventricular sequentially paced rhythm. Patient feeling well; B: Grouped beating with V paced beats and intermittent p-waves. Underlying intra-atrial reentry tachycardia with AV Wenkebach demonstrated on device tracing (not shown). Patient complaining palpitations.



**Figure 2** Electrocardiograms from a patient with a Mustard procedure. A: Sinus rhythm with 1<sup>st</sup> degree heart block. Patient feeling well; B: Intra-atrial reentry tachycardia with 2:1 ventricular conduction, alternate p-waves not seen as overlapping with QRS complexes. Patient complaining palpitations initially. Within 3 h unable to lie flat, requiring oxygen for desaturation and with pulmonary edema on chest X-ray. Note incorrect automated diagnosis of sinus tachycardia.

centre study of 471 electrical cardioversions in 149 CHD patients found that 78% were for IART and 22% for AF<sup>[23]</sup>. However, the prevalence of AF is increasing as the ACHD population ages such that this diagnosis is becoming the most common atrial arrhythmia in older cohorts. A recent study of 4781 TOF patients across the age spectrum reported the average age of onset of IART as 27 years vs 44 years for AF<sup>[20]</sup>. In the same study, AF was the diagnosis in 10% of arrhythmias seen in patients born prior to 1961 vs < 1% patients born after 1981<sup>[20]</sup>. In another cohort of TOF patients AF was the most prevalent atrial arrhythmia after 55 years of age<sup>[25]</sup>. The increasing risk of AF with age relates to the underlying mechanism, which is usually chronic hemodynamic atrial stress and remodeling as well as increase in conventional risk factors such as hypertension, diabetes mellitus, obesity, and sleep apnea. Patients with residual AV valve regurgitation or left-sided obstructive lesions as well as those with unrepaired, palliated CHD are particularly vulnerable to AF<sup>[23,24]</sup>. Patients who have undergone ablation for IART may go on to experience late atrial fibrillation in follow-up. During follow-up approximately 30% of patients with surgically closed ASD who had previously undergone successful catheter ablation for IART develop AF<sup>[40]</sup>.

**Atrioventricular reentrant tachycardia**

Wolff-Parkinson-White syndrome (WPW) occurs in 20% of cases with Ebstein anomaly of tricuspid valve<sup>[41]</sup>. The accessory pathway in Ebstein anomaly is usually located along the posterior and septal aspect of the tricuspid ring where the valve leaflets are most abnormal, and about half of these patients have multiple accessory pathways<sup>[42,43]</sup>. Ebstein-like malformation of a left-sided tricuspid valve is common in congenitally corrected TGA and often associated with accessory pathway(s)<sup>[36]</sup>. Tachycardia events for Ebstein patients are of concern in adult years when there is increased likelihood of coexisting atrial fibrillation and 1:1 anterograde conduction over the accessory pathway<sup>[36]</sup>.

**MANAGEMENT OF ACUTE ATRIAL ARRHYTHMIAS IN ACHD PATIENTS**

Acute management of atrial tachyarrhythmia in hemodynamically stable patients includes anticoagulation to prevent thromboembolism, rate control, and cardioversion to restore sinus rhythm. In ACHD patients with simple anatomy and an atrial arrhythmia of ≥ 48 h or unknown duration, ≥ 3 wk of anticoagulation or transesophageal

echocardiography (TEE) is recommended prior to cardioversion to rule out intra-cardiac thrombus<sup>[17]</sup>. In moderate and complex patients who are at higher risk of thrombosis formation, TEE or 3 wk of anticoagulation is recommended prior to cardioversion, even if the IART or atrial fibrillation is less than 48 h in duration<sup>[17,44]</sup>. In our own practice, we are reluctant to leave Fontan patients or those with a systemic right ventricle in an atrial tachyarrhythmia for a prolonged period of time, for fear of deteriorating hemodynamics and/or ventricular function. Therefore we rarely choose to anticoagulate and wait three weeks. In high-risk patients we prefer to perform TEE or low dose cardiac CT promptly followed by cardioversion within a day or two of diagnosis. Pharmacologic rate control can be useful for those who have a rapid ventricular response during their tachyarrhythmia while cardioversion is being planned. Options include use of beta-blockers, calcium channel blockers, or amiodarone<sup>[45]</sup>.

Termination of atrial tachyarrhythmia can be achieved by electrical cardioversion, overdrive pacing, or drug therapy. Urgent electrical cardioversion is recommended in adults with ACHD who are hemodynamically unstable regardless of arrhythmia duration or anticoagulation status<sup>[45]</sup>. Anterior-posterior pad positioning increases cardioversion success in the face of marked atrial dilatation<sup>[17]</sup> and is important in the many ACHD patients who have a pacemaker. Patients with Fontan palliation, Mustard or Senning, and Glenn shunts, are at risk of sinus node dysfunction and may develop prolonged sinus pause following rhythm conversion<sup>[17,9,46]</sup>. The team planning a cardioversion needs to be prepared for this possibility. Patients with an extra-cardiac or interatrial lateral tunnel Fontan circulation do not have ready venous access to enable ventricular pacing. The back-up plan for these patients should include percutaneous pacing and/or use of medications such as atropine or isopretrenol. Electrical cardioversion of complex CHD patients is best performed in the coronary care unit with continuous monitoring of heart rhythm post cardioversion till rhythm stability is established. Overdrive pacing of IART can be attempted in patients with either atrial or dual chamber pacemakers or defibrillators. Immediate anti-tachycardia pacing is effective in up to 50% of cases<sup>[47]</sup>. In pacemaker dependent patients, it is important to maintain back up ventricular pacing during attempted atrial overdrive pacing<sup>[17]</sup>.

Pharmacologic cardioversion can be used to terminate atrial arrhythmias acutely, however, concerns include risk of torsades de pointes in Class III and ventricular tachycardia in Class IA and IC antiarrhythmic medications<sup>[17]</sup>. Amiodarone is the medication we use most often for acute termination of atrial arrhythmias in ACHD patients. Cardioversion can sometimes be achieved by following an intravenous bolus dose with a maintenance infusion for 24-48 h. Amiodarone may restore sinus rhythm, or assist in slowing the ventricular rate if cardioversion fails. There are currently no efficacy or safety data regarding the acute use of amiodarone in treatment of atrial tachy-

arrhythmia in ACHD patients<sup>[17]</sup>. Ibutilide and sotalol have also been shown as effective in acute treatment of atrial tachyarrhythmia<sup>[48,49]</sup>. When compared in a randomized study in non-ACHD population, ibutilide was superior to sotalol in conversion of atrial arrhythmia<sup>[50]</sup>. If using ibutilide, one must be cautious of torsades de pointes which is reported to occur in 2%-8% of non-ACHD patients<sup>[51]</sup>. In ACHD patients presenting with IART or atrial fibrillation, 1 to 2 mg of IV ibutilide over 10 min may be given if used with continuous heart monitoring where emergency defibrillation and resuscitation is available<sup>[17]</sup>.

Patients with WPW, orthodromic atrioventricular reentrant tachycardia and AVNRT, who are hemodynamically stable can be treated with intravenous adenosine, which may terminate the tachycardia and restore sinus rhythm. This is because adenosine slows AV nodal conduction and these tachycardias include the AV node as an obligatory part of their circuit. In contrast, the effects of adenosine on atrial flutter, IART and atrial ectopic tachycardia are inconsistent<sup>[52]</sup>. Adenosine will not generally terminate these arrhythmias and is more likely to produce transient or increased AV block, which can unmask atrial activity on an ECG and aid diagnosis. It is important that adenosine be given rapidly and in a sufficient dose to reach the coronary circulation. Adenosine administration is generally safe but rare proarrhythmic and potentially life-threatening effects have been reported<sup>[53]</sup>. It can precipitate atrial fibrillation, which as already stated, is a risk in patients with an accessory pathway where the atrial rate may be conducted 1:1 to the ventricles. Patients with pre-excited atrial fibrillation are usually treated with urgent electrical cardioversion because of the risk of cardiovascular collapse<sup>[54]</sup>.

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## MANAGEMENT OF CHRONIC OR RECURRENT ATRIAL ARRHYTHMIAS IN ACHD PATIENTS

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### *Medical management*

Rhythm control is generally recommended as the initial strategy for patients with moderate or complex forms of CHD<sup>[17]</sup>. This is because loss of sinus rhythm, even with a controlled heart rate can adversely and importantly impact both hemodynamics and ventricular function in ACHD patients<sup>[17,27]</sup>. However, once an ACHD patient has experienced atrial arrhythmia, recurrences are often seen. In our experience, the initiation of antiarrhythmic drugs, before further cardioversion may be beneficial to the chances of reestablishing sinus rhythm and/or reducing the frequency of recurrence.

The pro-arrhythmic risk of Class I (fast sodium channel blockers) antiarrhythmic drugs in patients with CHD includes ventricular arrhythmias<sup>[55,56]</sup>. In addition, they are not recommended for maintenance of sinus rhythm in patients with coronary artery disease or moderately to severe systolic dysfunction of either ventricle<sup>[17,45]</sup>.

In general cardiology practice, sotalol is used for

maintenance of sinus rhythm in patients with AF who have normal baseline QT interval (< 460 ms) and minimal or no structural heart disease<sup>[45]</sup>. While some retrospective studies have suggested safety and efficacy of sotalol in adults with CHD<sup>[57-59]</sup>, a meta-analysis of antiarrhythmic drugs for AF which included 12 clinical trials showed that sotalol doubles all-cause mortality<sup>[60]</sup>. Based on the current evidence, sotalol can be used with caution for maintenance of sinus rhythm in IART or AF in patients with ACHD<sup>[17]</sup>.

In non-ACHD populations, amiodarone is the most effective antiarrhythmic medication in maintaining sinus rhythm in AF and is considered drug of choice in heart failure patients<sup>[61,62]</sup>. Expert consensus suggests amiodarone as first line for maintenance of sinus rhythm in ACHD patients with IART and those with AF in presence of ventricular hypertrophy or dysfunction, or coronary artery disease<sup>[17]</sup>. It is the drug we use most often across the spectrum in ACHD, including in patients with impaired ventricular function. Unfortunately, long-term treatment with amiodarone (which is often necessary in this population) can be complicated by pulmonary and liver toxicity, thyroid dysfunction, photosensitivity, and corneal microdeposits<sup>[63]</sup>. In our experience the most frequent problems in ACHD patients are thyroid related. Torsades de pointes is seen in fewer than 1% of non-ACHD patients<sup>[64]</sup>.

Dofetilide has been shown to be safe in adult patients with recent myocardial infarction or heart failure<sup>[65]</sup>. The major concern is risk of torsade de pointes, which is seen in 0.9% to 3.3% of patients<sup>[66,67]</sup>. Dofetilide was studied in a multicenter series of 20 ACHD patients with refractory atrial arrhythmia and reasonable success was noted<sup>[68]</sup>. However, we rarely use this drug in our center and prefer the use of sotalol.

### **Catheter ablation**

Catheter ablation is now used as an early treatment strategy for IART in many centers and is preferred over the long-term pharmacological management<sup>[17,69]</sup>. Advances in 3D mapping for improved circuit localization and irrigated-tip or large-tip ablation catheters which help with effective lesion creation has led to 81% acute success rate<sup>[69-72]</sup>. Newly developed software permits rapid automatic annotation of signals using multi-electrode catheters. This allows large chambers to be mapped rapidly and with a huge number of points reducing procedure time and potentially increasing success rates of ablation<sup>[73]</sup>. These needs to be interpreted in the context of programmed settings on the mapping system including the window of interest and electrogram annotation the discussion of which is beyond the scope of this review<sup>[74]</sup>.

The acute success rate is lower in Ebstein anomaly with higher recurrence rate<sup>[75,76]</sup> due to challenges of distorted anatomic landmarks, difficulty identifying the true AV groove, extremely fractionated electrograms, and the high incidence of multiple pathways<sup>[31,75,76]</sup>. Recurrence

rates following ablation are 34%-54%, mostly occurring within the first year and are higher in atriopulmonary anastomosis of Fontan palliation compared to other CHD patients<sup>[72,77,78]</sup>. Gaining access to the atrial tissue is difficult in patients with an interatrial lateral tunnel or extra-cardiac Fontan palliation and conduit puncture may be required<sup>[79]</sup>. When planning ablation, consideration should be given to the location of the AV node in the underlying CHD and the risk of AV block due to ablation. For example, the AV node is typically located anterior in the AV junction in congenitally corrected-TGA<sup>[80]</sup>. The AV node is displaced postero-inferiorly in inlet VSDs<sup>[81]</sup>. These should be kept in mind when planning ablations in that region as for typical slow fast AVNRT. The AV node does not have an intracardiac signal. The His bundle signal is used as its surrogate marker. Locating and identifying the His is often challenging in ACHD as the conduction system is often displaced in many conditions like AV canal defects and congenitally corrected transposition of great arteries. In other conditions like an extracardiac Fontan, the His bundle is not accessible unless a puncture is performed. If located, the His signal can be tagged by using 3D electroanatomic mapping systems. This is especially important in patients with single ventricle palliation where the complication of heart block would often require management with epicardial pacing<sup>[82]</sup>.

Specific recommendations for AF ablation in CHD population have not yet been developed due to scarcity of published data on mechanism of arrhythmia, unclear ablation targets, and efficacy<sup>[27]</sup>. One study reported a success rate of 42% compared to 53% in controls without CHD. The value of repeat ablations and role of pulmonary vein isolation in complex CHD patients remains to be determined<sup>[40,83]</sup>. Limited experience is available on AV nodal ablation followed by permanent pacing in symptomatic patient with poor rate control<sup>[84]</sup>.

### **Surgical treatment and percutaneous intervention**

A disturbance of hemodynamics often underlies (or is a significant contributor to) atrial arrhythmia in ACHD. Sometimes the hemodynamic issues are amenable to treatment by surgery or a percutaneous intervention and if successful, such procedures may extinguish or ameliorate the patient's arrhythmia burden. Examples would be replacement of a regurgitant left atrioventricular valve in a patient with an atrioventricular septal defect, pulmonary valve replacement in a patient with repaired tetralogy of Fallot and severe pulmonary regurgitation and replacement of a stenosed conduit for pulmonary blood flow. The decision to surgically revise or upgrade a Fontan circulation as an intervention for recurrent arrhythmia can have excellent results but is a specific example with unique considerations<sup>[85-87]</sup>. When patients with ACHD experience atrial arrhythmia consideration should not only be given to correction of residual hemodynamic lesions but also to the role of specific arrhythmia surgery, which can be performed either in conjunction with

other procedures or in isolation. Mavroudis *et al.*<sup>[88]</sup> have published an excellent and detailed review of arrhythmia surgery in ACHD based on their own experience in 248 patients. Most of the surgical procedures described are for the treatment of atrial arrhythmia in patients with repaired TOF or a single ventricle circulation. Operative techniques described include, methods for increasing the safety of repeat sternal reentry, direct ablation (cryoablation or radiofrequency), right atrial and biatrial Cox-maze procedures, as well as excision of automatic foci. The paper describes the differing anatomical and electrophysiological variations which need to be taken into account for each congenital cardiac diagnosis and arrhythmia<sup>[88]</sup>.

### Anticoagulation

Thromboembolic prevention in ACHD patients is an important aspect of pharmacological treatment of atrial arrhythmia. The prevalence of thromboembolic events in ACHD patients is estimated to be 10 to 100-fold higher than age-matched controls in the general population due to dilated chambers with sluggish flow, intra-cardiac prosthetic material, pacing/defibrillation leads, intracardiac shunts, and associated hypercoagulable states<sup>[89,90]</sup>. In particular, the risk of stroke is 10-fold higher in ACHD patients, with atrial arrhythmia being one of the strongest predictors<sup>[91,92]</sup>. In a small series of ACHD patients who underwent TEE prior to electrical cardioversion of an atrial arrhythmia, atrial thrombus was seen in 37%<sup>[93]</sup>.

Risk scoring systems (CHA2DS2, CHA2DS2-VASc, and HAS-BLED) are widely used to guide anticoagulant prescription in non-ACHD patients, balancing the risks of thromboembolism against the risks of bleeding<sup>[94-96]</sup>. Initially, these scoring systems were not developed or tested in ACHD patients and did not include any component relating to the type or severity of congenital cardiac lesion<sup>[17]</sup>. For many years there has been controversy about whether or not they have any value in decision-making for ACHD patients. In 2015 a Dutch study of 229 ACHD patients with atrial arrhythmias attempted to address this issue<sup>[97]</sup>. The authors evaluated dichotomized CHA2-DS2-VASc and HAS-BLED scores in their ACHD cohort and reported that thrombotic and bleeding events can be predicted by using scoring systems<sup>[97]</sup>. In moderate/complex patients with IART or AF, long-term oral anticoagulation is recommended with vitamin K antagonist (VKA) however, in simple nonvalvular CHD, the decision of anticoagulation risk can be guided by CHA2DS2-VASc score<sup>[17,98]</sup>. Patients with CHA2DS2-VASc score of  $\geq 2$  need oral anticoagulation with VKA or novel oral anticoagulants<sup>[17]</sup>.

The new oral anticoagulants (NOAC) have been introduced as an alternative to VKA in non-valvular atrial fibrillation. These drugs are either direct thrombin (Dabigatran) or factor Xa (Rivaroxaban, Apixaban) inhibitors. Limited data is available regarding the use of NOACs in ACHD population. One prospective study included data from 75 ACHD patients without prosthetic

heart valves taking one of three NOACs<sup>[99]</sup>. Twenty-one percent of participants had complex CHD and the main indication was thrombosis prevention in atrial arrhythmia<sup>[99]</sup>. During a mean follow-up duration of 12 mo, there were no thrombotic or major bleeding events<sup>[99]</sup>. Results from further multi-centre studies are anticipated. However, it may be reasonable to consider NOAC in lieu of VKA in simple CHD and without prosthetic valves or hemodynamically significant valve disease<sup>[17,99]</sup>.

## ATRIAL ARRHYTHMIAS DURING PREGNANCY IN ACHD PATIENTS

The risk of atrial arrhythmia is known to increase during pregnancy due to anticipated adaptive hemodynamic, hormonal, and autonomic changes<sup>[100,101]</sup>. The incidence of AF/IART in patients with structural heart disease was reported at 1.3% by the Registry on Pregnancy and Cardiac Disease with the majority of arrhythmias occurring during second trimester<sup>[102]</sup>. The frequency of arrhythmia during pregnancy is higher than this in other studies and certain ACHD subgroups. In a systematic review by Drenthen *et al.*<sup>[103]</sup>, the highest risk of arrhythmia was reported in patients with Fontan palliation, atrial redirection for TGA (Mustard or Senning) and repaired atrio-ventricular septal defect. In a multi-centre study of 157 pregnancies in 74 women with repaired TOF the incidence of arrhythmia was 6.5% vs < 1% in controls<sup>[104]</sup>. In a study of women with valvular heart disease the rate of arrhythmia during pregnancy was 15% vs 0% in controls ( $P = 0.001$ )<sup>[105]</sup>. The following have been identified as risk factors for the occurrence of atrial arrhythmias during pregnancy: Arrhythmia before pregnancy, mitral valve disease, beta-blocker use before pregnancy, and left-sided cardiac lesions<sup>[101,102]</sup>. Atrial arrhythmias during pregnancy are associated with pregnancy-related mortality and morbidity. This may be due to severity of underlying heart disease and also to an increased risk of thromboembolic events<sup>[102]</sup>.

Electrical cardioversion can be used in all trimesters of pregnancy and must not be delayed in hemodynamically unstable patients<sup>[106]</sup>. The risk of inducing fetal arrhythmias is minimal but unless cardioversion is emergent, fetal monitoring should be performed<sup>[101,106,107]</sup>. Most antiarrhythmic drugs are United States Food and Drug Administration class C medications; *i.e.*, animal studies have shown risk to the fetus, there are no controlled studies in women or studies in women and animals are not available. This is a confusing classification, meaning that there is insufficient data to make a statement regarding safety. Use of these drugs must be carefully discussed with pregnant women to allow them the ability to weigh potential pros and cons. Beta-blockers (often metoprolol) are commonly used as first line rate control therapy. Atenolol is an FDA class D medication (positive evidence of fetal risk) and should be avoided due to association with low birthweight. Oral verapamil and digoxin (FDA Class C) are used for atrial arrhythmia in pregnancy

but should not be used when an accessory pathway is suspected<sup>[106]</sup>. Sotalol (FDA class B - animal studies show no risk, no studies in humans) can be used to maintain sinus rhythm although, its side effects include fetal bradycardia and long QT in the mother and therefore, close monitoring is required. Due to its side effects on fetal thyroid function, amiodarone should not be used during pregnancy unless other antiarrhythmic agents are contraindicated or ineffective. Flecainide (FDA class C) is a drug which crosses the placenta and is often used for treatment of fetal tachycardia, however there are proarrhythmic risks in patients with structural heart disease<sup>[108,109]</sup>. Pregnancy is a prothrombotic state and sustained atrial arrhythmia will further increase risk of thromboembolic events in pregnancy, therefore anticoagulation should be considered<sup>[100,110]</sup> and any decision about anticoagulation during pregnancy should be made with the input of specialist advice and in full consultation with the patient. Different regimens can be recommended depending on patient preference and the individualized balance of risks: Obstetric risks (miscarriage, retro-placental hematoma, bleeding during delivery) vs offspring risks (warfarin associated embryopathy, premature birth, inter-cranial bleeding) vs maternal risks (thrombosis and bleeding). The risk of maternal thrombosis and thromboembolism are highest in women who in addition to their atrial arrhythmia also have either mechanical valves or Fontan circulations.

## CONCLUSION

The ACHD population continues to expand and is also aging. Atrial arrhythmias are common in these patients and the cause of significant morbidity. They also associated with increased risk of subsequent mortality. A comprehensive understanding of the underlying anatomy, previous surgeries and mechanism of the arrhythmia is essential to optimal management of arrhythmias in this population and clear, open communication between ACHD specialists, electrophysiologists and primary care providers necessary.

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## Influence of cardiac nerve status on cardiovascular regulation and cardioprotection

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### Abstract

Neural elements of the intrinsic cardiac nervous system transduce sensory inputs from the heart, blood vessels and other organs to ensure adequate cardiac function on a beat-to-beat basis. This inter-organ crosstalk is critical for normal function of the heart and other organs; derangements within the nervous system hierarchy contribute to pathogenesis of organ dysfunction. The role of intact cardiac nerves in development of, as well as protection against, ischemic injury is of current interest since it may involve recruitment of intrinsic cardiac ganglia. For instance, ischemic conditioning, a novel protection strategy against organ injury, and in particular remote conditioning, is likely mediated by activation of neural pathways or by endogenous cytoprotective blood-borne substances that stimulate different signalling pathways. This discovery reinforces the concept that inter-organ communication, and maintenance thereof, is key. As such, greater understanding of mechanisms and elucidation of treatment strategies is imperative to improve clinical outcomes particularly in patients with comorbidities. For instance, autonomic imbalance between sympathetic and parasympathetic nervous system regulation can initiate cardiovascular autonomic neuropathy that compromises cardiac stability and function. Neuromodulation therapies that directly target the intrinsic cardiac nervous system or other elements of the nervous system hierarchy are currently being investigated for treatment of different maladies in animal and human studies.

**Key words:** Intrinsic cardiac nervous system; Myocardial ischemia; Ischemic conditioning; Autonomic neuropathy; Coronary blood flow regulation

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**Core tip:** Neural elements within the intrinsic cardiac nervous system are known to transduce sensory inputs from the heart, blood vessels and surrounding organs

to ensure beat-to-beat regulation of cardiac function. Development of autonomic neurophathies in patients with comorbidities compromises clinical outcomes. Myocardial ischemia also significantly affects cardiocytes as well as cardiac neurons; post-ischemic remodeling might affect neuronal function and thereby contribute to cardiac instability. Different protection strategies including ischemic conditioning and neuromodulation interventions that limit neural injury and help maintain cardiovascular function are the subject of ongoing investigations.

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## INTRODUCTION

A dense network of parasympathetic, sympathetic and sensory neurons innervates the heart and cardiac conduction system; each population of neurons is distinct with respect to functional requirements of the heart. Increased attention is being focused on the complex anatomy and function of the cardiac neuroaxis and questions abound regarding the manner in which different neuronal populations communicate with each other and between different organ systems. Ardell *et al.*<sup>[1]</sup> recently made the case that the cardiac neural hierarchy functions as a distributive processor with multiple nested feedback control loops that involve peripheral and central aspects of the autonomic nervous system. Remodeling of the cardiac nervous system at morphological and phenotypic levels during disease development is also under scrutiny<sup>[2-5]</sup>; neural remodeling can cause electrical instability that increases the incidence of arrhythmogenesis. Neuromodulation-based treatments for cardiovascular disease are being investigated as evidenced by the increasing use of diverse cardiac sympathetic decentralization and bioelectric interventions<sup>[6]</sup>. Herein, we briefly discuss experimental and clinical findings that highlight a role for the intrinsic cardiac nervous system on cardiodynamics. We also discuss mechanisms relevant to diverse protection stratagems. Finally, we focus on autonomic neurophathies that accompany comorbidities (Figure 1). For this review, clinical and basic science reports were searched using MEDLINE, PubMed and Google Scholar with the keywords intrinsic cardiac nervous system, myocardial ischemia-reperfusion injury, heart and kidney disease, cardioprotection, preconditioning and combinations thereof. Findings from our own studies on this, and related subjects were also consulted.

### Developmental aspects

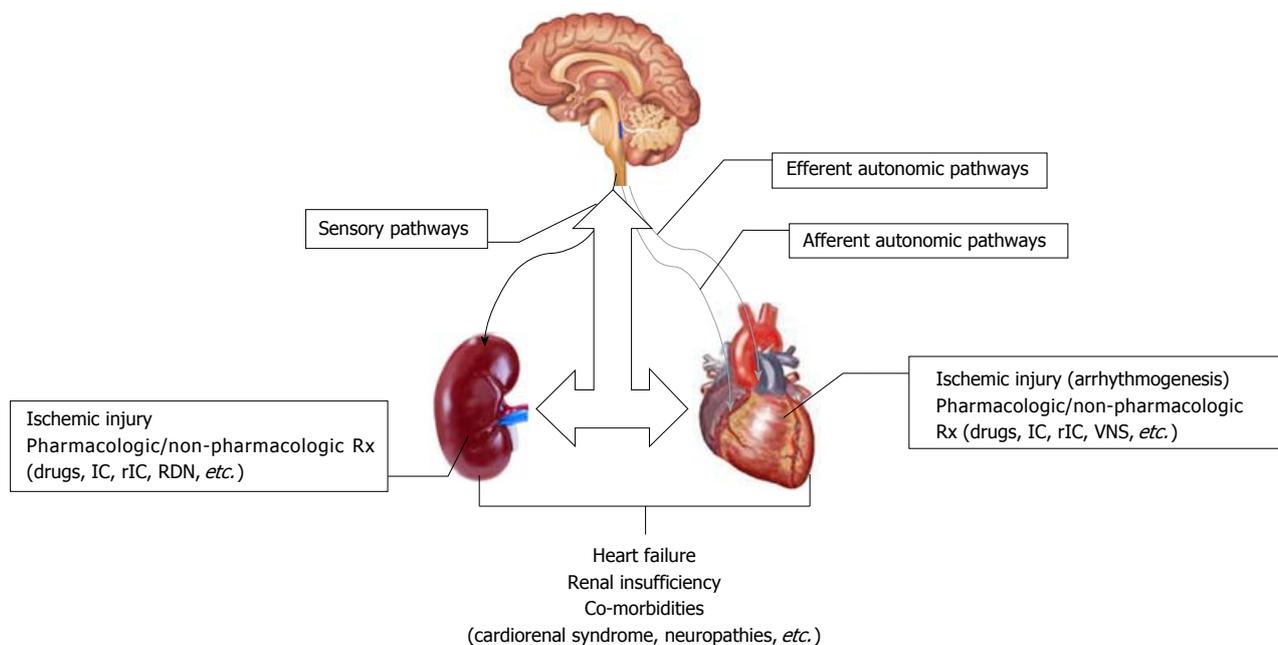
Development of the nervous and cardiovascular systems is synchronized during embryogenesis; neural crest cells in the dorsal neural tube form the parasympathetic and

sympathetic nervous systems that are important for cardiovascular function. Sympathetic interactions play a part in postnatal regulation of cardiocyte maturation; during life, cardiocytes remain quiescent and heart size increases by cellular hypertrophy<sup>[7]</sup>.

Cardiac neural crest cells furnish mesenchymal cells to the heart and great arteries that are involved in vascular remodeling and development of the cardiac conduction system<sup>[8-10]</sup>. The sympathetic component of the autonomic nervous system promotes cardiac conduction while the parasympathetic selectively exerts an inhibitory influence<sup>[11,12]</sup>. The integration of information for neurocardiac regulation involves the neuraxis that comprises the cortex, amygdala and various subcortical structures with an ability to modulate lower-level neurons within the hierarchy (for a detailed explanation see ref.<sup>[12]</sup>). Principal contacts between preganglionic neurons and the heart occur *via* the vagus nerves<sup>[2,13]</sup>. Neurons of the autonomic nervous system are: (1) characterized by chemical phenotyping (cholinergic, adrenergic, *etc.*); (2) located within intrathoracic extracardiac ganglia and intrinsic cardiac ganglia<sup>[14,15]</sup>; and (3) found within atrial epicardium and ganglionated plexi along major vessels and in the ventricular wall<sup>[16,17]</sup> depending on species<sup>[18]</sup>. Sensory neurons, interneurons and sensory fibers that originate from the nucleus ambiguus are also located therein<sup>[19,20]</sup>. Sensory information from all of these peripheral structures is integrated with higher central nervous system centers to coordinate regulation of cardiovascular responses. For example, descending signals from higher brain centers as well as afferent sensory signals from systemic arteries, cardiopulmonary regions and viscera have their first synapse in the nucleus tractus solarius (NTS) found in the dorsomedial region of the medulla<sup>[21]</sup>. Transmission of afferent inputs from other sources such as skin and skeletal muscle to medullary vasomotor centers occur *via* the spinal cord. Vagal outflow to the heart is mediated by NTS neurons that synapse to preganglionic parasympathetic neurons located in the dorsal motor nucleus. All of these neural inputs to medullary vasomotor centers are involved in autonomic control of the cardiovascular system, for example, the arterial baroreceptor reflex plays a major role in blood pressure homeostasis on a beat-to-beat basis and involves stretch receptors that can be found in the carotid sinus and aortic arch. Accordingly, afferent baroreceptor discharge is relayed from the carotid sinus (*via* glossopharyngeal nerve) and aorta (*via* vagus nerve) to the NTS that stimulates afferent baroreceptor discharge and promotes efferent sympathetic and parasympathetic outflow to the heart and blood vessels, this enables adjustments of cardiac output and vessel resistance and ultimately facilitates return of blood pressure to steady state levels.

## CORONARY BLOOD FLOW REGULATION AND MYOCARDIAL PERFUSION

Non-neural mechanisms (humoral, metabolic, mechanical,



**Figure 1** A schematic overview of efferent and afferent autonomic pathways on normal cardiac regulation, they also play a role in arrhythmogenesis caused by ischemic injury. Various pharmacologic/non-pharmacologic interventions that target autonomic pathways (IC: Ischemic conditioning; rIC: Remote IC; VNS: Vagus nerve stimulation) attenuate cardiac or renal symptoms. Sensory pathways are involved in renal regulation; injury (all cause) affects renal function that can be attenuated by different interventions (IC, rIC, RDN: Renal denervation). Inter-organ interactions also directly affect organ function; development of comorbidities is related to pathogenesis of disease in multiple organs (ex. heart-kidneys-brain, etc.). Pathology in one organ system can result in significant progression of disease in a distant organ; neuromodulation interventions may be beneficial to these patients.

etc.) that contribute to control of vascular regulation act independently from autonomic neural mechanisms. For example, under normal physiological conditions myocardial perfusion across the ventricles is uniform as long as coronary artery pressure is maintained within the range of autoregulation<sup>[22]</sup>. Shifts in the lower pressure limit are produced by changes in left ventricular pressure and volume as well as biochemical modifications by a host of endogenous compounds that exercise their effects on myocytes, conduction tissues, vascular smooth muscle, etc. The scientific literature that has examined coronary vasoregulation with a focus on cardiac nerve status is relatively sparse. Most studies have concentrated on control of regional cardiodynamics by the intrinsic cardiac nervous system in either normal or pathological conditions.

In healthy individuals during exercise, activation of the sympathetic nervous system stimulates metabolic vasodilatation due to increases in heart rate, cardiac contractility and ventricular work. Direct sympathetic stimulation of coronary vessels induces either vasoconstriction or vasodilatation depending on activation of either  $\alpha$ -, or  $\beta$ -adrenoreceptors, or vessel size. For example, large coronary vessels (> 100  $\mu\text{m}$ ) constrict when exposed to norepinephrine whereas small coronary vessels relax<sup>[23]</sup>; vasodilatation in arterioles permits coordination of oxygen delivery to myocardial oxygen demand<sup>[24]</sup>. On the other hand, simultaneous vasoconstriction in medium and large coronary arteries mediated by activation of  $\alpha$ -adrenoreceptors helps to preserve subendocardial blood flow when oxygen demand increases. In a canine study,

we examined myocardial perfusion following injection of select neuropeptides into active loci of the intrinsic cardiac nervous system and documented significant coronary vasodilatation secondary to increased myocardial metabolism and oxygen demand<sup>[25]</sup>. We also examined whether intact cardiac nerves were critical for coronary blood flow autoregulation; results confirmed a role for intrinsic cardiac neurons in autoregulatory control and myocardial perfusion even after ablation of extracardiac nerves from central nervous system control<sup>[26]</sup>. Ablation of external neuronal inputs to the heart also results in reduced myocardial efficiency that is consistent with impaired glucose utilization and depletion of cardiac catecholamine levels<sup>[27,28]</sup>; the latter directly affect myocardial oxygen demand<sup>[29-31]</sup>. Other animal studies reported that heterogeneity of myocardial perfusion is similar in innervated and denervated hearts<sup>[32-34]</sup>; possible explanations include: (1) the fact that regional denervation has little effect on vascular  $\alpha$ -adrenergic receptors (in part due to circulating catecholamines); or (2) preserved neural modulation and autoregulation at different levels of the microcirculation across the ventricular wall<sup>[35,36]</sup>.

Diverse central and peripheral elements within the cardiac nervous system act in sync to regulate cardiac function<sup>[20,37]</sup>; direct stimulation of intracardiac neurons occurs through central efferent neuronal inputs from the vagi or stellate ganglia<sup>[38]</sup>. G-protein coupled receptors are known to regulate cardiac function (see recent review by Capote *et al.*<sup>[39]</sup> on structure, function and signalling pathways solicited by G-protein-coupled receptors in the heart). Control of heart rate requires intricate

coordination between  $\beta$ -adrenergic and muscarinic cholinergic receptors found throughout the cardiac conduction system. Cardiac contraction controlled by  $\beta$ -adrenergic receptors are found in myocyte membranes while cardiac structure and morphology are coordinated by angiotensin II type 1 receptors in fibroblast and both endothelial cell and myocyte membranes<sup>[40,41]</sup>. Highly distinct processing capabilities of intracardiac neurons allow this complex network to respond to multiple inputs from all cardiac regions and major vessels near the heart. Disruption of these control networks by diverse cardiac pathologies ultimately increases the potential for sudden cardiac death<sup>[42-45]</sup>.

## MYOCARDIAL ISCHEMIA

Myocardial ischemia significantly influences cardiocytes as well as local and remote neurons that are involved in regulation of cardiac function<sup>[1,46]</sup>; the survival threshold of intra-/extra-cardiac sympathetic/parasympathetic neurons during development of coronary artery disease is not well established. However, viable nerves that course over an infarcted region tend to remain so oxygen and energy needs are fulfilled by an independent blood supply from extracardiac sources<sup>[47]</sup>. Reorganization of cardiocytes and nerves during development of diverse cardiac pathologies could occur in response to shifts of cardiac demand and function<sup>[3,48]</sup>. Mechanisms involved in the pathogenesis of cardiac dysfunction are multifactorial; a short list of possible factors include cardiac substrates, neural/cardiocyte interface, hormonal influences, inflammation and reflex responses between intra- and extra-cardiac nervous systems and their interactions with higher center neurons. Cardiocytes and cardiac neurons conceivably share common pathways for survival but this remains to be proven.

In the setting of transient ischemia, intact cardiac nerves are believed to play a key role on post-ischemic restoration of cardiac function<sup>[49]</sup>. Direct ischemic effects include progressive neuronal dysfunction and regional nerve terminal sprouting which ultimately diminishes local sensory and motor neurite function<sup>[50,51]</sup>. Indirect effects that modulate local neurite function are caused by local release of a host of endogenous chemicals (purinergic agents, peptides, hydroxyl radicals, *etc.*) that also affect neuronal function. Post-ischemic remodeling of cardiac neural networks could promote conflicts between central and peripheral reflexes that increases the risk of autonomic imbalances, arrhythmogenesis and sudden cardiac death<sup>[3,15,37,52]</sup>. A recent position paper by Ardell *et al.*<sup>[1]</sup> discussed the significance of remodeling of the cardiac neuronal hierarchy to cardiac arrhythmia induction. In addition, inotropic stimulation is deleterious to myocyte survival as it occasions an imbalance between oxygen demand and supply (*i.e.*, increased oxygen demand with limited coronary vascular reserve)<sup>[49,53]</sup>.

Acute occlusion of a coronary artery produces distinct alterations of myocyte pathology that lead to cell death unless blood flow is restored to the affected myocardium,

a transmural gradient of cell death occurs in relation to the duration of ischemia and degree of blood perfusion *via* coronary collateral vessels to the underperfused myocardium<sup>[54]</sup>. In animal models, necrosis is generally fully developed by 6 h after which tissue salvage is not possible (this time frame may not be the same for human myocardium) with currently available interventions. In addition, early restoration of blood flow to an infarct-related coronary vessel could cause "reperfusion injury" in already damaged or otherwise affected myocytes<sup>[55]</sup>. The physiopathology of ischemic, or reperfusion injury has been reviewed and discussed over the past several decades<sup>[56-59]</sup>; however, less attention has focused on the ability of the cardiac nervous system to accommodate the stress of ischemic, or reperfusion injury. Post-ischemic changes in peptide expression due to release of inflammatory cytokines combined with nerve damage could affect neuropeptide production in sympathetic cardiac neurons. In one study, Habecker *et al.*<sup>[60]</sup> documented extensive axon damage after infarction; they also reported a significant increase of galanin (promotes regeneration of sensory neurons<sup>[61]</sup>) in cardiac sympathetic neurons in the left ventricle. These findings indicate that cardiac sympathetic neurons retain a certain capability to respond to nerve growth factor which is increased during ischemia-reperfusion<sup>[62]</sup>.

While sympathetic dysinnervation has been reported secondary to myocardial infarction, the injury threshold of sympathetic and parasympathetic cardiac neurons within the ischemic region has not been established<sup>[63,64]</sup>. Several studies have documented that sympathetic impairment could exceed the area of underperfusion and necrosis<sup>[65,66]</sup>. Ischemic stress stimulates release of autocooids such as adenosine and bradykinin, along with nitric oxide and reactive oxygen species that can trigger cellular signal transduction pathways. These compounds can initiate responses in somata and axons within the intrinsic cardiac nervous system<sup>[37]</sup>. Indeed, oxidative stress, changes in growth factor expression and inflammatory cytokines released within the heart and vasculature contribute to neuronal remodelling<sup>[2,3,5,67]</sup>. As mentioned earlier, the regenerative capacity of cardiocytes is limited<sup>[68]</sup>; cardiocytes withdraw from the cell cycle early after birth and subsequently remain quiescent. Transition from proliferative to hypertrophic growth corresponds to the period of sympathetic growth into the heart tissues; *in vitro* studies with neonatal cardiocytes cultivated in the presence of innervating sympathetic fibers showed significant cellular proliferation<sup>[69]</sup> thereby confirming that early sympathetic signalling plays a role. In earlier *in vitro* studies, Horackova *et al.*<sup>[70]</sup> reported that adult ventricular myocytes co-cultured with intrathoracic neurons retained similar structural properties to those observed *in vivo*; cardiocytes and intrinsic cardiac neurons that were cultured alone displayed a variety of morphologies (unipolar, bipolar, multipolar).

Sympathetic regulation might also be involved in myocyte regeneration following ischemia, or reperfusion, injury; however, disruption of peripheral nerves inhibits

regeneration<sup>[71,72]</sup>. Chemical sympathectomy blocks early regeneration of damaged myocytes and increases tissue scarring<sup>[73]</sup>. Though additional studies are necessary, available data support the role of the intact cardiac nervous system on cardiocyte development and proliferation. On the other hand, post-ischemic regeneration and remodeling of the cardiac nervous system also merits further consideration and investigation. Rajendran *et al*<sup>[46]</sup> recently evaluated post-ischemic changes in neural signalling in a porcine model; they presented a “cardiac electroneurogram” between injured and adjacent non-injured myocardial tissue and reported: (1) that different intra-cardiac ganglia undergo morphological and phenotypic remodeling depending on the site of injury; (2) attenuation of afferent neural signals from the infarcted region to intra-cardiac neurons (activity in border and remote regions is apparently preserved); (3) maintenance of autonomic efferent inputs to the intrinsic cardiac nervous system; (4) augmented transduction capacity of convergent intrinsic cardiac local circuit neurons; and (5) reduced network connectivity within the intrinsic cardiac nervous system. The heterogeneity of afferent neural signals probably results from the presence of a “neural sensory border zone” (*i.e.*, analogous to the so-called myocardial border zone) caused by scar formation during post-ischemic myocardial healing. This infarct-induced asymmetry of afferent inputs probably contributes to reflex activation of the autonomic nervous system; recent findings from Wang *et al*<sup>[74]</sup> using resiniferatoxin (a potent agonist of transient receptor potential vanilloid 1) showed reductions in cardiac afferent nociceptive signalling, and sympatho-excitation along with preserved cardiac function in rat hearts.

The role of intact cardiac nerves in modulating responses to ischemia and post-ischemic ventricular function has been studied in a variety of experimental models. In a cardiac decentralized porcine model subject to acute coronary artery stenosis Huang *et al*<sup>[49]</sup> reported significant ventricular dysfunction accompanied by patchy subendocardial necrosis; they proposed that the impaired recovery of left ventricular function is mediated by nitric oxide (NO) and reactive oxygen species (ROS). Cardiac nerves may help to attenuate production of ROS and/or prevent conversion of NO to peroxynitrite (*via* release of still unknown mediators/scavengers); neurotransmitters from cardiac nerves could stimulate or upregulate different isoforms of nitric oxide synthase (*i.e.*, endothelial, neural)<sup>[75]</sup>. Myocardial perfusion-function relations are not altered by cardiac denervation<sup>[49]</sup>; this can be partly explained by the similarity between intact innervated and denervated hearts with regard to determinants of myocardial oxygen demand. In a recent study, we reported no significant change in coronary vascular reserve (intact cardiac nerves *vs* acute decentralized) in a canine model of ischemia-reperfusion injury<sup>[76]</sup>; these findings concur with most<sup>[77,78]</sup>, but not all, earlier studies<sup>[79]</sup>. Of particular note is that protection against ischemic injury occurred even when affected myocardium was disconnected from central command;

this suggests that local intrinsic cardiac neurons share common protection pathways to delay progression of cellular necrosis. Neurotransmitters that originate from cardiac nerves or intrinsic cardiac neurons might stimulate release of endogenous compounds that activate intracellular signalling pathways involved in cytoprotection; they could also inhibit peroxynitrite formation by modulating activation of various nitric oxide synthase isoforms. Indeed, many questions remain regarding the role of intact cardiac nerves within the context of cardioprotection against ischemia-reperfusion injury.

Myocardial ischemia also results in excessive activation of extracardiac cholinergic and adrenergic inputs of local circuit neurons within the intrinsic cardiac nervous system<sup>[38,80]</sup> that initiate cardiac arrhythmias<sup>[81]</sup>. A novel treatment for suppression of ventricular arrhythmias and treatment of refractory angina pectoris in current use in preclinical and clinical studies is spinal cord stimulation<sup>[80,82-84]</sup>; this intervention alters peripheral ganglia neural processing along the neural end-organ interface<sup>[85,86]</sup> and transduces neural signals to higher centers *via* the spinal cord<sup>[1,87,88]</sup>. Spinal cord stimulation influences autonomic reflexes within the neuroaxis and stimulates discharge of neuromodulators that limit release of select neurotransmitters and alter basal activity of sympathetic preganglionic neurons<sup>[89,90]</sup>. Intermittent spinal cord stimulation is suggested to stimulate neural memory and may be used for management of cardiac control and angina<sup>[91]</sup>; this could be akin to “electrical conditioning” and may be useful to limit cellular injury caused by ischemia. Vagus nerve stimulation is also being used to protect against ischemic injury and its consequences<sup>[92]</sup>; vagus nerve stimulation activates a host of signalling pathways and inhibits release of pro-inflammatory cytokines (see Ardell *et al*<sup>[1]</sup> for an up-to-date review). Vagus nerve stimulation might also affect myocardial energetics and maintain the equilibrium between energy supply and demand in the failing heart<sup>[93,94]</sup>. Interventions using vagus nerve stimulation favourably modulate cardiac disease as well as arrhythmogenesis; in several clinical studies this non-pharmacologic treatment is safe and well tolerated and is documented to improve cardiodynamics in patients with compromised ventricular function<sup>[95,96]</sup>.

## MYOCARDIAL PROTECTION

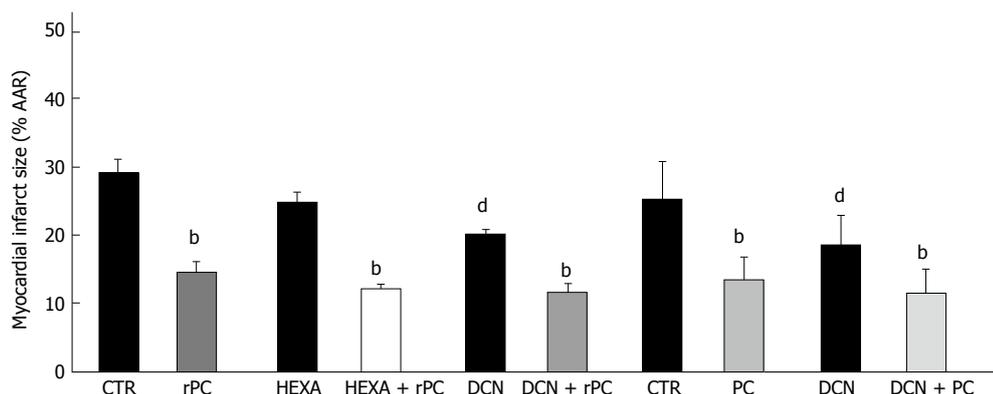
Sympathetic and parasympathetic nerves located near cardiocytes permit rapid crosstalk between cell types that may, or may not, activate cytoprotective pathways. Ischemic conditioning was first described by Murry *et al*<sup>[97]</sup> in 1986 in barbiturate-anesthetized dogs subjected to repeated episodes of sublethal coronary occlusion/reperfusion in advance of a prolonged period of acute ischemia. To date, ischemic conditioning has been reported to delay development of cellular necrosis in all organs examined in animals and in humans<sup>[98]</sup>; two distinct windows of cellular protection have been described but the causative mechanism(s) remain unanswered. The reader is referred to a recent review that summarizes

research into this cytoprotective intervention over the past 30 years<sup>[99]</sup>. Interestingly, Kudej *et al.*<sup>[100]</sup> showed that intact cardiac nerves were not required for first window protection in a porcine ischemia-reperfusion injury model; however, the presence of functional cardiac nerves was considered essential for development of second window protection. This delayed protection could occur through  $\alpha_1$ -adrenergic receptor pathways mediated by iNOS and COX-2<sup>[101]</sup>.

A host of conditioning strategies have been described in animal and clinical studies; however, the potential to translate conditioning-mediated protection in patients remains controversial<sup>[102,103]</sup>. Remote conditioning was first described in dogs subject to acute coronary occlusion and was referred to as "preconditioning at a distance"<sup>[104]</sup>. In that study, animals were subject to repetitive periods of non-lethal ischemia of the left circumflex artery vascular bed before exposure to a prolonged occlusion of the left anterior descending coronary artery; results demonstrated that a cytoprotective factor could be activated, produced, or transported from the heart or elsewhere to affected tissues to afford protection. Since the publication of these key findings numerous studies using remote conditioning either before, during or after coronary occlusion have been reported<sup>[105-109]</sup> but the mechanisms involved have not been established. An important but unanswered question that persists is how the protective signals are transferred from distant tissues to the target organ. Various hypotheses (not mutually exclusive) including: (1) communication *via* blood or perfusate borne humoral factors; (2) communication by neuronal stimulation and transmission; and (3) communication by systemic alteration of circulating immune cells have been proposed<sup>[106,110,111]</sup>. Intrinsic neural loops in the heart process sensory information from the myocardium that modulate efferent autonomic output from the intrinsic cardiac ganglia even in the absence of input from the central nervous system<sup>[37,38,93,112]</sup>. Transmission of sensory messages within intrinsic cardiac ganglia is regulated by release of acetylcholine into the synaptic cleft; nerve impulses are initiated by acetylcholine that activates specific receptors in post-ganglionic nerves<sup>[112-114]</sup>. The risk of injury or remodeling of these neural loops escalates during myocardial ischemia; studies with pharmacologic ganglionic blockade document abolition of remote conditioning-mediated cytoprotection and suggest that protective signals could transfer between organs *via* neural pathways<sup>[112,115-117]</sup>. Early preclinical studies in different experimental models (including heart failure) reported positive results with vagal nerve stimulation (VNS) with respect to ventricular remodeling, ejection fraction and biomarker levels<sup>[118-120]</sup>. In patients with advanced heart failure, VNS reportedly attenuates left ventricular contractile dysfunction<sup>[121]</sup> and may reduce ischemic injury<sup>[122-124]</sup>. Clinical studies show that diminished heart-rate responses and depressed sensitivity of vagal reflexes are associated with poor cardiovascular outcomes and cardiac-related mortality<sup>[125-127]</sup>. Smith *et al.*<sup>[127]</sup> recently reviewed efficacy of VNS for hypertension and heart failure in several small,

randomized clinical trials (ANTHEM-HF, NECTAR-HF, INOVATE-HF, *etc.*) and concluded that further studies are required; VNS titration studies are also needed to validate potential clinical benefits of these interventions<sup>[128]</sup>. Stimulation of vagal nerves activate a host of signalling pathways *via* increased release of acetylcholine that activates downstream receptors (cholinergic, muscarinic, *etc.*) to impact cardiodynamics and could also promote myocyte resistance to stress by improving myocyte energetics<sup>[93]</sup>. Cross-talk between humoral mediators and neural pathways could also produce cytoprotection by stimulation of local afferent nerves<sup>[129,130]</sup>; but it remains unclear whether intact, functional nerves are required to assure conditioning-mediated cytoprotection<sup>[131,132]</sup>. On the basis of data showing that intact sensory innervation of peripheral ischemic tissue is essential to remote conditioning protection, Mastitskaya *et al.*<sup>[133]</sup> proposed a "remote preconditioning reflex" that requires sensory input from remote ischemic tissue; recruitment of vagal pre-ganglionic neurons within the dorsal motor nucleus of the vagus nerve was considered to be critical for cytoprotection. While this data does not negate the concept that humoral factors are required for protection by remote conditioning, they strongly suggest that functional neurons within the parasympathetic nervous system are critical<sup>[134,135]</sup>. Bilateral vagotomy reportedly abolished protection afforded by remote conditioning<sup>[136]</sup>. On the other hand, findings from our laboratory (summarized in Figure 2) documented significant protection against ischemic injury independent of intact extrinsic cardiac nerves (note the similarity between groups with respect to reduction in infarct size) regardless of the conditioning protocol<sup>[76,137]</sup>. Briefly, in those studies isoflurane anesthetized dogs underwent remote conditioning (4 × 5-min renal artery occlusion/reperfusion) combined with/without treatment with the autonomic ganglionic blocker, hexamethonium (HEXA; 20 mg/kg, *IV*) or acute cardiac decentralization (DCN). Additional experiments were performed in dogs subject to classical preconditioning either before or after DCN. Based on these findings we suggested that neural pathways might not directly influence ischemic conditioning (either classical or remote) mediated cardioprotection. Moreover, others have brought forward the view that intact connections between the heart and central nervous system are not necessary for remote conditioning-mediated cardioprotection as long as recruitable parasympathetic neurons within a target organ can be activated. Use of remote conditioning as a potential therapeutic intervention for organ protection in man continues to merit investigation because it is non-invasive, cost-effective and easily applicable; however, the period for successful application of this intervention has yet to be determined and clinical strategies aimed at reducing myocardial damage by ischemic conditioning have been unsuccessful. While cellular protection by ischemic conditioning is possible in the presence of comorbidities, a stronger triggering stimulus appears necessary to assure cytoprotection<sup>[138]</sup>.

Understanding bidirectional interactions between



**Figure 2** Myocardial infarct size (% anatomic area at risk: AAR) is shown for different study groups subject to ischemia-reperfusion injury. Data are means  $\pm$  1SD; <sup>b</sup> $P \leq 0.01$  vs respective control (CTR), HEXA (hexmethonium; 20 mg/kg, IV), or DCN (acute cardiac decentralized) group; <sup>d</sup> $P \leq 0.01$  vs CTR groups. Group differences determined by ANOVA. PC: Ischemic preconditioning; rPC: Remote preconditioning. Data reported in earlier studies from our laboratory<sup>[76,137]</sup>.

elements of the nervous system and its remodeling during evolution of different comorbidities (senescence, kidney dysfunction, diabetes, *etc.*) is essential to help in the development of strategies to delay progression of disease not only in the heart but also in other organs. For instance, autonomic neuropathies defined by abnormalities of the sympathetic and parasympathetic nervous systems could be responsible for significant morbidity and mortality in patients; cardiovascular events are considered a primary risk factor for mortality. Cardiovascular autonomic dysfunction is the result of complex interplay between vascular, neural, cardiac, paracrine and endocrine entities; the outcome is tissue injury that compromises integrity of cardiac reflexes.

## HEART FAILURE

Heart failure subsequent to cardiac injury or chronic stress causes significant loss of contractile efficacy. Investigations into the role of autonomic imbalance between sympathetic and parasympathetic nervous systems and its contribution to pathogenesis of heart failure is ongoing for more than 25 years. Altered autonomic function also plays a role in other cardiac interrelated conditions such as hypertension, myocardial ischemia, cardiac arrhythmogenesis and sudden cardiac death<sup>[48]</sup>, see recent review by Florea and Cohn<sup>[139]</sup>. Dynamic interactions between cardiocytes and compensatory neurohumoral mechanisms allow the heart to maintain cardiac output; stimulation of the adrenergic nervous and renin-angiotensin-aldosterone systems along with activation of cytokines play a critical role to prevent progressive worsening of cardiac function associated with heart failure<sup>[140,141]</sup>. Lympelopoulous *et al.*<sup>[141]</sup> recently reviewed: (1) the actions of neurotransmitters on cell surface adrenergic and G-protein-coupled receptors; and (2) adrenergic receptor polymorphisms in the physiopathology of heart failure. They concluded that activation of the autonomic nervous system plays a critical role in compensatory responses to progressive cardiac dysfunction; however, excessive activation of these compensatory pathways could accelerate development

of heart failure. In addition, they examined various therapeutic approaches (*i.e.*, sympathomimetic drugs, activation of cardiac parasympathetic nervous system, increasing  $\beta$ -adrenergic receptor function using novel G-protein-coupled receptor blockade, *etc.*).

## CHRONIC KIDNEY DISEASE AND NEUROPATHY

Physiopathology of chronic kidney disease (CKD) is complex and results either from a primary renal disorder or from multisystem disorders related to various comorbidities such as diabetes. Indeed, diabetes is considered to be the most common cause of CKD in patients. Neurological derangements are a common occurrence in CKD<sup>[142]</sup>. The spectrum of CKD ranges from mild kidney damage (largely asymptomatic) to end-stage renal disease (potentially fatal); neurological complications that include cognitive dysfunction, stroke, as well as peripheral and autonomic neuropathy can markedly affect clinical outcomes<sup>[143]</sup>. Accumulation of urea, creatinine, parathyroid hormone in high concentrations provide a biochemical milieu that rapidly produces neurological dysfunction; however, most symptoms can be reversed with treatments such as hemodialysis<sup>[144]</sup>. Mechanisms responsible for increased cardiovascular risk in patients with CKD are multifactorial and include hypertension and diabetes<sup>[145]</sup>, along with increased oxidative stress, decreased bioavailability of nitric oxide, inflammation, abnormal calcium and phosphorous metabolism, overstimulation of the sympathetic nervous system, *etc.*<sup>[146-148]</sup>. Anemia is another major complication associated with both CKD and diabetes<sup>[149]</sup>; the latter may be present before overt evidence of symptoms of renal impairment<sup>[150]</sup>.

Essential structures of the kidneys (renal vessels, tubules, juxtaglomerular apparatus, *etc.*) are richly innervated. Renal afferent nerves transmit sensory information *via* chemo- and mechano-receptors to higher centers within the brain<sup>[151,152]</sup>, to maintain water retention, sodium reabsorption and blood flow. These

nerves might also play a role in renal inflammation and injury; suggested mechanisms include  $\beta$ -adrenergic receptor activation, release of neuropeptides (neuropeptide Y, vasoactive intestinal polypeptide, substance P, *etc.*), renin release from juxtaglomerular cells (increases plasma angiotensin II levels) and other pro-inflammatory cytokines (tumor necrosis factor, IL-1 $\beta$ , *etc.*).

Autonomic dysfunction is prevalent (> 60%) in CKD patients and is associated with vascular calcification, cardiac arrhythmias and sudden cardiac death<sup>[153]</sup>. Reduced sensitivity to baroreceptors in the vessel wall caused by autonomic dysfunction can modulate cardiac regulation and contribute to intradialytic hypotension (*i.e.*, no increase in heart rate to compensate the decrease in arterial pressure)<sup>[154]</sup>; these symptoms can be corrected with pharmaceuticals or, if necessary, renal transplantation.

## DIABETIC AUTONOMIC NEUROPATHY

Autonomic dysfunction is a recognized complication of diabetes mellitus; diverse contributory mechanisms to increased mortality includes medial hyperplasia at baroreceptor sites, impaired cardiac vagal function, left ventricular hypertrophy and endothelial dysfunction<sup>[155]</sup> due in part to oxidative stress and reduced availability of nitric oxide which can affect sympathetic nerve activity<sup>[156]</sup>. Endothelial nitric oxide synthesis is known to be defective in insulin resistant states and is a central factor to neuronal abnormalities during metabolic syndrome (increases cardiovascular risk to some extent due to sympathetic activation)<sup>[155]</sup>. Insulin also plays a key role in nitric oxide and autonomic nervous system interactions and is involved in regulation of peripheral vascular tone and arterial blood pressure. Significant evidence shows that nitric oxide is critical to the vasodilator actions of insulin<sup>[157]</sup>, sympathectomy and autonomic failure can severely limit insulin-induced vasodilatation in patients<sup>[158]</sup>. Vulnerability to lethal arrhythmias in diabetic patients with autonomic dysfunction is also elevated<sup>[159]</sup>. Cardiac autonomic dysfunction may occur more frequently when diabetes is coupled with micro albuminuria caused by microvascular damage and endothelial dysfunction<sup>[160-162]</sup>; however, it was reported in the Hoom Study that cardiovascular autonomic dysfunction and microalbuminuria were independently associated with mortality<sup>[163]</sup>. Additionally, in that study the presence of cardiovascular autonomic dysfunction doubled the 9-year mortality risk<sup>[155,164]</sup>; the ACCORD study also confirmed a significantly higher rate of mortality in patients with autonomic dysfunction<sup>[165]</sup>.

## CONCLUSION

Impaired sympathetic and parasympathetic nervous system regulation contributes to organ dysfunction and leads to significant morbidity and mortality particularly in patients with comorbidities. Early detection and management of these patients could markedly reduce adverse effects and thereby affect clinical outcomes. Prospectively, autonomic dysfunction develops because of

damage at multiple sites within organs but pathogenesis remains to be clarified. Cardiovascular autonomic dysfunction, for instance, reflects compromised interactions between vascular, neural, cardiac, inflammatory, paracrine and endocrine mechanisms. Restoration of autonomic equilibrium in animal and clinical studies using either pharmacologic or non-pharmacologic interventions is currently possible. Further investigations in neurocardiology should continue to provide important findings apropos connections between cardiac and neurohumoral control systems and thereby allow continued development of clinically relevant opportunities for neuroscience-based treatments.

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## Management of ventricular tachycardia storm in patients with structural heart disease

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### Abstract

Electrical storm (ES) is a medical emergency characterized by repetitive episodes of sustained ventricular

arrhythmias (VAs) in a limited amount of time (at least 3 within a 24-h period) leading to repeated appropriate implantable cardioverter defibrillator therapies. The occurrence of ES represents a major turning point in the natural history of patients with structural heart disease being associated with poor short- and long-term survival particularly in those with compromised left ventricular ejection fraction (LVEF) that can develop hemodynamic decompensation and multi-organ failure. Management of ES is challenging with limited available evidence coming from small retrospective series and a substantial lack of randomized-controlled trials. In general, a multidisciplinary approach including medical therapies such as anti-arrhythmic drugs, sedation, as well as interventional approaches like catheter ablation, may be required. Accurate patient risk stratification at admission for ES is pivotal and should take into account hemodynamic tolerability of VAs as well as comorbidities like low LVEF, advanced NYHA class and chronic pulmonary disease. In high risk patients, prophylactic mechanical circulatory support with left ventricular assistance devices or extracorporeal membrane oxygenation should be considered as bridge to ablation and recovery. In the present manuscript we review the available strategies for management of ES and the evidence supporting them.

**Key words:** Electrical storm; Ventricular tachycardia; Catheter ablation; Mechanical hemodynamic support; Anti-arrhythmic drugs

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**Core tip:** Electrical storm (ES) is a life-threatening condition characterized by ongoing ventricular arrhythmias leading to appropriate implantable cardioverter defibrillator therapies. It is associated with increased mortality and requires urgent medical care. In this review, we summarize the prognostic implications for ES as well as available treatment strategies to manage ES.

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## INTRODUCTION

Ventricular tachycardia (VT) electrical storm (ES) is a severe clinical condition characterized by clustering episodes of ventricular arrhythmia in a short amount of time. The current definition of ES implies at least 3 distinct episodes of sustained VT or ventricular fibrillation (VF) within the last 24-h or the occurrence of incessant VT for at least 12-h. In patients with ICD, ES is defined by  $\geq 3$  appropriate device interventions in the last 24-h (separated by at least 5-min one from the other) either with antitachycardia pacing (ATP) or direct-current shock<sup>[1]</sup>. Although ES mainly occurs in patients with structural heart disease and low left ventricular ejection fraction (LVEF), it may affect also patients with inherited arrhythmic syndromes and structurally normal heart (*i.e.*, Brugada syndrome and catecholaminergic polymorphic VT) representing a life-threatening condition requiring urgent medical care<sup>[2]</sup>. Several strategies have been proposed to manage ES with most of the data coming from small retrospective series, lacking large randomized-controlled trials. There are several substantial differences in the approach and treatment of ES in the setting of structural heart disease compared to primitive arrhythmic syndromes. In this review, we will focus on the management of ES in the setting of structural heart disease by summarizing the current therapeutic strategies in a stepwise approach based on available evidence (Figure 1).

## INITIAL CARE

Prolonged sustained VAs as well as multiple ICD shocks in the setting of ES, may contribute to worsening of systolic function and development of a low-output state leading to cardiogenic shock and multiple organ failure. In this setting, urgent ICD interrogation and reprogramming is mandatory. Documentation of appropriate ICD interventions triggered by VT/VF episodes is necessary to rule out all potentially reversible causes like electrolyte imbalances, acute ischemia, pro-arrhythmic drug effects, hyperthyroidism, infections and decompensated HF. However, reversible causes of ES account for less than 10%, and in the majority of cases no precipitating cause is identified (Table 1)<sup>[3]</sup>. Initial evaluation should include accurate patient risk stratification according to hemodynamic tolerability of the arrhythmia and presence of comorbidities (Figure 1)<sup>[4]</sup>. All patients with hemodynamic decompensation (persistent systolic blood pressure < 80-90 mmHg despite temporary resumption of sinus/paced rhythm and despite increasing doses of

vasopressors) as well as patients with hemodynamically tolerated VT but with major comorbidities (*i.e.*, LVEF  $\leq$  30%, moderate to severe chronic kidney disease and severe pulmonary obstructive disease) are considered at high risk and should be admitted to the intensive care unit in order to correct metabolic, respiratory and circulatory imbalances [mechanical ventilation and circulatory support with intra-aortic balloon pump (IABP), left ventricular assist device (LVAD), or extracorporeal membrane oxygenation (ECMO) may be required] and eventually undergo emergent CA. In both high and low-risk patients, every effort should be made to suppress VAs and avoid further ICD-shocks.

## ICD PROGRAMMING

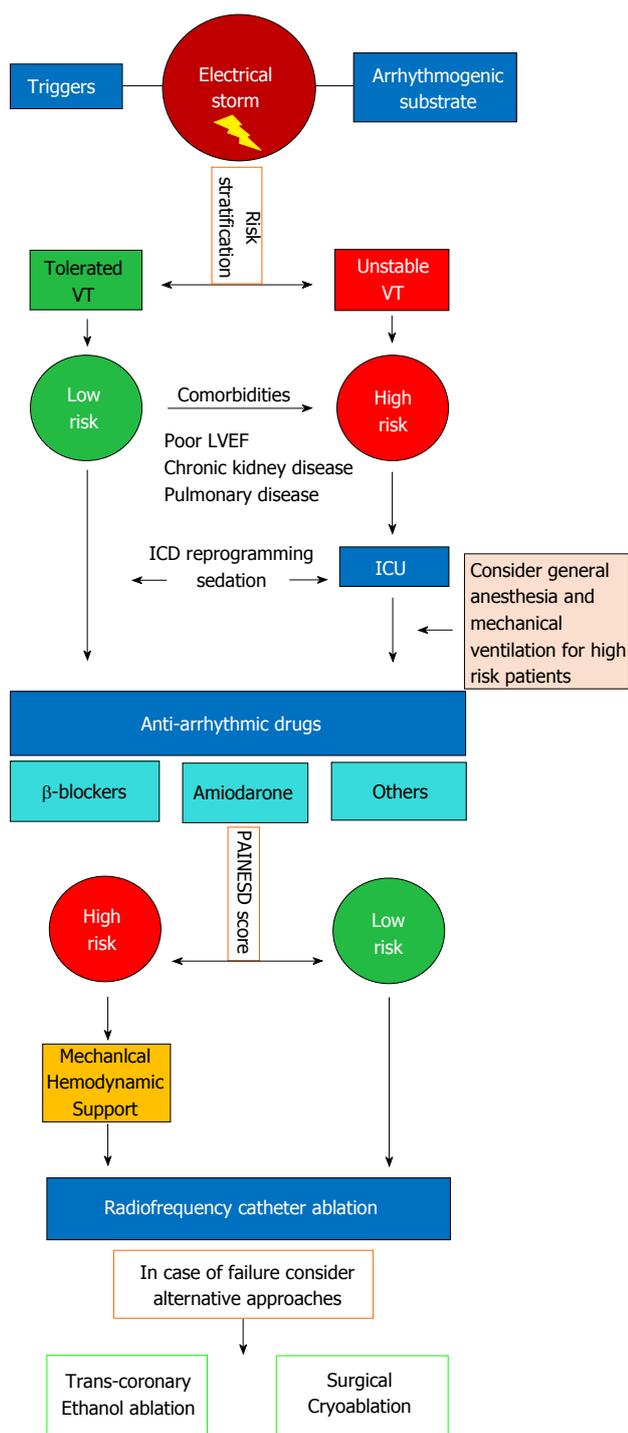
Reprogramming of ICD settings is of great importance in the initial workup of patients presenting with ES. Repeated ICD-shocks are associated with increased mortality and low quality of life<sup>[5,6]</sup>. The end-point of ICD reprogramming should be the reduction of ICD-shocks favoring interruption of VAs with ATP. In large trials, increases in both detection duration and heart rate detection threshold have been shown to reduce ICD-shocks without increasing mortality or the incidence of syncope<sup>[5,7,8]</sup>. Moreover, ATP can effectively terminate most slow VTs with a low risk of acceleration<sup>[9,10]</sup>.

## ANTIARRHYTHMIC DRUG THERAPY

Antiarrhythmic drugs (AADs) are usually required for the acute management of ES and are often used as an adjunctive therapy to prevent long-term recurrences. In a recent meta-analysis of randomized-controlled trials, we found a 1.5-fold reduction of appropriate ICD interventions with AADs compared to standard medical therapy with also a significant reduction of inappropriate ICD interventions. However, pooled analysis did not show a significant impact of AADs on all-cause mortality compared to standard medical therapy<sup>[11]</sup>. The choice of a particular drug and its dose should take into account its efficacy in controlling VA but also potential pro-arrhythmic effects as well as other side effects. Pro-arrhythmic effects have been reported in up to 7% of the patients treated with AADs for VT/VF with the higher incidence in patients with severely reduced LVEF<sup>[12]</sup>. A list of the most common AADs used in the acute and long-term management of ES as well as indications on the proper use of them and their therapeutic drug monitoring is presented in Table 2.

### **Beta-blockers**

A significant increase in the sympathetic tone is inevitably observed in patients experiencing ES, being responsible for the occurrence and maintenance of VAs. In these patients a spiral of events may occur: ICD shocks may precipitate increased sympathetic tone, resulting in further VAs and shocks, and so forth. Therefore, suppression of adrenergic tone with  $\beta$ -blockers represents



**Figure 1** Proposed algorithm for acute management of patients presenting with electrical storm. VT: Ventricular tachycardia; LVEF: Left ventricular ejection fraction; ICU: Intensive care unit.

the cornerstone of AAD therapy of ES<sup>[13]</sup>. Although most of the benefits of  $\beta$ -blockers are related to a class effect, in this setting there are some important advantages of nonselective  $\beta_1$  and  $\beta_2$  blockade. Ventricular remodeling in patients with chronic HF leads to a downregulation of  $\beta$ -receptors mostly involving  $\beta_1$ -receptors with relative sparing of  $\beta_2$ -receptors. Moreover, the lipophilic nature of some unselective  $\beta$ -blockers like propranolol, enables their penetration into the central nervous system where

**Table 1** Reversible causes of electrical storm

Acute myocardial ischemia
Electrolyte imbalances
Decompensated heart failure
Hyperthyroidism
Infections, fever
Pro-arrhythmic drug Effects
Early postoperative period

they act by blocking presynaptic adrenergic receptors<sup>[14,15]</sup>. Propranolol has been demonstrated to be effective in suppressing VAs refractory to both metoprolol and amiodarone<sup>[16]</sup>. Short-acting intravenous drugs like esmolol can also be used, especially in patients at highest risk for hemodynamic compromise such as those with severely reduced LVEF<sup>[17]</sup>.

**Amiodarone**

Amiodarone is widely used in the acute management of ES and can generally be safely administered unless hyperthyroidism or QT prolongation are present. Amiodarone has a mixed antiarrhythmic class action with a prevalent class III action (potassium channel blocker) prolonging the ventricular refractory period when administered orally and a prevalent class I (sodium channel), class IV (L-calcium channels) and class II (sympathetic blocker) action, not prolonging ventricular refractoriness, when is administered intravenously<sup>[18]</sup>. Amiodarone has demonstrated its efficacy in several trials being able to control VAs in up to 40% of patients within 24-h from intravenous administration as well as to reduce recurrent VT over follow-up<sup>[19-22]</sup>. The combined use of both amiodarone plus  $\beta$ -blockers significantly reduces the risk of recurrent ICD-shocks compared vs  $\beta$ -blockers alone<sup>[22]</sup>. In the specific setting of ES, amiodarone has been shown to reduce the risk of ES recurrence by 50% over 5-years follow-up<sup>[23]</sup>. Patients already under amiodarone treatment may benefit from a reloading dose or a dose adjustment based upon serum levels of amiodarone even if plasma concentration monitoring has been reported of very limited benefit because the drug and its active metabolite (desethylamiodarone) accumulates in tissues at higher concentrations than in plasma<sup>[24]</sup>. Importantly, amiodarone may increase defibrillation thresholds in patients with ICDs<sup>[25]</sup> and the risks and benefits of long-term administration of amiodarone should be carefully weighed because of its several side effects including liver dysfunction (elevated AST/ALT levels in up to 30% of patients but hepatitis requiring drug discontinuation in < 3% of the cases), thyroid disorders (hypothyroidism in up to 22%, hyperthyroidism in up to 12%), pulmonary fibrosis (2%), corneal deposits (> 90%, usually of no clinical importance), optic neuropathy (< 1%) and pro-arrhythmic effect (< 1%)<sup>[26]</sup>. A recent pooled analysis of randomized controlled trials comparing CA vs AADs demonstrated an association between amiodarone and increased mortality<sup>[11]</sup>. Furthermore, among patients

**Table 2 Anti-arrhythmic medications for acute and long-term treatment of electrical storm**

		Acute management	Long-term treatment	Desired plasma concentration
β-blockers	Propranolol	Bolus: 0.15 mg/kg IV over 10 min	10-40 mg by mouth three-four times a day	NA
	Metoprolol	Bolus: 2-5 mg IV every 5 min up to 3 doses in 15 min	25 mg by mouth twice a day up to 200 mg a day	NA
	Esmolol	Bolus: 300 to 500 mg/kg IV for 1 min Infusion: 25-50 mg/kg per minute up to a maximum dose of 250 mg/kg per minute (titration every 5-10 min)	Not recommended	NA
Class III agents	Amiodarone	Bolus: 150 mg IV over 10 min, up to total 2.2 g in 24 h  Infusion: 1 mg/min for 6 h, then 0.5 mg/min for 18 h	Oral load: 800 mg by mouth twice a day until 10 g total  Maintenance dose: 200-400 mg by mouth daily	1.0-2.5 µg/mL No efficacy proven for plasma concentrations < 0.5 µg/mL Serious toxicity risk for plasma concentrations > 2.5 µg/mL
	Sotalol	Not recommended	80 mg by mouth twice a day, up to 160 mg twice a day (serious side effects > 320 mg/d)	1-3 µg/mL (not of great value, usually monitored by QT prolongation with indication to reduction/discontinuation if prolongation > 15%-20%)
Class I agents	Procainamide	Bolus: 10 mg/kg IV over 20 min Infusion: up to 2-3 g/24 h	3-6 g by mouth daily fractionated in ≥ 3 administrations	4-12 µg/mL
	Lidocaine	Bolus: 1.0 to 1.5 mg/kg IV, repeat dose of 0.5-0.75 mg/kg IV up to a total dose of 3 mg/kg  Infusion: 20 µg/kg per minute IV	Not recommended	2-6 µg/mL
	Mexiletine	Not recommended	200 mg by mouth three times a day, up to 400 mg by mouth three times a day	0.6-1.7 µg/mL

undergoing CA for VT in the setting of structural heart disease, we have recently shown that higher amiodarone dose at discharge after CA was associated with increased mortality, suggesting that discontinuation or dose reduction of amiodarone should be considered in certain patients after successful CA<sup>[27]</sup>.

### Procainamide

Procainamide is a class IC agent no longer widely used (unavailable in most countries) that may be helpful to acutely terminate VAs and prevent recurrences. It acts as fast sodium channel blocker, while its active metabolite N-acetylprocainamide blocks potassium channels and accounts for much of the antiarrhythmic effect *in vivo* as well as side effects like QT interval prolongation. Up to date there are only two small randomized controlled trials analyzing its role in the acute treatment of tolerated VT. In the study by Gorgels *et al*<sup>[28]</sup>, procainamide demonstrated its superiority to lidocaine in acute VT termination in 29 patients while in the more recent PROCAMIO trial, intravenous administration of procainamide was shown to be safe and more effective compared to amiodarone in the treatment of tolerated monomorphic VT<sup>[29,30]</sup>. The most important acute adverse reaction is hypotension (up to 30% patients) which requires drug discontinuation in 11% of cases<sup>[28-30]</sup>. Data regarding the long-term efficacy of procainamide in preventing VT are lacking, moreover chronic therapy is limited by a number of systemic side effects including lupus-like syndrome, gastrointestinal disturbances, and autoimmune blood impairments. Plasma procainamide concentrations can be useful in initial dose titration;

however, monitoring of QRS and QT interval is a valid alternative to prevent drug toxicity.

### Lidocaine and mexiletine

Lidocaine and mexiletine are both class IB AADs, acting as rapid sodium channel blockers binding to the receptor in a use-dependent fashion. The main difference between them is the bioavailability of mexiletine (80%) that allows its oral administration. The use of lidocaine in ES is more limited due to its lower efficacy in terminating scar-related VTs. During ischemic VT, the altered membrane potential as well as pH reduction increase the rate of drug binding, making lidocaine more effective in terminating VAs<sup>[31]</sup>. For this reason lidocaine is currently recommended mostly for the suppression of VAs in the setting of acute ischemia<sup>[32]</sup>. Mexiletine has shown to reduce the burden of VAs but with a trend toward increased mortality and is mostly used as an adjunctive therapy to amiodarone being able to reduce appropriate therapies in patients with ICD in case of amiodarone inefficacy<sup>[33,34]</sup>. Side effects of lidocaine and mexiletine are dose dependent and predominantly related to central nervous system accumulation (particularly in patients with HF) including tremors, seizures and hallucinations. They are generally rapidly reversible with drug reduction or discontinuation.

### Sotalol

The commercially available form of Sotalol is a racemic mix of d-isomer (acting as a class III potassium channel blocker) and l-isomer (acting as a non-selective β-blocker). Most of its antiarrhythmic (as well as pro-arrhythmic) effects result from its action on potassium channels

resulting in prolongation of repolarization and the QT interval. While sotalol has shown to reduce the frequency of ICD-shocks among patients implanted for secondary prevention, it has failed to demonstrate his superiority to  $\beta$ -blocker therapy in preventing recurrent ICD-shocks in several randomized-controlled trials<sup>[22,35,36]</sup>. Moreover, an increased rate of arrhythmic deaths has been observed among patients with LV dysfunction and previous myocardial infarction treated with sotalol d-isomer alone for primary prevention of sudden death<sup>[37]</sup>. Basing upon this data it seems appropriate to consider sotalol only for VAs irresponsive to  $\beta$ -blockers. However, in patients with chronic kidney disease and severely depressed LVEF, it still should be avoided in favor of other medications like amiodarone<sup>[22]</sup>.

## GENERAL ANESTHESIA AND MECHANICAL HEMODYNAMIC SUPPORT

Sedation should be considered in all patients presenting with ES in order to minimize pain related to ICD-shocks and reduce the sympathetic surge triggered by repeated ICD therapies. Benzodiazepines such as midazolam in addition to short-acting analgesics such as remifentanyl should be the first choice being able to suppress the sympathetic hyperactivity and provide analgesia without negative inotropic effects<sup>[38,39]</sup>. Propofol has been reported to suppress ES but must be used carefully since its negative inotropic effects can lead to cardiogenic shock<sup>[40]</sup>. Dexmedetomidine is an  $\alpha_2$ -presynaptic receptor agonist that reduces sympathetic activity by enhancing central vagal tone and inhibiting presynaptic catecholamine release. It should be used cautiously, however, since it may result in severe hypotension and bradycardia<sup>[41,42]</sup>. General anesthesia and mechanical ventilation should be preferred for patients with hemodynamic unstable VTs, because drugs used for anesthesia induction and maintenance can further depress cardiac function<sup>[43]</sup>. Patients with unstable VTs may also benefit from mechanical hemodynamic support like IABP, LVAD and ECMO. Hemodynamic support can reduce the arrhythmic burden by increasing coronary perfusion, reducing afterload and therefore myocardial wall stress and prevent multiple organ failure guarantying and adequate cardiac output<sup>[44-46]</sup>.

## NEURAXIAL MODULATION

Sympathetic hyperactivity plays a critical role in the onset and maintenance of VAs. Therefore, modulation of neuraxial efferents to the heart with epidural anesthesia or cardiac sympathetic denervation (CSD) may be a valuable option in selected patients refractory to standard medical treatment and CA<sup>[47,48]</sup>. Sympathetic denervation has been effectively used in the setting of inherited arrhythmic syndromes like long QT syndrome and catecholaminergic polymorphic VT<sup>[49,50]</sup>. However, it has been recently applied even to ES in patients with structural heart disease<sup>[47,48]</sup>. Surgical CSD is usually

performed on the left side through a video-assisted thorascopic approach and entails removal of the lower third of the stellate ganglion (to avoid Horner syndrome) and T2-T4 thoracic ganglia. It has shown to suppress/ significantly decrease the arrhythmic burden in 56% of patients refractory to AADs and CA<sup>[47]</sup>. Bilateral CSD may be considered in cases of failure of left CSD. In a small study involving 6 patients undergoing bilateral CSD after failed medical therapy, CA and epidural anesthesia, a complete response was observed in 4 (67%) of them and a partial response in another one (17%)<sup>[48]</sup>. In a recent series of 41 patients with refractory VT undergoing either left (14) or bilateral (27) CSD, a significant reduction of ICD-shocks during a mean follow-up of  $367 \pm 251$  d was observed in 90% of the patients with a significantly higher ICD-shock free survival of 48% in the bilateral CSD group compared to 30% in the left CSD group<sup>[51]</sup>.

## CATHETER ABLATION

The last decade has seen a growing role for catheter ablation (CA) in the management of VT. Even if a mortality benefit has never been demonstrated in randomized-controlled trials, CA has repeatedly shown its superiority to medical therapy in reducing the arrhythmic burden<sup>[11,52,53]</sup>. Moreover, freedom from recurrent VT after CA ablation has been associated with improved survival<sup>[54,55]</sup>. For these reasons, CA should not be considered a bailout therapy but a valuable option in all patients presenting with ES related to structural heart disease. Radiofrequency CA is effective not only in the acute management of ES, leading to a control of VAs in up to 80%-90% of the patients but also over the long-term follow-up improving either VT- and ES-free survival (Table 3)<sup>[56,57]</sup>. In the recently published VANISH trial, a trend towards a 34% relative risk reduction of ES recurrences was observed in patients treated by CA compared to escalation of AADs<sup>[52]</sup>. In a pooled meta-analysis including 471 patients with ES treated invasively by different ablation strategies (*i.e.*, CA, ethanol ablation and surgical ablation), acute elimination of all inducible VAs was reached in 72% of the cases with the clinical arrhythmia effectively suppressed in 91% of the patients and a complication rate of 2% with a procedure-related death < 1%. In terms of long-term outcomes, after a median follow-up of 1.2 years, 94% of the patients were free from ES and 72% were free from any VT. Overall mortality was 17% at 1.2-years follow-up with most of the deaths related to progressive HF (62%)<sup>[58]</sup>. Similar positive results have recently been found by our group in a large series of 267 patients undergoing CA for drug-refractory ES with an acute procedural success (non inducibility of any VT with cycle length < 250 ms at the end of the procedure) of 73%, a 54% VT-free survival and a 93% ES-free survival at 60-mo follow-up. We also observed a significant reduction of VT burden in patients experiencing VT recurrence after CA<sup>[59]</sup>. Regardless, patients with ES tend to have worse prognosis after CA compared vs patients without ES, as evidenced by the fact that those with ES have higher VT recurrence rates

**Table 3** Principal studies analyzing the role of catheter ablation in controlling electrical storm

Ref.	No. of patients	Left ventricular ejection fraction	Epicardial procedures	Acute success	VT recurrence	ES recurrence	Death	Follow-up duration, mo
Sra <i>et al</i> <sup>[64]</sup>	19	27 ± 8	0%	87%	37%	-	0%	7 ± 2
Silva <i>et al</i> <sup>[65]</sup>	14	31 ± 13	20%	80%	13%	-	27%	12 ± 17
Carbucicchio <i>et al</i> <sup>[56]</sup>	95	36 ± 11	11%	89%	34%	8%	16%	Median 22
Arya <i>et al</i> <sup>[66]</sup>	13	33 ± 9	31%	100%	38%	-	31%	Median 23
Pluta <i>et al</i> <sup>[67]</sup>	21	-	0%	81%	19%	0%	0%	3
Deneke <i>et al</i> <sup>[68]</sup>	31	28 ± 15	9%	94%	25%	12%	9%	Median 15
Kozeluhova <i>et al</i> <sup>[69]</sup>	50	29 ± 11	0%	85%	52%	26%	29%	18 ± 16
Koźluk <i>et al</i> <sup>[70]</sup>	24	27 ± 7	7%	-	34%	12%	13%	28 ± 16
Di Biase <i>et al</i> <sup>[57]</sup>	92	27 ± 5	47%	100%	34%	0%	2%	25 ± 10
Izquierdo <i>et al</i> <sup>[71]</sup>	23	34 ± 10	0%	56%	-	35%	30%	Median 18
Jin <i>et al</i> <sup>[72]</sup>	40	21 ± 7	0%	80%	53%	-	25%	17 ± 17
Kumar <i>et al</i> <sup>[73]</sup>	287	27 ± 10 in ICM and 33 ± 16 in NICM	3.8% in ICM and 24% in NICM	60% in ICM and 50% in NICM	49% in ICM and 64% in NICM	17% in ICM and 27% in NICM	25% in ICM and 28% in NICM	Median 42
Muser <i>et al</i> <sup>[59]</sup>	267	29 ± 13	22%	73%	33%	5%	29%	Median 45

VT: Ventricular tachycardia; ES: Electrical storm.

PAINESD risk score			
Variable	Score		
Pulmonary disease (chronic obstructive)	5	Low risk	≤ 8
Age > 60 yr	3		
Ischemic cardiomyopathy	6	Intermediate risk	9-14
NYHA class III or IV	6		
Ejection fraction < 25%	3	High risk	≥ 15
Storm (VT)	5		
Diabetes mellitus	3		

**Figure 2** Proposed scoring system to identify patients at high risk of hemodynamic decompensation undergoing catheter ablation that may benefit from prophylactic mechanical circulatory support. Modified from Santangeli *et al*<sup>[43]</sup>. VT: Ventricular tachycardia.

and are more likely to die or require heart transplantation or surgical LVAD over long-term follow-up after CA<sup>[60]</sup>.

As patients with chronic HF are living longer with their condition, technological advances to CA and better understanding of VT substrate has led to an increased number of procedures performed in high risk patients. Patients with advanced HF, several comorbidities as well as patients with unstable VTs are at highest risk of hemodynamic collapse during the ablation procedure and subsequent post-procedural mortality<sup>[43,61]</sup>. In a preliminary study of our group, a simple score (PAINESD score) accounting for baseline patient characteristics such as pulmonary chronic obstructive disease, age, Ischemic cardiomyopathy, NYHA class, LVEF, ES at presentation and diabetes has been demonstrated able to predict acute decompensation during VT ablation procedures and therefore has been proposed to select patients who may benefit from prophylactic mechanical support (Figure 2)<sup>[43]</sup>. Recently, the PAINESD score has been validated in a study assessing the outcomes of prophylactic vs rescue percutaneous LVAD in a cohort of 93 patients undergoing CA for VT related to structural heart disease<sup>[61]</sup>. The authors reported a higher 30-d mortality in patients who underwent rescue LVAD (58%) compared to patients who underwent prophylactic LVAD (4%) placement

and patients who were ablated without LVAD (3%). Interestingly, patients who underwent rescue LVAD had similar PAINESD scores compared to those who underwent prophylactic LVAD insertion (mean 17.8 vs 16.5) while had a significantly higher score compared to the control group (mean 13.4), highlighting the importance of prophylactic mechanical support in high risk patients in order to improve post-procedural mortality<sup>[61]</sup>. Mechanical support is helpful in that it allows for prolonged mapping and ablation of inducible unstable arrhythmias. However, we have also found it to be useful when used prophylactically in high-risk patients with large areas of VT substrate undergoing a purely substrate-based ablation approach in which the long procedural times necessarily for complete substrate ablation and the consequent fluid overload related to irrigated CA may precipitate acute decompensation<sup>[43]</sup>. Importantly, some patients with advanced HF have significant biventricular dysfunction and LVAD support may be inadequate. In these cases, devices providing biventricular support like ECMO should be considered. In a recent study involving 64 patients undergoing CA of unstable VTs, the prophylactic use of ECMO has shown to allow to safely complete the procedure in 92% of the patients reaching the endpoint of VT non inducibility in 69% of them with a 88% overall survival after a median follow-up of 21 mo<sup>[46]</sup>.

## ALTERNATIVE APPROACHES

In cases in whom radiofrequency CA has failed or is challenging (*i.e.*, presence of mitral and aortic mechanical valves), alternative approaches like trans-coronary ethanol ablation and surgical cryoablation has been described<sup>[62]</sup>. Our group has recently reported a 73% VT-free survival at 1-year follow-up in a series of 20 consecutive patients with non-ischemic cardiomyopathy and VT refractory to conventional therapy who underwent surgical cryoablation<sup>[63]</sup>. Trans-coronary ethanol ablation performed through selective coronary angiography to identify the branches

supplying the putative VT site of origin has been recently reported in a series of 46 patients with VT related to structural heart disease and refractory to CA<sup>[62]</sup>. At least partial procedural success was reached in 66% of the patients with a 74% and 82% VT recurrence rate at 6- and 12-mo follow-up, respectively and a complication rate of 32% (1 procedure related death).

## CONCLUSION

Electrical storm is a life-threatening condition with an increasing incidence related to the wider use of ICD and the improved survival of patients with advanced HF. Management of ES requires a multimodality approach including optimal ICD-reprogramming, treatment of underlying conditions, anti-arrhythmic drug therapy, sedation and CA. Radiofrequency CA appears to be the most effective treatment option, being able to control arrhythmia burden in the acute phase and improve long-term arrhythmia free survival and therefore should be considered in all patients presenting with ES. A growing evidence supports the use of prophylactic mechanical hemodynamic support as a bridge to ablation and/or recovery in high risk patients.

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## Wearable cardioverter defibrillator: Bridge or alternative to implantation?

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### Abstract

The implantable cardioverter-defibrillator (ICD) is effective to prevent sudden cardiac death (SCD) in selected patients with heart disease known to be at high risk for ventricular arrhythmia. Nevertheless, this invasive and definitive therapy is not indicated in patients with potentially transient or reversible causes of sudden death, or in patients with temporary contraindication for ICD placement. The wearable cardioverter defibrillator (WCD) is increasingly used for SCD prevention both in patients awaiting ICD implantation or with an estimated high risk of ventricular arrhythmia though to be transient. We conducted a review of current clinical uses and benefits of the WCD, and described its technical aspects, limitations and perspectives.

**Key words:** Wearable cardioverter/defibrillator; Sudden cardiac death; Secondary prevention; Primary prevention; Ventricular arrhythmias

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**Core tip:** The wearable cardioverter defibrillator is increasingly used for sudden cardiac death prevention in patients thought to have a transient and/or reversible high risk for life-threatening ventricular arrhythmia. Evidences sustaining the use of this external device are growing. We provided an evidence base review in the light of new data.

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## INTRODUCTION

Sudden cardiac death (SCD) is an unpredictable event which leads to death in the absence of immediate resuscitation maneuvers and adequate therapies. Up to 23% of SCD are attributable to ventricular arrhythmias (VA)<sup>[1]</sup>. The implantable cardioverter-defibrillator (ICD) has proved to be highly effective for SCD secondary prevention. Otherwise, it has also been demonstrated to prevent SCD in selected patients with heart disease known to be at high risk for life-threatening VA<sup>[2-4]</sup>. However, long-term ICD-related complications, cost issues, social impact and quality of life force a rigorous evaluation of patients before ICD placement. Furthermore, some situations at high risk of VA-related SCD are known to be limited in time. For example, although SCD rate was 2.3% in patients with low left ventricular ejection fraction (LVEF) during the first month following myocardial infarction (MI), ICD implantation during the first 40 d post-MI failed to reduce total mortality. This result was essentially due to a large amount of non-arrhythmic death during this period<sup>[5]</sup>. In addition, up to 40% of patients with coronary artery disease and low LVEF do not meet the current criteria for ICD implantation after complete myocardial revascularization and/or optimization of medical therapy<sup>[6]</sup>.

The wearable cardioverter defibrillator (WCD) is increasingly used for SCD prevention both in patients awaiting ICD implantation or with an estimated high risk of VA though to be transient. This external device, which has been demonstrated to effectively terminate spontaneous and induced VA by automatic defibrillation shock delivery, requires no surgical intervention and is entirely removable. We conducted a review of current clinical uses and benefits of WCD, and described its technical aspects, limitations and perspectives.

## TECHNICAL ASPECT

Currently available WCD is the LifeVest 4000® [ZOLL Lifecor Corporation (ZOLL), Pittsburgh, PA, United States]. With the LifeVest 4000®, the chest is surrounded by an elastic belt including an electrocardiographic (ECG) monitoring system with four dry, non-adhesive electrodes and the defibrillation system consisting in two posterior and one apical electrodes (Figure 1). The whole is maintained by shoulder straps forming a light washable vest and connected to a monitor unit including the battery, an LCD screen for message display and two "response buttons" for patient defibrillation shock withholding. The monitor unit is held in a holster or around the waist (Figure 2). Two batteries are delivered with the WCD; each one lasts for 24 h so that one is always in charge during the use of the other. Total device weight is about 600 g. ECG electrodes provide two left-right and front-back bipolar ECG signals (Figure 3). The ECG is continuously recorded and analyzed. Following parameters can be programmed: (1) rate intervals for ventricular fibrillation (VF) zone: 120 to 250 bpm, default 200 bpm and ventricular tachycardia (VT) zone:

120 bpm to VF zone; (2) shock delay, *i.e.*, time from arrhythmia detection to shock delivery: 60 to 180 s in VT zone and 25 to 55 s for VF zone. Further delay up to 30 s may be added at night; and (3) shock energy: 75 to 150 J.

The WCD automatically delivers, *i.e.*, without neither patient nor witness intervention, defibrillation shocks for termination of life-threatening VA. Arrhythmia detection and discrimination (for arrhythmia detected in the VT zone) occur within few seconds after the rhythm disorder onset. In case of VA detection within the programmed VT or VF zone, the device alerts the patient of the imminence of a shock starting by vibrations of the defibrillation electrodes during 5 s, followed by a low monotonal sound signal then high bitonal sound signal. Finally, a voice warning during the few lasts s precedes the shock delivery. During this period, the patient, if still conscious, can withhold shock delivery by pressing the two response buttons on the monitor unit. Without this well-done intervention, defibrillation shock is delivered, synchronized to the R-wave signal in case of monomorphic VT. In order to improve shock impedance, and to prevent skin burns, the defibrillation electrodes release a conductive gel contained in small capsules before shock delivery (Figure 4). Up to five shocks can be delivered for the same episode. ECG signal is continuously recorded and reviewable 30 s prior to the detection of arrhythmia to 15 s after the alarms stop (Figure 5). Total duration from the onset of the arrhythmia to shock delivery, (including time of fulfilling detection criteria, confirmation, alarms and capacitor charging) is about 50 s. Daily remote monitoring advises medical staff about VA occurrence and therapies, daily ECGs, as well as patient compliance (assessed by the daily wear time).

## PATIENT EDUCATION AND COMPLIANCE

Patient education by specialized healthcare givers on how to properly wear the device, change the battery and disable shock delivery is a crucial step. In our experience, 10% to 15% patients eligible for this therapy are not able to understand instructions to withhold therapies or change battery and therefore are not treated with the WCD. In order to improve patient knowledge and handle of the WCD, we systematically schedule an additional patient education session 10 to 15 d after hospital discharge.

Similarly, understanding and knowledge of his cardiac disease and potentials benefits associated with the use of the WCD is a critical part of patient care, aiming high device compliance which is the prerequisite of effective SCD protection. Lack of compliance might have dramatic consequences. Indeed, in various studies, the majority of SCD observed during follow-up were observed in patients not or not-correctly wearing the WCD<sup>[7,8]</sup>. Weight and footprint of the device were the main reasons for low compliance. On the other hand, as high as 22.5% of patients discontinued the use of WCD due to comfort or lifestyle issues in study from Feldman *et al*<sup>[8]</sup>. A 40% reduction of size and weight of the device was associated with a significant decrease in the rate of WCD therapy



**Figure 1** Wearable cardioverter defibrillator. The two defibrillator electrodes are worn on the back of the garment, when the four monitoring electrodes are placed on the elastic belt around the chest. Both systems are connected to the monitor unit.



**Figure 2** Wearable cardioverter defibrillator worn by a patient under clothes; monitor unit is worn on waist belt or in a holster.

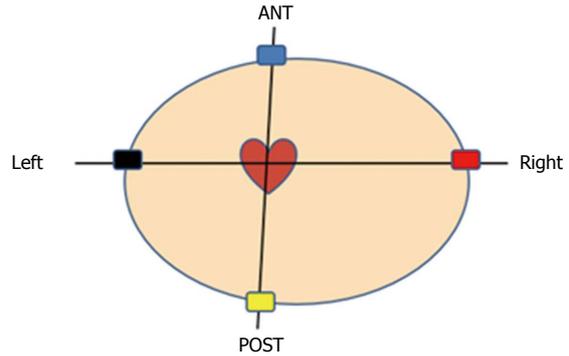
interruption (14.2%) in a more recent report<sup>[9]</sup>.

Overall, national registries showed good compliance with the actual WCD<sup>[6,10]</sup>. In United States' experience, of 3569 patients wearing WCD, > 50% of patients achieved a 90% wear time compliance<sup>[9]</sup>. In the German registry, this number grows to 72%<sup>[11]</sup>. In both studies, long period of therapy was associated with higher time of wearing. Otherwise, remote monitoring allows measurement of daily WCD wear time and medical staff is alerted in case of low patient compliance so that prompt corrective measures can be taken.

## CLINICAL STUDIES

### Efficacy

Auricchio *et al.*<sup>[12]</sup> were the firsts to report the efficacy of the first generation WCD (WCD™ device, LIFECOR, Pittsburgh, Pennsylvania) for termination of life-threatening VA. This device reliably stopped induced VT or VF by automatically delivering a 230 J defibrillation shock in 15 SCD survivors. The firsts prospective multicenter studies demonstrating clinical benefit of the WCD were the Wearable Defibrillator Investigate Trial (WEARIT) and Bridge to ICD in Patients at Risk Of Arrhythmic Death (BIROAT) studies<sup>[8]</sup>. Inclusion criteria for the WEARIT study was



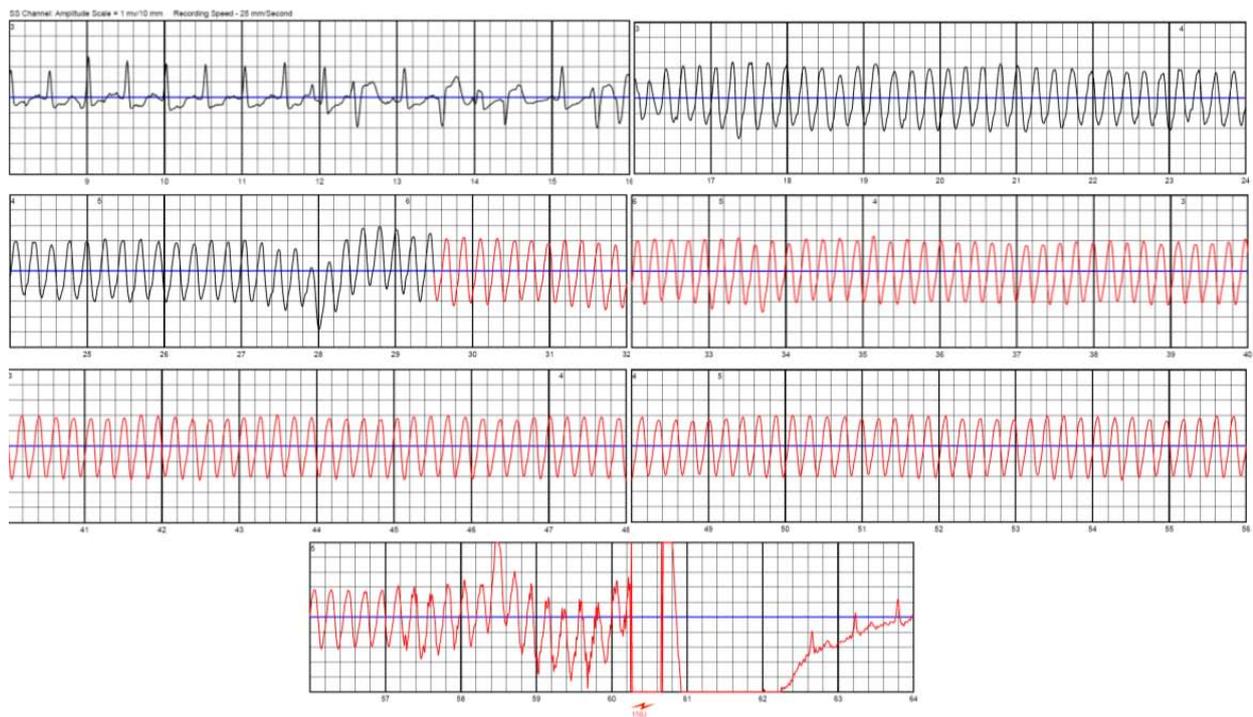
**Figure 3** Four electrocardiographic electrodes position, and two left-right and front-back bipolar electrocardiographic vectors.



**Figure 4** One defibrillator electrode with ten gel capsules inserted in, and one non-adhesive electrocardiogram electrode.

symptomatic NYHA III or IV ambulatory heart failure and LVEF < 0.30. Differently, the BIROAD study enrolled: (1) patients after a recent MI or coronary artery bypass grafting (CABG) and having complications such as VA, syncope or low LVEF < 0.30, but not receiving an ICD for up to 4 mo; and (2) patients who met criteria for an ICD but refused therapy or had to wait for at least 4 mo before implantation. A total of 289 patients were enrolled in both studies, united into one at the request of the Federal Drug Administration, and followed during a total of 901 mo of patient use. During the follow-up, 6 of 8 defibrillation attempts were successful. No patient died while correctly wearing the WCD.

Thereafter, some large studies validated the clinical benefit of this therapy and evaluated the occurrence of VA during the period of the WCD use in patients with low LVEF in the setting of ischemic heart disease. Rate of patients receiving appropriate shock within the 3 mo following percutaneous coronary intervention (PCI) or CABG varied from 1.3% to 1.7%<sup>[9,10]</sup>. Prolonging WCD wearing period to 15 mo resulted in increasing rate of appropriate WCD shock to 4.1%<sup>[13]</sup>. In the United States' experience, first shock success was of 99% for all VT/VF events, and survival after VT/VF events was 89.5%<sup>[9]</sup>. Importantly, no death could be attributed to WCD technical failure since its introduction. For note, at the end of the WCD period use, about 60% of patients were not



**Figure 5** Ventricular tachycardia correctly diagnosed and treated by wearable cardioverter defibrillator. Red line corresponds to sound signal. A 150-J defibrillation shock, automatically delivered by the device, terminated the arrhythmia.

eligible anymore for ICD implantation, mainly because of left ventricular ejection fraction improvement<sup>[6]</sup>.

**Inappropriate shock**

From 0.4% to 3% of patients experienced inappropriate WCD shock<sup>[6,9,10,14]</sup>. The WCD is an external device, which is dramatically exposed to noise detection. Inappropriate shocks are mainly related to noise artifacts or T wave oversensing<sup>[15]</sup>. Compared to conventional transvenous ICD, the rate of inappropriate shock with the WCD is low. This fact is explained by the possibility for the patient to withhold shock delivery while pressing the response buttons. Incidence of false alarms attributable to artifacts is unknown.

**Current indications**

According to current guidelines for management of patients presenting with VA and the prevention of SCD, “the WCD may be considered for adult patients with poor LV systolic function who are at risk of sudden arrhythmic death for a limited period, but are not candidates for an implantable defibrillator (e.g., bridge to transplant, bridge to transvenous implant, peripartum cardiomyopathy, active myocarditis and arrhythmias in the early post-myocardial infarction phase). In patients presenting with high risk of SCD, but non-indicated for an ICD implantation because of temporary contra-indication, in expectation of a diagnosis, or if the arrhythmic risk may evolve<sup>[16]</sup>. For the Heart Rhythm Society, the use of WCD is reasonable in patients with a clear indication of ICD placement but with temporary contra indication to the procedure (infection for example) or as a bridge therapy to heart transplantation.

Otherwise, the use of the WCD should be considered in additional clinical situations: In patients with high risk for SCD due to LV dysfunction that may resolve over time (following myocardial revascularization, myocarditis...) or with a potentially treatable cause (arrhythmia-induced or chemotherapy-induced LV dysfunction)<sup>[17]</sup>.

**Well-validated clinical situation to consider the WCD**

**After acute myocardial infarction:** Sudden cardiac death occurred in 2.3% of patients with severely depressed LVEF during the first month post-MI<sup>[18]</sup>. However, the risk of life-threatening VA significantly decreases with LVEF recovery after acute event<sup>[19]</sup>. Furthermore, in primary prevention studies, ICD benefit occurred years after implantation<sup>[3,20]</sup>. Former studies showed no impact of early implantation of ICD after AMI on overall mortality<sup>[5,21]</sup>. The DINAMIT was an open-label trial including 674 patients 6 to 40 d after an AMI, with LVEF > 0.35 and impaired cardiac autonomic function. Patients were randomized in a 1/1 fashion for medical treatment or medical treatment and ICD placement. This study did not found statistical difference in overall mortality between the 2 groups. Indeed, a smaller proportion of SCD observed in the ICD group was offset by an increase in the rate of non-arrhythmic deaths among these patients. These results are consistent with findings from the IRIS study<sup>[21]</sup>. The United States’ experience with the WCD was derived from a national database and included 8453 patients with ejection fraction < 0.35 early after acute MI<sup>[10]</sup>. One point four percent of patients were correctly treated by WCD, whose 75% in the first month of use. The median time to first WCD therapy was 9 d. The resuscitation

survival rate was of 91%. The VEST Prevention of Early Sudden Death Trial and VEST Registry (VEST) is a randomized simple blind trial currently enrolling patients with LVEF < 0.35 following AMI. This study aims to demonstrate a reduction of SCD within the first three mo following AMI. Enrollment exceeded 1700 patients in 2015, results are awaited<sup>[22]</sup>.

**After revascularization procedures:** Life-threatening VA are a frequent cause of SCD after elective revascularization CABG or PCI<sup>[23]</sup>. ICD implantation is mandated in patients with reduced LVEF < 0.35 evaluated at least 3 mo after revascularization because of possible LV systolic function recovery. In the setting of LV dysfunction <0.35 after CABG or PCI, Zishiri *et al.*<sup>[24]</sup> found a significant reduction in early mortality hazard in patients treated with the WCD (3% vs 7%,  $P < 0.05$ ). In this subset of patients, appropriate therapy rate was 1.3%.

**Terminal cardiomyopathy listed for heart transplantation:** The risk of SCD in patients awaiting heart transplantation is about 10% at one year<sup>[25]</sup>. Although ICD is largely used in this population of patients, complications, such as infection, are frequent, particularly in LV assist devices receivers<sup>[26]</sup>. The WCD was found to be a safe and efficient transitory solution to protect this population as a bridge to transplantation<sup>[27]</sup>.

**ICD infections, before re-implantation:** Cardiac implanted electronic devices infections require complete system removal, associated with antibiotic therapy for 2 to 6 wk. Period before re-implantation is long, so that patients could benefit from WCD protection without delaying hospital discharge, as the risk of SCD remains unchanged<sup>[7]</sup> during this period. Highest incidence rate of appropriate therapies remains to patients after ICD explantation for infection in expectation of reimplantation compared with other indications<sup>[14]</sup>. Therefore, the AHA guidelines sustain its use in this clinical setting with a Class II A recommendation (level of evidence C)<sup>[17]</sup>.

**Nonischemic cardiomyopathy:** Benefice of ICD in prevention of SCA in non-ischemic cardiomyopathy (NICM) patients is still a matter of debate. Low LVEF < 0.35 remains the only criterion validated to stratify the risk of SCD among these patients<sup>[4,28,29]</sup>. Plurality of etiologies, absence of criteria that define the likelihood of reversibility and potential for recovery after optimal medical therapy<sup>[30]</sup> make difficult the assessment of the long term risk of VA in this population of patients. Early ICD implantation, within the firsts mo after diagnosis failed to improve long term survival<sup>[28,31]</sup>. Therefore, LVEF assessment for SCD risk stratification is recommended at least 3 mo after optimal medical treatment<sup>[16]</sup>, and some studies tend to delay ICD placement to 9 mo<sup>[32-34]</sup>. Furthermore, in a recent large randomized study, prophylactic ICD implantation in patients with symptomatic NICM showed no impact on mortality<sup>[35]</sup>. Indeed, the

DANISH study included 556 patients with symptomatic systolic NICM and LVEF  $\leq 0.35$  who were assigned to receive an ICD, and 560 patients assigned to receive medical care, both group receiving CRT if indicated. Primary evaluation criteria was death from any cause. No difference was observed between the two groups after a median follow-up period of 67 mo. Only patients younger than 68 years of age showed a lower rate of death after ICD implantation, independent of CRT status.

Small cohorts aimed to evaluate the benefit of WCD in patients with NICM. Incidence of appropriate therapies varied from 0% to 5.5%<sup>[6,8,9,15,36]</sup>. Prospective studies are lacking in this heterogeneous population to specify real benefit.

### Unfrequent clinical presentation

**Tako-tsubo cardiomyopathy:** Tako-tsubo cardiomyopathy is a heterogeneous provider of SCD, and life-threatening VA occur during the first wk after disease onset. Prevalence of VA varies between 8% and 13.5%<sup>[37,38]</sup>. Patients with QT prolongation after stress cardiomyopathy demonstrated a higher risk of VA. This subset of patients might have substantial benefit of the WCD use<sup>[39,40]</sup>.

**Peripartum cardiomyopathy:** Peripartum cardiomyopathy patients with severely reduced LVEF have an elevated risk of VA<sup>[41,42]</sup>. Up to 38% of deaths in this population are sudden and most of them (87%) occur within the 6 mo following the diagnosis<sup>[43]</sup>. The WCD was found to correctly treat these VA during the first mo after diagnosis, until ICD implantation or systolic function recovery<sup>[44]</sup>.

Prediction of cardiomyopathy and evaluation of SCD risk after acute myocarditis is difficult. Assessment of the LVEF appears to be an insufficient criterion<sup>[45,46]</sup>. Similarly to Tako-tsubo cardiomyopathy or peripartum cardiomyopathy, myocarditis has a potentially high likelihood of cardiac recovery so that the WCD may be limited to patients in secondary prevention or with particularly high-risk features<sup>[17]</sup>.

Pharmacology-induced cardiomyopathies (alcohol, methamphetamine, trastuzumab) are associated with a great potential of recovery of LV systolic function after withdrawal of the putative agent and optimal medical therapy.

In all these various clinical settings known to result in both potentially transient LV dysfunction and high SCD risk, the WCD might be a valuable tool in both for SCD prevention and to provide additional information for subsequent SCD risk stratification.

### Clinical perspectives

**Unexplained syncope:** The diagnostic of syncope encompass various causes. First, it can be the precursor event of SCD. Then it is a major step in the rhythmic risk in patients presenting with inherited arrhythmia syndromes or structural heart diseases such as hypertrophic cardiomyopathy. During this time of evaluation, no rhythmic

protection can be offered by classical monitoring approaches, such as implantable cardiac monitors. The WCD may bridge this vulnerable period until diagnostic has been established. The Ambulatory Post-Syncope Arrhythmia Protection Feasibility Study currently enrolling patients, aims to assess utility of WCD in patients with high rhythmic risk after unexplained syncope<sup>[47]</sup>.

**End-stage renal disease:** Hemodialysed (HD) patients are known to be at high risk of SCD<sup>[48]</sup>. In a retrospective study, 75 hemodialysed patients presenting with SCD while wearing a WCD were included<sup>[49]</sup>. Seventy-eight point six percent of SCD were linked to VT/VF episodes. One-year survival after SCA was 31.4%. In comparison with historical data, the WCD therapy was associated with an improved survival ref. The ICD was associated with better survival in HD patients yet<sup>[50]</sup>, but is more exposed to complications such as device infections<sup>[51]</sup>.

### Limitations of the WCD

Although the WCD is able to automatically terminate VA, daily maintenance is necessary. A non-negligible proportion of patients are unable to correctly use and handle the device, change battery or respond to device alarms. This issue might be kept in mind before patient selection. The WCD cannot deliver antitachycardia and/or anti-bradycardia pacing. In patients with cardiac pacemakers, bipolar pacing mode should be programmed in order to avoid oversensing of pacing artifacts during VF leading to termination of the treatment algorithm<sup>[52]</sup>. In contrast, time to shock delivery, which is substantially longer compared to ICD, doesn't seem to be a limitation. As shown in the MADIT-RIT trial<sup>[53]</sup>, prolonged delays in therapy delivery were associated with reductions in inappropriate therapies and overall mortality. Finally, cost impact of this device has to be underlined. Few studies evaluated the cost-effectiveness of the WCD. After ICD removal for infection, WCD seemed to be cost-effective for SCD prevention compared to in-hospital monitoring or discharge to a skilled nursing facility before reimplantation<sup>[54]</sup>.

## CONCLUSION

The WCD is a life-saving therapy as it has been demonstrated to promptly detect and terminate VT/VF by automatically delivering defibrillation shock. This device represents a safe, easy to handle, non-invasive and reversible way to prevent SCD in patients with SCD risk though to be high for a limited period or having a transient contraindication to permanent ICD implantation. Data sustaining the use of the WCD therapy in patients with low LVEF following myocardial revascularization are strong. Similarly, current guidelines sustain the use of the WCD in patients with ICD infection requiring device removal. Further prospective and randomized studies are awaited to better guide its indications and its benefit in other clinical settings.

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## Clinical Trials Study

**Catheter ablation of atrial fibrillation facilitated by preprocedural three-dimensional transesophageal echocardiography: Long-term outcome**

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**Institutional review board statement:** The study was compatible with the regulations issued by the responsible University Review Board. No formal approval was required due to the retrospective character of the analysis.

**Informed consent statement:** All patients (or their legal guardians) gave informed consent prior to the ablation procedures.

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**Abstract****AIM**

To evaluate the long-term outcome of catheter ablation of atrial fibrillation (AF) facilitated by preprocedural three-dimensional (3-D) transesophageal echocardiography.

**METHODS**

In 50 patients, 3D transesophageal echocardiography (3D TEE) was performed immediately prior to an ablation procedure (paroxysmal AF: 30 patients, persistent AF: 20 patients). The images were available throughout the ablation procedure. Two different ablation strategies were used. In most of the patients with paroxysmal AF, the cryoablation technique was used (Arctic Front Balloon, CryoCath Technologies/Medtronic; group A2). In the other patients, a circumferential pulmonary vein ablation was performed using the CARTO system [Biosense Webster; group A1 (paroxysmal AF), group B (persistent AF)]. Success rates and complication rates were analysed at 4-year follow-up.

**RESULTS**

A 3D TEE could be performed successfully in all patients prior to the ablation procedure and all four pulmonary

vein ostia could be evaluated in 84% of patients. The image quality was excellent in the majority of patients and several variations of the pulmonary vein anatomy could be visualized precisely (*e.g.*, common pulmonary vein ostia, accessory pulmonary veins, varying diameter of the left atrial appendage and its distance to the left superior pulmonary vein). All ablation procedures could be performed as planned and almost all pulmonary veins could be isolated successfully. At 48-mo follow-up, 68.0% of all patients were free from an arrhythmia recurrence (group A1: 72.7%, group A2: 73.7%, group B: 60.0%). There were no major complications.

### CONCLUSION

3D TEE provides an excellent overview over the left atrial anatomy prior to AF ablation procedures and these procedures are associated with a favourable long-term outcome.

**Key words:** Pulmonary veins; Catheter ablation; Atrial fibrillation; Transesophageal echocardiography; Three-dimensional echocardiography

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**Core tip:** Three-dimensional (3-D) transesophageal echocardiography has been shown to be a useful tool for analysing the individual left atrial morphology prior to an ablation procedure. The aim of this study was to evaluate whether favourable long-term results can be obtained by catheter ablation of atrial fibrillation after prior pulmonary vein imaging using 3-D transesophageal echocardiography. In 50 patients, 3-D transesophageal echocardiography was performed immediately prior to an ablation procedure. The image quality was excellent in the majority of patients and several variations of the pulmonary vein anatomy could be visualized precisely. At 48-mo follow-up, 68.0% of all patients were free from an arrhythmia recurrence.

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## INTRODUCTION

Catheter ablation is an important therapeutic option in patients with symptomatic atrial fibrillation (AF)<sup>[1-21]</sup>. However, these procedures can be quite challenging because of the variability of the individual left atrial anatomy.

Magnetic resonance imaging (MRI) or multi-detector spiral computed tomography (MDCT) are frequently used prior to an ablation procedure. These three-

dimensional (3D) imaging systems provide insights into the morphology of the left atrium (LA). Obviously, the precise knowledge of the left atrial anatomy facilitates the ablation procedures and enhances the safety of these interventions. However, these imaging techniques are associated with significant limitations [*e.g.*, radiation exposure (MDCT), impaired image quality in patients suffering from AF with fast AV-nodal conduction (especially MRI) and additional costs]. Three-dimensional transesophageal echocardiography (3D TEE) provides excellent insights into the left atrial anatomy of individual patients and is free from most of the difficulties associated with MRI or MDCT<sup>[22-26]</sup>. It has been shown to be associated with a favourable short-term outcome after catheter ablation of AF<sup>[27]</sup>.

The target of this study was to analyse the long-term outcome of AF ablation procedures facilitated by preprocedural 3D TEE with regard to success rates and complication rates.

## MATERIALS AND METHODS

### Patient population

A total of 50 patients [35 men, 15 women; mean age 60.8 years (SD ± 9.2 years)] were enrolled in this study. All of them underwent 3D transesophageal echocardiography immediately before the ablation procedure, so that a 3D TEE reconstruction of the left atrium and the pulmonary veins (PVs) could be generated.

Catheter ablation was performed for paroxysmal AF in 30 patients and for persistent AF in 20 patients. All patients were highly symptomatic and at least one failed attempt of an antiarrhythmic drug therapy was a prerequisite for being accepted for catheter ablation. Table 1 summarizes clinical characteristics of the patients enrolled in our study. For all patients, this was the first AF ablation procedure.

The ablation procedures were performed at our University Hospital Center between October 2007 and May 2011.

Inclusion criteria were: (1) documented episodes of recurrent AF ( $\geq 30$  s); (2) severe symptoms despite antiarrhythmic drug therapy (including beta-blockers) or prior attempts of electrical cardioversion; (3) ability and willingness to give informed consent; and (4) age between 18 and 85 years. Patients were not accepted for catheter ablation if one of the following conditions was present: Severe valvular heart disease or any other concomitant cardiac disease requiring surgery, severely impaired left ventricular function (left ventricular ejection fraction < 20%), left atrial diameter > 65 mm (parasternal long-axis view), left atrial thrombus, hyperthyroidism, severe renal insufficiency (creatinine  $\geq 3$  mg/dL) or another severe concomitant illness.

### Cardiac imaging

In all patients, a 3D TEE was performed immediately before the ablation procedure (X7-2t, 7 MHz/IE 33;

Table 1 Clinical data

	Group A	Group A1	Group A2	Group B	P
Patients	30	11	19	20	0.07
Men:Women	18:12	5:6	13:6	17:3	
Age (yr), mean (SD)	60.0 (9.7)	61.6 (8.0)	59.1 (10.7)	62.1 (8.4)	0.57
Cardiac disease					0.05
None	13	8	5	2	
CAD	3	1	2	9	
DCM	0	0	0	1	
Valvular heart disease <sup>1</sup>	5	1	4	5	
Arterial hypertension	9	1	8	2	
Other	0	0	0	1	
Previous cardiac surgery	1	0	1	0	0.43
Left ventricular ejection fraction, mean (SD)	58.0% (5.8%)	59.1% (7.4%)	57.4% (4.8%)	52.6% (9.9%)	0.06
Antiarrhythmic drug therapy prior to the ablation procedure					0.68
Class I c (e.g., flecainide, propafenone)	1	0	1	2	
Class III (e.g., amiodarone, sotalol)	5	0	5	2	
Beta-blocker in combination with a class I c or class III antiarrhythmic drug	16/7	7/3	9/4	3/7	
Beta-blocker	1	1	0	6	
Digitalis	0	0	0	0	
Other	0	0	0	0	

<sup>1</sup>Not requiring surgery. CAD: Coronary artery disease; DCM: Dilated cardiomyopathy (left ventricular ejection fraction < 40%).

Philips Healthcare, Best, the Netherlands). The images were available throughout the ablation procedures. They were displayed in a synchronised way with the geometry created with the 3D mapping system (if available).

The echocardiographic examination was performed extensively to acquire all relevant information about the left/right atrium, all cardiac valves, the left/right ventricular function and the aorta. In addition, 3D reconstructions of the left atrium and the pulmonary vein ostia were generated. The image quality was classified as: (1) good; (2) acceptable; or (3) not appropriate (for each pulmonary vein ostium). If it was not possible to visualize the right-sided or left-sided PVs at all this was noted as well. The variations of the PV anatomy are summarized in Table 2. A detailed analysis of the 3D TEE findings concerning the left atrial anatomy has been published elsewhere<sup>[27]</sup>.

No other imaging techniques (MDCT or MRI) were used before or after the ablation procedures routinely.

### Ablation procedure

The ablation strategy was depending on the type of AF.

In patients with paroxysmal AF, two strategies were used. In some patients with paroxysmal AF, a circumferential pulmonary vein ablation was performed in combination with a potential-guided segmental approach in order to achieve complete pulmonary vein isolation [group A1; CARTO system (Biosense Webster, Diamond Bar, CA, United States)]. In most of the patients with paroxysmal AF, the cryoballoon technique (Medtronic, Minneapolis, MN, United States) was used (group A2). We refrained from using the cryoballoon technique if any variations of the pulmonary veins were detected by 3D TEE (e.g., common ostium, accessory pulmonary vein). In patients with persistent AF, a circumferential pulmonary vein ablation was performed in combination with a

potential-guided segmental approach to achieve complete pulmonary vein isolation (group B). Furthermore, a linear lesion was created at the roof of the left atrium in some patients. In addition, catheter ablation of the mitral isthmus was performed in selected cases [CARTO system (Biosense Webster)]. The ablation strategies have been described in detail in previous publications<sup>[20,27]</sup>.

In addition, catheter ablation of the right atrial isthmus was performed in patients with inducible or clinically documented episodes of typical atrial flutter. The completeness of the right atrial isthmus lines was confirmed by differential pacing maneuvers in all cases.

### Follow-up

After hospital discharge, patients were seen regularly on an outpatient basis. One month after the procedure, a physical examination, a resting electrocardiogram (ECG) and a transthoracic echocardiogram were performed. The patients were questioned whether there was any evidence for an arrhythmia recurrence. In addition, a long-term ECG recording (24-h) was performed.

Three months after the ablation procedure, the patients were re-examined in the same way except for the fact that a 7-d Holter monitoring was performed and that each patient underwent a repeat 3D TEE to rule out a pulmonary vein stenosis. Then, the patients were seen at 3-mo intervals if asymptomatic. If there was an arrhythmia recurrence or other problems occurred, the further follow-up and future strategy (e.g., medical therapy, electrical cardioversion, repeat ablation procedure) were planned on an individual basis.

Twelve months, twenty-four and forty-eight months after the ablation procedure another 7-d Holter monitoring was performed (or the results of repeated 24-h recordings obtained by the referring physicians were reviewed). A blanking period of 3 mo was employed after

**Table 2** Left atrial anatomy

	Total
Common PV ostium <sup>1,2</sup> (left PVs/right PVs)	2 (1/1)
Accessory PVs <sup>1,2</sup> (left PVs/right PVs)	1 (0/1)
Early PV branching <sup>2</sup>	3
LSPV	0
LIPV	0
RSPV	2
RIPV	1
Extremely short distance between the LAA and the LSPV <sup>1</sup>	3
Very prominent left atrial appendage <sup>1</sup>	2

<sup>1</sup>3D TEE; <sup>2</sup>Invasive PV angiography. LAA: Left atrial appendage; LIPV: Left inferior pulmonary vein; LSPV: Left superior pulmonary vein; PV(s): Pulmonary vein(s); RIPV: Right inferior pulmonary vein; RSPV: Right superior pulmonary vein.

ablation when evaluating the follow-up results.

Oral anticoagulation was continued for at least 3 mo after the procedure in all patients and was discontinued only in patients with a CHADS2 score  $\leq 1$  thereafter. Since October 2010 the CHADS2-VASc score was used for risk assessment and oral anticoagulation was only discontinued in patients with a CHADS2-VASc score  $\leq 1$  three months after the ablation procedure (vitamin K antagonist/novel oral anticoagulants). During the first three months after catheter ablation the patients received the same antiarrhythmic medication as prior to the ablation procedure. If there was no evidence for an arrhythmia recurrence all antiarrhythmic drugs were discontinued thereafter except for beta-blockers.

### Statistical analysis

Clinical characteristics of the three study groups were compared at baseline to discover potential sources of bias. All parameters with a normal distribution are given as mean ( $\pm 1$  SD). Age, left ventricular ejection fraction, total procedure time, fluoroscopy dosage and follow-up duration were compared using an one-way ANOVA. All other parameters (underlying cardiac disease, gender) were analysed using the  $\chi^2$  test. The  $\chi^2$  test was also used for analysing the clinical endpoints (arrhythmia recurrence rate at 48-mo follow-up). Significance was accepted if the *P* value was  $\leq 0.05$ . The statistical package of JMP (Version 3.2.6, SAS Institute, Cary, NC, United States) was used for data analysis. The data evaluation was reviewed by an expert in biostatistics of our institution.

## RESULTS

The study cohort consisted of fifty patients who were enrolled between October 2007 and May 2011. They had recurrent episodes of persistent or paroxysmal AF. Catheter ablation was performed in these patients after prior 3D TEE data acquisition. In all patients, this was the first AF ablation procedure. Catheter ablation of AF could be carried out as intended in all of them.

### Ablation strategy

In some patients with paroxysmal AF a circumferential pulmonary vein ablation in combination with a potential-guided segmental approach was carried out [group A1: 11 patients; Carto system (Biosense Webster)].

In the remaining 19 patients with paroxysmal AF, the cryoballoon technique was used (group A2; Medtronic). In all of them, a 28-mm cryoballoon was chosen at the beginning of the procedure. In 4 patients, a second cryoballoon (23 mm;  $n = 1$ ; poorly accessible right inferior pulmonary vein) or a standard cryoablation catheter (Freezor Max, Medtronic;  $n = 3$ ; rather large left-sided PVs as identified by 3D TEE) had to be used to achieve complete isolation of the PVs.

In all twenty patients with persistent AF, a circumferential pulmonary vein ablation in combination with a potential-guided segmental approach was the standard strategy (group B). Moreover, linear ablation across the left atrial roof was carried out in 7 patients with persistent AF. A mitral isthmus line was created in two patients in group B.

Additionally, catheter ablation of the cavotricuspid isthmus was carried out in 5 patients in group A (A1: 4 patients, A2: 1 patient) and in 2 patients in group B.

### Procedural results

The procedural results were published elsewhere<sup>[27]</sup>. In brief, a circumferential pulmonary vein ablation was carried out in all patients in group A1. This was combined with a potential-guided segmental approach if necessary. This resulted in the complete isolation of all 4 PVs in all patients in group A1.

In group A2, all cryoablation procedures could be completed successfully using this technique (mean number of successfully isolated PVs per patient: 3.9 (SD  $\pm 0.7$  PVs)).

The circumferential ablation strategy encircling the lateral and the septal PVs could be carried out successfully in all patients in group B [sometimes in combination with a potential-guided segmental approach (12 out of 20 patients)]. This resulted in complete isolation of a mean number of 3.8 PVs/patient [(SD  $\pm 0.9$  PVs); group B]. A complete linear lesion across the left atrial roof could be created in 7 patients in group B (7/7 patients). In addition, a continuous mitral isthmus line was achieved in two patients (10%) in this group B.

Successful ablation of the cavotricuspid isthmus was carried out in a total of 7 patients (group A1: 4 patients, group A2: 1 patient, group B: 2 patients).

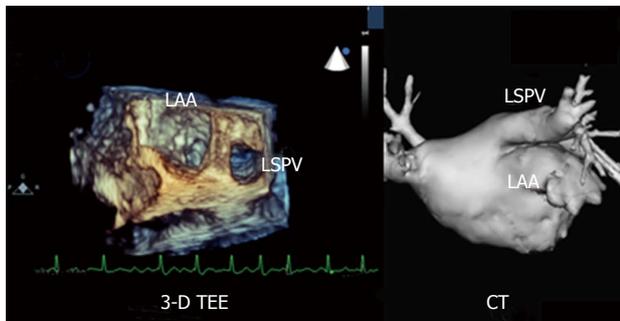
In both groups, no major complications (*e.g.*, neurologic disorders, significant pericardial effusion, PV stenosis  $\geq 70\%$ , periprocedural death) were observed during the procedure.

### Clinical outcomes

In group A, the mean follow-up duration was 1526 d (SD  $\pm 423$  d). In group B, the mean follow-up duration was 1697 d (SD  $\pm 208$  d;  $P = 0.1$ ). Thus, the mean overall

**Table 3 Long-term follow-up data**

	Group A	Group A1	Group A2	Group B	Total	P
Midterm follow-up (12 mo)	26/30	10/11	16/19	15/20	41/50	0.82
No. of patients without any arrhythmia recurrence	(86.7%)	(90.6%)	(84.2%)	(75.0%)	(82.0%)	
Long-term follow-up (4 yr)	22/30	8/11	14/19	12/20	34/50	0.62
No. of patients without any arrhythmia recurrence	(73.3%)	(72.7%)	(73.7%)	(60.0%)	(68.0%)	



**Figure 1 Three-dimensional transesophageal echocardiography-reconstruction providing an overview over the left atrial anatomy.** LSPV: Left superior pulmonary vein; LAA: Left atrial appendage; CT: Computed tomography; 3-D TEE: Three-dimensional transesophageal echocardiography.

follow-up duration was 1595 d (SD ± 360 d) (Table 3).

At 4-year follow-up, 73.3% of the study population in group A [22/30; A1: 72.7% (8/11)/A2: 73.7% (14/19)] and 60.0% of the study population in group B (12/20) were free from atrial tachyarrhythmias (*P* = 0.62). Thus, the overall rate of freedom from arrhythmia recurrences was 68.0% (no more atrial tachyarrhythmias in 34 out of 50 patients).

Four years after the procedure, 39/50 patients (78%) were clinically asymptomatic.

No major complications were observed within a follow-up period of 48 mo. Minor complications were observed in 10 patients (group: A1/A2/B: 3/2/5 patients; groin hematoma: 3 patients, pulmonary vein stenosis 30%: 1 patient, noninfectious pericarditis: 3 patients, minor pericardial effusion: 1 patient, hyperthyroidism; 1 patient, residual defect of the atrial septum; 1 patient).

In patients with recurrent atrial tachyarrhythmias, 7-d Holter monitoring demonstrated recurrent episodes of paroxysmal AF in 12 patients [group A: 9 patients (A1: 7/A2: 2); group B: 3 patients] and persistent AF in 4 patients [group A: 2 patients (A1: 1/A2: 1); group B: 2 patients]. No modification of the antiarrhythmic drug regimen and no redo procedure was necessary in 5 patients (group A1/A2/B: 1/1/3 patients) with recurrent atrial arrhythmias because they were almost free of symptoms. In 4 patients (group A1/A2/B: 1/0/3) relief of symptoms could be achieved by changing the antiarrhythmic drug regimen or an electrical cardioversion. In seven symptomatic patients a repeat ablation was necessary (group A1/A2/B: 1/4/2 patients).

**Cardiac imaging**

A 3D transesophageal echocardiography was carried out

in all 50 patients. All pulmonary veins could be visualized in 42/50 patients (84%; group A1/A2/B: 8/16/18 patients). In 8 patients (group A1/A2/B: 3/3/2), the right PVs could not be evaluated (RSPV: 0 patients; RIPV: 2 patients; RSPV+RIPV: 6 patients). The left-sided PVs could not be evaluated in 5/50 patients (group A1/A2/B: 3/0/2 patients). In all of these patients, both left-sided PVs could not be evaluated (Figures 1 and 2).

Some variations of the left atrial morphology were revealed (such as a right-sided accessory pulmonary vein or a common ostium of the left-sided or the right-sided PVs) (Table 2).

Based on the detailed knowledge of the individual left atrial anatomy the ablation strategy could be modified appropriately if necessary<sup>[27]</sup>. Thereby, major complications were avoided.

**DISCUSSION**

Catheter ablation is an important therapeutic tool in patients with recurrent symptomatic episodes of paroxysmal or persistent AF. This technique is effective in restoring and maintaining sinus rhythm even if antiarrhythmic drugs have failed or should be avoided. However, these ablation procedures are quite challenging. This is due to the fact that there are a lot of variations concerning the pulmonary vein and left atrial anatomy. 3D TEE provides detailed insights into the pulmonary vein anatomy of individual patients. In contrast to MDCT or MRI it is not associated with problems such as radiation exposure or impaired image quality if AF with rapid atrioventricular nodal conduction is present<sup>[27]</sup>.

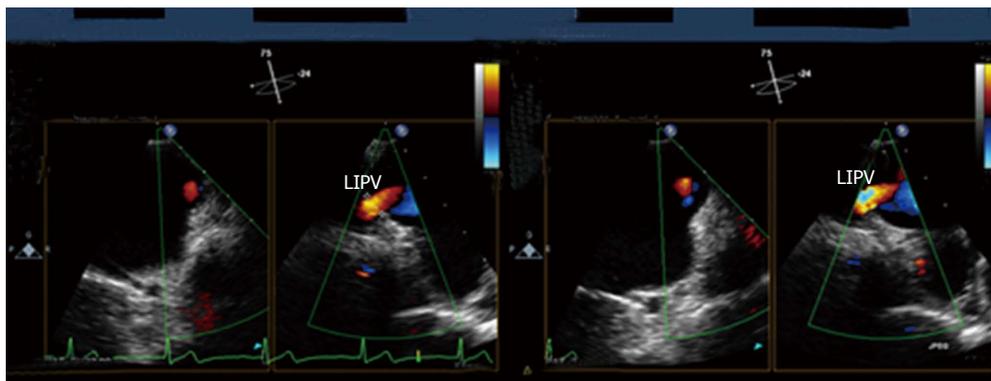
The study was performed to evaluate whether catheter ablation of atrial fibrillation facilitated by preprocedural 3D TEE is associated with a favourable long-term outcome.

**Main results**

The ablation procedures could be performed successfully in all patients in both groups after prior pulmonary vein imaging using 3D transesophageal echocardiography.

During a follow-up duration of 4 years, 73.3% of patients in group A (22/30) remained free from recurrent atrial tachyarrhythmias. In group B, 60.0% of patients (12/20, *P* = 0.62) remained free from an arrhythmia recurrence during a follow-up duration of 4 years. Thus, the overall rate of patients free from an arrhythmia recurrence was 68% at 4-year follow-up. No major complications were observed in both groups during long-term follow-up.

The data provided by our study shows that radio-



**Figure 2** Three-dimensional transesophageal echocardiography performed 3 years after catheter ablation of atrial fibrillation. Slightly increased flow velocity in the left inferior pulmonary vein (LIPV) ostium indicating a minor pulmonary vein stenosis [pulmonary vein diameter at 3-year follow-up: 2.1 mm (compared to 2.6 mm at baseline)].

frequency catheter ablation as well as cryoablation of AF can be performed effectively and safely after pre-procedural 3D TEE imaging. Pulmonary vein imaging prior to an ablation procedure using 3D TEE is associated with favourable long-term follow-up results concerning safety as well as efficacy of the procedures. Transesophageal echocardiography is recommended prior to catheter ablation of AF anyway (to rule out left atrial thrombus formation). Therefore, a 3D transesophageal echocardiography does not result in additional discomfort for the patient or additional cost. Furthermore, it is less time-consuming than performing an additional MDCT or MRI.

### Limitations

This is the long-term follow-up data of a feasibility study analysing our initial experience with AF ablation procedures facilitated by pre-procedural 3D TEE imaging. The target of our present study was to evaluate the usefulness of 3D TEE for LA visualization prior to an ablation procedure and to show that it is associated with a favourable outcome after catheter ablation of AF. The study was not designed to prove that this technique is equivalent to or superior to other imaging techniques (MDCT/MRI). Therefore, no comparison to MDCT or MRI data is provided.

Furthermore, this study was not designed to prove that pulmonary vein imaging (3D TEE, MDCT or MRI) does significantly improve the long-term outcome in comparison to patients not undergoing preprocedural PV imaging in a prospective randomized way.

Moreover, there are some technical limitations of 3D transesophageal echocardiography: First, the right pulmonary veins are sometimes difficult to visualize. Second, the 3D TEE images can only be displayed in a synchronized way during the ablation procedure and no direct image fusion with the geometry created with a 3D mapping system [Navx/Ensite (St. Jude Medical, Saint Paul, MN, United States) or CARTO (Biosense Webster)] is available so far.

In conclusion, Catheter ablation of AF can be performed with favourable results with regard to the

success rate as well as to the complication rate based on prior 3D TEE imaging. Three-dimensional TEE-models provide a good overview over the left atrial anatomy, thereby facilitating the procedure. Typical problems (such as atypical PV anatomy, variable relationship between the left atrial appendage and the left superior pulmonary vein) can be revealed. Then, the ablation strategy can be modified and complications can be avoided.

The results of our study demonstrate that pulmonary vein imaging prior to catheter ablation of AF is associated with a favourable long-term outcome with regard to a relatively high success rate and a very low complication rate. However, large randomized studies are needed to prove that this approach is superior to standard ablation procedures (either using 3D MRI-/MDCT reconstructions or no preprocedural imaging) with regard to various outcome parameters (*e.g.*, success and complication rates, procedure duration, radiation exposure).

## COMMENTS

### Background

Catheter ablation is an important therapeutic tool in patients with symptomatic atrial fibrillation (AF). However, these ablation procedures are quite challenging. This is due to the fact that there are a lot of variations concerning the pulmonary vein and left atrial anatomy. Three-dimensional transesophageal echocardiography (3D TEE) might be useful for analysing the individual left atrial morphology prior to an ablation procedure.

### Research frontiers

However, it is a matter of discussion whether the use of this technique is associated with a favourable long-term outcome with regard to the safety and efficacy of the procedures.

### Innovations and breakthroughs

A 3D TEE was performed successfully before the ablation procedure in all patients. All four pulmonary veins could be visualized in 84% of patients. The image quality was excellent in the majority of patients. Several pitfalls of the pulmonary vein morphology could be revealed (*e.g.*, accessory pulmonary veins, common pulmonary vein ostia, variable relationship between the left atrial appendage and the left superior pulmonary vein). All ablation procedures could be performed as planned. At 48-mo follow-up, 68.0% of all patients remained free from atrial tachyarrhythmias (group A1: 72.7%, group A2: 73.7%, group B: 60.0%). There was no major complications.

## Applications

The results of the study demonstrate that 3D TEE allows detailed insights into the left atrial anatomy. Catheter ablation of AF can be performed safely based on prior 3D TEE imaging.

## Terminology

Catheter ablation: Therapeutic option for the treatment of cardiac arrhythmias (catheter-based); atrial fibrillation: Atrial arrhythmia with a disorganized activation sequence.

## Peer-review

This is an interesting article. The authors have provided us with a semi-invasive method (first line or complementary) for monitoring the procedure during catheter ablation of paroxysmal and persistent AF.

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## Observational Study

**Entirely subcutaneous defibrillator and complex congenital heart disease: Data on long-term clinical follow-up**

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**Author contributions:** Ferrero P and Stuart AG developed the idea of the study; Ferrero P and Ali H equally contributed to collection of data; Ferrero P and Barman P wrote the paper; Foresti S and Lupo P contributed to interpret the data; D'Elia E and Cappato R reviewed and edited the manuscript.

**Institutional review board statement:** The study was reviewed and approved by the Adult Congenital Heart disease unit, Bristol Heart Institute Bristol United Kingdom.

**Informed consent statement:** All study participants, provided informed written consent prior to device implantation and verbally consented to collect follow-up data.

**Conflict-of-interest statement:** No conflict of interest relative to this research.

**Data sharing statement:** No additional data are available.

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**Abstract****AIM**

To describe the long-term follow-up of patients with complex congenital heart disease who underwent subcutaneous implantable cardiac defibrillator (S-ICD), focusing on local complications, appropriate and inappropriate shocks.

**METHODS**

Patients with complex congenital heart disease underwent S-ICD implant in two centers with the conventional technique. Data at follow-up were retrieved from clinical notes and institutional database.

**RESULTS**

Eight patients were implanted in two centres between 2010 and 2016. Median age at implant was 37.5 years (range 13-57). All patients who were deemed suitable for S-ICD implant passed the pre-procedural screening. Three patients were previously implanted with an anti-bradycardia device, one of whom with CRT. In one patient the device was explanted due to local infection. During

the total median follow-up of 874 d, one patient had an appropriate and one inappropriate shock triggered by fast atrial tachycardia. None of the patients had inappropriate shocks secondary to T wave oversensing or electrical interference with anti-bradycardia devices.

### CONCLUSION

S-ICD appears to be effective and safe in patients with complex congenital heart disease.

**Key words:** Subcutaneous defibrillator; Congenital heart disease; Outcomes

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**Core tip:** Implantation of subcutaneous implantable cardiac defibrillator in patients with complex congenital heart disease appears to be effective and reliable at long term follow-up. The high proportion of grossly abnormal baseline electrocardiogram and the significant incidence of atrial arrhythmias does not seem to affect the rate of inappropriate shocks.

Ferrero P, Ali H, Barman P, Foresti S, Lupo P, D'Elia E, Cappato R, Stuart AG. Entirely subcutaneous defibrillator and complex congenital heart disease: Data on long-term clinical follow-up. *World J Cardiol* 2017; 9(6): 547-552 Available from: URL: <http://www.wjgnet.com/1949-8462/full/v9/i6/547.htm> DOI: <http://dx.doi.org/10.4330/wjc.v9.i6.547>

## INTRODUCTION

Arrhythmic complications are common in patients with congenital heart disease (CHD) requiring implantation of an anti-tachycardic device<sup>[1]</sup>. Traditional endocardial approach can be particularly challenging in these patients due to limited vascular access, intracardiac shunts or abnormal cardiac chambers<sup>[2]</sup>. Furthermore the trans venous implantable cardiac defibrillator (ICD) implant carries a risk of long term lead related complication, which have been reported in up to 20% of cases at 10 years<sup>[3]</sup>. This figure is thought to be even higher in the pediatric and CHD population. Most of the long-term event in this clinical setting are lead related<sup>[4]</sup>. Alternative implant techniques have been devised in this population, including surgical epicardial or subcutaneous coils implant. Unfortunately, these non trans-venous approaches are associated with a higher procedural risk and have a significant failure rate during follow-up<sup>[5]</sup>. The entirely subcutaneous ICD (S-ICD) proved to be effective and safe in patients fulfilling both primary and secondary prevention indication<sup>[6]</sup>. This technology is particular appealing for CHD subjects, as it does not involve the implantation of lead within the cardiac chambers. Data about the performance of S-ICD in this subset of patients are still scant, particularly as far as the long-term outcomes are concerned. A major theoretical concern of the S-ICD in

this population is related to the presence of significant ventricular hypertrophy causing profound anomalies of both depolarization and repolarization phase on the surface electrocardiogram (ECG) and the high incidence of atrial tachycardia<sup>[7]</sup>. In theory, both these issues could lead to an inappropriate shock in the long-term follow-up. Furthermore, a significant proportion of patient with CHD develop atrial-ventricular conduction impairment either as the result of their specific congenital lesion or after cardiac surgery requiring long term pacing. A recent sub analysis from a pooled analysis of the IDE and EFFORTLESS registry showed the safety of S-ICD in patients with CHD<sup>[8]</sup>. However, during the median follow-up of 567 d none of the patients had any appropriate shocks, consequently no observations about the efficacy of this technology could be performed<sup>[9]</sup>.

In this article, we report medium and long term follow-up in eight patients with complex CHD implanted with a S-ICD, reflecting the experience of two adult CHD referral centres. The details of previous surgical history, the occurrence of either appropriate or inappropriate shocks, local complications, and interference with previously implanted anti-bradycardia and CRT devices are described.

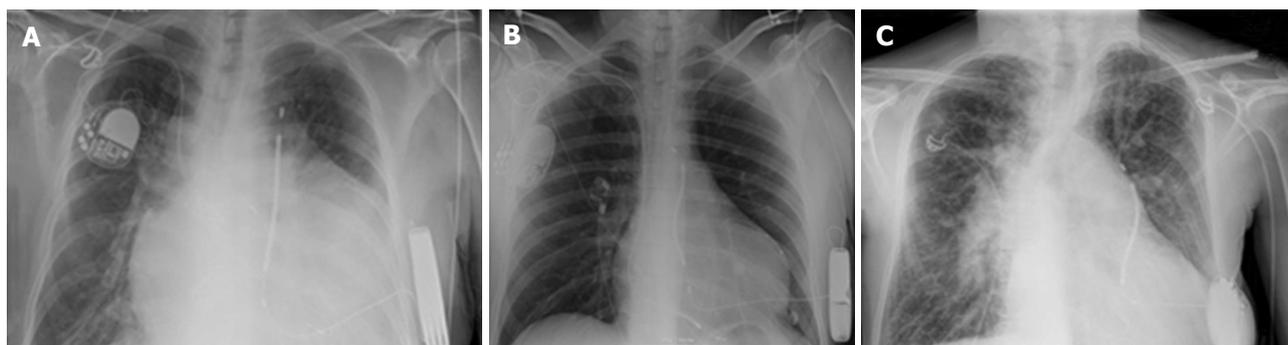
## MATERIALS AND METHODS

Patients with CHD were implanted with a S-ICD in two centres between 2010 and 2016. All patients underwent pre-implant eligibility screening. Suitability for S-ICD implantation was pre-assessed by a standardized protocol recommended by the manufacture, as previously published. This included assessment of the QRS and T wave amplitude ratio in at least two different postures (supine and standing), and during exercise on a treadmill<sup>[10]</sup>. Implant was performed under general anaesthesia with the conventional technique. Briefly, the device and lead positioning was guided by standard chest anatomical landmarks and fluoroscopy to ensure proper vector configuration across the cardiac silhouette. All devices but one were programmed from the beginning with a shock conditional zone (180-240 beats per minute, bpm) and a shock only zone above 240 bpm. All patients underwent defibrillation testing by induction of ventricular fibrillation using 50 Hz current to assess accurate detection and effective termination of the arrhythmia. Clinical and surgical details were retrieved from institutional databases. All patients implanted underwent regular follow-up at 1 and 6 mo thereafter. Data about patient clinical status, occurrence of local complication, arrhythmic burden, inappropriate and appropriate shocks were recorded.

## RESULTS

### Pre implant clinical details

Eight patients were implanted with a S-ICD device between 2010 and 2016 in two centres. Median age at implant was 37.5 years (range 13-57). Seven patients had a secondary prevention indication while one patient was implanted after one episode of syncope and documented



**Figure 1** A new transeptal endocardial lead was implanted in the left ventricle and the atrial septal defect was thereafter successfully closed with an occlude device. A: Subcutaneous implantable cardiac defibrillator and endocardial pacing system in a patient post Mustard operation; B: Patient with ASD and dilative DCM who previously underwent left ventricle lead implant; C: Patient with Eisenmenger syndrome. ASD: Atrial septal defect; DCM: Dilative cardiomyopathy.

Table 1 Pre implant clinical and anatomical characteristics							
Anatomical diagnosis	Sex	Age at implant (yr)	Pre implant ECG	Indication	Reason for SICD	Prev implant	F.U (d)
TOF	F	47	RBBB + RVH	VT	Tricuspid mech valve	No	360
VSD subaortic obstr.	M	52	LVH	Out hospital card arrest	Previous endocarditis	No	334
TGA, Mustard	M	36	RBBB + RVH	VF	SVC baffle stenosis	Yes	486
DILV TGA Eisenmenger	M	57	IVCD (aspecific)	Sustained VT	Right to left shunt	No	1139
ASD DCM	M	39	Paced LV endo	Syncope sustained VT	Previous leads implanted	Yes	1827
TGA, Mustard	M	24	Paced sub pulm vent.	Syncope NOT Sustained VT	SVC baffle occlusion	No	1890
HLVS Fontan	M	13	IVCD + RVH	Sustained VT	Extracardiac Fontan	No	1499
TGA VSD	M	23	RBBB + RVH	Sustained VT	TV repair	Yes	90

TOF: Tetralogy of Fallot; VSD: Ventricular septal defect; TGA: Transposition of great arteries; DILV: Double inlet left ventricle; ASD: Atrial septal defect; HLVS: Hypoplastic left ventricle syndrome; ECG: Electrocardiogram; RBBB: Right bundle branch block; RVH: Right ventricular hypertrophy; LVH: Left ventricular hypertrophy; IVCD: Inferior vena cava diameter; VF: Ventricular fibrillatio; LV: Left ventricular; DCM: Dilative cardiomyopathy; VT: Ventricular tachycardia; SICD: Subcutaneous implantable cardiac defibrillator; SVC: Superior vena cava; TV: Tricuspid Valve.

not-sustained ventricular tachycardia. The anatomical diagnoses were: Tetralogy of Fallot, repaired ventricular septal defect with subaortic obstruction, transposition of the great arteries that underwent Mustard repair, double inlet left ventricle with Eisenmenger physiology, atrial septal defect associated with cardiomyopathy. Three patients (37.5%) had previously undergone endocardial pacemaker implantation due to brady-tachyarrhythmic syndrome in two cases, and a CRT device in the other one (Figures 1A, B and 2). Four patients (50%) had a previous history of documented paroxysmal atrial tachyarrhythmia. The reasons for S-ICD vs conventional endocardial approach were limited or difficult access to the cardiac chambers in five patient, high infective risk in two patients and presence of right to left shunt in one patient (Table 1). In all patients, the option of conventional ICD was offered and discussed as part of the preoperative consent process.

**Pre implant ECG and screening details**

Pre implant ECG showed right bundle branch block in 3 patients (37.5 %), non specific interventricular conduction delay in two patients (28%), narrow QRS with left ventricular (LV) hypertrophy in one patient (12.5%), and paced QRS in two patients. Overall the QRS duration ranged from 110 ms to 180 ms (Table 1). All patients clinically deemed as good candidate for S-ICD passed the pre-implant screening (100% success rate). We did not

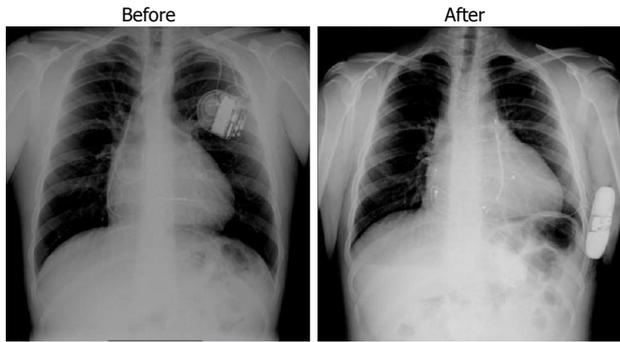
observe any difference in the QRS/T ratio between the left and right position of the electrodes.

**Operative issues**

Median procedural time was 65 min (range 58-90 min). The use of fluoroscopy was limited to check the proper position of the device and coil relative to the cardiac silhouette. In the patient with an epicardial pacing system, the coil was tunneled in the usual way without creating any mechanical interference with the previously implanted pacing lead (Figure 2). In one patient with a systemic right ventricle following Mustard operation the defibrillation test was effective only at 80 J despite repositioning of the pulse generator. None of the patients had significant bleeding during the procedure.

**Follow-up and outcomes**

Median follow-up was 812 d (range 90-1890). In four patients (50%) a follow-up longer than three years was available. Figure 3 depicts a summary of the events occurred in each individual patient according to the background anatomy. During follow-up, one patient underwent device extraction due to local infection secondary to hematoma eight months after the implant. This patient did not develop any signs of systemic infection and underwent subsequent surgical epicardial implantation. Three patients had multiple episodes of

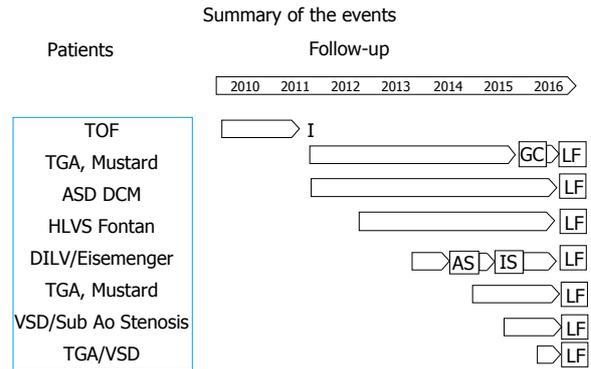


**Figure 2 Hybrid implant (subcutaneous implantable cardiac defibrillator and epicardial pacing).** The patient developed severe tricuspid regurgitation related to the endocardial lead previously implanted.

documented sustained atrial tachycardia (four clinically relevant episodes requiring admission and arrhythmia termination), triggering an inappropriate shock in one patient 18 mo after the implant (inappropriate discharge overall rate 12.5%). These patients had a history of atrial tachycardia before the implant. The same patient had an effective, appropriate shock due to fast ventricular tachycardia that occurred after eight months (appropriate discharge overall rate 12.5%). None of the patients had inappropriate shocks related to over-sensing. One patient underwent uncomplicated pulse generator replacement owing to battery depletion. One patient with large atrial septal defect associated with cardiomyopathy developed progressive LV dysfunction and underwent upgrading to biventricular stimulation. The trans-coronary sinus left LV lead was then switched off as it was causing diaphragmatic capture in the bipolar configuration and interference with the S-ICD in the unipolar one. A new transeptal endocardial lead was implanted in the left ventricle and the atrial septal defect was thereafter successfully closed with an occlude device (Figure 1). In the remaining two patients with conventional endocardial pacing system we did not observe any electrical interference during follow-up.

## DISCUSSION

Abnormal cardiac rhythm is the most common cause of hospital admission in adults with CHD. The absolute risk of sudden death and/or ventricular arrhythmias increases with prolonged follow-up, particularly in the subset of patients with reduced systemic ventricular function and evidence of extensive scar within the ventricular mass<sup>[11]</sup>. The risk of sudden death in the adult CHD population ranges from 0.1% and 0.5% per year<sup>[12,13]</sup>. However, there is no established guidance for ICD implantation in this group of patients apart from those fulfilling a secondary prevention indication. It is well recognized that ICD implantation in adult CHD might be particularly technically challenging due to vascular access issues or to the complex anatomy. Furthermore, complications at follow-up are significantly higher when compared to the general population of ICD recipients. These include



**Figure 3 Summary of the events during follow-up according to different anatomic background.** TOF: Tetralogy of Fallot; VSD: Ventricular septal defect; TGA: Transposition of great arteries; DILV: Double inlet left ventricle; ASD: Atrial septal defect; HLVS: Hypoplastic left ventricle syndrome; I: Infection; IS: Inappropriate shock; AS: Appropriate shock; GC: Generator change; LF: Last follow-up; DCM: Dilatative cardiomyopathy.

endocarditis in patient with prosthetic valve or residual native valve disease, baffle obstruction in patients who underwent atrial switch, and thromboembolism in patient with intracardiac shunts. S-ICD represents an attractive alternative for this population and may offer an effective protection against sudden death in a higher proportion of patients with reduced morbidity.

## Screening issues

Effective screening plays a pivotal role in selecting CHD subjects for the S-ICD. In congenital heart patients, a particular concern is the presence of a large percentage of T wave inversion or enlargement throughout the precordial leads, secondary to ventricular hypertrophy, right bundle branch block, or a paced QRS complex. These features, have been reported as a risk factor for ECG screening failure in the S-ICD<sup>[14,15]</sup>. Despite the fact that most of our patient had right bundle branch block and two had a paced ventricular complex, all passed the preimplant screening. Contrary to experience reported previously, all patients passed the screening with electrodes positioned on the left parasternal edge<sup>[16]</sup>. This finding should be interpreted cautiously owing to the small sample size, and might simply reflect the variability in ECG presentation in this population or the highly unpredictable vector configuration.

## Long-term outcomes

As expected, a significant proportion of patient (37%) had multiple episodes of sustained atrial tachycardia that were correctly discriminated by the device. Overall two patients had device related complications (an early local hematoma and an inappropriate shock). Only one patient had one appropriate and one inappropriate shock, accounting for a cumulative incidence of inappropriate shock over the follow-up of 1.5%. The device settings were optimized by activating the conditional shock zone. However, this percentage is consistent with the one reported in the IDE and EFFORTLESS, confirming

the reliability of the S-ICD algorithm in discriminating supraventricular from ventricular tachycardias, even in this clinical setting characterized by a high incidence of atrial arrhythmias<sup>[17]</sup>. One patient had an appropriate shock during the entire follow-up (cumulative prevalence 12.5%). Although consistent with the EFFORTLESS registry data, this percentage was lower compared with the population of patients with endocardial ICD<sup>[18]</sup>. Interestingly, a significant number of self-terminating ventricular tachycardia episodes were detected at follow-up, underscoring the appropriateness of a deliberate high cut-off rate and long time to therapy setting in this subset of patient. Furthermore, the low percentage of shocks also reflects the overall lower arrhythmic risk in patients with CHD as compared with patients with cardiomyopathies or ischaemic substrates, as already observed<sup>[12]</sup>.

### S-ICD in patients requiring anti-bradycardic pacing

A theoretical major limitation in the eligibility of CHD patient for S-ICD is the high likelihood of developing pacing dependency during follow-up. Data about the effect of a previously implanted endocardial pulse generator on the long term performance of the S-ICD are limited. In the EFFORTLESS registry, 2.8% of patients had a anti-bradycardic pacemaker implanted. In the CHD population, the experience of combined implantation of S-ICD and pacemaker did not raise concern regarding electrical interferences<sup>[19]</sup>. Although a significant proportion of patients had a pacemaker previously implanted, we did not reported clinical relevant electrical interferences in any patient but one in which the LV lead was temporarily programmed in the unipolar configuration. This finding suggest the long-term compatibility of the S-ICD with an endocardial anti-bradycardic device, provided that pacing configuration is bipolar. This safety issue, if consistently confirmed, may theoretically extend the indication to S-ICD in this particular subset of patients.

Our data suggest that S-ICD might represent a valid option for patient with complex CHD at high risk of sudden death. This technology may overcome some of the technical constrain and long-term risk related to the conventional transvenous ICD, eventually expanding the eligibility of this subset of patient for anti-tachycardic therapy.

### Limitations

A major limitation of this paper is the low number of patients, which reflect the experience of only two centres. Furthermore, we do not have a matched group of CHD patients who underwent transvenous ICD implant as control group. Systematic collection of prospective data is needed to support S-ICD as a routine alternative in this population.

## COMMENTS

### Background

Endocardial implant of devices in patients with congenital heart disease may pose a particular challenge owing to limited vascular access and complex

anatomy. Furthermore conventional endocardial pacing in this population is associated with a higher risk of lead related complications.

### Research frontiers

Subcutaneous implantable cardiac defibrillator (S-ICD) has been proved to be effective and safe in patients with a wide range of cardiomyopathies and arrhythmogenic syndromes. Limited evidences from subgroup of patients enrolled in clinical trials support the extension of the use of this technology in patients with structural heart disease.

### Innovations and breakthroughs

This paper report data relative to a uniquely long follow-up patients with congenital heart disease that underwent S-ICD implantation. Although the number of patients is low they represent a wide range of clinical settings, including single ventricle physiology.

### Applications

ICD implantation in patients with congenital heart disease is still a matter of debate, particularly concerning primary prevention indication. The development and optimization of subcutaneous technology might be a suitable tool to provide and extend the protection against sudden death in this group of patients.

### Terminology

S-ICD is a relative new technology made of a pulse generator connected with a coil. The whole system is implanted subcutaneously and is able to provide effective termination of fast rhythm by DC shock and only limited back up pacing.

### Peer-review

Very interesting and well written article. It gives an important overview of the topic in a subgroup of very complex patients.

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## Interferon related pericarditis: Review

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**Author contributions:** Nishio K drafted the manuscript, and assisted with data analysis; Arase T, Tada H and Tachibana H were involved with data collection and data analysis.

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### Abstract

#### AIM

To conduct a review of "interferon related pericarditis".

#### METHODS

We searched MEDLINE, EMBASE, Cinahl, and the Co-

chrane Database from the earliest available date through September 2016. A search strategy using the Medical Subject Headings and text keywords "interferon" and "pericarditis" were used.

#### RESULTS

Nine case reports were eligible for the present study. Six of 8 cases were women and the mean age was  $43.8 \pm 13.8$  years with chronic hepatitis C in 6 cases, malignant melanoma in 2 cases and chronic myelogenous leukemia in 1 case. The patients complained of chest pain in 6 cases, dyspnea in 5 cases and edema in 2 cases. Pericardial friction rub was heard in 3 of 9 cases. Congestive heart failure occurred in 3 of 9 cases. Two mechanisms for pericarditis were demonstrated, one is autoimmune included lupus like syndrome in 2 cases and the other is cardio toxicity in 4 cases. Treatment of interferon related pericarditis is discontinuation of Interferon treatment. Four of 9 cases were treated with prednisone and 4 with nonsteroidal anti-inflammatory drugs.

#### CONCLUSION

Interferon related pericarditis still remains uncertain. Treatment of interferon related pericarditis rests mainly on early recognition and drug discontinuation. Interferon related pericarditis was treated with steroid and/or non-steroidal anti-inflammatory drugs.

**Key words:** Chronic hepatitis C; Chronic myelogeneous leukemia; Interferon; Malignant lymphoma; Pericarditis

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**Core tip:** Interferon is considered to be one of the treatments for many diseases. However, interferon therapy is associated with side effects. Recently some reports demonstrated acute pericarditis complicating interferon therapy. Two mechanisms for pericarditis were demonstrated, one is autoimmune included lupus like syndrome and the other is cardio toxicity. However, these two mechanisms are controversial. The aim of this study is to review of "interferon related pericarditis".

Nishio K, Arase T, Tada H, Tachibana H. Interferon related pericarditis: Review. *World J Cardiol* 2017; 9(6): 553-557 Available from: URL: <http://www.wjgnet.com/1949-8462/full/v9/i6/553.htm> DOI: <http://dx.doi.org/10.4330/wjc.v9.i6.553>

## INTRODUCTION

Interferon is considered to be one of the treatments for many diseases. However, interferon therapy is associated with side effects, the most common being general symptoms such as fever, weight loss and headache. Some studies have demonstrated cardiac adverse effects of interferon for chronic hepatitis C (CHC)<sup>[1,2]</sup>. Most frequently reported are arrhythmia, congestive heart failure and sudden death. Reported with rarer frequency are polyneuropathy, paranoia and suicidal thoughts, diabetes mellitus, retinopathy, optical neuritis, diminution of hearing, seizures, loss of libido and cardio toxicity<sup>[3]</sup>. Recently some reports demonstrated acute pericarditis complicating interferon therapy<sup>[4-12]</sup>. We conducted a review of "interferon related pericarditis".

## MATERIALS AND METHODS

### Selection of case reports

We searched MEDLINE, EMBASE, Cinahl, and the Cochrane Database from the earliest available date through September 2016. A search strategy using the Medical Subject Headings and text keywords "interferon" and "pericarditis" were used. The retrieved studies were manually screened to assess their appropriateness for this study. All references cited in the studies were also reviewed to identify additional published articles not indexed in the database. The search was not restricted by language.

## RESULTS

### Patients

Nine case reports were eligible for the present study; seven were in English<sup>[4,5,7,8,10-12]</sup> and two in French<sup>[6,9]</sup>. Clinical characteristics of patients are shown in Table 1. Six of 8 cases were women and the mean age was  $43.8 \pm 13.8$  years with CHC in 6 cases, malignant melanoma in 2 cases and chronic myelogenous leukemia in 1 case. The patients complained of chest pain in 6 cases, dyspnea in 5 cases and edema in 2 cases. Pericardial friction rub was heard in 3 of 9 cases<sup>[5,8,9]</sup>. Congestive heart failure occurred in 3 of 9 cases<sup>[8-10]</sup>. Two mechanisms for pericarditis were demonstrated, one is autoimmune included lupus like syndrome (AI group) in 2 cases and the other is cardio toxicity (CT group) in 4 cases. Three of 9 articles didn't mention the mechanisms for pericarditis.

### Clinical history

Three cases had clinical history. The 28-year-old patient had allergic asthma since infancy<sup>[4]</sup>. The 24-year-old woman following therapy with interferon  $\alpha$  was diagnosed

with systemic lupus erythematosus (SLE), and she was treated with prednisone (40 mg/d)<sup>[5]</sup>. When prednisone had been stopped completely for 3 mo, a pericarditis occurred. The patient had a recurrence of SLE. The 63-year-old man was diagnosed as diffuse large B cell non-Hodgkin's lymphoma and was treated with a full course of chemotherapy consisting of cyclophosphamide, adriamycin, vincristine and dexamethasone<sup>[8]</sup>.

### Laboratory findings

The woman with SLE<sup>[5]</sup> experienced four episodes of fever and pain in the left shoulder while breathing. Antinuclear antibody and anti-ds DNA antibody tests were negative, whereas circulating immune complexes were positive at the second and the third episode. CH50 and C4 levels were decreased with slightly elevated C3d level. Laboratory results of the 63-year-old man with non-Hodgkin's lymphoma presented antinuclear antibodies (titer 1/40)<sup>[8]</sup>. The blood sample examination of the 67-year-old man with CHC showed anti-DNA antibody and anti-ds DNA IgM were positive<sup>[10]</sup>.

### Interferon daily dose and duration of treatment with interferon

Figure 1 showed a relationship between the daily dose of interferon and the duration of treatment with interferon. Autoimmune due to interferon does not dependent on the daily dose but developed within one month with interferon treatment. Cardio toxicity due to interferon does not dependent on the daily dose or the duration of treatment with interferon.

### Chest radiography

Chest radiography demonstrated abnormalities in three cases. Chest X-ray of the 63-year-old man showed an enlarged heart silhouette and bilateral pleural effusion<sup>[8]</sup>. Chest radiograph of the 53-year-old woman showed cardiomegaly<sup>[9]</sup>. Portable chest radiograph of the 67-year-old man revealed pulmonary vascular congestion without pleural effusion<sup>[10]</sup>.

### Electrocardiogram

Electrocardiogram (ECG) demonstrated abnormality in one case. ECG showed gradual ST-segment elevation in leads V1 through V6 without elevated myocardial enzyme in the 67-year-old man<sup>[10]</sup>. Coronary angiography showed that there was no significant coronary arterial stenosis in this case.

### Ultrasound cardiology

Ultrasound cardiology (UCG) demonstrated pericardial effusion in 7 of 9 cases; mild in 2 cases<sup>[6,12]</sup>, moderate in 2 cases<sup>[4,10]</sup>, severe in 1 case<sup>[9]</sup>, and no presentation in 2 cases<sup>[7,11]</sup>. The 53-year-old female was diagnosed with constructive pericarditis with pre-tamponade<sup>[9]</sup>.

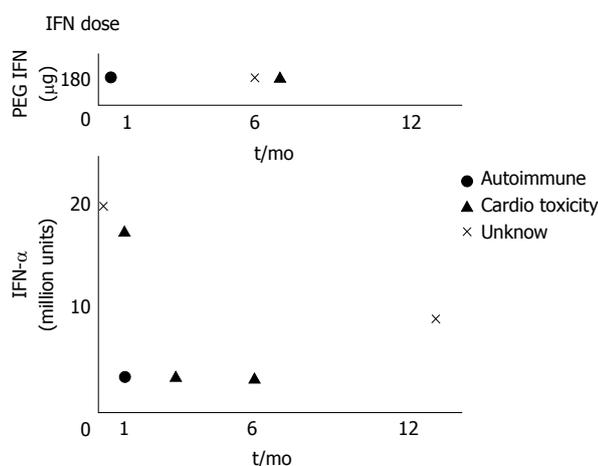
### Re-start and re-challenge test

The interferon treatment was restarted in three cases<sup>[4,6,11]</sup>. The 28-year-old patient suffered a pericarditis relapse at

**Table 1** Case reports of pericarditis associated with interferon

Ref.	Age/gender	Disease	Administered	Duration of IFN therapy	Mechanism
Fava <i>et al</i> <sup>[4]</sup>	28/NA	CML	IFN $\alpha$	13 mo	NA
Boonen <i>et al</i> <sup>[5]</sup>	24/F	CHC	IFN $\alpha$	1 mo	Autoimmune
Wisniewski <i>et al</i> <sup>[6]</sup>	42/F	CHC	IFN $\alpha$	6 h	Cardio toxicity
Gressens <i>et al</i> <sup>[7]</sup>	40/F	CHC	IFN $\alpha$ 2b	3 mo	Cardio toxicity
Benjamini <i>et al</i> <sup>[8]</sup>	63/M	MM	IFN $\alpha$ 2b	1 mo	Cardio toxicity
Hamdani <i>et al</i> <sup>[9]</sup>	53/F	CHC	PEG IFN $\alpha$ 2a	6 mo	NA
Nishio <i>et al</i> <sup>[10]</sup>	67/M	CHC	PEG IFN 2a	15 d	Lupus like syndrome
Popescu <i>et al</i> <sup>[11]</sup>	38/F	CHC	PEG IFN 2a	7 mo	Cardio toxicity
Ashraf <i>et al</i> <sup>[12]</sup>	39/F	MM	IFN $\alpha$	1 d	NA

CHC: Chronic hepatitis C; CML: Chronic myelogenous leukemia; F: Female; IFN: Interferon; M: Male; MM: Malignant melanoma; NA: Data not available; PEG IFN: Pegylated interferon.



**Figure 1** The relationship between interferon dose and duration of interferon therapy. PEG IFN: Pegylated interferon.

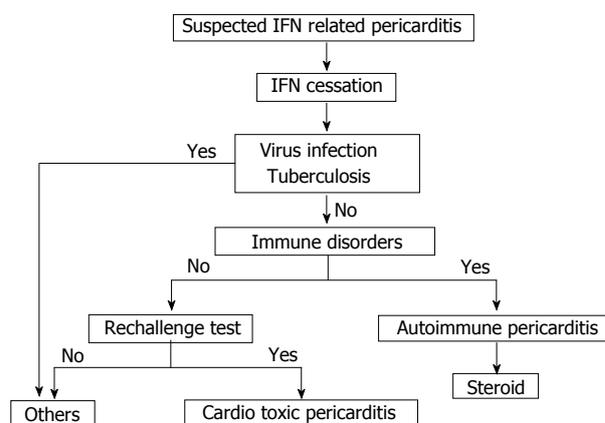
seven months after resumption of interferon  $\alpha$  therapy<sup>[4]</sup>. The 42-year-old female felt chest pain, after 7 h from administration of 1 million interferon  $\alpha$ <sup>[6]</sup>. After the first dose of interferon administration symptoms reappeared and UCG showed an increase of pericardial fluid in the 38-year-old female<sup>[11]</sup>. Re-challenge test was performed in one case<sup>[12]</sup>. Within ten hours of the re-initiation of interferon therapy, the 39-year-old woman developed chest pain identical to her previous pain.

### Complications

Two cases developed other complications. An electro-myography showed signs of polyneuropathy in the 40-year-old female<sup>[7]</sup>. The 67-year-old man developed chronic inflammatory demyelinating polyneuropathy during treatment with pegylated interferon-2a for chronic active hepatitis C viral infection<sup>[10]</sup>.

### Treatment

Treatment of drug-induced cardio toxicity rests mainly on early recognition and drug discontinuation. Interferon treatment was stopped in 7 of 9 cases. Four of 9 cases were treated with prednisone from 10 mg per day to 50 mg/d<sup>[4,5,8,10]</sup> and 4 with nonsteroidal anti-inflammatory drugs (NSAIDs)<sup>[5,7,11,12]</sup>. All of the AI group was treated with



**Figure 2** Algorithm of diagnoses and treatments for interferon related pericarditis. IFN: Interferon.

prednisone<sup>[5,10]</sup> and two of the CT group were treated with NSAIDs<sup>[7,11]</sup> and one of the CT group dexamethasone<sup>[8]</sup>. The 53-year-old female was treated with medications of anti-tuberculosis, but died because multiple organ failure<sup>[9]</sup>. Figure 2 showed an algorithm of the suspected interferon related pericarditis management.

## DISCUSSION

Cardiac adverse effects of interferon  $\alpha$  for CHC have been demonstrated<sup>[1,2]</sup>. Most frequently reported are arrhythmias, congestive heart failure and sudden death. These side effects occurred during treatment with interferon  $\alpha$ . However, pericarditis as a side effect of treatment with interferon is rare.

In 1988, the first report concerning interferon related pericarditis was presented by anonymity<sup>[13]</sup>. This report demonstrated two patients with continuous interferon therapy for chronic myelogenous leukemia had severe side effects consisting of pleural effusions and pericarditis. Montastruc *et al*<sup>[14]</sup> presented that there was an isolated pericarditis for which it was necessary to interrupt the interferon  $\alpha$  treatment. However, these two articles didn't describe in detail. Consequently, 9 articles were enrolled in the present study. Two mechanisms for pericarditis were demonstrated, one is autoimmune in 2 articles and

the other is cardio toxicity in 4 articles. Three of 9 articles didn't mention the mechanisms for pericarditis.

Prospective study reported on autoimmune phenomena in 987 patients treated with interferon for CHC. Twelve patients developed hyperthyroidism, 6 hypothyroidism, 3 interstitial pneumonia, 1 SLE, 2 rheumatoid arthritis, 2 autoimmune hepatitis and 1 autoimmune thrombocytopenic purpura<sup>[15]</sup>. In the present study, the appearance of lupus-like syndrome by the interferon treatment has been reported in 1 article and autoimmune in 1 article. The mechanism by which interferon  $\alpha$  induces autoimmune mediated complications is largely unknown. However, interferon alpha induces numerous target genes in antigen-presenting cells (APCs), such that APCs are stimulated and enhance humoral autoimmunity, promote isotype switching, and potentially activate autoreactive T cells. Moreover, interferon alpha can synergistically amplify T cell autoreactivity by directly promoting T-cell activation and keeping activated T cells alive. *Via* the latter mechanisms, interferon can trigger autoimmune diseases<sup>[16]</sup>. There is a possibility that interferon may damage endothelial cells, cause the thickening of capillary walls, and induce deposition of immune complexes. Interferon evokes the release of several cytokines, including tumor necrosis factor alpha, and interleukins 2, 6 and 1, affecting autonomic sympathetic nerve activity and vasopressor responses<sup>[17]</sup>. Interferon induces an autoimmune reaction through various mechanisms including production of gamma globulins and interleukin-6 (IL-6)<sup>[18]</sup> and inhibition of Allo-specific suppressor T lymphocytes, as well as activation of natural killer cells<sup>[19]</sup>. IL-6 was significantly increased in pericardial effusion<sup>[20]</sup>. Interferon has been associated with exacerbation or induction of a wide variety of clinical and serological immune disorders, including systemic lupus erythematosus, rheumatoid arthritis, autoimmune hepatitis, thyroid disease and diabetes mellitus. On the other hand, Orságová *et al.*<sup>[21]</sup> demonstrated that positivity of antinuclear antibodies and smooth muscle antibodies or increased rheumatoid factor and circulating immune complexes are often found in patients with chronic hepatitis B and CHC treated with interferon, but their presence does not correlate with the development of autoimmune diseases.

The cardiac toxicity of interferon alpha is also well known and uncommon. The mechanism of interferon cardio toxicity is unclear and probably multifactorial. There are no established predisposing factors for interferon cardio toxicity. The secondary effects of interferon described include arrhythmia (atrial fibrillation, sinus bradycardia, atrioventricular block), ischemic cardiomyopathy and cardiomyopathy with the dosage levels used in the treatment of hepatitis C<sup>[2]</sup>. Myocardial ischemia is mainly caused by cardio toxicity of interferon and antimetabolites<sup>[22]</sup>. Patients with previous heart disease are probably at higher risk for arrhythmia and ischemic manifestations<sup>[1]</sup>. Concerning drug toxicity, there have been reported cases of acute pericarditis after the administration of: Hydralazine, procainamide, izoniazid, phenylbutazone, dantrolene, doxorubicin, and penicillin.

These situations are extremely rare. Sonnenblick *et al.*<sup>[23]</sup> demonstrated that the cardiac effects of interferon were not related to the daily dose, cumulative total dose, or period of therapy and cardiac toxicity was reversible following the cessation of the drug therapy. Interferon inhibits cardiac cell function *in vitro*<sup>[24]</sup>.

The Naranjo adverse drug reactions (ADR) Probability Scale<sup>[25]</sup> is a validated tool used to determine the likelihood that the adverse drug reaction is caused by the implicated medication. The Naranjo algorithm requires a series of questions to be answered and scored. The total calculated score indicates the likelihood of causing an adverse drug reaction. Popescu *et al.*<sup>[11]</sup> used the Naranjo ADR Probability Scale to evaluate the correlation of pericarditis with interferon administration. This scale indicated a very probable association.

Treatment of interferon-induced cardio toxicity rests mainly on early recognition and drug discontinuation. There is a high degree of individual variation in toxicity, but most adverse events are reversible upon cessation of the drug<sup>[8]</sup>. In the present study, 4 of 9 patients were treated with prednisone and 4 with NSAIDs.

Chronic hepatitis C viral (HCV) infection and treatment with interferon are both associated with serological and clinical autoimmune manifestations<sup>[26,27]</sup>. The serological immune response to HCV infection may include the development of cryoglobulinemia, rheumatoid factor, anti-cardiolipin, antinuclear, anti-liver-kidney-microsome 1 and anti-smooth muscle antibodies. Serological autoimmune manifestations were explained by the lymphotropism of HCV and the polyclonal activation of B cells. Interferon-based treatment of HCV infection may precipitate or exacerbate the associated autoimmune disease. Classically, type II Cryoglobulinaemia, glomerulonephritis and thyroiditis are described.

Interferon related pericarditis still remains uncertain. There may be two mechanisms for pericarditis, one is autoimmune and the other is cardio toxicity. Treatment of interferon related pericarditis rests mainly on early recognition and drug discontinuation. Interferon related pericarditis was treated with steroid and/or NSAIDs.

## COMMENTS

### Background

When the authors examine a new unusual patient that the authors have never treated before, the authors need to research previous case reports. However, the case report is individual. The authors need to know what kind of examinations they need and what kind of treatments they need as soon as possible. This manuscript aimed to summarize those previous case reports concerning interferon related pericarditis.

### Research frontiers

There may be two mechanisms for interferon related pericarditis, one is autoimmune and the other is cardio toxicity. Treatment of interferon related pericarditis rests mainly on early recognition and drug discontinuation. Interferon related pericarditis was treated with steroid and/or nonsteroidal anti-inflammatory drugs.

### Innovations and breakthroughs

This is the first article that was summarized interferon related pericarditis.

## Applications

Readers will understand the previous case reports concerning interferon related pericarditis in a short time.

## Terminology

Interferon related pericarditis is one of the side effects of interferon treatment.

## Peer-review

In the current manuscript, the authors reviewed the 9 published interferon-related pericarditis cases. This interferon regimen complication is rare and this review is helpful to understand this rare complication.

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## Inadvertent cardiac phlebography

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**Author contributions:** Aznaouridis K and Alahmar A designed the report and revised the drafted manuscript; Masoura C collected the clinical data and drafted the manuscript; Kastellanos S collected the clinical data and drafted the manuscript.

**Institutional review board statement:** This case report was exempt from the Institutional Review Board standards at Hull and East Yorkshire NHS Trust, Hull, United Kingdom.

**Informed consent statement:** The involved patient gave her informed consent prior to study inclusion.

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### Abstract

We are reporting a case of a 80-year-old lady with effort angina who underwent coronary angiography through the right radial artery, using a dedicated radial multipurpose 5 French Optitorque Tiger catheter. The catheter was advanced into the left ventricle and a left ventriculogram was obtained, while the catheter appeared optimally placed at the centre of the ventricle and the pressure waveform was normal. A large posterior interventricular vein draining into the right atrium was opacified, presumably because the catheter's end hole inadvertently cannulated an endocardial opening of a small thebesian vein, with subsequent retrograde filling of the epicardial vein. Our case suggests that caution is needed when a dedicated radial catheter with both an end-hole and a side hole is used for a ventriculogram, as a normal left ventricular pressure waveform does not exclude malposition of the end-hole against the ventricular wall.

**Key words:** Thebesian vein; Radial access; Transradial; Cardiac phlebography

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**Core tip:** Use of a dedicated radial catheter with both an end-hole and a side hole to perform a left ventriculogram, can result in inadvertent cannulation of a small Thebesian vein and subsequent opacification of a large epicardial vein. When such catheters are used for ventriculogram, a normal ventricular pressure waveform does not exclude malposition of the end-hole against the ventricular wall and extra caution is needed in order to prevent iatrogenic myocardial injury. We review current literature on myocardial injury induced by end-hole catheters used for left ventriculograms.

Aznaouridis K, Masoura C, Kastellanos S, Alahmar A. Inadvertent cardiac phlebography. *World J Cardiol* 2017; 9(6): 558-561

## INTRODUCTION

In the last years, the use of radial artery as an arterial access site for coronary procedures has gained increasing popularity, as it is considered safer compared to transfemoral procedures. Recent data from large randomized trials suggest that the radial access is associated with a reduction of major adverse events in patients with acute coronary syndrome undergoing invasive management<sup>[1]</sup>. Furthermore, there is expanding use of dedicated "multipurpose" radial catheters, which enable the operator to cannulate both coronary arteries, and also to perform chamber injection and left ventriculogram. For transradial procedures, this single-catheter approach has been shown to decrease radiation exposure, fluoroscopy time, contrast volume and total procedure time compared with standard Judkins catheters<sup>[2]</sup>. Using a single catheter also reduces the risk of spasm of the radial artery. On the other hand, those dedicated radial catheters may rarely cause myocardial injury when used for a left ventriculogram. We present a rare angiographic finding in a patient who underwent cardiac catheterization through the radial artery using a dedicated radial catheter.

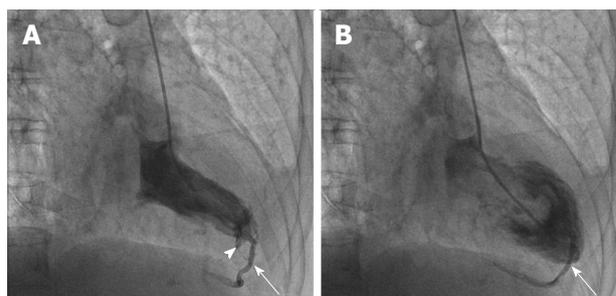
## CASE REPORT

A 80-year-old lady with effort angina underwent coronary angiography through the right radial artery, using a dedicated radial "multipurpose" 5 French Optitorque Tiger catheter (Terumo, Somerset, New Jersey). Coronary angiogram of the left and right coronary arteries demonstrated a significant stenosis in the ostium of a modest sized intermediate artery. The catheter was then advanced into the left ventricle (LV) and appeared optimally placed at the centre of the LV, while the LV pressure waveform was normal. A left ventriculogram was obtained after delivering 10 mL of contrast with a vigorous hand injection. Few ectopics were noticed at the beginning of the injection, followed by a small deflection of the catheter's tip, a minor subendocardial staining (arrowhead in panel A) and visualization of a large posterior interventricular vein, which seemed to drain directly into the right atrium (arrows in Figure 1 and supplementary Video 1).

We observed no persistent staining of the myocardium and the patient did not experience any discomfort, arrhythmia or electrocardiographic changes. The patient was monitored and was discharged few hours later.

## DISCUSSION

Dedicated radial "multipurpose" catheters such as the Tiger catheter have been specifically designed to minimise catheter exchange with ability to access both coronary ostia from the radial approach, and also provide



**Figure 1** Inadvertent phlebography of the posterior interventricular vein. Right anterior oblique image taken at time of left ventriculography. Arrows show the posterior interventricular vein in systole (A) and diastole (B). Arrowhead shows a minor subendocardial staining (A).

ability to perform chamber injection with the presence of both an end hole and a single side hole. In our case, we assume that the catheter's end hole cannulated an endocardial opening of a small Thebesian vein, with subsequent retrograde filling of the epicardial vein. Venae cordis minimae (Thebesian veins) are small valveless venous conduits that connect the coronary arteries, veins or capillaries with the cardiac chambers. Most Thebesian veins of the ventricles are connected to the cardiac venous system<sup>[3]</sup>, as was the case in our patient.

We screened the available literature and we identified a total of 7 reports with 8 cases of myocardial injury following contrast injection with end-hole catheters for left ventriculogram<sup>[4-10]</sup>. The characteristics of the patients and procedures and the type of myocardial injury and outcome are shown in Table 1. In 5 of those cases, a dedicated transradial end-hole catheter with one side hole near the tip (radial Tiger catheter) or two side holes (radial Jacky catheter) was used<sup>[4,6,7,9,10]</sup>. Traditional multipurpose (MPA) catheters with an end-hole and 2 side holes near the tip were used in 2 cases<sup>[4,5]</sup>, whereas a catheter with a single end-hole (Judkins right 4) was used from femoral access in 1 case<sup>[8]</sup>. The Thebesian venous network and/or cardiac veins were visualized in 4 cases<sup>[4,5,8,9]</sup>. A high-pressure power injection had been performed in most cases describing myocardial laceration/dissection and persistent myocardial staining<sup>[6,7,9,10]</sup>. Complete myocardial "perforation" with presence of contrast in the pericardial space was confirmed in 2 of those cases<sup>[6,10]</sup>, and emergency pericardiocentesis due to tamponade was performed in one patient<sup>[6]</sup>. No fatalities were reported (Table 1).

Even a pigtail catheter can rarely cause severe myocardial injury during ventriculography when its tip is inappropriately positioned<sup>[11]</sup>. However, apposition of the pigtail catheter's end-hole against the endocardium or cannulation of Thebesian veins is extremely unlikely, and therefore this catheter should be the preferred option for ventriculograms.

Caution is needed when a dedicated radial catheter with both an end-hole and side holes is used for a ventriculogram, as a normal left ventricular pressure waveform (likely from the side hole) does not exclude unsafe posi-

**Table 1 Patient and procedure-related characteristics and outcomes of published cases describing myocardial laceration or cannulation of Thebesian veins following left ventriculogram with end-hole catheters**

Case	Ref.	Demographics	Catheter, access	Injection characteristics	Complication	Clinical findings/outcome
1	Judkins <i>et al</i> <sup>[4]</sup>	72 yr, woman, aortic stenosis	Multipurpose-1 (right radial access)	Not provided	Opacification of Thebesian veins, coronary veins and coronary sinus	Not provided
2	Judkins <i>et al</i> <sup>[4]</sup>	77 yr, woman, chest pain	Optitorque Tiger (right radial access)	Not provided	Opacification of Thebesian veins and coronary veins	Not provided
3	Singhal <i>et al</i> <sup>[5]</sup>	46 yr, man, hypertrophic cardiomyopathy	Multipurpose-2 (femoral access)	Power injection, 25 mL of contrast, 10 mL/s	Opacification of Thebesian veins, coronary veins and coronary sinus	Ventricular tachycardia requiring cardioversion/uneventful recovery and next day discharge
4	Frizzell <i>et al</i> <sup>[6]</sup>	76 yr, woman, myocardial infarction	Optitorque Tiger (radial access)	Power injection, 30 mL of contrast over 10 s	Laceration/dissection of anterolateral myocardium and pericardial staining	Chest discomfort, pericardial effusion and cardiac tamponade/pericardiocentesis, uneventful recovery
5	Rosington <i>et al</i> <sup>[7]</sup>	71 yr, woman, angina	Optitorque Tiger (right radial access)	Power injection, 25 mL of contrast, 8 mL/s, 600 psi	Laceration/dissection of anterolateral myocardium	Chest discomfort, transient bundle branch block/uneventful course and next day discharge
6	Aqel <i>et al</i> <sup>[8]</sup>	50 yr, woman, chest pain	Judkins right 4 (femoral access)	Hand injection	Opacification of Thebesian veins, coronary veins and coronary sinus	Not provided
7	Kang <i>et al</i> <sup>[9]</sup>	66 yr, woman, angina	Optitorque Jacky radial (radial access)	Power injection, 30 mL of contrast over 2 s, 600 psi	Laceration/dissection of anterior myocardium and opacification of anterior interventricular vein and coronary sinus	Not provided
8	Basit <i>et al</i> <sup>[10]</sup>	69 yr, man, inferior wall ischemia	Optitorque Jacky radial (radial access)	Not provided	Laceration/dissection of myocardium with pericardial opacification	Chest pain, trivial pericardial effusion/uneventful recovery

tioning of the end-hole against the ventricular wall<sup>[6,7]</sup>. This malposition of the catheter may result in cannulation and injection in a Thebesian vein<sup>[4,5,8]</sup>, or injection against the endocardial layer. In our case, only a small volume of contrast was delivered in an endocardial opening of the Thebesian network with a hand injection, and this may partly explain the relatively “benign” outcome of opacifying an epicardial vein without causing any major myocardial injury. In this scenario, it seems that the injected contrast drains through the Thebesian network into the cardiac veins and therefore no significant intramyocardial shearing forces are generated. However, serious complications such as laceration/dissection of the myocardium or even catastrophic “perforation” of the ventricular wall<sup>[6,7,9,10]</sup> may occur when the contrast is injected against the endocardium, or when of a large contrast volume is injected in a Thebesian vein with high-pressure (with an automated power injector), as in this case the small Thebesian network would likely be unable to accommodate the forcefully injected large volume of contrast. Hence, we believe that our case indirectly supports the common practice of avoiding the use of radial multipurpose catheters with automated high-pressure power injectors and large volume of contrast for ventriculograms. Therefore, additional care should be taken to confirm that the catheter is optimally positioned at the centre of the left ventricular cavity and that the catheter’s tip is free before contrast injection,

and the operator should not rely only on a normal waveform of ventricular pressure. Finally, the injection of contrast must stop immediately when subendocardial or myocardial staining or opacification of an epicardial vein occurs during a ventriculogram with a dedicated radial multipurpose catheter, as this invariably indicates myocardial injury due to malposition of the catheter’s end hole against the endocardium.

## COMMENTS

### Case characteristics

This case shows that using a dedicated radial catheter with both an end-hole and a side hole for a left ventriculogram can result in inadvertent cannulation of a small Thebesian vein and subsequent opacification of an epicardial cardiac vein. This was not related to any symptoms or adverse outcomes.

### Clinical diagnosis

Minor catheter-induced endocardial staining and visualization of posterior interventricular vein.

### Differential diagnosis

Catheter-induced laceration/dissection of myocardial wall.

### Imaging diagnosis

Left ventriculogram with a dedicated radial Tiger catheter.

### Related reports

Current literature on myocardial injury induced by end-hole catheters used for

left ventriculogram is reviewed.

### Experiences and lessons

When dedicated radial end-hole catheters are used for ventriculogram, a normal ventricular pressure waveform does not exclude malposition of the end-hole against the ventricular wall and extra caution is needed in order to prevent iatrogenic myocardial injury.

### Peer-review

This is a case report about an unexpected cardiac phlebography. The manuscript is well written and describes an important aspect related to the use of multipurpose radial catheters.

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## Sudden cardiac death in patients with rheumatoid arthritis

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### Abstract

An increased cardiovascular morbidity and mortality, including the risk of sudden cardiac death (SCD), has been shown in patients with rheumatoid arthritis (RA). Abnormalities in autonomic markers such as heart rate variability and ventricular repolarization parameters, such as QTc interval and QT dispersion, have been associated with sudden death in patients with RA. The interplay between these parameters and inflammation that is known to exist with RA is of growing interest. In this article, we review the prevalence and predictors of SCD in patients with RA and describe the potential underlying mechanisms, which may contribute to this. We also review the impact of biologic agents on arrhythmic risk as well as cardiovascular morbidity and mortality.

**Key words:** Sudden death; Rheumatoid arthritis; Cardiovascular; QT; Autonomic nervous system; Arrhythmia

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**Core tip:** Patients with rheumatoid arthritis are twice as likely to experience sudden cardiac death (SCD). This excess risk can only partially be explained by the higher rates of heart failure and ischaemic heart disease. Abnormalities of the autonomic nervous system, such as decreased heart rate variability, and abnormalities of ventricular repolarization parameters, such as QTc interval and QT dispersion, have also been implicated. In this article we review the interplay between these parameters and inflammation, exploring whether biologic agents and disease modifying anti-rheumatic drugs may have a role in reducing the burden of SCD.

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## INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory condition which affects 0.8% of the adult population<sup>[1]</sup>. It causes significant morbidity as a result of synovial inflammation, joint destruction, and associated disability. In addition to articular manifestations, there is substantial data demonstrating excess cardiovascular morbidity and mortality in RA<sup>[2,3]</sup>. Studies as early as the 1950s have shown that RA is associated with premature death<sup>[4]</sup>, with 50% of excess deaths being attributed to cardiovascular disease<sup>[2,5]</sup>. Sudden cardiac death (SCD) is estimated to account for 50% of cardiovascular deaths in the general population<sup>[6,7]</sup>. Patients with RA are twice as likely to experience SCD<sup>[8]</sup>, a figure comparable to patients with diabetes mellitus<sup>[9]</sup>. This review will seek to explore the risk factors that make SCD more prevalent in RA, including coronary artery disease (CAD), structural heart disease, electrophysiological abnormalities including myocardial repolarization (QTc interval, QT dispersion) and autonomic dysfunction [heart rate variability (HRV) analysis], and the interplay of inflammation on all these factors<sup>[10]</sup>. We will also review the effect that the new biologic agents may have on the incidence of cardiovascular events and SCD.

## DEFINING SCD AND ITS PREVALENCE IN RA

Sudden death is defined as "non-traumatic, unexpected fatal event occurring within 1 h of the onset of symptoms in an apparently healthy subject. If death is not witnessed, the definition applies when the victim was in good health 24 h before the event"<sup>[11]</sup>. The term SCD is used when a congenital, or acquired, potentially fatal cardiac condition was known to be present during life, or an autopsy has identified a cardiac or vascular anomaly as the probable cause of the event, or no obvious extra-cardiac causes have been identified by post-mortem examination, and therefore an arrhythmic event is a likely cause of death<sup>[11]</sup>. SCD is largely thought to result from fatal arrhythmias, in particular, ventricular tachycardia degenerating to ventricular fibrillation<sup>[12,13]</sup>. Bradyarrhythmia or electromechanical dissociation can also be associated with SCD but these tend to occur in patients with advanced cardiac disease<sup>[12,14]</sup>.

In the general population sudden death accounts for 60% of cardiovascular deaths in those with known CAD<sup>[15]</sup>, and is the first presentation of CAD in 15% of cases<sup>[16]</sup>. Over 70% of fatal arrhythmias are thought to be secondary to CAD<sup>[12]</sup>. These arrhythmias can occur

acutely secondary to direct repolarisation changes occurring during ischaemia, or remotely, typically due to initiation of re-entry circuits within areas of electrically unexcitable scar tissue or diseased myocardium in patients with established myocardial infarction (MI)<sup>[17]</sup>. Dilated and hypertrophic cardiomyopathies account for the second largest number of sudden deaths followed by valvular, congenital, infiltrative, ion-channel disorders which only account for the small remainder<sup>[12,13]</sup>.

Within the RA population, there is a wealth of data regarding the rates of cardiovascular death, however few studies have looked specifically at the epidemiology of SCD. In an inception cohort of 1010 RA patients, Goodson *et al.*<sup>[18]</sup> found an excess of cardiovascular mortality without a corresponding increase in cardiovascular admission rates as compared to controls, suggesting that cardiovascular disease has a higher case fatality in the RA population, or that it often goes unrecognized before the fatal event. Indeed, Solomon *et al.*<sup>[19]</sup> found that the rate ratio for cardiovascular death was highest in young RA adults and those with no known prior cardiovascular events. Whilst Van Doornum *et al.*<sup>[20]</sup> demonstrated that RA patients have a higher 30-d case fatality following MI as compared to controls, 17.6% vs 10.8%. In a large population cohort study of 603 RA patients followed up for 15 years, Maradit-Kremers *et al.*<sup>[5]</sup> demonstrated that RA patients were twice as likely to experience SCD (hazard ratio 1.94, 95%CI: 1.06-3.55)<sup>[8]</sup>, a figure similar to the risk of SCD amongst patients with diabetes mellitus<sup>[21]</sup>. The authors also noted a higher risk of unrecognized MIs and a lower likelihood of angina symptoms, suggesting that CAD manifests differently in RA and is more likely to manifest as cardiovascular death<sup>[8]</sup>. Similarly Mantel *et al.*<sup>[22]</sup> demonstrated that RA is associated with higher risk acute coronary syndromes, higher cumulative incidence of SCD (0.2% vs 0.13% over 3 years), and higher short term case fatality rate at 7 and 30 d. Indeed, certain RA genetic polymorphisms have been linked to premature cardiovascular disease and mortality<sup>[23-26]</sup>, although none with a strong clinical implication<sup>[27,28]</sup>.

## RISK FACTORS FOR SCD IN RA

### **Accelerated CAD, congestive cardiac failure and inflammation**

Whilst there is a higher incidence of ischaemic heart disease (IHD) in RA, several authors have shown that this increased incidence cannot be explained by traditional risk factors alone<sup>[5,29]</sup>, as such there has been growing interest in the role of inflammation as novel risk factor for atherosclerosis<sup>[30]</sup>. Indeed, in the general population, modest increases in C-reactive protein (CRP) have been associated with increased cardiovascular events<sup>[31]</sup>, and RA has been likened to diabetes as a risk factor for CAD<sup>[32]</sup>.

Studies have also suggested different patterns of CAD in RA with chronic inflammation leading to early endothelial dysfunction<sup>[33,34]</sup>, and a higher incidence of unstable plaques attributed to inflammatory cytokines<sup>[35]</sup>. Indeed tumour necrosis factor alpha (TNF- $\alpha$ ) has been implicated in all stages of atherosclerosis including endothelial dysfunction, plaque formation, rupture and promotion of the clotting cascade<sup>[36,37]</sup>. Systemic inflammation has also been associated with dyslipidaemia, impaired glucose metabolism, platelet activation and increased clotting factors<sup>[36]</sup>. However, despite the evidence linking inflammation to accelerated atherosclerosis and IHD, Maradit-Kremers *et al*<sup>[8]</sup> demonstrated that the two-fold risk of SCD seen in the RA population persisted after adjustments for history of hospitalized, or unrecognized, MI, revascularization procedures and cardiovascular risk factors. This suggests that the increased risk of SCD in RA cannot be explained by increased rates of IHD alone<sup>[10,38]</sup>.

In two studies<sup>[39,40]</sup> the excess risk of congestive cardiac failure (CCF) among RA subjects could not be explained by the increased frequency, or effect of, either cardiovascular risk factors, or IHD. In the same cohort, Gabriel *et al*<sup>[41]</sup> demonstrated that whilst 80% of CCF in the general population is attributed to classical CVD risk factors, in RA, classical risk factors only explained 40% of the incident heart failure.

Amongst RA patients experiencing new-onset heart failure, ESR levels were highest in the 6 mo immediately preceding diagnosis, suggesting that ESR may signal the onset of heart failure in patients with RA<sup>[42]</sup>. However, the relationship between SCD and severity of CCF is not as clear-cut as that seen with SCD and IHD, and less is known about RA and CCF. Data from the general population suggests that as left ventricular (LV) systolic function deteriorates, all-cause mortality and the absolute number of sudden deaths increases, but the proportion of deaths due to arrhythmias decreases<sup>[14,43]</sup>. Thus, the degree of LV systolic dysfunction lacks specificity as a predictor of death secondary to cardiac arrhythmias, because it is also powerful measure of the risk of death<sup>[12]</sup>. In line with these results, Nicola *et al*<sup>[44]</sup> found CCF contributed to the excess cardiovascular mortality in RA, primarily through the increased incidence of CCF in RA rather than increased case fatality. Studies have also shown that patients with RA have higher rates of diastolic dysfunction<sup>[45]</sup>, and heart failure with preserved ejection fraction<sup>[46]</sup>.

### **Abnormal ventricular repolarization, autonomic dysfunction and inflammation**

Inflammation, as an independent predictor of cardiovascular mortality and sudden death, has been the focus of recent research<sup>[30,47,48]</sup>. Indicators of abnormal ventricular repolarization such as QTc prolongation, QT interval dispersion, and autonomic dysfunction have

been implicated in the aetiopathogenesis of SCD. The QT interval represents the time from onset of ventricular depolarization (beginning of the Q wave) to completion of repolarization (end of T wave). The corrected QT interval (QTc) estimates the QT at a standardized heart rate of 60 bpm, while QT interval dispersion (QTd) is measure of the dispersion of ventricular repolarization (maximum QT interval - minimum QT interval). In the general population both prolongation of QTc and increased QTd are known risk factors for SCD<sup>[49,50]</sup>, and there is data linking both CRP to prolongation of QTc<sup>[51]</sup> and to SCD<sup>[47]</sup>. In animal models, prolonged QTc is associated with depolarization during phases 2 and 3 of the action potential prior to completion of repolarization<sup>[52]</sup>. These premature action potentials also known as early after depolarizations (EADs) can generate fatal ventricular arrhythmias, such as torsade de pointes, which can progress to ventricular fibrillation and SCD<sup>[12,53]</sup>.

Several studies have also shown an association between RA and prolonged QTc or increased QT dispersion variables, as well as an association between RA disease activity and QTc length<sup>[54-62]</sup> (Table 1), with the strongest evidence available for CRP as a marker of disease activity, compared with clinical scoring systems and ESR<sup>[10]</sup>. Moreover, there is growing evidence from basic science studies demonstrating that pro-inflammatory cytokines, particularly TNF- $\alpha$ , directly prolong cardiomyocyte action potential duration (APD) by regulating ion channels involved in ventricular repolarization<sup>[10]</sup>. In particular, several experimental studies have shown that TNF- $\alpha$  prolongs APD, triggering re-entrant ventricular arrhythmias<sup>[63,64]</sup>. TNF- $\alpha$  prolongs APD by inhibiting both the transient outward potassium current<sup>[65]</sup>, and the rapid delayed-rectifier potassium current<sup>[10,66]</sup>. Similarly, animal studies have shown that the pro inflammatory cytokines IL-1 and IL-6, prolong APD in ventricular myocytes *via* their effects on calcium channels<sup>[67,68]</sup>. Interestingly both levels of CRP<sup>[48]</sup> and levels of soluble TNF- $\alpha$  receptors (sTNFR) are strong and independent predictors of cardiovascular death amongst RA patients<sup>[69]</sup>.

As early as 1998, a cross-sectional study by Gödeli *et al*<sup>[54]</sup>, demonstrated a significant increase in QT dispersion variables when comparing RA patients with matched controls, as well as an increase in complex premature ventricular beats. More recently a large prospective study of 357 RA patients demonstrated that prolonged QTc was a strong predictor of death, with a 50 ms increase in QTc being associated with a doubling of the hazard for all-cause mortality<sup>[60]</sup>. The authors also showed that QTc prolongation was independently associated with CRP levels, and that the association between QTc and mortality was lost after adjustment for CRP, further supporting the role of inflammation in the increased rates SCD seen in this patient group<sup>[60]</sup>. No association was found between QTc and the presence of cardiovascular disease at baseline,

**Table 1 Studies demonstrating associations between rheumatoid arthritis and QT parameters, inflammation and mortality**

Ref.	Design	RA patients	Controls	Impact of RA and QT dispersion (QTd) and QTc	Association between QT parameter, and disease activity/duration (1), arrhythmia (2), autonomic dysfunction (3), mortality (4)
[54]	Cross-sectional	42	42	↑ QTd variables (QTd, QTcD, JTD, JTcD) <i>vs</i> controls No difference in QTc <i>vs</i> controls	(1) ESR, CRP (2) Complex premature ventricular beats
[55]	Cross-sectional	40	48	↑ QTd variables (QTd, QTcD) <i>vs</i> controls	(1) Disease duration
[56]	Cross-sectional	40	40	↑ QTd <i>vs</i> controls	(1) Extra-articular manifestations, erosive disease
[57]	Cross-sectional	58	29	↑ QT <i>vs</i> controls	(1) Secondary Sjögren's syndrome
[58]	Cross-sectional	100	100	↑ QTd <i>vs</i> controls	(1) Disease duration, DAS28, ESR, number of joints involved
[59]	Cross-sectional	25	21 controls 76 with spondylarthopathy	↑ QTc <i>vs</i> controls and those with spondyloarthopathies Infliximab therapy duration inversely correlated to QTc ( $P < 0.01$ )	(1) CRP (3) ↑ QTC associated with ↑ HR, autonomic dysfunction, particularly sympathetic dysfunction as assessed by spectral parameters of heart rate variability
[60]	Prospective cohort	357	-	↑ QTc 10% males (QTc $\geq 450$ ms) and 5.6% of females (QTc $\geq 460$ ms)	(1) CRP (4) Doubled risk of all-cause mortality per 50 ms increase in QTc, (lost after adjustment for CRP) HR = 2.17 (95%CI: 1.21-3.90)
[61]	Retrospective cohort	417	422	↑ % of RA patients with QTc prolongation (> 450 ms males, > 460 ms females) <i>vs</i> controls 20 yr after disease onset (48% <i>vs</i> 38%, $P = 0.004$ )	(1) ESR (4) Any cause QTc prolongation was associated with ↑ all-cause mortality HR = 2.99 (95%CI: 1.93-4.65)
[62]	Prospective cohort	17	-	↑ QTc (> 440 ms) in 76% of patients Tocilizumab associated with 47% ↓ in No. patients with QTc prolongation ( $P = 0.006$ )	(1) CRP and TNF- $\alpha$
[70]	Cross-sectional	117	-		(1) CRP, TNF- $\alpha$ , IL-1 $\beta$ and IL 10 ( QTc BAZ) (1) IL-1 $\beta$ and IL 10, trend towards TNF- $\alpha$ (QTc FHS)

RA: Rheumatoid arthritis; QTd: QT interval dispersion; QTc: Heart-rate corrected QT interval; QTcD: Heart-rate corrected QT interval dispersion; JTD: JT interval dispersion; JTcD: Heart-rate corrected JT interval dispersion; DAS28: Disease activity score in 28 joints; ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein; ms: Milliseconds; QTc BAZ: QTc calculated using Bazett formula; QTc FHS: QTc calculated using Framingham formula.

ECG abnormalities suggestive of myocardial ischemia, LV hypertrophy, or the use of common cardiovascular medications<sup>[60]</sup>. Similarly, Chauhan *et al*<sup>[61]</sup> found a higher incidence of idiopathic QTc prolongation amongst RA patients and demonstrated that any cause QTc prolongation was significantly associated with all-cause mortality (HR = 2.99, 95%CI: 1.93-4.65) but only marginally associated with cardiovascular mortality (HR = 2.68, 95%CI: 0.84-5.6,  $P = 0.09$ ). The authors used a cut off of  $\geq 450$  ms in males and  $\geq 460$  ms in females to define QTc prolongation<sup>[61]</sup>, but interestingly, amongst the general over 55 population even a borderline increased QTc interval, defined as 451 to 470 ms in women, and 431 to 450 ms in men, was associated with a two-fold increase in the risk of SCD<sup>[53]</sup>. Following this, Lazzarini *et al*<sup>[62]</sup> showed that treating RA patients with 3 mo of the anti-IL 6-receptor

antibody, tocilizumab, was associated with a significant reduction in the QTc interval. The fact improvement was seen in such a short time frame suggests that QTc prolongation is driven by an inflammatory process rather than subclinical coronary atherosclerosis<sup>[62]</sup>.

There is also emerging data about the role of pro and anti-inflammatory cytokines in QTc prolongation amongst patients with RA. Lazzarini *et al*<sup>[62]</sup> recently demonstrated a strong association between QTc and circulating TNF- $\alpha$  levels, more so than CRP, although sample sizes were small. Adlan *et al*<sup>[70]</sup> performed a cross-sectional study of 112 patients with RA examining the relationship between QTc and cross-sectional sampling of several pro and anti-inflammatory cytokines. The authors demonstrated an association between QTc prolongation and CRP, TNF- $\alpha$ , IL-1 $\beta$  and the anti-inflammatory cytokine IL-10. A surge of IL-10

often follows the release of pro-inflammatory cytokines and its release is stimulated by adrenaline<sup>[70,71]</sup>.

Sympathetic excitation has been associated with prolongation of the QTc<sup>[72]</sup>, while cholinergic stimulation with pyridostigmine shortens QTc interval in patients with CAD<sup>[73]</sup>. RA has been associated with both reduced parasympathetic tone and increased sympathetic tone, with a recent systematic review demonstrating a 60% prevalence of autonomic dysfunction amongst patients with RA<sup>[52]</sup>. The majority of studies assessed autonomic dysfunction using clinical cardiovascular tests (CCTs) or by measuring HRV parameters<sup>[52]</sup>. CCTs include blood pressure and heart rate response to orthostasis, deep breathing and Valsalva manoeuvres, with many studies using Ewing's battery of CCTs<sup>[74]</sup>. HRV analysis attempts to assess cardiac autonomic regulation through quantification of variation in sino-atrial activity with rapid variations reflecting vagal modulation and slower variations reflecting a combination of both parasympathetic and sympathetic modulation and non-autonomic factors. HRV can be measured using time domain methods or frequency domain methods. Examples of time domain measures include; mean heart rate, AVNN (Average of all the NN intervals, with "NN" used in place of "RR" to emphasize that these are normal sinus beats), and the difference between the longest and shortest NN interval<sup>[75]</sup>. More complex statistically derived time domain measures include either those, derived from direct measurements of the NN intervals, such as SDNN (standard deviation of all NN intervals), SDANN (standard deviation of the average of NN intervals in all 5-min segments of a 24 h recording) or those derived from the differences between NN intervals such as RMSSD (square root of the mean of the squares of the differences between adjacent NN intervals) and pNN50 (percentage of differences between adjacent NN intervals that are > 50 ms)<sup>[75]</sup>. Conversely, frequency domain methods assign bands of frequency, and through fast Fourier transformation quantify the NN interval in each band<sup>[75]</sup>. The bands are typically high frequency (HF) from 0.15 to 0.4 Hz, low frequency (LF) from 0.04 to 0.15 Hz, and very low frequency from 0.0033 to 0.04 Hz. Vagal activity is the major contributor to the HF component with a combination of both sympathetic and parasympathetic activity contributing to the LF and LF/HF ratio<sup>[75]</sup>.

In the general population reduced HRV has been associated with a significantly increased risk of death post MI<sup>[76]</sup>, although as yet there are no studies demonstrating the association between autonomic dysfunction and mortality amongst RA patients. This said, there is data to show that autonomic dysfunction, namely reduced HRV is associated with prolongation of the QTc in patients with RA<sup>[59]</sup>. A study of 100 patients with chronic inflammatory arthritis (CIA) demonstrated that while CRP was independently associated with HRV, there was no association between CRP and QTc in the multivariate model, with HRV parameters and

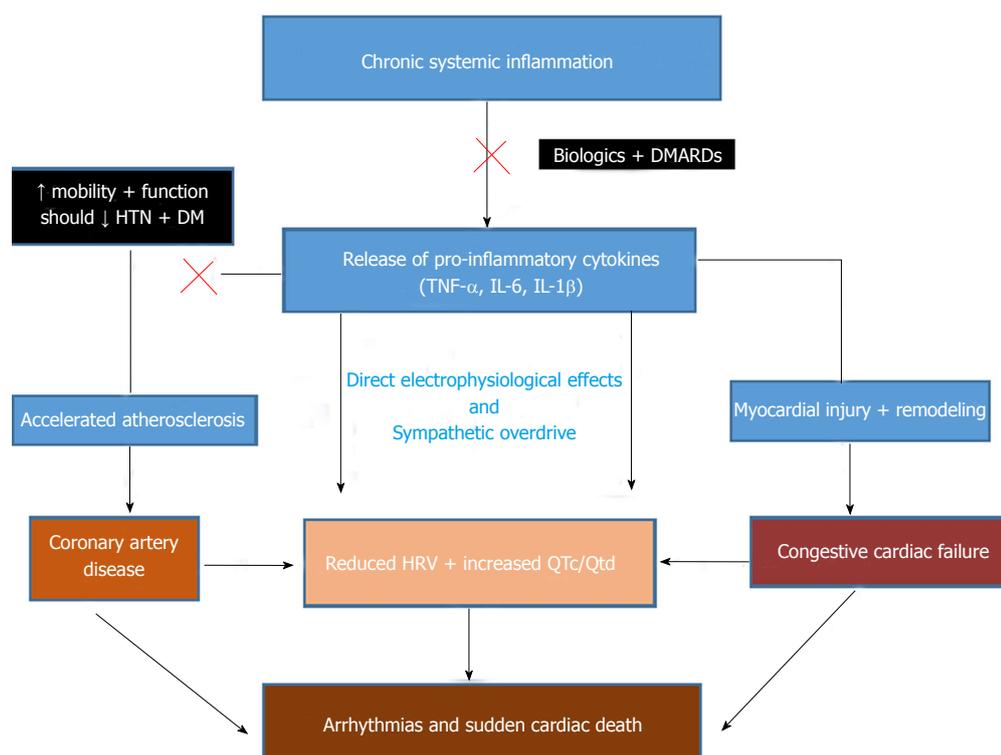
RR interval playing a predominant role in producing differences in QTc among the subjects<sup>[59]</sup>. These findings, together with the evidence that, even after sex-adjustment, QTc was correlated with heart rate and all HRV parameters suggests that the association between CRP and QTc prolongation is most likely an indirect consequence of the autonomic dysfunction and specifically increased sympathetic tone<sup>[59]</sup>. Indeed, there is growing evidence to show that the release of pro inflammatory cytokines in diseases such as RA increases sympathetic outflow activation *via* autonomic centres in brain<sup>[10]</sup>. This represents an adaptive response which dampens immuno-inflammatory activation and inhibits the release of further cytokines *via* stimulation of  $\beta$ 2-adrenoceptors in circulating lymphocytes and monocytes<sup>[77,78]</sup>. This negative feedback loop is known as the inflammatory reflex. However, sympathetic activation does not only affect the immune system, but all the systems throughout the body, and its effects may either directly<sup>[79]</sup>, or indirectly (by prolonging QT interval parameters *via* modification in calcium and/or potassium conductance) trigger the onset of arrhythmias and SCD<sup>[10]</sup>.

## IMPACT OF DISEASE-MODIFYING ANTI-RHEUMATIC DRUGS AND BIOLOGICS ON CARDIOVASCULAR OUTCOMES?

Disease-modifying anti-rheumatic drugs (DMARDs) are a category of otherwise unrelated drugs defined by their use in RA to slow down disease progression. Throughout this review the term DMARD will be used to refer to synthetic DMARDs such as methotrexate, whereas biologic DMARDs will be simply referred to as biologics.

Whilst currently there are no studies specifically evaluating the impact of synthetic DMARDs and biologics on the incidence of arrhythmias and SCD in RA, the European League Against Rheumatism advocate early aggressive treatment with these agents, for the purpose of reducing cardiovascular morbidity and mortality<sup>[3]</sup>. These agents are expected to exert their benefits *via* their direct effect on reducing inflammation, but also by improving joint inflammation and function they will potentially lead to increased levels of physical activity and reduce the incidence of other risk factors such as diabetes mellitus and hypertension<sup>[3]</sup> (Figure 1). Indeed, a prospective cohort study and concurrent literature review conducted by Meek *et al.*<sup>[80]</sup> showed a trend towards reducing cardiovascular case fatality since the advent of DMARDs and biologics. However, no comparison was made to a control population, to ensure that the findings were not just tagging the observed reduction in cardiovascular disease burden, in the general population.

In this section, we will explore whether the advent of DMARDs and particularly Biologics, has indeed reduced cardiovascular mortality and morbidity. We



**Figure 1 Proposed Mechanisms by which biologics and disease modifying anti-rheumatic drugs will reduce the risk of sudden cardiac death in patients with rheumatoid arthritis.** DMARD: Disease modifying anti-rheumatic drugs; HTN: Hypertension; DM: Diabetes; TNF: Tumour necrosis factor; IL: Interleukin; HRV: Heart rate variability; QTc: Corrected QT interval; QTd: QT interval dispersion.

will look closely at the data supporting both the anti-arrhythmic and pro-arrhythmic effects of biologics, as well as their influence on cardiac autonomic dysfunction and repolarisation parameters such as the QTc.

There is growing evidence from observational studies, including observational meta-analyses, to suggest that DMARDs in particular methotrexate<sup>[81,82]</sup> and biologics, particularly TNF inhibitors (TNFi)<sup>[37,83,84]</sup> are associated with decreased cardiovascular mortality and morbidity. To date, the largest meta-analysis has been conducted by Roubille *et al.*<sup>[84]</sup>, and included 28 observational studies, over 200000 RA patients and over 5000 cardiovascular adverse events. The authors found that TNFi were associated with a significant reduction in the risk of all cardiovascular events (CVE) (RR = 0.70,  $P = 0.005$ ), as well as MIs, strokes and major adverse cardiac events. Methotrexate was also associated with a reduction in the risk of all CVEs (RR = 0.72,  $P = 0.007$ ) and MIs. Moreover, a large observational study by Dixon *et al.*<sup>[85]</sup> suggested that patients who responded to TNFi experienced a 70% lower risk of MI than their non-responding counterparts. In addition, a recent retrospective post hoc analysis involving approximately 4000 patients with moderate to severe RA, demonstrated that during tocilizumab treatment, greater reductions in disease activity were inversely associated with future major cardiovascular events, including MIs and cardiovascular death<sup>[86]</sup>.

The lack of randomized controlled trials (RCTs)

specifically examining the impact of biologics and DMARDs on CVE is perhaps explained by the number of patients that would be required to adequately power the studies, and the duration of follow-up that would be needed to detect an effect. Some studies have examined the impact of biologics on surrogate markers of IHD such as carotid intimal thickness and brachial artery flow mediated dilatation with conflicting results<sup>[87]</sup>. A single center RCT conducted by Hsue *et al.*<sup>[88]</sup> demonstrated that depletion of B-cells with rituximab in RA patients improved both macrovascular (brachial artery flow-mediated dilation) and microvascular (reactive hyperemia) endothelial function, despite modest elevation in lipids. There is also an ongoing prospective imaging study, CADERA, bolted onto the single-center VEDERA RCT (very early vs delayed etanercept in RA, NCT 02433184), which will use cardiac MRI to explore the prevalence and change of cardiovascular abnormalities in patients receiving TNF inhibitors vs standard therapy over a 12-mo period<sup>[89]</sup>. The evidence for a link between inflammation and cardiovascular disease is so compelling that 2 RCTS, the Cardiovascular Inflammation Reduction Trial (CIRT) and the Canakinumab Anti-Inflammatory Thrombosis Outcomes Study (CANTOS), have been commenced. CIRT will investigate whether low-dose methotrexate will reduce rates of recurrent MI, stroke, and cardiovascular death among stable post MI patients with type 2 diabetes or metabolic syndrome, two conditions that are associated with an enhanced

inflammatory response (NCT01594333). CANTOS will evaluate whether interleukin-1 $\beta$  inhibition as compared to placebo can reduce rates of recurrent MI, stroke, and cardiovascular death among stable CAD patients who remain at high vascular risk due to persistent elevations of CRP (NCT01327846). In addition, tocilizumab and anakinra have been investigated as treatment for acute MIs with RCTs demonstrating an attenuation in CRP levels, CCF and cardiac remodeling following ST elevation MI<sup>[90,91]</sup>, and attenuation in CRP levels and post percutaneous intervention troponin release following non ST elevation MI<sup>[92]</sup>. There is a further ongoing trial TOCRIVA, which will assess the effects of tocilizumab on cardiovascular risk in RA patients (NCT 01752335).

The relationship between biologics and CCF is more complex and the data is conflicting. In the general population TNF- $\alpha$  levels are increased in CCF<sup>[93]</sup> and associated with severity of clinical signs and symptoms<sup>[94]</sup>. Experimental heart failure models have suggested that TNF inhibitors may improve ventricular dysfunction<sup>[95]</sup>; however, a large clinical trial assessing etanercept in the treatment of congestive heart failure showed no benefit<sup>[96]</sup>, while another one found that high-dose infliximab 10 mg/kg worsened heart failure in patients with moderate-to-severe chronic heart failure<sup>[97]</sup>. Consequently, a "black box" warning was introduced not to use these medications in patients with pre-existing heart failure<sup>[98]</sup>. The most recent data from the United States, which compared 8656 new users of synthetic DMARDs with 11587 new users of TNFi, suggested that TNFi were not associated with an increased risk of hospital admissions due to heart failure (HR = 0.85, 95%CI: 0.63 to 1.14), but identified that such a difference may well have existed prior to the introduction of the black box warning in 2002<sup>[99]</sup>. This study also noted a dose-dependent association between glucocorticoid use and heart failure. Importantly, the authors acknowledged that they were unable to adjust for potential differences in baseline disease severity between the TNFi and synthetic DMARD groups as this information was not collected<sup>[98]</sup>. The German RABBIT registry also reported similar results, with similar rates of heart failure reported in those receiving TNFi compared to those receiving combined synthetic DMARDs as well as a dose-dependent association with glucocorticoids<sup>[100]</sup>. The authors of that study suggested that the overall effect of TNFi is more beneficial than harmful, through improved control of disease activity and reduced need for glucocorticoid. Glucocorticoid use in RA patients has also been associated with a dose dependent increase in all-cause and cardiovascular mortality, at a threshold of 8 mg per day<sup>[101]</sup>. There is less data about the other biologics and CCF but a recent pilot study has shown that 12 mo of treatment with the anti-IL6 tocilizumab significantly increases LV ejection fraction and reduces LV mass index with a concomitant reduction in disease activity<sup>[102]</sup>. As aforementioned anakinra has also been associated with reduced heart

failure following ST elevation MIs<sup>[91]</sup>.

It has been suggested that by suppressing inflammation, biologics may attenuate the autonomic and electrophysiological disturbances that have been linked with SCD and arrhythmic risk amongst patients with RA. Indeed, in a small interventional study of 17 patients with active RA, 76% of which had a prolonged QTc, Lazzarini *et al.*<sup>[62]</sup> demonstrated that tocilizumab was associated with significant shortening of the QTc within a 3 to 6 mo period. This was also correlated with a decrease in both CRP and TNF- $\alpha$  levels. Similarly, Senel *et al.*<sup>[103]</sup> showed a reduction in both QTc interval, and inflammatory markers, amongst patients with Ankylosing spondylitis (AS), following 6 mo of treatment with infliximab. Amongst patient with CIA, infliximab therapy duration has also been shown to be inversely and independently associated with QTc duration<sup>[59]</sup>. Conversely, DI Franco *et al.*<sup>[104]</sup> found no significant difference in QTc interval duration amongst CIA patients treated with TNFi and rituximab. However, the authors did not report on disease activity and thus there may have been a large proportion of patients who did not achieve adequate disease control<sup>[105]</sup>. In the Diana study, 12 wk of treatment with combination synthetic DMARDs or biologics significantly improved cardiac autonomic dysfunction ( $P < 0.05$ ) in both RA and AS patients<sup>[106]</sup>. Inflammatory markers (ESR and CRP) correlated with variables of autonomic neuropathy before and after biologic treatment, suggesting that inflammatory markers may both predict the occurrence of autonomic neuropathy and response to treatment, especially with biologics<sup>[106]</sup>. Infliximab has also been associated with acute changes in HRV consistent with a decrease in sympathetic tone and shift towards relative vagal predominance<sup>[107]</sup>. Additionally, duration of treatment was also found to be correlated to increased HRV and improved cardiac autonomic function<sup>[59]</sup>.

However, the use of biologics is not without risk, and beyond the well-recognized risks of malignancy and infection, there have been reports of cardiac arrhythmias, in some cases life threatening, particularly following the use of anti-TNF monoclonal antibodies and rituximab<sup>[105]</sup>. Case reports have described ventricular arrhythmias<sup>[108,109]</sup>, supraventricular arrhythmias<sup>[110,111]</sup>, and various degrees of heart block<sup>[112-114]</sup>, associated with the use of infliximab, although in one case, the complete heart block did in fact resolve spontaneously<sup>[112]</sup>. It is thought that biologics and in particular TNF inhibiting monoclonal antibodies may be acutely unmasking the inflammation driven myocardial instability that characterizes RA, and other inflammatory conditions<sup>[105]</sup>. They could be doing this in one of three ways; firstly by worsening LV function, secondly by reducing coronary blood flow<sup>[115]</sup>, and thirdly, a mechanism which would be exclusive to monoclonal antibodies, *via* complement-mediated cytotoxic or inflammatory damage to the myocardium<sup>[105,116]</sup>. This is supported by two interesting studies in the literature.

The first, is a case report of 42-year-old AS patient who developed ventricular tachycardia requiring defibrillation following 3 doses of infliximab<sup>[117]</sup>. Despite this, the patient was retreated with infliximab given that there was no evidence of CAD on angiography and his inflammatory markers remained high. Over 2 mo a marked reduction in ventricular arrhythmias was noted with an associated attenuation of inflammatory response. The second study, a prospective, single-blind, crossover study of 75 patients with CIA, demonstrated that during acute infliximab infusion, there was 8% incidence of new-onset ventricular tachyarrhythmia vs 2.7% with placebo (OR = 3.17, 95%CI: 0.61-16.26)<sup>[107]</sup>. Although the difference was not statistically significant, the study was likely underpowered to detect this. Interestingly, those patients that experienced new onset ventricular arrhythmia showed baseline QTc and HRV values that were significantly prolonged and depressed, respectively, as compared to the patients who did not develop ventricular arrhythmia. Translating this into clinical practice, rituximab and monoclonal TNFi should be avoided in patients with significant CV risk factors, known structural heart disease or ECG abnormalities (conduction disease, QTc prolongation and HRV depression). If these drugs are still required, careful ECG monitoring should be performed in the early phases of administration, until disease activity is adequately controlled, to detect and treat any complications<sup>[105]</sup>.

## CONCLUSION

RA is a chronic inflammatory condition, which is associated with significant cardiovascular mortality and morbidity. Data suggests that RA patients are twice as likely to experience SCD compared to the general population<sup>[8]</sup>, a figure comparable to diabetics<sup>[9]</sup>. Whilst some of this excess risk can be explained by the higher rates of heart failure and IHD, thought to be partially triggered and mediated by inflammation, direct influence of inflammatory cytokines on electrophysiological parameters has been implicated in arrhythmogenesis leading to SCD in RA. Interest is growing in examining the interplay between QTc prolongation, autonomic dysfunction and the risk of SCD. Both autonomic dysfunction and QTc prolongation have been shown to be correlated to inflammation, with the best evidence in place for CRP<sup>[10]</sup>. The advent of DMARDs and biologics has improved cardiovascular morbidity and mortality<sup>[37,82]</sup>, with novel evidence demonstrating a direct normalisation effect on repolarization parameters such as QTc<sup>[62]</sup>, as well as improvement in parameters of autonomic dysfunction<sup>[106]</sup>. Randomised controlled trials assessing the impact of DMARDs and biologics on autonomic dysfunction and repolarization parameters, such as QTc or QT dispersion, are urgently required to demonstrate the potential for reduction of SCD in this patient population.

## Key messages

Patients with RA are twice as likely to experience SCD compared to the general population; This excess risk can be partially explained by the higher rates of heart failure and IHD, thought to be partially triggered and mediated by inflammation; Direct influence of inflammatory cytokines and autonomic dysfunction on electrophysiological parameters has been implicated in arrhythmogenesis in this patient group; Biologic agents and disease modifying anti-rheumatic drugs may have a role in reducing the burden of SCD by controlling inflammation.

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## Vascular complications of transcatheter aortic valve replacement: A concise literature review

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### Abstract

Transcatheter aortic valve replacement (TAVR) is a relatively newer therapeutic modality which offers a promising alternative to surgical aortic valve replacement

for patients with prohibitive, high and intermediate surgical risk. The increasing trend to pursue TAVR in these patients has also led to growing awareness of the associated potential vascular complications. The significant impact of these complications on eventual clinical outcome and mortality makes prompt recognition and timely management a critical factor in TAVR patients. We hereby present a concise review with emphasis on diverse vascular complications associated with TAVR and their effective management to improve overall clinical outcomes.

**Key words:** Vascular; Transcatheter; Aortic valve; Concise; Review

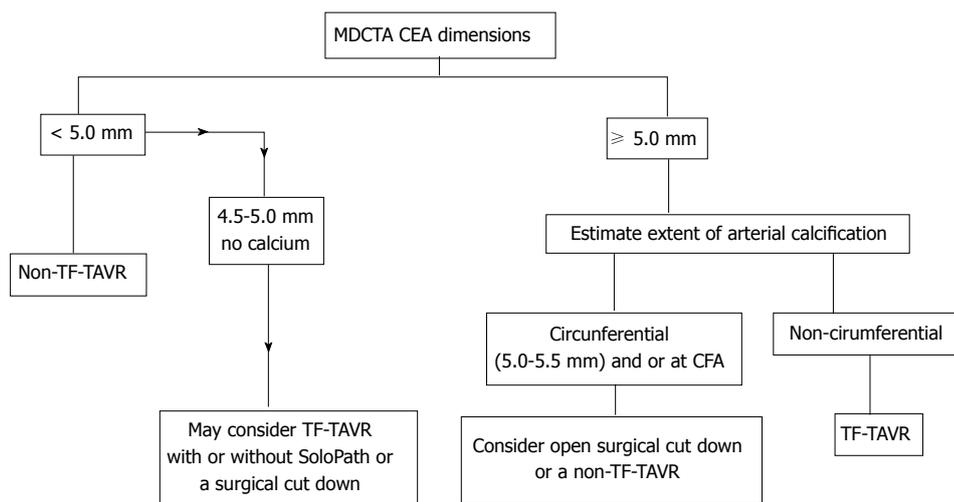
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**Core tip:** Latest review of literature regarding vascular complications of transcatheter aortic valve replacement, optimum access techniques, key technical considerations and potential management strategies have been addressed.

Chaudhry MA, Sardar MR. Vascular complications of transcatheter aortic valve replacement: A concise literature review. *World J Cardiol* 2017; 9(7): 574-582 Available from: URL: <http://www.wjgnet.com/1949-8462/full/v9/i7/574.htm> DOI: <http://dx.doi.org/10.4330/wjc.v9.i7.574>

### INTRODUCTION

Transcatheter aortic valve replacement (TAVR) is an evolving percutaneous valve replacement procedure especially with the new improved low profile sheaths. The most widely used approach for TAVR is retrograde access through a common femoral artery (CFA). Although there is a striking decrease in all-cause morta-



**Figure 1** Schematic representation of trans catheter aortic valve replacement access approach based on common femoral artery dimensions as seen on multidetector computed tomography angiography. TAVR: Transcatheter aortic valve replacement; CFA: Common femoral artery; MDCTA: Multidetector computed tomography angiography. Republished with permission of Sage from Sardar *et al.*<sup>[39]</sup>.

lity and cardiovascular outcomes between TAVR and standard therapy at 5 years in high risk patients<sup>[1]</sup>, there is a significant component of associated major vascular complications such as annular rupture, vessel dissection, major bleeding (16.7%)<sup>[2]</sup>. Analysis of the PARTNER trial showed the rate of major and minor complications as 15.3% and 11.9% respectively which was associated with a higher rate of 30 d and 1 year mortality especially among cohort B<sup>[3]</sup>. In comparison to this historic trend, newer temporal data from the STS/ACC TVT registry has shown a significant decrease in the annual rate of vascular complications to as low as 4.2%<sup>[4]</sup>. Effective management of vascular complications to improve outcomes is of paramount importance as recent studies have shown TAVR to be non-inferior to surgical aortic valve replacement in moderate risk patients<sup>[5]</sup> and that reflects a higher potential patient pool who could benefit from this procedure.

## RISK FACTORS FOR VASCULAR ACCESS

Risk factors associated with increased risk of vascular complications in TAVR include female gender, renal failure, peripheral vascular disease with significant calcification (especially when circumferential) and concomitant peripheral vascular disease. The sheath to femoral artery diameter ratio (SFAR) greater than 1.05 also compounds risk<sup>[6]</sup>. Newer delivery systems such as Edwards SAPIEN XT and S3 decrease the risk as does operator experience and skill<sup>[7]</sup>. The subclavian approach is comparable to transfemoral TAVR<sup>[8]</sup>. Most well-known complication of caval-aortic access is caval-aortic fistula but there is paucity of data regarding vascular complications as this approach is not used commonly.

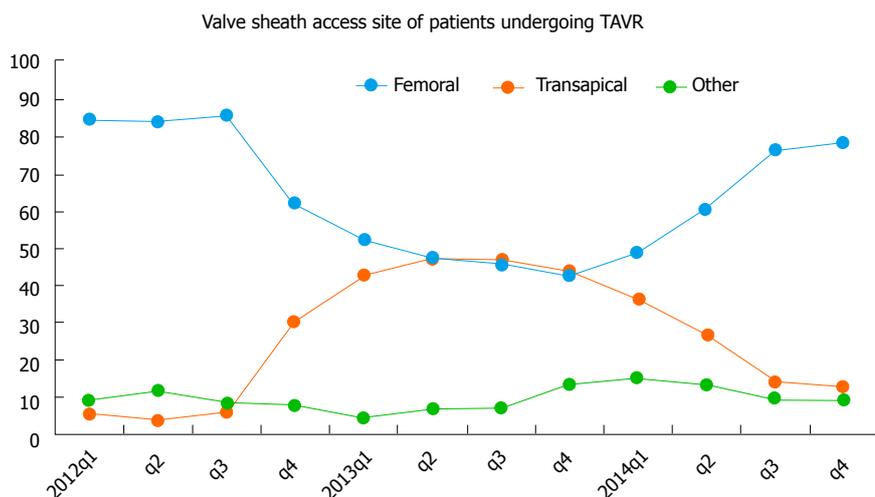
## ACCESS TECHNIQUES

### Femoral

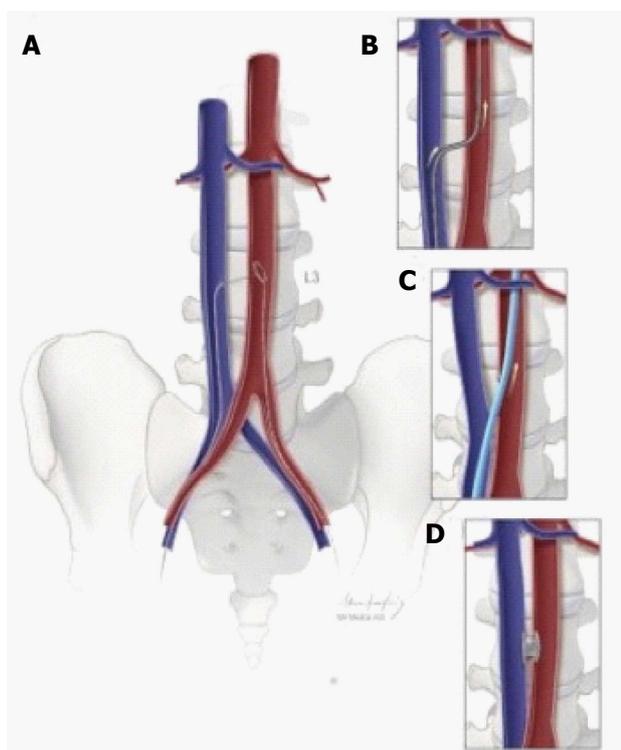
Pre-procedural multidetector computed tomography (MDCT) can help assess CFA calcification, determine the distance from skin to artery, and the vessel diameter, all of which can aid in selecting the optimal vessel entry site. A general schematic for femoral access based on MDCT is outlined in Figure 1. In recent times, there has been a significant surge in transfemoral approach as reflected by TVT registry results (Figure 2). In many centers, TF TAVR is performed using a micropuncture needle and 4 or 5 Fr sheath<sup>[9]</sup> but there is wide variability of approach dependent on an operator.

The micropuncture technique avoids potential large bore needle trauma at an unwanted CFA site (low, high or otherwise suboptimal), which may ultimately culminate in development of vascular complications. Fluoroscopy or ultrasound can be utilized to assist with identification of the appropriate site of entry, although the latter provides greater anatomic detail. A radio-opaque marker (*e.g.*, a hemostat) can be placed on the groin to mark the femoral head, facilitating guidance of needle entry under fluoroscopy. The level of sheath entry relative to the femoral head can be confirmed using fluoroscopy in an antero-posterior (AP) projection and its relation to the superficial-profunda femoral bifurcation ascertained using angiography performed from an ipsilateral oblique projection (*i.e.*, right or left anterior oblique for right- and left-sided access, respectively). B-mode ultrasound can be used as well and may result in less frequent vascular complications and higher first pass access success<sup>[10]</sup>.

Finally, needle puncture may be guided using real time digital subtraction angiography (DSA) or "road mapping" by using contralateral common femoral



**Figure 2** Transcatheter aortic valve replacement vascular access site in the transcatheter valve therapy Registry, 2012 to 2014. The changing valve sheath access site over time has resulted from multiple factors, including FDA instructions for use, and changing technology. TAVR: Transcatheter aortic valve replacement. Republished with permission of Elsevier, from Holmes DR, Nishimura RA, Holmes *et al*<sup>[4]</sup>.



**Figure 3** Schematic depiction of caval-aortic access. A: Using transfemoral venous access, a catheter directs a guidewire from the inferior vena cava toward a snare positioned in the adjacent abdominal aorta; B: The catheter is advanced over the guidewire into the aorta and used to introduce a more rigid guidewire; C: The valve introducer sheath is advanced from the vena cava into the aorta; D: After completion of transcatheter aortic valve replacement, the aorto-caval access tract is closed with a nitinol occluder. Republished with permission of Elsevier from A.B Greenbaum, *J Am Coll Cardiol* 2014; 63: 2795-2804.

access and placing a cross over sheath or catheter in the common or external iliac artery on the side to be accessed. Regardless of the method employed, after confirming appropriate CFA access, the micropuncture sheath can then be exchanged over guidewire to a

larger sheath as required.

### Subclavian

Subclavian access is an alternative option with a prerequisite vessel diameter of greater than 6 mm. Increased angulation, ectasia and calcification are all adverse risk factors. With history of coronary artery bypass grafting and a left internal mammary graft, subclavian vasculature diameter should be greater than 7 mm with no significant atherosclerotic disease and no ostial stenosis to consider it feasible for TAVR access. Surgical cut-down for proper visualization and ease of access is commonly used<sup>[11]</sup>.

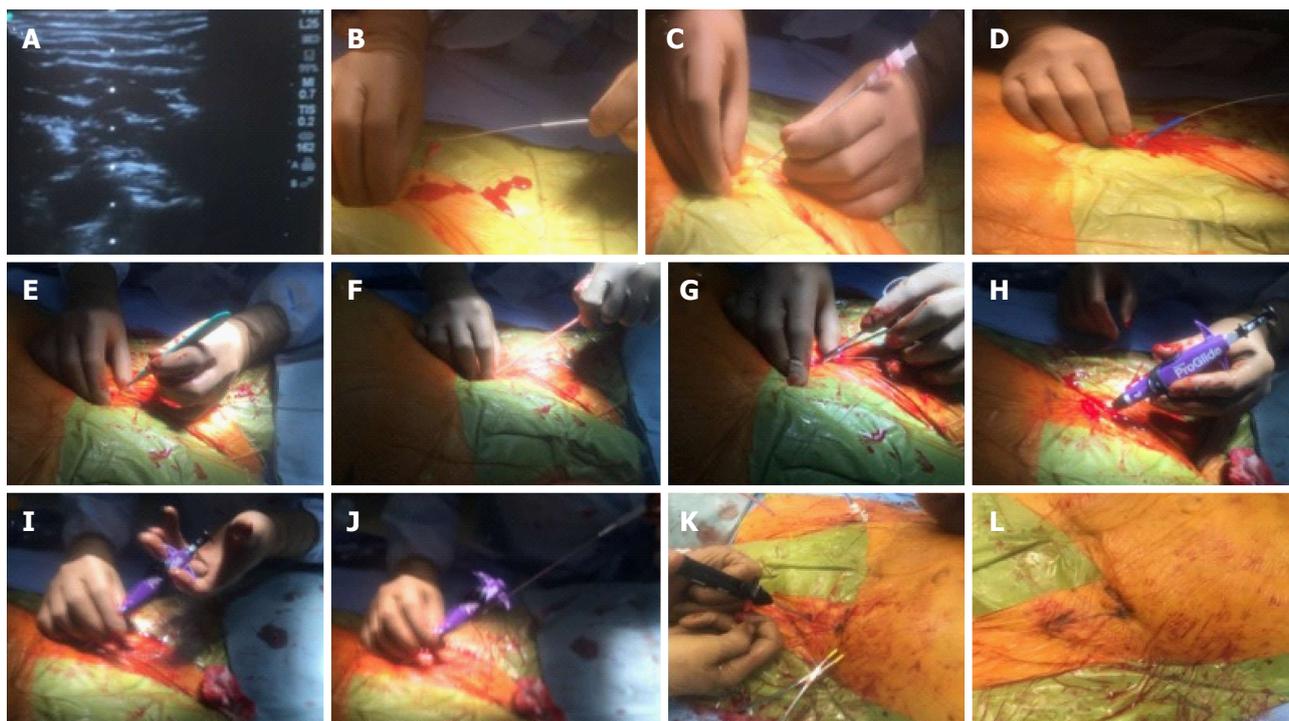
### Caval-aortic

This is an option for TAVR in patients with significant peripheral vascular disease in the femoral and iliac systems thereby limiting arterial access. The caliber and pliability of venous system provides advancement of the delivery system through the femoral vein into the inferior vena cava followed by puncture of the descending aorta and sealing the pathway with a nitinol plug on completion of the procedure<sup>[12]</sup>. A stepwise illustration is provided in Figure 3.

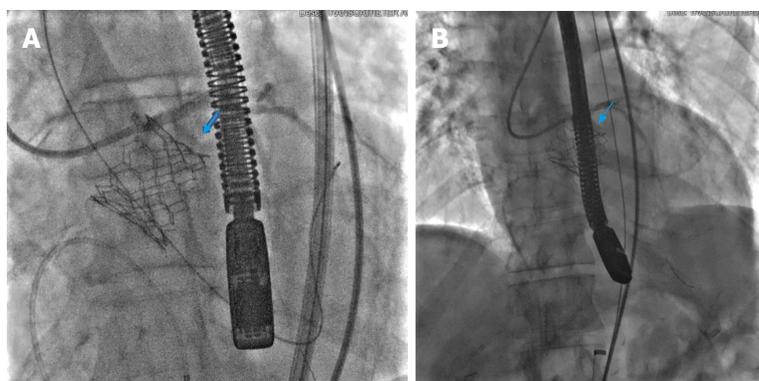
## HEMOSTASIS METHODS

Hemostasis following removal of the sheath is usually achieved with Prostar XL10F and Perclose ProGlide (Abbott Vascular Devices, Redwood City, CA, United States) in which the mechanism of action is a suture release and delivery. This method greatly decreases the incidence of access site complications<sup>[10]</sup>.

The Prostar XL and 6 Fr ProGlide are used for closure of upto 10F and 8F arteriotomies. If the devices are initially used at the time of initial access and sheath placement, hemostasis can be achieved in a more predictable and effective fashion. This is termed as the



**Figure 4** Pre-close hemostasis technique during a transcatheter aortic valve replacement procedure. A-C: A calcium-free zone is visualized using real time ultrasound and access is obtained using a micropuncture needle system; D-G: The micropuncture system is exchanged for a 180 cm 0.035 wire and the skin tract is sequentially dilated with scalpel, 7 F sheath dilator and later a forceps; H: A Proglide is advanced over the wire into the arterial lumen, and return of pulsatile blood flow confirmed; I and J: After ensuring stable Proglide position, two sequential sutures are deployed at 10 and 2 O'clock; K and L: After the removal of transcatheter aortic valve replacement sheath and guide wire, pre-close sutures are sequentially locked to ensure hemostasis.



**Figure 5** Annular rupture post transcatheter aortic valve deployment with the rupture site marked by blue arrows (A, B).

“Preclose” method and is illustrated in Figure 4. After TAVR completion, a 0.035” guidewire is always left in the artery while removing the sheath, to maintain continuous access in case an upstream perforation becomes apparent. Once sufficient hemostasis is achieved, the 0.035 wire can be removed and suture knots locked to ensure complete hemostasis. Occasionally a third Proglide or 8 Fr Angio-Seal (Abbott Vascular, Redwood City, California) can be used to adequately achieve hemostasis if required<sup>[13]</sup>.

Cross over balloon technique (COBT) is an alternative method to achieve hemostasis. COBT involves inflating a balloon above the access site prior to the

retrieval of TAVR sheath and closure of arteriotomy. COBT can be performed over 0.018” or 0.035” guidewires, and the hemostasis balloon can be inflated at low pressure to ensure safe deployment of the suture-mediated closure device<sup>[14]</sup>.

## GUIDEWIRES

There are different guidewires with varying degrees of stiffness and flexibility which can be employed during the TAVR procedure. Wires used for TAVR delivery are usually 0.035” diameter and have an inner core with a tapered distal tip that is easily shapeable to

**Table 1 Traditionally used transcatheter aortic valve replacement guidewires (permission obtained)**

Guidewire	Core material and coating	Wire guide diameter inch	Wire guide length (cm)	Taper length (cm)	Floppy tip length (cm)	Stiffness	Preshaped curve	Use
Amplatz Extra Stiff wire (Cook Medical Inc.)	PTFE-coated stainless steel	0.035	260	7	3	Least stiff	3 cm	TAVR device delivery Straightening of tortuous vessels Sheath insertion
Amplatz Super Stiff wire (Boston Scientific)	PTFE-Coated Stainless Steel	0.035	260	6	3	Stiffer than Extra stiff	1 and 3 cm	Straightening of tortuous vessels Sheath insertion
Lunderquist Extra Stiff wire (Cook Medical Inc.)	PTFE-Coated Stainless Steel	0.035	260 and 300	7.5	4	Stiffer than Amplatz extrastiff and superstiff	4 cm	Straightening of tortuous vessels Sheath insertion
Safari Guide wire (Boston Scientific)	LUBRIGREEN™ PTFE-Coated Stainless Steel	0.035	260 and 300			Stiffness equal to Amplatz extrastiff	Small curve - 16 cm distal grind and 1.7 inch/4.25 cm curve Large curve - 18 cm distal grind and 1.9 inch/4.90 cm curve	TAVR device delivery

TAVR: Transcatheter aortic valve replacement; PTFE: Polytetrafluoroethylene.

facilitate steerability. Length is usually in the range of 260 cm and some are coated to reduce resistance to minimize vessel trauma during catheter and device exchange in TAVR procedures. One should be wary of the fact that verbal description of guidewires does not co-relate with actual wire stiffness. Objective parameters such as “flexural modulus” co-relate well with wire stiffness and are more reliable as shown by Harrison et al in a retrospective analysis<sup>[15]</sup> rather than market terminology such as “super stiff” or “extra stiff”. If higher stiffness is required as in cases with significant vessel tortuosity, a pig tail curve is typically placed at the distal tip of the wire to prevent vascular or left ventricular trauma. Table 1 shows important characteristics of guidewires commonly used during TAVR.

## TAVR DEVICES

Balloon-expandable Edwards SAPIEN S3 and Edwards SAPIEN XT™ valves (Edwards Lifesciences Inc., Irvine, CA) and the self-expanding Medtronic CoreValve® Evolut™ R System valves (Medtronic, Minneapolis, MN) are United States Food and Drug Administration (FDA)-approved TAVR devices which are being used nowadays. Core Valve and Edwards Sapien S3 have a range of 23-32 mm and 20-29 mm valve size respectively with sheath size either 14 or 16 French. Currently there are two CE mark approved TAVR devices, the Lotus™ valve system (Boston Scientific Corporation,) available in 23, 25 and 27 mm sizes and the Portico Valve (St. Jude Medical, Minneapolis, Minnesota), available in 27 and 29 mm sizes<sup>[16]</sup>.

## SHEATHS

The risk of vascular trauma increases with bigger sheath sizes and has shown a downward trend with the new generation TAVR delivery systems<sup>[17]</sup>.

Older generation Edwards SAPIEN and SAPIEN XT valves required up to 24 Fr and 20 Fr sheaths, respectively, while the first Medtronic CoreValve required up to a 25 Fr sheath. Newer generation valves require 14-16 Fr sheaths.

The SoloPath sheath (Terumo Medical Corporation, Irvine, CA, United States) is a balloon expandable and re-collapsible sheath, available in various internal diameters/outer diameters of 14/17, 16/19, 18/21, 19/22, 20/23 and 21/24 Fr, in working lengths of 25 and 35 cm, and balloon expandable lengths of 20 and 30 cm respectively. The sheath is inserted into the vessel in a folded state over a balloon-expandable dilator. Once the sheath is in the desired position, the dilator is inflated, the sheath expands, and later dilator is removed. Upon completion of the procedure, balloon is deflated and sheath returns to its original OD. The safety and efficacy of the 19F SoloPath sheath was investigated for TF-TAVR in a single arm study of 90 patients. When patients were dichotomized into those with a sheath to femoral artery ratio (SFAR) of  $\leq 1.05$  vs  $> 1.05$ , the 19 F Solopath sheath appeared feasible and safe even in patients with SFAR  $> 1.05$  (a traditional indicator of increased vascular risk) and there was no difference in technical or procedural success, total vascular complications, or total bleeding rates between groups<sup>[18]</sup>. The safety of the SoloPath access sheath was confirmed in a recent multicenter

**Table 2 Internal and external diameter of large percutaneous sheaths (permission obtained)**

Manufacturer	Sheath	Sheath internal diameter (F)	Sheath outer diameter (mm)/ prosthesis size	Minimum vessel diameter (mm)
Edwards Lifesciences	RetroFlex 3 introducer sheath	22	8.4/23 Sapien	7.0
		24	9.2/26 Sapien	8.0
	NovaFlex introducer sheath	16	6.7/23 Sapien XT	6.0
		18	7.2/26 Sapien XT	6.5
		20	8.0/29 Sapien XT	7.0
	Expandable Sheath <sup>1</sup>	14	6.0/20	5.0
		14	6.0/23	5.5
14		6.0/26	5.5	
16		6.7/29	6.0	
Medtronic	InLine Sheath for Evolut R System <sup>1</sup>	14 F equivalent <sup>2</sup>	6.0	5.0
Gore medical	GORE® DrySeal Sheath <sup>1,3</sup>	14	5.5	5.0
		16	6.2	5.5
		18	6.8	6.0
		20	7.5	6.0
Terumo medical corporation	SoloPath sheath <sup>1,3</sup>	14 <sup>4</sup>	3.83 <sup>5</sup> /5.67 <sup>4</sup> (11.5-17F)	
		16 <sup>4</sup>	5.0 <sup>5</sup> /6.33 <sup>4</sup> (15-19F)	
		18 <sup>4</sup>	5.0 <sup>5</sup> /7.0 <sup>4</sup> (15-21F)	
		19 <sup>4</sup>	5.0 <sup>5</sup> /7.3 <sup>4</sup> (15-22F)	

<sup>1</sup>Currently used introducer or delivery sheath for TAVR. <sup>2</sup>Internal dimension is 14 Fr-equivalent systems with InLine™ Sheath. True outer diameter of the sheath is 18 Fr/6 mm. <sup>3</sup>Most commonly used sizes for TAVR. <sup>4</sup>Expanded internal and external dimensions of the sheath. <sup>5</sup>Unexpanded or folded SoloPath sheath dimension. TAVR: Transcatheter aortic valve replacement.

study of patients with  $\leq 5.0$  mm ilio-femoral access undergoing TF-TAVR using the CoreValve device<sup>[19]</sup>. A detailed list of different access sheaths used during TAVR is given in Table 2.

## ACCESS SITE INFECTION

There are variable reports of access site infection after TF-TAVR, ranging from 1.6% to 12.1% with 90% of access site infections encountered after surgical cut down with a 10% associated mortality<sup>[20]</sup>. In many practices, all patients undergoing TAVR are pretreated with broad spectrum antibiotics and the access site skin incision is closed with a topical skin adhesive. It provides a flexible microbial barrier with wound support that may prevent infection better than traditional wound dressings<sup>[21]</sup>.

## ACCESS SITE HEMATOMA

Hematomas at point of access can occur ranging from a few minutes to days following completion of TAVR procedure. Careful attention must be paid to the access site as the ideal point is the mid femoral head above the femoral bifurcation. Prolonged hospital stay as well as increased morbidity and mortality are potential associations<sup>[22]</sup>. The occurrence has continued to decrease due to enhanced center experience, operator skill and smaller delivery systems over the last few years. Manual pressure and anti-coagulation reversal is sufficient for successful management in majority of cases. In case of compressive symptoms or profound blood loss indicated by rapid drop in hemoglobin, contralateral femoral access with balloon tamponade

is usually employed. Viabahn covered stent placement (W.L. Gore and Associates, Newark, DE) has been shown to co- relate with an efficacy of 98%<sup>[23]</sup>.

## PSEUDOANEURYSMS

Pseudoaneurysm (PSA) is a contained rupture can occur with arterial puncture below the femoral bifurcation involving superficial or deep femoral arteries or the iliac system<sup>[24]</sup>. The frequency of pseudoaneurysm ranges from 2%-6%. PSA can thrombose spontaneously in upto 90% of cases at 3 wk if the size is less than 3 cm<sup>[25]</sup>. Size greater than 2 cm along with aggressive anticoagulation are potential predisposing risk factors and can lead to persistent discomfort and act as nidus of infection to increase risk of septic embolism<sup>[26]</sup>. Rupture can occur with devastating consequences with major bleeding and hypovolemic shock and diameter greater than 3 cm potentiates the possibility<sup>[27]</sup>.

Palpation of a pulsatile mass at the access site or the auscultation of a systolic bruit are suggestive of a possible PSA. For diagnostic purposes, doppler ultrasound has a 94% sensitivity and 97% specificity for PSA<sup>[28]</sup>.

Usually a 5-7 MHz frequency probe is used and the depth should be greater than 4 cm from the skin. Color Doppler shows a turbulent flow pattern in the PSA tract and pulse Doppler shows constant flow shift towards and away from the probe which is diagnostic. Ultrasound guided compression when used has a success rate of 30%-70%. Multiple attempts are mostly needed to obtain sustained compression and thrombosis with a mean time of 33 min<sup>[29,30]</sup>. Ultrasound guided thrombin injection is an effective treatment

modality with a 97% success rate. It facilitates the conversion of fibrinogen to fibrin<sup>[31]</sup>. Injections are usually given in incremental doses of 0.2-0.4 mL till no flow is observed on the pulse Doppler.

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## ILEO-FEMORAL DISSECTION

Ileo-femoral dissection in transfemoral TAVR has an incidence of approximately 7% even in high volume centers. External iliac artery is the most commonly involved vessel and can occur during initial advancement of the delivery system or during sheath withdrawal.

Diagnosis can be made with careful review of DSA with either retrograde or contralateral antegrade contrast injections. Significant dissections can lead to lower limb ischemia which can be critical or subcritical depending on the spread of dissection and the vessel territory involved. This can predispose to thrombus formation and vessel occlusion or compression symptoms with blood extravasation.

Computed tomographic angiography (CTA) with distal runoff can be used to identify the focus of dissection.

Contained dissections can be managed by careful monitoring as mostly they resolve on their own with course of time. In case of extensive dissections, endovascular repair can be pursued. Ballooning alone with appropriate stent placement as needed is the preferred approach. Balloon inflation can tamponade the bleeding site and in addition maintenance stents are used for vessel patency. If the dissection is unable to be sealed with this modality, surgical repair is required. Follow up imaging with CTA as indicated can be used<sup>[32]</sup>.

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## ILEO-FEMORAL RUPTURE

Ileo-femoral rupture is another feared complication of TAVR but the occurrence has decreased significantly with the use of smaller and compact delivery systems as compared to initial TAVR procedures when the frequency was roughly 4%. As long as the sheath is in place, pelvic vascular rupture is not evident but as soon as the sheath is withdrawn, the pressure seal is taken off and huge pelvic bleed can occur with rapid clinical deterioration and death<sup>[33]</sup>.

During the sheath withdrawal, the patient's clinical status should be monitored closely. Sudden hemodynamic compromise may be evident if there is a significant defect although small tears can extend and cause clinical instability within a few hours post procedure. Angiography prior to complete sheath removal is usually performed to assess for any focal dissection or to detect any extra-luminal contrast flow.

Management includes quick sheath reintroduction to seal the site of dissection while contralateral balloon delivery and inflation can be attempted. Massive fluid repletion, quick anticoagulation reversal and

covered stent placement is required although in cases of complex dissections, surgical intervention is indicated<sup>[34]</sup>.

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## ARTERIAL AVULSION

In cases of extensive atheromatous and calcified vessels, vessel avulsion can rarely occur during sheath withdrawal. Urgent proximal occlusive balloon placement and prompt surgical intervention needed in his scenario<sup>[35]</sup>.

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## ARTERIAL STENOSIS, THROMBOSIS AND OCCLUSION

CFA stenosis can occur following device closure of the arteriotomy site. If there is evidence of significant flow limitation, angioplasty can be done to reduce the stenosis. In cases of arterial thrombosis and occlusion, critical limb ischemia can occur and thrombectomy is needed to restore vessel patency.

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## AORTIC DISSECTION

Aortic dissection is an uncommon but potentially fatal complication of TAVR procedure, Incidence has been reported in the range of 0.6%-1.9%<sup>[36]</sup>.

As the access approach varies from transfemoral and transapical to transaortic, any segment can be involved including the ascending or descending aorta. In a study of 412 patients reported by Lange *et al*<sup>[37]</sup> who were treated with transapical and transfemoral approach, annular and abdominal aortic rupture occurred in four patients. Generally, continuous transesophageal monitoring is done throughout the procedure, and Type A dissections can be diagnosed promptly. If aortic dissection is suspected post procedure, aortic angiography is pursued.

The clinical manifestation of aortic dissection may manifest at any time during or after the procedure. Symptoms vary from chest pain and abdominal pain to neurological deficits depending on the extent of involvement (mesenteric, renal, carotid arteries). Clinically, hypotension and pressure difference of greater than 20 mmHg between the arms can be suggestive. Imaging modalities such as computed tomography, magnetic resonance imaging and transesophageal echocardiography (TEE) can be used depending on availability and the complexity of the clinical scenario.

The management of aortic dissection depends on initial site of dissection, extent and vascular compromise. Strict blood pressure control with systolic less than 110 mmHg by using beta blocker with alpha blocking additive effect such as Labetalol or Carvedilol is preferred. Non-dihydropyridine calcium channel blockers can be used as well. In case of hypotension, volume repletion is done to maintain mean arterial

pressure of greater than 70 mmHg. Type A dissections should be treated with prompt surgical repair while Type B dissections are medically managed and uncommonly endovascular repair is considered<sup>[38]</sup>.

## AORTIC RUPTURE

Aortic rupture is a dreaded, rare complication with extremely poor prognosis. It has an incidence of less than 1%. Commonly the presentation is acute with rapid hemodynamic instability and circulatory shock. The rupture extends quickly along tissue planes and hemorrhagic tamponade can be seen on TEE quite frequently. Infrequently, there is a subacute clinical picture as the initial aortic tear takes time to extend and manifest clinically. The mechanisms includes trauma by the device catheter if it overshoots the guidewire or forceful attempts made to manoeuvre the catheter through vessels with steep angulation and tortuosity. It can be spotted on fluoroscopy at the time of valve deployment as shown in Figure 5. There should be an extremely low threshold of suspicion in TAVR patients with even mild hemodynamic instability as prompt intervention with open surgical or endovascular approach with covered stents is needed to stabilize or repair the ruptured focus. The overall prognosis is strikingly dismal even in skilled hands as rupture extension can take place exponentially with dramatic reduction in chances of recovery.

## CONCLUSION

TAVR has certainly evolved exponentially since its initial days. Improved device profiles, equipment design and operator expertise are major factors which have significantly improved success rates by reducing possible procedure complications. Nonetheless continuing awareness, meticulous technique, timely management and availability of even better delivery systems in the future would be the key to better clinical outcomes.

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## Peripheral interventions and antiplatelet therapy: Role in current practice

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### Abstract

Peripheral arterial disease (PAD) is a common disorder associated with a high risk of cardiovascular mortality and continues to be under-recognized. The major risk factors for PAD are similar to those for coronary and cerebrovascular disease. Management includes exercise program, pharmacologic therapy and revascularization including endovascular and surgical approach. The optimal revascularization strategy, endovascular or surgical intervention, is often debated due to the paucity of head to head randomized controlled studies. Despite significant advances in endovascular interventions resulting in increased utilization over surgical bypass, significant challenges still remain. Platelet activation and aggregation after percutaneous transluminal angioplasty of atherosclerotic arteries are important risk factors for re-occlusion/restenosis and life-threatening thrombosis following endovascular procedures. Antiplatelet agents are commonly prescribed to reduce the risk of myocardial infarction, stroke and death from cardiovascular causes in patients with PAD. Despite an abundance of data demonstrating efficacy of antiplatelet therapy in coronary artery disease and cerebrovascular disease, there is a paucity of clinical information, clinical guidelines and randomized controlled studies in the PAD population. Hence, data on antiplatelet therapy in coronary interventions is frequently extrapolated to peripheral interventions. The aim of this review article is to elucidate the current data on revascularization and

the role and duration of antiplatelet and anticoagulant therapy in re-vascularized lower limb PAD patients.

**Key words:** Peripheral arterial disease; Peripheral vascular disease; Antiplatelet therapy; Revascularization

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**Core tip:** Peripheral arterial disease (PAD) is nearly a pandemic disorder which carries a high morbidity and mortality. Treatment includes risk factor modification, revascularization whenever feasible and medical management including antiplatelet therapy being a crucial element. Despite improvements in endovascular techniques and equipment for revascularization in PAD patients, current data regarding antiplatelet therapy in this population is limited. Our objective is to consolidate the current data on role and duration of antiplatelet and anticoagulant therapy in re-vascularized lower limb PAD patients.

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## INTRODUCTION

Peripheral arterial disease (PAD) represents a major clinical problem affecting millions of people worldwide, which carries high morbidity and mortality and an increased risk of major adverse cardiovascular events including myocardial infarction (MI), stroke, premature death and impaired quality of life. The incidence of PAD is globally estimated to be between 3% and 12%<sup>[1-3]</sup>. This incidence has increased to as high as 29% in low to middle income areas, becoming one of the global problems of the 21<sup>st</sup> century<sup>[4]</sup>. Atherosclerosis in the peripheral arteries is a chronic, slowly developing disorder causing narrowing of the arteries. Depending on the degree of narrowing, clinical presentations vary from classic intermittent claudication, exercise limitations, or ischemic pain, to lower extremity ulceration or gangrene of the toes from chronic limb ischemia. Other patients found to have PAD from ankle brachial index (ABI) screening can remain asymptomatic throughout their life. Occasionally, acute events occur, frequently associated with thrombosis, embolism and/or major arterial occlusion.

Therapy for PAD includes both a pharmacologic and revascularization approach if possible. Antiplatelet therapy is the cornerstone of pharmacologic therapy in addition to risk factor reduction. The purpose of this paper is to discuss revascularization strategies and review clinical trial data for antiplatelet therapy in

patients with PAD.

## REVASCULARIZATION STRATEGY: ENDOVASCULAR THERAPY VS SURGICAL BYPASS

The optimal treatment strategy, endovascular or surgical intervention, is often debated due to the lack of head to head randomized controlled studies. Of the studies conducted, most are underpowered and lack uniform endpoint definitions making a direct comparison among studies difficult<sup>[5]</sup>.

Remarkable advancement in technology in the past decade has shifted the paradigm of revascularization strategies in PAD from an open surgical approach to percutaneous endovascular treatments including percutaneous atherectomy, percutaneous transluminal angioplasty (PTA) and stenting. Analysis conducted by Goodney *et al*<sup>[6]</sup>, provides statistical evidence based on Medicare claims between 1996 and 2006 that endovascular interventions are now performed more commonly than bypass surgery. The rate of major lower extremity amputation declined significantly more than 25% and endovascular interventions increased more than threefold [138 to 455 per 100000; relative risk (RR) = 3.30; 95%CI: 2.9-3.7], while surgery decreased by 42% (219 to 126 per 100000; RR = 0.58; 95%CI: 0.5-0.7)<sup>[6]</sup>. However, caution must be used to interpret this data as more research is warranted to determine if there is an association between lower extremity vascular procedures and improved rates of limb salvage in this population.

The BASIL trial was first published in 2005 followed by an intention-to-treat analysis published in 2010 evaluating amputation-free survival and overall survival. This was a prospective randomized controlled trial comparing the effectiveness of endovascular therapy vs open surgical approach in patients with severe limb ischemia due to infra-inguinal disease. Similar short term outcomes were found comparing both treatment modalities<sup>[7,8]</sup>. However, data also suggests that the results of angioplasty are less durable than that of surgical grafting. The primary patency rate after angioplasty is greatest for lesions in the common iliac artery and decreases distally. Additionally, the rates of patency are lower in cases with increasing lesion length, multiple and diffuse lesions, poor-quality run-off and in patients with concomitant diabetes and renal failure<sup>[9]</sup>.

The BEST-CLI trial is currently underway and designed to clarify this clinical conundrum for critical limb ischemia patients. This is a multi-center trial with a planned enrollment of 2100 patients that includes interventional cardiologists, interventional radiologists and vascular surgeons. The trial emphasizes a team based treatment approach and will compare patients eligible for both endovascular and open surgical bypass. All contemporary endovascular therapeutic modalities

**Table 1 Results of clinical trials initially designed for patients with coronary artery disease, with subgroup analysis in peripheral arterial disease**

Clinical trial	No. of patients	Patient population	Drugs studied	Primary end point	Outcomes
PEGASUS TIMI-54 subgroup analysis <sup>[40]</sup> (2016)	1143	CAD and concomitant PAD	Ticagrelor 90 mg BID + aspirin <i>vs</i> Ticagrelor 60 mg BID + aspirin <i>vs</i> Placebo + aspirin	Cardiovascular death, MI and stroke  Acute limb ischemia and peripheral revascularization for ischemia	15.2% in ticagrelor (pooled group) and 19.3% in placebo. ARR 4.1% in ticagrelor (pooled group) 60 mg dose more beneficial (ARR of 5.2%)  0.46% in ticagrelor (pooled group) and 0.71% in placebo (HR 0.65; 95%CI: 0.44-0.95; <i>P</i> = 0.026)
PLATO-subgroup analysis <sup>[32]</sup> (2015)	1144	CAD and concomitant PAD	Ticagrelor <i>vs</i> clopidogrel	Cardiovascular death, MI and stroke	18% in ticagrelor group and 20.6% in clopidogrel group (HR: 0.85; 95%CI: 0.64-1.11; <i>P</i> = 0.99)
TRA 2P-TIMI 50 <sup>[35]</sup> (2012)	26449	Previous history of MI or ischemic stroke within the previous 2 wk-12 mo or PAD	Vorapaxar <i>vs</i> placebo	Cardiovascular death, MI, and stroke	9.3% in vorapaxar group and 10.5% in placebo ( <i>P</i> < 0.001)  Subgroup analysis in PAD patients showed no difference between groups for the primary endpoint Rate of intracranial hemorrhage (1% vorapaxar <i>vs</i> 0.5% placebo; <i>P</i> < 0.001) 6.8% in clopidogrel plus aspirin group and 7.3% in aspirin group ( <i>P</i> = 0.22) Subgroup analysis in PAD patients: no benefit was derived from dual antiplatelet therapy
CHARISMA <sup>[38]</sup> (2006)	15603	Patients with either clinically documented vascular disease or risk factors for atherothrombotic disease	Aspirin plus clopidogrel <i>vs</i> aspirin monotherapy	MI, stroke or cardiovascular death	6.8% in clopidogrel plus aspirin group and 7.3% in aspirin group ( <i>P</i> = 0.22) Subgroup analysis in PAD patients: no benefit was derived from dual antiplatelet therapy
CAPRIE <sup>[15]</sup> (1996)	19185	Recent MI, recent ischemic stroke or symptomatic PAD	Aspirin <i>vs</i> clopidogrel	MI, stroke and vascular death	RRR of 8.7% clopidogrel group ( <i>P</i> = 0.043; 95%CI: 0.3-16.5) Subgroup analysis in PAD patients: 23.8% RRR in clopidogrel over aspirin ( <i>P</i> = 0.0028; 95%CI: 8.9-36.2)

MI: Myocardial infarction; PAD: Peripheral arterial disease; ARR: Absolute risk reduction; RRR: Relative risk reduction.

and surgical bypass conduits will be compared and chosen by enrollment site and physician preference. The revascularization strategy will be selected for each case in a specialized vascular center in close cooperation with an endovascular specialist and a vascular surgeon<sup>[10]</sup>.

## ANTIPLATELET THERAPY

Platelets have a fundamental role in the development of atherothrombosis<sup>[11]</sup>. Although percutaneous revascularization therapies have evolved significantly with dramatic improvement in interventional devices and techniques, the most appropriate antiplatelet therapy regimen in PAD is understudied compared to the coronary artery disease (CAD) population. Multiple antiplatelet agents have been studied in the PAD population, including aspirin, the combination of aspirin and dipyridamole, clopidogrel, ticagrelor, cilostazol and vorapaxar. Results from randomized clinical trials in patients with CAD and subgroup analysis in the PAD population and PAD alone are summarized in Tables 1 and 2 respectively. Given the number of agents studied, there is a wide discrepancy in the management of patients with PAD. Meta-analysis conducted by the Antithrombotic Trialists Collaboration Group in 2002 evaluated 287 randomized studies, and concluded that antiplatelet therapy reduced the risk of

serious vascular events (non-fatal MI, non-fatal stroke, or vascular death) by about 23%, not just among the population with unstable angina, acute MI or stroke but also among patients with CAD, PAD, and those at high risk of embolism<sup>[12]</sup>.

## ASPIRIN

Aspirin is a commonly used antiplatelet agent, which irreversibly inhibits the cyclooxygenase-1 and 2 enzymes resulting in decreased formation of thromboxane A<sub>2</sub>, thus inhibiting platelet aggregation. However, compelling evidence to support a reduction in cardiovascular events in the setting of PAD is lacking<sup>[12]</sup>. In a meta-analysis published by Berger *et al.*<sup>[13]</sup> in 2009, 18 trials comprising 5269 participants with PAD were evaluated. Cardiovascular events occurred at a rate of 8.9% (251/2823 subjects) in the aspirin or aspirin plus dipyridamole group and 11% (269/2446 subjects) in the control group (95%CI: 0.76-1.04). This finding was a 12% relative risk reduction in non-fatal MI, non-fatal stroke and cardiovascular death with aspirin, but it failed to reach statistical difference<sup>[13]</sup>. Despite these results, aspirin (dose 75-325 mg) is given a class I recommendation in the 2016 AHA/ACC PAD guidelines for management of symptomatic patients largely due to benefit of aspirin in other vascular diseases<sup>[3,14]</sup>.

**Table 2** Results of clinical trials designed for patients with peripheral arterial disease

Clinical trial	No. of patients	Patient population	Drugs studied	Primary end point	Outcomes
COMPASS <sup>[44,45]</sup> (2017)	27402	Peripheral arterial disease or coronary artery disease	Rivaroxaban plus aspirin or rivaroxaban alone <i>vs</i> aspirin alone	Myocardial infarction, stroke, CV death and the time from randomization to the first occurrence of major bleeding	Preliminary results: Trial stopped prematurely. One of rivaroxaban arms proved to be superior to aspirin alone No disclosed information on the primary bleeding endpoint or the regimen that showed superiority to aspirin alone
EUCLID <sup>[41]</sup> (2016)	13885	PAD (ABI $\leq$ 0.80 or prior (> 30 d) revascularization of the lower extremities)	Ticagrelor <i>vs</i> clopidogrel	CV death, MI, or ischemic stroke	10.8% in ticagrelor group <i>vs</i> 10.6% in clopidogrel group ( $P = 0.65$ )
MIRROR <sup>[39]</sup> (2012)	80	PAD treated with endovascular therapy	Dual antiplatelet therapy (aspirin plus clopidogrel) <i>vs</i> aspirin monotherapy	Local concentrations of platelet activation markers $\beta$ -thromboglobulin and CD40L	Reduced peri-interventional platelet activation and improved functional outcome in the dual antiplatelet therapy group
Berger <i>et al</i> <sup>[13]</sup> (Meta-analysis-2009)	5269	PAD (patients with claudication, those undergoing percutaneous intervention or bypass surgery, and asymptomatic patients with an ABI of 0.99 or less)	Aspirin or combination of aspirin plus dipyridamole <i>vs</i> placebo	Composite end point of non-fatal MI, nonfatal stroke, and CV death	8.9% in aspirin or combination of aspirin and dipyridamole, 11% in placebo (95%CI: 0.76-1.04)
WAVE <sup>[43]</sup> (2007)	2161	PAD (atherosclerosis of the arteries of lower extremities, carotid arteries or subclavian arteries)	Antiplatelet agent plus oral anticoagulant <i>vs</i> antiplatelet therapy in patients with PAD	CV death, MI and stroke	12.2% in combination therapy group and 13.3% in antiplatelet therapy alone (95%CI: 0.73 to 1.16; $P = 0.48$ )
Thompson <i>et al</i> <sup>[29]</sup> (Meta-analysis-2002)	2702	PAD (stable, moderate to severe claudication)	Cilostazol <i>vs</i> placebo	MWD, pain free walking distance	MWD: 44% and 50% (cilostazol 50 mg and 100 mg respectively) and 21.4% in placebo ( $P < 0.05$ ) Pain-free walking distance: 60% and 67% (cilostazol 50 and 100 mg respectively) and 40% in placebo group ( $P < 0.05$ )
BOA <sup>[42]</sup> (2000)	2690	Patients undergone infra-inguinal bypass surgery	Warfarin <i>vs</i> aspirin	Graft occlusion	No observed difference in warfarin compared to aspirin (HR = 0.95; 95%CI: 0.82-1.11)

ABI: Ankle brachial index; CV: Cardiovascular; HR: Hazard ratio; MI: Myocardial infarction; MWD: Mean walking distance.

## CLOPIDOGREL

Clopidogrel is a thienopyridine derivative which inhibits platelet activation by adenosine diphosphate (ADP). There is data to support the effectiveness of clopidogrel as monotherapy in PAD. The first trial to establish this benefit was the CAPRIE trial, a randomized, blinded trial which compared the relative efficacy of clopidogrel (75 mg once daily) and aspirin (325 mg once daily) in patients with high risk of ischemic events. It included 19185 subjects (recent MI, recent ischemic stroke or symptomatic PAD), followed over 1-3 years with mean follow up of 1.9 years. There was a statistically significant 8.7% relative risk reduction ( $P = 0.043$ ; 95%CI: 0.3-16.5) in the composite endpoint of MI, stroke and vascular death in the clopidogrel group. In a subgroup analysis of the PAD population from the CAPRIE trial, the average event rate per year was 3.71% in the clopidogrel arm compared to 4.86% in the

aspirin arm, resulting in a 23.8% relative risk reduction ( $P = 0.0028$ ; 95%CI: 8.9-36.2)<sup>[15]</sup>. This outcome provides support for the inclusion of clopidogrel as a class I recommended antiplatelet agent in the 2016 AHA/ACC guidelines for the management of PAD<sup>[3]</sup>.

We are currently in an era where individualized antiplatelet therapy is becoming an important concept due to the fact that significant major adverse cardiovascular events (MACE) still occur despite clopidogrel use<sup>[16]</sup>. It is possible that clopidogrel resistance due to poor metabolism may contribute to this problem<sup>[17,18]</sup>. Clopidogrel resistance has been demonstrated in populations of patients also identified to have risk factors for PAD, including diabetics<sup>[19]</sup>, smokers<sup>[20]</sup>, and chronic kidney disease patients<sup>[21]</sup>. Doubling the dose of clopidogrel in these patients has proved ineffective<sup>[22]</sup>. In these cases, a more potent P2Y<sub>12</sub> inhibitor such as prasugrel or ticagrelor should be considered as these agents have enhanced platelet inhibition<sup>[23,24]</sup>. This

concept has been validated by Spiliopoulos *et al*<sup>[25]</sup>, who measured platelet reactivity after switching from clopidogrel to ticagrelor in clopidogrel resistant patients and found a significant response in platelet inhibition.

## DIPYRIDAMOLE AND ASPIRIN

The role of dipyridamole, an inhibitor of platelet adenosine uptake, in the management of PAD is debatable. Numerous small studies have shown benefit of combining dipyridamole and aspirin compared to aspirin alone<sup>[26,27]</sup>. The ESPRIT trial published in 2006 was a large randomized controlled trial which compared the efficacy of aspirin and dipyridamole combination therapy against aspirin alone to prevent vascular events within six months after ischemic stroke or TIA. The primary outcome was the composite of death from all vascular causes, non-fatal stroke, non-fatal MI or major bleeding, which occurred at a rate of 13% in the aspirin and dipyridamole group and 16% aspirin alone group [hazard ratio (HR) = 0.80, 95%CI: 0.66-0.98; absolute risk reduction 1.0% per year, 95%CI: 0.1-1.8]<sup>[28]</sup>. However, it is uncertain if dipyridamole monotherapy would be superior to aspirin since there is no data available. Additionally, this study was not conducted in the PAD population.

## CILOSTAZOL

Cilostazol, a unique antiplatelet agent, is a phosphodiesterase III inhibitor which reversibly inhibits platelet aggregation and also possesses vasodilatory and antiproliferative properties. It has been widely studied in PAD. A meta-analysis of 8 randomized trials including 2702 PAD subjects with claudication found improvement in maximum and pain-free treadmill walking distance with cilostazol. The mean walking distance of patients taking cilostazol 50 and 100 mg twice daily increased by 44% and 50%, respectively compared to 21.4% in placebo ( $P < 0.05$ ). The pain-free walking distance increased by 60% and 67% in the cilostazol 50 and 100 mg twice daily groups respectively, compared to 40% in the placebo group ( $P < 0.05$ )<sup>[29]</sup>. Hence cilostazol has class IA recommendation to improve symptoms and walking distance in patients with claudication<sup>[3]</sup>. There are some available studies that support an additional value of cilostazol in reducing restenosis and repeat revascularization following endovascular therapy, although these studies are very small and thus hypothesis generating<sup>[30,31]</sup>.

## TICAGRELOR

Ticagrelor is a cyclopentyltriazolopyrimidine which reversibly binds to the platelet ADP P2Y<sub>12</sub> receptor, unlike the thienopyridines. Ticagrelor is metabolized by Cytochrome P450 3A4/5. Its metabolite AR-C124910XX is equally active and potent, reversibly interacting with the platelet P2Y<sub>12</sub> ADP receptor, resulting in the

inhibition of platelet aggregation. Ticagrelor has been reported to have a faster onset of action compared to clopidogrel and, like prasugrel, results in greater platelet inhibition than clopidogrel.

The PLATO trial established the benefit of ticagrelor over clopidogrel in the ACS population. In this study, 18624 ACS patients with or without ST-segment elevation were randomized to receive ticagrelor (180 mg loading dose, then 90 mg twice daily) or clopidogrel (300-600 mg loading dose, then 75 mg daily). All patients received low dose aspirin (75-100 mg daily), although 325 mg was permitted for 6 mo following PCI with stenting. There was a significant reduction in the rate of death from vascular causes, MI, or stroke with ticagrelor compared to clopidogrel (9.8% vs 11.7%,  $P < 0.001$ ), although the rate of non-CABG related major bleeding was higher (4.5% vs 3.8%,  $P = 0.03$ )<sup>[23]</sup>. An analysis of the PLATO population ( $n = 1144$ ) with concomitant PAD, found similar results to the overall trial although it did not reach statistical significance. It also showed a significantly higher rate of the primary endpoint compared to patients without PAD<sup>[32]</sup>.

The recently published EUCLID trial is a direct comparison of ticagrelor and clopidogrel in the PAD population. This is a large, multicenter, randomized, parallel blinded study that enrolled 13885 patients 50 years or older with PAD defined as ABI  $\leq 0.80$  or prior ( $> 30$  d) revascularization of the lower extremities. Patients were randomized to ticagrelor 90 mg twice daily ( $n = 6930$ ) or clopidogrel 75 mg daily ( $n = 6955$ ) and followed for 30 mo. The primary outcome of the study was the incidence of cardiovascular death, MI, or ischemic stroke, which occurred at a rate of 10.8% of the ticagrelor group and 10.6% of the clopidogrel group ( $P = 0.65$ ). There was also no noted difference in secondary outcomes including acute limb ischemia and major bleeding between the two groups. Not surprisingly, there was a higher rate of medication discontinuation in the ticagrelor group due to dyspnea. In summary, among patients with symptomatic PAD, ticagrelor was not superior to clopidogrel in preventing MACE<sup>[33]</sup>.

The THEMIS Study (Effect of Ticagrelor on Health Outcomes in Diabetes Mellitus Patients Intervention Study) is another ongoing trial which is evaluating the efficacy of ticagrelor vs placebo, in addition to standard care including aspirin, for the long-term prevention of major vascular events in patients with type 2 diabetes and coronary atherosclerosis<sup>[34]</sup>.

## VORAPAXAR

Vorapaxar is a protease activator receptor-1 (PAR-1) antagonist, inhibiting the interaction of thrombin with the PAR-1 receptor, thus inhibiting platelet aggregation. The Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic events-Thrombolysis in Myocardial Infarction 50 (TRA

2P-TIMI 50) trial published was a double blinded placebo controlled trial which evaluated vorapaxar for the secondary prevention of atherothrombosis. It included 26449 subjects with a previous history of MI or ischemic stroke within the previous 2 wk-12 mo or PAD, randomized to either vorapaxar 2.5 mg daily or placebo. Concomitant antiplatelet therapy was permitted. The primary endpoint included a composite of cardiovascular death, MI and stroke. Results revealed that the composite endpoint occurred in 9.3% of patients receiving vorapaxar vs 10.5% of patients receiving placebo (HR = 0.87; 95%CI: 0.80-0.94;  $P < 0.001$ ). Subgroup analysis in the PAD population showed no difference in the primary endpoint, however the vorapaxar group showed a significant reduction in limb ischemic events (vorapaxar 2.3% vs placebo 3.9%; HR = 0.58; 95%CI: 0.39-0.86;  $P = 0.006$ ) and the need for peripheral artery revascularization (vorapaxar 18.4% vs placebo 22.2%; HR = 0.84; 95%CI: 0.73-0.97;  $P = 0.017$ ). However, the clinical benefit offered by vorapaxar was offset by a significant increase in the rate of intracranial hemorrhage (vorapaxar 1% vs placebo 0.5%,  $P < 0.001$ )<sup>[35]</sup>.

## DUAL VS MONO ANTIPLATELET THERAPY

Data behind optimal antiplatelet therapy following peripheral endovascular treatment is limited. A recent meta-analysis reviewed dual vs mono antiplatelet therapy trials after endovascular therapy in coronary, carotid and peripheral vascular territories. The authors did not find conclusive data proving superiority of dual antiplatelet therapy over monotherapy in peripheral vascular interventions, however they did note the paucity of data in this regard<sup>[36]</sup>.

The Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance trial compared the effect of combination aspirin and clopidogrel vs aspirin monotherapy in patients with either clinically documented vascular disease or risk factors for atherothrombotic disease. It included 15603 patients randomized to either clopidogrel (75 mg/d) plus low dose aspirin (75-162 mg) or placebo plus low dose aspirin for a mean follow up of 28 mo. Dual antiplatelet therapy did not significantly reduce the rate of MI, stroke or cardiovascular death (6.8% in clopidogrel plus aspirin group and 7.3% in aspirin monotherapy group,  $P = 0.22$ )<sup>[37]</sup>. In a subgroup analysis of patients with symptomatic PAD, no benefit was derived from dual antiplatelet therapy<sup>[38]</sup>.

The MIRROR study was a randomized double blinded trial, enrolling only 80 patients, which assessed the influence of dual antiplatelet therapy with aspirin and clopidogrel vs aspirin alone on local platelet activation in patients with PAD treated with endovascular therapy. Primary endpoints were local concentrations of platelet activation markers  $\beta$ -throm-

boglobulin and CD40L and the rate of clopidogrel resistance. Secondary endpoints included the clinical development of target lesion revascularization (TLR), stenosis, ABI, adverse events and days spent in hospital because of TLR, 6 mo after the intervention. The duration of therapy was 6 mo post intervention and results showed reduced peri-interventional platelet activation and improved functional outcome in the dual antiplatelet therapy group. The median peri-interventional concentration of  $\beta$ -TG was 224.5 vs 365.5 ( $P = 0.03$ ) in the clopidogrel and placebo group respectively. The concentration of CD40L was 127 in the clopidogrel group and 206.5 in the placebo group ( $P = 0.05$ )<sup>[39]</sup>.

Finally, the combination of ticagrelor and aspirin was studied against aspirin alone in the PEGASUS-TIMI 54 trial to evaluate the benefit of prolonged treatment with dual antiplatelet therapy. A total of 21162 patients with a history of myocardial infarction 1 to 3 years prior, were randomized to receive placebo or two different regimens of ticagrelor, 60 mg twice daily or 90 mg twice daily. All patients were recommended to take aspirin, with 97% taking aspirin 75-100 mg daily. The trial continued for a median of 33 mo with a primary composite endpoint of cardiovascular death, MI or stroke. The rate of the primary endpoint was 9.04% in the placebo (aspirin only) arm, 7.77% in the ticagrelor 60 mg arm and 7.85% in the ticagrelor 90 mg arm ( $P = 0.004$  ticagrelor 60 mg vs placebo;  $P = 0.008$  ticagrelor 90 mg vs placebo). This benefit was counterbalanced by a significant increase in TIMI major bleeding with both ticagrelor groups compared to placebo<sup>[40]</sup>.

The symptomatic PAD population from this trial included 1143 patients and was separately analyzed. As expected, the PAD population had a higher rate of major cardiovascular events compared to the population without PAD (19.3% vs 8.4%,  $P < 0.001$ ). Both ticagrelor groups had a lower incidence of the primary endpoint compared to placebo, but only the 60 mg arm had a statistically significant reduction. There was no difference in the rates of major bleeding between the three groups, although the numbers of patients in each group were small<sup>[41]</sup>.

## ROLE OF ANTICOAGULANT THERAPY

### Vitamin K antagonists

There is limited information describing the role of oral anticoagulation, with or without antiplatelet therapy, in patients with PAD. Warfarin and acenocoumarol, both vitamin K antagonists, have been studied in a few PAD population based studies. The Dutch Bypass Oral Anticoagulants or Aspirin (BOA) trial evaluated anticoagulation with warfarin (INR goal 3.0-4.5) compared to aspirin 80 mg daily in 2690 patients undergoing infra-inguinal bypass surgery. There was no observed difference in the patency rates with warfarin

compared to aspirin, respectively (HR = 0.95; 95%CI: 0.82-1.11). Subgroup analysis revealed that patients with vein grafts benefited from lower rates of graft occlusion (HR = 0.69; 95%CI: 0.54-0.88) in the warfarin group. However, patients with prosthetic grafts experienced higher rates of graft occlusion on warfarin (HR = 1.26; 95%CI: 0.82-1.11). As predicted, the warfarin population experienced an increased number of major bleeding episodes compared to aspirin (HR = 1.96; 95%CI: 1.42-2.71). The BOA trial reiterated that only selected patients with PAD stand to benefit from chronic warfarin therapy, particularly patients undergoing lower extremity bypass with vein grafts<sup>[42]</sup>.

The WAVE trial compared the efficacy and safety of combination therapy with an antiplatelet agent (aspirin 81-325 mg, ticlopidine or clopidogrel) and a vitamin K antagonist (warfarin or acenocoumarol) (target INR, 2.0 to 3.0) to antiplatelet therapy (aspirin, ticlopidine or clopidogrel) alone in patients with PAD. Results showed that the use of combination therapy did not prevent major cardiovascular complications to a greater extent than antiplatelet therapy alone (combination therapy group 12.2% and antiplatelet therapy alone 13.3%; 95%CI: 0.73-1.16;  $P = 0.48$ ). Instead, combination therapy was associated with a significantly higher incidence of life-threatening bleeding (4.0% vs 1.2%; 95%CI: 1.84-6.35;  $P < 0.001$ ) and moderate bleeding (2.9% vs 1.0%; 95%CI: 1.43-5.58;  $P = 0.002$ )<sup>[43]</sup>. Due to lack of evidence to support any benefit of the addition of warfarin to antiplatelet therapy in the reduction of thrombotic events in patients with PAD, oral anticoagulant therapy is highlighted as a class III (no benefit and possible harm) recommendation in the most recent AHA/ACC guidelines<sup>[3]</sup>.

## DIRECT ACTING ORAL ANTICOAGULANT AGENTS

Studies are currently ongoing to investigate the potential role of direct acting oral anticoagulant agents (DOAC) (dabigatran, rivaroxaban, apixaban and edoxaban) therapy in the PAD population. Apixaban, edoxaban and rivaroxaban are all factor Xa inhibitors, while dabigatran is a direct thrombin inhibitor. Preliminary results from the Cardiovascular Outcomes for People using Anticoagulation Strategies trial have recently been released, following early termination due to clinical benefit. In this study, 27402 patients with documented atherosclerosis (coronary and/or peripheral) were randomized to either 2.5 mg of rivaroxaban twice-daily plus aspirin 100 mg daily, 5 mg rivaroxaban twice-daily monotherapy or aspirin 100 mg once daily monotherapy. Primary endpoints were defined as the time from randomization to the first occurrence of either myocardial infarction, stroke or cardiovascular death and the time from randomization to the first occurrence of major bleeding. The primary efficacy outcome data was not released, but the

company stated that the trial reached its prespecified criteria for superiority in at least one of the rivaroxaban-based arms compared to aspirin alone. Bleeding information was not disclosed, although the company release mentioned "confirmation of the existing safety profile"<sup>[44,45]</sup>. In a similar trial, edoxaban, a once-daily factor Xa inhibitor is being evaluated in a randomized multicenter study in patients with PAD to assess the efficacy of its addition to aspirin compared to a clopidogrel plus aspirin regimen in preventing stenosis or occlusion in patients undergoing femoro-popliteal endovascular intervention<sup>[46]</sup>.

## ANTIPLATELET THERAPY AND PATENCY POST PERIPHERAL ENDOVASCULAR TREATMENT

Restenosis after percutaneous transluminal angioplasty is a major limitation for favorable outcomes, and is influenced by a number of factors such as vascular inflammation, platelet activation and aggregation. Data on post endovascular intervention duration of treatment with antiplatelet therapy is insufficient. There is high rate of re-occlusion and target lesion stenosis post angioplasty. Patency rate after PTA is impacted by variables; such as length of diseased segments, severity of the disease in run-off arteries, the number of lesions treated and presence of cardiovascular risk factors<sup>[1,47]</sup>.

The ideal antiplatelet regimen and appropriate duration of treatment has not been well validated in clinical trials. The combination of aspirin and dipyridamole trended toward a superior impact on patency after femoro-popliteal angioplasty compared with vitamin K antagonists at 3, 6, and 12 mo. Aspirin 50 to 300 mg, with or without dipyridamole, given before femoro-popliteal endovascular treatment, reduced the incidence of re-occlusion at 6 and 12 mo without any safety concerns when compared with no therapy or vitamin K antagonists<sup>[48]</sup>. The Clopidogrel and Aspirin in the Management of Peripheral Endovascular Revascularization study which was designed to assess the efficacy and safety of this regimen after femoro-popliteal PTA was stopped prematurely because of insufficient randomization numbers. Off-label use of dual antiplatelet therapy in many patients led to its failure. The combination of clopidogrel and aspirin showed higher inhibition of platelets before and after angioplasty in patients undergoing endovascular intervention for claudication<sup>[49]</sup>. As mentioned previously, in the MIRROR study, treatment with clopidogrel and aspirin reduced target lesion revascularization improving the patency of treated lesions and decrease the need for revascularization<sup>[39]</sup>.

Lower extremity bypass is another important treatment for patients with symptomatic PAD when less-invasive endovascular procedures are not an

**Table 3** Current available guidelines addressing antiplatelet therapy for peripheral arterial disease

Class of recommendation	Guidelines
Class Ia	Aspirin in daily doses of 75 to 325 mg or clopidogrel 75 mg/d is recommended to reduce the risk of MI, stroke, or vascular death in individuals with symptomatic atherosclerotic lower extremity PAD
Class IIa	Antiplatelet therapy is reasonable to manage asymptomatic individuals with an ABI less than or equal to 0.90 to reduce the risk of MI, stroke, or vascular death
Class IIb	Dual-antiplatelet therapy (aspirin and clopidogrel) may be reasonable to reduce the risk of limb-related events in patients with symptomatic PAD after lower extremity revascularization

PAD: Peripheral arterial disease; MI: Myocardial infarction.

option because of anatomic or technical considerations. Graft failure is related to multiple factors including type of graft material, site of anastomosis, rate of stenosis, type of antiplatelet used post procedure and duration of medical treatment post intervention. Prosthetic grafts with anastomosis to the tibial arteries seem to have highest rate of failures. Most grafts fail in the first two years, mainly attributed to graft stenosis<sup>[50]</sup>.

Antiplatelet therapy with aspirin improves grafts patency and limb salvage. Patients receiving a prosthetic graft were more likely to benefit from administration of antiplatelet agents than those treated with a venous graft<sup>[51]</sup>. Risk of graft occlusion while on single antiplatelet therapy; typically aspirin, still remains high. Incidence reported to be 15% per year when a vein is used and 20% with synthetic material (polytetrafluoroethylene) rising to 45% and 75%, respectively, for below-knee grafts<sup>[52,53]</sup>. In the CASPAR trial, combination of aspirin and clopidogrel showed statistically significant decrease in prosthetic graft failure with decreasing rate of occlusion and amputation to levels similar to those seen with venous grafts<sup>[54]</sup>.

## DISCUSSION

### Current practice

Dual antiplatelet therapy is often used in patients undergoing infra-inguinal angioplasty and stenting as mentioned in a survey by Allemang *et al*<sup>[55]</sup> from the vascular surgery community itself, which revealed that the most common antiplatelet therapy after lower extremity endo-luminal therapy was a combination of aspirin and clopidogrel. Duration of therapy also varied, with 1 to 3 mo as the most common time frame. Therapy use increased with distal endovascular treatment and with the placement of stents and there was no consensus over the duration of therapy<sup>[55]</sup>. However, there is no robust data to support such practice. Rationale for shorter duration of antiplatelet therapy post endovascular interventions in patients with PAD is primarily drawn from the fact that there is endothelial damage from balloon angioplasty and stenting is generally reserved as a last resort for treating flow limiting localized complications. However, in the current era, peripheral vascular intervention invariably involves atherectomy and significantly longer length of lesions

compared to those seen in the coronary realm. This translates to more extensive endothelial damage and subsequent re-endothelialization which would make longer duration of dual antiplatelet therapy appear intuitive.

### Current guidelines

The recently updated AHA/ACC guidelines for the management of patients with PAD, recommend either aspirin in daily doses of 75 to 325 mg or clopidogrel 75 mg per day as safe and effective antiplatelet therapy to reduce the risk of MI, stroke, or vascular death in individuals with symptomatic atherosclerotic lower extremity PAD (class IA). A Class IIa recommendation is given for considering antiplatelet therapy to manage asymptomatic individuals with an ABI less than or equal to 0.90. Dual antiplatelet therapy with aspirin and clopidogrel may be reasonable after lower extremity revascularization (class IIb), due to the lack of well designed, large clinical trials<sup>[3]</sup>. A summary of the current AHA/ACC Guideline recommendations for antiplatelet therapy in PAD is provided in Table 3.

## CONCLUSION

There have been significant advances in open surgical and endovascular modalities for the treatment of peripheral vascular disease. Long term patency rates for either modality continue to improve, however, randomized controlled trial data comparing the two options head to head are lacking. There appears to be a consensus emerging that endovascular therapy when feasible should be attempted first, although robust randomized data is still needed to support this approach. With contemporary atherectomy techniques, drug coated balloons and stents, a bigger armamentarium is available for immediate and long term success of endovascular therapy. Similarly there is lack of data regarding post intervention medical therapy. Although dual antiplatelet therapy with aspirin and clopidogrel is commonly used, the duration of such therapy is highly variable without a strong recommendation in practice guidelines. Practice patterns for dual antiplatelet therapy are influenced and extrapolated from data available for PCI. It is apparent that there is paucity of clinical trial data for the treatment of peripheral vascular disease

and subsequent care. Additional data is warranted from large scale multicenter randomized controlled trials and observational studies to assess the optimal medical treatment and duration of medical therapy across the spectrum of PAD.

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## Is Entresto good for the brain?

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### Abstract

The main stay pharmacotherapy for heart failure (HF) is targeted towards rennin-angiotensin-aldosterone (RAAS) and neprilysin pathways (NP). Both therapeutic strategies decreases morbidity and mortality but also

carry considerable adverse effects. This review of the literature highlights the new generation of HF drug, sacubitril-valsartan (SV), trade name Entresto (researched as LCZ696, Novartis) which simultaneously blocks RAAS and NP. This dual action of angiotensin receptors blocker and neprilysin inhibitor (NPI) has improved HF prognosis and it is an evolution in the management of HF. Although the initial follow-up of patients treated with SV has yielded promising results, there are concerns regarding potential side effects especially an increase in the risk of Alzheimer's disease (AD) and young onset of AD. NPI interferes with the breakdown and clearing of beta-amyloid peptides, the plaques seen in AD, raising concern for AD in SV patients. On the other hand, hypertension and cardiovascular diseases are established risk factors for AD which can be decreased by SV therapy. It is therefore essential that SV treated patients are followed up over an extended period of time to detect any adverse cognitive changes.

**Key words:** Heart failure; Sacubitril-valsartan; Entresto; LCZ696; Neprilysin inhibitor; Alzheimer's disease

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**Core tip:** We are discussing an innovative and exciting new treatment for heart failure (HF). This advance in pharmacotherapy has shown promising results and is rapidly incorporating into standard medical therapy for HF. There is, however, a theoretical concern for cognitive dysfunction and early onset Alzheimer's disease particularly in the young. This review informs clinicians of the mechanism and potential for cognitive dysfunction, thereby increasing awareness and promoting informed prescribing.

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## INTRODUCTION

Heart failure (HF) is typified by the reduced ability of the heart to deliver an adequate supply of blood and oxygen to the tissues. Its causes are numerous including ischemic heart disease, diabetes, hypertension, cigarette smoking, obesity and valvular heart disease<sup>[1]</sup>. Over 5 million individuals worldwide suffer from HF and its incidence is rising with 550000 new diagnoses annually<sup>[1,2]</sup>. With a steadily aging population, HF incidence is projected to increase to 46% by the year 2030<sup>[1,2]</sup>. HF is associated with increased morbidity, mortality and cost<sup>[1,3]</sup>.

HF occurring due to depressed left ventricular function [ejection fraction (EF)  $\leq$  40%] is known as HF with reduced EF (HFrEF)<sup>[4]</sup>. Pharmacological intervention for HF largely depended on angiotensin inhibitors such as angiotensin receptor blockers (ARBs) and angiotensin converter enzyme inhibitors (ACEi). Recently, a new strategy using a Neprilysin inhibition (NIs) and recombinant natriuretic peptides was proven as a therapeutic option to target HF pathophysiology<sup>[5]</sup>. The new generation of HF pharmacotherapy entails the simultaneous inhibition of both the angiotensin and Neprilysin pathways, the latest version of which is Entresto<sup>®</sup> - the combination of sacubitril and valsartan (SV) (researched as LCZ696)<sup>[6,7]</sup>. In this concise review, we highlight the mechanisms of SV activity, the results of the successful clinical trial and the potential adverse effects, highlighting those on cognitive function.

## METHODS

The search for the relevant articles was conducted on Medline. The following terms "Entresto", "neprilysin inhibitors", "angiotensin inhibitors", "dementia" and "Alzheimer's Disease" "cognitive impairment" were searched in different combinations. The search was limited to articles in English language but no search filters were used for timeline and subjects.

## INCLUSION CRITERIA

Articles that met our following inclusion criteria were included in this review: (1) discussed pathophysiology of HF and target pharmacotherapy mechanism; (2) discussed pathophysiology of development of AD; (3) ongoing trials of Entresto; (4) reported link between neprilysin inhibitors and development of AD; and (5) articles that were published full and in English language.

## PATHOPHYSIOLOGY OF HF

The pathophysiology of HFrEF results mainly from the activation of the renin-angiotensin-aldosterone (RAAS) neuro-hormonal compensatory mechanism. Although the peripheral vasoconstriction initiated by the RAAS mechanism maintains blood pressure and cardiac output for a short time, sustained activation of

RAAS leads to ventricular hypertrophy, hypertension and angioedema, ultimately worsening myocardial dysfunction<sup>[8,9]</sup>. A second compensatory mechanism, the natriuretic peptide (NP) system, counteracts the vasoconstrictive and sodium/water retentive effects of the RAAS system<sup>[10]</sup>.

## GOALS OF PHARMACOTHERAPY

The initial HF pharmacotherapy targeted the RAAS circuit using ARBs<sup>[11]</sup>, ACEi<sup>[12]</sup>, beta-blockers<sup>[13]</sup>, diuretics<sup>[14]</sup> and aldosterone inhibitors<sup>[15]</sup>. All of these drugs have proven to be effective in lowering the morbidity and mortality in HFrEF. The NP system consists of four related peptides (Atrial, Brain, C-Type, and Dendroaspis NP) and a membrane bound peptidase called Neprilysin that degrades these vasoactive peptides<sup>[16]</sup>. NP system targeting drugs have included a recombinant form of BNP (Nesiritide)<sup>[17]</sup> as well as NIs, *e.g.*, candoxatril, recedodotril, *etc*<sup>[18,19]</sup>. HF pharmacotherapy targeting the NP system and the respective clinical trials are summarized in Table 1<sup>[20-32]</sup>. Although strategies blocking either of these two pathways have reduced mortality and morbidity in HF<sup>[12,28,32]</sup>, the prognosis still remains poor due to long term ineffectiveness of the drugs as well as adverse physiological effects<sup>[5]</sup>.

The newest strategy in HFrEF pharmaco-intervention is the combination of ARB and NI (ARNI) that causes a dual inhibition of the RAAS pathway and Neprilysin: The prototype drug was LCZ696<sup>[6,7]</sup> which is made up of 1:1 ratio of the ARB valsartan<sup>[33]</sup> and the NI sacubitril (AHU 377)<sup>[34]</sup>. The action of SV is multimodal. Sacubitril is a pro-drug which is activated to Sacubitrilat (LBQ657), the active metabolite that inhibits NP while valsartan simultaneously blocks the angiotensin receptor. The dual action of Sacubitril and valsartan augment the beneficial actions of the NPs and inhibits the deleterious effects of the RAAS system<sup>[7]</sup>. The PARADIGM-HF trial was conducted by McMurray *et al*<sup>[31]</sup> to determine the efficacy of SV compared to the ACE inhibitor Enalapril<sup>[35,36]</sup>, which improves mortality and morbidity. The median follow-up duration was 27 mo and SV reduced HF related symptoms and overall survival by 20%<sup>[31]</sup>. Additionally, the ARNI approach avoids the common side-effects of ACEi such as cough and angioedema that result from impaired degradation and elevated levels of bradykinin<sup>[37]</sup>. In the ONTARGET trial, ARBs were documented to result in a lower rate of cough and angioedema compared to ACEi: Therefore, combination therapy prefers ARBs over ACEi<sup>[38]</sup>.

The United States Food and Drug Administration had approved SV for clinical use and at present it is produced under the name of Entresto<sup>®</sup> by Novartis<sup>[39]</sup>. The recommended dose of Entresto is 49 mg sacubitril/51 mg valsartan twice daily increased to 97 mg sacubitril/103 mg valsartan after 2-4 wk. It is contraindicated in patients with history of angioedema, hypotension, hyperkalemia or renal dysfunction and in pregnant women due to fetal toxicity<sup>[40]</sup>. In the

**Table 1** Overview of drugs targeting the neprilysin pathways and its pathways

Drug	Mechanism	Clinical trials and year	Results on HF symptoms
Nestiride	Increasing natriuretic peptide activity	VMAC, 2000 <sup>[20]</sup> PRECEDENT, 2002 <sup>[21]</sup> ASCENT-HF, 2009 <sup>[22]</sup>	Improved BP and dyspnea Less cardiac arrhythmias More hypotension
Candoxatril	NPi	Single-centered investigation with only a limited number of patients <sup>[23-25]</sup>	More exercise tolerance Increase in vascular resistance
Omapatrilat	NPi	IMPRESS, 2000 <sup>[26]</sup> OVERTURE, 2002 <sup>[27]</sup> OCTAVE, 2004 <sup>[28]</sup>	More exercise tolerance Increase in angioedema Reduction in BP Lower mortality
LCZ696	NPi	PARAMOUNT, 2012 <sup>[29]</sup> PARADIGM, 2014 <sup>[30,31]</sup> PARAGON, ongoing <sup>[32]</sup>	Reduction in BP Improved ejection fraction Lower mortality No change in angioedema

BP: Blood pressure; HF: Heart failure; NPi: Neprilysin inhibitors.

PARADIGM-HF trial, 10.7% of the patients reported at least one of the following adverse effects hypotension, renal failure, hyperkalemia, fatigue and dizziness<sup>[31]</sup>.

In clinical practice, approximately 50% of the HF patients have a preserved left ventricular ejection fraction (HFpEF) and present with similar morbidity and mortality as seen in patients with HFrEF<sup>[2-4]</sup>. Sacubitril/valsartan is validated in HFrEF but is being evaluated for HFpEF in the PARAMOUNT-HF (The Prospective comparison of ARNI with ARB on Management of Heart Failure with Preserved Ejection Fraction) trial. Patients who treated with sacubitril/valsartan showed a reduction in NYHA class and left atrial volumes<sup>[29]</sup>. At present, the PARAGON-HF trial is ongoing comparing the effects of sacubitril/valsartan versus valsartan in the HFpEF patients<sup>[32]</sup>.

## NEPRILYSIN INHIBITORS AND ALZHEIMER'S DISEASE

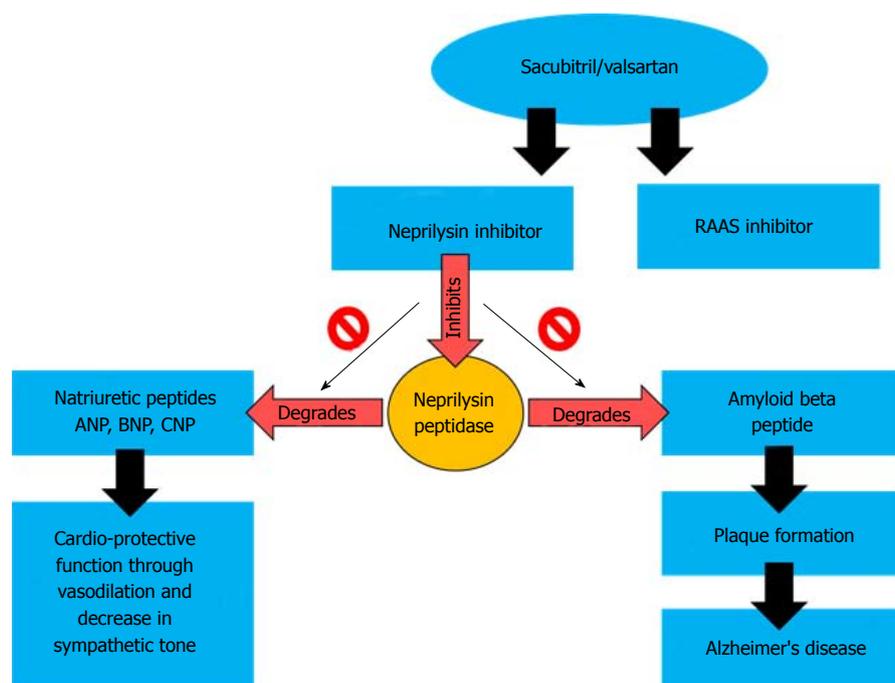
An interesting facet of the use of NIs in the treatment of cardiovascular diseases is their potential role in the development or progression of Alzheimer's disease (AD), as there is considerable overlap between the populations suffering from HF and AD<sup>[41]</sup>. The hallmark of AD is the accumulation of beta amyloid ( $\beta$ A) peptide in the brain causing neurotoxic plaques that are supposedly responsible for the pathology of AD<sup>[42]</sup>. Under normal physiological conditions, the  $\beta$ A peptide is degraded by proteases such as ACE, NP and insulin degrading enzyme<sup>[43]</sup>. NP has a broad range of substrates apart from the NPs such as bradykinin, enkephalins as well as the  $\beta$ A peptide<sup>[44]</sup>. Additionally, patients with AD have lower expression of NP compared to healthy subjects<sup>[45]</sup>, and NP deficient mice develop the murine form of AD<sup>[46]</sup>. This possible correlation was further highlighted when intracerebral infusion of NPi lead to the development of AD-like lesions in rabbits<sup>[47]</sup>. Lastly, certain polymorphisms in the NP gene (NEP) were associated with a higher propensity

for AD in a Finnish cohort<sup>[48]</sup>. Therefore, NP is as much a pharmaceutical target for the treatment of AD as for HF, except that the strategies are opposite for both pathologies (Figure 1). Indeed, NP centered therapies have been developed independently for AD and tested at the pre-clinical levels. CNS targeted recombinant human NP was able to reduce  $\beta$ A peptide toxicity in the mouse model of AD<sup>[49,50]</sup>.

## ENTRESTO® AND ALZHEIMER'S DISEASE

Clinicians should be aware of the possible inhibitory action of SV in the clearing of  $\beta$ A peptide while considering it for HF treatment. In patients who are at the risk of developing AD, whether due to age or genetic predisposition, the chronic exposure to SV may accelerate the clinical onset of the disease. Critical to this hypothesis is the ability of SV to cross the blood brain barrier (BBB) in order to block brain NP. There is evidence that certain NIs like S-acetyltiorphan can cross the BBB<sup>[51]</sup> while some like candoxatril cannot<sup>[52]</sup>. Both Sacubitril and its active metabolite LBQ657<sup>[7]</sup> are under the threshold size of 400 kD which makes them fit to cross the BBB<sup>[53,54]</sup>. It is noteworthy that the PARADIGM-HF trial<sup>[31]</sup> had excluded patients with AD and did not include any cognitive function tests to evaluate drug safety. McMurray *et al.*<sup>[55]</sup> have confirmed some correlation between EN treatment and  $\beta$ A peptide levels in a recent review article. While cynomolgus monkeys treated with SV had increased levels of  $\beta$ A peptide in the CSF, the healthy volunteers treated with EN for two weeks had no change in  $\beta$ A peptide levels. McMurray *et al.*<sup>[31]</sup> showed that the dementia and cognitive defects were not increased in the EN treated patients during the trial. However, it should be noted that the earliest symptoms of AD can take as long as 8-10 years to manifest<sup>[56]</sup>. If there is a correlation between EN therapy and AD, one would predict an earlier onset of symptoms.

It is therefore imperative that patients on SV are followed up for cognitive abilities and potentially



**Figure 1** Schematic representation of the contradictory effects of angiotensin receptor and neprilysin inhibitors on cerebrovascular disease and Alzheimer's disease. ANP: Atrial natriuretic peptide; BNP: Brain natriuretic peptide; CNP: C-type natriuretic peptide.

evaluated for AD. One can consider cerebrospinal fluid (CSF) analysis for  $\beta$ A peptide levels and amyloid plaques through PET scans if early signs of dementia ensue<sup>[57]</sup>. In the ongoing PARAGON-HF<sup>[32]</sup> trial, AD patients have not been excluded and serial cognitive tests have also been included as part of initial follow-up.

Another concern is that the proportion of HF patients younger than 40 years old is increasing<sup>[58]</sup>. Younger patients receiving SV have the potential for a longer term exposure and the consequent potential for increased risk of young onset Alzheimer's disease (YOAD) is noteworthy. YOAD is described in subjects less than 65 years of age and has a more rapid progression than the typical late onset Alzheimer's<sup>[59]</sup>.

Interestingly, one can also describe SV as having protective effect against AD since hypertension and cardiovascular diseases are established risk factors for AD<sup>[60]</sup>, is decreased by SV therapy. ACEi or ARBs have also been shown to decrease in dementia and other symptoms of AD through reducing hypertension and cardiovascular disease<sup>[61]</sup>. It will be interesting to follow the neuro-cognitive outcomes from PARAGON-HF trial.

## CONCLUSION

Clinicians should be aware of the potential adverse effects of SV and make informed decisions in prescribing SV, particularly to patients with existing neuro-degenerative diseases or the very young. As there are no definitive answers yet about the long term effects of SV, we await the results from PARAGON-HF and reports to follow with interest. Patients who are currently

receiving SV treatment should be well monitored for potential adverse events with particular attention to dementia. A low threshold for testing for AD if/when dementia symptoms occur seems warranted. More study on the implications for young HF patients is warranted.

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## Cardiac and pericardial tumors: A potential application of positron emission tomography-magnetic resonance imaging

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### Abstract

Cardiac and pericardial masses may be neoplastic, benign and malignant, non-neoplastic such as thrombus or simple pericardial cysts, or normal variants cardiac

structure can also be a diagnostic challenge. Currently, there are several imaging modalities for diagnosis of cardiac masses; each technique has its inherent advantages and disadvantages. Echocardiography, is typically the initial test utilizes in such cases, Echocardiography is considered the test of choice for evaluation and detection of cardiac mass, it is widely available, portable, with no ionizing radiation and provides comprehensive evaluation of cardiac function and valves, however, echocardiography is not very helpful in many cases such as evaluation of extracardiac extension of mass, poor tissue characterization, and it is non diagnostic in some cases. Cross sectional imaging with cardiac computed tomography provides a three dimensional data set with excellent spatial resolution but utilizes ionizing radiation, intravenous iodinated contrast and relatively limited functional evaluation of the heart. Cardiac magnetic resonance imaging (CMR) has excellent contrast resolution that allows superior soft tissue characterization. CMR offers comprehensive evaluation of morphology, function, tissue characterization. The great benefits of CMR make CMR a highly useful tool in the assessment of cardiac masses. (Fluorine 18) fluorodeoxyglucose (FDG) positron emission tomography (PET) has become a corner stone in several oncological application such as tumor staging, restaging, treatment efficiency, FDG is a very useful imaging modality in evaluation of cardiac masses. A recent advance in the imaging technology has been the development of integrated PET-MRI system that utilizes the advantages of PET and MRI in a single examination. FDG PET-MRI provides complementary information on evaluation of cardiac masses. The purpose of this review is to provide several clinical scenarios on the incremental value of PET and MRI in the evaluation of cardiac masses.

**Key words:** Cardiac; Pericardial tumors; Echocardiography

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**Core tip:** With the commercial availability of positron emission tomography- magnetic resonance imaging (PET-MRI) true simultaneous PET and MRI in a single study is real. Several studies have demonstrated the feasibility and incremental value of combined PET and MRI in many clinical applications. A combination of PET and MRI can provide incremental information in many cardiovascular scenarios. Evaluation of cardiac tumors may be most straightforward application for PET-MRI because it offers a unique opportunity to evaluate the tumor morphology, characterization, infiltration to adjacent structures, local and M staging and comprehensive cardiac evaluation in a single study. The purpose of this review is to provide several clinical scenarios on the incremental value of PET and MRI in the evaluation of cardiac masses.

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## INTRODUCTION

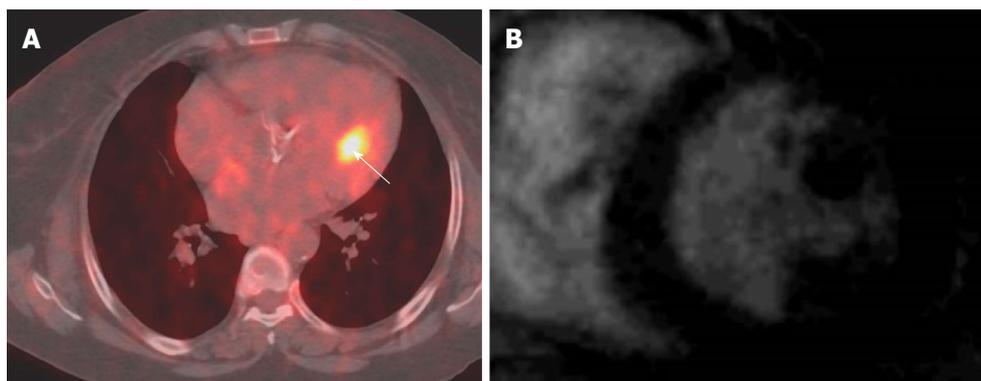
Primary cardiac tumors, Benign and Malignant, are rare with an estimated prevalence of 0.002%-0.3% at autopsy<sup>[1]</sup>. The primary benign cardiac tumors are common and include myxomas, fibromas, rhabdomyomas, lipoma, fibroelastomas, hemangioma, and paragangliomas. The primary malignant cardiac neoplasm is generally sarcomas, mesotheliomas, or lymphoma. Cardiac metastases involving the heart and pericardium (secondary cardiac tumors) from direct invasion or hematological spread are 20%-40% more common than primary cardiac tumors and usually associated with poor prognosis primary related to advanced stage of primary malignancy<sup>[2]</sup>. However, the most common type of cardiac mass is in fact pseudotumors or tumors like structures such as intracardiac thrombus, pericardial cyst, valvular vegetation, perivalvular abscess, or normal cardiac variant such as crista terminalis.

Patients with primary cardiac tumors may present with a range of symptoms that can simulate cardiac disease. The clinical presentation is determined mostly by location, size, and texture, the rate of growth and invasiveness of the tumor. For example, patients with mechanical obstruction related to cardiac mass in outflow tract may present with heart failure or valvular disease, systolic dysfunction or diastolic dysfunction related to impaired contractility. Pericardial disease may present as pericardial effusion, pericardial tamponade, or pericardial thickening and nodularities.

Several imaging modalities are used in the evaluation of cardiac and Pericardial tumors with their inherent advantages and disadvantages. Transthoracic

echocardiography is widely available and is considered the procedure of choice for diagnosis of intracardiac tumors. It provides information on the size, mobility, shape and location of the cardiac mass but limited information on mass tissue characterization. In certain patients, such as obese patients or patients with chronic obstructive lung disease trans esophageal echocardiography offers a diagnostic alternative<sup>[3]</sup>. Cardiac computed tomography (CT) is a noninvasive technique which offers a high spatial resolution and sufficient temporal resolution. Both cardiac and intracardiac mass can be very clearly depicted as well as their degree of myocardial and pericardial involvement; however, radiation and iodinated contrast injection are some of CT imaging<sup>[4]</sup>. Cardiac magnetic resonance (CMR) has several advantages in the diagnosis of patients with cardiac tumors. The greatest advantages of CMR over various imaging modalities, is that CMR have a unique ability to characterize tissue composition based on the inherent T1 and T2 relaxation of different tissue; in addition CMR provides excellent temporal and spatial resolution, multiplanar 3D imaging capabilities, large field of view, evaluating adjacent vascular structures, lymph nodes involvement and mediastinum<sup>[5,6]</sup>. Positron emissions tomography (PET) offers an accurate evaluation of the metabolic activity of the tumors *via* utilizing (fluorine 18) fluorodeoxyglucose (FDG). FDG PET is very helpful for staging malignancies, optimizing biopsy location, radiation therapy planning and detection of tumors recurrence and response to therapy. In cases of cardiac metastases FDG pet can detect both primary lesions such as lung cancer and cardiac metastases. The extent of FDG uptake by tumors is useful for differentiation between benign and malignant tumors<sup>[7]</sup>.

Positron emission tomography-magnetic resonance imaging (PET-MRI) hybrid scanners are a newly developed type of clinical imaging system. PET-MRI benefits from the advantages of both PET and MRI. MRI provides tumors tissue characterization with T1 and T2, and different pulse sequence with and without gadolinium injection, extent of the tumors invasion and local metastasis, in addition, CMR offers a comprehensive examination of the heart and any complication related to the tumors such as pericardial effusion or valvular dysfunction. PET assesses the metabolic evaluation of the tumors, and evaluation of the primary extracardiac tumors or other distant metastases. Integrated PET-MRI systems provide improved spatial and temporal alignment, CMR image based motion correction is also improved, artefacts such as motion and partial volume effect in PET scanning. Integrated PET-MRI system significantly reduces time of imaging acquisition compared to performing two separate examinations, improve throughput and also reduce patient's discomfort<sup>[8,9]</sup>. In this review, we will discuss several clinical scenarios in which CMR and PET provides additive information, these illustrated cases performed as sequential examinations, not



**Figure 1** Localization of abnormal fluorodeoxyglucose activity in the heart. A: Axial fused PET-CT image shows focal intense FDG uptake in the heart (arrow) in patient with melanoma that thought represents cardiac metastases; B: Selected delayed enhancement short axis image of the same patient with other images (not shown) shows no abnormal enhancement or tissue infiltration, the FDG uptake was corresponding to hypertrophic papillary muscle, follow PET-CT was normal. PET: Positron emission tomography; CT: Computed tomography; FDG: Fluorodeoxyglucose.

on integrated PET-MRI scan, these includes: (1) characterization and Localization of abnormal FDG uptake in the heart; (2) characterization and Localization of abnormal FDG uptake adjacent to the heart; (3) differentiation between tumoral thrombus from bland thrombus; (4) distant Metastasis (M staging); (5) evaluation of aggressiveness of the lesion and assessment of cardiac involvement; and (6) other potential indications.

### CHARACTERIZATION AND LOCALIZATION OF ABNORMAL FDG UPTAKE IN THE HEART

The patterns and distribution of FDG in the normal myocardium may be classified into three types; no to faint uptake, regional uptake, and diffuse uptake. There is no specific pattern myocardial FDG uptake<sup>[10]</sup>. Furthermore, myocardial FDG uptake in the same individual is neither stable nor reproducible unless under the same fasting condition. The PM has a characteristic location on axial and coronal images. PM uptake can occasionally be seen without myocardial uptake, this appearance can mimic an intraventricular thrombus or tumor<sup>[11]</sup>. Focal intense FDG uptake is frequently observed in the basal septal region in patients with active cardiac sarcoidosis<sup>[12]</sup>. Several reports describing FDG patterns in cardiac tumors have been published<sup>[13,14]</sup>. However, the usefulness of FDG in the differentiation between benign (including thrombus) and malignant tumors.

Different imaging modalities are often necessary for approaching final diagnosis of primary or metastatic cardiac tumors. The differential diagnosis can be narrowed down by clinical history, signs and symptoms of the clinical presentation, history of primary neoplasm. Normal cardiac variants and variable myocardial uptake of FDG may raise the suspicion of cardiac metastasis in some PET-CT studies in patients with cancer. In such clinical circumstances, CMR is very

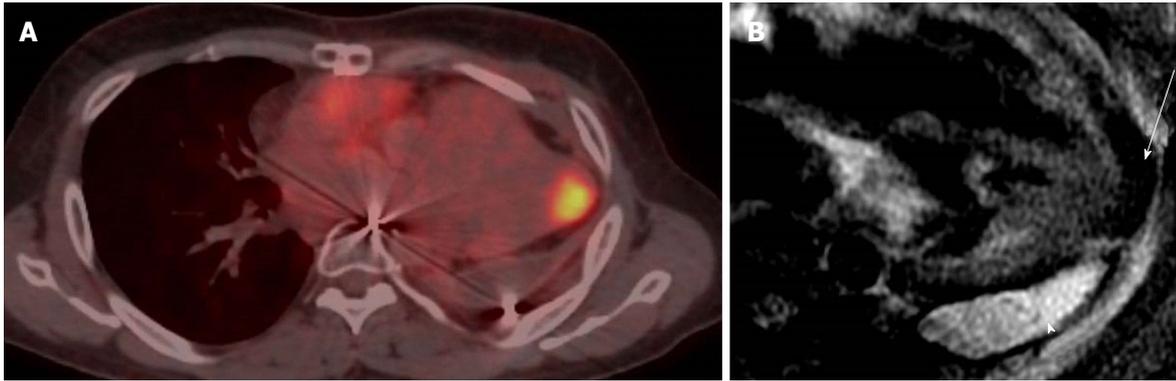
useful (Figures 1 and 2).

### CHARACTERIZATION AND LOCALIZATION OF ABNORMAL FDG UPTAKE ADJACENT TO THE HEART

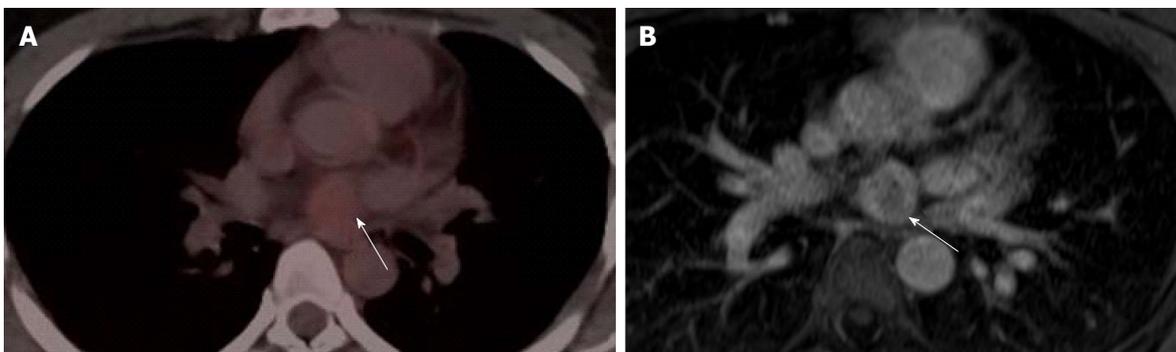
One of the most and frequent artefact in PET-CT is due to respiratory motion during scanning. It typically creates mismatch between a specific stage of breath cycle during the CT and average of many breath cycles of the PET images. The diaphragm that is visualized in a single position during fast CT acquisition is different from mean position of PET images or in case of respiratory motion. misregistration of CT and PET images disrupts images fusion of normal organ and may cause erroneous localization of FDG avid lesion in the liver, upper abdomen, base of the lung, or adjacent to the heart. The best way to correct for respiratory motion between CT and PET images would be acquired gated images to discriminate different interval for a breath cycle<sup>[15]</sup>. There are some techniques in integrated PET-MRI that correct for motion artifact, motion can be derived from MR data without the need for navigators, an approach called self-navigation, and these techniques require that K-space be sampled in a motion sensitive scanner<sup>[16]</sup>. The motion control and gating approaches will continue to be used in integrated PET-MRI scanner, the field will likely move towards data-derived approaches<sup>[17]</sup>. Oncologic PET-CT scans may reveal abnormal focus of hypermetabolism in the chest, either in or adjacent to the heart. It is often not possible to accurately localize this lesion using PET or the corresponding low-dose CT scan. In such situations, MRI can provide additional information in localizing and characterizing these masses (Figures 3 and 4).

### DIFFERENTIATION BETWEEN TUMORAL THROMBUS FROM BLAND THROMBUS

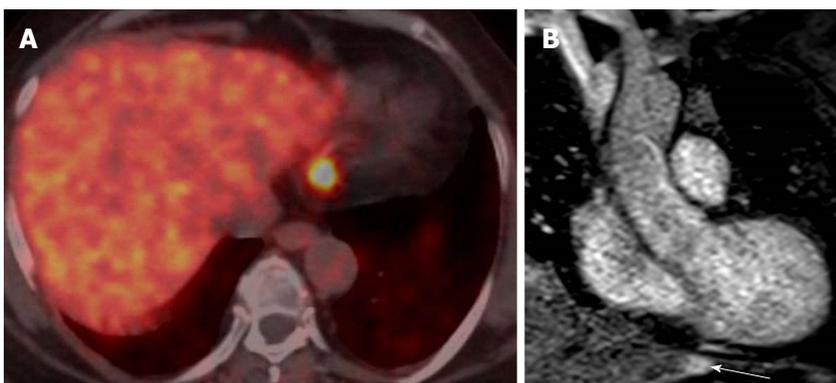
Tumor thrombosis is often clinically asymptomatic,



**Figure 2** Localization and characterization of abnormal fluorodeoxyglucose activity in the heart. A: Axial PET-CT images in patient with history of invasive thymoma underwent surgical resection shows intense FDG focal uptake in the cardiac apex highly suspicious for cardiac metastases, review CT component of PET-CT shows area of and soft tissue; B: Four-chamber DE image with triple inversion recovery shows complete fat suppression of the apical activity in keeping with brown fat (arrow), with high signal fluid intensity consistent with post-operative lobulated fluid collection (arrowhead). PET: Positron emission tomography; CT: Computed tomography; FDG: Fluorodeoxyglucose.



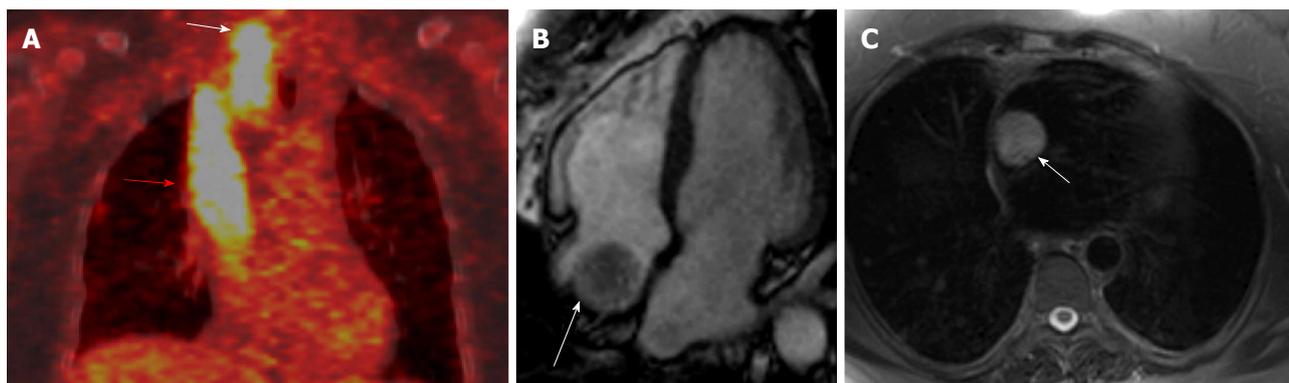
**Figure 3** Localization and characterization of abnormal fluorodeoxyglucose activity adjacent to the heart. A: Localization and characterization of abnormal FDG activity adjacent to the heart. Axial PET-CT image of the heart shows a non-FDG avid nodule near the base of the heart (arrow), PET-CT was performed for incidentally discovered nodule mass on Echocardiography. The study was otherwise unremarkable; B: Axial first pass perfusion image shows highly vascular intrapericardial tumors with no evidence of tissue invasion (arrow); this lesion was surgically removed and pathologically proven schwannoma. PET: Positron emission tomography; CT: Computed tomography; FDG: Fluorodeoxyglucose.



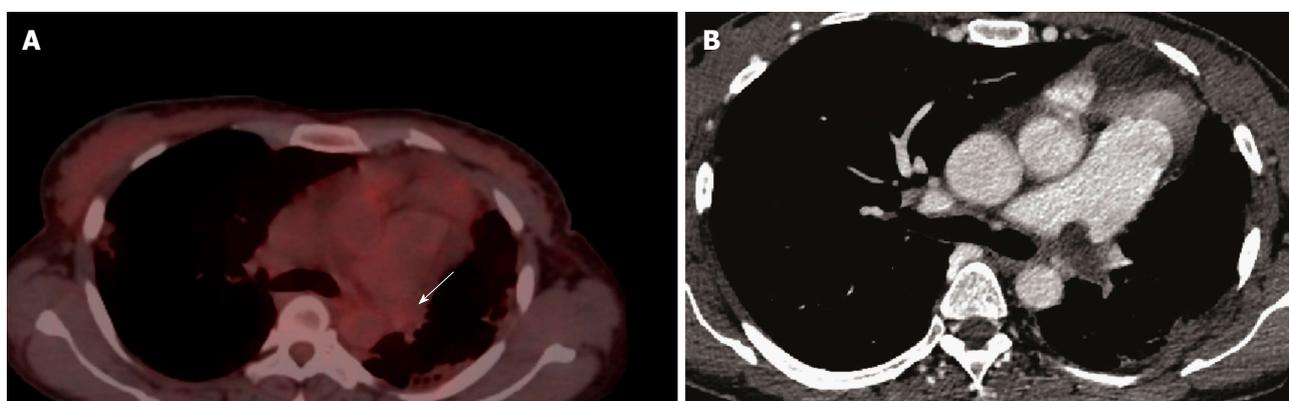
**Figure 4** Localization and characterization of abnormal fluorodeoxyglucose activity adjacent to the heart. A: Axial Ga-68 DOTATATE PET/CT shows a focal intense radiotracer uptake adjacent to the heart with difficulty to accurately localize; patient is known to have history of ileocecal area carcinoid and underwent surgery; B: Coronal first pass perfusion images show highly vascular lesion in the tip of the left lobe of the liver corresponding to abnormal radiotracer uptake, this location is very common for PET-CT misregistration and there was no focal lesion identified in CT component of PET-CT. PET: Positron emission tomography; CT: Computed tomography; FDG: Fluorodeoxyglucose.

the diagnosis of tumoral thrombus is usually made incidentally, discrimination between benign, and tumor thrombus can have significant implications in patient's management. In general, tumor thrombus

is a rare complication of solid cancers, with occult inferior vena cava tumor thrombosis having a reported incidence of 0.11%. Few case reports have described the diagnosis of tumor thrombus by PET-CT in



**Figure 5** Differentiation between tumoral thrombus from bland thrombus. A: Differentiation between tumoral thrombus from bland thrombus in patient with history of thyroid cancer treated with total thyroidectomy presented with neck mass. Coronal fused FDG-PET image shows intense linear FDG uptake from in the thyroid bed (white arrow) and spreading through SCV to the right atrium (red arrow); B: Four chamber cine image shows irregularly defined mass in the right atrium (arrow), the rest of cardiac examination was unremarkable; C: Axial HASTE at the junction of superior vena cava and right atrium shows a high signal intensity mass (arrow). PET: Positron emission tomography; CT: Computed tomography; FDG: Fluorodeoxyglucose.



**Figure 6** Differentiation between tumoral thrombus from bland thrombus. A: Differentiation between tumoral thrombus from bland thrombus in female patient with history ovarian cancer, patient was known to have chronic pulmonary embolism, there was a bland thrombus almost occluding the left pulmonary artery was no FDG uptake (arrow); B: Axial CT image shows a left pulmonary artery thrombus. CT: Computed tomography; FDG: Fluorodeoxyglucose.

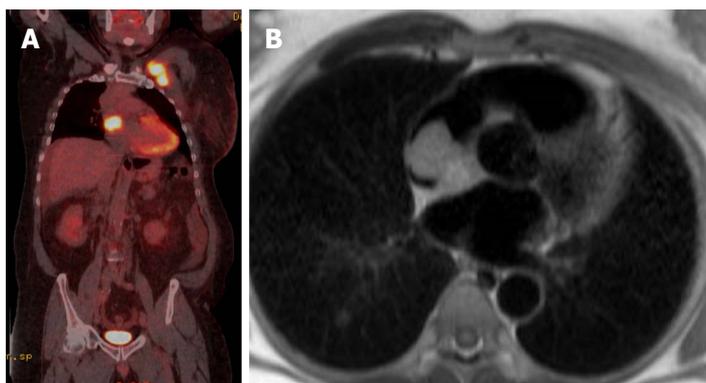
various cancer including pancreatic, colon, renal cell cancer and adrenocortical cancer. In contrast, venous thromboembolism (VTE) is relatively common than tumor thrombosis in patients with cancer. Cancer has been associated with 18% of all cases of incidental VTE. Across all patients with cancer, the risk for VTE has elevated seven folds, in certain malignances the risk for VTE may increase up to 28-folds<sup>[18]</sup>.

Tumor thrombosis is composed mainly of viable tumor cells and usually has high metabolic neoplastic activity<sup>[19]</sup> with subsequent high FDG uptake. FDG uptake in malignant cells is mediated through glucose transporters receptors. In contrast, benign thrombus is composed of activated of platelets, macrophages and fibrin. Therefore, benign thrombus is none metabolically active, simple, non-infected thrombus called bland thrombus. On PET-CT images, bland thrombus appear as intravascular filling defect without FDG uptake and can be found in veins of any size and location.

Distinguishing between benign thrombus and tumor thrombus on basis of presence or absence of FDG uptake may be difficult, it is quite reasonable for

inflammatory or infectious thrombus to demonstrate some degree of FDG uptake. It is reported that inflammatory cells cause significant increase in FDG uptake in presence of platelet-aggregation factors and cytokines including growth factors<sup>[20]</sup>. In addition, expression of the glucose transporter is also increased in activated granulocytes and macrophages<sup>[21]</sup>. The differential diagnosis can be narrowed down by correlating clinical presentation, distinctive clinical features, demographics, and relevant laboratory findings in association with imaging characterization of the thrombus.

Different imaging modalities are available for distinguishing between benign and malignant thrombus. PET-CT offers comprehensive anatomical and metabolic evaluation of the thrombus, particularly, if CT component performed with IV iodinated contrast. On MRI, the signal intensity of the thrombus may vary depending on the age of the thrombus. Gadolinium contrast is useful for differentiating thrombus from tumor, Thrombus typically does not enhance but tumors usually enhance on delayed imaging<sup>[22]</sup>. One



**Figure 7 M staging.** A: M staging: Coronal PET-CT image of patient with lymphoma with unexpected cardiac involvement; B: Axial T1-weighted image at the level of interatrial septum shows well defined mass attached to the atrial septum and nearly fills the right atrium and was proved to be lymphoma. PET: Positron emission tomography; CT: Computed tomography.

study reported, diffusion weighted (DW) imaging enables differentiation between portal vein tumoral thrombus from bland thrombus in patients with hepatocellular carcinoma (HCC), when apparent diffusion coefficient (ADC) of the thrombus to ADC of HCC is less than 2 and when the thrombus showed signal intensity similar to HCC, DW imaging may be very helpful in certain patients, such as patients with contraindication for contrast material injection and/or history of previous reaction to contrast media<sup>[23]</sup> (Figures 5 and 6).

## M STAGING

CMR is a very helpful imaging technique for diagnosis of cardiac tumors which enables evaluation of anatomy, function, tissue type, and vascularity and relationship to adjacent structures. It also allows searching for primary tumors in case of cardiac metastases and detection for metastases in the thorax and liver/abdomen. However, CMR is not adequate for M staging, PET-CT is useful technique for M staging of wide varieties of cancers, several studies reported that PET-CT is more accurate than other conventional imaging staging in several cancer such as several types of lymphoma, solid cancer such as breast, lung, ovary, and head and neck cancers. The newer MRI technique, whole body diffusion weighted imaging is used for tumors detection, characterization, therapy monitoring. In certain with low FDG, uptakes such as neuroendocrine tumors, thyroid cancer and several low malignancy lymphomas, whole body DW is additive for PET-CT for tumors detection, staging, and assessment for response for therapy<sup>[24,25]</sup> (Figure 7).

## EVALUATION OF AGGRESSIVENESS OF THE LESION AND ASSESSMENT OF CARDIAC INVOLVEMENT

FDG PET uptake reflects the metabolic glycolysis in tumors and supplies additional information to mor-

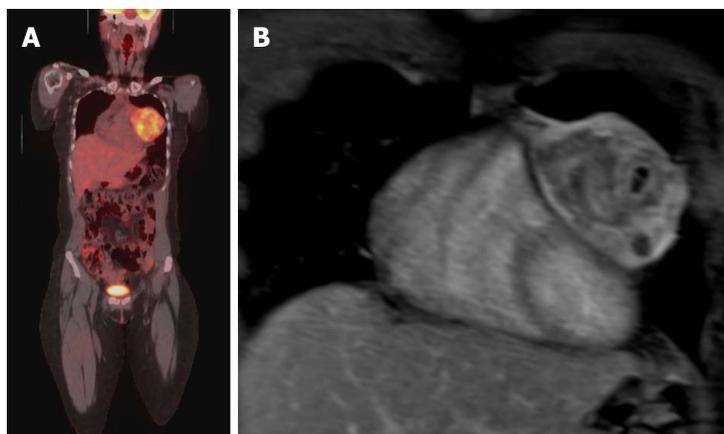
phological imaging. Generally, there is correlation between glucose accumulation in tumors tissue and degree of malignancy, with some exceptions<sup>[26,27]</sup>. However, PET has not yet systematically evaluated for characterization of cardiac tumors, furthermore, PET imaging can assess the local extent of the tumors and tumor infiltration to adjacent tissue. In addition, it is not often possible to accurately localize the lesion using low dose CT component of PET-CT. Contrast-enhanced CT visualizes several morphological features of cardiac tumors and helps to discriminate between benign and malignant tumors. CT high sensitive markers for malignancy includes location of the tumors outside the heart, tissue inhomogeneity and contrast enhancement. The presence of pericardial effusion is a high specific feature for malignancy, but tumors size is neither specific nor sensitive for malignancy<sup>[28]</sup>. A well-defined tumor without infiltration to adjacent structures is highly suggestive for benignity. CMR may have benefit over CT in the assessment of local tumor extension because MRI provides high soft tissue contrast<sup>[29,30]</sup>. Therefore PET-MRI can have role in the detection of T-stage and assessment of local invasion and infiltration (Figures 8 and 9).

## OTHER POTENTIAL INTEGRATED PET-MRI APPLICATIONS RELATED TO CARDIAC TUMORS

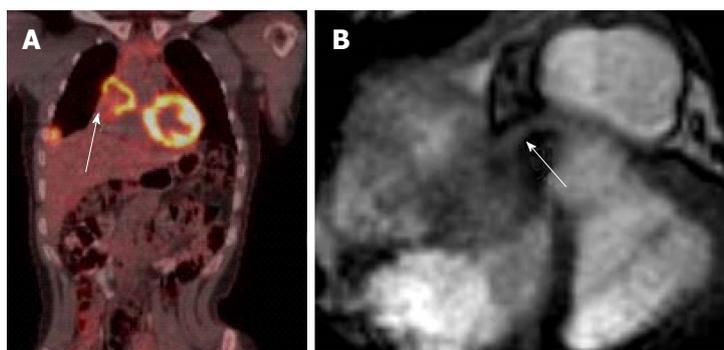
PET-MRI with optimal coregistration is essential to differentiate between residual scar tissue and tumors relapse, integrated PET-MRI imaging obviously combines the advantage of both methods in a single examination. FDG PET- and MRI-imaging yielded 100% sensitivity and 92% specificity in detecting tumors malignancy, but combined PET-MR yielded 100% sensitivity and specificity in one small study, one of the limitations of this study was small ample size<sup>[31]</sup>. In addition, in integrated PET-MRI, MRI component can assess the cardiac function, volume, morphology, and metabolism, and accurately assess tumors infiltration to



**Figure 8** Evaluation of the aggressiveness of the lesion and assessment of cardiac involvement. A: Evaluation of the aggressiveness of the lesion and assessment of cardiac involvement; whole body PET-CT image of patient with extensive Ewing sarcoma of the left hemithorax, PET-CT images are not sufficient to evaluate local extension of the tumor to the heart; B: Axial delayed enhancement image shows large necrotic mass occupying the left hemithorax with direct left ventricle (upper arrow) the arrow without circle and left atrial invasion (lower arrow). PET: Positron emission tomography; CT: Computed tomography.



**Figure 9** Evaluation of the aggressiveness of the lesion and assessment of cardiac involvement. A: Evaluation of the aggressiveness of the lesion and assessment of cardiac involvement; Coronal PET-CT image in a patient with Ewing sarcoma of the left chest wall with direct compression of the left side of the heart; B: Coronal Post contrast T1-weighted image of the heart shows no evidence of cardiac invasion with clear separation of the mass from the heart, the mass was surgically removed and there was no evidence of cardiac invasion. PET: Positron emission tomography; CT: Computed tomography.



**Figure 10** Evaluation of coronary artery involvement by the tumor. A: Coronal PET-CT image in a female patient with history of breast cancer with mediastinal and lung metastasis and recurrent chest pain; B: Axial cine image at the base of the heart shows metastatic lesion invading the heart causing mechanical obstruction of the right coronary artery (arrow). PET: Positron emission tomography; CT: Computed tomography.

various cardiac struts such as valves, papillary muscle, or coronary artery (Figure 10).

## CONCLUSION

With the commercial availability of PET-MRI true

simultaneous PET and MRI in a single study is real. Several studies have demonstrated the feasibility and incremental value of combined PET and MRI in many clinical applications. A combination of PET and MRI can provide incremental information in many cardiovascular scenarios. Evaluation of cardiac tumors may be most

straightforward application for PET-MRI because it offers a unique opportunity to evaluate the tumor morphology, characterization, infiltration to adjacent structures, local and M staging and comprehensive cardiac evaluation in a single study.

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## Hand dysfunction after transradial artery catheterization for coronary procedures

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**Author contributions:** Nolan J and Mamas MA conceived the idea and designed the study protocol; Kwok CS conducted the literature; Ul Haq MA and Wong CW reviewed search results; Kwok CS analyzed the data; Ul Haq MA and Rashid M wrote the first draft and all authors contributed in final completion of manuscript.

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### Abstract

#### AIM

To synthesize the available literature on hand dysfunction after transradial catheterization.

#### METHODS

We searched MEDLINE and EMBASE. The search results were reviewed by two independent judicators for studies that met the inclusion criteria and relevant reviews. We included studies that evaluated any transradial procedure and evaluated hand function outcomes post transradial procedure. There were no restrictions based on sample size. There was no restriction on method of assessing hand function which included disability, nerve damage, motor or sensory loss. There was no restriction based on language of study. Data was extracted, these results were narratively synthesized.

#### RESULTS

Out of 555 total studies 13 studies were finally included in review. A total of 3815 participants with mean age of 62.5 years were included in this review. A variety of methods were used to assess sensory and motor dysfunction of hand. Out of 13 studies included, only 3 studies reported nerve damage with a combined incidence of 0.16%, 5 studies reported sensory loss, tingling and numbness with a pooled incidence of 1.52%. Pain after transradial access was the most common form of hand dysfunction (6.67%) reported in 3 studies. The incidence of hand dysfunction defined as disability, grip strength change, power loss or any other hand complication was incredibly low at 0.26%. Although radial artery occlusion was not our primary end point for

this review, it was observed in 2.41% of the participants in total of five studies included.

### CONCLUSION

Hand dysfunction may occur post transradial catheterisation and majority of symptoms resolve without any clinical sequel.

**Key words:** Transradial access; Transfemoral access; Hand dysfunction

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**Core tip:** Transradial access (TRA) is default access site in many countries to perform coronary procedures. Hand function may occur post TRA, however our review shows that its incidence is exceedingly low and most symptoms resolve without any clinical sequel.

Ul Haq MA, Rashid M, Kwok CS, Wong CW, Nolan J, Mamas MA. Hand dysfunction after transradial artery catheterization for coronary procedures. *World J Cardiol* 2017; 9(7): 609-619 Available from: URL: <http://www.wjgnet.com/1949-8462/full/v9/i7/609.htm> DOI: <http://dx.doi.org/10.4330/wjc.v9.i7.609>

## INTRODUCTION

Coronary angiography is the current gold standard in providing anatomical information regarding the extent and severity of coronary artery disease<sup>[1,2]</sup>. Access site practice has changed in a number of European and Asian countries from mainly being transfemoral (TFA) to transradial (TRA)<sup>[3,4]</sup> in view of less access site related bleeding complications, mortality and shorter hospital stay associated with TRA<sup>[5-11]</sup>. For instance, in the United Kingdom use of radial access has increased from 14% to 80% between 2005 and 2014 in patients undergoing percutaneous coronary intervention (PCI) and it is estimated that this practice change has saved an estimated 450 lives nationally<sup>[12]</sup>. In the most recent European Society of Cardiology guidelines for management of non-ST elevation myocardial infarction (NSTEMI), TRA received class 1A indication for invasive management of NSTEMI with PCI<sup>[2]</sup>. Furthermore national bodies have formulated recommendations to prevent and minimize procedure related complications of TRA such as reducing the risk of radial artery occlusion (RAO), minimizing patient and operator radiation exposure and transitioning to TRA for primary PCI<sup>[13,14]</sup>.

Nevertheless, despite of its clear advantages over TFA, TRA is not without limitations and is associated with longer operator learning curve<sup>[15,16]</sup>, increased radiation exposure in individual operators at the start of their learning curves<sup>[17,18]</sup> and higher case radial proportion to translate the better results of randomized trials into clinical practice<sup>[11,19,20]</sup>. Moreover, vas-

cular complications such as RAO<sup>[21]</sup> and radial artery spasm<sup>[22]</sup> are not uncommon and very recently concerns have been raised that patients undergoing TRA PCI may encounter hand dysfunction<sup>[23]</sup>.

Whether access site related complications can lead to hand dysfunction is unclear and studies have reported inconsistency results. A study by van Leeuwen *et al*<sup>[24]</sup> investigated the impact of TRA on limb function at long term follow up, reported 9% and 11% of the patients develop temporary or permanent hand dysfunction respectively. Whereas Zwaan *et al*<sup>[25]</sup> reported a pooled incidence of 0.32% in 14 studies evaluating hand dysfunction post TRA.

Considering that the TRA is the predominant access site for cardiac catheterization procedures in many countries, there is little data around hand dysfunction post procedure. In view of the limited published data we conducted a systematic review to evaluate the hand dysfunction post TRA.

## MATERIALS AND METHODS

We searched MEDLINE and EMBASE on 23 August 2016 using the search terms: [(radial or transradial or radial artery) AND (catheterisation or catheterization or angiography or angiogram or angioplasty or percutaneous coronary intervention or PCI)] AND (hand function or grip strength or disability or dysfunction or sensation or paraesthesia or paralysis). The search results were reviewed by two independent adjudicators (MAU, CWW) for studies that met the inclusion criteria and relevant reviews. The bibliographies of included studies and relevant reviewers were screened for additional studies.

We included studies with patients undergoing transradial procedure and evaluated hand function outcomes post procedure. No control group was required so studies could be single arm. There were no restrictions based on language, sample size or method of assessing hand function which included disability, nerve damage, motor or sensory loss. These results were then narratively synthesized.

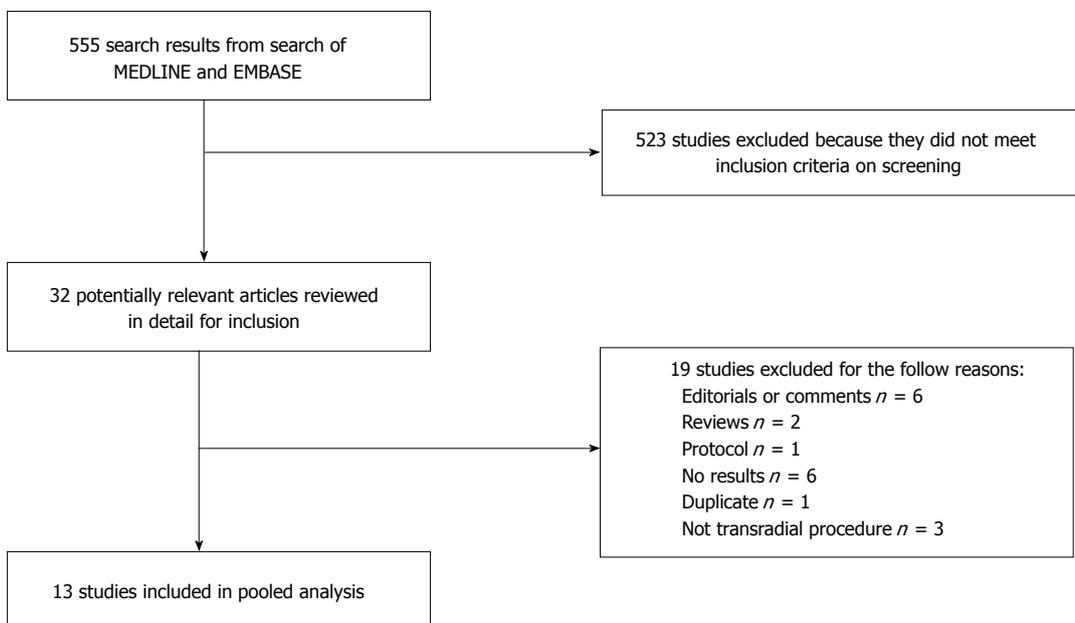
## RESULTS

Our search yielded 555 related studies out of which after screening and reviewing the full manuscripts, 13<sup>[24,26-38]</sup> studies were included in the final review. Detail process of inclusion and exclusion is illustrated in Figure 1.

Table 1 provides the description of studies, year of study, percentage of males and number of participants. A total of 3815 participants with mean age of 62.5 years were included in the studies. Table 2 describes the various methods of assessment employed to assess hand dysfunction, follow up time and results. We observed significant heterogeneity in the methods of assessment hand function and follow

**Table 1 Study design and participant characteristics**

Ref.	Study design/country/year	No. of participants	Mean age	% male	Participant inclusion criteria and procedural details
Benit <i>et al</i> <sup>[26]</sup>	Randomized trial; Belgium; 1994-1995	50	57.7	100%	Participants had transradial coronary angioplasty with 6-Fr catheters and Palmaz-Schatz stent
Campeau <i>et al</i> <sup>[27]</sup>	Cohort study; Canada; Unclear	100	58 (median)	90%	Participants had transradial coronary angiogram with 5-Fr, 6-Fr and 7-Fr sheath
Chatelain <i>et al</i> <sup>[28]</sup>	Cohort study; Switzerland; 1995-1997	159	60	82%	Participants had transradial diagnostic and interventional cardiac procedures with 4-Fr, 5-Fr or 6-Fr introducer sheath and guide catheters with RadiStop radial compression system
De Belder <i>et al</i> <sup>[29]</sup>	Cohort study; United Kingdom; Unclear	75	Unclear	69%	Participants had transradial coronary angiography and intervention and severe peripheral vascular disease with 5-Fr or 6-Fr sheath and 6-Fr guide catheter
Kiemeneij <i>et al</i> <sup>[30]</sup>	Cohort study; The Netherlands; 1992-1993	100	62	77%	Participants had transradial coronary angiography with 6-Fr introducer and 6-Fr-guide catheters
Lotan <i>et al</i> <sup>[31]</sup>	Cohort study; Israel; 1994	100	61	79%	Participants had transradial coronary angiography and angioplasty with 6-Fr introducer and 6-Fr guide catheters
Prull <i>et al</i> <sup>[32]</sup>	Cohort study; Germany; Unclear	93	62.5	80.6%	Participants had transradial diagnostic cardiac catheterization with 5-Fr or 6-Fr sheath or transradial coronary intervention with 7-Fr sheath
Sciahbasi <i>et al</i> <sup>[33]</sup>	Prospective cohort study; Italy; Unclear	99	65	72%	Participants had transradial coronary angiography and angioplasty with 6-Fr introducer sheath
Tharmaratnam <i>et al</i> <sup>[35]</sup>	Retrospective case control study; United Kingdom; 2005-2006	1283	65.5	79%	Participants had transradial coronary angiography and angioplasty
Valgimigli <i>et al</i> <sup>[39]</sup>	Prospective cohort study; The Netherlands, Italy; 2014	942	70	73%	Participants had transradial coronary angiography and angioplasty
Van Leeuwen <i>et al</i> <sup>[24]</sup>	Prospective cohort study; The Netherlands; 2015	286	64	72%	Participants had transradial coronary angiography and angioplasty with 6-Fr introducer sheath
Wu <i>et al</i> <sup>[37]</sup>	Cohort study; United States; 1996-1998	40	65	88%	Participants underwent 6-Fr and 8-Fr transradial procedure
Zankl <i>et al</i> <sup>[34]</sup>	Prospective cohort study; Germany; 2010	488	Unclear	Unclear	Participants had transradial coronary angiography and angioplasty with 5- and 6-Fr introducer, 4-, 5- and 6-Fr catheters



**Figure 1 Flow diagram of study inclusion/ exclusion.**

up time. For instance, the follow up of assessment varied from anytime between the day procedure was undertaken up to a year post TRA. Similarly, an array

of methods were employed to assess the sensory and motor component of hand function such as questionnaire based surveys in the form of Disabilities

**Table 2 Results of studies**

Ref.	Measure of hand function and vascular complications	Follow up post procedure	Results
Benit <i>et al</i> <sup>[26]</sup>	Local complications assessed in clinic by history and EMG	1 mo	Nerve damage documented by EMG: 0/50 Local pain: 0/50
Campeau <i>et al</i> <sup>[27]</sup>	Patients were re-examined or questioned over telephone about local complications	1 to 3 mo	No nerve injury: 0/100
Chatelain <i>et al</i> <sup>[28]</sup>	Physicians assessed for any clinical events	Assessment prior to discharge	Paraesthesia of right thumb during exercise: 1/159
De Belder <i>et al</i> <sup>[29]</sup>	Clinical evaluation	4-6 wk	Haematoma and paraesthesia post procedure: 1/75 Hand sensation and function at 4-6 wk: 0/75
Kiemeneij <i>et al</i> <sup>[30]</sup>	Examination and ultrasound study performed if radial artery pulsations or flow were absent	1 to 3 mo	Functional disability of the hand: 0/100
Lotan <i>et al</i> <sup>[31]</sup>	Assessment methods unclear	1 mo follow up	Small hematoma in wrist: 3/100 Small pseudoaneurysm: 2/100 Numbness of the thumb and index finger: 1/100 No flow on Doppler: 2/100
Prull <i>et al</i> <sup>[32]</sup>	Clinical evaluation with ultrasound	Post-procedure assessment	Vascular complication: 9/93 Motor skills, coordination or force reduction of hand after procedure: 0/93
Sciahbasi <i>et al</i> <sup>[33]</sup>	Radial artery occlusion by ultrasound test. Handgrip strength by Jamar Plus dynamometer. Thumb and forefinger pinch test by Jamar Plus electronic pinch gauge	Day of procedure and at least 30 d follow up	No pseudoaneurysm: 0/93 Radial artery occlusion: 9/99 Hand grip strength change at follow up: 0/99 Thumb and forefinger pinch test change at follow up: 0/99
Tharmaratnam <i>et al</i> <sup>[35]</sup>	Questionnaire posted to address and clinical notes for significant clinical events	Unclear	Problem with radial access site: 166/1283 (12.9%) Pain at puncture site: 95/1283 (7.4%) Swelling: 46/1283 (3.6%) Bruising: 30/1283 (2.3%) Non-specific sensory abnormalities either pain or paraesthesia in hand: 22/1283 (1.71%)
Valgimigli <i>et al</i> <sup>[39]</sup>	Radial artery occlusion by duplex echocardiographic examination. Hand grip strength test with dynamometer	Just after procedure, 1 d, 30 d and 1 yr	Radial artery occlusions at day 1: 5/942 Radial artery occlusions at 1 year: 3/942 Change in handgrip strength test: 0/942
Van Leeuwen <i>et al</i> <sup>[24]</sup>	Quick DASH questionnaire and CISS questionnaire. Patients were asked to describe any procedure-related extremity complaints or loss of function at 1 mo	Pre, 30 d and 1 yr post procedure	Ischemic vascular or bleeding complications: 0/942 Temporary upper limb complaint (< 30 d): 26/286 (9%) Persisting upper limb complaint (> 30 d): 31/286 (11%) Pain: 13/286 Numbness: 2/286 Tingling: 3/286 Stiffness: 2/286 Less power: 2/286
Wu <i>et al</i> <sup>[37]</sup>	Ultrasound assessment for radial artery occlusion, aneurysm or dissection. Grip strength based on dynamometer results. Palmar pinch, key pinch and tip pinch strength tests were assessed by dynamic endurance test	Late follow up 315 d	Upper limb function by QuickDASH at 30 d: No change over time, baseline 4.55 (IQR 0-13.64), follow up 2.27 (IQR 0-9.32) Upper limb function by CISS at 30 d: No change over time Upper limb function by QuickDASH at 1 yr: no change over time, baseline 2.39 (IQR 0-13.64), follow up 0 (0-11.02) Cold intolerance was not associated with access route at 1 yr Hand complication in hospital: 0/40 Radial occlusion: 1/40 Late radial occlusions: 5/34 Radial artery aneurysm: 0/40 Radial artery dissection 0/40 Grip strength: Baseline 68 ± 34, post-catheterization 69 ± 35 Palmar pinch: Baseline 18 ± 10, post-catheterization 17 ± 6 Key pinch: Baseline 19 ± 7, post-catheterization 19 ± 6 Tip pinch: Baseline 14 ± 6, post-catheterization 14 ± 4 Endurance: Median for 6 Fr and 8 Fr is 78 (IQR 53, 108) and 58 (IQR 32, 68) respectively, post-catheterization 58 (IQR 47, 84) and 56 (IQR 38, 80), respectively
Zankl <i>et al</i> <sup>[34]</sup>	Assessment with ultrasound	4 wk follow up	Radial artery occlusion at 1 d: 51/488 Persistent radial artery occlusion at 4 wk: 21/488 Radial nerve paralysis: 1/488

CISS: Cold intolerance symptom severity; EMG: Electromyography.

**Table 3 Summary of pooled results for hand dysfunction or vascular complications post transradial procedure**

Hand dysfunction or vascular complication	No. of studies	No of events	No of participants	Percentage of events
Nerve damage	3 <sup>[26,27,34]</sup>	1	638	0.16%
Sensory loss, tingling and numbness	5 <sup>[24,28,29,31,35]</sup>	29	1903	1.52%
Pain	3 <sup>[24,26,35]</sup>	108	1619	6.67%
Hand function, disability, grip strength change, stiffness, power loss and hand complications	6 <sup>[24,30,32,33,37,39]</sup>	4	1560	0.26%
Vascular complications including occlusions, hematoma, pseudoaneurysm and dissection	6 <sup>[29,31,32,35,37,39]</sup>	54	1762	3.06%
Radial artery occlusion	5 <sup>[31,33,34,37,39]</sup>	40	1663	2.41%

**Table 4 Disabilities of Arm, Shoulder and Hand (QuickDASH) Questionnaire**

	No difficulty	Mild difficulty	Moderate difficulty	Severe difficulty	Unable
1 Open a tight or new jar	1	2	3	4	5
2 Do heavy house hold chores eg. Wash walls, floors	1	2	3	4	5
3 Carry a shopping bag or briefcase	1	2	3	4	5
4 Wash your back	1	2	3	4	5
5 Use a knife to cut food	1	2	3	4	5
6 Recreational activities in which you take some force or impact through your arm shoulder or hand	1	2	3	4	5
7 During the past week to what extent has your arm, shoulder or hand problem interfered with your normal social activities with family, friends, neighbors or groups?	1	2	3	4	5
8 During the past week, were you limited in your work or other daily activities as a result of your arm, shoulder or hand problem?	1	2	3	4	5
9 Arm, shoulder or hand pain	1	2	3	4	5
10 Tingling	1	2	3	4	5
11 Sleep	1	2	3	4	5

of Arm, Shoulder and Hand (Quick DASH) or Cold Intolerance and Symptom Severity (CISS) or postal surveys, electromyography (EMG), dynamometer and forefinger pinch grip tests.

Table 3 presents pooled results of various form of limb dysfunction described by the studies. Out of 13 studies included, only 3 studies reported nerve damage<sup>[26,27,34]</sup> with a combined incidence of 0.16%, 5 studies reported sensory loss, tingling and numbness<sup>[24,28,29,31,35]</sup> with a pooled incidence of 1.52%. Pain after TRA was the most common form of hand dysfunction (6.67%) reported in 3 studies<sup>[24,26,35]</sup>. The incidence of hand dysfunction defined as disability, grip strength change, power loss or any other hand complication was incredibly low at 0.26%<sup>[24,30,32,33,37,39]</sup>. Although RAO was not our primary end point for this review, it was observed in 2.41% of the participants in total of five studies included<sup>[31,33,34,37,39]</sup>.

In one the very early studies from pre-stent era, Campeau *et al.*<sup>[27]</sup> assessed the neurological damage to hand following TRA using 5 Fr, 6 Fr or 7 Fr sheath. Patients were assessed at 1 and 3 mo either clinically or *via* telephone reported no nerve injury. It is not clear how the nerve damage was assessed in patients reviewed by telephone. Another study employing a more subjective assessment of nerve function using EMG in 150 patients receiving TRA using a 6

Fr sheath reported no damage to the median nerve at 1 mo follow up. In a large retrospective analysis of 1283 patients undergoing TRA using hydrophilic sheaths, 13.2% patients reported non-specific sensory symptoms post procedure<sup>[35]</sup>. However, the results were dependent on a questionnaire based postal survey and no objective method was used to assess for the sensory loss. Similarly two other studies<sup>[28,29]</sup> assessing the neurological dysfunction post TRA, reported only 1 case of paraesthesia of right thumb and 1 case of forearm haematoma resulting in some sensory disturbance of hand but no loss of function. More importantly, both cases made full recovery without any clinical sequel.

In a prospective study of 203 patients after TRA, Valgimigli *et al.*<sup>[39]</sup> assessed the motor component of hand function by performing handgrip strength tests using a dynamometer at 30 d and 1 year, maximal isometric strength on handgrip test did not change over time. Van Leeuwen *et al.*<sup>[24]</sup> conducted a randomised study of 338 patients to evaluate motor component of upper limb function using self-reported shortened version of Disabilities of Arm, Shoulder and Hand (Quick DASH, Table 4) and sensory component using Cold Intolerance and Symptom Severity (CISS, Table 5) questionnaires at baseline and 30 d. There was no statistically significant change in Quick DASH score at baseline to follow up in patients undergoing

**Table 5 Cold Intolerance symptoms severity Questionnaire**

Questions	Score
Which of the following symptoms of cold intolerance do you experience in your injured limb on exposure to cold? Pain, numbness, stiffness, weakness, aching, skin colour change (white/bluish white/blue)	
How often do you experience these symptoms? (Please tick)	
Continuously/all the time	
Several times a day	
Once a day	
Once a week	
Once a month or less	
Never	
When you develop cold induced symptoms, on your return to a warm environment are the symptoms relieved? (Please tick)	
Not applicably	
Within a few minutes	
Within 30 min	
After more than 30 min	
What do you do to ease or prevent your symptoms occurring? (Please tick)	
Take no special action	
Keep hand in pocket	
Wear gloves in cold weather	
Wear gloves all the time	
Avoid cold weather/stay indoors	
Other (please specify)	
How much does cold bother your injured hand in the following situations? (Please score 0-10)	
Holding a glass of ice water	
Holding a frozen package from the freezer	
Washing in cold water	
When you get out of a hot bath/shower with air room temperature	
During cold wintry weather	
Please state how each of the following activities have been affected as a consequence of cold induced symptoms in your injured hand and score each (please score 0-4)	
Domestic chores	
Hobbies and interests	
Dressing and undressing	
Tying your	

TRA (baseline 4.55; IQR: 0.00 to 13.64; follow-up 2.27 IQR: 0.00 to 9.32,  $P = 0.06$ ). Similarly there was no change in the CISS score over time. An important feature of the study was they included patients undergoing TFA to make a comparison between the two access sites. More recently, HANGAR (HAND Grip test After tRansradial percutaneous coronary procedures) study investigated 108 patients with stable angina undergoing PCI using 6Fr sheath with a primary endpoint of variation in hand grip strength measured with the Jamar Plus dynamometer after the procedure<sup>[33]</sup>. The secondary endpoints of interest were thumb and forefinger pinch measured using key pinch and electronic pinch gauge respectively. Out of 99 patients, 9 patients developed radial artery occlusion after the procedure, the patients were then divided in two groups according to the radial patency (group 1) or occlusion (group 2) The hand grip test values were significantly reduced compared with baseline values ( $40 \pm 11$  kg in group 1,  $P < 0.0001$  and  $37 \pm 17$  kg in group 2,  $P = 0.007$ ) after the procedure but returned back to baseline at follow up. Interestingly thumb and finger pinch function was unaffected at baseline, after the procedure and follow up. Finally ARCUS (Effects of transradial percutaneous coronary intervention on upper extremity function) is an ongoing trial assessing

the effects of TRA on hand function by taking various measurement such as Echo Doppler for radial artery occlusion, Questionnaires testing including Quick DASH (Table 4), Boston Carpal Tunnel Questionnaire (BCTQ, Table 6) and Visual Analogue Scale (VAS), volumetry of hand and forearm, sensibility of fingertips, key and palmar grips and isometric strength of wrist and elbow<sup>[40]</sup>. The interim results were published recently suggesting that 143 of 191 (74.9%) patients had some form of upper limb dysfunction defined as a compiled binary score of various measurements taken<sup>[38]</sup>. Furthermore, RAO was 9.8% in upper limb dysfunction group as compared to 0% RAO in non-upper limb dysfunction group.

## DISCUSSION

In the current review, we synthesize the evidence on the incidence and clinical impact of hand dysfunction after TRA. We observe a very low incidence of hand dysfunction in limited literature and importantly, we observe significant heterogeneity in the definition and method of assessment of hand dysfunction amongst the studies, with no internationally accepted measure of hand dysfunction that can be used as the gold standard for such studies. Many of these studies are

**Table 6 Boston Carpal Tunnel Syndrome Questionnaire**

	1	2	3	4	5
A: Symptom severity scale (11 items)					
1 How severe is the hand or wrist pain that you have at night?	Normal	Slight	Medium	Serious	Very serious
2 How often did hand or wrist pain wake you up during a typical night in the past two weeks?	Normal	Once	2-3	4-5	> 5
3 Do you typically have pain in your hand or wrist during the daytime?	No Pain	Slight	Medium	Serious	Very Serious
4 How often do you have hand or wrist pain during daytime?	Normal	1-2 times/d	1 times/d	> 5 times/d	Continued
5 How long on average does an episode of pain last during the daytime?	Normal	< 10 min	10-60 continued	> 60 min	Continued
6 Do you have numbness (loss of sensation) in your hand?	Normal	Slight	Medium	Severe	Very Serious
7 Do you have weakness in your hand or wrist?	Normal	Slight	Medium	Severe	Very Serious
8 Do you have tingling sensations in your hand?	Normal	Slight	Medium	Severe	Very Serious
9 How severe is numbness (loss of sensation) or tingling at night?	Normal	Slight	Medium	Severe	Very Serious
10 How often did hand numbness or tingling wake you up during a typical night during the past two weeks?	Normal	Once	2-3 times	4-5 times	> 5
11 Do you have difficulty with the grasping and use of small objects such as keys or pens?	Without difficulty	Little difficulty	Moderate difficulty	Very difficulty	Very difficult
B: Functional status scale (8 items)					
Writing					
Buttoning of cloths					
Holding a book while reading					
Gripping of a telephone handle					
Opening of jars					
House hold chores					
Carrying of grocery basket					
Bathing and dressing					

poorly conducted and subjective reports of sensory/hand dysfunction with only few studies quantifying any changes in a robust manner. Finally, we find no evidence of widespread clinically significant hand dysfunction post TRA and the potential benefits of TRA in reducing major bleeding, access site related complications and mortality outweigh such rare events.

The majority of studies that reported cases of neurological deficits following TRA were underpowered<sup>[26,29,37]</sup>. In most circumstances, studies relied on subjective reporting of symptoms by patients, rather than quantifying the neurologic deficit with proper neurophysiological or other robust objective testing<sup>[24,27-31,34,35]</sup>. Benit *et al*<sup>[26]</sup> assessed nerve damage clinically and quantified this using EMG. Valgimigli *et al*<sup>[39]</sup> and Sciahbasi *et al*<sup>[33]</sup> used dynamometer to assess hand grip function whereas only Sciahbasi *et al*<sup>[33]</sup> used electronic pinch gauge to check for thumb and finger pinch tests. Van Leeuwen *et al*<sup>[24]</sup> used QuickDASH questionnaire and Cold Intolerance Symptom Severity (CISS) questionnaire based assessment of hand function post TRA.

The clinical significance of neurological and motor injuries leading to hand dysfunction must be con-

sidered. Many neurological injuries are known to be transient and resolve over time. For instance, van Leeuwen *et al*<sup>[24]</sup> reported that almost 20% patients developed subjective neurological complications in the form of numbness, tingling, stiffness and less power, more importantly nearly 50% resolved by 30 d at follow up. Similarly, pain is commonly reported by patients regardless of the access site practice but long term sequel of such symptoms is unclear. In addition, there is no consensus on the optimal method of assessing hand function and studies so far have used various methods such VAS, BCTQ, Disabilities of Arm, Shoulder and Hand (QuickDASH) and CISS (Tables 4-6).

Visual analogue scale is measure of pain intensity on a continuous scale anchored by pain descriptor ranging from "no pain (0 score)" to worst pain (score 10)<sup>[41]</sup>. BCTQ questionnaire comprises of a symptom severity scale and a functional status scale (Table 6). The symptom severity scale has 11 questions scored from 1 point (mildest) to 5 points (most severe). Likewise, functional status scale has eight questions scored from 1 point (no difficulty with activity) to 5 points (cannot perform the activity at all)<sup>[42]</sup>. Similarly,

CISS score is usually employed to detect cold intolerance. It consists of 6 questions and based on response, patient with a score of 30 or higher is said to have pathological CISS score<sup>[43,44]</sup>. There is a need of internationally agreed, sensitive method of assessing hand function amongst the radial community to evaluate and monitor for such complications.

The mechanisms that may underlie hand dysfunction after TRA remains unclear though there are several possible explanations. For instance, Flexor Carpi Radialis, Flexor Pollicis Longus tendons and Median nerve lies next to radial artery at wrist from lateral to medial respectively. Neurological deficits may occur from direct damage to these structures during cannulation of the radial artery. There also may be indirect extrinsic compression of these structures due to haematomas which may result in motor or sensory deficit of the hand. Endothelial dysfunction, intimal hyperplasia and medial dissections resulting in radial artery stenosis and occlusion are well known complications associated with TRA<sup>[45,46]</sup>. Haematoma or pseudoaneurysm is another relatively rare complications encountered after TRA. There is a possibility that such vascular complications may lead to transient or permanent ischemia of the nervous supply of hand leading to sensory deficit or directly cause motor dysfunction of small muscles of hand. Additionally, there are anatomic variations of neurovascular bundles of hand<sup>[47]</sup> which might be injured during the puncture leading to hand dysfunction such as sensory or motor symptoms. There are isolated case reports that describe this mechanism of nerve damage<sup>[48-50]</sup>. RAO may occur post TRA<sup>[21]</sup>, however it is usually asymptomatic and rarely causes ischemia due to the excellent collateral supply of hand from ulnar and intermediate artery<sup>[45,51]</sup>. Notably, recent results of ACRUS trial suggested that hand dysfunction was very common in patients developing RAO compared to the ones with a patent radial artery post procedure<sup>[38]</sup>. However, in the study conducted by Valgimigli *et al.*<sup>[39]</sup> across whole spectrum of Allen test, there were no differences in serial lactate measurement after the procedure suggesting that it is unlikely such mechanism can lead to clinically significant hand dysfunction.

It is unclear what factors are associated with hand dysfunction after TRA. It could very well be that certain patient factors, such as baseline hand muscle strength, history of musculoskeletal disorders, gender, atypical anatomy may be a risk factor but no studies have evaluated such predictors. Another important point how minor changes in hand function may impact on a patient's life. For example individuals that require very fine manual dexterity for their profession such as watchmakers, pianists, and surgeons may notice very minor changes in hand function whilst in other patient groups this may be less relevant. Finally, the way in which complications are managed may also affect hand function such as how quickly a haematoma

is identified and compressed. Future studies should be focused in assessing both patient and procedure related factors which may lead to development of hand dysfunction with clinically relevant end points. Finally, current literature does not provide an insight around the prevalence and significance of lower limb function in patients undergoing transfemoral access. Adequately powered randomized trial with a control group is required to better understand the incidence and mechanisms involved in the development of hand dysfunction post TRA.

In conclusion, hand dysfunction is an exceedingly rare complication post TRA. There is significant heterogeneity in the methodology and reporting of the studies investigating hand function after TRA. Patients may develop non-specific sensory symptoms or muscle weakness but majority of these symptoms resolve over time. Future studies should be focused around assessing such complications using robust methodology and more importantly reporting on the clinical relevance of hand function. Given the reductions in mortality, MACE and major bleeding complications associated with use of TRA in high risk groups undergoing PCI, TRA should remain the default access site for PCI in such high risk groups of patients at risk of bleeding complications, in line with international guidelines and consensus statements.

## COMMENTS

### Background

The uptake of transradial access (TRA) for cardiac procedures is growing with both observational and randomized controlled trial data showing decreases in mortality and access site related bleeding complications across the whole spectrum of acute coronary syndromes compared to procedures undertaken through the femoral approach.

### Research frontiers

Recently, concerns have been raised around hand dysfunction following transradial procedures.

### Innovations and breakthroughs

The review of the literature suggests that hand dysfunction after TRA has been reported in several studies and case reports. The quality of the evidence describing these complications is poor as many studies are underpowered and do not report any events. These complications appear to be rare and of uncertain clinical impact in most cases. Isolated case reports have reported rare complications such as compartment syndrome requiring emergency surgery or complex regional pain syndrome which can be disabling due to chronic pain.

### Applications

The current literature is limited as there is no standardized method of assessment of hand function with very few studies that provide mechanistic insight. Higher quality studies with clinically relevant endpoints are needed to better understand the incidence and clinical significance of the hand dysfunction following TRA.

### Terminology

TRA: Transradial access; TFA: Transfemoral access; PCI: Percutaneous coronary intervention; UED: Upper Extremity dysfunction.

**Peer-review**

It is an excellent review.

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## Infective endocarditis and thoracic aortic disease: A review on forgotten psychological aspects

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### Abstract

#### AIM

To summarize the current evidence on psychological issues in thoracic aortic disease (TAD) and infective endocarditis (IE) setting.

#### METHODS

We performed a narrative review about psychological issues in adults with IE and TAD. Through the electronic databases, PubMed and PsycINFO, we searched full manuscripts in English and published until September 1, 2014.

#### RESULTS

We found sixteen studies exploring psychological issues in patients with IE (six studies) and in TAD (ten papers). Psychological issues assessed were quality of life, depression, anxiety and posttraumatic stress disorder. Quality of life was explored in IE (four papers) and in TAD (eight papers). Depression and anxiety were analyzed in TAD only (five papers). Post-traumatic stress disorder was assessed in IE (one study). Quality of life was found impaired in three of four studies about IE and in three of eight studies about TAD. Posttraumatic stress disorder was present in 11% and was associated with lower levels of quality of life in IE patients. In TAD patients, anxiety and depression levels after different invasive interventions did not differ.

#### CONCLUSION

Sixteen studies report about psychological issues in IE and TAD. Most of them explore quality of life and to a less extent anxiety and depression.

**Key words:** Infective endocarditis; Thoracic aortic disease; Psychology; Depression; Anxiety; Quality of life; Posttraumatic stress disorder

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**Core tip:** Some papers and guidelines have recently reported that psychosocial factors such as depression, anxiety and other mental disorders like personality disorders and post-traumatic stress disorder are related to morbidity and mortality due to cardiovascular diseases. Chronic heart failure, arrhythmias, and acute myocardial infarction are one of the most studied pathologies. However, other cardiovascular diseases are poorly or not yet studied from a psychological point of view, including infective endocarditis and thoracic aortic disease. The study of psychological issues in these severe diseases could bring us information about specific needs to cover with psychological interventions and to design specialized care training and practice.

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## INTRODUCTION

Infective endocarditis (IE) is an inflammatory disease of the heart, an infection of the endocardium that usually involves valves and adjacent structures. The incidence of IE ranges from one country to another within 3-10 episodes/100000 person-years. It is higher in patients with underlying valvular heart diseases, prosthesis and those with intravenous drug abuse. IE with positive blood cultures represents 85% of all IE. Causative microorganisms are most often staphylococci, streptococci, and enterococci<sup>[1-7]</sup>. This disorder presents in a variety of clinical forms according to the initial clinical manifestation, underlying cardiac disease, microorganism involved, prosthesis presence, and development of complications. It may present as an acute and rapidly progressive infection or as sub-acute with low-grade fever and non-specific symptoms. With a modern combination of antimicrobial therapy and heart valve surgery, the in-hospital mortality rate of patients with or chronic disease IE varies from 9.6 to more than 26% (1-8)<sup>[1-8]</sup>. Psychological factors such as depression, anxiety and some personality traits could negative influence IE development and prognosis.

On the other hand, thoracic aortic diseases (TAD) include a wide spectrum of degenerative, structural, acquired, genetic-based, and traumatic disease states and presentations. The overall global death rate from aortic aneurysms and aortic dissection increased from 2.49 per 100000, to 2.79 per 100000 inhabitants between 1990 and 2010. TAD may be diagnosed after a long period of subclinical development or after an acute presentation such as acute aortic syndromes. Acute aortic syndromes are often the first sign of the disease, requiring rapid diagnosis and decision-making to improve prognosis. Medical therapy aims to reduce

shear stress on the diseased segment of the aorta by reducing blood pressure and cardiac contractibility. Further management options include endovascular therapy and surgery<sup>[9,10]</sup>. Psychological factors such as anxiety, depression and personality, could promote subclinical development and could negatively influence medical outcome after surgery and endovascular therapy, as well.

The aim of this review is to summarize the current evidence on psychological issues in TAD and IE setting. Thus, we performed a narrative review about psychological issues in adults with both TAD and IE.

## MATERIALS AND METHODS

Through the electronic databases PubMed and PsycINFO we searched all full manuscripts published in English until September 1, 2014.

The main data search terms were: Infective endocarditis + psychology, infective endocarditis + psychiatry, infective endocarditis + depression, infective endocarditis + anxiety, infective endocarditis + quality of life, infective endocarditis + personality, infective endocarditis + illness perception, infective endocarditis + therapeutic adherence, infective endocarditis + coping, thoracic aortic disease + psychology, thoracic aortic disease + psychiatry, thoracic aortic disease + depression, thoracic aortic disease + anxiety, thoracic aortic disease + personality, thoracic aortic disease + quality of life, thoracic aortic disease + therapeutic adherence, thoracic aortic disease + illness perception, thoracic aortic disease + coping.

## RESULTS

We found sixteen studies exploring psychological issues in patients with IE and TAD: Six about IE and ten about TAD. Main results are summarized in Tables 1 (IE) and 2 (TAD). Psychological issues assessed were mainly quality of life, depression, anxiety and post-traumatic stress disorder.

Quality of life was reviewed in 4 papers for IE and for TAD in 8 papers using Short Form 36 Health Survey questionnaire (SF-36) or EuroQol five dimensions questionnaire (EQ-5D).

Post-traumatic stress disorder was assessed in IE (one study) using the Post-traumatic stress disorder questionnaire. Depression and anxiety were analyzed in TAD (five papers) using Hospital Anxiety and Depression Scale (HADS).

### IE

We included six manuscripts about psychological issues in IE, all published in the last 5 years. Two papers used a qualitative method and four studies used a quantitative prospective design.

**Quantitative studies:** Quantitative studies assessed quality of life using standardized questionnaires.

Table 1 Scheme of main findings about infective endocarditis

Ref.	Methods and materials	Main results
Verhagen <i>et al</i> <sup>[11]</sup> , 2009	Prospective, 67 treated for left-sided native valve endocarditis complete Short Form 36 Health Survey questionnaire and Posttraumatic Stress Disorder questionnaire	Quality of life was significantly impaired in IE patients, compared with an age- and sex-matched population. Posttraumatic stress disorder 11%
Perrotta <i>et al</i> <sup>[12]</sup> , 2010	Prospective, 40 infective prosthetic valve endocarditis or native endocarditis with abscess operated with homograft replacement. Short Form 36 Health Survey questionnaire	Statistically significant differences in quality of life were found between IE patients and an age-matched and gender-matched general population
Berg <i>et al</i> <sup>[15]</sup> , 2010	Qualitative, 10 patients. Semi-structured interview	Patients explain that a sudden unexpected physical change occurred that is difficult to understand and interpret. During the hospital admission, time is spent thinking about choices and lost possibilities before admission. They talk about investing their energy and attention on getting well
Yeates <i>et al</i> <sup>[13]</sup> , 2010	Prospective, 9 active native left sided valve endocarditis and cerebrovascular complications. EuroQol five dimensions questionnaire	6 reported some problems with mobility, 5 reported some problems with usual activities and 5 pain or discomfort
Nayak <i>et al</i> <sup>[14]</sup> , 2011	Prospective, 85 active endocarditis, native valve endocarditis or prosthetic valve endocarditis. EuroQol five dimensions questionnaire	Quality of life was not impaired
Rasmussen <i>et al</i> <sup>[16]</sup> , 2014	Qualitative, 11 patients. Semi-structured interview	Patients felt physically weak and mentally imbalanced to a varying degree. Uncertainty of recovery trajectory and future capacity was considered stressful

Three of four studies reported quality of life impaired in IE patients. One study reported the presence of a posttraumatic stress disorder in 11% of the cases.

In 2009, a prospective and multicenter follow-up study was performed aiming to assess quality of life and posttraumatic stress disorder of adults treated because a left-sided native valve endocarditis. Twelve months after the end of the antimicrobial treatment 67 adults completed both the SF-36 and the Posttraumatic stress disorder questionnaires. The quality of life was significantly impaired in IE patients, compared with an age- and sex-matched population. A posttraumatic stress disorder was present in 11% of the cases. The type of infecting microorganism, the length of hospitalization, type of cardiac surgery, and infective complications did not affect the result of the quality of life scores<sup>[11]</sup>.

In 2010, another study reported the outcomes and quality of life after homograft replacement for IE. After a mean follow-up of 37 ± 11 mo, the quality of life was assessed using a SF-36 form. Forty five patients completed a specific questionnaire.

Statistically significant differences between patients operated with homograft and an age-matched and gender-matched general population were depicted in four subscales: Role-physical, general health, vitality, mental health<sup>[12]</sup>.

In the same year, Yeates *et al*<sup>[13]</sup> assessed the quality of life of IE patients who suffered cerebrovascular complications using the EQ-5D questionnaire. After a mean follow-up of 37.2 mo, 9 adults responded EQ-5D questionnaire by telephone: 7 reported no problems with self-care, 6 reported some problems with mobility, 5 reported some problems with usual

activities and 5 pain or discomfort.

In 2011, another study evaluated the early and mid-term outcomes, mortality and morbidity and quality of life of patients operated for IE. After a mean follow-up time of 37.2 mo, 85 patients answered a EQ-5D questionnaire. In that study, the patient's quality of life was not impaired<sup>[14]</sup>.

**Qualitative studies:** Qualitative studies review patient's experiences after IE diagnoses. Berg *et al*<sup>[15]</sup> described in 2010 IE experiences before and during hospital admission, including experience of physical symptoms and expectations for future health. Ten patients were included just before or after discharge, after a mean of 51.5 d of hospital admission. IE was perceived as an "intermezzo in life": Presage and appearance of IE, reaction to IE, living through IE, the little life with IE, body change and loved ones at distance.

The patients explained that perceived a sudden unexpected physical change, difficult to understand and interpret. This happens after a very long hospital admission, far different from one's normal way of life. During the hospital admission, they spent some time thinking about choices and lost possibilities before admission. They mentioned the idea of investing their energy and attention on getting well. Patients felt like not being able to interpret their body's signals, or that they did not receive clear signals whatsoever from the body that there is something wrong. Symptoms of IE are similar to and are often misinterpreted as a common infection or virus, such as a lung infection or influenza. Another important idea reported was that the disease does not only affect the patients, but can

Table 2 Scheme of main findings about thoracic aortic disease

Ref.	Methods and materials	Main results
Immer <i>et al</i> <sup>[22]</sup> , 2004	Prospective, 363 patients. 176 acute type A dissections, 187 aortic aneurysms. Antegrade cerebral perfusion 41 cases. Short Form 36 Health Survey questionnaire	Averaged quality life score was higher with the use of antegrade cerebral perfusion, independently of the duration of deep hypothermic circulatory arrest
Stalder <i>et al</i> <sup>[23]</sup> , 2007	Prospective, 244 patients. 76 isolated replacement of the ascending aorta, 42 separate aortic valve replacement and supracoronary replacement of the ascending aorta, 86 mechanical composite graft, 40 biologic composite graft. Short Form 36 Health Survey questionnaire	No difference in quality of life between groups was found
Dick <i>et al</i> <sup>[17]</sup> , 2008	Post hoc analysis, 122 patients. 52 thoracic endovascular aortic repair, 70 open aortic repair. Short Form 36 Health Survey questionnaire and Hospital Anxiety and Depression Scale	Anxiety and depression scores were not significantly different between group
Immer <i>et al</i> <sup>[26]</sup> , 2008	Prospective, 567 patients. 387 deep hypothermic circulatory arrest with pharmacologic protection with pentothal only, 91 selective antegrade cerebral perfusion and pentothal, 89 continuous cerebral perfusion through the right subclavian artery and pentothal. Short Form 36 Health Survey questionnaire	No statistical differences in quality life scores Average quality of life after an arrest time between 30 and 50 min with continuous cerebral perfusion through the right subclavian artery was significantly better than selective antegrade cerebral perfusion
Krähenbühl <i>et al</i> <sup>[24]</sup> , 2008	Prospective, 907 patients. 219 acute aortic dissection type A, 617 aortic aneurysm. Transient neurological dysfunction 89 cases. Short Form 36 Health Survey questionnaire	Patients with transient neurological dysfunction showed a significantly impaired quality of life
Dick <i>et al</i> <sup>[18]</sup> , 2009	Post hoc analysis, 52 patients. 27 treated electively, 25 emergency indications. Short Form 36 Health Survey questionnaire and Hospital Anxiety and Depression Scale	Anxiety and depression scores were in normal range and not increased after emergency situations No statistical differences between groups in quality of life were found
Lohse <i>et al</i> <sup>[25]</sup> , 2009	Prospective, 124 patients. 45 supracoronary replacement of the ascending aorta, 59 Wheat procedure, 15 David procedure, 12 Bentall-De Bono procedure, 3 Cabrol procedure. Short Form 36 Health Survey questionnaire	Different surgical techniques had no statistically significant influence on postoperative quality of life
Aicher <i>et al</i> <sup>[19]</sup> , 2011	Prospective, 166 patients. 86 aortic valve repair, 41 valve replacement with mechanical prosthesis, 39 valve replacement with pulmonary autograft. Short Form 36 Health Survey questionnaire and Hospital Anxiety and Depression Scale	No differences were found in anxiety or depression scores between groups Patients after aortic valve repair <i>vs</i> replacement with pulmonary autograft revealed similar quality of life scores
Lehr <i>et al</i> <sup>[20]</sup> , 2011	Prospective, 144 patients. 51 mechanical conduit, 93 biological valve conduit. Hospital Anxiety and Depression Scale	No significant differences were found between groups for either anxiety and depression
Okamoto <i>et al</i> <sup>[21]</sup> , 2013	Prospective, 128 patients. 49 aortic surgery, 79 coronary artery bypass. Hospital Anxiety and Depression Scale	No statistical differences were found in depression or anxiety scores

also have a great impact on the life of their families<sup>[15]</sup>.

In 2014, a qualitative study described patient experiences during recovery after IE. Eleven patients were interviewed 3 to 6 mo after discharge. Patients talked of IE as an unpredictable disease. They described a phase of adaptation to a new life situation, which some perceived as manageable and temporary, whereas others found it extremely distressing and prolonged. Most of them experienced a persisting weakness and felt frustrated about the prolonged recovery phase. Patients felt physically weak and mentally imbalanced to a varying degree. They described a time of emotional instability and different psychological reactions, ranging from mild mood swings to severe anxiety. Uncertainty of recovery trajectory and future capacity was considered stressful. They worried about sources of infections; open wounds and they recognized that even a hemorrhoid could become a cause for concern. Most of them described how significant the support from family and friends had been during hospital admission and recovery. Some also described feeling concerned and guilty; being the cause of the stress and strain their loved ones had been through<sup>[16]</sup>.

### TAD

We found ten suitable manuscripts that studied psychological issues using standardized questionnaires in TAD patients, after surgery or endovascular therapy and a variable follow up period.

**Depression and anxiety:** Five papers studied depression and anxiety in patients treated with surgery or endovascular therapy. No statistical differences were found in anxiety and depression scores after aortic valve repair using mechanical replacement *vs* after aortic valve repair using pulmonary autograft; after underwent thoracic aortic surgery *vs* after coronary artery bypass grafting; after thoracic endovascular aortic repair *vs* after open aortic repair or after thoracic endovascular aortic repair which indication was done electively *vs* emergency.

In 2008, a study assessed anxiety and depression on diseases of descending thoracic aorta, in patients treated either by thoracic endovascular aortic repair or open aortic repair. After mean follow-up of  $34 \pm 18$  mo, 75 adults fulfilled a HADS form. Although depression and anxiety scores tended to be more elevated in patients that underwent thoracic endovascular aortic

repair than in patients that underwent open aortic repair patients, statistical significances were not found<sup>[17]</sup>.

In 2009, Dick *et al*<sup>[18]</sup> studied the impact of urgency procedures on quality of life in patients with descending thoracic aorta disease. Twenty seven patients completed the HADS after mean follow-up of  $29 \pm 16$  mo. Anxiety and depression scores were in normal range and did not increase after emergency situations.

In 2011, a study was conducted to assess and compare anxiety and depression after aortic valve repair using two replacement alternatives: Mechanical valve and pulmonary autograft. After a follow up interval that ranged between 3 and 7 years, 166 subjects responded the HADS questionnaire. No differences were found regarding anxiety or depression scores between groups<sup>[19]</sup>.

In the same year, anxiety and depression over a group of patients who underwent aortic root replacement with mechanical and biological conduits were assessed and compared by Lehr *et al*<sup>[20]</sup>. Seventy four patients completed a HADS form after a median follow-up of 40 mo. Anxiety and depression scores were not significantly different between groups.

In 2013, other study compared anxiety and depression in patients undergoing thoracic aortic surgery with another cohort of patients undergoing coronary artery bypass grafting. Hospital anxiety and depression scale was complete at 1-5 years postoperatively by 98 patients. Twenty-eight percent of thoracic aortic surgery patients had depression and 14% anxiety. Twenty percent of coronary bypass patients had depression and 16% anxiety. No statistical differences were found in depression or anxiety scores either in this study<sup>[21]</sup>.

**Quality of life:** Over ten, eight studies analyzed the impact of different surgical procedures and endovascular therapy on the quality of life of patients with diseases of aortic root and aortic valve, ascending aorta, aortic arch, and descending aorta.

One study assessed the quality of life after aortic valve replacement comparing two replacement alternatives: Mechanical and pulmonary autograft. Over a follow-up interval between 3 and 7 years, 166 subjects completed a SF-36 questionnaire. Patients who had undergone aortic valve repair and replacement with pulmonary autograft depicted similar quality of life scores, but this matter was better in patients after replacement with mechanical prosthesis regarding physical functioning, general health, and mental health<sup>[19]</sup>.

**Ascending aorta:** Four papers studied the quality of life of patients with diseases of ascending aorta.

In 2004 a study analyzed the impact of the duration of the deep hypothermic circulatory arrest and the potential effects of antegrade cerebral perfusion

on quality of life in patients undergoing surgery of the thoracic aorta. Two hundred and ninety adults completed the SF-36 questionnaire after mean follow up of  $2.4 \pm 1.2$  years. Averaged quality life score was significantly better with the use of antegrade cerebral perfusion, independently of the duration of deep hypothermic circulatory arrest<sup>[22]</sup>.

In 2007 another manuscript analyzed the impact of different surgical procedures on quality of life in patients with ascending aorta diseases. Patients were divided according to the operative procedure: Isolated replacement of the ascending aorta, separate aortic valve replacement and supracoronary replacement of the ascending aorta, mechanical composite graft, and biologic composite graft. After mean follow-up of  $26.6 \pm 8.8$  mo, 176 patients completed a SF-36 questionnaire. No difference in quality of life between groups was found<sup>[23]</sup>.

Krähenbühl *et al*<sup>[24]</sup>, in 2008, assessed the influence of transient neurological dysfunction (defined as a Glasgow coma scale value  $< 13$ ) on the quality of life of patients undergoing surgery of ascending aorta and proximal aortic arch. Over a mean follow-up interval of  $27 \pm 14$  mo, 79 subjects completed a SF-36 questionnaire. Patients with transient neurological dysfunction showed a significantly impaired quality of life except for bodily pain.

In 2009, a study assessed the quality of life among patients who underwent replacement of a dilated ascending aorta. Patients were divided according to the operative procedure. Operative procedures consisted of supracoronary replacement of the ascending aorta, the Wheat procedure, the David procedure, the Bentall-De Bono procedure, and the Cabrol procedure. One hundred and twenty two patients completed a SF-36 questionnaire after mean follow-up of  $36.4 \pm 15.5$  mo. Different surgical techniques had no statistically significant influence on postoperative quality of life. However, many subscales of SF-36 were below the norm when compared with a standard population, in particular physical pain and physical function<sup>[25]</sup>.

**Aortic arch:** Two studies assessed quality of life of patients with diseases of aortic arch.

Immer *et al*<sup>[26]</sup> published (2008) a study assessing the impact of continuous cerebral perfusion through the right subclavian artery on quality of life. With a mean follow-up of  $2.4 \pm 1.2$  years, 453 adults respond SF-36 questionnaire. Interestingly, the average quality of life after an arrest time between 30 and 50 min with continuous cerebral perfusion through the right subclavian artery was significantly better than when selective antegrade cerebral perfusion was used.

As we mentioned previously, in 2008, Krähenbühl *et al*<sup>[24]</sup> assessed the influence of transient neurological dysfunction on quality of life of patients undergoing surgery of proximal aortic arch and ascending aorta, showing that patients with transient neurological

dysfunction showed a significantly impaired quality of life later.

**Descending aorta:** Two studies explored quality of life of patients with diseases of descending aorta. Dick *et al.*<sup>[17]</sup>, in 2008 analyzed quality of life in patients treated either by thoracic endovascular aortic repair or by open aortic repair for diseases of the descending thoracic aorta. Seventy-five adults completed the SF-36 questionnaire after a mean follow-up of  $34 \pm 18$  mo. Quality of life scores of open aortic repair in the patients included in this study ranged from 63 to 110; the median was 93. Quality of life scores of thoracic endovascular aortic repair ranged from 60 to 112, with a median of 83. Thus, the authors concluded that after thoracic aortic repair the quality of life was reduced.

One year later, Dick *et al.*<sup>[18]</sup>, published another paper regarding the impact of urgency procedures on quality of life in patients with descending thoracic aorta disease. After a mean follow-up of  $29 \pm 16$  mo, 27 adults responded the SF-36 questionnaire. Quality of life scores after emergency range between 58 and 124, with a median of 72. Quality of life scores after elective endovascular aortic repair range between 61 and 105, median: 85. No statistical differences between groups in quality of life were found.

## DISCUSSION

We summarize the results of a small number of studies dealing with psychological issues in IE and TAD. Despite the high impact that psychological conditions might cause in these severe diseases, we could verify that there is not much information available on these matters. Thus, we aimed to review the available evidence on this context.

Some papers<sup>[27-29]</sup> and guidelines<sup>[30-33]</sup> previously reported that psychosocial factors such as depression, anxiety and other mental disorders such as personality disorders and post-traumatic stress disorders are related to morbidity and mortality due to cardiovascular diseases. Chronic heart failure, arrhythmias, and acute myocardial infarction are one of the most studied pathologies in that setting. Otherwise, other cardiovascular diseases are poorly or not studied from a psychological point of view, such as IE and TAD. We found four studies comparing anxiety and depression scores in patients with TAD after treatment and only one paper assessing post-traumatic stress disorder after IE treatment.

When specialists choose a specific type of invasive intervention, psychological aspects are usually ignored. The identification of interventions that increase anxiety and/or depression could be of interest from a medical point of view because anxiety and/or depression might negatively influence patient recuperation after the intervention. In TAD patients, anxiety and depression levels after different invasive interventions did not differ. No statistical differences were found in anxiety

and depression scores: After aortic valve repair using mechanical replacement vs after aortic valve repair using pulmonary autograft; after underwent thoracic aortic surgery vs after coronary artery bypass grafting; after thoracic endovascular aortic repair vs after open aortic repair, after thoracic endovascular aortic repair which indication was done electively vs emergency. Moreover, baseline anxiety and depression scores had not been reported. Depression or/and anxiety before invasive intervention, might negatively influence coping and recuperation after intervention.

A posttraumatic stress disorder was present in 11% and was associated with lower levels of quality of life in IE patients. IE patients with posttraumatic stress disorder reported feeling nervousness and depressive, having problems with work or other daily activities and having frequent interference with social activities due to physical or emotional problems. Although the percentage of posttraumatic stress disorder in IE might be considered low, IE patients with posttraumatic stress disorder need specialized mental health care and interventions to improve their quality of life.

Most of the studies assessed IE and TAD quality of life after treatment. Quality of life was reported to be impaired in three of four studies about infectious endocarditis and in three of eight studies about TAD. However, recent clinical guidelines about infectious endocarditis did not mention quality of life and recent guidelines about TAD did not make the slightest reference to quality of life either.

Most of quantitative studies about IE reported that after 12 or 37 mo after IE diagnosis, quality of life was clearly impaired. Only one study explored the possible influence of the causal microorganism, length of hospitalization, type of cardiac surgery, and infective complications in quality of life scores. The authors concluded that those issues did not clearly affect quality of life scores. In two studies, the patients evaluated their personal health as poor mentioning that it was likely to get worse. In one study, patients reported feeling tired, worn out all, nervousness and depressive. Since depression was not assessed, we can not know if those IE patients had depression, although this is a possibility. Moreover, elevated pro-inflammatory cytokines in IE could promote psychological alterations such as depression, especially in vulnerable patients, and this might compromise prognosis and the ability to cope the disease.

The cerebral perfusion technique used in invasive intervention of TAD patients might have neurological consequences and could influence the perceived quality of life as well. After a surgery of thoracic aorta, patients might postoperatively develop confusion, agitation and delirium, also named "temporary neurological dysfunction". Although resolution of these symptoms usually occur before hospital discharge, patients with temporary neurological dysfunction had lower scores in quality of life than patients without temporary neurological dysfunction. Patients with temporary

neurological dysfunction evaluate their personal health as poor and believe that it is likely to get worse. This way, they reported feeling nervousness, depressive, and having problems with work or other daily activities. The incidence of neurological complications might be decreased using selective antegrade cerebral perfusion. A study reported that the average quality of life after an arrest time between 30 and 50 min with continuous cerebral perfusion through the right subclavian artery was significantly better than selective antegrade cerebral perfusion. One important limitation was that all the studies revised did not include assessment before treatment or a proper control group. In addition, detailed medical records about patients that answered these mentioned questionnaires used to assess psychological issues are frequently not available.

Sixteen studies have been published about psychological issues in IE and TAD. Most of them explored quality of life and to a less extent anxiety and depression. Papers reviewed were heterogeneous in patients and procedures; they included few participants, they did not include control groups and they did not evaluate patients before treatment. Thus, we feel that more studies are needed, especially with a prospective design. The study of psychological issues is relevant and could bring us information about specific needs to be covered by psychological interventions and to design specialized care training and practice.

## COMMENTS

### Background

Some papers and guidelines reported that psychosocial factors such as depression, anxiety and other mental disorders such as personality disorders and post-traumatic stress disorder are related to morbidity and mortality due to cardiovascular diseases. Chronic heart failure, arrhythmias, and acute myocardial infarction are one of the most studied pathologies. Otherwise, other cardiovascular diseases are poorly or not yet studied from a psychological point of view, such as infective endocarditis (IE) and thoracic aortic disease (TAD). The study of psychological issues in these severe diseases could bring people valuable information about specific needs to cover with psychological interventions and to design specialized care training and practice. The aim of this review is to summarize the current evidence on psychological issues in TAD and IE setting. The authors performed a narrative review about psychological issues in adults with both TAD and IE.

### Research frontiers

From the health-psychology standpoint, both IE and TAD are almost forgotten research subjects. Patients with medical disorders usually require specialized medical attention and psychological care. It might be expected that patients with severe cardiovascular diseases will not be the exception, especially in the cases of IE and TAD, which generally require several invasive interventions. This area of interest is pretty new. All the papers revised in this research were published in the present century. Nevertheless, precise data on the psychological disorders that could be associated with IE and TAD is still lacking.

### Innovations and breakthroughs

Sixteen studies have been published about psychological issues in IE (six studies) and TAD (ten papers). Psychological issues assessed were quality of life, depression, anxiety and posttraumatic stress disorder. Quality of life was reported impaired in three of four studies about infectious endocarditis and in three of eight studies about TAD. However, recent clinical guidelines about infectious endocarditis did not mention quality of life and recent guidelines

about TAD made slightest reference to quality of life. Depression and anxiety were analyzed in TAD only (five papers). Anxiety and depression levels after different invasive interventions did not differ. No statistical differences were found in anxiety and depression scores: After aortic valve repair using mechanical replacement vs after aortic valve repair using pulmonary autograft; after underwent thoracic aortic surgery vs after coronary artery bypass grafting; after thoracic endovascular aortic repair vs after open aortic repair, after thoracic endovascular aortic repair which indication was done electively vs emergency. Moreover, baseline anxiety and depression scores had not been reported. Depression or/and anxiety before invasive intervention, might negatively influence patient recuperation after intervention. Regarding to IE, since depression was not properly assessed in the published manuscripts we do not have precise data. However, elevated pro-inflammatory cytokines in IE could promote psychological alterations such as depression, especially, in vulnerable patients, and this might compromise prognosis and coping disease. Post-traumatic stress disorder was assessed in IE (one study). It was present in 11% and was associated with lower levels of quality of life in IE patients. Although percentage of posttraumatic stress disorder in IE might be considered low, IE patients with posttraumatic stress disorder need specialized mental health care and interventions to improve quality of life.

### Applications

Despite the high impact that psychological conditions might cause in these severe diseases, the authors could verify that there is not much information available. It would be desirable that future studies used prospective designs, included control group and completed psychological assessment before and after treatments/interventions.

### Terminology

Psychological aspects revised in this paper include depression, anxiety, personality, coping, therapeutic adherence, illness perception and quality of life.

### Peer-review

The focus on IE is very timely and important, and the author presents the data in a very meaningful and useful manner.

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## Endovascular treatment of paravisceral mycotic aneurysm: Chimney endovascular sealing the end of de road

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**Author contributions:** All authors contributed to the acquisition of data, writing, and revision of this manuscript.

**Institutional review board statement:** This case report was exempt from the Institutional Review Board standards at Hospital Italiano of Buenos Aires.

**Informed consent statement:** The patient involved in this study gave her written informed consent authorizing use and disclosure of her protected health information.

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### Abstract

Open surgery is the elective treatment for mycotic aneurysms of the aorta. This surgery consists of resection of the aneurysm, debridement and revascularization with an *in situ* or extra-anatomic bypass. Even when surgery has been successful, the morbidity is raised and the endovascular treatment has become an alternative for specific patients. When mycotic aneurysms involved the visceral arteries, more complex techniques are necessary such as fenestrated endovascular aortic repair or chimney endovascular aortic repair and the most frequent complications of this are endoleaks and occlusion the visceral arteries. We present a case of a patient with a paravisceral abdominal mycotic aneurysms that was result with 2 chimney technique (in the right renal and superior mesenteric arteries) and a single Nellix EVAS (Endologix, Irvine, Calif) of 12 cm long without evidence of endoleaks in the follow-up.

**Key words:** Mycotic aneurysms; Edovascular repair; Aorta; Endoleaks; Para visceral aneurysms

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**Core tip:** The interesting of the case that we present is the resolution of the mycotic aneurysms throw a new techniques calls chimney endovascular sealing (Ch-EVAS). This case it would be the first case treated with Ch-EVAS that has been reported since in the

bibliographical review that we made we do not find cases of paravisceral abdominal mycotic aneurysms treated with this technology.

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Rabellino M, Moltini PN, Di Caro VG, Chas JG, Marenchino R, Garcia-Monaco RD. Endovascular treatment of paravisceral mycotic aneurysm: Chimney endovascular sealing the end of de road. *World J Cardiol* 2017; 9(7): 629-633 Available from: URL: <http://www.wjgnet.com/1949-8462/full/v9/i7/629.htm> DOI: <http://dx.doi.org/10.4330/wjc.v9.i7.629>

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## INTRODUCTION

Open surgery is the elective treatment for mycotic aneurysms of the aorta. This surgery consists of resection of the aneurysm, debridement and revascularization with an *in situ* or extra-anatomic bypass<sup>[1]</sup>. Even when surgery has been successful, the morbi-mortality is raised and the endovascular treatment has become an alternative for specific patients<sup>[2]</sup>.

The main problem of this kind of pseudoaneurysms is the location. When the mycotic aneurysm is in the descending aorta or infrarenal aorta without compromising the supra-aortic trunks or the visceral arteries, endovascular treatment is possible with a successful outcome<sup>[2]</sup>. Nevertheless, it has not been well described in the literature this type of procedure for paravisceral abdominal aortic aneurysm.

When mycotic aneurysms involved the visceral arteries, more complex techniques are necessary such as Fenestrated endovascular aortic repair (f-EVAR) or chimney endovascular aortic repair (Ch-EVAR) and the most frequent complications of this are endoleaks and occlusion the visceral arteries<sup>[3,4]</sup>.

We present a case of a patient with a paravisceral abdominal mycotic aneurysms with absolute contraindication for open surgery with two unsuccessful endovascular treatments, that was result with chimney technique and Nellix (Endologix, Irvine, Calif) chimney endovascular sealing (Ch-EVAS).

## CASE REPORT

A 72-year-old woman was admitted in the emergency department presented with acute abdominal pain. She had a medical history of former smoker, multiple coronary by-pass with dehiscence of the chest wound, pulmonary embolism treated with anticoagulants and respiratory failure (SpO<sub>2</sub> 82%).

To the physical examination, the patient was presenting an acute abdominal pain with rigidity, guarding and peritoneal irritation so an AngioCT scan was performed and showed gastrointestinal perforation and a 4.9 cm paravisceral abdominal aneurysms with intraluminal thrombus (Figure 1A). Small bowel resection and jejunostomy was done.

Anatomopathology showed miliary tuberculosis with intestinal involvement and peritoneal implants.

With this result and the presence of the aortic aneurysms we made the diagnosis of tuberculous mycotic aneurysm with compromise of the four visceral branches. Although, the endovascular treatment was decided because of the clinical situation of the patient, the endovascular options have not been simple because of the location of the aneurysms. The options were a f-EVAR, which was impossible for the time confection or a Ch-EVAR with the risk of endoleaks in the pseudoaneurysms that needs 4 chimney.

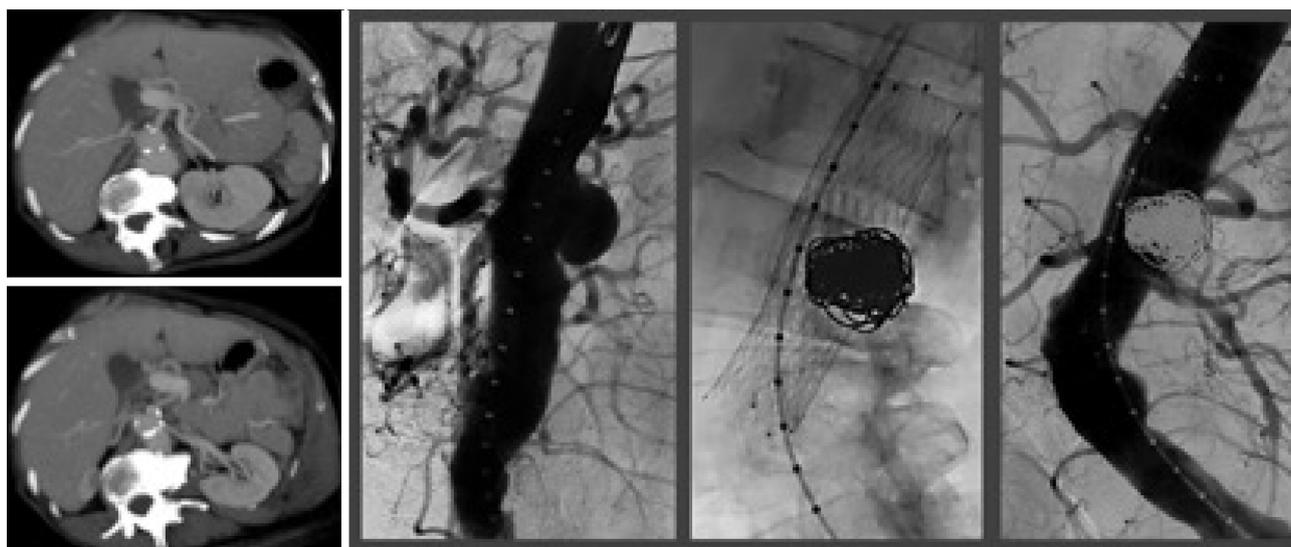
Another therapeutic option was Ch-EVAS which was not available in our country. Base on the foregoing, and knowing that it was not a definitive treatment, the decision was to perform stent assisted coil embolization technique of the aneurysms.

In the procedure, for a femoral access a Sinus XL stent (OptiMed, Ettlingen, Germany) was placed in the aortic visceral topography and across it embolization of the pseudoaneurysm with coils was performed with a successful initial first result (Figure 1B and D) and without complications. The patient was discharged 48 h later with parenteral nutrition, aspirin 100 mg/d and antibiotics therapy for tuberculosis.

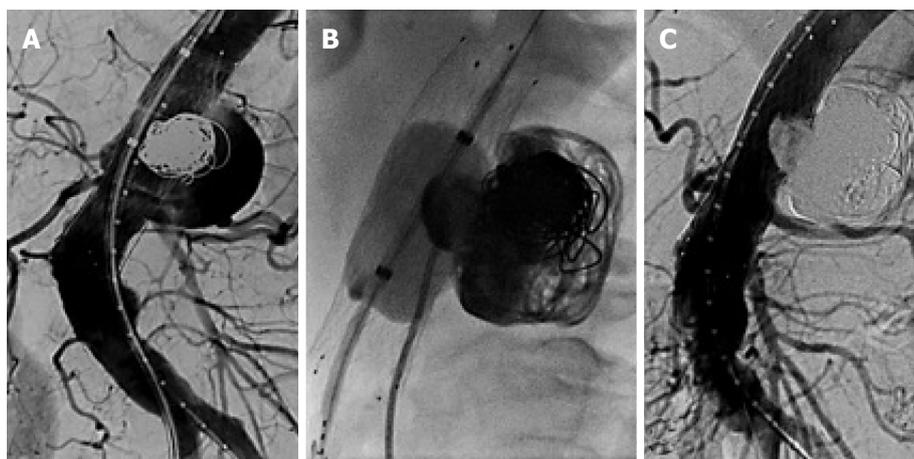
Four month later, an AngioCT scan revealed that the mycotic aneurysm had grown and a for a percutaneous femoral access a balloon-assisted coils and n-butyl 2-cyanoacrylate embolization was performed with good angiographic outcomes (Figure 2). The patient was still undergoing treatment for her infection disease and was discharged 24 h later without complications. Bowel transit and abdominal wall reconstruction was made a month later. Two month after surgery, the patient was admitted with low back pain and the CT angiogram showed an endoleak with aneurysm sac enlargement and extravasation of the embolic agents used previously that indicated rupture, so an endovascular treatment with Ch-EVAS was decided, because it was already available in our country.

Under general anesthesia a percutaneous femoral access was done for the introduction of a single Nellix EVAS of 12 cm long (the aortic diameter was normal and it was not necessary to spread up to the iliac arteries) and a open left subclavian access to place the chimneys for the right renal and superior mesenteric arteries. Both chimneys were performed with a Viabahn covered stent (Gore and Associates, Flagstaff, AZ) of 7 mm × 100 mm for the right renal artery and 8 mm × 100 mm for the superior mesenteric artery. Inside the chimneys a nitinol self-expanding stent was placed to give them a greater radial force strength and to avoid the chimney collapse by the polymer (Figure 3).

The left renal artery was catheterized but it was not possible to advance a catheter across the strut of the Sinus stent, so an angioplasty with a 6-mm low-profile coronary balloon was performed. Despite these, it was not possible to introduce a 4 Fr diagnostic catheter



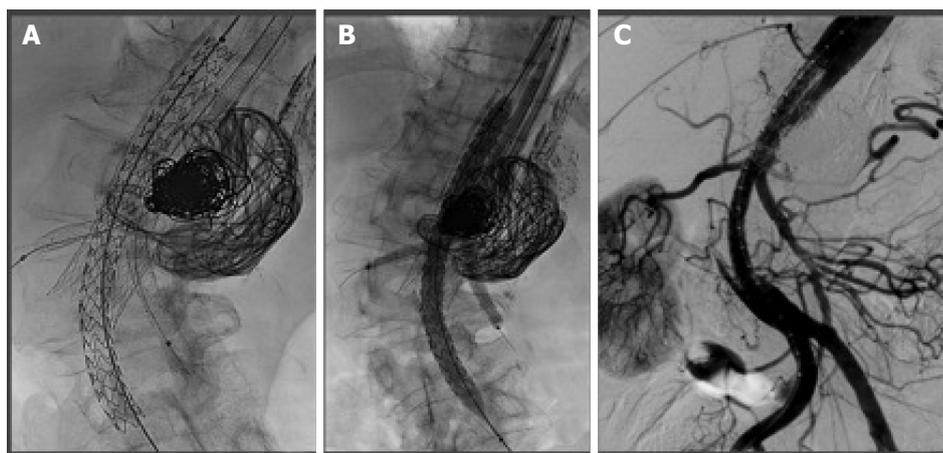
**Figure 1** AngioCT scan and digital subtraction angiography. Mycotic aneurysm and the relation with the visceral branches, stent assisted coil embolization of aneurysms with a Sinus XL stent and complete embolization of the mycotic aneurysms without evidence of flow inside the sac.



**Figure 2** Digital subtraction angiography (A-C). Flow in the mycotic aneurysms an increased de diameter of the sac. Coils and n-butyl 2-cyanoacrylate embolization performed with the balloon-assisted technique and final angiographic control shows absence of flow in the interior of the aneurysms.



**Figure 3** Digital subtraction angiography. Rechanneling of the pseudoaneurysms. Renals and superior mesenteric arteries catheterization (the left renal artery with a coronary balloon angioplasty) and the presence of n-butyl 2-cyanoacrylate out of the pseudoaneurysms. Chimney in the right renal artery and superior mesenteric artery.



**Figure 4** Single Nellix endovascular sealing and the chimneys (A-C). Fluoroscopy of the balloons inflated during the filling of the bag of the Nellix EVAS with the polymer. Permeability of the endograft, both chimneys and the celiac trunk without evidence of endoleaks.

so it was decided to abandon the left renal artery. It was decided not to be catheterized the celtrunk for the idea that it would be compensated for the superior mesenteric artery, as it happened.

The final angiographic control showed the exclusion of the mycotic aneurysms with permeability of the right renal artery and superior mesenteric artery which supply the celiac trunk and its branches (Figure 4). After the procedure, the patient was discharged 5 d later without complications, normal renal function, clopidogrel 75 mg, aspirin 100 mg a day and antibiotic therapy. AngioCT scan follow-up at 3 mo, showed absence of endoleaks and permeability of the right renal artery, superior mesenteric artery and the celiac trunk.

## DISCUSSION

Open surgery is the elective treatment for mycotic aneurysms of the aorta, however in patient with absolute contraindication for surgery, the endovascular treatment become an important alternative for this patients that have been well described in the multicentric European study which concluded that endovascular treatment it is a feasible and lasting option in most patients<sup>[2]</sup>. Nevertheless, in this study of all treated aneurysms only in the 7% of them it was used f-EVAR techniques, not having specific comments about the follow-up in these patients. Another endovascular option for the treatment of paravisceral abdominal mycotic aneurysms is the Ch-EVAR. However, the rate of endoleaks with this technique in a review by Patel *et al*<sup>[4]</sup> was estimated at 5% to 37.5%.

In a recent review by Li *et al*<sup>[5]</sup> the rate of endoleaks type IA was 11.8% with a permeability of the branches of 96.6% at 6 mo. Because of these, in our case we this alternative was scorned in view of the high percentage of endoleaks (4 or 3 chimneys were necessary) and the consequent risk of rupture. In this location, the f-EVAR is a good choice to treat this

aneurysm. The only problem is the time of confection that limits the use in pseudoaneurysms that need an early resolution. In the last 2 years, it has been reported some cases of paravisceral aneurysms treated with Ch-EVAS technique that show promising result<sup>[6-8]</sup>. Torella *et al*<sup>[7]</sup> presented 2 cases of juxtarenal aortic aneurysms treated with Ch-EVAS with 2 chimneys in each case and without evidence of endoleaks type IA. Youssef *et al*<sup>[6]</sup> published recently a series of 7 patients treated with Ch-EVAS with four chimneys for patient in which they reported no early endoleaks with a permeability of 96% of the branches to 6 mo of follow-up.

The Ch-EVAS turns out to be an interesting concept since the polymer realizes a copy of the aortic anatomy occupying the space of the gutters that they originate with the conventional Ch-EVAR technique reducing the risk of endoleaks. The case that we presented it would be the first case treated with Ch-EVAS that has been reported since in the bibliographical review that we made we do not find cases of paravisceral abdominal mycotic aneurysms treated with this technology. While so far, the reports on Ch-EVAS are only clinical case reports, they represent encouraging results as a future alternative of first choice for the treatment of paravisceral aortic aneurysms.

## COMMENTS

### Case characteristics

A 72-year-old woman with a medical history of military tuberculosis with abdominal involvement that was treated in two opportunities for a mycotic aortic aneurysm with compromise of the four visceral branches with endovascular technique was admitted at the emergency department with low back pain two months after the second treatment.

### Imaging diagnosis

Computed tomography angiogram showed an endoleak with mycotic aneurysm enlargement.

### Treatment

Endovascular treatment performed with Chimney endovascular aneurysm

sealing (Ch-EVAS) with good result with exclusion and absent of endoleaks in the final angiography control. In the follow up the patient continuous asymptomatic with no evidence of endoleaks or another complication.

### Experiences and lessons

A mycotic aneurysm of the aorta with involvement of the visceral arteries is a dreadful condition and repair it can be quite challenging. The endovascular treatment has become an important alternative. The Ch-EVAS turns out to be an interesting concept because it solves the endoleak problems with the conventional chimney endovascular aneurysm repair. In the authors' bibliographical review, the authors did not find cases of paravisceral abdominal mycotic aneurysms treated with this technology.

### Peer-review

This is an interesting case report about the endovascular treatment of paravisceral mycotic aneurysm.

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**L- Editor:** Logan S **E- Editor:** Wu HL



## Percutaneous closure of congenital Gerbode defect using Nit-Occlud® Lê VSD coil

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**Author contributions:** All authors contributed to the acquisition of data, writing, and revision of this manuscript.

**Institutional review board statement:** This case report was reviewed and approved by Quang Nam Central General Hospital Institutional Review Board.

**Informed consent statement:** The patient involved in this case report gave his written informed consent authorizing use and disclosure of her protected health information.

**Conflict-of-interest statement:** All the authors have no conflicts of interests to declare.

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### Abstract

We present a case report about percutaneous closure of a congenital Gerbode defect using Nit-Occlud® Lê VSD coil. The patient was referred to our hospital with a diagnosis of ventricular septal defect (VSD) and severe pulmonary arterial hypertension. But transthoracic echocardiography revealed a communication between the left ventricle (LV) and the right atrial (RA), called Gerbode defect. Catheterization confirmed the shunt from the LV to the RA. We successfully closed the defect with a VSD coil. After uneventful 6 mo follow-up, the patient was out of dyspnea, the symptom urged him to have medical attention. This case report is to discuss the diagnosis and percutaneous treatment approach for this rare congenital heart disease.

**Key words:** Congenital Gerbode defect; Nit-Occlud® Lê VSD coil; Congenital heart disease; Transcatheter device closure; Device embolization

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**Core tip:** Congenital Gerbode defect is rare, only accounts for about 0.08% among congenital heart diseases. The diagnosis is easily misinterpreted with others condition on clinical examination and echocardiography. The treatment of this disease is also lack of recommendation. There are several approaches can be applied for this kind of defect such as conservation, cardiac surgery, intravascular intervention or intra-operative device closure. There are several devices can be used for transcatheter closure such as ventricular septal occluder, atrial septal occluder, ADO I or ADO II. This is the first report using Nit-Occlud® Lê VSD coil to close Gerbode defect successfully.

Phan QT, Kim SW, Nguyen HL. Percutaneous closure of congenital Gerbode defect using Nit-Occlud® Lê VSD coil. *World J Cardiol* 2017; 9(7): 634-639 Available from: URL: <http://www.wjgnet.com/1949-8462/full/v9/i7/634.htm> DOI: <http://dx.doi.org/10.4330/wjc.v9.i7.634>

## INTRODUCTION

The left ventricular to right atrial (LV-RA) communication was first described by Frank Gerbode in 1958<sup>[1]</sup>. This defect can be either congenital or acquired. While congenital LV-RA shunt is very rare, acquired LV-RA shunt is reported more common, can be induced by endocarditis, trauma, valve replacement, myocardial infarction, *etc*<sup>[2]</sup>. There are several varieties of Gerbode defect<sup>[1]</sup>: Supravalvular (direct) type, subvalvular (indirect) type and a combination of these two lesions.

The diagnosis of congenital Gerbode defects is quite challenging: While the clinical symptoms may mimic ventricular septal defect (VSD), it can be misinterpreted on TTE with tricuspid regurgitation and pulmonary arterial hypertension. Further investigation by transesophageal echocardiography (TEE), magnetic resonance imaging (MRI), computed tomographic angiography (CTA), ... may help to determine the right diagnosis.

## CASE REPORT

A 31-year-old male who had dyspnea on exertion 3 mo before hospitalization, was referred to our hospital with a diagnosis of heart failure in patient with VSD and severe pulmonary hypertension. He had healthy active lifestyle, normal physical and mental development. The clinical examination showed a loud harsh holosystolic murmur (4/6 Levine scale) at 4<sup>th</sup> intercostal spaces along left sternal border, radiated downward and a systolic thrill could be palpated. His blood pressure was 125/85 mmHg. The ECG showed sinus rhythm. The BNP was slightly increased. Chest X-ray, ionogram, creatinine, glucose, blood count and clotting times were in normal range. The TTE revealed a shunt between the LV and the RA. The jet went into the RA looked similar to the tricuspid valve regurgitation flow with high velocity, about 4.8 m/s. The other findings included slight dilation of the right heart chambers, mild RV systolic dysfunction and Qp:Qs was 1.6.

Cardiac catheterization was performed. LV contrast injection illustrated quite large shunt from the LV to the RA. The defect was in long conical figuration with diameters of 9.5 mm at the biggest LV ampulla, 4.0 mm at the narrowest position and 8.5 mm length. It was quite far from the aortic valve and coronaries. The pulmonary arterial pressure was 56/22/35 mmHg.

After getting across the defect with a Terumo wire from LV and snaring the wire at the superior vena cava for making the arteriovenous loop, an 8F deli-

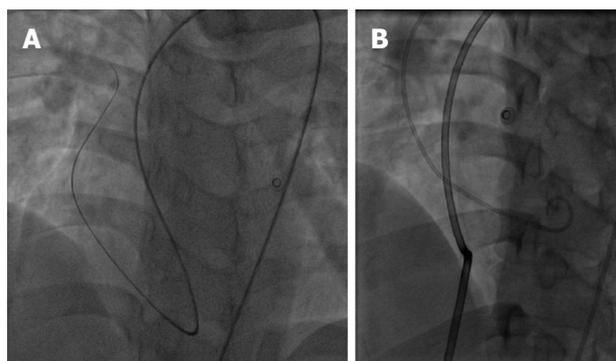


Figure 1 Through the defect, the Terumo wire was introduced to the right atrial and superior vena cava from left ventricular (A) and the 8F delivery catheter went from inferior vena cava and right atrial to the left atrial and aorta (B).



Figure 2 The Nit-Occlud® Lê VSD coil.

very catheter was introduced to LV and aorta from RA through the defect (Figure 1). Then, a 12 mm × 6 mm Nit-Occlud® Lê VSD coil (Figure 2) was deployed to close the defect with aortic approach (Figure 3). The procedure was quite similar to perimembranous VSD occlusion with likely satisfied result (Figure 4). There was only small residual shunt from LV to RA on LV contrast injections and echocardiography, no aortic regurgitation, no cardiac arrhythmia on ECG and the hemodynamic was stable.

But while the patient was kept following on cathlab table for complications, mostly concerning bradycardia and heart block, we detected some free bizarre movement of device distal part (Video 1). The device was going to drift out of the defect at 15 minutes after coil release. We quickly retrieved the coil with multi-snare and 10F catheter from the RA through inferior vena cava (Figure 5). Another attempt to close the defect with a bigger 14 mm × 8 mm Nit-Occlud® Lê VSD coil was performed (Figure 6). The final result looked fine with mild residual LV-RA shunt, no aortic regurgitation, no arrhythmia. Six hours after the procedure, there was still a grade 2/6 murmur can be found on auscultation and mild shunt from LV to RA on echocardiography. After 24 h, both the murmur and residual shunt flow were gone. After 5 d of close

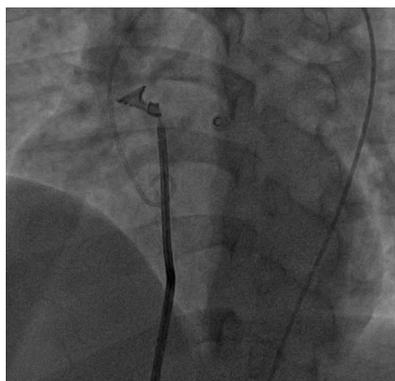


Figure 3 The 12 mm × 6 mm Nit-Occlud® Lê VSD coil was deployed with aortic approach.

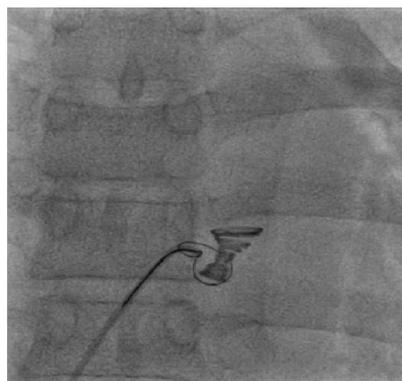


Figure 5 The drifting coil was retrieved with a multi-snare from the atrial side.



Figure 4 The 12 mm × 6 mm Nit-Occlud® Lê VSD coil immediately after release.

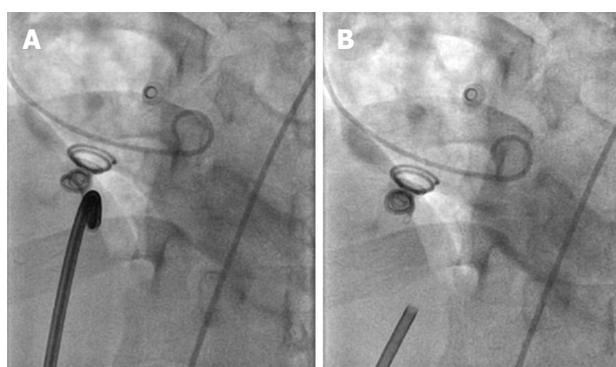


Figure 6 The bigger 14 mm × 8 mm Nit-Occlud® Lê VSD coil before (A) and immediately after release (B).

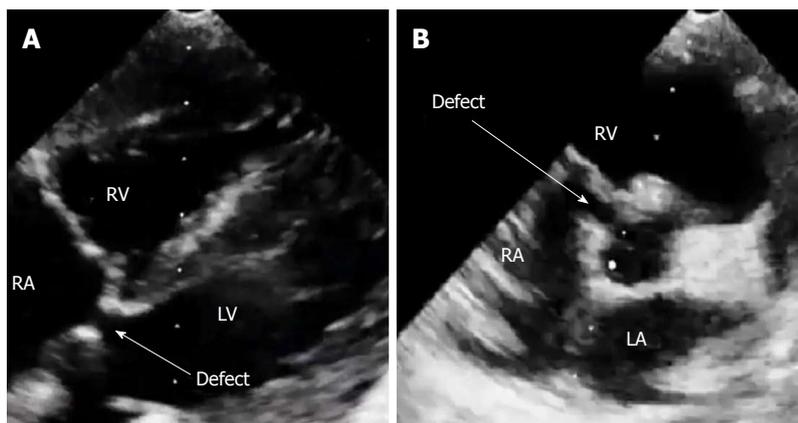
following up uneventful, the patient was discharged in good physical and mental condition. We have been checking the patient at 1 mo, 3 mo and 6 mo after the procedure. Till now, the patient has no symptom on exertion, the device is in good position without any shunt on echocardiography and there is no murmur on heart auscultation.

## DISCUSSION

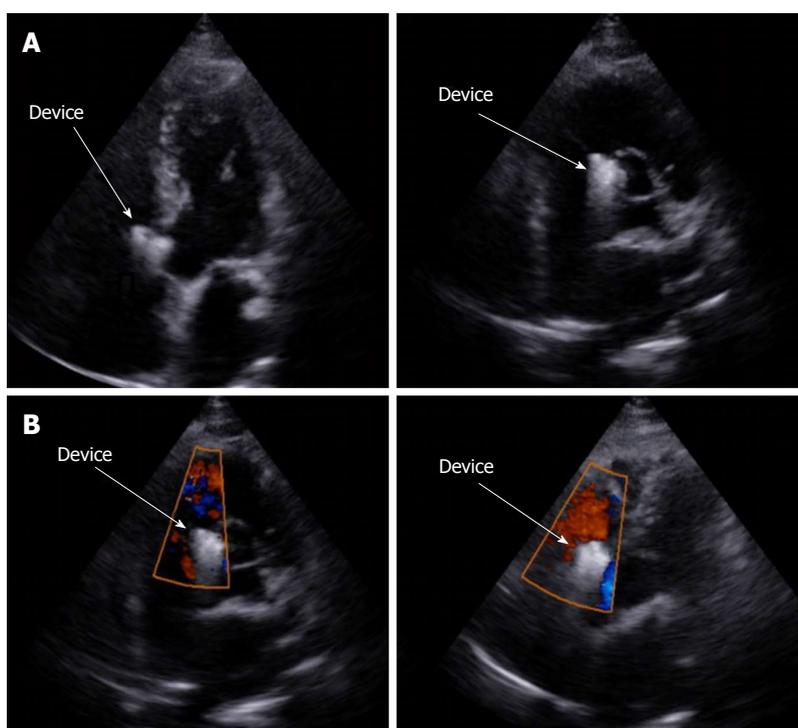
Congenital Gerbode defect is rare, only accounts for about 0.08% among congenital heart diseases<sup>[1]</sup>. Patients may have symptoms or not depends on the defect size and the shunt from LV to RA. Heart auscultation can detect a systolic murmur with position and intensity similar to the VSD but slightly lower and radiating downward.

TTE is useful for diagnosis of Gerbode defect. In 2D mode, the LV-RA shunt may be detected in some views, such as parasternal short axis, four and five chambers or subcostal views (Figure 7). The image quality was better in subcostal view as there was no bone or lung tissue to obstruct the view. Pulsed wave Doppler was helpful in detecting the shunt by the high turbulent audio signal. Continuous wave Doppler helped detect and measure peak systolic velocities across the shunt. Color flow imaging was useful in

localizing defect position and shunt flow. However, in Gerbode defect, the shunt flow, affected by the septal leaflet of the tricuspid valve, may change direction unexpectedly. So, it can mimic the direction of tricuspid regurgitation flow and made sonographers misrecognize as tricuspid regurgitation in the setting of severe pulmonary artery hypertension<sup>[3]</sup>. In this case, at first, the clinical physician thought about VSD and sent the patient to the sonographer for more detail. The conclusion they received was VSD with very high systolic pulmonary arterial pressure, about 115 mmHg. Both the clinical physician and sonographer were cheated by the shunt flow. So quick clinical examination and echocardiography in this kind of defect may easily lead to a misdiagnosis. The sonographer should meticulously look for Gerbode defect if physical examination suspects VSD but echocardiography can not detect any high velocity flow or aliasing in the right ventricle. The presence of normal diastolic pulmonary arterial pressure using pulmonic regurgitation jet is also very useful to distinguish the true pulmonary arterial hypertension from high velocity jet in the RA caused by Gerbode defect<sup>[4,5]</sup>. Actually, only about 2/3 of the LV-RA shunts of either congenital or acquired origin can be well diagnosed with TTE<sup>[6]</sup>. The 1/3 of others have to rely on other means like contrast echo, TEE, MRI, CTA or catheterization for accurate diagnosis.



**Figure 7** The Gerbode defect were best seen on echocardiography at subcostal five chamber view (A) or parasternal short axis view (B).



**Figure 8** Six months following up showed steady result with good device position and no shunt on echocardiography. A: Transthoracic echocardiography performed 6 mo after the procedure showed good device position at apical five chamber view (left) and parasternal short axis view (right); B: Colour doppler showed no residual shunt at apical five chamber view (left) and parasternal short axis view (right) 6 mo after device deployment.

Till now, there has been no clear official guidance for optimal treatment of Gerbode defect. Physicians may personally choose suitable therapy among conservation, cardiac surgery, intravascular intervention or intraoperative device closure. Patients without symptom and right ventricular volume overload, due to a small LV-RA shunt, may not need the treatment<sup>[7]</sup>. But if left untreated, the significant LV-RA shunt may lead to progressive congestive heart failure<sup>[8]</sup> and up to 8.7% of patients with LV-RA shunt developed infectious endocarditis in long-term follow-up<sup>[9]</sup>. So, some authors<sup>[10-14]</sup> suggested that correction of this type of defect with significant LV-RA shunt is necessary.

Even though the surgical closure is accepted as a treatment of choice<sup>[12]</sup>, some successful transcatheter closures for Gerbode defect have been reported. There is a paucity of information in the existing literature on transcatheter therapy for this type of defect. Indications of intervention may be same as those in the left to

right shunt lesion<sup>[14]</sup>. The devices used for occlusion this kind of defect varies from centers to centers. The first device reported used to close of an acquired Gerbode defect following VSD surgical correction was Amplatzer ventricular septal occluder<sup>[11]</sup>. Another device, amplatzer septal occluder (ASO) commonly used for atrial septal defect closure, also being used to close Gerbode defect complicated from mitral valve surgery with marked improvement in exercise tolerance<sup>[13]</sup>. The smallest patient reported, a 3-mo old baby with an acquired Gerbode shunt after VSD patch closure, was treated using an amplatzer duct occluder (ADO) with complete closure achieved 2 wk after device deployment and good long term follow-up<sup>[12]</sup>. Recently, a report of 12 Gerbode defect patients that were transcatheterly closed with ADO II showed satisfactory outcomes<sup>[14]</sup>. Until now, there is no specific device purposely manufactured for Gerbode defects closure. The devices used to occlude this kind of defects are borrowed from

products created for other defect types such as atrial septal defect, VSD, patent ductus arteriosus, etc. In this case, giving the size and shape of the defect, a suitable device could be chosen for transcatheter occlusion among ADO, ADO II, membranous or muscular VSD occluder, VSD Coil or ASO. With a quite big and long defect like that, heart block and injuring adjacent structures could likely happen when using ADO, VSD occluder or ASO. A good device might be ADO II, but it was not available in our center at that time. So, we finally decided to use the Nit-Occlud® Lê VSD coil (PFM Medical, Germany), which are commonly used for VSD closure. This device is made of Nitinol coils with securely attached polyester fibers and a cone-in-cone configuration (Figure 2). The bigger proximal cone is more flexible and will be partially deployed on the left ventricular side of the defect. The smaller distal cone will be deployed on the other side of the defect and its diameter should be at least twice the defect smallest diameter. The first device chosen might be undersized purposely, for minimizing surrounding structures injury. That could explain for device embolization after deployment. The second bigger device was appropriate for the defect with firmly sitting in the correct position. So, choosing a suitable device with correct size is very important to prevent device embolization in transcatheter Gerbode defect closure.

After device successfully released, there was rising concern of hemolysis and hematuria because the contrast ejection and echocardiography showed small residual shunt. But after 24 h, the murmur on heart auscultation and residual shunt on echocardiography was completely gone. Six months following up also showed steady result with no heart murmur, good device position, no shunt on echocardiography (Figure 8) and the patient achieved almost normal life.

In conclusion, the diagnosis of congenital Gerbode defect is quite challenging, can be easily misinterpreted. Percutaneous device occlusion offers a feasible, safe and effective therapy for this type of defect. Among devices used for transcatheter closure of Gerbode defects, the Nit-Occlud® Lê VSD coil may be a good candidate.

## COMMENTS

### Case characteristics

A 31-year-old male who had normal physical and mental development presented with dyspnea on exertion and a loud harsh holosystolic murmur at 4<sup>th</sup> intercostal spaces along the left sternal border with a systolic thrill could be palpated.

### Clinical diagnosis

Ventricular septal defect.

### Differential diagnosis

Tricuspid regurgitation, mitral regurgitation, pulmonic stenosis, patent ductus arteriosus.

### Laboratory diagnosis

The BNP was slightly increased. Other labs were within normal limits.

### Imaging diagnosis

Echocardiography showed a shunt from left ventricle to the right atrium.

### Pathological diagnosis

Communication between the left ventricle and right atrium (congenital Gerbode defect).

### Treatment

The defect was transcatheterly closed using a Nit-Occlud® Lê VSD coil with no residual shunt at 6 mo follow-up.

### Related reports

Congenital Gerbode defect is a rare congenital heart disease and can be easily misinterpreted. Percutaneous device occlusion offers a feasible, safe and effective therapy for this disease.

### Experiences and lessons

In congenital Gerbode defect, careful review of echocardiography is an important key to avoid misdiagnosis and the transcatheter closure with an appropriate device is a crucial factor to ensure the procedural success.

### Peer-review

The reported case is well described and interesting.

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## Diagnosis and management challenges of in-stent restenosis in coronary arteries

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### Abstract

Over the course of the 3 decades, percutaneous coronary intervention (PCI) with stent implantation transformed the practice of cardiology. PCI with stenting is currently the most widely performed procedure for the treatment of symptomatic coronary disease. In large trials, drug-eluting stents (DES) have led to a significant reduction in in-stent restenosis (ISR) rates, one of the major limitations of bare-metal stents. Due to these favorable findings, DES was rapidly and widely adopted enabling more complex coronary interventions. Nevertheless, ISR remains a serious concern as late stent complications. ISR mainly results from aggressive neointimal proliferation and neoatherosclerosis. DES-ISR treatment continues to be challenging complications for interventional cardiologists.

**Key words:** Stent; In-stent; Restenosis; Percutaneous coronary intervention

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**Core tip:** Percutaneous coronary intervention with stenting is currently the most widely performed procedure for the treatment of symptomatic coronary disease. In large trials, drug-eluting stents (DES) have led to a significant reduction in in-stent restenosis (ISR) rates, one of the major limitations of bare-metal stents. However, ISR remains a serious concern as late stent complications. ISR mainly results from aggressive neointimal proliferation and neoatherosclerosis. DES-ISR treatment continues to be challenging complications for interventional cardiologists. This review focuses on pathogenesis, diagnosis and treatment options for ISR in the current era of advanced intravascular imaging and intervention.

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## INTRODUCTION

Percutaneous coronary intervention (PCI) with stenting is currently the most widely performed procedure for the treatment of symptomatic coronary disease<sup>[1]</sup>. Over the course of the 3 decades, PCI with stent implantation transformed the practice of cardiology. In large trials, drug-eluting stents (DES) have led to a significant reduction in in-stent restenosis (ISR) rates, one of the major limitations of bare-metal stents (BMS)<sup>[2]</sup>. Due to these favorable findings, DES was rapidly and widely adopted enabling more complex coronary interventions. Nevertheless, ISR remains a serious concern as late stent complications.

## DEFINITION

ISR is defined as the gradual re-narrowing of a stented coronary artery lesion due to arterial damage with subsequent neointimal tissue proliferation<sup>[3,4]</sup>. Angiographically IRS is a binary event defined as recurrent diameter stenosis at the stent segment more than 50% of the vessel diameter as determined by coronary angiography<sup>[4]</sup>. The angiographic definition remains the main definition since it allows determination of ISR severity and morphological pattern. The clinical definition of ISR requires the presence of greater than 50% diameter in-stent stenosis and one of the following: Clinical symptoms of recurrent angina, objective signs of ischemia (EKG changes), positive coronary hemodynamic assessment with fractional flow reserve (FFR) less than 0.80, intravascular ultrasonography (IVUS) minimum cross-sectional area less than 4 mm<sup>2</sup> (6 mm<sup>2</sup> for left main), or restenosis with  $\geq 70\%$  reduction in lumen diameter even in the absence of clinical symptoms or signs.

## CLASSIFICATION

Multiple classification systems have been identified to address the severity of ISR. Mehran system<sup>[5]</sup> is a morphologic classification of ISR lesions in to four patterns. Pattern I (focal) is ISR ( $\leq 10$  mm in length) lesion within the stent, pattern II (diffuse) is ISR greater than 10 mm within the stent, pattern III (proliferative) is ISR greater than 10 mm extending outside the stent, and pattern IV (occlusion) is totally occluded ISR. This classification system predicts the need for repeat revascularization after intervention (19%, 35%, 50%, and 98%, respectively)<sup>[5]</sup>. American College of Cardiology/American Heart Association lesion

classification has been also validated in patients with ISR<sup>[6]</sup>. Type A lesions had a probability of success of more than 85% and a low risk of acute occlusion. Type B lesions had a probability of success of between 60% and 85% and a moderate risk of abrupt occlusion. Finally, type C lesions had a probability of success of less than 60% and a high risk of abrupt occlusion following the procedure (Table 1). Lesions B2 and C have been reported to be frequently associated with suboptimal acute results with a higher restenosis rate and poorer long-term clinical outcomes<sup>[7]</sup>.

## INCIDENCE

In general, rates of ISR range from 3% to 20% with drug-eluting stents and 16% and 44% with BMS. This occurs mostly between 3 to 20 mo after stent placement<sup>[3,8]</sup>. The incidence of ISR depends on the definition, stent type, location, patient comorbidities and lesion complexity (*i.e.*, lesion length, vessel size, and bifurcation lesions). The introduction of DES has significantly reduced the occurrence of neointimal proliferation, which is considered the main mechanism for ISR. The decrease in ISR was translated into decreased clinical need for subsequent repeat revascularization<sup>[9-11]</sup>. A meta-analysis of 38 randomized controlled trials with more than 18000 patients showed significant reduction in TLR with both sirolimus-eluting stent (SES) and paclitaxel-eluting stents (PES) compared with BMS<sup>[10]</sup>. However, due to the complexity of ISR beyond device and stent design, the rates of ISR in both BMS and DES are still relatively high<sup>[12]</sup>. Routine angiographic surveillance 6 to 8 mo after stent implantation was done in one study that revealed ISR rates of 30.1%, 14.6%, and 12.2% for BMS, first-generation DES, and second-generation DES, respectively<sup>[13]</sup>.

### **Bare-metal stents ISR**

Despite relatively high restenosis rates, bare-metal stents are still frequently used in clinical practice during PCI<sup>[14]</sup>. This is related to unaffordable prices of DES and more importantly, lower risk of bleeding due to shorter duration of dual antiplatelet therapy (DAPT) that is required after BMS compared with DES. BMS-ISR causes a significant therapeutic burden in current clinical practice. One pooled analysis reported a one-year TLR and TVR rates after BMS of 12% and 14.1% respectively<sup>[15,16]</sup>. Clinical restenosis was evident within 6-12 wk after BMS implantation<sup>[16]</sup>. Beyond 1 year, rate of BMS restenosis is negligible and most stenting events are related to disease progression in vessel segments other than the stented lesion<sup>[16]</sup>.

### **Drug-eluting stents ISR**

Restenosis rate of DES increased in the recent years due to expanded use to include high-risk patients with complex coronary lesions. The DES-ISR rate has been reported in 3%-20% depending on DES type, the duration of follow-up, and the complexity of the lesions

**Table 1 ACC/AHA lesion-specific classification of the primary target stenosis**

Lesion type		Lesion characteristic according to AHA/ACC classification				
Type A lesions	Discrete (< 10 mm length)	Concentric	Readily accessible	Non angulated segment < 45°	Smooth contour	Little or no calcification
	Less than totally occlusive	Not ostial in location	No major branch involvement	Absence of thrombus		
Type B1 lesions	Tubular (10-20 mm length)	Eccentric	Moderate tortuosity of proximal segment	Moderately angulated segment, 45°-90°	Irregular contour	Moderate to heavy calcification
	Total occlusion < 3-mo-old	Ostial in location	Bifurcation lesions requiring double Guidewires	Some thrombus present		
Type B2 lesions	Two or more "B" characteristics					
Type C lesions	Diffuse (> 2 cm length)	Total occlusion > 3-mo-old	Excessive tortuosity of proximal segment	Extremely angulated segments, > 90°	Inability to protect major side branches	Degenerated vein grafts with friable lesions

in which the stents were placed<sup>[3]</sup>. When compared with BMS, DES is associated with lower ISR. At one-year follow up, SES markedly reduced the incidence TLR from 16.6% to 4.1% when compared with BMS<sup>[17]</sup>. For first-generation DES, j-Cypher registry of 12812 patients who received SES, the TLR rate was 7.3% at 1 year, and 15.9% at 5 years<sup>[18]</sup>. Ischemia-driven TLR was also the same in patients randomly assigned to SES or PES (13.1% vs 15.1%) in the SIRTAX LATE study<sup>[19]</sup>. Second generation stents have been associated with lower death and myocardial infarction compared with first-generation DES. However, zotarolimus-eluting stent (ZES) found to be noninferior to PES for TVR at 1 and 5 years<sup>[20]</sup>. In a pooled analysis of multiple studies comparing everolimus-eluting with ZES, the rates of TVR at up to five years of follow-up were 6.3% and 5.0%, respectively<sup>[21]</sup>.

## PREDICTORS OF IN-STENT RESTENOSIS

Patient comorbidities, lesion characteristic, and procedural characteristics are the main predictors of ISR.

### Patient characteristics

Patient characteristics and comorbidities that are associated with higher rate of ISR include; metal allergy, local hypersensitivity reactions with immunologic and inflammatory response to the drug or the polymer, age, female gender, diabetes mellitus, chronic kidney disease (including hemodialysis), and multivessel coronary artery disease<sup>[3,22,23]</sup>.

### Lesion characteristics

Lesion characteristics associated with ISR include; lesion length, smaller reference artery diameter, ostial lesion, initial plaque burden and residual plaque after implantation. In contrast with BMS, DES tends to have a more focal pattern of ISR, except in diabetics, where the ISR tends to be more confined to the stent edges<sup>[24,25]</sup>. Focal ISR (Mehran pattern I) has been associated with a lower rate of ISR recurrence than nonfocal (Mehran pattern > I) ISR<sup>[25]</sup>.

### Procedural characteristics

Operator and technique dependent characteristics include stent undersizing, incomplete lesion coverage, stent under expansion, and malapposition. Mechanical properties of stents that may lead to recoil because of loss of radial force, stent fractures, and altering increase in shear stress are all associated with higher rates of ISR. For every 10 mm of excess stent length beyond lesion has been independently associated with increased post-procedural percent diameter stenosis by 4% and increased TLR at 9 mo (OR = 1.12, 95%CI: 1.02-1.24)<sup>[26-29]</sup>. Stent fracture, on the other hand, can trigger focal ISR or thrombosis<sup>[30-32]</sup> which can result in a reduction in drug delivery at the breakage point of the stent. Stent fracture occurs more frequently in the right coronary artery, overlapping stents, longer stents, SESs (because of the ridged closed cell structure), and excessively tortuous angulated vessels<sup>[33]</sup>. Malapposition, also known as incomplete stent apposition (ISA), is defined as the absence of contact between stent struts and the vessel wall not overlying a side branch. Malapposition seems to be related to procedural technique due to under-sizing the stent, use of low deployment pressures, and severely calcified lesions, which do not allow for homogenous stent expansion<sup>[34]</sup>. Oversized stents can also lead to extensive trauma to the vessel wall and increased proliferative reaction<sup>[35]</sup>. Geographic miss occurs when the stent does not fully cover the injured or diseased segment of the artery (axial miss) or the ratio of balloon to artery size is less than 0.9 or greater than 1.3 (longitudinal miss). Geographic miss is associated with increased risk of TLR and MI at 1 year<sup>[36]</sup>. DESs decrease neointimal growth. As a result, geographic miss or strut fracture may be larger factors of ISR in DESs compared with BMSs<sup>[12]</sup>.

## PATHOGENESIS

The main mechanism of ISR following stent implantation is neointimal tissue proliferation because of arterial wall damage<sup>[21,22]</sup>. Neointimal tissue proliferation could be focal or distributed uniformly along the

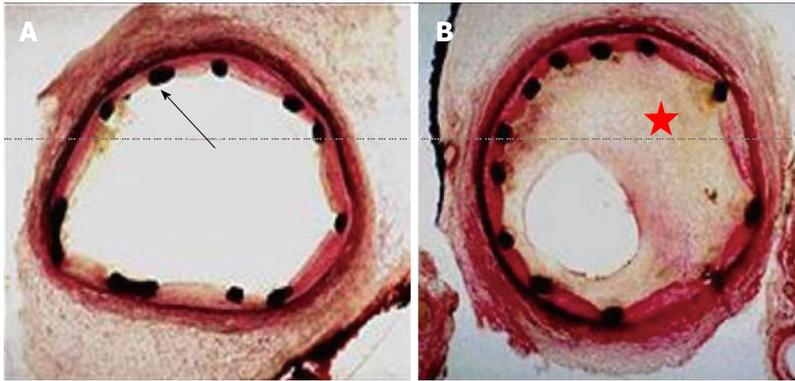


Figure 1 The figure showing cross-section of coronary artery immediately after implantation of a bare metal stent black dots represent the stent struts (red arrow) (A); the figure showing significant in-stent restenosis with neointimal hyperplasia (red star) 6 mo after the implantation of a bare metal stent (B).

length of the stent (Figure 1). ISR, which happens early within days of stent deployment, is due to elastic recoil and relocation of axially transmitted plaque. The causes of late (weeks to months) ISR commonly are reorganization of thrombus, neointima formation and remodeling<sup>[37]</sup>.

Neoatherosclerosis yet is another contributing factor to ISR. The stimulation of neointima formation happens due to injury to the vessel during the PCI and stent deployment. A cascade of events are triggered by the intimal and medial damage, leading to proliferation and migration of vascular smooth muscle cells, extracellular matrix formation which ultimately activates the coagulation-fibrinolysis system<sup>[38]</sup>. The local inflammation can lead to the development of neoatherosclerosis characterized by accumulation of lipid-laden foamy macrophages within the neointima with or without a necrotic core formation and calcification, which can occur years after stent placement<sup>[39]</sup>. Neoatherosclerosis is associated with a higher proportion of in-stent atherosclerotic plaque, which could explain unstable symptoms and myocardial infarction presentation of patients with ISR years after PCI. The incidence of neoatherosclerosis was significantly greater in DES compared with BMS (31% vs 16%,  $P < 0.001$ )<sup>[40]</sup>. Younger age, longer implant durations, SES usage, PES usage and underlying unstable plaques, are independent risk factors for neoatherosclerosis<sup>[14,40]</sup>.

## CLINICAL PRESENTATION

Due to the gradual and slow progression of ISR compared with stent thrombosis, majority of ISR presents as progressive recurrent angina<sup>[40]</sup>. The time for symptoms to develop due to DES-ISR is 3 to 12 mo after stent placement<sup>[41]</sup>. BMS stent on the other hand develop ISR symptoms sooner with reported average period of 6 mo post-PCI<sup>[42]</sup>. BMS-ISR presented as MI in 3.5%-20% of patients<sup>[43]</sup>. DES-ISR is similar to that of BMS with approximately 16%-66% of patients presenting with unstable angina and 1%-20% with MI<sup>[44,45]</sup>.

## ANATOMIC ASSESSMENT

### Routine surveillance

Routine angiographic surveillance is not recommended

because it has been shown to increase the rates of oculostenotic revascularization.

### Intravascular ultrasonography

IVUS is considered a fundamental intracoronary imaging modality to assess ISR. The stent and procedures characteristics can be readily assessed as contributing mechanism of ISR using IVUS<sup>[35]</sup>. IVUS delineate external elastic lamina behind the stent struts very well, which provides valuable insights on vessel sizing for optimization of stent expansion (Figure 2F and G). IVUS does help detect the presence of neointimal hyperplasia obstructing the stent, stent underexpansion, stent fracture, or edge restenosis. In addition, it can provide insights into optimal vessel sizing for choosing the appropriate stent size (Figure 2K and L). However, IVUS has limited axial resolution (150  $\mu\text{m}$ ), which makes neointimal interface hard to define<sup>[12]</sup>.

### Optical coherence tomography

Optical coherence tomography (OCT) provides better axial resolution (15  $\mu\text{m}$ ), allowing better resolution of the vessel lumen, neointimal tissue, and stent struts distribution. The morphology of ISR can be identified using OCT which could show macrophage infiltration, necrotic core, in-stent calcification and neoatherosclerotic plaque rupture<sup>[46,47]</sup>. The weakness of the OCT resides in the poor tissue penetration, which cause poor visualization of the residual plaque that is beyond the stent<sup>[12]</sup>.

## HEMODYNAMIC ASSESSMENT

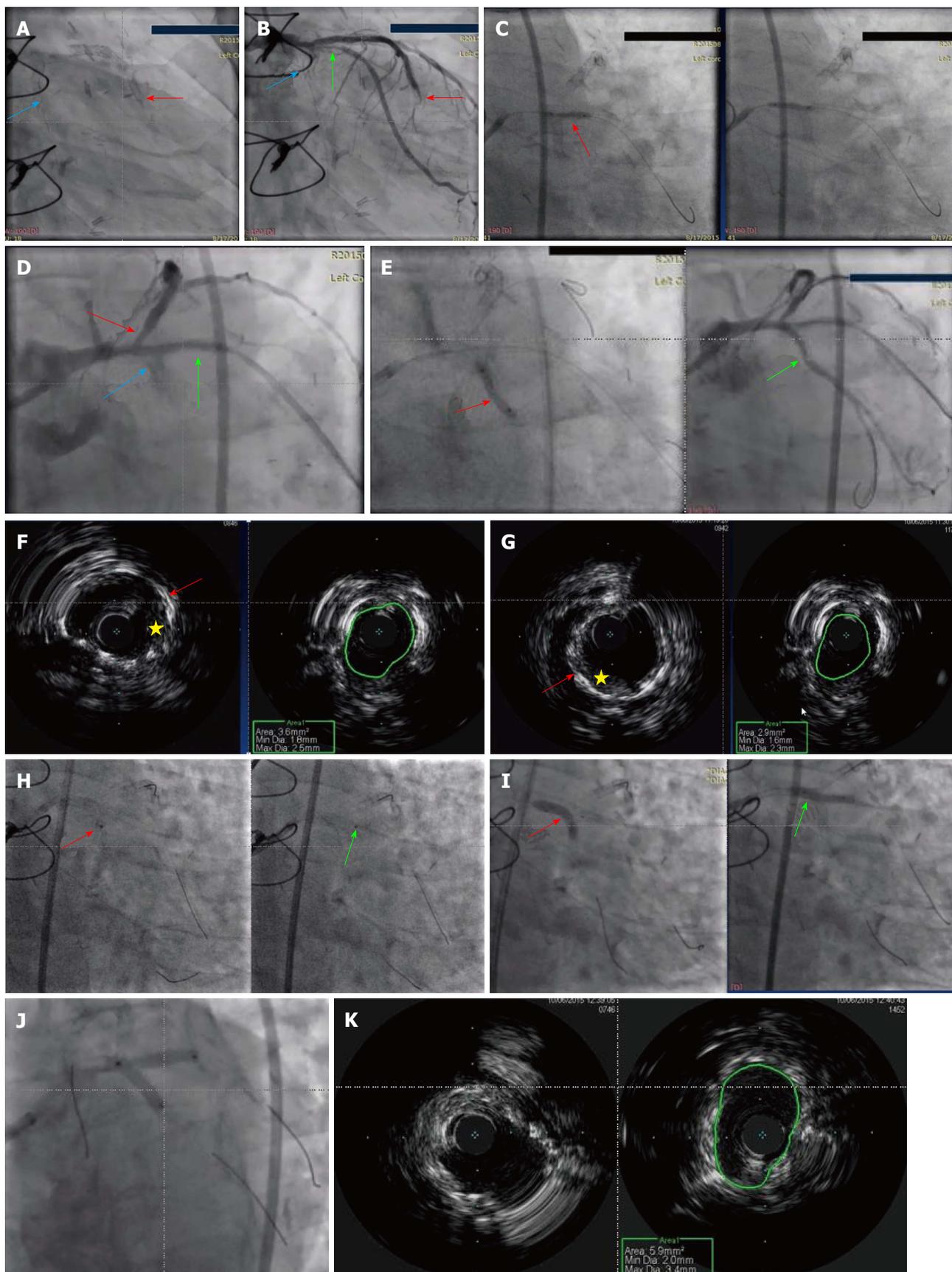
### Fractional flow reserve

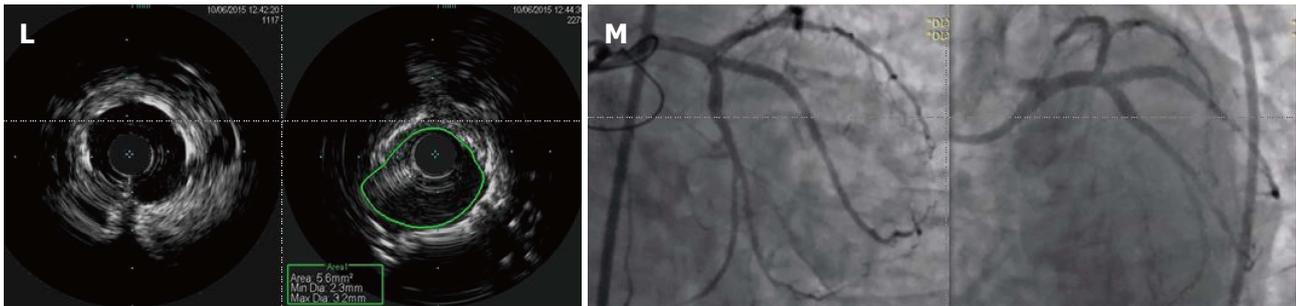
FFR has been validated for clinical decision making in patients with ISR. The clinical outcome of patients with ISR with deferred interventions based on a FFR > 0.75 is excellent<sup>[48]</sup>. This diagnostic strategy is useful in controversial cases with angiographically moderate or inconclusive ISR.

## TREATMENT

### Balloon angioplasty

Balloon angioplasty (BA) is one of the earliest interventions that were used to treat ISR by displacing in-





**Figure 2** Sixty-seven-year-old man presented with increasing chest pain at rest. He has past medical history significant for coronary artery disease with PCI and coronary artery bypass grafting. He had PCI with (3.0 mm × 12 mm) DES to LCx, (2.5 mm × 16 mm) DES to RI and (2.5 mm × 16 mm) DES to obtuse marginal a year prior to his presentation. The left internal mammary artery to LAD is patent, however, he is known to have occluded SVG to RI and SVG to first diagonal (D1). Given his increasing chest pain, coronary angiogram was done. A: Coronary stents before contrast injection in LAD (red arrow), LCx (blue arrow); B: Coronary angiogram of the same patient showing severe proximal LCx ISR (blue arrow) with no flow, severe proximal RI ISR (green arrow) with slow flow, and mid LAD severe ISR (red arrow); C: Dilation of the RI coronary artery with 2.5 mm × 22 mm NC balloon with 22 atm inflation pressures was done; D: Coronary angiogram showing the proximal RI ISR (green arrow) post balloon dilation. Red arrow shows severe proximal LAD stenosis with poor flow. LCx has completely occluded ISR (blue arrow); E: The left circumflex ISR lesion (red arrow) was wired and with balloon dilation the flow was restored in the LCx (green arrow); F: IVUS imaging of the underexpanded stent in the proximal LCx lesion. Left panel shows stent struts (red arrow) with evidence of neointimal hyperplasia (yellow star). The right panel shows small stent CSA of only 3.6 mm<sup>2</sup> which is below the target 5 mm<sup>2</sup> in Asians and 6 mm<sup>2</sup> in non-Asians; G: IVUS imaging of the underexpanded stent in the proximal ramus coronary artery. Left panel shows severely under-expanded stent (red arrow) with evidence of neointimal hyperplasia (yellow star). The right panel shows small stent CSA of only 2.9 mm<sup>2</sup>; H: Excimer Laser Coronary Angioplasty treatment of LCx (left panel - red arrow) and ramus artery (right panel - green arrow) using 0.9 mm coronary laser and the heparinized flush technique. Laser catheter was advanced slowly at 0.2-0.5 m/s during laser emission with careful monitoring of heart rate and blood pressure. Vessel injury such as perforation, dissections and acute closure are the main side effects; I: Post laser balloon dilation with (3.5 mm × 20 mm) NC balloon of both LCx (red arrow) and ramus (green arrow) arteries; J: Sequential kissing stenting technique in the proximal LCx and ramus arteries with DES 3.5 mm × 18 mm in Ramus and 3.5 mm × 15 mm in LCx; K: IVUS imaging of the stent in the proximal LCx coronary artery that shows good expansion of the stent with great increase in CSA to 5.9 mm<sup>2</sup>; L: IVUS imaging of the stent in the proximal ramus coronary artery that shows good expansion of the stent with great increase in CSA to 5.6 mm<sup>2</sup>; M: TIMI III flow was achieved in the LCx and Ramus coronary arteries without any compromise of LAD. PCI: Percutaneous coronary intervention; DES: Drug-eluting stents; LCx: Left circumflex; RI: Ramus intermedius; LAD: Left anterior descending artery; SVG: Saphenous vein graft; ISR: In-stent restenosis; NC: Non-compliant; IVUS: Intravascular ultrasound; CSA: Cross-sectional area.

stent tissue from the lumen in axial and longitudinal direction to the outer portion of the vessel wall as well as further expanding the stent<sup>[49]</sup> (Figure 2). This intervention could be useful in focal ISR. The outcome of BA for focal ISR. However, during balloon inflation, slippage or watermelon seeding can occur, leading to edge-related complications. Cutting or scoring balloons can help minimize this, but also have limitations in delivery through stented regions or distal areas<sup>[50]</sup>. Lateral blades or atherotomes anchor the balloon in the lesion and minimize slippage<sup>[51]</sup>. Progressive balloon dilations and small/short balloons can also prevent side effects from balloon slippage<sup>[52]</sup>. One of the limitations of BA is that subacute tissue re-intrusion back to the lumen tends to occur within minutes after the last balloon inflation. This explains the early lumen loss phenomenon detected in BA studies in this setting, a finding also associated with subsequent recurrent restenosis.

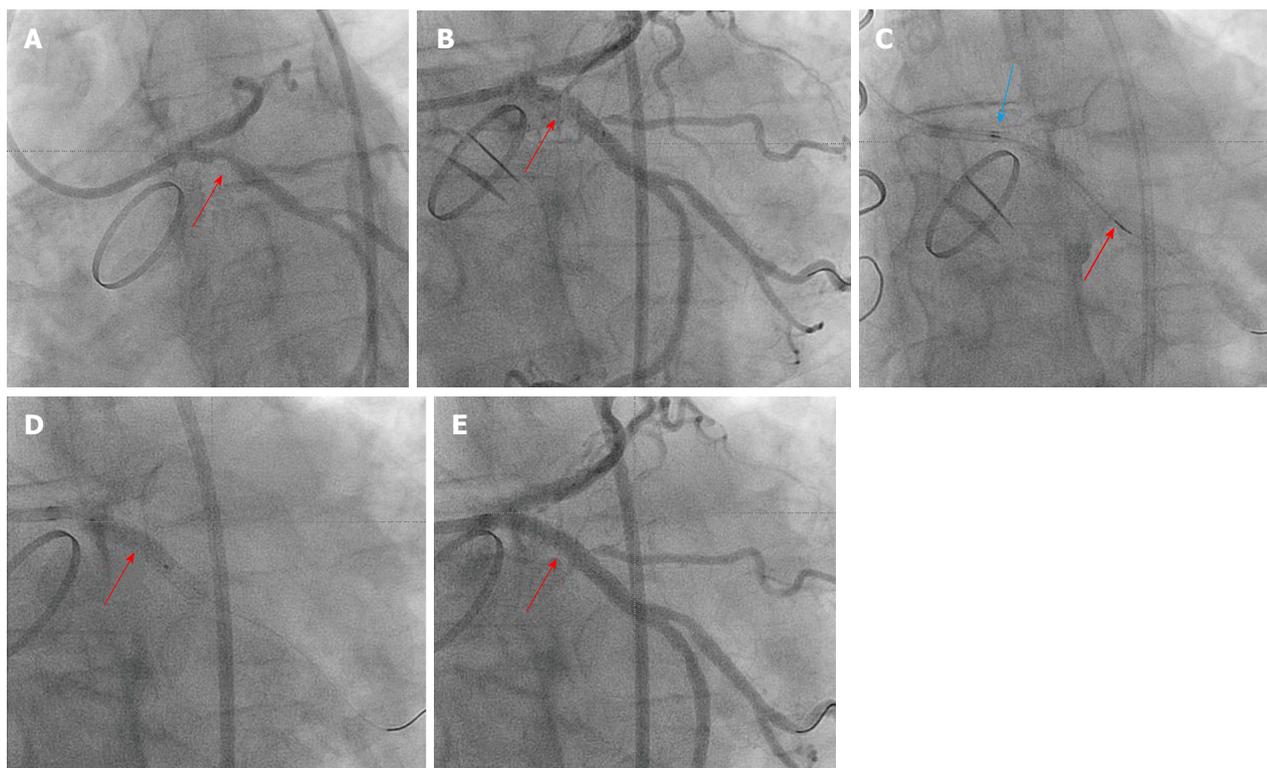
### Vascular brachytherapy

Brachytherapy inhibits neointimal formation within the stent, but not the stent edges, by delivering radiation to the areas of ISR. Brachytherapy effectively suppressed the proliferative response and significantly reduced clinical and angiographic restenosis rates (Figure 3C). Both beta and gamma radiation sources could achieve major reductions in the angiographic restenosis rates<sup>[53]</sup>. Gamma emitters had profound tissue penetration, whereas beta emitters had less tissue penetration

(Figure 3E). Randomized clinical trials in patients with ISR demonstrated the superiority of brachytherapy compared with conventional BA or atheroablative techniques<sup>[53-55]</sup>. Adding an extra layer of metal to treat DES or BMS-ISR is not ideal and will continue to place patients at future risk for ISR. Therefore, DEB and vascular brachytherapy are better options compared with DES. Vascular brachytherapy is available in few centers in the United States and is used primarily for recurrence of DES-ISR, but logistic issues and lack of radiation oncology support impede its uses. Therefore, restenting with second-generation DES became the default therapy for DES-ISR.

### Excimer laser angioplasty

Excimer laser angioplasty (ELA) produces monochromatic light energy, which generates heat and shock waves that disrupt plaque (Figure 2H). Mehran *et al.*<sup>[56]</sup> compared results of ELA vs rotational atherectomy (RA), both followed by percutaneous transluminal coronary angioplasty (PTCA). 119 patients with 158 ISR lesions were treated with ELA plus PTCA and 130 patients with 161 ISR lesions were treated with RA plus PTCA. Volumetric IVUS analysis showed a greater reduction in intimal hyperplasia volume after RA than after ELA (43 mm<sup>3</sup> vs 19 mm<sup>3</sup>,  $P < 0.001$ ). However, the 1-year TLR rates were similar: 26% with ELA plus PTCA vs 28% with RA plus PTCA ( $P =$  nonsignificant). ELA is not currently a well-accepted treatment for ISR, but the ultimate role of this therapy



**Figure 3** Fifty-five-years-old caucasian male with mantle cell radiation for Hodgkin's lymphoma complicated with radiation heart valve disease with severe aortic valve stenosis status post mehanical aortic valve replacement surgery. Few years later he presented with chest pain and had PCI to the proximal LAD and LCx with DES. However, both few months later he developed ISR and underwent another PCI with DES to the proximal LAD and LCx. Patient was referred for vascular brachytherapy for the treatment of ISR of the LCx due to increased chest pain at rest and recurrent ISR of proximal LCx. A: Coronary angiogram showing 90% focal proximal LCx ISR (red arrow); B: Balloon angioplasty of the proximal LCx lesion (red arrow) to prepare the lesion before brachytherapy delivery; C: Coronary angiogram showing the Novoste Beta-Cath™ System that was used to deliver a source train that contains 12 individual radioactive seeds blue arrow to red arrow). Once properly positioned, 23 Gy from the center of the source center was prescribed. The patient was monitored during the dwell time which required 4 min and 49 s; D: Another balloon angioplasty was done after the radioactive seeds are pulled from LCx; E: Final TIMI-III flow in the LCx. PCI: Percutaneous coronary intervention; LAD: Left anterior descending artery; LCx: Left circumflex; DES: Drug-eluting stents; ISR: In-stent restenosis.

is still unclear.

### **Drug-eluting balloon angioplasty**

It was proposed that repeat stenting for ISR raises concerns for creating multiple stent layers. Therefore, the use of DEB angioplasty should minimize the metal layer and eventually decrease future ISR. For that purpose, multiple randomized studies have been done to evaluate the efficacy and durability of DEB compared with DES in treating BMS or DES-ISR. Few studies have shown that DEB is non-inferior to DES for BMS and DES-ISR<sup>[52-61]</sup>. However, none of these studies have been powered for clinical endpoints. DEB is currently not available for use in the United States. In addition, their use has been associated with issues that may limit their use mostly related to the use of paclitaxel and potential of particulates showering to the distal vessel bed, as well as the high profile of the device. Comparison of DEB with DES for treatment of ISR will be discussed in the following section.

### **Drug-eluting stents**

Balloon angioplasty alone carries a high risk of recurrent stenosis, especially in diffuse and/or severe ISR<sup>[44,62,63]</sup>.

The randomized trials Paclitaxel-eluting Stents vs Brachytherapy for In-stent Restenosis (TAXUS V ISR) and Sirolimus-eluting Stents vs Vascular brachytherapy (SISR) trial showed better outcomes for DES compared with brachytherapy<sup>[64,65]</sup>. Two major randomized trials compared DES with DEB for patients with ISR. The ISAR-DESIRE 3 trial randomized 402 patients with ISR in DES to paclitaxel-eluting balloon (PEB) vs first generation DES (PES) vs balloon angioplasty<sup>[52]</sup>. At a median follow-up of 3 years, the risk of TLR was similar with PEB vs PES (HR = 1.46, 95%CI: 0.91-2.33,  $P = 0.11$ ) and lower with PEB vs balloon angioplasty (HR = 0.51, 95%CI: 0.34-0.74,  $P < 0.001$ ). The risk of death/MI was lower, but not statistically significant, with PEB vs PES (HR = 0.55, 95%CI: 0.28-1.07,  $P = 0.08$ ). This finding was driven by a lower risk of death (HR = 0.38, 95%CI: 0.17-0.87,  $P = 0.02$ ). The risk of death/MI was similar with PEB vs balloon angioplasty (HR = 0.96, 95%CI: 0.46-2.0,  $P = 0.91$ ). Using the second generation DES, Restenosis Intra-Stent of Drug-Eluting Stents: Drug-Eluting Balloon vs Everolimus-Eluting Stent (RIBS IV) trial, evaluated the comparative efficacy of DEB and EES in patients presenting with DES-ISR<sup>[66,67]</sup>. A total of 309 patients with DES-ISR

were randomly allocated to DEB, or second generation DES (EES) patients in the EES arm had a significantly larger minimal lumen diameter ( $2.03 \pm 0.7$  mm vs  $1.80 \pm 0.6$  mm,  $P < 0.01$ ) net lumen gain ( $1.28 \pm 0.7$  mm vs  $1.01 \pm 0.7$  mm,  $P < 0.01$ ), and lower percent diameter stenosis ( $23\% \pm 22\%$  vs  $30\% \pm 22\%$ ,  $P < 0.01$ ) and binary restenosis rate ( $11\%$  vs  $19\%$ ,  $P = 0.06$ ), compared with patients in the DEB arm. At the 1-year clinical follow-up (100% of patients), the main clinical outcome measure (composite of cardiac death, myocardial infarction, and target vessel revascularization) was significantly reduced in the EES arm ( $10\%$  vs  $18\%$ ,  $P = 0.04$ , HR = 0.58, 95%CI: 0.35-0.98), mainly driven by a lower need for target vessel revascularization ( $8\%$  vs  $16\%$ ,  $P = 0.035$ ).

A meta-analysis looked into treatment of ISR comparing DEB, DES, and BA reported that treatment with DEB had a trend toward better outcomes than with DES<sup>[68-72]</sup>. The risk of TLR was lower in patients treated with DEB (OR = 0.22, 95%CI: 0.10-0.42) or DES (OR = 0.24, 95%CI: 0.11-0.47) than in those treated with BA. In a comparison of DEB and DES, the risk of TLR (OR = 0.92, 95%CI: 0.43-1.90) was similar. The risk of major adverse cardiac events, which was mainly driven by TLR, was also significantly lower in the DEB and DES groups (OR = 0.28, 95%CI: 0.14-0.53) than in the BA group, but it was similar between the DEB and DES groups (OR = 0.84, 95%CI: 0.45-1.50). For TLR, the probability of being ranked as the best treatment was 59.9% (DEB), 40.1% (DES), and 0.1% (BA).

There is no clear evidence on which type of DES should be used to treat ISR of a DES. Some experts argue that using a different type of DES helps to overcome drug resistance, but no strong data support this practice. A recently published network meta-analysis addressed the question of which strategy is preferred for the treatment of ISR, with the primary outcome defined as the percent diameter stenosis at angiographic follow-up<sup>[73]</sup>. This analysis suggested that PCI with second-generation DES (EES) was the most effective treatment, whereas percutaneous coronary intervention with DEB was ranked as the second most effective treatment but without significant differences from first-generation DES. Two additional similar design meta-analyses have reported similar findings suggesting second generation DES as treatment of choice for BMS and DES-ISR<sup>[74,75]</sup>. As a result, the 2009 update of the American College of Cardiology/American Heart Association/Society for Cardiovascular Angiography and Interventions guideline update for PCI and the 2005 European Society of Cardiology Task Force recommend DES for ISR whether the initial stent was BMS or DES<sup>[76-78]</sup>.

A recently published pooled analysis of the RIBS V and RIBS IV compared the efficacy of EES in patients with BMS-ISR and DES-ISR<sup>[79-82]</sup>. The study detected clinical and morphological differences of ISR in BMS vs DES, including for the later more focal ISR pattern and delayed onset of presentation. Nevertheless, the

outcome of the patients with DES restenosis was less favorable with regard to the angiographic indices, including lumen diameter post procedure and at follow-up. DES-ISR group treated with EES had both increased mortality and need for target vessel revascularization as compared with BMS-ISR group at one year follow up. The authors conclude that EES provides favorable outcomes in patients with ISR and that the results of EES are less satisfactory in patients with DES-ISR than in those with BMS-ISR.

## CONCLUSION

In-stent restenosis remains a prevailing clinical problem. The substrate of ISR includes a pathological spectrum ranging from smooth muscle cell proliferation to neoatherosclerosis. Optimal stent deployment, utilization of imaging-guided implantation by IVUS or OCT, adequate coverage of the lesion, verifying stent expansion and apposition to the vessel wall and minimal use of BMS are considered the main strategies to decrease ISR. Based on the currently available literature, the use of BMS should be minimal in clinical practice and replaced with second generation DES. For patients presenting with first ISR, vascular brachytherapy should be considered in patients with focal ISR, or high bleeding risk or requiring DAPT interruption. 2<sup>nd</sup> generation DES should be a second line therapy to avoid adding an extra layer of metal to treat DES. For patients presenting with recurrent ISR, second generation DES have better long-term outcomes specially if combined with DEB. DEB should be used as first line therapy for bifurcation restenosis to prevent excess metal at the carina.

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## Cardiovascular involvement in celiac disease

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### Abstract

Celiac disease (CD) is an autoimmune response to

ingestion of gluten protein, which is found in wheat, rye, and barley grains, and results in both small intestinal manifestations, including villous atrophy, as well as systemic manifestations. The main treatment for the disease is a gluten-free diet (GFD), which typically results in the restoration of the small intestinal villi, and restoration of other affected organ systems, to their normal functioning. In an increasing number of recently published studies, there has been great interest in the occurrence of alterations in the cardiovascular system in untreated CD. Herein, published studies in which CD and cardiovascular terms appear in the title of the study were reviewed. The publications were categorized into one of several types: (1) articles (including cohort and case-control studies); (2) reviews and meta-analyses; (3) case studies (one to three patient reports); (4) letters; (5) editorials; and (6) abstracts (used when no full-length work had been published). The studies were subdivided as either heart or vascular studies, and were further characterized by the particular condition that was evident in conjunction with CD. Publication information was determined using the Google Scholar search tool. For each publication, its type and year of publication were tabulated. Salient information from each article was then compiled. It was determined that there has been a sharp increase in the number of CD - cardiovascular studies since 2000. Most of the publications are either of the type "article" or "case study". The largest number of documents published concerned CD in conjunction with cardiomyopathy (33 studies), and there have also been substantial numbers of studies published on CD and thrombosis (27), cardiovascular risk (17), atherosclerosis (13), stroke (12), arterial function (11), and ischemic heart disease (11). Based on the published research, it can be concluded that many types of cardiovascular issues can occur in untreated CD patients, but that most tend to resolve on a GFD, often in conjunction with the healing of small intestinal villous atrophy. However, in some cases the alterations are irreversible, underscoring the need for CD screening and treatment when cardiovascular issues arise of unknown etiology.

**Key words:** Cardiovascular; Celiac disease; Gluten;

Heart; Vascular

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**Core tip:** Celiac disease (CD) is a public health concern suffered by about 1% of the population worldwide. It often goes undetected even in developed countries, owing to the varied and occult presentation which can make diagnosis difficult. Untreated, systemic manifestations including cardiovascular ailments can occur. In this review, information concerning the cardiovascular involvement in CD patients is described and discussed. Treatment of CD patients with a gluten free diet can reverse some, but not all of the cardiovascular involvement. Thus the need for prompt diagnosis and treatment.

Ciaccio EJ, Lewis SK, Biviano AB, Iyer V, Garan H, Green PH. Cardiovascular involvement in celiac disease. *World J Cardiol* 2017; 9(8): 652-666 Available from: URL: <http://www.wjgnet.com/1949-8462/full/v9/i8/652.htm> DOI: <http://dx.doi.org/10.4330/wjc.v9.i8.652>

## INTRODUCTION

Celiac disease (CD) is characterized by an immunologic response to gluten, which often results in diffuse inflammatory damage to the small intestinal mucosa, and malabsorption of nutrients<sup>[1]</sup>. CD is of special interest among chronic diseases due to several factors: (1) it is associated with specific comorbidities; (2) it involves a compromised absorption of nutrients; and (3) a gluten-free diet (GFD) is currently the main long-term treatment<sup>[2]</sup>. Studies have shown that certain cardiovascular maladies, including cardiomyopathy, myocarditis, arrhythmias, and premature atherosclerosis, are more prevalent in individuals with CD as compared to individuals without the disease<sup>[3,4]</sup>. In this article, published works concerning the effects of CD on the cardiovascular system, and the risk of cardiovascular disease, are reviewed. The method of some previous analyses is followed to quantitatively characterize the published articles<sup>[5-7]</sup>, and to then compile the most salient information for review.

## RESEARCH

The Google Scholar search tool was used to find associations between CD and the heart and vascular systems. Keywords pertaining to the heart and vascular system, tabulated in Table 1, were used for search in conjunction with "celiac disease", "coeliac disease", or "gluten". The searches were limited to the co-detection of these terms in the publication title, which is suggestive of the importance of the keywords. The cardiovascular keywords used for

search were derived from encyclopedic descriptions of the heart, vascular, and cardiovascular systems. Under these headings, all relevant terms were extracted as keywords. They were categorized as heart terms and vascular terms. The format used for search in Google Scholar was, for example: (1) allintitle: "celiac disease" "myocardial"; (2) allintitle: "coeliac disease" "myocardial"; and (3) allintitle: "gluten" "myocardial", where the results for the three forms of expression pertaining to CD were then combined. Heart and vascular keywords, tabulated in Table 1, were then combined to form summary topics for analysis. The number of CD/cardiovascular publications per year was then graphed for all of the summary topics.

The type of published document was also recorded for each keyword entry. Each citation used was categorized by type of published documentation as shown in Table 2. There are six possible publication types according to the list. All published documents were categorized as one of the types noted in Table 2. Graphical displays were utilized to separately show the number of CD/cardiovascular documents of each type noted in Table 2 that were published per year. Then for each of the summary topics, the total number of publications of each type in Table 2 were compiled. Also for each of the summary topics, the total number of studies and the mean publication year of the studies for the journals the studies were published in were tabulated. The essential points in each study were then condensed and described in review form, in separate sections, for each of the summary topics.

## PUBLICATION SUMMARY STATISTICS

In Figure 1 is presented a graph of the number of publications per year in which CD and cardiovascular terms appeared. The earliest studies in which CD was investigated for cardiovascular function were published in 1970. However until the year 1998, only a handful of such studies were published, after which there began a substantial increase in the publishing of CD/cardiovascular studies. Although there were fluctuations in the number of studies in the 2000s and 2010s, the overall trend was a sharp upward swing in published studies. The data for 2017 only includes the first few weeks of the year.

The number of studies for selected types that was published per year is shown in bar graph form in Figure 2. The results are shown for articles (cohort), case studies, abstracts, and letters, and review and editorial publications. Many of the CD/cardiovascular published studies were either articles or case studies. As for graphs of the total studies published that were shown in Figure 1, the graphs of individual published document types in Figure 2 begin to exhibit substantial increases about the year 2000. There were also a number of abstracts and case reports published in the late 1980s and 1990s, as is notable in the case reports

**Table 1 Cardiovascular terms used for search in the study**

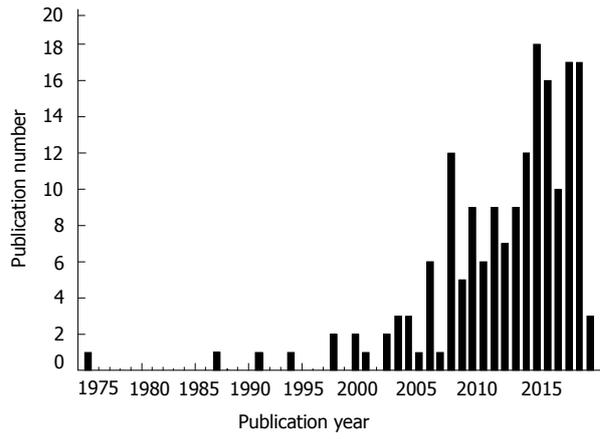
Heart terms	Vascular terms
Afterload, preload	Angiogenesis
Arrhythmia, rhythm	Aorta, aortic
Atrial, atrium	Arterial, arteries, artery
Atrioventricular	Arteriosclerosis, atherosclerosis
Bachmann's	Atherogenesis, atherogenic
Cardiac, cardio	Blood pressure
Cardiologist	Cardiovascular
Cardiomyopathies, cardiomyopathy	Circulatory
Congenital	Circumflex
Contractility	Coronary
Depolarization	Embolism
Effusion	Haemoptysis, hemoptysis
Ejection	Hemorrhage
Electromechanical	Haemodynamics, Hemodynamics
Endocardium, epicardium	Haemosiderosis, hemosiderosis
Fibrillation	Stroke
Foramen ovale	Thrombosis, thromboembolism
Frank-Starling	Vascular
Heart	Vein, veins
Infarction	Vena cava
Ischaemic, ischemic	Venous
Mitral	Venule, venules
Myocardial, myocardium	
Myocarditis	
Myocyte	
Pericardial, pericardium	
Purkinje	
QT	
Septum	
Sinoatrial	
Stenosis	

**Table 2 Categories of published documents**

Type	Description
Articles	Includes research articles, cohort studies and case control studies
Reviews	These included reviews of the literature and meta-analyses
Case studies	Limited to $n = 1-3$ patients in the study
Letters	These could include comments on other articles as well as case reports in letter form
Abstracts	When no full paper had been published, abstracts were included in the references
Editorials	These were typically comments on papers published in the same journal issue

graph in Figure 2. There are only a few review and editorial publications to date, but they are recent.

Based on all of this data, in Table 3 are provided, for each document type, the number of published studies for each topic, with the totals for all articles shown in the last row. Most of the published works are either articles (74) or case studies (62). There are also substantial numbers of letters (23) and abstracts (20). The totals for each term are given to the right in the table. The sum total, 190, is greater than the number of cited articles in this review, 180, because a particular citation could be used in more than one review topics



**Figure 1 Overall published studies on celiac disease/cardiovascular by year.**

section. Furthermore, several citations used in the Introduction were not cardiovascular studies and were not included in Table 3. A number of topics were particularly of interest for CD/cardiovascular publishing. These include papers on CD and cardiomyopathy (33 studies), thrombosis (27), cardiovascular risk (17), atherosclerosis (13), stroke (12), and arterial function and ischemic heart disease (11 each). In Table 4 are shown keyword terms and total number of studies, and median (range) study year of the journal. The median year for all of the studies is 2004 or later, except for the term "haemodynamics" (1998). Thus the possible connection between CD and "haemodynamics" tended to be investigated at earlier dates, as compared with other cardiovascular conditions.

**Compilation of the celiac disease - cardiovascular literature**

In this section, the study results for each keyword of Table 1 are combined into summary topics, to show the general consensus and trends for CD/cardiovascular publications. Thus the most pertinent information from all studies belonging to a particular cardiovascular term was collated by topic. The total number of studies (#) and median and range in years (median year) are shown for published studies concerning each topic. The terms are separated and noted as belonging to vascular or heart categories, followed by cardiovascular risk assessment.

**Vascular - arterial function [# = 11, median year = 2014 (2011-2016)]**

Arterial function is of great concern in CD. Measurements to quantify alterations are made using echocardiography and pulse wave velocity<sup>[8,9]</sup>. In untreated CD, aortic function can deteriorate, and this deterioration is predictive of subclinical atherosclerosis and future cardiovascular events<sup>[8]</sup>. Aortic strain and distensibility tend to be significantly lower, and the aortic stiffness index significantly higher, in untreated CD patients vs controls<sup>[8,10]</sup>. CD patients are at increased risk for

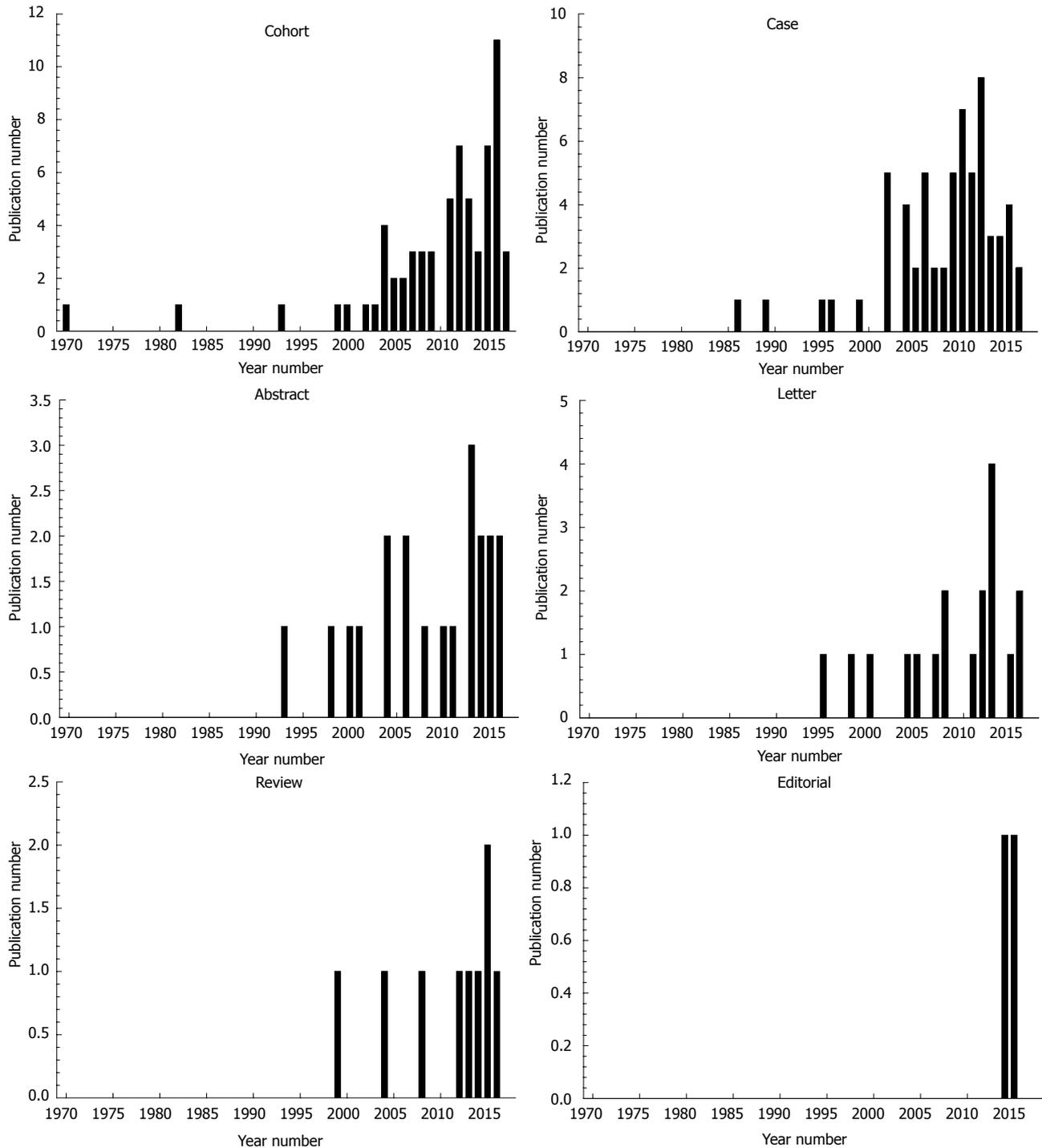


Figure 2 Published studies per year according to document type.

coronary artery disease<sup>[9]</sup>, which may have a genetic association<sup>[11]</sup>. Occlusion of the brachiocephalic trunk and right and left common carotid artery has been noted in CD<sup>[12]</sup>. In adult CD patients lacking cardiovascular risk factors, abnormal homocysteine, erythrocyte sedimentation rate, C-reactive protein, and insulin levels may, along with inflammation, be contributive to arterial stiffening<sup>[9]</sup>. Spontaneous coronary artery dissections have been observed as a cause of acute myocardial infarction in CD patients<sup>[3]</sup>. There is also some support

for an association between CD and cerebrovascular disease<sup>[13]</sup>. Correlation has been shown between restoration of the small intestinal villous atrophy and normalization of vascular parameters in gluten-abstinent CD patients<sup>[14]</sup>. Yet after onset of the GFD, the lack of a significant reduction in aortic elastic properties suggests that some risk of cardiovascular disease may persist<sup>[10]</sup>. Type 1 diabetic patients with early presence of micro- or macrovascular complications should always be screened for CD<sup>[15]</sup>. Type I diabetes mellitus and CD can coexist,

**Table 3** Types of studies associated with each keyword

Keyword	Article	Review	Case	Letter	Abstract	Editorial	Total
Arterial function	6	1	2	2			11
Atherosclerosis	4		1	5	3		13
Angiogenesis	6				1		7
Thrombosis	4	2	15	5	1		27
Stroke	2	2	7		1		12
Hemorrhage			7	3			10
Haemodynamics	1			1	2		4
Vascular - other	2		3				5
Pericardial effusion	2		1		1		4
Myocarditis	3	1	1	1			6
Cardiomyopathy	8	1	21	0	2	1	33
Infarction	4			1			5
Electromechanical	6				1		7
Ischemic heart disease	6			3	1	1	11
Rhythm disturbances	3		1	1	3		8
Congenital heart defect	3		1				4
Heart - other	3		2		1		6
Cardiovascular risk	11	2		1	3		17
Total	74	9	62	23	20	2	190

**Table 4** Characteristics of the published studies by keyword

Category	Topic	Studies <sup>1</sup>	Median year	Range
Vascular	Arterial function	11	2014	2011-2016
Vascular	Atherosclerosis	13	2013	2008-2016
Vascular	Angiogenesis	7	2009	1970-2013
Vascular	Thrombosis	27	2007	1995-2016
Vascular	Stroke	12	2008	2001-2017
Vascular	Hemorrhage	10	2007	1997-2012
Vascular	Haemodynamics	4	1998	1993-2005
Vascular	Other	5	2004	1993-2013
Heart	Pericardial effusion	4	2008	2000-2014
Heart	Myocarditis	6	2004	2002-2012
Heart	Cardiomyopathy	33	2010	1986-2016
Heart	Infarction	5	2009	2008-2015
Heart	Electromechanical	7	2014	2008-2016
Heart	Ischemic heart disease	11	2014	2004-2016
Heart	Rhythm disturbances	8	2014	1989-2016
Heart	Congenital heart defect	4	2014	1982-2016
Heart	Other	6	2012	2004-2016
Cardiovascular disease	Risk factors	17	2013	2007-2017

<sup>1</sup>Studies: Total number of studies published on the topic. Studies could be used as references for more than one topic.

and there is evidence that microvascular complications are more severe in patients with both conditions<sup>[16,17]</sup>.

**Vascular - atherosclerosis [# = 13, median year = 2013 (2008-2016)]**

Atherosclerosis has been linked to myocardial infarction and ischemic stroke, with chronic inflammation being a likely pathogenic factor<sup>[18]</sup>. Untreated adults with CD are at increased risk of early atherosclerosis, as suggested by the presence of chronic inflammation, vascular impairment, unfavorable biochemical patterns<sup>[19-21]</sup>,

and relative lack of the classical risk factors. Carotid intima-media thickness values are significantly higher in patients with coexisting diabetes and CD as compared to those patients with diabetes or CD alone<sup>[16,22]</sup>. CD youth have also been associated with increased risk of developing early atherosclerosis<sup>[19]</sup>. They are also more likely to have greater mean low density lipoprotein (LDL) cholesterol and thicker carotid intima media as compared with controls, and their endothelium-dependent dilatation is decreased, all of which negatively affect vascular function<sup>[23,24]</sup>. The GFD enables a reduction in inflammatory parameters, oxidative stress, and insulin resistance, factors that when unchecked can lead to atherosclerosis<sup>[10,25]</sup>. Gluten avoidance followed by restoration of the intestinal villi to normal function is likely to revert cardiovascular dysfunction in less than 1 years' time<sup>[2,20,21,23,24]</sup>. Areas with improved markers on a GFD include the common carotid arteries for intima media thickness, and the humeral artery for endothelium-dependent dilatation<sup>[26]</sup>. However, patients on the GFD often show weight gain and increase in triglyceride blood levels, which suggests a risk to atherogenicity<sup>[27]</sup>, although alterations of other risk factors do not necessarily support this supposition<sup>[28]</sup>. CD patients should always be encouraged to choose a healthy GFD<sup>[27]</sup>.

**Vascular - angiogenesis [# = 7, median year = 2009 (1970-2013)]**

In untreated CD, the overall architecture of the small-bowel mucosal vasculature may be altered, leading to inhibition of angiogenesis<sup>[29]</sup>. On the GFD, the vasculature normalizes as compared to healthy subjects, in parallel to mucosal recovery, and mucosal autoantibody deposits diminish in the small intestine<sup>[29,30]</sup>. Autoantibody production in CD mainly targets against transglutaminase 2 (TG2)<sup>[29]</sup>. These autoantibodies are found in untreated

CD patients' serum<sup>[31]</sup>, but also bound to extracellular TG2 below the epithelial basement membrane and around capillaries in the small intestinal mucosa, as well as in extra-intestinal organs. The autoantibodies can interfere with angiogenesis, including changes in transendothelial migration of lymphocytes<sup>[29,32,33]</sup>, which is probably influenced by common genetic variants in angiogenesis-related genes<sup>[34]</sup>. *In vitro*, CD autoantibodies reduce endothelial branching, increase endothelial permeability to macromolecules and lymphocytes, and enhance lymphocyte adhesion to the endothelium<sup>[29,35]</sup>. Ultrastructural alterations of the small blood vessels embedded in the subepithelial connective tissue of the jejunal mucosa are most severe in CD patients not on the GFD. Similar changes occur when gluten is administered to pediatric CD patients previously on a GFD, and are one of the earliest pathological changes seen in the biopsy material<sup>[35]</sup>.

#### **Vascular - thrombosis [# = 27, median year = 2007 (1995-2016)]**

Thrombotic events are increased in CD<sup>[36]</sup>, can be recurrent<sup>[37]</sup>, and may be present at multiple locations<sup>[38]</sup> which are observable *via* Doppler ultrasonographic examination<sup>[39]</sup>. Thrombophilia may result from hyperhomocysteinemia and deficiencies in protein S, folate, and vitamin B2<sup>[40-42]</sup>. The thrombotic events in CD may also result from dehydration due to diarrhea<sup>[43]</sup>. Cerebral venous sinus thrombosis can occur in CD patients<sup>[40,44-46]</sup>, even in absence of gastrointestinal symptoms<sup>[45]</sup>, but can resolve with symptomatic treatment<sup>[40]</sup>. Venous thrombosis can be a sequela of undetected CD<sup>[42,47-54]</sup>, and may result in thromboembolic events<sup>[48,55]</sup>. CD may be accompanied by portal vein thrombosis<sup>[56,57]</sup>, and mesenteric<sup>[58]</sup> or splenic<sup>[59]</sup> vein thrombosis may present in occult or subclinical celiac disease<sup>[58]</sup>. There is an increased risk of developing venous thromboembolism from chronic inflammation and vitamin deficiency in CD<sup>[44,60,61]</sup>. On a GFD, there is favorable evolution of young CD patients with thrombosis<sup>[62]</sup>. CD should be considered in young patients with thrombosis, especially if the event occurs in an unusual location<sup>[62]</sup>.

#### **Vascular - stroke [# = 12, median year = 2008 (2001-2017)]**

Patients with CD have been found to be at an increased risk for stroke, which can persist after onset of the GFD<sup>[63,64]</sup>. Stroke events can be recurrent<sup>[65]</sup>. Cerebral infarction and transient hemiplegia may also present in untreated asymptomatic CD patients<sup>[66]</sup>. CD should be considered as a possible etiology for stroke cases of unknown cause, particularly in youth, whether gastrointestinal manifestations are evident or not<sup>[67]</sup>. The pathogenesis of stroke in CD youth may involve vitamin B12 deficiency<sup>[68]</sup> and possibly hyperhomocysteinemia, which may be secondary to folic acid deficiency<sup>[69]</sup>, cerebral arterial vasculopathy, and antiphospholipid

syndrome, a secondary autoimmune disorder<sup>[70-72]</sup>. Children with recurrent acute ischemic stroke should be screened for CD<sup>[73]</sup>. Because CD is a potentially treatable cause of cerebral vasculopathy and stroke<sup>[74]</sup>, serology-specifically anti TTG antibodies should be included in the evaluation for cryptogenic stroke in childhood, even in the absence of typical gastrointestinal symptoms<sup>[72]</sup>.

#### **Vascular - hemorrhage [# = 10, median year = 2007 (1997-2012)]**

When unresponsive CD is treated with corticosteroids and immunosuppression therapy, it can be complicated by the presence of small intestinal lymphoma, and result in hemorrhage<sup>[75,76]</sup>. During hemorrhage, coagulopathy can occur, which is attributable to vitamin K deficiency associated with malabsorption of multiple fat soluble vitamins in these patients<sup>[75]</sup>. The immune response to CD, triggered by gluten, can lead to deposition of circulating immune complexes on the membrane of alveolar capillaries, resulting in pulmonary hemosiderosis<sup>[77]</sup>. Lane-Hamilton syndrome refers to the co-occurrence of idiopathic pulmonary hemosiderosis and CD<sup>[78]</sup>. Idiopathic pulmonary hemosiderosis is severe and potentially fatal, and is characterized by recurrent episodes of alveolar hemorrhage, hemoptysis, and anemia, and can share a common immune pathway with CD<sup>[79]</sup>. Left untreated, it can lead to poor prognosis, with progression to pulmonary fibrosis and chronic respiratory limitation<sup>[80]</sup>. In patients with diffuse alveolar hemorrhage, even in the absence of gastrointestinal symptoms, screening for CD should be done using anti-transglutaminase antibodies<sup>[79,81]</sup>. If CD is found, the GFD helps control symptoms, enables a reduction of immunosuppressive treatment, and improves clinical course<sup>[79]</sup>. Improvement of the co-occurrence of CD and pulmonary hemosiderosis over a period of months is found when patients are placed on the GFD<sup>[82,83]</sup>. Thus patients with pulmonary hemosiderosis should always be screened for CD<sup>[80,82]</sup>. Patients with hereditary hemorrhagic telangiectasia with unexplained iron malabsorption should also be screened for CD<sup>[84]</sup>.

#### **Vascular - haemodynamics [# = 4, median year = 1998 (1993-2005)]**

Alteration of blood flow is an important issue. The pathophysiological changes in the small bowel mucosa during the active phase of CD can induce haemodynamic changes<sup>[85]</sup> including an abnormal splanchnic circulation<sup>[86]</sup>, and splenic vein obstruction may be present<sup>[47]</sup>. The postprandial mesenteric blood flow can be significantly increased and delayed in time<sup>[86]</sup>. A hyperdynamic mesenteric circulation and higher peak systolic velocity of the superior mesenteric artery is often manifested in untreated CD patients as compared with healthy controls and treated celiac patients<sup>[85,87]</sup>. Treatment with the GFD can improve haemodynamics<sup>[85,87]</sup>.

**Vascular - other [# = 5, median year = 2004 (1993-2013)]**

Several other vascular maladies have been noted to occur in conjunction with CD. The combination of CD, epilepsy, and cerebral calcification is a rare condition known as CEC syndrome<sup>[88]</sup>. Folate malabsorption is a suggested mechanism, because cerebral calcification can be seen in other conditions related to folate deficiency<sup>[88]</sup>. Membranous obstruction of the inferior vena cava can also occur<sup>[89]</sup>. In patients with hyperhomocysteinaemia and sub-clinical CD, endothelial dysfunction is associated with increased systemic vascular resistance that can lead to a reversible form of hypertension<sup>[90]</sup>. CD adults tend to have a lower prevalence of hypertension and hypercholesterolaemia as compared with the general population<sup>[91]</sup>. However in patients with hypertension, CD, and hyperhomocysteinaemia (*via* malabsorption of essential cofactors), CD treatment can improve blood pressure control<sup>[90]</sup>. Covert hemoptysis may be responsible for disproportionately severe anemia in CD patients<sup>[92]</sup>.

**Heart - pericardial effusion [# = 4, median year = 2008 (2000-2014)]**

The heart itself can be greatly affected in CD patients. Echocardiography has been used to show that there is a higher incidence of pericardial effusion in CD<sup>[93]</sup>. In adults, this phenomenon can be asymptomatic<sup>[94]</sup>. The predisposing factors for pericardial effusion include vessel dysfunction in the presence of high antibody titer, selenium deficiency, and viral infection due to reduced immunological competence, in conjunction with a diminished ability to eliminate toxic free radicals<sup>[93,95]</sup>. After onset of the GFD and with iron supplement, pericardial effusion, along with peripheral edema and fatigue, decreases<sup>[94,96]</sup>. Presence of left ventricle dilation, suggesting an initial phase of heart damage, is reversible on the GFD<sup>[96]</sup>. CD children may also have pericardial fluid, and show no difference compared to those lacking effusion with respect to ECG, chest X-ray, blood cell count, serum enzymes, serum protein, and iron levels<sup>[95]</sup>. Pericardial effusion is reversible in children when they are treated with a GFD<sup>[95,96]</sup>. Thus pediatric cardiologists should be alerted to the possibility that mild left ventricular enlargement can be caused by CD<sup>[96]</sup>.

**Heart - Myocarditis [# = 6, median year = 2004 (2002-2012)]**

Autoimmune myocarditis may be a complication of CD<sup>[97]</sup>. Biopsy-proven granulocytic myocarditis of unknown etiology can be found in the setting of silent CD<sup>[98]</sup>. Progressive heart failure may accompany viral myocarditis in untreated CD; patient condition can improve following standard heart failure treatment and GFD<sup>[99]</sup>. A strong fluorescence around heart muscle fibers has been noted in untreated CD patients but not in patients on the diet or in controls<sup>[100]</sup>. This suggests that an autoimmune process toward antigenic components of the myocardium can occur in untreated

CD, and lead to cardiac tissue injury, resulting in myocarditis<sup>[101]</sup>. In these patients, immunosuppression and GFD are often effective therapeutic options<sup>[101]</sup>. It is thus highly important to screen for CD in patients with these conditions to avoid progression and clinical deterioration<sup>[102]</sup>. It has been found that the CD prevalence in children with myocarditis is greater than in children without myocarditis<sup>[102]</sup>, who should therefore also receive CD screening.

**Heart - cardiomyopathy [# = 33, median year = 2010 (1986-2016)]**

Cardiomyopathy associated with CD is a serious and potentially lethal condition which requires a multi-disciplinary approach involving both a gastroenterologist and a cardiologist<sup>[103-106]</sup>. There is a higher prevalence of CD in patients with dilated cardiomyopathy<sup>[107-109]</sup>, idiopathic cardiomyopathy<sup>[110-113]</sup> and ischaemic or valvular cardiomyopathy<sup>[110]</sup>. There is also a higher prevalence of CD in the relatives of patients with sporadic and inherited dilated cardiomyopathy<sup>[114]</sup>. Severely dilated left ventricle, concomitant left ventricular dysfunction, very low ejection fraction, pulmonary hemosiderosis, heart block, and/or heart failure have been reported in cardiomyopathy patients with CD<sup>[112,115-120]</sup>. Severe progressive dilated cardiomyopathy, requiring heart transplantation, can occur<sup>[121]</sup>. Dilated cardiomyopathy in CD may be accompanied by congestive heart failure and is also becoming increasingly recognized in the pediatric population<sup>[122,123]</sup>. These children may also present with acute onset congestive heart failure, as well as severe left ventricular systolic dysfunction<sup>[123]</sup>. Upper limb venous thrombosis and recurrent haemoptysis secondary to pulmonary haemosiderosis may be present<sup>[123]</sup>. Cirrhotic cardiomyopathy without gastrointestinal symptoms has also been found in pediatric patients<sup>[124]</sup>.

Although a serious condition, the precise cause-and-effect relationship between CD and cardiomyopathy when they occur in tandem is currently unknown<sup>[125]</sup>. Dilated cardiomyopathy may evolve due to carnitine deficiency<sup>[126,127]</sup>, which is related to CD, but may also develop after onset of the GFD, particularly in patients lacking carnitine supplementation<sup>[126]</sup>. Idiopathic dilated cardiomyopathy may have an autoimmune mechanism<sup>[110,128]</sup>. The tTG-positive serology in relatives with echocardiographic abnormalities suggests that immune-mediated mechanisms are at work in subsets of these patients and their families<sup>[106]</sup>. In individuals with idiopathic congestive cardiomyopathy and CD, ultrastructural and electrophoretic examination of myocardial samples shows a selective loss of actin, and electron microscopy reveals characteristic alterations of enterocyte microvilli<sup>[129]</sup>. Hence there can be an involvement of the microfilament system in both the myocardial sarcomeres and the enterocytes of these patients<sup>[129]</sup>. Ischemic cardiomyopathy can occur due to an accelerated atherosclerosis when chronic inflammation is present in CD<sup>[130]</sup>.

Compliance with a GFD is mandatory if patients are

to avoid progression of their cardiomyopathy<sup>[105,131]</sup>. The GFD has been shown to have a beneficial effect on cardiac performance in CD patients with dilated cardiomyopathy<sup>[132]</sup>. After start of the GFD, abnormal left ventricular dimensions, and diminished cardiac function, including decreased ejection fraction, can improve markedly and may even be completely reversible<sup>[103,108,118,128,133]</sup>. After two years on a GFD, patients presenting with dilated cardiomyopathy associated with CD show progressive increase in mean serum carnitine levels as compared to values observed prior to the diet<sup>[127]</sup>. Children with CD and dilated cardiomyopathy also have improved cardiac function once adherent to the GFD<sup>[109]</sup>. In CD patients on the GFD, there is no association with later onset of myocarditis, cardiomyopathy or pericarditis<sup>[134]</sup>.

Screening for CD in patients with dilated cardiomyopathy, pulmonary haemosiderosis, and iron deficiency anemia in the absence of known etiology is advisable regardless of the intestinal symptoms<sup>[105,108,116,123,133]</sup>. Serologic tests for IgA-EmA and tissue transglutaminase antibodies should be used to screen for CD<sup>[106]</sup>. Comorbidities including iron-deficiency anemia in patients with dilated cardiomyopathy should arouse suspicion of CD<sup>[117]</sup>. All patients diagnosed with cardiomyopathy and CD should be offered an endomyocardial biopsy for better histological and diagnostic definition<sup>[128]</sup>. It is beneficial to assess CD in children with dilated cardiomyopathy in the absence of known etiologies<sup>[104,135]</sup>.

#### **Heart - infarction [# = 5, median year = 2009 (2008-2015)]**

Acute myocardial infarction with ST-elevation and spontaneous coronary artery dissection can occur in young patients with CD<sup>[3,136]</sup>. However, chronic hypocalcemia in untreated CD patients due to poor absorption of minerals can result in electrocardiographic changes that mimic acute myocardial infarction<sup>[120]</sup>. In CD, there is a higher all-cause mortality one year post-myocardial infarction as compared with the general population<sup>[20]</sup>. Mesenteric infarction has also occurred as a consequence of CD, and clinicians should be aware of this possibility<sup>[137]</sup>.

#### **Heart - electromechanical functioning [# = 7, median year = 2014 (2008-2016)]**

Measurement of electromechanical parameters is beneficial to determine the degree of cardiac involvement in CD<sup>[138]</sup>. Atrial conduction delays are significantly higher in untreated CD as compared with healthy individuals, and may lead to atrial fibrillation<sup>[139]</sup>. Measurement of atrial electromechanical delay parameters might therefore be useful to predict atrial fibrillation risk<sup>[139]</sup>. Statistically significant differences in left ventricular function as assessed by echocardiography imaging are found in CD patients vs controls<sup>[140]</sup>. Patients with CD can have impaired diastolic and systolic function as measured by tissue Doppler echocardiography<sup>[141]</sup>. Mitral valve prolapse<sup>[142]</sup> and subclinical myocardial dysfunction of

both ventricles<sup>[143]</sup> can be present in both the pediatric and adult CD population. In children, significantly lower contractility indices and higher left ventricular dimensions are evident as compared with controls<sup>[144]</sup>. On the GFD, valve regurgitations resolve, and echocardiographic parameters significantly improve<sup>[144]</sup>.

#### **Heart - ischemic heart disease [# = 11, median year = 2014 (2004-2016)]**

There is an increased risk of ischemic heart disease and higher cardiovascular mortality in CD<sup>[145,146]</sup> despite the lack of traditional risk factors<sup>[26,147]</sup> including blood pressure, body mass index, serum cholesterol, lipids, exercise, and smoking<sup>[4,148]</sup>. First-degree relatives of CD patients are also at an increased risk of ischemic heart disease, but the excess risk is slight<sup>[149]</sup>. CD and ischemic heart disease may share a common underlying link, rather than a cause-and-effect relationship<sup>[18,150]</sup>. The underlying association between CD and ischemic heart disease may be chronic inflammation, a major risk factor in the general population; however, potential confounders may also be involved<sup>[18,146,148]</sup>. After onset of the GFD, persistent villous atrophy detected during follow-up biopsy was not associated with increased risk of ischemic heart disease<sup>[151,152]</sup>.

#### **Rhythm disturbances [# = 8, median year = 2014 (1989-2016)]**

Compared to controls, untreated CD patients have increased P-wave dispersion and higher interatrial, intra-left atrial, and intra-right atrial conduction delay<sup>[153]</sup>. Tp-e interval, Tp-e/QT and Tp-e/QTc ratios are also increased in CD<sup>[154]</sup>. There is a higher prevalence of atrial fibrillation among CD patients<sup>[153,155]</sup>. Atrial fibrillation, when it occurs, is associated with an increased risk of ischaemic stroke and heart failure<sup>[156]</sup>. The chronic inflammation that can occur in untreated CD is a recognized risk factor for atrial fibrillation<sup>[155,156]</sup>. CD patients have slower atrial electrical conduction, which may also increase the risk of atrial fibrillation<sup>[153]</sup>. However, persistent villous atrophy on follow-up biopsy was not associated with any increased risk of atrial fibrillation<sup>[151,152]</sup>. It has been reported that CD patients with pulmonary hemosiderosis can develop infranodal heart block, necessitating implantation of a pacemaker<sup>[77,157]</sup>. These patients may lack digestive manifestations but have iron deficiency and vitamin deficiency anemia<sup>[77]</sup>. Rhythm alterations in CD can thus result from other pathogenic mechanisms including electrolyte disturbances caused by malabsorption, which can normalize on the GFD<sup>[77]</sup>. Patients with rhythm disturbances and chronic anemia of unclear origin should therefore be tested for CD<sup>[77]</sup>.

#### **Heart - congenital heart defect [# = 4, median year = 2014 (1982-2016)]**

CD patients are likely to more commonly have atrial septal defect as compared to controls<sup>[158]</sup>. Screening

for CD in children with congenital heart defect is recommended, since serum TTG IgA levels are significantly higher in patients with congenital heart defect vs control children<sup>[159]</sup>. Down syndrome patients with congenital heart defect have higher CD prevalence as compared to patients without congenital heart defect, and CD prevalence in Down syndrome patients is higher than in controls<sup>[160]</sup>. In children with congenital heart disease and CD, growth improves on a GFD<sup>[161]</sup>.

#### **Heart - other [# = 6, median year = 2012 (2004-2016)]**

Chronic hypocalcemia, which may occur in untreated CD due to malabsorption, has been associated with reversible cardiac dysfunction<sup>[120]</sup>. Untreated CD children tend to show an imbalance of cardiac sympathetic and parasympathetic activity due to enhanced sympathetic tone<sup>[162]</sup>. This imbalance is still detected after a six months period of GFD<sup>[162]</sup>. This suggests the presence of a subclinical autonomic nervous system dysfunction<sup>[162]</sup>. There is a higher prevalence of CD in patients with Postural Orthostatic Tachycardia Syndrome (POTS)<sup>[163]</sup>, thus these patients should also be screened for CD<sup>[164]</sup>. Left ventricular hypertrabeculation/noncompaction may be associated with CD<sup>[165]</sup>. Subclinical systolic dysfunction of the left ventricle may be present in CD children<sup>[166]</sup>.

#### **Cardiovascular disease risk factors [# = 17, median year = 2013 (2007-2017)]**

Cardiovascular disease (CVD) as a whole has many etiologies and is the leading cause of death in developed countries<sup>[167,168]</sup>. There is a modestly increased risk of CVD in CD patients<sup>[63]</sup>. Both male and female CD patients may have higher estimated risk for CVD as compared to controls<sup>[169,170]</sup>. However, CVD risk factors conferred by CD have not been well-defined<sup>[171]</sup>. This has led to conflicting evidence as to whether CD patients actually have increased baseline risk<sup>[172]</sup>. CD patients are susceptible to increased platelet activation and increased mean platelet volume and RDW values, factors that contribute to increased risk<sup>[173,174]</sup>. Using the Framingham Heart Study (FRS) 10-year general CVD risk score, lower values were found among CD patients as compared with controls, which may be due to a lesser body mass index and reduced tobacco use among CD patients<sup>[171]</sup>. Risk factors other than those measured by the FRS may be observed as increased risk of CVD in CD patients<sup>[171]</sup>. There can also be a positive association between CD and CVD risk due to ascertainment bias<sup>[175]</sup>. In CD children, risk factors can be frequently observed as compared with healthy subjects<sup>[18]</sup>. Overall, certain CVD risk factors have been found to be higher in CD youth as compared with the general population, although neither blood pressure nor overweight and obesity rates were increased<sup>[176]</sup>. Youth with type 1 diabetes and CD had lower high density lipoprotein (HDL) cholesterol, increasing CVD risk, as compared with non CD patients<sup>[177]</sup>.

The lack of a uniform set of risk factors can influence whether CVD risk is affected by a GFD<sup>[172]</sup>. In actuality, both risk and protective factors for CVD are likely to be present in CD, at baseline and also on a GFD<sup>[172]</sup>. Modifiable risk factors for CVD can include body mass index and cholesterol, which have been shown to increase on the GFD<sup>[168]</sup>. In CD individuals with type 1 diabetes on a GFD, improvement in HDL-cholesterol, and a lower resting heart rate, has been demonstrated as compared with those CD patients without diabetes<sup>[178]</sup>. On a GFD, the lipid profile of CD patients can also improve<sup>[17]</sup>. At one year on a GFD, waist circumference may increase, but without significant rise in total or LDL cholesterol<sup>[173,174]</sup>. The GFD should therefore ideally go beyond gluten exclusion and include body weight control and high quality nutrients<sup>[172]</sup>. A relatively high proportion of CD children on the GFD had one or more CVD risk factors<sup>[179]</sup>. The most common CVD risk factors are high fasting triglycerides, elevated blood pressure, and high LDL cholesterol concentrations<sup>[179]</sup>. Insulin resistance is also found, underscoring the need for CVD screening and dietary counseling targeting the pediatric CD population<sup>[179]</sup>. Screening for CD and monitoring of HDL cholesterol is recommended in youth with type 1 diabetes<sup>[177]</sup>. CVD risk factors also include metabolic disorders caused by malabsorption in pediatric CD patients<sup>[180]</sup>. Hence timely correction of water and electrolyte imbalance, and administration of cardiometabolic therapy, is necessary<sup>[180]</sup>.

## **CONCLUSION**

Published studies pertaining to the connection between cardiovascular conditions and CD began in the late 1960's, consisting of a few studies each year, and was followed by a substantial increase beginning about the year 2000. Many of the published studies are either articles (including cohort and case control studies) or case studies consisting of one to three patients. Often, as might be expected, a number of case studies appeared in the literature prior to the cohort studies. Based on the evidence presented in these papers, it is apparent that cardiovascular involvement in CD is a real phenomenon and that there are many manifestations, owing to the multifaceted, systemic physiological changes that can occur in CD. A number of the cardiovascular issues that can occur in untreated CD patients, will resolve on a GFD, often in conjunction with healing of the small intestinal villi. Cardiomyopathy is the most frequently documented cardiovascular condition observed in conjunction with CD, and seems to mostly or completely resolve with appropriate treatment, including a GFD. However, if CD is left unrecognized until a late stage, damage done to the heart may not be entirely reversible. Similarly, to the present time there has been substantial documentation of a number of other cardiovascular conditions found in conjunction with untreated CD including

thrombosis and thromboembolism, ischemic heart disease, stroke, and arrhythmia. There has also been significant investigation of CD and risk of cardiovascular disease. On this topic, a current problem is that there is no uniform set of cardiovascular risk factors used for analysis. Future studies should settle the question of how to best treat these co-occurring conditions, and to determine if other cardiovascular manifestations of CD are common phenomena.

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## Is there evidence for statins in the treatment of aortic valve stenosis?

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### Abstract

Research revealed that the pathogenesis of aortic stenosis (AS) not merely comprises of a mechanical wear and tear process yet that active biological processes, similar to

those of coronary artery disease are involved, a promising role for statins in disease-modifying therapy was suggested. However, recently, many prospective studies could not observe decreased progression nor regression of the disease. Here, we review the current knowledge on the pathomechanisms of AS and its similarities and differences with atherosclerosis. Moreover, we discuss whether there is still a place for statins in the treatment of particular AS patient subgroups.

**Key words:** Aortic stenosis; Statins; HMG-CoA enzyme inhibitor; Coronary artery stenosis; Aortic valve surgery

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**Core tip:** Aortic stenosis is a age-dependent and growing disease. As there are several similarities with atherosclerotic disease of other regions there are growing research on underlying pathophysiology. The treatment benefit of classic atherosclerosis treatment is evaluated in case of aortic valve stenosis.

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### INTRODUCTION

Aortic stenosis (AS) is the most common heart valve disease in Western countries. It affects 12.4% of the population over the age of 75 years<sup>[1]</sup> with a male predominance of 80% in symptomatic AS<sup>[2]</sup>. AS is usually characterized by an asymptomatic latent period of several years or even decades before patients suffer from discomforts. However, once patients with severe AS display symptoms (typically

syncope, angina and/or dyspnoea), the prognosis is poor with a 2-year and 5-year survival rate of 50% and 20%, respectively; hence valve replacement surgery is usually mandated<sup>[3]</sup>. Since the elderly population in Western countries is expected to double by 2050, it is imperative to define early diagnostic and treatment strategies. Even though AS or the fibrous thickening and calcification of the valves is a widespread disease, its underlying molecular mechanisms are still unknown<sup>[4]</sup>. Traditionally, it was accepted that AS is caused by the progression of calcium deposition continued to aortic valvular leaflets. However, research demonstrating the involvement of active cellular processes over the past 15 years<sup>[5]</sup>. Genetic polymorphism seems to influence the degree of aortic valve sclerosis<sup>[6]</sup>, with a focus on chronic inflammatory processes. Moreover, it has become clear that the development of AS shows many similarities with atherosclerosis including infiltration and retention of lipoproteins, lipids, T-lymphocyte and other inflammatory cells, as well as osteoblastic activation<sup>[7-9]</sup>. Accordingly, numerous studies demonstrated a strong association to coronary artery disease (CAD) and many of its risk factors, including hypercholesterolemia<sup>[10,11]</sup>. This opened the field to develop effective disease-modifying strategies, which would halt or even regress the disease, thus avoiding the need of surgical or interventional replacement. At first, statins seem to be the most obvious medical treatment choice since its use is well-established for the primary and secondary prevention of CAD<sup>[12]</sup>. Moreover, statins have been shown to exert pleiotropic effects beyond their cholesterol-lowering effect, such as anti-oxidation, plaques stabilization and reduction of vascular inflammatory processes<sup>[13,14]</sup>. Numerous retrospective observational studies showed a delay in AS progression when statins were administered concomitantly which encouraged the use of statins for treatment of AS<sup>[15-19]</sup>. However, 3 recent large-scale prospective randomized clinical trials investigating the effects of intense lipid-lowering therapy with statins showed no effect on neither progression, nor regression of AS. Meanwhile, new insights are emerging, demonstrating distinct differences in (molecular) pathology between CAD and AS. Here, we review what is known today about the pathogenesis of AS and the potential influence of statin therapy in AS patients, with a distinction between degenerative or calcific AS, congenital AS, AS with coronary heart disease as comorbidity, and, treatment before and after aortic valve surgery.

## PATHOMECHANISMS OF DEGENERATIVE OR CALCIFIC AS AND CAD: SIMILARITIES AND DIFFERENCES

Since it became clear that AS is not merely the result of mechanical stress and ageing, but rather an active biological processes involving inflammatory contributing

to the disease; pharmacological treatment possibilities were completely opposed to valve replacement surgery inevitable at the time when AS has reached a severe symptomatic status. What has been revealed of the current knowledge of the pathogenesis of AS so far, revealed many similarities with CAD. Hence, it was obvious to turn to statins for the treatment of AS since they have proven efficacy for the primary and secondary prevention of CAD. Nevertheless, it is shown that, besides lipid-lowering, statins display pleiotropic effects such as anti-inflammatory and antioxidant effects as well as plaque-stabilization and improvement of endothelium dysfunction<sup>[20]</sup> (Figure 1). The potential use of statins was initially encouraged by positive results from numerous retrospective studies. Yet recently, three prospective randomized studies showed neither regression, nor reduction in progression of AS: SEAS (Simvastatin and Ezetimibe in Aortic Stenosis), SALTIRE (Scottish Aortic Stenosis and Lipid Lowering Trial, Impact on Regression) and ASTRONOMER (Aortic Stenosis Progression Observation: Measuring Effects of Rosuvastatin)<sup>[21-23]</sup>. All three trials demonstrated that extensive lipid-lowering induced by statins failed to correlate with neither improvement of aortic-jet velocity of the valve, nor with regression of valvular calcification. Such disappointing results were surprising because of the many well recognized similarities between CAD and AS in terms of pathogenesis. Moreover, statin use has become an established principle for CAD. Furthermore, similar risk factors have been identified for both diseases such as age, sex (male gender), dyslipidaemia, hypertension, smoking, diabetes and renal dysfunction<sup>[24,25]</sup>. Aortic valve stenosis can be characterized an 'early lesion', which are similar to those of atherosclerotic plaques in vessels<sup>[8]</sup> and both CAD and AS are characterized by infiltration and accumulation of (oxidized) low-density lipoproteins (LDL) and T-lymphocytes, thus filling tissue inflammation and the release of pro-inflammatory cytokines such as tumour necrosis factor (TNF)- $\alpha$  and interleukin (IL)-1 $\alpha$  which in turn induce cell proliferation<sup>[7,9,26]</sup>. Calcification and osteogenesis, mediated by inflammation and processes involving metalloproteinases, have been identified as players in the pathogenesis of AS<sup>[27-29]</sup>. Finally, neo-angiogenesis contributes to AS development<sup>[30,31]</sup> and is responsible for reduced concentrations of the anti-angiogenesis protein chondromodulin-1 in damaged aortic valve tissue<sup>[32]</sup>. The resulting cell apoptosis, extracellular matrix formation and consequent thickening and calcification of the cusps, decreases aortic valve mobility and orifice areas, ultimately leading to an increased pressure gradient<sup>[33]</sup>. Nevertheless, there are some fundamental differences in the underlying molecular mechanisms with an early inflammation affecting fibroblasts in AS as opposed to late onset of inflammation in smooth muscle cells in CAD. Yet, plaque instability is not the leading clinical problem with AS; however clearly the main cause of symptoms with CAD<sup>[34]</sup>. It is important to note that

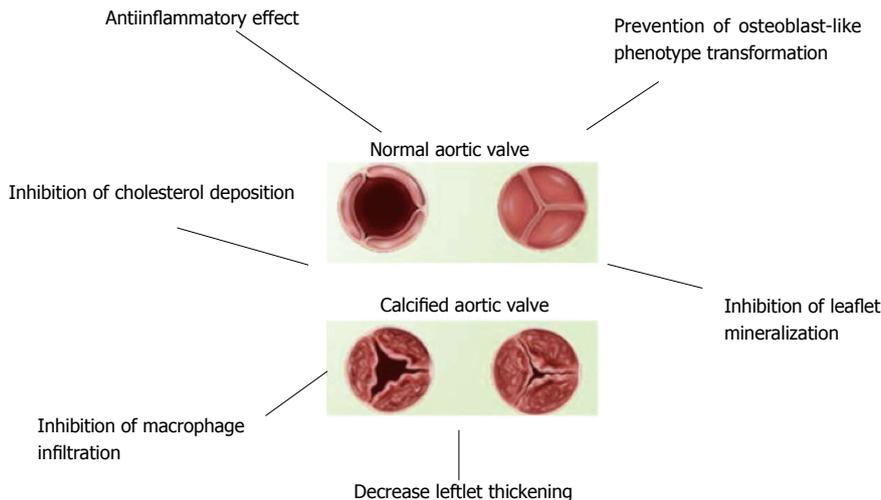


Figure 1 Schematic overview of statin effects on aortic valve calcification.

those retrospective studies on the effect of statins in AS included patients already exposed to statins prescribed for primary or secondary prevention of CAD. Moreover, study patients had only mild to moderate AS as severe AS was excluded. Based on sub-analyses of the 3 RCT's, several research groups support the lipid hypothesis as a common denominator of both diseases, with similarities between atherosclerosis and AS seen in initial stages of AS. Later on, disease progression is mostly determined by plasticity and structure of the leaflets, and by mechanical stress<sup>[35,36]</sup>. Yet, results of a recent meta-analysis challenged suggested role of statins to prevent the onset of AS in non-symptomatic patients<sup>[37]</sup>. They pooled high risk patients without known AS from 3 large scale RCT's who evaluated the effect of high (80 mg) and normal (10 mg) daily doses of atorvastatin and found no significant differences between placebo, low or high atorvastatin with regards to the onset of AS. Furthermore, across the board any subtle correlation between hyperlipidaemia and AS progression<sup>[15,17]</sup> turned out to be inconsistent<sup>[18,19]</sup>.

#### Effect of statins on AS in patients with CAD

As much as 40% of patients undergoing aortic valve replacement surgery suffers from atherosclerosis as well. Moreover, AS progresses faster in older patients with CAD<sup>[2]</sup>. There is evidence of beneficial effects of statins in presence of CAD<sup>[38]</sup>. Dyslipidaemia is an independent predictor of AS progression and adequate lipid-lowering by statin use in patients with CAD has beneficial effects on valve integrity<sup>[39]</sup>. Yet, a quantitative relationship between lipid-lowering and changes in AS progression has not been found. It is worth mentioning that most studies investigated patients with intermediate or advanced AS which appears difficult to modify by drugs; however, a potential effect in early AS could still be debated<sup>[40]</sup>. Another point to address is patient selection bias, especially in the SEAS trial that excluded patients

with diabetes or CAD. Even though no correlation between statin use and beneficial effects on AS have been shown, it is highly likely that patients with AS and relevant comorbidities such as atherosclerosis, which is a common clinical scenario, may be positively affected<sup>[41,42]</sup>. Indeed, statins would mitigate AS progression only when hyperlipidaemia is present<sup>[43]</sup> but more profound research is needed. Current guidelines suggest offering patients with comorbidities such as CAD, diabetes or hyperlipidaemia statins. Conversely, untreated metabolic syndrome in patients with AS is related to faster stenosis progression and worse prognosis<sup>[44]</sup>. These observations were more pronounced in younger patients (< 57 years of age). Interestingly, however, statins in younger patients with metabolic syndrome and AS turned out to be disadvantageous with AS progression and lower insulin resistance supporting the notion that lipophilic statins may actually induce diabetes type II<sup>[45,46]</sup>; this effect is even more pronounced when patients suffer from metabolic syndrome as well<sup>[47]</sup>. This effect was not seen in older patients, suggesting that the pathophysiological mechanisms of AS progression may be related to the patient's age<sup>[44]</sup>.

## CONGENITAL AORTIC STENOSIS

Congenital defects resulting in AS include partially fused leaflets, thickened leaflets, narrowing of the supra- or subvalvular area, and, most frequently, bicuspidity. A bicuspid aortic valve is the result of the fusion of two of the three leaflets during the developmental phase and is with an incidence of almost 2% the most common congenital cardiac malformation<sup>[48]</sup>. The abnormal structure of the bicuspid aortic valve results in excess stress onto leaflets, resulting in valvular thickening, calcification, and increased rigidity and restricted aortic orifice. For that reason, AS is the most frequent complication of bicuspid aortic valve. While randomized prospective

trials mainly included older AS patients, the PROCAS (Progression of Stenosis in Adult Patients with Congenital Aortic Stenosis) trial was designed to evaluate the effect of statins on the progression of stenosis in young asymptomatic adults (aged between 18 and 45) with congenital AS. Not surprising, the investigators did not find any benefit from extensive lipid-lowering by 10 mg rosuvastatin, independent of the degree of valve calcification<sup>[49]</sup>. These findings are in line with those of the bicuspid valve patients subgroup of the ASTRONOMER trial<sup>[23]</sup>.

## STATIN THERAPY AND AORTIC VALVE SURGERY

Because of their anti-ischemic and anti-inflammatory effects and protection of the endothelium statins have been suggested to reduce atrial fibrillation after aortic valve surgery, yet with conflicting<sup>[50,51]</sup>. Some beneficial effects of perioperative statin therapy on mortality, stroke, renal insufficiency, length of ICU and hospital stay were found<sup>[52,53]</sup> however leading to the conclusion that preoperative statin use is justified in case of coronary artery bypass grafting (CABG). Indeed, advantageous effects on the above-mentioned endpoints have been demonstrated in only CABG patients and not in others<sup>[54-56]</sup>. Conversely, just to add to the confusion statin were also reported to delay restenosis after balloon aortic valvuloplasty or bioprosthetic valve replacement<sup>[57-59]</sup>, but findings were not<sup>[60]</sup>. With pre- and postoperative statin therapy in patients undergoing aortic valve replacement an increased long-term survival was found with biological valve replacement but not with mitral valve repair or mechanical valve replacement<sup>[61]</sup>. Finally, a retrospective study of bicuspid aortic valve patients undergoing surgery showed a significant decrease in ascending aortic dilatation when exposed to statins preoperatively<sup>[62]</sup>. Clearly, more clinical data are required to justify perioperative use of statin therapy.

## FUTURE CONSIDERATIONS

Future research in this context needs to focus both, elucidating the molecular pathways involved in the pathogenesis of AS and developing potential pharmacological treatment strategies. In that regard, it is of interest to determine both vascular and valvular aspects and when they occur during the evolution of AS. As such, different treatment approaches might apply for distinct stages of the disease. In addition, defining predisposing genetic deviations may help define preventative and curative approaches to slow disease progression. Additionally, in the quest for new pharmacological agents to treat AS, low-cost accurate animal model are missing; only ageing swine can develop AS<sup>[34]</sup>. At present, there is no evidence that statins halt the progression or induce the

regression of AS. The notion that their administration is harmless and devoid any side effects is untrue as we know adverse effects of statins in asymptomatic AS patients without concomitant diseases may in fact induce new risk factors (diabetes mellitus, aortic valve calcification)<sup>[44,63]</sup>. In conclusion, the general consensus to date is that treatment with statins is not recommended in patients with valvular aortic stenosis and in absence of standard indications to lipid-lowering treatment.

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## Basic Study

## Interleukin-19 is cardioprotective in dominant negative cyclic adenosine monophosphate response-element binding protein-mediated heart failure in a sex-specific manner

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### Abstract

#### AIM

To investigate the role of interleukin-19 (IL-19) in a murine model of female-dominant heart failure (HF).

## METHODS

Expression of one copy of a phosphorylation-deficient cyclic adenosine monophosphate response-element binding protein (dnCREB) causes HF, with accelerated morbidity and mortality in female mice compared to males. We assessed expression of IL-19, its receptor isoforms IL-20R  $\alpha/\beta$ , and downstream IL-19 signaling in this model of female-dominant HF. To test the hypothesis that IL-19 is cardioprotective in dnCREB-mediated HF, we generated a novel double transgenic (DTG) mouse of dnCREB and IL-19 knockout and assessed cardiac morbidity by echocardiography and survival of male and female mice.

## RESULTS

IL-19 is expressed in the murine heart with decreased expression in dnCREB female compared to male mice. Further, the relative expression of the two IL-19 receptor isoforms manifests differently in the heart by sex and by disease. Male DTG mice had accelerated mortality and cardiac morbidity compared to dnCREB males, while female DTG mice showed no additional detriment, supporting the hypothesis that IL-19 is cardioprotective in this model.

## CONCLUSION

Together, these data suggest IL-19 is an important cytokine mediating sex-specific cardiac (dys) function. Ongoing investigations will elucidate the mechanism(s) of sex-specific IL-19 mediated cardiac remodeling.

**Key words:** Cardiac dysfunction; Sex differences; Heart failure; Interleukin-19

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**Core tip:** Heart failure (HF) is a sexually dimorphic disease. In a female-dominant model of HF, the dominant negative cyclic AMP response-element binding protein (dnCREB) mouse, female mice show accelerated cardiac morbidity and mortality alongside downregulated interleukin-19 (IL-19) expression, while male mice maintain IL-19 expression and are protected against cardiac dysfunction. We generated a novel double transgenic mouse with dnCREB and IL-19 knockout to test the hypothesis that IL-19 is cardioprotective. We show accelerated cardiac morbidity only in male mice, supporting the hypothesis that IL-19 is a sex-specific cardioprotective cytokine.

Bruns DR, Ghincea AR, Ghincea CV, Azuma YT, Watson PA, Autieri MV, Walker LA. Interleukin-19 is cardioprotective in dominant negative cyclic adenosine monophosphate response-element binding protein-mediated heart failure in a sex-specific manner. *World J Cardiol* 2017; 9(8): 673-684 Available from: URL: <http://www.wjgnet.com/1949-8462/full/v9/i8/673.htm> DOI: <http://dx.doi.org/10.4330/wjc.v9.i8.673>

## INTRODUCTION

Heart failure (HF) is the leading cause of mortality within the United States, affecting more than 5 million Americans<sup>[1]</sup>. HF is frequently perceived as a disease with poorer prognosis in male patients, perhaps since women are protected against cardiovascular disease premenopausally. However, many large-scale epidemiological studies do not support this conclusion. Sexually divergent manifestation of HF is observed regarding etiological factors, in response to a variety of HF therapies, and in presentation of HF and its comorbidities. Although the prevalence of HF is lower in women compared to men, treatment and survival outcomes for female patients are poorer with females having disproportionately higher morbidity and mortality<sup>[1]</sup>. Women are more likely to be symptomatic and functionally limited<sup>[2]</sup>, experience less improvement following hospitalization<sup>[3]</sup>, and show higher level of disability at similar levels of left ventricular (LV) dysfunction with worse quality of life<sup>[4]</sup> than male counter-parts. Together, the sex differences in HF highlight the necessity to understand female disease to close the gap in treatment and prognosis.

The deleterious effects of inflammatory cytokines in the context of HF are well documented as elevated circulating levels of cytokines predict adverse outcomes in patients with HF<sup>[5]</sup>. Inflammatory cytokines directly affect cardiomyocyte contractility<sup>[6]</sup>, as well as influence LV remodeling and hypertrophy. Few studies, however, have examined sex-specific differences in cytokine expression, though sparse data indicate inflammatory profiles may be sexually dimorphic<sup>[7]</sup>. Interleukin-19 (IL-19) is a member of the IL-10 subfamily of interleukins. IL-19 signals through an IL-20 receptor heterodimer IL-20R $\alpha$  and  $\beta$  to activate cytoplasmic tyrosine kinases of the Janus family signal transducer activator of transcription (JAK-STAT)<sup>[8]</sup>. Differential relative expression of IL-20R subunits has been reported in different tissue types<sup>[9]</sup> and is suggested as a potential mechanism of differential downstream IL-19 signaling, though this hypothesis has not yet been tested in the heart. While initially thought to be restricted to immune cells, IL-19 expression has since been observed in a wide variety of tissue types. IL-19 exerts both pro-inflammatory and anti-inflammatory properties, depending on tissue and disease specific factors<sup>[10]</sup>. Previous work has demonstrated anti-inflammatory properties of IL-19 in endothelial and vascular smooth muscle cells<sup>[8]</sup>, but its role in the heart remains unknown.

Here, we investigated the expression of IL-19 and its receptor complex in a female dominant model of HF. Cardiac-specific expression of a dominant negative cyclic AMP response element-binding protein (dnCREB) results in dilated cardiomyopathy with accelerated mortality in female mice<sup>[11]</sup>. In this model, the transcription factor CREB is rendered phosphorylation inactive *via* mutation of a critical Ser residue located

in the kinase-inducible domain the protein<sup>[12]</sup>. In the unphosphorylated state, CREB can bind to DNA but cannot activate transcription, thus rendering the transcription factor inactive. This single nucleotide mutation results in significant cardiac dysfunction and accelerated morbidity and mortality in female mice compared to males. In comparison to male dnCREB mice, female dnCREB have significantly worse LV systolic function, higher heart rate, and diminished cardiac output, resulting in overall greater cardiac morbidity compared to male mice with the same genetic mutation<sup>[11]</sup>. This exaggerated pathology in female dnCREB is particularly interesting, as the majority of HF models involving genetically manipulated mice demonstrate more profound morbidity in the male sex<sup>[13]</sup>. In addition to this novel sexual divergence, the role of CREB in cardiac dysfunction is important, as CREB is functionally lost in rodent models of HF<sup>[14]</sup> and loss of CREB-regulated genes is observed early in the failing human heart<sup>[15]</sup>. Here, we show for the first time that IL-19 is expressed in the rodent heart, and is expressed in a sexually dimorphic manner in HF. Further, we demonstrate dysregulated downstream IL-19 signaling in female-dominant HF and suggest that IL-19 is cardioprotective in this model.

## MATERIALS AND METHODS

### Animals

The mouse model used in this study was a heterozygous, phosphorylation-deficient (Ser<sup>133</sup> to Ala<sup>133</sup>) mutant CREB (dnCREB) transgenic mouse<sup>[16]</sup> and non-transgenic (control, Con) littermates. dnCREB mice begin showing signs of contractile dysfunction at eight weeks of age. By 12 wk, female mice display significant mortality compared to males<sup>[11]</sup>. Homozygous IL-19 knockout (IL-19 KO) mice were generated as previously described<sup>[17]</sup> and show no overt signs of cardiac dysfunction or early morbidity and mortality. To have dnCREB and IL-19 KO mice on the same background, dnCREB mice were back-bred onto the C57 background for a minimum of 6 lineage passages. Male dnCREB mice were then crossed with female IL-19 KO to create heterozygous IL-19 KO. Male dnCREB IL-19 heterozygous mice from this F1 generation were then crossed with IL-19 KO female mice to create homozygous IL-19 KO and heterozygous dnCREB double transgenic male and female mice (DTG). Mice were housed at 4 per cage after weaning. Cages were inspected daily, and date of death noted for those mice found dead. Experiments were conducted in accordance with the National Institutes of Health "Guide for the Care and Use of Laboratory Animals", and were approved by the Institutional Animal Care and Use Committee at the University of Colorado-Denver.

### Echocardiography

Cardiac function was assessed by two-dimensional transthoracic echocardiography using a VisualSonics

Vevo 770 high-resolution ultrasound imager equipped with a 35-MHz transducer. Mice were lightly sedated with isoflurane and body temperature was maintained at 37 °C. Parasternal long- and short-axis B-mode videos and M-modes images (at the level of the midpapillary short axis) were routinely acquired. LV wall thicknesses and inner dimensions at diastole and systole were measured from the parasternal short-axis M-mode images.

### Isolation of primary ventricular cardiac myocytes and fibroblasts

Cardiomyocytes were isolated from C57BL/6 male and female mice (approximately 14 wk of age) by enzymatic dissociation of the whole heart on a Langendorff apparatus as previously described<sup>[18]</sup>. Briefly, hearts were rapidly removed and rinsed in a control buffer (133.5 mmol/L NaCl, 4mmol/L KCl, 1.2 mmol/L NaH<sub>2</sub>PO<sub>4</sub>, 10 mmol/L HEPES, 1.2 mmol/L MgSO<sub>4</sub>, and 1% bovine serum albumin) to remove blood, weighed and mounted on a Langendorff apparatus. The isolated heart was then perfused at 37 °C for 3 min with control buffer before switching to enzyme solution (control solution containing collagenase type II (2.4 mg/mL) and 25 μmol/L CaCl<sub>2</sub>). After perfusion, ventricles were removed, minced in control solution and incubated at 37 °C for an additional 3 min with titration. Dissociated cells were then filtered through a nylon mesh to remove big pieces of undigested tissues. Isolated cells were rinsed in control solution and allowed to settle by gravity to remove debris and non-cardiomyocytes. Calcium was added to the myocytes in step-wise fashion by settling/resuspension in 4 steps. Purified myocytes were resuspended in Medium 199 supplemented with 110 mg/L sodium pyruvate, 0.1 mmol/L β-mercaptoethanol, 100 U/mL penicillin, 100 μg/mL streptomycin, and 10% fetal calf serum and cultured on laminin-coated culture plates at a density of approximately 6000 cells/cm<sup>2</sup> at 37 °C for 2 h before washing to remove dead and non-adherent cells. Cells were maintained overnight in serum-containing medium before experimentation. Ventricular fibroblasts were isolated following the first low-speed spin to sediment myocytes. Fibroblasts were plated in Dulbecco's modified eagle medium (DMEM) plus 10% fetal calf serum and 1% penicillin/streptomycin and allowed to culture until confluence. Upon reaching confluence, the media was changed to serum-free DMEM for one hour. Cells were then washed one time with PBS and harvested for subsequent experimentation.

### Western blot analysis

The LV was carefully dissected away from the right ventricle and atria, and flash-frozen in liquid nitrogen. LV were homogenized in isoelectric focusing buffer (8 mol/L urea, 2.5 mol/L thiourea, 4% Chaps, 2 mmol/L EDTA) containing 2 mmol/L tributylphosphine, 10 mmol/L DTT and protease inhibitors. The homogenate was centrifuged at 14000 g for 5 min, and the super-

natant saved for protein analyses. Protein concentration was determined using a modified protein assay (Bio-Rad) and prepared in Laemmli sample buffer (Bio-Rad). Proteins were resolved on 7.5% SDS-PAGE gels and transferred to PVDF. Following blocking in 5% bovine serum albumin for one hour at room temperature, membranes were incubated with primary antibody overnight at 4 °C. The following primary antibodies were used: Phospho-Stat3 (Tyr705) (Cell Signaling 9131; 1:1000), Stat3 (Cell Signaling 9139; 1:1000). Membranes were washed and incubated with secondary antibody for one hour at room temperature. Protein bands were visualized using a chemiluminescent substrate and autoradiography. Membranes were probed first with phospho signal transducer and activator of transcription 3 (STAT3), stripped, and then re-probed for total STAT3. Equal loading of proteins was verified by Ponceau-S staining.

### Real-time RT-PCR

RNA was extracted from LV and isolated cells using standard TRIzol protocol (Thermo Fisher) and reverse transcribed using iScript cDNA synthesis kit (BioRad). For detection of murine IL-19 and IL-20R, real-time RT-PCR was performed with the iCycler My iQ using iQ SYBR Green Supermix (BioRad), normalized to the housekeeping gene 18S ribosomal RNA (18S). Primer sequences were as follows. IL-19 forward: 5'-GGCTAAAAGTATGTTTCAGTTCTCC-3', IL-19 reverse: 5'-AAATCTCTGGAGCGATGTCAG-3', IL-20R $\alpha$  forward: 5'-AACTGGCAGGCTGTGTATCC-3', IL-20R $\alpha$  reverse: 5'-TTGTCAGGTGCCTGGTTCTC-3', IL-20R $\beta$  forward: 5'-CGAGGAGGGACGGAAGAATG-3', IL-20R $\beta$  reverse: 5'-TACGGCCTCTCTCGATGTCA-3', 18S forward: 5'-GCCGCTAGAGGTGAAATTCTTG-3', 18S reverse: 5'-CTTTCGCTCTGGTCCGTCTT-3'. Myosin heavy chain  $\beta$  (MYHC $\beta$ ), atrial natriuretic factor (ANF), brain natriuretic peptide (BNP), myosin heavy chain  $\alpha$  (MYHC $\alpha$ ), and sarcoplasmic reticulum Ca<sup>2+</sup> ATPase (SERCA) oligonucleotide sequences were used as previously published<sup>[19]</sup>.  $\Delta$ Ct were calculated relative to the housekeeping gene 18S to allow comparisons across all groups (genotype and sex). As such, a lower  $\Delta$ Ct indicates higher expression.

### Statistical analysis

Significance was set a priori at  $P < 0.05$ . Data were analyzed by Students t-test using GraphPad and 2-way ANOVA (genotype by sex) using IBM SPSS Statistics Version 24. Data with unequal variance were log-transformed to meet assumptions for homoscedasticity. Data are expressed as means  $\pm$  SE of the mean. Where statistical analyses trend towards significance ( $P < 0.1$ ), values are also noted above figures. Kaplan-Maier survival curves were generated for survival data, and differences in survival were assessed with log rank test. The statistical methods of this study were reviewed by David Kao, MD from the University of Colorado-Denver.

## RESULTS

### IL-19 signaling in the female dominant dnCREB model of HF

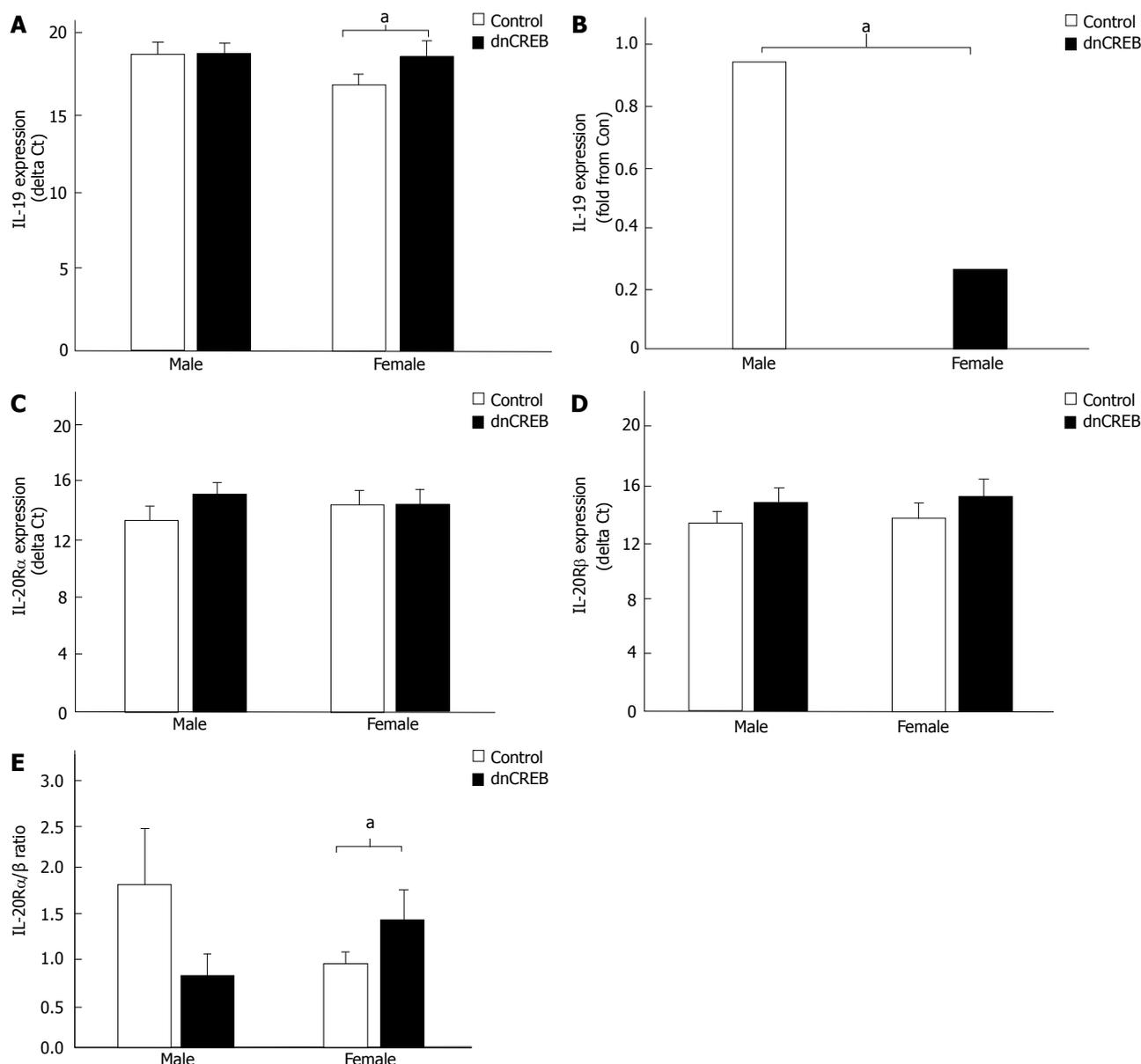
To begin to delineate the role of IL-19 in dnCREB-mediated HF, we assessed the expression of IL-19 and its receptor subunits in the LV from dnCREB mice compared to controls. Male dnCREB mice showed no change in IL-19 expression (Figure 1A); however, female dnCREB mice demonstrate significantly downregulated IL-19 expression (Figure 1A) with disease, a statistically different outcome in male and female mice (Figure 1B). Neither male nor female mice showed significant changes in expression of IL-20R $\alpha$  or  $\beta$  with disease (Figure 1C and D). However, the ratio of  $\alpha/\beta$  was significantly upregulated only in female dnCREB (Figure 1E). We then assessed activation of STAT3 as a downstream mediator of IL-19 signaling. Both male and female dnCREB mice showed downregulated STAT3 activation compared to control mice (Figure 2); however female dnCREB mice STAT3 activation was suppressed to 40% of control, while male dnCREB mice were suppressed to 70% of control.

### Survival of IL-19 KO and dnCREB double transgenic mice

The sexual dimorphic regulation of IL-19 and its receptor subunits in dnCREB-mediated suggests that IL-19 is cardioprotective in the setting of dnCREB, since female mice in this model suffer premature morbidity and mortality compared to males and express significantly attenuated IL-19. To test this hypothesis, we generated a novel double transgenic model (DTG) of IL-19 knockout in dnCREB-mediated HF. Survival analyses show that DTG males died from HF earlier in the development of disease than dnCREB male mice; with nearly identical survival curves to dnCREB females and female DTG (Figure 3). During this time, there was no morbidity in the Con or IL-19 KO mice (data not shown). Thus, knockout of IL-19 in this model accelerates mortality only in male mice, with no additional effect in females.

### Assessment of cardiac function in DTG mice

To confirm that accelerated mortality in DTG mice is due to cardiac dysfunction, we examined contractile function in male and female DTG mice at 10 wk of age by echocardiography. Representative M-mode echocardiographs are shown in Figure 4, and quantification (no hyphen) of echocardiography is reported in Table 1. Previous reports of the dnCREB model of female-dominant HF reported diminished fractional shortening (19.4% and 8.79%) and cardiac output (17.4 and 14.6 mL/min) in male and female mice respectively, with a significant difference between sexes<sup>[11]</sup>. Consistent with the dnCREB model, our DTG mice showed evidence of significant cardiac contractile dysfunction, with low fractional shortening (14% and 12%), stroke volume (24 and 23  $\mu$ L), and cardiac output (13.59 and 14.35 mL/



**Figure 1** Expression of interleukin-19 and interleukin-20R in the dominant negative cyclic AMP response-element binding protein model of female-dominant heart failure. A: Female male significantly downregulated IL-19 expression in the setting of dnCREB-mediated heart failure compared to male mice which maintained IL-19 expression; B: A significant difference between sexes; C: IL-20R $\alpha$  and IL-20R $\beta$  (D) expression were unchanged in either sex; D: However, the ratio between IL-20R $\alpha$ / $\beta$  was significantly upregulated in female dnCREB mice. Expression of IL-19 and IL-20R was assessed by qRT-PCR, and  $\Delta$ Ct calculated relative to 18S. The ratio of IL-20R $\alpha$ / $\beta$  was calculated as a fold change of  $\alpha$ - $\beta$  within each sex. Data are expressed as mean  $\pm$  SEM. <sup>a</sup>*P* < 0.05, *n* = 5-9 mice per group. dnCREB: Do-minant negative cyclic AMP response-element binding protein.

min) in male and female mice, respectively. However, genetic ablation of IL-19 completely abrogated the previously reported sex difference in the dnCREB model. That is, male DTG mice display similar levels of cardiac morbidity as female DTG, suggesting that IL-19 is cardioprotective in the dnCREB model of HF.

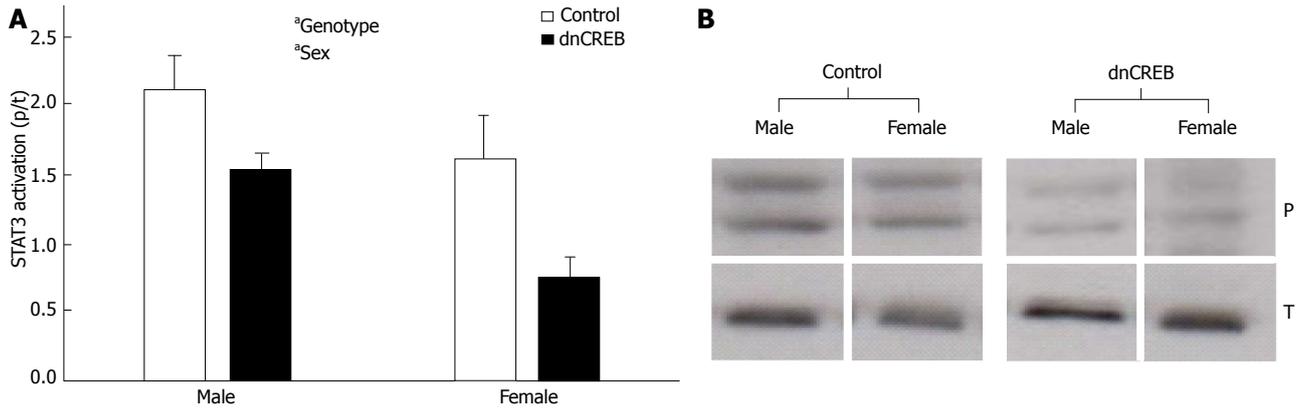
**IL-20R expression and STAT3 activation in DTG mice**

We assessed the relative expression of IL-20R $\alpha$  and  $\beta$  subunits in DTG male and female mice. We found male and female DTG mice to express similar levels of both subunits, with no difference in the ratio of the receptor subunits (Figure 5A and B). In addition, we assessed activation of STAT3 in male and female DTG mice and

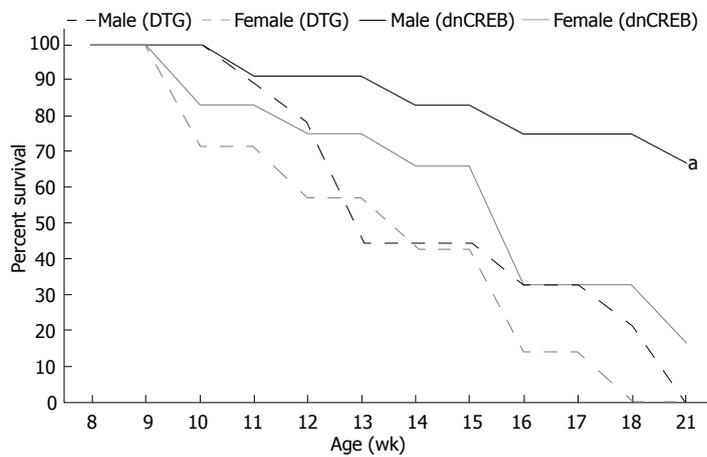
found STAT3 activation to be similar between sexes (Figure 5C and D). Expression of IL-20R and STAT3 activation in DTG male and female mice contrast with dnCREB mice, where downstream IL-19 signaling was significantly different between sexes.

**Biochemical responses to dnCREB-mediated HF**

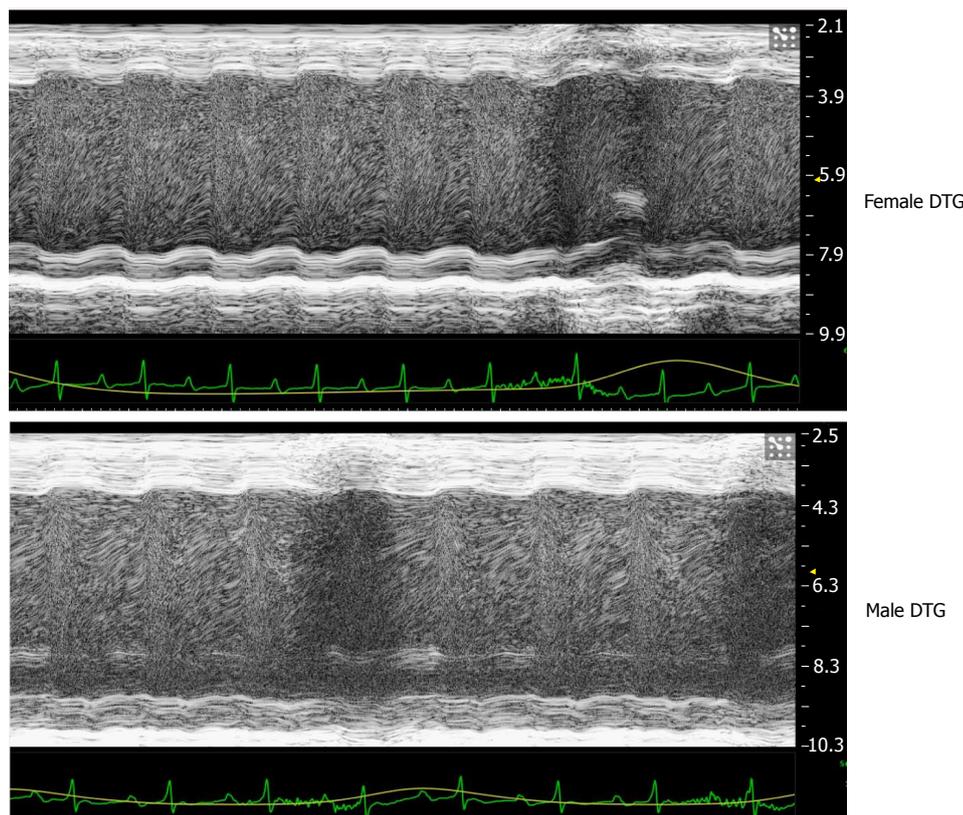
We assessed the expression of five genes in the hypertrophic gene program. These genes, components of the fetal gene program, are differentially expressed in established pathologic cardiac hypertrophy. While myosin heavy chain  $\alpha$  (MYHC $\alpha$ ) expression was unchanged by either sex or genotype (Figure 6A), myosin heavy chain  $\beta$  (MYHC $\beta$ ), atrial natriuretic factor (ANF) and



**Figure 2** Activation of signal transducer and activator of transcription 3 in the dominant negative cyclic AMP response-element binding protein model of female-dominant heart failure. **A:** Male and female dnCREB mice show attenuated STAT3 activation compared to controls; **B:** Representative immunoblotting images. Activation of STAT3 was assessed by immunoblotting of phospho STAT3/total STAT3. Data are expressed as mean  $\pm$  SEM and analyzed by 2-way ANOVA. All four conditions were run on the same gel, and non-essential lanes were removed for generation of the representative images. <sup>a</sup> $P < 0.05$ ,  $n = 2-6$  mice per group. a: Significant effect of genotype. dnCREB: Do-minant negative cyclic AMP response-element binding protein; STAT3: Signal transducer and activator of transcription 3.



**Figure 3** Kaplan-Meier survival curve of dominant negative cyclic AMP response-element binding protein and double transgenic male and female mice. IL-19 knockout in the setting of dnCREB accelerates male mouse mortality, while not affecting female dnCREB survival. No mortality was observed in Control or IL-19 KO mice during this period. Log-rank analyses were performed to compare survival between groups. <sup>a</sup> $P < 0.05$  vs female DTG, female dnCREB, and male DTG;  $n = 7-10$  mice per group. dnCREB: Do-minant negative cyclic AMP response-element binding protein; DTG: Double transgenic.

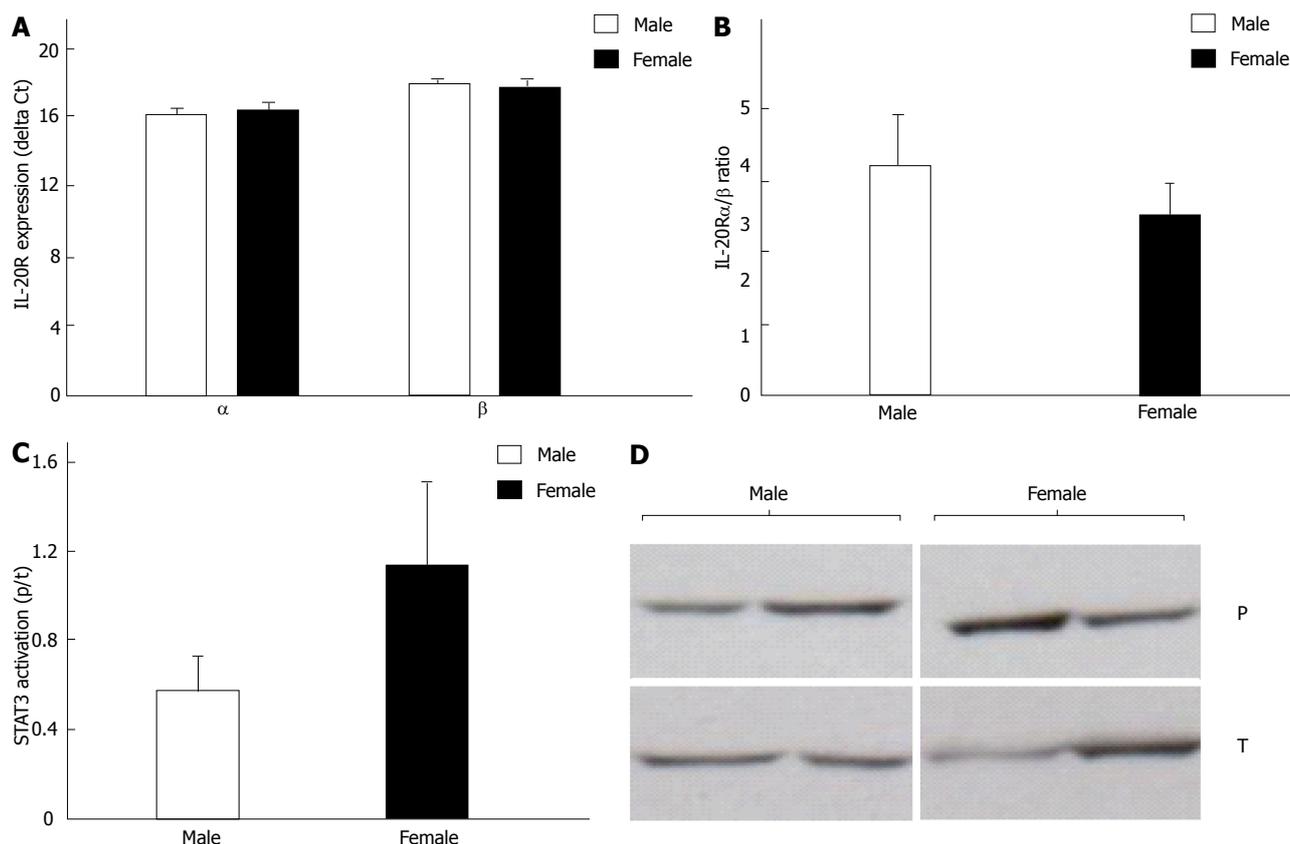


**Figure 4** Representative images from M-mode echocardiographic analysis of cardiac function in male and female double transgenic mice. Quantification of echocardiographic analyses are presented in Table 1. DTG: Double transgenic.

**Table 1 Cardiac function in dominant negative cyclic AMP response-element binding protein/interleukin-19 KO double transgenic male and female mice<sup>1</sup>**

		LVID; d (mm)	LVID; s (mm)	FS (%)	SV ( $\mu$ L)	HR (bpm)	CO (mL/min)
DTG	Male	4.49 $\pm$ 0.47	3.90 $\pm$ 0.60	13.95 $\pm$ 4.2	24.10 $\pm$ 2.60	566 $\pm$ 30	13.59 $\pm$ 1.33
	Female	4.53 $\pm$ 0.18	3.99 $\pm$ 0.29	12.02 $\pm$ 3.05	23.34 $\pm$ 3.11	621 $\pm$ 24	14.35 $\pm$ 1.30

<sup>1</sup>Values are presented as mean  $\pm$  SEM. Animals are 10 wk of age; *n* = 3 of each sex. All comparisons between sexes are *P* > 0.05 as assessed by Student's *t*-test. LVID; d: Left ventricular internal diameter at diastole; LVID; s: Left ventricular internal diameter at systole; FS: Fractional shortening; SV: Stroke volume; HR: Heart rate; CO: Cardiac output. DTG: Double transgenic.



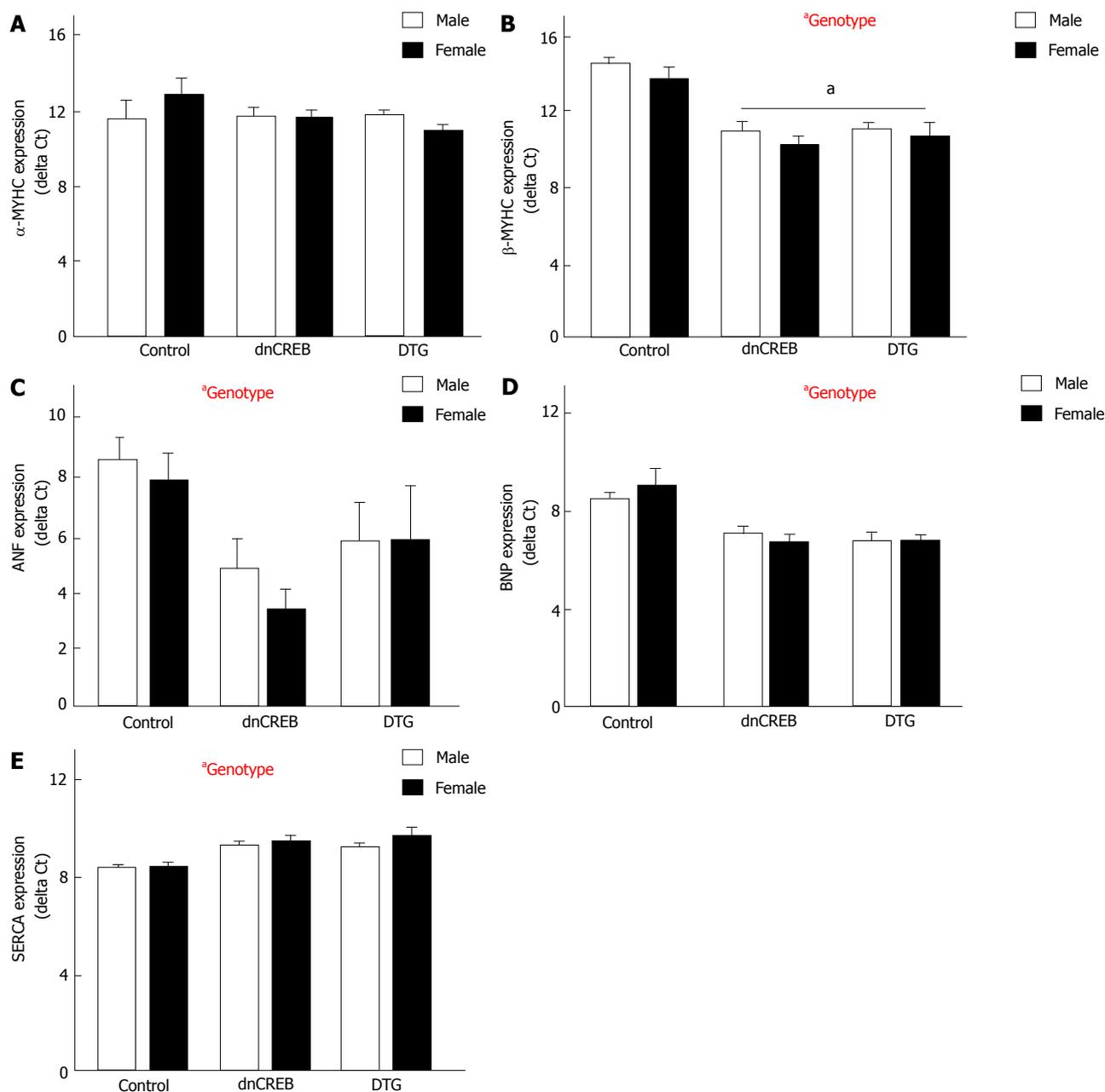
**Figure 5 Expression of interleukin-20R $\alpha/\beta$  and activation of signal transducer and activator of transcription 3 in male and female double transgenic mice.** A: IL-20R $\alpha$  and IL-20R $\beta$  expression were similar in male and female DTG mice; B: Similarly, the ratio of IL-20R $\alpha/\beta$  did not differ between sexes; C: STAT3 activation did not differ between male and female DTG mice; D: Representative immunoblotting images. Expression of IL-20R was assessed by qRT-PCR and expressed and  $\Delta$ Ct calculated relative to 18S. The ratio of IL-20R $\alpha/\beta$  was calculated as a fold change of  $\alpha/\beta$  within each sex. Activation of STAT3 was assessed by immunoblotting of phospho STAT3/total STAT3. Both male and female mice were run on the same gel, and non-essential lanes were cropped for generation of the representative image. Data are expressed as mean  $\pm$  SEM; *n* = 4-7 mice per group. STAT3: Signal transducer and activator of transcription 3; DTG: Double transgenic.

brain natriuretic peptide (BNP) were all significantly upregulated in dnCREB and DTG mice (Figure 6B-D), while sarcoplasmic reticulum Ca<sup>2+</sup> ATPase (SERCA) expression was significantly downregulated (Figure 6E). Surprisingly, we observed no overall effect of sex on fetal gene program expression; however, BNP expression was more robustly induced in female dnCREB mice compared to male dnCREB (4.8 fold vs 2.6 fold, *P* < 0.05, data not shown).

**Expression of IL-19 and IL-20R in isolated cardiac myocytes and fibroblasts**

IL-19 signaling is uncharacterized in the heart. It is

imperative we understand IL-19 signaling in the male and female heart to understand the dysregulation that occurs with disease. Therefore, we isolated primary cardiac myocytes and fibroblasts from male and female mice to assess IL-19 signaling in these two cell types. Both fibroblasts (Cfib) and myocytes (CM) expressed IL-19, with no differences between sexes in either cell type (Figure 7A). Both cell types also express IL-20R $\alpha$ , with higher expression in CM than Cfib, and a trend towards lower expression in female myocytes than males (Figure 7B). Fibroblasts and myocytes similarly express IL-20R $\beta$ , with no difference between sexes (Figure 7C), however the ratio of IL-20R $\alpha/\beta$



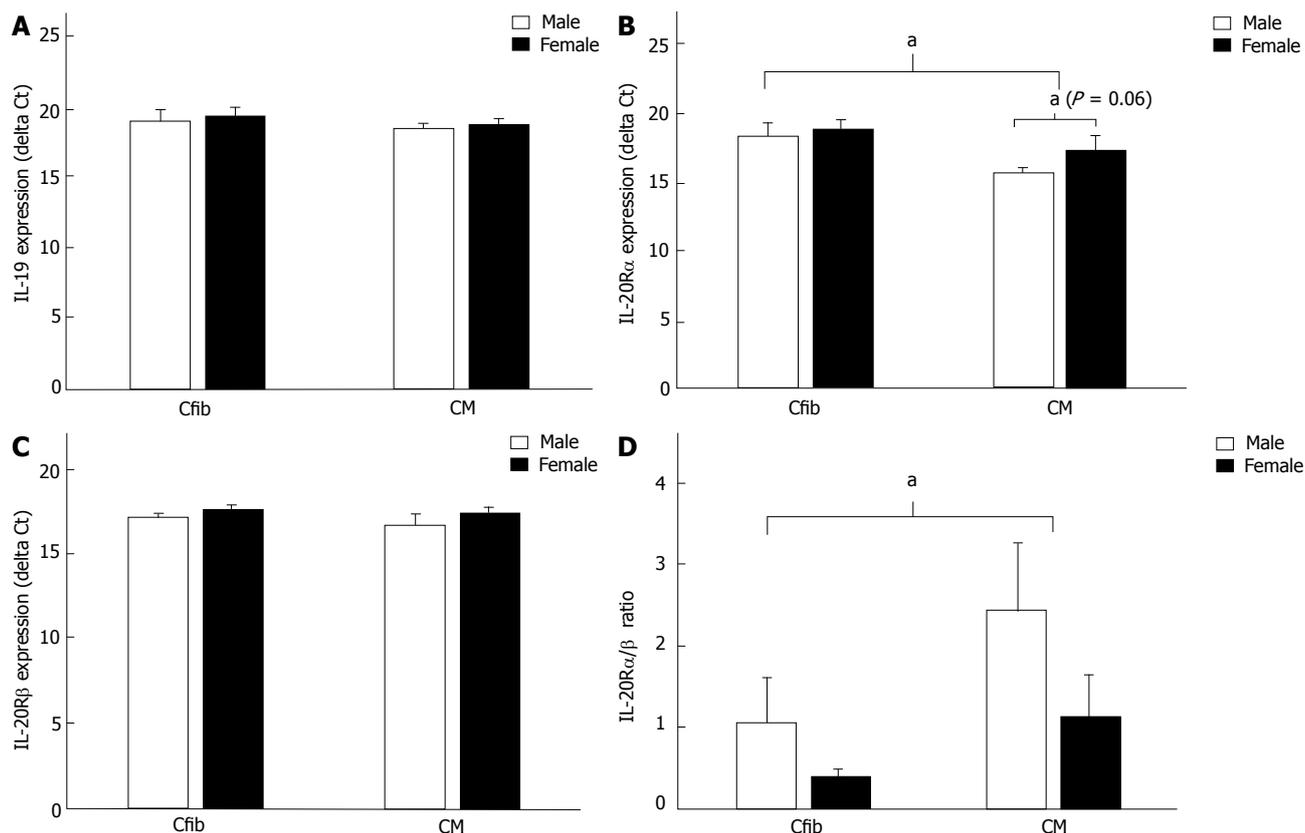
**Figure 6** Activation of the fetal hypertrophic gene program in dominant negative cyclic AMP response-element binding protein and double transgenic mice. A: Myosin heavy chain  $\alpha$  (MYHC $\alpha$ ) expression was unchanged by either sex or genotype; B: Myosin heavy chain  $\beta$  (MYHC $\beta$ ); C: Atrial natriuretic factor (ANF); D: Brain natriuretic peptide (BNP) were all significantly upregulated in both male and female dnCREB and DTG mice; E: Sarcoplasmic reticulum Ca<sup>2+</sup> ATPase (SERCA) expression was significantly downregulated in both sexes with disease. Expression of fetal hypertrophic genes was assessed by qRT-PCR, relative to the housekeeping gene 18S. Data are expressed as mean  $\pm$  SEM and assessed by 2-way ANOVA. <sup>a</sup>*P* < 0.05 vs Control; *n* = 4-7 mice per group. a: Significant effect of genotype. dnCREB: Do-minant negative cyclic AMP response-element binding protein; DTG: Double transgenic.

was significantly higher in CM than Cfib (Figure 7D), suggesting the potential for cell-type specific responses to IL-19 signaling in the heart.

## DISCUSSION

HF is a sexually dimorphic disease, adversely affecting female patients regarding morbidity and mortality. The maladaptive role of cytokines in HF is well documented; however, only a few studies have considered sex differences in cytokine expression or signaling. We show for the first time that IL-19, a previously

undescribed cytokine in the heart, is expressed in rodent cardiac tissue and two previously unexamined cardiac cell types: Cardiac myocytes and fibroblasts. Further, we report dysregulation of IL-19 signaling in a female-dominant model of HF, suggesting a cardioprotective role of IL-19 in the heart. We propose the following model, as summarized in Figure 8, where IL-19 signaling through IL-20R $\alpha/\beta$  activates STAT3 and canonical downstream cardioprotective mechanisms. This pathway is significantly downregulated in female dnCREB mice, resulting in attenuated STAT3 activation, LV remodeling, cardiac dysfunction, and premature

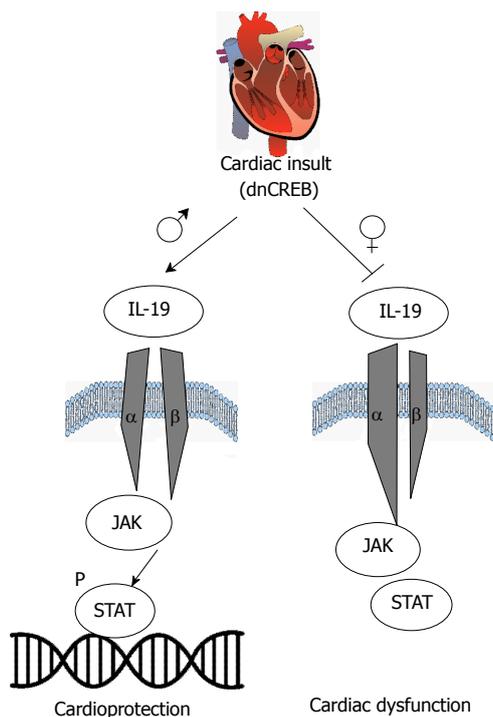


**Figure 7 Interleukin-19 and interleukin-20R expression in male and female cardiac fibroblasts and myocytes.** A: Both male and female Cfib and CM express IL-19, with no differences between sexes or cell types; B: Both Cfib and CM express IL-20R $\alpha$ , with higher expression in CM than Cfib, as evident by the lower delta Ct. Male CM tended to express higher IL-20R $\alpha$  than female CM ( $P = 0.06$ ); C: Both Cfib and CM express IL-20R $\beta$ , with no differences between cell types or sex; D: The ratio of IL-20R $\alpha$ / $\beta$  was significantly higher in CM than Cfib. IL-19 and IL-20R expression were assessed by qRT-PCR and normalized to the housekeeping gene 18S. Data are expressed as mean  $\pm$  SEM and assessed by 2-way ANOVA;  $n = 7-8$  mice per group. Cfib: Cardiac fibroblasts; CM: Cardiac myocytes.

mortality. However, male dnCREB mice maintain IL-19 expression with disease, resulting in heightened cardioprotection and significantly less morbidity and mortality compared to female mice. Ongoing investigations will elucidate further mechanistic insight into sexually divergent downstream IL-19 mediated cardiac signaling and whether this novel cytokine represents a new therapeutic target for the treatment of women's heart disease.

IL-19 was first discovered over a decade ago and classified as a member of the IL-10 family based on structure and location of the IL-19 gene and the use of similar receptor complexes<sup>[20]</sup>. Since its discovery, however, the function of IL-19 has remained unclear. In a number of disease states including asthma<sup>[21]</sup>, sepsis<sup>[22]</sup>, and acute kidney injury<sup>[23]</sup> IL-19 acts as a pro-inflammatory factor. Conversely, in inflammatory bowel disease<sup>[17]</sup> and vascular disease<sup>[24]</sup>, IL-19 appears to be anti-inflammatory and protect against disease progression. These data imply that IL-19 may function as either pro- or anti-inflammatory depending on the tissue and disease context. Further, it suggests that downstream IL-19 signaling including receptor subunit expression may be implicated in the disparate biological outcomes. A study examining IL-20R expression in 24 different human tissues reports significant differential  $\alpha$ /

$\beta$  subunit expression between tissue types<sup>[9]</sup> suggesting differential relative expression of these two subunits may be implicated in the varying biological outcomes of IL-19 signaling. Various groups have attempted to define the binding kinetics and receptor requirements for IL-19 signaling. While most report a requirement for the IL-20R heterodimer and the rapid formation of a stable 1:1:1 complex in the presence of a ligand, other evidence also supports less stable homodimer formation<sup>[25]</sup>. In support of homodimer IL-20R signaling, IL-19 has clear effects on lymphocytes derived from IL-20R $\beta$  knockout mice<sup>[26]</sup>. Thus the specific requirement for receptor dimerization remains controversial, as does the effect of subunit expression on IL-19 downstream function. We assessed IL-20R subunit expression in isolated primary cardiac myocytes and fibroblasts and found differential expression of the receptor subunits, suggesting that IL-19 may modulate IL-20R in a cell-type specific manner. These data are consistent with previous reports of IL-19 signaling in the vasculature which demonstrate that IL-19 stimulation of vascular smooth muscle cells induces expression of IL-20R $\beta$  with no effect on endothelial cells<sup>[27]</sup>. Further, receptor subunit expression may be regulated in a sex-specific manner during disease progression as evidenced by differential IL-20R $\alpha$ / $\beta$  ratios in male and female dnCREB



**Figure 8 Working model of interleukin-19 in sex-specific heart failure.** Cardiac insult (inactivation of cyclic AMP response-element binding protein) results in maintained interleukin-19 (IL-19) expression in male mice, with maintained expression of IL-20 receptor subunits. Activation of downstream JAK-STAT signaling in male hearts is cardioprotective. However, cardiac insult in female mice results in attenuated IL-19 signaling, dysregulated expression of IL-20R subunits, and cardiac dysfunction. Ongoing investigations will delineate the downstream mediators implicated in IL-19 cardioprotection in a sex-specific manner.

mice. Together, these data suggest that cell and context-specific regulation of IL-20 receptor isoforms may be important in disease, and may do so in a sexually dimorphic manner. Elucidation of the effects of IL-19 on specific cardiac cell populations (including inflammatory cells, endothelial, and vascular smooth muscle unexamined here) from male and female models warrants future investigation.

IL-19 treatment of IL-20R $\alpha/\beta$  expressing cells leads to tyrosine phosphorylation of STAT3<sup>[28]</sup>. STAT3 is universally cardioprotective in response to a number of cardiac insults including ischemia-reperfusion injury<sup>[29]</sup> and hypertrophy<sup>[30]</sup>. Myocyte-specific STAT3 knockout mice develop cardiac fibrosis and myocardial dysfunction even in the absence of stress<sup>[31]</sup>. These mice are also more susceptible to inflammation-induced cardiac damage and greater contractile dysfunction<sup>[32]</sup>, and ultimately lack of myocyte STAT3 leads to age-related HF<sup>[31,32]</sup>. Furthermore, human failing hearts exhibit reduced STAT3 levels and activity compared to healthy controls<sup>[33]</sup>. Thus, STAT3 is crucial for cardiac resistance to inflammation and other acute injuries. We show attenuated STAT3 activation in the LV from dnCREB male and female mice. Further, this effect is more robust in female dnCREB mice, correlating with the female-dominance of the dnCREB model and the early mortality of female mice. The mechanisms

of STAT3-mediated cardiac protection in our model are not yet characterized; though canonical (Tyr705) STAT3 activation has proposed anti-oxidant, anti-apoptotic, and pro-angiogenic target genes (Reviewed in<sup>[34]</sup>). In addition, STAT3 also enhances mitochondrial respiration and acts on complex I to inhibit reactive oxygen species formation; mechanisms which are augmented by non-canonical phosphorylation of STAT3 at Ser727<sup>[35]</sup>. The action of STAT3 on mitochondrial function is particularly interesting and warrants future investigation, as dnCREB female mice have increased oxidant production, attenuated antioxidant defenses, and disrupted mitochondrial structure and function compared to male dnCREB<sup>[11]</sup>.

In summary, we show for the first time that IL-19 demonstrates clear sexually dimorphic expression in the female-dominant dnCREB model of HF. Ablation of IL-19 in this model accelerates male mortality and causes severe cardiac morbidity, suggesting a cardioprotective role for IL-19 in the heart. Elucidation of IL-19 signaling in this model and in other models of female-dominant HF will facilitate the identification of novel therapeutics for women’s heart disease.

## ACKNOWLEDGMENTS

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## COMMENTS

### Background

Heart failure (HF) is a sexually dimorphic disease, with worse morbidity and mortality in female patients compared to males. Inflammation is hypothesized to play a detrimental role in HF development, though whether it is regulated in a sexually dimorphic manner remains unknown. Interleukin-19 (IL-19) is an inflammatory cytokine with an unknown function in the healthy heart or in HF. Therefore, the authors set out to assess the role of IL-19 in female dominant HF.

### Research frontiers

HF is characterized by inflammatory signaling, though how this may be regulated in a sex-specific manner is unknown. Since HF is a sexually dimorphic disease, it is imperative that understand molecular mechanisms which contribute to disease in a sex-specific approach.

### Innovations and breakthroughs

Although IL-19 has been studied in the vasculature, few reports exist regarding cardiac signaling. The authors show for the first time that IL-19 demonstrates clear sexually dimorphic expression in a model of female-dominant HF. Genetic ablation of IL-19 in this model accelerates male mortality, suggesting IL-19 is cardioprotective.

### Applications

Development of sex-specific therapies will improve HF outcomes, and is a primary goal of personalized medicine. To develop sex-specific therapies, the authors must understand mechanisms which underlie HF in both males and females. Although the impact of IL-19 in the human heart remains unknown, the data identify sex-specific mediators of cardiac function, and suggest that therapies for the failing human heart be explored in both sexes.

### Peer-review

This is a very interesting topic. The paper is well written, clear and interesting. The results provide adequate grounds for the conclusion.

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**E-Editor:** Lu YJ



## Case Control Study

**Effects of hypertonic saline solution on body weight and serum creatinine in patients with acute decompensated heart failure**

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**Informed consent statement:** Informed consent was not

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**Abstract****AIM**

To test the safety and effectiveness of hypertonic saline solution (HSS + F) as a strategy for weight loss and

prevention of further deterioration of renal function.

### METHODS

Patients admitted with acute decompensated heart failure (ADHF) who received HSS + F were included in the study. After a period of a standard ADHF treatment, our patients received an intravenous infusion of furosemide (250 mg) combined with HSS (150 mL of 3% NaCl) twice a day for a mean duration of 2.3 d. Our primary outcomes were weight loss and a change in serum creatinine per day of treatment. The parameters of the period prior to treatment with HSS + F were compared with those of the period with HSS + F.

### RESULTS

A total of 47 patients were included. The mean creatinine on admission was  $155 \mu\text{mol/L} \pm 65 \mu\text{mol/L}$ , the ejection fraction was  $40\% \pm 17\%$ . The experimental treatment (HSS + F) resulted in greater weight loss per day of treatment than the standard treatment ( $-1.4 \text{ kg/d} \pm 1.4 \text{ kg/d}$  vs  $-0.4 \text{ kg/d} \pm 1.0 \text{ kg/d}$ ,  $P = 0.0168$ ). Importantly, the change in creatinine was not significantly different.

### CONCLUSION

This study supports the effectiveness of HSS + F on weight loss in patients with ADHF. The safety profile, particularly with regard to renal function, leads us to believe that HSS + F may be a valuable option for those patients presenting with ADHF who do not respond to conventional treatment with intravenous furosemide alone.

**Key words:** Heart failure; Decompensated; Hypertonic saline; Renal failure; Fluid overload

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**Core tip:** Hypertonic saline solution (HSS) has been proposed in recent years as a potential therapy to facilitate diuresis in patients with decompensated heart failure and to overcome diuretic resistance. This study supports the effectiveness of HSS + F on weight loss in patients with acute decompensated heart failure and a high burden of comorbidities, despite a proportion of patients having preserved ejection fraction, right heart failure and advanced renal failure. The administration of small intravenous boluses of HSS in conjunction with intravenous furosemide can be a feasible and inexpensive therapeutic option which can prevent the use of costlier and more invasive treatments such as ultrafiltration, hemodialysis and inotropic infusion.

Lafrenière G, Béliveau P, Bégin JY, Simonyan D, Côté S, Gaudreault V, Israeli Z, Lavi S, Bagur R. Effects of hypertonic saline solution on body weight and serum creatinine in patients with acute decompensated heart failure. *World J Cardiol* 2017; 9(8): 685-692 Available from: URL: <http://www.wjgnet.com/1949-8462/full/v9/i8/685.htm> DOI: <http://dx.doi.org/10.4330/wjc.v9.i8.685>

## INTRODUCTION

Heart failure (HF) is a well-recognized major public health problem affecting about 26 million people worldwide<sup>[1]</sup>. Its impact in terms of mortality, morbidity, quality of life and cost is considerable. Acute decompensated heart failure (ADHF) is a leading cause of hospitalization and a common issue in emergency departments. Loop diuretics have long been recognized as the key for the treatment of ADHF<sup>[2]</sup>, however, high doses can cause adverse effects, including electrolyte abnormalities and deterioration of renal function. In addition, patients can develop resistance to diuretics and congestive symptoms can persist despite treatment with high doses<sup>[3]</sup>. Currently available treatment options include higher doses or a continuous infusion of intravenous diuretics<sup>[4,5]</sup>, a combination of different classes of diuretics for their synergistic effects<sup>[6,7]</sup>, and in severe/advanced cases, parenteral inotropes<sup>[8-10]</sup> and ultrafiltration<sup>[11,12]</sup>. The last two options are not associated with a better prognosis, and in fact, can cause deleterious effects and their use is limited by the cost and availability<sup>[11-14]</sup>.

The hypertonic saline solution (HSS) has been proposed in recent years as an adjunctive therapy for intravenous loop diuretics to improve or restore their initial pharmacological efficacy<sup>[3]</sup>. Among the proposed mechanisms to explain the benefits of HSS, it has been reported that it would prevent intravascular depletion due to diuretics<sup>[15,16]</sup> and thus would maintain renal flow and the glomerular filtration rate (GFR) during intensive treatment of intravenous furosemide<sup>[17]</sup>.

Compared to the administration of high doses of intravenous furosemide alone, concomitant use of HSS (HSS + F) has shown, in patients with ADHF, a more rapid and complete resolution of the signs and symptoms of congestion by increasing urine volume and by potentiating weight loss<sup>[16,18,19]</sup>, the potential to protect against deterioration of renal function during intensive diuretic therapy<sup>[15,20]</sup>, an improvement of cardiac biomarkers and echocardiographic parameters<sup>[19,21,22]</sup>, a reduced length of hospital stay and frequency of re-hospitalizations<sup>[23]</sup> and a good safety profile<sup>[24]</sup>.

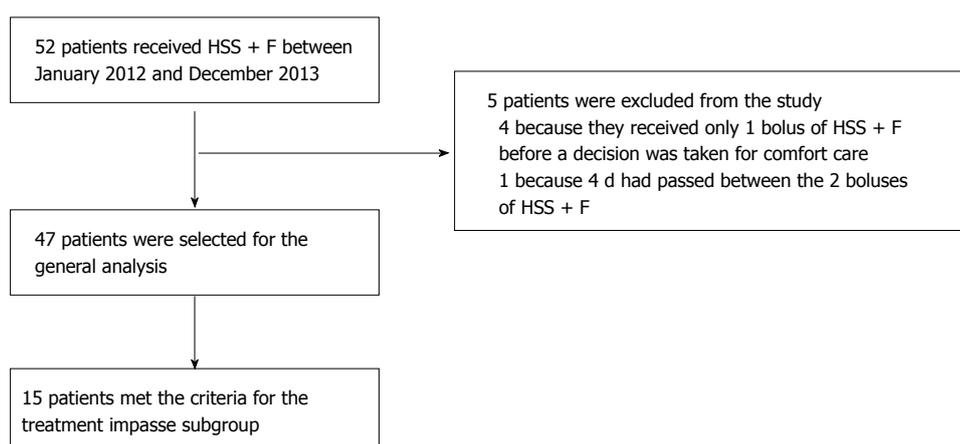
Therefore, the aim of the present report was to test the safety and effectiveness of HSS + F as a strategy for weight loss and prevention of further deterioration of renal function compared to the usual intensive treatment with intravenous furosemide alone.

## MATERIALS AND METHODS

Patients admitted with ADHF and who received HSS + F between January 2012 and December 2013 at the Quebec University Hospital Centre were included for the analysis. The decision to prescribe HSS + F following the standard treatment for a given patient was left to the discretion of the treating cardiologist,

<p>Eligible patients</p> <ul style="list-style-type: none"> <li>Men or women older than 18 years</li> <li>ADHF with congestive symptoms and signs</li> <li>Refractory to standard treatment of ADHF <ul style="list-style-type: none"> <li>Worsening renal function due to increased diuretics doses</li> <li>Poor responsiveness to treatment with furosemide <ul style="list-style-type: none"> <li>Constant increase of body weight</li> <li>Persistence of peripheral or pulmonary edema</li> <li>Reduction of urine volume</li> </ul> </li> <li>Orthostatic hypotension with increased diuretic doses</li> </ul> </li> </ul> <p>Patients who should not receive protocol</p> <ul style="list-style-type: none"> <li>Hypertensive crisis</li> <li>Baseline hyponatremia</li> <li>No congestive symptoms and signs</li> </ul> <p>Prescription protocol</p> <ul style="list-style-type: none"> <li>Infusion of HSS + F: 150 mL of 3% NaCl + 250 mg of furosemide</li> <li>Administered over one hour</li> <li>Twice a day for a suggested period of 48 h</li> </ul> <p>Other prescriptions</p> <ul style="list-style-type: none"> <li>Fluid restriction of 1.5 L/d</li> <li>Vital signs and weight must be recorded daily</li> <li>Serum Na, serum K and creatinine must be recorded daily</li> </ul>
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**Figure 1 Study protocol.** ADHF: Acute decompensated heart failure; HSS: Hypertonic saline solution.



**Figure 2 Data collection protocol and observation periods.**

who had received at the beginning of the study a list of the suggested inclusion and exclusion criteria (Figure 1). All clinical, echocardiographic and laboratory data were prospectively collected in a dedicated database. Institutional review board approval and patient consent were not required because of the nature of this study.

### Intervention

On admission for ADHF, most patients were on fluid restriction of 1.5 L/d, received an intravenous furosemide dose that was adjusted according to the clinical response and the conventional HF treatment that was considered appropriate by the treating physician based on current recommendations<sup>[25,26]</sup>. When patients were considered to be refractory to this treatment, based on a poor response to standard therapy (weight, creatinine, clinical judgment), intravenous furosemide was replaced by an intravenous infusion of HSS + F (150 mL of 3% NaCl + 250 mg of furosemide) administered

over one hour twice a day for a suggested period of 48 h that could be extended or shortened depending on the clinical response. Patients underwent the usual daily medical examination for the evaluation of the signs and symptoms of HF. Vital signs and weight were recorded daily; serum creatinine, sodium (Na) and potassium (K) levels were closely monitored during treatment. Moreover, the clinician's impression concerning the treatment effectiveness was recorded in the medical notes. Patients were all compared to themselves with a before and after study design. The effects of treatment with intravenous furosemide alone (standard treatment) were compared to the treatment with intravenous furosemide plus HSS (HSS + F) (experimental treatment) administered following the standard treatment. The results available from days one to four prior to the initiation of saline treatment were analyzed and compared to the experimental treatment d (Figure 2).

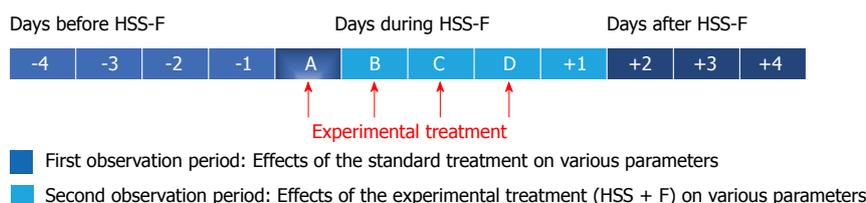


Figure 3 Flow diagram of participants in the study. HSS: Hypertonic saline solution.

### Outcomes

Our primary outcomes were the decrease in weight and the change of creatinine per day of treatment. Secondary outcomes were the effect of the experimental treatment on the serum Na and K levels and its safety profile regarding neurological events.

### Subgroup analysis

The effects of HSS + F on weight and creatinine were studied in the “treatment impasse” subgroup defined as all patients with increased weight and creatinine per day of treatment despite standard therapy.

### Statistical analysis

Continuous data are presented as mean  $\pm$  SD or median [interquartile range (IQR)] depending on variable distribution, and categorical data are presented as frequencies (percentage). Differences between the weight reduction in the experimental treatment and the standard treatment periods were assessed by Wilcoxon Signed Rank test for paired samples. The same approach was used for all other analyses as the change of creatinine per day of treatment between these two periods and analyses in the “treatment impasse” subgroup. The level of statistical significance was set as  $P < 0.05$ . Data were analyzed using the SAS statistical software, version 9.3.

## RESULTS

A total of 52 patients received HSS + F for ADHF. Five patients were excluded from the study; four because they received one bolus of HSS + F before the decision of giving end-of-life comfort care only, and one patient was not selected because four d had elapsed between the two boluses of HSS + F, making interpretation difficult.

Hence, a total of 47 patients (32 men, 68%), mean age of  $77.6 \pm 9.5$  years, were included in the study (Figure 3). Thirty-two (68%) patients had chronic kidney disease based on an estimated GFR (eGFR)  $\leq 60$  mL/min per  $1.73 \text{ m}^2$ . Moreover, the mean creatinine was  $155 \pm 65 \mu\text{mol/L}$ , leading to an eGFR of  $42 \pm 22$  mL/min per  $1.73 \text{ m}^2$  on admission. Of note, 12 (25.5%) presented with a serum Na  $< 135$  mmol/L. The left ventricle ejection fraction (LVEF) was  $40\% \pm 17\%$  and half of the patients had  $\leq 40\%$  (Table 1). In addition, 31 patients had pleural effusion, 11 had ascites, 11 presented with arterial hypotension and/or orthostatic

hypotension and 13 had acute kidney injury defined as a 1.5-fold increase in serum creatinine or absolute increase in serum creatinine of  $\geq 26.4 \mu\text{mol/L}$  from their baseline value<sup>[27,28]</sup>.

Before receiving HSS + F, six (12.8%) patients required non-invasive ventilation and three (6.4%) patients were intubated for respiratory failure, but no form of mechanical ventilation was initiated during treatment with HSS + F. In addition, eight (17%) patients had a thoracentesis during hospitalization (two during the HSS + F treatment period and six outside of the observation period) and four (8.5%) patients had a paracentesis (two during the standard treatment and none during the HSS + F treatment). Moreover, eight (17%) patients received an infusion of inotropes, but only three during the observation period (one during the experimental treatment, one throughout the two treatments studied and the remaining during the standard treatment only). Six (12.8%) patients underwent coronary angiography during hospitalization, but only two patients had it during the observation period (one during the standard treatment and the other had two coronary angiograms: One before and another during treatment with HSS + F).

### Intervention

Patients received a mean of  $5.1 \pm 2.0$  doses of HSS + F for a mean duration of  $2.3 \pm 1.0$  d. During the treatment period with HSS + F, patients lost  $3.9 \pm 3.8$  kg. Interestingly, the treating physician reported a significant improvement in signs and symptoms of congestion with this experimental treatment on 38 (81%) patients. In addition, weight loss per day of treatment was significantly greater with HSS + F treatment than with the standard treatment ( $-1.4 \pm 1.4$  kg/d vs  $-0.4 \pm 1.0$  kg/d, mean difference of  $0.8 \pm 1.8$  kg/d,  $P = 0.0168$ ) (Table 2). The change in creatinine per day of treatment was not statistically different between treatments (Table 2). The mean serum Na increased by 2.4 mmol/L (95%CI: 1.6-3.1,  $P < 0.0001$ ) and the mean serum K decreased by 0.2 mmol/L (95%CI: -0.4 to -0.1,  $P = 0.0001$ ) with the experimental treatment compared to the standard treatment. The mean daily dose of intravenous furosemide given during the standard treatment period was  $106 \pm 67$  mg. Four patients received an additional continuous infusion of furosemide for a mean duration of 2.3 d. Nine patients received mainly oral furosemide, with a correspondingly larger mean daily

**Table 1** Baseline characteristics of the study population *n* (%)

Variables	<i>n</i> = 47
Age (yr)	77.6 ± 9.5
Males	32 (68.1)
Body mass index (kg/m <sup>2</sup> )	28.2 ± 7.2
Hypertension	46 (97.9)
Diabetes	28 (59.6)
NYHA functional class (admission)	
III	16 (38.1)
IV	23 (54.8)
Coronary artery disease	33 (70.2)
Ischemic heart failure	29 (61.7)
Stroke or transient ischemic attack	11 (23.4)
Vascular disease	22 (46.8)
Atrial fibrillation	27 (57.4)
Oxygen-dependent COPD	4 (8.5)
Active cancer	11 (23.4)
Baseline creatinine (μmol/L) <sup>1</sup>	140.1 ± 65.5
Chronic kidney disease (eGFR ≤ 60 mL/min per 1.73 m <sup>2</sup> ) <sup>1</sup>	32 (68.1)
Admission creatinine (μmol/L)	154.8 ± 65.4
Admission eGFR using MDRD (mL/min per 1.73 m <sup>2</sup> )	42.2 ± 22.3
Admission serum Na concentration < 135 mmol/L	12 (25.5)
Echocardiographic data	
Left ventricle ejection fraction	39.9 ± 17.4
LVEF > 40%	23 (48.9)
LVEF ≤ 40%	24 (51.0)
Severe aortic stenosis	1 (2.2)
Moderate and/or severe mitral regurgitation	16 (34.8)
Severe tricuspid regurgitation	6 (13.0)
Pulmonary hypertension ≥ 50 mmHg	19 (41.3)
Severe diastolic dysfunction	11 (23.9)
Right ventricular dysfunction/dilatation	28 (60.9)
Medications	
ACEI/ARBs	28 (59.6)
Hydralazine	3 (6.4)
Beta-blocker	39 (83.0)
Diuretics	
Oral furosemide	39 (83.0)
Thiazide	9 (19.1)
Spironolactone	8 (17.0)
Zaroxolyn	1 (2.1)
Furosemide dose per day (mg)	128.2 ± 106.7

<sup>1</sup>Average of the five most recent creatinine values before hospitalization. Values are expressed as mean ± SD or *n* (%). NYHA: New York Heart Association; COPD: Chronic obstructive pulmonary disease; eGFR: Estimated glomerular filtration rate; MDRD: Modification of Diet in Renal Disease equation; LVEF: Left ventricle ejection fraction; ACEI: Angiotensin-converting-enzyme inhibitor; ARBs: Angiotensin II receptor blockers.

dose of 196 ± 165 mg. Seven doses of metolazone were given during the standard treatment and 7 doses during the experimental treatment.

The administration of HSS + F was well tolerated by all patients and no major adverse events were observed. It is noteworthy to be highlighted that there was no pulmonary congestion or neurological consequences due to HSS + F strategy. However, the HSS + F treatment was discontinued in 2 (4.3%) patients due to an excessive increase in serum Na (*i.e.*, from 120 mmol/L to 128 mmol/L) in 1 patient and a significant decrease in blood pressure for the other.

A total of 7 (15%) patients died during the hospital stay. The median time between death and the end

**Table 2** Weight loss and creatinine change per day of treatment (*n* = 47)

Variable	mean ± SD	95%CI	<i>P</i> value
Weight loss (kg/d)			
Standard treatment	-0.39 ± 1.02	(-0.77, -0.03)	
Experimental treatment	-1.43 ± 1.43	(-1.86, -1.02)	
Standard-experimental difference	0.80 ± 1.77	(0.15, 1.44)	0.0168
Change in creatinine (μmol/L per day)			
Standard treatment	3.48 ± 9.89	(0.51, 6.68)	
Experimental treatment	-0.69 ± 9.62	(-3.51, 2.00)	
Standard-experimental difference	4.20 ± 14.25	(-0.49, 8.88)	0.331

of treatment with HSS + F was 3 (IQR: 1-33) d. However, two of these deaths were attributed to a shift to end-of-life palliative care requested by the family (treatment with HSS + F originally scheduled for 48 h was discontinued). The average hospital stay was 20 ± 12 d with a median of 16 (IQR: 11-24) d.

Notably, in the impasse treatment subgroup (*n* = 15), consisting of patients selected because of their negative response to the standard treatment, in addition to a significant weight loss achieved with the experimental treatment (-1.2 kg/d ± 1.3 kg/d vs -0.3 kg/d ± 0.6 kg/d with the standard treatment, mean difference of 1.5 kg/d ± 1.7 kg/d, *P* = 0.0026), there was an increase in creatinine level with the standard therapy that was not seen with the experimental therapy; indeed, the mean creatinine difference was also statistically significant (11 ± 13 μmol/L per day, *P* = 0.008) (Table 3).

## DISCUSSION

In a population of patients admitted with ADHF, the administration of HSS + F led to a greater weight loss per day of treatment compared to the standard intravenous furosemide strategy; even if a considerable proportion of them presented HF with preserved LVEF and/or advanced renal failure.

The difference in weight loss achieved through treatment with HSS + F is comparable to that demonstrated in previous studies<sup>[16,18,19,21-23,29,30]</sup>. Among these studies, the difference between the average in weight loss in the group treated with HSS + F compared to the group treated with intravenous furosemide alone ranged from 0.3-5.6 kg<sup>[21,30]</sup>. Because patients generally had some weight loss with the treatment with intravenous furosemide alone before starting treatment with HSS + F, it is possible that we have underestimated the weight loss due to HSS + F that could have been achieved without the prior use of intravenous furosemide alone.

We were unable to demonstrate a statistically significant difference in terms of creatinine, although it tended to decrease with the experimental treatment while the trend was reversed with the standard treatment. It has been previously shown an increase in

**Table 3** Weight loss and creatinine change per day of treatment in the impasse subgroup (*n* = 15)

Variable	mean ± SD	95%CI	P value
Weight loss (kg/d)			
Standard treatment	0.25 ± 0.64	(-0.04, 0.58)	
Experimental treatment	-1.20 ± 1.30	(-1.89, -0.57)	
Standard-experimental difference	1.45 ± 1.65	(0.54, 2.36)	0.0026
Change in creatinine (μmol/L per day)			
Standard treatment	7.33 ± 8.65	(3.01, 11.70)	
Experimental treatment	-3.79 ± 11.34	(-10.41, 1.63)	
Standard-experimental difference	11.13 ± 13.29	(3.77, 18.49)	0.008

creatinine among those treated with intravenous furosemide alone, while there is either a decrease in creatinine in patients treated with HSS + F<sup>[16,18,22,23]</sup> or a mild increase that is less than furosemide alone<sup>[19,21,30]</sup>. It is noteworthy to be outlined that the lack of statistical significant in creatinine levels may be explained in part by the inclusion of patients with advanced renal failure. Indeed, Engelmeier *et al.*<sup>[29]</sup> recruited patients with advanced renal failure (eGFR < 40 mL/min) and did not demonstrate a significant advantage of using HSS for the prevention of worsening renal function. Moreover, another study showed that HSS affords a protective role in the deterioration of renal function induced by loop diuretics, but does not exert a substantial protective effect in patients with ADHF who have pre-existing advanced renal failure and exhibiting a mean creatinine  $\geq 194$  μmol/L<sup>[15]</sup>. However, in our study, the renal function of many patients worsened during treatment with intravenous furosemide alone, so the change in creatinine during treatment with HSS + F could be a reflection of the previous treatment.

Treatment with HSS + F was well tolerated and its safety profile was reassuring as demonstrated in previous studies<sup>[18,24]</sup>. Of note, although we did not adjust the Na concentration in the HSS depending on the patient's serum Na as done in most studies, there were no severe electrolyte disturbances, except in one patient who had an increase in serum Na of 8 mmol/L within 24 h, but without any neurological symptoms or further consequences. Our results indicate that serum Na levels should be monitored, but adjusting the tonicity of the HSS based on the serum Na level may not be necessary. This facilitates the administration of HSS and reduces the risk of errors.

The result for the impasse subgroup, with few available treatment options, is of particular interest. Those patients, who increased their weight and creatinine while treated with intravenous furosemide alone, had benefited from the therapy in terms of weight loss and renal function.

The use of parenteral inotropes in a number of patients hospitalized for HF is potentially deleterious and requires tighter monitoring<sup>[31]</sup>. Moreover, the treatment of advanced ADHF by ultrafiltration or intravenous inotropes is not associated with a better prognosis and is limited

by the cost and availability<sup>[11-14]</sup>. Therefore, according to some studies<sup>[19,30]</sup>, simultaneous administration of appropriate doses of HSS during treatment with intravenous diuretics reduce diuretic resistance, which in fact, is the phenomenon of a decrease in the natriuretic response and thus, requires the use of further increasing doses of diuretics that often results in the deterioration of renal function<sup>[3]</sup>. Hence, the administration of small intravenous boluses of HSS associated with intravenous furosemide is a valid and inexpensive therapeutic option.

### Limitations

The main limitation of this study lies with the fact of a small sample size and even prospective, the non-randomized nature of the study. Therefore, the fact that certain clinical variables that appeared to account more frequently in some group but finally did not reach statistical significance were related to the small sample size. Patients were compared to themselves under the standard and experimental treatments, and the latter being influenced by the previous one. In addition, since the standard treatment was at the discretion of the clinician, the doses of furosemide, the doses of other drugs and the use of thoracentesis or paracentesis were not the same for both treatments. Thus, confirming these results in a larger series of randomized patients might have a high impact on patient selection and clinical decision-making in this high-risk group of patients.

In conclusion, the results of this study support the effectiveness of HSS + F on weight loss. The safety profile, particularly with regard to renal function, leads us to believe that HSS + F may be a valuable option for those patients presenting with ADHF who do not respond to conventional treatment with intravenous furosemide alone.

## COMMENTS

### Background

Compared to the administration of high doses of furosemide monotherapy, the concomitant use of hypertonic saline solution (HSS + F) has shown, in some single-centre studies, clinical benefits and a good safety profile in patients with acute decompensated heart failure (ADHF).

### Research frontiers

Patients can develop resistance to diuretics and congestive symptoms may persist despite treatment with high doses of furosemide.

### Innovations and breakthroughs

This study supports the effectiveness of HSS + F on weight loss in patients with ADHF.

### Applications

The safety profile, particularly regarding renal function, leads us to believe that HSS + F may be a valuable option for those patients presenting with ADHF who do not respond to conventional treatment with intravenous furosemide alone.

### Terminology

This study aims to test the safety and effectiveness of HSS + F as a strategy for

weight loss and prevention of further deterioration of renal function.

### Peer-review

This is a well-written manuscript about the treatment of severe acute heart failure.

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## Observational Study

# Estimating pressure gradients by auscultation: How technology (echocardiography) can help improve clinical skills

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**Conflict-of-interest statement:** We report no conflicts of interest, real or perceived, financial or otherwise.

**Data sharing statement:** Dataset is available from the corresponding author at [colin.phoon@nyumc.org](mailto:colin.phoon@nyumc.org). No additional data are available.

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## Abstract

### AIM

To extend our previously-published experience in estimating pressure gradients (PG) *via* physical examination in a large patient cohort.

### METHODS

From January 1, 1997 through December 31, 2009, an attending pediatric cardiologist compared clinical examination (EXAM) with Doppler-echo (ECHO), in 1193 patients with pulmonic stenosis (PS, including tetralogy of Fallot), aortic stenosis (AS), and ventricular septal defect (VSD). EXAM PG estimates were based primarily on a murmur's pitch, grade, and length. ECHO peak instantaneous PG was derived from the modified Bernoulli equation. Patients were 0-38.4 years old (median 4.8).

### RESULTS

For all patients, EXAM correlated highly with ECHO: ECHO = 0.99 (EXAM) + 3.2 mmHg;  $r = +0.89$ ;  $P < 0.0001$ . Agreement was excellent (mean difference =  $-2.9 \pm 16.1$  mmHg). In 78% of all patients, agreement between EXAM and ECHO was within 15 mmHg and within 5 mmHg in 45%. Clinical estimates of PS PG were more accurate than of AS and VSD. A palpable precordial thrill and increasing loudness of the murmur predicted higher

gradients ( $P < 0.0001$ ). Weight did not influence accuracy. A learning curve was evident, such that the most recent quartile of patients showed  $ECHO = 1.01 (EXAM) + 1.9$ ,  $r = +0.92$ ,  $P < 0.0001$ ; during this time, the attending pediatric cardiologist had been  $> 10$  years in practice.

### CONCLUSION

Clinical examination can accurately estimate PG in PS, AS, or VSD. Continual correlation of clinical findings with echocardiography can lead to highly accurate diagnostic skills.

**Key words:** Physical examination; Ventricular septal defect; Clinical skills; Echocardiography; Aortic stenosis; Pulmonary stenosis

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**Core tip:** Knowing pressure gradients across valves, arteries, and ventricular septal defects is important to clinical management of patients. In a large cohort of patients, we have determined the high degree of accuracy of the physical examination against the benchmark Doppler echocardiography. We discuss this clinical approach in the context of clinical practice, technology, and healthcare costs.

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## INTRODUCTION

Strong clinical skills, including history-taking and physical diagnostic skills, remain an important part of patient evaluation - central to the practice of medicine. The clinical skills required for auscultation are especially important in childhood, when more than 50% of children have heart murmurs, most of which are benign<sup>[1,2]</sup>. In recent years however, there have been a decline in clinical examination skills and an increasing reliance on diagnostic testing<sup>[3-7]</sup>.

The gradual loss of emphasis on physical exam skills has several implications<sup>[8-11]</sup>. The physical exam is an integral part of the doctor-patient relationship, and can also garner otherwise unattainable observations and findings. Additionally, the information obtained from the physical exam can help delineate the need for further testing. Although there have been several initiatives to minimize wasteful testing by focus on clinical examination<sup>[12-14]</sup>, few groups have described specific and learnable techniques to do so.

In this follow-up to a small pilot study<sup>[15]</sup>, our objectives of this study were several-fold. We hoped

to further validate our technique of estimating peak pressure gradients through auscultation with a much larger cohort of patients. We also hoped to debunk the idea that the physical exam has a dwindling role in medicine; we believe its use in conjunction with technology can allow for a more accurate clinical assessment. We also hoped to determine the specific situations and characteristics associated with a more accurate physical exam, allowing others to learn this technique as well.

## MATERIALS AND METHODS

The methods are essentially as detailed in our previous report<sup>[15]</sup>. This study was approved by the Institutional Review Boards at NYU Langone Medical Center and Bellevue Hospital Center (both located in New York, NY, United States). Including our initial cohort of 151 patients<sup>[15]</sup>, a total of 1193 consecutive patients with pulmonary stenosis (PS,  $n = 563$ ), aortic stenosis (AS,  $n = 234$ ), or ventricular septal defect (VSD,  $n = 396$ ) were studied by both auscultation and Doppler echocardiography over a 13-year period between February 1997 and December 2009. Not all patients were diagnosed with these lesions at the visits; some were "first" visits, but the physical examination was characteristic for valvar stenosis or VSD, and therefore a clinical estimate of the pressure gradient could be made even before a diagnosis was established by echocardiography. All levels of PS (including tetralogy of Fallot) and AS, all types of VSDs, and residual lesions after surgical or transcatheter interventions were included. In our patient population, the AS seen was congenital, rheumatic, or postoperative, not the fibrocalcific AS seen in older patients. "Complex" AS or PS (as opposed to valvar AS or PS) denotes non-valvar stenosis, or multi-level stenosis; examples include the PS in patients with tetralogy of Fallot, subvalvular AS and supra-valvular AS. It has been standard clinical practice in our pediatric echocardiography laboratory for the author (CKLP), an attending echocardiographer, to examine every patient briefly as time permits; it is felt by at least some echocardiographers, including the author, that this preliminary examination (which may include palpation and auscultation, especially of the heart sounds and murmurs) improves the reliability of the echocardiographic study. This physical examination helps to assess the degree of clinical suspicion and to focus the requested echocardiogram. For lesions with pressure gradients, the author routinely estimates a pressure gradient (see below) before the echocardiographic study. It should be noted this study was started (1997) only 1.5 years following the completion of clinical fellowship training by CKLP; therefore, at the completion of data acquisition (2009), 13.5 years had elapsed since completion of training.

The auscultatory pressure gradient was estimated by an "auscultatory scale" based predominantly on

**Table 1 Summary table of key findings for pulmonary stenosis, aortic stenosis, and ventricular septal defect**

Lesion	<i>n</i>	Mean gradient (mmHg)	Agreement to: ≤ 15 mmHg	≤ 10 mmHg	≤ 5 mmHg	<i>r</i>
Pulmonary stenosis						
PS (all)	563	42 ± 28	82%	70%	49%	0.85
Valvar PS	313	36 ± 22	89%	77%	56%	0.85
Complex PS	250	49 ± 32	72%	61%	40%	0.84
PVR	81	48 ± 25	84%	65%	42%	0.86
Aortic stenosis						
AS (all)	234	38 ± 24	81%	71%	49%	0.8
Valvar AS	112	42 ± 24	77%	68%	46%	0.76
Complex AS	122	34 ± 23	85%	75%	52%	0.85
AVR	34	46 ± 22	71%	65%	38%	0.71
Ventricular septal defect						
VSD	396	83 ± 31	70%	60%	36%	0.82

“Complex” AS or PS denotes non-valvar stenosis or multi-level stenosis, such as the PS observed in patients with tetralogy of Fallot. AS: Aortic stenosis; AVR: Aortic valve replacement; CHD: Congenital heart defects; PS: Pulmonary stenosis; PVR: Pulmonary valve replacement; VSD: Ventricular septal defect.

a murmur’s perceived predominant frequencies and frequency spread<sup>[15,16]</sup>. A stethoscope is inched around the chest until the highest frequencies of a murmur are heard. These frequencies are then used to estimate the pressure gradient. As the examiner continued to gain clinical experience, other components of auscultation were incorporated into the clinical estimate of the pressure gradients, including murmur loudness and length. Short murmurs generally comprised < 50% of systole, medium-length 50% to < 100% of systole with a crescendo-decrescendo quality, and long/holosystolic 100% of systole. Gradients were estimated in 5 mmHg range increments (for example, 5-10 mmHg or 25-30 mmHg) and then recorded as a midpoint value [5-10 (= 8 mmHg), 25-30 (= 28 mmHg), etc.]. In the remainder of this article, the terms “auscultation” and “auscultatory gradient” will refer to this technique of assessing the frequency composition of a murmur unless otherwise specified.

To avoid bias, the auscultatory gradient was recorded before Doppler echocardiography, and the Doppler examination was performed by a pediatric cardiac sonographer who was unaware of the auscultatory estimate. Echocardiograms performed solely by the author were excluded. In standard fashion, the Doppler beam was aligned as parallel as possible with the blood flow jet, without angle correction, interrogating for the maximal flow velocity from multiple views. The peak instantaneous Doppler pressure gradient was calculated with the modified Bernoulli equation. Any perceived inconsistencies between the auscultatory gradient and the echocardiographic results were resolved with further imaging.

Ideally, patients should be in a calm resting state for both the auscultatory examination and the echocardiogram because changes in activity level will change the cardiac output and therefore flow characteristics, including gradients. Because we do not routinely use conscious sedation, we examined patients in as calm a state as possible, recognizing that

variability in the resting state will introduce variability into our assessments.

Age, weight, diagnoses, and history of interventions were obtained from the patient reports.

The relationship between the auscultatory and Doppler pressure gradients was assessed by simple linear regression. Agreement was assessed by Bland-Altman analysis<sup>[17]</sup>. Results are expressed as mean ± SD. Differences were analyzed with a 2-tailed Student *t* test. Comparison of categorical variables was performed with chi-square analysis or Fisher’s exact test. Statistical significance was set at *P* < 0.05.

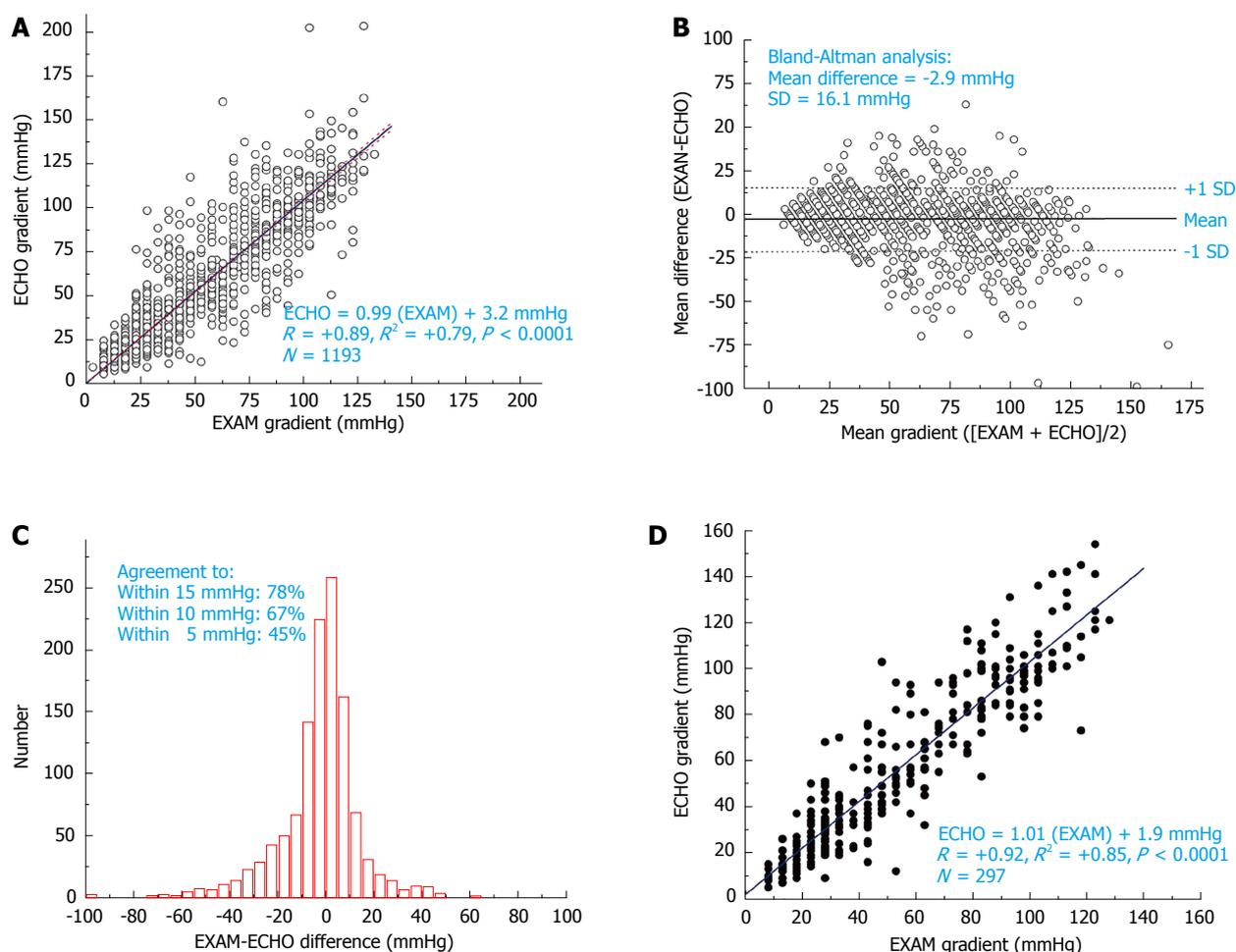
## RESULTS

### Patient demographics

Patients were 0-38.4 years old (mean 6.8 years, median 4.8), weighing 0.83-129 kg (mean 26.8 kg, median 18.2). There were 339 patients between 0-1 years of age (infants); 270 patients > 1 year-5 years (toddlers and young children); 311 patients between > 5 years-12 years (school-age children); 200 patients between 12-18 years (adolescents); and 73 patients older than 18 years (adults).

### Accuracy and correlations of various congenital cardiac conditions

For all patients, auscultation correlated highly with echocardiography: ECHO= 0.99 (AUSC) + 3.2 mmHg; *r* = +0.89 (*r*<sup>2</sup> = +0.79); *P* < 0.0001 (Figure 1A). Agreement was excellent [mean difference between clinical exam and echo = -2.9 ± 16.1 mmHg (SD), also as seen in the Bland-Altman analysis, Figure 1B]. In 78% of all patients, agreement between auscultation and echocardiography was within 15 mm Hg; in 67%, within 10 mmHg; and in 45%, within 5 mmHg (Figure 1C). Clinical estimates of PS pressure gradients were more accurate than of AS and VSD (Table 1). Valvar PS appeared to be more accurately estimated than other lesions, and VSD showed the worst agreement overall.



**Figure 1 Accuracy and correlations of various congenital cardiac conditions.** A: Regression plot of all patients; B: Bland-Altman plot; C: Histogram displaying spread between the Doppler and physical examination gradients, and the agreement between Doppler and physical examination to within 15, 10, and 5 mmHg; D: Regression plot of most recent quartile of patients.

A learning curve was evident. Overall agreement and correlation in the original published cohort of 151 patients [ $ECHO = 0.99 (AUSC) + 7.12$ ,  $r = +0.84$  ( $r^2 = +0.71$ )] were worse (Phoon 2001); the most recent quartile of patients showed  $ECHO = 1.01 (AUSC) + 1.9$ ,  $r = +0.92$  ( $r^2 = +0.85$ ),  $P < 0.0001$  ( $n = 297$ ) (Figure 1D). The initial cohort<sup>[15]</sup> corresponded to a time period from early 1997 through mid-1998, while the most recent quartile of data corresponded to a time period from mid-2007 through end of 2009; thus, there was a 10-year difference in clinical experience.

**Correlates with patient factors affecting accuracy**

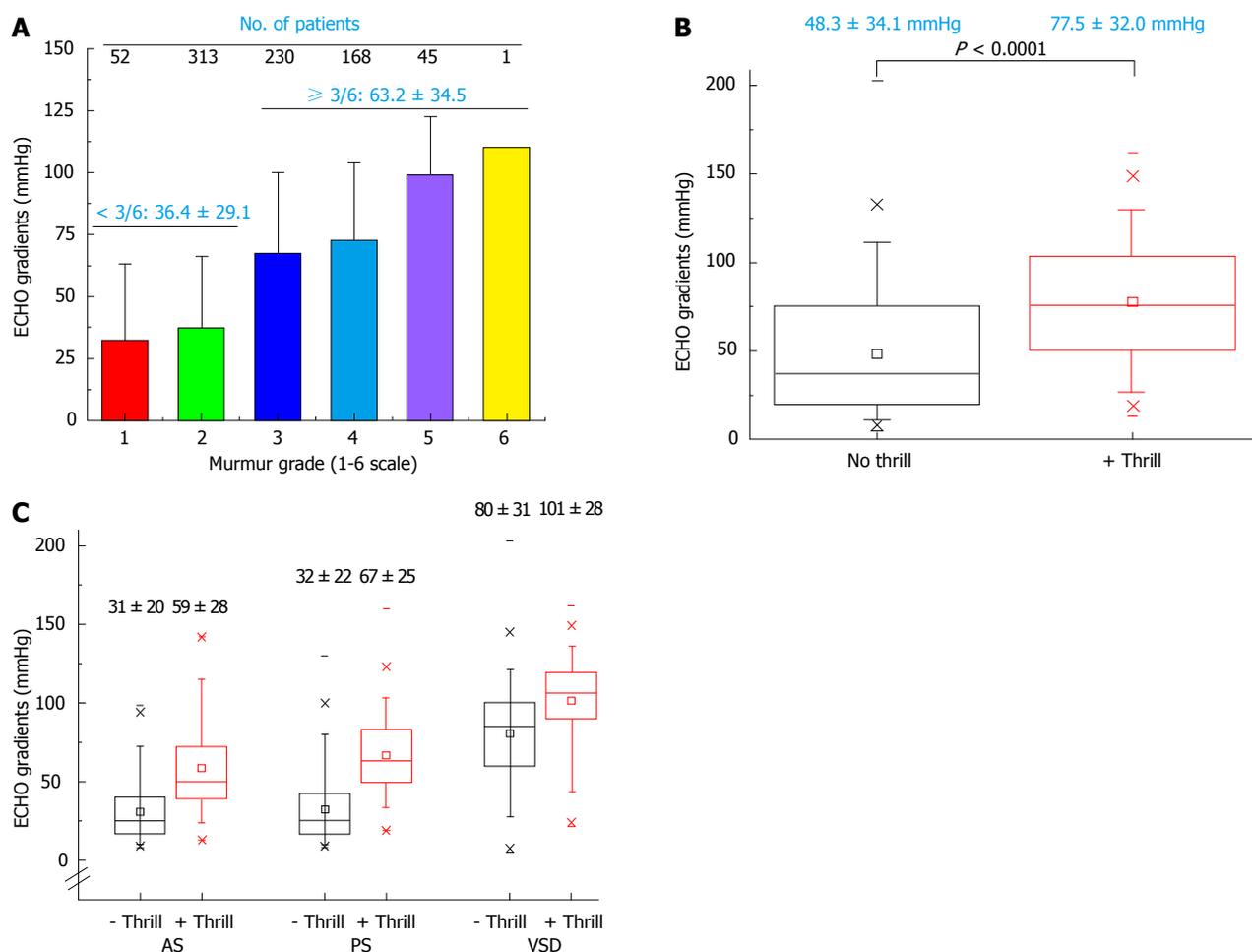
Increasing loudness of the murmur (standard 1-6 grade scale) predicted higher gradients ( $r = +0.54$ ,  $P < 0.0001$ ), with the largest gap occurring between grades 2 (mean PG:  $36 \pm 29$  mmHg) and 3 (mean PG:  $63 \pm 35$  mmHg) (Figure 2A). Similarly and as expected, a palpable precordial thrill predicted significantly higher gradients [all  $P < 0.0001$ : PS:  $32 \pm 22$  mmHg (no thrill) vs  $67 \pm 25$  (+thrill); AS:  $31 \pm 20$  vs  $59 \pm 29$ ; VSD:  $80 \pm 31$  vs  $101 \pm 28$ ] (Figure 2B, C). Despite the highly significant differences in patients

with and without a palpable precordial thrill, there was considerable overlap in the pressure gradients. Possible influencing factors are shown in Table 2. Heavier weight and prior surgery did not appear to influence accuracy. Infants and young toddlers appeared to be less accurately assessed. Although a previous echocardiogram (and therefore possibly knowledge of the previous gradient) exhibited a better correlation, the correlation coefficient even during a “first” visit was very high (Table 2).

In several cases, the physical examination “trumped” the echocardiogram, although this represented a small percentage of all patients. Nearly all were VSD’s, for which Doppler echocardiography underestimated the predicted peak gradient due to a suboptimal Doppler incident angle (Table 3). In such cases, the VSD gradient alone would have predicted the presence of pulmonary hypertension.

**DISCUSSION**

This large dataset extends our previous observations and confirms that physical examination, relying mainly



**Figure 2** Correlates with patient factors affecting accuracy. A: Loudness of heart murmur (standard grade system, 1-6) plotted against peak Doppler (“ECHO”) gradient; B: Box-and-whiskers plot of Doppler peak gradients in the absence and presence of a palpable thrill, all patients; C: Box-and-whiskers plots of specific congenital lesions (aortic stenosis, pulmonic stenosis, ventricular septal defect), thrill absent vs thrill present.

on auscultation, can be very accurate in determining pressure gradients. We emphasize that our purpose was not to diagnose specific conditions *de novo*, but to evaluate pressure gradients clinically. Other studies have previously demonstrated that the cardiac physical exam, specifically auscultation, can accurately distinguish benign from pathologic murmurs<sup>[15,18-24]</sup>. Although these studies look at auscultation in general, they do not specifically analyze pressure gradients. We have now in more detail analyzed some of those aspects of clinical auscultation, as well as patient characteristics, which impact the accuracy of the physical examination. A key finding in this study is how technology - in this case, echocardiography - can help improve clinical skills, presumably by providing feedback to the examiner.

#### Comparison of different lesions: PS, AS, VSD

Pressure gradients have been examined in dogs, and have been found to both correlate with echocardiographic findings<sup>[25-28]</sup> and be associated with severity of disease<sup>[29]</sup>. These studies corroborate the validity of our findings, and we further show its applicability to human subjects. Several groups have

shown that examination can diagnose both AS and PS successfully<sup>[30-36]</sup>. Diagnosis of VSDs by clinical exam is also accurate but can be imperfect for major VSDs<sup>[37]</sup>. Our study takes these analyses further by laying out a specific auscultatory technique to assess heart murmurs, and by continually correlating clinical findings with echocardiographic data to improve accuracy. We demonstrate that auscultation has the greatest accuracy in predicting pressure gradients in PS, and is still accurate but less so in VSD. We speculate that the murmur of PS is consistently directed in a similar direction in nearly all patients, whereas VSD jets would exhibit far more variability that may change their auscultatory characteristics. We additionally experienced several cases in which echocardiography underestimated the severity of the murmur, or missed the etiology of a murmur completely, demonstrating the significance of auscultation in a clinical exam.

#### When to be careful: Accuracy is affected by certain patient variables

Several auscultatory characteristics have been identified to predict pathologic disease, such as holosystolic timing, harshness, grade 3 or more, or palpable

**Table 2 Summary table of variables that might affect accuracy of clinical estimates of gradients**

Variable	n	Mean gradient (mmHg)	Agreement to: ≤ 15 mmHg	≤ 10 mmHg	≤ 5 mmHg	r
Weight						
≤ 10 kg	367	61 ± 32	71%	61%	42%	+0.81
> 10 to 20 kg	270	57 ± 36	79%	69%	46%	+0.92
> 20 to 40 kg	236	53 ± 38	81%	71%	48%	+0.91
> 40 to 70 kg	237	49 ± 34	81%	67%	42%	+0.91
> 70 kg	82	45 ± 35	85%	74%	48%	+0.88
Age						
< 2 yr	414	60 ± 32	71%	62%	42%	+0.83
≥ 2 yr	779	52 ± 36	81%	70%	46%	+0.91
Prior echo?						
No prior	321	61 ± 36	72%	64%	43%	+0.85
+Prior	872	53 ± 35	79%	68%	45%	+0.90
Operative status (all CHD)						
No operative	688	65 ± 37	74%	64%	43%	+0.89
Post-operative	505	42 ± 27	82%	70%	46%	+0.87

CHD: Congenital heart defects.

**Table 3 Examples of cases when physical examination “trumped” echocardiography or echocardiography presented misleading data**

Case	Age (yr)	Lesion	Clinical Gradient	DOPP Gradient	Comment
1	6.7	Supravalvar PS s/p repair of TOF with homograft from RV to PA	63	24	Homograft poorly visualized; tricuspid regurgitation jet predicted a systolic RV pressure of 66 mmHg plus the right atrial v-wave, so the PS gradient was significantly underestimated by DOPP
2	6.9	VSD, s/p repair of TOF	70	66	Prior echocardiograms did not visualize VSD; exam led to finding of a tiny residual VSD
3	10.8	VSD	88	63	Poor DOPP incident angle predicted pulmonary hypertension
4	0.005	VSD	68	NA	VSD was so tiny and anterior, a jet could not be obtained for a DOPP gradient
5	4.3	VSD	73	61	BP 104/50; poor DOPP incident angle predicted pulmonary hypertension
6	0.01	VSD	88	48	Technician obtained initial VSD DOPP gradient of 28 mmHg; exam prompted a search for a better DOPP angle
7	2.8	VSD	83	55	Poor DOPP incident angle predicted pulmonary hypertension; tricuspid regurgitation jet predicted normal PA pressures
8	5.5	VSD, s/p repair	98	62	Poor DOPP incident angle predicted pulmonary hypertension; tricuspid and pulmonary regurgitation jets predicted normal PA pressures
9	3.8	VSD	73	53	Poor DOPP incident angle predicted pulmonary hypertension; tricuspid regurgitation jet predicted normal PA pressures
10	15.4	VSD, Shone’s complex with minimal LV outflow tract obstruction	93	63	Poor DOPP incident angle predicted pulmonary hypertension
11	15.7	VSD	118	73	Poor DOPP incident angle predicted pulmonary hypertension, even though the VSD was 2.8 mm in diameter; tricuspid and pulmonary regurgitation jets predicted normal PA pressures

BP: Blood pressure; DOPP: Doppler echocardiography; LV: Left ventricular; PA: Pulmonary artery; PS: Pulmonary stenosis; RV: Right ventricular; TOF: Tetralogy of Fallot; VSD: Ventricular septal defect.

precordial thrill<sup>[24,38]</sup>. We confirmed such factors can be used to estimate pressure gradients clinically, specifically the loudness of the murmur and the presence of a palpable thrill. Somewhat surprisingly, neither heavier weight nor prior surgery worsened clinical accuracy, even though we had wondered if adipose or scar tissue would impact the auscultated frequency spectrum of heart murmurs.

We believe several teaching points can be made from our data. Although the data exhibit much overlap, the presence of a precordial thrill may help differentiate higher gradients in PS and AS, although this appears to be much less useful with VSD’s. For both PS and AS,

the presence of a thrill is likely to indicate a pressure gradient of > 40-45 mmHg. Infants and toddlers also are more difficult to assess clinically.

**Philosophical and practical issues**

Our study raises the question of whether clinical skills such as these are important in the current era of medical practice. It is debatable or even unlikely a study such as this will impact use of technology or healthcare costs significantly. Nevertheless, it is our impression that: (1) some cases were diagnosed based primarily on clinical findings, and echocardiography played a limited or initially misleading role; and (2)

our data exposes some strengths and weaknesses of the cardiac physical examination with regards to estimating pressure gradients. We and others continue to believe the gradual loss of emphasis on physical exam skills has several implications.

The physical exam is a central part of the doctor-patient relationship. The intimate contact of a physical exam not only gives the patient a sense of comfort and confidence in their physician, but can itself help the patient heal<sup>[10,11,39,40]</sup>. Besides the desired dynamic bedside skills help to create, there is also a great deal of information obtained through the physical exam that might otherwise be lost<sup>[11,41]</sup>. Many clinical signs and symptoms cannot be classified by technology alone, and can only be appreciated with a thorough physical exam. Fred discussed the implications of over-reliance on CT scans in the diagnosis of patients, including delays in treatment by waiting for a CT scan to confirm a diagnosis that can be made by physical examination alone<sup>[9]</sup>. McGee described several instances where the physical exam bested technological testing, including reactive arthritis and pericarditis<sup>[42]</sup>.

However, as Verghese *et al.*<sup>[39]</sup> argue, it is not a fight of physical exam skills vs technology, but the attempt to merge these two to produce the optimal comprehensive exam. Ippisch *et al.*<sup>[43]</sup> demonstrated this with regards to cardiology specifically. Neither the physical exam nor a hand-carried echocardiography machine were as accurate as the two used together<sup>[6]</sup>. We conclude that technology does not erode physical exam skills but in fact improves both bedside skills and clinical judgment. Technology and clinical examination can and should go hand-in-hand for optimal patient care. "It has to make sense"<sup>[16]</sup>.

### **Balancing exam with technology**

Recently, several groups have discussed the development of technologies that can assist physicians in analyzing heart murmurs, including computer-assisted auscultation and artificial neural networks<sup>[44,45]</sup>. Heart murmurs are complex sounds that can nevertheless be analyzed by a simple frequency analysis, which can be done either with advanced technologies or with a trained ear and a stethoscope.

It has been shown that physicians listening to recorded heart sounds can accurately distinguish innocent from pathologic murmurs<sup>[46-48]</sup>. Therefore, telecardiology (tele-auscultation) may find potential use in areas where access to echocardiography is limited. Many rural areas, both in the United States and around the world, do not have either an echocardiography machine or a trained echocardiographer. Doctors trained to auscultate for peak pressures could feasibly receive digital heart sounds from remote areas, and improve remote diagnostic capabilities.

### **Cost considerations**

As physicians move away from their stethoscopes,

they increasingly rely on diagnostic testing that may be unnecessary and is often uninformed, and certainly costly. Unfortunately in our study, it is impossible to know how many patients could have avoided an echocardiogram, based purely on auscultatory estimation of a pressure gradient; other clinical questions may also prompt an echocardiogram. Nevertheless, in response to the increasing impact of echocardiography on health care costs, the ACCF and the ASE prepared a 2011 revision on appropriate use criteria (AUC) for echocardiography<sup>[14]</sup>. More recently AUC has also been described for pediatric echocardiography, specifically to determine the need for TTE as an initial diagnostic tool in the outpatient setting<sup>[13]</sup>. The AUC are not absolute, but should be applied to clinical exams to determine when an echocardiogram is appropriate. We believe that an increased focus on auscultation would aid in this.

### **Limitations**

This technique has been proven rigorously for one cardiologist only. The study period corresponded to this cardiologist's early and middle career. Of note, in our original study, we validated the auscultatory scale using a senior pediatric cardiology fellow. In our anecdotal experience, several other individuals have mastered this technique to some degree. Similar to our findings, others have shown that attention to clinical examination skills can allow residents and students to improve their physical exam skills and diagnoses<sup>[1]</sup>. Moreover, similar findings in animal studies as cited above further validate our approach<sup>[25-29]</sup>.

This study was performed primarily in children but included heavier children as well as some adults. Still, this data may not be applicable to adults with calcific valve disease or other pathologies not addressed in this study. In addition, pressure gradients depend on flow, and the true severity of a valvar or arterial obstruction may not be reliably assessed when there is myocardial failure. For instance, severe AS in adults may present with only a short, unimpressive midsystolic murmur or even no murmur at all. Finally, we did not test this technique for diastolic gradients.

### **Conclusions and future directions**

Physical examination can accurately estimate pressure gradients in most patients with PS, AS, or VSD. An accurate physical examination may provide data that may be missed by technology, contribute to the patient-doctor relationship, and has a role for the cost-conscious physician. And it may prove useful in areas with limited access to technological resources. We do not propose that the physical exam should replace echocardiography, but believe that the use of the two in conjunction allows for the optimal patient assessment. Contrary to the belief that technology erodes clinical skills, continual correlation of clinical findings with a technological "gold standard" such as echocardiography can lead to highly accurate

diagnostic skills and improved clinical judgment, thereby enhancing clinical skills training and further substantiating the value of clinical examination.

## COMMENTS

### Background

Strong clinical skills, including physical examination skills, remain central to the practice of medicine. In recent years, there has been a much-decried decline in clinical examination skills. The authors had performed a small pilot study over 15 years ago with 151 patients that indicated that physical examination can be very accurate in determining pressure gradients across stenosis or septal defects.

### Research frontiers

Very little research is being performed to help clinicians improve clinical skills, or to determine the strengths and/or weaknesses of clinical examination. Moreover, very little is known about how technology such as imaging can help clinicians improve their physical examination skills.

### Innovations and breakthroughs

In pediatric cardiology, physical examination is felt to be very accurate in determining normal from abnormal heart murmurs. What is not known, however, is whether the physical examination can accurately predict pressure gradients in aortic stenosis, pulmonary stenosis, and ventricular septal defect. Knowledge of such pressure gradients helps guide clinical management. Almost no work has been done on this area.

### Applications

Honing physical examination skills such as being able to predict pressure gradients has two potential benefits: (1) The clinician may rely less on technology and therefore may reduce the use of expensive testing (imaging); and (2) The clinician may use the physical examination findings in conjunction with testing (imaging) to come to a better overall evaluation of the patient.

### Terminology

Aortic stenosis (AS): Anatomical obstruction to blood flow at any level, including subaortic stenosis, valvar aortic stenosis, supra-aortic stenosis (narrowing of the ascending aorta). In this project, aortic stenosis did not include coarctation of the aorta; Pulmonary stenosis (PS): Anatomical obstruction to blood flow at any level, including subpulmonary or infundibular stenosis, valvar stenosis, and supra-aortic stenosis (narrowing of the main pulmonary artery). For the purposes of this project, the authors did not include stenoses of the peripheral branch pulmonary arteries; Ventricular septal defect (VSD): the authors included VSD's at any site, including perimembranous, muscular, and supracristal (subpulmonary) VSD's; Doppler echocardiography, peak instantaneous pressure gradient: For aortic or pulmonary stenosis, there will be a higher-pressure site (proximal to the obstruction) and a lower-pressure site (distal to the obstruction). For ventricular septal defects, the higher-pressure site is generally the left ventricle, while the lower-pressure site is the right ventricle. The difference in pressures ( $\Delta P$ ) between the two sites in the heart or arteries can be estimated using the Doppler principle on echocardiography systems; most commonly, one uses the modified Bernoulli equation,  $\Delta P = 4V^2$ , where V is the maximal velocity across the region of interest (stenosis or VSD) as acquired from the Doppler ultrasound transducer.

### Peer-review

This is a well-written and interesting paper demonstrating how clinical auscultation in expert hands may approximate echo results. The results are important in an era of considerable expenses in technology and of looking down on clinical examination.

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## Observational Study

**Coronary angiography findings in cardiac arrest patients with non-diagnostic post-resuscitation electrocardiogram: A comparison of shockable and non-shockable initial rhythms**

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Pedro Martínez-Losas, Pablo Salinas, Carlos Ferrera, María Teresa Nogales-Romo, Francisco Noriega, María Del Trigo, Iván Javier Núñez-Gil, Luis Nombela-Franco, Nieves Gonzalo, Pilar Jiménez-Quevedo, Javier Escaned, Antonio Fernández-Ortiz, Carlos Macaya, Ana Viana-Tejedor, Interventional Cardiology and Coronary Care Unit, Cardiovascular Institute, Hospital Universitario Clínico San Carlos, 28040 Madrid, Spain

**Author contributions:** Martínez-Losas P, Salinas P, Ferrera C and Nogales-Romo MT contributed equally to this work; Salinas P and Ferrera C designed the study; Martínez-Losas P, Nogales-Romo MT, Salinas P and Ferrera C participated in the follow up; all authors participated in clinical and/or interventional care, prospective data acquisition and realized a critical revision of the manuscript; Martínez Losas P, Salinas P, Ferrera C, Nogales-Romo MT and Viana-Tejedor A revised the final version.

**Institutional review board statement:** The institutional ethics review committee approved the retrospective anonymous analysis of the patients, in accordance with European guidelines for good clinical practice.

**Informed consent statement:** All patients' relatives signed informed consents for the clinical procedures performed during admission. No special tests were done for this study. Therefore, no specific informed consent was obtained for this anonymous observational study.

**Conflict-of-interest statement:** There are no conflicts of interest to report.

**Data sharing statement:** Technical details and statistical methods are available from the corresponding author at [salinas.pablo@gmail.com](mailto:salinas.pablo@gmail.com).

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**Abstract****AIM**

To investigate the impact of coronary artery disease in a cohort of patients resuscitated from cardiac arrest with non-diagnostic electrocardiogram.

**METHODS**

From March 2004 to February 2016, 203 consecutive patients resuscitated from in or out-of-hospital sudden cardiac arrest and non-diagnostic post-resuscitation electrocardiogram (defined as ST segment elevation or pre-sumably new left bundle branch block) who

underwent invasive coronary angiogram during hospitalization were included. For purpose of analysis and comparison, patients were classified in two groups: Initial shockable rhythm (ventricular tachycardia or ventricular fibrillation;  $n = 148$ , 72.9%) and initial non-shockable rhythm ( $n = 55$ , 27.1%). Baseline characteristics, coronary angiogram findings including Syntax Score and long-term survival rates were compared.

## RESULTS

Sudden cardiac arrest was witnessed in 95.2% of cases, 66.7% were out-of-hospital patients and 72.4% were male. There were no significant differences in baseline characteristics between groups except for higher mean age (68.1 years vs 61 years,  $P = 0.001$ ) in the non-shockable rhythm group. Overall 5-year mortality of the resuscitated patients was 37.4%. Patients with non-shockable rhythms had higher mortality (60% vs 29.1%,  $P < 0.001$ ) and a worst neurological status at hospital discharge based on cerebral performance category score (CPC 1-2: 32.7% vs 53.4%,  $P = 0.02$ ). Although there were no significant differences in global burden of coronary artery disease defined by Syntax Score (mean Syntax Score: 10.2 vs 10.3,  $P = 0.96$ ) there was a trend towards a higher incidence of acute coronary lesions in patients with shockable rhythm (29.7% vs 16.4%,  $P = 0.054$ ). There was also a higher need for *ad-hoc* percutaneous coronary intervention in this group (21.9% vs 9.1%,  $P = 0.03$ ).

## CONCLUSION

Initial shockable group of patients had a trend towards higher incidence of acute coronary lesions and higher need of *ad-hoc* percutaneous intervention vs non-shockable group.

**Key words:** Sudden cardiac arrest; Electrocardiogram; Invasive coronary angiography; Percutaneous coronary intervention; Syntax score; Coronary artery disease

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**Core tip:** Coronary artery disease represents the most common cause of sudden cardiac arrest. Current resuscitation guidelines recommend emergency coronary angiography in patients with cardiac arrest and ST elevation or new left bundle branch block on post-resuscitation electrocardiogram. However, electrocardiogram findings may be a poor predictor of an acute coronary lesion in this context and nowadays, the benefit of early coronary angiography is still under debate in patients without ST elevation. In this study, we analyzed our single-center data of patients with cardiac arrest and non-diagnostic electrocardiogram to describe the burden of coronary artery disease and their prognosis depending on initial rhythm.

Noriega F, Del Trigo M, Núñez-Gil JJ, Nombela-Franco L, Gonzalo N, Jiménez-Quevedo P, Escaned J, Fernández-Ortiz A, Macaya C, Viana-Tejedor A. Coronary angiography findings in cardiac arrest patients with non-diagnostic post-resuscitation electrocardiogram: A comparison of shockable and non-shockable initial rhythms. *World J Cardiol* 2017; 9(8): 702-709 Available from: URL: <http://www.wjgnet.com/1949-8462/full/v9/i8/702.htm> DOI: <http://dx.doi.org/10.4330/wjc.v9.i8.702>

## INTRODUCTION

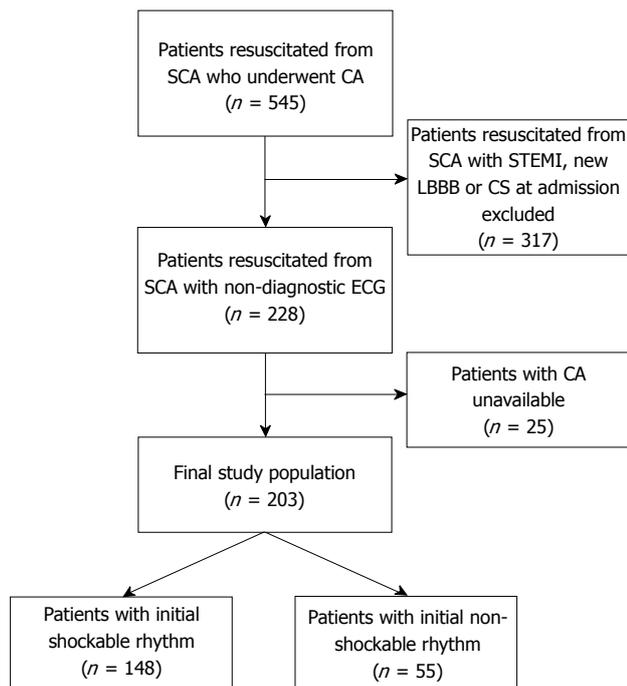
Sudden cardiac arrest (SCA) is one of the most common causes of death in the developed world, affecting nearly 560000 people annually in the United States. Although a majority of deaths occur during the initial resuscitation, a substantial proportion of cardiac arrest deaths occur in patients who have been initially successfully resuscitated after first medical contact. Despite the important advances in emergency medical services and post cardiac arrest syndrome care over the last decades, survival free from neurological deficit is still low<sup>[1]</sup>.

Coronary artery disease (CAD) represents the most common cause of SCA and current resuscitation guidelines recommend the performance of an emergency coronary angiography (CA) and appropriate percutaneous coronary interventions (PCI) in patients with SCA and ST segment elevation or presumably new left bundle branch block (LBBB) on post-resuscitation electrocardiogram (ECG). In patients without ST elevation after SCA but with suspected or with a high risk of cardiac origin, emergency CA is reasonable in selected situations (for example, electrically or hemodynamically unstable patients)<sup>[2,3]</sup>. Such "suspicion of cardiac origin" is not well defined and therefore the recommendation remains somewhat ambiguous.

Regarding the likelihood of a cardiac origin of the SCA, the ECG may be a poor predictor of acute coronary occlusion in resuscitated patients<sup>[4-7]</sup>. Also, a recent meta-analysis showed a high prevalence of significant CAD ranging from 59% to 71% in patients resuscitated from SCA without an obvious non-cardiac etiology<sup>[8]</sup>. Furthermore, pre-arrest symptoms reported in this setting are unreliable and dependent on the presence of by-standers. In summary, the suspicion of cardiac origin is largely subjective or uncertain for most patients. For these reasons, and without available randomized data, the justification for use of an early invasive strategy in survivors of SCA without an obvious non-cardiac cause of arrest is based on observational data<sup>[9-11]</sup>.

From a single-center registry of patients resuscitated from SCA undergoing CA, we present in this paper the results of a sub-analysis comparing patients with shockable and non-shockable initial rhythms<sup>[12]</sup>. The aim of this sub-analysis was to investigate the impact of CAD in a cohort of SCA patients with non-diagnostic

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**Figure 1 Patient flowchart.** CA: Coronary angiography; CS: Cardiogenic shock; ECG: Electrocardiogram; LBBB: Left bundle branch block; SCA: Sudden cardiac arrest.

ECG depending on initial rhythm.

## MATERIALS AND METHODS

### Study population

All patients recovered from in or out-of-hospital SCA and admitted to a tertiary care center with 24/7 emergent PCI availability that underwent invasive CA were extracted from a multipurpose database including data from interventional procedures, critical care unit and hospital admission.

From March 2004 to February 2016, 545 consecutive SCA patients were identified. For this study, we focused on patients without emergent indication for CA. Therefore, patients with ST segment elevation or presumably new LBBB on post-resuscitation ECG, or cardiogenic shock at admission were excluded ( $n = 317$ ). Of the remaining 228 patients, 25 had unavailable or incomplete CA films. Thus, our final study population was 203 patients. For the purpose of this sub-analysis, patients were classified into two groups depending on initial ECG: Shockable [ventricular tachycardia or ventricular fibrillation ( $n = 148$ , 72.9%)] and non-shockable rhythm ( $n = 55$ , 27.1%) (Figure 1).

Clinical and outcome data were collected from clinical record, patient's charts or telephone contact with patients or their relatives. Follow-up was completed up to 5-year after index admission.

### Cardiac catheterization

The indication and timing of CA in our study population was individualized for each patient based on treating

physician's criterion. CA was classified as early when performed  $< 24$  h after hospital admission or late when performed  $\geq 24$  h after admission. Two interventional cardiologist reviewed all CA blinded to original reports. The percentage diameter stenosis (DS%) was visually estimated for each lesion. Quantitative CA was used if discordances  $> 10\%$  were found between both investigators. Significant stenosis was defined as  $\geq 50$  DS%, severe stenosis when DS% was  $\geq 70\%$  and non-obstructive CAD when DS% was  $< 50\%$ . A normal coronary angiogram was defined as 0 DS% in all arteries with no other pathological findings. Culprit lesion was defined as the presence of an acute arterial occlusion (plaque rupture with occlusive thrombus) or an incomplete coronary artery occlusion in presence of complex lesion morphology as previously defined<sup>[13]</sup>. Chronic total occlusion (CTO) was defined as a Thrombolysis In Myocardial Infarction (TIMI) grade 0 flow for at least 3 mo of estimated duration. Estimation of occlusion duration was based on at least one of the following: Prior history of myocardial infarction in the target vessel territory, comparison with a previous angiogram, or the presence of collateral circulation or bridging collaterals. Critical stenosis was considered when DS% was  $\geq 90\%$  but  $< 100\%$  and there were no CTO features. Acute coronary lesion was defined as critical or culprit lesion for the purpose of this investigation. *Ad-hoc* PCI was defined if performed at the moment of the index CA at the operator's discretion. Procedural success was defined as complete restoration of antegrade blood flow (TIMI 3) and  $< 30\%$  residual diameter stenosis by visual assessment.

Burden of CAD was measured using the Synergy Between Percutaneous Coronary Intervention With Taxus And Cardiac Surgery (SYNTAX) Score and number of vessels with significant and/or severe stenosis. We calculated the Syntax Score for each patient, as previously reported<sup>[14,15]</sup>. If the patient had previous PCI we used residual Syntax score (rSS) defined as the SYNTAX score remaining after PCI. If the patient had previous coronary artery bypass graft (CABG) surgery we calculated the CABG-SYNTAX score proposed by Farooq *et al*<sup>[16]</sup>. Both rSS and CABG-SYNTAX score reflect the current burden of CAD (successfully revascularized segments are equalized to segments with CAD  $< 50\%$ , thus not incrementing SYNTAX score).

### Statistical analysis

Statistical analysis was performed using SPSS 21 (SPSS Inc, Illinois, Chicago, United States). Continuous variables are presented as mean and standard deviation. Categorical variables are expressed as frequency and percentage. In quantitative variables, the groups were compared using a two-tailed Student's *t*-test for independent samples. Categorical variables were compared with the  $\chi^2$  test. The Kaplan-Meier method was used to estimate the cumulative patient survival rates and log-rank test for comparison. All test were two

**Table 1** Baseline characteristics of study patients *n* (%)

	All patients ( <i>n</i> = 203)	Non-shockable rhythm ( <i>n</i> = 55)	Shockable rhythm ( <i>n</i> = 148)	<i>P</i> value
Age (mean ± SD)	62.9 ± 14	68.1 ± 13	61 ± 13.9	0.001
Male sex	147 (72.4)	36 (65.5)	111 (75)	0.176
Arterial hypertension	123 (60.6)	37 (67.3)	86 (58.1)	0.235
Diabetes mellitus	65 (32)	22 (40)	43 (29.1)	0.137
Dyslipidemia	80 (39.4)	26 (47.3)	54 (36.5)	0.162
Smoking	103 (50.7)	27 (49.1)	76 (51.4)	0.775
Peripheral vascular disease	23 (11.3)	7 (12.7)	16 (10.8)	0.702
Cerebrovascular disease	18 (8.9)	6 (10.9)	12 (8.1)	0.533
Prior MI	45 (22.2)	14 (25.5)	31 (20.9)	0.780
Prior PCI	35 (17.2)	10 (18.2)	25 (16.9)	0.829
Prior CABG	22 (10.8)	7 (12.7)	15 (10.1)	0.597
Out-of-hospital SCA	124 (66.7)	30 (58.8)	94 (69.6)	0.163
Time to ROSC	17.8 ± 12.7	14.8 ± 11.9	19 ± 12.9	0.122
Witnessed arrest	157 (95.2)	40 (93)	117 (95.9)	0.450
Coma status at admission	148 (84.6)	40 (88.9)	108 (83.1)	0.352
Cardiogenic shock	48 (23.6)	18 (32.7)	30 (20.3)	0.063
Therapeutic hypothermia	71 (41.8)	14 (32.6)	57 (44.9)	0.402

Values are given as mean ± SD or *n* (%). MI: Myocardial infarction; PCI: Percutaneous coronary intervention; CABG: Coronary artery bypass grafting; SCA: Sudden cardiac arrest; ROSC: Return of spontaneous circulation.

**Table 2** Angiographic characteristics *n* (%)

	All patients ( <i>n</i> = 203)	Non-shockable rhythm ( <i>n</i> = 55)	Shockable rhythm ( <i>n</i> = 148)	<i>P</i> value
Normal coronaries	71 (35)	20 (36.4)	51 (34.5)	0.800
Mean Syntax Score	10.3 ± 12.4	10.2 ± 13.6	10.3 ± 11.9	0.961
Any vessel with significant stenosis (DS ≥ 50%)	125 (61.6)	33 (60)	92 (62.2)	0.778
Significant stenosis				
None	79 (38.9)	22 (40)	57 (38.5)	0.710
One vessel	46 (22.7)	15 (27.3)	31 (20.9)	
Two vessels	40 (19.7)	9 (16.4)	31 (20.9)	
Three vessels	38 (18.7)	9 (16.4)	29 (19.6)	
Any vessel with severe stenosis (DS ≥ 70%)	111 (54.7)	28 (50.9)	83 (56.1)	0.480
Any CTO	60 (29.6)	14 (25.5)	46 (31.1)	0.388
Critical stenosis	51 (25.1)	9 (16.4)	42 (28.4)	0.079
Culprit lesion	25 (12.3)	4 (7.3)	21 (14.2)	0.173
Acute lesion	53 (26.1)	9 (16.4)	44 (29.7)	0.054
<i>Ad hoc</i> PCI	37 (18.2)	5 (9.1)	32 (21.6)	0.036

Values are given as mean ± SD or *n* (%). CTO: Chronic total occlusion; DS%: Percentage diameter stenosis; PCI: Percutaneous coronary intervention.

sided and  $P < 0.05$  was considered significant.

## RESULTS

### Baseline characteristics

Of 203 consecutive patients resuscitated from SCA with non-diagnostic ECG, 148 had initial shockable rhythm and 55 had non-shockable rhythm. Table 1 shows the baseline characteristics of the study cohort. There were no statistical differences between groups in baseline characteristics except for higher mean age in the initial non-shockable group (68.1 years vs 61 years,  $P = 0.001$ ).

### CA findings

Early CA was performed in 115 patients (56.9%). The most relevant angiography findings are reproduced in Table 2. Overall, mean value of Syntax Score

calculated was 10.30 with no statistical differences between groups (10.33 vs 10.23,  $P = 0.95$ ). There were also no differences ( $P = 0.71$ ) in the percentage of vessels with significant stenosis (0, 1, 2 or 3 vessels with  $\geq 50$  DS%). However, patients with initial shockable rhythm showed a trend towards a higher incidence of acute coronary lesions (29.7% vs 16.4%,  $P = 0.054$ ) and higher rate of *ad-hoc* PCI (21.9% vs 9.1%,  $P = 0.03$ ), mainly for left anterior descending artery lesions (45.9%).

The prognostic value of acute coronary lesions as defined by this study was assessed through a stratified Kaplan Meier analysis. Figure 2 shows Kaplan Meier curves for all cause 5-year survival depending on the finding of an acute coronary lesion. Patients with shockable rhythm and with acute coronary lesions had a non-significant increased mortality, whereas no significant differences or trends were found in the

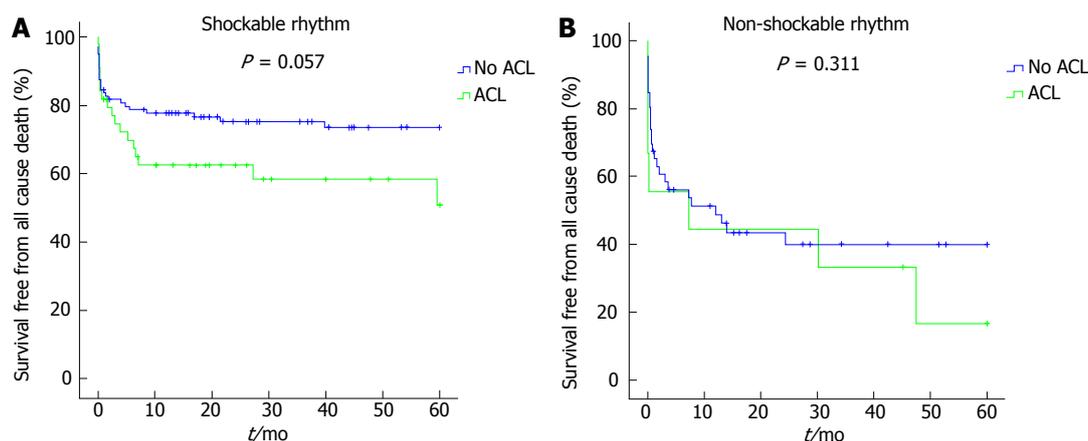


Figure 2 Kaplan Meier curves for all cause 5-year survival depending on the finding of an acute coronary lesion. ACL: Acute coronary lesion.

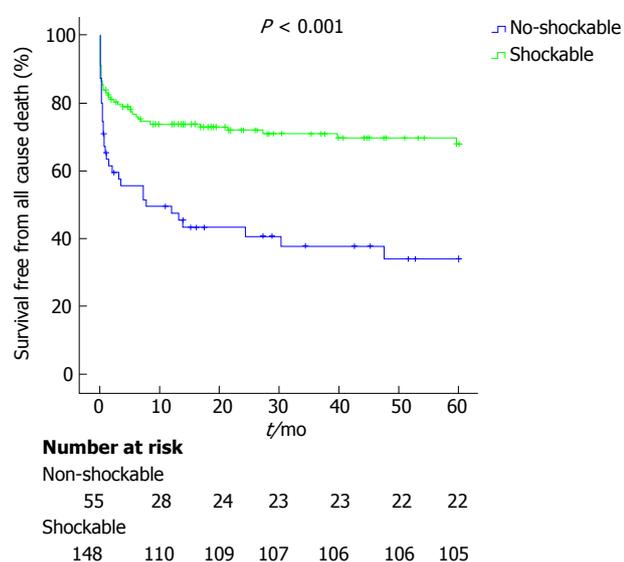


Figure 3 Kaplan-Meier curves for 5 years survival.

non-shockable group. Interestingly, in patients with shockable rhythm, those who underwent *ad hoc* PCI of the acute coronary lesions had a trend towards improved survival compared to patients with untreated acute coronary lesions (mean all-cause survival  $41.3 \pm 5.4$  mo vs  $29.7 \pm 6.9$  mo,  $P = 0.147$ ). However, in patients with initial non-shockable rhythm, *ad hoc* PCI did not improve survival rates ( $P = 0.948$ ).

### In-hospital and long-term survival

Overall, 151 (74.4%) patients survived until hospital discharge and 97 (64.2%) survived with a favorable neurological outcome based on cerebral performance category score (CPC). Patients with initial shockable rhythm had a better prognosis, with higher survival rates to discharge compared with those with non-shockable rhythm (56.4% vs 81.1%,  $P < 0.001$ ). Patients with shockable rhythm also had a better neurological status at discharge (CPC 1-2: 32.7% vs 53.4%,  $P = 0.02$ ). Five-years mortality was 37.4% in the global cohort. Patients with non-shockable rhythm

had a higher five-year mortality (60% vs 29.1%,  $P < 0.001$ , Figure 3).

## DISCUSSION

This study is a sub-analysis of a large single-center registry of selected SCA patients with CA and non-diagnostic post resuscitation ECG<sup>[12]</sup>. The present study compares shockable vs non-shockable rhythms and reveals a similar high burden of CAD in both groups. Although these findings are consistent with previous observational studies<sup>[8]</sup>, our study is novel because it is the first to explore differences between shockable and non-shockable rhythms in this setting. Since the publication in 1997 of a seminal study by Spaulding *et al*<sup>[17]</sup>, many studies with important methodological limitations have reported the possible survival impact of an early invasive approach in this context<sup>[9,18-21]</sup>. However, other studies did not find any benefit from such an invasive strategy and proposed to restrict its use to highly selected patients<sup>[10,11,22]</sup>. Besides, in contrast to the usual presentation of acute coronary syndromes, the standard tools to evaluate coronary ischemia in post cardiac arrest patients are less accurate. The sensitivity and specificity of the usual clinical data, ECG or biomarkers to predict an acute coronary artery occlusion are unclear<sup>[4-6,23]</sup>. For these reasons, there is still an ongoing debate on the use of an early invasive strategy in all survivors of SCA without an obvious non-cardiac cause. We conducted this sub-analysis in order to assess if the initial rhythm after resuscitation could be a predictor of CAD burden and acute coronary lesions.

Given the high probability of CAD (measured as mean Syntax Score), our data supports a low threshold for CA regardless of initial rhythm. According to current resuscitation guidelines, it is reasonable to discuss and consider emergent cardiac catheterization in patients with a high risk of a coronary cause for their cardiac arrest<sup>[3]</sup>. However, definitive data will come with the results of several ongoing randomized trials designed to determine whether early CA improves outcomes in

out-of-hospital cardiac arrest, in patients without ST elevation [one of those (COUPE trial) conducted by our group]<sup>[24-27]</sup>.

Some differences in acute coronary lesions were found between the two groups. Those patients with initial shockable rhythm had a higher incidence of acute coronary lesions (29.7% vs 16.4%,  $P = 0.054$ ) and consequently a greater requirement of *ad-hoc* PCI (21.9% vs 9.1%,  $P = 0.03$ ). These acute coronary lesions might also have a potential impact on prognosis (Figure 2). Unfortunately, our study was underpowered to show the effect of revascularization on these lesions, but this should be considered a relevant research target for future studies. These findings are in accordance with the observed trend that reveals that CA and PCI after ventricular tachycardia or ventricular fibrillation has substantially increased over the last years, regardless of the presence of ST elevation<sup>[28]</sup>.

Regarding the prognosis of initial ECG rhythm analysis, SCA patients are usually divided into non-shockable rhythms (pulseless electrical activity and asystole) or shockable rhythms (ventricular tachycardia and ventricular fibrillation). Non-shockable rhythms are the most prevalent first recorder rhythm and survival rates of this group are worst compared with initial shockable rhythm<sup>[1]</sup>. Studies have shown that increased age, female gender, and prolonged ROSC are associated with a non-shockable rhythm while public location and witnessed arrest are associated with a shockable rhythm<sup>[29]</sup>. In our study, survival rates were also higher in patients with initial shockable rhythms (60% vs 29.1%,  $P < 0.001$ ), as previously reported<sup>[1]</sup>. However, there were no statistical differences in baseline characteristic except for higher mean age (68.1 years vs 61 years,  $P = 0.001$ ) in the non-shockable rhythm group, probably due to the study design and patients selection.

The present study should be interpreted within the context of several limitations of a single-center observational study and relatively small size of the study population. The cohort included in this study was selected from consecutive patients who survived to in or out-of-hospital SCA and were subsequently selected for CA by clinicians upon admission. Patients with an explicit non-cardiac etiology of SCA would not be selected for CA and the final decision to proceed with CA was based on the clinical judgment of individual physicians. It is likely that CA was selectively more frequently offered to patients with a better likelihood of neurological recovery.

In conclusion, in our cohort of patients with SCA and non-diagnostic ECG, initial shockable rhythm group of patients had a similar burden of CAD compared to those with non-shockable rhythms. Patients with initial shockable rhythm had a trend towards a higher incidence of acute coronary lesions and a higher need of *ad-hoc* percutaneous coronary intervention. A low threshold for early CA should be considered in this subgroup of resuscitated SCA patients.

## ACKNOWLEDGMENTS

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## COMMENTS

### Background

Acute coronary syndromes are a common cause of sudden cardiac arrest (SCA). Based on observational studies, current resuscitation guidelines recommend emergency coronary angiography (CA) in patients with SCA and ST segment elevation on post-resuscitation electrocardiogram (Class I, level B). However, because of fewer data available, in patients without ST segment elevation, emergency CA is reasonable in selected patients with suspected cardiac origin (Class II a, level C), regardless of initial rhythm.

### Research frontiers

Electrocardiogram findings may be a poor predictor of an acute coronary lesion in patients after a SCA. Without randomized data, the benefit of early CA in patients without ST elevation remains controversial.

### Innovations and breakthroughs

In patients with SCA and non-diagnostic post-resuscitation electrocardiogram, initial shockable rhythms show a trend towards a higher incidence of acute coronary lesions and higher need of *ad-hoc* percutaneous coronary intervention.

### Applications

The results of the study suggest that a low threshold for early CA should be considered in this subgroup of resuscitated SCA patients.

### Terminology

Shockable rhythms include ventricular tachycardia and ventricular fibrillation in opposition to non-shockable rhythm that include asystole and pulseless electrical activity.

### Peer-review

The manuscript is well-written, the statistical analysis is appropriate, and the data support the conclusions. This work will be of interest to the readership, and is potentially impactful regarding acute treatment of initially resuscitated, hospitalized cardiac arrest patients.

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## Very late bioresorbable scaffold thrombosis and reoccurrence of dissection two years later chronic total occlusion recanalization of the left anterior descending artery

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### Abstract

We describe the case of a patient presenting with ST-segment elevation myocardial infarction due to very late scaffold thrombosis. The patient was already admitted for an elective percutaneous recanalization of a chronically occluded left anterior descending artery (LAD). The procedure was performed according the sub-intimal tracking and re-entry (STAR) technique with 4 bioresorbable vascular scaffolds implantation. However, even though the coronary flow was preserved at the end of the procedure, the dissected segment was only partially sealed at the distal segment of the LAD. After 18 mo of regular assumption, dual antiplatelet therapy was discontinued for 10 mo before his presentation at the emergency room. This is the first reported case of a very late scaffold thrombosis after coronary chronic total occlusion (CTO) recanalization performed according to the STAR technique. This case raises concerns about the risk of very late scaffold thrombosis after complex CTO revascularization.

**Key words:** Bioresorbable vascular scaffolds; Scaffold dismantling; Scaffold thrombosis

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**Core tip:** We describe a case of a 53-year-old male patient who was admitted with anterior ST-elevation myocardial infarction 28 mo after elective percutaneous revascularization of a chronically occluded left anterior descending (LAD) threatened with 4 bioresorbable vascular scaffolds (BVS) in order to seal a long flow limiting dissection after sub-intimal tracking and re-entry technique. Coronary angiography showed a large thrombus at the proximal segment of the proximal BVS and a long dissection was evident from mid to distal LAD. In this case, the progressive reduction of both scaffolds radial strength and structure dismantling might have been responsible for both intraluminal thrombosis and reoccurrence of vessel dissection.

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## INTRODUCTION

Bioresorbable vascular scaffolds (BVS) represents the latest revolution in the field of interventional cardiology. Providing temporary scaffolding and disappearing few years later, BVS results particularly appealing for the treatment of long segments of coronary arteries such as it usually occurs for percutaneous revascularization (PCI) of chronic total occlusions (CTO). However, limited data are available about the long-term efficacy of BVS in this particular setting. Herein we report a case of a very late scaffold thrombosis after CTO revascularization.

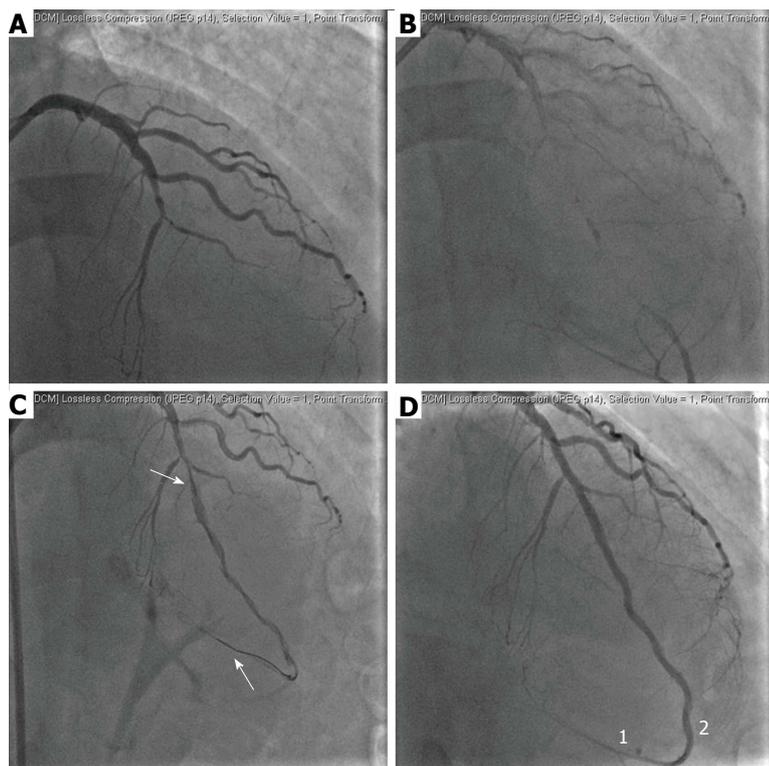
## CASE REPORT

A 53-year-old male patient, with hypertension and dyslipidemia, presented with anterior ST-elevation myocardial infarction, 28 mo after elective percutaneous coronary intervention (PCI) of the chronically occluded left anterior descending artery (LAD), with implantation of 4 marker-to-marker bioresorbable vascular scaffolds (BVS, Absorb Abbott Vascular, Abbott Park, Illinois), performed in another cath-lab. BVS implantation followed chronic total occlusion (CTO) recanalization unintentionally performed according the subintimal tracking and re-entry (STAR) technique. The dissected segment was only partially sealed up to the distal segment of the LAD (Figure 1). The patient completed 18 mo of dual antiplatelet therapy (DAPT) 10 mo before his presentation at the emergency room. The

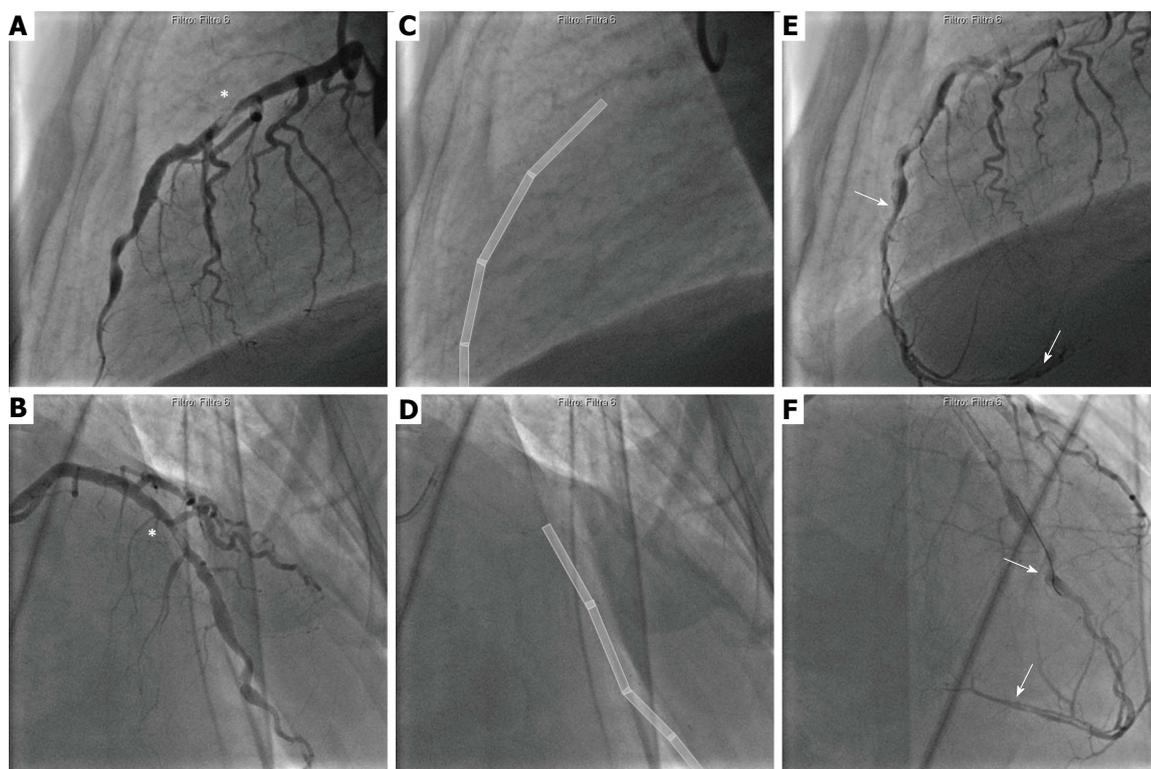
index coronary angiography showed a large thrombus at the proximal segment of the proximal BVS followed by a long dissection up to the very distal LAD segment (Figure 2). Thrombus aspiration and proximal drug eluting stent (DES) implantation was performed, while medical treatment was suggested for the distal chronic dissection (Figure 3). DAPT with ASA and Ticagrelor was finally resumed and clinical follow up planned.

## DISCUSSION

To the best of our knowledge, this is the first clinical case reporting on a very late scaffold thrombosis and reoccurrence of coronary dissection after PCI of a chronic coronary total occlusion. Since neither optical coherence tomography (OCT) nor intravascular ultrasound (IVUS) were available at the time of both baseline and index procedures, the mechanism subtending the BVS failure in this particular case remains unknown. However, we might speculate that intraluminal scaffold dismantling together with scaffold discontinuity and restenosis during the resorption process, might have been responsible of thrombus formation at the mid-LAD, as previously described<sup>[1-3]</sup>. In addition, the gradual scaffold resorption process, together with the incomplete scaffold coverage of the dissected segment at the time of the CTO PCI, might have been responsible of incomplete dissection healing, with progressive expansion of the subintimal hematoma, resulting in a "dual lumen" coronary artery<sup>[4,5]</sup>. CTOs are the most challenging coronary lesions for PCI, mainly because of two reasons: (1) Procedure related: CTO remains technically challenging, in fact PCI failure is reported in up to 35% of CTOs and > 40% of CTOs are not attempted and treated either with medical therapy or with CABG; (2) Patient related: Identification of those patients for whom PCI of CTO does not bring any significant clinical benefit, despite successful revascularization, is still debatable<sup>[6]</sup>. By the way, the use of BVS for CTO revascularization is particularly appealing mainly because PCI normally involves long coronary segments, thereby limiting future surgical interventions and increasing the risk of late malapposition after Drug Eluting Stents (DES) implantation<sup>[7,8]</sup>. However, limited data are available about the use of BVS for PCI of CTOs. In fact, most of the randomized controlled trials conducted so far compared BVS and DES in simple or intermediate coronary artery stenosis, thereby the long-term efficacy of such new devices for percutaneous revascularization of complex stenosis, such as CTOs is still not clear. Recently, a propensity score adjusted analysis of 537 patients undergoing to PCI of a CTO showed a trend toward a higher adjusted risk of ischemia-driven target lesion revascularization for patients undergoing to BVS implantation as compared with DES<sup>[9]</sup>. However, larger randomized studies are warrant in order to better define the role of BVS in CTO-PCI.



**Figure 1** Baseline chronic total occlusion-percutaneous revascularization of the left anterior descending. A and B: Mid-LAD occlusion with omolateral reperfusion of the distal segment; C: Dissected segment after CTO recanalization and balloon dilation (white arrows); D: Final result after four BVS implantation and (2) contrast staining at the distal LAD suggesting the presence of subintimal hematoma with the occlusion of the distal apical branch (1). BVS: Bioresorbable vascular scaffolds; LAD: Left anterior descending; CTO: Chronic total occlusion.

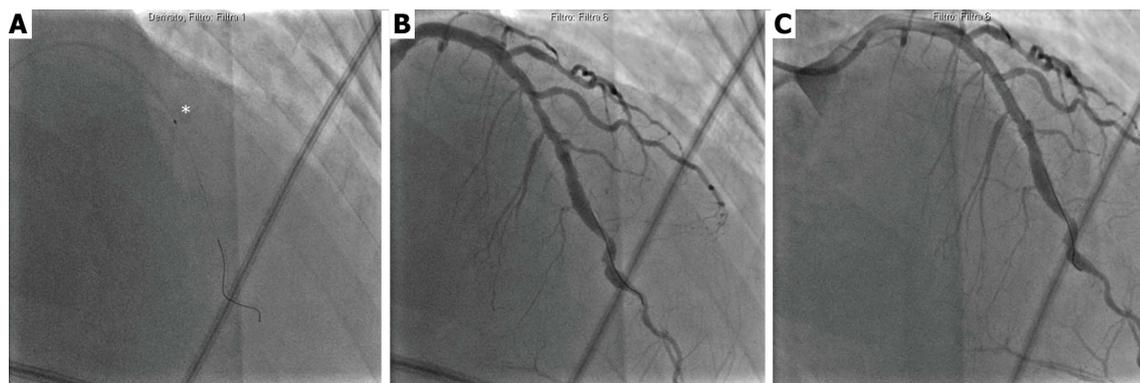


**Figure 2** Coronary angiography of the left anterior descending at 28 mo after chronic total occlusion recanalization. A and B: Large in-scaffold thrombus at the proximal edge of the previously implanted BVS (C, D, white boxes), at the mid LAD (\*); E and F: Dissected segment (white arrows) from the mid-LAD up to the distal segment, with a resulting image of a “dual lumen” LAD. LAD: Left anterior descending; BVS: Bioresorbable vascular scaffolds.

**Conclusion**

This case raises concerns about the risk of very late scaffold thrombosis and the use of BVS in complex CTO-PCI, particularly when “full polymer jacket” is not

warranted for the entire dissected coronary segment. A prolonged DAPT should be encouraged while a complete sealing of the dissected segment should be considered<sup>[10]</sup>.



**Figure 3** Percutaneous revascularization of the left anterior descending. A and B: After coronary wire crossing, thrombus aspiration was successfully performed (\*) and a drug eluting stent was finally implanted with good final result (C).

## COMMENTS

### Case characteristics

A 53-year-old male patient presenting with chest pain for an anterior ST-elevation myocardial infarction.

### Clinical diagnosis

Anterior ST-elevation myocardial infarction due to very late scaffold thrombosis.

### Differential diagnosis

Clinical characteristic, patient's medical history and echocardiography were useful for differential diagnosis between pericarditis and aortic dissection.

### Laboratory diagnosis

High sensitive Troponin-I increased together with myoglobin and creatine kinase-MB.

### Imaging diagnosis

Definite diagnosis was possible with invasive coronary angiography which showed a large thrombus at the proximal segment of the proximal bioresorbable vascular scaffolds (BVS) followed by a long dissection up to the very distal left anterior descending segment.

### Pathological diagnosis

In the acute setting of the coronary syndrome, no thrombus was kept for pathological analysis.

### Treatment

Thrombus aspiration and proximal drug eluting stent implantation was performed, while medical treatment was suggested for the distal chronic dissection.

### Related reports

To our knowledge, there are only few case reports about very late scaffold thrombosis.

### Experiences and lessons

This case raises concerns about the use of BVS in complex chronic total occlusion percutaneous revascularization (PCI), thereby suggesting a prolonged dual-antiplatelet therapy tailored according to both patients' clinical characteristics and PCI procedures.

### Peer-review

This case report of late thrombosis after chronic total occlusion recanalization with bioabsorbable scaffold is well organized.

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## Use of carbon dioxide as an intravascular contrast agent: A review of current literature

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### Abstract

Use of X-ray contrast allows us to differentiate between two or more adjacent structures on radiographic studies. The X-ray contrast agent can be the one with increase X-ray absorption, like iodine and a barium X-ray contrast agent or the one with decrease X-ray absorption like air and carbon dioxide contrast agent. Each contrast agent possesses different risks and benefits in various ways. Carbon dioxide as an intravascular contrast agent can be used as an alternative intravascular contrast agent and has superior results in some cases. In patients with renal dysfunction or iodinated contrast allergy, the use of Iodinated Contrast Agent poses the risk of considerable morbidity. Similarly, use of Gadolinium is discouraged in subject with severe renal dysfunction. Use of carbon dioxide (CO<sub>2</sub>) as an intravascular contrast, offers an alternative in such patients for certain procedures, as it is not nephrotoxic and it does not incite allergic reactions. It is inexpensive, readily available and due to its unique physical properties, it can be used to image a wide variety of vascular beds and chambers. The aim of this paper is to systemically review the current literature to describe the indications, contraindications, adverse effects, instruments, precautions, latest methodologies and data supporting for the use of CO<sub>2</sub> as a contrast agent.

**Key words:** Iodinated; Carbon dioxide; Contrast; Vascular; Gadolinium

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**Core tip:** In patients with renal dysfunction or iodinated contrast allergy, use of iodinated contrast agent poses the risk of considerable morbidity. Similarly, use of gadolinium is discouraged in subject with severe renal dysfunction. Use of carbon dioxide (CO<sub>2</sub>) as an intravascular contrast offers an alternative in such patients for certain procedures, as it is not nephrotoxic and it does not incite

allergic reactions. It is inexpensive, readily available and due to its unique physical properties it can be used to image a wide variety of vascular beds and chambers. This article describes the indications, contraindications, adverse effects, instruments, precautions, latest methodologies and data supporting for the use of CO<sub>2</sub> as a contrast agent.

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## INTRODUCTION

In medical parlance, contrast is a mean which allows us to differentiate between two or more adjacent elements on a radiographic study. There are essentially two prototypes of X-ray contrast agents: (1) Positive agents (which increase X-ray absorption: Iodine or barium based); and (2) negative agents [decrease X-ray absorption: Air, carbon dioxide (CO<sub>2</sub>)]<sup>[1]</sup>. In animal experiments (1940s) and later in human studies (1950s), CO<sub>2</sub> enabled investigators to delineate both right and left heart structures. With the introduction of digital subtraction angiography (DSA) in 1980s, the image quality improved significantly<sup>[1]</sup>. Conditions where use of iodinated contrast agent (ICA) are precluded such as impaired kidney functions, dye allergy, CO<sub>2</sub> may be used as an alternate contrast agent with comparable results and in some cases superior results<sup>[2-4]</sup>.

### Physical properties

Understanding of physical properties of CO<sub>2</sub> is central for its use. Administration of CO<sub>2</sub> needs extreme care. It is a colorless, odorless and significantly compressible gas. CO<sub>2</sub> has low molecular weight as compared to ICA, is less viscous than blood and ICA and due to this property it can be used to image small collateral vessels. It displaces the blood in the vessels and acts as a negative contrast agent. This property creates a significant gradient between the radiographic density of the vessel wall and the lumen. DSA technique uses this difference in the densities to provide a contrast image. CO<sub>2</sub> is more soluble than oxygen (O<sub>2</sub>) and dissolves in the blood within 2-3 min after injection. When mixed with water it creates carbonic acid (H<sub>2</sub>CO<sub>3</sub>) which dissociates into bicarbonate (HCO<sub>3</sub><sup>-</sup>) and hydrogen (H<sup>+</sup>) ions carried by blood flow to the lungs. Reverse reaction happens in the lungs where the breakdown product of H<sub>2</sub>CO<sub>3</sub>, CO<sub>2</sub> is then exhaled. These chemical reactions are facilitated by enzymes called carbonic anhydrases.

During its use, monitoring of vital signs is required. Capnography if available would be useful in monitoring the ventilation.

### Administration

There are 3 commonly used methods of administering CO<sub>2</sub>. Preferred method is *via* automated injectors (automated CO<sub>2</sub> mmanders). Hand held syringes have been used in the past but are not commonly used now due to increased risk of complications such as air contamination and explosive over dosage<sup>[5,6]</sup>.

**Automated CO<sub>2</sub> mmanders:** Have the utility of being handy, portable, safe and easy to use but their high cost (approximately 3000 USD)<sup>[7]</sup> make them an unpopular choice.

**The modified plastic bag system with O-ring:** Is a preferred method by some experts. Kit packs consisting of bag, tube and valves are available commercially (custom waste management kit by Merit Medical, South Jordan, UT; or Angio-Dynamics Queensbury, NY)<sup>[8,9]</sup>. The usual source of CO<sub>2</sub> is an Aluminum or steel cylinder of medical grade CO<sub>2</sub> which is about 99.99% pure, fitted in a series circuit with a valve, a gauge, a regulator, a diaphragm and an antibacterial filter. A 1500 mL plastic bag with a single port connected with a low pressure tube and a 2-way stopcock at the distal end of the tube is then connected to the CO<sub>2</sub> cylinder. It is then filled and manually purged at least 3 times. The filled bag is then connected at its 2-way stopcock end with an O-ring connector which on the other end is connected with the delivery syringe (20-60 mL). There is a 1-way valve between the O-ring and the syringe. The syringe is then connected with another 1-way valve and then with a 100 cm connecting tube. The distal end of this tube has one more 1-way valve which is then connected with a 3-way valve. This 3-way valve can then be connected with the angiographic catheter. On the other port an additional syringe for back-bleeding or eliminating the air from the system can be attached (Figure 1). To fill the delivery syringe the plunger is simply retracted. The 1-way valves will allow the CO<sub>2</sub> in the plastic bag to move into the syringe. The plunger can then be advanced at the desired rate and amount. The 1-way valves will allow the gas to move towards the 3-way valve which can then be adjusted depending on the ports required to be used. The angiographic catheter is at times filled with blood which can be cleared by using the additional syringe attached at the 3-way valve. Forceful boluses of 3-5 mL CO<sub>2</sub> can be used to clear the catheter from any remaining fluid. The catheter can then be flushed with 1-3 mL of CO<sub>2</sub> every 2-3 min. All the connections of the circuit need to be air tight to avoid any air aspiration or embolism. The plastic bag should be filled enough to remain flaccid as tightly filled bag may pose risk of overdose due to gas compression<sup>[9]</sup>.

**Underwater seal:** This is a relatively simple, inexpensive and easier method but there may be a slight risk of air contamination and or inadvertent explosive

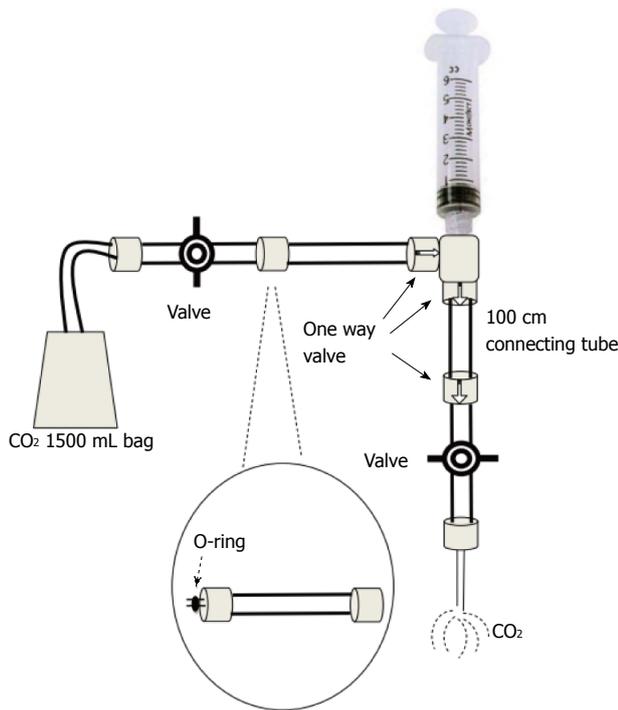


Figure 1 The modified plastic bag system with O-ring.

administration of CO<sub>2</sub> into the patient<sup>[10]</sup>. In this system, the CO<sub>2</sub> source is connected to a regulator, a particle filter and a 3-way tap by connecting tubes. One end of 3-way valve has a sliding 2-way valve connected to a 60 cc syringe. The other end of 3-way valve has a tube serving as a simple under water seal by having the other end of the tube dipped in a bowl of saline. When the CO<sub>2</sub> source is turned on and the 3-way valve is on to the syringe, the syringe will get filled without pulling the plunger, by the positive pressure of the CO<sub>2</sub> coming from the source. Once the syringe is filled the 2-way valve is turned off and 3-way valve is turned to the under-water seal. Bubbles of CO<sub>2</sub> would be seen in the bowl of saline coming out of the tube's end. The CO<sub>2</sub> source is then turned off and the 3-way valve is then turned on to the syringe and the water seal. The CO<sub>2</sub> can then be purged through the water seal. This process of filling and purging can be repeated at least 3 times to make sure that there is only CO<sub>2</sub> and no air in the tubing and syringe system. Then the filled syringe along with a 2-way valve turned off, can then be disconnected and attached to the angiography catheter. Right before it is connected to the angiography catheter, the 2-way valve is turned on to release the positive pressure in the syringe to come down to atmospheric pressure. This will avoid explosive administration and or over dosing of pressurized CO<sub>2</sub> in the syringe but at the same time this may create a very small risk of air contamination. Only fully filled syringes should be used while using this method as half-filled syringes when opened to atmospheric pressure will certainly lead to higher risk of air contamination. The innovators of this system also described their experience of 5 years in

over 250 patients and no directly related complications were noticed<sup>[10]</sup>.

### Dosage

Typically 30-40 mL of CO<sub>2</sub> is injected for abdominal aortography or IVC visualization. Twenty to thirty milliliter is used for lower extremity vessels and other aortic branches like celiac, superior mesenteric or renal arteries. The left renal artery which is more posteriorly located can be filled even with 10 mL if injected with patient lying on the right side. Injections can be repeated at approximately 3 min intervals. Thirty to fifty milliliter may be used for runoff studies by injecting at low rate of 10 mL/s.

### Potential uses of CO<sub>2</sub>-based angiography (Figure 2)

The diagnostic accuracy is acceptable in comparison to contemporary ICA and in some conditions such as TIPS, CO<sub>2</sub> is even rendered superior to the ICA.

**Aortic aneurysm repairs:** CO<sub>2</sub> has been used in endovascular repairs of aortic aneurysms<sup>[11-14]</sup>. A recent prospective study of 72 patients with abdominal aortic aneurysm (AAA) endovascular repair demonstrated that CO<sub>2</sub> has overall sensitivity of 84% and specificity of 72% as compared to ICA as the standard criterion for detection of endoleaks and in patients who are at risk of nephrotoxicity from ICA, CO<sub>2</sub> can be used as an acceptable alternative to ICA<sup>[15]</sup>. Another study describes the outcomes of CO<sub>2</sub>-guided procedures are similar to those which are ICA-guided<sup>[14]</sup>. Additional benefit of CO<sub>2</sub> use in endovascular repair of AAA is that an accessory catheter which is otherwise required for ICA may not be required for CO<sub>2</sub> injection as it can be administered through the endograft sheath or femoral access sheath<sup>[13]</sup>.

**Aortography:** CO<sub>2</sub> may be used for aortography and for runoff studies in most patients<sup>[16]</sup>. If needed supplemental ICA imaging may be used in order to obtain additional information. To get the retrograde aortogram, CO<sub>2</sub> may be injected retrograde through the femoral artery by percutaneous catheterization with a 4-Fr end-hold catheter (Cobra-shaped or shepherd hook catheter) or catheters with side-holes (Omni-flush, pigtail, Racquet, multipurpose). Contra-lateral superficial femoral arterial views can also be taken through the same port by moving the catheter into the contralateral superficial femoral artery. For antegrade views micro-catheters of 3-Fr may be used for popliteal, tibial and peroneal arteries. Use of intra-arterial nitroglycerine and or leg elevation may be done for better visualization of smaller vessels such as tibial and plantar branches.

**Renal artery angiography (Figure 3):** CO<sub>2</sub> can be used in the assessment of renal artery stenosis, aneurysms, AV (arterio-venous) malformations, AV fistulas, renal artery stenting, invading tumors in renal

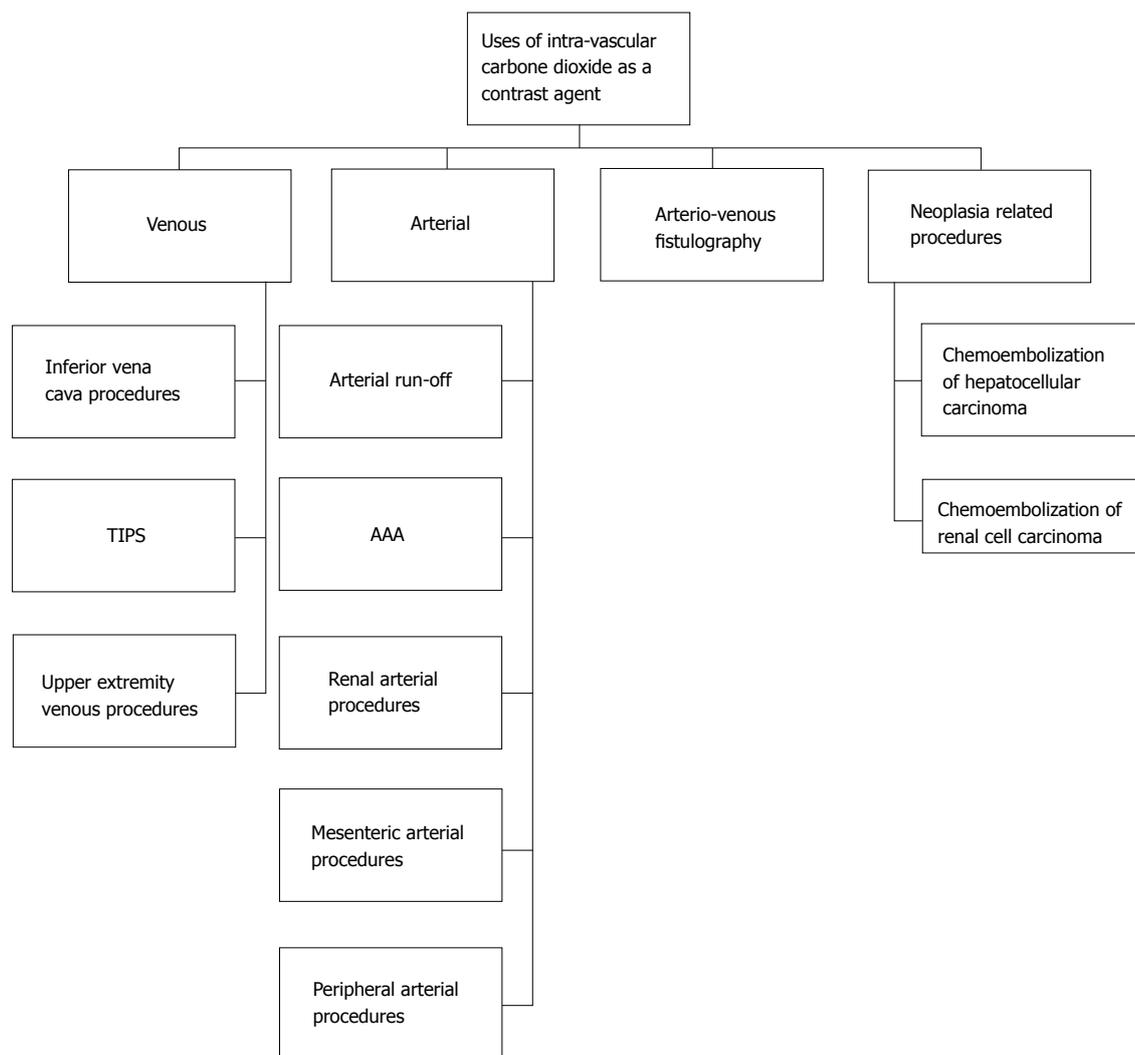


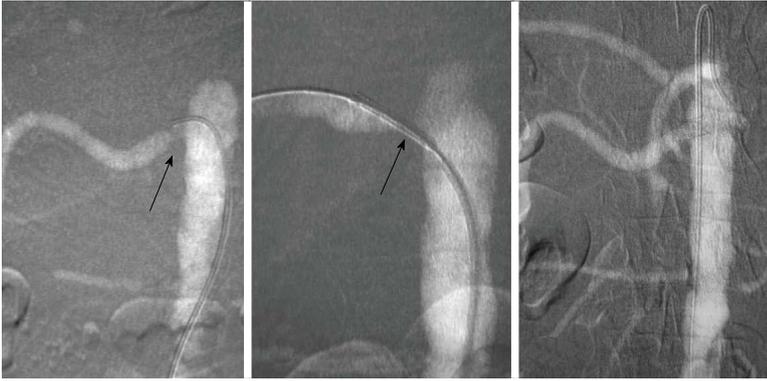
Figure 2 Potential uses of carbon dioxide angiography. AAA: Abdominal aortic aneurysm.

veins or arteries, renal cell carcinomas, evaluation of transplanted kidney vascular stenosis and for its angioplasty and/or stenting, anastomotic stenosis, diffuse arterial disease related to chronic rejection and AV fistulas after renal transplant biopsy (in which case it may be superior to ICA)<sup>[17,18]</sup>. In such cases CO<sub>2</sub> may be used as initial imaging modality to get an overview and then small dose ICA may be used for confirmation of the findings<sup>[11]</sup>. CO<sub>2</sub> does not adequately fill the distal portion of renal artery very well in a supine patient, as it is located posterior to the aorta. In this situation, the patient may be turned on the side to bring the renal arteries superior with respect to the aorta. Recent studies have also demonstrated the use of CO<sub>2</sub> in combination with intravascular ultrasound for successful vascular stenting. In a study of 18 patients, 27 successful renal artery stenting procedures were done using CO<sub>2</sub> and intravascular ultrasound with good outcomes<sup>[19,20]</sup>.

**Inferior venae cava imaging:** CO<sub>2</sub> can be used for the placement of inferior venae cava (IVC) filters, IVC venous

anomalies and thrombus visualization, recanalization of occlusion and estimation of IVC diameters (accuracy of about 97%). In a study of 50 patients, CO<sub>2</sub> was used for IVC filter placement at the bedside in ICU setting. Only 2 of these patients required additional ICA for better visualization. The study concluded with positive results and favored the use of CO<sub>2</sub> as first line contrast agent in ICU patients requiring IVC filter<sup>[21]</sup>.

**Portal vein imaging (portography):** A very important utility of CO<sub>2</sub> is in the delineation of the portal vein anatomy (wedged hepatic venography) during TIPS procedure (Figure 4). CO<sub>2</sub> is found to be superior to ICA for this use and can be used as first line contrast agent for portography<sup>[22]</sup>. The reason is buoyancy and low viscosity of CO<sub>2</sub> making it travelling through the sinusoids easily and deeply. In liver transplants, anastomosis can also be visualized using CO<sub>2</sub>. In a study of 16 patients, the utility of CO<sub>2</sub> was compared with ICA for balloon-occluded retrograde trans-venous venography (BRTV) and obliteration (BRTO) for gastric varices and it was found that varices were visualized



**Figure 3** A carbon dioxide renal arteriogram showing renal artery orifice stenosis with subsequent stent placement and resolution of the stenosis with good flow. The carbon dioxide contrast is injected through the sheath. Adapted with permission from Dr. Kyung Cho.



**Figure 4** Carbon dioxide wedged hepatic protogram showing portal vein stenosis (arrow). Adapted with permission from Dr. Kyung Cho.

better with CO<sub>2</sub> than with ICA and even in cases where ICA could not reach the varices, CO<sub>2</sub> successfully delineated these varices (in 7 out of 16 patients), leading to successful obliteration of the varices<sup>[23]</sup>. According to some estimates, success rate of portal vein visualization with CO<sub>2</sub> wedged hepatic venography is approximately 90%. A diagnostic catheter of 5-Fr can be used for wedged hepatic venography. Using the femoral or jugular vein approach, catheter can be advanced into a peripheral hepatic vein for wedging. It is also being used for multi-detector CT cholangiopancreatography. In a study of 73 patients, the feasibility of CO<sub>2</sub> enhanced CT cholangiopancreatography was assessed and found to be very useful for interventional procedures<sup>[24]</sup>.

**Splenoportography:** Can also be done by using CO<sub>2</sub> in selected patients<sup>[25]</sup> such as a patient in which portal vein imaging study for patency is inconclusive<sup>[26]</sup>. Twenty-two to twenty-five gauge needle can be used to inject CO<sub>2</sub> into the parenchyma of spleen. This is useful in pediatric patients as it obviates the catheterization of femoral artery for arterial portography. Endoscopic ultrasound guided direct portal venography with CO<sub>2</sub> by using a small FNA needle has also been used in animal studies with favorable results<sup>[27]</sup>.

**Tumor embolization procedures:** CO<sub>2</sub> can be used

for the following oncological embolization procedures: Embolization of renal cell carcinoma and its metastatic lesions in the bone, hepatocellular carcinoma<sup>[28,29]</sup>, radiofrequency ablation and transcatheter arterial chemo-embolization of hepatocellular carcinoma (by using intra-arterial CO<sub>2</sub> for enhancement for ultrasonography guidance)<sup>[30]</sup>, uterine artery embolization in uterine leiomyoma<sup>[31]</sup>. These procedures can be optimized by using super-selective angiographic techniques with help of micro-catheters of 3 Fr.

**Upper extremity venography:** Can be performed using the CO<sub>2</sub><sup>[32]</sup>. It can be useful for AV-fistula formation<sup>[33]</sup>, insertions of trans-venous pacer wires<sup>[34]</sup>, central venous catheters and for the delineation of any atypical vascular anatomy. The preferable site of injection is antecubital vein and a 21 gauge catheter may be used. In a series of 146 AV fistulography procedures using CO<sub>2</sub> as the first line contrast agent, 141 cases required AV fistula intervention and in 115 of these cases intervention was performed successfully using CO<sub>2</sub> alone. Rest of the cases required ICA for various reasons in addition to CO<sub>2</sub> for intervention<sup>[35]</sup>. For AV fistula assessment, one needs to be careful of not letting CO<sub>2</sub> reflux into arterial system due to potential risk of neurologic sequelae including infarction. Also there is a potential of overestimation of fistula stenosis.

**Gastrointestinal bleeding:** Due to increased compressibility and low viscosity it may be useful in detecting the site of occult bleeding or ongoing blood loss such as the gastrointestinal tract, with higher sensitivity than ICA. CO<sub>2</sub> can also be used in selected angiographies for chronic mesenteric ischemia<sup>[36]</sup>.

**Contrast ultrasonography:** CO<sub>2</sub> can be used to enhance sonography by employing CO<sub>2</sub> microbubbles. In a study where conventional sonography was compared with CO<sub>2</sub> micro-bubble enhanced sonography; the former detected only 6 tumors however with CO<sub>2</sub>-microbubble enhanced sonography 14 tumors were detected and then treated successfully with radiofrequency ablation

**Table 1 Summary of the characteristics of carbon dioxide and against iodinated contrast agents**

Characteristics	Carbon dioxide	Iodinated contrast agents
Overall sensitivity	Less	Higher
Overall specificity	Less	Higher
Nephrotoxicity	No	Yes
Allergenic	No	Yes
Cost	Low	High
Ease of administration	Cumbersome	Easier
Limitations	Visibility and air contamination	Dose related toxicity and allergy
Delivery <i>via</i> small caliber catheters	Possible	Difficult
Radiation exposure	Increased if digital subtraction angiography used	Standard
Dose	Rate related toxicity	Volume related nephrotoxicity
Contraindications	Pulmonary-systemic communications; not for use in heart, brain or spinal vasculature	Allergy, nephrotoxicity
Hepatotoxicity	Rare	Rare
Quality of image	Good	Better
Procedure duration	Increased	Standard

using CO<sub>2</sub>-microbubbles enhanced sonography<sup>[37]</sup>.

## LIMITATIONS

Overall CO<sub>2</sub> is a relatively safe agent<sup>[38]</sup>. In a study of 800 subjects, only one complication of transient colonic ischemia was reported. In another study of 1200 subjects only 7 subjects developed some kind complication. Livedo reticularis, bowel ischemia and renal dysfunction have been described after in 1 patient with CREST syndrome<sup>[38]</sup> (Table 1).

The adverse effects are primarily either dose related or buoyancy related. Majority of the adverse effects are due to "vapor-lock phenomenon" which result when large amounts of CO<sub>2</sub> are injected or a small amount is injected too frequently with very short intervals causing trapping of CO<sub>2</sub> gas column in the vessel and consequently obstructing the vessel. This may lead to ischemia of the tissues. Cases with transient mesenteric ischemia and ischemic colitis secondary to "vapor lock phenomenon" have been described in the literature. Similar mechanism may potentially precipitate right sided heart failure. Sometimes CO<sub>2</sub> bubbles may accumulate in an aortic aneurysm and may cause blood flow obstruction, leading to tissue ischemia. Even a transient occlusion of inferior mesenteric artery may result in mesenteric ischemia. Typically, this happens with the use of excessive dose of CO<sub>2</sub>. Similarly a vapor lock may happen in the pulmonary artery and this may lead to significant hypotension. Air contamination may also cause vapor-lock phenomenon that is typically worse and more persistent. Usually CO<sub>2</sub> bubbles in the pulmonary artery dissolve within 30 s. If they persist beyond 30 s then either air contamination or CO<sub>2</sub> over-dosage should be suspected and the tubing system should be checked for any air leak. For hypotension secondary to vapor lock phenomenon, patient should be placed in Trendelenburg position or lateral decubitus positions. Aspirating the air using a catheter from the pulmonary artery should also be considered.

Due to its buoyancy the visualization of a dependent

(inferior or caudal positioned) vessels may be sub-optimal (such as visualization of renal arteries in supine position). This problem can be circumvented by putting the patient in lateral decubitus position. CO<sub>2</sub> may get trapped in organs which are non-dependant and cause decreased blood flow or ischemia such as in transplanted kidneys or mesenteric vessels. If we place the patient in lateral decubitus position, the CO<sub>2</sub> may remain trapped in right atrium instead of moving into pulmonary arteries. Changing the body position may help clearance in these situations. Similarly using low volumes of CO<sub>2</sub> with adequate time intervals may help avoiding these adverse effects. Although 100 mL is the recommended maximum volume for arterial use and 50 mL for venous use, by using above mentioned precautions, larger total volume may be used. Vessels which are more anterior such as superior mesenteric artery (SMA), CO<sub>2</sub> is useful in their evaluation, particularly for proximal mesenteric stenosis. For more distal assessment ICA probably provides superior imaging.

Due to its dissolution in blood soon after injection vessels with slower flow may not have adequate visualization and this may lead to overestimation of stenosis. Similarly due to the expansive nature of CO<sub>2</sub> and elasticity of vessels, CO<sub>2</sub> may lead to overestimation of the vessel diameter. This may cause errors in estimation of balloon or stent size during intervention procedures.

The use of CO<sub>2</sub> for cerebral, spinal and or cardiac procedures should be avoided as there is a potential risk of ischemia to vital organs<sup>[39]</sup>. In animal models neurotoxicity has been reported after cerebral use. For the same reasons, before the use of CO<sub>2</sub> presence of atrial or ventricular septal defects or pulmonary arterio-venous malformation should be ruled out to avoid the risk of paradoxical embolism to CNS and or coronary embolization. CO<sub>2</sub> may also aggravate or worsen pulmonary arterial pressure therefore the use of this agent should be avoided in pulmonary hypertension. There are some relative contraindications for the use of CO<sub>2</sub> for upper extremity which are similar for other uses

as well and these are the presence of cardiac septal defects, pulmonary AV malformations, pulmonary hypertension and severe emphysema. In a series of 146 arteriovenous fistulography procedures, in 3 cases when manual injection of CO<sub>2</sub> into the brachial artery was performed, a reflux of the gas into the thoracic aorta occurred precipitating transient loss of consciousness<sup>[35]</sup>.

Typically, CO<sub>2</sub> angiography does not cause any significant changes in the serum osmolality or blood gas values<sup>[40]</sup> unless excessive quantities of CO<sub>2</sub> are used or significant derangements of pulmonary function happen. Caution is required in cases where pulmonary functions are compromised such as in chronic obstructive pulmonary disease, as clearance of CO<sub>2</sub> may be decreased. Doses of CO<sub>2</sub> for diagnostic purposes are typically between 20–40 cc and it has no effect on vital signs. Any change in vital signs should prompt the considerations for air contamination or air trapping.

Peristaltic and breathing movements sometime may decrease the image quality of mesenteric CO<sub>2</sub> angiography. This problem may be avoided by selective or superselective CO<sub>2</sub> injection into the mesenteric arterial branch, getting additional mask images or using intravenous glucagon to suppress the peristalsis. While using CO<sub>2</sub>, sedation should be avoided or minimized as any of the side effects of CO<sub>2</sub> overdosing or air contamination may be missed in the presence of heavy sedation. During the procedure patients vital signs (pulse-oxymetry, blood pressure, heart rate, respiratory rate, ECG, and if possible capnography) need to be monitored closely. Any change in these parameters should raise the suspicion of CO<sub>2</sub> over dosage or air contamination.

The utility of CO<sub>2</sub> as contrast agent for CT angiography for abdominal aorta and peripheral vessels is also currently being evaluated<sup>[41,42]</sup>. In an animal study the use of CO<sub>2</sub> micro-bubbles mixed in saline was compared with conventional CO<sub>2</sub> gas and ICA and demonstrated that vessels can be depicted using X-ray angiography and CO<sub>2</sub> micro-bubbles as enhancement<sup>[43]</sup>. CO<sub>2</sub> bubbles sometimes may provide better visualization than plain CO<sub>2</sub> gas with additional benefit of low dose requirement<sup>[44]</sup>.

## CONCLUSION

CO<sub>2</sub> is useful in cases where ICA cannot be used due to allergy or impaired kidney functions. CO<sub>2</sub> may be superior to ICA in certain procedures such as in TIPS.

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## Takotsubo cardiomyopathy: Pathophysiology and role of cardiac biomarkers in differential diagnosis

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### Abstract

Takotsubo cardiomyopathy (TC) is characterized by reversible ventricular dysfunction, not limited to the distribution of an epicardial coronary artery. A disease

primarily afflicting post-menopausal women, it is frequently mistaken for acute anterior wall myocardial infarction. Alternatively called Stress Cardiomyopathy, physical or emotional triggers are identified in only three fourths of TC patients. Long considered a benign condition, recent findings suggest poor short term prognosis similar to acute coronary syndrome (ACS). Despite the widely recognized pathophysiological role of catecholamine excess, its diagnostic role is uncertain. TC is suspected based on typical wall motion abnormalities in ventriculogram or echocardiogram. Several additional electrocardiographic, laboratory and imaging parameters have been studied with the goal of clinical diagnosis of TC. While several clinical clues differentiate it from ACS, a clinical diagnosis is often elusive leading to avoidable cardiac catheterizations. Natriuretic peptides (NPs), a family of peptide hormones released primarily in response to myocardial stretch, play a significant role in pathophysiology, diagnosis as well as treatment of congestive heart failure. TC with its prominent ventricular dysfunction is associated with a significant elevation of NPs. NPs are elevated in ACS as well but the degree of elevation is typically lesser than in TC. Markers of myocardial injury such as troponin are usually elevated to a higher degree in ACS than in TC. This differential elevation of NPs and markers of myocardial injury may play a role in early clinical recognition of TC.

**Key words:** Takotsubo cardiomyopathy; Natriuretic peptide; Brain natriuretic peptide; N-terminal-pro brain natriuretic peptide; Troponin; Cardiac biomarkers; Acute myocardial infarction

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**Core tip:** Takotsubo cardiomyopathy (TC) characterized by reversible ventricular dysfunction is frequently mistaken for acute anterior wall myocardial infarction often leading to avoidable cardiac catheterizations. While several clinical clues differentiate TC and acute coronary syndrome

(ACS), a clinical diagnosis still remains elusive. We review the pathophysiology and diagnosis of TC with a focus on role of cardiac biomarkers [natriuretic peptides - brain natriuretic peptide (BNP) and NT-proBNP and cardiac myonecrosis markers - Troponin, CKMB and Myoglobin]. We have done a review of several studies looking at diagnostic utility of cardiac biomarkers in differentiating TC and ACS.

Gopalakrishnan P, Zaidi R, Sardar MR. Takotsubo cardiomyopathy: Pathophysiology and role of cardiac biomarkers in differential diagnosis. *World J Cardiol* 2017; 9(9): 723-730 Available from: URL: <http://www.wjgnet.com/1949-8462/full/v9/i9/723.htm> DOI: <http://dx.doi.org/10.4330/wjc.v9.i9.723>

## INTRODUCTION

Takotsubo cardiomyopathy (TC), originally described by Sato *et al*<sup>[1]</sup> in 1990, is variably known as stress cardiomyopathy, broken heart syndrome, and apical ballooning syndrome. A disease process primarily affecting post-menopausal women, it is characterized by transient left ventricular (LV) dysfunction, not limited to distribution of an epicardial coronary artery. Clinical presentation of TC most often has a significant overlap with acute coronary syndrome (ACS) with symptoms, cardiac biomarker profiles and EKG changes suggesting myocardial ischemia or infarction. TC is estimated to occur in 1%-2% of patients presenting as ACS. With prevalence in 2008 reported as 0.02% of hospitalizations in United States<sup>[2]</sup>, TC incidence has increased with a 3-fold increase in TC hospitalization in United States between 2007 and 2012<sup>[3]</sup>. The inability to confidently diagnose TC based on clinical presentation leads to almost universal use of cardiac catheterization in these patients. Several indicators including cardiac biomarker elevation have been studied with the goal of making a clinical diagnosis of TC (Table 1).

## EPIDEMIOLOGY

Women have a 9-fold higher risk of TC compared to men<sup>[4]</sup>. Women > 55 years have about 5-fold higher risk than women < 55 years<sup>[4]</sup>. While a physical or emotional trigger is often identified, no specific triggers have been reported in little over a fourth of TC patients<sup>[4]</sup>. Reported stressors include surgery, critical illness, death of dear ones, dobutamine or ergonovine stress test, lightning strike, prolonged immobilization and thyrotoxicosis. TC recurrence has been reported in greater than 10% of the patients in the first four years<sup>[5]</sup>. Initially thought to have a benign course, recent data show short term prognosis for TC is similar to ACS. In the InterTAK registry, severe in-hospital complications, such as shock and death were similar in TC and ACS<sup>[4]</sup>. According to the SWEDEHEART study, prognosis of takotsubo syndrome is poor, with early and late mortality similar

to STEMI and NSTEMI<sup>[6]</sup>.

## PATHOPHYSIOLOGY

### Clinical findings

Four different morphotypes of TC have been described: (1) Classical - apical ballooning with basal hyperkinesis; (2) Mid-ventricular - basal hyperkinesis, mid-ventricular hypokinesis and normal or hyperkinetic apex; (3) Basal (inverted) - basal and mid-ventricular hypokinesis with apical hyperkinesis; and (4) Focal - hypokinesis of a focal myocardial segment<sup>[4]</sup>. TC predominantly affects the left ventricle but right ventricular (RV) involvement with a more malignant course has been described as well<sup>[7]</sup>. The classic type characterized by basal hyperkinesis is often associated with left ventricular outflow tract (LVOT) obstruction and shock<sup>[8]</sup>. Significant reversible mitral regurgitation (MR) and higher brain natriuretic peptide (BNP) levels related to the ventricular dilation have been described in the classic form. The inverted (basal) form seems to have higher levels of troponin and lower levels of BNP as well as lower incidence of LVOT obstruction and MR<sup>[8]</sup>.

### Mechanisms

Several etiologies have been proposed including catecholamine excess, derangement of myocardial glucose and fatty acid metabolism, microcirculatory dysfunction, coronary vasospasm, estrogen deficiency *etc.* Norepinephrine may trigger  $\alpha$ 1-mediated coronary vasospasm and  $\beta$ 1-mediated hyperdynamic basal contraction, as basal myocardium has higher density of sympathetic nerve endings and higher content of norepinephrine. The biased agonism of epinephrine and apical-basal gradient of  $\beta$ 2-adrenergic receptor ( $\beta$ 2AR) may explain the apical stunning. High level of epinephrine could trigger signal switching of  $\beta$ 2AR from stimulatory G-protein to inhibitory G-protein. Apical myocardium with higher concentrations of  $\beta$ 2AR may be more susceptible, compared to basal myocardium leading to apical stunning<sup>[9]</sup>. The histological changes of TC mirror catecholamine toxicity seen in pheochromocytoma. Loss of cardioprotective action of estrogen against catecholamine excess may explain higher incidence of TC in postmenopausal women. Positron emission tomography (PET) studies have suggested disturbances in glucose and fatty acid metabolism in TC patients<sup>[10]</sup>. Findings suggestive of coronary vasospasm as well as microcirculatory dysfunction have been described in coronary angiograms of TC patients.

## DIFFERENTIAL DIAGNOSIS

ACS is the primary differential diagnosis as both disease states have significant overlap in their clinical presentation. TC is often mistook for acute anterior wall ST elevation myocardial infarction (occlusion of proximal left anterior descending artery). Other differential diagnoses include myocarditis, endogenous catecholamine excess

**Table 1** Diagnostic clues for differentiating takotsubo cardiomyopathy and acute coronary syndrome

History	Stressful stimulus Female sex Age > 55 yr Neuropsychiatric conditions	
EKG findings	Absence or paucity of reciprocal ST depression Widespread T wave inversion QTc prolongation	
Laboratory findings	Catecholamine levels Natriuretic peptides Myonecrosis markers Others	Metanephrine, Normetanephrine BNP, NT-proBNP Myoglobin, CK-MB, Troponin I, Troponin T Copeptin, sST2, soluble lectin like oxidized LDL receptor-1 (sLOX-1), IMA
Imaging	Echocardiogram  Coronary angiogram  SPECT  PET CMR	Reversible wall motion abnormalities > distribution of a epicardial coronary artery Reversible mitral regurgitation, Left ventricular outflow tract obstruction Absence of ruptured plaque Diminished flow Coronary vasospasm Reduced Thallium uptake Reduced fatty acid metabolism in BMIPP imaging Reduced myocardial MIBG uptake Reverse metabolism perfusion mismatch T2 hyperintensity; lack of first pass hypoperfusion; LGE (may be seen if MRI done early)

sST2: Soluble suppression of tumorigenicity-2; sLOX-1: Soluble lectin like oxidized LDL receptor-1; IMA: Ischemic modified albumin; SPECT: Single photon emission computed tomography; BMIPP:  $\beta$ -Methyliodophenyl-pentadecanoic acid; MIBG: Metaiodobenzylguanidine; PET: Positron emission computed tomography; CMR: Cardiac Magnetic resonance imaging; LGE: Late gadolinium enhancement; MRI: Magnetic resonance imaging; LDL: Low-density lipoprotein; BNP: Brain natriuretic peptide.

(pheochromocytoma), exogenous catecholamine excess (Cocaine, Amphetamine), peripartum cardiomyopathy and cerebrovascular disease (Japanese guidelines have cerebrovascular disease as exclusionary criteria unlike the commonly used Mayo criteria). Other differential diagnosis for chest pain such as aortic dissection, pulmonary embolism should be considered as well.

## DIAGNOSIS

Several diagnostic criteria including the Modified Mayo<sup>[11]</sup> and Japanese<sup>[12]</sup> criteria have been proposed underlining the difficulty in diagnosis of TC. As per the widely used Modified Mayo criteria, all of the following 4 criteria must be met for diagnosing TC: (1) transient hypokinesia, akinesia, or dyskinesia of the LV mid segments with or without apical involvement; the regional wall motion abnormalities extend beyond a single epicardial vascular distribution; a stressful trigger is often, but not always present; (2) absence of obstructive coronary disease or angiographic evidence of acute plaque rupture; (3) new electrocardiographic abnormalities (either ST-segment elevation and/or T-wave inversion) or modest elevation in cardiac troponin; and (4) absence of pheochromocytoma and myocarditis. Several approaches have been proposed to facilitate differentiating TC from ACS. They include use of laboratory findings [catecholamine levels, cardiac biomarkers, lipid levels and investigational markers such as soluble lectin like oxidized LDL receptor-1 (sLOX-1), Copeptin, ischemic modified albumin (IMA), sST2 (soluble suppression of tumorigenicity-2), etc.], imaging

modalities [echocardiography, computed tomography (CT) coronary angiogram, invasive coronary angiogram, cardiac magnetic resonance imaging (CMR), single photon emission computed tomography (SPECT) and PET], EKG findings and risk scores.

## LABORATORY FINDINGS

More studies have focused on laboratory findings due to their universal availability at the time of presentation as well as availability of repeat measurements. Several markers including Copeptin<sup>[13]</sup>, lipid profile<sup>[14]</sup>, sLOX-1<sup>[15]</sup>, IMA<sup>[16]</sup>, sST-2<sup>[17]</sup> have been proposed for differentiating TC from ACS. High HDL-C and lower levels of LDL and triglycerides have been reported in TC compared to MI<sup>[14]</sup>. Forty percent of TC pts had hyperalphalipoproteinemia or hypotriglyceridemia. sLOX-1 elevation has been found comparable to troponin rise in ACS and is lower in non-ACS patients including TC<sup>[15]</sup>. Changes in level of sST2 have additional predictive value for TC in patients with normal Troponin I<sup>[17]</sup>. The most studied laboratory findings though are natriuretic peptides (NP), markers of cardiomyonecrosis (troponin I and T, creatine kinase and myoglobin) and catecholamines.

### NP

NP belong to a family of peptide hormones with natriuretic and vasodilatory properties in addition to other pleiotropic effects<sup>[18]</sup>. Atrial natriuretic peptide (ANP), BNP and C-type natriuretic peptide (CNP) constitute the natriuretic peptide family. Under normal conditions

ANP is primarily released from atria, BNP from both atria and ventricles (ventricles more than atria) and CNP from nervous tissue and vascular endothelium<sup>[19,20]</sup>. The NPs act *via* the natriuretic peptide receptors (NPR) NPR-A, NPR-B and NPR-C<sup>[18]</sup>. ANP and BNP act primarily through NPR-A leading to natriuresis, vasodilation, inhibition of aldosterone synthesis, thirst suppression, sympatholysis and inhibition of release of vasopressin and adrenocorticotrophic hormone<sup>[18,20]</sup>. Additional effects on pulmonary vasculature and airway smooth muscle cells have been described<sup>[20]</sup>. CNP which has less potent natriuretic effect, acts primarily *via* NPR-B and modulates vascular tone, cardiac remodeling and proliferation of vascular smooth muscle cells. Primary mechanism of NP clearance is by NPR-C mediated internalization and lysosomal degradation<sup>[21]</sup>. While ANP was discovered earlier in the 1980s, BNP and amino terminal proBNP (NT-proBNP) - an inactive by-product of BNP formation, have been more widely studied for their role in pathophysiology, diagnosis as well as treatment of heart failure.

### BNP

BNP is initially produced in the form of preproBNP a 134 amino acid (AA) peptide. Cleavage of the 26 AA signal peptide forms the proBNP which is further cleaved by enzyme Corin into active 32 AA BNP and inactive 76 AA amino terminal proBNP (NT-proBNP). BNP has a short half-life (about 20 min) and is cleared by neutral endopeptidase (Nepilysin) and by NPR-C mediated clearance. NT-proBNP has a longer half-life (120 min) and is cleared renally<sup>[22]</sup>. Use of neprilysin inhibitor (sacubitril) increases BNP levels by inhibiting its clearance but does not affect clearance of NT-proBNP<sup>[23]</sup>. Upper limit of normal in the non-acute setting is 35 pg/mL for BNP and 125 pg/mL for NT-proBNP<sup>[24]</sup>. In acute setting, higher cut-off values are recommended (BNP < 100 pg/mL and NT-proBNP < 300 pg/mL)<sup>[24]</sup>. In the Breathing Not Properly trial, BNP < 100 pg/mL had a high diagnostic accuracy of 83.4% to distinguish other causes of dyspnea from heart failure<sup>[25]</sup>. The PRIDE (ProBNP Investigation of Dyspnea) study proposed an age based cut-off for NT-proBNP (> 450 pg/mL for age < 50, > 900 pg/mL for age > 50) for diagnosing HF and < 300 pg/mL for ruling out CHF<sup>[26]</sup>. International Collaborative of NT-proBNP (ICON) study, a pooled analysis recommended a cut off of > 1800 pg/mL for age > 75<sup>[27]</sup>. Asians and african americans have higher levels compared to caucasians and hispanics<sup>[28]</sup>. Obese patients tend to have lower levels and heart failure with preserved ejection fraction (HfPEF) patients have levels lower than heart failure with reduced ejection fraction (HfrEF) patients<sup>[29,30]</sup>. Causes of BNP and NT-proBNP elevation include cardiac causes such as heart failure, ACS, valvular heart disease, pericardial diseases, atrial fibrillation, myocarditis, and cardioversion and non-cardiac causes such as advancing age, anemia, renal failure, pulmonary diseases, critical illness, sepsis,

burns, etc<sup>[24]</sup>.

### NP in TC

Reversible LV dysfunction without significant myocardial ischemia and or necrosis is the hallmark of TC, leading to significant elevation of NP. Among TC patients, the classic form of TC with basal hyperkinesis and apical ballooning appears to have higher degree of NP elevation compared to the basal (inverted) variant<sup>[8]</sup>. BNP has been correlated with the degree of basal hyperkinesis, measured by  $\delta$ Base (difference between end systolic and end diastolic dimension of the LV base measured 10 mm below aortic valve)<sup>[31]</sup>. NT-proBNP levels rise within first 24 h after the onset of symptoms with slow and incomplete resolution during the 3 mo thereafter<sup>[32]</sup>. NT-proBNP levels have been shown to correlate with plasma catecholamine levels and the severity of LV dysfunction, as measured by the wall motion score index and LV ejection fraction<sup>[32]</sup>.

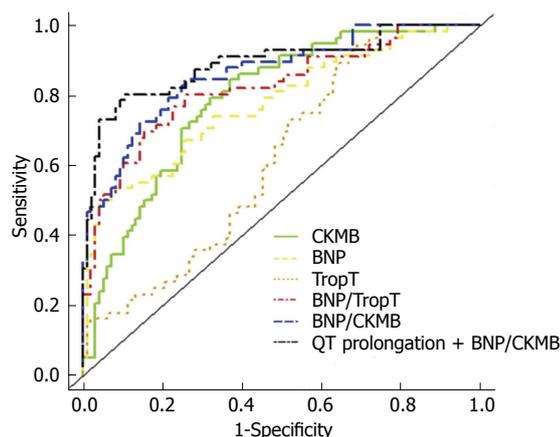
### Myonecrosis markers in TC

With lack of significant myonecrosis, TC patients usually have lesser degree of elevation of cardiac myonecrosis markers such as myoglobin, creatine kinase and troponin when compared to ACS patients. Studies comparing TC with anterior ST elevation myocardial infarction (STEMI) showed significantly lower mean peak troponin T levels in TC patients<sup>[33]</sup>. Some studies suggested threshold values for troponin to rule out TC while other studies contradicted it. Ramaraj *et al.*<sup>[34]</sup> found troponin T > 6 ng/mL or troponin I > 15 ng/mL were unlikely in TC but Song *et al.*<sup>[8]</sup> found about 20% of patients included in their study of TC patients had troponin I > 15 ng/mL. Among TC patients, inverted (basal) type TC patients tend to have higher elevation of myonecrosis markers<sup>[8]</sup>.

### Relative elevation of NP and Myonecrosis markers in TC

Comparing TC to STEMI, Madhavan *et al.*<sup>[35]</sup> found lower troponin (0.62 ng/mL vs 3.8 ng/mL), higher BNP (944 pg/mL vs 206 pg/mL) but no significant differences in plasma normetanephrine, metanephrine, cortisol or hs-CRP levels. Fröhlich *et al.*<sup>[36]</sup> found NT-proBNP (ng/L)/myoglobin ( $\mu$ g/L) ratio of 3.8, distinguished TC from STEMI, while a NT-proBNP (ng/L)/myoglobin ( $\mu$ g/L) ratio of 14, distinguished TC from NSTEMI. NT-proBNP (ng/L)/TnT ( $\mu$ g/L) ratio of 2889, distinguished TC from STEMI, while a NT-proBNP (ng/L)/TnT ( $\mu$ g/L) ratio of 5000 distinguished TC from NSTEMI. NT-proBNP levels usually peaked 22 to 26 h after a cardiac event, whereas TnT levels peaked 8 to 13 h after the first manifestation of chest pain. In a study of 52 patients with TC, Lahoti *et al.*<sup>[37]</sup> found higher NT-proBNP/troponin T in TC than in ACS patients (5154 vs 183). Peak BNP/peak troponin ratio > 2500 yielded a 90% sensitivity and specificity for TC.

Randhawa *et al.*<sup>[38]</sup> compared 58 patients and 97 acute myocardial infarction patients and found early

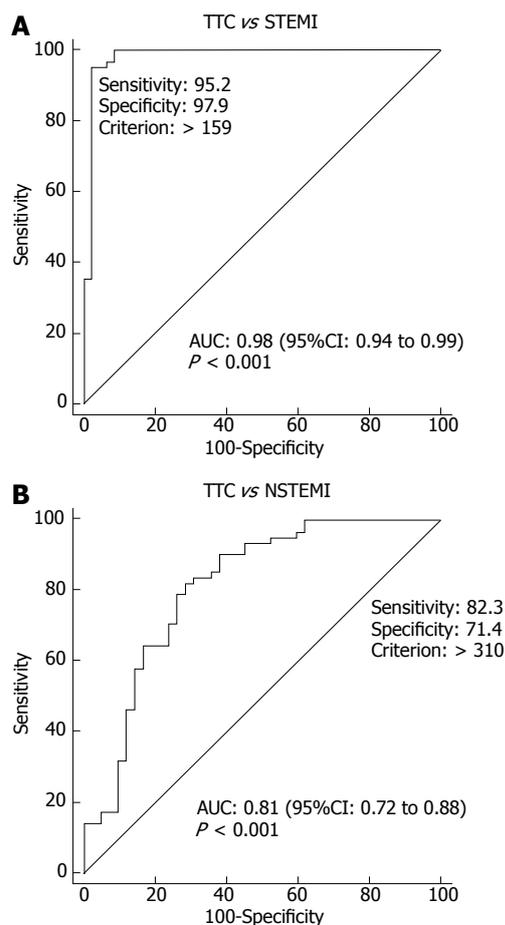


**Figure 1** Receiver operator characteristic analysis to distinguish acute myocardial infarction and takotsubo cardiomyopathy (Reproduced from Randhawa *et al.*<sup>[39]</sup>; Permission requested). BNP: Brain natriuretic peptide; CKMB: Creatine kinase - MB fraction.

BNP/TnT and BNP/CKMB ratios help to differentiate TC from AMI with greater accuracy than BNP alone. Median BNP/TnT and BNP/CKMB ratios were, respectively, 1292 and 28.44 in the TC group and 226.9 and 3.63 in the AMI group. TC was distinguished from AMI with 95% specificity with the use of BNP/TnT ratio of  $\geq 1272$  (sensitivity 52%) with area under the curve (AUC) of 0.822 and BNP/CKMB ratio  $\geq 29.9$  (sensitivity 50%) with AUC of 0.862. When QT prolongation was combined with BNP/CKMB, the AUC was even higher (Figure 1). Doyen *et al.*<sup>[39]</sup> found TnI elevations in TC comparable to anterior NSTEMI but lower than anterior STEMI, earlier peaking of troponin in TC than ACS (6 h vs 12 h) and higher BNP/TnI ratio (642) than anterior NSTEMI (184.5) or anterior STEMI (7.5). BNP/TnI ratio showed high area under the curve (AUC) in receiver operating characteristic (ROC) analysis. The AUC for TC vs STEMI was 0.98 (0.94 to 0.99) and TC vs NSTEMI was 0.81 (0.72 to 0.88) (Figure 2). The InterTAK registry study group<sup>[40]</sup> compared matched cohorts of 455 TC (out of 1750 TC patients in InterTAK registry) and 455 ACS patients. Median troponin levels in TC were not significantly different from ACS but CK and BNP levels were significantly different.

### InterTAK Diagnostic Score

InterTAK Diagnostic Score<sup>[39]</sup> was developed using a derivation cohort with TC patients recruited from the International Takotsubo Registry and ACS patients from a Zurich hospital (TC,  $n = 218$ ; ACS,  $n = 436$ ). The score has seven variables each with an assigned score value: Female sex 25, emotional trigger 24, physical trigger 13, absence of ST-segment depression (except in lead aVR) 12, psychiatric disorders 11, neurologic disorders 9, and QTc prolongation 6 points. A cut-off value of 40 score points yielded a sensitivity of 89% and specificity 91%. With a score of  $\geq 50$ , nearly 95% of TC patients were correctly diagnosed and with a score  $\leq 31$ , approximately 95% of ACS patients were diagnosed



**Figure 2** Receiver operating characteristic analysis for brain natriuretic peptide/ troponin I ratio to differentiate takotsubo cardiomyopathy from acute coronary syndrome in patients with (A) ST-segment elevation and (B) without ST-segment elevation (Reproduced from Doyen *et al.*<sup>[39]</sup>; Permission requested).

correctly<sup>[39]</sup>. The score was subsequently validated in an independent validation cohort (TTS,  $n = 173$ ; ACS,  $n = 226$ )<sup>[39]</sup>.

While several studies have reported higher levels of NPs in TC and higher troponin in ACS, utilizing ratio of NP to troponin, CKMB or myoglobin to differentiate TC from ACS in clinical practice is more complicated. As discussed earlier the cut off values used in different studies varied widely (Table 2). In general the ratio is higher for TC than ACS and among ACS the ratio is higher for NSTEMI compared to STEMI. The use of different markers for myonecrosis - troponin I and T, CKMB or myoglobin as well as ventricular stretch - BNP or NT-proBNP in different studies affects the wider applicability. Also, most of the studies used peak troponin and or NP levels instead of levels at presentation, which limits the utility of this ratio in avoiding cardiac catheterizations in acute settings. In addition, all these studies were retrospective. The InterTAK score derived from a large cohort study did not include cardiac biomarkers. In the derivation cohort, while the CK was higher in ACS patients and BNP higher in TC patients, the troponin levels were surprisingly higher in TC patients ( $6.67 \times$  ULN) compared to ACS

**Table 2** Natriuretic peptide/cardiac myonecrosis marker ratio in takotsubo cardiomyopathy and acute coronary syndrome

Ref.	Biomarker and time of collection	Takotsubo cardiomyopathy		Acute coronary syndrome	
Frölich <i>et al</i> <sup>[36]</sup>	NT-proBNP (peak)	Cutoff NT-proBNP/TnT to differentiate TC and NSTEMI		Cutoff NT-proBNP/TnT to differentiate TC and STEMI	
	TnT (peak)	5000		2889	
Lahoti <i>et al</i> <sup>[37]</sup>	NT-proBNP (mean)	NT-proBNP/TnT		NT-proBNP/TnT (STEMI)	
	TnT (peak)	5154 ± 1891.2		183 ± 128.9	
Randhawa <i>et al</i> <sup>[38]</sup>	First simultaneous BNP and TnT	BNP/TnT	BNP/CKMB	BNP/TnT (AMI)	BNP/CKMB (AMI)
		1292 (443.4-2657.9)	28.44 (13.7-94.8)	226.9 (69.9-426.3)	3.63 (1.1-10.0)
Doyen <i>et al</i> <sup>[39]</sup>	BNP (admission)	BNP/TnI		BNP/TnI (NSTEMI)	
	TnI (peak)	642 (331.8-1226.5)		184.5 (50.5-372.3)	
				7.5 (2.0-29.6)	

BNP: Brain natriuretic peptide; NT-proBNP: N-terminal proBNP; TnT: Troponin T; TnI: Troponin I; NSTEMI: Non-ST elevation myocardial infarction; STEMI: ST elevation myocardial infarction; CKMB: Creatine kinase-MB fraction.

patients (3.75).

### Catecholamines

With catecholamine excess thought to underlie the pathogenesis of TC, several studies have looked at catecholamine measurements with mixed results. Nguyen *et al*<sup>[32]</sup> reported correlation of peak NT-proBNP levels in TC patients with simultaneous plasma normetanephrine levels as well as LV ejection fraction. On the contrary Madhavan *et al*<sup>[35]</sup> found significantly higher elevation of BNP in TC patients compared to STEMI patients but similar plasma normetanephrine, metanephrine and cortisol levels. In their study majority of TC patients had normal 24-h urine metanephrines, catecholamines and cortisol.

### IMAGING

Echocardiographic findings in TC include reversible wall motion abnormalities extending beyond distribution of an epicardial coronary artery, basal hyperkinesis, LVOT obstruction, reversible MR and RV dysfunction. Reverse McConnell's sign with RV basal hyperkinesis and hypokinesis of RV apex has been described in TC<sup>[41]</sup>. Common coronary angiogram findings include absence of ruptured plaque or obstructive coronary artery disease. Coronary vasospasm with provocative maneuvers as well as delayed filling has been reported in TC patients. Ventriculogram often demonstrates the typical takotsubo-like shape. Microcirculatory dysfunction has been demonstrated in TC using index of microvascular resistance<sup>[42]</sup>. CMR findings include enhancement in T2-weighted images representing myocardial edema in the hypocontractile segments during acute phase and absence of first-pass perfusion hypoenhancement<sup>[43]</sup>. Evidence on late gadolinium enhancement (LGE) findings in TC are conflicting. Some studies suggest absence of LGE differentiates TC from ACS and myocarditis while other studies have reported reversible LGE in TC, if CMR is done in acute phase (< 72 h)<sup>[44,45]</sup>. Reduction of fatty acid metabolism during acute phase has been reported using <sup>123</sup>I-β-methyliodophenylpentadecanoic acid (BMIPP) imaging<sup>[46]</sup>. Reduced intramyocardial uptake

during <sup>123</sup>I-metaiodobenzylguanidine (MIBG) imaging suggests sympathetic denervation<sup>[46]</sup>. A reverse perfusion metabolism mismatch in PET with normal perfusion and reduced <sup>18</sup>F-fluoro deoxyglucose (FDG) uptake has been described in TC patients<sup>[43]</sup>.

### ELECTROCARDIOGRAM

Several EKG criteria have been proposed to help differentiate TC from ACS. These include lack or rarity of reciprocal ST depression, widespread T wave inversion, low QRS voltage on presentation, attenuation of QRS voltage in serial EKGs, QTc prolongation, frontal plane ST vector, ST segment elevation (STE) in aVR without STE in V1, lower rate of Q-waves, more frequent STE in the inferior leads, higher ratio of the sums of STEs in leads V4-V6 to the sums of STEs in leads in V1-V3, lower amplitude of STE (< 1.5 mm) and a summated amplitude of the S-wave in V1 plus the R-wave in V6 < 1.5 mV<sup>[47,48]</sup>. While these EKG findings could have additive value in diagnosis of TC, their diagnostic accuracy for TC diagnosis have been found wanting in some studies<sup>[49,50]</sup>.

### CONCLUSION

TC presents a diagnostic challenge by virtue of its similarity in clinical presentation with anterior wall STEMI. The different pathophysiology underlying these two processes leads to a differential degree of elevation in NP and troponin with NP relatively higher in TC and troponin relatively higher in STEMI. While conceptually sound, the use of various assays (BNP vs NT-proBNP, Troponin I vs Troponin T) and wide range in elevation of NPs and Troponin with significant overlap in these two conditions, limits the diagnostic utility of ratio of NPs and troponin. Use of uniform assays for NP and myonecrosis markers and larger trials could pave the way for wider use of NP/troponin ratio in clinical decision making in future.

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## Obesity paradox in patients undergoing coronary intervention: A review

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### Abstract

There is strong relationship between obesity and cardiovascular disease including coronary artery disease (CAD). However, the literature has shown better outcomes in higher obese patients who undergo percutaneous cardiovascular interventions for CAD, a phenomenon known as the obesity paradox (OX). In this review, we performed extensive search for OX in patients undergoing percutaneous coronary intervention. We also discussed possible mechanism OX and disparities in different race and sex.

**Key words:** Obesity paradox; Coronary artery disease; Obesity; Percutaneous coronary intervention; Racial disparities

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**Core tip:** Literatures have shown strong association between obesity and coronary artery disease (CAD). However, a phenomenon known as obesity paradox (OX) exist which means that obese patients who undergo percutaneous coronary intervention for CAD, they have better outcome compared to normal and underweight patients. New studies also suggest racial and sexual disparities in OX. Multiple mechanisms and patho-physiology have been implicated for OX. In this review, we performed literature search of OX undergoing percutaneous intervention, propose mechanism of OX and racial and sexual disparities.

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## INTRODUCTION

Obesity is a condition in which the body mass index (BMI) is above 30.0 kg/m<sup>2</sup><sup>[1]</sup>. According to the Centers for Disease Control and Prevention (CDC), more than one-third of United States adults, which account for 78.6 million people, are obese<sup>[1]</sup>. It is one of the leading health problems in the United States<sup>[2]</sup> and is strongly associated with a higher risk of developing cardiovascular diseases such as hypertension, coronary artery disease (CAD), heart failure (HF), and arrhythmias like atrial fibrillation<sup>[3]</sup>.

Obese individuals generally have increased total blood volume which is associated with hypertension, high stroke volume, and increased cardiac output as the heart has to pump blood against high pressure<sup>[4]</sup>. Increased cardiovascular workloads typically lead to left ventricular hypertrophy and dilation which can further contribute to dyslipidemia and diabetes mellitus - syndromes typically associated with obesity. In addition, obesity is also an independent risk factor for CAD, a condition which arises when blood flow through the arteries becomes constricted following a steady buildup of atherosclerotic plaques along the arterial walls. CAD also increases the cardiovascular workload and leads to the pathologies discussed above. A common strategy of treating CAD is through percutaneous coronary intervention (PCI), a non-surgical approach that involves catheterization of the coronary arteries. Interestingly, research has shown that obese people have better outcomes and fewer complications following a PCI, despite the high health risk of CAD, a phenomenon that has been termed as the obesity paradox<sup>[5]</sup>.

Since most studies suggest a significant relationship between obesity and cardiovascular risks, it is imperative to review the information available in case studies and controlled trials. Thus, the aim of the study is to present a better understanding of how obesity relates to specific medical conditions and their associated outcomes.

## RESEARCH METHODS

We searched PubMed, Ovid, and Google Scholar for English language articles using terms obesity, paradox, PCI, CAD in various combinations. The abstracts were reviewed and articles related to OX and PCI were examined in detail.

## OBESITY AND PCI

Obese individuals are at a higher risk of developing (CVD)<sup>[6]</sup> and obesity is a poor prognostic factor for cardiovascular mortality<sup>[7]</sup>. Nevertheless, a growing body of evidence suggest better outcome and prognosis

in this very population following some forms of intervention<sup>[5,8-13]</sup>. This obesity paradox basically refers to the observation that while the risk of developing coronary heart disease is greater in obese individuals, the clinical outcomes - including cardiovascular mortality, myocardial infarction (MI), and related complications - are less common in these individuals after a PCI (Table 1).

A systemic review by Gurm *et al*<sup>[14]</sup> of four different randomized controlled trials of platelet glycoprotein II b/III a inhibition showed that the 30-d and one-year post-PCI complications were worse in patients with low (below 18.4 kg/m<sup>2</sup>), normal (18.5-24.9 kg/m<sup>2</sup>), overweight (25-29.9 kg/m<sup>2</sup>), and excessive (above 40 kg/m<sup>2</sup>) BMI compared to the obese individuals (BMI 30-39.9 kg/m<sup>2</sup>). They analyzed the Prevention of Ischemic Complication (EPIC) trial, the Long-term Outcome with Abciximab GP II b/III a blockade (EPILOB) trial, the Integrilin to Minimise Platelet Aggregation and Coronary Thrombosis- II (IMPACT- II) trial and The Evaluation of Platelet II b/III A Inhibitor for Stenting (EPISTENT) trial. They analyzed 11300 patients for 30-d morbidity and mortality and 7290 patients for a 12-mo follow-up. They also observed a paradoxical effect in the obese group compared to the low, normal and overweight BMI patients after PCI. The 30-d mortality was statistically significantly lower and similar results were detected in the long-term follow-up.

In a cohort study, Angerås *et al*<sup>[15]</sup> analyzed 64436 patients from the Swedish Coronary Angiography and Angioplasty Registry. They divided the patients into two groups based on the significance of CAD and the treatment options (PCI, coronary artery bypass, or medical treatment). These patients were followed for up to 3 years for overall mortality. Their analysis showed a U-shaped mortality curve, with the least mortality in obese and overweight patients compared with normal, underweight, and morbidly obese patients. Hence, this study provides additional evidence of an obesity paradox.

In the Using the Rapamycin-Eluting Stent Evaluated at Rotterdam Cardiology Hospital (RESEARCH) registry, Younge *et al*<sup>[16]</sup> analyzed 1019 patients who underwent PCI and followed them for 7 years for all-cause mortality to determine the association between health status, BMI, and mortality. They found that the overall mortality was decreased in overweight compared with obese and normal weight patients.

Lazzeri *et al*<sup>[17]</sup> conducted a retrospective analysis to study the relationship between age and obesity in the outcome of ST-elevation MI (STEMI) in patients treated with primary PCI therapy. The study included 1268 patients who were divided based on their BMI and age. The study had 2.9% patients with a lean BMI, 31.8% with normal, 51.7% with overweight, and 13.6% with an obese BMI, out of which 68.1% were less than 75 years of age and 31.9% were above 75 years of age. All-cause mortality was measured during in-hospital stay and at 1-year follow-up. They

**Table 1** Summary of association between percutaneous coronary intervention and obesity

Ref.	Study population	Study design	Outcome measures	Relationship with obesity
Akin <i>et al</i> <sup>[2]</sup>	1436 normal weight, 2839 overweight, and 1531 obese patients	Retrospective Cohort Study	Primary endpoints were the rate of major adverse cardiac and cerebrovascular events and target vessel revascularization	Baseline clinical parameters were more severe in overweight and obese patients
Angerås <i>et al</i> <sup>[13]</sup>	64436 patients going under angiography. Patients were divided into 9 groups based upon BMI	Cohort Study	To investigate the relationship between BMI and mortality in patients with ACSs	Obese and overweight patients have least mortality compared with normal, underweight, and morbidly obese patients
Gurm <i>et al</i> <sup>[14]</sup>	4 randomized, controlled trials	Systematic Review	To study the impact of BMI on outcome patients undergoing PCI	Increased BMI is associated with reduced risk of complications after PCI
Kaneko <i>et al</i> <sup>[11]</sup>	1205 patients: 92 lean, 640 normal-weight; 417 overweight, and 56 obese	Retrospective Cohort Study	Impact of obesity on Japanese patients who undergo primary PCI	Over-weight and obese patients were independently associated with favorable long-term clinical outcomes after PCI
Lazzeri <i>et al</i> <sup>[17]</sup>	1268 patients: 37 lean, 403 normal, 656 overweight, 172 obese patients	Case Series	Impact of age on the prognostic value of BMI	In patients < 75 yr, overweight patients showed increased in-hospital mortality rate and a poorer long-term survival rate
Kosuge <i>et al</i> <sup>[20]</sup>	3076 patients undergoing PCI	Case Control Study	In-hospital mortality	BMI itself had no impact on in-hospital mortality in patients undergoing primary PCI
Sharma <i>et al</i> <sup>[19]</sup>	36 studies (12 CABG; 26 PCI)	Meta-Analysis	Total mortality, CV mortality, and myocardial infarction	The risk of total mortality, CV mortality, and MI was highest among underweight patients as defined by low BMI and CV mortality was lowest among overweight patients
Stähli <i>et al</i> <sup>[9]</sup>	1993 patients: 461 (23.1%) were of normal weight, 985 (49.4%) overweight, 396 (19.9%) obese, and 144 (7.2%) very obese	Retrospective Cohort Study	All-cause mortality	Overweight and obese patients had lower all-cause mortality
Lancefield <i>et al</i> <sup>[10]</sup>	4762 patients undergoing PCI	Meta-Analysis	In-hospital and 12-mo MACE and mortality rates after PCI	Overweight and obese patients had lower in-hospital and 12-mo MACE and mortality rates after PCI
Uretsky <i>et al</i> <sup>[5]</sup>	22576 hypertensive patients with coronary artery disease	Randomized Control Trial	Primary outcomes include first occurrence of death, nonfatal myocardial infarction, or nonfatal stroke	Obese patients had a decreased risk of primary outcomes
Kang <i>et al</i> <sup>[12]</sup>	3824 STEMI patients: 129 underweight, 1253 normal weight, 1959 overweight, 483 obese	Retrospective Cohort Study	In-hospital mortality, revascularization in 1 yr, mortality in 1 yr, and overall mortality	Obese patients had significantly lower in-hospital and overall mortalities
Numasawa <i>et al</i> <sup>[13]</sup>	10142 patients: 462 underweight, 5945 normal, 3100 overweight and 635 obese	Retrospective Cohort Study	In-hospital outcomes	Obese patients are at a lower risk for in-hospital complications during and after PCI
Younge <i>et al</i> <sup>[16]</sup>	1019 patients: 354 normal, 468 overweight, and 197 obese	Prospective Cohort Study	All-cause mortality	Overweight, but not obesity, was associated with a lower risk for 7-yr mortality in PCI patients
Wang <i>et al</i> <sup>[21]</sup>	6083 patients (normal: 1592; overweight: 3026; obese: 1465)	Retrospective Cohort Study	Clinical-driven repeat revascularization, including TLR and non-TLR	Obesity was not associated with TLR, but was associated with a higher risk of non-TLR

ACS: Acute coronary syndrome; BMI: Body mass index; CV: Cardiovascular; CABG: Coronary artery bypass grafting; MACE: Major adverse cardiac event; PCI: Percutaneous coronary intervention; STEMI: ST-segment elevation myocardial infarction; TLR: Target lesion revascularization.

concluded that patients with a lean BMI had the highest mortality across all age subgroups at short and long-term follow-ups, and younger obese patients (age < 75 years) showed the lowest mortality only at short-term follow-up. Their findings indicate that obese populations develop cardiovascular heart disease at a younger age compared with the lean population and therefore, have less all-cause mortality at short-term. They also concluded that the obesity paradox is age-related because most of the obese individuals included in the study were in the younger age groups and their current medical condition was based on their consistent weight in the obese range. Therefore, with intervention

and appropriate weight loss regimen, a majority of the health problems could potentially dissipate with the decrease in the patients' weights. The lowest mortality at short-term observed in the younger obese patients is an expected result because the medical intervention helped them to recover from their medical conditions. Therefore, based on the above findings, it can be inferred that the obesity paradox is related to age in some instances.

A study by Akin *et al*<sup>[2]</sup> analyzed the relationship between BMIs after PCI with drug-eluting stent (DES). The investigators followed patients who underwent PCI with DES to determine if they had major cardiac,

cerebrovascular events (MACCE), such as death, MI, or cerebrovascular accident, and target vessel revascularization (TVR) during their in-hospital stay and at 1-year follow-up. A total of 5806 patients were enrolled in this study, out of which 24.7% had normal BMI, 48.9% were overweight, and 26.4% obese. No difference was observed in overall in-hospital MACCE rate in relation to BMI. However, in-hospital death was noted to be significantly higher in patients with normal BMI compared with overweight and obese patients. At one-year follow-up, there was no significant difference in MACCE-free and TVR-free survival in relation to BMI. It can be concluded that no "obesity paradox" was observed in patients after PCI with DES.

Sharma *et al*<sup>[19]</sup> conducted a meta-analysis of 36 studies [12 coronary artery bypass graft (CABG) and 26 PCI] to investigate the relationship of BMI with total mortality, cardiovascular mortality, and MI post-PCI and CABG. They reported that the relative risk of total mortality, cardiovascular mortality, and MI was the highest among patients with low BMI and lowest among overweight patients<sup>[19]</sup>.

In another analysis limited to post-PCI patients, Sharma *et al*<sup>[19]</sup> noted that the total mortality, CV mortality, and MI were the highest among patients with low BMI at the end of a mean follow-up period of 1.6 years. The CV mortality was the lowest among overweight patients. The investigators explained that better outcomes in overweight and obese patients could have been influenced by age, as the severely obese patients in the study were younger than the normal-weight patients on average by 7 years for PCI and 4 years for CABG. Because their study was not a randomized trial, patients could have had unmeasured CVD risk factors that affected outcomes. They also reported that in the CABG subgroup, CV mortality was highest among severely obese patients; therefore, they stated that prospective studies were needed to determine associations between weight and outcomes and to explore any underlying mechanisms.

Stähli *et al*<sup>[9]</sup> assessed long-term mortality of 1993 patients undergoing chronic total occlusion (CTO) PCI at a tertiary care center. They studied patients according to different BMI categories: 23.1% were of normal weight, 49.4% were overweight, 19.9% were obese, and 7.2% were very obese. They found that compared with normal weight BMI patients (16.3%), overweight patients had a lower all-cause mortality (10.2%, log-rank  $P = 0.001$ ), while obese (11.1%, log-rank  $P = 0.08$ ) and severely obese (13.2%, log-rank  $P = 0.39$ ) patients had similar mortality rates. Being overweight was significantly associated with lower all-cause mortality. They concluded that overweight is associated with an improved survival in patients undergoing PCI for CTO, particularly in men.

Kosuge *et al*<sup>[20]</sup> studied 3076 patients to determine the impact of BMI on outcomes after PCI for acute myocardial infarction (AMI). They reported that obese patients had a higher frequency of diabetes mellitus,

hyperlipidemia, hypertension and smoking.

Wang *et al*<sup>[21]</sup> examined 6083 patients who were divided into three groups according to BMI: Normal ( $n = 1592$ ), overweight ( $n = 3026$ ), and obese ( $n = 1465$ ). The follow-up focused on clinical-driven repeat revascularization, including target lesion revascularization (TLR) and non-TLR. There was no significant difference in the incidence of TLR among normal, overweight, and obese patients (6.3% vs 6.1% vs 7.1%,  $P = 0.423$ ). In contrast, the incidence of non-TLR was significantly higher in obese patients compared with normal and overweight (8.4% vs 6.0% vs 5.8%,  $P = 0.003$ ). They concluded that, among patients undergoing PCI with DES, obesity was not associated with TLR but was associated with a higher risk of non-TLR.

## MECHANISM OF OBESITY PARADOX

Various possible mechanisms have been proposed for the observed obesity paradox in coronary heart disease. As BMI increases the size of coronary artery proportionally increase as well and small coronary artery are associated with worse outcome after PCI and CABG<sup>[22]</sup>. Another possible explanation could be that the obese patients are protected against malnutrition and wastage of energy, therefore cardiac remodeling after MI would be greater in obese compared to underweight patients. Obese patients have a high calorie reserve which is beneficial in case CAD induces cachexia, a known adverse prognostic factor in HF. The resulting weight loss also improves disease prognosis; in non-obese individuals however, any non-purposeful weight loss due to cachexia will have a detrimental effect on the patients' overall health<sup>[23]</sup>. In addition, the obese patients with heart disease are likely to make lifestyle changes that include better diet, caloric restrictions, daily exercise which can positively shift the disease prognosis. Obese patients also have an altered cytokine and hormonal profile which can be cardio-protective and to neutralize the harmful effects of other biological factors that are upregulated in acute and chronic heart disease. The high levels of the inflammatory TNF- $\alpha$  can be quenched by the high density of TNF- $\alpha$  receptors on the adipose tissues<sup>[24]</sup>. In addition, obese individuals have been shown to have significantly lower levels of circulating natriuretic peptides, which are associated with HF pathophysiology<sup>[25]</sup>. The higher levels of free lipoproteins in the obese also help block LPS and other inflammatory cytokines<sup>[26]</sup>.

## GENDER AND RACIAL DISPARITY IN OBESITY PARADOX

A recent cohort study by Vest *et al*<sup>[27]</sup> showed that overweight females with HF had a survival advantage compared to overweight males. They reviewed 3811 HF patients and determined the impact of BMI on mortality. When the data was adjusted for potential confounders,

the overweight and obese males did not show any significant survival advantage; in the females however, the mortality associated with HF was higher in normal weight group compared to the obese even after the confounding factors were adjusted.

An association between race and obesity paradox has also been explored. A retrospective study by Kokkinos *et al.*<sup>[28]</sup> correlated BMI with mortality in 2013 African-American and 2000 Caucasian males with a mean age 60 years. A correlation was observed between BMI and mortality in the entire cohort, the healthy weight participants had a significantly higher risk, a hazard ratio (HR) of 1.7, compared to the obese subjects. This association was stronger in the African-American group (HR 1.95) compared to the Caucasian group (HR 1.53). However, the study was not focused on the obesity paradox specifically among CVD patients as presence of a cardiovascular disease was not considered as an inclusion or an exclusion factor for the participants.

## LIMITATIONS

The hypothesis of obesity paradox is controversial as the respective studies are limited by various biases and limitations. Most studies on the obesity paradox are retrospective in nature and therefore do not present any evidence of a direct link between obesity and better CAD treatment prognosis. Obese patients with CAD usually present earlier to the clinicians compare to their leaner counterparts. Therefore, the prolonged survival seen in the obese may simply be an earlier detection. There is evidence that the higher blood pressures seen in obese individuals makes them tolerate and respond better to CAD medications<sup>[29]</sup>. This may be easily confused with an inherent cardio-protective mechanism in the obese. Smoking is a common risk factor for CAD onset and poor prognosis and is most correlated with individuals with leaner BMIs: This could be another reason for a perceived better prognosis in the obese<sup>[30]</sup>. CAD prognosis is often confounded by the presence of other patho-physiological conditions like cancer<sup>[30]</sup>. The obesity paradox has been negated in one study that used X-ray absorptiometry to directly assess body fat levels instead of using the BMI index<sup>[31]</sup>.

## CONCLUSION

There is an obesity epidemic and obese patients have higher prevalence of co-morbid conditions such as arrhythmia, hypertension, hyperlipidemia, diabetes mellitus, which then increase the risk for CAD. Studies have shown favorable outcome after coronary intervention in obese patients proving phenomenon OX. There is an also strong disparity between different sex and race for OX and further studies are needed to investigate these disparities.

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## Brugada type 1 electrocardiogram: Should we treat the electrocardiogram or the patient?

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syncope of presumed arrhythmic origin. Familial sudden cardiac death (f-SCD) is not a recognized independent risk factor. Finally, positive electrophysiologic study (+EPS) has a controversial prognostic value. Current ESC guidelines recommend implantable cardioverter defibrillator (ICD) implantation in patients with a Brugada type 1 ECG pattern if they have suffered a previous resuscitated cardiac arrest (class I recommendation) or if they have syncope of presumed cardiac origin (class IIa recommendation). In clinical practice, however, many other patients undergo ICD implantation despite the suggestions of the guidelines. In a 2014 cumulative analysis of the largest available studies (including over 2000 patients), we found that 1/3 of patients received an ICD in primary prevention. Interestingly, 55% of these latter were asymptomatic, while 80% had a + EPS. This means that over 30% of subjects with a Brugada type 1 ECG pattern were considered at high risk of SCD mainly on the basis of EPS, to which a class II b indication for ICD is assigned by the current ESC guidelines. Follow-up data confirm that in clinical practice single, and often frail, risk factors overestimate the real risk in subjects with the Brugada type 1 ECG pattern. We can argue that, in clinical practice, many cardiology centers adopt an aggressive treatment in subjects with a Brugada type 1 ECG pattern who are not at high risk. As a result, many healthy persons may be treated in order to save a few patients with a true Brugada Syndrome. Better risk stratification is needed. A multi-parametric approach that considers the contemporary presence of multiple risk factors is a promising one.

**Key words:** Brugada syndrome; Brugada type 1 electrocardiogram; Sudden cardiac death

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### Abstract

Patients with a Brugada type 1 electrocardiogram (ECG) pattern may suffer sudden cardiac death (SCD). Recognized risk factors are spontaneous type 1 ECG and

**Core tip:** On the basis of frail risk factors, many cardiology centers adopt an aggressive treatment in subjects with a Brugada type 1 electrocardiogram pattern who are not at high risk. As a result, many healthy persons may

be treated in order to save a few patients with a true Brugada Syndrome. Better risk stratification is needed, for example the adoption of a multiparametric approach.

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## INTRODUCTION

Brugada syndrome was first described by the Brugada brothers in 1992<sup>[1]</sup> as a distinct heritable clinical entity characterized by malignant arrhythmias in patients without organic heart disease and by a peculiar electrocardiogram (ECG) pattern consisting of coved-type ST elevation  $\geq 2$  mm in one or more leads from V1 to V3 (Brugada type 1 ECG pattern).

During the last 25 years, both in scientific papers and in current practice, the terms "Brugada type 1 ECG pattern" and "Brugada Syndrome" have frequently been used synonymously. Even the recent ESC guidelines on the prevention of sudden cardiac death (SCD)<sup>[2]</sup> equate the Brugada type 1 ECG pattern with Brugada Syndrome, basing the diagnosis of Brugada syndrome only on ECG criteria. This is, to say the least, curious, as the definition of any syndrome includes symptoms and various clinical and instrumental signs.

This semantic error has the deleterious consequence that any subject with a Brugada type 1 ECG pattern is considered to be at risk of SCD, both in the presence and in the absence of symptomatic or asymptomatic arrhythmias.

In medicine, similar mistakes have been made many times in the past when an ECG sign has been equated to a disease. For example, more than 60 years ago, negative T waves were defined by the Mexican School<sup>[3]</sup> as "ischemia", and this ECG anomaly was identified with coronary artery disease. This error was corrected only after many years, when it was demonstrated that negative T waves were not always a manifestation of myocardial ischemia; rather, they may be a nonspecific finding or may be due to various heart diseases (hypertrophic cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy, pulmonary embolism, *etc.*).

Likewise, a so-called Brugada type 1 ECG pattern, in addition to indicating a Brugada syndrome, may be a nonspecific, benign finding or the consequence of a right ventricular cardiomyopathy<sup>[4]</sup>, pulmonary embolism, *etc.* (Brugada phenocopies)<sup>[5]</sup>.

It follows that "Brugada type 1 ECG pattern" and "Brugada syndrome" should not be used as synonyms, even though, in the presence of a Brugada type 1 ECG, a Brugada syndrome in its asymptomatic phase may be suspected.

## CURRENT INDICATIONS FOR IMPLANTABLE CARDIOVERTER DEFIBRILLATOR IN PRIMARY PREVENTION IN SUBJECTS WITH BRUGADA TYPE 1 ECG PATTERN

Current ESC guidelines<sup>[2]</sup> recommend implantable cardioverter defibrillator (ICD) implantation in patients with a Brugada type 1 ECG pattern if they have suffered a previous resuscitated cardiac arrest (class I recommendation) or if they have syncope of presumed cardiac origin (class II a recommendation). In clinical practice, however, many other patients undergo ICD implantation despite the suggestions of the guidelines.

In 2014, Delise *et al.*<sup>[6]</sup> performed a cumulative analysis of the largest available studies<sup>[7-16]</sup>, which included a total of 2176 patients with a Brugada type 1 ECG pattern who had no history of cardiac arrest. In this study, we found that 1/3 of patients received an ICD in primary prevention.

In addition, our cumulative data<sup>[6]</sup> (Table 1) show that, frequently in clinical practice, indications for ICD implantation not only do not completely follow current guidelines, but also do not fully consider the weight of the various potential risk factors. Indeed, recognized risk factors are spontaneous type 1 ECG and syncope of presumed arrhythmic origin. In contrast, a drug-induced type 1 ECG pattern and the absence of symptoms identify a low risk<sup>[12-21]</sup>. Familial SCD is not a recognized independent risk factor<sup>[16,17,20]</sup>. Finally, +EPS has a controversial prognostic value<sup>[11,12,17,19,20]</sup>.

Interestingly, in our cumulative analysis<sup>[6]</sup>, of 566 patients who received an ICD in primary prevention, only 45% were symptomatic for syncope. In addition 65% had a spontaneous Brugada type 1 ECG pattern, while 35% had a drug-induced Brugada type 1 ECG. In contrast, 80% had a positive EPS (Table 1). In other words, ICD indication was mainly guided by EPS, to which a class IIb indication for ICD is assigned by the current ESC guidelines<sup>[2]</sup>.

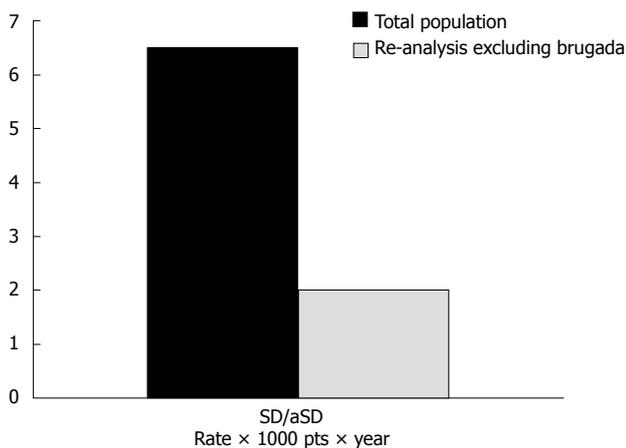
Further data come from a recent paper by Conte *et al.*<sup>[17]</sup>, of the Group of Pedro Brugada, who published their 20-year single-center experience of ICD implantation in patients with Brugada ECG pattern/syndrome. In this population, 151 patients received an ICD in primary prevention, 30% of whom were asymptomatic. In these 30 asymptomatic patients, the indication for ICD was mainly guided by a family history of Brugada syndrome (59%), f-SCD (59%) and +EPS (61%). Of note, the vast majority (76%) had a drug-induced type 1 ECG.

The main reason why many cardiologists do not follow guidelines and overestimate the risk of subjects with a Brugada type 1 ECG pattern stems from the frail scientific basis of currently used risk factors. Indeed, all prospective studies (ours included) which have

**Table 1** Prevalence of risk factors in patients without previous cardiac arrest who underwent implantable cardioverter defibrillator implantation in primary prevention, cumulative analysis of 5 large studies<sup>1</sup>

Studies	n. pts	Spont. type 1 ECG	Drug-I type 1 ECG	Fam. SCD	Syncope	Asympt.	+EPS/EPS performed
Sacher <i>et al</i> <sup>[6]</sup>	202	61% (124)	49% (78)	42% (85)	35% (70)	65% (132)	82% (153/187)
Kamakura <i>et al</i> <sup>[9]</sup>	70	66% (44)	34% (26)	23% (16)	46% (32)	54% (38)	87% (58/67)
Sarkozy <i>et al</i> <sup>[10]</sup>	47	62% (29)	38% (18)	55% (26)	55% (26)	45% (21)	83% (38/46)
Delise <i>et al</i> <sup>[11]</sup>	110	74% (82)	26% (28)	38% (42)	58% (64)	42%	85% (90/106)
Priori <i>et al</i> <sup>[12]</sup>	137	NA	NA	NA	NA	NA	72% (98/137)
Total	566	65% (279/429)	35% (150/429)	39% (169/429)	45% (192/429)	65% (237/429)	80% (437/543)

<sup>1</sup>From Delise *et al*<sup>[6]</sup>, modified. Spont.: Spontaneous; Drug-I: Drug-induced; Fam. SD: Familial sudden death; Asympt.: Asymptomatic; EPS: Electrophysiologic study; NA: Not available.



**Figure 1** Incidence of sudden cardiac death/aborted sudden cardiac death × 1000 patients × year in subjects with type 1 Brugada type 1 electrocardiogram pattern without implantable cardioverter defibrillator. Cumulative analysis of 1366 patients including and excluding the paper of Brugada *et al*<sup>[7]</sup> from Delise *et al*<sup>[6]</sup> modified. SD: Sudden death.

evaluated risk factors have been based on population registries<sup>[6]</sup>. Furthermore, all these studies have evaluated a combined end-point constituted by fast ventricular arrhythmias (FVA) recorded by ICD, and by SCD in subjects without ICD<sup>[6]</sup>. However, ICD-recorded FVA are only a surrogate of SCD<sup>[22,23]</sup>, as FVA are frequently self-terminating and do not necessarily lead to SCD. It follows that, in all these studies, any single risk factor probably overestimates the real risk of SCD.

In addition, all recognized and possible risk factors (spontaneous type 1 ECG, syncope, familial SD, +EPS), when tested singly against recorded FVA in patients with ICD, show an unsatisfactory performance: Variable sensitivity (ranging from 39% to 86%), low specificity (21%-61%) and low positive predictive value (ranging from 9% to 15%)<sup>[6]</sup>.

## CLINICAL OUTCOME OF SUBJECTS WITH BRUGADA TYPE 1 ECG

As all prospective studies have evaluated a combined end-point constituted by fast ventricular arrhythmias (FVA) recorded by ICD, and sudden death (SD) in subjects without ICD<sup>[6]</sup>, it is impossible to say what the

outcome of patients would be if they did not undergo ICD implantation. Indeed, no randomized studies have been performed that are able to establish the real risk of SCD and the ability of ICD to prevent it.

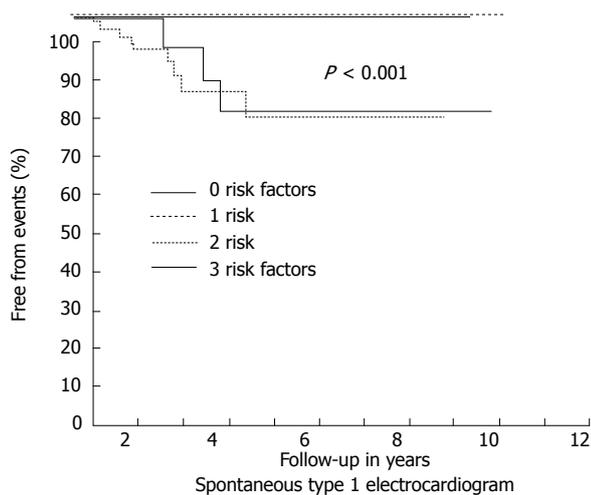
Despite these limitations, most prospective studies have shown that, in general, the risk of arrhythmias is low in asymptomatic patients, in those with drug-induced type 1 ECG and in those with negative EPS<sup>[6-17]</sup>. For example, in the study by Conte *et al*<sup>[17]</sup>, asymptomatic patients with ICD in primary prevention had an incidence of appropriate shocks of only 0.16 per year.

No prospective study has focused on the risk of SCD in patients without ICD. However, in our cumulative analysis<sup>[6]</sup>, we also analyzed 1366 patients without ICD separately. These patients were generally asymptomatic (84%) and did not have familial SCD (82%); about half (54%) had a spontaneous and about half (46%) a drug-induced type 1 ECG. EPS was positive in only 22%. In other words, most of them were correctly classified as being at low risk according to the guidelines. In these patients, SCD occurred in 6.5 per 1000 patients per year.

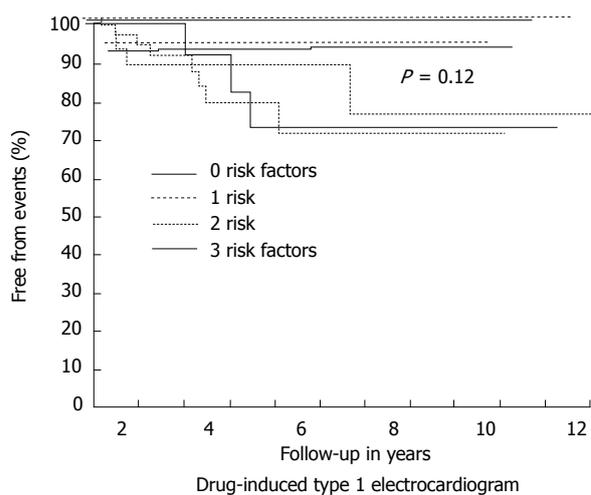
In a subsequent re-analysis of this population<sup>[24]</sup>, we excluded the 2003 paper by Brugada, because his population had a much higher risk than those of the remaining authors (high prevalence of familial SD, multiple risk factors, three-fold higher incidence of SCD). In this re-analysis, the incidence of SCD fell to 2 per 1000 patients per year (Figure 1). We can argue that patients classified as being at low risk according to the guidelines generally have a benign outcome.

## USEFULNESS OF A MULTIPARAMETRIC APPROACH FOR RISK STRATIFICATION

In 2011, our group<sup>[11]</sup> suggested that selecting patients on the basis of the presence of single or multiple risk factors could better stratify the risk of events. Specifically, on considering f-SCD, syncope and +EPS as risk factors, we found that, during follow-up, no events occurred in patients with either 0 or 1 risk factor, while events occurred only in patients with 2 or 3 risk factors. This was observed whether the patients had a spontaneous or a drug-induced Brugada type 1 ECG



**Figure 2** Incidence of events (appropriate implantable cardioverter defibrillator shocks + sudden cardiac death) in patients without implantable cardioverter defibrillator) in subjects with spontaneous Brugada type 1 electrocardiogram (from Delise *et al*<sup>[11]</sup> modified).



**Figure 3** Incidence of events (appropriate implantable cardioverter defibrillator shocks + sudden cardiac death) in patients without implantable cardioverter defibrillator) in subjects with drug-induced Brugada type 1 electrocardiogram (from Delise *et al*<sup>[11]</sup> modified).

(Figures 2 and 3). Similar results were reported by Okamura *et al*<sup>[25]</sup> in 2015.

Recently, Sieira *et al*<sup>[26]</sup>, from Pedro Brugada’s group, proposed a score model to predict the risk of events in patients with Brugada Syndrome. The model includes several risk factors: Spontaneous type 1 ECG (1 point), early f-SCD (1 point), +EPS (2 points), syncope (2 points), sinus node dysfunction (3 points) and previous aborted SCD (4 points). Interestingly, in line with our data, a significantly increased risk was observed in subjects with more than 2 points.

## CONCLUSION

In current clinical practice, many cardiology centers adopt an aggressive treatment in subjects with a Brugada type 1 ECG pattern who are not at high risk. Thus, these subjects undergo ICD implantation or experimental therapies such as ablation of the right ventricular outflow tract<sup>[27,28]</sup>. As a result, many healthy persons may be treated in order to save a few patients with a true Brugada Syndrome. The consequences of such a policy are deleterious in terms of the psychological impact on the subjects treated, the procedural risks involved and the costs accruing to the community.

The solution to this problem is not easy. However, it is reasonable to restrict indications only to high-risk patients, as indicated by the guidelines. Moreover, in addition to the indications provided in the guidelines, ICD implantation might be reasonable in subjects with multiple risk factors<sup>[11,25,26]</sup>. Finally, in controversial cases and/or in cases at low risk, it is a good rule to discuss indications, contraindications and complications with patients and their families, so that they are aware that there is still a risk, even though it is small.

In the future, only new scientific data will help us to better identify the risk of SCD in subjects with a

Brugada type 1 ECG pattern, a possibly misleading ECG sign.

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## Retrospective Cohort Study

**Clinical and anatomic predictors of need for repeat atrial fibrillation ablation**

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**Informed consent statement:** Consent was not obtained but the presented data are anonymized and risk of identification is low. Waiver for requirement of informed consent was obtained from the Emory University Institutional Review Board.

**Conflict-of-interest statement:** None reported.

**Data sharing statement:** Technical appendix, statistical code, and dataset available from the corresponding author at [faisal.merchant@emoryhealthcare.org](mailto:faisal.merchant@emoryhealthcare.org).

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**Abstract****AIM**

To identify predictors of need for repeat procedures after initial atrial fibrillation (AF) ablation.

**METHODS**

We identified a cohort undergoing first time AF ablation at our institution from January 2004 to February 2014 who had cardiac magnetic resonance (CMR) imaging performed prior to ablation. Clinical variables and anatomic characteristics (determined from CMR) were assessed as predictors of need for repeat ablation. The decision regarding need for and timing of repeat ablation was at the discretion of the treating physician.

**RESULTS**

From a cohort of 331 patients, 142 patients (43%) underwent repeat ablation at a mean of  $13.6 \pm 18.4$  mo after

the index procedure. Both male gender (81% vs 71%,  $P = 0.05$ ) and lower ejection fraction ( $57.4\% \pm 10.3\%$  vs  $59.8\% \pm 9.4\%$ ,  $P = 0.04$ ) were associated with need for repeat ablation. On pre-ablation CMR, mean pulmonary vein (PV) diameters were significantly larger in all four PVs among patients requiring repeat procedures. In multivariate analysis, increased right superior PV diameter significantly predicted need for repeat ablation (odds ratio 1.08 per millimeter increase in diameter, 95%CI: 1.00-1.16,  $P = 0.05$ ). There were also trends toward significance for increased left and right inferior PV sizes among those requiring repeat procedures.

### CONCLUSION

Increased PV size predicts the need for repeat AF ablation, with each millimeter increase in PV diameter associated with an approximately 5%-10% increased risk of requiring repeat procedures.

**Key words:** Atrial fibrillation ablation; Repeat ablation; Cardiac magnetic resonance imaging; Pulmonary veins; Imaging

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**Core tip:** Among patients undergoing initial atrial fibrillation ablation, those with larger pulmonary vein (PV) size determined by pre-procedure cardiac magnetic resonance imaging had an increased likelihood of needing repeat ablation procedures. Each millimeter increase in PV diameter was associated with an approximately 5%-10% increased risk of requiring repeat procedures.

Desai Y, Levy MR, Iravanian S, Clermont EC, Kelli HM, Eisner RL, El-Chami MF, Leon AR, Delurgio DB, Merchant FM. Clinical and anatomic predictors of need for repeat atrial fibrillation ablation. *World J Cardiol* 2017; 9(9): 742-748 Available from: URL: <http://www.wjgnet.com/1949-8462/full/v9/i9/742.htm> DOI: <http://dx.doi.org/10.4330/wjc.v9.i9.742>

### INTRODUCTION

Although catheter ablation can be an effective treatment strategy for atrial fibrillation (AF), approximately 1 in 6 patients will undergo repeat ablation within 1 year of their initial ablation procedure<sup>[1]</sup>. This has motivated the search for clinical and demographic parameters that might predict an increased likelihood of AF recurrence and need for repeat ablation.

Although many studies have assessed predictors of AF recurrence after ablation, it is unclear whether there are additional relevant predictors of need for repeat ablation. Among clinical variables, the pattern of AF (paroxysmal vs persistent), congestive heart failure, hypertension, tobacco use and gender have all been associated with risk of AF recurrence<sup>[2-4]</sup>, as have serum biomarkers such as C-reactive protein (CRP)<sup>[5]</sup>. Anatomic

characteristics identified on cardiac imaging have also been evaluated as predictors of AF recurrence. Prior studies have suggested that larger left atrial (LA) size and lower left ventricle ejection fraction (LVEF) are associated with increased AF recurrence after ablation, although a meta-analysis demonstrated significant heterogeneity across studies in the predictive capacity of these parameters<sup>[6]</sup>. Although the pulmonary veins (PVs) are known to play an important role in the pathophysiology of AF and prior studies have assessed differences in PV anatomy and geometry between patients with and without AF, the role of PV anatomic features as predictors of AF recurrence and need for repeat ablation have not been well characterized.

In this analysis, we sought to identify predictors of the need for repeat ablation in a cohort of patients undergoing initial AF ablation.

### MATERIALS AND METHODS

The Emory University institutional review board approved the study protocol. Patients at Emory University Hospital Midtown undergoing initial catheter ablation for AF between January 2004 and February 2014 who had pre-procedure cardiac magnetic resonance (CMR) imaging performed were included in this analysis. Baseline demographic data, clinical covariates, and procedural details were ascertained by review of electronic medical records. The decision to perform AF ablation along with specific details of the ablation strategy and peri-procedural management was performed at the discretion of the treating physician. PV isolation was the primary goal of all procedures, with additional substrate modification performed at operator discretion. The decision regarding need for and timing of repeat ablation was also left to the discretion of each operator.

All patients included in this analysis underwent pre-procedure gadolinium-enhanced CMR to delineate LA and PV anatomy. CMR was performed on a 1.5 Tesla Philips Intera® magnetic resonance imaging (MRI) scanner (Amsterdam, The Netherlands) using a five-element phased-array cardiac coil. PV anatomy was defined using turbo spin echo and gradient echo imaging in axial and double oblique planes following administration of gadopentetate dimeglumine (Magnevist®) or gadobenate dimeglumine (MultiHance®) at a dose of 0.075-0.10 mmol/kg. Orthogonal projections of angiographic images were used to measure PV and LA dimensions<sup>[7]</sup>.

### Statistical analysis

Continuous variables are presented as mean  $\pm$  SD, and categorical data are summarized as frequencies and percentages. Comparisons across groups were performed using the Student's *t* test or  $\chi^2$  test, as appropriate. A binomial logistic regression of variables with univariate  $P$ -value  $\leq 0.1$  was used for the multivariate analysis. For all comparisons, a two-tailed  $P < 0.05$  was considered to be statistically significant. Analysis was performed using MATLAB software (Mathworks, Inc., Natick, MA, United

**Table 1 Clinical predictors of need for repeat ablation *n* (%)**

Parameter	Single ablation ( <i>n</i> = 189)	Repeat ablation ( <i>n</i> = 142)	<i>P</i> value
Age (yr)	59.2 ± 10.8	57.4 ± 9.5	0.12
Male gender	135 (71)	115 (81)	0.05
Left ventricular ejection fraction	59.8 ± 9.4	57.4 ± 10.3	0.04
Hypertension	114 (61)	79 (57)	0.46
Coronary artery disease	29 (16)	15 (11)	0.22
Diabetes mellitus, type II	13 (7)	13 (9)	0.43
CVA or TIA	3 (2)	1 (1)	0.47
Obstructive sleep apnea	39 (21)	24 (17)	0.42
Congestive heart failure	13 (7)	7 (5)	0.48
Persistent atrial fibrillation	41 (22)	37 (27)	0.31
Medications at initial ablation			
Beta blocker	90 (49)	72 (53)	0.45
Calcium channel blocker	28 (15)	24 (18)	0.53
ACE-I or ARB	45 (24)	32 (24)	0.89
Statin	66 (35)	43 (32)	0.47
Warfarin	100 (54)	88 (64)	0.06
Direct OAC	62 (33)	33 (24)	0.07
Anti-arrhythmic drug			
Class III			
Amiodarone	19 (10)	12 (9)	0.68
Dronedarone	27 (15)	19 (14)	0.89
Sotalol	33 (18)	23 (17)	0.85
Dofetilide	9 (5)	12 (9)	0.15
Class Ic (Flecainide or Propafenone)	54 (29)	41 (30)	0.83
Procedural data			
Ablation time (min)	138.3 ± 55.2	148.4 ± 53.5	0.11

Age, left ventricular ejection fraction, and ablation time data presented as mean ± SD. For other clinical parameters, data presented as *n* (%). Demographic and clinical parameters stratified by patients who received single ablation procedure *vs* repeat ablation during study period.

States).

## RESULTS

A cohort of 331 patients underwent first time AF ablation with pre-ablation CMR scans. Of the entire cohort, 142 (43%) underwent repeat ablation at a mean of 13.6 ± 18.4 mo after the initial procedure. Among repeat procedures, 61% were performed primarily for recurrent AF and the remaining were performed primarily for organized atrial tachycardias. Touch-up lesions were performed on at least one PV for 69% of patients upon repeat ablation.

Across the entire cohort at the initial procedure, mean age was 58.4 ± 10.3 years and 24% had persistent AF, without significant differences between those undergoing a single *vs* repeat procedures. During the index ablation, 91% of patients had radiofrequency (RF) ablation and the remaining had Cryoballoon ablation, again without significant differences in the single *vs* repeat procedure groups. In addition to PV isolation, 101 (31%) patients underwent additional substrate modification during the initial procedure, including 79 patients who underwent linear lesions (either mitral annulus or LA roof) and 55 patients who

**Table 2 Anatomic predictors of need for repeat ablation**

Pre-ablation size parameters	Single ablation ( <i>n</i> = 189)	Repeat ablation ( <i>n</i> = 142)	<i>P</i> value
Right atrial area (cm <sup>2</sup> ) <sup>1</sup>	23.0 ± 5.8	24.4 ± 5.4	0.08
Left atrial area (cm <sup>2</sup> ) <sup>1</sup>	28.0 ± 5.3	29.3 ± 6.2	0.13
Pulmonary vein ostial diameter (mm)			
Right superior vein	19.4 ± 4.0	21.5 ± 4.3	< 0.01
Right inferior vein	18.0 ± 3.5	19.6 ± 5.8	< 0.01
Left superior vein	17.7 ± 3.4	18.7 ± 3.0	< 0.01
Left inferior vein	17.0 ± 2.7	18.6 ± 5.0	< 0.01

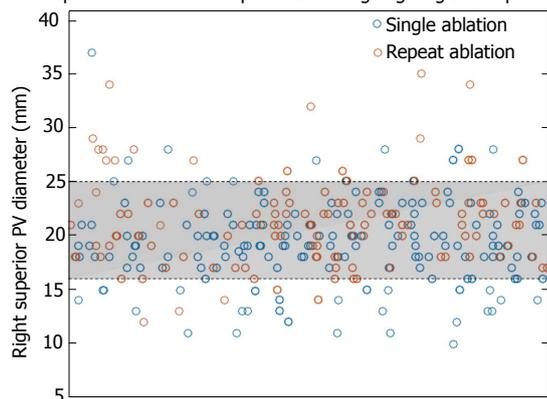
Data presented as mean ± SD. <sup>1</sup>Data reported for 123 patients in single ablation group and 81 patients in repeat group. Comparison of cardiac magnetic resonance parameters stratified by patients who received single ablation procedure *vs* repeat ablation during study period.

had LA complex fractionated atrial electrograms (CFAEs) ablated. Duration of the first ablation procedure, defined as the elapsed time between initial and final ablation lesions, was longer in patients who required repeat procedures, although the difference was not significant (148.4 ± 53.5 min *vs* 138.3 ± 55.2 min, *P* = 0.11).

Baseline clinical characteristics, stratified by patients with and without repeat ablation are shown in Table 1. Males were more likely to undergo repeat ablation (81% *vs* 71%, *P* = 0.05). Left ventricular ejection fraction was lower in patients undergoing repeat ablation, although the absolute difference between groups was small (57.4% ± 10.3% *vs* 59.8% ± 9.4%, *P* = 0.04). Other clinical parameters, including the prevalence of hypertension, coronary artery disease, diabetes mellitus and obstructive sleep apnea were similar between groups. Medications at the time of initial ablation were also similar.

Anatomic predictors of need for repeat ablation identified by CMR are presented in Table 2. Mean left and right PV ostial diameters were significantly larger in patients undergoing repeat ablation: Right superior PV, 21.5 mm ± 4.3 mm *vs* 19.4 mm ± 4.0 mm (*P* < 0.01); right inferior PV, 19.6 mm ± 5.8 mm *vs* 18.0 mm ± 3.5 mm (*P* < 0.01); left superior PV, 18.7 mm ± 3.0 mm *vs* 17.7 mm ± 3.4 mm (*P* < 0.01); left inferior PV, 18.6 mm ± 5.0 mm *vs* 17.0 mm ± 2.7 mm (*P* < 0.01). Although on average patients requiring repeat procedures had larger PVs, there was significant overlap in the distributions, making it difficult to identify clinically meaningful thresholds to predict an increased risk of need for repeat ablation. For example, in the distribution of right superior PV diameter, only 5% of patients with a single ablation had diameters > 25 mm, and among patients requiring repeat procedures, only 4% had right superior PV diameters < 16 mm (Figure 1). However, 80% of the measurements fell between 16 and 25 mm with significant overlap between those undergoing a single *vs* repeat procedures (Figure 1). Cumulative PV diameter was also significantly larger in patients who required repeat ablation: 78.5 ± 11.2 mm *vs* 71.6 ± 9.5 mm (*P* < 0.01), although there was

Overlap between PV size in patients undergoing single vs repeat ablation



**Figure 1** Distribution of right superior pulmonary vein ostial diameter measurements. There was significant overlap in the distributions of patients with single and repeat procedure, with 80% of all measurements falling between 16 and 25 mm. PV: Pulmonary vein.

still significant overlap in size compared with those who did not undergo repeat procedures. Of the 142 patients in the repeat ablation group, 96 (68%) required PV touch-up lesions during the second ablation. Patients who required touch-up lesions were more likely to have larger left inferior PV diameter on MRI before initial ablation:  $19.1 \pm 5.7$  mm vs  $17.5 \pm 3.0$  mm ( $P = 0.045$ ). Sizes of the other PVs were not significantly different between those who did and did not require PV touch-up at the second procedure.

Mean right ( $24.4 \pm 5.4$  cm<sup>2</sup> vs  $23.0 \pm 5.8$  cm<sup>2</sup>,  $P = 0.08$ ) and left ( $29.3 \pm 6.2$  cm<sup>2</sup> vs  $28.0 \pm 5.3$  cm<sup>2</sup>,  $P = 0.13$ ) atrial areas assessed by CMR were numerically larger in patients with repeat ablation, although the differences were not significant. Of note, due to evolution in the protocol for measuring atrial volumes by CMR at our institution, right and LA area data were only available for 204 out of 331 patients. There was a statistically significant but modest direct correlation between PV size and LA area for all but the left inferior PV (Figure 2). A multivariate linear regression of all 4 PVs with LA area was also significant ( $R^2 = 0.11$ ,  $P < 0.01$ ), demonstrating a direct relationship between PV and LA size. Male gender was also associated with larger PV size, although the results were only significant for the right superior PV [odds ratio (OR) = 1.10, 95%CI: 1.03-1.18,  $P < 0.01$ ] and left superior PV (OR = 1.19, 95%CI: 1.09-1.31,  $P < 0.01$ ).

Results of an analysis to identify multivariate clinical and anatomic predictors of need for repeat ablation are presented in Table 3. The only multivariate predictor of need for repeat ablation was larger right superior PV diameter (OR = 1.08 per millimeter increase in diameter, 95%CI: 1.00-1.16,  $P = 0.05$ ). There were also trends toward significance in multivariate analysis for increased left and right inferior PV dimensions as predictors of need for repeat ablation. Clinical variables including male gender and LVEF were no longer significant predictors of need for repeat ablation after

**Table 3** Multivariate analysis of anatomic and clinical predictors

Variable	Odds ratio (95%CI)	P value
Clinical parameters		
Male gender	1.53 (0.77-3.05)	0.23
LVEF	0.98 (0.95-1.01)	0.25
Warfarin	1.04 (0.43-2.51)	0.92
Direct OAC	0.59 (0.24-1.46)	0.25
Anatomic parameters		
Right superior PV diameter	1.08 (1.00-1.16)	0.05
Right inferior PV diameter	1.07 (0.99-1.15)	0.09
Left superior PV diameter	1.05 (0.95-1.16)	0.36
Left inferior PV diameter	1.10 (0.99-1.22)	0.07

Multivariate binomial logistic regression of clinical and anatomic variables with univariate  $P$  values  $\leq 0.1$ . LVEF: Left ventricle ejection fraction; PV: Pulmonary vein.

multivariate adjustment. It should be noted that despite a univariate  $P < 0.1$  ( $P = 0.08$ ), we excluded RA area from the multivariate analysis because only a small percentage of patients had data available.

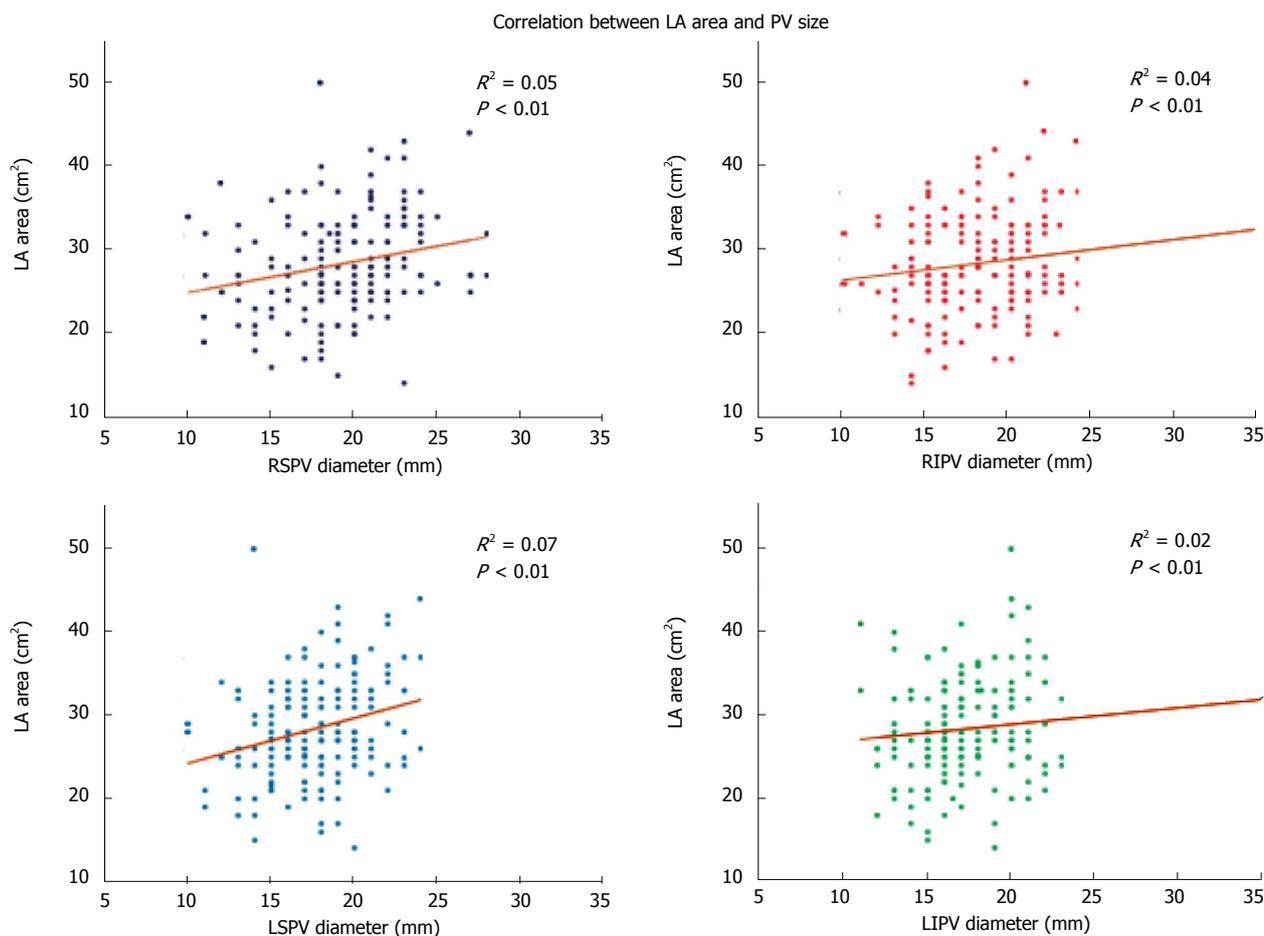
## DISCUSSION

In this cohort of 331 patients undergoing first time AF ablation, both clinical parameters including male gender and LVEF and anatomic characteristics assessed by CMR, most notably increased PV size, were associated with need for repeat ablation. However, in multivariate analysis, only increased PV size remained a significant predictor, suggesting that clinical factors may have limited utility in predicting the likelihood of repeat ablation. These findings also highlight the possibility that pre-procedure imaging may be useful in counseling patients undergoing initial AF ablation on the likelihood of needing repeat procedures and may facilitate more informed decision-making.

### Clinical predictors of need for repeat ablation

In our cohort, male gender was more prevalent among those requiring repeat ablation. Our findings regarding male gender are consistent with the results from the STOP-AF trial, in which the only clinical parameter predictive of early recurrence was male sex<sup>[4]</sup>. Interestingly, in our analysis, male gender was correlated with PV diameter, so it is conceivable that male gender is a marker for larger PV size and was thus no longer significant in multivariate analysis once PV size was taken into account.

Left ventricular ejection fraction was lower in patients undergoing repeat ablation, which is also consistent with previous findings looking at predictors of AF recurrence<sup>[8]</sup>. It should be noted, however, that in our analysis mean ejection fractions were in the normal range in both groups (single and repeat ablations) and the absolute difference in LVEF, although significant, was small. Such small differences in LVEF within the normal range are unlikely to have any clinically meaningful impact in helping to risk stratify patients likely to need



**Figure 2** Correlation between pulmonary vein size and left atrial area among all patients in the cohort. All but the left inferior pulmonary vein (PV) were significantly correlated with left atrial (LA) area, although the correlation coefficients were small. RSPV: Right superior pulmonary vein; RIPV: Right inferior pulmonary vein; LSPV: Left superior pulmonary vein; LIPV: Left inferior pulmonary vein.

multiple procedures.

None of the other clinical parameters in our study were significantly different between the cohorts who had a single ablation vs those who required repeat procedures. This corroborates the recent findings of Al-Hijji *et al*<sup>[9]</sup>, who studied predictors of repeat catheter ablation in a large study of over 8600 patients, and found no association between congestive heart failure, hypertension and diabetes and need for repeat ablation. Other studies have implicated obstructive sleep apnea in the pathophysiology of AF<sup>[10]</sup>, and, indeed, the total prevalence within our study population was 19%-greater than typical estimates of between 3%-7% in the general population<sup>[11]</sup>. However, the proportion of patients with OSA was not significantly different among patients requiring repeat ablation in our cohort. Broadly speaking, our data along with others suggest that clinical variables likely have limited utility in identifying those patients most likely to require repeat ablation procedures.

#### **Anatomic predictors of need for repeat ablation**

In contrast to clinical variables, several anatomic predictors assessed by pre-ablation CMR were signi-

ficantly different between those undergoing single vs. repeat ablations in our cohort. Previous studies have assessed anatomic predictors of AF recurrence after ablation. Two studies which used pre-ablation CT to characterize PV and LA anatomy found that anomalous PV anatomy (*e.g.*, presence of left common PV trunk or presence of middle accessory PVs) was not correlated with procedure outcome<sup>[12,13]</sup>. To our knowledge, only one other study investigated the effect of PV size. Our findings corroborate the results of Hauser *et al*<sup>[14]</sup> who reported that patients with at least one PV ostial area larger than 461 mm<sup>2</sup> were more likely to have early recurrence of AF and those with at least one PV area larger than 371 mm<sup>2</sup> were more likely to have late recurrence. The results of our multivariate analysis suggest that an increase in PV diameter of one millimeter is associated with a roughly 5%-10% increased likelihood of requiring a repeat ablation.

Although the pathophysiology of AF is not fully understood, it is known that the myocardial sleeves extending around the PVs are sites of enhanced automaticity and anisotropic conduction which may facilitate re-entry and provide some of the triggers and substrate necessary for AF<sup>[15]</sup>. Several hypotheses may explain why

larger PVs are associated with an increased likelihood of need for repeat ablation. Since the majority of patients in our study had point-by-point RF ablation, it is conceivable that with larger veins, permanent and transmural isolation is more difficult to achieve due to the need for larger/wider circumferential lesions resulting in a higher likelihood of gaps or recovery of conduction. Patients who required repeat ablation had numerically (although not statistically significant) longer initial ablation times, which may reflect a wider area requiring ablation around larger PVs. In contrast, rather than a purely anatomic explanation, it is also conceivable that larger PV size may be associated with larger LA size and reflect a more advanced atrial substrate or a higher prevalence of risk factors which may contribute to recurrence after ablation and need for repeat procedures.

Previous studies have shown that LA size is larger in patients with AF, and that larger LA size is an independent predictor of AF recurrence after ablation<sup>[16]</sup>. However, the association between LA size and PV size is inconsistent and not all studies have demonstrated a direct relationship<sup>[17]</sup>. In our cohort, LA size was weakly correlated with PV diameter. LA size was numerically larger in patients requiring repeat ablation, but the difference was not statistically significant. However, due to an evolution in the technique for measurement and reporting of atrial volumes at our institution during the course of this study, we were only able to report LA area in 204 of the 331 patients (61%), which raises the possibility that we were underpowered to detect a significant difference in LA size.

### Limitations

We used repeat ablation, as opposed to AF recurrence, as the primary endpoint for this study. Whereas AF recurrence is an objective measure and much has been reported about predictors of AF recurrence after ablation, need for repeat ablation is a more subjective endpoint and has been less well validated. Although thresholds for performing repeat ablation may vary between providers and across different patient circumstances, the need for repeat procedures has an important impact on resource utilization and is an important metric when counseling patients on expected outcomes after an initial procedure. We chose not to report data on AF recurrence in this cohort. During the time course covered by this analysis, many institutions, including ours, have evolved to more rigorous monitoring for recurrent arrhythmias after ablation, as reflected in the most recent HRS/EHRA/ECAS consensus statement on AF ablation<sup>[18]</sup>. Given this evolution, along with increasing numbers of patients with implantable devices capable of detecting AF, it is likely that our ability to detect clinically silent recurrent AF has improved significantly which would confound the results of any analysis looking at AF recurrence as an endpoint.

As an additional limitation, we cannot rule out the possibility that some patients underwent repeat procedures at another facility after having an initial ablation performed at our institution and therefore, would not

have been captured as needing repeat procedures for the purpose of this analysis.

Due to evolution in the technique for measuring and reporting atrial volumes on CMR at our institution, we were only able to report right and LA volumes on a subset of patients in the cohort and therefore, may have been underpowered for analyses involving atrial volumes. Lastly, we did not have data available to assess other anatomic parameters that may affect ablation outcomes, such as mitral valve pathology and PV anatomic variants.

### Conclusion

Our data demonstrate that increased PV size is an important predictor of outcomes after AF ablation, with each millimeter increase in PV diameter associated with a roughly 5%-10% increased risk of needing a repeat procedure. These findings suggest that results of pre-procedure cross-sectional imaging may be useful in counseling patients undergoing initial AF ablation on the likelihood of needing repeat procedures and may facilitate more informed decision-making. Additional study will be needed to determine whether ablation strategies can be altered at the time of initial ablation in patients with large PVs to mitigate the increased risk of needing repeat procedures.

## COMMENTS

### Background

Although many studies have assessed predictors of atrial fibrillation (AF) recurrence after ablation, it is unclear whether there are additional relevant predictors of need for repeat ablation. In this study, the authors analyzed clinical and anatomic predictors of need for repeat AF ablation.

### Research frontiers

A significant percentage of patients require repeat procedures after initial AF ablation and tools to identify those at highest risk of needing repeat procedures would be useful.

### Innovations and breakthroughs

Larger pulmonary vein (PV) size determined by pre-procedure cardiac magnetic resonance imaging had an increased likelihood of needing repeat ablation procedures. Each millimeter increase in PV diameter was associated with an approximately 5%-10% increased risk of requiring repeat procedures.

### Applications

The data suggest that pre-procedure magnetic resonance imaging may be useful in identifying individuals at highest risk for needing repeat AF ablation procedures.

### Peer-review

The manuscript is well written and highlights a popular topic with AF recurrence after pulmonary vein isolation.

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## Retrospective Study

**Utility and correlation of known anticoagulation parameters in the management of pediatric ventricular assist devices**

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**Informed consent statement:** Not applicable, retrospective study. Institutional review board waived need for consent for retrospective study.

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**Abstract****AIM**

To assess utility and correlation of known anticoagulation parameters in the management of pediatric ventricular assist device (VAD).

**METHODS**

Retrospective study of pediatric patients supported with a Berlin EXCOR VAD at a single pediatric tertiary care center during a single year.

**RESULTS**

We demonstrated associations between activated thromboplastin time (aPTT) and R-thromboelastography (R-TEG) values ( $r_s = 0.65$ ,  $P < 0.001$ ) and between anti-Xa assay and R-TEG values ( $r_s = 0.54$ ,  $P < 0.001$ ). The strongest correlation was seen between aPTT and anti-

Xa assays ( $r_s = 0.71$ ,  $P < 0.001$ ). There was also a statistically significant correlation between platelet counts and the maximum amplitude of TEG ( $r_s = 0.71$ ,  $P < 0.001$ ). Importantly, there was no association between dose of unfractionated heparin and either measure of anticoagulation (aPTT, anti-Xa or R-TEG value).

### CONCLUSION

This study suggests that while there is strong correlation between aPTT, anti-Xa assay and R-TEG values for patients requiring VAD support, there is a lack of relevant correlation between heparin dose and degree of effect. This raises concern as various guidelines continue to recommend using these parameters to titrate heparin therapy.

**Key words:** Ventricular assist device; Anticoagulation; BERLIN-EXCOR; Pediatric; Thromboelastography

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**Core tip:** This study suggests that while there is strong correlation between activated thromboplastin time, anti-Xa assay and R-thromboelastography values for patients requiring ventricular assist device support, there is a lack of relevant correlation between heparin dose and degree of effect. This raises concern as various guidelines continue to recommend using these parameters to titrate heparin therapy. A comprehensive strategy for appropriate anticoagulation may therefore warrant a combination of parameter monitoring and warrants further study.

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## INTRODUCTION

Appropriate anticoagulation continues to be a significant challenge in pediatric patients supported with ventricular assist devices (VADs). VAD implantation leads to dysregulation of hemostasis through contact of blood with foreign materials and introduction of shear forces that activate vascular endothelium, platelets, leukocytes and the coagulation cascade. This constellation of events increases the generation of thrombin and thus greatly increases the risk of thrombosis. Clinicians attempt to address the resultant imbalance between the pro- and anti-thrombotic states through the administration of anticoagulation and antiplatelet therapy. However, appropriate titration of these therapies in the pediatric population is challenging and resulting in various complications related to either a pro-thrombotic state leading to embolic complications or an overly anti-

thrombotic state presenting as post-operative bleeding, gastrointestinal bleeding or hemorrhagic stroke.

Despite technological advances in VAD design and development of new methods of anticoagulation, complication rates remain significant. Adults on VAD support have bleeding rate of 15%-50% while the risk of stroke has been reported at 5%<sup>[1,2]</sup>. Unfortunately the overall incidence of these complications in children with VAD appears to be higher<sup>[3-5]</sup>. While the VAD technology and anticoagulation agents are the same as those for adult patients, there are marked differences in dosing of medications, device performance characteristics in children and intrinsic differences in the maturity of the hemostatic system in children as they develop<sup>[6-9]</sup>. One retrospective study of 28 pediatric patients with various types of VAD demonstrated major bleeding in 29% and stroke in 25%. Given that there are several types of VAD that can be used in the pediatric population, and technology is constantly evolving, interpretation of older studies is challenging. The Berlin Heart EXCOR Pediatric VAD, a pulsatile extracorporeal device, is currently the most commonly used in pediatrics as it can accommodate a wide range of patient sizes and can support both the right and left heart as necessary. A prospective study comparing the Berlin Heart Pediatric EXCOR device to extracorporeal membrane oxygenation (ECMO) as bridge-to-transplantation demonstrated bleeding in 50% of patients and stroke in 29%<sup>[3]</sup> in the setting of a prescribed anticoagulation protocol with high degree of adherence.

The major obstacle to achieving adequate anticoagulation while minimizing the risk of hemorrhagic complications revolves around ineffective monitoring strategies and the lack of evidence-based pediatric guidelines to assist clinicians in modifying therapy. Various laboratory tests exist that measure specific components of the hemostatic system, including anti-Xa, activated thromboplastin time (aPTT), prothrombin time (PT), and international normalized ratio (INR), but none of these gives a complete picture of hemostasis<sup>[7,10-12]</sup>. Thromboelastography (TEG) has been proposed to more accurately demonstrate the *in vivo* state of hemostasis<sup>[13,14]</sup>. Specifically the R-value is thought to reflect the anticoagulant effect of heparin. Current VAD anticoagulation guidelines, including those adopted for clinical trials, lack standardization to guide heparin therapy<sup>[15]</sup>. In addition, there is very limited data on coagulation parameters in pediatric patients supported on VADs. This disconnect may explain why, in many cases, using target lab values to indicate degree of anticoagulation does not prevent poor clinical outcomes. This study attempts to assess the utility and correlation between various measures of anti-coagulation, including the value of TEG, in a cohort of patients who received the Berlin Heart Pediatric EXCOR VAD.

## MATERIALS AND METHODS

Anticoagulation parameters from four patients su-

Table 1 Patient demographics

	Patient 1 K	Patient 2 S	Patient 3 P	Patient 4 N
Diagnosis	DCM	DCM	CHB, DCM	DCM
Age	13 mo	5 mo	8 mo	10 yr
Weight	8.4 kg	7.2 kg	8.1 kg	24.5 kg
Gender	F	M	M	F
Type of VAD	LVAD	LVAD	LVAD	LVAD
Days on VAD	141	69	13	54
Outcome	OHT	OHT	OHT	OHT

Relevant clinical data from the four patients studied including diagnosis prior to receiving VAD, type of ventricular support (LVAD), absolute number of days on VAD support and eventual patient outcome. All patients received Berlin EXCOR devices as bridge to successful transplantation. DCM: Dilated cardiomyopathy; CHB: Congenital heart block; OHT: Orthotopic heart transplantation; LVAD: Left ventricular assist device.

supported with a Berlin Heart EXCOR VAD at a single center during 2013 were studied retrospectively. The study was approved by the institutional review board. Standard anticoagulation therapy was initiated for all of these patients after the implantation of the Berlin EXCOR VAD in accordance with the published guidelines<sup>[15]</sup>. All management decisions for anticoagulation and anti-platelet therapy were made by the VAD team, again with target levels for various parameters consistent with the published protocol. Briefly, our standard regimen included unfractionated heparin initiated typically about 12 h post-operative, followed by initiation of anti-platelet therapy with aspirin and dipyridamole typically, 48 h post-operative in the setting of good surgical hemostasis. This was followed by dose adjustments as needed based on monitoring parameters. Patients were monitored closely by assessing various anticoagulation parameters such as PT, aPTT, anti-Xa assay, complete blood count, fibrinogen level daily. TEG was performed using a TEG<sup>®</sup> 5000 Thrombelastograph<sup>®</sup> Hemostasis Analyzer system (Haemonetics Corporation, MA, United States). Kaolin TEG as well as heparinase TEG were both performed as part of a standard approach to assess whole blood anticoagulation related to heparin as well as the health of coagulation system without the heparin effect. Additionally, TEG was also used to perform platelet-mapping studies using the platelet agonists arachidonic acid (AA) and adenosine diphosphate (ADP) to study platelet inhibition achieved by aspirin and dipyridamole. We tabulated all laboratory tests that were ordered to both assess their coagulation system and to direct their anticoagulation therapy. Additionally, we tabulated incidental heparin dose at time of laboratory collection, as well as clinical data reflecting outcomes, adverse events, morbidities and mortality. Statistical analysis was performed using SPSS 21 software (SPSS Inc., Chicago, IL, United States). Continuous data are reported as mean  $\pm$  SD, categorical data are reported as frequency (%). Continuous data was compared using student *t*-test while  $\chi^2$  test was used for categorical

Table 2 Distribution of values for various measures of coagulation status

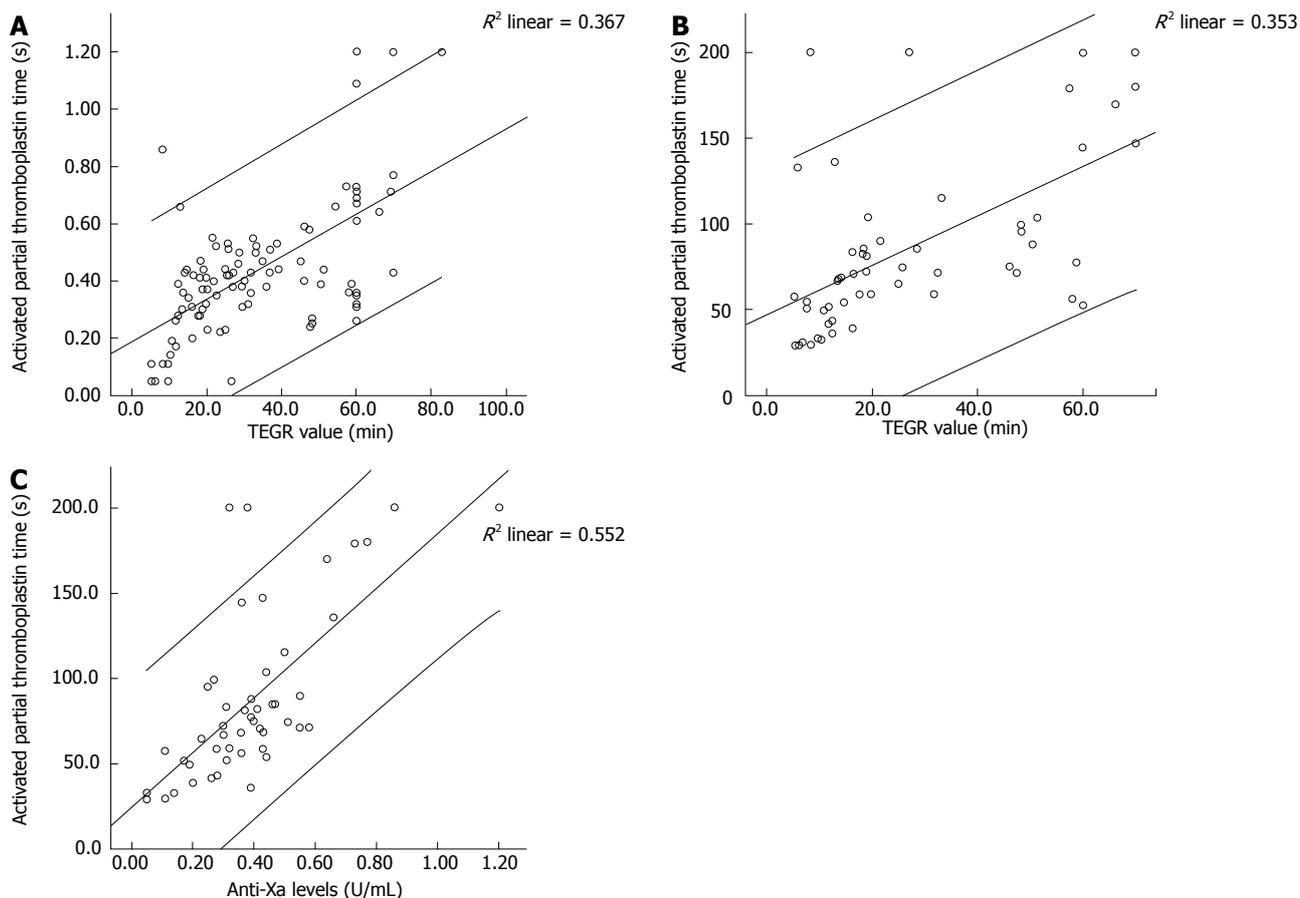
Test	<i>n</i>	Minimum	Maximum	mean	SD
Prothrombin time	97	12.5	30.8	14.542	2.34
Activated partial thromboplastin time (s)	98	26.1	200	79.779	44.62
INR	98	0.9	3	1.132	0.25
Anti-Xa levels (U/mL)	97	0.05	1.2	0.4381	0.24
TEG-R (min)	102	5.2	82.8	32.464	19.77
TEG-alpha angle	99	5.9	71.8	28.83	18
TEG-MA	98	10	75	46.002	18.08
TEG R (heparinase) (min)	102	5.1	34.5	8.455	3.2
TEG-K (heparinase)	102	0.8	12	2.029	1.12
TEG- $\alpha$ angle (heparinase)	102	17.8	74.4	63.306	7.3
TEG-MA (heparinase)	102	45.1	73	59.696	6.03
TEG-G (heparinase)	100	4.1	13.5	7.712	2.01
Platelet inhibition-ADP (%)	90	0	100	41.113	33.73
Platelet inhibition-AA (%)	91	0	100	43.69	37.05
Platelet count (k/ $\mu$ L)	131	77	451	267.05	89.6
Platelet volume	121	6.8	10.1	8.46	0.69
Heparin dose (units/kg per hour)	131	15	46	33.66	7.15

Summary of data are presented as number of individual data points (*n*) with value ranges, mean value and standard deviation given. TEG values without heparinase are represented by R (reaction time), ANGLE (alpha-angle), MA (mean amplitude). TEG values with heparinase are noted as RHEP, KHEP (K = coagulation time), ANGLEHEP, MAHEP and GAHEP (GA = overall clot strength). Percent of platelet inhibition *via* the AA and ADP pathways are shown. The range of administered heparin dose at the time of laboratory value collection is also presented. AA: Arachidonic acid; ADP: Adenosine phosphate; PT: Prothrombin time; aPTT: Activated thromboplastin time; INR: International normalized ratio.

variables. Spearman's Correlation was used to assess correlation between various tests. Statistical significance was defined as  $P < 0.05$ .

## RESULTS

Chart review of anticoagulation parameters from a total of four patients who were supported with the Berlin EXCOR Pediatric VAD during a single year yielded nearly 100 data points for every test. Three of the four patients had the primary diagnosis of dilated cardiomyopathy while the fourth patient carried a diagnosis of congenital heart block and developed pacemaker induced cardiomyopathy (Table 1). No other significant comorbidities, genetic syndrome or coagulation disorders noted prior to the implants. Indications for VAD placement were heart failure non-responsive to standard inotropic therapy with milrinone and need for a second agent (dobutamine), along with evidence of end-organ injury. The later was extremely poor tolerance of enteral feeds in 3 patients while it was increased need for respiratory support (including intubation) in one patient. Berlin EXCOR VAD implantation was performed in the standard fashion



**Figure 1** Scatterplots demonstrating correlation between standard measures of anticoagulation for patients on left ventricular assist device support. The estimated linear regression line (line of best fit) is shown along with 95%CI for individual value predictions for (A) anti-Xa and TEG-R levels, (B) aPTT and TEG-R levels, and (C) aPTT and anti-Xa levels. The  $R^2$  values are shown alongside each panel (all  $P < 0.001$ ). aPTT: Activated thromboplastin time; TEG: Thromboelastogram.

	aPTT correlation coefficient	<i>P</i>	Anti-Xa correlation coefficient	<i>P</i>	R-TEG correlation coefficient	<i>P</i>
aPTT	1		0.71	< 0.001	0.65	< 0.001
Anti Xa	0.71	< 0.001	1		0.54	< 0.001
R-TEG	0.65	< 0.001	0.54	< 0.001	1	

Spearman correlation analyses were used to determine the degree of correlation between aPTT, anti-Xa and R values (R-TEG). aPTT: Activated thromboplastin time; TEG: Thromboelastogram.

per manufacturer’s detailed instructions. There were no intraoperative complications.

**Measures of anticoagulation and correlations**

The results for the various tests are shown in Table 2. As noted, there was wide variation in the degree of anticoagulation achieved. We performed Spearman correlation testing to assess the relationship between individual tests measuring degree of anticoagulation, namely, aPTT, anti-Xa assay and R value on TEG. There was a strong and statistically significant correlation between all of these three parameters, with the strongest

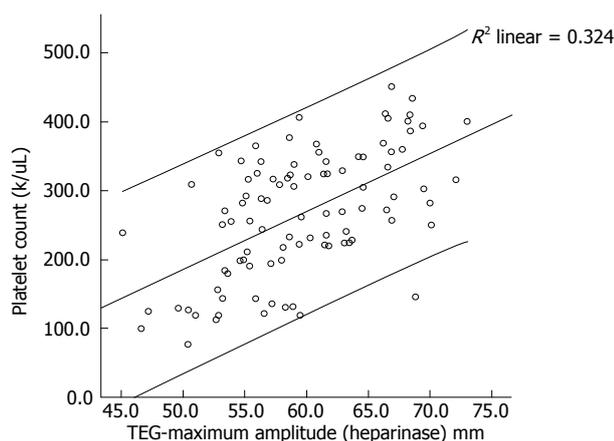
correlation existing between the aPTT value and anti-Xa assays ( $R^2 = 0.55$ , Spearman correlation coefficient of 0.71,  $P < 0.001$ ). R-TEG had correlation coefficients of 0.54 and 0.65 with anti-Xa and aPTT, respectively. These correlations are summarized in Table 3 and demonstrated in Figure 1.

**Role of platelets**

We also assessed the correlation between platelet count (PLT) and the maximum amplitude (MA) on TEG with heparinase added to nullify the heparin effect. We demonstrated that there was a strong and statistically significant correlation between the two values (Spearman correlation coefficient of 0.71,  $P < 0.001$ ) (Figure 2).

**Heparin dose and effect**

Similar to previous studies, we found no clinically relevant association between heparin dose and the degree of anticoagulation measured by the tests. There was no relationship between aPTT and Heparin dose (Figure 3A) giving a Spearman’s rho correlation coefficient of 0.152 and a  $P$  value of 0.168. Similarly, there was no correlation between the heparin dose and



**Figure 2 Correlation between platelet count and maximum amplitude after treatment with heparinase.** The estimated linear regression line (line of best fit along with 95%CI) is shown for platelet counts and TEG-MA (heparinase). Correlation coefficient of 0.541 ( $P < 0.001$ ). TEG: Thromboelastogram.

anti-Xa levels (Spearman's rho of  $-0.004$ ,  $P = 0.971$ ). There was weak correlation between heparin dose and TEG-R values (Spearman's rho of  $0.24$ ,  $P = 0.015$ ). To account for patient variation in response to heparin as well as inherent differences in the coagulation system in pediatric patients, we also performed a correlation analyses by patient. In this case, there was a large variation in correlation between heparin dosing and aPTT or anti-Xa levels for a given patient. The  $R^2$  value ranged from  $0.0318$  to  $0.108$  with a  $P$  value between  $0.01$  to  $0.18$  giving a statistically unstable model.

### VAD associated coagulopathy

It has been widely hypothesized that the circulatory support devices themselves induce a coagulopathic state beyond that induced by anti-coagulant therapy<sup>[7,16]</sup>. The degree and nature of coagulopathy was assessed using heparinase-TEG to neutralize the heparin effect. Figure 4 shows dot-density plots of the distribution of individual values for individual parameters such as R, K, Angle, Maximum Amplitude value obtained on heparinase TEG. As demonstrated in the panel, we found a wide variation in the health of the underlying coagulation system with variable demonstration of factor deficiencies as well as clot strength. Four point nine to 13.72% of all values for individual parameters were out of the normal range (represented by solid grey circles in the plots) suggesting significant coagulopathy or factor deficiencies. These findings were used to guide therapy for correcting the coagulopathy by administering appropriate factors in the form of cryoprecipitate or fresh frozen plasma.

### Outcomes

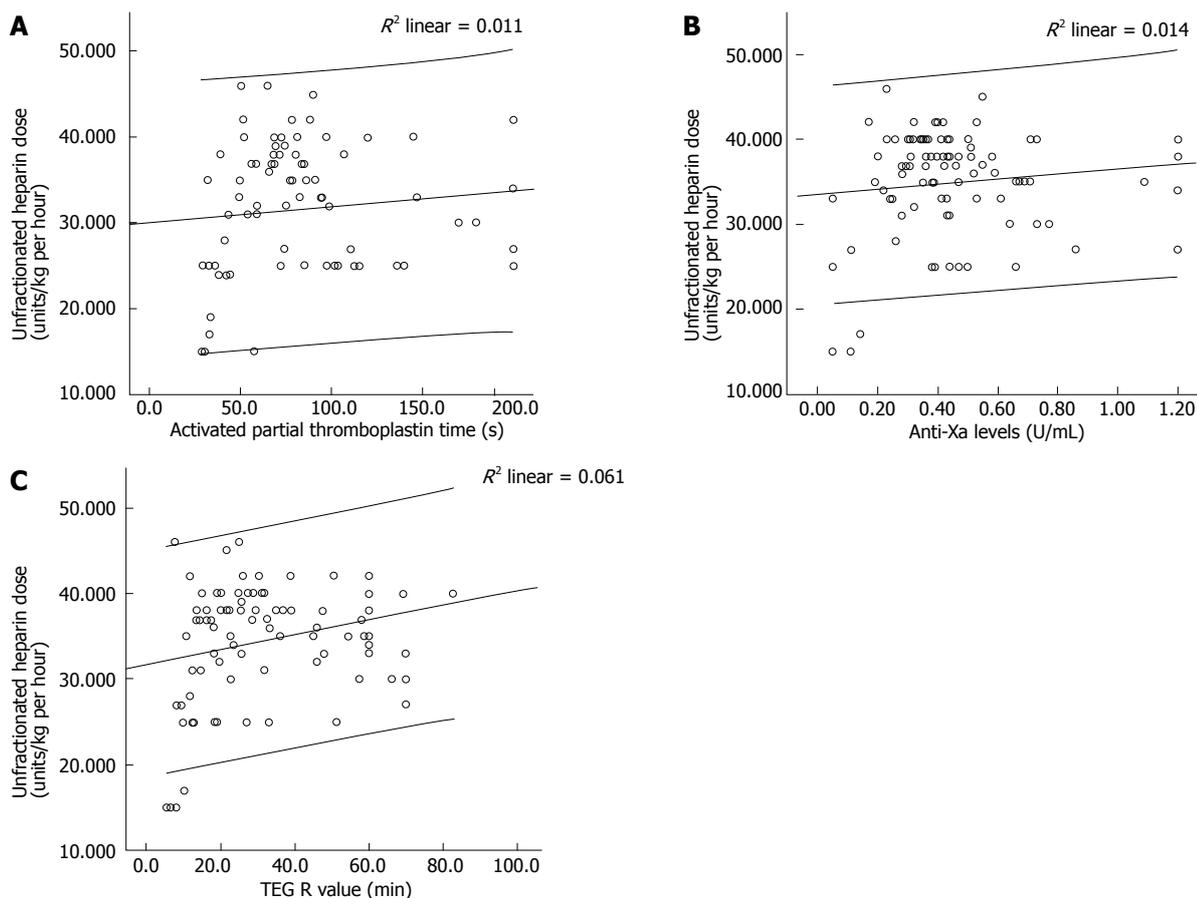
The mean duration of VAD support was 69.25 d (range 13 to 141 d). Two patients suffered stroke. One patient suffered an ischemic stroke with hemorrhagic conversion, a second patient suffered an ischemic stroke diagnosed by computed tomography (CT). Although the

exact timing of the strokes could not be ascertained, the degree of anticoagulation was within prescribed ranges for the 12 h before the CT scan and or clinical detection of the event. Both these patients made complete clinical recovery. A secondary endpoint was need for VAD pump change-out. A total of 8 pump exchanges were performed. The indications for pump change were made by the VAD team based on rate of clot growth, visualization of a dark clot measuring greater than 4 mm and subjective mobility of the clots. White clots and fibrin deposits in the blood chamber did not initiate pump exchanges, per manufacturer guidelines. Pump exchanges were well tolerated and did not result in any procedural complication. We were unable to identify predictors, such as degree of anticoagulation, fibrinogen levels, heparin dosing and the occurrence of either stroke or need for pump change. There were no mortalities in the cohort. All four patients underwent successful heart transplantation and at follow-up are alive and well.

## DISCUSSION

Managing anticoagulation in the pediatric VAD patient remains a challenging task. Failure to provide adequate anticoagulation results in thromboembolic events. Unfortunately, if the balance is tipped too far, devastating hemorrhagic complications may ensue. Clinicians are further stymied by the lack of evidence-based guidelines to direct therapy based on available laboratory data. The current study provides a direct comparison of these laboratory tests to determine their degree of correlation with one another as well as with anticoagulant effect. In a robust comparison sample of greater than 100 individual data points from four patients, our study showed very strong correlations between aPTT, anti-Xa assay and R-TEG (Figure 1). This is not unexpected, but demonstrates that these tests segregate together and may be substituted for one another, especially in the clinically relevant ranges.

The role of TEG in routine monitoring remains controversial<sup>[17]</sup>. While TEG has limitations, including difficulty with reproducibility, the utilization of TEG may be beneficial when employed routinely by experienced practitioners within a single center. Interestingly, we found a significant and clinically important correlation between platelet count and MA-TEG (Figure 2). This supports the importance of maintaining a normal platelet count and need for increased anti-platelet agents in the setting of thrombocytosis to manage the strength of clot formation. Additionally, TEG with- and without heparinase is important for diagnosing coagulopathy on VAD and guiding therapy. Furthermore, the presence of a wide range of values suggests a significant underlying coagulopathy that would otherwise be under-appreciated. This may be secondary to multiple factor deficiencies, prothrombotic microparticles or activation of coagulation factors. TEG may enable clinicians to monitor underlying VAD-induced coagulopathy and thereby explain how



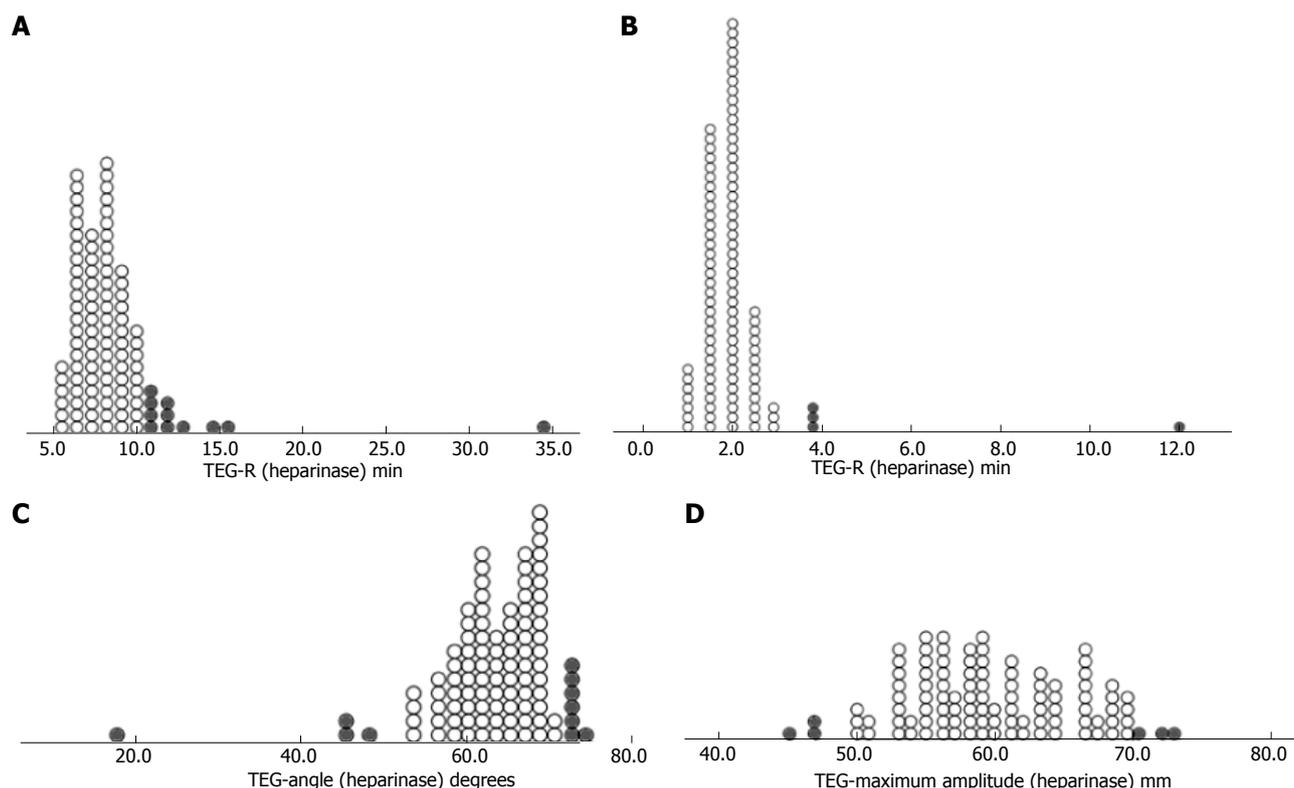
**Figure 3** Scatterplots demonstrating correlation between unfractionated heparin dose and (A) activated thromboplastin time (B) Anti-Xa levels and (C) thromboelastogram-R value. The estimated linear regression line (line of best fit) is shown along with 95%CI for individual value predictions. aPTT: Activated thromboplastin time; TEG: Thromboelastogram.

complications of anticoagulation therapy arise despite achievement of target levels for other coagulation parameters. We are currently validating this hypothesis using a larger cohort of patients that includes those dependent upon mechanical circulatory support devices as well as those requiring extracorporeal membrane oxygenation support.

One important observation from our investigation is the lack of relevant correlation between unfractionated heparin (UNFH) dose and degree of effect as measured by aPTT, anti-Xa or R value (Figure 3). This potentially reflects a significant variation in response to heparin by patient as well as by the coagulation milieu at any given time. These results differ somewhat from data that suggests good correlation between aPTT and UNFH levels in adults on extracorporeal life support (ECLS)<sup>[18]</sup> as well as a recent study in a small cohort of pediatric patients on ECLS<sup>[19]</sup>. These discrepancies may reflect variations in heparin response amongst patients due to developmental differences in hemostasis and genetic variability<sup>[20,21]</sup>. Lastly, none of these tests are specific in their assessment of the effect of unfractionated heparin *in vivo*. A lack of correlation between heparin dose and PTT or anti-Xa assay has also been noted in other settings, including a cohort of critically ill children<sup>[10]</sup>.

This is extremely relevant as various guidelines continue to recommend use of these monitoring parameters to titrate heparin therapy.

We also noted timing and significance of thrombotic or hemorrhagic events in our patient cohort. Three patients experienced significant morbidities. Two had an ischemic stroke and one had a hemorrhagic stroke. The older patient had an uneventful course. All patients eventually underwent successful bridge to transplantation and were discharged to home. At follow-up, all of them are alive. The patients with ischemic strokes have made a complete functional recovery, albeit after extensive rehabilitation. The patient who had hemorrhagic stroke still has speech delay and motor delay, but no deficits. Unfortunately, due to a small number of events, predictive modeling could not be performed to analyze further risk factors. Correlation of TEG and anticoagulation values with thromboembolic or hemorrhagic events in a larger patient cohort will provide valuable data as to the predictive ability of these tests. This study was also limited only to a single type of VAD. Future studies will include non-pulsatile and implantable devices such as Heartmate II or HeartWare HVAD in an effort to not only provide device-specific information, but also to determine if standards can be



**Figure 4** Dot-density plots of thromboelastogram (heparinase) parameters R (panel A), K (panel B), angle (panel C) and maximum amplitude (panel D) showing distribution of individual values. Abnormal values are represented by solid grey circles. TEG: Thromboelastogram.

applied across all devices.

This study provides valuable data regarding the utility of common laboratories to monitor the state of hemostasis in VAD patients, as suggested by existing guidelines. It also highlights the imprecise nature of current means of monitoring and demonstrates that multiple targets in the hemostatic pathway need to be targeted in order to achieve the desired balance between prevention of device thrombosis and hemorrhagic consequences.

## COMMENTS

### Background

Appropriate anticoagulation continues to be a significant challenge in pediatric patients supported with ventricular assist devices (VADs) resulting in high rate of complications related to bleeding or clotting related complications. Clinicians attempt to address the imbalance between the pro- and anti-thrombotic states through the administration of anticoagulation and antiplatelet therapy. However, the data regarding monitoring parameters is largely an extension of adult experience with very little data to support any pediatric monitoring strategies.

### Research frontiers

There is therefore an immediate need for improving our understanding of coagulation and anticoagulation parameters in pediatric patients on VAD as well as for studies that validated anticoagulation strategies.

### Innovations and breakthroughs

The current study provides a direct comparison of various laboratory tests to determine their degree of correlation with one another as well as with anticoagulant effect. In a robust comparison sample, this study showed very

strong correlations between activated thromboplastin time (aPTT), anti-Xa assay and R-thromboelastography (R-TEG). Additionally, the authors show that the dose-response relationship between heparin and these monitoring parameters is very weak, underscoring the authors' presumption that current guidelines for dose-titration based on anti-Xa levels may not be appropriate. Lastly, for the first time, the authors show the degree of underlying coagulopathy that can be assessed using TEG and underline the utility of the same.

### Applications

The study underscores the need for continued research in pediatric coagulation system especially within hitherto unexplored world of pediatric VAD and hopefully improves understanding of monitoring and management parameters to improve the morbidity and mortality associated with VADs.

### Terminology

VAD: Ventricular assist device, mechanical support as a circulatory assist; TEG: Thromboelastogram - a whole blood test for assessing the coagulation system in real time.

### Peer-review

This is an interesting manuscript about the utility and correlation of anticoagulation parameters such as aPTT, anti-Xa, and R-TEG in the management of pediatric VADs.

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## Observational Study

**Geometric comparison of the mitral and tricuspid valve annulus: Insights from three dimensional transesophageal echocardiography**

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Author contributions: Makaryus AN, Ismail H, Makaryus JN and Fan D were authors and researchers.

**Institutional review board statement:** This study protocol was approved by the North Shore University Hospital/Northwell Institutional Review Board and met criteria for expedited review under U.S. 45 CFR 46.110(5) for research involving materials (data, documents, records, or specimens) that have been collected, or will be collected solely for the non-research purposes (such as medical treatment or diagnosis).

**Informed consent statement:** This study was granted a Waiver of Consent and HIPAA Authorization by the North Shore University Hospital/Northwell Institutional Review Board.

**Conflict-of-interest statement:** No conflicts of Interest exist for any of the authors with respect to the publication of this article.

**Data sharing statement:** No additional data are available.

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**Abstract****AIM**

To apply real time three-dimensional transesophageal echocardiography (RT3D TEE) for quantitative and qualitative assessment of the mitral valve annulus (MVA) and tricuspid valve annulus (TVA) in the same patient.

**METHODS**

Our retrospective cohort study examined the MVA and TVA in 49 patients by RT3D TEE. MVA and TVA shape were examined by TEE. The MVA and TVA volume data set images were acquired in the mid esophageal 4-chamber view. The MVA and TVA were acquired separately, with optimization of each for the highest frame rate and image quality. The 3D shape of the annuli was reconstructed using the Philips® Q lab, MVQ ver. 6.0 MVA model software. The end-systolic frame was used. The parameters measured and compared were annular area, circumference, high-low distances (height), anterolateral-posterolateral (ALPM), and anteroposterior (AP) axes.

**RESULTS**

A total of 49 patients (mean age 61 ± 14 years, 45%

males) were studied. The ALPM and the AP axes of the MVA and TVA are not significantly different. The ALPM axis of the MVA was  $37.9 \pm 6.4$  mm and  $38.0 \pm 5.6$  mm for the TVA ( $P = 0.70$ ). The AP axis of the MVA was  $34.8 \pm 5.7$  mm and  $34.9 \pm 6.2$  mm for the TVA ( $P = 0.90$ ). The MVA and the TVA had similar circumference and area. The circumference of the MVA was  $127.9 \pm 16.8$  mm and  $125.92 \pm 16.12$  mm for the TVA ( $P = 0.23$ ). The area of the MVA was  $1103.7 \pm 307.8$  mm<sup>2</sup> and  $1131.7 \pm 302.0$  mm<sup>2</sup> for the TVA ( $P = 0.41$ ). The MVA and TVA are similar oval structures, but with significantly different heights. The ALPM/AP ratio for the MVA was  $1.08 \pm 0.33$  and  $1.09 \pm 0.28$  for the TVA ( $P < 0.001$ ). The height for the MVA and TVA was  $9.23 \pm 2.11$  mm and  $4.37 \pm 1.48$  mm, respectively ( $P < 0.0001$ ).

### CONCLUSION

RT3D TEE plays an unprecedented role in the management of valvular heart disease. The specific and exclusive shape of the MVA and TVA was revealed in our study of patients studied. Moreover, the intricate codependence of the MVA and the TVA depends on their distinctive shapes. This realization seen from our study will allow us to better understand the role valvular disease plays in disease states such as hypertrophic cardiomyopathy and pulmonary hypertension.

**Key words:** Mitral valve annulus; Tricuspid valve annulus; Three dimensional imaging; Real time three-dimensional transesophageal echocardiography

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**Core tip:** Three dimensional (3D) imaging of the heart has allowed for improved understanding and delineation of cardiac structure and function. Real time three-dimensional transesophageal echocardiography (RT3D TEE) has been on the forefront of allowing this 3D imaging to be used in mainstream cardiac practice for many years. The mitral valve annulus (MVA) and the tricuspid valve annulus (TVA) are multi-component complex structures and 3D imaging has allowed better understanding of their structure. Our study aims to apply RT3D TEE for quantitative and qualitative assessment and comparison of the MVA and TVA in the same patient. Gaining an understanding of the similarities and differences between these two valves will provide a better understanding of cardiac physiology and pathophysiology and thereby hopefully lead to improvements in clinical practice.

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## INTRODUCTION

The mitral valve annulus (MVA) and the tricuspid

valve annulus (TVA) are multi-component complex structures<sup>[1]</sup>. The anatomy and geometry of the MVA has been previously described in many studies that utilized advanced imaging techniques<sup>[2-5]</sup>. This allowed for a better comprehension of valve dysfunction and provided significant implications for surgical repair<sup>[5]</sup>. Similarly, the geometry of the TVA has been previously assessed in numerous studies utilizing real time three-dimensional transesophageal echocardiography (RT3D TEE) to allow for complete visualization of the cusps of this complex structure<sup>[1]</sup>. Furthermore, RT3D TEE can visualize atrio-ventricular valves from both the atrial and ventricular side in great detail<sup>[1]</sup>. Measurements of the MVA and TVA, both researched and documented in the literature, have not been routinely measured and compared in the same person. This study aimed to apply RT3D TEE for quantitative and qualitative assessment and comparison of the MVA and TVA in the same patients. Gaining an understanding of the similarities and differences between these two valves will likely provide a better understanding of cardiac physiology and pathophysiology and lead to improvements in clinical practice.

## MATERIALS AND METHODS

### Study population

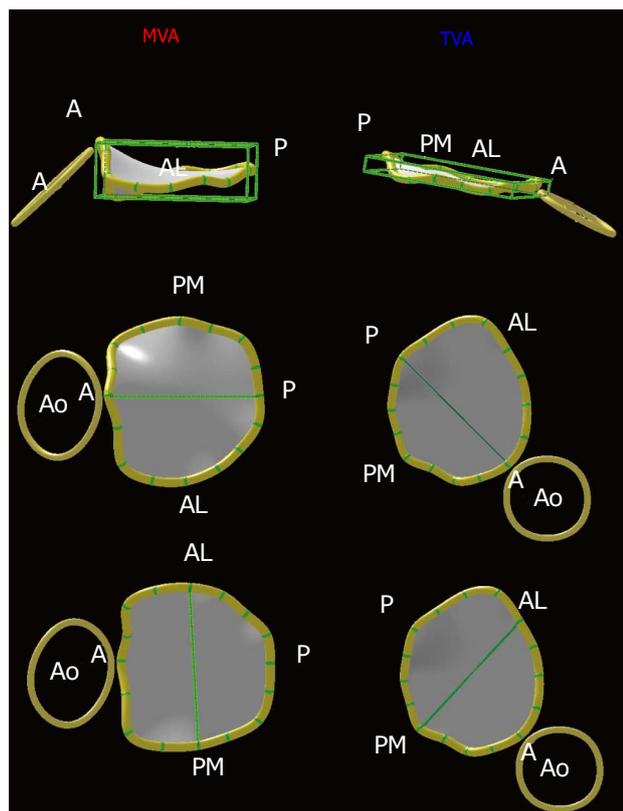
In this retrospective cohort study, the MVA and TVA were examined in forty-nine patients by RT3D TEE after institutional review board approval was obtained. The study population included all patients that were referred to the North Shore University Hospital Echocardiography lab for standard TEE during a three month period. The TEE performing physician was capable of performing RT3D TEE. All patients had sinus rhythm, no prosthetic rings, no mechanical/bioprosthetic valves, no  $> 2+$  MR or  $> 2+$  TR, no more than moderate MS/AS, no more than moderate chamber dilation, and no regional wall abnormalities. Only patients with optimal studies were included.

### Data acquisition and analysis

MVA and TVA shape were examined by TEE. The MVA and TVA volume data set images were acquired in the mid esophageal 4-chamber view. The MVA and TVA were acquired separately, with optimization of each for the highest frame rate and image quality. The MVA and TVA were never acquired in the same image because the frame rate was too low. The 3D shape of the annuli was reconstructed using the MVA model software (Figure 1, Philips® Q lab, MVQ ver. 6.0). The end-systolic frame was used. The parameters measured and compared were annular area, circumference, high-low distances (height), anterolateral-posterolateral (ALPM), and anteroposterior (AP) axes.

## RESULTS

A total of 49 patients (mean age  $61 \pm 14$  years, 45% males) were studied. Among the 49 patients 59% had hypertension, 18% had diabetes mellitus, 31% had



**Figure 1** Comparison of the mitral valve annulus to the tricuspid valve annulus using three-dimensional analysis software to provide detailed measurements of three-dimensional structure. MVA: Mitral valve annulus; TVA: Tricuspid valve annulus; AL: Anterolateral; PM: Posterolateral.

coronary artery disease, and 57% had dyslipidemia. Furthermore, 51% were on a beta blocker, 24% were on a calcium channel blocker, 39% were on an angiotensin converting enzyme inhibitor or angiotensin receptor blocker, and 57% were on a statin. The ALPM and the AP axes of the MVA and TVA are not significantly different. The ALPM axis of the MVA was  $37.9 \pm 6.4$  mm and  $38.0 \pm 5.6$  mm for the TVA ( $P = 0.70$ ). The AP axis of the MVA was  $34.8 \pm 5.7$  mm and  $34.9 \pm 6.2$  mm for the TVA ( $P = 0.90$ ). Similarly, the MVA and the TVA had similar circumference and area. The circumference of the MVA was  $127.9 \pm 16.8$  mm and  $125.92 \pm 16.12$  mm for the TVA ( $P = 0.23$ ). The area of the MVA was  $1103.7 \pm 307.8$  mm<sup>2</sup> and  $1131.7 \pm 302.0$  mm<sup>2</sup> for the TVA ( $P = 0.41$ ). The MVA and TVA are similar oval structures, but with significantly different heights. The ALPM/AP ratio for the MVA was  $1.08 \pm 0.33$  and  $1.09 \pm 0.28$  for the TVA ( $P < 0.001$ ). The height for the MVA and TVA was  $9.23 \pm 2.11$  mm and  $4.37 \pm 1.48$  mm, respectively ( $P < 0.0001$ ; Table 1).

## DISCUSSION

Two-dimensional echocardiography (2DE) has been utilized in previous studies and proved to be a valuable imaging modality for the functional assessment of the MVA and TVA<sup>[3-7]</sup>. However, 2DE did not provide detailed anatomical information of the MVA or TVA. Previous

**Table 1** Mitral and tricuspid annulus geometric measurement dimension comparison

Dimension	MV (mean $\pm$ SD)	TV (mean $\pm$ SD)	<i>P</i> -value
Circumference	$127.9 \pm 16.8$ mm	$125.9 \pm 16.1$ mm	0.23
Area	$1103.7 \pm 307.8$ mm <sup>2</sup>	$1131.7 \pm 302.0$ mm <sup>2</sup>	0.41
Height	$9.23 \pm 2.11$ mm	$4.37 \pm 1.48$ mm	$< 0.0001$
ALPM axis	$37.9 \pm 6.4$ mm	$38.0 \pm 5.6$ mm	0.7
AP axis	$34.8 \pm 5.7$ mm	$34.9 \pm 6.2$ mm	0.9
ALPM/AP ratio	$1.08 \pm 0.33$	$1.09 \pm 0.28$	$< 0.0001$

MV: Mitral valve; TV: Tricuspid valve; ALPM: Anterolateral-posterolateral; AP: Anteroposterior.

case studies exploited the advanced imaging technique of RT3D TEE in visualizing the MVA and TVA in different patients<sup>[1]</sup>. This present study demonstrates that RT3D TEE allows for the comprehensive analysis and exact characterization of the anatomy of the MVA and TVA in the same patient.

One of the salient findings in our study was that, although the MVA and TVA had similar annular areas, circumference, ALPM axes, and AP axes, they both have a bimodal pattern with significantly different heights. The MVA is more elevated, circular and saddle shaped. This property allows for a secure anchoring of the leaflets that may minimize leaflet stress<sup>[8,9]</sup>. This unique shape of the MVA may also be due to the common location of the anterior mitral leaflet and the right coronary aortic leaflet which are united by a fibrous region. On the other hand, the posterior part of the MVA appears to be more flexible from the muscular fiber received from the proximal aspect of the posterior leaflet<sup>[8]</sup>. These unique assets contribute to the dynamic nature of the MVA for its proper functioning. RT3D TEE allows us to understand the anatomy which is necessary for reconstructive surgery of the MVA in mitral valve (MV) disease. The aim is such to restore the normal MVA shape and dynamics to enhance repair durability.

The MVA has more of an elliptical-saddle shape that is planar and ovoid. The shape of the TVA stems from its bicuspid embryology<sup>[9,10]</sup>. The TVA has two high points and two low points oriented to the right atrium and the right ventricular apex, respectively. The elliptical shape contributes to the competency of the tricuspid valve (TV) throughout the cardiac cycle. The preservation of the unique shape of the TVA also depends on the normal and unique shape of the MVA during the cardiac cycle. RT3D TEE demonstrates that anatomically the TVA and MVA form a figure eight across the ventricular septum. The shape of the TVA is requisite during ventricular systole when the high pressure of the left ventricle bends the interventricular septum and mitral annulus towards the right ventricle. RT3D TEE allows for better dynamic imaging to help in surgical planning in TV stenosis and regurgitation<sup>[8-10]</sup>.

RT3D TEE plays an unprecedented role in the management of valvular heart disease. It allows for superior characterization of specific components of the valvular apparatus. Several studies have utilized RT3D TEE to

evaluate the MVA and TVA in different patients. The aim of this study was to evaluate the native MVA and TVA using RT3D TEE in the same patients. The specific and exclusive shape of the MVA and TVA was revealed in the patients studied. Moreover, the intricate codependence of the MVA and the TVA depends on their distinctive shapes. This realization seen from our study will allow us to better understand the role valvular disease plays in disease states such as hypertrophic cardiomyopathy and pulmonary hypertension.

## COMMENTS

### Background

Three dimensional (3D) imaging of the heart has allowed for improved understanding and delineation of cardiac structure and function. Real time three-dimensional transesophageal echocardiography (RT3D TEE) has been on the forefront of allowing this 3D imaging to be used in mainstream cardiac practice for many years. The mitral valve annulus (MVA) and the tricuspid valve annulus (TVA) are multi-component complex structures and 3D imaging has allowed better understanding of their structure.

### Research frontiers

Measurements of the MVA and TVA, both researched and documented in the literature, have not been routinely measured and compared in the same person.

### Innovations and breakthroughs

The study aims to apply RT3D TEE for quantitative and qualitative assessment and comparison of the MVA and TVA in the same patient. Measurements in the same patient with comparison of the MVA and TVA have not been routinely performed and documented. The authors used an innovative comparison of these two valve areas in the same patient.

### Applications

Gaining an understanding of the similarities and differences between these two valves will provide a better understanding of cardiac physiology and pathophysiology and thereby hopefully lead to improvements in clinical practice.

### Terminology

MVA: This is the fibrous ring that comprises the structural skeleton of the two mitral valve leaflets. The mitral annulus is generally saddle-shaped and its shape is dynamic throughout the cardiac cycle; TVA: This is the fibrous ring that comprises the structural skeleton of the three tricuspid valve leaflets. The tricuspid annulus is generally saddle-shaped and its shape is dynamic throughout the cardiac cycle; RT3D TEE: Three-dimensional visual tool employing echocardiography to achieve a better understanding and assessment of normal and pathological cardiac function and anatomy and the spatial relationships of the structures identified.

## Peer-review

This is an interesting manuscript.

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## Safety, efficiency and cost effectiveness of Bivalirudin: A systematic review

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### Abstract

#### AIM

To review the early and more recent studies of Bivalirudin,

to assess the safety, effectiveness, and cost benefits of this drug.

#### METHODS

Literature search of MEDLINE and PubMed databases from 1990 to 2017 using keywords as "bivalirubin" and "angiomax", combined with the words "safety", "effectiveness", "efficiency", "side effects", "toxicity", "adverse effect", and "adverse drug reaction".

#### RESULTS

A total of 66 publications were reviewed. The changes in clinical practice and differences in clinical protocols make it difficult to do direct comparisons of studies among each other. However, most trials showed decreased bleeding complications with bivalirudin, although ischemic complications and mortality were mostly comparable, with some favor towards bivalirudin.

#### CONCLUSION

Bivalirudin and heparin are both acceptable options according to current ACA/AHA guidelines. Authors conclude however, that due to bivalirudin safer bleeding profile, it should be the preferred medication for anticoagulation.

**Key words:** Efficiency; Cost effectiveness; Bivalirudin; Safety

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**Core tip:** Bivalirudin is a direct thrombin inhibitor used in clinical practice since 1990's. It was initially introduced as an alternative medication to heparin during percutaneous coronary intervention. Early studies showed advantages of bivalirudin over heparin. We did a systematic review of the literature since 1990 and summarized all relevant trials. The majority showed better outcomes with bivalirudin. However, some trials are difficult to compare directly as protocols and patient populations differ. Bivalirudin and heparin are both acceptable options according to current

ACA/AHA guidelines. Authors conclude however, that due to bivalirudin safer bleeding profile, it should be the preferred medication for anticoagulation.

Mehrzhad M, Tuktamyshov R, Mehrzhad R. Safety, efficiency and cost effectiveness of Bivalirudin: A systematic review. *World J Cardiol* 2017; 9(9): 761-772 Available from: URL: <http://www.wjgnet.com/1949-8462/full/v9/i9/761.htm> DOI: <http://dx.doi.org/10.4330/wjc.v9.i9.761>

## INTRODUCTION

To prevent peri-procedural thrombotic complications, anticoagulation is required during percutaneous coronary intervention (PCI) and other percutaneous transluminal coronary angioplasty. The most common anticoagulant regimens are unfractionated heparin (UFH) and low molecular weight heparins (LMWHs)<sup>[1]</sup>. Bivalirudin (Angiomax) is a specific and reversible direct thrombin inhibitor, used for anticoagulant in patients with unstable angina undergoing percutaneous transluminal coronary angioplasty, patients undergoing PCI, or in patients with, or at risk of heparin-induced thrombocytopenia (HIT), undergoing PCI<sup>[2]</sup>. Evidence from early trials has pointed unique advantages with this drug with predictable pharmacokinetics, avoidance of HIT, and perhaps most importantly, a reduction in bleeding complications. The purpose of this study is to review the early and more recent studies of Bivalirudin, to assess the safety, effectiveness, and cost benefits of this drug.

## MATERIALS AND METHODS

A literature search was performed of the MEDLINE and PubMed database from 1990-2017, using keywords as "Bivalirudin" or "angiomax", combined with the words "safety", "effectiveness", "efficiency", "side effects", "toxicity", "adverse effect", and "adverse drug reaction".

## RESULTS

### Drug information

Drug information was showed in Table 1.

### Early trials comparing bivalirudin to other anticoagulant drugs

In 1993, bivalirudin was introduced in a multicenter dose escalation study to overcome the theoretical limitations of heparin. The appropriate dose was set to 1.8-2.2 mg/kg per hour, and was suggested as a feasible sole anticoagulant drug in patients with stable or unstable patients undergoing elective coronary angioplasty. They documented that it was associated with rapid onset of action, dose dependent anticoagulant effect and minimal bleeding complications<sup>[3]</sup>.

In 1995, Bittl *et al*<sup>[4]</sup> performed a randomized, double

blind, multicenter study comparing bivalirudin with high dose [UFH (initial bolus of 175 U/kg)] in patients undergoing urgent coronary angioplasty for unstable angina, or post-infarction (< 2 wk after myocardial infarction) angina. The results showed that the overall safety profile of bivalirudin was found to be superior<sup>[5]</sup>. This study was also reproduced in 2001, with an intention to treat principle, using contemporary and more clinically accepted endpoints and reducing the proportion of the missing data. The results of this re-analysis showed, again, that bivalirudin reduced ischemic complications, defined as death, myocardial infarction (MI) or repeat revascularization, at 7 d (6.2% vs 7.9%,  $P = 0.039$ ), 90 d (17.5% vs 24.3%,  $P < 0.001$ ) and 180 d (24.5% vs 30.3%,  $P < 0.001$ ) follow-ups. This benefit was more apparent and persistent in the post-infarction angina patient group at 7 d (4.9% vs 9.9%,  $P < 0.009$ ), 90 d (13.3% vs 27.2%,  $P < 0.001$ ) and 180 d (20.3% vs 32.0%,  $P < 0.001$ ) follow-ups. This reanalysis also documented significantly lesser major hemorrhagic events with bivalirudin at 7-d, 90-d and 180-d follow-ups (3.5% vs 3.7% vs 9.3%,  $P < 0.001$ ). Thus, this study determined bivalirudin's unique and unexpected uncoupling of outcomes for an anticoagulant, *i.e.*, lesser ischemic events as well as lesser bleeding complications<sup>[6]</sup>. However, this study used a high dose UFH that might have exaggerated the benefits seen in major bleeding rates with bivalirudin.

The results of a double-blind, randomized HERO study in 1997 showed that bivalirudin can be used as an adjunct to improve the early patency achieved with streptokinase in STEMI patients presenting within 12 h. This effect of bivalirudin was found to be more effective than using UFH as an adjunct, and was achieved at a lower aPTT levels. Furthermore, it was not associated with increased bleeding risk<sup>[7]</sup>. The bolus dose of UFH in this study was 5000 U, which is approximately 71 U/kg in a 70 kg patient.

A meta-analysis was done, analyzing 11 studies with a total number of 35970 patients, comparing different direct thrombin inhibitors with UFH in patients with acute coronary syndrome (ACS) (including patients who underwent PCI). In this analysis, it was found that bivalirudin reduced the composite of death and MI and also reduced the major bleeding events<sup>[8]</sup>. But none of these eleven studies used glycoprotein II b/IIIa inhibitor.

Before Thienopyridine introduction, in 2001, Kleiman *et al*<sup>[9]</sup> performed a study on 42 patients who underwent elective PCI and they found that combining bivalirudin with eptifibatid is a feasible drug combination of choice. There were no major bleeding events, and only a single non-Q-wave MI occurred in a patient treated with bivalirudin. The CACHET study in 2001 was an open label, randomized trial performed on patients who underwent PCI for elective coronary balloon angioplasty or stenting. Patients with acute MI (< 12 h) were excluded. It showed that bivalirudin with planned or provisional abciximab was at least as

**Table 1 Dose information**

Dose	0.75 mg/kg IV bolus then 1.75 mg/kg per hour if no prior antithrombotic therapy is administered
Half life	For patients who have received UFH, wait 30 min, then give 0.75 mg/kg IV bolus, then 1.75 mg/kg per hour IV infusion Healthy patients: 25 min. The half-life is increased in patients with CKD, and is estimated to 3.5 h in dialysis-dependent patients
Mechanism of action	Reversible direct thrombin inhibitor. Thus, inhibits thrombin by directly binding to it
Theoretical advantages over heparin-	Directly inhibits thrombin Binds to clot-bound thrombin also Lab monitoring of efficacy is not required Does not cause HIT Short half life Almost nil thrombin induced platelet aggregation
Antidote and toxicity	No known antidote Should be discontinued 3 h before CABG In cases of toxicity, hemodialysis should be considered
CKD	Dose is reduced in patients with renal failure
Recommendations from the American College of Cardiology/ American Heart Association and European Society of Cardiology for the use of bivalirudin in patients undergoing PCI	Class of recommendation - I, level of Evidence-B For patients undergoing PCI: Bivalirudin is useful as an anticoagulant with or without prior treatment with UFH Class of recommendation - I, level of Evidence-C With HIT: It is recommended that bivalirudin or argatroban be used to replace UFH Class of recommendation - I, level of Evidence-B Either discontinue bivalirudin or continue at 0.25 mg/kg per hour for up to 72 h at the physician's discretion if given before diagnostic angiography and no PCI or CABG

PCI: Percutaneous coronary intervention; CKD: Chronic kidney disease; HIT: Heparin-induced thrombocytopenia; UFH: Unfractionated heparin.

safe and effective as UFH (initial bolus of 70 U/kg), plus planned abciximab in reducing the composite clinical endpoint of death, MI, repeat revascularization or major bleeding. However, this was a pilot study with a small sample size of only 268 patients<sup>[10]</sup>. The REPLACE-2 trial from 2003 was a randomized, double blind, active-controlled trial conducted among 6010 patients undergoing urgent or elective PCI. Patients presenting with acute MI were excluded. Study patients received either bivalirudin or UFH (65 U/kg initial bolus) plus glycoprotein II b/IIIa inhibitors (GPI). GPI were used provisionally in the bivalirudin group. This study showed that bivalirudin was not inferior to UFH plus GPI in reducing the incidence of ischemic events (death, MI and repeat revascularization) at 30-d (7.6% vs 7.1%,  $P = 0.40$ ) and 6 mo (18.8% vs 17.5%,  $P = 0.21$ ) follow-ups. The mortality in the bivalirudin group at 30-d (0.2% vs 0.4%,  $P = 0.26$ ), 6 mo (1.0% vs 1.4%,  $P = 0.15$ ) and 1 year (1.89% vs 2.46%,  $P = 0.16$ ) follow-ups is non-inferior to UFH plus GPI. However, the results were not statistically significant. The 30-d major bleeding episodes were statistically significantly lower in bivalirudin group (2.4% vs 4.1%,  $P < 0.001$ )<sup>[11]</sup>.

The, PROTECT-TIMI 30 from 2005, evaluated glycoprotein II b/IIIa inhibition role with eptifibatide when administered with indirect thrombin inhibition as compared with monotherapy with bivalirudin among patients with non-ST-segment elevation. 857 moderate to high risk patients with at least one or more of the following risk factors: Diabetes, a positive cardiac biomarker either CK-MB or troponin T/I, ST-segment deviation  $> 0.5$  mm,

or TIMI risk score  $\geq 3$ , was evaluated when presenting with chest pain or an anginal equivalent symptom at rest  $\geq 10$  min in the setting of a non ST elevation acute coronary syndrome, which were anticipated to undergo PCI of a native coronary artery. This study compared the combination of eptifibatide and heparin (UFH/enoxaparin) with bivalirudin. Results showed that the primary end point of post-PCI coronary flow reserve was significantly higher with bivalirudin (1.43 vs 1.33,  $P = 0.036$ ). The myocardial perfusion (post-PCI TMPG) was found to be better in eptifibatide group (57.9% vs 50.9%,  $P = 0.048$ ) and the 48 h post-PCI composite of death and MI was lower in eptifibatide group (8.8% vs 6.6%,  $P = 0.246$ ). Duration of post-PCI ischemia was also lower in eptifibatide group (36 min vs 169 min,  $P = 0.013$ ). In the UFH plus eptifibatide group, there were increased bleeding episodes, more notably TIMI minor bleeding episodes, (2.5% vs 0.4%,  $P = 0.027$ ) and bleeding episodes that required transfusion (4.4% vs 0.4%,  $P < 0.001$ ). This study showed that, moderate- to high-risk patients with ACS undergoing PCI, bivalirudin therapy lowers bleeding and the need for blood transfusion and is thus safer than heparin plus eptifibatide therapy<sup>[12]</sup>.

The ACUITY trial evaluated the role of bivalirudin in patients with moderate or high-risk ACS patients. Patients with acute ST elevation or shock were the important exclusion criteria in this study. The anti-thrombotic regimens used in this study were heparin (UFH or enoxaparin) plus GPI, bivalirudin plus GPI, and bivalirudin monotherapy. This trial was a 13819 patient, open label study in which the patients were randomized

to receive one of the above three antithrombotic regimens. Bivalirudin had comparable clinical outcomes in patients with moderate and high-risk acute coronary syndromes treated with glycoprotein II b/IIIa inhibitors in whom percutaneous coronary intervention is done as unfractionated heparin or enoxaparin. Moreover, anticoagulation with bivalirudin alone suppressed adverse ischemic events to a similar extent as does glycoprotein II b/IIIa inhibitors plus heparin, while also significantly lowering the risk of major hemorrhagic complications<sup>[13]</sup>.

The ARMYDA-7 BIVALVE study compared bivalirudin with UFH in 401 high-risk patients undergoing PCI. The inclusion criteria in this study was the following: Age > 75 years, diabetes mellitus (definitions according to the American Diabetes Association criteria), chronic renal failure (CrCl between 30 and 60 mL/min). Clopidogrel 600 mg was preloaded in all patients in this study. At 30-d follow-up, it was found that bivalirudin caused similar rates of MACE, *i.e.*, cardiac death, MI, stent thrombosis, or target vessel revascularization (11.1% vs 8.9%  $P = 0.56$ ) with significantly lower rates of bleeding (1.5% vs 9.9%,  $P = 0.0001$ )<sup>[14]</sup>. One of the important exclusion criteria was to exclude patients who were undergoing primary PCI for acute MI.

The HORIZONS-AMI (Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction) was, open-label, randomized trial done on 3602 patients who were undergoing primary PCI for STEMI (presentation from onset of symptoms < 12 h). Patients were randomized to receive bivalirudin or UFH (initial bolus of 60 U/kg) plus GPI (control). Patients then underwent randomization to bare metal or paclitaxel-eluting stents. Ninety-two point seven percent of patients underwent primary PCI and the rest were treated either medically or by primary CABG. A very small portion of patients were deferred PCI (0.2%). Ninety-four point five percent of patients received GPI in patients who were assigned to UFH plus GPI. Seven point two percent of patients in the patients assigned to bivalirudin group required GPI (mainly because of absence of reflow or giant thrombus after PCI). At 30 d, the MACE rates were significantly lower in bivalirudin group (9.2% vs 12.1%,  $P = 0.005$ ). Bivalirudin group patients also had lower rates of non-CABG-related major bleeding (NCRMB 4.9% vs 8.3%,  $P < 0.005$ ) and all-cause mortality (2.1% vs 3.1%,  $P = 0.047$ ). The significant benefit in the NACE rates was mainly due to the lower major bleeding rates in the bivalirudin group<sup>[15]</sup>. At one year, reductions in MACE (15.6% vs 18.3%,  $P = 0.022$ ), NCRMB (5.8% vs 9.2%,  $P < 0.0001$ ) and all-cause mortality (3.5% vs 4.8%,  $P = 0.037$ ) rates were noted with bivalirudin. MACE rates were similar between the two groups (11.9% vs 11.9%,  $P = 0.98$ )<sup>[16]</sup>. Reduction in one-year mortality (8.4% vs 15.9%,  $P = 0.01$ ) and MI recurrence (3.6% vs 7.9%,  $P = 0.042$ ) was also found in high risk patients<sup>[17]</sup>. In patients with diabetes mellitus, significant benefit was seen in terms of reduction in cardiac death at 30 d with bivalirudin compared with the control group

(2.1% vs 5.5%,  $P = 0.01$ ). At one year, similar benefit in reduction of cardiac death was noted which was more evident in insulin dependent-DM patients (1.4% vs 9.4%,  $P = 0.04$ ). However, no benefit was seen in NCRMB rates (8.7% vs 10.7%,  $P = 0.42$ )<sup>[18]</sup>.

### **Studies on bleeding profile and other outcomes**

A subanalysis of the REPLACE-2 study showed that pretreatment with antithrombin therapy before randomization did not affect the bleeding outcomes in patients treated with bivalirudin<sup>[19]</sup>. Even in the subanalysis of patients with renal impairment (creatinine clearance < 60 mL/min), lower bleeding incidence and efficacy that was non-inferior to UFH plus GPI, showed in another subanalysis of the REPLACE-2 trial<sup>[20]</sup>. However, it should be noted that none of the individual subgroup in this trial was sufficiently powered to support definitive conclusions. This study documented that using bivalirudin with provisional GPI was easy to administer, as well as simple because only 7.2% ( $P = 0.001$ ) patients in this group required provisional GPI inhibitors compared with 5.2% ( $P = 0.001$ ) of provisional use and 96.5% ( $P$  value not significant) of planned use of GPI inhibitors in patients of the UFH group<sup>[11]</sup>. However, this study did not include patients with acute MI or unstable ischemic syndromes who often require empiric GPI. This study determined with certainty that using bivalirudin with provisional GPI is appropriate in the subgroup of patients with low to moderate risk characteristics for periprocedural or long-term ischemic complications of PCI, especially if these patients have more risk factors for bleeding. This approach was cost effective with savings from \$375 to \$400 per patient in the 4651 United States patients studied<sup>[21]</sup>. Since almost one fourth of the patients undergoing PCI are diabetic patients, a post hoc analysis of REPLACE-2 was done only on patients with diabetes mellitus and found that no difference in both short and long term ischemic events in the bivalirudin and UFH plus GPI groups<sup>[22]</sup>. Moreover, in patients with diabetes mellitus who underwent PCI, bivalirudin as a monotherapy resulted in similar 30 d composite ischemia (8.5% vs 9.7%,  $P = 0.63-1.22$ ) and lower major bleeding rates (4.6% vs 8.5%,  $P = 0.36-0.81$ ) when compared with heparin plus GPI group<sup>[23]</sup>. Furthermore, a study analyzed the outcomes in NSTEMI patients of this trial who were pretreated with heparin and then switched to bivalirudin. Though the composite ischemia was similar in these patients when compared with patients on consistent heparin plus GPI (9.0% vs 8.2%,  $P = 0.47$ ), these patients had lesser rates of 30 d major bleeding episodes (3.5% vs 6.7%,  $P < 0.01$ )<sup>[24]</sup>.

The NAPLES trial from 2009 was done on 355 diabetic patients undergoing elective PCI for asymptomatic/stable/unstable angina. It compared bivalirudin monotherapy with the combination of UFH and tirofiban in these patients. After 30-d follow up, the composite endpoint (death, MI, revascularization and all bleeding) was found to be lower in the bivalirudin group (18.0% vs 31.5%,  $P = 0.004$ )<sup>[25]</sup>. At that time, evidence was

increasing that pretreatment with 300 mg or 600 mg clopidogrel improves outcomes<sup>[13,15,26-28]</sup>. The ISAR-REACT 3 and 4 trials, studied the efficacy and safety of bivalirudin compared with that of UFH in patients with stable or unstable angina (cardiac biomarker negative), pretreated with 600 mg clopidogrel, undergoing PCI. Overall, the rates of major bleeding were significantly lower with bivalirudin (3.1% vs 4.6%,  $P = 0.008$ ).

The 30-d primary outcome (composite of death, MI, urgent target-vessel revascularization and major bleeding) with bivalirudin was similar to that of UFH (8.3% vs 8.7%,  $P = 0.57$ ), showed in a study with 4570 enrolled patients with stable or unstable angina. The rates of major bleeding were significantly lower with bivalirudin (3.1% vs 4.6%,  $P = 0.008$ )<sup>[29]</sup>. No significant differences in the primary outcome was found between the two groups even after one year of follow up (17.1% vs 17.5%,  $P = 0.816$ )<sup>[30]</sup>. In the subgroup of unstable angina patients (836 patients) of this study, the 30-d primary outcome with bivalirudin was similar to that of UFH (10.0% vs 10.8%,  $P = 0.88$ )<sup>[29]</sup>. No significant differences in the primary outcome was found in this subgroup of patients between the two groups even after one year of follow up (21.5% vs 20.1%,  $P = 0.458$ )<sup>[30]</sup>. In this study the dose of heparin was high (140U/kg initial bolus). This might have made the benefit with bivalirudin in reducing major bleeding rates more apparent. ISAR-REACT 3A study compared the reduced dose of UFH (initial bolus of 100 U/kg) with bivalirudin in 2505 stable (cardiac biomarker negative) patients undergoing PCI. UFH at 100 U/kg showed net clinical benefit in these patients when compared with bivalirudin<sup>[31]</sup>.

ISAR-REACT 4, a randomized, double blind study done in 2011, on 1721 patients compared the combination of abciximab plus UFH (70 U/kg initial bolus) with bivalirudin in patients with NSTEMI undergoing PCI. All patients received pretreatment with 600 mg clopidogrel. The primary end point of net clinical outcome (death, large recurrent MI, urgent target-vessel revascularization and major bleeding) was similar in both the groups at 30 d (10.9% vs 11.0%,  $P = 0.94$ ). The relative risk of major bleeding was lower with bivalirudin (approximately 0.55)<sup>[32]</sup>.

ISAR-REACT 3 and 4 trials showed that bivalirudin was non-inferior in reducing ischemic complications, and safer than UFH in clopidogrel pretreated patients. A pooled analysis from the ACUITY and ISAR-REACT 4 NSTEMI patients who underwent PCI after clopidogrel pretreatment found that bivalirudin monotherapy was as efficient as heparin (UFH/enoxaparin) plus GPI in reducing net adverse clinical events (13.4% vs 14.7%,  $P = 0.21$ ) and superior to heparin plus GPI in reducing major bleeding events (3.4% vs 6.3%,  $P = 0.21$ )<sup>[31]</sup>. However, a recent meta-analysis did not support that pretreatment with clopidogrel, improved outcomes<sup>[33]</sup>.

The Naples III was a double blind, randomized trial that included 837 patients with increased risk of to receive either bivalirudin or heparin infusion for

transfemoral elective coronary stenting. Patients had to be cardiac biomarkers negative without any EKG changes, suggesting ongoing acute or recent MI. The primary endpoint was the rate of in-hospital major bleed, which occurred in 2.6% (11 patients) in the heparin group vs 3.3% (14 patients) in the bivalirudin group. The authors concluded that there was no difference between these two groups in the rate of major bleeding<sup>[34]</sup>.

### Safety with combination drug use

The REPLACE-1 study was done to evaluate whether bivalirudin in combination with planned GPI was an effective and safe approach or not. The patients were randomized in an open-label fashion to receive bivalirudin or UFH during the procedure. Seventy-six percent of patients received GPI blockade in this study in which 71.7% of patients received it in a planned fashion (almost identical percentage of patients in bivalirudin and UFH groups). Overall, the composite efficacy endpoint of death, MI and revascularization occurred in 5.6% of patients in the bivalirudin group compared with 6.9% of patients in the UFH group. The major bleeding rates with bivalirudin were non-inferior to that of UFH (2.1% vs 2.7%,  $P = 0.52$ ). In patients who received GPI, 7.2% of patients in the bivalirudin group experienced the composite of death, MI and revascularization compared with 6.1% of patients in the UFH group and the major bleeding episodes were the same (2.9% vs 2.9%) in both the groups. Thus, this study showed that, regardless of whether patients received GPI or not, bivalirudin reduces the ischemic events. Furthermore, this trial represented the largest prospective dataset of bivalirudin administered concomitantly with planned GP II b/III a blockade and provided evidence of the safety and efficacy of this combined antithrombotic approach<sup>[35]</sup>. These end points were recorded during the hospital stay or within 48 h, whichever came first, which was different from a set time duration used in CACHET trial (7 d). Also, this was a blinded study unlike CACHET trial. REPLACE-2 supported the findings in CACHET trial.

The PROTECT-TIMI 30 trial was a randomized, open label, parallel group study on 857 moderate to high risk patients (having at least one or more of these risk features, *i.e.*, diabetes, a positive cardiac biomarker either CK-MB or troponin T/I, ST-segment deviation > 0.5 mm, or TIMI risk score  $\geq 3$ ) with non ST elevation acute coronary syndromes presenting with chest discomfort or an anginal equivalent at rest  $\geq 10$  min and were anticipated to undergo PCI of a native coronary artery. This study compared the combination of eptifibatide and heparin (UFH/enoxaparin) with bivalirudin. Results showed that the primary end point of post-PCI coronary flow reserve was significantly higher with bivalirudin (1.43 vs 1.33,  $P = 0.036$ ). The myocardial perfusion (post-PCI TMPG) was found to be better in eptifibatide group (57.9% vs 50.9%,  $P = 0.048$ ) and the 48 h post-PCI composite of death and MI was lower in eptifibatide

group (8.8% vs 6.6%,  $P = 0.246$ ). Duration of post-PCI ischemia was also lower in eptifibatide group (36 min vs 169 min,  $P = 0.013$ ). In the UFH plus eptifibatide group, there were increased bleeding episodes more notably TIMI minor bleeding episodes (2.5% vs 0.4%,  $P = 0.027$ ) and bleeding episodes that required transfusion (4.4% vs 0.4%,  $P < 0.001$ ). This study showed that bivalirudin therapy lowers bleeding and the need for blood transfusion and thus safer than heparin plus eptifibatide therapy<sup>[12]</sup>.

### Mortality rates

When bivalirudin plus GPI was compared with heparin plus GPI in the ACUTY trial in a subgroup analysis of 7780 patients undergoing urgent PCI that there were no significant difference in 30 d rates of composite ischemia, *i.e.*, death, MI or revascularization (9% vs 8%,  $P = 0.16$ ) and major bleeding (8% vs 7%,  $P = 0.32$ ). In this subgroup analysis, when bivalirudin monotherapy group was compared with heparin plus GPI, the proportion of individuals with composite ischemia was found to be very much the same (8.8% vs 8.2%,  $P = 0.45$ ) but the major bleeding events were significantly lower in the bivalirudin monotherapy patients (4.5% vs 7.8%  $P < 0.0001$ )<sup>[13]</sup>. In naive patients who were administered heparin plus GPI ( $n = 1462$ ), similar rates of composite ischemia (5.5% vs 6.2%,  $P = 0.47$ ) and more major bleeding rates (4.9% vs 2.5%,  $P = 0.28$  to 0.75), were noted at 30 d when compared with patients naive to antithrombin therapy who were administered bivalirudin monotherapy ( $n = 1427$ ). The one-year follow up of PCI subgroup patients showed similar rates of composite ischemia and mortality in all the 3 regimen groups<sup>[24]</sup>. In a major review, although the study demonstrated that using bivalirudin had several advantages such as being more cost effective, and lesser major bleeding events, it received criticism from researchers due to the open-label design, not including patients with acute STEMI, stating that using such definitions of bleeding endpoints made comparison between studies tough, considering hematoma > 5 cm at the puncture site as a major bleeding event among other factors<sup>[36]</sup>. Dangas *et al*<sup>[37]</sup> showed that patients who received UFH as early treatment and were switched to bivalirudin, 30 d (7.6% vs 12.3%,  $P = 0.0001$ ) and 2 years (8.4% vs 13.0%,  $P = 0.0003$ ), major bleeding rates were found to be lower than that of the control group. These patients also had lower 30-d (1.6% vs 2.9%,  $P = 0.04$ ) and 2 year (2.3% vs 3.8%,  $P = 0.04$ ) rates of cardiac mortality. MI recurrence rate (4.0% vs 7.1%,  $P = 0.0002$ ) was also found to be lower at 2-year follow-up<sup>[37]</sup>. At 3 years, lower rates of all-cause mortality (5.9% vs 7.7%,  $P = 0.03$ ) and NCRMB (6.9% vs 10.5%,  $P = 0.0001$ ) were found with bivalirudin. For every 1000 patients treated with bivalirudin, 18 lives were saved. MACE (21.9% vs 21.8%,  $P = 0.95$ ) and NACE (25.5% vs 27.6%) rates were similar between the two groups<sup>[38]</sup>. A pooled analysis of the patients who underwent PCI in

REPLACE-2, ACUTY and HORIZONS-AMI trials showed that there is a strong positive association between NCRMB within 30 d and the 1 year mortality risk, post PCI<sup>[2]</sup>. This study supported the conclusions derived by the researchers in other similar analysis<sup>[39]</sup>. In the integer based risk score for NCRMB (TIMI) developed by this pooled analysis researchers, bivalirudin monotherapy was the only variable that received a negative score (-6) among all the 28 variables<sup>[2]</sup>.

### Timing studies

A *post-hoc* analysis was done to assess whether the timing of clopidogrel administration had any influence on safety and efficacy. They found that, in patients who received clopidogrel before or within 30 min after PCI, treatment with bivalirudin monotherapy resulted in significantly less bleeding rates (3.5% vs 6.6%,  $P < 0.0001$ ) and similar 30-d composite ischemia (8.2% vs 8.3%, risk ratio: 0.98, 95% confidence interval: 0.81 to 1.20) when compared with heparin plus GPI treatment. They also found that, in the patients who receive clopidogrel > 30 min or not at all after PCI, bivalirudin monotherapy might be associated with worst ischemic outcomes (14.1% vs 8.5%, risk ratio: 1.66, 95%CI: 1.05 to 2.63)<sup>[40]</sup>. This might have been due to the short half-life of bivalirudin. A subset of high risk patients undergoing PCI of the left anterior descending artery (LAD), was studied separately. Among 1445 patients who underwent PCI to the LAD, in the HORIZONS-AMI trial, the use of bivalirudin was associated with significantly lower rates of cardiac death (3.8% vs 6.8%,  $P = 0.01$ ), reinfarction (5.3% vs 9.5%,  $P < 0.004$ ), and major bleeding events (7.3% vs 11.8%,  $P = 0.004$ ) compared to UFH plus GPI<sup>[41]</sup>.

Ideally, the treatment for STEMI should be started when patients are on their way to the hospital. The EUROMAX study addressed this question by comparing the use of bivalirudin vs heparin plus optional GPI (control group) during emergency transport to the hospital for primary PCI. A total 2218 patients were enrolled. The primary outcome of death and non-CABG major bleeding occurred in 5.1% in bivalirudin group vs 8.5% in control group ( $P = 0.001$ ). The study specified that bivalirudin had to be continued for at least 4 h after PCI. One of the limitations of the study was that GPI administration was not randomized and 11.5% of patients in bivalirudin group received it comparing to 69.1% in heparin group<sup>[42]</sup>.

In contrast, the HEAT-PPCI study showed that bivalirudin was not beneficial over heparin in PCI. This was an open-label, single center, randomized trial where 1829 patients were randomized to either receive bivalirudin or heparin. The primary outcome of MACE occurred in 8.7% of patients in bivalirudin group and 5.7% in heparin group (95%CI: 1.09-2.13,  $P = 0.01$ ). The superiority of heparin was primarily due to decreased rate of reinfarction. Both groups were given GPIs at same rate. Patients were given a bolus of bivalirudin at the end of the procedure if activated clotting time was less than

225 s but the drip was not continued after procedure<sup>[43]</sup>.

The Bright trial was conducted at 82 centers in China. In this trial, 2194 patients with MI, both STEMI and NSTEMI, were randomized into three groups: The first group received bivalirudin alone, the second group heparin alone and the third group received heparin plus tirofiban infusion. In the bivalirudin group the medication had to be given for at least 30 min and no more than 4 h post PCI, and reduced dose of infusion (0.2 mg/kg per hour comparing to mandatory rate 1.75 mg/kg per hour right after PCI) could be administered for up to 20 h post PCI at physician discretion (15.6% patients of bivalirudin group). In the third group tirofiban infusion was given for 18 to 36 h total. The primary outcome of the study was net clinical adverse events (NACE) at 30 d consisting of major adverse cardiac or cerebral events (all-cause death, reinfarction, ischemia-driven target vessel revascularization, or stroke) and bleeding. NACE occurred in 65 patients (8.8%) in bivalirudin group compared to 96 patients (13.2%) in heparin alone group ( $P = 0.008$ ). The 30-d bleeding rate was also less frequent in bivalirudin group at 4.1% comparing to 7.5% in heparin alone group and 12.3% in bivalirudin plus tirofiban group ( $P < 0.001$ )<sup>[44]</sup>.

The Matrix trial studied patients with ACS undergoing PCI and compared heparin infusion to bivalirudin with or without post-PCI continuation of bivalirudin. The primary outcomes of the study were MACE and NACE. There was no significant difference in MACE in bivalirudin group and heparin group (10.3% vs 10.9%,  $P = 0.44$ ), or in NACE (11.2% vs 12.4%, respectively,  $P = 0.12$ ). Bivalirudin was associated with a lower rate of death from any cause than was heparin (1.7% vs 2.3%,  $P = 0.04$ ), as well as lower rate of death from cardiac causes (1.5% vs 2.2%,  $P = 0.03$ ). Post-PCI infusion of bivalirudin did not significantly change the outcome in comparison to stopping the infusion after completing procedure. In this study the use of transfusion without overt bleeding did not satisfy the criteria for major bleeding<sup>[45]</sup>.

Bivalirudin was compared to heparin not only during PCI but also during transcatheter valve replacement (TAVR). In this Bravo-3 trial, 802 patients with aortic stenosis were randomized to receive bivalirudin or UFH during the procedure. Although bivalirudin group showed slightly better results in the number of major bleedings at 48 h (6.9% vs 9.0%,  $P = 0.27$ ) and net adverse cardiovascular events at 30 d (14.4% vs 16.1%,  $P = 0.35$ ), these results were not statistically significant. Authors concluded that UFH should be used during the procedure because of the lower cost<sup>[46]</sup>.

### Stent thrombosis comparison trials

Within the first 24 h post-PCI stent thrombosis rates were more in patients assigned to bivalirudin compared with the control group (1.4% vs 0.3%,  $P < 0.001$ ). The stent thrombosis rates after 24 h were more in the control group than with bivalirudin (4.4% vs 2.8%;  $P$

= 0.02). Stent thrombosis occurred at a higher rate in patients who received higher loading dose (600 mg) of clopidogrel<sup>[47]</sup>. Stent thrombosis rates were similar in both the groups at 30 d, one year and 3-year follow ups. When compared to bare metal stents, stent thrombosis rates were lesser with paclitaxel-eluting stents at 3 years (9.4% vs 15.1%,  $P < 0.0001$ )<sup>[38]</sup>.

### Bivalirudin in fondaparinux pre-treated patients undergoing PCI

Fondaparinux is a factor Xa inhibitor, given subcutaneously. Today, this drug is approved in patients undergoing orthopedic surgery and as initial therapy for venous thromboembolisms. The clinical value of fondaparinux in patients with ACS has also been investigated<sup>[48]</sup>. The PENTUA (Pentasaccharide in Unstable Angina) study on NSTEMI patients compared different doses of fondaparinux against enoxaparin in patients with non-ST elevation ACS. In PCI patients, there were no significant differences between the groups in the primary endpoint of death, MI, or recurrent ischemia at the end of 9 d<sup>[49]</sup>. A study done on 20078 patients with ACS were randomly assigned to receive either Fondaparinux (2.5 mg daily) or enoxaparin (1 mg per kilogram of body weight twice daily) for a mean of six days and evaluated death, myocardial infarction, or refractory ischemia at nine days (the primary outcome); major bleeding; and their combination. Patients were followed for up to 6 mo. Fondaparinux was found to be similar to enoxaparin in reducing the risk of ischemic events at nine days, but it substantially reduced major bleeding complications and improved long term mortality and morbidity<sup>[50]</sup>.

The OASIS-5 study compared 2.5 mg daily fondaparinux with enoxaparin 1 mg/kg twice daily for a mean of 6 d in over 20000 patients with ACS. The primary endpoint of death, MI, or refractory ischemia at 9 d was similar between the groups and there was a non-significant trend toward lower event rates with fondaparinux at 30 d. Furthermore, Fondaparinux markedly lowered the rates of bleeding (2.2 % vs 4.1%). The mortality rates with fondaparinux were lower at both 30 and 180 d follow-up<sup>[51]</sup>. However, OASIS-6 (Sixth Organization to Assess Strategies in Acute Ischemic Syndromes) was a randomized, double-blind study performed on STEMI patients. Two point five milligram dose fondaparinux was compared to UFH. It showed that the patients in the fondaparinux group had excess PCI complications and catheter thrombosis rates. In this study, no benefit was seen in death and reinfarction rates with fondaparinux in patients undergoing primary PCI<sup>[52]</sup>.

SWITCH III was an open-label, randomized, multi-center pilot study done on 100 patients with non-ST-segment elevation ACS initially treated with fondaparinux and undergoing early invasive strategy. It compared treatment with bivalirudin vs UFH in these patients. Results in this study suggest that bivalirudin when compared to standard-dose UFH, had a similar safety profile in terms of thrombotic events and peri-PCI

**Table 2 Major studies comparing bivalirudin and heparin**

Trial name	Type of trial	Number of patients	Bleeding risk	Thrombosis risk	Mortality benefit	Comments
REPLACE-2	Randomized, double blind	6010	Favors bivalirudin	Bivalirudin noninferior	Bivalirudin noninferior	
ACUTY	Randomized, open-label	13819	Favors bivalirudin	Comparable	Comparable	
ARMYDA-7	Randomized, open-label	401	Favors bivalirudin	Comparable	Comparable	Primarily decrease in access site bleeding in bivalirudin group
BIVALVE						
HORIZONS-AMI	Randomized, open-label, multicenter	3602	Favors bivalirudin	Comparable	Favors bivalirudin	Heparin group was given glycoprotein II b/IIIa inhibitors
NAPLES	Randomized, open-label	355	Favors bivalirudin	Comparable	No deaths in study period	All patients with diabetes mellitus. Heparin group was given tirofiban
ISAR-REACT 4	Randomized, double-blind	1721	Favors bivalirudin	Comparable	Comparable	Heparin group was given abciximab
NAPLES III	Randomized, double-blind	837	Comparable	Not studied	Not studied	Femoral approach access in PCI
EUROMAX	Randomized, open-label	2218	Favors bivalirudin	Favors heparin	Comparable	GP II b/IIIa inhibitor was optional in heparin group
HEAT-PPCI	Randomized, open-label	1829	Comparable	Favors heparin	Favors heparin	Use of GP II b/IIIa was option in both groups
BRIGHT	Randomized, open-label	2194	Favors bivalirudin	Comparable	Comparable	
MATRIX	Randomized, open-label	7213	Favors bivalirudin	Favors heparin	Favors bivalirudin	Post-PCI infusion of bivalirudin didn't affect the outcome

PCI: Percutaneous coronary intervention.

bleeding. Thus, in NSTEMI patients initially treated with upstream fondaparinux who undergo PCI, bivalirudin can be used<sup>[53]</sup>.

**Trials on newer antiplatelet drugs with bivalirudin**

Prasugrel and ticagrelor are the novel antiplatelet drugs. In patients undergoing PCI for ACS, dual antiplatelet therapy with aspirin and prasugrel reduced the ischemic events in TRITON-TIMI 38 study<sup>[54]</sup>. Another study showed that prasugrel was found to be as safe and effective as clopidogrel in ACS patients undergoing PCI with bivalirudin anticoagulation<sup>[55]</sup>. The benefit of reduction in ischemic events was more in STEMI patients. BRAVE-4 trial on patients undergoing urgent PCI for STEMI demonstrated a more pronounced inhibition of platelet aggregation as well as platelet adhesion and aggregate formation to collagen under flow in prasugrel plus bivalirudin treated patients<sup>[56]</sup>.

**DISCUSSION**

In conclusion, bivalirudin is now the most commonly used anticoagulant for transradial PCI in the United States, while weight adjusted unfractionated heparin remains the most common choice outside the United States<sup>[57]</sup>. Table 2 outlines the biggest studies comparing bivalirudin to heparin. Bivalirudin reduced both ischemic and bleeding events in femoral-treated patients, even though no such clinical benefit was observed in the radial-treated patients<sup>[58]</sup>. Except in stable (cardiac biomarker negative) patients where heparin could be used, bivalirudin should

be considered for anticoagulation in patients undergoing PCI especially if a patient has increased risk of bleeding. Switching from UFH or enoxaparin or fondaparinux to bivalirudin is also an option. Furthermore bivalirudin is safe to use in patients with HIT. The combination of newer antiplatelet drugs with bivalirudin in PCI patients has shown promising results. The cost of bivalirudin is high. However, this therapy reduces the overall costs since it lowers complications, hospital stays, and all over mortality<sup>[59,60]</sup>. Moreover, the combination of bivalirudin and drug eluting stents has resulted in better outcomes. Peri-procedural PCI bleeding avoidance strategies have become paramount to optimize the clinical benefit, and the interaction between bivalirudin and radial approach deserves additional investigations. There are numerous studies comparing heparin against bivalirudin. Unfortunately, many of them are difficult to compare because of difference in protocols and definitions. Some of the studies, like HORIZONS AMI, were conducted in the era when administration of GPIs was routine and newer P2Y12 inhibitors like ticagrelor and prasugrel were not yet available. The HEAT-PPCI trial showed the heparin to be superior over bivalirudin in preventing major adverse ischemic events. Heparin's longer half-life may partially explain the decreased rate of ischemic events in HEAT-PPCI trial. Many trials defined the requirement for the transfusion as a major bleeding but this was not the case in MATRIX trial unless there was overt bleeding. Recent ACC/AHA guidelines do not specify the preference of one medication over another during PCI for NSTEMI or STEMI, and both heparin and bivalirudin are acceptable

options in these guidelines. Each individual patient's ischemic and bleeding risks should be taken into account. However, in spite of some minor conflicting data, we conclude that bivalirudin should be used as preferred method of anticoagulation during PCI for ACS as the majority of randomized trials showed more superior long-term advantages over heparin, including safety, efficiency and cost-effectiveness. This will likely bring higher value to patients, defined as better outcomes for less cost, which is the ultimate goal in healthcare.

## COMMENTS

### Background

Anticoagulation is required during (PCI) and other percutaneous transluminal coronary angioplasty. Historically, heparin was used for this purpose until 1990's when bivalirudin was introduced to clinical practice. There is still ongoing debate about the drug of choice for peri-PCI anticoagulation.

### Research frontiers

Bivalirudin is a direct thrombin inhibitor with a short half-life and this quality may decrease bleeding complications during PCI. There is extensive amount of literature comparing bivalirudin to heparin.

### Innovations and breakthroughs

In this article the authors reviewed the literature comparing bivalirudin to heparin.

### Applications

The article will help to understand the literature comparing bivalirudin to heparin and to make conscious and medical decision making between these medication.

### Terminology

Bivalirudin is a direct thrombin inhibitor widely used to prevent thrombotic complication during PCI.

### Peer-review

This is an excellent review about the safety, effectiveness, and cost benefits of bivalirudin. This manuscript is nicely structured and well written.

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## Cardiac magnetic resonance imaging: Which information is useful for the arrhythmologist?

Elia De Maria, Annachiara Aldrovandi, Ambra Borghi, Letizia Modonesi, Stefano Cappelli

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### Abstract

Cardiac magnetic resonance (CMR) is a non-invasive, non-ionizing, diagnostic technique that uses magnetic fields,

radio waves and field gradients to generate images with high spatial and temporal resolution. After administration of contrast media (*e.g.*, gadolinium chelate), it is also possible to acquire late images, which make possible the identification and quantification of myocardial areas with scar/fibrosis (late gadolinium enhancement, LGE). CMR is currently a useful instrument in clinical cardiovascular practice for the assessment of several pathological conditions, including ischemic and non-ischemic cardiomyopathies and congenital heart disease. In recent years, its field of application has also extended to arrhythmology, both in diagnostic and prognostic evaluation of arrhythmic risk and in therapeutic decision-making. In this review, we discuss the possible useful applications of CMR for the arrhythmologist. It is possible to identify three main fields of application of CMR in this context: (1) arrhythmic and sudden cardiac death risk stratification in different heart diseases; (2) decision-making in cardiac resynchronization therapy device implantation, presence and extent of myocardial fibrosis for left ventricular lead placement and cardiac venous anatomy; and (3) substrate identification for guiding ablation of complex arrhythmias (atrial fibrillation and ventricular tachycardias).

**Key words:** Cardiac magnetic resonance; Ablation; Sudden cardiac death; Cardiac resynchronization therapy; Arrhythmic risk stratification

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**Core tip:** Cardiac magnetic resonance (CMR) is a non-ionizing diagnostic technique that generates images with high spatial and temporal resolution. After administration of contrast media (*e.g.*, gadolinium chelate), it is also possible to acquire late images, which make possible the identification and quantification of myocardial areas with scar/fibrosis (late gadolinium enhancement). In recent years, its field of application has extended to arrhythmology, both in diagnostic and prognostic evaluation of arrhythmic

risk and in therapeutic decision-making. In this review, we discuss the applications of CMR for the arrhythmologist. It is possible to identify three main fields of application in this context: (1) arrhythmic and sudden cardiac death risk stratification; (2) decision making in cardiac resynchronization therapy device implantation; and (3) substrate identification for guiding ablation of complex arrhythmias.

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## INTRODUCTION

Cardiac magnetic resonance (CMR) is a non-invasive, non-ionizing, diagnostic technique that uses magnetic fields, radio waves and field gradients to generate images with high spatial and temporal resolution and without limitations due to the acoustic window, compared to other imaging techniques<sup>[1,2]</sup>. It provides a very precise "in vivo" tissue characterization through the different quantity of protons in different chemical environments, identifying the presence of fat, water (oedema), blood, fibrosis and scar<sup>[1,2]</sup>. In particular, after the administration of contrast media (*e.g.*, gadolinium chelate), it is possible to acquire late images which make possible the identification and quantification of myocardial areas with scar/fibrosis (late gadolinium enhancement, LGE)<sup>[1]</sup>. First used as a research tool, CMR has become a daily instrument in clinical cardiovascular practice for the assessment of several pathological conditions, including ischemic and non-ischemic cardiomyopathies and congenital heart disease<sup>[1]</sup>.

In recent years, its field of application has also extended to arrhythmology, both in diagnostic and prognostic evaluation of arrhythmic risk and in therapeutic decision-making. It is possible to identify three main fields of application of CMR in arrhythmology: (1) arrhythmic and sudden cardiac death (SCD) risk stratification in different heart diseases; (2) decision-making in cardiac resynchronization therapy (CRT) device implantation [cardiac vein anatomy, scar burden and left ventricular (LV) lead placement]; and (3) substrate identification for guiding ablation of complex arrhythmias [atrial fibrillation and ventricular tachycardias (VTs)].

In this review, we discuss the possible useful applications of CMR that can help the arrhythmologist in the management of patients with this broad spectrum of arrhythmological conditions.

## ARRHYTHMIC AND SCD RISK STRATIFICATION

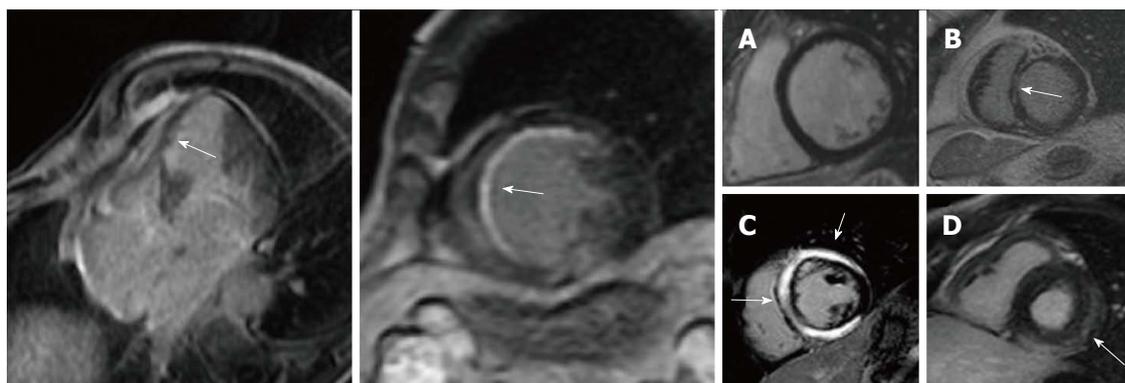
SCD is responsible for 25% of 17 million cardiovascular

deaths every year in the world. The great majority of these deaths (> 90%) have an arrhythmic origin, namely, VT degenerating into ventricular fibrillation (VF), primary VF or torsade de pointes<sup>[3]</sup>.

The underlying causes vary in different age groups, with channelopathies and cardiomyopathies prevailing in young people, while degenerative diseases are more common in older people. In general, the main causes are: Acute and chronic coronary heart disease (75%-80%); cardiomyopathies (10%-15%); valvular, inflammatory and infiltrative diseases (5%-10%); and molecular/genetic conditions (< 5%)<sup>[3]</sup>. Prevention can be made with pharmacological or device therapy. This latter consists in ICD (implantable cardioverter defibrillator) implantation that is recommended in different groups of high risk patients with ischemic or non-ischemic heart diseases. However, risk stratification is sometimes very challenging, especially in primary prevention. Current approaches have limited sensitivity and specificity in many clinical settings, identifying only a very small portion of future cardiac arrests with sufficient precision to justify ICD therapy<sup>[3,4]</sup>. Moreover, ICD implantation is not without complications and many patients will not benefit even if implanted according to guidelines<sup>[3,4]</sup>. Lately, scientific interest is pointing to a polyparametric approach, using a combination of different risk markers to better dichotomize high and low risk patients<sup>[4,5]</sup>. In this context, CMR can give its contribution, especially through the identification and quantification of myocardial areas with scar and fibrosis. Ventricular fibrosis is an important substrate for the genesis of ventricular arrhythmias (VA): Within fibrotic tissue the slow and heterogeneous conduction favors re-entrant circuits, increasing vulnerability to VT and VF<sup>[6-8]</sup>.

### **Dilated ischemic and non-ischemic cardiomyopathies**

A left ventricular ejection fraction (LVEF) of 35% or less is the major determinant of ICD implantation for SCD primary prevention in patients with ischemic or nonischemic LV dysfunction<sup>[3]</sup>. Even in the recent European Society of Cardiology (ESC) guidelines<sup>[3]</sup>, the only suggested markers of arrhythmic risk to guide ICD implant are LVEF and NYHA functional class (Table 1). However, it is now well-known that ejection fraction alone has limited sensitivity and specificity as a risk marker for SCD, because it is not able to distinguish the risk of sudden death from death caused by heart failure or other non-cardiac diseases. Subsequently, many patients implanted for primary prevention according to current guidelines will have little benefit from their ICD, with a low rate of appropriate ICD therapy (2%-4%/year)<sup>[9]</sup>, while they can suffer from side effects (even > 10%/year overall), in particular inappropriate shocks, lead failure and infections<sup>[10,11]</sup>. On the other side, many patients who are at risk of SCD are missed when using only LVEF, because the largest part of sudden arrhythmic death patients have only mildly depressed ejection fraction<sup>[9,12,13]</sup>. Anyway, the substrates of SCD are particularly complex, so it is unlikely for a single test to achieve significantly better predictive accuracy than LVEF. To overcome this



**Figure 1** Late gadolinium-enhanced cardiac magnetic resonance images of ischemic (left panel) and non-ischemic (right panel) dilated cardiomyopathy. In ischemic cardiomyopathy LGE has a subendocardial or transmural distribution in myocardial segments following a coronary artery. In non-ischemic etiology, it shows a “midwall” pattern (panel B, C) or subepicardial distribution (panel D). LGE: Late gadolinium enhancement.

**Table 1** Current European Society of Cardiology recommendations for implantable cardioverter defibrillator implantation for primary prevention in patients with ischemic and non-ischemic left ventricular dysfunction

Recommendations
Class I: ICD therapy is recommended to reduce SCD in patients with symptomatic HF (NYHA class II–III) and LVEF $\leq$ 35% after $\geq$ 3 mo of optimal medical therapy who are expected to survive for at least 1 yr with good functional status
Level of evidence A: Ischemic etiology (at least 6 wk after myocardial infarction)
Level of evidence B: Non-ischemic etiology

From ref. [3]. ICD: Implantable cardioverter defibrillator; SCD: Sudden cardiac death; LVEF: Left ventricular ejection fraction; HF: Heart failure; NYHA: New York Heart Association.

limitation, a combination of markers has been proposed<sup>[9]</sup>, for example, combining ejection fraction with different tests that investigate different arrhythmic mechanisms (LGE-CMR, T-wave alternans, programmed ventricular stimulation, evaluation of autonomic tone, etc.).

The pathophysiology of VA in structural heart diseases is due - in most cases - to re-entrant circuits. Electrophysiological studies and anatomic mapping have highlighted, in these cases, the presence of extensive areas where the electrical potentials are absent (indicating the absence of viable myocardium, scar and fibrosis) and areas with low-amplitude, fragmented, late potentials compared to healthy myocardium (conduction with high anisotropy and low speed)<sup>[6-8]</sup>. The classic arrhythmogenic substrate of re-entry arrhythmias is represented by a mix of these areas, with inflammation often acting as a trigger. Thanks to its ability to identify both areas of myocardial scar/fibrosis and inflammation, CMR can provide essential information in this context<sup>[8,9]</sup>.

Myocardial fibrosis can be evaluated with the LGE imaging technique. Gadolinium-based contrast agents are washed out by viable myocytes and accumulate in extracellular spaces, such as areas of fibrotic tissue, where cardiomyocytes have been replaced by collagen, or in areas of acutely damaged myocardium<sup>[7,8]</sup>. The LGE imaging techniques have been validated by histology in several studies with animal models<sup>[14]</sup>. To date, due to the high spatial resolution (approximately 2 mm), it is the most accurate method to detect myocardial fibrosis and to precisely identify its location and extension, distinguishing

in particular endocardial, epicardial or transmural involvement. The pattern of LGE distribution is particularly useful in the differential diagnosis between ischemic and non-ischemic fibrosis<sup>[15-17]</sup>. Virtually all patients with ischemic cardiomyopathy have LGE, presenting with a subendocardial or transmural distribution in myocardial segments following a coronary artery territory<sup>[16]</sup>; the most common pattern consists of core dense fibrosis within a heterogeneous peri-infarct (gray) zone, indicating the presence of both viable and nonviable myocardium<sup>[9]</sup>. On the other side, in non-ischemic dilated cardiomyopathy fibrosis is present only in about 30%-40% of cases and it shows a “midwall” pattern, mostly located in the interventricular septum<sup>[17]</sup> (Figure 1). From an etiological and therapeutical point of view, this is a very important issue: non-ischemic cardiomyopathy on the basis of a traditional definition (clinical history, ECG, echocardiogram and coronary angiography) may be reclassified as ischemic cardiomyopathy thanks to CMR in about 20% of cases<sup>[15]</sup>.

Numerous studies have demonstrated that LGE is a powerful predictor of VA events both in ischemic and non-ischemic cardiomyopathy patients, with moderately to severely depressed LVEF<sup>[18-21]</sup>. An overview of 19 studies, all with an arrhythmic endpoint, for a total of 2692 patients, indicated that the presence and extension of myocardial fibrosis, documented by LGE, predicted VA both in ischemic and non-ischemic diseases, even in patients with only mildly depressed LVEF<sup>[9,18,19]</sup>. Furthermore, CMR increased the negative predictive

value for SCD prediction to 95%<sup>[9,20-22]</sup>.

Taking into account only non-ischemic dilated cardiomyopathy, the cut-off for risk definition was the presence or absence of fibrosis and its midwall location. These markers were successfully used to dichotomize patients at high vs low risk of ventricular arrhythmic events<sup>[23-32]</sup>. The largest prospective study in non-ischemic cardiomyopathy by Gulati *et al.*<sup>[26]</sup> included 472 patients followed for > 5 years. In this paper midwall fibrosis was an independent risk factor for ventricular tachyarrhythmias [hazard ratio (HR) = 4.61], while combining ventricular fibrosis with LVEF significantly improved risk reclassification for the arrhythmic endpoint. A recent meta-analysis of 29 studies including 2948 patients with idiopathic dilated cardiomyopathy<sup>[32,33]</sup> confirmed that the presence of ventricular fibrosis, identified by LGE, was an important risk factor for arrhythmic endpoints (SCD, VT, VF and ICD therapies): Clinical events occurred in 21% of LGE positive vs 4.7% of LGE negative patients, with an annual event rate of 6.9% and 1.6%, respectively.

In ischemic dilated cardiomyopathy, the issue is more complex: The majority of studies evaluating total LGE or "gray zone" (peri-infarct area) reported a statistically significant dose-response effect for arrhythmic risk, with larger and more heterogeneous scar associated with the higher risk of VA during follow-up<sup>[34-39]</sup>. Currently, there is not a definite cut-off value of fibrosis/scar extent to adequately differentiate patients at high vs low risk of arrhythmic events, especially in ischemic etiology<sup>[18]</sup>. The presence of a large amount of ventricular fibrosis/scar has been generally used as a marker of higher risk. However, a great variety of analysis methods and diagnostic thresholds exists<sup>[34-39]</sup>: Standardization of LGE-CMR should be a target to reach before spreading practical use of this technique for arrhythmic risk stratification. Moreover, no randomized study has been concluded so far: The DETERMINE study<sup>[40]</sup> was planned to demonstrate the role of LGE-CMR in decision-making for ICD implantation in patients with ischemic cardiomyopathy, but it was prematurely terminated due to a low rate of patient enrollment.

Even with the above limitations, a polyparametric approach, using a combination of different risk markers (including LGE-CMR), could help to refine risk stratification in at least two subsets of patients who are not adequately assessed by current guidelines<sup>[9]</sup>.

The first group is represented by patients with LVEF less than 35% and high risk of death due to heart failure or non-cardiac causes. In this setting, the absence of LGE-CMR (non-ischemic etiology) or a small extension of fibrosis/scar (ischemic etiology), especially if coupled with negative T-wave alternans test, identifies patients with a relatively low risk of sudden arrhythmic death (about 1%/year) for whom ICD implantation should be critically considered because they will hardly have a benefit<sup>[9,21,22,32]</sup>.

The second group includes patients with LVEF of 35%-50% and high risk of SCD defined by: (1) presence

or high burden of fibrosis on LGE-CMR; (2) VT/VF inducibility by programmed ventricular stimulation in post-infarction etiology; and (3) lamin A/C pathological mutation associated with familial sudden death in idiopathic cardiomyopathy. For these patients, even if the current guidelines do not recommend the use of ICD, such a therapy could be critically evaluated, discussed and offered case by case<sup>[9,37,38]</sup>.

Finally, a small portion of patients without LGE at CMR will suffer from sudden death, especially in non-ischemic disease. LGE imaging is not suited to detect diffuse fibrosis that may be present in idiopathic dilated cardiomyopathy. New imaging techniques, such as T1 mapping, are able to detect and quantify diffuse fibrosis by means of extracellular volume fraction and preliminary data show that this pattern is associated with worse outcome in non-ischemic patients<sup>[41]</sup>.

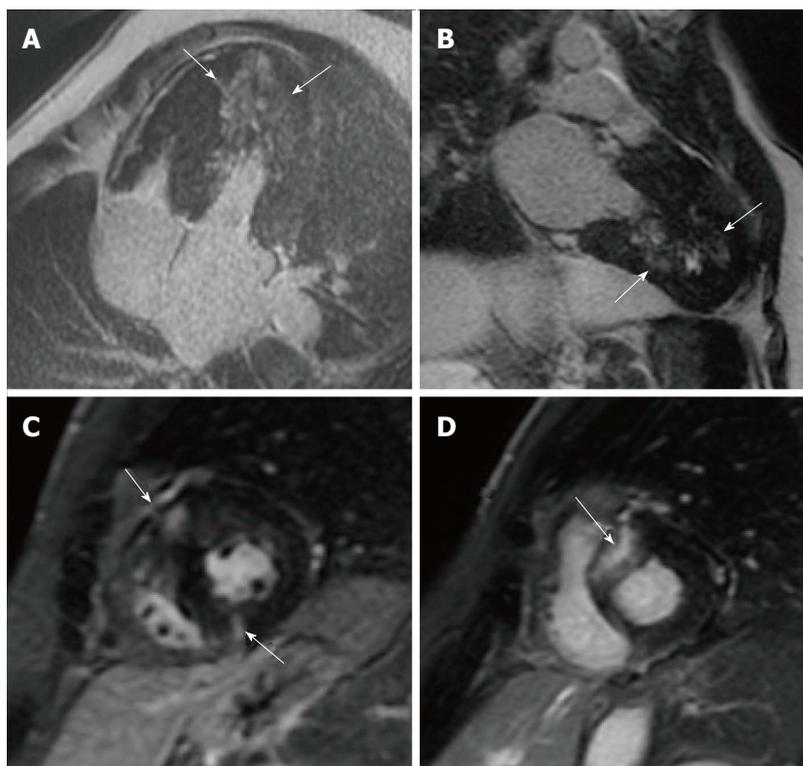
Currently, neither American nor European guidelines support CMR as a first-line tool for risk stratification in dilated cardiomyopathies, so further studies are needed to define its role in this context.

### **Hypertrophic cardiomyopathy**

Hypertrophic cardiomyopathy (HCM) is the most common genetic cardiomyopathy and cause of SCD in young people, including competitive athletes. It is caused by mutations in genes encoding cardiac sarcomere proteins and has a prevalence of 1:500 in the general population<sup>[42]</sup>. HCM is defined by the presence of unexplained LV hypertrophy (wall thickness  $\geq 15$  mm), associated with non-dilated ventricular chambers, in the absence of other cardiac or systemic diseases that might cause hypertrophy<sup>[42,43]</sup>. Hypertrophied myocytes are arranged in a chaotic architecture with increased extracellular matrix<sup>[42]</sup>. The myocardium may also present ischemic areas, caused by microvasculature obstruction, with replacement fibrosis and scar<sup>[42-44]</sup>. This modified cardiac structure predisposes to the risk of malignant VA such as VT and VF<sup>[42,43]</sup>.

SCD represents the most feared complication, occurring in about 5% of patients<sup>[43,44]</sup>. In patients with HCM, at high risk for SCD, ICD reduces mortality rate to 0.5% per year<sup>[44]</sup>. A primary prevention risk model has been proposed to identify high risk patients and guide ICD implant<sup>[43,44]</sup>, based on: (1) family history of premature HCM-related SCD, in close or multiple relatives; (2) unexplained non-reflex syncope, particularly if recent and in young patients; (3) nonsustained VTs on ambulatory ECG, particularly if multiple, repetitive or prolonged; (4) hypotensive or attenuated blood pressure in response to exercise; and (5) extreme hypertrophy (wall thickness  $\geq 30$  mm). Although current risk factor model is effective, not all high-risk patients are identified and the absence of conventional risk factors does not eliminate the risk of SCD.

In this context, CMR is increasingly considered an important tool, in particular for the evaluation of fibrotic areas (LGE-CMR) and wall thickness<sup>[44]</sup>. Moreover, it allows more precise characterization of the phenotype,



**Figure 2** Late gadolinium enhancement patterns in hypertrophic cardiomyopathy patients. A: LGE in the lateral wall (small arrows) and in the interventricular ventricular septum; B: LGE in the LV apex and inferior wall; C: LGE localized to the insertion area of the RV wall into the anterior and posterior ventricular septum; D: Transmurular LGE involving the ventricular septum. LGE: Late gadolinium enhancement.

which helps to differentiate HCM from other causes of LV hypertrophy.

Approximately 50%-60% of HCM patients demonstrate LGE-CMR which, when present, occupies on average 10% of the LV myocardial mass. LGE can be observed in any location or distribution, although most frequently in the ventricular septum and free wall (> 30% of patients), with mid-myocardial distribution, and less often involving the apex and the right ventricular insertion into ventricular septum<sup>[42]</sup> (Figure 2). Moreover, patients with LGE have greater maximal LV wall thickness and LV mass index than patients without<sup>[43]</sup>. A large number of studies demonstrated that the presence of LGE-CMR identifies areas of myocardial fibrosis where life-threatening VA can originate and is associated with a significant higher risk of SCD, even in patients without conventional risk factors<sup>[45-50]</sup>. LGE extension, expressed as a percentage of myocardial mass, correlates with the risk of developing life-threatening VA, in particular if LGE exceeds 15% of LV mass<sup>[50]</sup>. On the contrary, patients without LGE have a low arrhythmic risk and can be reassured.

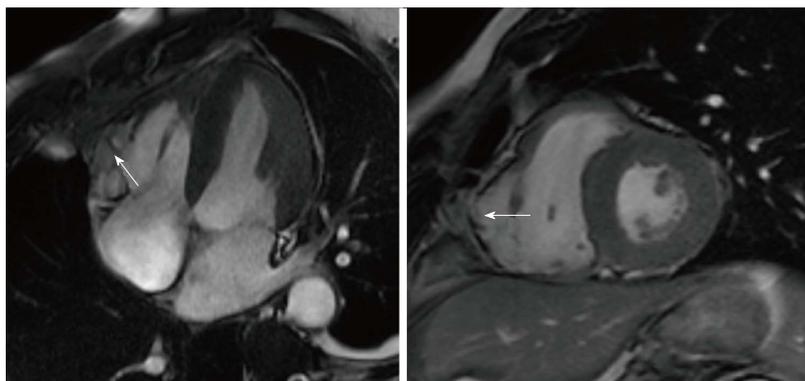
CMR also enables the identification of other high-risk subsets of patients such as those with massive LV hypertrophy and apical aneurysms (the latter being a subgroup at increased risk for VA and thromboembolic stroke)<sup>[51,52]</sup>. Notably apical HCM may be overlooked by echocardiography, while CMR can precisely visualize apical segments and detect hypertrophy and aneurysms.

Current schemes for SCD risk determination, such

as American algorithm<sup>[51]</sup> and ESC risk calculator<sup>[53]</sup>, are not completely effective and precise in risk evaluation. CMR, instead, has shown to improve stratification, providing additional information in patients for whom the current markers underestimate the risk (for example, young asymptomatic patients without conventional risk factors but with LGE) and in patients for whom decision-making about ICD implantation is difficult and ambiguous (for example, patients with a single risk factor and at intermediated risk), and potentially acting as an "arbitrator". Anyway, at the moment, neither American nor European guidelines support CMR as a first-line tool for risk stratification in HCM<sup>[51,53]</sup>.

### **Arrhythmogenic cardiomyopathy**

Arrhythmogenic cardiomyopathy (AC) is a group of heart muscle disease clinically characterized by life-threatening VA and pathologically by a progressive dystrophy of the ventricular myocardium with fibrofatty replacement<sup>[54,55]</sup>. AC affects mostly young males < 40 years old. Its estimated prevalence ranges between 1:2000 and 1:5000, therefore it is considered among rare diseases<sup>[54,55]</sup>. It is mostly caused by autosomal dominant genetic mutations (with incomplete penetrance and variable expressivity) of desmosomal proteins like desmoplakin and plakoglobin<sup>[56,57]</sup>. The desmosomal complex, situated in the cardiac intercalated disk, is responsible for tissue strength and stability, binding cells to one another. Consequently, a defective desmosomal complex can cause cell loss with fibro-fatty tissue



**Figure 3** Subtricuspid involvement in arrhythmogenic right ventricular cardiomyopathy. Dilated right ventricle with bulging of the subtricuspid region (arrow). The right ventricular apex is relatively spared.

replacement<sup>[58-60]</sup>. In its most common form the disease affects the right ventricle, but in a minority of patients it may affect both ventricles or only the left ventricle, thus supporting the use of the more general term AC<sup>[54,55]</sup>. Clinical manifestations differ in the different phases of the disease, from asymptomatic patients to patients with heart failure and VA or SCD<sup>[56-60]</sup>. AC is a major cause of sudden death in young and athletes, with VT and VF occurring at any stage<sup>[54-61]</sup>.

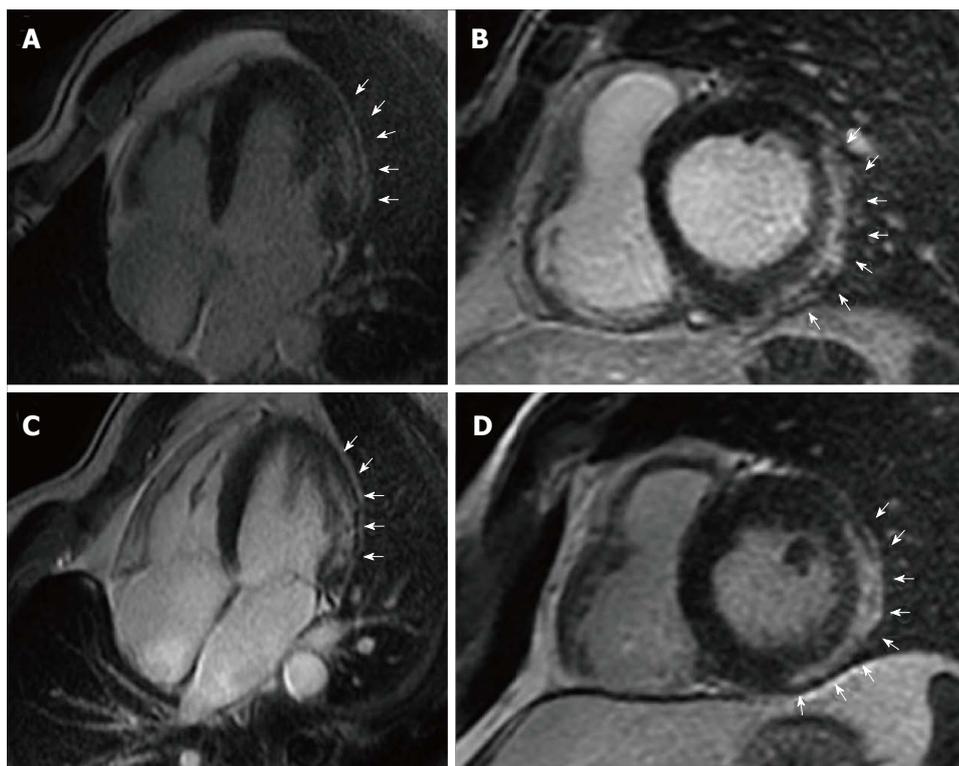
Considering the most frequent variant, arrhythmogenic right ventricular cardiomyopathy (ARVC), the diagnosis is based on a score obtained from the assessment of several parameters combined into major and minor criteria<sup>[56-59]</sup>, as there is no single gold standard diagnostic test. CMR has an important role for a comprehensive and precise assessment of right ventricular volumes, function and kinesis<sup>[56-59]</sup>. Typically, in ARVC myocardial disarray involves the entire ventricular wall, in particular the subtricuspid region and the right ventricle outflow tract ("triangle of dysplasia"), leading to aneurysm formation. In these regions wall motion abnormalities (akinesia or dyskinesia) and aneurysms can be detected by CMR, representing one of the criteria for diagnosis (Figure 3). The usefulness of CMR to detect fatty replacement or fibrosis is limited because the right ventricle has a thin wall and the differentiation between normal epicardial and intramyocardial infiltration is challenging. Therefore, to date, tissue characterization by CMR is not considered in the diagnostic work-up for ARVC<sup>[54-59]</sup>. Arrhythmic risk stratification in ARVC is based on multiparametric evaluation mainly based on clinical variables; patients at higher risk indicated for ICD implantation are those resuscitated after cardiac arrest, those with sustained and unstable monomorphic VT or exercise-induced unexplained syncope<sup>[60,61]</sup>. The role of CMR for risk stratification in ARVC is marginal, although significant: the extension of the disease to the left ventricle, identified by LGE-CMR, seems to be associated with a worse arrhythmic outcome and must be looked for<sup>[60-62]</sup>.

On the other side, and even more rare, left-dominant arrhythmogenic cardiomyopathy (LDAC) is characterized by epicardial or midmyocardial fibrotic or fibro-fatty replacement in postero-infero-lateral LV wall ("isolated

nonischemic scar") associated with life-threatening VA exceeding the degree of LV dysfunction (LVEF is often normal)<sup>[63-65]</sup>. LDAC is increasingly recognized as a cause of SCD in young athletes<sup>[66-68]</sup>. ECG often shows T-wave inversion in infero-lateral leads and low-voltage QRS complexes; VTs have right bundle branch block configuration and are often exercise-induced. In genetic familiar forms, usually autosomal-dominant, gene mutation mostly concerns components of cardiac desmosomes. In non-familiar forms LDAC phenotype can be the result of myocarditis leading to disruption of desmosomal architecture<sup>[63-65]</sup>. LGE-CMR plays a major diagnostic role because subepicardial/midmyocardial scar location is usually missed by echocardiography (Figure 4). Risk stratification is not well defined: By extrapolation from ARVC, ICD is indicated in patients who survived VF, with poorly tolerated sustained VT, or exercise-induced syncope. LGE-CMR also helps in risk stratification because a "stria" pattern in postero-lateral LV wall has been recently associated with a higher arrhythmic risk compared to the "benign" junctional "spotty" pattern, in a population of young athletes<sup>[68]</sup>.

#### **Some other pathological conditions at risk of SCD**

Sarcoidosis is an idiopathic non-caseating granulomatous disease that affects several organs, mostly the lungs, but also the heart, skin, liver, spleen, eye, and lymph nodes. Sarcoidosis occurs worldwide, being more frequent in African-American and Northern Europeans, especially women. Disease prevalence ranges between 4.7 and 64 in 100000<sup>[69]</sup>. Cardiac involvement is clinically evident in approximately 5% of patients, in form of: (1) conduction abnormalities; (2) VA including unexpected SCD; and (3) heart failure with reduced LVEF. Moreover, about 25% of patients with systemic sarcoidosis have asymptomatic cardiac involvement. At CMR cardiac sarcoidosis can appear as LGE in a patchy pattern or in longitudinal striae in the midwall or subepicardium, usually located in basal septum or LV wall. Delayed enhancement represents focal scarring, while inflammation areas can be detected with T2-weighted and STIR sequences<sup>[70,71]</sup>. CMR is also useful for differential diagnosis with ARVC that sometimes can resemble cardiac sarcoidosis. A recent



**Figure 4** Left dominant arrhythmogenic cardiomyopathy. Long-axis (A and C) and short-axis (B and D) postcontrast CMR views of two 34-year-old identical twin brothers showing a subepicardial/midmyocardial stria of LGE involving the lateral and inferolateral left ventricular wall (white arrows). CMR: Cardiac magnetic resonance; LGE: Late gadolinium enhancement.

consensus document<sup>[69]</sup> provided guidance for diagnosis and management of this disease, with a particular focus on arrhythmias. There are few data to help with SCD risk stratification<sup>[71]</sup>; in general, evidence from major randomized ICD trials of dilated cardiomyopathy is applicable, both in primary and secondary prevention. The presence of inflammation in both ventricles may increase ventricular arrhythmic risk; indeed, patients with implanted ICD have more frequent therapies from their devices, compared to other non-ischemic cardiomyopathies<sup>[69,70]</sup>. Current consensus recommendations<sup>[69]</sup> consider the use of CMR and the presence/absence of LGE (combined with electrophysiological study) to guide decision-making about ICD implant.

Amyloidosis is a disease characterized by protein misfold, aggregating into fibrils, and depositing extracellularly with disruption of organ architecture and function. There are two main types which affect the heart: Light chain (AL) amyloidosis and transthyretin cardiac amyloidosis (ATTR), both associated with the risk of VA and SCD<sup>[72,73]</sup>. Systemic amyloidosis occurs in more than 10 per million person-years in the United States population, with about 2000 new cases of AL amyloidosis occurring each year, approximately half of whom with significant cardiac involvement. The median age at presentation is 55–60 years, especially affecting women. The gold standard for diagnosis is endomyocardial biopsy, but CMR is increasingly used because it provides an accurate tissue characterization without the invasiveness of biopsy. At CMR the most frequent finding is a global

subendocardial and circumferential LGE that is specific for cardiac amyloidosis. CMR findings (in particular LGE) have also been associated with prognosis and arrhythmic risk stratification, with the potential for guiding decision about ICD implant<sup>[73]</sup>.

Left ventricular non-compaction (LVNC) is a relatively rare congenital disease, caused by an embryogenesis arrest, in which LV seems to be spongy. Ventricular wall anatomy is characterized by prominent LV trabeculae, a thin compacted layer, and deep intertrabecular recesses<sup>[74]</sup>. Clinical symptoms are related to neuromuscular disorders, heart failure with reduced LVEF, ventricular arrhythmic events and systemic thromboembolism. CMR can accurately identify this pathology, delineating hypertrabeculations of the apex and the LV lateral wall with subendocardial, midwall or transmural LGE<sup>[75]</sup>. CMR also helps to differentiate true LVNC from normal variants of increased trabeculations that can be found especially in young athletes. There are also recent data about the role of CMR for risk stratification. In a recent prospective multicenter study<sup>[75]</sup>, 113 patients underwent CMR, looking for diagnostic criterion of noncompacted/compacted ratio > 2.3 in end-diastole and LGE assessment. At a mean follow-up of  $48 \pm 24$  mo the degree of LV trabeculation had no prognostic impact on the primary outcome (a composite of thromboembolic events, heart failure hospitalizations, VA and cardiac death) above LV dilation and dysfunction. LGE-CMR, instead, showed a significant correlation with life-threatening VA events and SCD.

Myocarditis is a group of heart-specific immune diseases

classified by clinical and histopathological manifestations. Myocarditis may resolve spontaneously, recur or become chronic, leading about 30%-40% of biopsy-proven cases to dilated cardiomyopathy (DCM), death or heart transplantation. In the 2013 ESC myocarditis Task Force report<sup>[76]</sup>, the disease was defined histologically as an inflammatory disease of the myocardium diagnosed on endomyocardial biopsy (EMB). Although EMB remains the diagnostic gold standard for diagnosis, it is not widely used. Traditionally, when the diagnosis is only based upon the histological Dallas criteria, myocarditis results to be a relatively rare disease. However, the use of highly sensitive immunohistochemical and molecular tools applied to EMB and of CMR suggests that there is a substantial clinical underestimation of its frequency and of its role in DCM<sup>[77,78]</sup>. CMR sequences have important diagnostic and prognostic value. T<sub>2</sub>-weighted CMR sequences detect edema or water, and T<sub>1</sub>-weighted sequences detect inflammation or fibrosis. LGE imaging can help in distinguishing nonischemic patterns of myocyte damage and fibrosis from ischemic injury, and T<sub>2</sub>-weighted and early gadolinium enhancement imaging detect other inflammatory features of edema, capillary leakage and hyperemia<sup>[78,79]</sup>. LGE has been associated with a higher (3.7%/year) risk of a composite of cardiovascular adverse events and its extent also predicted a composite endpoint of cardiac death, heart failure hospitalization, VT, and sudden death<sup>[80]</sup>.

Anderson-Fabry disease is a X-linked disorder due to a deficiency of the alpha-galactosidase enzyme that causes an inability to catabolize glycosphingolipids, leading to their accumulation in several organs, including the heart<sup>[81]</sup>. The storage of lipids causes an increase of the ventricular wall thickness that simulates HCM and leads to heart failure<sup>[81,82]</sup>. Diagnosis can be made with CMR showing LGE within the basal infero-lateral wall but typically sparing the endocardium, related to myocardial collagen scarring that represents the substrate for re-entry mechanism and SCD. Patients who have significant fibrosis on MRI and those with nonsustained VT are at higher risk for arrhythmic complications and may be considered for ICD<sup>[82,83]</sup>.

## DECISION-MAKING IN CRT DEVICE IMPLANTATION

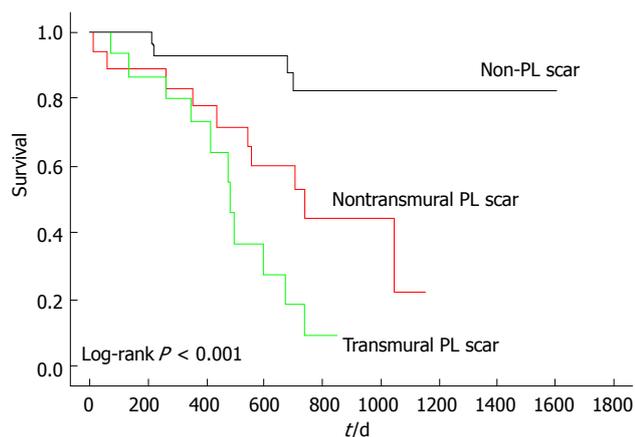
CRT is a well-established therapy in patients with heart failure with reduced LVEF (< 35%) and a wide QRS (> 120 ms), usually with left bundle branch block<sup>[84]</sup>. In this setting, compared to optimal medical therapy, CRT reduces all-cause mortality and heart failure hospitalization, both in ischemic and non-ischemic cardiomyopathy, with larger benefit in non-ischemic etiology<sup>[84,85]</sup>. However, about 30%-40% of patients implanted according to current guidelines<sup>[86]</sup> do not show any benefit from CRT or even get worse<sup>[87]</sup>. This is hardly acceptable considering costs and risk of the procedure. There are several reasons explaining suboptimal CRT response: (1) patient's characteristics (absence of ventricular dyssynchrony,

too advanced heart disease to get a benefit, severe right ventricular dysfunction, untreated arrhythmias, severe medical co-pathologies, etc.); (2) suboptimal LV lead position at implant; (3) suboptimal CRT device programming during subsequent course<sup>[87,88]</sup>.

The LV pacing site is an important determinant of a good outcome after CRT<sup>[88]</sup>. According to current guidelines, LV lead should be placed in non-apical posterolateral region to pace the latest activated areas<sup>[86]</sup>. Intuitively, deploying the LV lead over the latest electrical or (preferably) mechanical activated segments is likely to maximize the effects of CRT. However, recent evidence suggests that there is a large interindividual variability as concerns the latest activated areas and, subsequently, optimal LV pacing site<sup>[89-91]</sup>. Indeed, the latest mechanical activation is localized in posterolateral regions in 85%-90% of patients with non-ischemic dilated cardiomyopathy, but only in 10% of those with ischemic etiology<sup>[15]</sup>.

Moreover, scar in proximity of LV pacing stimulus interferes with resynchronization, leading to QRS fragmentation and prolongation, and this is true both in ischemic and non-ischemic etiologies<sup>[92,93]</sup>. Chalil<sup>[94]</sup> showed that pacing over scar was associated with a higher risk of cardiac mortality or heart failure hospitalizations compared with pacing viable myocardium (Figure 5). In a study of 559 patients undergoing CRT, Leyva<sup>[95]</sup> found that LV lead positions over scar was associated with poorer CRT response, higher risk of cardiovascular death, heart failure hospitalizations and SCD at follow-up.

In this context, a multimodality imaging approach<sup>[96-98]</sup> is emerging with a dedicated "CRT team"<sup>[99-102]</sup>, composed of electrophysiologists, cardiac imaging specialists and radiologists working together to identify the target areas (the most delayed and viable region) for LV pacing, by using CMR, myocardial perfusion imaging and newer echocardiographic techniques (such as longitudinal myocardial strain). Recent studies applying this method have demonstrated better clinical outcomes with the LV lead positioned at the latest mechanically activated region and away from myocardial scar<sup>[99-102]</sup>. In a study by Bertini *et al.*<sup>[102]</sup>, 100 patients with ischemic and non-ischemic dilated cardiomyopathy were enrolled: Group 1 with 50 consecutive patients scheduled for CRT and prospectively included, and group 2 (control) including 50 patients with a CRT device implanted according to standard clinical practice. In group 1, patients underwent two-dimensional speckle-tracking assessment of longitudinal myocardial strain and CMR imaging to identify the target area for LV lead. A positive response to CRT was defined as a  $\geq 15\%$  reduction of LV end-systolic volume at 6-mo follow-up. The result was that 78% of patients in group 1 were classified as responders to CRT compared to only 56% in group 2 ( $P = 0.019$ ). The "CRT team" identified as target for LV pacing the lateral area in 60% of patients, but notably, in 16% of patients, the target was far from the lateral area, in the anterior or posterior regions. The patients with concordant position showed the highest positive response (93.1%) to CRT. These encouraging results need further



**Figure 5** Left ventricular lead position, transmuralty of scar, and outcome after cardiac resynchronization therapy. PL: Posterolateral.

validation in future larger multicenter trials with longer follow-up.

Placement of the LV lead is restricted by variable cardiac venous anatomy. Retrograde cardiac venography *via* the coronary sinus, at the time of implantation, is the gold-standard approach to imaging the coronary veins. It has been suggested that coronary vein imaging before CRT implantation could be useful and, in this respect, coronary venography is feasible with both CMR and computed tomography (CT)<sup>[15,96]</sup>. However, this approach has major limitations because it is technically challenging and can miss little veins that are beyond the spatial resolution of CMR and CT, but anyway these veins could be suitable for implantation. In addition, neither CMR nor CT provides adequate imaging of Thebesian and Vieussens valves or vein stenoses<sup>[15,96]</sup>.

## ARRHYTHMIC SUBSTRATE IDENTIFICATION AND ABLATION

Catheter ablation is a well-established therapy for patients with scar-related sustained monomorphic VT, usually seen after myocardial infarction, and for atrial fibrillation (AF), the most common cardiac arrhythmia. Anyway, these arrhythmias are the most complex and challenging for the electrophysiologist<sup>[103]</sup>.

For a successful ablation, the correct identification of underlying arrhythmogenic substrates is critical. With the use of standard electroanatomic mapping techniques, substrates are identified only indirectly, with local voltage amplitudes as a surrogate of the state of surrounding myocardium<sup>[103]</sup>. This approach, in addition to being time-consuming, lacks sensitivity for deep scar and lacks specificity when there is poor catheter contact or thinner myocardium<sup>[103]</sup>. Therefore, improved strategies to define arrhythmogenic scar substrates would be welcome. In this context, CMR could give an important contribution due to its ability to characterize cardiac anatomy and function without exposing the patient to additional radiation<sup>[7,41]</sup>. As validated histopathologically,

CMR can visualize fibrosis and scar by delayed imaging of gadolinium contrast agents that accumulate in the extracellular matrix and have slower washout from scar than from normal myocardium<sup>[7,8,14]</sup>. Thanks to newer mapping technologies, CMR images can be merged with electrograms acquired from the conventional electrophysiologic study, thus creating an anatomic roadmap to guide ablation procedure<sup>[103]</sup>.

Myocardial scar, the most common substrate for reentrant VA, can be easily displayed by LGE-CMR, allowing to shorten the procedure time devoted to substrate identification and enabling ablation of hemodynamically unstable VT (when conventional electrophysiologic and point-by-point voltage mapping is impossible)<sup>[104]</sup>. Moreover, a better understanding of the physiologic conduction characteristics associated with various anatomic scar substrates may improve patient selection for ablation, avoiding the procedure when scar burden is too high and complex, with few chances of success<sup>[105]</sup>.

In the setting of AF ablation, LGE-CMR could be useful for patient selection, guidance of ablation procedure and post-ablation follow-up. Importantly, atrial LGE-CMR may allow improved patient selection so that unnecessary procedures are avoided in cases with little chance of procedural success<sup>[106]</sup>: Extensive left atrial LGE (> 35%) has been associated with a high rate (96%) of AF recurrence after catheter ablation<sup>[107]</sup>. Moreover, when procedure is planned in patients with a high burden of LGE, a more extensive ablation strategy could be pursued in addition to isolation of the pulmonary veins<sup>[108]</sup>. During the follow-up period, CMR can be useful to assess ablation success, for example, in terms of complete/incomplete isolation of pulmonary veins.

The main limitations for such approach are the added costs and expertise required for adequate image acquisition and analyses, the need for dedicated software, as well as inadequate spatial resolution in the atria. Moreover, CMR can create potential problems in patients already implanted with a cardiac device (pacemaker, ICD and CRT). Even when the device is "MRI safe" and CMR is technically feasible, lead artifacts can significantly alter image integrity and its clinical utility.

Hopefully, with improving techniques, accurate pre-procedural identification of the arrhythmogenic substrate by CMR may become in the near future an important adjunct for patient selection, procedural planning and post-procedural evaluation.

## CONCLUSION

Cardiac MRI is revolutionizing the approach to the arrhythmologic patients both in diagnostic and therapeutic work-up. It provides information that other diagnostic imaging techniques do not allow to obtain, without radiation exposure, facilitating the initial evaluation and, once established a diagnosis, the choice of the most appropriate treatment. Current limitations are: (1) the paucity of randomized studies evaluating the outcome of

patients treated with a CMR-based approach; (2) CMR is time-consuming, expensive, and requires experienced personnel for image acquisition and analysis; and (3) CMR still has inadequate spatial resolution in the left atrium and right ventricle, limiting its routine use for most arrhythmias arising from these chambers.

Lastly, a mention has to be made to nephrogenic systemic fibrosis that is a devastating (albeit extremely rare) potential complication in patients exposed to gadolinium-based contrast agents. This complication occurs almost exclusively in patients with moderate to severe kidney disease, particularly those on dialysis with incidences, in this latter group, ranging from 2.5% to 5%<sup>[109]</sup>.

Based on the current literature and waiting for more data from future studies, it is foreseeable that CMR use in daily arrhythmologic practice will be increasingly implemented.

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## Retrospective Study

**Clinical outcomes of tricuspid valve repair accompanying left-sided heart disease**

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**Informed consent statement:** All involved persons (subjects or legally authorized representative) gave their informed consent (written or verbal, as appropriate) prior to study inclusion.

**Conflict-of-interest statement:** All authors declare having no conflicts of interest.

**Data sharing statement:** The statistical methods and original anonymous dataset are available on request from the corresponding author at [kazarnoush@chu-clermontferrand.fr](mailto:kazarnoush@chu-clermontferrand.fr).

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**Abstract****AIM**

To determine whether the need for additional tricuspid valve repair is an independent risk factor when surgery is required for a left-sided heart disease.

**METHODS**

One hundred and eighty patients (68 ± 12 years, 79 males) underwent tricuspid annuoplasty. Cox proportional-hazards regression model for multivariate analysis was performed for variables found significant in univariate analyses.

**RESULTS**

Tricuspid regurgitation etiology was functional in 154 cases (86%), organic in 16 cases (9%), and mixed in

10 cases (6%), respectively. Postoperative mortality at 30 days was 11.7%. Mean follow-up was 51.7 mo with survival at 5 years of 73.5%. Risk factors for mortality were acute endocarditis [hazard ratio (HR) = 9.22 (95%CI: 2.87-29.62),  $P < 0.001$ ], ischemic heart disease requiring myocardial revascularization [HR = 2.79 (1.26-6.20),  $P = 0.012$ ], and aortic valve stenosis [HR = 2.6 (1.15-5.85),  $P = 0.021$ ]. Significant predictive factors from univariate analyses were double-valve replacement combined with tricuspid annuloplasty [HR = 2.21 (1.11-4.39),  $P = 0.003$ ] and preoperatively impaired ejection fraction [HR = 1.98 (1.04-3.92),  $P = 0.044$ ]. However, successful mitral valve repair showed a protective effect [HR = 0.32 (0.10-0.98),  $P = 0.046$ ]. Additionally, in instances where tricuspid regurgitation required the need for concomitant tricuspid valve repair, mortality predictor scores such as Euroscore 2 could be shortened to a simple Euroscore-tricuspid comprised of only 7 inputs. The explanation may lie in the fact that significant tricuspid regurgitation following left-sided heart disease represents an independent risk factor encompassing several other factors such as pulmonary arterial hypertension and dyspnea.

### CONCLUSION

Tricuspid annuloplasty should be used more often as a concomitant procedure in the presence of relevant tricuspid regurgitation, although it usually reveals an overly delayed correction of a left-sided heart disease.

**Key words:** Tricuspid regurgitation; Patient outcome assessment; Valvular annuloplasty; Infective endocarditis; Mitral valve annuloplasty

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**Core tip:** Tricuspid valve repair with flexible ring is easy to achieve in patients undergoing heart surgery. Predictor scores such as Euroscore 2 could be shortened to a simple Euroscore-tricuspid of only 7 inputs. A significant tricuspid regurgitation following a left-sided heart disease is an independent risk factor that encompasses several other factors such as pulmonary arterial hypertension and dyspnea. Patients with functional damage of the right side of the heart and significant functional tricuspid regurgitation have poor mid-term results with high mortality. A concomitant tricuspid regurgitation usually reveals a delayed correction of a left-sided heart disease.

Azarnoush K, Nadeemy AS, Pereira B, Leesar MA, Lambert C, Azhari A, Eljezi V, Dauphin N, Geoffroy E, Camilleri L. Clinical outcomes of tricuspid valve repair accompanying left-sided heart disease. *World J Cardiol* 2017; 9(10): 787-793 Available from: URL: <http://www.wjgnet.com/1949-8462/full/v9/i10/787.htm> DOI: <http://dx.doi.org/10.4330/wjc.v9.i10.787>

### INTRODUCTION

The concomitant correction of functional tricuspid regur-

gitation secondary to left heart disease requiring surgery remains underused<sup>[1]</sup> despite recent data showing late development of severe tricuspid regurgitation in patients with mild regurgitation at the time of cardiac procedures (e.g., mitral valve surgery)<sup>[2]</sup>. Several factors including pulmonary arterial hypertension, right ventricular dilatation, increased tricuspid annulus diameter and the occurrence of right-sided heart failure promote persistent or even deteriorating functional tricuspid insufficiency<sup>[3,4]</sup>. Associated tricuspid regurgitation is present in almost 50% of patients undergoing mitral-valve surgery<sup>[5]</sup>. Most patients presenting with significant tricuspid regurgitation suffer from functional regurgitation due to dilatation of the tricuspid annulus, caused by dilatation of the right ventricle<sup>[6]</sup>.

Rare organic tricuspid insufficiencies may be secondary to iatrogenic injury (*i.e.*, pacing leads), or of rheumatic, infectious, congenital or carcinoid origin<sup>[7]</sup>.

Data on concomitant tricuspid valve annuloplasty are rare and usually focus on different techniques for repair. A recent review seemingly demonstrated evidence for tricuspid annuloplasty to be a low-risk procedure<sup>[8]</sup>. However, as highlighted in the present work, a concomitant tricuspid regurgitation reveals a delayed correction of left-sided heart disease. Our data demonstrate that standard Euroscore 2 mortality risk factors such as gender, pulmonary hypertension, renal impairment or weight of the intervention should no longer be taken into account when significant tricuspid regurgitation appears prior to surgery of left-sided heart disease and the need for tricuspid repair becomes an independent mortality risk factor.

The present study aimed to confirm that the need of concomitant tricuspid annuloplasty according to guidelines represents a far too late treatment. Patients should be addressed to heart surgery centers for an early correction of the left-side heart disease before the need of additional tricuspid valve repair procedure.

### MATERIALS AND METHODS

All patients undergoing concomitant tricuspid valve annuloplasty between January 2005 and December 2009 were included in this retrospective, single-center study. The study was approved by the local ethics committee and all patients gave their written informed consent for the procedure as well as for inclusion in this retrospective study<sup>[9]</sup>.

All surgeries were performed using full median sternotomy and extracorporeal circulation with cardiac arrest using blood cardioplegia. Tricuspid annuloplasty was performed either with a De Vega tricuspid repair<sup>[10]</sup>, a flexible Sovering® ring (Sorin Biomedica Cardio S.r.l., Saluggia, Italy) sized 26 to 36 mm<sup>[11]</sup>, or a flexible Bex® linear reducer (Gamida, France)<sup>[12]</sup>, respectively. If necessary, annuloplasty was combined with concomitant procedures to the tricuspid valve such as resection of vegetations in case of endocarditis, implantation of artificial chords or tricuspid pillar reinsertion in case of prolapse.

**Table 1** Characteristics and cardiovascular risk factors of the study patients

	<i>n</i> (%)
Age (yr)	68.3 ± 12.4
Gender	
Female	101 (56)
Male	79 (44)
Dyspnea (New York Heart Association)	
Class I	7 (4)
Class II	25 (14)
Class III	125 (69)
Class IV	23 (13)
Cardiac rhythm	
Sinus rhythm	77 (43)
Atrial fibrillation	87 (48)
Branch block	40 (22)
Pacemaker	16 (9)
Risk factors	
Arterial hypertension	79 (44)
Hypercholesterolemia	77 (43)
Tobacco	44 (24)
Diabetes	42 (23)
Lower limb or supra-aortic obstructive arteriopathy	20 (11)
Pulmonary disease	25 (14)
Cerebrovascular accident or transient ischemic attack	19 (11)
Rheumatic valve disease	40 (22)
Myocardial infarction	12 (7)
Pacemaker implantation	16 (9)
Reoperation	26 (14)
Other heart disease	
Aortic regurgitation	19 (11)
Aortic stenosis	30 (17)
Combined aortic stenosis/regurgitation	15 (8)
Mitral regurgitation	99 (55)
Mitral stenosis	21 (12)
Combined mitral stenosis/regurgitation	21 (12)
Pulmonary valve regurgitation	1 (0.6)
Coronary artery disease	28 (16)
Acute endocarditis	9 (5)
Interventricular or interatrial septal defect	3 (1.7)

The patients' health status was obtained through a questionnaire submitted to the cardiologist, to the attending physician or, in the absence of the latter, by interviewing the patient or his/her relatives by phone (if the patient was deceased).

### Statistical analysis

Data are presented as the mean ± SD for continuous data and as the number of patients and associated percentages for categorical parameters. Cox proportional-hazards regression model was performed to evaluate the impact of several covariates on mortality in a multivariate context and define prognostic factors (using a stepwise backward and forward algorithm, from variables with a  $P < 0.10$  in univariate analyses) according to the results of univariate analysis and clinical relevance.

All analyses were conducted using Stata v12® (Stata Corp, College Station, United States). The tests were two-sided, with a type I error set at  $\alpha = 0.05$  (except for multiple comparisons).

## RESULTS

Between January 2005 and December 2009, a total 180 consecutive patients underwent tricuspid valve annuloplasty in our institution. During the same period, another 3 patients underwent isolated tricuspid valve replacement and were not included in the present study. Among the 180 included patients, there were 79 males (44%) and 101 females (56%). Age ranged from 12 to 89 years; mean age was  $68.3 \pm 12.4$  years (Table 1).

Tricuspid valve regurgitation etiology was classified as functional in 154 cases (86%), organic in 16 cases (9%) and mixed in 10 cases (6%). In instances of functional tricuspid regurgitation, the main cause was degenerative mitral valve disease. In instances of organic tricuspid regurgitation, the predominant pathologies were rheumatism disease and infectious endocarditis, 9 of which required urgent surgery for acute endocarditis (Table 1).

Ninety-seven patients (45%) suffered from at least one heart failure episode, 22 with left-sided HF, 15 with right-sided HF, and 60 with global heart failure, respectively. Eighty-five patients (47%) suffered from persistent atrial fibrillation preoperatively. Further cardiovascular risk factors of the study patients are summarized in Table 1, along with preoperative echocardiographic findings in Table 2.

Tricuspid annuloplasty with a prosthetic ring was performed in 176 patients; a Sovering® ring was used in 156 cases and a Bex® linear reducer in 20 cases. In 20 cases, annuloplasty was combined with concomitant procedures for tricuspid valve: Valve repair (leaflet slit or cleft closure), vegetation resection, implantation of a Gore-Tex® cord, and one tricuspid pillar reinsertion for iatrogenic tricuspid incompetence as a consequence of pacemaker lead removal. Four 4 De Vega tricuspid repairs were performed while the remaining procedures consisted of the following: Aortic valve replacement in 29 cases (16%), mitral valve replacement in 67 cases (37%), double mitro-aortic valvular replacement in 42 cases (23%), mitral valve repair in 38 cases (21%), pulmonary valve replacement in one case (0.6%), coronary artery bypass grafting in 26 cases (14%), and other procedures in 21 cases. Only 9 patients (5%) underwent surgery for isolated tricuspid regurgitation. These patients presented with preoperative grade III or IV tricuspid incompetence. Three of these patients had a previous history of mitral or aortic valvular surgery, with tricuspid insufficiency appearing within two years postoperatively. Two of these patients had a preoperative pulmonary artery hypertension with peak gradients over 60 mmHg at their first operation. The other five patients did not present any associated left-sided heart disease.

Mean hospital stay was  $17.8 \pm 19.3$  d (range 2 to 165 d). Postoperative complications were reoperation for bleeding in 15 cases (8%) and one postoperative stroke. A total of 21 patients (11.7%) died within 30 d.

**Table 2** Preoperative and postoperative characteristics of the study patients

	mean $\pm$ SD	n (%)
Preoperative parameter		
Left ventricular ejection fraction (%)	58.6 $\pm$ 12.5	
Systolic pulmonary arterial pressure (mmHg)	58.0 $\pm$ 16.7	
Tricuspid regurgitation		
I		9 (5)
II		69 (38)
III		70 (39)
IV		32 (18)
Left ventricular end-diastolic diameter (mm)	52.7 $\pm$ 9.5 (29-74)	
Left ventricular end-systolic diameter (mm)	34.4 $\pm$ 9.3 (17-63)	
Postoperative parameter		
Left ventricular ejection fraction (%)	54.4 $\pm$ 12.2 (10-82)	
Systolic pulmonary arterial pressure (mmHg)	38.6 $\pm$ 10.6 (19-76)	
Tricuspid regurgitation		
0- I		150 (83)
II		28 (15)
III		1 (0.6)
IV		1 (0.6)
Left ventricular end-diastolic diameter (mm)	50.4 $\pm$ 7.4	
Left ventricular end-systolic diameter (mm)	35.2 $\pm$ 8.3	

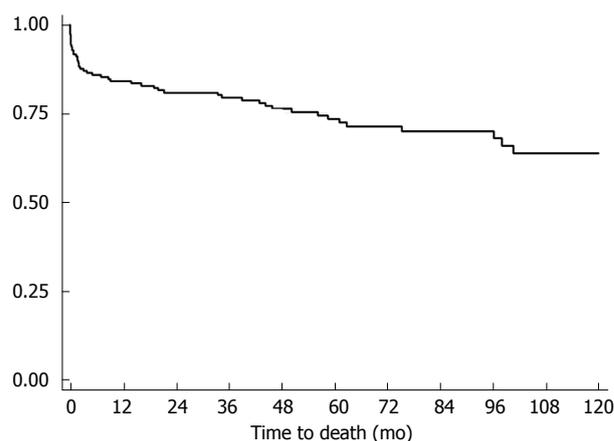
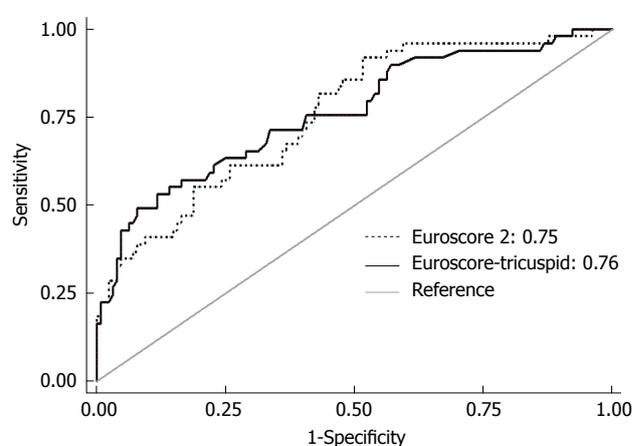
The main causes of death were multi-organ failure in 20 cases, two of whom were from massive bleeding, and one unexplained sudden death.

All patients underwent early postoperative echocardiography, demonstrating marked reduction in both tricuspid insufficiency and in systolic pulmonary artery pressure (Table 2).

Among hospital survivors, two patients (1%) were lost at follow-up, the initial analysis thus resulting in a 99% follow-up. Data from these two patients were subsequently collected in 2014. One patient living in Kathmandu returned for a control cardiology visit in our university hospital and the second patient had a control consultation in the thoracic surgery department in Clermont-Ferrand, allowing us to complete the initial follow-up. Mean follow-up was 51.7  $\pm$  39 mo with 5-year survival at 73.5% and 10-year survival at 63.8% (Figure 1). The main cause of death during the follow-up was heart failure. Only one tricuspid valve repair failed. Eight patients had a cerebrovascular event during the study period and seven patients presented with a late complete atrioventricular block requiring pacemaker implantation.

Univariate and multivariate analyses and parameters affecting global mortality (in-hospital and post-discharge) are detailed in Tables 3 and 4.

Of note, there was no significant correlation between death and several Euroscore factors such as gender, pulmonary hypertension, NYHA dyspnea level, chronic lung disease, renal impairment or weight of the intervention (Table 3). From multivariate analyses (Table 4), the adverse factors for mortality were the presence

**Figure 1** Overall patient survival.**Figure 2** ROC curve comparing Euroscore 2 and Euroscore-tricuspid.

of acute endocarditis, ischemic heart disease that required myocardial revascularization, and aortic valve stenosis, respectively. In contrast, a successful mitral valve repair appeared to have a protective effect.

When taking into account a tricuspid valve regurgitation requiring an additional tricuspid valve repair accompanying a left-sided heart disease surgery, the 18 predictive risk factors of Euroscore 2 could be reduced to a Euroscore-tricuspid of only 7 factors with an at least equivalent statistical power (Figure 2). This new Euroscore-tricuspid would require only the following patient data: Age, ischemic heart disease, insulin-treated diabetes, previous cardiac surgery (redo intervention), active endocarditis, critical preoperative state and left ventricle function less than 50%.

## DISCUSSION

Both the current American and European guidelines recommend correction of relevant functional tricuspid insufficiency if other cardiac diseases are corrected surgically<sup>[4,7]</sup> since functional tricuspid regurgitation, a frequent finding in patients undergoing cardiac surgery for other reasons<sup>[5]</sup>, has proven to increase over time when not corrected during first surgery<sup>[2]</sup>, mainly due to

**Table 3** Univariate analyses: Parameters affecting global mortality

Variable	n (%)	Univariate HR	P
Gender (male)	79 (44)	1.38 [0.77-2.44]	0.27
Age ( $\geq$ 75 yr)	63 (35)	1.75 [0.98-3.11]	0.06
Tobacco use	44 (24)	1.16 [0.60-2.24]	0.66
Pulmonary disease	25 (14)	1.58 [0.74-3.40]	0.24
Pacemaker	16 (9)	2.40 [1.12-5.13]	0.02
Branch block	40 (22)	1.88 [1.01-3.47]	0.04
Previous heart failure	75 (42)	1.67 [0.94-2.95]	0.08
Ejection fraction ( $>$ 50%)	132 (73)	0.49 [0.25-0.98]	0.044
Hypertension	79 (44)	1.81 [1.01-3.20]	0.04
Diabetes on insulin	8 (4)	2.33 [0.83-6.51]	0.11
Aortic regurgitation	19 (11)	0.52 [0.16-1.67]	0.27
Aortic disease	15 (8)	1.29 [0.51-3.26]	0.59
Mitral regurgitation	99 (55)	1.01 [0.56-1.79]	0.98
Mitral stenosis	21 (12)	0.96 [0.38-2.44]	0.93
Mitral disease	21 (12)	0.55 [0.19-1.54]	0.26
Dyslipidemia	77 (43)	0.88 [0.49-1.57]	0.67
NIDD	34 (19)	1.31 [0.64-2.64]	0.45
Cerebrovascular accident	19 (11)	1.44 [0.60-3.40]	0.41
Myocardial infarction	12 (7)	1.70 [0.67-4.30]	0.26
New York Heart Association (III/IV)	148 (82)	1.99 [0.78-5.04]	0.14
Redo vs Tridux	26 (14)	1.49 [0.74-3.00]	0.26
Double valve replacement associated with tricuspid repair	43 (24)	2.21 [1.11-4.39]	0.024
Sinus rhythm	77 (43)	0.74 [0.41-1.35]	0.33
Sovering ring	156 (87)	1.10 [0.49-2.46]	0.81
Bex device	20 (11)	1.16 [0.52-2.60]	0.71
Systolic pulmonary artery pressure ( $>$ 59 mmHg)	98 (54)	1.06 [0.60-1.88]	0.83
Systolic pulmonary artery pressure ( $>$ 49 mmHg)	31 (17)	1.16 [0.56-2.40]	0.69
Tricuspid annulus diameter ( $>$ 40 mm)	20 (11)	0.31 [0.07-1.27]	0.10
Postoperative ejection fraction ( $>$ 50%)	98 (66)	2.58 [1.31-5.08]	0.006

HR: Hazard ratio.

**Table 4** Prognostic factors for mortality in multivariate analyses

Variable	n (%)	Univariate		Multivariate	
		HR	P	HR	P
Aortic stenosis	30 (17)	2.69 [1.24-5.42]	0.011	2.60 [1.15-5.85]	0.021
Coronary disease	28 (16)	4.12 [2.06-8.21]	$<$ 0.001	2.79 [1.26-6.20]	0.012
Mitral-valve repair	38 (21)	0.27 [0.08-0.88]	0.03	0.32 [0.10-0.98]	0.046
Infective endocarditis	9 (5)	5.06 [1.7-14.62]	0.003	9.22 [2.87-29.62]	$<$ 0.001

HR: Hazard ratio.

progressive annular dilatation<sup>[3]</sup>. However, although factors influencing the natural course of tricuspid regurgitation over time<sup>[4]</sup> and even during long-term follow-up of over 5 years<sup>[13]</sup> as well as its deleterious effect on mortality<sup>[14]</sup> are well known, its concomitant correction has yet to be performed to an adequate extent<sup>[1]</sup>. In the present study, the conducting of a successful mitral valve repair was found to be a protective factor when tricuspid annuloplasty was performed in patients with significant mitral regurgitation.

Acute endocarditis, associated ischemic heart disease and double valve replacement combined with tricuspid regurgitation were the main risk factors for hospital mortality in this study. Surprisingly, there was no correlation between elevated pulmonary arterial pressure, advanced age, preexisting arrhythmias and mid-term mortality results as conversely reported by

others<sup>[15]</sup>.

The 11.7% hospital mortality rate observed herein, mainly driven by multi-organ failure, is a reflection of the high rate of concomitant procedures. Other studies have reported hospital mortality rates of up to 35% in patients undergoing tricuspid valve repair as a concomitant procedure to other cardiac surgery<sup>[16,17]</sup>.

The use of a flexible ring represented the technique of choice in the present series. Easy implantation, avoidance of a suture close to the conduction system, measured reduction of the tricuspid annulus and preservation of the valve's normal physiological shape are among the related advantages of this approach<sup>[18]</sup>. For dilatation of the tricuspid annulus, annuloplasty alone provides excellent results in the absence of valvular or subvalvular disease<sup>[3]</sup>; however, it is no longer effective in correcting tricuspid regurgitation if there is also damage

of the leaflets and of the subvalvular apparatus, and/or in instances where additional procedures are required<sup>[18,19]</sup>. Accordingly, less-than-moderate tricuspid regurgitation prior to discharge after tricuspid annuloplasty during redo valve surgery additionally proved to be an independent risk factor for better long-term outcome in terms of survival in a recent retrospective analysis<sup>[20]</sup>. Furthermore, concomitant tricuspid annuloplasty using flexible bands offered improved durability as compared to suture annuloplasty for preventing postoperative tricuspid regurgitation progression in two retrospective comparative analyses<sup>[21,22]</sup>. In the current series, 20 patients underwent a concomitant valvular or subvalvular procedure, without any added mortality or morbidity.

Recent clinical studies have demonstrated that moderate to severe residual tricuspid regurgitation still persists in 10% of patients who have undergone surgical repair<sup>[18]</sup>. Tricuspid regurgitation is related to the degree of limited leaflet motion and to the severity of the dilatation of the tricuspid annulus. The severity of preoperative tricuspid regurgitation, together with right ventricular dysfunction, contributes to postoperative residual insufficiency. Risk factors for recurrent tricuspid regurgitation are preoperative severe regurgitation, tricuspid repair without a prosthetic ring or with an oversized ring (large tricuspid valve), pacemaker catheters that pass through the tricuspid valve, mitral valve replacement rather than mitral repair, left ventricular dysfunction associated or not with advanced remodeling, cardiomegaly and atrial fibrillation<sup>[19]</sup>.

Finally and surprisingly, we found that mortality predictor scores such as Euroscore 2 could be shortened to a simple Euroscore-tricuspid of only 7 inputs. From our standpoint, the explanation may reside in the fact that significant tricuspid regurgitation following a left-sided heart disease is an independent risk factor encompassing several other factors such as pulmonary arterial hypertension and dyspnea. Such finding has been reported in several studies of other diseases with regard to aortic and mitral valve diseases which also corroborate the present data embodying multiple diseases at once<sup>[23-25]</sup>.

The present study demonstrates the efficacy and durability of tricuspid annuloplasty with an open flexible ring. This procedure may be performed in patients with severe left-sided valve disease. Patients with functional damage of the right side of the heart combined with significant functional tricuspid regurgitation have poor mid-term results along with high mortality. A concomitant tricuspid regurgitation typically reveals a delayed correction of left-sided heart disease.

## COMMENTS

### Background

The concomitant correction of functional tricuspid regurgitation secondary to left heart disease requiring surgery remains underused and an associated functional tricuspid regurgitation typically reveals a delayed correction of left-sided heart disease.

### Research frontiers

Functional tricuspid valve regurgitation concerns patients who are referred

to heart surgery for left-sided heart disease too late. Results of this study contribute to clarify these patients' clinical situation.

### Innovations and breakthroughs

In this study, when a tricuspid regurgitation required the need for concomitant tricuspid valve repair, mortality predictor scores such as Euroscore 2 could be shortened to a simple Euroscore-tricuspid comprised of only 7 inputs. The explanation may lie in the fact that significant tricuspid regurgitation following left-sided heart disease represents an independent risk factor encompassing several other factors such as pulmonary arterial hypertension and dyspnea.

### Applications

The present study demonstrates the efficacy and durability of tricuspid annuloplasty with an open flexible ring.

### Peer-review

The study aimed the need of concomitant tricuspid annuloplasty for an early correction of the left-side heart disease. The author conducted retrospective multivariate analysis for significant variables in univariate analyses in 180 cases with tricuspid annuloplasty. The 5-10 years follow-up observation find out the risk factors for mortality were acute endocarditis, ischemic heart disease requiring myocardial revascularization, and aortic valve stenosis. Significant predictive factors from univariate analyses were double-valve replacement combined with tricuspid annuloplasty and preoperatively impaired erection fraction. The author concluded that tricuspid annuloplasty should be used more often as concomitant procedure if relevant tricuspid regurgitation is present. The study suggests that the predictor scores could be shorten to a simple Euroscore-tricuspid of only 7 inputs. Functional tricuspid regurgitation may be frequently found in patients undergoing cardiac surgery from other reasons. It will become more severe over time if not corrected during first surgery. It is significant to have a investigation on the outcomes of tricuspid valve repair accompanying left-sided heart disease surgery. This manuscript retrospectively investigated this topic, discussed the advantages of the correction surgery at the same time, analyzed the risk factors and concluded to simplify using the predictive factors.

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## Mining twitter to understand the smoking cessation barriers

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### Abstract

Smoking cessation is challenging and lack of positive support is a known major barrier to quitting cigarettes. Previous studies have suggested that social influences might increase smokers' awareness of social norms for appropriate behavior, which might lead to smoking cessation. Although social media use is increasing among young adults in the United States, research on the relationship between social media use and smoking cessation is lacking. Twitter has provided a rich source of information for researchers, but no overview exists as to how the field uses Twitter in smoking cessation research. To the best of our knowledge, this study conducted a data mining analysis of Twitter to assess barriers to smoking cessation. In conclusion, Twitter is a cost-effective tool with the potential to disseminate information on the benefits of smoking cessation and updated research to the Twitter community on a global scale.

**Key words:** Smoking cessation; Stop smoking; Smoking; Twitter; Tweets

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**Core tip:** Twitter use is increasing globally, research on the relationship between Twitter use and smoking cessation is lacking. This study is to the best of our knowledge the first Twitter analytic study of smoking cessation. Twitter is a cost-effective tool with the potential to disseminate information on the benefits of smoking cessation and updated research to the Twitter community on a global scale. Digital health interventions through Twitter that educate the health community are still needed.

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## TO THE EDITOR

Smoking cessation is challenging and lack of positive support is a known major barrier to quitting cigarettes. Previous studies have suggested that social influences might increase smokers' awareness of social norms for appropriate behavior, which might lead to smoking cessation<sup>[1,2]</sup>. Although social media use is increasing among young adults in the United States, research on the relationship between social media use and smoking cessation is lacking. Recent studies have shown that Twitter data mining can have broad implications on cardiovascular health research<sup>[3,4]</sup>. We report on an assessment of barriers to smoking cessation by performing data mining in Twitter.

Twitter (<https://twitter.com/>) postings containing the terms "quit smoking", "smoking cessation", and "stop smoking" were obtained for July 23, 2009, through November 22, 2016. All analyses relied on public, anonymized data and adhere to the terms and conditions, terms of use, and privacy policies of Twitter. No exact tweets are included in this report. Data mining were performed with R version 3.2.3.

We identified 39731 tweets associated with smoking cessation and identified insights into people's perceptions of quitting smoking and some barriers to cessation. In the sample, 12375 retweets (reposted or forwarded messages) were excluded from the analysis. The results found 13099 negative statements, 4425 positive statements, and 9832 ambiguous or unclear statements. Reasons to not quit smoking were found in 965 tweets. For example, "someone dies from smoking, someone dies from a heart attack, what's the difference both are dead". Some tweets reported a social influence on smoking

cessation, such as "sometimes I think people only quit smoking for the Facebook likes". Some tweets did not report barriers to smoking cessation. For example, "I wonder how many times I'm going to quit smoking". A few tweets stated a need for more information from the community, such as "yoo is there anyone on here who has quit smoking successfully and can give me sum tips". Several academic institutions have been using Twitter to deliver health messages to the community. For example, "smoking increases the risk of death from lung cancer, heart attack and stroke by 200%".

Overall, Twitter is a cost-effective tool with the potential to disseminate information on the benefits of smoking cessation and updated research to the Twitter community on a global scale. Digital health interventions through Twitter that educate the health community are still needed.

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## Effects of energy drinks on the cardiovascular system

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### Abstract

Throughout the last decade, the use of energy drinks has been increasingly looked upon with caution as potentially dangerous due to their perceived strong concentration of caffeine aside from other substances such as taurine, guarana, and L-carnitine that are largely unknown to the general public. In addition, a large number of energy drink intoxications have been reported all over the world including cases of seizures and arrhythmias. In this paper, we focus on the effect of energy drinks on the cardiovascular system and whether the current ongoing call for the products' sales and regulation of their contents should continue.

**Key words:** Energy drinks; Caffeine; Taurine; Guarana; Cardiovascular effects

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**Core tip:** The last decade has witnessed a great surge in the consumption of energy drinks which coincided with an increased rate of reported cases of intoxications resulting in cardiovascular adverse effects especially arrhythmias, although most of such cases were associated with alcohol, stimulants, or rapid consumption in a short period of time. In our paper, we summarized the research pertaining to the most common components of the energy drinks in an attempt to evaluate whether the call for control of the products is merited, some of which had surprising possible health benefits.

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## INTRODUCTION

The last decade has witnessed the greatest rise in the consumption of non-steroidal energy supplements for the specific purpose of boosting athletic performance and concentration. For many years, the use of energy drinks (ED) has been perceived as potentially dangerous due to their strong concentration of caffeine and presence of other substances such as taurine, guarana, and L-carnitine amongst others. In France, the use of Red Bull™ was banned at one point until the rule was reversed by the European Union on claims of the lack of evidence for its toxicity. The controversy surrounding energy drinks heightened recently due to the increasing reports of energy drink toxicities, most alarmingly in regard to heart rhythm and central nervous system abnormalities such as atrial fibrillation and seizures, respectively. We aim to focus on the effect of energy drinks on the cardiovascular system and whether the call for the products' sales and regulation of their contents has merit.

## SCOPE OF THE ISSUE

In recent years, the market for energy drinks has thrived and after 50 years in the market, the consumption of these beverages has increased exponentially<sup>[1]</sup>. Along with a growing global market, emergency room visits due to the consumption of energy drinks have increased as well. The Substance Abuse and Mental Health Services Administration revealed that 20783 people visited the emergency department with complaints involving caffeine rich energy drinks in 2011. Over the period from 2007-2011, ED-related emergency department visits in the United States doubled<sup>[2]</sup>. Due to their high consumption, lack of evidence, and occasional acute adverse health effects, the safety of energy drinks has been called into question. Our review will specifically focus on the cardiovascular effects of the ingredients contained in EDs.

As promisors of prolonged arousal, boosted athletic performance, and increased concentration, energy drinks have become popular supplements in the past few years. A recent study of 1620 nursing students noted 78.1% reported ED use. The students consumed an average of 1.6 cans per week, ranging from 1 to 30 cans per week<sup>[3]</sup>. Certain ED company claims have been found to be true. One placebo controlled study found that certain important aspects of cognitive function can be improved by a single energy shot. The study was performed on partially sleep-deprived healthy individuals and the effect was noted to last

for up to 6 h<sup>[4]</sup>. Another study found that subjective ratings of vigor and fatigue were improved after the consumption of energy drinks, although, objective performance did not improve and, in fact, seemed to worsen over time<sup>[5]</sup>.

With increased stress to perform academically, athletically, and socially, it is not surprising that most consumers of EDs are teenagers and young male adults<sup>[6,7]</sup>. It should be noted that ED consumption cannot be looked at as a separate entity as co-ingestion with alcohol, drugs, and other pharmaceuticals has become a widespread practice. A cross-sectional survey conducted in 2012 reported that 85 emergency department patients, that were there for ED related events, showed that illicit stimulants such as cocaine and methamphetamine were often co-ingested<sup>[8]</sup>. Another study found that males were more likely to co-ingest alcohol or drugs, whereas in females, co-ingestion of other medications was more common<sup>[9]</sup>. It should be noted that the half-life of caffeine was found to increase by up to 72% with its coingestion with alcohol, thereby enhancing the effects of EDs<sup>[10]</sup>.

## PURPORTED EFFECTS OF ENERGY DRINKS AND THEIR CAFFEINE-RELATED CAUSAL ROLES ON THE CARDIOVASCULAR SYSTEM (FIGURE 1)

### *Physiologic effects on vital signs*

Evidence of reported energy drinks-related cardiovascular adverse effects has helped to further raise suspicion of these beverages. It is widely believed that caffeine, particularly at high doses, is associated with multiple cardiac comorbidities including palpitations and a number of arrhythmias such as atrial fibrillation and supraventricular and ventricular ectopy. Caffeine's effect in acutely raising the blood pressure is also thought to stress the cardiovascular system, furthering the likelihood of it causing arrhythmia. Such an elevation in blood pressure has been also shown to be more prominent in the elderly and those with underlying hypertension. A study of 20 young healthy humans explored the effects of Red Bull along with induced mental stress. It was found that compared with the ingestion of water, ingestion of a 355 mL can of Red Bull imposes a cumulative cardiovascular load, increasing systolic BP by about 10 mmHg, diastolic BP by about 7 mmHg, and heart rate by 20 beats/min, and decreasing cerebral blood flow velocity by -7 cm/s<sup>[11]</sup>.

Several studies have found energy drinks have been shown to induce hypertension compared to placebo. A recent study asked fifteen recreational runners to complete five exercise trials. The subjects ingested one of three energy drinks or a placebo one hour prior to testing. Results showed that the fifteen minute systolic BP readings were significantly higher in the three energy drink trials (163.87, 166.47, and

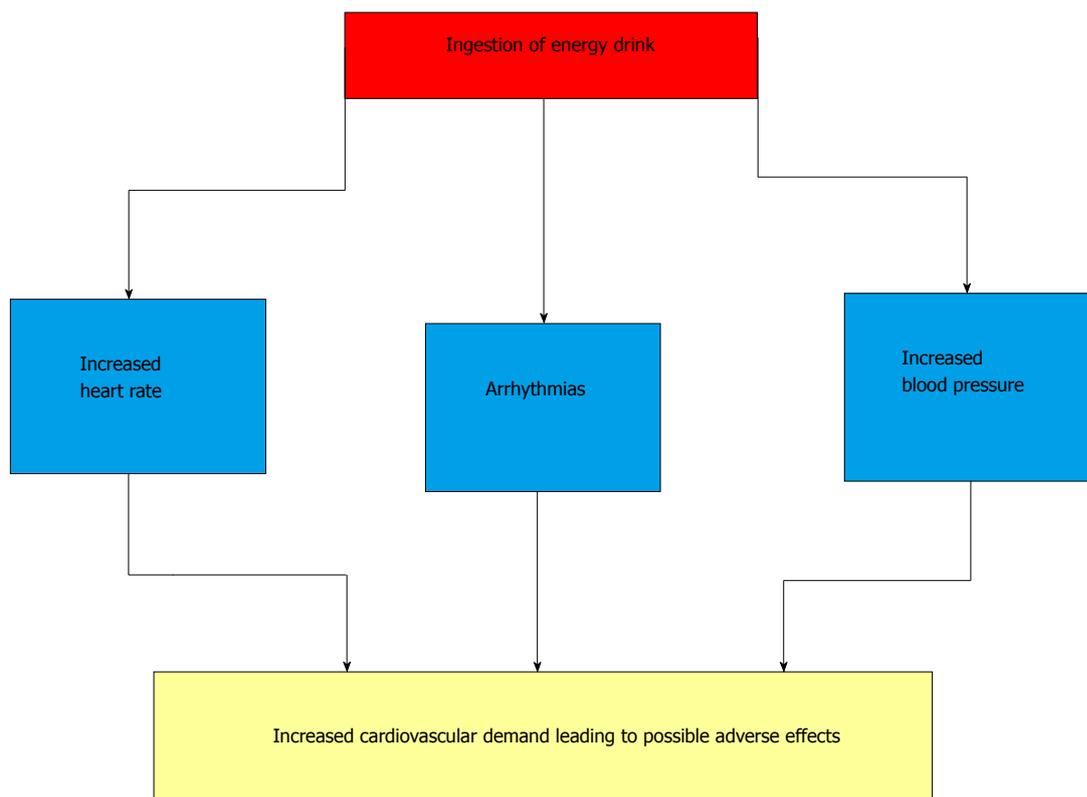


Figure 1 Effects of energy drinks on the cardiovascular system.

165.00) compared to the placebo trials (156)<sup>[12]</sup>. Other studies have found the same effect as well. Elitok *et al*<sup>[13]</sup> studied 50 young, healthy subjects and found that 2 h after consumption of 355 mL of Red Bull their systolic blood pressure increased from 112 to 121 mmHg, and diastolic blood pressure 73 to 76 mmHg. Grasser *et al*<sup>[14]</sup> conducted a randomized crossover study of twenty-five young non-obese and healthy subjects and showed that both systolic and diastolic blood pressure increased as a result of Red Bull consumption. The water control load did not. The study also showed increases in cerebrovascular resistance and breathing frequency, in addition to decreases in cerebral blood flow velocity and end-tidal carbon dioxide<sup>[14]</sup>.

A recent comprehensive and systematic review of case studies related to EDs and their adverse health effects has found that the most common adverse events affect the neurological and cardiovascular systems. The neurological effects were most commonly seizures but also included neuro psychotic agitation, aggressive behavior, and suicidal ideation. That may be because caffeine and taurine are known psychoactive agents. The cardiac related events included reports of: Arrhythmias (highest percent 35% with the others being rare), coronary vasospasm, aortic aneurysm dissection, cardiac arrest, QT prolongation, acute cardiomyopathies, accelerated hypertension, reversible postural tachycardia syndrome, acute coronary thrombosis, and ST-elevation myocardial infarction.

The authors attribute the cardiovascular adverse effects to the ingredients in ED, such as caffeine and taurine which have shown to increase platelet aggregation, disturb the endothelial function, and possibly causing vasospasm in association with hypertension<sup>[15]</sup>. Although there has been a link between energy drink consumption and platelet aggregation and endothelial dysfunction, the exact agent that is causing the effects is still unknown<sup>[16]</sup>. It should be noted that many of the adverse events described in these case reports have been linked to haphazard use of ED's and ED use combined with alcohol and other substances. Thus, emergency department case reports offer a hurdle to clearly understanding the adverse effects of EDs alone.

Another study was conducted with fifteen healthy adults. Their blood pressures were taken after abstaining from caffeine for 48 h, and, baseline BP, HR, and electrocardiographic (ECG) parameters were measured. Participants were asked to consume 500 mL of an energy drink and measurements were repeated 30 min, 1 h, 2 h, 3 h, and 4 h later, then drank 500 mL of energy drink daily for the next 5 d and measurements taken again on the final day. No significant ECG changes were noted, yet HR and SBP measurements increased by 5-7 beats/min and 10 mmHg, respectively. The cardiovascular effects were greater after five days of consumption than after the first day of consumption<sup>[17]</sup>.

Another study enrolled fourteen volunteers, who completed a three-session study. In each session,

they received a 2oz. 5-h Energy shot, 2oz. Ocean Spray™ Diet Cranberry Juice as the placebo, or no drink with BP readings measured each hour. The energy shot condition showed diastolic BP readings that were significantly higher when compared to both the no drink and placebo drink conditions. Interestingly, it was also significantly higher at 240 and 360 min when compared to 60 min. There was no difference in BP between the placebo and no drink<sup>[5]</sup>.

### **Physiologic effects on heart rhythm and induction of arrhythmia**

A number of documented cases correlated the consumption of energy drinks to the development of atrial fibrillation such as: Atrial fibrillation in a 16-year-old Caucasian boy after consuming an unknown amount of Red Bull™ mixed with vodka<sup>[18]</sup>. A case of atrial fibrillation in a patient with dilated cardiomyopathy that experienced seizures after the cessation of his excessive caffeine consumption<sup>[19]</sup>, and, atrial fibrillation in a 14-year-old Caucasian boy after an athletic event where he consumed an unknown amount of energy drink. He noted that he felt the same fluttering feeling 5 d before as well when he ingested a Red Bull™<sup>[18]</sup>. It is noteworthy that in all of such cases, there is a high suspicion for the excessive consumption of the beverages as the causal event.

## **CAFFEINE CONTENT AND DOSE**

The caffeine content of energy drinks has been the center of the controversy, as it is widely believed that most such products contain a significantly higher concentration of caffeine than what is found in an average cup of coffee. The cardiovascular effects of caffeine have been heavily studied. Caffeine's inotropic effect on the heart muscle has been long looked at with suspicion as a possible culprit for heart disease in some people<sup>[20]</sup>. The last couple of decades saw coffee be linked with various harmful effects such as hypertension, gastric ulcers, palpitations, anxiety, tremulousness, and, ultimately, heart disease<sup>[21-23]</sup>. Hence, caffeine has an essential role in understanding the possible dangers of energy drinks.

In healthy individuals, caffeine, a methylxanthine, increases sympathetic nerve activity. Caffeine's molecular mechanism lies in its competitive inhibition of phosphodiesterase. This results in an elevation in myocardial cyclic AMP and, as a consequence, the positive inotropic action on the myocardium. On the other hand, the inhibition of adenosine receptors prevents the negative inotropic effect elicited by adenosine, namely, blocking the vasodilatory effect of adenosine and adenosine's inhibitory effects in platelet aggregation, catecholamine levels, renin release, and lipolysis. Thus, acute caffeine administration may increase blood pressure and increase levels of plasma

catecholamine, renin, and free fatty acid<sup>[24]</sup>.

As noted above, there is an extensive amount of literature that reveals that caffeine moderately increases blood pressure and heart rate<sup>[25-28]</sup> and also linked to a drop in myocardial blood flow<sup>[29,30]</sup>. However, caffeine has also been shown to have some positive benefits as well. One study showed that caffeine consumption was associated with a significant increase in flow-mediated dilation and a decrease in hs-CRP level in healthy volunteers and volunteers with coronary artery disease alike. It is noteworthy that these positive effects in endothelial dysfunction and inflammation were not seen with nitroglycerin application<sup>[31]</sup>. While these results seem promising, other studies have found negative effects that caffeine may have on endothelial function, such as a study conducted by Papamichael *et al.*<sup>[32]</sup> they found that after ingestion of 80 mg of caffeine by healthy individuals, flow-mediated dilation was decreased in these individuals, most acutely in the first hour after ingestion. These results may not come as a surprise, as caffeine has been known to promote endothelial dysfunction through sympathetic activation<sup>[33]</sup>.

A large prospective study followed 130054 members of a healthcare plan in Northern California gathering subjects from 1978 to 1985 and following them until 2008 to note the amount of coffee consumed by each individual and whether that added a risk for hospitalization for arrhythmias or any other cardiomyopathy. Results showed a strong inverse relationship of coffee consumption to risk of hospitalization for arrhythmia. The inverse relationship was consistent in men, women, whites, blacks, and persons younger or older than 60 years old at baseline<sup>[34]</sup>. This result shows that participants who consumed more cups of coffee generally were significantly less likely to develop cardiac arrhythmias. This shows the reverse of the idea traditionally held of increased caffeine consumption leading to more cardiac arrhythmias. Additionally, a comprehensive literature review dealing with the effects of habitual caffeine consumption on the cardiovascular system found that moderate consumption resulted in beneficial to neutral effects<sup>[35]</sup>.

There is evidence, however, that point to caffeine's possible adverse effects especially when consumed at high doses. Toxic doses may affect conductance and refractoriness on the heart, which results in the development of various arrhythmias<sup>[36]</sup>. Symptoms of caffeine overdose also include palpitation, hypertension, irritability, insomnia, tremors, and seizures. In addition, the hypertensive effects of caffeine should not be overlooked as they may lead to hazardous cardiovascular events. The HARVEST study found that when after adjusting for possible confounding variables, cardiovascular events were more common among coffee drinkers than non-coffee drinkers. The authors suggested that hypertensive patients should be discouraged from drinking coffee<sup>[6]</sup>.

Table 1 Caffeine concentration in common drinks

Caffeinated beverage	Amount of caffeine/drink, mg
5-h energy™ bottle	215
Arizona Iced Black Tea (16oz)	30
Bang Energy (16oz)	357
Caffeine Powder (1/16 Tsp.)	200
Coca Cola, Coke Zero, Diet Pepsi (12oz)	34
Dannon Coffee Yogurt (6oz)	30
Dunkin Donuts™ Medium Brewed Coffee (14oz)	178
Dunkin Donuts™ Medium Latte (14oz)	97
FDA official limit for cola and pepper soft drinks(12oz)	71
Herbal Tea (8oz)	0
Lipton Decaffeinated Black Tea (8oz)	5
Maxwell House Decaf Ground Coffee (2 Tbs. makes 12oz)	2-10
Maxwell House Light Ground Coffee (2 Tbs. makes 12oz)	50-100
Monster Energy™ (16oz)	160
Mountain Dew (12oz)	54
Pepsi (12oz)	38
Red Bull™ (8.4oz)	80
Rockstar™ (16oz)	160
Snapple Lemon Tea (16 oz)	37
Starbucks Grande Chai Latte (16oz)	95
Starbucks Hot Chocolate (16oz)	25
Starbucks Refreshers Can (12oz)	50
Starbucks™ Grande Caffè Americano (16oz)	225
Starbucks™ Grande Caffè Mocha (16oz)	175
Starbucks™ Grande Coffee Frappuccino (16oz)	95
Starbucks™ Grande Ice coffee (16oz)	165

There is a widespread belief that caffeine may be arrhythmogenic in those who regularly consume it. However, a large-scale Danish study did not find a higher risk for atrial fibrillation/flutter with different amounts of caffeine consumed<sup>[37]</sup>. In addition, the stimulant effects of caffeine seems to vary amongst individuals, in fact, the degree of tolerance and dependence to it is likely heritable and may be linked to polymorphisms<sup>[38]</sup>.

Two comprehensive meta-analyses both determined that caffeine is unlikely to promote cardiovascular disease. In fact, the opposite may be true. The first review, conducted by Cheng *et al.*<sup>[39]</sup> found an inverse relation was found between habitual caffeine intake and risk of atrial fibrillation. For every 300 mg per day increment in habitual caffeine intake, incidence of AF was found to drop by 6%. One explanation for these results is caffeine's association with lower risks of obesity, and metabolic disease. Thus, adverse cardiovascular effects of caffeine seem to represent itself with a J-shaped curve, with higher doses increasing the risks of heart disease, and normal doses proving to be beneficial<sup>[40]</sup>.

The discrepancies in these studies can be difficult to reconcile although some of the variation in results may be attributed to differences in study design, varied caffeine dosages administered, and different study cohorts. Most studies do an inclusion criteria exercise for their cohorts. However, many did not take into account the regular coffee consumption

of volunteers prior to the study. This is important because coffee metabolism is extremely variable in humans; thus, the effects of caffeine are not uniform. The half-life is 4.9 h, however absorption rates are largely based on the individual's genes, age, sex, liver health, and drug uptake, such as use of oral contraception, antidepressants, and antiarrhythmics, as well as their tolerance to the stimulant<sup>[41]</sup>. Caffeine is primarily metabolized through the liver's cytochrome P450 1A2 (CYP1A2) enzyme and defects in such an enzyme have been implicated in the population's variation in metabolism and half-life. Hence, genetic polymorphisms in the CYP1A2 pathway may explain some of the inconsistencies in studies of coffee and its effects on health<sup>[42]</sup>.

To examine the caffeine amounts, Table 1 shows the caffeine concentrations of some popular drinks at Starbucks™ and Dunkin Donuts™ along with some of the most popular caffeine containing drinks<sup>[43]</sup>. Note that all EDs or energy shots surpass the FDA official soft drink concentration limit of 71 mg per twelve-ounce drink, sometimes by over triple the amount. According to the Mayo Clinic and the US food and Drug Administration up to 400 mg of caffeine a day appears to be safe for most healthy adults<sup>[44,45]</sup>. One study that supports this quantity mentions that maximum safe caffeine intake for pregnant women, children, and those taking medications is still undetermined<sup>[9,46]</sup>. Unfortunately, proper labeling has also been an issue, with companies reportedly falsely labeling caffeine content on their products, and

misguiding consumers<sup>[47]</sup>.

## OTHER ACTIVE INGREDIENTS IN ENERGY DRINKS AND THEIR ADDED EFFECTS

### Taurine

Taurine is a derivative of the amino acid cysteine, and is found in high quantities in heart and skeletal muscle<sup>[48]</sup>. It is added in a large number of energy drinks such as 5-h energy™ and Red Bull™. Although taurine is considered an essential nutrient for humans, clinical studies evaluating the effects of taurine are limited. Taurine has been shown to be beneficial in improving the lipid profile by increasing the transcription of CYP7A1, an important enzyme in bile conjugation<sup>[49]</sup>, as well increasing the liver's LDL uptake and up-regulation of LDL receptors<sup>[50]</sup>. Its supplementation has also been linked with a decrease in blood pressure possibly through the attenuation of angiotensin II, which causes vasoconstriction<sup>[51]</sup> or by "enhancing" the kinin-kallikrein system, which normally causes vasodilation<sup>[52]</sup>. An ethnic Chinese study found an inverse correlation between twenty-four hour taurine excretion and diastolic blood pressure in Han (the major Chinese ethnic group) individuals and a decrease in both systolic and diastolic BPs in Tibetan subjects when consumed<sup>[53]</sup>. Similarly, there was a significant decrease in systolic and diastolic BPs in 19 borderline hypertensive subjects<sup>[54]</sup>.

In addition, taurine deficiency was found to be associated with a decrease in the sensitivity of the cardiac muscle to Ca<sup>2+</sup>, and, hence, a decreased inotropic capability of the organ<sup>[48]</sup>. This may be the reason for the supplements alleged boost in physical performance through an improved blood supply to the rest of the organs, specifically the musculoskeletal system. Interestingly, concentration of taurine have been found to be higher in the left ventricular muscle of hearts of patients who died of chronic congestive heart failure than that of patients who died of other causes and had no cardiac pathology<sup>[55]</sup>. The study hints that taurine may, in fact, have an inotropic effect which may shed some light on the cardiovascular adverse effects of energy drinks.

Certain studies have compared the effects of energy drinks containing just caffeine, and those containing caffeine and taurine. One study randomized nine volunteers to receive either an ED containing 80 mg of caffeine and 1000 mg of taurine or a control that contained 80 mg of caffeine solution in water. They were asked to consume their respective drink every 3-4 h for a single day. Mean 24-h systolic blood pressure, diastolic blood pressure, and mean arterial pressure recordings were significantly higher in the ED group than in the control (123.2 mmHg vs 117.4 mmHg, 73.6 mmHg vs 68.2 mmHg, 90.1

mmHg vs 84.8 mmHg, respectively)<sup>[56]</sup>. Another study asked 13 athletes to ingest either Red Bull, a similar caffeinated drink without taurine, or a placebo prior to performance of exhaustive endurance exercises. ECGs performed before ingestion, before exercise, after ingestion, during the recovery period showed that the only significant increase in stroke volume during the recovery period was the group that consumed taurine containing Red Bull. This study suggests that taurine and caffeine may interact together to increase cardiac contractility<sup>[57]</sup>. A third study explored the peak systolic strain in 32 healthy individuals at baseline, and one hour after consumption of an ED containing caffeine and taurine, or just caffeine. While the drink with caffeine did not seem to have any significant cardiovascular effects shown by magnetic resonance imaging, those that ingested the combination of caffeine and taurine had a significant increase in peak systolic strain<sup>[58]</sup>.

Schaffer *et al.*<sup>[59]</sup> conducted a comprehensive literature review regarding the interaction between taurine and caffeine and in agreement with the European Union's Scientific Committee on Food, they concluded that taurine should neutralize several untoward effects of caffeine excess. They noted that the physiological functions of taurine appear to be inconsistent with the adverse cardiovascular symptoms associated with excessive consumption of beverages containing caffeine and taurine.

### B vitamins

Referred to as vitamin B complex, the eight B vitamins, thiamine (B1), riboflavin (B2), niacin (B3), pantothenic acid (B5), pyridoxine hydrochloride (B6), biotin (B7), inositol (B8), and cyanocobalamin (B12), act as coenzymes for proper cell function, especially mitochondrial function and energy production. Thus, some believe that B vitamins may increase energy expenditure<sup>[60]</sup>. One study has shown lower fat mass in men who regularly consumed multivitamins<sup>[61]</sup>. Energy drinks often contain a large quantity of B-group vitamins, often at larger doses than the recommended daily intake for healthy individuals.

Studies have shown that high dietary intakes of folate and vitamin B6 has been linked with reduced risk of mortality from stroke, coronary heart disease, and heart failure<sup>[62]</sup>. B vitamins have also been shown to reduce levels of the amino acid homocysteine whose elevation have been linked to numerous comorbidities including pregnancy complications, cognitive impairment and mental disorders, as well as cardiovascular risks<sup>[63-65]</sup>.

A meta-analysis established that while B vitamin supplementation the B vitamin reduced homocysteine levels and has a significant protective effect on stroke, no benefit was found to reduce cardiovascular disease, myocardial infarction, coronary artery disease,

cardiovascular death, or all-cause mortality<sup>[66]</sup>.

### **Guarana**

*Paullinia cupana*, also known as guarana, is a South American plant that has been mentioned as early as 1872 for the treatment of "Sick-Headache"<sup>[67]</sup>. The Amazonians have used the seeds of its fruit to increase awareness and energy<sup>[68]</sup>. Guarana's stimulant effect is due to its similar chemical composition to that of caffeine. There is 2%-4.5% caffeine in the guarana seeds, compared to 1%-2% in the coffee bean<sup>[69]</sup>. The effect of guarana is not yet known. Whether it is of additive or synergistic effect when combined with caffeine is not clear. Guarana in a 16 ounce energy drink ranges from 1.4 mg to as much as 300 mg. The FDA generally recognizes guarana as safe, although there are no established dosages and it is unclear how much guarana is in each drink because many companies do not list a milligram amount. Therefore, it should be assumed that the amount of caffeine in the products is, in reality, larger than the amount of caffeine noted especially when guarana is present. It is not surprising that young adults have been admitted to emergency departments with cardiovascular adverse effects after excessive ingestion of guarana-based EDs<sup>[70]</sup>.

### **L-carnitine**

A meta-analysis on the effect of the L-carnitine supplement on the cardiovascular system found a 40% reduction in angina (RR, 0.60; 95%CI, 0.50-0.72;  $P < 0.00001$ ;  $I^2 = 0\%$ ). Compared with placebo or control, L-carnitine was found to be associated with a highly significant 65% reduction in ventricular arrhythmias (RR = 0.35; 95%CI: 0.21-0.58,  $P < 0.0001$ ,  $I^2 = 0\%$ )<sup>[71]</sup>. An increase in cardiac output after intravenous administration of L-carnitine in normotensive coronary artery disease patients has also been observed<sup>[72]</sup>. Another study showed that L-carnitine supplementation increased the left ventricular ejection fraction in studied individuals. The mean percent of increase of ejection fraction in the L-carnitine group was  $12.5\% \pm 8.3\%$  ( $P < 0.01$ ), while the control group had an increase of ejection fraction of  $6.1\% \pm 4.3\%$  ( $P < 0.01$ )<sup>[73]</sup>. In addition, the supplementation of L-carnitine has been shown to decrease left ventricular remodeling in post-myocardial infarction patients<sup>[74]</sup>. However, Koeth *et al.*<sup>[75]</sup> recently found a possible link of L-carnitine in red meat with cardiovascular disease through the development of atherosclerosis. This effect may simply be due to the long acknowledged negative effect of red meat on the cardiovascular system instead of L-carnitine itself.

L-carnitine is a naturally occurring amino acid made predominantly by the liver and kidneys. It is involved in B-oxidation of fatty acids and is thus linked to changes in metabolism and energy levels. It is commonly added to energy drinks to help promote

muscle function and physical performance. It is found in energy drinks such as Monster™ and Rockstar™ energy drinks.

L-carnitine's popularity in EDs is due to its possible ability to burn more fat and increase endurance during exercise, however, those claims remain elusive. Some data has indicated that L-carnitine plays an important role in the prevention of cellular damage and positively affects recovery from exercise stress. Uptake of L-carnitine by blood cells has been implicated in stimulation of hematopoiesis, a dose-dependent inhibition of collagen-induced platelet aggregation; and the prevention of programmed cell death in immune cells. Carnitine was recently shown to have direct effects in the regulation of gene expression and is potentially involved in modulating intracellular fatty acid concentration. Hence, there is evidence for a positive effect of L-carnitine supplementation. It may be especially beneficial in training and recovery from strenuous exercise<sup>[76]</sup>. In high doses, L-carnitine has been shown to have a side effect of nausea, vomiting, abdominal pain, and diarrhea; in addition, it has been associated with seizures in patients with no known disease and to increase seizure frequency in patients with seizure disorder<sup>[9]</sup>. However, as with ginseng, the amount of L-carnitine in energy drinks is likely not high enough to be of concern.

### **Ginseng**

This East Asian herb is one of the most popular herbal supplements in the world and has also been a popular additive in EDs. The claims about ginseng range far and wide-reducing stress, curing diabetes, insomnia, erectile dysfunction, improving memory, and increasing stamina are all purported benefits of the herb. However, very few claims are rooted in scientific research. A recent review concluded that evidence of enhanced physical performance after ginseng administration in well-designed investigations remains to be demonstrated<sup>[77]</sup>.

In 2013, one Mayo Clinic study did show that after eight weeks of taking 2000 milligrams of pure American ginseng root in a capsule, patients undergoing cancer treatment found a sudden jump in the general energy levels reported by the group on ginseng when compared to the placebo control group<sup>[78]</sup>.

Interestingly, several studies in rats have results suggesting that oral administration of ginseng root may increase insulin sensitivity and help with weight loss. Researchers at the University of Chicago administered daily intraperitoneal injections of Panax ginseng berry extract to rats and on day 12, extract-treated *ob/ob* mice became normoglycemic and were found to have significantly improved glucose tolerance. A more than twofold increase in the rate of insulin-stimulated glucose disposal in treated *ob/ob* mice was noted in hyperinsulinemic-euglycemic clamp study. The mice also lost a significant amount of weight which was

believed to be associated with the reduced food intake and the increase in body temperature and energy expenditure. Other studies revealed that ginsenoside Re plays a significant role in antihyperglycemic action. Interestingly, this antidiabetic effect of ginsenoside Re was not associated with body weight changes, suggesting that other components in the extract have distinct pharmacological mechanisms on energy metabolism. Additionally, plasma cholesterol levels were notably reduced following the treatment with the extract<sup>[79]</sup>.

Excessive amounts of ginseng ingestion may cause diarrhea, vaginal bleeding, headache, vertigo, mania, hypertension, rashes, insomnia, irritability, Stevens-Johnson syndrome, and agranulocytosis. However, some of these symptoms may be related to contaminants, such as phenylbutazone and aminopyrine that are used in its production<sup>[6]</sup>. However, the amounts of ginseng found in EDs are thought to be less than the amount needed to deliver the suggested therapeutic benefits or cause adverse events<sup>[80]</sup>.

### **Glucuronolactone**

Glucuronolactone is a glucose derivative, metabolized in the liver. In the sixties, the Japanese were particularly interested in its performance enhancing properties. They conducted one published study by injecting glucuronolactone, glucose, glycogen, and some other substances directly into the gut of lab rats, and recording the rats' ability to swim 30 min post injection. They repeated the procedure three times. In two of the three trials, the animals injected with glucuronolactone were able to swim longer than those injected with the other substances. The study also noted that the human equivalent of the dose would be between 1 and 2 g of glucuronolactone compared to the 600 mg found in a can of Red Bull<sup>[81]</sup>. These results may be due to glucuronolactone detoxification effects as supplementation with glucuronolactone may favor the body's natural defense mechanism for eliminating carcinogens and tumor promoters and their effects<sup>[82]</sup>.

Glucuronolactone has shown to act as an anti-platelet aggregative compound<sup>[83]</sup>, however, this outcome has not been proven to be effective when mixed in energy drinks, as after consumption an overall increase in platelet aggregation appears without any apparent effect of platelet anti-aggregation of the glucuronolactone<sup>[16]</sup>. There has been minimal suggested significant contribution towards energy by glucuronolactone on humans in the scientific literature and, therefore, no definitive conclusion can be made of its safety<sup>[84]</sup>.

## **OVERALL ASSESSMENT**

The increasing number of energy drink and caffeine-related overdoses clearly shows that there seems to be a real risk for adverse health effects such as

arrhythmias. However, under moderate use and without combining other stimulants or alcohol, the lack of a similar number of case reports makes the risk for such side effects seem negligible. It is noteworthy that a large number of serious health risks resulted were due to overconsumption of the products or their ingestion in a short period of time. Therefore, it may well be important for energy drink companies to place warnings on their products to avoid such habits.

The exact amounts and concentrations that are ideal in order to minimize the health risks are largely unknown. Patients with underlying illnesses such as hepatic failure or cardiomyopathy should likely avoid such products or, at least, be cautious by consuming small amounts. In addition, since there seems to be variation amongst individuals in the enzymatic activity of CYP1A2 and since testing for such enzymatic activity is not routinely performed, it is of great importance for each consumer to cease consuming the energy drinks if symptoms of an overdose develop. Producers should place a warning that includes such symptoms.

As for the constituents of the energy drinks themselves, the concentrations of caffeine seem to be comparable or even lower than many popular coffee drinks making the amount of caffeine itself an unlikely reason to not consume the products. In fact, medical research has shown that moderate consumption of caffeine is strongly related to a reduced risk of arrhythmias.

As for taurine and L-carnitine, the medical literature shows an overall positive health effect especially for the cardiovascular system, hence, making it unlikely that they can cause harm to that same system. In fact, it may be reasonable to consider those two compounds for future supplementation to those at risk for hyperlipidemia, hypertension, and cardiomyopathy. Guarana, on the other hand, may have a synergistic caffeine-like effect added to the caffeine already in these products and more information is needed on their combined effect.

## **CONCLUSION**

The last decade has seen an exponential increase in the number of energy drink products as well as the number of reported cases of arrhythmias and other health hazards caused by their consumption. Our review has found that the vast majority of the cases were due to excessive consumption of the drinks in a short period of time or when co-ingested with other stimulants such as alcohol and indicates that such drinks may be relatively safe when consumed moderately and separately. Additionally, the research covering the components of the beverages, such as caffeine, taurine, L-carnitine, glucuronolactone, ginseng, and guarana, seems to have a neutral to positive health effect unlike previously thought. However, it may be important for energy drink

producers to place warning labels of symptoms associated with an overdose in order to promote their recognition. Until the FDA sanctions these energy drink products, it is strongly encouraged that individuals research energy drink consumption and consult their physician in order to ensure safe consumption. Also, those with underlying cardiovascular disease should be careful by limiting the amount consumed or avoiding altogether, as they may be at increased risk for arrhythmias or other cardiovascular events.

With the exception of the effects of caffeine, the ingredients in energy drinks have not been thoroughly studied to confirm the cardiovascular safety or the proclaimed energy-boosting benefits. There is an overwhelming lack of evidence to substantiate claims that components of EDs, contribute to the enhancement of physical or cognitive performance. Additional well-designed, randomized, placebo-controlled studies are needed in order to assess claims made for these products and further elucidate potential adverse effects.

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## Randomized Clinical Trial

**Randomized study comparing incidence of radial artery occlusion post-percutaneous coronary intervention between two conventional compression devices using a novel air-inflation technique**

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**Institutional review board statement:** This study was reviewed and approved by the Ethics Committee of University Hospital Limerick, Dooradoyle, Limerick, Ireland.

**Informed consent statement:** All eligible patients gave written informed consent to participate in the study, prior enrollment.

**Conflict-of-interest statement:** All authors declare no potential conflicting interests related to this paper.

**Data sharing statement:** No additional data are available. Technical appendix, statistical code, and dataset available from the corresponding author at [victor.voon@gmail.com](mailto:victor.voon@gmail.com). Presented data are anonymized and risk of identification is low.

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**Abstract****AIM**

To compare post-percutaneous coronary intervention (PCI) radial artery occlusion (RAO) incidence between two conventional radial artery compression devices using a novel air-inflation technique.

**METHODS**

One hundred consecutive patients post-PCI were randomized 1:1 to Safeguard or TR band compression devices. Post-radial sheath removal, each compression device was inflated with additional 2 mL of air above index bleeding point during air-filled device application and gradually down-titrated accordingly. RAO was defined as absence of Doppler flow signal performed at 24 h and at 6 wk post-PCI. Patients with missing data were excluded. Statistical significance was defined as  $P < 0.05$ .

## RESULTS

All patients had 6F radial sheath inserted. No significant differences were observed between Safeguard Radial ( $n = 42$ ) vs TR band ( $n = 42$ ) in terms of age ( $63 \pm 11$  years vs  $67 \pm 11$  years), clinical presentation (electives,  $n = 18$  vs  $n = 16$ ; acute coronary syndrome,  $n = 24$  vs  $n = 26$ ) and total procedural heparin ( $7778 \pm 2704$  IU vs  $7825 \pm 2450$  IU). RAO incidence was not significantly different between groups at 24 h (2% vs 0%,  $P = 0.32$ ) and 6 wk (0%, both).

## CONCLUSION

Safeguard Radial and TR band did not demonstrate significant between-group differences in short-term RAO incidence. Lack of evidence of RAO in all post-PCI patients at 6 wk follow-up, regardless of radial compression device indicate advantage of using the novel and pragmatic air-inflation technique. Further work is required to more accurately confirm these findings.

**Key words:** Radial artery; Arterial occlusive disease; Cardiac catheterization

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**Core tip:** Radial artery occlusion (RAO) is a rare but significant complication post-transradial percutaneous coronary intervention (PCI). We found that post-PCI Doppler flow signal-detected RAO incidence was not significantly different between Safeguard Radial and TR band compression devices. However, with the use of a novel air-inflation technique, we observed significantly lower incidence of RAO in all patients regardless radial compression device, in the short-term compared to current literature. Therefore, this novel air-inflation technique may offer a pragmatic and effective solution in reducing RAO incidence.

Voon V, Ayyaz Ul Haq M, Cahill C, Mannix K, Ahern C, Hennessy T, Arnous S, Kiernan T. Randomized study comparing incidence of radial artery occlusion post-percutaneous coronary intervention between two conventional compression devices using a novel air-inflation technique. *World J Cardiol* 2017; 9(11): 807-812 Available from: URL: <http://www.wjgnet.com/1949-8462/full/v9/i11/807.htm> DOI: <http://dx.doi.org/10.4330/wjc.v9.i11.807>

## INTRODUCTION

Radial artery occlusion (RAO) is an increasingly recognized and significant vascular complication among those observed post-hemostatic compression device application for transradial percutaneous coronary intervention (PCI), the recommended access route in current guidelines<sup>[1]</sup>. As a consequence of RAO, ipsilateral limb transradial access may be

rendered unusable for future procedures. This may be particularly crucial in post-PCI patients, a cohort at higher risk of requiring further coronary angiography, conduit for coronary artery bypass surgery or arterio-venous fistula formation for hemodialysis. Furthermore, ipsilateral ulnar artery access may be unusable due to ischemic limb risk on arterial cannulation.

Several studies have reported rates of RAO from 1%-30%<sup>[2-9]</sup>. These figures reflect the complex pathophysiology involved in RAO, particularly impaired vascular remodeling and thrombo-inflammatory alterations post-arterial injury. In addition, reports to date have been confounded by multiple external factors. These factors include heterogeneity of study designs, targeted patient populations, parameters for assessing RAO, anticoagulation as well as compression devices and techniques<sup>[10]</sup>.

While several compression bands and techniques tested have demonstrated a modest reduction in RAO, a more pragmatic and effective approach remains to be defined<sup>[11]</sup>. Therefore, we aimed to prospectively compare incidence of RAO between two conventional hemostatic compression devices (Safeguard Radial and TR band) using a pragmatic and novel air-inflation technique, in patients post-transradial PCI.

## MATERIALS AND METHODS

Ethics approval was obtained from University Hospital Limerick Ethics committee for our study, which conformed to the principles of the Helsinki Declaration. A total of 107 consecutive patients who had undergone transradial percutaneous coronary intervention at University Hospital Limerick, were screened and eligible patients were recruited into the study. Patients gave written informed consent prior to PCI and were prospectively randomized to either Safeguard Radial or TR band compression device *via* a pre-specified 1:1 automated randomization. Exclusion criteria were patients less than 18 years old, pregnancy, inability to consent, inability to attend follow-up clinic and difficult radial access requiring femoral access. Patient demographics and angiographic profiles were collected. All patients received dual anti-platelet therapy prior to PCI. Radial artery procedural preparation and management as well as RAO assessment are described below.

### Radial artery cannulation

After sterile preparation, 1% lidocaine was injected at puncture site. The radial artery was punctured at the anterior wall with a 21-gauge arterial needle through which a 0.018-inch straight floppy tip guidewire (40-cm length) was advanced upon appearance of pulsatile flow. Following this, the needle was withdrawn and a hydrophilic 6F introducer sheath (11-cm length) with dilator length of 16 cm (Prelude, Merit Medical



Figure 1 TR band compression device.

Systems) was inserted over the guidewire into the radial artery. Subsequently, the wire and dilator were removed. According to operator preference, a “radial cocktail” consisting of intra-arterial 100-200 mcg nitroglycerin, 250 mcg verapamil and heparin 2000-4000 IU, was given. All patients had total procedural heparin 70-100 IU/kg given as part of the PCI procedure.

#### **Radial sheath removal and hemostatic compression technique**

Patients were randomized to either TR band (Terumo Interventional Systems) or Safeguard Radial (Merit Medical) hemostatic compression device groups (Figures 1 and 2). Immediately post-PCI, the radial sheaths were pulled out 4-5 cm and chosen hemostatic compression device band was placed around wrist, with the transparent bladder immediately over the puncture site. We utilized a novel and pragmatic air-inflation technique that involved initial syringe-guided inflation of 2-5 mL of air into device transparent bladder *via* a cuff-valve system, with careful simultaneous removal of sheath. Continued inflation up to 5-10 mL of air was done to stop bleeding after complete removal of sheath. This was followed by immediate release of air, using similar syringe until bleeding/oozing point, at which an additional 2 mL of air was inflated into device bladder. This is contrary to current non-personalized air-inflation techniques utilizing standard 15 mL and 7 mL of air in TR band and Safeguard respectively, as per manufacturer’s instructions. Subsequent gradual down-titration of air (1 mL of air removed every 30 min) was performed by nursing staff until completion of hemostasis.

#### **Activated clotting time measurement**

Activated clotting time (ACT) is the routine method of choice for monitoring heparin therapy during

PCI. At the end of PCI, for all patients, 5 mL of fresh arterial blood sample was obtained in a 5 mL syringe after initially discarding 10 mL of blood from radial sheath prior to sheath removal. The fresh blood was immediately measured for ACT, by using a disposable single-use point-of-care assay. The assay consists of a cuvette containing manufacturer reagents and is measured by the accompanying battery-operated, hand-held device Hemochron Jr Signature + Whole Blood Microcoagulation System (International Technidyne) as per manufacturer’s instructions.

#### **RAO assessment**

The handheld ultrasonic Doppler signal flow detector 2 MHz (FD1, Huntleigh, Sonicaid) probe was applied above the puncture site of radial artery of resting and extended forearm. RAO was defined as absence of Doppler signal flow. This was performed at 24 h and 6 wk post-PCI by operators blinded to randomization process.

#### **Outcome measures**

Primary endpoint was RAO at 24 h post-procedure and 6 wk follow-up. Secondary endpoints were bleeding requiring transfusion/surgical intervention, hematoma and pain/numbness at radial access site.

#### **Statistical analysis**

As a pilot study evaluating this technique, exploratory analyses was performed. Continuous normal data were expressed as mean  $\pm$  SD. Continuous non-normal and categorical variables were expressed as mean (25<sup>th</sup>, 75<sup>th</sup> percentile) or frequencies (and percentages). Accordingly, between-group comparisons were compared using unpaired t-testing, Mann-Whitney rank sum test or Pearson chi-square tests. All patients with missing data were excluded from analyses. All analyses were performed using SPSS version 18 statistical software (SPSS Inc, Chicago, IL, United states).  $P < 0.05$  was considered significant (two-tailed significance).

## **RESULTS**

Baseline demographics of patient cohort are presented in Table 1. A total 84 patients were included for analyses after excluding patients who were not eligible ( $n = 5$ )/refused ( $n = 2$ ), had missing data ( $n = 16$ ). No significant differences were observed between-groups in terms of demographics or procedural profiles (Table 2). Approximately 60% of patients presented with an acute coronary syndrome. All patients had 6F radial sheaths inserted. Despite no significant between-group differences in post-procedural outcomes measures, both Safeguard Radial and TR band groups demonstrated very low incidence of RAO at 24 h (2% vs 0%) and 6 wk (0%, both) (Table 3). No significant



Figure 2 Safeguard Radial compression device.

**Table 1 Clinical and angiographic profiles of Safeguard Radial vs TR band groups at baseline-total patient cohort**

Variables	Safeguard radial, n = 42	TR band, n = 42	P value
Age, years	63.8 ± 10.9	66.8 ± 10.8	0.21
Gender, male/female ratio	31/11	37/5	0.16
BMI, kg/m <sup>2</sup>	29.2 ± 3.9	29.0 ± 5.7	0.88
Diabetes	4 (10%)	8 (19%)	0.22
CKD	1 (2%)	2 (5%)	0.56
PAD	0%	1 (2%)	0.32
Indication			
Elective	18	16	0.88
UA	6	8	0.9
NSTEMI	13	8	0.7
STEMI	5	10	0.6

BMI: Body mass index; CKD: Chronic kidney disease; PAD: Peripheral arterial disease; UA: Unstable angina; NSTEMI: Non-ST elevation myocardial infarction; STEMI: ST-elevation myocardial infarction.

differences in secondary outcome measures were observed.

## DISCUSSION

This study has demonstrated no significant difference in incidence of short-term RAO between Safeguard and TR band devices. However, we have for the first time demonstrated significantly lower incidence of RAO at 24 h and at 6 wk post-PCI compared to current literature, regardless of type of conventional hemostatic compression device using the novel air-inflation technique. Among the few studies that have reported short-term RAO, some have observed RAO incidence as high as 9.2% at discharge<sup>[9]</sup>. Pancholy and colleagues reported RAO incidence of 4.4% at 24 h and 3.2% at 30 d using TR band in a cohort using 5F radial sheaths<sup>[8]</sup>. Dai *et al.*<sup>[11]</sup> demonstrated that in post-transradial PCI patients, incidence of RAO was at least 11% at 24 h and 10% at 30 d. The study showed that air titration based compression strategy using TR band was superior to non-air titration strategies. However, the study utilized a non-specific, non-personalized method using manufacturer’s instructions.

In our experience, additional 2 mL of air above point

of bleeding/oozing provides personalized and adequate temporary patent hemostasis without the need of conventional methods to monitor radial patency. This has been shown despite different surface area of compression bladder of both devices. This magnitude of air may provide sufficient compression on muscle, adipose tissue and artery although impact of higher magnitudes of air remains to be determined. This technique requires confirmation in future studies.

To further support this technique, our study involved a cohort presenting predominantly with acute coronary syndrome, a more prothrombotic state, compared to previous studies. Only 29.7% of transradial PCI-treated patients presented with acute coronary syndrome in a study by Rathore and colleagues<sup>[9]</sup>. The study demonstrated a higher incidence of RAO as aforementioned with manufacturer’s technique of compression device air inflation. However, several techniques to measure RAO were used and only 50% of patients had hydrophilic radial sheaths compared to our study. Some may argue that lack of sheath hydrophilicity may account for such results.

Furthermore, sheath size has also been regarded as a contributing factor to RAO. Larger diameter sheaths have been reported to have increase RAO

**Table 2** Procedural profiles of Safeguard Radial *vs* TR band groups

Variables	Safeguard radial, <i>n</i> = 42	TR band, <i>n</i> = 42	<i>P</i> value
Pre-procedure			
IR verapamil, %	(86%)	(83%)	0.77
IR nitroglycerine, %	(31%)	(45%)	0.18
Procedural			
Heparin, IU	7778 ± 2704	7825 ± 2450	0.94
Number of target vessels treated with PCI			
1			
2	39	39	1
≥ 3	3	3	1
	0	0	1
Target vessels			
LM	1	0	0.98
LAD/Diagonal	19	22	0.87
LCx/OM	7	7	0.96
RCA	18	12	0.64
IM	0	2	0.77
VG	0	2	0.77
Fluoroscopy times, min	15.3 ± 8.4	15.0 ± 6.9	0.88
Post-procedure			
GP2B3A inhibitor, %	1 (2%)	0%	0.32
ACT (s)	197 ± 38	197 ± 47	0.97

IR: Intra-radial; LM: Left main artery; LAD: Left anterior descending artery; LCx: Left circumflex artery; OM: Obtuse marginal artery; RCA: Right coronary artery; IM: Intermediate artery; VG: Vein graft; GP2B3A: Glycoprotein 2B 3A receptor; ACT: Activated clotting time.

**Table 3** Post-procedural outcomes in Safeguard Radial *vs* TR band groups

Variables	Safeguard radial, <i>n</i> = 42	TR band, <i>n</i> = 42	<i>P</i> value
Bleeding requiring blood transfusion/surgical intervention	0%	0%	1
Hematoma	7%	0%	0.07
Pain/numbness	2%	0%	0.32
Radial artery occlusion at 24 h	2%	0%	0.32
Radial artery occlusion at 6 wk	0%	0%	1

incidence<sup>[12-14]</sup>. This effect was not observed in our study which used 6F sheaths in all patients who required PCI. Despite that, further studies involving improved imaging modalities are required to more accurately characterize vessel to sheath ratio. This is because the higher prothrombotic effects due to possible oversized sheaths may be offset by heparin therapy that all patients received in our study.

Heparin itself has been shown to reduce incidence of RAO. The lack of procedural heparin is an independent predictor of RAO<sup>[9]</sup>. Rathore and colleagues demonstrated RAO incidence of 24.1% at 4-6 mo follow-up in those without heparin administration. The study showed that in 92% of patients who had transradial PCI with 6F sheaths, RAO incidence was 8.9% at discharge and 5.6% at follow-up in the TR band group, which demonstrated lesser RAO between compression devices compared. Lefvre *et al*<sup>[15]</sup> reported 30% RAO with 1000 IU of heparin. This requires further confirmation, particularly at different comparator doses. However, the results of our study again emphasize the impact of the novel air-inflation technique in reducing RAO beyond conventional anticoagulation.

Several limitations were observed during the study. Firstly, we observed a high prevalence of missing data due to procedures performed out-of-hours. However, both groups were well matched in baseline demographics to negate group bias effects. Second, as with all exploratory studies, type I error may contribute to the results. Despite our study demonstrating consistent results at discharge and follow-up, this requires further confirmation. Third, Allen's test was not routinely performed pre-PCI. However, conventional methods of assessment *via* plethysmography and oximetry have not yielded consistent results due to influence of collaterals from palmar arches and recanalization<sup>[6,16]</sup>. Lastly, a known confounding factor that was not measured but critical for vascular management, was increased vigilance using our personalized air-inflation strategy to reduce RAO.

In conclusion, Safeguard Radial and TR band did not demonstrate significant between-group differences in short-term RAO incidence. Lack of evidence of RAO in all post-PCI patients at 6 wk follow-up, regardless of radial compression device indicate advantage of

using the novel and pragmatic air-inflation technique. Further work is required to more accurately confirm these findings.

## COMMENTS

### Background

Radial artery occlusion is a rare but significant complication post-transradial percutaneous coronary intervention, which is increasing in its use, globally. Therefore, better radial artery compression techniques are required to reduce such complication.

### Research frontiers

Conventional radial artery compression devices by varying air-inflation techniques have shown different results in reducing the incidence of radial artery occlusion post-percutaneous coronary intervention. These suggest that novel air-inflation techniques using such devices may yield better results in reducing incidence of radial artery occlusion.

### Innovations and breakthroughs

The authors have shown a much lower short-term incidence of post-percutaneous coronary intervention radial artery occlusion, compared to current literature, using a novel and pragmatic air-inflation technique in two conventional radial compression devices, Safeguard Radial and TR band.

### Applications

This pilot study's methods and results of this study could be used in a larger prospective study aiming to the impact of this novel air-inflation technique with two conventional radial compression devices in different settings of transradial percutaneous coronary intervention.

### Terminology

Radial artery occlusion is a rare but significant complication of transradial percutaneous coronary intervention. Novel and pragmatic radial compression techniques are required to reduce the incidence of such complication.

### Peer-review

This is an interesting manuscript about the comparison of post-percutaneous coronary intervention radial artery occlusion incidence between two conventional radial artery compression devices using a novel air-inflation technique, Safeguard Radial and TR band.

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## Clinical Trials Study

**Delineation of epicardial stenosis in patients with microvascular disease using pressure drop coefficient: A pilot outcome study**

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**Author contributions:** Hebbar UU, Effat MA, Peelukhana SV and Banerjee RK designed the research; Effat MA and Arif I performed the interventions; Banerjee RK assimilated the data; Hebbar UU and Peelukhana SV performed the data analysis; Hebbar UU, Effat MA, Peelukhana SV and Banerjee RK wrote the paper.

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## Abstract

### AIM

To investigate the patient-outcomes of newly developed pressure drop coefficient (CDP) in diagnosing epicardial stenosis (ES) in the presence of concomitant microvascular disease (MVD).

### METHODS

Patients from our clinical trial were divided into two subgroups with: (1) cut-off of coronary flow reserve

(CFR) < 2.0; and (2) diabetes. First, correlations were performed for both subgroups between CDP and hyperemic microvascular resistance (HMR), a diagnostic parameter for assessing the severity of MVD. Linear regression analysis was used for these correlations. Further, in each of the subgroups, comparisons were made between fractional flow reserve (FFR) < 0.75 and CDP > 27.9 groups for assessing major adverse cardiac events (MACE: Primary outcome). Comparisons were also made between the survival curves for FFR < 0.75 and CDP > 27.9 groups. Two tailed chi-squared and Fischer's exact tests were performed for comparison of the primary outcomes, and the log-rank test was used to compare the Kaplan-Meier survival curves.  $P < 0.05$  for all tests was considered statistically significant.

### RESULTS

Significant linear correlations were observed between CDP and HMR for both CFR < 2.0 ( $r = 0.58$ ,  $P < 0.001$ ) and diabetic ( $r = 0.61$ ,  $P < 0.001$ ) patients. In the CFR < 2.0 subgroup, the %MACE (primary outcomes) for CDP > 27.9 group (7.7%, 2/26) was lower than FFR < 0.75 group (3/14, 21.4%);  $P = 0.21$ . Similarly, in the diabetic subgroup, the %MACE for CDP > 27.9 group (12.5%, 2/16) was lower than FFR < 0.75 group (18.2%, 2/11);  $P = 0.69$ . Survival analysis for CFR < 2.0 subgroup indicated better event-free survival for CDP > 27.9 group ( $n = 26$ ) when compared with FFR < 0.75 group ( $n = 14$ );  $P = 0.10$ . Similarly, for the diabetic subgroup, CDP > 27.9 group ( $n = 16$ ) showed higher survival times compared to FFR group ( $n = 11$ );  $P = 0.58$ .

### CONCLUSION

CDP correlated significantly with HMR and resulted in better %MACE as well as survival rates in comparison to FFR. These positive trends demonstrate that CDP could be a potential diagnostic endpoint for delineating MVD with or without ES.

**Key words:** Fractional flow reserve; Pressure drop coefficient; Microvascular disease; Intermediate coronary stenosis; Interventional cardiology

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**Core tip:** Fractional flow reserve (FFR), a functional diagnostic index, is currently the gold standard for decision making in the catheterization laboratory. However, FFR can be confounded by concomitant microvascular disease (MVD). In this subgroup analysis study, pressure drop coefficient (CDP) showed improved clinical outcomes for patients with MVD compared to FFR, potentially making CDP a better diagnostic endpoint compared to FFR.

Hebbar UU, Effat MA, Peelukhana SV, Arif I, Banerjee RK. Delineation of epicardial stenosis in patients with microvascular disease using pressure drop coefficient: A pilot outcome study. *World J Cardiol* 2017; 9(12): 813-821 Available from: URL: <http://www.wjgnet.com/1949-8462/full/v9/i12/813.htm> DOI:

## INTRODUCTION

A persistent clinical challenge for interventional cardiologists today is the accurate assessment of intermediate coronary stenosis. While multiple quantitative anatomical methods were proposed, their applicability remains in question<sup>[1]</sup>. Functional diagnostic indices such as fractional flow reserve (FFR) and coronary flow reserve (CFR) agree well with non-invasive stress testing<sup>[2-4]</sup>, although their efficacy is limited in the presence of significant microvascular disease (MVD) as FFR and CFR depend solely on either pressure or flow measurements<sup>[5,6]</sup>.

### Current functional diagnostic indices

FFR, the current gold standard for the functional evaluation of epicardial stenosis (ES) is defined as the ratio of distal and proximal pressures along an ES<sup>[7-9]</sup>. The parameter ranges from "0", indicating a completely blocked vessel to "1" which indicates no obstruction. Earlier clinical outcome trials have established a cut-off value of 0.75<sup>[8]</sup> for significant coronary stenosis in the presence of single-vessel disease. However, FFR suffers from limitations, such as the zero-central venous pressure assumption as well as its dependence on the patient achieving maximal hyperemia. Also, constant minimum microvascular resistance may not be achieved in the case of sub-maximal hyperemia, leading to under-estimation of pressure drop and overestimation of FFR across the lesion<sup>[10]</sup>.

CFR, the flow-derived parameter is defined as the ratio of hyperemic blood flow to basal (or resting) flow. The CFR values agreed well with non-invasive stress testing at a cut-off value of 2.0<sup>[2]</sup>, and CFR < 2.0 was associated with reversible myocardial perfusion defects with high sensitivity and specificity<sup>[2]</sup>. It is worth noting that while CFR can provide the combined effect of ES and MVD, it cannot differentiate between the two conditions.

### Need for alternate functional indices

FFR and CFR are based solely on pressure measurements and flow measurements, respectively. Thus, both the indices can be misleading in the presence of extended MVD<sup>[5,6]</sup>. Hybrid parameters based on pressure and flow were proposed to overcome these limitations of FFR and CFR. However, such a parameter, *e.g.*, hyperemic stenosis resistance index (HSR; ratio of pressure drop across the lesion to the distal velocity)<sup>[3]</sup> evaluates only ES. On a similar note, hyperemic microvascular resistance index (HMR; ratio of mean distal pressure and distal hyperemic velocity)<sup>[11]</sup> assesses MVD only.

To simultaneously detect ES and MVD using a single parameter, we recently introduced pressure drop coefficient (CDP), a functional diagnostic index which utilizes pressure as well as flow measurements. CDP

was validated *via in vitro*<sup>[12,13]</sup> as well as *in vivo* animal studies<sup>[12-18]</sup>, and could differentiate between ES and MVD. The CDP was recently employed to differentiate between degrees of stenotic severity in a patient population<sup>[19]</sup>. In order to make interventional decisions, an equivalent cut-off to FFR < 0.75 for single vessel disease was established for CDP (CDP > 27.9)<sup>[20,21]</sup> as a marker for significant ES.

Our earlier pilot clinical study<sup>[22]</sup> validated the proposed cut-off value for CDP with positive clinical outcomes associated with the CDP > 27.9 group when compared with the FFR < 0.75 group. The objective of the current study is to assess the efficacy of CDP in delineating ES within patient subgroups suffering from MVD only. Therefore, this follow-up pilot study compares the outcomes between CDP > 27.9 and FFR < 0.75 for MVD patient subgroups extracted from the complete patient data analyzed previously<sup>[22]</sup>. Accordingly, two subgroups having possible MVD were studied: One consisting of patients with abnormal CFR (CFR < 2.0), and the other consisting of patients suffering from diabetes. Both of these subgroups were correlated with possible microvascular dysfunction in literature<sup>[23-28]</sup>. Survival curves were also compared between the FFR < 0.75 and CDP > 27.9 groups for both subgroups. Additionally, CDP was correlated with HMR - another index that uses both pressure and flow measurements to evaluate MVD. This correlation was done in both subgroups to evaluate CDP's ability to delineate MVD in the presence of ES.

## MATERIALS AND METHODS

### Study patients

The protocol<sup>[19]</sup> for the study was approved by the institutional review board at the University of Cincinnati (UC) and Cincinnati Veteran Affairs Medical Center (CVAMC), and informed consent was obtained from all the participants. Patients who underwent exercise testing and myocardial perfusion scans were consented based on the inclusion and exclusion criteria, which are reported in detail in our earlier study for the complete patient group<sup>[22]</sup>. The study population consisted of 86 patients enrolled at the UC and CVAMC. Table 1 summarizes the clinical characteristics of the enrolled patients in the complete patient group.

### Cardiac catheterization and hemodynamic measurement

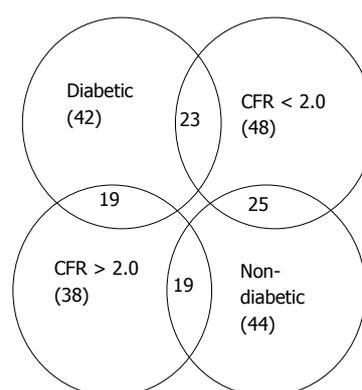
Standard-of-care catheterization techniques<sup>[22]</sup> were utilized to obtain intra-coronary pressure and flow measurements across the stenosis. All signals were recorded continuously through rest, and induction as well as decline of maximal hyperemia.

### CDP calculation

CDP is defined as the ratio of trans-stenotic pressure drop to distal dynamic pressure.

$$CDP = \Delta p / (0.5 \times \rho \times APV^2) \quad (1)$$

where,  $\Delta p$  is the pressure drop across the lesion; the



**Figure 1** Overlap of the various patient subgroups. The graphic highlights the intersection of the diabetic and CFR < 2.0 patient subgroups as well as the overlap between other subgroups. CFR: Coronary flow reserve.

distal dynamic pressure is the product of  $\rho$ , blood density (assumed to be a constant value of 1.05 g/cm<sup>3</sup>), the square of average peak flow velocity (APV) and a constant value of 0.5.

### Patient follow-up and study endpoints

The follow-up for the consented patients was performed through either chart review, a phone call, and/or a questionnaire. A minimum of 1-year follow-up was ensured. Over the follow-up period, the primary outcomes, which consisted of major adverse cardiac events (MACE) were determined. MACE was defined as the composite of all-cause mortality, myocardial infarction (MI), and repeat revascularization (Table 2).

### Sub-group methodology

In order to perform the subgroup analysis for patients suffering from possible MVD, two subgroups were extracted from the complete patient group data: One subgroup was composed of patients who exhibited an abnormal CFR value (CFR < 2.0); the other subgroup was composed of patients suffering from diabetes. Figure 1 summarizes the patient data *via* a Venn diagram showing overlap of the various patient subgroups.

### Statistical analysis

The authors had sufficient prior biostatistics background, as evidenced by previous publications<sup>[19-22]</sup>. First, correlations were performed between CDP and HMR in the diabetic and CFR < 2.0 subgroups using linear regression to evaluate the agreement of CDP with HMR, a parameter reported to identify the severity of MVD.

The patient data for each subgroup was then divided per the cut-off value of FFR < 0.75 for significant ES. On a similar note, CDP > 27.9<sup>[20,21]</sup> was used as an equivalent cut-off for significant stenosis. In the primary outcome study, for each subgroup (CFR < 2.0 and diabetic), the %MACE in the FFR < 0.75 group was quantified and compared with the %MACE in the corresponding CDP > 27.9 group. All comparisons were performed using the two-tailed  $\chi^2$  test and further

**Table 1** Summary of clinical data and characteristics of the recruited patients

Variable	Study/group
Sex (M/F)	77/9
Age (yr)	61 ± 9
Ejection fraction (%)	58 ± 10
Clinical history	
Diabetes	42/86
Hypertension	70/86
Dyslipidemia	60/86
Previous myocardial infarction	21/86
Smoking history	52/86
Family history of CAD	23/86
LV hypertrophy	4/86
Affected artery	
LAD	43
LCX	17
RCA	26

CAD: Coronary artery disease; LAD: Left descending artery; LCX: Left circumflex; RCA: Right coronary artery; M: Male; F: Female.

evaluated using the Fischer’s exact test.

Kaplan-Meier survival curves were generated to compare the long-term event free survival of the FFR < 0.75 patient group and the CDP > 27.9 patient group. This analysis was performed for both subgroups in the study. The duration between the index procedure, and the time when the patient was last followed-up was recorded. Any patient who reached the primary outcome (MACE) was recorded as positive. Patients lost to follow-up or who did not reach the primary outcome were considered as censored data. The generated survival curves were compared using the log-rank test for statistically significant difference.

All statistical analyses were performed using MedCalc (V10.2, Mariakerke, Belgium). All results obtained were considered statistically significant if *P* < 0.05.

## RESULTS

CDP was first correlated with HMR to identify its efficacy in evaluating MVD in patients suffering from concomitant ES. Further, to test the efficacy of CDP cut-off values (CDP > 27.9) as a guide for decisions on clinical intervention in patients with ES in presence of microvascular impairment, the %MACE outcomes for a CDP based strategy were statistically compared with those for a FFR based strategy (FFR < 0.75) using the two-tailed  $\chi^2$  test. The results for the Fischer’s exact test were also computed to account for the lower sample size. Comparisons were performed for both subgroup methodologies: The diabetic subgroup, and the CFR < 2.0 subgroup. Further, Kaplan-Meier survival curves were generated and comparisons were made for both subgroups.

### Correlation with HMR

The results for the correlation between CDP and HMR

**Table 2** Summary of the %MACE outcomes for the recruited patients at a minimum of 1-year follow-up

	FFR < 0.75	FFR > 0.75	CDP > 27.9	CDP < 27.9
CFR < 2.0				
All-cause mortality	3/14	2/34	2/26	3/22
Myocardial infarction				
Revascularization				
Diabetic				
All-cause mortality	1/11	3/31	2/16	2/26
Myocardial infarction				
Revascularization	1/11			1/26

CFR: Coronary flow reserve; CDP: Pressure drop coefficient; FFR: Fractional flow reserve.

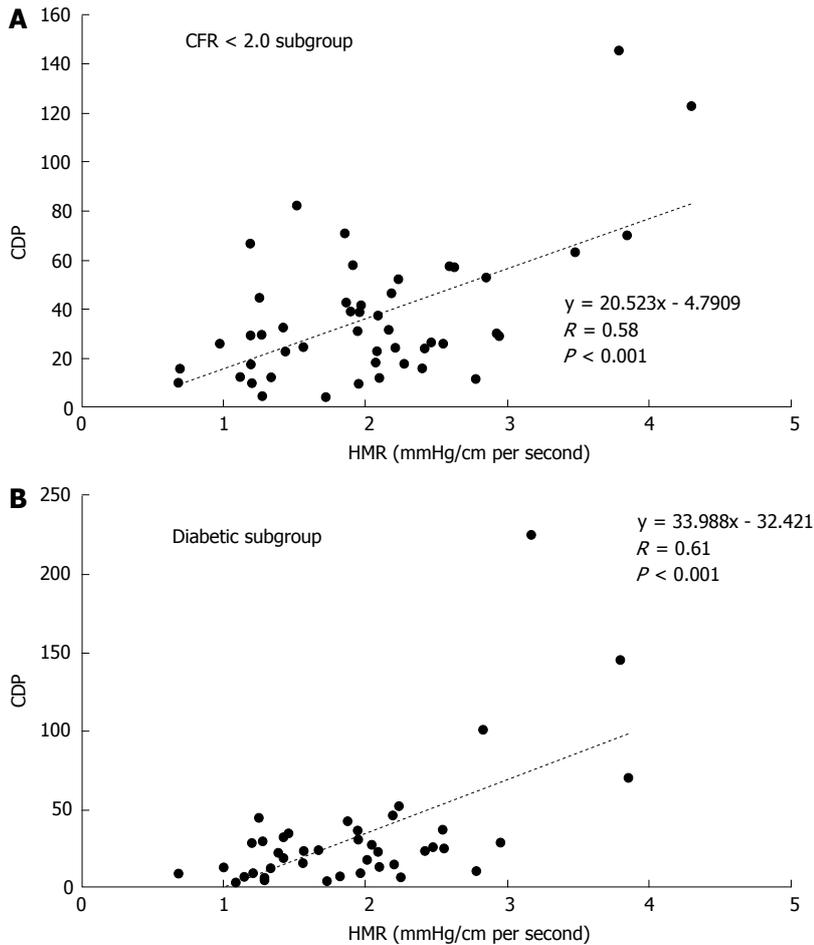
are presented in Figure 2. For the CFR < 2.0 subgroup, CDP showed a moderate but significant correlation (Figure 2A) with HMR (*r* = 0.58, *P* < 0.001). In the diabetic subgroup (Figure 2B), CDP again correlated moderately with HMR and the correlation was statistically significant (*r* = 0.61, *P* < 0.001). These results further highlight the ability of CDP to delineate severity of MVD in patients who suffer from concomitant epicardial lesions.

### Comparison of %MACE outcomes

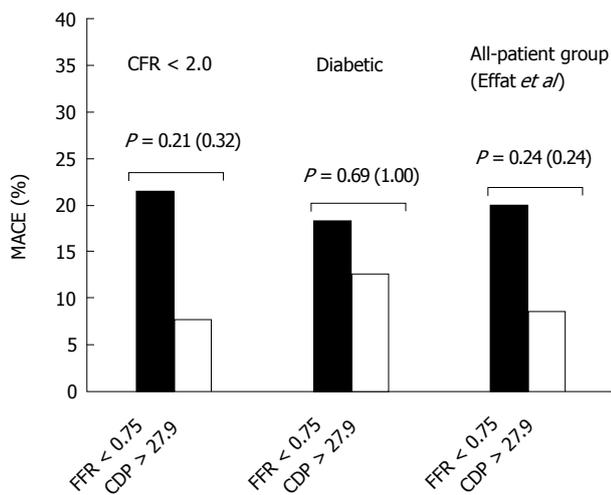
The comparison of %MACE outcomes between the FFR and CDP based cut-offs for the two subgroup analyses are summarized in Figure 3. Further, the comparison performed in our earlier outcome study<sup>[22]</sup> for the complete patient group is also presented. For the CFR < 2.0 subgroup, the %MACE outcomes in the FFR < 0.75 group (3 out of 14, 21.4%) were higher than the corresponding values for the CDP > 27.9 group (7.7%, 2 out of 26) although the results were not statistically significant as per the chi-squared test (*P* = 0.21) and the Fischer’s exact test (*P* = 0.32). On a similar note, for the diabetic subgroup, the %MACE in the FFR < 0.75 group (18.2%, 2 out of 11) was higher than the %MACE seen in the CDP > 27.9 group (12.5%, 2 out of 16), but the results were not statistically significant as per the chi-squared test (*P* = 0.69). The Fischer’s exact test resulted in a *P*-value of 1 due to the smaller sample size. Similar to the findings in this study, the analysis performed in our earlier study<sup>[22]</sup> for the complete patient group yielded a lower %MACE outcome for the CDP > 27.9 group though the results were not significant (*P* = 0.24) for both the chi-squared test and the Fischer’s exact test. These initial results suggest that if a CDP-based strategy were to be implemented, reduced %MACE outcomes would be observed when compared with the FFR-based strategy for the patient group with lower CFR values, as well as diabetic patients, who are known to suffer from MVD.

### Survival analysis

Figure 4A summarizes the Kaplan-Meier survival analysis



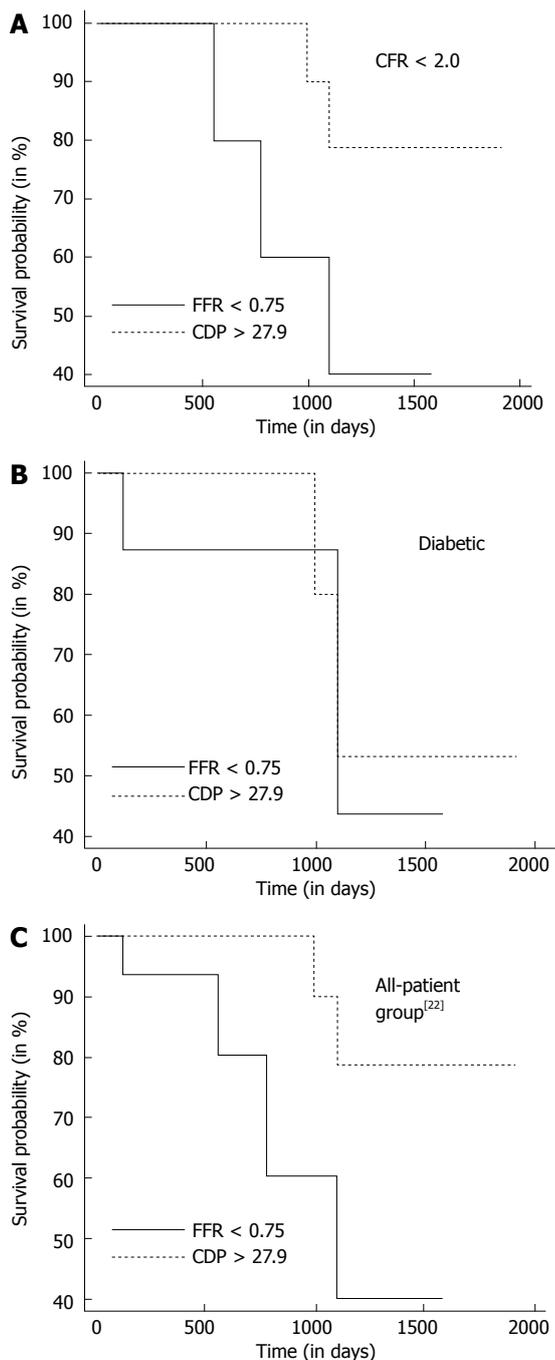
**Figure 2** Correlation of pressure drop coefficient with hyperemic microvascular resistance. A: The linear regression performed between CDP and HMR for the CFR < 2.0 subgroup. The equation, *R*-value and the *P*-value are provided for the comparison; B: Similar regression performed for the diabetic subgroup. CFR: Coronary flow reserve; CDP: Pressure drop coefficient; HMR: Hyperemic microvascular resistance.



**Figure 3** Comparison of %MACE between fractional flow reserve < 0.75 and pressure drop coefficient > 27.9 groups for the coronary flow reserve < 2.0 subgroup and diabetic subgroup. These patient subgroups are obtained from the complete patient group analyzed in Effat *et al*<sup>[22]</sup>. The *P*-values are provided for the  $\chi^2$  test, and the *P*-values for the Fischer's exact test are provided in parentheses. CDP: Pressure drop coefficient; FFR: Fractional flow reserve.

was computed to be 0.26 (95%CI: 0.04-1.82) implying that the survival probability in the CDP > 27.9 group is 3.85 times the corresponding probability in the FFR < 0.75 group. The difference in survival time for the FFR < 0.75 group (*n* = 14) compared with the CDP > 27.9 group (*n* = 26) was borderline significant (*P* = 0.10). On a similar note, Figure 4B summarizes the survival analysis performed for the diabetic subgroup. The computed hazard ratio was 0.60 (95%CI: 0.08-4.57), indicating higher survival probability for the CDP > 27.9 group. The survival time for the FFR < 0.75 group (*n* = 11) was not statistically different (*P* = 0.58) compared to the CDP > 27.9 group (*n* = 16). Figure 4C shows the survival analysis performed for the complete patient group in our previous study<sup>[22]</sup>. The hazard ratio was computed to be 0.22 (95%CI: 0.06-1.24), again indicating higher survival probability for the CDP > 27.9 group. In this comparison, a statistically significant improvement in survival time for the CDP > 27.9 group was observed when compared with the FFR < 0.75 group (*P* = 0.048). In summary, the survival analysis indicates better survival times for the CDP > 27.9 group when compared with the FFR < 0.75 group for the complete patient group as well as for patients suffering

performed for the CFR < 2.0 subgroup. The hazard ratio



**Figure 4** Comparison of Kaplan - Meier survival curves between fractional flow reserve < 0.75 and pressure drop coefficient > 27.9 groups. A: CFR < 2.0 subgroup; B: Diabetic subgroup; C: Complete patient group in Effat *et al*<sup>[22]</sup>. CFR: Coronary flow reserve; CDP: Pressure drop coefficient; FFR: Fractional flow reserve.

from MVD.

## DISCUSSION

The advantages of using CDP, a combined pressure-flow diagnostic endpoint, have been reported in earlier studies<sup>[14,20-22]</sup>. However, the applicability of such a parameter in clinically relevant scenarios, particularly in the presence of MVD needs further assessment.

### Correlation with HMR

HMR is a dimensional diagnostic index which utilizes pressure and flow measurements to specifically evaluate the severity of MVD in patients. In contrast, CDP is a unique non-dimensional parameter developed from fluid dynamics principles that combines pressure and flow measurements to evaluate the severity of both ES and MVD. CDP showed a moderate but significant correlation with HMR for both CFR < 2.0 and diabetic patient-subgroups, further strengthening the hypothesis that CDP can be used to evaluate the severity of MVD, with or without the presence of concomitant ES.

### Comparison of %MACE outcomes

One of the significant contributors to improved quality of life is reduced incidence of MACE. Therefore, the comparison of %MACE in the FFR-based group and the CDP-based group was one of the primary results of this study. The first methodology used in the subgroup analysis was based on CFR values. It is well documented that abnormally low CFR (< 2.0) values is associated with possible MVD<sup>[23]</sup> and an inability to achieve peak hyperemia. Under this scenario, constant minimal microvascular resistance is not assured, leading to an underestimation of the pressure drop which in turn results in an overestimation of FFR values<sup>[24]</sup>. It is worth noting that in the presence of MVD and submaximal hyperemia, both blood flow as well as pressure drop over the stenosis are affected in a similar manner. Physiologically, the reduction seen in the peak hyperemic blood flow due to MVD dominates over the corresponding reduction effected by ES<sup>[14]</sup>. The formulation of CDP accounts for this effect though the square of the maximal hyperemic flow in the denominator, thus providing improved resolution for accurate evaluation of the status of the stenosis. The results for the %MACE comparisons between the FFR-based strategy and the CDP-based strategy in the study show the improved resolving power for the CDP-based patient group *via* the lower %MACE. However, considering the low rates of MACE and the relatively lower sample size in this study, a prospective randomized trial with larger patient population is required to confirm the outcomes of this pilot study.

Similar to patients with abnormal CFR, patients with diabetes are also associated with potential MVD. Previous studies of the arterioles and small arteries of diabetic patients have indicated functional microvasculature damage evidenced by reduced vasodilation of the coronary arterioles. This could be the result of a decrease in activity of ATP sensitive potassium channels<sup>[25-28]</sup>. As an additional confirmation of our hypothesis, a subsequent analysis was performed on a subgroup consisting of diabetic patients by evaluating and comparing the %MACE outcomes between the FFR-based strategy and the CDP-based strategy. The results indicated a similar trend as in the case of the CFR (< 2.0) based subgroup analysis. Additionally, the comparisons performed for the complete patient group in our previous study<sup>[22]</sup> report

similar results of reduced %MACE outcomes for the CDP group, thereby strengthening the argument that CDP can accurately delineate the status of ES, particularly in the presence of concomitant MVD. Again, these results require further assessment using a prospective randomized clinical trial with larger sample size.

### Survival analysis

Another significant measure which affects the quality of life for patients suffering from cardiovascular disease is long-term event-free survival. Comparisons of the Kaplan-Meier survival curves using the log-rank test were performed between the FFR based group and the CDP based group for both subgroup methodologies discussed above. The results indicated improved long-term event free survival for the CDP-based groups in both the subgroup analyses. Furthermore, the survival curves comparison performed for the complete patient group in our previous study<sup>[22]</sup> indicated a significant improvement in long-term event free survival for the CDP group, lending further strength to the resolving power of CDP in diagnosing the status of ES with concomitant MVD.

### Clinical advantages of CDP

CDP, a non-dimensional parameter based on fundamental fluid dynamics is defined as the ratio of coronary trans-lesional pressure drop ( $\Delta p$ ) to the distal dynamic pressure ( $0.5 \text{ blood density APV}^2$ ) where APV (average peak blood flow velocity) is measured during peak hyperemia. In the presence of increased microvascular resistance, FFR and CFR along an ES are affected in opposite directions. Therefore, ischemic assessment performed by measuring FFR and CFR in such a coronary artery with concomitant diseases might potentially lead to discordant results in up to 40% of the cases<sup>[29]</sup>. A possible explanation would be the presence of diffuse epicardial lesions wherein lower CFR would be observed without notable changes in FFR values. On the other hand, healthy microvasculature and auto-regulatory function could allow for normal CFR values while leading to abnormal FFR values. The complex interaction of pressure and flow seen in such scenarios may not be captured adequately by FFR or CFR alone, since these parameters depend solely on pressure and flow, respectively. In contrast, CDP is a combined physiological parameter derived from fundamental fluid dynamics principles involving both pressure and flow measurements, and can adequately distinguish between ES and MVD<sup>[20]</sup>.

Considering the numerous advantages afforded by CDP, we believe that this parameter has a potentially significant role in modern clinical practice. However, it is worth mentioning that the dual-sensor wires necessary for computing CDP has not become prevalent in catheterization laboratories. Nevertheless, the use of these guidewires is expected to increase with: (1) technological advancement; and (2) mounting evidence of better clinical outcomes. This would make

the measurement of functional diagnostic indices such as CDP standard-of-care with reduced complexities. Several prior studies have validated the clinical application of functional measures such as FFR in treatment of coronary stenosis. These include the DEFER study<sup>[24]</sup>, the FAME trial<sup>[30]</sup> and the FAME 2 trial<sup>[31]</sup>, which confirmed the role of FFR as a guide to management of coronary artery disease. This study proposes CDP as an improved measure over FFR for accurate prediction of major ischemic events as well as long-term event-free survival in the presence of confounding scenarios such as MVD. While statistical significance was not reached, consistent improved outcomes were observed over all the measures. Significant statistical significance in the comparisons may be observed on repeating the analysis for a larger patient group and longer follow-up periods.

### Limitations

All the clinical decisions in this study were made based on FFR values alone. Thus, a larger sample size and a prospective randomized clinical trial is needed. This will allow improved evaluation of the performance of CDP compared to FFR under clinical settings and confirm the patient outcomes of this current cohort study.

In this follow-up pilot study to our earlier clinical trial<sup>[22]</sup>, a subgroup analysis was performed with two subgroups: one consisting of patients exhibiting CFR < 2.0, and the other consisting of diabetic patients. CDP showed moderate but significant correlation with HMR in both the diabetic and CFR < 2.0 subgroups. Comparison of primary (%MACE) outcomes led to lower %MACE in the CDP > 27.9 groups in comparison to the FFR < 0.75 groups for both subgroups, although statistical significance was not reached. Further, event-free survival rates in the CDP > 27.9 group were higher when compared with the FFR < 0.75 group for both subgroups, with the difference being borderline significant for the CFR < 2.0 subgroup. Further clinical trials with a larger patient population and longer follow-up periods could validate the positive trends seen for the CDP group in this study, while proving the efficacy of CDP as a useful clinical endpoint for decision making in the cardiac catheterization laboratory.

## ARTICLE HIGHLIGHTS

### Research background

Accurate assessment of coronary stenosis is an important aspect of interventional cardiology. Although existing functional diagnostic indices such as fractional flow reserve (FFR) and coronary flow reserve (CFR) have been validated extensively via clinical trials, their efficacy is limited in the presence of concomitant microvascular disease (MVD) as they depend solely on pressure or flow measurements. This pilot study explores the efficacy of a combined pressure-flow diagnostic endpoint, pressure drop coefficient (CDP) compared to pressure-based FFR. It was hypothesized that CDP would show better clinical outcomes compared to FFR for patient subgroups with MVD.

### Research motivation

Diagnosis of epicardial stenosis (ES) with concomitant MVD is a challenge with existing diagnostic indices (such as FFR, CFR) as they depend solely on

pressure or flow. Pressure-based FFR can be overestimated in the presence of concomitant MVD, leading to possible misdiagnosis of severity of the stenosis, while CFR cannot differentiate between the effects of the stenosis and MVD. There is a need for combined pressure-flow diagnostic endpoints (such as CDP) to better diagnose coronary stenosis, particularly in the presence of MVD.

### Research objectives

The primary objective of this research was to compare the clinical outcomes of patients with stenosis and possible MVD evaluated using FFR and CDP. Secondly, CDP was correlated with an existing index (HMR) used to evaluate the severity of MVD. CDP showed better clinical outcomes compared to FFR, as well as longer survival times for the patients. Also, CDP showed significant correlation with HMR, validating its efficacy at evaluation of MVD. It is to be noted that larger sample sizes and a randomized clinical trial is required to further confirm the results of this exploratory pilot study.

### Research methods

Patients from our clinical trial was divided into two subgroups with: (1) cut-off of CFR < 2.0; and (2) diabetes. First, correlations were performed for both subgroups between CDP and HMR, a diagnostic parameter for assessing the severity of MVD. Linear regression analysis was used for these correlations. Further, in each of the subgroups, comparisons were made between FFR < 0.75 and CDP > 27.9 groups for assessing major adverse cardiac events (MACE: primary outcome). Comparisons were also made between the survival curves for FFR < 0.75 and CDP > 27.9 groups. Two tailed chi-squared and Fischer's exact tests were performed for comparison of the primary outcomes, and the log-rank test was used to compare the Kaplan-Meier survival curves.  $P < 0.05$  for all tests was considered statistically significant.

### Research results

Significant linear correlations were observed between CDP and HMR for both CFR < 2.0 ( $r = 0.58$ ,  $P < 0.001$ ) and diabetic ( $r = 0.61$ ,  $P < 0.001$ ) patients. In the CFR < 2.0 subgroup, the %MACE (primary outcomes) for CDP > 27.9 group (7.7%, 2/26) was lower than FFR < 0.75 group (3/14, 21.4%);  $P = 0.21$ . Similarly, in the diabetic subgroup, the %MACE for CDP > 27.9 group (12.5%, 2/16) was lower than FFR < 0.75 group (18.2%, 2/11);  $P = 0.69$ . Survival analysis for CFR < 2.0 subgroup indicated better event-free survival for CDP > 27.9 group ( $n = 26$ ) when compared with FFR < 0.75 group ( $n = 14$ );  $P = 0.10$ . Similarly, for the diabetic subgroup, CDP > 27.9 group ( $n = 16$ ) showed higher survival times compared to FFR group ( $n = 11$ );  $P = 0.58$ .

### Research conclusions

CDP correlated significantly with HMR and resulted in better %MACE as well as survival rates in comparison to FFR. These positive trends demonstrate that CDP could be a potential diagnostic endpoint for delineating MVD with or without ES.

### Research perspectives

This study highlights the ability of CDP in delineating MVD in patients with or without ES. In this patient subgroup analysis, CDP showed better clinical outcomes and higher survival rates compared to FFR, which is the current gold standard in functional diagnosis of coronary artery disease. There is a clear need for functional diagnostic endpoints which can better evaluate ES with concomitant MVD. In future, a large scale randomized clinical trial comparing the outcomes of CDP and FFR is required.

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## Observational Study

**Endothelin-1 activation in pediatric patients undergoing surgical coarctation of the aorta repair**

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## Abstract

### AIM

To determine endothelin-1 (ET-1) concentration before and after surgical coarctectomy and evaluate its association with left ventricular geometric change.

### METHODS

A prospective, cohort study of 24 patients aged 2 d to 10 years with coarctation of the aorta undergoing surgical repair. A sub-cohort of patients with age < 1 mo was classified as "neonates". Echocardiograms were performed just prior to surgery and in the immediate post-op period to assess left ventricle mass index and relative wall thickness (RWT). Plasma ET-1 levels were assessed at both time points. Association between ET-1 levels and ventricular remodeling was assessed.

### RESULTS

Patients < 1 year demonstrated higher pre-op ET-1 than post-op (2.8 pg/mL *vs* 1.9 pg/mL,  $P = 0.02$ ). Conversely, patients > 1 year had no change in ET-1 concentration before and after surgery (1.1 *vs* 1.4, NS). Pre-op, patients < 1 year demonstrated significantly higher ET-1 than older children (2.8 *vs* 1.1,  $P = 0.001$ ). Post-op there was no difference between the age groups (1.9 *vs* 1.4, NS). Neither RWT nor left ventricle mass index (LVMI) varied from pre-op to post-op. The subset of neonates showed a strong positive correlation between pre-op ET-1 and RWT ( $r = 0.92$ ,  $P = 0.001$ ). Patients with ET-1 > 2 pg/mL pre-op demonstrated higher LVMI (65.7 g/m<sup>2.7</sup> *vs* 38.5 g/m<sup>2.7</sup>,  $P = 0.004$ ) and a trend towards higher RWT (45% *vs* 39%,  $P = 0.07$ ) prior to repair than those with lower ET-1 concentration.

### CONCLUSION

ET-1 concentration is significantly variable in the perioperative period surrounding coarctectomy. Older children and infants have different responses to surgical repair suggesting different mechanisms of activation.

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**Key words:** Biomarkers; Cardiac remodeling; Pediatric; Neonate; Left ventricular hypertrophy

**Core tip:** Patients with coarctation of the aorta are at risk for a variety of short- and long-term complications after surgical repair. Endothelin-1 (ET-1) is a peptide hormone known to cause both cardiac myocyte hypertrophy and vasoconstriction that has been linked to late ventricular hypertrophy in this population. Peri-operative endothelin concentration in this population has not been previously defined. We demonstrate that neonates with coarctation of the aorta have high pre-operative ET-1 levels that decrease post-operatively. Older coarctation patients have more modest ET-1 activation that is unchanged post-operatively. These findings suggest two distinct patterns of ET-1 activation within this population.

Frank BS, Urban TT, Tong S, Cassidy C, Mitchell MB, Nichols CS, Davidson JA. Endothelin-1 activation in pediatric patients undergoing surgical coarctation of the aorta repair. *World J Cardiol* 2017; 9(12): 822-829 Available from: URL: <http://www.wjgnet.com/1949-8462/full/v9/i12/822.htm> DOI: <http://dx.doi.org/10.4330/wjc.v9.i12.822>

## INTRODUCTION

Isolated coarctation of the aorta (CoA) is found in 800 of every million live births, approximately 8% of all congenital heart disease<sup>[1]</sup>. Open surgical repair *via* thoracotomy or sternotomy is required for most patients presenting with severe obstruction. Although perioperative mortality is low in the modern era, the post-operative course is frequently complicated by either low cardiac output syndrome or recalcitrant hypertension<sup>[2,3]</sup>. Additionally, these children are at significant risk for long-term complications including persistent hypertension, a hypertensive response to exercise, altered cardiac mechanics, and left ventricular (LV) hypertrophy<sup>[4,5]</sup>.

Vascular and cardiac changes are, in many cases, already present at the time of initial surgery. Pre-operatively, approximately 65% of all children with CoA will have LV hypertrophy and 33% of the subset who are diagnosed as neonates will have evidence of pulmonary hypertension<sup>[6]</sup>. Such echocardiographic evidence of physiologic derangements, present at diagnosis, suggests that there may be early activation of critical pathologic pathways. Better understanding of such pathways and their patterns of activation offers significant promise to understand the mechanisms of disease progression, improve prognostic accuracy, and guide future therapy.

Endothelin-1 (ET-1) is a 21-amino acid vasoactive peptide hormone with endocrine and paracrine effects. Previous mechanistic *in vitro* studies have demonstrated the capacity for ET-1 to cause vasoconstriction in both the pulmonary and systemic vasculature<sup>[7]</sup> as well as cardiac myocyte hypertrophy<sup>[8,9]</sup>. Additionally, a recent study showed increased ET-1 blood concentration was associated with left ventricular hypertrophy in a mouse model of coarctation of the aorta<sup>[10]</sup>. Clinical data in human subjects, however, are quite limited. While ET-1 concentration is increased compared to controls at late follow-up after coarctation repair<sup>[11]</sup>, the clinical implications of this finding are yet to be evaluated. Further, no prior study has assessed either ET-1 concentration or its association with cardiovascular pathology at the time of initial surgery for CoA. While ET-1 activation is not thought to be causative of coarctation of the aorta, defining ET-1 activation in the perioperative period could offer significant insight as a marker of the variable short and long term physiologic responses to coarctation seen in this population.

**Table 1** Demographics *n* (%)

Age (d)	356 (24039)
Age class	
≤ 1 yr	12 (50)
> 1 yr	12 (50)
Age class	
≤ 28 d	7 (29.2)
28 d-1 yr	5 (20.8)
> 1 yr	12 (50)
Weight preop	7.9 (3.1, 81.8)
Weight postop	8.0 (2.9, 81.8)
Race	
African American	1 (4.2)
White	20 (83.3)
Hispanic	3 (12.5)
Gender	
Male	17 (70.8)
Female	7 (29.2)

Here we present a prospective, cohort study of ET-1 concentration and pathologic myocardial remodeling both prior to surgical correction of coarctation/aortic arch obstruction and in the immediate post-operative period. We sought to define pre-operative ET-1 activation, perioperative changes in concentrations with surgical relief, and the association with early myocardial change.

## MATERIALS AND METHODS

The Colorado Multiple Institution Review Board approved this study. Written informed consent was obtained from the study subjects' parents in all cases. Written assent was obtained from all subjects aged between seven years and eighteen years.

### Subjects

We prospectively enrolled consecutive subjects (aged 0 to 18 years) undergoing surgical relief of coarctation of the aorta with or without associated transverse arch hypoplasia at Children's Hospital Colorado from September 2015 through January 2017. Exclusion criteria included patients with significant co-morbid heart disease, those with a prior intervention (surgical or trans-catheter) on their aortic arch, and those weighing less than 2 kg, due to limitations in acceptable sample blood volumes for research.

### Clinical data

Clinical information was extracted from the electronic medical record (Epic Systems, Verona, WI). Demographic variables, peri-operative details, and key clinical variables were recorded. Study data were collected and managed using REDCap electronic data capture tools hosted at University of Colorado<sup>[12]</sup>.

### Laboratory data

Blood samples were obtained immediately prior to surgery and between 12-48 h post-operatively. Extracted plasma aliquots were then stored at -80 °C for batch analysis.

ET-1 and B-type natriuretic peptide (BNP) analysis were performed by enzyme-linked immunosorbent assay (ELISA) per manufacturer's recommendations (R and D Systems, Inc. Minneapolis, MN).

### Echocardiographic data

Echocardiograms were obtained immediately prior to surgical repair and between 24 and 72 h post-operatively. All images were obtained with a GE Vivid E9 or E95 machine (General Electric, Chicago, Ill). Relative wall thickness (RWT) was measured at end-diastole from the parasternal short axis view as the ratio of the sum of the posterior and septal mural thickness to the left ventricular internal end-diastolic diameter; a value of 41% is conventionally taken as the upper limit of normal for RWT<sup>[4]</sup>. LV mass was calculated by the area-length (AL) method, indexed to height<sup>2.7</sup>, and compared to previously published normal values<sup>[13,14]</sup>.

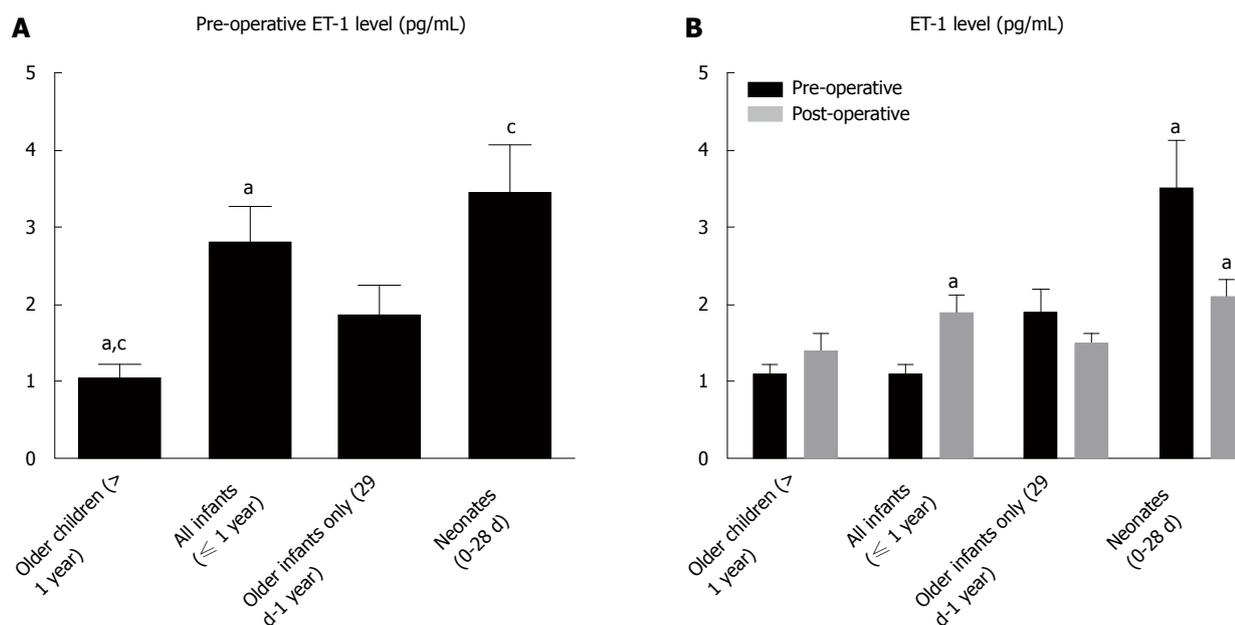
### Statistical analysis

Demographics were summarized using descriptive statistics as indicated by the distribution of the data. Changes in echocardiographic indices were compared using the Signed-Rank test. Pearson's correlation test, two-sample *T*-Test, and general linear modeling compared ET-1 levels among groups and correlation with echocardiographic indices. All the statistical analyses were performed with SAS V9.4. The primary outcome for analysis was change in ET-1 concentration from the pre-operative to the post-operative sample. Other associations were tested as secondary outcomes. Statistician S Tong from University of Colorado, Denver reviewed the statistical methods of this study.

## RESULTS

Twenty-four patients were enrolled in the study. Their demographics and baseline/surgical characteristics are presented in Table 1, represented as median (range) or *n* (%). Five patients, all < 1 mo in age, underwent aortic arch reconstruction on cardio-pulmonary bypass, while the other nineteen underwent coarctectomy by lateral thoracotomy without bypass. Six patients (all in the neonatal cohort) had evidence of a patent ductus arteriosus on echocardiogram and were on prostaglandin infusion at the time of repair. In each of those six patients, ductal flow was right-to-left in systole, indicating that pressure in the pulmonary artery was equal to or greater than pressure in the aorta. One patient was on continuous milrinone. No patient received an endothelin receptor antagonist during the study period.

Clinical presentation varied by age at diagnosis. Five of the neonates were diagnosed prenatally, started on prostaglandin within the first hours of life, and remained stable until repair. Two neonates presented within the first week of life with clinical evidence of decreased systemic perfusion and were medically stabilized before proceeding to operative repair. The patients between one month and one year of life had the greatest variability in



**Figure 1 Serum endothelin-1 concentration.** A: Pre-operative ET-1 concentration by age group; B: Comparison between pre-operative and post-operative levels for each age group. <sup>a,c</sup>*P* < 0.05. Scale bars represent standard deviation. ET-1: Endothelin-1.

clinical presentation, ranging from asymptomatic murmur to symptomatic left ventricular failure with decreased tissue oxygen delivery. Children older than one year were all clinically stable at presentation, referred for right upper extremity hypertension, decreased femoral pulses, or an asymptomatic murmur.

#### Pre-operative ET-1 concentration

Pre-op ET-1 level in our entire cohort was 1.9 pg/mL (Figure 1). Patients < 1-year-old showed significantly higher concentrations when compared to the older cohort. This effect was most pronounced among neonates, who demonstrated the highest levels.

#### Post-operative change in ET-1 concentration

Analysis within age cohorts demonstrated two distinct patterns. Patients < 1-year-old showed an immediate decline in ET-1 level post-op (Figure 1). Conversely, older children demonstrated no significant change between pre-op and post-op. Overall, patients with the highest levels of ET-1 pre-op demonstrated the greatest post-op decline while those with more modest ET-1 concentration pre-op tended to have unchanged levels after repair (Figure 2).

#### B-type natriuretic peptide concentration

For the entire population taken together, BNP concentration followed a right skewed distribution. Median pre-op BNP concentration was 73 pg/mL (upper limit of normal 99 pg/mL, range 21-4915). Neonatal subjects demonstrated significantly higher BNP levels than older children [1752 (30-4915) pg/mL vs 35 (21-74) pg/mL, *P* < 0.0001, represented as median (range)]. Pre-operative BNP was moderately correlated with pre-operative ET-1 (*r* = 0.65; *P* = 0.0002). Post-operatively,

neonatal patients demonstrated a significant decrease in BNP level [1752 (30-4915) pg/mL vs 977 (192-2732) pg/mL, *P* = 0.02] while the concentration was unchanged among older children [35 (21-74) pg/mL vs 161 (124-451) pg/mL, NS]. Post-operative BNP was moderately correlated with post-operative ET-1 (*r* = 0.73; *P* = 0.0001).

#### Echocardiography

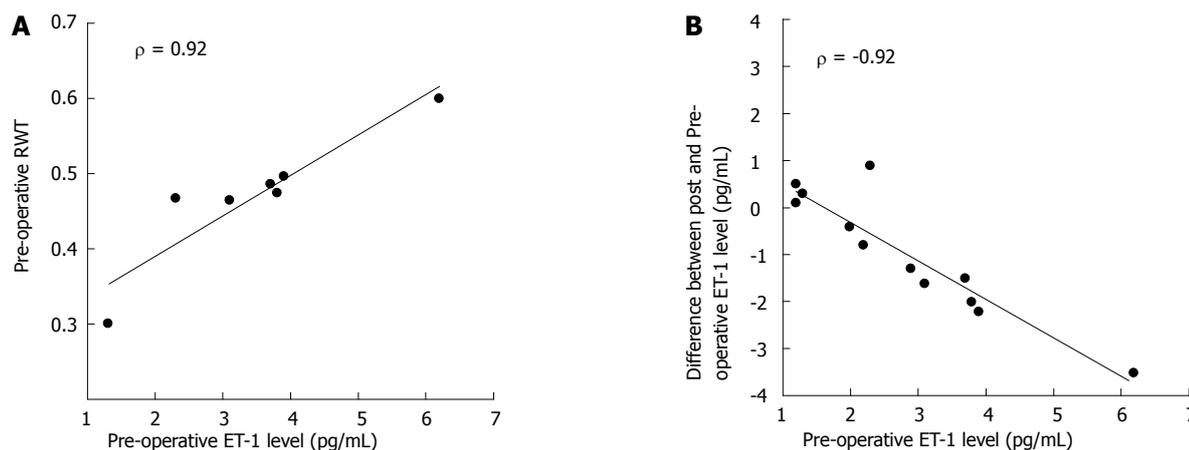
Mean RWT (%) and left ventricle mass index (LVMI) (g/m<sup>2.7</sup>) were increased compared to normal values for all time points (Table 2). As expected, there was no significant change in RWT or LVMI between the pre-op and post-operative echocardiograms. Overall, infants showed higher LVMI compared to older children but no significant difference in RWT.

#### ET-1 as a biomarker of remodeling

Including the entire cohort, RWT and LVMI were compared between patients with lower and higher levels of ET-1. Patients with ET-1 > 2 pg/mL pre-op demonstrated higher LVMI (65.7 g/m<sup>2.7</sup> vs 38.5 g/m<sup>2.7</sup>, *P* = 0.004) and a trend towards higher RWT (45% vs 39%, *P* = 0.07) prior to repair. Additionally, pre-op ET-1 > 2 pg/mL was associated with higher post-op LVMI and RWT. Among the neonatal cohort, pre-operative ET-1 showed a strong positive correlation with post-op RWT (Figure 2).

## DISCUSSION

This study is the first to assess early ET-1 activation and its association with LV remodeling at the time of surgery for coarctation of the aorta. Key findings include increased concentration among neonates preoperatively



**Figure 2 Pre-Operative Endothelin-1 as a predictor.** A: Correlation between pre-operative ET-1 concentration and post-operative RWT in the subset cohort of neonatal patients; B: Correlation between pre-operative ET-1 concentration and change in level from pre-operative to post-operative sample in the full cohort of patients. Points represent individual patients. ET-1: Endothelin-1; RWT: Relative wall thickness.

**Table 2 Echocardiographic markers of left ventricle remodeling prior to and immediately following surgical coarctectomy**

	Subjects	Preop	Posop	P value
Relative wall thickness				
All subjects	24	0.41 (0.09)	0.42 (0.10)	NS
Neonates (0-28 d)	7	0.44 (0.09)	0.47 (0.09)	NS
Infants (29 d-1 yr)	5	0.43 (0.08)	0.40 (0.14)	NS
Children (> 1 yr)	12	0.39 (0.09)	0.39 (0.09)	NS
LV mass index				
All subjects	24	49.4 (24.6)	51.6 (17.5)	NS
Neonates (0-28 d)	7	50.2 (22.3)	57.6 (12.9)	NS
Infants (29 d-1 yr)	5	79.7 (31.1)	72.0 (19.9)	NS
Children (> 1 yr)	12	36.4 (6.3)	39.6 (7.1)	NS

LV: Left ventricle.

with a decline after anatomic correction. This pattern is contrasted with more modest ET-1 level before surgery in older children and no significant post-operative change. Taking all patients together, our population also shows higher levels of ET-1 concentration than previously reported normal controls<sup>[11]</sup>. Similar changes in ET-1 level surrounding anatomic correction of a congenital heart lesion have not previously been described. The variable pattern of ET-1 concentration seen among patients with similar anatomic lesions but different physiologies is also a novel finding.

Increasing evidence suggests that ET-1 activation is regulated in part by pulmonary vascular stress. While data conflict on whether pulmonary artery pressure or pulmonary blood flow is the primary effector, abnormalities in pulmonary vascular physiology are known to associate with alterations in serum ET-1 concentration<sup>[15-18]</sup>. Sub-group analysis of our data supports this relationship. The youngest subset of patients demonstrated the highest pre-operative ET-1 levels; these patients, in addition to manifesting high LV afterload, all demonstrated elevated pressure in the pulmonary arteries due either to ductal dependent systemic blood flow or as an upstream consequence of left atrial hypertension. Those same

patients also had a post-operative decline in ET-1 level associated with the acute physiologic change (rapid normalization of pulmonary hemodynamics). The older children, with isolated high LV afterload physiology that is slower to resolve, experienced no change in ET-1 concentration from pre-op to post-op. The variable activation pattern between neonatal and older patients supports a role for the different pulmonary artery mechanics between the two subgroups affecting the variable ET-1 levels seen.

One potential confounder in the different pre-op to post-op ET-1 patterns described is the role of cardio-pulmonary bypass in post-op ET-1 concentration (a majority of neonates were repaired on bypass while all older children were repaired off pump). However, prior studies of pediatric patients undergoing bypass for the Fontan operation<sup>[19]</sup> and adult patients undergoing bypass for coronary artery bypass grafting<sup>[20]</sup> have demonstrated, on average, higher plasma ET-1 concentrations after bypass. And, the two neonates who underwent coarctectomy without bypass showed the same pattern of ET-1 concentration as the rest of the neonatal cohort. The observation that patients with different pre- and post-op physiologies undergoing bypass have widely variable peri-op ET-1 concentration patterns further supports the conclusion that the peri-op physiology likely plays the dominant role in ET-1 level, rather than bypass alone.

Our data also provide preliminary evidence for a separate pathway of ET-1 regulation associated with LV afterload. All patients in our cohort, including older coarctation subjects with isolated high LV afterload and otherwise normal physiology, have higher ET-1 concentration than previously reported normal controls<sup>[11]</sup>. Previous studies have suggested such a correlation in a similar population, showing increased ET-1 levels compared to controls in hypertensive adults with high afterload physiology<sup>[21]</sup>. One possible driver of ET-1 activation in this group is sympathetic nervous system activation. Norepinephrine, an endogenous catecholamine

and effector of the sympathetic nervous system, is known both to be over-expressed in hypertensive patients<sup>[22]</sup> and to stimulate ET-1 production by the vascular endothelium<sup>[23]</sup>. Given the normal pulmonary hemodynamics in our older cohort and the mechanistic explanation offered by previous work, we posit that the ET-1 levels seen in this sub-group could reflect sympathetic activation due to the abnormality in LV and systemic vascular physiology. Future studies will be needed to confirm this hypothesis.

Individual patients who deviated from the typical clinical presentation for their age cohort provide further evidence for the two distinct mechanisms of ET-1 regulation. A neonate with a severe coarctation, acutely decreased LV function, and normal pulmonary artery pressure developed post-operative low cardiac output syndrome and his function was slow to recover. His ET-1 concentration increased slightly from the pre-operative to post-operative sample, consistent with the pattern typical of older children whose ET-1 level is likely driven by LV stress. An eight month old with severe coarctation, a dilated LV with poor systolic function, and near-systemic pulmonary artery pressure secondary to longstanding LV failure demonstrated rapidly improved pulmonary hypertension and LV function post-operatively. As would be expected, ET-1 activation in this patient more closely mirrored those in the neonatal cohort: Pre-operative ET-1 concentration was quite high and post-operative level was well below the pre-operative value.

Measured BNP concentration follows a similar trend to ET-1 concentration in this patient population. Neonatal patients have higher pre-operative BNP levels than their older counterparts and show a significant post-operative decline. Older children have lower BNP levels (normal in many cases) pre-operatively with no statistical change after surgical correction. These data suggest that neonates and some older infants experience a broad neuro-hormonal activation prior to coarctation repair in response to ventricular and potentially pulmonary artery stress and that surgical repair can result in early reversal of this neuro-hormonal activation in many patients. The specific role of BNP in this pathophysiology is not fully defined, and future studies will be needed to clarify the relationship with ET-1 and other markers of neuro-hormonal activation.

The echocardiographic data provide another layer of evidence for ET-1's potential role in the physiologic response to coarctation. Average LVMI and RWT in our patient population were significantly higher than previously published normal values and did not vary significantly through the perioperative period. This finding supports prior work demonstrating concentric LV remodeling and hypertrophy in the face of chronically high afterload with no immediate resolution following afterload reduction<sup>[6,24,25]</sup>. Mechanistically, animal studies have demonstrated that chronic ET-1 exposure induces cardiomyocyte hypertrophy *via* increased production of Extracellular Signal-Regulated Kinases 1 and 2 (ERK

1/2)<sup>[8,9,26]</sup>. Our data aligns with this finding, as patients with higher levels of ET-1 had more abnormal cardiac geometry. This novel finding combined with a biologically plausible link between ET-1 and myocyte hypertrophy raises the possibility that ET-1 could be not only a useful marker of LV remodeling but potentially an effector as well. Further, longitudinal studies will be needed to evaluate ET-1's role both in myocyte hypertrophy prior to repair and reverse remodeling after surgical correction.

In summary, we conclude that ET-1 concentration is significantly altered in patients with coarctation of the aorta undergoing surgical repair. We find preliminary evidence supporting two potentially distinct stimuli for ET-1: One mechanism, associated with high LV afterload and sympathetic nervous system activation, persists through the immediate post-operative period and the other, likely driven by altered pulmonary artery physiology, is rapidly reversible. We further find preliminary evidence supporting an association between ET-1 activity and early pathologic LV remodeling.

### Limitations

This study is prospective, single center, and targets a relatively rare patient population. As such, statistical power was limited, particularly in sub-cohort analysis. Biological heterogeneity, particularly among patients between 1 mo and 1 year of age, also limited statistical analysis. Therefore, validation of these findings in similar cohorts at other centers will be of great importance. Our study design does not allow for conclusions regarding causality in the relationship between ET-1 level and LV remodeling. Due to the young age of the subject population, control serum samples for ET-1 analysis were not obtained. While historical controls from previous studies were noted for discussion, an ideal comparison including unaffected, age-matched controls will be a goal of future studies. Additionally, small patient size and safety concerns preclude routine direct clinical monitoring of pulmonary artery and left atrial pressure in the perioperative period. While hemodynamic inferences can be drawn from available clinical data, future animal studies will be helpful to directly measure these pressures and more precisely elucidate their role in the physiology described.

## ARTICLE HIGHLIGHTS

### Research background

Patients with coarctation of the aorta are at risk for a variety of short- and long-term complications after surgical repair. Endothelin-1 (ET-1) is a peptide hormone known to cause both cardiac myocyte hypertrophy and vasoconstriction that has been linked to late ventricular hypertrophy in this population. Peri-operative endothelin concentration in this population has not been previously defined.

### Research motivation

Defining ET-1 activation in the perioperative period could offer significant insight into the variable short and long term physiologic responses to coarctation seen in this population.

### Research objectives

The authors sought to define pre-operative ET-1 activation, perioperative changes in concentrations with surgical relief, and the association with early myocardial change.

### Research methods

Here authors present a prospective, cohort study of ET-1 concentration and pathologic myocardial remodeling both prior to surgical correction of coarctation/aortic arch obstruction and in the immediate post-operative period. ET-1 analysis was performed by ELISA. Echocardiograms were obtained immediately prior to surgical repair and between 24 and 72 h post-operatively. All images were obtained with a GE Vivid E9 or E95 machine (General Electric, Chicago, Ill). Relative wall thickness (RWT) was measured at end-diastole from the parasternal short axis view as the ratio of the sum of the posterior and septal mural thickness to the left ventricular internal end-diastolic diameter; a value of 41% is conventionally taken as the upper limit of normal for RWT. LV mass was calculated by the area-length (AL) method, indexed to height<sup>2.7</sup>, and compared to previously published normal values.

### Research results

The authors demonstrate that neonates with coarctation of the aorta have high pre-operative ET-1 levels that decrease post-operatively. Older coarctation patients have more modest ET-1 activation that is unchanged post-operatively.

### Research conclusions

This study is the first to assess early ET-1 activation and its association with LV remodeling at the time of surgery for coarctation of the aorta. Key findings include increased concentration among neonates preoperatively with a decline after anatomic correction. This pattern is contrasted with more modest ET-1 level before surgery in older children and no significant post-operative change. The authors find preliminary evidence supporting two potentially distinct stimuli for ET-1: One mechanism, associated with high LV afterload and sympathetic nervous system activation, persists through the immediate post-operative period and the other, likely driven by altered pulmonary artery physiology, is rapidly reversible. The authors further find preliminary evidence supporting an association between ET-1 activity and early pathologic LV remodeling.

### Research perspectives

Longitudinal studies will be needed to evaluate ET-1's role both in myocyte hypertrophy prior to repair and reverse remodeling after surgical correction. Given the normal pulmonary hemodynamics in the author's older cohort and the mechanistic explanation offered by previous work, the authors posit that the ET-1 levels seen in this sub-group could reflect sympathetic activation due to the abnormality in LV and systemic vascular physiology. Future studies will be needed to confirm this hypothesis. The variable activation pattern between neonatal and older patients supports a role for the different pulmonary artery mechanics between the two subgroups affecting the variable ET-1 levels seen. Further studies will be needed to clarify the role of pulmonary artery pressure and pulmonary blood flow on ET-1 concentration.

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## Erythropoietin therapy after out-of-hospital cardiac arrest: A systematic review and meta-analysis

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### Abstract

#### AIM

To assess safety and efficacy of early erythropoietin (Epo) administration in patients with out-of-hospital cardiac arrest (OHCA).

#### METHODS

A systematic literature search was performed using PubMed, MEDLINE, EMBASE, EBSCO, CINAHL, Web of Science and Cochrane databases, of all studies published from the inception through October 10, 2016. Inclusion criteria included: (1) Adult humans with OHCA and successful sustained return of spontaneous circulation; and (2) studies including mortality/brain death, acute thrombotic events as their end points. Primary efficacy

outcome was "brain death or Cerebral Performance Category (CPC) score of 5". Secondary outcomes were "CPC score 1, and 2-4", "overall thrombotic events" and "acute coronary stent thrombosis".

### RESULTS

We analyzed a total of 606 participants ( $n = 276$  received Epo and  $n = 330$  with standard of care alone) who experienced OHCA enrolled in 3 clinical trials. No significant difference was observed between the Epo and no Epo group in brain death or CPC score 5 (OR = 0.77; 95%CI: 0.42-1.39), CPC score 1 (OR = 1.16, 95%CI: 0.82-1.64), and CPC score 2-4 (OR = 0.77, 95%CI: 0.44-1.36). Epo group was associated with increased thrombotic complications (OR = 2.41, 95%CI: 1.26-4.62) and acute coronary stent thrombosis (OR = 8.16, 95%CI: 1.39-47.99). No publication bias was observed.

### CONCLUSION

Our study demonstrates no improvement in neurological outcomes and increased incidence of thrombotic events and acute coronary stent thrombosis in OHCA patients who were treated with Epo in addition to standard therapy.

**Key words:** Erythropoietin; Thrombosis; Cardiac arrest; Cardiopulmonary resuscitation

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**Core tip:** This manuscript suggested that: (1) No improvement in neurological outcomes with erythropoietin (Epo) administration after out of hospital cardiac arrest; and (2) Epo administration was also associated with increased thrombotic events and acute stent thrombosis.

Chaudhary R, Garg J, Krishnamoorthy P, Bliden K, Shah N, Agarwal N, Gupta R, Sharma A, Kern KB, Patel NC, Gurbel P. Erythropoietin therapy after out-of-hospital cardiac arrest: A systematic review and meta-analysis. *World J Cardiol* 2017; 9(12): 830-837 Available from: URL: <http://www.wjgnet.com/1949-8462/full/v9/i12/830.htm> DOI: <http://dx.doi.org/10.4330/wjc.v9.i12.830>

## INTRODUCTION

Patients who undergo out-of-hospital cardiac arrest (OHCA) frequently have post-anoxic encephalopathy, even after successful initial resuscitation. This brain insult can be either transient or definitive, and is the major cause of mortality<sup>[1]</sup>. Even after successful resuscitation and restoration of cerebral perfusion, brain injury continues to progress due to reperfusion injury. At present, apart from targeted therapeutic hypothermia, no other modalities have demonstrated a reduction in cerebral anoxic brain ischemia after OHCA<sup>[2,3]</sup>. In

recent years, pre-clinical studies have suggested tissue protective effects of erythropoietin (Epo) and its analogues especially after brain and myocardial damage from ischemia-reperfusion injury<sup>[4,5]</sup>. However, this did not translate into a significant clinical benefit in patients with either acute myocardial infarction or stroke<sup>[6-8]</sup>. In the setting of OHCA, there is whole body ischemia and clinical studies have shown conflicting results with 2 studies demonstrating mortality benefit with early Epo administration<sup>[9,10]</sup> and a recent randomized controlled trial with no significant benefit<sup>[11]</sup>. In view of these studies, we aim to perform a meta-analysis to assess for any significant mortality benefit of early Epo administration in patients with OHCA.

## MATERIALS AND METHODS

The present review was performed according to Cochrane Collaboration and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statements<sup>[12]</sup>.

### Search strategy

We carried out a literature search using PubMed, MEDLINE, EMBASE, EBSCO, CINAHL, Web of Science and Cochrane databases, of all studies published from the inception through October 10, 2016 comparing early Epo administration in addition to standard care in patients with OHCA with standard care alone. We combined the terms ("out of hospital cardiac arrest" OR "cardiac arrest" OR "OHCA") AND ("erythropoietin" OR "EPO") as keywords or medical subject heading terms in different combinations. All references of the retrieved articles were reviewed for further identification of potentially relevant studies. The identified studies were systematically assessed using the inclusion and exclusion criteria described below.

The studies had to fulfill the following criteria to be included in the analysis: (1) adult human subjects with OHCA and successful sustained return of spontaneous circulation (ROSC); and (2) studies including mortality/brain death, acute thrombotic events as their end points. All studies with retrospective design, abstracts, case reports, conference presentations, editorials, reviews, and expert opinions were excluded from our analysis. Longest available follow-up data from individual studies was used for our analysis.

### Data extractions and quality appraisal

Two authors (Rahul Chaudhary and Jalaj Garg) searched the studies and extracted the data independently and in duplicate. The abstractors (Jalaj Garg and Rahul Chaudhary) independently assessed the quality items, and any discrepancies were resolved by discussion and consensus with the third author (PK). Final results were reviewed by senior investigator (NP) (Figure 1).

Assessment of risk of bias for each selected study was performed according to PRISMA 2009 guidelines.

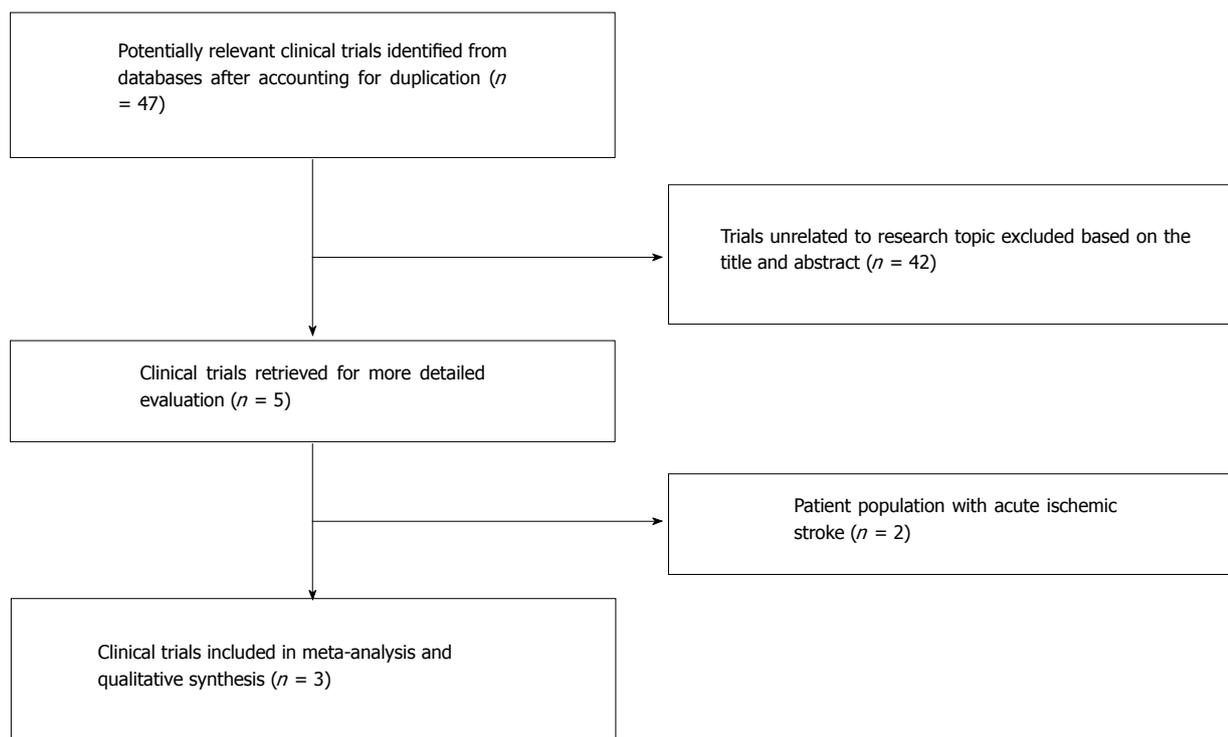


Figure 1 Process of study selection for randomized and prospective trials (PRISMA Statement).

Qualitative evaluation of bias using the following key parameters were performed for each study: (1) clear definition of study population; (2) clear definition of outcomes and outcome assessment; (3) independent assessment of outcome parameters; (4) sufficient duration of follow-up; (5) selective loss during follow-up; and (6) important confounders and prognostic factors identified. The quality of non-randomized studies were evaluated using the Newcastle-Ottawa quality assessment scale<sup>[13]</sup> and randomized controlled trials were evaluated using Cochrane Risk of Bias tool.

### Outcomes

The primary efficacy outcome in our study was "brain death or Cerebral Performance Category (CPC) score of 5". Briefly, the CPC scale ranges between 1 and 5. A score of 1 represents good cerebral performance or minor disability, 2 moderate disability, 3 severe disability, 4 coma or vegetative state, and 5 represent brain death<sup>[14]</sup>. Secondary outcome assessed in our study were "CPC score 1 and 2-4", "overall thrombotic events" (defined as a combination of venous thrombosis, acute coronary stent thrombosis and other arterial thrombosis) and "acute coronary stent thrombosis".

### Statistical analysis

Descriptive statistics are presented as means and SDs for continuous variables and as number of cases and percentages for dichotomous and categorical variables. Data were summarized across treatment arms using the Mantel-Haenszel odds ratio (OR) fixed effects model. Between-study heterogeneity was analyzed by means of

Higgins  $I^2$  statistic<sup>[15]</sup>. In cases of heterogeneity (defined as  $I^2 > 25\%$ ), random effects models of DerSimonian and Laird were used<sup>[16]</sup>. Funnel plot were evaluated visually to assess for any publication bias<sup>[17]</sup>. If any bias was observed, further bias quantification was measured using the Begg-Mazumdar Test<sup>[18]</sup>, Egger Test<sup>[19]</sup> and Duval-Tweedie test<sup>[20]</sup>. The statistical analysis was performed using the Cochrane Collaborative software, RevMan 5.3.

## RESULTS

A total of 47 studies were identified after exclusion of duplicate or irrelevant references (Figure 1). After detailed evaluation, 3 clinical trials (2 case-controlled studies and 1 randomized controlled study) with a total of 606 patients (276 patients received Epo in conjunction to standard of care compared to 330 patients with standard of care alone) were included in our analysis<sup>[9-11]</sup>. The characteristics of these trials and mean follow-up periods are described in Table 1.

### Quality assessment and publication bias

Overall, there were clear definitions of the study population, outcomes, and assessment in the component studies. The quality assessment of individual trials is listed in Table 2. Funnel plots did not reveal publication bias for comparison of CPC score 5 and CPC score 1-4 (Figure 2).

### Baseline characteristics

In the participant studies, there were no significant

**Table 1 Characteristics of the included studies**

Name of study	Cariou <i>et al</i> <sup>[9]</sup> , 2008	Grmec <i>et al</i> <sup>[10]</sup> , 2009	Cariou <i>et al</i> <sup>[11]</sup> , 2016
Study design	Single center, case-control	Single center, case-control	Multicenter, single blind RCT
Total dose of Epo administered	200000 IU	90000 IU	200000 IU
Timing of Epo administration	Immediately after ROSC	Within 1 or 2 min of physician assisted CPR	Immediately after ROSC
No. of participants, <i>n</i> (intervention/control)	18/40	24/48	234/242
Mean age, yr (intervention/control)	59/58	59/60	60.5/58.6
Male gender, <i>n</i> (intervention/control)	16/39	16/34	192/184
Initial rhythm PEA/asystole, <i>n</i> (intervention/control)	2/8	12/17	94/100
Initial rhythm shockable (VF/VT), <i>n</i> (intervention/control)	16/32	12/31	115/110
Perfusing rhythm after bystander defibrillation, <i>n</i> (intervention/control)	0/0	0/0	24/31
Unknown rhythm, <i>n</i> (intervention/control)	0/0	0/0	1/3
Follow-up duration	28 d	Till hospital discharge	60 d

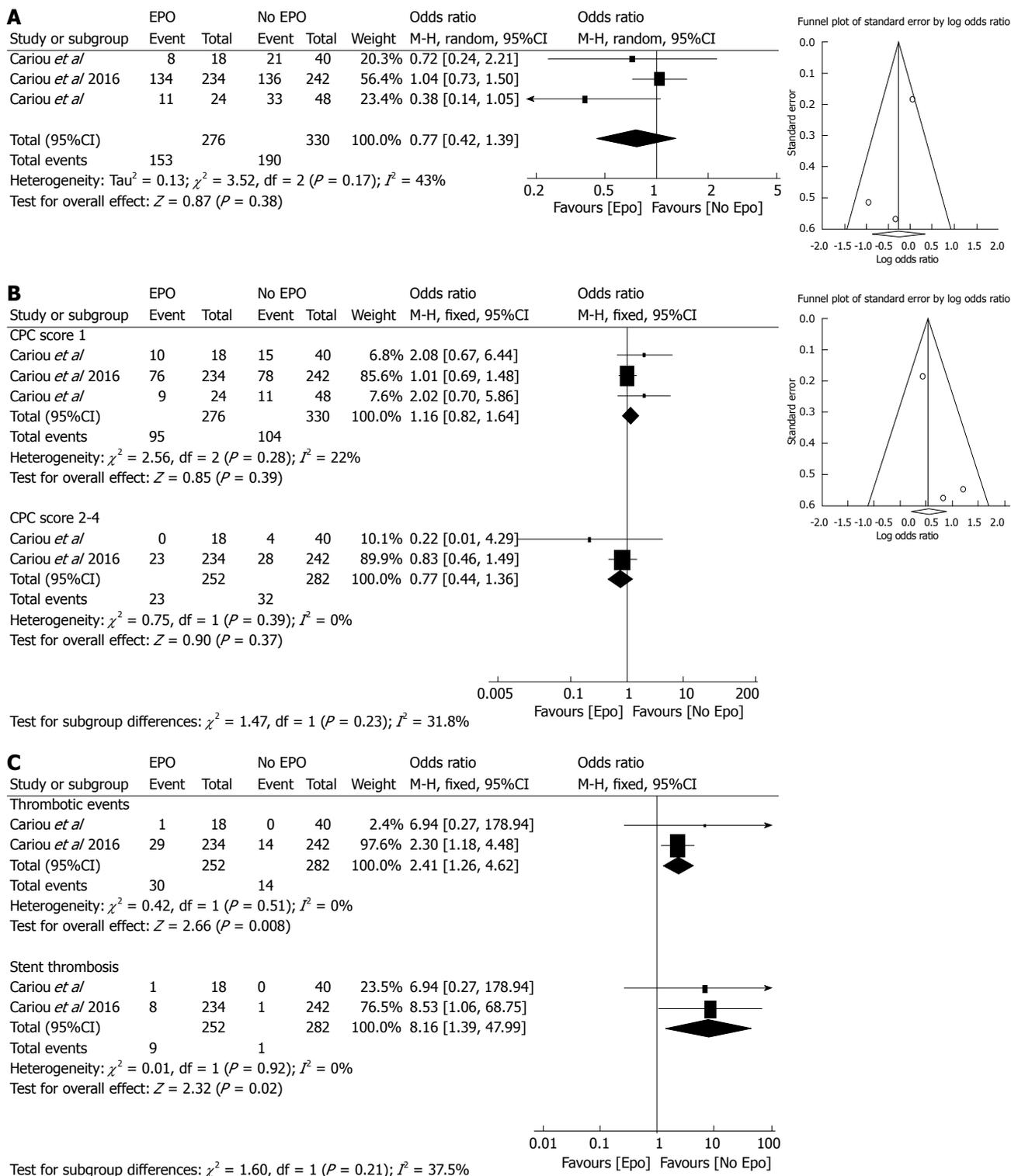
RCT: Randomized control trial; Epo: Erythropoietin; IU: International units; ROSC: Return of spontaneous circulation; CPR: Cardiopulmonary resuscitation; PEA: Pulseless electrical activity; VF: Ventricular fibrillation; VT: Ventricular tachycardia.

**Table 2 Assessment of quality for the included studies**

Newcastle-Ottawa scale for bias assessment for case-controlled studies		
Newcastle-Ottawa scale for bias assessment	Cariou <i>et al</i> <sup>[9]</sup> , 2008	Grmec <i>et al</i> <sup>[10]</sup> , 2009
Selection	3	2
Comparability	2	2
Exposure	3	3
Cochrane Risk of Bias tool for the Randomized controlled study (Cariou <i>et al</i> <sup>[11]</sup> )		
Entry	Judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomly assigned in a 1:1 ratio to the intervention or the control group"
Allocation concealment (selection bias)	Low risk	Quote: "Randomization was performed centrally with the use of a computer-generated assignment sequence Intervention assignments were made in permuted blocks of varying size and were stratified according to site"
Blinding of participants and personnel (performance bias)	High risk	Comment: Probably done Quote: "Single-blinded"; "physicians performing neurological follow-up and final outcome measurement, as well as study administrators and statisticians, were unaware of the intervention assignments" Comment: Probably done. However, only single blinding performed
Blinding of outcome assessment (detection bias) (patient-reported outcomes)	Low risk	Quote: "Single-blinded"
Blinding of outcome assessment (detection bias) (mortality)	Low risk	Comment: Probably done Obtained from medical records; Quote "CPC was assessed by face-to-face contact with patients still hospitalized, and through phone interviews in discharged patients using a standardized protocol"
Incomplete outcome data addressed (attrition bias) (Longer-term outcomes, > 6 wk)	Low risk	Review authors do not believe this will introduce bias 60 d: 1/234 missing from intervention group ("lost to follow-up"); 0/242 missing from control group
Selective reporting (reporting bias)	Low risk	A single scale to assess neurological outcomes was used and reported (CPC score)

differences between the two groups in terms of age, gender, and initial rhythm (pulseless electrical activity or asystole and ventricular fibrillation or ventricular tachycardia). No significant heterogeneity was observed (Table 3). The mean age of our study population was 59.1 years (range 58 to 60.5 years) with 80% males.

In the component studies, standard of care included use of therapeutic hypothermia immediately upon ICU admission (or continued if initiated pre-hospital) using external or internal cooling during the first 24 h in order to obtain a target temperature between 32 °C and 34 °C. Normothermia between 37 °C and 37.5 °C



**Figure 2 Forest plot demonstrating the primary and secondary outcomes in patients with out of hospital cardiac arrest who received erythropoietin compared to no erythropoietin group. A: Primary Outcomes: Brain death or CPC score 5; B: Secondary outcome: CPC score 1, and 2-4; C: Secondary outcome: Thrombotic events and acute stent thrombosis.**

was then achieved using passive rewarming and maintained for the next 48 h. In patients with a high suspicion of acute coronary syndrome as the cause of OHCA, coronary angiograms were performed at hospital admission and followed by immediate percutaneous coronary interventions (PCIs) when indicated. Vaso-pressor agents were used, when indicated to keep the

mean arterial blood pressure above 65 mmHg.

**Summary of results from individual trials**

In the first clinical trial evaluating use of Epo, in addition to standard therapy, for patients with OHCA, Cariou *et al*<sup>[9]</sup> showed a non-significant improvement in survival rates (55% vs 47.5%,  $P = 0.17$ ) and rates of full

**Table 3** Baseline demographics of study population

Baseline characteristic	Epo	No Epo	n	Studies (n)	P for overall effect
Age, yr	59.5	58.9	606	3	0.22
Males, %	79.2	81.4	606	3	0.93
Initial rhythm PEA/asystole, %	33.8	32.2	606	3	0.85
Initial rhythm VF/VT, %	62.7	63.3	606	3	0.45

Epo: Erythropoietin; PEA: Pulseless electrical activity; VF: Ventricular fibrillation; VT: Ventricular tachycardia.

neurological recovery (55% vs 37.5%,  $P > 0.05$ ) in a case-control study of 58 patients ( $n = 18$  in Epo group and  $n = 40$  in control group)<sup>[9]</sup>. In 2009, Grmec *et al*<sup>[10]</sup> showed an association of early Epo administration in patients with OHCA with higher incidence of return of spontaneous circulation (92% vs 71%,  $P = 0.06$ ), 24-h survival (83% vs 52%,  $P = 0.01$ ) and hospital survival (54% vs 31%,  $P = 0.06$ ) in a study of 72 patients ( $n = 24$  in Epo group and  $n = 48$  in control group). After adjustment for pretreatment covariates all the above-mentioned outcomes were statistically significant<sup>[7]</sup>. In 2016, Cariou *et al*<sup>[11]</sup> performed a large-scale multicenter, single blind, randomized controlled trial (RCT), of 476 patients followed for a period of 60 d. They demonstrated no improvement in neurological outcomes (CPC score 1 in patients in Epo group 32.4% vs 43.1% in no Epo group; OR = 1.01, 95%CI: 0.68-1.48) and reported no differences between the mortality rate and proportion of patients in each CPC level between the two groups at any time points. Additionally, they observed a higher incidence of more serious adverse events with Epo administration compared to controls (22.6% vs 14.9%;  $P = 0.03$ ), particularly thrombotic complications (12.4% vs 5.8%;  $P = 0.01$ )<sup>[11]</sup>.

### Primary outcomes

Brain death or CPC score of 5 was observed in 55% (153/276) of patients in Epo group compared to 57% (190/330) in control with no significant difference between the two groups (OR = 0.77; 95%CI: 0.42-1.39;  $I^2 = 43%$ ) (Figure 2A).

### Secondary outcomes

No significant differences were observed between the Epo and No Epo group with CPC scores 1 (34% vs 31% respectively, OR = 1.16, 95%CI: 0.82-1.64;  $I^2 = 22%$ ), and CPC score 2-4 (9% vs 11% respectively; OR = 0.77, 95%CI: 0.44-1.36;  $I^2 = 0%$ ) (Figure 2B).

Erythropoietin therapy was associated with a significant increase in overall thrombotic events (12% vs 5% for Epo and control group respectively; OR = 2.41, 95%CI: 1.26-4.62;  $I^2 = 0%$ ) and acute coronary stent thrombosis (3% vs 0.3% for Epo and control group respectively; OR = 8.16, 95%CI: 1.39-47.99;  $I^2 = 0%$ ) (Figure 2C).

## DISCUSSION

To best of our knowledge, this is the first meta-analysis

comparing early use of Epo in conjunction to standard therapy with standard therapy alone in patients with out-of-hospital cardiac arrest. The major findings in our study are as follows: (1) Epo plus standard therapy was not associated with any improved neurologic recovery (brain death, *i.e.*, CPC score 5, CPC score 1-4); and (2) Epo plus standard therapy was significantly associated with increased incidence of overall thrombotic complications and acute coronary stent thrombosis.

Use of Epo as a neuroprotective agent emerged from animal models demonstrating Epo induced neuronal and vascular protection from ischemia-reperfusion injury<sup>[4,21]</sup>. Although promising, these results did not translate into improvement in clinical outcomes in patients with ischemic stroke or acute MI<sup>[6-8]</sup>. In 2008, Cariou *et al*<sup>[9]</sup> reported the first clinical study evaluating early use of Epo plus standard therapy in patients with OHCA. This study demonstrated encouraging results with a higher rate of full neurological recovery in Epo treated patients (55% vs 37.5%) with no significant difference mortality benefit. Similarly, Ehrenreich *et al*<sup>[7]</sup>, in 2009 observed higher incidence of return of spontaneous circulation, 24-h survival and hospital survival with early administration of Epo in patients with OHCA. However, both these studies were case-control, single centered and non-randomized with a small patient population. Recently, Cariou *et al*<sup>[11]</sup> performed a large-scale multicenter, single blind, randomized controlled trial (RCT), which did not show any improvement in neurological outcomes with early administration of Epo. The results in our study are consistent with this recent RCT and other major RCTs evaluating the role of Epo in a similar setting, *i.e.*, acute MI and acute ischemic stroke<sup>[6-8]</sup>. The discrepancy between animal and human studies could be due to inter-species variability in action of Epo and mechanism of neurological injury<sup>[11]</sup>.

In addition, our study demonstrated an increased incidence of overall thrombotic events and acute coronary stent thrombosis. In prior studies, Epo has been associated with increased thrombotic events including stent thrombosis in patients treated for cancer associated anemia<sup>[22]</sup> and acute myocardial infarction<sup>[6]</sup>. The underlying mechanisms involved with increased thrombogenicity with Epo in patients with OHCA remains unclear. Several mechanism have been proposed to explain stent thrombosis in patients undergoing therapeutic hypothermia - impaired drug metabolism and reduced bioavailability<sup>[23,24]</sup>, increased platelet

activation<sup>[25]</sup>, ineffective platelet inhibition, hypothermia induced mast cell degranulation<sup>[26]</sup>. In a recently published article from our group, we demonstrated no statistical significant difference in stent thrombosis in patients undergoing therapeutic hypothermia<sup>[27]</sup>. Also, Epo or its analogues have not been shown to enhance platelet activation<sup>[28]</sup> or activation of coagulation factors<sup>[29]</sup>. Thus it is possible increased thrombotic events in the Epo arm may be due to additional factors that were not accounted in our study (*i.e.*, erythropoietin induced increase in blood viscosity, vasoconstriction and elevated blood pressure<sup>[22,30]</sup>, timing of dual antiplatelet therapy, hemodynamic circulatory support, presence of congestive heart failure, cardiogenic shock and number of stents)<sup>[27]</sup>.

A major limitation of the current meta-analysis includes paucity of data from RCT's - with data from 2 case-controlled studies and only 1 RCT with a small patient population. Despite, differences in trials design, no significant heterogeneity was observed.

In conclusion, this study demonstrates no improvement in neurological outcomes and increased incidence of thrombotic events and acute coronary stent thrombosis in OHCA patients who were treated with Epo in addition to standard therapy.

## ARTICLE HIGHLIGHTS

### Research background

Patients with out-of-hospital cardiac arrest (OHCA) frequently have post-anoxic encephalopathy, even after successful initial resuscitation. This brain insult can be either transient or definitive, and is the major cause of mortality. Even after successful resuscitation and restoration of cerebral perfusion, brain injury continues to progress due to reperfusion injury.

### Research motivation

In the setting of OHCA, there is whole body ischemia and clinical studies have shown conflicting results with 2 studies demonstrating mortality benefit with early Erythropoietin (Epo) administration and a recent randomized controlled trial with no significant benefit. In view of these studies, the authors aim to perform a meta-analysis to assess for any significant mortality benefit of early Epo administration in patients with OHCA.

### Research objectives

The primary efficacy outcome in this study was "brain death or Cerebral Performance Category (CPC) score of 5". Secondary outcomes assessed in this study were "CPC scores 1 and 2-4", "overall thrombotic events" and "acute coronary stent thrombosis".

### Research methods

A systematic literature search was performed using PubMed, MEDLINE, EMBASE, EBSCO, CINAHL, Web of Science and Cochrane databases, of all studies published from the inception through October 10, 2016. The included trials were evaluated for publication bias and data summarized across treatment arms using the random effects model as odds ratio (OR).

### Research results

No significant differences were observed between the two groups in brain death or CPC score of 5 (OR = 0.77; 95%CI: 0.42-1.39;  $I^2 = 43\%$ ), CPC score 1 (OR = 1.16, 95%CI: 0.82-1.64;  $I^2 = 22\%$ ), and CPC score 2-4 (OR = 0.77, 95%CI: 0.44-1.36;  $I^2 = 0\%$ ). Epo therapy was associated with a significant increase in overall thrombotic events (OR = 2.41, 95%CI: 1.26-4.62;  $I^2 = 0\%$ ) and acute coronary stent thrombosis (OR = 8.16, 95%CI: 1.39-47.99;  $I^2 = 0\%$ ).

## Research conclusions

This study demonstrates no improvement in neurological outcomes and increased incidence of thrombotic events and acute coronary stent thrombosis in OHCA patients who were treated with Epo in addition to standard therapy.

## Research perspectives

Epo administration in patients with OHCA demonstrated an increase in adverse events with no mortality benefit in addition to current standard of care. Based on the currently available literature and this systematic review, further studies are needed in order to assess the safety and efficacy of Epo in Out-Of-Cardiac-Arrest patients.

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## Artefactual angulated lesion on angiography: A case report and review of literature

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### Abstract

We present a case of a patient who presented with chest pain, and on diagnostic coronary angiography appeared to have a grossly angulated yet significant coronary stenosis. This was proven to be an artefactual appearance on further assessment with intravascular ultrasound imaging. We describe the causes and associations of coronary tortuosity with other arteriopathy, and highlight challenges in the interpretation of tortuous vessels to accurately assess luminal narrowing and suitability for coronary intervention. We describe a case of artefactual coronary stenosis, and its thorough assessment with intravascular ultrasound. A literature review describes the pathogenesis of coronary tortuosity, and links with other cardiovascular disease. Readers will gain an understanding of the challenge in determining the severity of luminal stenosis based on coronary angiography alone in tortuous coronary anatomy, the use of intravascular ultrasound in this setting, and the allied vasculopathies of interest.

**Key words:** Coronary tortuosity; Intravascular ultrasound; Spontaneous coronary artery dissection; Diagnostic coronary angiography

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**Core tip:** Coronary arteries are inherently tortuous, and are assessed at angiography, compressing a 3D structure into a 2D picture. An overly tortuous artery may resemble true luminal stenosis, rather than mere angulation, and may be interpreted as a significant coronary stenosis. We present a remarkably angulated coronary artery, which appeared to bear a significant stenosis. On further assessment with pressure wire study and intravascular ultrasound we found there to be no significant lesion. We demonstrate an artefactual false-positive finding, and describe our clinical approach to avoid mistaking such a lesion for one that requires intervention, with a review of

the literature.

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## INTRODUCTION

Coronary artery tortuosity poses many challenges in its assessment and further investigation. We present a case with ambiguous appearances at coronary angiography, clarified with intravascular imaging, and discuss the possible underpinning causes to consider when evaluating a tortuous epicardial artery.

## CASE REPORT

An 80-year-old Caucasian hypertensive patient presented with atypical chest discomfort that was present both at rest and on exercise. She had no cardiovascular risk factors. She was normotensive, with BP 126/72, and heart rate 70. Her ECG was normal. Transthoracic echocardiography demonstrated preserved left ventricular function. A coronary angiogram appeared to show a severe lesion in the proximal left anterior descending coronary artery, at its origin (Figure 1). She underwent a pressure wire study to this territory, to confirm its significance, with plans to carry out further intracoronary imaging to determine whether percutaneous intervention was feasible in view of the lesion's ostial location and extreme angulation.

The pressure wire study was repeatedly negative, with instantaneous wave-free ratio of 0.97 and fractional flow reserve of 0.92 at maximal hyperaemia with systemic adenosine. Intravascular ultrasound demonstrated a normal calibre vessel throughout, with no significant atheroma seen (Video 1), contrary to the angiographic profile of the vessel.

## DISCUSSION

Arteries are rarely straight, and a degree of curvature is inevitable in their path from the heart to distal tissue beds. Angulated or widespread coronary tortuosity is often seen, though its relevance is dependent on the context in which it is found, with coexistent congenital diseases and the possibility of an artefactual appearance, as described here, complicating interpretation.

### **Degenerative coronary tortuosity**

An inordinate degree of tortuosity has been observed in ageing, hypertension, diabetes mellitus and atherosclerosis, where it may be seen in all arterial vessels, from aorta to arteriole, and throughout the venous system. Arterial tortuosity may be quantified by a number of

tortuosity indices, which in general assimilate the number of curvatures of an artery away from its overall direction of travel, measured in end-diastole. Though arterial curvature is usually benign, severe tortuosity may impede blood flow in coexistent atherosclerotic disease, embolus or systemic hypoperfusion predisposing to end organ ischaemia<sup>[1]</sup>.

### **Heritable syndromes with arterial tortuosity**

Degenerative arterial tortuosity is distinct from a group of inherited arteriopathies. Extreme arterial tortuosity has been seen in a number of congenital syndromes, including Loeys-Dietz syndrome, with genetic mutations of the transforming growth factor- $\beta$  receptor, Marfan Syndrome, affecting fibrillin-1, and Arterial Tortuosity Syndrome, with mutation of the SLC2A10 gene. The underlying mechanism for the effects of these deletions is unclear. They manifest as gross, diffuse arterial sinuosity affecting coronary, great vessels, carotid and vertebral arteries, and are associated with cerebrovascular infarct or aneurysm, aortic dissection and adverse overall cardiovascular outcomes<sup>[2]</sup>.

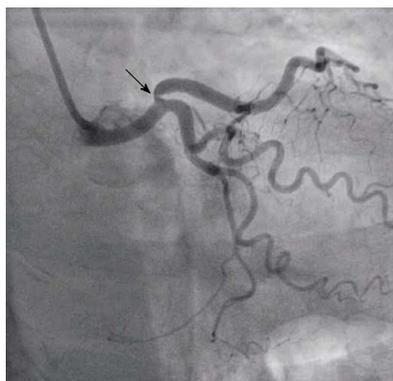
### **Cardiovascular events in patients with coronary tortuosity**

In a prospective study of coronary tortuosity in 1010 patients presenting for diagnostic coronary angiography, the incidence of epicardial coronary artery tortuosity appears to be higher in females, and its presence was correlated with hypertension yet negatively correlated with hyperlipidaemia, smoking and atherosclerosis. No significant difference was seen in major adverse cardiovascular events over a 4 year follow-up period between those with or without coronary tortuosity<sup>[3]</sup>. Conversely tortuous microvessels induce increased shear forces on blood transiting through its conduit, inducing platelet activation. This is thought to be thrombogenic, with higher mural thrombus and platelet activation seen in preclinical modelling of tortuous arterioles<sup>[4]</sup>.

There appears to be an underlying genetic cause linking a continuum of arterial phenotypes from coronary tortuosity, *via* fibromuscular dysplasia and culminating in spontaneous coronary artery dissection (SCAD) with myocardial infarction. Patients with SCAD have been observed to have a high prevalence of coronary tortuosity, and this is higher still in those with recurrent SCAD. Fibromuscular dysplasia is associated with SCAD, with a recent report of *SMAD3* gene deletion underpinning a presentation of SCAD<sup>[5-7]</sup>.

### **Challenges of assessing coronary atherosclerosis in arterial tortuosity**

Native tortuosity of an epicardial coronary artery may resemble a significant luminal stenosis when straightened through passage of a guidewire. The guidewire induces a linear shape to a conduit that is normally curved, and there is invagination of the redundant tissue which impinges on the vessel lumen. This appearance disappears when the



**Figure 1 Artefactual angulated lesion on angiography.** The coronary angiogram, shown here in the AP caudal view, appears to demonstrate a significant lesion in the proximal left anterior descending coronary artery (arrow). There was no significant impediment to flow on pressure wire study, with no significant lesion seen on intravascular ultrasound.

guidewire is retracted and the natural curvature of the vessel is restored, confirming an artefactual stenosis. This has been termed the “accordion effect”. The right coronary artery has scant surrounding tissue in the atrioventricular groove in comparison to the left coronary system, and is thought to be particularly prone to this appearance with instrumentation<sup>[8]</sup>. Our case demonstrates a normal vessel lumen that appears to resemble coronary stenosis on angiographic views due to its angulation.

We demonstrate the importance of intravascular imaging in excluding a significant atherosclerotic process. The use of intravascular ultrasound has previously been described as a gold standard test, above coronary angiography, in clarifying the course of a segment of ambiguous coronary anatomy and its relationship with other vessels<sup>[9]</sup>. However these measurements are reliant on the passage of a guidewire through a curved artery, and care must be taken in intracoronary measurements in tortuous vessels. Coronary tortuosity has recently been described as a potential cause of foreshortening of vessel length in Optical Coherence Tomography (OCT), and overestimation of vessel diameter by up to 12%, due an eccentric position of the OCT catheter in a nonlinear segment of vessel, and/or the straightening effect and movement of redundant tissues as seen with the accordion effect. This effect was minimised by using a floppy rather than a stiff guidewire in this OCT study<sup>[10]</sup>.

We conclude that the appearances of severe coronary stenosis in this angulated and tortuous vessel is an artefactual appearance, which was proven to have neither arteriosclerosis nor significant intraluminal narrowing on further assessment. This case highlights the importance of multimodality assessment of tortuous vessels, where luminal stenosis may be overestimated by coronary angiography. The accordion effect at coronary angiography, and underestimation of vessel length with overestimation of vessel diameter at intracoronary imaging, require careful interpretation of data for correct diagnosis. The links between coronary tortuosity and other arteriopathies are currently the

subject of investigation, with a possible underpinning genetic aetiology.

## ARTICLE HIGHLIGHTS

### Case characteristics

The patient described atypical exertional chest pain, with no prior cardiovascular risk factors.

### Clinical diagnosis

Coronary angiography initially appeared to demonstrate a severe lesion in the proximal left anterior descending coronary artery, which was demonstrated to be a false positive finding in an angulated artery with no significant coronary stenosis, through further physiological and anatomical testing.

### Differential diagnosis

Further assessment of a lesion of this nature may be carried out using functional assessment, with a pressure wire study, or anatomical assessment, with intravascular ultrasound, as demonstrated here.

### Imaging diagnosis

The authors used intravascular ultrasound to demonstrate a normal calibre of coronary artery. An alternative modality of optical coherence tomography may be used.

### Treatment

The above approach identified a false positive finding of possible coronary stenosis, which when ruled out prevented inappropriate treatment with a coronary artery stent.

### Related reports

The authors describe the aetiology of coronary angulation, which may be degenerative or heritable, and though epicardial tortuosity has not been shown to be associated with an increase in major adverse cardiovascular events an association with spontaneous coronary artery dissection, and the potential for misinterpretation of angulation as luminal stenosis, are important considerations when assessing lesions.

### Experiences and lessons

The authors learned the importance of multimodality assessment of apparent coronary lesions to justify, and subsequently rule out, the need for intervention in a case of marked coronary artery curvature, and present an approach to prevent mis-interpretation.

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## Successful recanalization of long femoro-crural occlusive disease after failed bypass surgery

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### Abstract

Patients with critical limb ischemia necessitate immediate intervention to restore blood flow to the affected limb. Endovascular procedures are currently preferred for these patients. We describe the case of an 80-year-old female patient who presented to our department with ischemic rest pain and ulceration of the left limb. The patient had history of left femoral popliteal bypass surgery, femoral thromboendarterectomy and patch angioplasty of the same limb 2 years ago. Doppler sonography and magnetic resonance angiography revealed an occlusion of the left superficial femoral artery (SFA) and popliteal artery and of all three infra-popliteal arteries. Due to severe comorbidities, the patient was scheduled for a digital subtraction angiography. An antegrade approach was first attempted, however the occlusion could not be passed. After revision of the angiography acquisition, a stent was identified at the level of the mid SFA, which was subsequently directly punctured, facilitating the retrograde crossing of the occlusion. Thereafter, balloon angioplasty was performed in the SFA, popliteal artery and posterior tibial artery. The result was considered suboptimal, but due to the large amount of contrast agent used, a second angiography was planned in 4 wk. In the second session, drug coated balloons were used to optimize treatment of the SFA, combined with recanalization of the left fibular artery, to optimize outflow. The post-procedural course was uneventful. Ischemic pain resolved completely after the procedure and at 8 wk of follow-up and the foot ulceration completely healed.

**Key words:** Critical limb ischemia; Chronic occlusion; Duplex sonography; Lower limb

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**Core tip:** Herein, we present a patient with critical ischemia of the lower limb, due to long occlusive disease of the femoro-popliteal and below-the-knee arteries who was successfully treated using an endovascular approach after failed bypass surgery and using the direct stent puncture technique. This case demonstrates that an endovascular approach may be extremely valuable even in very long, complex occlusive peripheral artery disease. This may further shift treatment from surgical to endovascular treatment in the near future.

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## INTRODUCTION

The prevalence and mortality of peripheral artery disease (PAD) rapidly increased during the last years due to prolonged life expectancy and is estimated to affect  $\geq 30\%$  of older patients within the next few years<sup>[1,2]</sup>. Particularly patients with critical limb ischemia (CLI) show poor outcome with high risk for major amputation and high death rates within the first year after diagnosis<sup>[3,4]</sup>. Such patients very frequently suffer from comorbidities, like renal failure and diabetes mellitus<sup>[5]</sup> and are at high risk for septic shock if perfusion is not promptly re-established.

In patients with CLI, arterial revascularization should be performed without delay. Current guidelines provided by the task force for the treatment of PAD recommend an "endovascular first" approach in patients with CLI, taking the potential risk and the anticipated success rate of interventional treatment option into account<sup>[6]</sup>. Procedural decision should also consider the localization, complexity and length of the vascular lesions, as well as local expertise, comorbidities such as diabetes mellitus and renal failure and patients' preferences<sup>[7]</sup>.

Herein, we present the case of an 80-year-old female patient with CLI due to long occlusive disease of the femoral superficial, popliteal and all 3 infra-popliteal arteries, who was successfully treated endovascularly in 2 sessions.

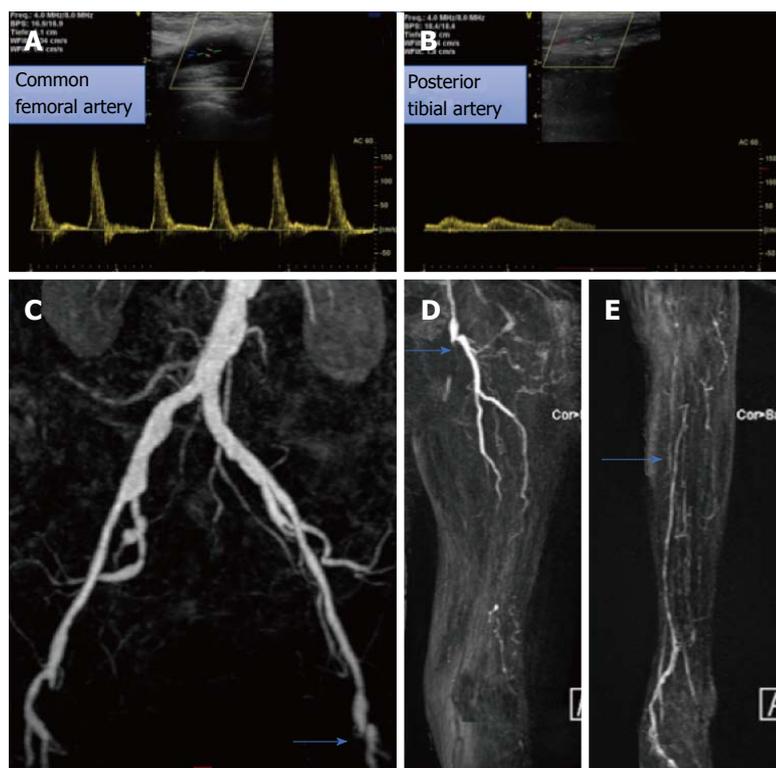
## CASE REPORT

An 80-year-old female patient was referred to our department due to CLI with ulceration of the left limb (Rutherford Class 5), accompanied by ischemic rest pain.

The patient had history of multi-vessel coronary artery disease with non-ST elevation myocardial infarction 3 mo ago. Left ventricular function was moderately reduced. In addition, she had history of arterial hypertension, hyperlipidemia, prior cigarette smoking and type 2 diabetes mellitus. Furthermore, atrial fibrillation was present. The laboratory markers showed reduced renal function with a creatinine of 1.4 mg/dL with an estimated glomerular filtration rate of  $GFR = 36 \text{ mL/min per } 1.73 \text{ m}^2$ . White blood count and C-reactive protein were increased (12300/ $\mu\text{L}$  and 18.3 mg/L, respectively) at the time of presentation. Clinical inspection revealed the presence of a forefoot ulcer without presence of gangrenous necrosis. The patient had history of left femoral popliteal bypass surgery as well as femoral thromboendarterectomy and patch angioplasty surgery 2 years ago. Duplex sonography relieved biphasic flow in the left iliac external and common femoral artery and a long occlusion of the femoral and popliteal artery with blunted monophasic flow in the posterior tibial artery (Figure 1A and B). No flow was present in the anterior tibial and in the fibular arteries. The ankle-brachial-index was severely reduced at 0.30. Magnetic resonance angiography (MRA) confirmed these findings, exhibiting no stenosis of the iliac arteries (Figure 1C), a long total occlusion of the left superficial femoral (SFA) (blue arrow in D showing flush occlusion of the SFA) and of the popliteal artery with collateral filling to the proximal part of the posterior tibial artery (blue arrow in Figure 1E) and occlusion of the anterior tibial, the tibiofibular tract and of the fibular artery (Figure 1D and E).

The patient had a history of chronic renal disease (creatinine = 1.4 mg/dL,  $GFR = 35 \text{ mL/min per } 1.73 \text{ m}^2$ ), atrial fibrillation, chronic obstructive lung disease (GOLD Class 3), type 2 diabetes mellitus and multi-vessel coronary artery disease with prior non-ST elevation infarction 3 mo ago.

Due to history of failed bypass surgery and severe cardio-pulmonary comorbidities the patient was scheduled for invasive digital subtraction angiography (DSA). After inserting a 6F guiding cross-over introducer sheath (Terumo Destination®, Terumo interventional systems, Eschborn, Germany) by puncture of the right CFA, DSA confirmed flush occlusion of the left SFA (Figure 2A) with no native vessels depicted in the upper leg and in the proximal lower leg (Figure 2B and C) and with scarce filling of the posterior tibial artery (blue arrow in Figure 2D) (Video 1). Subsequently, 500 mg aspirin and 5000 IU of heparin were injected and antegrade recanalization was attempted using different hydrophilic tapered and non-tapered guidewires. However, antegrade crossing of the occlusion failed, possibly due to presence of scarred tissue in this area after surgery. After careful revision of the initial moving table non-DSA acquisition (Video 1), a stent was identified at the level of the mid SFA, which was subsequently directly punctured, facilitating the retrograde insertion of a 0.035" advantage guidewire (Terumo interventional systems, Eschborn, Germany) (Figure 2E



**Figure 1 Duplex sonography and magnetic resonance angiography findings.** A: Biphasic flow in the left common femoral artery; B: Blunted monophasic flow in the posterior tibial artery due to long occlusive disease; C: Absence of flow limiting stenosis in iliac arteries by magnetic resonance angiography; D: Long total occlusion of the SFA (blue arrow) and of the popliteal artery; E: Collateral filling in the proximal part of the posterior tibial artery (blue arrow). SFA: Superficial femoral artery.

and Video 1). Subsequently, retrograde passage of a 0.018" advantage guidewire was achieved over a 0.035" TrailBlazer support catheter, which was then snared in the 6F guiding cross-over sheath. Then, the retrograde 0.035" support catheter was pulled back and a second antegrade 0.035" support catheter was inserted over the 6F guiding cross-over sheath, which passed over the SFA through the punctured stent and was advanced to the level of the popliteal artery (blue arrow in Figure 2F). Over this 0.035" support catheter, a 0.014" advantage guidewire was advanced to the proximal anterior tibial artery and its intraluminal localization was confirmed by DSA (Figure 2G). Balloon angioplasty was then performed using a 2.5 mm × 200 mm Armada balloon (Figure 2H) in the infra-popliteal level and 5.0 mm × 200 mm and 6.0 mm × 200 mm Armada balloons (Figure 2I) (Abbott Vascular Deutschland GmbH) in the popliteal and SFA, respectively. Due to extensive dissection of the proximal SFA a 6.0 mm × 80 mm Innova self-expanding bare metal stent was placed (Boston Scientific, Ratingen, Germany). The final angiographic result, which can be depicted in Figure 2J-L was judged as suboptimal due to the absence of outflow in the lower leg. However, intervention was stopped at this point due to contrast agent administration of approximately 200 mL with chronic renal disease. The patient was put on treatment with 100 mg aspirin, 75 mg clopidogrel and 5 mg fondaparinux daily and was scheduled for re-angiography after 4 wk.

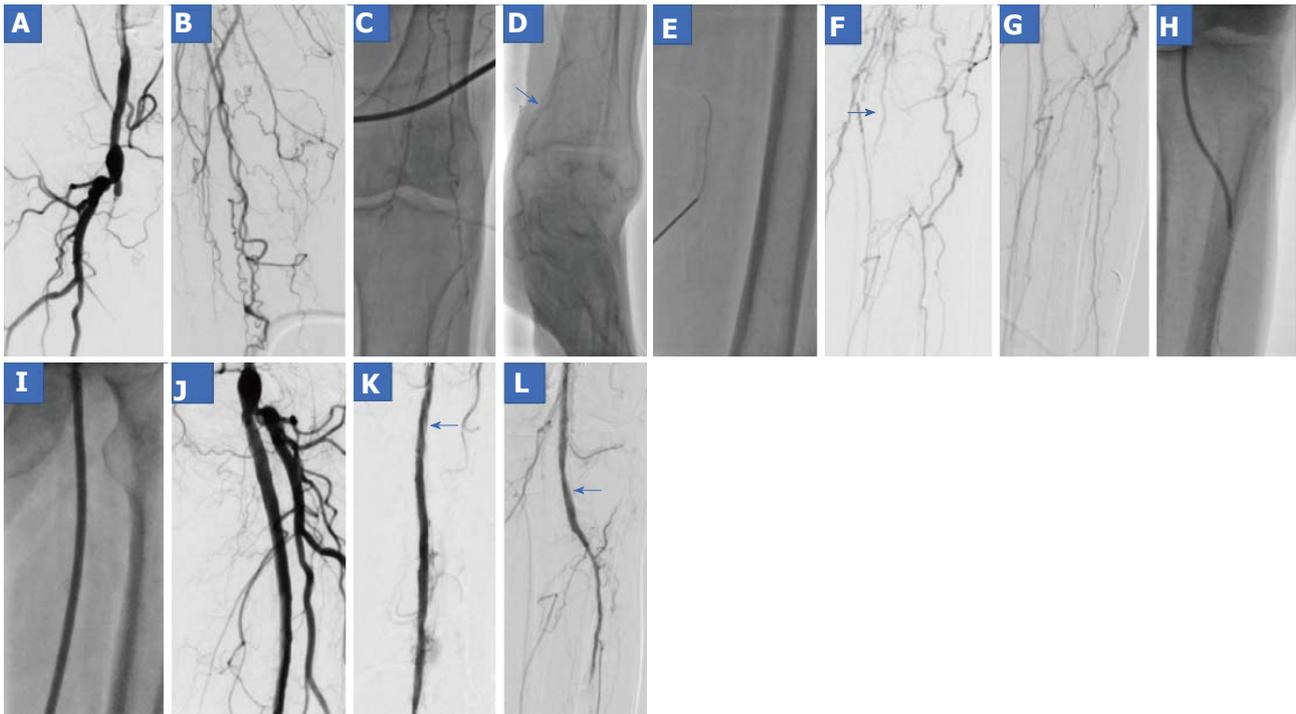
In the second session antegrade puncture of the

left CFA was performed directly above the implanted stent in the proximal SFA with subsequent insertion of a short 6F guiding introducer sheath. DSA revealed moderate restenosis of the mid SFA and of the popliteal artery, which were treated using 5.0 mm × 120 mm and 6.0 mm × 120 mm Impact Pacific (Medtronic GmbH, Meerbusch, Germany) drug coated balloons, respectively. In addition, recanalization of the fibular artery was performed, resulting in functional 2 vessel out-flow of the shortly occluded posterior tibial and of the fibular artery to the left foot. Final DSA images can be appreciated in Figure 3.

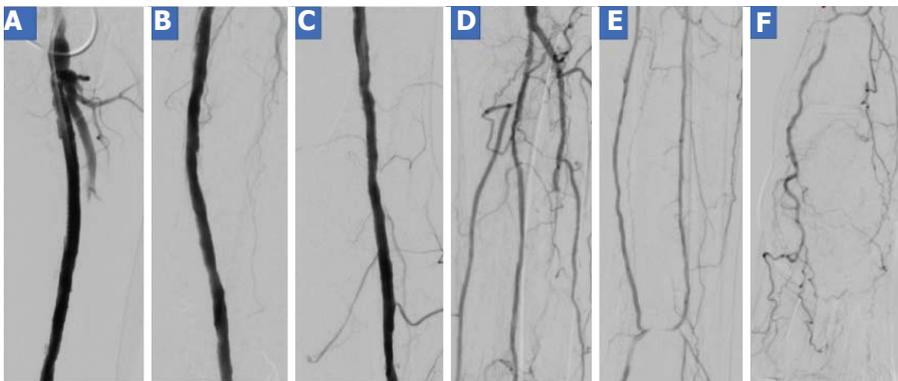
The clinical course of the patient was uneventful, and she was discharged at the following day. Ischemic pain had resolved completely, and the foot ulceration healed after 3 wk. The ankle-brachial-index increased to 0.98. The patient was set on treatment with 5 mg ramipril, 20 mg atorvastatin, 5 mg bisoprolol, 75 mg clopidogrel and 15 mg rivaroxaban per day. After 8 wk, duplex sonography exhibited a well perfused SFA with biphasic flow in the distal SFA and in the popliteal artery and monophasic flow of the distal fibular and posterior tibial artery (Figure 4).

## DISCUSSION

This is a case reporting on the usefulness of interventional treatment by the direct stent puncture technique in a very complex lesion with long occlusive disease of the



**Figure 2** Digital subtraction angiography in the first interventional session. A-D: Long occlusion of the left SFA and of the popliteal artery with scarce filling of the posterior tibial artery (blue arrow in D); E: After failed antegrade crossing direct stent puncture at the level of the mid SFA was performed, achieving retrograde intraluminal passage; F: After snaring the guidewire, a 0.035" TrailBlazer support catheter was antegrade advanced to the level of the popliteal artery (blue arrow); G: A 0.014" advantage guidewire was used to wire the anterior tibial artery; H-I: Balloon angioplasty; J-L: Final angiographic result. SFA: Superficial femoral artery.

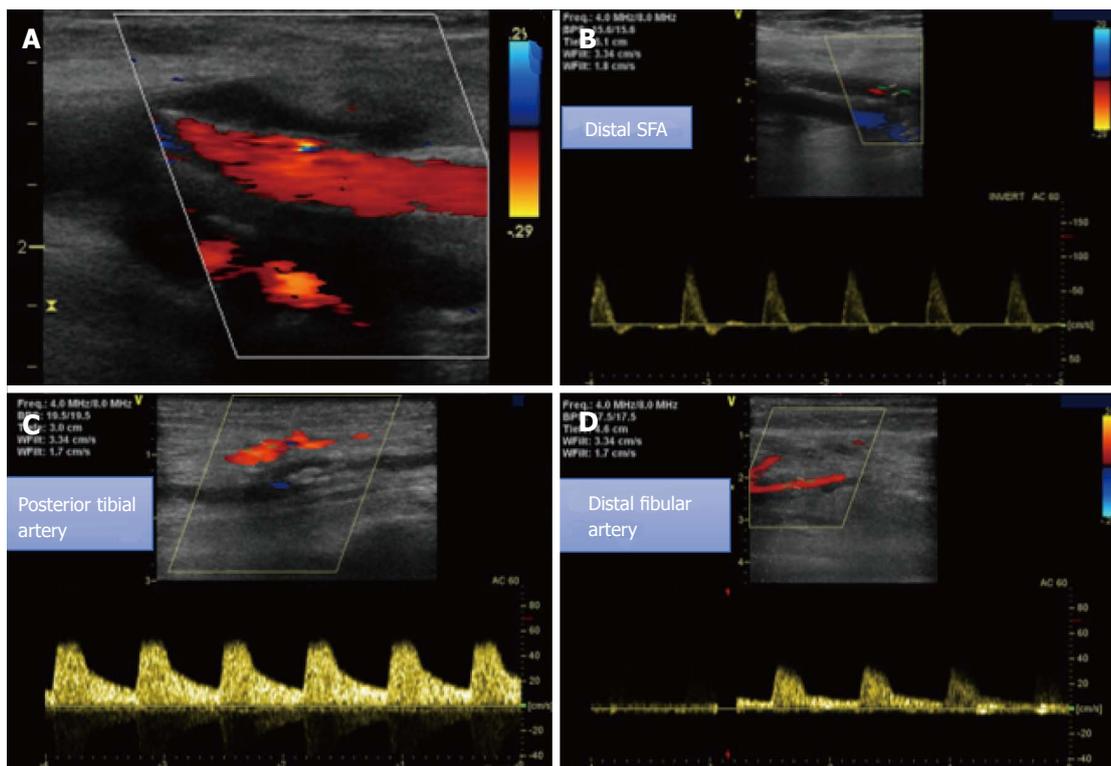


**Figure 3** Digital subtraction angiography in the second interventional session. A, B: DSA images of the SFA; C: DSA image of popliteal artery; D-F: DSA images of crural and foot arteries after the second angiographic procedure. SFA: Superficial femoral artery; DSA: Digital subtraction angiography.

SFA, popliteal artery and below-the-knee arteries.

CLI is associated with high amputation and mortality rates, depending on concomitant risk factors and treatment options<sup>[8]</sup>. From a pathophysiologic point of view, ischemia of the limb is reversible, but causes irreversible tissue death, if left untreated. In patients presenting with CLI, current guidelines by the task force for the treatment of PAD recommend an "endovascular first" approach depending on the anatomy and complexity of the underlying lesions. However, with long occlusion of the SFA and popliteal artery bypass surgery should be considered due to rather poor technical success rates and high risk for re-occlusion, especially in segments with predicted poor patency rates

in the distal downstream segments<sup>[7]</sup>. In our case, long femoro-popliteal occlusive disease was present along with occlusion of the proximal tibial posterior artery and total occlusion of the tibiofibular tract, of the fibular and the anterior tibial artery. Despite the complexity of the lesion, we chose an interventional approach due to failed bypass surgery and cardiac comorbidities. We used the direct stent puncture technique, which was previously described as an efficient and safe option for intraluminal stent recanalization in femoro-popliteal occlusive lesions<sup>[9,10]</sup>, exhibiting high technical success rates and low rates of peri- and postprocedural complications, such as distal embolization and hematoma at the puncture site<sup>[11]</sup>. Like previously reported cases, we punctured



**Figure 4 Duplex sonography at follow-up.** A, B: Well perfused SFA with biphasic flow in the distal SFA and in the popliteal artery; C, D: Monophasic flow in the distal posterior tibial and fibular arteries. SFA: Superficial femoral artery.

an occluded stent in the mid SFA, facilitating retrograde recanalization. In contrast to most of the reported cases however, the lesion in our patient was more complex, as it did not end in the femoro-popliteal segment, but also involved the proximal and mid part of crural arteries. Thus, due lesion complexity and chronic renal disease, we decided to tackle the lesion in 2 sessions to minimize the risk for contrast induced nephropathy. Indeed, a high amount of contrast agent was necessary within the first recanalization session. Although the final angiographic results after the first session was not optimal due to remaining dissections in the SFA and poor outflow in the crural arteries, vasculature remained open during pharmacologic treatment with aspirin, clopidogrel and fondaparinux for 4 wk. During the second session, further treatment with drug coated balloons was possible, along with recanalization of a crural artery, leading to much better outflow to the foot. This case demonstrates that an “endovascular first” approach may be a valuable and ultimately successful even in very long, complex occlusive lesions, which may further shift treatment from surgical to endovascular treatment procedures in the future.

**ARTICLE HIGHLIGHTS**

**Case characteristics**

An 80-year-old female patient with peripheral artery disease (PAD) and long occlusion of the femoro-popliteal artery and below-the-knee arteries after failed bypass surgery, who presented with critical limb ischemia (CLI).

**Clinical diagnosis**

PAD with CLI (Rutherford Class 5).

**Differential diagnosis**

Venous ulcer, neuropathic diabetic ulcer.

**Laboratory diagnosis**

Laboratory markers showed increased inflammation due to the arterial ulcer. In addition, a reduced renal function with an estimated glomerular filtration rate of 36 mL/min per 1.73 m<sup>2</sup> was noticed.

**Imaging diagnosis**

PAD was diagnosed by duplex sonography and magnetic resonance angiography (MRA) and was confirmed by digital subtraction angiography (DSA).

**Pathological diagnosis**

PAD with CLI (Rutherford Class 5).

**Treatment**

Endovascular strategy using percutaneous balloon angioplasty and without stent placement.

**Related reports**

The direct stent puncture technique has been used for the recanalization of complex femoro-popliteal occlusive disease in cases where an antegrade recanalization is not successful. The lesion in the patient was more complex, as it did not end in the femoro-popliteal segment, but also involved the proximal and mid part of crural arteries.

**Term explanation**

CLI is a life-threatening condition due to advanced occlusive PAD, usually

accompanied by ischemic rest pain, arterial ulcers and gangrene. If left untreated this condition will in major amputation, sepsis and death.

### Experiences and lessons

In patients with complex femoro-popliteal occlusive disease, the direct stent puncture technique may facilitate recanalization of very long occlusive lesions without the need of bypass surgery. An endovascular first approach needs to be considered in such patients, who usually are bad candidates for surgery due to cardiopulmonary disease and other comorbidities.

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## Transposition of the great arteries - a phenotype associated with 16p11.2 duplications?

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**Author contributions:** Lauridsen MH conducted the primary research, selected the patients, obtained informed consent from the parents and children, retrieved the blood samples, and communicated the genetic results to the families; Vestergaard EM performed and interpreted the chromosomal microarray analyses; Karunanithi Z collected the patient information from medical records; Karunanithi Z, Vestergaard EM and Lauridsen MH collectively summarized the data and wrote the manuscript.

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### Abstract

Genetic analyses of patients with transposition of the great arteries have identified rare copy number variations, suggesting that they may be significant to the aetiology of the disease. This paper reports the identification of a 16p11.2 microduplication, a variation that has yet to be reported in association with transposition of the great arteries. The 16p11.2 microduplication is associated with autism spectrum disorder and developmental delay, but with highly variable phenotypic effects. Autism and attention deficit disorders are observed more frequently in children with congenital heart disease than in the general population. Neonatal surgery is proposed as a risk factor, but as yet unidentified genetic abnormalities should also be taken into account. Thus, congenital heart abnormalities may constitute a part of the phenotypic spectrum associated with duplications at 16p11.2. We suggest chromosomal microarray be considered part of the diagnostic work-up in patients with transposition of the great arteries.

**Key words:** Transposition of the great arteries; Copy number variation; Genetics; 16p11.2; Microduplication

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**Core tip:** Rare copy number variations may be of significance to the aetiology of transposition of the great arteries. This paper reports, for the first time, the finding of a 16p11.2 microduplication in a patient with transposition of the great arteries. Recognizing a possible genetic association to transposition of the great arteries will spur investigations into associated phenotypic effects such as developmental delays, thus allowing for earlier identification and treatment. We recommend that chromosomal microarray be considered part of the diagnostic work-up in patients with transposition of the great arteries.

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## INTRODUCTION

Structural gene mutations are emerging as important causes of congenital heart diseases<sup>[1]</sup>. Transposition of the great arteries is a rare, life-threatening form of congenital heart disease. In contrast to some congenital heart defects, such as atrioventricular septal defects and tetralogy of Fallot, simple transposition of the great arteries is rarely associated with syndromes<sup>[2]</sup>.

Although the aetiology of the disease is currently unknown, rare copy number variations have recently been identified in patients with transposition of the great arteries<sup>[1,3-5]</sup> (Table 1). To investigate this further, we screened 13 patients with transposition of the great arteries for copy number variations using high-resolution chromosomal microarray analyses. Approximately half of the screened patients had additional congenital heart diseases.

## CASE REPORT

Here, we present the case of a young patient with a genetic mutation that has yet to be reported in association with transposition of the great arteries.

Blood samples were collected from patients and their parents during planned visits. Informed consent to perform chromosomal microarray was obtained. Chromosomal microarray (Agilent Technologies Inc., Santa Clara, CA, United States; 180K CGH for nine patients or 400K CGH + SNP for four patients) was performed on DNA extracted from blood leucocytes as per the manufacturer's protocol.

In one patient, the chromosomal microarray revealed

a 0.5 Mb duplication at chromosome 16p11.2 {arr(hg19) 16p11.2 [(29664529-30198600)] × 3 mat} covering the region involved in chromosome 16p11.2 duplication syndrome (OMIM 614671). This microduplication was subsequently detected in the patient's 35-year-old Caucasian mother, who was phenotypically unaffected. The mother was without any cardiac symptoms or murmurs and was not interested in further examinations of her heart.

The patient was born at gestational age 40 wk, weighing 3.06 kg and measuring 50 cm in length. The patient's Apgar score was 9 at one minute and 10 at five minutes. In addition to transposition of the great arteries, a pulmonary valve stenosis and ventricular and atrial septal defects were present. The patient had an arterial switch operation at birth and the Nikaidoh procedure at 7 years of age. Postoperatively, the patient achieved a relatively high level of activity and had no cardiac or respiratory discomfort. At 8 years of age, the patient was diagnosed with attention deficit hyperactive disorder. The patient was followed until the age of 9.5 years.

The 16p11.2 microduplication is associated with autism spectrum disorder and developmental delay, but with highly variable phenotypic effects. This duplication does not always result in severe impairment and may be inherited from a parent with minimal or no clinical features<sup>[6]</sup>. The 16p11.2 microduplication has not previously been associated with transposition of the great arteries. In the Decipher database, two cases of persistent arterial duct and one case of ventricular septal defect were seen among all patients with a 16p11.2 microduplication<sup>[7]</sup>.

## DISCUSSION

Transposition of the great arteries is one of the more severe congenital cardiac defects, but only few studies have investigated the possible aetiology of this defect<sup>[1,2]</sup>. Two clinical reports have documented a variety of genetic variations associated with transposition of the great arteries<sup>[4,5]</sup>. On a review of the literature, Unolt *et al.*<sup>[3]</sup> identified frequent syndromes, such as Turner and Noonan, that were rarely associated with transposition of the great arteries; however, a sporadic association with several other genetic variations is possible (Table 1). Costain *et al.*<sup>[2]</sup> studied a cohort of patients with transposition of the great arteries ( $n = 101$ ) and identified 11 different rare copy number variations, none of which were found in the control group ( $n = 10528$ )<sup>[2]</sup>. Osoegawa *et al.*<sup>[8]</sup> searched for candidate gene loci and sex chromosome aneuploidy among patients with conotruncal cardiac anomalies, of which 194 patients had transposition of the great arteries. They identified a 22q11.22 microdeletion in one patient, an 8p23.2 micro duplication in another patient, and sex chromosome abnormalities (47XYY and

**Table 1 Known genetic associations with transposition of the great arteries**

		Cytoband	Ref.
Non-syndromic	ZIC3	Xq26.3	Bamford <i>et al</i> <sup>[12]</sup>
	Nodal	10q22.1	Nomura <i>et al</i> <sup>[13]</sup>
	CFC1	2q21.1	Bamford <i>et al</i> <sup>[12]</sup>
	Smad2	18q21.1	Nomura <i>et al</i> <sup>[13]</sup>
		1p31.1	Costain <i>et al</i> <sup>[2]</sup>
		3q25.33-q25.32	Costain <i>et al</i> <sup>[2]</sup>
		4q28.3-4q28.2	Costain <i>et al</i> <sup>[2]</sup>
		7q21.11	Costain <i>et al</i> <sup>[2]</sup>
		8p22	Costain <i>et al</i> <sup>[2]</sup>
		12q24.33	Costain <i>et al</i> <sup>[2]</sup>
		13q13.1-13q13.2	Costain <i>et al</i> <sup>[2]</sup>
		16p12.3-16p13.11	Costain <i>et al</i> <sup>[2]</sup>
		16p12.2	Costain <i>et al</i> <sup>[2]</sup>
		Xp22.12	Costain <i>et al</i> <sup>[2]</sup>
		16p11.2	Current paper
Syndromic	CHARGE		Unolt <i>et al</i> <sup>[3]</sup>
	Deletion 11q		Jacobsen <i>et al</i> <sup>[14]</sup>
	Deletion 18p		Digilio <i>et al</i> <sup>[15]</sup>
	DiGeorge/ deletion 22q11		Van Mierop <i>et al</i> <sup>[16]</sup>
	Heterotaxy (right isomerism)		Marino <i>et al</i> <sup>[17]</sup>
	Marfan syndrome		Unolt <i>et al</i> <sup>[3]</sup>
	Noonan syndrome		Unolt <i>et al</i> <sup>[3]</sup>
	Trisomy 18		Unolt <i>et al</i> <sup>[3]</sup>
	Trisomy 8		Unolt <i>et al</i> <sup>[3]</sup>
	Tuberous sclerosis		Jiang <i>et al</i> <sup>[18]</sup>
	Turner syndrome		Unolt <i>et al</i> <sup>[3]</sup>
	VACTERL		Unolt <i>et al</i> <sup>[3]</sup>
Williams syndrome		Unolt <i>et al</i> <sup>[3]</sup>	

47XXY) in two patients with transposition of the great arteries.

We are the first to document the presence of a 16p 11.2 microduplication in a patient with transposition of the great arteries. Deletions and duplications of the recurrent 600 base pair region on chromosome 16p11.2 are frequent findings in patients with autism spectrum disorders and the concomitant finding of congenital heart disease may be an incidental finding not caused by the microduplication<sup>[9]</sup>. It is, however, well known that congenital abnormalities can occur in the context of recurrent duplications associated with susceptibility to intellectual disability.

Autism and attention deficit disorders are observed more frequently in children with congenital heart disease than in the general population<sup>[10]</sup>. Neonatal surgery is proposed as a risk factor<sup>[11]</sup>, but as yet unidentified genetic abnormalities should also be taken into account.

Thus, congenital heart abnormalities may constitute a part of the phenotypic spectrum associated with duplications at 16p11.2. We suggest chromosomal microarray be considered part of the diagnostic work-up in patients with transposition of the great arteries.

In conclusion, rare copy number variations may be of significance to the aetiology of transposition of the great arteries. This paper reports, for the first time, the finding of a 16p11.2 microduplication in a patient with transposition of the great arteries. Recognizing

a possible genetic association to transposition of the great arteries will spur investigations into associated phenotypic effects such as developmental delays, thus allowing for earlier identification and treatment. We therefore recommend that chromosomal microarray be considered part of the diagnostic work-up in patients with transposition of the great arteries.

**ARTICLE HIGHLIGHTS**

**Case characteristics**

Young patient diagnosed with transposition of the great arteries and a 16p11.2 microduplication.

**Clinical diagnosis**

The child deteriorated after birth, when the arterial duct closed. Echocardiography revealed transposition of the great arteries, pulmonary valve stenosis and ventricular and atrial septal defects. Around school age the child was diagnosed with attention deficit disorder.

**Differential diagnosis**

Regarding deterioration after birth, differential diagnoses are: Neonatal sepsis, metabolic disease, and other cyanotic heart defects. Neonatal surgery is a risk factor for attention deficit disorder.

**Laboratory diagnosis**

Chromosomal microarray revealed the 0.5 Mb chromosomal duplication at chromosome 16p11.2.

**Imaging diagnosis**

The congenital heart diseases were diagnosed using echocardiography.

### Treatment

The transposition of the great arteries was treated with an arterial switch operation at birth and the Nikaidoh procedure at the age of 7 years.

### Related reports

Transposition of the great arteries is rarely associated with genetic variations. Transposition of the great arteries have once before been associated with a 16p13.11 duplication (Ref. [19]). The authors are the first to report the 16p11.2 microduplication in association with transposition of the great arteries.

### Term explanation

Copy number variation: A structural variation in the DNA that results in the cell having an abnormal number of copies of one or more sections of the DNA.

### Experiences and lessons

The case document that copy number variations may be of significance in transposition of the great arteries and chromosomal microarray should be considered part of the diagnostic work-up in these patients.

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## Transcatheter aortic valve implantation operators - get involved in imaging!

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### Abstract

Pre-procedural planning is the key element of trans-

catheter aortic valve implantation (TAVI). Multislice computed tomography of the chest, abdomen and pelvis with the ability to perform a 3-dimensional reconstruction has become the cornerstone of pre-procedural planning. We would like to encourage TAVI operators (interventional cardiologist and surgeons) to get involved in imaging. All TAVI operators should know how to assess the annulus, the annular root, and the iliofemoral access. We strongly believe that this will improve outcomes of this evolving procedure.

**Key words:** Aortic stenosis; Transcatheter aortic valve implantation; Transcatheter aortic valve replacement; Imaging; Computed tomography

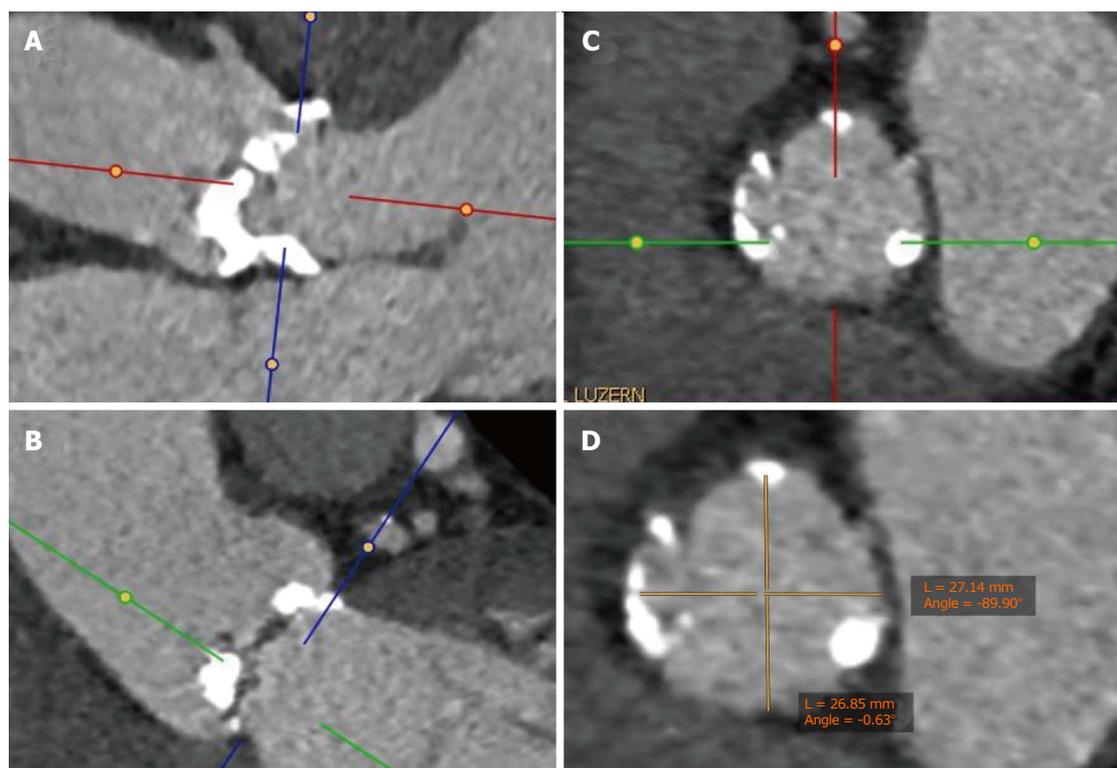
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**Core tip:** We have noticed that only a minority of interventional cardiologists and cardiac surgeons routinely look at their patients MDCTs and know how to perform a three dimensional multiplanar reconstruction. With this editorial, we would like to encourage all transcatheter aortic valve implantation (TAVI) operators to get involved in cardiac imaging. We do believe that this will improve outcomes. In case a complication occurs, TAVI operators will be more likely to understand the nature of the complication and learn from it. And this again will lead to improved outcomes in future.

Brinkert M, Toggweiler S. Transcatheter aortic valve implantation operators - get involved in imaging! *World J Cardiol* 2017; 9(12): 853-857 Available from: URL: <http://www.wjgnet.com/1949-8462/full/v9/i12/853.htm> DOI: <http://dx.doi.org/10.4330/wjc.v9.i12.853>

### TO THE EDITOR

Transcatheter aortic valve implantation (TAVI) is now routinely performed in inoperable, high-risk, and



**Figure 1** Example of a multiplanar reconstruction of the aortic annulus. A and B: Double-oblique MSCT images at the basal insertion of the calcified native cusps; C: Double-oblique reconstruction at the level of the aortic annulus. The aortic valve leaflets are just barely visible at the level of the ventriculoarterial junction; D: Measurement of the short and long diameter at the level of the aortic annulus. MSCT: Multislice computed tomography.

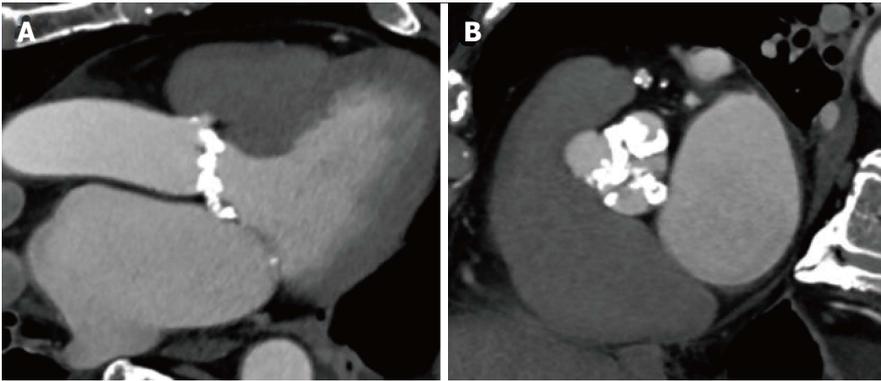
intermediate risk patients with low mortality- and complication rates<sup>[1,2]</sup>. Some of the key elements contributing to these impressive results are pre-procedural patient evaluation by the multidisciplinary HeartTeam, and pre-procedural imaging<sup>[3,4]</sup>.

The important role of multislice computed tomography (MSCT). MSCT of the chest, abdomen and pelvis with 3-dimensional reconstruction has become the cornerstone of pre-procedural planning. MSCT is now routinely performed to assess the aortic annulus, the distance between the aortic annulus and the coronary ostia and the suitability for the transfemoral access<sup>[3,5]</sup>. Nowadays matured post-processing imaging software is widely available to perform these measurements automatically and create standardized reports<sup>[6]</sup>. However, automatic measurements may not include the degree and distribution of calcification and may not take into account all aspects of the anatomy. Most of the TAVI operators rely on such reports or on numbers and measurements reported by the radiologist<sup>[7-9]</sup>. Therefore, we would like to encourage all TAVI operators to get involved in imaging and learn how to perform a 3-dimensional multiplanar reconstruction.

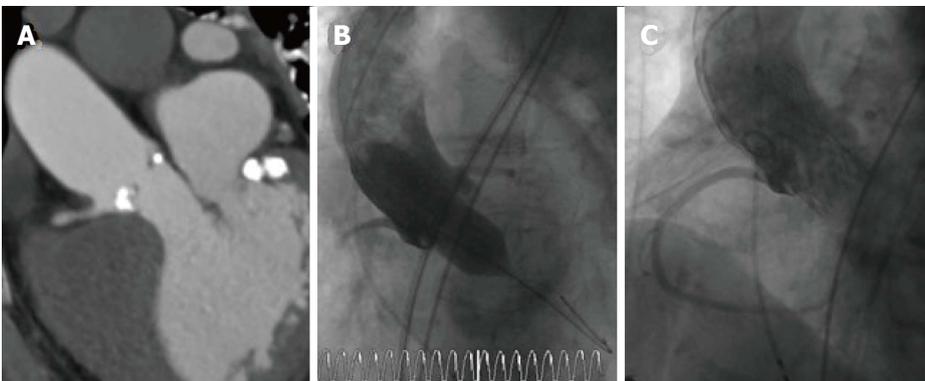
Choosing the valve type and size. It has been shown that left ventricular outflow tract (LVOT) calcification is associated with an increased risk for annular rupture during TAVI with balloon-expandable prostheses<sup>[10]</sup>. Extensive calcifications at the native aortic valve may increase the risk for paravalvular regurgitation or need for a permanent pacemaker<sup>[11,12]</sup>. As an interventional

cardiologist or cardiac surgeon, we can easily perform multiplanar reconstructions of the aortic annulus not only to measure the dimensions of the annulus but also to get an impression of the distribution of calcification of the valve leaflets and the LVOT (Figure 1)<sup>[13]</sup>. Based on all information including the annular perimeter, area, distribution of calcification and anatomy of the aortic root, valve type and size can be chosen more specifically as part of a patient tailored therapy (Figure 2).

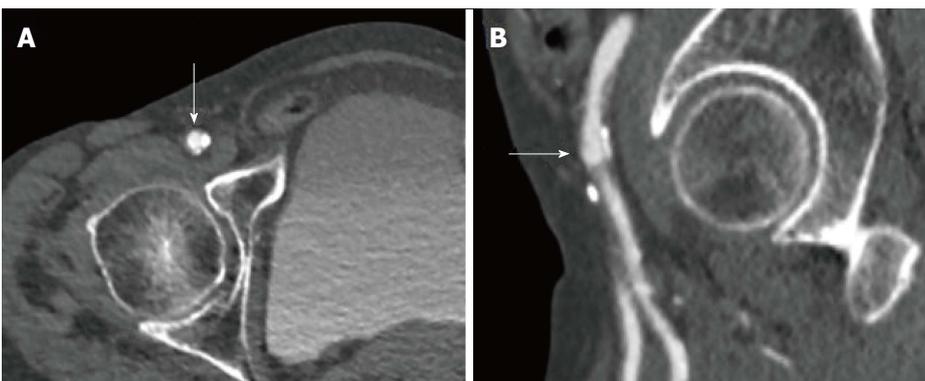
Assessment of the coronary artery height. The "Instructions for use" of different valves include specific recommendations for the minimal coronary artery height. However, the risk for coronary obstruction is greatly increased in patients with bulky atheroma or calcifications at the tip of the leaflets, a smaller sinus of valsalva diameter, narrow sinotubular junction and different patient characteristics like female gender or patients with previous surgical bioprosthesis<sup>[14]</sup>. Measuring the coronary artery height with MSCT is a great screening tool, but "virtual implantation" by the operator comparing the length of the leaflets with the distance between annulus and coronary ostia and also assessing the distribution of calcifications may allow much better risk stratification (Figure 3). Radial strength depends largely on the valve type. Whereas the widely used balloon-expandable valves consist of cobalt chromium, self-expanding valves are composed of nitinol thus applying less radial force to the tissue<sup>[14]</sup>. Accordingly, a self-expandable and retrievable valve might be preferable in patients at risk for coronary obstruction. Moreover, in case of borderline



**Figure 2** Cardiac multislice computed tomography showing a patient with heavy calcifications extending into the left ventricular outflow tract and a shallow sinus. This anatomy is associated with increased risk for annular rupture in patients undergoing TAVI with a balloon expandable valve. A: Three chamber view of the heart showing a patient with heavy calcification extending from the aortic annulus into the LVOT and a shallow sinus; B: Short axis view of the aortic valve showing heavy calcified aortic leaflets. LVOT: Left ventricular outflow tract; TAVI: Transcatheter aortic valve implantation.



**Figure 3** Patient undergoing transfemoral transcatheter aortic valve implantation with a very low ostium of the right coronary artery. A: Patient with a very low ostium of the right coronary artery but potentially a large enough sinus valsalva for TAVI; B: Balloonvalvuloplasty with simultaneous injection of contrast media to estimate the risk for coronary obstruction; C: Successful implantation of an Evolut R. Supraannular injection shows a patent right coronary artery. TAVI: Transcatheter aortic valve implantation.



**Figure 4** Multislice computed tomography showing calcified right common femoral artery in a patient undergoing transfemoral transcatheter aortic valve implantation. A: Right common femoral artery with an arrow pointing at the ideal puncture site above the calcification; B: Right common femoral artery with an arrow pointing at the ideal puncture site above the height of bifurcation of the common femoral artery in relationship to the femoral head.

anatomy, balloonvalvuloplasty with simultaneous contrast media injection may allow to estimate the risk for coronary obstruction during valve deployment. In patients considered at high risk for coronary obstruction placing a coaxial guiding catheter extension such as the GuideLiner catheter (Cascular Solutions Inc., Minneapolis,

MN, United States) in the coronary artery during valve deployment may allow emergent percutaneous coronary intervention.

Choosing the ideal puncture site. Finally MSCT is routinely used to evaluate size, tortuosity and calcifications of the iliofemoral arteries and to determine

the feasibility of transfemoral access<sup>[15]</sup>. MSCT provides detailed information about the height of the bifurcation of the common femoral artery in relationship to the femoral head. Furthermore, it allows visualization of the inferior epigastric artery which is located within the inguinal ligament. Finally, MSCT shows the extent of calcification at the level of the potential puncture site (Figure 4). Knowing your patients anatomy allows to perform a precise puncture under fluoroscopy guidance thus minimizing the risk for vascular injury<sup>[16,17]</sup>.

How to get involved in imaging, and why? Potential TAVI candidates are discussed by the interdisciplinary HeartTeam consisting of non-invasive cardiologists specialized in cardiac imaging, interventional cardiologists and cardiac surgeon to define the best treatment option for the individual patient. Evaluation of associated comorbidities that may limit the life expectancy or the recovery after the procedure is of particular importance. Results from pre-procedural invasive angiogram, echocardiogram and MSCT are reviewed for each patient. We would like to encourage all TAVI operators to review their patients MSCT again immediately before the procedure. Look at the iliofemoral access to choose the better side with less calcification or tortuosity, and choose the ideal puncture site. Then, perform a three dimensional multiplanar reconstruction of the annulus, measure the annular diameters, perimeter, and the area. Look for calcification at the level of the annulus, but also at the level of the LVOT. Finally, review the root and the coronary arteries. With routine, this can be performed in 2-3 min in most patients. There are two potential advantages of being able to analyze your patient's images. First, you may improve your patient's outcomes. Second, if you have a complication, you are more likely to understand it and learn from it. And this will again lead to better outcomes in the future.

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