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Essential hypertension and oxidative stress: New insights

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Abstract

Essential hypertension is a highly prevalent pathological condition that is considered as one of the most relevant cardiovascular risk factors and is an important cause of morbidity and mortality around the world. Despite the fact that mechanisms underlying hypertension are not yet fully elucidated, a large amount of evidence shows that oxidative stress plays a central role in its pathophysiology. Oxidative stress can be defined as an imbalance between oxidant agents, such as superoxide anion, and antioxidant molecules, and leads to a decrease in nitric oxide bioavailability, which is the main factor responsible for maintaining the vascular tone. Several vasoconstrictor peptides, such as angiotensin II, endothelin-1 and urotensin II, act through their receptors to stimulate the production of reactive oxygen species, by activating enzymes like NADPH oxidase and

xanthine oxidase. The knowledge of the mechanism described above has allowed generating new therapeutic strategies against hypertension based on the use of antioxidants agents, including vitamin C and E, N-Acetylcysteine, polyphenols and selenium, among others. These substances have different therapeutic targets, but all represent antioxidant reinforcement. Several clinical trials using antioxidants have been made. The aim of the present review is to provide new insights about the key role of oxidative stress in the pathophysiology of essential hypertension and new clinical attempts to demonstrate the usefulness of antioxidant therapy in the treatment of hypertension.

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Key words: Hypertension; Oxidative stress; Endothelial dysfunction; Antioxidants

Core tip: This review focuses on one of the most prevalent diseases worldwide: hypertension, providing new insights about the key role of oxidative stress in the pathophysiology of essential hypertension and new clinical attempts to demonstrate the usefulness of antioxidant therapy in its treatment.

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INTRODUCTION

Hypertension is considered the most important risk factor for the occurrence of cardiovascular disease^[1]. Oxidative stress has gained attention as one of the fundamental mechanisms responsible for the development of hypertension. Reactive oxygen species (ROS) have an important

role in the homeostasis of the vascular wall, hence they could contribute to the mechanism of hypertension^[2-4]. Thus, increased ROS production, and reduced nitric oxide (NO) and antioxidants bioavailability were demonstrated in experimental and human hypertension. Vascular superoxide is derived primarily from NADPH oxidase (NOX) when stimulated by hormones such as angiotensin II (AT-II), endothelin-1 (ET-1) and urotensin II (UT-II), among others. In addition, increased ROS production may be generated by mechanical forces, which increase with hypertension. ROS-induced vasoconstriction results from increased intracellular calcium concentration, thereby contributing to the pathogenesis of hypertension^[2]. Vasomotor tone is dependent upon a delicate balance between vasoconstrictor and vasodilator forces resulting from the interaction of the components of the vascular wall and the blood, and both of them can be altered by oxidative stress. These findings have stimulated the interest on antihypertensive therapies targeted to decrease ROS generation and/or increase NO bioavailability. This review examines the available studies pointing to a role of oxidative stress in the mechanism of production of high blood pressure, as well as the use of antioxidants in the prevention or treatment of this disorder.

PATHOPHYSIOLOGY OF HYPERTENSION

Endothelial dysfunction

Endothelial dysfunction has been implicated in the pathophysiology of different forms of cardiovascular disease, including hypertension. It may be defined as impairment characterized by a shift of the actions of the endothelium toward reduced vasodilation, a proinflammatory state, and prothrombotic setting. These events lead to a state of vascular inflammation, which may be mediated, partly, by ROS formed by activated mononuclear cells.

Vascular oxidative stress and hypertension

Oxidative stress constitutes a unifying mechanism of injury of many types of disease processes, it occurs when there is an imbalance between the generation of ROS and the antioxidant defense systems in the body. The ROS family comprises many molecules that have divergent effects on cellular function. Importantly, many of these actions are associated with pathological changes observed in cardiovascular disease. The effects of ROS are mediated through redox-sensitive regulation of multiple signaling molecules and second messengers^[5-7]. Several studies have demonstrated that essential hypertensive patients and various animal models of hypertension produce excessive amount of ROS^[8-12], and have abnormal levels of antioxidant status^[13], thereby contributing to the accumulating evidence that increased vascular oxidative stress could be involved in the pathogenesis of essential hypertension^[2,3,14]. Recently, it was demonstrated a strong association between blood pressure and some oxidative stress-related parameters^[15]. Other studies show that mouse models with genetic deficient in ROS-

generating enzymes have lower blood pressure compared with wild-type counterparts^[16,17]. In addition, in cultured vascular smooth muscle cells (VSMC) and isolated arteries from hypertensive rats and humans, ROS production is enhanced, redox-dependent signaling is amplified, and antioxidant bioactivity is reduced^[18]. Classical antihypertensive agents such as β -adrenergic blockers, angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor antagonists, and calcium channel blockers may be mediated, in part, by decreasing vascular oxidative stress^[19,20].

Sources of ROS in vascular wall

A variety of enzymatic and non-enzymatic sources of ROS exist in blood vessels. The best characterized source of ROS is NOX. In addition to NOX, several other enzymes may contribute to ROS generation, including xanthine oxidase, NO synthase and the mitochondrion.

NOX: NOX is the primary biochemical source of ROS in the vasculature, particularly of superoxide. The kidney and vasculature are rich sources of NOX-derived ROS, which under pathological conditions play an important role in renal dysfunction and vascular damage^[12,21]. This system catalyses the reduction of molecular oxygen by NADPH as electron donor, thus generating superoxide. NOX is up-regulated in hypertension by humoral and mechanical signals. AT-II is the most studied stimulus, but ET-1 and UT-II may also participate in activation of NOX, thereby resulting in increased ROS. Likely the most well-known function of NOX derived superoxide is inactivation of NO to form peroxynitrite, leading to impaired endothelium dependent vasodilation and uncoupling of endothelial nitric oxide synthase (eNOS) to produce additional superoxide^[16,22]. In the vasculature, NOX activation has been strongly associated with hypertension^[23].

Uncoupled endothelial NO synthase: The primary function of eNOS is NO production which regulates vasodilation. Nevertheless, L-arginine and tetrahydrobiopterin (BH₄)-two essential cofactors for its action-deficiency or oxidation are associated with uncoupling of the L-arginine-NO pathway resulting in decreased formation of NO, and increased eNOS-mediated generation of superoxide. NOX is the initial source of ROS. Superoxide combines with NO, which is synthesized by eNOS, to form peroxynitrite^[24]. In turn, peroxynitrite oxidizes and destabilizes eNOS to produce more superoxide^[22,25]. Superoxide also leads to BH₄ oxidation (in fact, BH₄ is highly sensitive to oxidation), which promotes eNOS uncoupling and ROS production.

Xanthine oxidase: Xanthine oxidase is also an important source for oxygen free radical present in the vascular endothelium^[23,26]. It catalyzes the last two steps of purine metabolism. During this process oxygen is reduced to superoxide. There is evidence suggesting involvement of this enzyme in hypertension. Spontaneously hypertensive rats demonstrate elevated levels of endothelial xanthine

oxidase and increased ROS production, which is associated with increased arteriolar tone^[21]. In addition to effects on the vasculature, xanthine oxidase may play a role in end-organ damage in hypertension^[27].

Mitochondrion: The mitochondrion is a major source and target of ROS. Part of the superoxide produced in the intermembrane space may be carried to the cytoplasm^[28]. Ubiquinol or coenzyme Q is a source of superoxide when partially reduced (semiquinone form) and an antioxidant when fully reduced^[29]. Complex I produces most of the superoxide generated by mammalian mitochondria *in vitro*. Complexes II and IV are not normally significant sites of ROS production. Mild uncoupling very effectively decreases the high superoxide production that occurs from complex I. A reduction in antioxidant enzymatic activity in patients with hypertension has been reported^[30].

Role of the vascular wall components

The endothelium senses mechanical and hormonal stimuli. In response, it releases agents that regulate vasomotor function. There is no doubt that endothelium plays a regulatory and protective role by generating vasorelaxing substances. Under some pathophysiological circumstances, endothelium derived vasoconstricting factors, such as ET-1, AT-II, UT-II, superoxide anions, vasoconstrictor prostaglandins and thromboxane A₂, can be released and contribute to the paradoxical vasoconstrictor effects. VSMC are fit not only for short-term regulation of the blood vessel diameter and therefore of blood pressure, but also for long-term adaptation, *via* structural remodeling. ROS mediate many of these pathophysiological processes. The adventitia can contribute to hypertension by either reducing NO bioavailability or participating in vascular remodeling through ROS.

Role of vascular hormones and factors

NO: NO is known to play an important role as a key paracrine regulator of vascular tone. Physiologically, NO inhibits leukocyte-endothelial cell adhesion, VSMC proliferation and migration, and platelet aggregation to maintain the health of the vascular endothelium. Therefore it has many beneficial effects. The decrease in bioavailability of NO in the vasculature reduces vasodilatory capacity and contributes to hypertension. The enzyme that catalyzes the formation of NO from oxygen and arginine is NOS, which in fact is a whole family of enzymes. eNOS is the predominant NOS isoform in the vessel wall. Receptor-mediated agonist stimulation leads to rapid enzyme activation. In addition, shear stress and allosteric modulators are also an important modulator of eNOS activity^[31]. Except the vasorelaxing and antiproliferative properties *per se*, NO plays an important role in antagonizing the effects of AT-II, endothelins and ROS. Nitric oxide diffuses as a gas to the adjacent smooth muscle where it interacts with different receptor molecules such as the soluble guanylyl cyclase. It is accepted

that the normal production of NO plays a crucial role in the maintenance of the physiologic conditions within the cardiovascular system. L-arginine, a substrate for eNOS, seems to be promising in preserving NO formation. However, L-arginine failed to prevent blood pressure increase and left ventricle remodeling due to chronic treatment with L-methyl ester of N-nitro-L-arginin (NAME), an inhibitor of eNOS^[32]. The ACE inhibitor captopril completely prevented NO-deficient hypertension, yet without improving NOS activity. NO also has an ACE down-regulation effect. Thiols protect NO from oxidation by scavenging oxygen-free radicals and by forming nitrosothiols, both effects prolonging NO half-life and duration of NO action^[33,34]. Reduced NO levels can be attributed to elevated levels of ROS. Superoxide combines with NO to form peroxynitrite that oxidizes BH₄ and destabilizes eNOS to produce more superoxide^[22,24,25] thus further enhancing the development of oxidative stress. The balance between NO and AT-II in the vasomotor centers seems to play important role in the regulation of the sympathetic tone.

Renin-angiotensin system: The renin-angiotensin system plays a key role in the development of cardiovascular disease. AT-II is a potent vasoactive peptide that can be formed in vascular beds rich in ACE. When AT-II production increases above normal levels, it induces vascular remodeling and endothelial dysfunction in association with increases in levels of blood pressure. As a potent activator of NOX, AT-II contributes to the production of ROS^[35,36]. In rats and mice made hypertensive by AT-II infusion, expression of NOX subunits, oxidase activity, and generation of ROS are all increased^[37]. AT-II not only increases NOX activity but also upregulates superoxide dismutase activity, possibly to compensate for the increased ROS. In situations where this compensatory effect is efficient, ROS levels may appear normal even in the face of prooxidant. However, when ROS production becomes overwhelming, compensatory mechanisms are inadequate and pathophysiological consequences ensue^[38]. Captopril and enalapril prevented blood pressure rise in young spontaneously hypertensive rats inhibiting ACE. Captopril, probably due to the antioxidant role of its thiol group, had more effective hypotensive effect than enalapril^[39,40]. In contrast, NO not solely antagonizes the effects of AT-II on vascular tone, cell growth, and renal sodium excretion, but also down-regulates the synthesis of ACE and AT₁ receptors. On the other hand, ACE inhibition up-regulates eNOS expression. The ability of AT-II to induce endothelial dysfunction is also due to its ability to down-regulate soluble guanylyl cyclase, thereby leading to impaired NO/cGMP signaling. Recently, it has been proposed that Ca²⁺/calmodulin-dependent protein kinase II is an important molecule linking AT-II, ROS and cardiovascular pathological conditions^[41].

Acetylcholine: In vascular vessels, acetylcholine induces endothelium-dependent dilation *via* production of endo-

thelial factors, mainly NO. NO then diffuses to underlying VSMC, where it induces vascular smooth muscle cell relaxation. The diminution in NO bioavailability will lead to significantly reduced acetylcholine-mediated vasodilation^[39,40]. The consequence of an overall increase in ROS is a reduce bioavailability of NO.

ET-1: Endothelins are potent vasoconstrictor isopeptides produced in different vascular tissues, including vascular endothelium. ET-1 is the main endothelin generated by the endothelium and the most important in the cardiovascular system. When ET-1 is administered in large concentrations, it behaves as a potent vasoconstrictor capable of exerting an array of physiological effects, including the potential to alter arterial pressure. ET-1 mediates its effects through two receptors, ET_A and ET_B. ET_A mediates contractions *via* activation of NOX, xanthine oxidase, lipoxygenase, uncoupled NO synthase, and mitochondrial respiratory chain enzymes. The ET_B induces relaxation on endothelial cells^[42]. Many factors that normally stimulate ET-1 synthesis, (*e.g.*, thrombin, AT- II) also cause the release of vasodilators such as prostacyclin (PGI₂) and/or NO, which oppose the vasoconstricting action of ET-1. It was reported that essential hypertension is characterized by increased ET-1 vasoconstrictor tone, an effect that seems to be dependent on decreased endothelial ET_B-mediated NO production attributable to the impaired NO bioavailability.

UT- II: UT- II is a potent vasoactive peptide^[43], indeed the most potent vasoconstrictor identified. It acts through activation of NOX. The role of UT- II in disease is not well elucidated. The constrictor response to UT- II appears to be variable and highly dependent on the vascular bed examined. Vasoconstriction is not its only effect, because UT receptors have been found in other organs^[44,45]. UT- II has also been shown to act as a potent vasodilator in some isolated vessels^[46].

Norepinephrine: VSMC is innervated primarily by the sympathetic nervous system through adrenergic receptors. Three types of adrenoceptors are present within VSMC: α_1 , α_2 and β_2 . Norepinephrine stimulates VSMC proliferation. In addition, over-expression of inducible NOS increases blood pressure *via* central activation of the sympathetic nervous system, which is mediated by an increase in oxidative stress^[5].

Prostaglandins: PGI₂, another endothelium-dependent vasodilator, relaxes the VSMC. PGI₂ is released in higher amount in response to ligand binding such as thrombin, arachidonic acid, histamine, or serotonin. The enzymes prostaglandin H₂ synthase uses arachidonic acid as a substrate, forming prostaglandin H₂. Prostaglandin H₂ is converted to vasoactive molecules, such as PGI₂. The isoform prostaglandin H₂ synthase-2 may mediate vascular dysfunction in conditions characterized by oxidative stress. Thus, peroxynitrite inhibits the enzymatic activity

of prostacyclin synthase, thereby causing impairment in the PGI₂-mediated vasodilation.

Homocysteine: This molecule may play an important role in the pathogenesis of essential hypertension^[3]. Elevated homocysteinemia diminishes the vasodilation by nitric oxide, increases oxidative stress, stimulates the proliferation of VSMC, and alters the elastic properties of the vascular wall. Thus, homocysteine contributes to elevate the blood pressure^[47]. It is also known that elevated homocysteine levels could lead to oxidant injury of the endothelium^[3]. The correction of elevated homocysteinemia by administration of vitamins B12 and B6 plus folic acid, could be a useful adjuvant therapy of hypertension^[3,48]. However, further controlled randomized trials are necessary to establish the efficacy of these therapeutic agents.

A hypothesis for the role of vascular oxidative stress in hypertension is depicted in Figure 1.

This review has discussed the importance of ROS in the vasculature and its relation to hypertension, but it is important to emphasize the evidence that hypertensive stimuli, such as high salt and AT- II, promote the production of ROS not only in the vasculature, but also in kidney and the central nervous system (CNS) and that each of these sites contributes either to hypertension or to the untoward sequels of this disease^[48].

Role of oxidative stress in kidney

Evidence proposes that ROS play a key role in the pathophysiological processes of several renal diseases; these diseases are considered to be cause and consequence of hypertension. Regarding glomerular alterations, ROS mediates lipoprotein glomerulopathy and other inflammatory glomerular lesions^[49]. A recent study demonstrates that NOX activation and production of ROS through lipid raft clustering is an important molecular mechanism triggering oxidative injury of podocytes induced by homocysteine. This may represent an early event initiating glomerulosclerosis during hyperhomocysteinemia^[50]. Concerning ROS mediated tubulointerstitial injury, one of the mechanisms is the exposure of tubular cells to low-density lipoproteins which may result in tubulointerstitial damage due to ROS production mediated by NOX^[51]. AT- II also plays a pivotal role in the progression of tubulointerstitial injury but also in obstructive nephropathy^[52,53]. It activates NOX and, subsequently, generates superoxide that leads to hypertrophy of renal tubular cells^[54].

There is evidence suggesting that a high-fat diet induces renal inflammation and aggravation of blood pressure in spontaneously hypertensive rats, *via* ROS^[55]. It is also known that the metabolic syndrome is a risk factor for chronic kidney disease (CKD) at least in part independent of diabetes and hypertension *per se*, probably mediated by ROS. Moreover, the onset and maintenance of renal damage may worsen metabolic syndrome features like hypertension, leading to potential vicious cycles^[56].

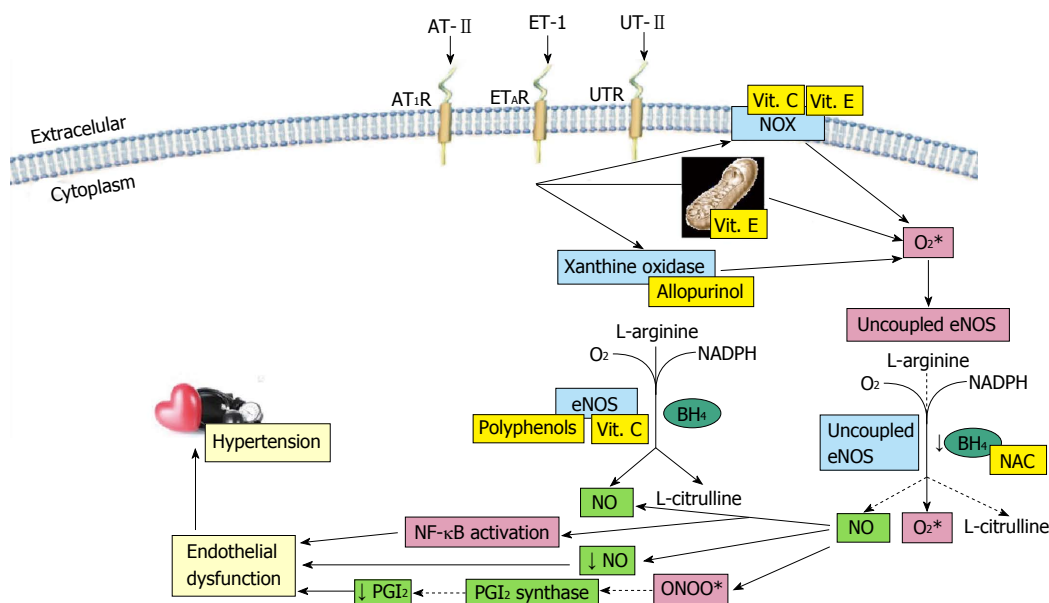


Figure 1 Schematic summary of the role of vascular oxidative stress in the pathogenesis of hypertension and the mechanisms of exogenous antioxidant accounting for anti-hypertensive effects. AT-II: Angiotensin II; AT1R: Type 1 angiotensin II receptor; ET-1: Endothelin 1; ETAR: Type A endothelin receptor; UT-II: Urotensin II; UTR: Urotensin-II receptor; NO: Nitric oxide; eNOS: Endothelial nitric oxide synthase; PGI₂: Prostacyclin; NAC: N-Acetylcysteine; NOX: NADPH oxidase; NF-κB: Nuclear factor kappa B.

There are several oxidative stress-mediated mechanisms involved in endothelial dysfunction in CKD^[57]. ROS are elevated in CKD and related to endothelium-dependent vascular reactivity and systolic blood pressure^[58]. High ROS and increased level of the endogenous asymmetric dimethylarginine (ADMA) was reported to be a novel risk factor for endothelial dysfunction^[59]. Moreover, high levels of ADMA were reported in CKD and were associated with higher intima-media thickness and cardiovascular events^[60]. In renovascular hypertension, oxidative stress in the ischemic kidney plays a major role in the maintenance of hypertension in two kidney-one clip rats^[61].

Role of oxidative stress in central nervous system

Just like the kidney and the vasculature itself, the sympathetic nervous system (SNS), regulated in the CNS, plays an important role in the pathogenesis of hypertension^[62]. Recent studies strongly suggest that central sympathetic outflow is increased in hypertension^[63]. There is also evidence that increased ROS generation in the brainstem contributes to the neural mechanisms of hypertension in hypertensive rats^[64].

The rostral ventrolateral medulla (RVLM) is the major vasomotor center and is essential for the maintenance of basal vasomotor tone^[65,66]. There are findings that strongly indicate that ROS in the RVLM is increased in stroke-prone spontaneously hypertensive rats and thereby contributes to the neural mechanisms of hypertension through activation of the SNS^[65]. The paraventricular nucleus of the hypothalamus is most likely also involved in the ROS mediated neural mechanism of hypertension^[61,67]. There is evidence that other regions of the brain are also involved in ROS mediated hypertension. These investigations suggest that increased

intracellular superoxide production in the subfornical organ is critical in the development of AT-II-induced hypertension^[68].

Antioxidants in hypertension

This section refers to the antihypertensive role of endogenous and exogenous antioxidants that have demonstrated their ability to alter the blood vessels function and to participate in the main redox reactions involved in the pathophysiology of hypertension.

Vitamin C: Vitamin C is a potent water-soluble antioxidant. On the vascular wall behaves as enzyme modulator exerting up-regulation on eNOS and down regulation of NOX^[69]. Most studies have demonstrated an inverse relationship between plasma ascorbate levels and blood pressure in both normotensive and hypertensive populations^[15]. It has been shown that treatment with antioxidants improves the vascular function and reduces the blood pressure in animal models^[70,71] and in human hypertension^[72,73]. Vitamin C may have favorable effects on vascular dilation, possibly through its antioxidant effects on NO^[74-76].

Nevertheless, there are several small and short-term clinical trials in which the effect of vitamin C supplements on blood pressure have yielded inconsistent findings^[77-82]. The lack of antihypertensive efficacy observed in studies using supplementation with vitamin C alone could be due to the decreased bioavailability of NO under conditions of oxidative stress. It was shown that these effects are mediated in part by the ability of vitamin C to protect BH₄ from oxidation and thereby increase the enzymatic activity of eNOS^[83]. In addition, this uncertain clinical beneficial effect of vitamin C *in vivo* as an antihypertensive agent could be due to the lack of

consideration of their pharmacokinetic properties. It was experimentally determined that the antihypertensive effect of vitamin C is expected to occur at a concentration by $10\mu\text{mo/L}$ ^[75], a plasma level unreachable in humans through oral administration, but that would be required to compete efficiently with the reaction of NO with superoxide. The renal ascorbic acid threshold occurs at vitamin C dose between 60 and 100 mg daily. Plasma is completely saturated at doses of 400 mg daily and higher, producing a steady-state plasma concentration of approximately $80\mu\text{mo/L}$ ^[84]. Thus, the antihypertensive effect may only be active in plasma following vitamin C infusion at high doses.

Vitamin E: This major lipid-soluble antioxidant has received considerable attention for their antioxidant potential. Epidemiological data support a role of high dietary vitamin E intake and a reduced incidence of cardiovascular disease^[57]. Increasing evidence indicates that vitamin E can act as a biological modifier independently of its antioxidant activity. Experimental evidence available shows that vitamin E is capable of dose-dependently regulating mitochondrial generation of superoxide and hydrogen peroxide.

However, intervention trials have not been convincing, with a number of studies demonstrating no beneficial effect of vitamin E on cardiovascular disease outcomes^[85-88]. Moreover, a study using supplementation with vitamin E, either as α -tocopherol or mixed tocopherols, showed a significant increase in blood pressure, pulse pressure and heart rate in individuals with type 2 diabetes^[89]. It should be noted that it is unlikely to achieve sufficiently high concentrations in the vascular microenvironment to interfere effectively with all components of oxidative stress^[90].

Association of vitamins C and E: Ascorbic acid may reduce the α -tocoperoxyl radical and may be required for beneficial vascular effects of α -tocopherol^[91]. In fact, the effect of α -tocopherol seems to be dependent on tissue saturation with vitamin C, and both vitamins may act synergistically to provide optimal conditions for endothelial NO formation^[92]. Thus, the association of vitamins C and E is expected to have an antihypertensive effect probably because this combined therapy provides a reinforcement of their individual properties through a complementary effect^[93].

Despite the biological effects of both vitamin C and E, long-term clinical trials have failed to consistently support their antihypertensive effects in patients at high cardiovascular risk. Some short-term trials have shown that supplemental antioxidant vitamin intake lowers blood pressure^[78,81,82,94] but the majority of clinical long-term trials did not find any antihypertensive effects of antioxidant vitamins. However, most of these studies lack rigorous exclusion criteria in the selection of subjects to avoid the influence of confounders^[95]. It deserves special mention that regarding cohorts included in large trials,

most subjects had irreversible cardiovascular disease.

Allopurinol: Xanthine oxidase is an important source of ROS in the vascular endothelium^[24]. It catalyzes the last two steps of purine metabolism, producing uric acid. Xanthine oxidase activity is associated with an increasing arteriolar tone and therefore, hypertension^[96,97]. Xanthine oxidase inhibitors such as allopurinol have shown marked improvements in endothelial function in various cohorts at risk of cardiovascular events. Treatment with allopurinol result in reduction of blood pressure in adolescents^[98], spontaneously hypertensive rats^[99] and patients with CKD^[100]. Nevertheless, most of the evidence so far comes from smaller mechanistic studies, and the few large randomized controlled trials have not shown significant mortality benefit using these agents^[101].

Selenium: Selenium is an essential trace element and an integral part of many proteins with catalytic and structural functions. It exerts an antioxidant function mainly in the form of selenocysteine residues, an integral constituent of ROS-detoxifying selenoenzymes, such as glutathione peroxidase (GSH-Px), thioredoxin reductases (TR) and selenoprotein P^[102]. Maintenance of full GSH-Px and TR activity by adequate dietary selenium supply has been proposed to be useful for the prevention of several cardiovascular disorders^[83]. In addition, selenium is capable of preventing the union of nuclear factor kappa B (NF- κ B) to its nuclear response elements in DNA^[103]. NF- κ B has a key role in inflammation and production of ROS. The inhibition of NF- κ B is presumed to be the result of the binding of the selenium to the essential thiols of this transcription factor^[104].

Its antioxidant properties have been documented in several trials^[103,105-110]. Selenium at low doses can provide significant protection of the human coronary artery endothelium against damage by oxidative stress^[102]. In an animal model, dietary supplementation with selenium was associated with lower levels of cardiac oxidative damage and increased antioxidant expression, as well as a reduction in disease severity and mortality in spontaneously hypertensive rats^[111]. A reduced selenium concentration in hypertensive pregnancies has been associated with a diminution of GSH-Px activity^[112]. Thus it is reasonable to say that deficiency of selenium might be an underestimated risk factor for the development of high blood pressure^[113].

N-acetylcysteine: The antioxidant N-acetylcysteine (NAC), a sulfhydryl group donor, improves renal dysfunction and decreases arterial pressure and renal injury in salt-sensitive hypertension^[114]. The inhibition of oxidative stress in hypertensive states probably contributes to the therapeutic effects of NAC, an effect likely mediated by an NO-dependent mechanism^[115]. This protective mechanism is exerted by prevention of BH₄ oxidation by the increased superoxide^[116]. In addition, this molecule can protect against oxidative damage inhibiting lipid per-

oxidation and scavenging ROS^[117,118].

Polyphenols: Polyphenols are the most abundant antioxidant in diet. They can act as ROS scavengers, iron chelators, enzyme modulators^[119,120], and possibly enhancing the production of NO^[121,122]. In humans, after the consumption of polyphenols, circulating NO concentration increases^[123]. Polyphenols also increase glutathione, and inhibit ROS-producing enzymes such as NADPH and xanthine oxidases. These pathways lead to improved endothelial function^[124]. However, some studies have shown increased blood pressure by association of polyphenols with vitamin C^[125].

Diet: There is sufficient evidence to suggest that dietary approaches may help to prevent and control high blood pressure. There are dietary approaches regarding the prevention and management of hypertension: *i.e.*, moderate use of sodium, alcohol, an increased potassium intake, plant fibers, calcium, and foods like salmon, nuts, wine, among others^[126]. In a Mediterranean population with an elevated fat consumption, a high fruit and vegetable intake is inversely associated with blood pressure levels^[127]. Short-term studies indicate that specialized diets may prevent or ameliorate mild hypertension, most notable are the Dietary Approaches to Stop Hypertension (DASH) diet, which is high in fruits, vegetables, and low-fat dairy products^[128]. It has been reported that a low sodium DASH diet is effective in reducing blood pressure in hypertensive patients, particularly in those taking antihypertensive medications^[129]. In addition, DASH diet had significant beneficial effects on cardiovascular risk^[130-132]. In overweight or obese persons with above-normal blood pressure, the addition of exercise and weight loss to the DASH diet resulted in even larger blood pressure reductions, greater improvements in vascular and autonomic function, and reduced left ventricular mass^[133,134].

Pharmacological attempts aimed to reduce blood pressure with antioxidant therapies

Recent advances in understanding the complexity of redox signaling in the vascular system points to a central role of oxidative stress in the pathogenesis of vascular dysfunction. This is how hypertension is associated with impaired endothelium-dependent vasodilation with inactivation of endothelium-derived nitric oxide by oxygen free radicals. In this regard, it has arisen a growing interest concerning the therapeutic possibilities to target ROS in the management of essential hypertension.

In support of this view, epidemiological studies suggest that individuals with higher antioxidant intake have reduced cardiovascular risk. In fact, population-based observational studies have shown an inverse association between diverse plasma antioxidant concentrations, obtained by dietary intake, with blood pressure^[113,135], providing justification for trials evaluating antioxidant supplementation as adjunct anti-hypertensive therapy favoring blood pressure reduction.

Antihypertensive effects of vitamin C were hypothesized as early as 1946^[136], and it has been proven that vitamin C enhances endothelial function through effects on nitric oxide production^[75]. Most studies have demonstrated an inverse relation between vitamin C plasma levels and blood pressure, in normotensive and hypertensive populations^[27,137]. However, evidence for blood pressure-lowering effects of vitamin C in clinical trials is still inconsistent. Nevertheless, laboratory^[138,139] and human studies^[140,141] have established biological plausibility for a clinical use of antioxidants concerning hypertension.

Taddei *et al.*^[142] made one of the first trials in 1998, where patients with essential hypertension received intra-arterial infusion of vitamin C, and showing that in essential hypertensive patients vitamin C significantly increased the vasodilation effect of the muscarinic agonist, acetylcholine, indicating that antioxidant vitamin C improves endothelium-dependent vasodilation in hypertensive patients. As ratifying evidence, On *et al.*^[143] in 2002 conducted a study that achieved similar results on endothelium dysfunction, using vitamin C as an adjunctive therapy to Amlodipine.

Despite the evidence points to the use of vitamin C as an adjunct in the treatment on essential hypertension, there is still lack of long-term studies that support its use. Up to date there are few trials that have used chronic supplementation. In a small randomized, double-blind controlled trial^[144], patients were followed for 8 mo and were randomized to receive 500, 1000 and 2000 mg of vitamin C once daily. Results of this study showed a significant diminution of both, mean systolic blood pressure and diastolic blood pressure, with no differences between the increasing doses of vitamin C. Additionally, these effects were only seen during the first month of supplementation, suggesting only a short term benefit. Besides this, other trial aimed to study the effects of ascorbic acid on ambulatory blood pressure in elderly patients, showing that chronic supplementation of vitamin C (600 mg/daily) markedly reduced systolic blood pressure and pulse pressure in ambulatory patients^[145]. Furthermore, this was accompanied by decreases of oxidative stress biomarkers such as levels of 8-isoprostane and malondialdehyde.

The strongest evidence of the possible role of vitamin C on hypertension treatment was handed by a recent meta-analysis that included twenty-nine trials, concluding that in short-term trials, vitamin C supplementation reduces systolic and diastolic blood pressure. But it also highlights that long-term trials on the effects of vitamin C on blood pressure and clinical events are still needed to elucidate its true benefit^[146].

Because supplementation made only with vitamin C has achieved inconsistent clinical outcomes, the scientific rational approach has led to the suggestion that the combined intake of antioxidants could achieve better clinical results. To prove this concept, a small randomized double-blind placebo-controlled trial was made including 38 subjects, 21 hypertensive and 17 normotensive^[81]. Groups

Table 1 Clinical trials accounting for strategies using antioxidants in essential hypertension

Details of Study	Study	n	Results	Ref.
Intrabrachial vitamin C (2.4 mg/100 mL forearm tissue per minute)	Randomized placebo-controlled trial	28	In hypertensive patients but not in control subjects, vitamin C increased the impaired vasodilation to acetylcholine	[141]
Intra-arterial infusion of vitamin C at 24 mg/min for 10 min	Randomized trial	16	Forearm blood flow response to acetylcholine was significantly enhanced with intra-arterial infusion of vitamin C in hypertensive group before antihypertensive treatment	[142]
Oral administration of 500, 1000 or 2000 mg of vitamin C once daily	Randomized double-blind, placebo-controlled trial	31	Significant diminution of mean systolic blood pressure and diastolic blood pressure, with no differences between the increasing doses of vitamin C	[143]
Chronic supplementation of 600 mg/daily of vitamin C	Randomized placebo-controlled trial	24	Reduced systolic blood pressure and pulse pressure in ambulatory elderly patients, but not in adult group	[144]
Included 29 trials of vitamin C supplementation	Meta-analysis	-	In short-term trials, vitamin C supplementation reduces systolic and diastolic blood pressure	[145]
Crossover design Placebo or antioxidant combination: 200 mg zinc 500 mg vitamin C 600 mg vitamin E 30 mg of β -carotene	Randomized double-blind placebo-controlled trial	38	Combined therapy of antioxidants showed that systolic blood pressure fell significantly on hypertensive subjects	[80]
Oral supplementation: 1 g vitamin C 400 UI vitamin E or Placebo for 8 wk	Randomized double-blind, placebo-controlled, crossover study	30	Treatment with vitamins C and E has beneficial effects on endothelium-dependent vasodilation in untreated essential hypertensive patients	[153]
Oral supplementation: 1 g vitamin C 400 UI vitamin E or Placebo for 8 wk	Randomized double-blind placebo-controlled trial	110	Specific association between oxidative-stress related parameters and blood pressure Patients with essential hypertension had significantly lower systolic, diastolic and mean arterial blood pressure	[146]
ACEI plus NAC (600 mg three times a day) or ACEI only	Randomized controlled trial, crossover study	18	Significant decrease in systolic and diastolic blood pressure with the combination of ACEI and NAC compared to ACEI-only	[147]
Standard therapy or Melatonin plus antihypertensive standard therapy	Randomized controlled trial	170	Combined therapy had better outcomes than standard therapy alone on essential hypertensive patients	[148]
Intra-arterial administration: NAC (48 g/min) or vitamin C (18 mg/min)	Cross-over randomized study	30	The intra-arterial administration of NAC had no effect on endothelium-dependent vasodilation Intra-arterial vitamin C improved endothelium-dependent vasodilation	[151]
Coenzyme Q10, 100 mg twice daily or placebo	Randomized, double-blind, placebo-controlled crossover study	30	There was not statistically significant reductions systolic or diastolic blood pressure	[150]
Vitamin C supplement daily Either 50 mg or 500 mg, for 5 yr	Randomized double-blind controlled trial	244	Neither systolic nor diastolic blood pressure was significantly related with the serum vitamin C concentration	[152]

ACEI: Angiotensin-converting enzyme inhibitors; NAC: N-Acetylcysteine.

were assigned to receive in a crossover design placebo or a combination of antioxidants consisting of zinc, ascorbic acid, alpha-tocopherol and beta-carotene daily for 8 wk. Although it was a short-term following, this combined therapy of antioxidants showed that systolic blood pressure fell significantly on hypertensive subjects while been on the antioxidant phase compared with placebo. Additional evidence was given by another study aimed to evaluate the effect of short-term combined treatment with antioxidants vitamin C and E^[95]: 30 essential hypertensive patients were assigned randomly either to vitamin C plus vitamin E or placebo for 8 wk. Results showed that parameters of flow-mediated dilation of the brachial artery and central pulse wave velocity were significantly improved after antioxidant supplementation, concluding that treatment with vitamins C and E has beneficial effects on endothelium-dependent vasodilation in untreated essential hypertensive patients.

Following the same consideration, recently a randomized double-blind placebo-controlled clinical trial was conducted to test the hypothesis that oral administration of vitamin C and E together causes decrease in blood pressure in patients with mild-to-moderate essential hypertension, 110 men with recent diagnosis of grade 1 essential hypertension were randomly assigned to receive either vitamin C (1 gr) plus Vitamin E (400 UI) daily or placebo for 8 wk. The results of this study, showed for the first time a specific association between oxidative-stress related parameters and blood pressure. Following administration of vitamins C plus E, patients with essential hypertension had significantly lower systolic, diastolic and mean arterial blood pressure^[147].

According to the theoretical possibility of the role of antioxidants, further trials have been performed using different compounds with antioxidant activity. This is how Barrios *et al*^[148] in 2002 conducted a patient cross-

over study with the aim to investigate the potential effect of NAC added to the Angiotensin-converting enzyme inhibitors (ACEI) antihypertensive action. A significant decrease in systolic and diastolic blood pressure was achieved with the combination of ACEI and NAC compared to ACEI-only period^[148].

A more recent study tried the use of melatonin to evaluate its effectiveness as an adjunct for a combined treatment adding melatonin to standard anti-hypertensive drugs^[149]. This study showed that combined therapy had better outcomes than standard therapy alone on essential hypertensive patients.

Although there is objective compelling evidence supporting the use of antioxidants in the management of hypertensive patients, there are also several studies that have not shown beneficial effects. As an example: Vitamin E^[150], Coenzyme Q10^[151], NAC^[152] and vitamin C^[153] have failed to obtain beneficial effects on clinical settings.

A summary of the antioxidant approaches as clinical interventions on essential hypertension is presented on Table 1.

CONCLUSION

There is considerable evidence supporting the view that oxidative stress is involved in the pathophysiology of hypertension. ROS are mediators of the major physiological vasoconstrictors, increasing intracellular calcium concentration. In addition, superoxide reduces the bioavailability of NO and enhances superoxide production *via* uncoupled eNOS, further enhancing oxidative stress, a major factor of hypertension.

Antioxidant therapy can curtail the development of hypertension in animal models, but remains controversial in humans. Possible confounding factors in patients include co-existing pathologies and treatments, lack of selection of treatments according to ROS levels, among others. However, the dietary intake of antioxidants and polyphenols could have an effect in the primary prevention or reduction of hypertension. Despite existing molecular basis and *in-vitro* evidence supports the use of diverse antioxidants, clinical evidence continues to be controversial. It is necessary to collect efforts in performing basic/clinical trials that augment the current, which could eventually help to elucidate the role of antioxidants as novel therapy for essential hypertension. Also available data lead us to think that antioxidants may not play the same role in different stages of disease, suggesting that supplementation could be only beneficial during the phase of endothelial dysfunction, which precedes an established vascular damage. In this setting antioxidants would be more likely to have a role on early stages of hypertension with the potential to reverse or counteract deleterious effects of ROS. In contrast, it should not be expected an anti-hypertensive effect in patients having an advanced state of cardiovascular disease, in which chronic damaging effects of oxidative stress may be unreachable for antioxidant approach.

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WJC 6th Anniversary Special Issues (2): Coronary artery disease

G-protein-coupled estrogen receptor as a new therapeutic target for treating coronary artery disease

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Abstract

Coronary heart disease (CHD) continues to be the greatest mortality risk factor in the developed world. Estrogens are recognized to have great therapeutic potential to treat CHD and other cardiovascular diseases; however, a significant array of potentially debilitating side effects continues to limit their use. Moreover, recent clinical trials have indicated that long-term postmenopausal estrogen therapy may actually be detrimental to cardiovascular health. An exciting new development is the finding that the more recently discovered G-protein-coupled estrogen receptor (GPER) is expressed in coronary arteries-both in coronary endothelium and in smooth muscle within the vascular wall. Accumulating evidence indicates that GPER activation dilates coronary arteries and can also inhibit the proliferation and migration of coronary smooth muscle cells.

Thus, selective GPER activation has the potential to increase coronary blood flow and possibly limit the debilitating consequences of coronary atherosclerotic disease. This review will highlight what is currently known regarding the impact of GPER activation on coronary arteries and the potential signaling mechanisms stimulated by GPER agonists in these vessels. A thorough understanding of GPER function in coronary arteries may promote the development of new therapies that would help alleviate CHD, while limiting the potentially dangerous side effects of estrogen therapy.

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Key words: G-protein-coupled estrogen receptor; Coronary arteries; G-1; Atherosclerosis; Estrogen

Core tip: A continuing controversy in cardiology is the impact of estrogen on coronary arteries. This review provides the latest information on the discovery of a novel estrogen receptor in these vessels: the G-protein-coupled estrogen receptor (GPER). Recent findings demonstrate that GPER activation induces coronary artery relaxation and attenuates the proliferation and migration of coronary smooth muscle cells. Thus, GPER appears to be a promising, novel pharmacological target that could increase coronary blood flow in diseased arteries and prevent or reverse the progression of coronary atherosclerotic disease, and do so with potentially fewer dangerous side effects associated with traditional estrogen therapy.

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INTRODUCTION

Evidence that ovarian hormones can influence blood flow in other vascular beds was provided well over a century ago^[1]; yet the overall impact of estrogens on cardiovascular function is still quite controversial. For example, there are conflicting reports regarding the potential therapeutic uses of estrogens to alleviate or prevent cardiovascular disease, as clinical trials have found both preventative^[2] and deleterious^[3] effects of conjugated equine estrogens (a mixture of at least 10 different estrogens) on coronary heart disease (CHD) in menopausal women. More directly, 17 β -estradiol (E2), the predominant and most potent circulating estrogen in premenopausal women, has clearly defined effects on blood vessel function. For example, numerous studies have demonstrated that estradiol dilates coronary arteries from humans or other species, and does so by specifically targeting both vascular smooth muscle (VSM) and endothelial cells. Estradiol increases coronary blood flow in intact hearts^[4,5], dilates coronary arteries *in situ*^[6-8], and relaxes coronary arteries isolated *in vitro*^[9-12]. Such studies strongly suggest an inherent therapeutic potential of E2 for alleviating or possibly even preventing coronary insufficiency. As a caution, however, it should be noted that we have demonstrated that E2 can also constrict coronary arteries under experimental^[13] or pathological^[14] conditions *via* a non-genomic mechanism. Thus, E2, a “well-known vasodilator”, is actually a powerful, multifunctional vasoactive hormone whose signaling mechanisms are heterogeneous and complicated, and whose overall physiological effect on coronary arteries apparently depends upon the biochemical disposition of cells located in the vascular wall.

In addition to directly modulating coronary artery function, estrogens may also slow the progression of coronary atherosclerotic disease. Young women are normally protected from significant atherosclerotic plaque accumulation in coronary arteries. Menopause, however, brings unhealthy changes in plasma lipoproteins [*i.e.*, increased low-density lipoproteins (LDLs), and decreased high-density lipoproteins (HDLs), respectively], whereas postmenopausal estrogen replacement therapy (ERT) reverses these potentially harmful changes by decreasing LDL and increasing HDL^[15-17]. More specifically, the phenolic ring structure of estrogens appears to exert an antioxidant effect that may attenuate oxidation of lipids^[18,19] and LDLs^[20-22], and it is oxidized LDLs are accumulated by macrophages in the early stages of atherosclerosis leading to foam cell formation and atherogenesis. Further, E2 can lower the activity and expression of vascular NADPH oxidase, a potent source of reactive oxygen species^[23-25]. Thus, there is increasing evidence that an antioxidant effect of estrogen may attenuate the development of coronary atherosclerosis to help preserve optimal cardiac function throughout a woman's reproductive years^[26].

One might expect oxidant stress to increase during menopause as the antioxidant influence of estrogen begins to wane. Indeed, menopausal women do exhibit greater levels of oxidative stress compared to women of

childbearing age^[27]. In light of the demonstrated beneficial effects of E2 on plasma lipoproteins, it is puzzling that recent clinical trials continue to indicate a mostly deleterious effect of long-term postmenopausal hormone therapy on cardiovascular health. A potential reason for this apparent contradiction is that ERT, while reducing total LDL cholesterol level, does not reduce the number of LDL particles—which, become smaller, therefore more atherogenic^[28]. In addition, we have demonstrated that E2 can actually promote oxidative stress in coronary arteries by enhancing the activity of uncoupled nitric oxide synthase expressed in VSM cells^[13]. Thus, it seems likely that the influence of estrogens on cardiovascular health cannot be explained solely by an antioxidant effect on plasma lipids or blood vessels.

In summary, there is convincing evidence that estrogens can exert powerful effects on both the structure and function of coronary arteries, and that E2 can produce both beneficial and harmful effects on cardiovascular function. As our appreciation of estrogen grows, so should the potential to develop estrogen-like compounds as novel therapeutic agents to prevent or treat CHD. The current challenge remains to fully elucidate the cellular/molecular basis of estrogen action on coronary arteries. At present, however, our understanding of these mechanisms is far from complete, and is at times quite controversial. An important first step is to understand the nature of the specific estrogen receptor molecules that bind E2 and thereby initiate the complicated process of estrogen signaling in coronary arteries.

G-PROTEIN-COUPLED ESTROGEN RECEPTOR AND CORONARY ARTERY TONE

For years it was believed that E2 action on coronary arteries was mediated only *via* activation of one or both of the “classic” estrogen receptors (ER), ER α or ER β . For example, both ERs are expressed in human coronary artery smooth muscle cells (CASMC); but it is ER α that appears to play a great role in mediating acute responses to E2 in these cells *via* increased nitric oxide (NO) generation^[29]. Similarly, porcine coronary arteries were relaxed *via* a NO-dependent mechanism *in vitro* by an ER α -selective agonist, whereas an ER β -selective agonist appeared to induce an NO-independent relaxation response^[30]. It is the ER α subtype that helps protect against ischemia/reperfusion injury in rabbit hearts^[31], whereas ER β did not impact ischemic tolerance significantly^[32]. In addition, optimal functioning of coronary artery endothelial cells is abrogated in mice lacking expression of ER α ^[33]. On the other hand, studies of coronary arteries obtained from human females indicated that it was ER β , which was associated with coronary calcification and atherosclerosis, not ER α ^[34]. These studies suggest that although ER α and ER β are both expressed in coronary arteries, it is ER α that may play the greater role in an acute vasodilatory response to E2 and possibly cardio-

protection as well.

It is the dependency of estrogen on ER α and ER β activation that has limited the potential use of estrogen as a therapeutic agent to alleviate coronary artery dysfunction. Estrogens are powerful endocrine hormones, and these endocrine effects (*e.g.*, secondary sex characteristics) are mediated primarily by classic ERs which are expressed in most cell types. In terms of specifically treating cardiovascular disease the need is to pharmacologically mimic the beneficial effects of estrogens on coronary arteries while minimizing the oftentimes unwanted endocrine side effects in other tissues. Selective ER modulators (SERMs)-agents which act as ER agonists in some target tissues but not in others-have had some success in meeting this therapeutic ideal, but their use still falls short of providing protection against coronary artery disease without endocrine and other side effects. An exciting new development in this important field of investigation is the discovery of a novel G-protein-coupled estrogen receptor (GPR30, now GPER). GPER activation constitutes an acute, non-genomic mechanism of estrogen action that may avoid many, if not most, potential effects of estrogen on endocrine target tissues. Discovery of GPER expression and function in blood vessels has opened the potential for this receptor to serve as a novel therapeutic target.

What was often noticed, yet seldom appreciated, was that some commonly employed ER “antagonists” did not always attenuate the vasodilatory effect of E2 on coronary arteries, and sometimes actually exhibited a direct vascular action themselves. For example, ICI182,780 (fulvestrant) has long been considered a “pure” ER α /ER β antagonist, an estrogen receptor down regulator (SERD); however, this ER blocker did not significantly affect E2-induced coronary dilation or blood flow in canine hearts^[8]. These studies suggested a vasodilatory effect of E2 on coronary arteries that was not mediated by either of the classic ERs. Moreover, we^[35] and others^[36] have demonstrated that ICI182,780 can itself relax porcine coronary arteries *in vitro* (*i.e.*, an effect independent of ER α or ER β activation). In addition, ICI182,780 does not inhibit coronary artery relaxation induced by the SERM raloxifene, which acts directly on CSMC^[37]. Taken together, these findings strongly suggest that E2 (and possibly ICI182,780 and raloxifene as well) can relax coronary arteries *via* a mechanism that does not involve activation of ER α or ER β . Interestingly, it is now known that ICI182,780 and raloxifene are agonists for GPER^[36,38-40].

GPER was originally cloned in 1997 from breast cancer^[41] and other cells, including endothelial cells^[42,43], and was found to exhibit the canonical seven transmembrane spanning regions common to all G-protein-coupled receptors. GPER is expressed in the heart and in a variety of blood vessels^[44,45], and GPER mRNA and protein have been detected in porcine and human CSMC^[46-48]. Functionally, studies employing the selective GPER agonist, G-1, have indicated a vasodilatory response to G-1 stimulation. Acute treatment with G-1 relaxes rat aorta^[49], rat mesenteric arteries^[50], human internal mammary arteries^[50], and rat carotid arteries^[40,51], whereas infusion

of G-1 induces an acute decrease in arterial pressure^[50]. In addition, recent studies have demonstrated that G-1 induces an acute relaxation response in porcine coronary arteries^[36,46]. These pharmacological studies have been bolstered by use of G15, a selective GPER antagonist, which attenuates vascular relaxation induced by E2^[52] or G-1^[46,52]. Thus, there is increasingly consistent evidence obtained from both protein and pharmacological studies that activation of GPER exerts a vasodilatory effect, particularly in coronary arteries. These findings also substantiate the putative role of GPER in mediating E2-induced coronary artery relaxation.

Relatively few studies have investigated the signaling mechanisms mediating GPER-induced coronary artery relaxation, and these reveal that GPER can relax coronary arteries acutely *via* diverse mechanisms. There is good agreement that G-1 induces a maximal 30%-40% relaxation of porcine epicardial coronary arteries *in vitro* (after taking into account the effect of ethanol or dimethylsulfoxide vehicle on these vessels); however, this relaxant effect of G-1 may be endothelium-dependent or -independent. Meyer *et al.*^[36] report that activation of GPER induces a rapid relaxation of coronary arteries, and that this process is mediated by NO release from endothelial cells. In contrast, Yu *et al.*^[46] provide evidence for a direct relaxant effect of G-1 on CSMC, which is bolstered by patch-clamp experiments demonstrating that G-1 opens calcium-activated potassium (BK_{Ca}) channels in isolated porcine and human CSMC (*i.e.*, in the absence of endothelium). In this later study G-1-induced relaxation was inhibited by blocking these same potassium channels, but was not attenuated by inhibiting NO or cyclic guanosine monophosphate synthesis. Thus, there appears to be a redundancy of mechanisms mediating GPER-induced coronary artery relaxation: indirect (endothelial cells) and direct (CSMC), and may or may not involve production of NO. Because E2 is a very lipophilic hormone that easily traverses biological membrane, it is likely that both cell types mediate GPER-induced coronary artery relaxation *in vivo* (unless there is significant endothelial dysfunction in which case the direct action on CSMC should predominate). In addition, there is significant expression of aromatase in both endothelial and VSM cells allowing estrogen to be synthesized directly within the coronary artery wall (*i.e.*, independent of plasma E2 levels)^[53].

As mentioned above, raloxifene is also an agonist for GPER and stimulates an endothelium-independent relaxation of porcine coronary arteries^[37]. In this study the presence of high extracellular potassium (*i.e.*, 30 or 60 mmol) significantly reduced raloxifene-induced relaxation, as did iberiotoxin, a highly specific inhibitor BK_{Ca} channels. In contrast, inhibiting ER α or ER β with ICI182,780 had no effect on the response to raloxifene. Further patch-clamp studies demonstrated that raloxifene elevates iberiotoxin-sensitive outward currents in isolated CSMC. Thus, the endothelium-independent relaxation effect of raloxifene on porcine coronary arteries appears very similar to that of G-1 on CSMC in that stimulation of BK_{Ca} channels is likely an important effector of

GPER-induced coronary artery relaxation. In contrast to these findings, however, are previous studies indicating that ICI182,780 can inhibit raloxifene-induced, endothelium-dependent relaxation of rabbit coronary arteries^[54], also attenuates raloxifene-induced NO production from human endothelial cells^[55]. Thus, it seems likely that endothelium-dependent effects of raloxifene are mediated primarily by classic ERs, whereas the direct effects on CASC are *via* GPER.

It is interesting that the diverse mechanisms mediating acute, non-genomic estrogen-induced coronary artery relaxation often converge upon a common cellular effector-the BK_{Ca} channel. Nearly 20 years ago we first demonstrated that E2 could activate this powerful hyperpolarizing mechanism in CASC^[11], and a number of studies have since confirmed and extended the role this protein plays in mediating acute estrogen signaling in coronary arteries. An exciting new development is that there is now increasing evidence that coronary artery relaxation induced by GPER activation appears to involve BK_{Ca} activity as well. In addition to E2, single-channel and whole-cell patch-clamp studies have demonstrated that agents known to stimulate GPER, *i.e.*, G-1^[46], raloxifene^[37], tamoxifen^[10], also exert significant stimulatory effects on BK_{Ca} channel activity in isolated CASC. Although not tested directly, it is also quite likely that the endothelium-dependent coronary artery relaxation effect of G-1^[36] may also indirectly open BK_{Ca} channels in CASC *via* release of NO^[10,11,56]. These cellular studies are bolstered by the fact that ibuprofen attenuates coronary relaxation induced by either G-1^[46] or raloxifene^[37]. At present, mechanisms coupling GPER activation to BK_{Ca} channel activity remain undefined; however, there is likely to be significant therapeutic potential here. For example, identification of the BK_{Ca} channel as a molecular effector of rapid estrogen signaling in CASC could lead to the development of new agents which could specifically target these proteins in coronary arteries to provide the beneficial vasodilatory effect of E2 without the substantial endocrine side effects of hormone treatment.

GPER AND CORONARY ARTERY CELL PROLIFERATION

In healthy arteries CASC retain a contractile phenotype and are localized in the medial layer; however, intimal injury (*e.g.*, atherosclerosis, angioplasty) causes CASC to dedifferentiate, lose their contractile phenotype, and proliferate^[57,58]. Dedifferentiated CASC can then migrate into the intimal region and contribute to the narrowing of the coronary artery lumen. Estrogen is known to inhibit injury-induced VSM proliferation^[46,59-64], but, interestingly, genetic deletion of classic ERs does not abolish this anti-proliferative effect of E2^[65,66]. Thus, it is likely that the protective, anti-proliferative effect of estrogens is due, at least in part, to activation of another ER-quite possibly GPER-in coronary arteries.

We recently reported that stimulation of GPER by G-1

inhibits proliferation of human and porcine CASC^[47]. In this study we found that 24-h exposure of primary porcine CASC to G-1 inhibited serum-induced cell growth *via* repression of cell cycle progression. Further, we found that G-1 completely inhibited CASC migration, and this inhibitory effect was attenuated by G-15. Similarly, Haas *et al.*^[50] found that G-1 decreased proliferation of human umbilical vein VSM. Further, VSM proliferation, assessed by measuring the media-to-lumen ratio, in murine resistance vessels was significantly increased in animals lacking the GPER gene^[67]. Thus, it is very likely that GPER helps maintain VSM cells in a differentiated, contractile phenotype, and may thereby help retard the development of atherosclerotic buildup in the vascular intima.

Estrogen is also known to regulate the proliferation of vascular endothelial cells, and, specifically, can influence endothelial cell growth and re-endothelialization^[68]. For example, direct delivery of E2 promotes reendothelialization and endothelial nitric oxide synthase expression in coronary arteries after damage due to coronary angioplasty^[69]. In addition to this protective effect that may promote healing of endothelial damage, there is also evidence that GPER may prevent excessive proliferation of endothelial cells. G-1 reduces proliferation, DNA synthesis, and number of microvascular endothelial cells^[70]. These studies suggest that an important role of GPER may be to provide an optimal balance for the effects of E2 on endothelial cell proliferation, and thereby prevent excessive endothelial cell proliferation; for instance, as occurs in tumor-associated angiogenesis.

The mechanism(s) of how GPER attenuates vascular cell growth remain to be elucidated, although several lines of evidence point to specific alterations in mitogenic signaling pathway such as extracellular signal-regulated protein kinases (ERKs) and protein kinase B (Akt). For example, E2 has been shown to phosphorylate ERK-1 and ERK-2 in breast cancer cells expressing GPER^[71], thus enhancing cell proliferation. In contrast, we recently reported that GPER activation decreases phosphorylation of ERK1/2 and Akt activity in human and porcine CASC^[47], thus suppressing proliferation. This decreased kinase activity was consistent with a similar inhibitory effect of GPER stimulation on ERK1/2 activity in breast cancer cells^[72]. Further, Gros *et al.*^[45] reported that E2 enhanced apoptosis in rat aortic VSM cells in which GPER was overexpressed, and did so in an ERK1/2-dependent manner. GPER overexpression altered downstream signaling from protein kinase A to a pertussis toxin-sensitive pathway which increased Akt phosphorylation and ERK1/2 activation, resulting in VSM cell apoptosis. In these VSM cells, G-1 stimulated ERK1/2 phosphorylation; however, other GPER agonists (*i.e.*, tamoxifen, ICI182,780) failed to do so. These studies indicate that E2 can induce cell apoptosis *via* GPER signaling; however, the signaling mechanisms underlying this effect are complicated and require further study. A summary of the currently known effects of GPER activation is presented in Table 1 and the proposed mechanisms mediating the effects of GPER activation in coronary arteries is sum-

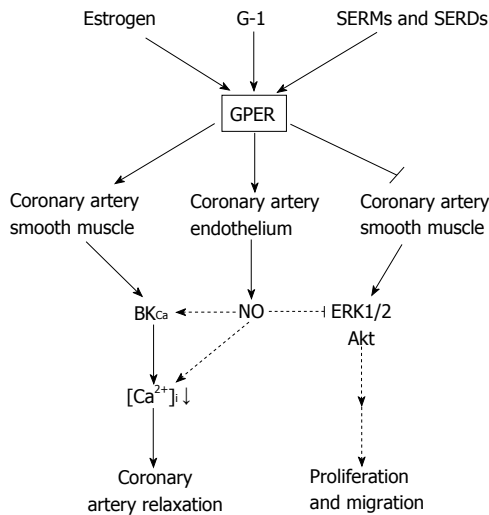


Figure 1 Summary of proposed mechanisms mediating the effects of G-protein-coupled estrogen receptor activation in coronary arteries. GPER is activated by 17 β -estradiol and the selective agonist, G-1. In addition, selective estrogen receptor modulators (e.g., raloxifene, tamoxifen) and selective estrogen receptor down regulators (e.g., ICI182,780) also appear to be agonists for GPER. GPER activation induces an endothelium-independent relaxation of coronary artery smooth muscle mediated by the large-conductance, calcium-activated potassium channel. In addition, GPER activation can stimulate release of NO from coronary endothelial cells to relax these arteries. Besides this vasodilatory effect, GPER activation can attenuate proliferation and migration of coronary artery smooth muscle cells by inhibiting signaling via the ERK1/2 and Akt pathways. GPER: G-protein-coupled estrogen receptor; SERMs: Selective estrogen receptor modulators; SERD: Estrogen receptor down regulator; ERK: Extracellular signal-regulated protein kinase.

marized in Figure 1.

GPER: A NOVEL THERAPEUTIC TARGET FOR CORONARY ARTERY DISEASE

The first rule of medical practice is to “do no harm”. Despite the considerable therapeutic potential of estrogen and estrogen-like compounds, fear of potentially dangerous ancillary effects continues to limit their usage. A primary obstacle to overcome is the pleiotropic effects of E2 on a wide diversity of tissues, most of which express one or more classes of ERs. For several years an important goal was to define the levels of ER expression in target tissues, and then deliver a receptor- or tissue-specific agonist that would produce the desired therapeutic response with limited side effects on non-target sites. However, because of the ubiquitous expression of ERs and the fact that multiple ERs are often expressed in the same cells, this goal has not been realized to any significant extent. With the more recent discovery of GPER, pursuit of this goal has been reinvigorated. In particular, the findings that GPER is highly expressed in both coronary endothelial cells and CASC has opened the search to understand the importance of this non-genomic estrogen signaling mechanism and explore pharmacological means whereby GPER activity could be modulated for therapeutic benefit. A summary of experimental evidence suggesting possible therapeutic benefits of GPER activa-

Table 1 Primary effects of G-protein-coupled estrogen receptor activation on coronary arteries

Effect	Species	Drug
Relaxation	Porcine	G-1 ^[36,46]
		ICI182,780 ^[35,36]
		Raloxifene ^[37]
		Tamoxifen ^[73]
		Raloxifene ^[54]
Endothelial NO production	Porcine	Tamoxifen ^[74]
		G-1 ^[36]
		Raloxifene ^[54]
CASC BKCa channel opening	Porcine	Tamoxifen ^[74]
		G-1 ^[46]
		Raloxifene ^[37]
Inhibition of CASC proliferation	Human	Tamoxifen ^[10]
	Porcine	G-1 ^[46]
	Human	G-1 ^[47]
Inhibition of CASC migration	Porcine	G-1 ^[47]

CASC: Coronary artery smooth muscle cells; BKCa: G-1 opens calcium-activated potassium; NO: Nitric oxide.

Table 2 Evidence for possible therapeutic effects of G-protein-coupled estrogen receptor agonists and selective estrogen receptor modulators

	Species	Drug
Coronary artery relaxation		
Endothelium-dependent, <i>in vitro</i>	Porcine	G-1 ^[36]
	Rabbit	Raloxifene ^[54]
Endothelium-independent, <i>in vitro</i>	Porcine	Tamoxifen ^[73,74]
		G-1 ^[46]
Reduced cardiac ischemic injury/infarct	Rat	Raloxifene ^[37]
		G-1 ^[75,76]
Reduced cerebral ischemic injury/infarct	Mice	G-1 ^[77]
Middle cerebral artery relaxation, <i>in vitro</i>	Rat	G-1 ^[78]
Systemic artery relaxation, <i>in vitro</i>	Mice	G-1 ^[40]
		G-1 ^[49]
		G-1 ^[50]
		G-1 ^[79]
	Rat	G-1 ^[51]
		G-1 ^[52]
Reduced systemic blood pressure, infusion	Human	G-1 ^[50]
		G-1 ^[49]
Inhibit VSM cell proliferation	Porcine	G-1 ^[50]
		G-1 ^[47]
Inhibit endothelial cell proliferation	Human	G-1 ^[50]
Prevents calcium-induced increases in plasma cholesterol	Mice	G-1 ^[70]
	Rats	G-1 ^[80]

VSM: Vascular smooth muscle.

tion is presented in Table 2.

CHD continues to be the greatest mortality risk factor in the developed world. Although our understanding of the causes of CHD continues to increase, therapeutic measures to prevent and treat this serious health problem have not improved dramatically over the past several decades. Invasive procedures such as bypass grafting or balloon angioplasty have been refined, but are still routinely practiced. Pharmacological measures (e.g., nitrates, calcium channel antagonists, beta blockers) can be effective at

treating the symptoms of CHD (*e.g.*, angina pectoris), but are seldom a viable long-term option, much less a cure. Ideally, what is needed is a widely-available therapeutic agent which might slow or reverse the progression of atherosclerosis, restore endothelial function, and induce coronary vasodilation in cases where blood flow was compromised significantly; and this agent would produce these beneficial cardiac effects with few side effects on other organs. In light of current research, it is possible that activation of GPER might be a promising new approach to achieving this desired therapeutic end.

Evidence is clear that activation of GPER produces an acute (*i.e.*, in minutes) dilation of coronary arteries due to relaxation of CSMC. This action appears to be both direct (acting on and relaxing CSMC) and indirect (*via* NO release from endothelial cells), and this dual action could prove to be very important as many CHD patients have dysfunctional or damaged coronary endothelium. Thus, stimulation of GPER has the potential to induce a direct coronary artery dilation, as well as lowering afterload due to its ability to decrease peripheral vascular resistance. As a consequence of GPER activation myocardial oxygen supply should increase with increased coronary blood flow as metabolic oxygen demand declines in face of lower peripheral vascular resistance. In addition, relaxation of venous smooth muscle could lower venous return and preload, thus further lowering myocardial oxygen demand. Thus, the vasodilatory potential of GPER activation could influence a number of favorable hemodynamic parameters to alleviate the pain and risk of CHD, and could be used acutely or prophylactically. In addition, there is similar evidence that GPER activation may also reduce the risk of ischemic stroke due to dilation of cerebral arteries^[77,78], and that GPER exerts a tonic suppression of arterial tone^[79].

Although we are only beginning to understand the mechanisms whereby GPER activation influences cell proliferation, there is accumulating evidence that GPER agonists exert an anti-proliferative and anti-migratory effect on CSMC-as it does for human urothelial cells^[81] and endothelial cells^[70]. Because CSMC dedifferentiation, proliferation, intimal migration, and secretion are important steps in the process of atherogenesis, these studies strongly suggest a potentially important protective effect of GPER activation on coronary atherosclerotic disease. Further, it appears that GPER activation can also help heal intimal damage and quite possibly help restore normal function to dysfunctional coronary endothelial cells-particularly because of its ability to enhance NO synthesis and release from endothelium. These intimal effects involving NO release would likely prevent coronary vasospasm and also help to further limit CSMC proliferation/migration, as well as attenuate the formation of coronary thrombi that could precipitate an acute ischemic attack or infarction. Although the potential effects of GPER stimulation of plasma lipoproteins are as yet unknown, a recent study has reported that GPER activation prevents increases in plasma total cholesterol levels in postmenopausal women taking calcium supplements^[80].

Thus, a new and promising effect of GPER activation may be outside the vascular system to help promote optimal cardiovascular health. Clearly then, there are potentially multiple sites of action for agents that would selectively stimulate GPER and produce beneficial effects on cardiovascular function-particularly treatment of CHD.

As always, potential side effects of GPER action must be considered. Initially, however, it could be predicted that GPER stimulation might produce significantly less risk of limiting side effects compared to E2 therapy or currently prescribed estrogenic agents (*e.g.*, breast or uterine cancer, venothromboembolism). For example, raloxifene has been demonstrated to lower overall risk of cardiovascular disease or breast cancer and strengthen bones in younger postmenopausal women^[82]; however, raloxifene does not lower blood pressure in these women, and its anti-estrogen side effects (*e.g.*, hot flashes, vaginal dryness) continue to limit its use somewhat. Tamoxifen has been widely employed as a treatment for estrogen-sensitive breast tumors. As a SERM, tamoxifen can increase bone density and produce beneficial changes in plasma lipids; however, its anti-estrogenic effects can increase the risk of uterine cancer and produce many negative symptoms of menopausal^[83]. It is likely that action on classic ERs (sometimes agonistic; other times antagonistic) mediates many of the undesirable side effects of SERM action.

At present, we are unaware of any reports from clinical trials evaluating the potential of G-1 (or another GPER agonist) as a therapeutic agent. As noted above, there appears to be great potential for GPER activation to enhance cardiovascular health. These effects, particularly those on coronary arteries, appear to be mediated almost exclusively *via* GPER with little or no concomitant activation of ER α or ER β . If so, then this more specific pharmacodynamic profile should do much to help limit the potential side effects of GPER activation on targets outside the cardiovascular system. A caveat, however, is that we are only beginning to understand the impact of GPER activation and its signaling mechanisms in a diversity of cell types. Thus, caution must be exercised in promoting GPER as a therapeutic target. Nonetheless, there is a substantial cautious optimism that pharmacological targeting of this novel non-genomic estrogen signaling mechanism may finally provide a means of producing the many beneficial effects of estrogen on the cardiovascular system while eliciting fewer side effects on the reproductive and other non-cardiovascular systems that continue to limit the use of other less specific estrogenic compounds.

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WJC 6th Anniversary Special Issues (2): Coronary artery disease

Effect of genetic factors on the association between coronary artery disease and PTPN22 polymorphism

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without CAD. A similar pattern is observed in carriers of *Pro allele of p53 codon 72 with a higher proportion of *T allele carriers in non diabetic subjects with CAD as compared to other groups. A highly significant association between PTPN22 and CAD is observed in carriers of ADA₂ *2 allele with higher proportion of *T allele carriers in non diabetic subjects with CAD as compared to other group. There is a high significant correlation between the number of factors that contributes to increase the strength of association between PTPN22 *T and CAD and the proportion of *T carriers in CAD. ACP₁, p53 codon 72 and ADA are involved in immune reaction and give an important additive contribution to the strength of association between PTPN22 and CAD. This study stresses the importance of the simultaneous analysis of multiple genes functionally related to a specific disease: the approach may give important hints to understand multifactorial disorders.

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Key words: Coronary artery disease; PTPN22; Acid phosphatase locus 1; Adenosine deaminase 2; p53 codon 72

Core tip: Acid phosphatase locus 1, p53 codon 72 and adenosine deaminase have an important role in immune reactions and influence the strength of association between coronary artery disease (CAD) and PTPN22 an enzyme involved in autoimmunity. These results agree with multifactorial origin of CAD.

Abstract

PTPN22 has been previously found associated with coronary artery disease (CAD). In the present note we have studied the effect of p53 codon 72, acid phosphatase locus 1 (ACP₁) and adenosine deaminase (ADA) genetic polymorphism on the strength of association between PTPN22 and CAD. We have studied 133 non diabetic subjects with CAD, 122 non diabetic cardiovascular patients without CAD and 269 healthy blood donors. Informed written consent was obtained from all subjects and the study was approved by the Ethical Committee. A high significant association between PTPN22 and CAD is observed in carriers of *A allele of ACP₁ with a higher proportion of *T allele carriers in non diabetic subjects with CAD as compared to controls and to non diabetic subjects with cardiovascular disease

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INTRODUCTION

PTPN22 gene encodes a protein tyrosine phosphatase expressed principally in lymphoid tissue and it is also named Lyp. PTPN22 protein is involved in the control of immune system activity. The gene shows a single nucleotide polymorphism C/T at +1858 resulting in the W620 variant that is associated to autoimmune diseases. We have previously found in non diabetic subjects an association of PTPN22 with coronary artery diseases (CAD)^[1] confirming the relationship observed by Pertovaara *et al*^[2] between PTPN22 and atherosclerosis.

p53 codon 72 shows a single nucleotide substitution resulting in the presence of either arginine or proline in the aminoacid sequence. Proline variant is a stronger transcriptional activator, while the arginine variant is a stronger apoptosis inducer. The impact of this polymorphism within the context of a living organism is poorly understood but several data indicate that it is involved in immunity and inflammation by regulating STAT 1 and pro-inflammatory cytokines^[3,4]. We have recently reported a statistically significant effect of this polymorphism on the association between PTPN22 and CAD in non diabetic subjects^[5].

Acid phosphatase locus 1 shows a genetic polymorphism that controls the synthesis of a low molecular weight protein tyrosine phosphatase. The protein is composed by two isoforms called F (fast) and S (slow). The polymorphism is due to the presence of three codominant alleles *A, *B and *C at an autosomic locus. The corresponding six genotypes show an increasing enzymatic activity in the order *A/*A < *A/*B < *B/*B ≤ *A/*C < *B/*C < *C/*C^[6]. The enzyme dephosphorylate a negative regulatory phosphorylation site of the ZAP70 tyrosine kinase in T cells that leads to increased activation of the kinase resulting in enhanced signaling from T-cell antigen receptor^[7]. This suggests that acid phosphatase locus 1 (ACP₁) could have an important role in immune functions. An association between ACP₁ and CAD has been reported^[8].

Adenosine deaminase (ADA) structural gene consists of 12 exons distributed in approximately 32 kb of DNA on chromosome 20^[9]. A number of differences among normal sequences have been found within exonic and intronic regions of the gene^[10]. The enzyme contributes to control the concentration of adenosine that in turn regulates T cell activation with important effects on immune reactions. As ectoenzyme ADA acts as a costimulatory molecule that facilitates specific signaling events in various cell types^[11].

We have studied three intragenic ADA polymorphisms (PCRP_s). The three PCRP_s spanning over about 28 kb have a known molecular basis and include the presence/absence of a Taq I site (ADA₁) (nt 4050-4053-exons 1), of Pst I site (ADA₂) (nt 19465-19470, intron 2) and a Mlu NI site (ADA₆) (nt 31230-31235, exon 6)^[10]. In non diabetic subjects with CAD a preliminary analysis of association of PTPN22 with the three ADA locus has revealed a statistically significant association with ADA₂

locus.

In the present note we have examined the cooperative effects of ACP₁, p53 codon 72 and ADA₂ genetic polymorphisms on the association of PTPN22 and CAD in non diabetic subjects.

EMPIRICAL STUDY

PTPN22 and ACP₁ genotype were determined in 133 non diabetic subjects admitted to hospital for CAD, in 122 non diabetic cardiovascular patients without CAD and in 269 healthy blood donors. PTPN22 and p53 codon 72 genotype were determined in 129 non diabetic subjects with CAD, in 117 non diabetic admitted for cardiovascular disease without CAD and in 256 healthy blood donors. PTPN22 and ADA₂ genotypes were determined in 132 non diabetic subjects with CAD, 121 non diabetic subjects with cardiovascular diseases without CAD and in 147 healthy blood donors. All the four polymorphisms, PTPN22, ACP₁, p53 codon 72 and ADA₂ were determined in 128 non diabetic subjects with CAD and in 117 non diabetic subjects admitted for cardiovascular diseases without CAD.

Informed written consent was obtained from all subjects to participate to this study that was approved by the Ethical Committee of the Hospital.

ACP₁, p53 codon 72, PTPN22 and ADA₂ genotypes was determined by DNA analysis. Technical details about the determination of the four polymorphisms have been described in previous papers^[12,13].

Statistical analysis was performed by using SPSS programs.

RESEARCH

Table 1 shows the proportion of *T allele of PTPN22 polymorphism in relation to the presence of *A allele of ACP₁ polymorphism in non diabetic subjects with CAD, in non diabetic cardiovascular patients with no CAD and in healthy subjects. A high significant association is observed in carriers of *A allele with a very high proportion of *T allele carriers in non diabetic subjects with CAD as compared to controls and to non diabetic subjects with cardiovascular diseases without CAD. Such association is not observed in subjects who do not carry the *A allele of ACP₁.

Table 2 shows the proportion of PTPN22 *T allele carriers in relation to the presence of *Pro allele of p53 codon 72 polymorphism in the three groups of subjects. A high significant association is observed in carriers of *Pro allele with a very high proportion of *T allele carriers in non diabetic subjects with CAD as compared to controls and to non diabetic subjects with cardiovascular diseases without CAD. Such association is not observed in subjects carrying the *Arg/*Arg genotype.

Table 3 shows the proportion of *T allele carriers in relation to the presence of the ADA₂ *2 allele of ADA₂ polymorphism in non diabetic subjects with CAD, in non diabetic subjects with cardiovascular diseases without

Table 1 Proportion of *T allele of PTPN22 in relation to the presence of *A allele of acid phosphatase locus 1 polymorphism

	Proportion of carriers of *T allele of PTPN22		Total of subjects, <i>n</i>
Non diabetic subjects with CAD			
Subjects carrying the *A allele	19.3%		62
Other ACP ₁ genotypes	7.0%		71
Non diabetic subjects with cardiovascular diseases without CAD			
Subjects carrying the *A allele	3.4%		59
Other ACP ₁ genotypes	6.3%		63
Blood donors			
Subjects carrying the *A allele	7.2%		138
Other ACP ₁ genotypes	4.6%		131
Statistical analysis	χ^2 test of independence		
	χ^2	df	P
Carriers of *A allele	10.598	2	0.005
Other ACP ₁ genotypes	0.998	2	0.742

CAD: Coronary artery disease; ACP₁: Acid phosphatase locus 1.**Table 2** Proportion of carriers of *T allele of PTPN22 in relation to the presence of the *Pro allele of p53 codon 72 polymorphism

	Proportion of carriers of *T allele of PTPN22		Total of subjects, <i>n</i>
Non diabetic subjects with CAD			
*Arg/*Arg genotype	7.6%		66
Carriers of *Pro allele	17.5%		63
Non diabetic subjects with cardiovascular diseases without CAD			
*Arg/*Arg genotype	9.2%		65
Carriers of *Pro allele	0.0%		52
Blood donors			
*Arg/*Arg genotype	7.2%		139
Carriers of *Pro allele	5.1%		117
Statistical analysis	χ^2 test of independence		
	χ^2	df	P
*Arg/*Arg genotype	1.212	2	0.545
Carriers of *Pro allele	11.248	2	0.004

CAD: Coronary artery disease. Adapted from reference [13].

Table 3 Proportion of carriers of *T allele of PTPN22 in relation to the presence of the adenosine deaminase locus 2 *2 allele of adenosine deaminase locus 2 polymorphism

	Proportion of carriers of *T allele of PTPN22		Total of subjects, <i>n</i>
Non diabetic subjects with CAD			
ADA ₂ *1/*1 genotype	8.3%		84
Carriers of ADA ₂ *2 allele	20.8%		48
Non diabetic subjects with cardiovascular diseases without CAD			
ADA ₂ *1/*1 genotype	6.7%		75
Carriers of ADA ₂ *2 allele	2.2%		46
Blood donors			
ADA ₂ *1/*1 genotype	4.5%		88
Carriers of ADA ₂ *2 allele	5.1%		59
Statistical analysis	χ^2 test of independence		
	χ^2	df	P
ADA ₂ *1/*1 genotype	1.024	2	0.599
Carriers of ADA ₂ *2 allele	11.747	2	0.003

CAD: Coronary artery disease; ADA₂: Adenosine deaminase locus 2.

CAD and in healthy blood donors. A high significant association is observed in carriers of ADA₂ *2 allele with a very high proportion of *T allele carriers in non diabetic subjects with CAD as compared to controls and to non diabetic subjects with cardiovascular diseases without CAD. Such association is not observed in subjects who

do not carry the ADA₂ *2 allele.

Figure 1 shows in non diabetic subjects with CAD the relationship between the number of factors (*i.e.*, *A allele of ACP₁, *Pro allele of p53 and ADA₂ *2 allele) which contributes to the increase of PTPN22 *T allele carriers, and the proportion of *T carriers. There is a highly

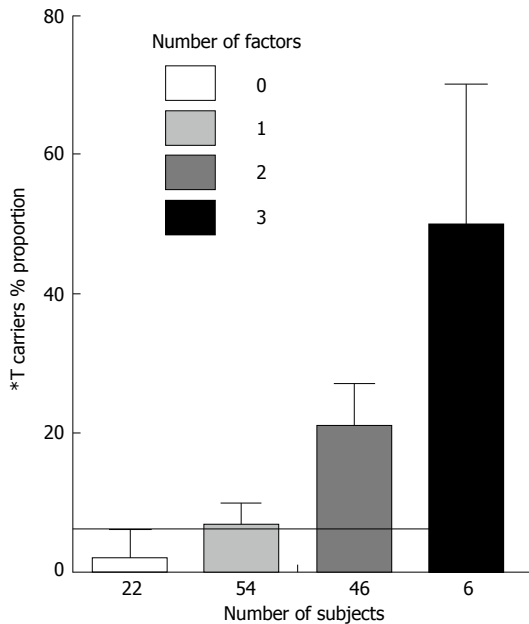


Figure 1 Twenty-two non diabetic subjects with coronary artery disease had no factor contributing to increase the proportion of *T carriers, 54 subjects had 1 factor, 46 had 2 factors and 6 had 3 factors.

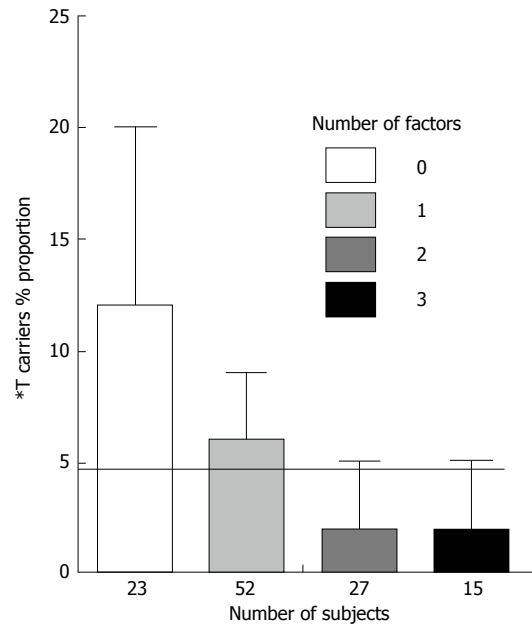


Figure 2 Twenty-three non diabetic subjects with cardiovascular diseases without coronary artery disease had no factor contributing to increase the proportion of *T carriers, 52 subjects had 1 factor, 27 had 2 factors and 15 had 3 factors.

significant linear correlation between the number of factors and the proportion of *T carriers (0.0004). The relationship is compatible with an exponential function $y = 5^x/100$ in which y = *T carriers proportion and x = the number of factors that influence the proportion of *T allele carriers.

Figure 2 shows a similar analysis in non diabetic subjects with cardiovascular disease without CAD. The relationship appears opposite to that observed in non diabetic subjects with CAD.

In non diabetic subjects with CAD we have examined the relationship of PTPN22 with sex, hypertension, magnetic resonance imaging, age and total cholesterol level. No statistical significant association has been observed.

CONCLUSION

The strength of association between PTPN22 and CAD in non diabetic subjects is dependent on other genetic variables. A similar phenomenon has been recently reported also in endometriosis, a disease in which immunological factors could have a important role^[14]. The data point to a multifactorial origin of CAD with a contribution of several genes involved in immune reactions.

It has been suggested that the increased susceptibility to autoimmune disorders observed in carriers of W620 variant of PTPN22 is due to failure to delete autoreactive T cells during intrathymic selection^[15,16]. The Proline variant with its stronger transcriptional activity could increase the production of autoreactive T cells enhancing the effect of W620 variant of PTPN22.

Low ACP1 activity decreasing ZAP70 activity, results in a weakening of T cell receptor signaling that may contribute with W620 variant to the failure to delete autore-

active T cells during intrathymic induction.

ADA2 polymorphism could influence ADA activity and in turn the concentration of adenosine and T cell activity. The polymorphism also may have a role on ADA activity as ectoenzyme. The strength of the signal on lymphocyte would depend on the concentration of ecto-ADA available. Modulation of ecto-ADA function could influence the development and functionality of lymphoid tissue.

The simultaneous analysis of multiple genes functionally related to a specific disease would provide a productive approach to the analysis of multifactorial diseases. The mechanisms of the observed associations presented in this paper, however, remain to be elucidated.

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WJC 6th Anniversary Special Issues (2): Coronary artery disease

Coronary thrombus in patients undergoing primary PCI for STEMI: Prognostic significance and management

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Abstract

Acute ST-elevation myocardial infarction (STEMI) usually results from coronary atherosclerotic plaque disruption with superimposed thrombus formation. Detection of coronary thrombi is a poor prognostic indicator, which is mostly proportional to their size and composition. Particularly, intracoronary thrombi impair both epicardial blood flow and myocardial perfusion, by occluding major coronary arteries and causing distal embolization, respectively. Thus, although primary percutaneous coronary intervention is the preferred treatment strategy in STEMI setting, the associated use of adjunctive anti-thrombotic drugs and/or percutaneous thrombectomy is crucial to optimize therapy of STEMI patients, by improving either angiographical and clinical outcomes. This review article will focus on the prognostic significance of intracoronary thrombi and on current antithrombotic pharmacological and interventional strategies used in

the setting of STEMI to manage thrombotic lesions.

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Key words: ST-elevation myocardial infarction; Intracoronary thrombosis; Primary percutaneous coronary intervention; Antithrombotic therapies; Coronary thrombectomy

Core tip: Intracoronary thrombosis, is the basic pathophysiologic event in acute ST-elevation myocardial infarction (STEMI), and thrombi are very frequently detected in STEMI patients undergoing primary percutaneous coronary intervention (PPCI). Thrombus burden and components are important determinants of prognosis in STEMI, being well-known risk factors for long-term adverse cardiovascular events, distal embolization and stent thrombosis. As a result, percutaneous management of lesions with a consistent thrombotic burden is still challenging in the setting of PPCI for STEMI. Therefore, several pharmacological and interventional strategies, such as thrombectomy have been developed in order to improve PPCI's safety and efficacy, by reducing thrombus burden.

Vecchio S, Varani E, Chechi T, Balducelli M, Vecchi G, Aquilina M, Ricci Lucchi G, Dal Monte A, Margheri M. Coronary thrombus in patients undergoing primary PCI for STEMI: Prognostic significance and management. *World J Cardiol* 2014; 6(6): 381-392 Available from: URL: <http://www.wjgnet.com/1949-8462/full/v6/i6/381.htm> DOI: <http://dx.doi.org/10.4330/wjc.v6.i6.381>

INTRODUCTION

Intracoronary thrombosis, subsequent to plaque rupture and causing partial or complete occlusion of a coronary

artery, is the basic pathophysiologic event in acute ST-elevation myocardial infarction (STEMI)^[1]. Actually, although angiography seems to underestimate the presence of thrombi, they are very frequently detected in STEMI patients undergoing primary percutaneous coronary intervention (PPCI) and tend to be larger than in non ST-elevation acute coronary syndromes (ACS). Sianos *et al*^[2] reported that up to 91.6% of STEMI patients undergoing PPCI showed intracoronary thrombosis at angiography.

Intracoronary thrombus burden and components are important determinants of prognosis in STEMI, being well-known risk factors for long-term adverse cardiovascular events, distal embolization and stent thrombosis^[2-8]. As a result, percutaneous management of lesions with a consistent thrombotic burden is still challenging in the setting of PPCI for STEMI. Therefore, several pharmacological and interventional strategies, such as thrombectomy, aiming at reducing thrombus burden, have been developed in order to improve PPCI's safety and efficacy, patients' survival and their quality of life.

CORONARY THROMBOSIS IN STEMI PATIENTS

Atherosclerotic plaque rupture or erosion are usually followed by hemorrhage into the plaque, luminal thrombosis, and vasospasm, which may cause sudden, partial or total, flow obstruction, and hence the onset of ischemic symptoms in the setting of STEMI^[1,9,10]. Inflammation and increased oxidative stress seem to play an important role in the pathogenesis of plaque instability^[11-13], while the clinical manifestation of an acute thrombotic event is determined by the balance between the propensity for thrombus formation, proportional to the kind and extent of exposed plaque components and to the local flow disturbances, and the efficacy of endogenous thrombolytic processes^[14]. However, plaque disruption and thrombosis do not always coincide with the onset of symptoms^[15,16]. Actually, post-mortem investigation and, more recently, histological studies of *in vivo*-derived thrombectomy specimens of STEMI patients, revealed that approximately 50% of the aspirated thrombi were days to even weeks old, which further suggests that thrombus formation starts at a variable time before symptoms onset^[17,18].

Pathological analyses revealed that coronary thrombi consist of platelets, erythrocytes and fibrin, and often contain atherosclerotic inflammatory cells^[19,20]. Initially, at the site of plaque disruption, platelets aggregate forming a platelet-rich thrombus which begins to protrude into the lumen. Then, the thrombus grows in association with the formation of a fibrin network entrapping a lot of erythrocytes and inflammatory cells, and forming an erythrocyte-rich thrombus^[19-21], which can partially or totally occlude the vessel.

ANGIOGRAPHIC CORONARY THROMBI: DEFINITION AND CLASSIFICATION

Angiography seems to underestimate the presence of

thrombi. Nevertheless, intracoronary thrombi are angiographically defined as the presence of a filling defect with either a total occlusion with convex, irregular, or hazy distal margins and post injection contrast retention or staining, or a partial occlusion circumferentially outlined by contrast medium^[22].

When angiographically detected, the thrombus burden can be classified according to the thrombolysis in myocardial infarction (TIMI) thrombus grade (TG)^[23]. TIMI TG 0 corresponds to no angiographic evidence of thrombus; in TIMI TG 1, angiographic characteristics suggestive of thrombus are detected (*i.e.*, reduced contrast density, haziness, irregular lesion contour or a smooth convex meniscus at the site of total occlusion suggestive but not diagnostic of thrombus); in TG 2, there is definite thrombus, with greatest dimensions $\leq 1/2$ the vessel diameter; in TG 3, there is definite thrombus but with greatest linear dimension $> 1/2$ but < 2 times the vessel diameter; in TG 4, there is definite thrombus, with the largest dimension ≥ 2 vessel diameter; and in TIMI TG 5, there is total occlusion and the size of thrombus cannot be assessed.

In STEMI setting, there is a high incidence of total coronary occlusion, thus, as was shown by Sianos *et al*^[2], the prevalence of TG 5 and unknown thrombus size is almost 60% of the patients. Therefore, a modified TG classification was recently suggested by Sianos *et al*^[2], where, grade 5 lesions are reclassified into one of the other TIMI grade categories, after flow achievement with either guidewire crossing or a small (diameter 1.5 mm) deflated balloon passage or dilation. According to this new classification, most lesions (99%) can be classified. Particularly, TIMI TG 0-3 are defined as small thrombus burden (STB), while TIMI TG 4 is defined as large thrombus burden (LTB).

PROGNOSTIC SIGNIFICANCE OF ANGIOGRAPHICALLY DETECTED CORONARY THROMBI

Angiographically detection of coronary thrombi in the setting of PPCI for STEMI is a well known negative prognostic factor, associated with a higher incidence of in-hospital and long-term adverse cardiac events^[2,6,24,25]. Actually, intracoronary thrombi can impair both epicardial and myocardial perfusion, by spontaneous or PPCI-induced occlusion of an epicardial vessel or its branches, or distal embolization of plaque and thrombotic components. Data derived from PPCI for STEMI studies, showed that PPCI resulted in about 6% to 18% distal embolization rate^[3,4,25-28]. Moreover, patients with distal embolization, compared to those without, showed lower procedural success rates with higher slow/no-reflow rates, lower left ventricular ejection fraction (LVEF), larger enzymatic infarctions, with increased in-hospital and late mortality rates^[25,29].

Size and thrombus composition are the major predictors of distal embolization, as well as slow TIMI flow

grade before PCI, long target lesion and large vessel diameter^[3,4,30]. A LTB and a high plaque burden were shown to be independent predictors of distal embolization^[2,5,7,29], and correlated with worse final TIMI flow/myocardial blush grades, as well as 2-year mortality and major adverse cardiac event (MACE) rates^[2]. In STEMI setting, thrombus burden is higher than in the other types of ACS. Particularly, a significant association between TG and vessel size has been reported (*i.e.*, large right coronary arteries, aneurismatic coronary arteries and aged degenerated saphenous vein grafts). Moreover, some clinical scenarios, such as STEMI occurring for stent thrombosis (ST), are associated with the presence of a LTB. Actually, Chechi *et al.*^[31] reported a significantly higher incidence of LTB (TG ≥ 3) in patients with STEMI due to ST, compared to those with STEMI due to *de novo* coronary thrombosis.

Recently, the development of thrombectomy and distal protection devices has enabled the evaluation of ante-mortem coronary thrombi, thus facilitating analysis of thrombi components, given that previous autopsy studies were unable to differentiate coronary thrombi responsible for STEMI from post-mortem clots. However, even for in vivo-derived thrombectomy thrombi, a sampling bias must be considered, related to the inability to determine whether retrieval of the thrombus was complete and which part of the thrombus has been extracted, and to the potential distortion of the samples that might have occurred during aspiration through a catheter lumen. Nevertheless, recent studies have demonstrated that erythrocyte-rich component in aspirated coronary thrombi is closely associated with thrombus size that increases the incidence of distal embolization during PPCI in STEMI patients^[4,32]. Actually, data on aspirated thrombi from 164 STEMI patients within 12 h from symptoms onset, revealed that thrombi from patients with distal embolization had a greater erythrocyte-positive area and more myeloperoxidase (MPO)-positive cells than those from patients without distal embolization, and that thrombus size was positively correlated with the erythrocyte component and the numbers of MPO-positive cells^[32]. These results reflect the above mentioned mechanism of thrombosis whereby the thrombus, initially platelet-rich, becomes erythrocyte-rich with inflammatory cells entrapped during thrombus growth^[21,33,34]. Moreover, MPO-positive cells, constituted by neutrophils and only occasionally by macrophages^[35], and erythrocyte-rich thrombi were shown to be associated with impaired coronary microcirculation, as assessed by ST-segment resolution and myocardial blush grade after PPCI in STEMI patients^[36,37]. Finally, independently from the histopathology of aspirated thrombi, patients with fresh thrombus tended to have better ST-segment resolution than patients with older thrombus^[38].

Prediction of thrombus burden and composition, as well as plaque volume and composition, before the procedure in patients with STEMI undergoing PPCI, may contribute to optimize percutaneous treatment of these highly thrombotic lesions, guiding utilization of pharma-

cological agents or interventional strategies, in order to reduce thrombus burden and improve both epicardial and myocardial perfusion. Grade III ischemia on electrocardiogram, defined as distortion of the terminal portion of the QRS complex, and red cell distribution width (RDW), a marker of variation in the size of circulating red cells routinely reported as a part of blood count analysis, were shown to be independent predictors of coronary thrombus burden in STEMI patients undergoing PPCI, and to be associated with angiographic no-reflow and impaired epicardial and myocardial perfusion^[39-41]. Probably, also the evaluation of thrombus burden using, not only coronary angiography, but also intravascular imaging modalities, such as ultrasound, optical coherence tomography or virtual histology, may provide important informations about the amount and composition of coronary thrombi, thus facilitating the choice of treatment strategies.

PHARMACOLOGIC AND PERCUTANEOUS INTERVENTIONAL MANAGEMENT OF CORONARY THROMBI

PPCI is the preferred treatment option, compared to thrombolytic therapy, in STEMI patients, being effective in obtaining patency of the infarct-related artery (IRA)^[42], and resulting in smaller infarcts, less acute and long-term clinical events, including recurrent myocardial infarction and death^[43,44]. However, a substantial number of STEMI patients, up to 40%, treated with PPCI shows poor procedural outcomes^[25], above all because of the presence of intracoronary thrombi that can lead to micro and macro distal embolization, thus reducing the benefits of PCI^[25]. Actually, although PPCI effectively restores flow in the IRA, myocardial perfusion often remains sub-optimal, with persistent ST-segment elevation, abnormal myocardial blush grade and abnormal TIMI frame count, due to microvascular obstruction, mostly attributed to distal embolization^[45]. As a result, management of lesions with a consistent thrombotic burden is still challenging during PPCI for STEMI. This has led to the employment and development of drugs and adjunctive percutaneous devices, aiming at reducing distal embolization and therefore improve myocardial perfusion. Particular subgroups of STEMI patients may benefit more from these adjunctive pharmacological and interventional strategies; these include patients with large anterior myocardial infarction, LTB, residual thrombus, side-branch involvement, and those with slow or no-reflow. Finally, attention must be paid on stenting strategies in order to further reduce PCI complications.

Pharmacologic agents

Several pharmacologic agents, delivered intravenously or *via* the intracoronary route, can be used in the catheterization laboratory, to manage lesions with consistent thrombus burden during PPCI for STEMI. When possible, STEMI patients undergoing PPCI should receive dual

antiplatelet therapy (aspirin plus one of the ADP receptor blockers) and one parenteral anticoagulant. Moreover glycoprotein II b/IIIa inhibitors (GPI) and vasodilators drugs may be useful to manage lesions with consistent thrombus burden and to improve epicardial and myocardial perfusion. Particularly, these pharmacological measures are useful in the presence of slow or no-reflow, which is related to a combination of distal embolization of plaque debris and thrombus, vasoconstriction and reperfusion injury^[25].

Anticoagulants

Anticoagulant options for PPCI include unfractionated heparin (UFH), enoxaparin and bivalirudin. UFH titrated to an appropriate activated clotting time is a familiar and well-tested strategy for anticoagulant therapy in the setting of PPCI^[46,47], compared to enoxaparin which has been studied less extensively in this setting. Moreover, the ATOLL trial comparing intravenous enoxaparin with UFH for PPCI failed to meet its primary composite endpoint (30-d death, complication of myocardial infarction, procedural failure and major bleeding)^[48]. Thus, European guidelines recommend UFH in Class I, level of evidence C, while enoxaparin has an indication of Class II b, level of evidence B^[42]. However, European guidelines stated that enoxaparin should be preferred over UFH^[42], based on the considerable clinical experience with enoxaparin in other PCI settings^[42] and on considerations derived from the ATOLL trial^[48]. Particularly, although the primary endpoint was not reached, there were reductions in the composite main secondary endpoint of death, recurrent myocardial infarction or ACS or urgent revascularization, and in other secondary composite endpoints, such as death, or resuscitated cardiac arrest and death, or complication of myocardial infarction, and there was no indication of increased bleeding from use of enoxaparin over UFH^[48]. Moreover, a recent meta-analysis of 23 trials, including 30966 patients undergoing PCI (33.1% PPCI for STEMI, 28.2% rescue PCI, and 38.7% with non ST-elevation ACS or stable patients), showed that enoxaparin was associated with a significant relative and absolute risk reduction of mortality, along with a significant reduction of major bleeding, especially in patients treated with PPCI for STEMI^[49]. Bivalirudin is a direct thrombin inhibitor. In the HORIZONS-AMI trial^[50], reporting on 3602 STEMI patients randomized to UFH plus a GPI or to bivalirudin alone, the later showed lower major bleeding rates at 30-d, 1 and 3 years^[50-52], with significantly lower rates of death from cardiac causes and all causes^[50]. Conversely, the use of bivalirudin was associated with an initial increase in ST, which disappeared after 30 d^[50]. Based on these data, European guidelines recommend the use of bivalirudin, over UFH, in STEMI patients, with a Class I indication, level of evidence B, with use of GPI restricted only to bailout^[42].

GPIs

GPIs (abciximab, tirofiban and eptifibatide) inhibit final

common pathway of aggregation process by preventing fibrinogen from binding to activated platelets and forming white thrombus. All GPI agents have been found to achieve their benefits by reducing the clot burden at the epicardial coronary level, by improving microvascular flow and reducing no-reflow and infarct size, and thus by improving short- and long-term outcomes^[53,54]. Although, GPIs are frequently administered to ACS patients undergoing PCI, a strategy supported by several randomized clinical trials, their role in STEMI patients, treated with PPCI and dual antiplatelet therapy, has been conflicting, especially because of bleeding concerns^[50,55-57]. The most profound evidence has been found for abciximab, which remains the drug of choice in PPCI, in combination with heparin^[58,59]. The recent 2013 ACC/AHA guidelines^[47] have given the routine use of upstream GPIs in STEMI patients undergoing PPCI, a Class II b recommendation. However, upstream administration of GPIs, may be considered among high-risk patients within the first 4 h from symptoms onset, when the larger amount of myocardium at risk and viable myocardium may justify this approach^[60]. Actually, the On-TIME 2 trial showed that upstream administration of GPI was associated with a higher rate of an open artery and a lower initial thrombus burden, with these benefits restricted only to early presenters (< 76 min)^[61]. Therefore, GPIs, as stated by European guidelines^[42], should be considered only for bailout therapy (Class II a, C) if there is evidence of LTB, slow or no-reflow or a thrombotic complication, or could be administered upstream only in high-risk patients undergoing transfer for PPCI (Class II b, B). Generally, GPIs are administered intravenously. Recently, intracoronary bolus of abciximab has been tested, with the rationale that intracoronary drug concentration may increase drug efficacy, and that the continuous intravenous infusion may not be beneficial to further improve outcomes, but may increase the risk of bleeding, especially in the contemporary era of PPCI, in which more potent ADP receptor blockers and thrombus aspiration are available for most of the STEMI patients. However, to achieve these favorable effects, it is advisable to administer intracoronary abciximab bolus after thrombus penetration by the PCI guidewire, and when the risk of bleeding is an issue, intracoronary bolus of GPI and no infusion strategy may be useful. Some small studies showed infarct size reduction, decrease in microvascular obstruction, improvement in the LVEF, and improvement in myocardial blush, but no significant difference in the clinical outcomes with intracoronary bolus administration of abciximab, with and without subsequent infusion^[62-65]. However, meta-analyses published recently, demonstrated not only a favorable effect of intracoronary bolus on TIMI flow, but also on target vessel revascularization and short-term mortality after PCI with no increase of bleeding complications^[66,67]. In summary, the role of intracoronary bolus of GPIs still need to be established by randomized trials comparing intravenous and intracoronary GPIs administration, with and without subsequent infusion, in combination with

modern PPCI strategies.

Vasodilators

Vasodilators that have been used in PPCI setting include nitroprusside, adenosine and diltiazem or verapamil. When used, they are administered intracoronary, in order to achieve a higher local concentration. Thus, they can be delivered directly through the guiding catheter, or *via* a distal over-the-wire balloon, infusion catheters or infusion balloons^[68].

Adenosine is considered a cardio-protective agent, because it antagonizes many of the factors implicated in the reperfusion injury, and has been shown to reduce post-ischemic ventricular dysfunction and myocyte necrosis and apoptosis. Moreover, several studies showed beneficial effects on coronary flow^[69,70]. Compared to the other drugs, adenosine has the advantage to have a very short half-life, and therefore, adverse effects are rapidly resolved.

Nitroprusside is a direct donor of nitric oxide, functioning as a potent venous and arterial vasodilator. Selective intracoronary nitroprusside administration is safe, generally well-tolerated, and provides stimulus to promote vascular dilation and improve tissue perfusion, especially in patients who develop slow or no-reflow after PCI. Moreover, if administered before balloon or stenting angioplasty, intracoronary nitroprusside, as well as adenosine, may decrease rates of no-reflow, increase myocardial blush scores, and shorten procedural times. In cases of impaired flow during PCI, combination therapy of adenosine and nitroprusside has been shown to be safe and provides better improvement in coronary flow and MACE, as compared with adenosine alone^[68].

Small trials suggest that there may be a role for prophylactic use of intracoronary calcium channel blockers, especially verapamil, because they seem to prevent no-reflow in some patients by reversing the calcium-mediated distal microvascular spasm^[71,72].

Although the benefit of intracoronary delivery of adjunctive pharmacologic agents such as calcium channel blockers, adenosine and nitroprusside is limited to small studies showing reduction of embolization rates and not clinical outcomes, they are still useful in the catheterization laboratory.

Percutaneous devices

The rationale for thrombectomy and embolic protection devices use is the reduction of the incidence of distal embolization, and improvement of myocardial perfusion and clinical outcomes. Particularly, thrombectomy devices aim at reducing thrombus burden, while embolic protection devices aim at capturing the debris liberated during PCI.

Thrombectomy devices

In the last years thrombectomy has emerged as a useful tool to reduce thrombus burden and thus distal embolization, further enhancing benefits of PPCI. Various throm-

bectomy devices have been developed allowing manual or mechanical removal of intracoronary thrombi. All thrombectomy devices have shown benefits compared with conventional PPCI, when surrogate endpoints, such as angiographic flow assessment, LVEF assessment, infarct size reduction by perfusion imaging, enzymatic analysis and ST-segment resolution were used^[26,29,73-79]. To date evidences about hard endpoints from randomized controlled trials, comparing manual and mechanical thrombectomy, are limited and even conflicting.

The REMEDIA trial, comparing thrombus aspiration with the Diver CE (Invatec, Brescia, Italy) before PCI *vs* conventional PPCI^[73], showed no difference in clinical outcomes or peak creatine kinase, muscle and brain (CK-MB) elevation, but a significant improvement in perfusion grades and in ST-segment resolution. The EXPIRA trial, evaluating the Export catheter (Medtronic, Inc, Minneapolis, MN) in PPCI, demonstrated improvement in surrogate markers, including myocardial blush grade and ST-segment resolution^[78]. The TAPAS trial is the largest randomized trial to date evaluating thrombus aspiration in PPCI for STEMI^[26]. It randomized 1071 patients and demonstrated effective manual thrombus aspiration in 73% in the treatment group. There was a trend toward less MACE at 30 d.

Recently, a direct and adjusted indirect meta-analysis of studies on manual and mechanical thrombectomy in PPCI for STEMI has been published^[80]. The direct meta-analysis showed comparable rates of survival, re-infarction and procedural outcomes between the two groups, even though these results are limited in sample size. On the contrary, the indirect meta-analysis showed a superior reduction in mortality with manual compared to mechanical thrombectomy. When trials, such as TAPAS and AIMI, with low percentage of patients with intracoronary thrombus (< 50%) at baseline, were excluded from the analysis, the two strategies were comparable in survival, but mechanical thrombectomy was associated with a significant reduction in re-infarction and stroke^[80]. This report lends support to mechanical thrombectomy, which until now was looked upon with suspicion. Actually, despite more bulky and complex to use, mechanical thrombectomy devices may provide more consistent advantages in removal thrombus, because of their intrinsic properties. To date, the negative results associated with the use of mechanical thrombectomy devices, are mostly driven by the results of the AIMI trial^[81], reporting on 480 patients randomized to AngioJet rheolytic thrombectomy (RT) and standard PPCI. In this study, the AngioJet RT group reported a higher final infarct size, a lower final TIMI flow grade 3 and a higher 30-d MACE rate. It has been speculated that the higher mortality observed in these patients may be related to a very low (and unexpected) mortality of patients treated only by PPCI (0.8% *vs* 4.6%; $P = 0.02$)^[81]. Moreover, both operator experience and the technique used, might have influenced mortality in patients treated with AngioJet RT. Actually, in the AIMI trial enrolling centers were low-volume centers without

extensive AngioJet experience, as resulted from the high rate of coronary perforation. Furthermore, a retrograde thrombectomy technique was used without activation of the device prior to crossing the lesion, which might have promoted distal embolization. Finally, angiographic evidence of thrombus was absent in a large percentage of both groups^[81]. Conversely, the recently published JET-STENT trial, evaluating 501 patients with LTB (thrombus grade ≥ 3) in large vessels (≥ 2.5 mm), randomized to AngioJet RT prior to direct stent *vs* direct stent alone, reported that patients treated with AngioJet showed a better myocardial reperfusion, with a higher rate of early ST-segment resolution ($P = 0.043$), without any significant differences in secondary surrogate endpoints, such as infarct size at 1-mo scintigraphy, post-procedural TIMI flow and corrected TIMI frame count. On the contrary, the rate of MACE (*i.e.*, death, myocardial infarction, repeated revascularization and stroke) was significantly lower in patients treated with AngioJet either at 1-mo ($P = 0.043$), or 6-mo ($P = 0.011$) or 12-mo ($P = 0.036$) follow-up, primarily driven by a lower incidence of death and time to target vessel revascularization. This was attributed to better myocardial perfusion and to better stent length and diameter assessment following RT^[82].

Therefore, current evidences support the routine use of manual thrombectomy devices in PPCI, and consequently, manual thrombectomy received a Class IIa indication in PPCI in the recent ESC guidelines^[42]. However, when LTB is present, especially in large vessels and when experienced operators are available, mechanical thrombectomy with AngioJet system should be considered. Particularly, AngioJet may be very useful in patients with STEMI due to stent thrombosis, in which the thrombotic burden seems to be huge. A study published by Chechi *et al*^[31] showed that thrombus grade ≥ 3 was observed in all patients with STEMI due to stent thrombosis, compared to 93.9% of patients with STEMI and de-novo coronary thrombosis ($P = 0.01$). The OPTIMIST study, in which 110 patients with stent thrombosis treated by PCI have been evaluated, showed that a sub-optimal coronary reperfusion was related to a worse outcome, even though GPIs, intra-aortic balloon pump and mechanical thrombectomy devices were used. In this study, mechanical thrombectomy devices were under-used: only 30% of patients have been treated with these devices, and among them few have been treated with AngioJet^[83]. Patients treated with mechanical thrombectomy showed a better coronary reperfusion, compared to patients in which mechanical thrombectomy devices were not used^[83].

Embolic protection devices

Embolic protection devices (EPD) can be divided into proximal and distal devices. Distal EPDs consist in filter-wire or occlusive distal balloon systems, while the principal proximal EPD is represented by an occlusive proximal balloon system (*i.e.*, Proxis system). Few data are available on proximal EPDs, while most of the data regard distal EPDs. Distal EPDs were first used to protect from em-

bolization associated with PCI in diseased saphenous vein grafts, then after they were applied in PPCI setting for STEMI to protect myocardium during intervention on highly thrombotic lesions in native vessels.

The EMERALD trial demonstrated no significant improvements in the primary end points of myocardial reperfusion or infarct size with the use of the distal balloon occlusion and aspiration system, GuardWire, despite the removal of visible debris in a high proportion of patients (73%)^[84]. The DEDICATION trial, evaluating patients randomized to distal protection using a filter wire (Filter-Wire-EZ), or a SpiderFX protection device, *vs* standard PPCI without distal protection, showed no significant difference in the primary endpoint of ST-segment resolution or in cardiac biomarker elevation or left ventricular wall motion index, and found a higher MACCE rate with distal protection^[85]. Thus, although, distal EPDs showed favorable clinical benefits during PCI in saphenous vein grafts, the results in PPCI setting for native vessel were not so good. Resuming, no differences were reported on ST-segment resolution, infarct size and MACE rates with distal EPDs compared to standard PPCI^[84-86]. These data were confirmed by the meta-analysis by Kunadian *et al*^[87], where the use of distal EPDs resulted in no decrease of early mortality or recurrent myocardial infarction rate. Probably, the absence of benefits with the use of distal EPDs could be explained by the fact that such devices can themselves induce distal embolization when crossing highly thrombotic lesions and may not be completely effective in preventing all debris from embolizing. Theoretically, compared to distal EPDs, proximal ones offer the benefit of embolic protection without crossing the thrombus, therefore avoiding added distal embolization, while allowing effective thrombus removal. Conversely, proximal EPDs, such as the Proxis device, have several technical limitations contraindicating their use during PPCI (*i.e.*, the presence of a stenosis within 15 mm of the ostium or IRA proximal segment diameter < 2.5 or > 4.5 mm, contraindicate the use of Proxis system), and therefore making results on their use inconclusive. In the setting of STEMI, use of the Proxis device demonstrated an initial benefit in ST-resolution; however, this benefit was not maintained over time with a late catch-up in the control group.

Based on the above data, European guidelines did not recommend routine use of distal EPDs^[42].

Stenting strategies

PCI strategies, including selection of vascular access, timing of stenting, sizing and type of stent, are crucial to further improve angiographic and clinical outcomes during PPCI for STEMI, along with the use of adjunctive pharmacologic drugs and thrombectomy devices.

Compared to elective procedure, PPCI is associated with a higher rate of bleeding, because of the need for potent antithrombotic and antiplatelet agents, mostly related to the arterial puncture site. Radial approach has been shown to reduce the incidence of acute bleeding

events, both in ACS and STEMI patients, especially when operators are skilled with this arterial approach^[42].

The presence of a LTB in STEMI setting, may affect stent apposition, correct stent sizing and final TIMI flow, all of which are predictors of acute ST. Thus, the best approach to stenting in PPCI seems to be thrombus guided, as reported in the SINCERE database^[88]. Based on this strategy, if the extent of thrombus is small (TG 0-1), direct stenting may be sufficient. Conversely, if more significant thrombus burden is present (TG 2-3), initial aspiration with a manual device is usually prudent, by decreasing distal embolization and no-reflow, and facilitating subsequent stenting. If thrombus burden is unchanged after 2 passes, it is advisable to switch to a more aggressive thrombectomy device, such as the AngioJet system. If a very LTB is present (TG 4-5), manual thrombectomy may be insufficient and AngioJet RT may be warranted^[88]. Actually, a LTB has been related to a very high rate of ST (2); moreover, if not removed, thrombus compression or displacement by the stent struts may cause distal embolization and no-reflow in the acute phase during PPCI, and in the long-term, with abluminal thrombus resolution, may cause late stent malapposition, thus increasing the risk of late ST. Therefore, a strategy of delayed stent implantation (DSI) after thrombus removal, compared to immediate stent implantation (ISI), appears attractive. To date, only few and small studies have been published comparing these two strategies^[89-91], but they all showed that DSI is associated with better microvascular perfusion, less frequent distal embolization and no-reflow, compared with ISI. Certainly, in STEMI setting with LTB, DSI has to be weighed against the potential risk of recurrent ischemia and bleeding episodes during the waiting period before PCI. On the other hand, DSI could allow to perform PCI after full antithrombotic preparation, enhancing clot lysis and thrombus dissolution, and after enough time to “cool off” the culprit lesion, thus becoming more stable with a reduced incidence of adverse angiographic events.

When a stenting strategy is applied, selection of the appropriate stent diameter may be of particular importance during PPCI, since stent undersizing is one of the most powerful predictor of ST among non-elective PCI^[92]. Actually, the reference vessel diameter of the IRA may be difficult to accurately assess during PPCI, because of thrombus burden, catecholamine stimulation and inflammatory substances, that can contribute to general and localized vasoconstriction^[93]. Therefore, intracoronary administration of nitrates is recommended before starting the coronary angiographic sequence used for stent size selection^[42].

Drug-eluting stents (DES) can be implanted during PPCI for STEMI, with a reduced risk of repeated target vessel revascularization, compared with bare-metal stents (BMS)^[94]. There have been concerns about increased risks of very late ST and reinfarction with DES, compared with BMS^[94]. However, use of DES has not been associated with an increased risk of death, myocardial infar-

tion or ST on long-term follow-up^[52]. Moreover, newer generations of DES seem to provide improved clinical outcomes following PPCI, with a reduced incidence of ST. The often spastic reaction of the IRA and the presence of LTB, may be the rationale for implanting stents with progressive self-apposing after their implantation. Interim results of the APPPOSITION III trial, using self-expanding BMS, are promising with a lower 30-d MACE rate. Moreover, when a LTB is present, the use of special mesh-covered stents can be useful in managing thrombi and preventing distal embolization. There are some small studies reporting on the use of the MGuard stent in STEMI setting, documented promising surrogate results, such as a better ST-resolution and a higher post-procedural TIMI 3 flow rate, when compared to standard types of stents^[95-98].

CONCLUSION

Since detection of intracoronary thrombi is associated with distal embolization, myocardial damage and poor clinical outcomes, several pharmacologic agents and interventional adjunctive techniques need to be taken in consideration during PPCI for STEMI, as well as a correct stenting strategy. The treatment during PPCI needs to be modified with respect to the risk profile, thrombotic burden, availability of medical resources and operators' experience.

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WJC 6th Anniversary Special Issues (2): Coronary artery disease

Use of intravascular imaging in managing coronary artery disease

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Abstract

For many years, coronary angiography has been considered "the gold standard" for evaluating patients with coronary artery disease. However, angiography only provides a planar two-dimensional silhouette of the lumen and is unsuitable for the precise assessment of atherosclerosis. With the introduction of intravascular imaging, direct visualization of the arterial wall is now feasible. Intravascular imaging modalities extend diagnostic information, thereby enabling more precise evaluation of plaque burden and vessel remodeling. Of all technologies, intravascular ultrasound (IVUS) is the most mature and widely used intravascular imaging technique. Optical coherence tomography (OCT) is an evolving technology that has the highest spatial resolution of existing imaging methods, and it is becoming increasingly widespread. These methods are useful tools for planning interventional strategies and optimizing stent deployment, particularly when stenting complex lesions. We strongly support the mandatory use of IVUS for left main percutaneous coronary intervention (PCI). In addition, it can be used to evaluate vascular

responses, including neointimal growth and strut apposition, during follow-ups. Adequately powered randomized trials are needed to support IVUS or OCT use in routine clinical practice and to answer whether OCT is superior to IVUS in reducing adverse events when used to guide PCI. The current perception and adoption of innovative interventional devices, such as bioabsorbable scaffolds, will increase the need for intravascular imaging in the future.

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Key words: Imaging; Ultrasonics; Optical coherence tomography; Stent; Restenosis; Thrombosis

Core tip: Intravascular ultrasound (IVUS) and optical coherence tomography (OCT) are imaging methods that allow the direct visualization of the arterial wall and atherosclerosis. These methods are useful tools for planning interventional strategies and optimizing stent deployment and for evaluating vascular responses during follow-ups. In this review, we focus on the potential clinical utility of IVUS and OCT in patients with coronary artery disease.

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INTRODUCTION

Intravascular ultrasound (IVUS) is the first widely applied catheter-based imaging technology that provides valuable diagnostic information to angiography (*i.e.*, vessel and lumen dimensions, plaque burden and morphology)^[1]. IVUS uses a miniaturized ultrasound transducer mounted

on the tip of a catheter. In principle, IVUS is based on the emission, attenuation, and backscattering of ultrasonic waves that are converted to electrical signals and then processed as an image. The envelope (amplitude) of the radiofrequency signal is used to form the grey-scale IVUS image. In recent years, information derived from the spectral analysis of IVUS backscattered data has been added to grey-scale reconstructions to obtain a more detailed characterization of plaque morphology as a color-coded map^[2]. Three main post-processing methods for tissue characterization are virtual histology IVUS (VH-IVUS, Volcano Therapeutics, Rancho Cordova, CA, United States), iMAP-IVUS (Boston Scientific Corp, Fremont, CA, United States), and integrated backscatter IVUS (IB-IVUS)^[3-5]. Intravascular palpography, which measures mechanical strain of the arterial wall and has the potential to differentiate between fibrous and fatty plaque components and detect high-stress regions^[6], is a technique that is also based on IVUS. Recently, new intravascular imaging techniques with other energy sources (*e.g.*, light) have been introduced. Optical coherence tomography (OCT) is an optical technology that is based on the emission and reflection of near-infrared light. OCT has approximately 10-fold greater resolution than ultrasound-based approaches. However, the higher resolution (10 to 15- μ m axial and 20 to 25- μ m lateral) comes at the expense of poorer penetration through blood and tissue (1 to 3 mm). Recently, the earlier time-domain OCT has been replaced by frequency-domain OCT (FD-OCT) technology to reduce ischemia during blood-free optical imaging. This technique does not require proximal balloon occlusion and allows for the comprehensive scanning of long arterial segments within a few seconds^[7]. Intracoronary angioscopy is an endoscopic technology that allows direct visualization of the surface color and superficial morphology^[8]. Near-infrared spectroscopy (NIRS) uses a laser light source to detect lipid-rich plaques^[9]. A combined NIRS-IVUS catheter has recently been introduced; it provides simultaneous acquisition of grey-scale IVUS and identification of lipid core-containing plaques.

In this review, we focus on the potential clinical utility of IVUS and OCT in patients with coronary artery disease for planning interventions and percutaneous coronary intervention (PCI) guidance.

ASSESSMENT OF ANGIOGRAPHIC INTERMEDIATE LESIONS

Intravascular imaging methods enable more precise assessments of lesion severity in cases of angiographic intermediate coronary lesions. Fractional flow reserve (FFR) is the gold standard for invasive assessments of the functional significance of intermediate lesions^[10]; however, there have been attempts to correspond IVUS or OCT measurements to the functional significance of a stenosis.

Relationship between IVUS measurements and FFR

Several studies have shown good correlation between

IVUS measurements and FFR values. In a study of 53 angiographic intermediate coronary lesions, a minimum lumen area (MLA) of ≤ 4.0 mm² (by IVUS) was reported to be the best cut-off value in identifying FFR < 0.75 , with 92% sensitivity and 56% specificity^[11]. Moreover, low event rates (a mean follow-up time of 13 mo) were reported in 300 patients for whom PCI was deferred on the basis of an IVUS MLA ≥ 4.0 mm² or a minimum lumen diameter ≥ 2.0 mm, and the event rate decreased as the MLA increased^[12]. An MLA cutoff of 4.0 mm² has been the IVUS parameter that is more frequently applied in the clinical setting. However, recent studies have found different MLA cutoff values and have used a combination of other IVUS parameters to predict FFR. Recently, in a population of 201 patients with 236 coronary lesions, the best cutoff value to predict a FFR < 0.80 was an MLA < 2.4 mm², with a diagnostic accuracy of 68%, a high sensitivity of 90% and a poor specificity of 60%. Plaque burden and lesion length measured by IVUS were also the independent determinants for FFR^[13]. An IVUS-derived MLA < 2.0 mm² has been reported as the best cutoff value to predict FFR < 0.75 in vessels with reference diameters measuring < 3 mm^[14].

Few studies have validated IVUS measurements as anatomic predictors for the functional significance of left main lesions. In an analysis of 55 patients, Jasti *et al*^[15] reported that an MLA of 5.9 mm² and a minimum lumen diameter of 2.8 mm strongly predicted FFR < 0.75 . In the LITRO study, which enrolled 354 patients with intermediate left main lesions, an MLA > 6 mm² was a safe value for deferring revascularization. In the 2-year period, there was no significant difference between the deferred and revascularized groups in terms of cardiac death-free survival (97.7% *vs* 94.5%, respectively, $P = 0.5$) and event-free survival (87.3% *vs* 80.6%, respectively, $P = 0.3$)^[16]. Recently, Kang *et al*^[17] addressed this issue in 55 patients with isolated intermediate left main lesions. The IVUS MLA value that best predicted FFR < 0.80 was 4.8 mm², with 89% sensitivity and 83% specificity. In contrast with studies of non-left main stenosis, the specificity was acceptable high.

Based on this evidence, most intermediate non-left main lesions with an MLA ≥ 4 mm² are non-significant, and PCI may be deferred. However, physiological evaluation is still recommended for lesions with MLA < 4.0 mm² because of poor specificity of IVUS parameters. Other IVUS parameters should be considered in combination with the MLA to justify revascularization, including reference vessel size, lesion length, plaque burden and area stenosis. Revascularization may be deferred in patients with left main MLA ≥ 6.0 mm². FFR or non-invasive stress tests should be performed for an MLA < 6.0 mm². IVUS, therefore, should be used with caution as a tool to investigate the functional significance of intermediate lesions; the accuracy of IVUS measurements in predicting abnormal FFR remains debatable.

Recently the Society of Cardiovascular Angiography and Interventions released an expert consensus statement

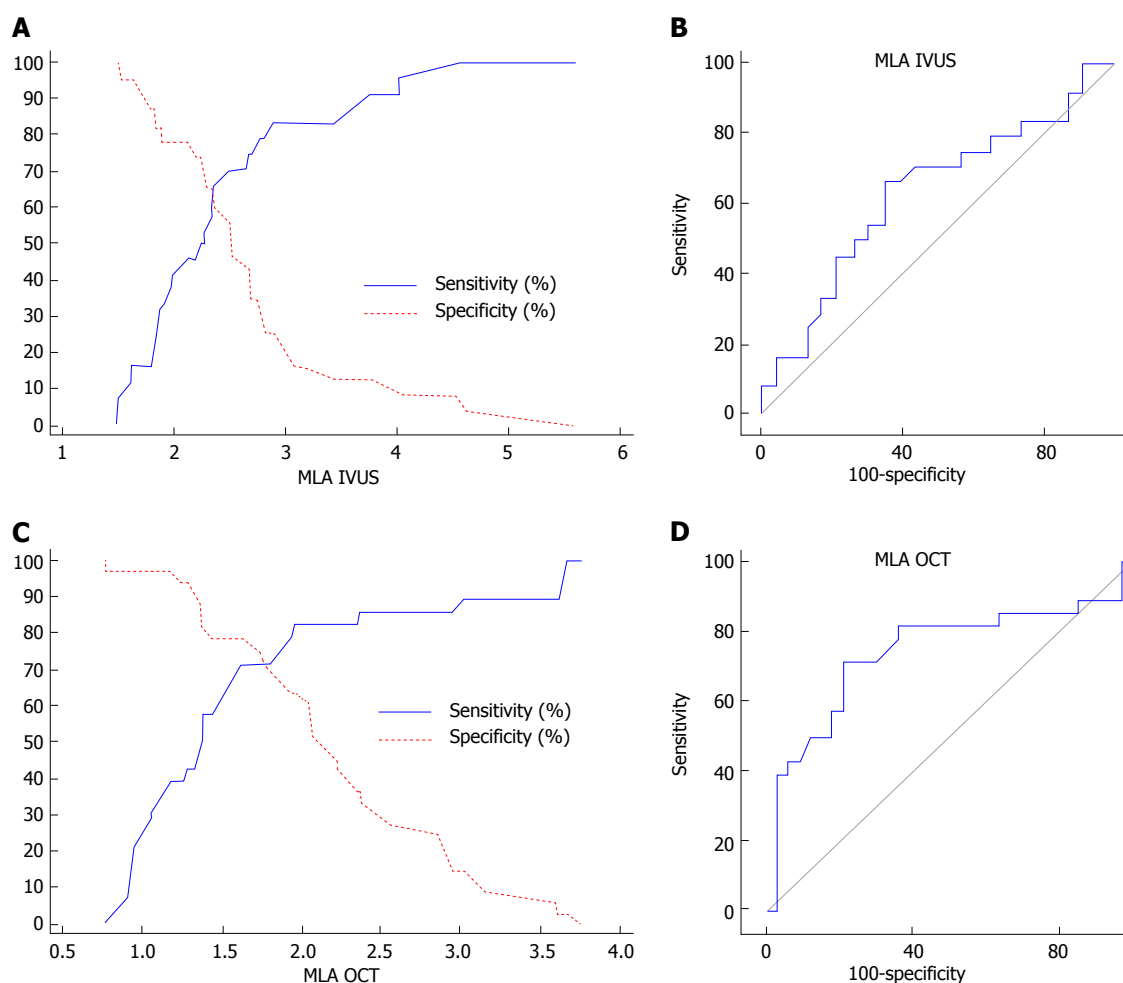


Figure 1 Intravascular ultrasound and optical coherence tomography derived minimum lumen area and fractional flow reserve. A: Sensitivity and specificity curve for IVUS-derived MLA to predict FFR ≤ 0.80 ; B: Receiver-operating characteristic curve for IVUS-derived MLA to predict FFR ≤ 0.80 ; C: Sensitivity and specificity curve for OCT-derived MLA to predict FFR ≤ 0.80 ; D: Receiver-operating characteristic curve for OCT-derived MLA to predict FFR ≤ 0.80 ^[19]. MLA: Minimum lumen area; IVUS: Intravascular ultrasound; OCT: Optical coherence tomography; FFR: Fractional flow reserve.

on the use of FFR, IVUS, and OCT. Experts recommend using IVUS to appraise the significance of left main lesions and employing a cutoff MLA value of 6.0 mm² to assess whether revascularization is warranted. However, the use of IVUS should be discouraged when evaluating non-left main lesions^[18].

Relationship between OCT measurements and FFR

Few studies have examined the potential of OCT to demonstrate the functional significance of coronary artery disease and the new expert statement does not recommend using OCT to determine stenosis functional significance^[18]. Recently, one study of 56 patients with 61 non-left main intermediate stenoses analyzed the value of OCT in identifying hemodynamically significant stenosis using FFR as a standard of reference. OCT showed moderate diagnostic efficiency in identifying coronary stenoses with FFR ≤ 0.80 (area under the curve 0.74; 95%CI: 0.61-0.84). The best OCT-derived measurements to predict FFR ≤ 0.80 were 1.95 mm² for the MLA (82% sensitivity, 63% specificity, and 72% accuracy) and 1.34 mm for the minimum lumen diameter (82% sensitivity, 67% specificity, and 73% accuracy). In addition 77% of

the stenoses were studied with IVUS. The IVUS cut-off value for MLA was 2.36 mm² (67% sensitivity, 65% specificity, and 66% accuracy). In patients with simultaneous IVUS and OCT, there were no significant differences in the diagnostic efficiency of OCT and IVUS, but in a subgroup of small vessels (reference diameter < 3 mm), OCT showed a significantly better diagnostic efficiency (Figure 1)^[19]. The moderate diagnostic efficiency demonstrated by OCT and IVUS in this study may be related to the reference diameter of 2.60 ± 0.6 mm, and 49.2% of the target vessels had reference diameters measuring < 2.5 mm. Thus, although an OCT-derived MLA may be a useful criterion for excluding hemodynamically significant stenoses, direct FFR measurements or stress tests may be necessary to identify the ischemia-inducible lesion.

INTRAVASCULAR IMAGING FOR PCI GUIDANCE

Pre-intervention imaging provides valuable information regarding the severity of stenosis, lesion length, vessel size, and plaque characteristics. It has been used to plan

Table 1 Intravascular ultrasound criteria for optimal stent deployment

MUSIC criteria
Complete apposition of the stent over its entire length against the vessel wall
MLA:
In-stent MLA $\geq 90\%$ of the average reference lumen area or $\geq 100\%$ of the reference segment with the lowest lumen area
In-stent MLA of proximal stent entrance $\geq 90\%$ of proximal reference lumen area
If the in-stent MLA is $> 9.0 \text{ mm}^2$:
In-stent MLA $\geq 80\%$ of the average reference lumen area or $\geq 90\%$ of the reference segment with the lowest lumen area
In-stent MLA of proximal stent entrance $\geq 90\%$ of the proximal reference lumen area
Symmetric stent expansion defined by the minimum lumen diameter divided by the maximum lumen diameter ≥ 0.7
AVIO study criteria
Final minimum stent cross sectional area of at least 70% of the hypothetical cross sectional area of the fully inflated balloon used for post-dilatation
The optimal balloon size that should be used for post-dilatation is the average of the media to media diameters of the distal and proximal stent segments, as well as at the sites of maximal narrowing within the stent. The value is rounded to the lowest 0.00 or 0.50 mm. For values $\geq 3.5 \text{ mm}$, the operator could downsize the balloon diameter based on clinical judgment

MUSIC: Multicenter Ultrasound Stenting in Coronaries Study; MLA: Minimum lumen area; AVIO: Angiography *vs* IVUS Optimization; IVUS: Intravascular ultrasound.

and guide PCI and also provides information on the extent of calcium, the need for vessel preparation and the selection of device size and type. The presence of circumferential calcium can lead to plaque pretreatment with rotablation or cutting/scoring balloon prior to stent implantation. Post-intervention imaging has the potential to detect PCI complication, including the presence of edge dissections and plaque protrusion. It verifies stent expansion and apposition, as well as the need for post-dilatation or additional stent implantation. Randomized clinical studies of IVUS guidance for stent implantation have used various criteria to define an optimal result (Table 1)^[20,21].

Impact of IVUS on restenosis and adverse events

Several post-intervention IVUS findings have been associated with restenosis and stent thrombosis. Smaller post-procedure lumen dimensions, residual reference segment stenosis, stent underexpansion, thrombus and dissections have been reported to be IVUS predictors of restenosis or stent thrombosis^[22-25].

Stent underexpansion has been the most important mechanism of stent failure (Figure 2). In a large study of 550 patients treated with sirolimus-eluting stent implantation, the target IVUS criterion for stent expansion was a post-procedural final in-stent MLA measuring $\geq 5.0 \text{ mm}^2$ more than the distal reference segment lumen area. The only independent predictors of angiographic restenosis were final in-stent MLA by IVUS (OR = 0.586, 95%CI: 0.387-0.888, $P = 0.012$) and IVUS-measured stent length (OR = 1.029, 95%CI: 1.002-1.056, $P = 0.035$). The final in-stent MLA that best predicted restenosis was 5.5 mm^2 ^[26]. In IVUS substudies of the TAXUS IV, V, and VI and TAXUS ATLAS Workhorse, Long Lesion, and Direct Stent trials, which comprised 1580 patients, the optimal thresholds of post-intervention IVUS in-stent MLA that best predicted angiographic in-stent restenosis at 9 mo were 5.7 mm^2 for paclitaxel-eluting stents and 6.4 mm^2 for bare metal stents (BMS)^[27]. Consistent with these observations, the optimal post-intervention in-stent MLA to predict angiographic restenosis of the

second generation drug-eluting stents was 5.3 mm^2 for zotarolimus-eluting stents and 5.4 mm^2 for everolimus-eluting stents^[28]. However, a single cutoff value to define optimal stent implantation or to predict restenosis should be used cautiously because these studies enrolled patients with different risks for restenosis or lesion complexity.

Recently, Kang *et al.*^[29] reported the best IVUS-MLA criteria that predicted angiographic in-stent restenosis on a segmental basis after left main intervention. Underexpansion was defined as post-stenting IVUS-MLA $< 5.0 \text{ mm}^2$ at the ostial left circumflex, $< 6.3 \text{ mm}^2$ at the ostial left anterior descending, $< 7.2 \text{ mm}^2$ at the polygon of confluence, and $< 8.2 \text{ mm}^2$ at the proximal left main above the polygon of confluence. Post-stenting underexpansion was an independent predictor of 2-year major adverse cardiac events, particularly repeat revascularization, while stent malapposition did not predict restenosis or major adverse cardiac events.

Few studies have reported stent malapposition as a predictor of early^[30] or very late stent thrombosis^[31]. However, several IVUS studies have failed to identify incomplete stent apposition as a predictor of clinical adverse events^[32,33]. The IVUS substudy of the HORIZONS-AMI trial reported smaller final lumen dimensions because of tissue protrusion through stent struts and/or stent underexpansion and inflow/outflow disease (residual stenosis or stent edge dissections) but not acute malapposition as a predisposing factor of early stent thrombosis in acute myocardial infarction^[34].

IVUS-guided PCI

In the pre-drug-eluting stent era, several studies assessed whether IVUS-guided stent implantation improves clinical outcomes compared with standard, angiography-guided PCI. However, these studies enrolled relatively small numbers of patients and were underpowered to definitively assess the role of IVUS guidance on clinical endpoints. In a meta-analysis of 7 randomized trials ($n = 2193$) IVUS-guided BMS implantation was associated with a significantly lower rate of angiographic restenosis compared with angiographic-guided strategy (22% *vs*

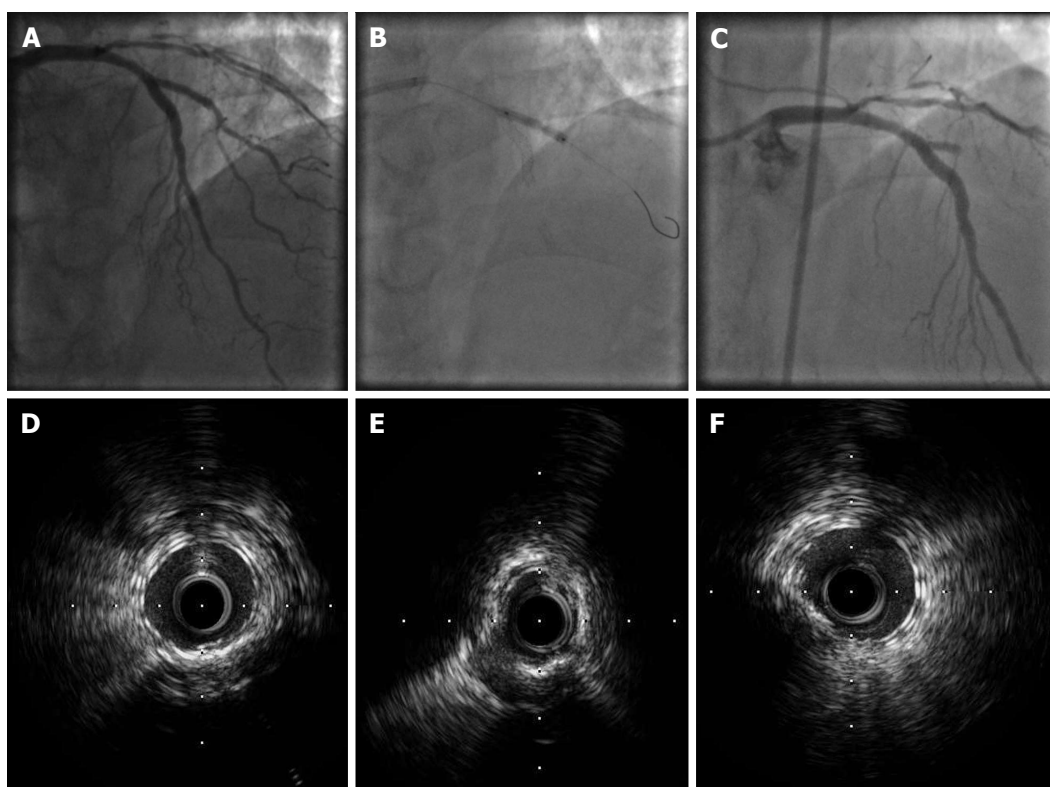


Figure 2 Intravascular ultrasound findings in patient with stent failure. A: Left anterior descending-Diagonal bifurcation treated with everolimus-eluting stent implantation in the left anterior descending and bioabsorbable everolimus-eluting scaffold implantation (T-stenting) in the diagonal branch; B: Post-dilatation with a noncompliant balloon in the diagonal branch; C: Four days later, the patient presented with acute myocardial infarction and stent thrombosis in the diagonal branch; D-E: Post-intervention IVUS showed stent underexpansion in the mid part of the diagonal branch (E) with good stent expansion at the proximal part (D) and at the distal part (F) of the diagonal branch. IVUS: Intravascular ultrasound.

29%, respectively, $P = 0.02$), with no significant effect for myocardial infarction (3.6% *vs* 4.4%, respectively $P = 0.51$) or mortality (2.4% *vs* 1.6%, respectively, $P = 0.18$)^[35]. In a larger meta-analysis of 2972 patients, IVUS-guided strategy demonstrated a reduced risk of binary restenosis, repeat revascularization and major adverse cardiac events, without significant benefits in death or myocardial infarction^[36].

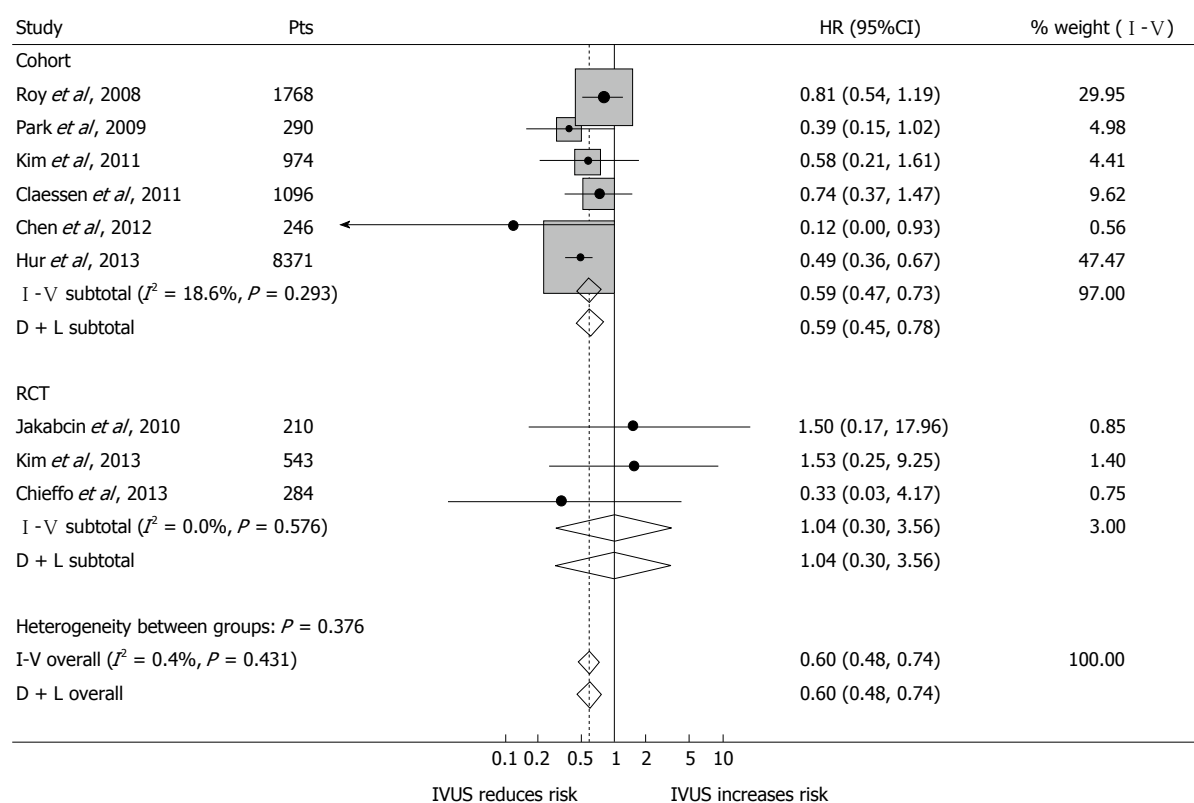
In the drug-eluting stent (DES) era, limited data from randomized trials on IVUS-guided DES are available. Recently, the Angiography *vs* IVUS Optimization (AVIO) study evaluated the safety and efficacy of IVUS *vs* angiography-guided DES post-dilatation in 284 patients with complex lesions (bifurcation, long lesions, chronic total occlusions or small vessels). IVUS guidance showed a larger final in-lesion minimum lumen diameter ($2.70 \text{ mm} \pm 0.46 \text{ mm}$ *vs* $2.51 \pm 0.46 \text{ mm}$, $P = 0.0002$), with no impact on major adverse cardiac events or target lesions revascularization at 24 mo. However, an angiographic follow-up was performed in only one-third of the patients, and in this group the restenosis rates were 17.5% in the IVUS group and 28.6% in the angiography group. Moreover, the top enrollment centers had substantial experience with IVUS, and operators may develop an “IVUS eye” that leads to the ability to perform aggressive post-dilatation even with angiography guidance alone^[21]. A meta-analysis of 18707 patients from 3 randomized

IVUS *vs* angiography-guided studies and 9 high quality cohort studies found that IVUS guidance reduced the risk of major adverse cardiac events (RR = 0.80, 95%CI: 0.71-0.89, $P = 0.001$). This technique was associated with a reduced risk of mortality (RR = 0.60, 95%CI: 0.48-0.74, $P = 0.001$), myocardial infarction (RR = 0.59, 95%CI: 0.44-0.80, $P = 0.001$) and thrombosis (RR = 0.50, 95%CI: 0.32-0.80, $P = 0.007$) but not of revascularization (RR = 0.95, 95%CI: 0.82-1.09, $P = 0.75$) (Figure 3)^[37]. This meta-analysis is supported by a recently published large-scale prospective, multicenter, non-randomized ADAPT-DES study of 8583 “all-comers” patients. In propensity adjusted multivariable analysis, IVUS guidance compared to angiography reduced the risk of stent thrombosis (0.6% *vs* 1.0%, respectively, $P = 0.003$), myocardial infarction (2.5% *vs* 3.7%, respectively, $P = 0.004$) and major adverse cardiac events (3.1% *vs* 4.7%, respectively, $P = 0.002$) within 1 year following DES implantation^[38]. IVUS guidance was particularly beneficial among patients with acute coronary syndromes and complex lesions, including left main, bifurcations and multivessel disease. In contrast, Ahmed *et al*^[39] reported that the use of IVUS guidance for stent deployment failed to improve 12-mo mortality rates in patients presenting with acute myocardial infarction.

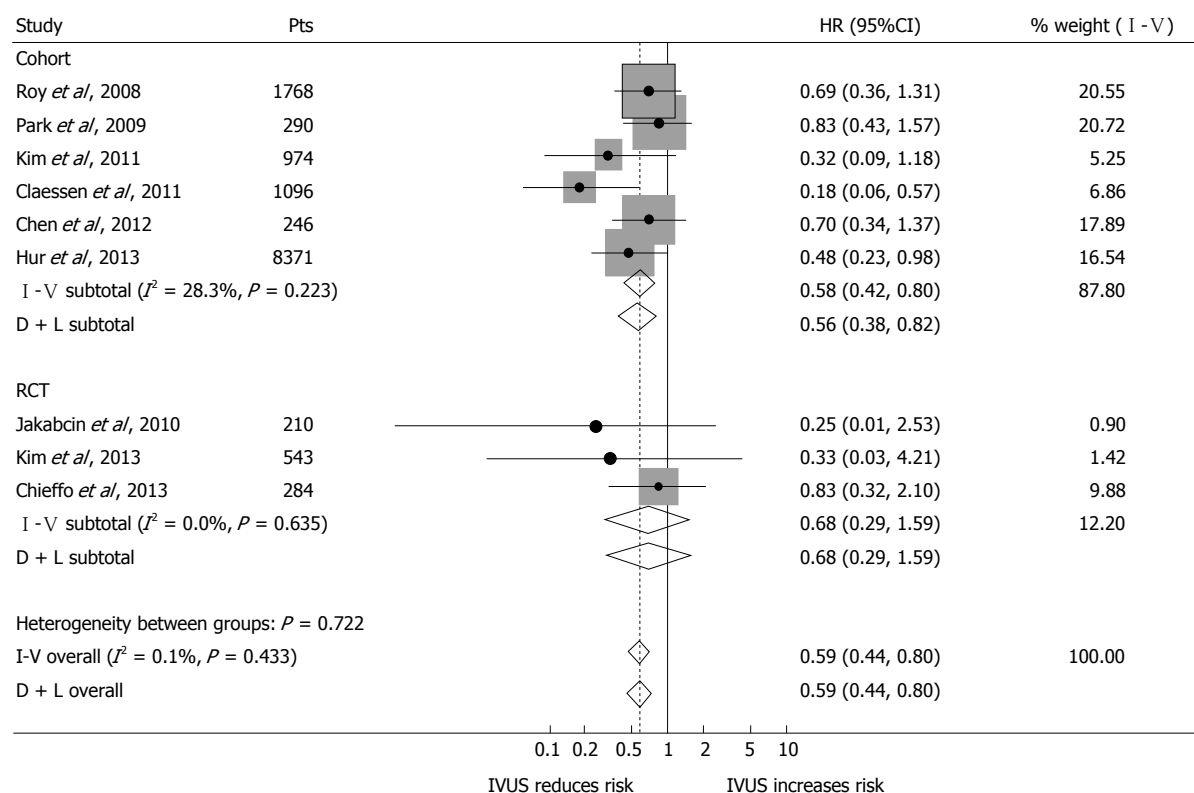
IVUS-guided PCI of left main lesions

In the MAIN-COMPARE multicenter registry, 975 pa-

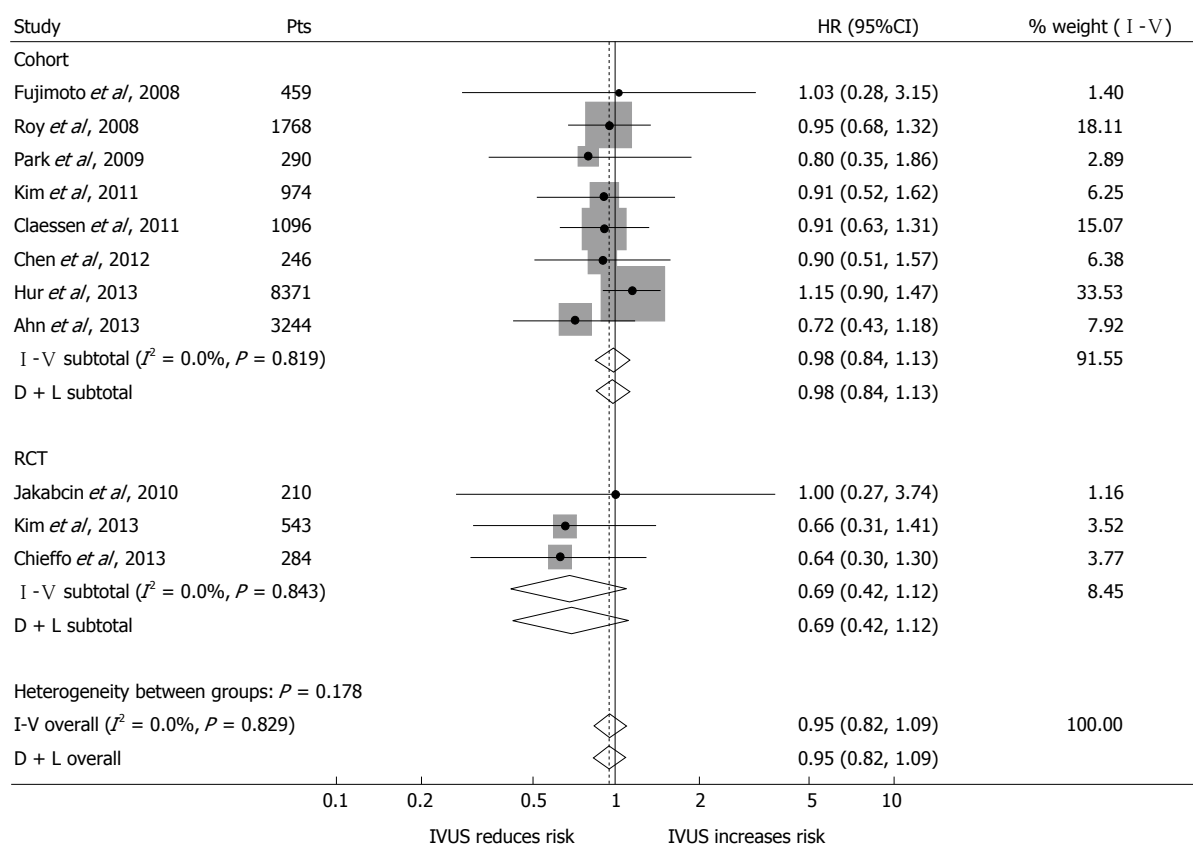
IVUS and dead (primary population)



IVUS and MI (primary population)



IVUS and TVR_TLR (primary population)



IVUS and thromb (primary population)

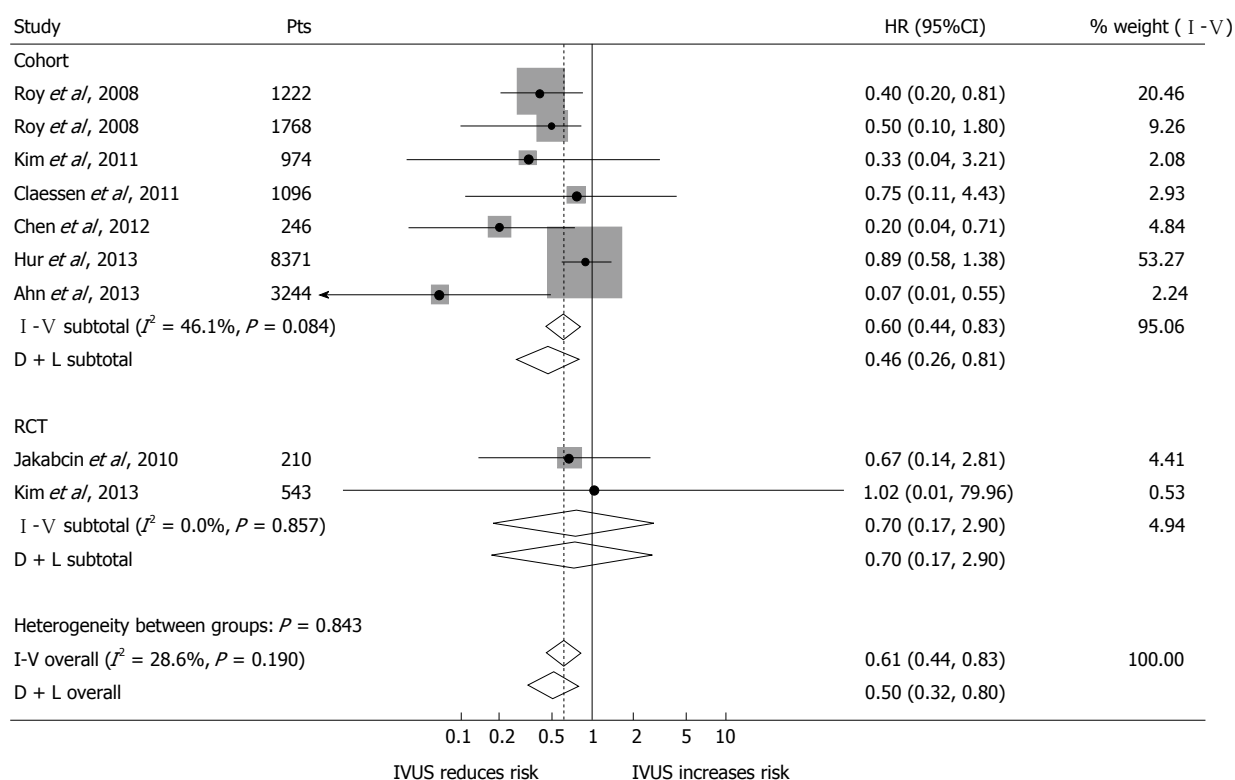


Figure 3 Impact of intravascular ultrasound vs angiography guidance of percutaneous coronary intervention on clinical outcomes. A Forrest plot of the secondary endpoints [*i.e.*, death, myocardial infarction (MI), target vessel and lesion revascularization (TVR_TLR), thrombosis]. Diamonds represent the meta-analytic estimates and 95%CI. Adapted from [37]. IVUS: Intravascular ultrasound.

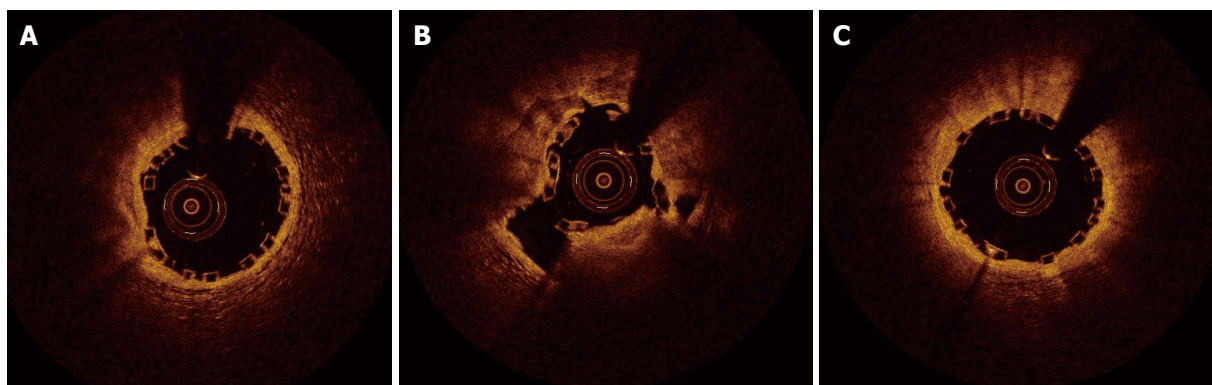


Figure 4 Optical coherence tomography findings in patient with stent underexpansion. A-C: Post-intervention OCT of the diagonal branch after bioabsorbable scaffold implantation in a patient who presented 4 d later with stent thrombosis and acute myocardial infarction. OCT showed stent underexpansion of the mid part of the diagonal branch (B) with good stent expansion at the proximal (A) and distal (C) part of the diagonal branch. OCT: Optical coherence tomography.

tients with unprotected left main coronary artery stenosis underwent PCI under the guidance of IVUS or angiography alone. In the propensity-score matched comparison, IVUS guidance showed a trend towards lower 3-year mortality rates (6.0% in the IVUS group *vs* 13.6% in the angiography group, log-rank $P = 0.063$; HR = 0.54; 95%CI: 0.28-1.03; Cox-model $P = 0.061$). In particular, patients receiving DES had significantly lower mortality rates with IVUS guidance (4.7% *vs* 16.0%, log-rank $P = 0.048$; HR = 0.39; 95%CI: 0.15-1.02; Cox model $P = 0.055$), but after BMS implantation, the IVUS guidance did not reduce the risk of death^[40]. Our Latvian randomized trial comparing paclitaxel-eluting stents to BMS in treating unprotected left main coronary artery stenosis demonstrated that PCI with IVUS guidance and cutting balloon pre-treatment is safe and effective for up to 3 years after intervention^[41,42]. Therefore, we strongly support the mandatory use of IVUS for left main PCI.

Although large prospective studies appear to support IVUS-guided DES implantation, randomized trials have been underpowered to definitively assess the clinical utility of IVUS guidance because of their small sample sizes and low event rates, including restenosis or highly morbid complications.

OCT-guided PCI

OCT has evolved from time-domain to frequency-domain imaging, which does not require proximal balloon occlusion and allows imaging of long coronary segment in a few seconds. OCT provides greater resolution than IVUS and excellent contrast between lumen and vessel wall imaging. Therefore, OCT can assess coronary plaque morphologies and identify suboptimal stent failure (*e.g.*, incomplete stent apposition, intrastent tissue protrusion, stent edge dissection, and intrastent thrombus) that is missed by IVUS. Similar to IVUS, OCT can be used to identify stent underexpansion (Figure 4). In 73 consecutive patients (80 vessels) evaluated by OCT, the incidence of edge dissection was 25%, but this incidence were not associated with clinical events during hospitalization^[43]. The clinical significance of edge dissections and other parameters identified by OCT must be addressed by pro-

spective trials.

FD-OCT provides more accurate quantitative analysis of lumen. In the OPUS-CLASS study, the *in vivo* minimum lumen diameter and area measured by FD-OCT was significantly greater than those measured by quantitative coronary angiography (QCA) but smaller than those measured by IVUS. In a phantom model, the mean lumen area by FD-OCT was equal to the actual lumen area of the phantom model, while IVUS overestimated the area measurements^[44]. The difference in lumen measurements between the 2 techniques is likely caused by the superior ability of FD-OCT to visualize the lumen-intima interface. Therefore, caution should be exercised before using the recommended IVUS parameters to assess lesion significance and to guide PCI by FD-OCT. The disadvantage of OCT is its limited far-field penetration. Thus, it may be more difficult to measure the true vessel size (external elastic membrane) and to identify a landing zone with the smallest plaque burden to minimize geographical miss.

In the CLI-OPCI study, Prati *et al*^[45] compared OCT guidance on top of angiography for routine PCI to angiographic guidance alone in 670 patients. OCT guidance was associated with a significantly lower risk of cardiac death (3.3% *vs* 6.9%, respectively, $P = 0.035$) and the composite of cardiac death, myocardial infarction, or repeat revascularization at 1 year. Thus, OCT is a safe and feasible tool for PCI guidance. However, further investigations are needed to confirm whether the use of FD-OCT will improve clinical outcomes.

OCT vs IVUS for PCI guidance

There are ongoing discussions as to whether FD-OCT has the potential to replace IVUS for PCI guidance. In a small prospective, single center study of 70 patients, FD-OCT guidance was compared with IVUS guidance for coronary stent implantation. Although both devices showed similar accessibility and there was no significant difference for stent apposition, FD-OCT guidance demonstrated a smaller final minimum stent area, as well as smaller stent expansion and more frequent significant residual reference segment stenosis. Researchers con-

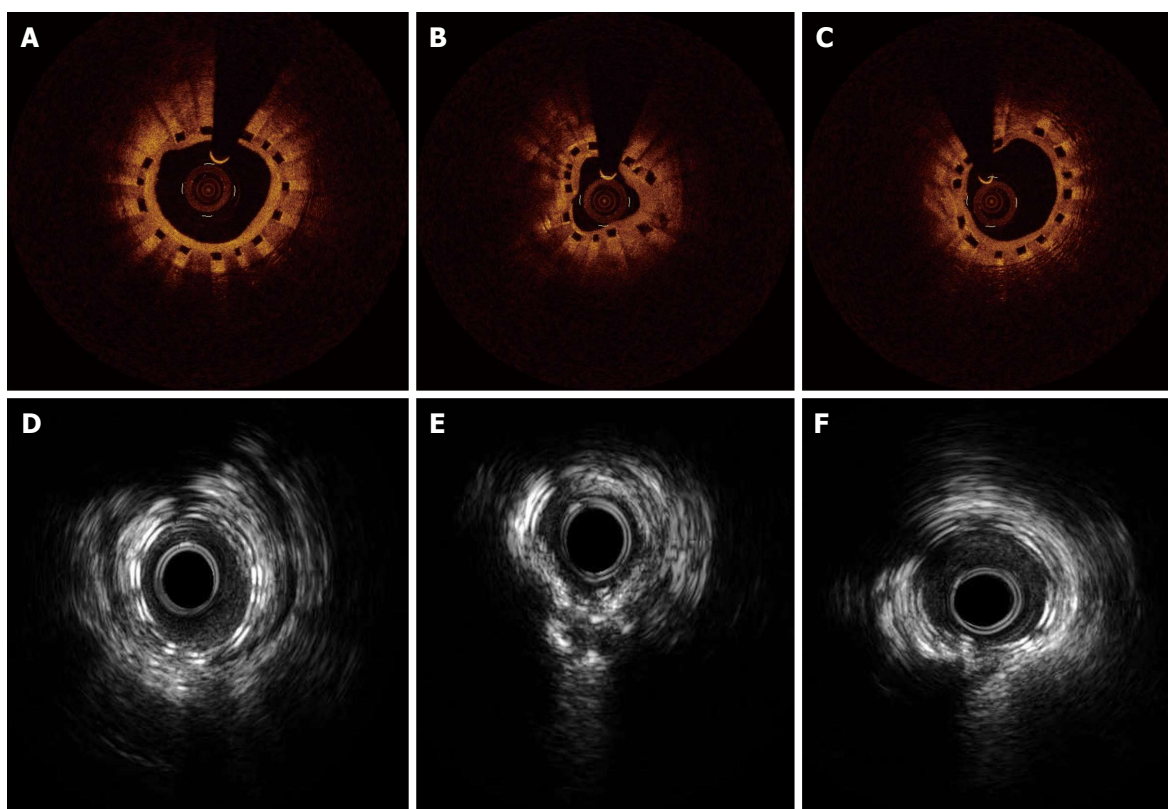


Figure 5 Intravascular ultrasound and optical coherence tomography findings 1 yr after bioabsorbable stent implantation. A-C: The OCT findings 12 mo after bioabsorbable scaffold implantation showed complete strut coverage; D-E: IVUS also shows uncovered struts in the same patient. IVUS: Intravascular ultrasound; OCT: Optical coherence tomography.

cluded that OCT has several limitations for optimal stent deployment because of the poor visibility of the vessel border. Good vessel border visibility at the MLA site was more frequently observed in the IVUS group both prior to intervention (94.3% *vs* 8.6%, $P < 0.001$) and post-intervention (94.3% *vs* 11.4%, $P < 0.001$). This difference in visibility resulted in a lower frequency of post-dilatation and lower stenting and post-dilatation pressure in the OCT group^[46]. Further studies are warranted to determine whether IVUS or OCT is better suited to improve clinical outcomes after stent implantation.

EVALUATION OF NEOINTIMAL COVERAGE AFTER PCI

Intravascular imaging methods have been used to assess the vascular response to stent implantation during follow-up. Endothelial coverage is a powerful histological predictor of stent thrombosis. Post-mortem studies have shown that uncovered struts are strongly associated with late stent thrombosis^[47]. With the introduction of OCT, it is possible to perform strut level analysis and to evaluate neointimal growth and stent apposition on each stent strut. Because OCT has higher resolution compared to IVUS, it is more sensitive for detailed strut-level analysis of tissue coverage and apposition (Figure 5). Stent struts are classified on OCT into four main categories: embedded-covered, protruding-covered, uncovered-

apposed, uncovered malapposed struts. In a subanalysis of the ODESSA trial, 8% of the stented segments with no detectable neointimal coverage by IVUS were found to have tissue coverage of the stent struts by OCT^[48]. In a study of 34 patients (6840 struts), the prevalence of struts covered by neointima that were undetectable by IVUS was 64% at the 6-mo follow-up after sirolimus-eluting stent implantation. A total of 16% of the struts showed full coverage by neointima, whereas the average rate of neointima-covered struts in an individual stents was 89%^[49]. In a formal substudy of HORIZONS-AMI trial, OCT was performed at 13 mo in 118 patients after paclitaxel-eluting stent or BMS implantation. An analysis of 44139 struts revealed reduced neointimal hyperplasia and a greater percentage of uncovered struts, as well as higher percentage of malapposed struts in paclitaxel-eluting stents compared with BMS. While these observations are important in term of stent design, further studies are needed to determine the clinical significance of these findings^[50].

OCT also plays a critical role in assessing bioabsorbable scaffolds. OCT is capable of an accurate assessment of polymeric struts, which are seen as “boxes”, scaffold degradation and neointimal formation at follow-up^[51].

CONCLUSION

Compared to angiography, intravascular imaging provides additional anatomic information regarding vessel wall

changes in atherosclerosis, but these methods should be used cautiously for the physiologic assessment of coronary artery disease. Therefore, the use of intravascular imaging and FFR should be complementary to guide decision making in certain coronary lesions. Because of their excellent imaging quality and spatial resolution, IVUS and OCT are the best tools for evaluating optimal stent deployment. Successful PCI of complex lesions often requires IVUS guidance, novel devices and advanced operator skills. The current perception and adoption of innovative interventional devices, such as bioabsorbable stents, will increase the need for intravascular imaging. Today, the routine use of intravascular imaging in daily practice remains controversial. Adequately powered randomized trials are needed to support IVUS or OCT use in routine clinical practice and to determine whether OCT is superior to IVUS in reducing adverse events when used to guide PCI. Selective angiography will remain vital for managing coronary artery disease. Intravascular modalities will complement rather than replace this “gold standard” and will be routinely used in selected patients. The future of intravascular imaging is the integration of functional and anatomical assessment and the usage of multiple imaging modalities in a complementary manner to diagnose and manage coronary artery disease.

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WJC 6th Anniversary Special Issues (2): Coronary artery disease

Role of cardiovascular magnetic resonance in assessment of acute coronary syndrome

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Abstract

Cardiovascular disease (CVD) is the leading cause of death in the western world and is becoming more important in the developing world. Recently, advances in monitoring, revascularisation and pharmacotherapy have resulted in a reduction in mortality. However, although mortality rates have declined, the burden of disease remains large resulting in high direct and indirect healthcare costs related to CVDs. In Australia, acute coronary syndrome (ACS) accounts for more than 300000 years of life lost due to premature death and a total cost exceeding eight billion dollars annually. It is also the main contributor towards the discrepancy in life expectancy between indigenous and non-indigenous Australians. The high prevalence of CVD along with its associated cost urgently requires a reliable but non-invasive and cost-effective imaging modality. The imaging modality of choice should be able to accelerate the diagnosis of ACS, aid in the risk stratification of de novo coronary artery disease and avail incremental

information of prognostic value such as viability which cardiovascular magnetic resonance (CMR) allows. Despite its manifold benefits, there are limitations to its wider use in routine clinical assessment and more studies are required into assessing its cost-effectiveness. It is hoped that with greater development in the technology and imaging protocols, CMR could be made less cumbersome, its imaging protocols less lengthy, the technology more inexpensive and easily applied in routine clinical practice.

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Key words: Cardiovascular disease; Acute coronary syndrome; Cardiac imaging

Core tip: This review focuses on cardiovascular magnetic resonance in achieving speedy diagnosis, risk stratification and prognostication in acute coronary syndrome. It discusses the modalities already available towards achieving this end and the incremental information availed by cardiac magnetic resonance. The paper also discusses new imaging techniques and their contribution towards the cardiac magnetic resonance imaging assessment of patients with acute coronary syndrome.

Azarisman SM, Teo KS, Worthley MI, Worthley SG. Role of cardiovascular magnetic resonance in assessment of acute coronary syndrome. *World J Cardiol* 2014; 6(6): 405-414 Available from: URL: <http://www.wjgnet.com/1949-8462/full/v6/i6/405.htm> DOI: <http://dx.doi.org/10.4330/wjc.v6.i6.405>

INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of death in the western world and is becoming more im-

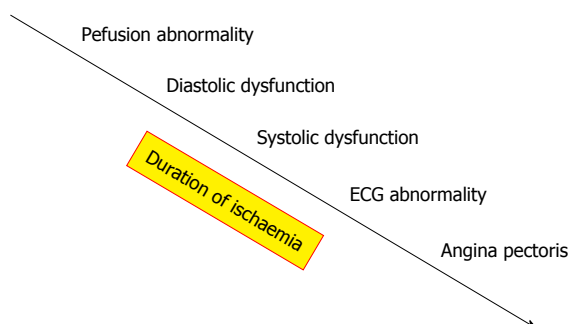


Figure 1 Cascade of events following coronary artery occlusion. (Adapted from Gani *et al*^[14]). ECG: Electrocardiography.

portant in the developing world^[1,2]. Recently, advances in monitoring, revascularisation and pharmacotherapy have resulted in a reduction in mortality. However, although mortality rates have declined, the burden of disease remains large resulting in high direct and indirect healthcare costs related to CVDs^[3-5]. In Australia, acute coronary syndrome (ACS) accounts for more than 300000 years of life lost due to premature death and a total cost exceeding eight billion dollars annually. It is also the main contributor towards the discrepancy in life expectancy between indigenous and non-indigenous Australians^[6]. In the United States and Europe, approximately 15 million patients are treated annually for chest pain and suspicion of myocardial infarction (MI) and upwards of 20% are eventually diagnosed to have ACS^[2,7].

The high prevalence of CVD along with its associated cost urgently requires a reliable but non-invasive and cost-effective imaging modality. The imaging modality of choice should be able to accelerate the diagnosis of ACS, aid in the risk stratification of de novo coronary artery disease (CAD) and avail incremental information of prognostic value such as viability.

ACUTE CORONARY SYNDROME

It is well established that ACS refers to a spectrum of clinical presentations ranging from unstable angina to non ST-elevation myocardial infarction and ST-elevation myocardial infarction. These presentations refer to clinical symptoms compatible with myocardial ischaemia resulting from acute thrombosis induced by a ruptured or eroded atherosclerotic coronary artery plaque^[1-4].

The main management strategy for ACS is prompt diagnosis leading to early coronary reperfusion. The usual assessment sequence involves a detailed case history delineating the patient's risk factor profile, appropriate physical examination, electrocardiography (ECG) and laboratory risk markers such as creatine kinase and troponin levels.

Early reperfusion limits the final infarct size, halts progression of myocardial necrosis and and optimises myocardial salvage thereby improving both short and long term outcomes^[8,9]. Pertaining to these established aims, several questions need to be answered. What is the regional and global ventricular function, what is the

extent of myocardial necrosis, is there any viable myocardium and are the epicardial coronary arteries patent?^[10-12].

Over the past two decades, noninvasive imaging has emerged as the investigative modality of choice for ACS. It allows comprehensive cardiac assessment of patients, risk stratification of patients with ACS at an early management time point and provides diverse and complementary information regarding possible differential diagnoses and prognosis^[13-15].

NONINVASIVE ASSESSMENT

Early coronary reperfusion following diagnosis of ACS results in myocardial salvage and prevents irreversible injury^[16,17]. Usual investigative tools such as ECG and Troponin assays are helpful but may be negative early. Echocardiography, although useful in establishing regional wall motion abnormalities and quantifying ventricular ejection fraction, can also be negative early as these abnormalities appear later in the temporal cascade of events following coronary artery occlusion (Figure 1). Furthermore, echocardiographic assessment lacks the tissue characterisation ability needed to rule out differentials such as myocarditis. Over the past two decades, computed tomography (CT) has emerged as a potentially useful imaging modality for ACS.

COMPUTED TOMOGRAPHY BASED IMAGING

Positron emission tomography

Positron emission tomography (PET) utilises several radionuclides namely ¹⁸F-Fluorodeoxyglucose (¹⁸FDG) for myocardial metabolism and ¹³N-Ammonia (¹³NH₃) for myocardial perfusion assessment^[18]. Myocardial segments with normal glucose metabolism and preserved myocardial flow indicate viable and adequately perfused myocardium. ¹⁸FDG allows differentiation between hibernating but viable, with infarcted and non-viable myocardium in regions with wall motion abnormalities when interpreted together with ¹³NH₃^[19,20]. Although clinically useful in identifying metabolism/perfusion mismatch in stable CAD, its utility in the setting of ACS is limited due to restricted availability, high costs, and limited data supporting its application^[21].

Coronary angiography

Computed tomography coronary angiogram (CTCA) is becoming a useful tool for evaluation of patients with ACS. It can be utilised both in the diagnosis and risk stratification of ACS^[22,23]. Three recent trials affirmed the utility of employing CTCA for rapid triage *via* radiographic demonstration of the absence of coronary artery disease in low to intermediate risk patients^[24-26]. Whilst all three trials reported more rapid and cost efficient discharge from the Emergency Department with the use of CTCA, the CT-STAT and ROMICAT II trials reported an increase in downstream testing and radiation exposure

with no decrease in the overall costs of care^[25,26]. Although the appropriate use criteria endorses its use in low to intermediate risk patients, it is primarily an exclusion tool with limited suitability for higher cardiac risk patients or pathological stress testing^[27].

Calcium score

Coronary artery calcification can be evaluated by electron beam CT and multi-detector CT. It describes the extent of coronary arteriosclerosis and is correlated with increased cardiac risk. It has a high negatively predictive value, and can reliably exclude ACS in low to intermediate risk patients presenting with chest pain^[28-30]. Unfortunately, its positive predictive value is unsatisfactory and a positive result usually warrants further downstream investigation. Moreover, conclusive evidence on its use in conjunction with other CT modalities such myocardial perfusion imaging (MPI) is still deficient^[14,31].

MPI

Rest MPI becomes abnormal at the onset of impaired myocardial blood flow and therefore precedes other symptoms and signs of ACS. The non-invasive detection of a resting perfusion defect can be achieved with single-photon emission CT (SPECT), PET, cardiovascular magnetic resonance (CMR) and contrast enhanced echocardiography^[32-34].

Resting myocardial perfusion is preserved with increasing severity of coronary stenosis through autoregulatory mechanisms in the microcirculation. This is exhausted when critical coronary artery stenosis develops and a resting myocardial perfusion abnormality will appear with complete occlusion of the coronary artery^[35].

Cardiac CT based MPI has been utilised in animals since the late 1970s but its use in detection of MI only took off in mid-2000^[36-38]. Resting MPI in addition to CTCA improves its diagnostic accuracy for detecting significant coronary artery disease. Studies have shown that in patients with chest pain, MPI with CTCA helps clarify the diagnosis of ACS^[39-41]. Unfortunately rest MPI is not sensitive enough to identify the majority of ischaemic segments and vasodilator-induced hyperemia is required to detect significant disease^[42-44].

Stress MPI detects the presence of a flow-limiting coronary stenosis by detecting regional variations in perfusion reserve. During vasodilator-induced hyperaemia, blood flow will not increase in already dilated arteriolar bed of stenosed coronary arteries. However, perfusion of normal coronaries will increase significantly and the resultant increase over resting blood flow is referred as the perfusion reserve. Consequently, the perfusion reserve of normal coronary territories will be greater than that of critically stenosed coronary territories and this regional discrepancy is detected by stress MPI^[32-34].

Stress MPI is especially helpful in patients with coronary calcification and stents, with studies reporting a sensitivity and specificity of at least 95%^[45,46]. Most studies however, report a sensitivity of between 50%-90%

and specificity of 50%-98% when compared with either SPECT, CMR or invasive fractional-flow reserve (FFR) studies^[32,45-50].

The major limitation to CT based rest and stress MPI, as with other CT based modalities, especially in research with comprehensive protocols remains exposure to ionizing radiation. Lack of long-term follow-up data of patients presenting to Emergency Department with chest pain and subsequently diagnosed with ACS is also compelling. Furthermore, although more recent studies have shown greater ability of different CT-based modalities in diagnosing and risk stratifying ACS, their utility remains only with those in the low to intermediate risk group. Cost effectiveness also becomes questionable with greater need for downstream investigation and greater overall cost of care especially in those with moderate to high risk of ACS.

Magnetic resonance imaging

In an Emergency setting, accurate early diagnosis of ACS along with efficacious institution of treatment is the main objective. As aforementioned, ECG and biomarkers are all helpful but may not be able to pick out early or equivocal ACS. Furthermore, these tests are presently unable to distinguish with certainty, ACS from other potential differentials, establish the extent of myocardial involvement, determine whether the damage is reversible, or even define the culprit artery with any reliability.

CMR offers high spatial resolution, accuracy and high reproducibility thereby allowing detailed volume and functional assessment, excellent tissue characterization in any tomographic plane and exceptional prognostic ability with late gadolinium enhancement (LGE) imaging (Figure 2). Radiation free examination also affords the CMR with the ability to incorporate extensive imaging protocols and repeated imaging necessary for both clinical and research imperatives.

Studies have already shown that CMR techniques such as myocardial function, perfusion imaging and LGE is able to provide a more accurate diagnosis of ACS compared with standard clinical assessment that includes ECG and biomarkers^[51]. The use of new imaging techniques such as T2-weighted sequences for oedema detection also increases its diagnostic performance^[52]. Moreover, unlike CT-based imaging, CMR utility can be extended to patients with intermediate to high risk for ACS but without ECG or biomarker evidence of MI^[53].

In essence, CMR represents a "one-stop-shop" for early and comprehensive assessment towards accurate and reliable diagnosis, risk stratification and prognostication of patients with ACS.

Standard magnetic resonance imaging techniques

Rest cine magnetic resonance imaging utilises steady-state free precession sequences to acquire a series of consecutive, breath-hold, long and short-axis slices (Figure 3). The excellent spatial resolution, coupled with the high contrast between blood and myocardium allows the en-

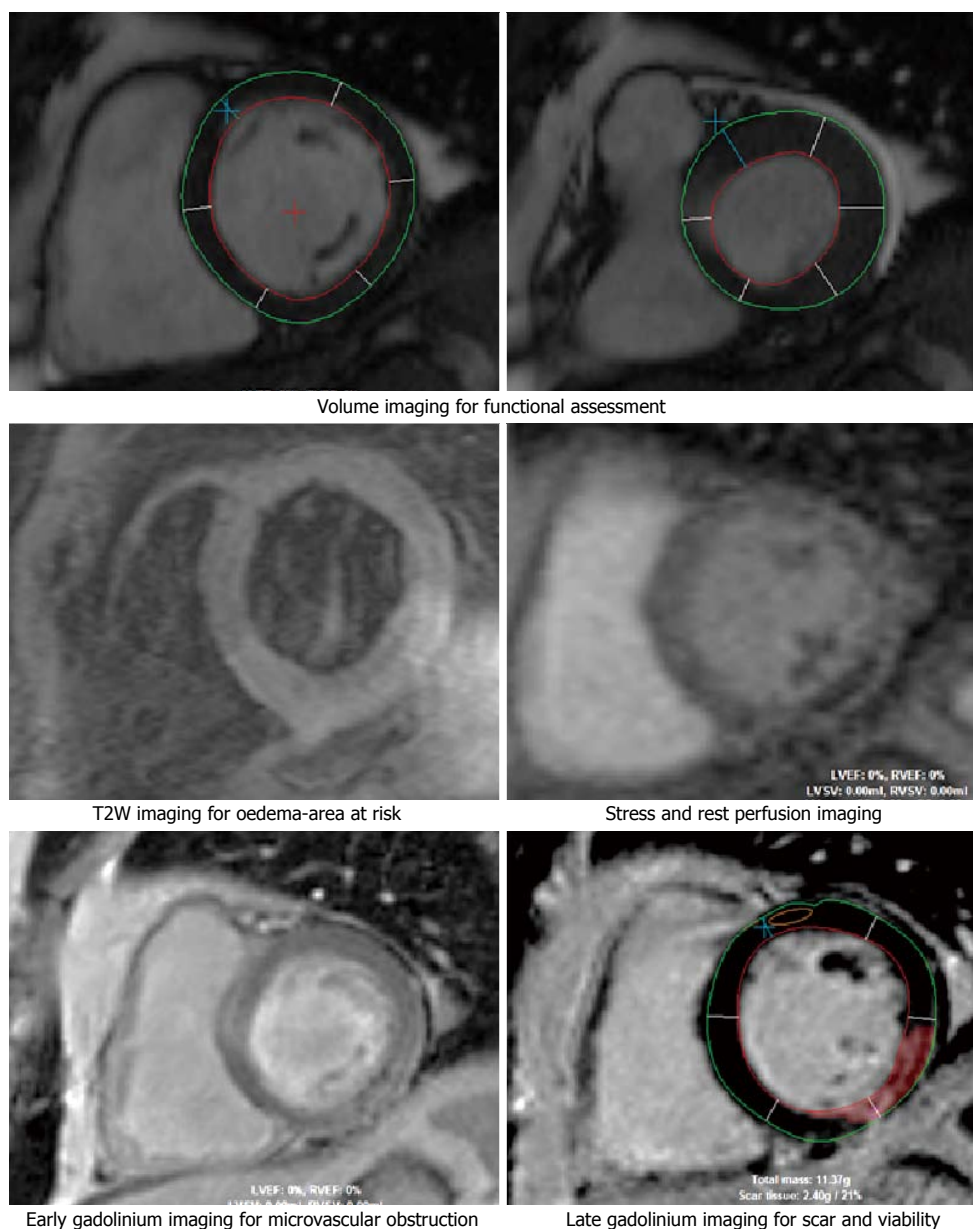


Figure 2 Cardiovascular magnetic resonance imaging sequence employed for the diagnosis of acute coronary syndrome. T2W: T2-weighted.

docardial border to be detected easily. This allows easy assessment of ventricular wall motion, ventricular volumes, ejection fraction, myocardial mass and anatomy of the extracardiac structures. These CMR assessments are accurate, reproducible and well validated^[54,55].

In the Emergency Department, these initial CMR imaging sequences can also be utilized to detect diseases of the aorta that may mimic ACS such as dissection or penetrating ulcer^[56]. Findings typical of myocarditis and Takotsubo cardiomyopathy can also be seen and confirmed by LGE^[57-60]. Initial review of the right ventricle and ventricular outflow tract, interventricular septum and pulmonary vasculature may also yield signs characteristic of acute pulmonary embolism which can then be subsequently confirmed with MR angiography^[61].

T2-weighted imaging

T2-weighted (T2W) imaging with short tau inversion re-

covery (STIR) sequences is used to detect myocardial oedema which has increased signal intensity. The presence of oedematous myocardial segments on T2W imaging is a sign of ischaemic myocardium and a negative prognostic indicator for cardiovascular events^[62]. Oedematous segments also allow acute-on-chronic differentiation of myocardial segments in established CAD patients^[63]. Acutely, T2W imaging also identifies the area-at-risk (AAR) which is defined as an area of potentially reversible myocardial injury but at risk of infarction. The extent of the AAR has been validated against histopathological and angiographic measurements and is predictive of the risk of further cardiovascular event or death^[62,64-66].

Perfusion imaging

Perfusion imaging is performed both at rest and stress (with Adenosine infusion) and assesses myocardial blood flow by capturing the transit of contrast medium through

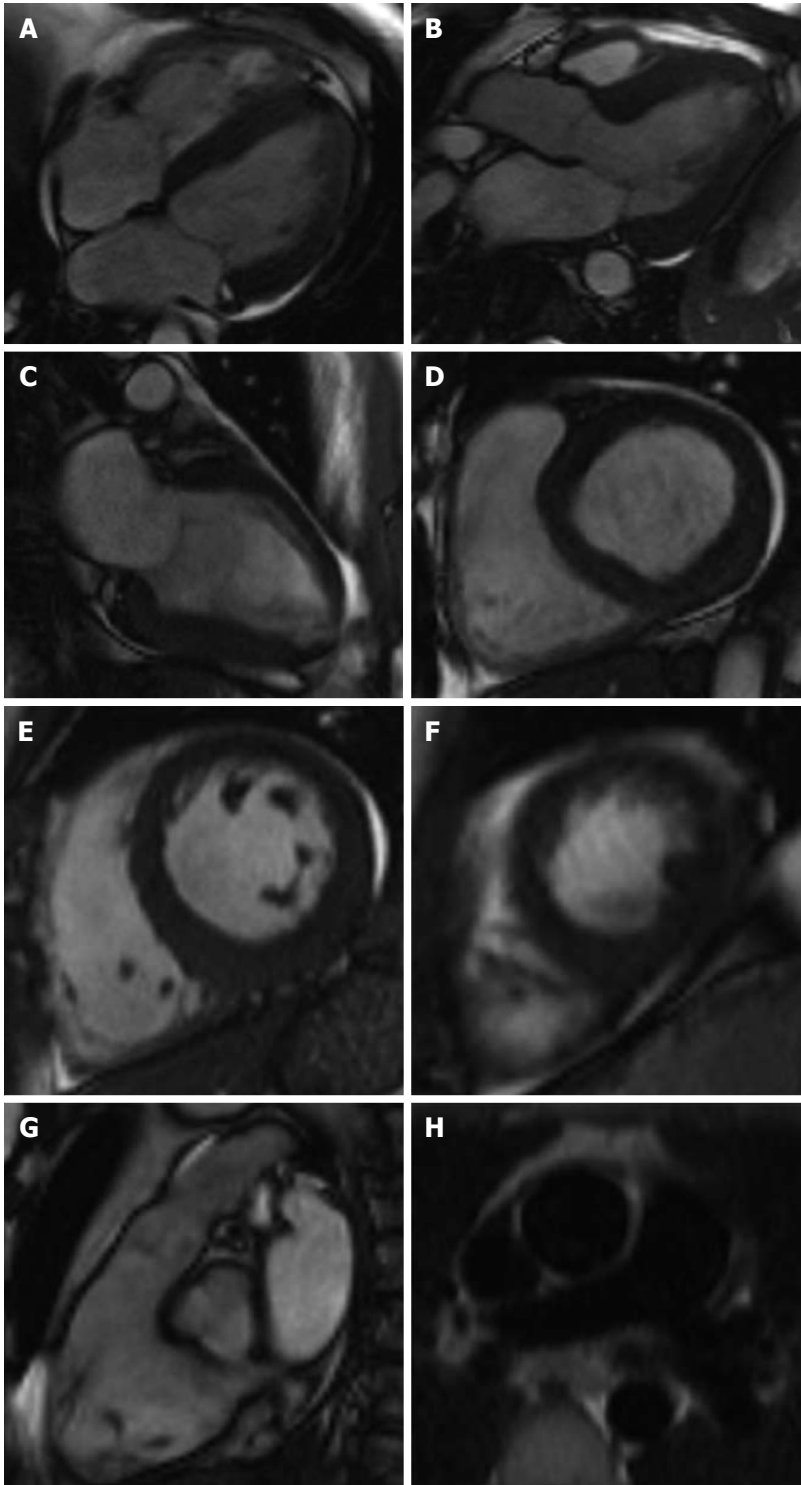


Figure 3 Standard imaging technique showing cine magnetic resonance imaging long axis views (A-C) and followed by short axis (D-F) and RVOT (G). Half-Fourier acquisition single-shot turbo spin-echo image shows the main, left and right pulmonary arteries (H).

the myocardium. It is a well established tool for assessing acute impairment in myocardial blood flow, patency of microvasculature, myocardial perfusion reserve and viability^[51,67]. In patients with chest pain with intermediate to high probability of ACS and a paucity of ischaemic signs, stress perfusion has a high negative predictive value with high diagnostic and prognostic value^[53,68].

CMR perfusion imaging is a potential alternative to

CT-based perfusion imaging due to improved subendocardial resolution, lack of ionizing radiation and cost effectiveness with reduced downstream investigation. Comparison with SPECT, PET and/or coronary angiography have shown good sensitivity and specificity of CMR in detecting perfusion defects of 87%-90% and 85%, respectively^[69,70]. Rest and stress perfusion imaging is well complemented by LGE and adds to a comprehen-

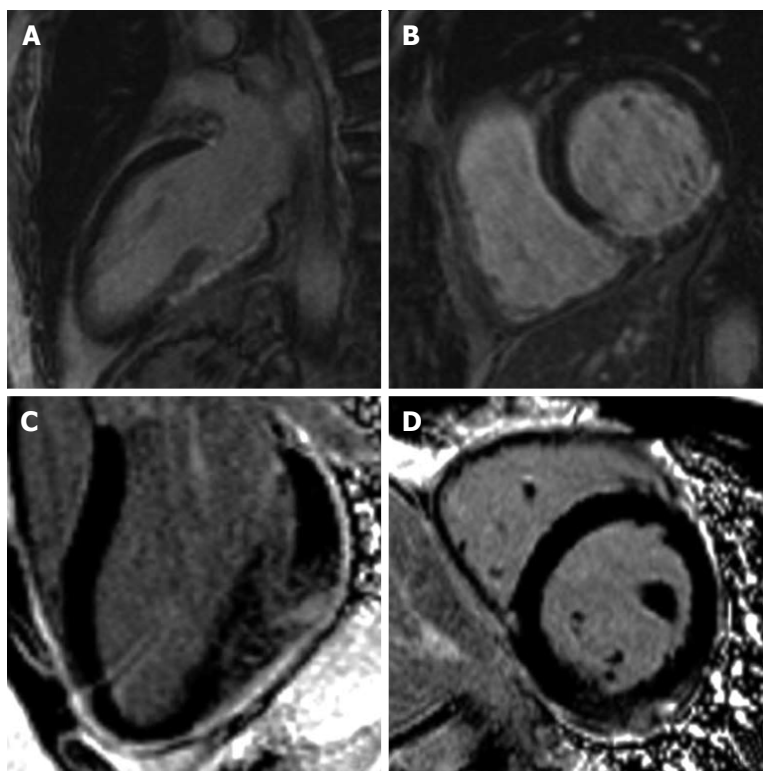


Figure 4 Late gadolinium enhancement showing two distinct hyperenhancement patterns. Subendo cardial for myocardial infarction (A and B) and epicardial for myocarditis (C and D).

sive assessment of patients with ACS. Its utility, reliability and accuracy in patients with intermediate to high risk of ACS also puts it ahead of CT-based perfusion studies.

LGE

Gadolinium based contrast is an extracellular contrast agent that accumulates in the interstitial space following myocardial death and replacement with fibrosis. Increased signal intensity denotes myocardial injury and scarring^[71]. Positive gadolinium enhancement coupled with CMRs high spatial resolution allows accurate and reliable quantification of the volume of injury and the transmural extent of the scarring^[72,73]. This is crucial in estimating the extent of the scar as a percentage of wall thickness with ramifications towards viability and therefore, reversibility of the underlying myocardial dysfunction^[74].

LGE essentially differentiates between irreversibly damaged (and thus non-viable) myocardium, from stunned myocardium which is ischaemic but viable. Acutely ischaemic but viable myocardium will have high signal intensity on T2W imaging but will be LGE negative. Generally, in a patient with MI, a transmural extent of scarring greater than 50% will signal a poor likelihood of functional recovery following revascularization^[75]. This has an important clinical ramification, as the prevalence of non-viable myocardial segments subtending the occluded epicardial artery will negate the need for immediate revascularization in an emergency setting.

LGE also has a role earlier in the diagnostic milieu of ACS by differentiating between ischaemic and non-

ischaemic causes of chest pain with biomarker rise. Differentials such as myocarditis and cardiomyopathy will have a different pattern of hyperenhancement. Ischaemia typically causes a more coalescent and subendocardial distribution of gadolinium enhancement confined to a particular vascular territory. Myocarditis has a typically epicardial or mid-myocardial distribution and cardiomyopathy has a patchy, mid-wall distribution (Figure 4).

LGE is also used in identifying microvascular obstruction (MVO) which is known angiographically as the “no reflow” phenomenon. Pathologically it is caused by failure of reperfusion at a microvascular level despite patent coronary arteries following revascularization. It is seen as a hypoenhanced core surrounded by hyperenhanced, scarred myocardium. MVO is well established as a negative prognostic marker and have been shown to be predictors of adverse remodeling following myocardial infarction^[76-78].

On another note, LGE is also of use for the detection of left ventricular (LV) thrombus which is a serious complication post-MI. It has a higher sensitivity and specificity than echocardiography for the detection of LV thrombus especially laminar, mural and apical thrombi^[79,80].

Prospect for clinical studies

CMR is already the gold-standard imaging modality for assessing left ventricular volumes, ventricular function and tissue characterization in cardiomyopathies. These factors along with infarct size and MVO are common surrogate end-points in many clinical trials and strong

predictors of clinical outcome. Other imaging sequences coming to the fore include T1 relaxation times with modified look-locker imaging, myocardial tagging and phase contrast imaging for flow assessment. These sequences are especially pertinent in assessing diastolic function which is becoming more routinely assessed and thus gaining greater importance in post-MI imaging.

Limitations of CMR

The main obstruction to incorporating CMR as a routine assessment for ACS in Emergency Department is the high capital outlay required both in terms of hardware and human resource. This limits the CMRs ability to accommodate emergency studies in an Emergency Department setting despite the manifold benefits that it offers. Likewise, newer imaging protocols introduced as part of clinical studies may lengthen the scan time beyond what is acceptable for revascularization targets and thus rule out its relevance in the Emergency setting. Having a strong magnetic field also negates its use in patients with metallic implants, aside from those who are claustrophobic. It is also not as mobile and easy to use as an echocardiogram and thus may not be usable in an intensive care unit setting for those who may gain the most from its use. More research is required into establishing the cost-effectiveness of CMR in routine clinical practice.

CONCLUSION

CMR allows comprehensive assessment of patients presenting to the Emergency department with chest pain. Its ability to accurately and reliably diagnose, risk stratify and prognosticate ACS puts it ahead of other imaging modalities currently available. Despite its manifold benefits, there are limitations to its wider use in routine clinical assessment and more studies are required into assessing its cost-effectiveness. It is hoped that with greater development in the technology and imaging protocols, CMR could be made less cumbersome, its imaging protocols less lengthy, the technology more inexpensive and easily applied in routine clinical practice.

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Clinical disease registries in acute myocardial infarction

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Core tip: Clinical disease registries are one of the oldest types of research methodology. They have been particularly important in the researching and guiding the management of myocardial infarction. Registries in multi-site studies can often be cheaper and simpler to undertake and less demanding of patients, and allow huge volumes of data to be collected from which many landmark studies already have been published.

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Abstract

Disease registries, containing systematic records of cases, have for nearly 100 years been valuable in exploring and understanding various aspects of cardiology. This is particularly true for myocardial infarction, where such registries have provided both epidemiological and clinical information that was not readily available from randomised controlled trials in highly-selected populations. Registries, whether mandated or voluntary, prospective or retrospective in their analysis, have at their core a common study population and common data definitions. In this review we highlight how registries have diversified to offer information on epidemiology, risk modelling, quality assurance/improvement and original research-through data mining, transnational comparisons and the facilitation of enrolment in, and follow-up during registry-based randomised clinical trials.

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Key words: Myocardial infarction; Acute coronary syn-

INTRODUCTION

Despite improvements in prognosis, myocardial infarction (MI) remains a major cause of death and morbidity^[1]. Significant structural, human and financial resources (nearly two billion euros/year in the United Kingdom) continue to be devoted to its management^[2]. This aspect of cardiological practice has been particularly well served by rigorous research using large randomised control trials (RCTs) of specific interventions or strategies-many of which have informed national and international guidelines^[3-5]. However, such guidelines are not automatically adopted. Clinicians may be slow to change, or uncertain where new findings fit into, their existing practice. They may fail to recognise, within a well-designed RCT, with its controlled environment, narrow inclusion criteria and intention to treat analyses, their own patient populations and complex (messy) working conditions, where what matters is not what treatment is “intended” but rather what is “given”, and the subsequent outcome. Registries

illuminate what is actually happening in practice.

Registries existed before the contemporary dominance of the RCT, and continue to flourish, as clinicians, researchers, healthcare companies, policymakers and patient advocacy groups recognise their importance. They complement the RCT, in as much as they allow an understanding of the extent to which the findings of RCTs are implemented in practice. Their analysis fills in some of the “gaps in evidence” concerning interventions for which RCTs have not been, or cannot be, performed or have not provided definitive answers. Additionally, they have a role in quality assurance, through clinical audit, and quality improvement initiatives and will play a central role in describing the outcomes of clinical care, from patient and payer perspectives.

There is no unified definition of a disease (or clinical) registry. While many registries fail to provide comprehensive outcome information the following two definitions highlight some of the key features:

“An organized system that uses observational study methods to collect uniform data (clinical and other) to evaluate specified outcomes for a population defined by a particular disease, condition or exposure, and that serves one or more predetermined scientific, clinical, or policy purposes”^[6].

“... a systematic collection of a clearly defined set of health and demographic data for patients with specific health characteristics, held in a central database for a pre-defined purpose”^[7].

So a registry is characterised by an intention to explore what is happening to patients with a particular condition or health need, pre-planning, explicit definitions of data items, a systematic approach to data collection, and a clear purpose.

In this anniversary edition, we review the historical background of registries, their characteristics, practical issues and future development in the management of myocardial infarction. Necessarily we will draw on our experience within the United Kingdom, but will also discuss other established national and international registries. We do not intend to provide an exhaustive catalogue of such registries, and mean no disrespect to colleagues whose registries we do not mention.

HISTORICAL DEVELOPMENT

The earliest registries were the personal records of individual physicians formed through their review of patient cases. These were presented and published as case series of particular conditions for the education of the wider medical community. The emphasis was on presentation and prognosis, rather than treatment of the recently recognised condition of coronary thrombosis. Examples of these early series, the precursors of the modern registry, can be found in the 1920s such as a seminal series of papers from Boston on MI and angina^[8]. By 1931, White and Bland^[9] were able to report on the prognosis of 200 cases of coronary thrombosis.

Collaborative, small scale, hospital registries began

to appear, normally containing observational reports on changing patterns of disease or outcomes of patients with MI^[10]. Interestingly, many of the most common clinical practices such as the use of the coronary care unit^[11] and description of Killip class^[12] were introduced following publication of analyses of disease registries.

In the late 1960s, there was great interest in a more collaborative international approach, to better understand the epidemiology of MI. The World Health Organisation (WHO) set up and co-ordinated a number of local MI registries (the MONICA project) which yielded much valuable information at a local level^[13]. This WHO initiative focussed on communities rather than hospitals, and was therefore able to capture information about those who died before reaching hospital and those who (as was common practice at that time) were managed at home by their general practitioners^[14]. Importantly, it promoted the collection of common datasets of information. The primary purpose remained “educational”-to more precisely describe the incidence of coronary events in a community, to categorise the various manifestations of heart attack and to compare fatality rates between communities. While others more recently have attempted to perform exhaustive community-based prospective studies of MI^[15,16] with an emphasis on expressing the “burden” of disease within a population-most existing registries are hospital-based (*i.e.*, patients are included/enrolled upon admission to hospital); the emphasis is on describing the provision of care and its effect on outcomes.

The need for a change in emphasis to allow such analysis was recognised by Hugh Tustall Pedoe in 1978 (echoing the thoughts of Osler, above): “The collection of information for its own sake is of doubtful value unless it is acted upon. Community registries should not become the equivalent of village war memorials”^[17].

He further stated that such information could be used in “monitoring the effects of treatment” and ensuring that it was “reaching those who needed it”. Here was an aspiration for registries to be used to assure provision of appropriate care and to record outcomes.

Long established, single-centre, registries (*e.g.*, the enduring Nottingham Heart Attack Registry, which began in 1972), instigated by interested clinicians rather than imposed by healthcare managers or professional bodies, provided fascinating insights into the changing management of MI^[18] but did not allow direct comparison with other units.

In some countries it was recognised that the administrative records generated to support well-developed insurance-based healthcare systems could be used for a secondary purpose: to create registries to compare care between hospitals (as “provider units”). In the United States, the Co-operative Cardiovascular Care project used billing information to investigate improvements in care, particularly for MI^[19]. The use of administrative data is now a common and cost-effective approach to data collection within registries.

More recently, there has been a general shift from registries as a mechanism for the “passive” reporting of

Table 1 Examples of key or historic exemplar registries of myocardial infarction

Registry/author	First publication year	Location	Setting	Key outcome
White ^[8]	1926	United States	Hospital	Prognosis of MI
Killip <i>et al</i> ^[12]	1967	United States	Hospital	Importance of coronary care unit
Tower Hamlets coronary project ^[14]	1972	United Kingdom	Community	Community based treatment and outcomes of MI
MONICA Project ^[23]	1987	Global	Various	Geographical variation, mortality and epidemiological trends
Second National Registry of Myocardial Infarction ^[24]	2000	United States	Hospital	Importance of door to balloon time in angioplasty
GRACE ^[25]	2002	Global	Hospital	Risk stratification in acute MI
EuroHeart Survey ^[26]	2002	European	Hospital	Quality improvement and assurance
MINAP ^[27]	2004	United Kingdom	Hospital	Epidemiology and quality improvement

MI: Myocardial infarction; MINAP: Myocardial Ischaemia National Audit Project; GRACE: Global Registry of Acute Coronary Events.

epidemiologic characteristics and the provision of treatments towards their use in an “active” process that assures and improves quality of care. Such an initiative can be appreciated in the Global Registry of Acute Coronary Events (GRACE)-a collaboration of over 100 volunteer hospitals in 14 countries to produce the largest multinational register of patients hospitalised with acute coronary syndrome^[20]. The development of this influential registry has been a milestone in the use of such data, not only in its “worldwide reach” but also in the underlying intention, to improve the care of MI.

Similar strategies of quality improvement and audit have been introduced in many countries. In the United Kingdom, the Myocardial Ischaemia National Audit Project (MINAP) began in 1998 with the intention to audit the management of all patients admitted to hospital in England and Wales following MI^[21]. The results of this project have allowed cardiologists to audit the performance of their hospital and focus on areas of inadequate performance in order to improve care^[22].

A selection of exemplar registries in MI through the years is shown in Table 1.

TYPES OF REGISTRY

MINAP is a (1) mandated, (2) continuous registry that uses a (3) unique data collection system to describe the (4) “whole-pathway” of care of acute coronary syndrome-from the onset of symptoms until discharge from hospital. It is designed to collect data on every case, regardless of where the patient is admitted within a hospital, though case ascertainment is incomplete. While some registries share these four attributes (*e.g.*, the Swedish SWEDE-Heart registry^[28]), others differ in this regard.

So, for example, in Italy the BLITZ programme consists four separate voluntary, time-limited, “snapshot” audits of care provided to a limited number of patients admitted to cardiac care units-the most recent being for a 10 wk period in 2010^[29]. In France the FAST-MI audit programme has, every five years since 1995, organised a month-long, nationwide, voluntary registry of consecutive patients admitted, with either STEMI or NSTEMI, to cardiac or intensive care units, within 48 h of symptom onset^[30]. The Acute Coronary Syndrome Israeli Survey is a biennial nationwide survey of acute coronary syndrome patients admitted to all 26 public hospitals in Israel dur-

ing a 2 mo period^[31]. An advantage of such intermittent (snapshot) data collection is the ability to collect very detailed and extensive data for a limited number of patients over a relatively short time (*e.g.*, 3079 patients over 1 mo in FAST MI 2010 compared with 79863 in the 12 mo from April 2010 in MINAP^[32]) without causing undue fatigue for data collectors. The long interval between snapshots allows adequate time for follow up of patients, for careful analysis of results and for the re-design of the next registry.

Some registries are designed to capture data for only certain sub-groups of patients with MI. So the ALERT-CZ registry reported on aspects of the pre-hospital treatment of patients admitted to 32 non-interventional hospitals in the Czech Republic^[33]; The Austrian Acute Percutaneous Coronary Intervention (PCI) Registry restricts analysis to those patients with acute coronary syndrome undergoing PCI, and so can provide accurate data on particular adjunctive drug treatments during such interventions^[34]; The Spanish EPICOR, a large registry sponsored by a pharmaceutical company, concentrates only on survivors of MI^[35].

As mentioned earlier, while many registries require active collection of data as an additional task, others use (or “mine”) routinely-collected administrative data, either as the sole data source, or, as in the case of MINAP, as the mechanism to provide basic follow-up information. Using administrative data restricts the types of question that can be answered through subsequent analysis, but considerably reduces the effort involved in collection. In many cases, at the local (hospital) level, there is no financial incentive to collect data and so anything that makes data collection less onerous is greatly advantageous.

Provision of data to registries may be voluntary on the part of the patient, such as the STENT registry on treatment of vein graft disease^[36], voluntary on the part of the hospital such as the Danish registry on mortality in ST-elevation and non-ST elevation MI^[37] or mandatory as part of a local legal or business framework-in some cases the successful completion of data is necessary if a hospital is to receive payment for the care provided.

FUNCTIONS OF REGISTRIES

Epidemiological information

Provision of epidemiological information-incidence and

prevalence, patient characteristics, intervention rates-the national Swiss AMIS Plus, and CZECH 1 and CZECH-2, being key examples of projects that can evaluate changes in epidemiology^[38,39].

Risk modelling and prognostication

Risk modelling and prognostication-as in the national MINAP registry^[40] and the multi-national GRACE-risk scores derived from such registries, and validated in others^[41], allow interventions to be targeted at those at highest risk, and therefore most likely to benefit, and, through use in case-mix adjustment, allow meaningful comparisons between hospitals and health systems.

Quality assurance

Quality assurance-registries can be used to measure performance against “best practice”, as described in national or international guidelines. In Europe, the first Euro Heart Survey on acute coronary syndromes was a large registry that looked prospectively at adherence to guidelines^[26] a second survey, repeated several years later, showed improved guideline adherence and superior outcomes^[42]. This has been confirmed in the Swedish registry where the adoption of evidence-based interventions (those shown to be beneficial in randomised trials) was shown to be associated with increased survival in those with STEMI^[43], and in MINAP where delivery of best and timely care (as expressed by a composite performance score) was associated with improved outcomes^[44].

Quality improvement

Quality improvement-registries can be designed, or opportunistically used, to monitor changes in process and outcomes of care, and so provide a good platform for assessing the effectiveness of quality improvement initiatives^[45]. Rather than being a passive tool to facilitate quality improvement, or a surrogate marker of a willingness to improve care (whereby voluntary participation in the registry is a sign of openness to change for the better), some have suggested that registries themselves provide the stimulus for instigating such initiatives. Major improvements in hospital performance and mortality rates have been reported following the public disclosure of hospital-specific results, with a substantial narrowing of the gap between the best and worst performing hospitals^[46].

Pursuit of research

Pursuit of research-while not their primary purpose, most registries lend themselves to the creation of generalizable knowledge^[47] and so to observational research. Such research, while adequate for hypothesis generation, for example the link between non-steroidal anti-inflammatory drugs and adverse cardiovascular events^[48], lacks the power to prove causality, but can be used to support findings from RCTs by reproducing the results of a trial in the large unselected captured in a registry population^[49]. However, analysis of registry data is complex, and often requires sophisticated multivariate analysis, sensitiv-

ity analysis and, because of incomplete data collection, imputation of missing values^[50] or propensity analysis^[51]. Notwithstanding these difficulties, the large volume of data held within a registry may be mined to yield important information. So, confirmation that earlier reopening of a coronary occlusion is beneficial was obtained not from a randomised trial of early *vs* delayed primary percutaneous intervention but from analysis of a registry that recorded door-to balloon times^[24]. Also, many registries have been used to show which pharmacological treatments are important in the MI population and how discontinuation can have significant negative outcomes for patients and have used this as a driver for improved post MI care^[22,52].

KEY PRACTICAL ISSUES IN REGISTRIES

With most registries there is a “trade-off”, or balance, between the richness of the data and data completion and case ascertainment rates. As the amount of information required for each case increases so do the demands placed upon local data collectors and, unless there is an explicit link between reimbursement for care and data collection, the likelihood that some cases will be included with incomplete data, and others will be missed altogether. This is of importance because there is evidence that those hospitals with poorer recording systems are also those with poorer outcomes^[53]. The extent of missing data is associated with 30-d mortality for STEMI and NSTEMI^[54]. This is less likely to be problematic in snapshot-type registries. Others have responded to this by introducing differing levels of participation, (*e.g.*, ACTION Registry-GWTG Premier and Limited levels of participation-the latter having 50% reduction in the amount of data collected^[55]) to allow centers that are experiencing particular problems with data entry to continue to register patients.

Some of the key properties of good registry design and performance and their practical aspects are shown in Table 2. A review of the advantages and disadvantages of the most common registry types is shown in Table 3.

ETHICAL AND GOVERNANCE ISSUES IN REGISTRIES

Data that can be collected from administrative records or medical case notes can be recorded without the individual patient’s knowledge or consent. Is this ethical? This is a point of significant controversy. Consideration of the principle of individual autonomy and right to personal privacy balanced against the greater good of future patients, as well as national statute, lead to significant variation in practice. Patients who refuse to give consent are systematically different from those who do not and their exclusion from registries is likely to skew findings^[59]. For this, and other reasons, some authors have argued that a regulatory insistence on individual choice is counterproductive, and that the standards suggested for

Table 2 Some key attributes of good registry design

Attributes of a good registry	Practical aspects
Standardised data collection and definitions	Pre-project agreement of common data definitions (<i>e.g.</i> , use of the Cardiology Audit and Registration Data standards ^[56]) and, where possible, standardised data collecting techniques
Rapid data collection	Computer web based data collection allowing rapid data accrual and transmission; agreed timeliness of data entry
Case ascertainment/ data completeness	Built in data checking during submission; regular data validation exercises (<i>e.g.</i> , the NCDR Data Quality Program ^[57]); comparison of case numbers with some other measure of unit activity; regular audit of participating sites to identify areas for improvement; explicit definition of participation in the registry and of a minimum dataset for each record; linkage to other complementary dataset ^[58]
Sequential enrolment	Allows for representative data without cherry-picking
Appointment of key stakeholders to a formal Steering Committee	Effective coordination of registry with oversight to share good practice and important results; guarantee analyses; clinical leadership and endorsement by professional bodies; regular revisions of the dataset reflect changes in practice
Random multi-site collection or mandated participation	Reduces the risk of population or site bias (as is common with RCTs in large academic city centres); enables comparisons between sites
Appropriate ethical considerations	Addresses both legal and ethical issues of patient consent; confidentiality; anonymity; data linkage (see below)
Clear and comprehensive result presentation	Clear and full results with meaningful and appropriate conclusions that reflect the findings and are presented in a way the target audience understands (<i>e.g.</i> , funnel plots); easy access to data and reports; clear explanations of any statistical adjustments
Transparent study background and funding	Prospective declarations of any issues

RCTs: Randomised control trials.

Table 3 Advantages and disadvantages of common registry types

Registry type	Benefits	Negatives
Academic	Limited external pressures for study; more flexibility in developing the dataset; lends itself to research; collaboration with many academic institutions and with Professional Bodies	Access to data provided by external sites may be limited; potentially limited funding; danger of “mission creep”-increasing data required; participating clinicians may become divorced from the academic group; difficult to enforce participation
Insurance	Ready access to data through billing information; large amounts of data held; potential for internal data linkage; large populations to study; excellent case ascertainment	Inability to expand dataset outside that determined by insurance company/HMO; difficult to influence/alter datafield definitions; full access to data may not be available due to commercial sensitivity
Industry sponsored	Well-funded; support for training of data collectors and encouragement of data entry; often based on access to new treatments	Limited sites; confidentiality clauses may restrict dissemination of findings; not all data widely available; may have strict patient selection (restricted to those receiving particular intervention); often time limited; less direct clinician control
Government	National “reach”; can promote and mandate high levels of participation and data collection; collaboration between multiple agencies; large population for study	Limited sense of clinical ownership

HMO: Health maintenance organization.

fully informed consent are too stringent and harm both research and public health^[60-62]. In the United Kingdom, the impact is low on patients whose data is included in a registry whose primary purpose is quality assurance and improvement and in which there is no intention to treat differently by virtue of participation, and so written consent is not required. The MINAP group, for example, has a legal exemption to hold patient-identifiable data without direct consent. As a result third party research access requires formal application of proposals to an academic steering committee and then only anonymised or pseudo-anonymised data is released after full academic review.

FUTURE DEVELOPMENTS

Registries will continue to develop beyond their original functions, becoming increasingly influential with respect

to quality improvement, regulation and research. This is predicated on an increased emphasis on professional accountability, the provision of safe, effective patient-centred care, and a shift of focus from the performance of particular interventions to the outcomes of the entire process of care. Increasingly, comparisons between clinicians, institutions and healthcare systems will be enabled through the implementation of common definitions for particular data fields across a range of registries. An international consortium of policy makers, clinicians, patient advocates and academics has identified registries as the mechanism through which to measure and report specific outcomes of the care of patients with coronary artery disease (including acute myocardial infarction) in a standardised way^[63], pointing to the need to share and to publicly report risk-adjusted data. Such transnational comparisons have recently been published following

painstaking analysis of two large national registries^[64]. Further, by understanding more about outcomes and costs of care it is hoped that patients will derive the maximum possible value of their interactions with clinicians in what has been called a “value-based” system^[65].

In addition to hard, readily/reliably measureable outcomes, such as death or length of stay in hospital, patients will be encouraged to report on their own outcomes following, and experiences of, care using a number of generic or disease-specific tools. These patient reported outcome measures or patient reported experience measures could potentially be gathered *via* integrated web services (with patient prompts), and provide a method of identifying important late complications which maybe outside the original data capture window^[66]. Furthermore, the social and emotional information contained within patient feedback may prove useful for the future design of services, and help understanding of adverse outcomes or difficulties in compliance with treatment.

If the ethical, legal and practical issues concerning the linkage of cases held in large datasets^[67] can be overcome, there will be further opportunities to appreciate the experiences and health needs of patients both before their index admission and thereafter. For example, the continuation of secondary preventive drugs following discharge from hospital with acute coronary syndrome has been assessed through linking the MINAP registry to a primary care dataset^[22]. It should be possible to link registries of heart attack to those of heart failure and cardiac rehabilitation, and so understand more fully the longer-term consequences of myocardial infarction.

Just as registries can provide information regarding the effects of quality improvement initiatives, so they can provide both a platform for enrolment and a mechanism for follow-up of patients participating in randomised trials of particular interventions; for example the TASTE trial of routine aspiration of intracoronary thrombus during primary percutaneous intervention^[68]. This technique, of registry-based randomised clinical trials, will significantly reduce the cost of interventional studies (to as little as 10% of the probable cost of an orthodox RCT in the case of TASTE) and maximise recruitment, while readily demonstrating the selective nature of the participating population through comparing the characteristics and outcomes of those enrolled with those excluded. The reduction in cost might also make possible important investigations of the utility of interventions for which there is no financial interest of the pharmaceutical or device industry—the usual sponsors of large trials—such as the role of supplemental oxygen in acute myocardial infarction^[69]. More investigator-initiated (either prospective/open-ended or time-limited/fixed-term) registries will be instigated to monitor the implementation of new technologies and to answer specific clinical questions^[70].

CONCLUSION

Registries have evolved greatly over the years from sources of epidemiological information to datasets whose analy-

sis can provide key information to clinicians, patients, researchers and medical policy makers. Registries will continue to provide important information on disease epidemiology, treatment and guideline adherence while being integral to quality improvement strategies in many disease states, as is already the case for MI.

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WJC 6th Anniversary Special Issues (5): Myocardial infarction

Timely reperfusion for ST-segment elevation myocardial infarction: Effect of direct transfer to primary angioplasty on time delays and clinical outcomes

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attractive way of diminishing delays. The purpose of this review is to address the effect of direct transfer on time delays and clinical events of patients with STEMI treated by PPCI.

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Key words: Primary angioplasty; Direct transfer; ST-segment elevation myocardial infarction network; Primary percutaneous coronary intervention; Myocardial infarction

Core tip: Primary angioplasty has emerged as the preferred reperfusion modality for patients with ST-segment elevation myocardial infarction. However, this treatment is associated with longer delays. Several strategies have been proposed to overcome these drawbacks. This review aimed to highlight the effect of a direct transfer strategy on time delays reduction and in the prognosis of this subgroup of patients.

Abstract

Primary percutaneous coronary intervention (PPCI) is the preferred reperfusion therapy for patients presenting with ST-segment elevation myocardial infarction (STEMI) when it can be performed expeditiously and by experienced operators. In spite of excellent clinical results this technique is associated with longer delays than thrombolysis and this fact may nullify the benefit of selecting this therapeutic option. Several strategies have been proposed to decrease the temporal delays to deliver PPCI. Among them, prehospital diagnosis and direct transfer to the cath lab, by-passing the emergency department of hospitals, has emerged as an

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INTRODUCTION

Primary percutaneous coronary intervention (PPCI) is the current preferred strategy to treat ST-segment eleva-

tion myocardial infarction (STEMI) when performed in a timely-fashion and by experienced operators. This technique has yielded superior results over thrombolytic therapy even when long transfer distances are accomplished^[1-6].

It has been demonstrated a relevant prognostic role of reperfusion delays in STEMI and both door-to-balloon and total ischemic time have been linked to increasing mortality^[7-9]. Current guidelines recommend that door-to-balloon delay must be inferior to 90-120 min^[10,11]. However, time delays to deliver PPCI are usually longer than recommended in practice guidelines^[12,13] and this may nullify the advantages of mechanical reperfusion over lysis^[14,15]. To overcome this problem, several strategies have been proposed^[16-18] and national efforts have been claimed to address all organizational issues either in United States or in Europe^[19,20].

Among these strategies, direct transfer from the field, bypassing the emergency department, to the catheterization laboratory has emerged as a safe and effective protocol for minimizing PPCI-related delays^[21-28]. We aimed to review the current evidence regarding the effect of DT on time delays and on clinical outcomes.

TIME EFFECT IN REPERFUSION THERAPY

Experimental models have clearly shown that there is a close relationship between the extension of myocardial necrosis and the time elapsed since the coronary artery occlusion^[29-31]. The myocardial damage extends as a “wavefront phenomenon” from the subendocardium to the subepicardium and the amount of muscle that can be saved by reperfusion is related to the time that flow can be restored^[32].

In the clinical setting, this relationship was evident in the first studies where a reperfusion method was tested: the thrombolytic therapy. The GISSI trial compared the use of streptokinase against placebo in patients with STEMI and less than 12 h from symptom onset. The overall results showed a net clinical benefit of the thrombolytic therapy^[33]. But when results were divided between time delay categories the significant benefit was observed only in those patients that received the lytic in the first 6 h since the start of the symptoms. This finding was subsequently confirmed in the fibrinolytic therapy trials’ analyses where all studies including > 1000 STEMI patients and randomized to thrombolytic or placebo were included^[34]. This metaanalysis showed that there was a linear relationship between the time to lytic therapy and the benefit in terms of mortality. The benefit was greater in the first hour (35 lives saved/1000 patients treated) and progressively decline every hour until 12 h since symptom onset. It was calculated that the loss of benefit of every hour of delay was 1.6 lives per every 1000 patients treated. No survival benefit was observed for those patients randomized after 12 h. However, this concept was challenged in a similar analysis but with more studies included by Boersma *et al.*^[35] (22 studies, every study with > 100 patients randomized). Authors showed that this

time-survival relationship with lytics was better represented by a non-linear regression curve. Survival benefit was maximal in the first two h and thereafter it suffered a steep decline, maintaining the benefit until 12 h of delay.

The relationship between time delays and mortality was as well observed in the setting of PPCI. To assess this association two time intervals have been defined: time to treatment (TTT, interval elapsed between symptom onset and mechanical reperfusion) and door-to-balloon (DTB, time from arrival to interventional hospital and mechanical reperfusion). Both time intervals have been linked to mortality in STEMI patients treated by PPCI. De Luca *et al.*^[9] showed that every 30 min of delay in the delivery of PPCI increased the mortality by 7.5%. Cannon *et al.*^[7] analyzing the data from the NRMI-2 registry demonstrated as well that the DTB interval was associated with an increasing mortality, above all when it was greater than 120 min. This fact was confirmed subsequently in a more contemporary analysis of the NRMI-3 and 4 registries, noting that a DTB interval > 90 min was associated with worse prognosis^[8]. However, several publications have addressed the issue that the time delay effect is related to the risk profile of the patients. In this sense, those patients exhibiting high risk features [anterior wall myocardial infarction (MI), previous MI, advanced Killip class, data of hemodynamic instability], those presenting very early after symptom onset (< 2-3 h) and those in cardiogenic shock, time delays play a key role in their prognosis. On the other hand, those patients of low risk or presenting late are less affected by the delays in reperfusion^[36-39].

The aforementioned data allowed the establishment in the practice guidelines the recommended time intervals to deliver PPCI: a DTB time of \leq 90-120 min^[10,40,41]. If mechanical reperfusion cannot be achieved in this time frame, then a selection of thrombolytic therapy might be advisable. However, with the growing evidence of PPCI being superior to lytic therapy in terms of mortality and cardiac events, this mode of reperfusion rapidly gained adoption in the medical community^[1]. Notwithstanding, it was rapidly pointed out that the widespread use of PPCI was translated into the fact that most of the patients received their reperfusion treatment out of the time schedule proposed by guidelines. In an analysis of the NRMI-4 registry, Nallamothu *et al.*^[12] showed that only 4.2% of patients treated by means of PPCI had a DTB time of less than 90 min. In a more recent analysis by Chakrabarti, including as well transferred patients from non-PPCI hospitals, only 9.9% of patients were into the boundaries of practice guidelines^[13]. In Europe, even with a more organized system, delays are as well longer than suggested. Moreover, the retardation induced by the system of care is an independent factor associated with worse prognosis^[42]. Several retrospective studies have tried to elucidate the exact delay with PPCI which will nullify the clinical benefit compared to thrombolysis^[14,15,43,44]. This time frame has varied from 60 to 120 min, but all studies have limitations inherent

Table 1 Effect of direct transfer on time delays *n* (%)

<i>n</i>	DTB	TTT	FP	Staff	Ref.
161 (DT 13)	87 vs 168	-	14%	Physician	[24]
658 (DT 25.2)	-	146 vs 191	-	Physician	[25]
401 (DT 59.9)	124 vs 154	-	-	Paramedics	[55]
301 (DT 35.8)	74 vs 116	150 vs 203	7%	Paramedics (teletransmission)	[28]
344 (DT 39.2)	69 vs 123	158 vs 230	-	Paramedics	[21]
1437 (DT 42.9)	83 vs 103	150 vs 200	-	Paramedics (teletransmission)	[26]
581 (DT 78)	69 vs 118	149 vs 219	-	Paramedics (computed algorithm)	[61]
1194 (DT 21)	102 vs 125	189 vs 259	4.7%	Physician	[27]
1859 (DT 23)	105 vs 122	185 vs 255	-	Physician	[67]

DT: Direct transfer; DTB: Door-to-balloon; FP: False positives; TTT: Time to treatment; PPCI: Primary percutaneous coronary intervention.

to post-hoc analysis and registries. Therefore, the exact delay assumable is still elusive and, moreover, it may depend on the risk profile of the individual patient^[43,45]. Given the evidence supporting the benefit of PPCI over thrombolysis (even though when the patient should be transferred from a non-PPCI facility^[6], and likely related to a more stable effect of reperfusion^[46,47]) most of efforts of national societies is to implement STEMI networks well organized and strategies in order to minimize delays for a timely PPCI^[19,20,48-50].

STRATEGIES TO REDUCE TIME DELAYS IN STEMI NETWORKS

Taking the previous information into account, several efforts have been claimed to reduce the delays involved in the delivery of PPCI and there have been conducted studies to address the strategies associated with the greater reductions in time delays performing PPCI. Most of these studies have been conducted in United States through surveys to hospitals across the country and through analysis of how top hospitals develop their programs of PPCI^[16,17,51-53]. The most comprehensive analysis of all studies published has been reported by Bradley *et al*^[18]. Authors conducted a survey in 365 hospitals of United States trying to identify the independent predictors of lower DTB time. In their results 6 strategies were significantly associated with faster door-to-balloon interval: (1) Having an emergency physician activating the catheterization laboratory; (2) Having a single call to a central page operator activate the laboratory; (3) Having the emergency department activate the catheterization laboratory while the patient is en route to the hospital; (4) Expecting staff to arrive in the catheterization laboratory within 20 min after being paged; (5) Having an attending cardiologist always on site; and (6) Having staff in the emergency department and the catheterization laboratory use real-time data feedback.

Interestingly, the use of prehospital electrocardiogram (ECG) was not associated with lower delays in the overall

population. However, this strategy was associated with significantly lower time intervals if the emergency medical system activated the cath lab team while the patient was on route to the hospital. Simply diagnosing STEMI in the prehospital setting, activate the interventional team and move the patient directly to the catheterization theater avoiding the emergency department or the coronary care unit is what we call direct transfer strategy (DT).

DT IN PPCI

In recent years there have been several studies that have investigated the association of DT for PPCI with shorter time delays in the delivery of reperfusion. The publications differ in their geographic location, method of ECG interpretation, distance between the reference point and the cath lab and the definitions of the different intervals analyzed^[21-26,28,54-63]. Furthermore, it is noteworthy that there is no randomized study on the subject and the evidence that we have rests on observational studies. That is why the results are heterogeneous and difficult to compare.

Role of direct transfer on time delays

The results of the main studies regarding the effect of DT on time delays in PPCI are summarized in Table 1.

The most relevant publications in terms of number of patients, methodology and results are those published by Le May *et al*^[21], Pedersen *et al*^[26], Dieker *et al*^[61] and our group^[27]. Le May *et al*^[21] analyzed the effect of DT in 344 patients with STEMI treated in the metropolitan area of Ottawa. The farthest distance to the PPCI hospital was 59.5 km. In this publication 39.2% of patients were directly transferred to the catheterization laboratory. Notably, for various reasons 2% received fibrinolytic therapy. DT significantly shortened the time delays, with median DTB of 69 min compared to 123 min in the standard admission. A significant reduction in total ischemic time (median 158 min vs 230 min, $P < 0.001$) was also observed. Ambulances were handled by paramedics. Pedersen *et al*^[26] analyzed their records of STEMI from 2005 to 2008 and included in the analysis 1437 patients of whom 42.9% were transferred directly to the catheterization laboratory. The study region covers a large population nucleus but investigators stress that the maximum transfer distance was 10 km and 90% within 60 min of the interventional hospital. For DTB interval definition the first medical contact instead of the arrival to the interventional hospital was selected. This is in accordance with the new recommendations for measuring these intervals when transferred patients from non-PCI facilities are included^[64]. Direct transfer patients consistently showed less delay compared to the conventional admission strategy in the DTB interval (median 83 min vs 103 min, $P < 0.001$) and in the TTT time (median 150 min vs 200 min, $P < 0.001$). Sixty-one percent of patients were in the range of DTB < 90 min recommended by the guidelines. In this study, ambulances were equipped with ECG tele-

transmission and were staffed by paramedics. Dieker *et al*^[61] analyzed 581 patients from a region of Holland with transport distance of 77 km. DT was associated with lower time delays and a higher proportion of patients in the recommended time frame of guidelines (82% *vs* 23%, $P < 0.001$). In the publication by our group^[27], we studied the role of DT in 1194 patients with STEMI who underwent PPCI at our regional STEMI program. From that group, 255 (21%) experienced DT from the field. It must be stressed that our network has its farthest point of reference located 154 km from the PPCI-hospital. Our data showed that DT was as well associated with lower DTB and total ischemic time compared to those referred through emergency department route. And this finding was consistent for both patients from the catchment area of the PPCI-hospital and for that from catchment areas of non-PPCI hospitals. Furthermore, the longer the distance to the PPCI the greater the time saved by this strategy. Our results confirm and expand the previous observations to those regions with a STEMI network involving large transfer distances.

Role of direct transfer on clinical outcomes

While it is clear that DT reduces temporal delays, it is still more debatable if this strategy is associated with better clinical outcomes. Since the overall ischemic time is diminished a greater myocardial salvage is expected and this should impact prognosis of patients. However, we must take into account that publications of DT are retrospective and observational and the association between DT and clinical events may be biased. Moreover, in the early publications of the topic DT was associated with a negative impact on survival. In the publication of So *et al*^[55] DT group showed significantly higher mortality (13.3% *vs* 5%, $P = 0.001$) despite having less delay to reperfusion. But, we should highlight that these figures of mortality are unadjusted and DT patients presented cardiogenic shock more frequently and had higher percentage of intracranial hemorrhage. And even in 2009 a systematic review of studies published to that date with 980 patients concluded that there was still insufficient evidence to confirm that DT improved prognosis^[65]. However, this meta-analysis did not include the most recent studies and pooled together trials where fibrinolytic therapy and primary angioplasty were used. These features may explain why this meta-analysis failed to show benefit of DT on prognosis.

However, the most contemporary researches have changed this tendency and consistently pointed to a net clinical benefit with this strategy. In the study by Steg *et al*^[57], avoiding the emergency department was associated with lower early mortality (4.9% *vs* 8.6%, $P = 0.01$), being the Emergency service use a factor associated with a worse prognosis (OR = 1.67). At one year there was still benefit in mortality in the direct admission group (11.5% *vs* 15.6%, $P < 0.05$). In a post-hoc analysis of the On-Time trial^[23] patients in the DT group had a significant improvement in ejection fraction, less ventricular dysfunction [left ventricular ejection fraction (LVEF) <

40%] and lower 30-d mortality (1% *vs* 3.2%), although this finding was not statistically significant ($P = 0.2$). However at 1 year, DT was associated with lower mortality (2.1% *vs* 5.6%, $P = 0.04$), being direct admission an independent predictor of better clinical outcome (OR = 0.3). Pedersen *et al*^[26] were the first researchers to report an independent clinical benefit of DT. Authors showed a significant reduction in the composite endpoint of death or non-fatal myocardial infarction at 1 year (HR = 0.67). On the other hand, this study present the limitation that the individual figures of the clinical variables were not provided and they found no decrease in both “end points” individually. In the ACTION registry^[62], a registry regarding the use of prehospital ECG, which included patients not undergoing PPCI, a trend towards lower adjusted hospital mortality in prehospital diagnosis group was as well observed (6.7% *vs* 9.5%, OR = 0.80, $P = 0.06$). Dieker *et al*^[61] observed a lower mortality in the group of DT (7% *vs* 13%, $P = 0.03$). However the mortality reported was unadjusted and DT group were younger, with less diabetes mellitus and lower percentage of previous myocardial infarctions. In a novel study by Le May *et al*^[66] DT strategy was analyzed in 1389 patients. Death at 180 days occurred in 5.0% of patients transferred directly from the field, and in 11.5% of patients transported from the field to a non-PPCI-capable hospital ($P < 0.0001$). After adjusting for baseline characteristics mortality remained lower among DT group (OR = 0.52, 95%CI: 0.31-0.88, $P = 0.01$).

The most exhaustive analysis of the effect of DT on mortality was carried out by our group in two separate reports analyzing short (30-d) and long-term mortality (after a median follow-up of 2.4 years)^[27,67]. In the first study, we analyzed the effect of DT on 30-d mortality in 1194 patients. Patients transported directly had lower 30-d mortality (2.7% *vs* 6.8%, $P = 0.017$). After adjustment in a multivariable logistic regression analysis, DT remained as an independent predictor for improved outcome (OR = 0.33, 95%CI: 0.12-0.92). Subsequently we reported the effect of DT in a larger cohort and with the longest follow-up in the literature. In a multivariable Cox regression model the DT strategy persisted as an independent variable associated with a better prognosis (HR = 0.71, 95%CI: 0.50-0.99) (Figure 1).

And finally, as we previously stated, the effect of time delays may be related to risk profile of patients. Therefore, the effect of DT on mortality might be influenced as well by some of the baseline characteristics. In this sense, Ortolani found a positive effect on survival of patients with cardiogenic shock who experienced direct transfer^[25,59] and our group found a suggested better outcomes in those patients with cardiogenic shock, diabetes mellitus, anterior wall myocardial infarction and those presenting ≤ 2 h from symptom onset (Figure 2)^[67]. The evidence of the effect of DT on clinical events is summarized in Table 2.

There are various reasons that may explain this survival benefit. First, patients have an earlier contact with

Table 2 Effect of direct transfer on clinical events *n* (%)

<i>n</i>	Short-term mortality	Late mortality	Adjusted mortality	Ref.
401 (DT 59.9)	13.3% vs 5%, <i>P</i> = 0.001	-	-	[55]
1204 (DT 66.9)	4.9% vs 8.6%, <i>P</i> = 0.01	11.5% vs 15.6%, <i>P</i> < 0.05	OR = 1.67 use ED	[57]
467 (DT 44.7)	1% vs 3.2%, <i>P</i> = NS	2.1% vs 5.6%, <i>P</i> = 0.04	OR = 0.3 if DT	[23]
344 (DT 39.2)	3.7% vs 5.7%, <i>P</i> = 0.3	6% vs 7.7%, <i>P</i> = 0.67	-	[21]
1437 (DT 42.9)	-	-	HR = 0.67 at 1 yr for death/reMI in DT	[26]
7098 (DT 27.4)	6.7% vs 9.5%, <i>P</i> = NS	-	OR = 0.80, <i>P</i> = NS in DT	[62]
581 (DT 78)	7% vs 13%, <i>P</i> = 0.03	-	-	[61]
1389 (DT 59.2)	3% vs 8.1%, <i>P</i> > 0.001	5% vs 11.5%, <i>P</i> < 0.001	OR = 0.52 at 180 d	[66]
1194 (DT 21)	2.7% vs 6.8%, <i>P</i> = 0.017	9% vs 16%, <i>P</i> = 0.005	OR = 0.33 at 30 d	[27]
1859 (DT 23)	3% vs 6%, <i>P</i> = 0.049	9.4% vs 14.4%, <i>P</i> = 0.008 at a median 2.4 yr	HR = 0.71 at 2.4 yr	[67]

DT: Direct transfer; ED: Emergency department; NS: Not significant.

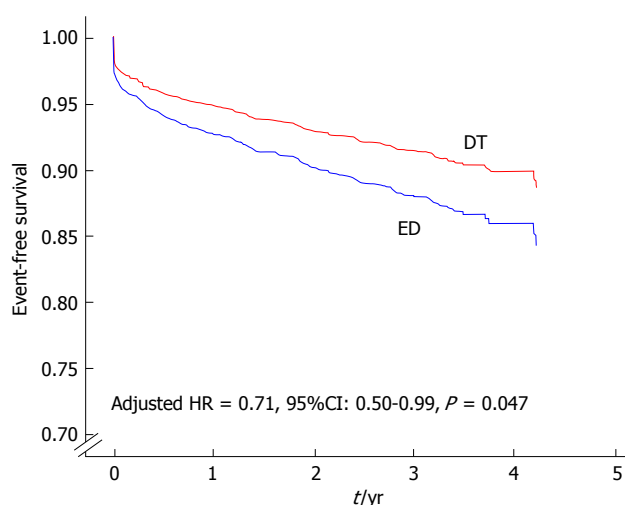


Figure 1 Cox regression survival curves. There is an adjusted survival benefit of direct transfer (DT). With permission, from reference [67]. ED: Emergency department.

the system, which provides a higher possibility of being in contact with staff that can deliver cardiac defibrillation and resuscitation if necessary, since it has been estimated that 50% of deaths occur in the prehospital phase^[68]. It is pertinent to recall that it has been observed consistently in the literature that the time from onset of symptoms to the contact with medical system is lower in DT group. It is possible that the DT group may represent a lower risk profile than those who come or are derived through emergency departments. They usually are younger, probably with clearer symptoms and possibly with a more definite ECG. This fact was shown previously^[69] and it is for this reason that when the effect of DT on mortality is assessed, it must be adjusted by this and other relevant variables. Despite this adjustment, the DT is still significantly associated with lower mortality. Second, it is clear that this strategy consistently reduces time delays and following the aphorism that “time is muscle” it is logical to find a prognostic benefit in these patients. The benefit of reperfusion regarding myocardial salvage is maximal in the first h of STEMI^[70] and this strategy allows greater diagnosis and treatment in the early stages, therefore driving to a more preserved LVEF. Moreover, the earlier treatment of patients with STEMI has been linked to a

better degree of “myocardial blush”^[71] and has also reported to significantly increase the percentage of thrombolysis in myocardial infarction 3 flow after PPCI^[61], both facts associated with improvement in LV function and prognosis. A recent publication has challenged the concept that lower DTB times are associated with lower in-hospital mortality^[72]. However, the retrospective nature of the study, the exclusion of transferred patients, the short DTB times and follow-up and the unadjustment for time from symptom onset to presentation may have affected the results. Since DT decreases all temporal delays in PPCI and not only DTB, we believe that this fact impacts positively the prognosis of patients. In addition, the prehospital diagnosis allows early initiation of antiplatelet and antithrombotic treatment. Drugs such as aspirin, clopidogrel, heparin and II b/IIIa inhibitors have been associated with an increased permeability of the infarct related artery preangioplasty^[73-76], a fact that has been associated with a better prognosis^[77].

CURRENT LIMITATIONS OF THE DT STRATEGY

This strategy, although in our view of enormous clinical benefit, has several limitations. First, it can only be applied in areas where a well-organized STEMI network is present. Second, despite having shown that the prehospital diagnosis by emergency medical system (EMS) ambulances and subsequent activation of the interventional cardiology team reduces delays, the use of these resources is underutilized. The main reason is probably related to the difficulty of general population awareness to call the EMS when there is a case of chest pain suggestive of myocardial infarction. Third, despite activating the EMS ambulances, not all of them have the capability to perform and transmit an ECG. In the ACTION registry^[62] done on more than 12000 patients, only 58.7% of the patients analyzed had contacted the EMS and only 27.4% had a prehospital ECG available. And together with the low frequency of prehospital ECG there is still the problem of its interpretation, raising the possibility of false activations of the cath lab with the consumption of unnecessary resources. In the literature false positive activations of the PPCI team with DT strategy have

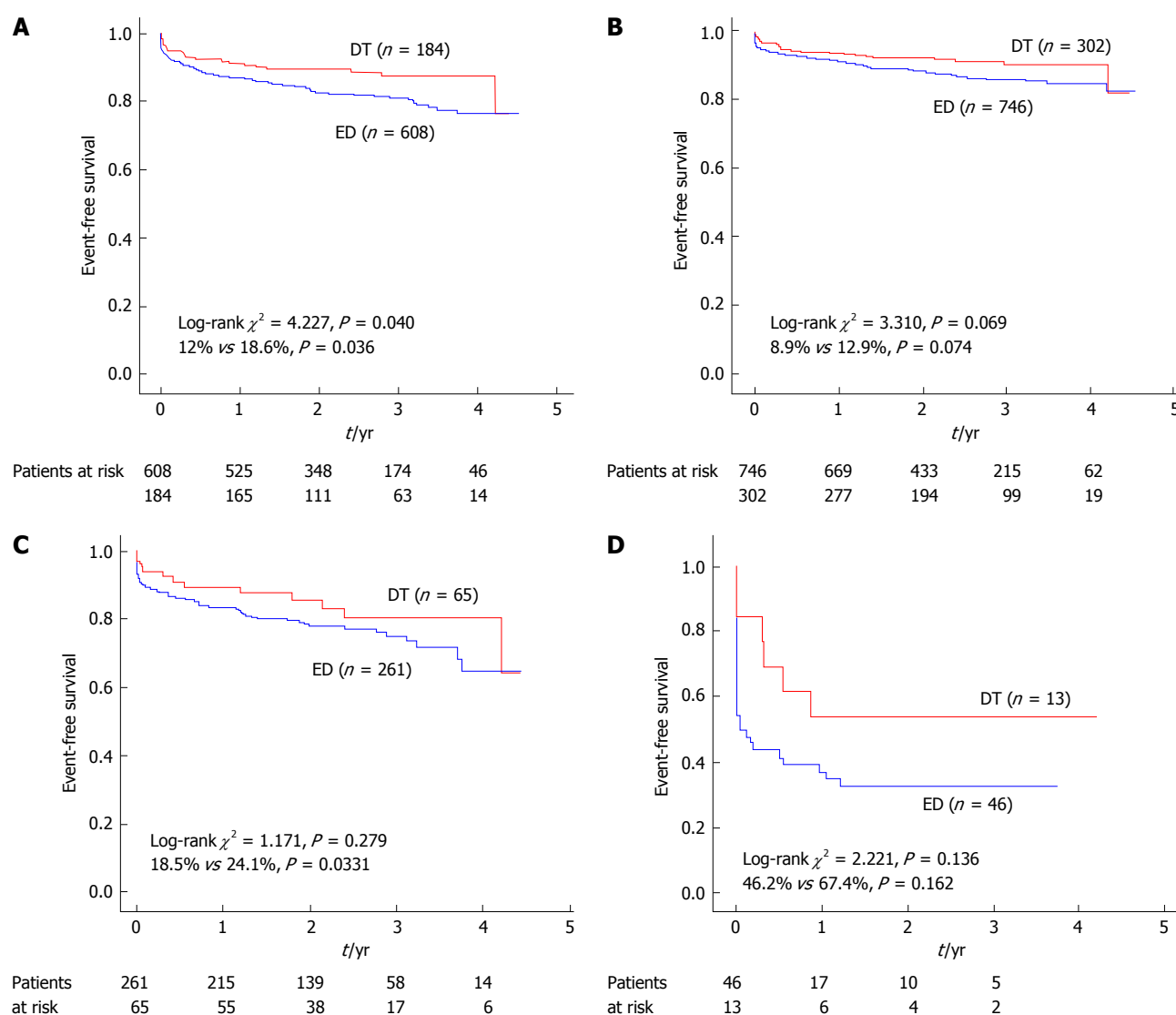


Figure 2 Kaplan-Meier survival curves for the different subgroups of higher risk. There is a trend to prognostic benefit in all subgroups that reaches significance in the group of anterior-wall myocardial infarction (MI). With permission, from reference [67]. A: Anterior wall MI; B: Early presenters; C: Diabetic patients; D: Cardiogenic shock. DT: Direct transfer; ED: Emergency department.

ranged from 0% to as high as 17%^[54]. However, when a STEMI network is well organized the false positive referrals from the EMS ambulances performing DT do not differ from those observed in the PPCI-hospitals and it is not associated with an increase in mortality^[78]. And finally, it is remarkable that, despite the benefits demonstrated and that is recommended in practice guidelines^[41], this strategy is underutilized in most of angioplasty networks. In a recent study in Canada^[79], and more than 15000 paramedics surveyed, only 18% (95%CI: 10%-25%) of EMS operators had protocols allowing the bypass of emergency departments in case of STEMI. We must work to increase the use of a technique that can offer prognostic benefits.

CONCLUSION

PPCI is the preferred reperfusion strategy in patients experiencing STEMI. On the other hand, it is associated

with longer time delays and most of patients do not meet the DTB limit recommended in practice guidelines. DT has emerged as a strategy that has consistently proved to reduce time delays and that is associated with an improved survival. However, it is still underutilized in most STEMI networks, so efforts must be done to increase the percentage of utilization.

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WJC 6th Anniversary Special Issues (5): Myocardial infarction

Novel adjunctive treatments of myocardial infarction

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Abstract

Myocardial infarction is a major cause of death and disability worldwide and myocardial infarct size is a major determinant of prognosis. Early and successful restoration of myocardial reperfusion following an ischemic event is the most effective strategy to reduce final infarct size and improve clinical outcome, but reperfusion may induce further myocardial damage itself. Development of adjunctive therapies to limit myocardial reperfusion injury beyond opening of the coronary artery gains increasing attention. A vast number of experimental studies have shown cardioprotective effects of ischemic and pharmacological conditioning, but despite decades of research, the translation into clinical effects has been challenging. Recently published clinical studies, however, prompt optimism as novel techniques allow for improved clinical applicability. Cyclosporine A, the GLP-1 analogue exenatide and rapid cooling by endovascular infusion of cold saline all reduce infarct size and may confer clinical benefit for patients admitted with acute myocardial infarcts. Equally promising, three follow-up studies of the effect of remote ischemic conditioning (RIC) show clinical prognostic benefit in patients undergoing coronary surgery and percutaneous coronary intervention. The discovery that RIC can

be performed noninvasively using a blood pressure cuff on the upper arm to induce brief episodes of limb ischemia and reperfusion has facilitated the translation of RIC into the clinical arena. This review focus on novel advances in adjunctive therapies in relation to acute and elective coronary procedures.

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Key words: Myocardial infarction; Primary percutaneous intervention; Coronary artery by-pass graft; Ischemia-reperfusion injury; Ischemic preconditioning; Remote ischemic conditioning; Cyclosporine; Cooling; Exenatide

Core tip: Patients with ischemic heart disease have a high risk of developing myocardial infarction, which is associated with considerable morbidity and mortality. Limiting the detrimental consequences of myocardial infarction is a major focus of cardiovascular research. Recent clinical studies suggest that novel adjunctive therapy with pharmacological and ischemic conditioning reduce ischemia-reperfusion injury in patients during coronary procedures. In three independent randomized trials, remote ischemic conditioning (RIC) improves clinical outcome in patients undergoing acute or elective percutaneous intervention or coronary artery by-pass surgery. RIC can be performed safely and non-invasively by intermittent inflation of a blood-pressure cuff on the upper arm and is easily applicable in most clinical settings.

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INTRODUCTION

Heart disease and stroke are the leading causes of death

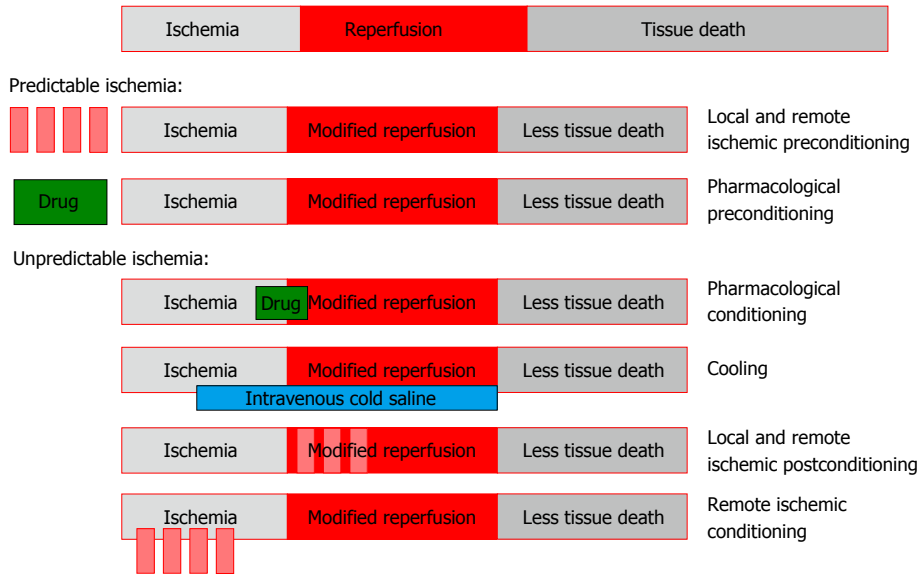


Figure 1 Overview of interventional strategies for achieving cardioprotection as adjunct to thrombolysis or primary percutaneous coronary intervention, see text for details.

worldwide^[1,2]. Since 1990, more people have died from coronary artery disease than any other death cause^[3,4].

In China, a staggering 230 million are estimated to suffer from cardiovascular disease, and three million Chinese die of cardiovascular disease annually, accounting for 41% of all deaths^[5,6]. In the United States alone, cardiovascular diseases, including ischemic heart disease and stroke, account for more than one-third deaths and an estimated 900000 heart attacks and 800000 strokes occur each year. In the remaining parts of the world, from the Sub-Saharan developing countries over booming South America to affluent areas in Europe and Asia, similar patterns are seen^[7,8].

Globally, socio-demographic factors, unhealthy life style, escalating obesity and suboptimal control of risk factors are likely to further aggravate the disease burden over the coming decades^[9]. In the Western world, nearly half of the male and a third of the female population will develop coronary artery disease^[10]. Partly driven by urbanization and adoption of Western life style, China undergoes a transition towards a similar health statistic^[11].

The pandemic of cardiovascular disease has immense negative effects on global population health and life expectancy. While attempts to modify risk factor and life style related growth in cardiovascular disease are important and have been successful in some parts of the world^[8], improved treatment of acute and chronic cardiovascular disease is also crucial to alleviate the disease burden.

This review will focus on novel advances in the treatment of coronary artery disease, particularly the recent reports of successful adjunctive therapy in relation to elective percutaneous coronary intervention (PCI), coronary artery by-pass graft surgery (CABG), and acute angioplasty (primary PCI) for ST-elevation myocardial infarction (STEMI).

PROTECTING THE HEART AGAINST ISCHEMIA-REPERFUSION INJURY

Ischemia-reperfusion injury is the essence of myocardial infarction in relation to acute coronary events, but ischemia-reperfusion injury also occurs during planned procedures such as elective PCI and CABG, although usually to a lesser extent. As the term implies, not just the ischemia itself but also the following reperfusion harms the myocardium. Although reperfusion ultimately saves the ischemic myocardium and it may seem paradoxical that reperfusion induces myocardial injury, several biological phenomena explain for this effect [for detailed reviews, please see Hausenloy *et al*^[12] (2013) and Heusch *et al*^[13] (2013)]. Of potential clinical importance, ischemic and pharmacological conditioning of the myocardium can modify reperfusion injury and significantly reduce the tissue damage (Figure 1).

LOCAL ISCHEMIC CONDITIONING

Local ischemic preconditioning, induced by brief periods of ischemia before a sustained ischemic insult, has long been known to afford potent protection against ischemia-reperfusion injury^[14]. However, the technique has inherent limitations as it requires interruption of blood flow to the target organ and, thus, can only be achieved in the operating room or during coronary angioplasty. Furthermore, additional time for the preconditioning procedure is required during surgery or during intervention. Preconditioning itself might cause deterioration of organ function or cause complications, such as emboli of atheroma, because of the intermittent aortic clamping or intermittent coronary balloon inflation. Hence, local ischemic preconditioning has not found widespread clinical use.

However, by instead applying the local ischemic con-

ditioning stimulus after the ischemic event (*e.g.*, at the time of reperfusion in primary PCI), so-called ischemic postconditioning, most of these obstacles for clinical use are overcome. In an experimental setting, ischemic postconditioning inhibits ischemia-reperfusion injury almost as efficiently as ischemic preconditioning^[15,16]. Some clinical studies suggest that local ischemic postconditioning reduces myocardial injury in patients undergoing primary PCI for acute myocardial infarction^[17,18], but another recently published trial did not confirm this effect^[19]. Furthermore, a large-scale trial of 700 patients admitted with STEMI randomized to either standard primary PCI or primary PCI followed by postconditioning, failed to show any effect on myocardial reperfusion and clinical endpoints^[20].

REMOTE ISCHEMIC CONDITIONING

Remote ischemic conditioning (RIC) by repeated short-lasting ischemia in a distant tissue—mostly achieved by intermittent interruption of circulation in a limb—has recently emerged as a promising adjunctive therapy to avoid organ damage, thereby improving the outcomes of well-established therapies.

From the site of the remote stimulus, through humoral^[21] and neuronal^[22,23] pathways, RIC activates several protective mechanisms in the target organ similar to those activated by local preconditioning. They include the reperfusion-injury salvage kinase^[24] and survivor activating factor enhancement^[25,26] signaling pathways. Furthermore, RIC modifies systemic inflammatory response^[27,28], prevents endothelial dysfunction^[29] and platelet activation^[30] following ischemia-reperfusion injury.

In experimental studies, RIC has been shown to afford protection against ischemia-reperfusion in the liver^[31], lung^[32], kidney^[33], brain^[34], and heart^[29].

The ability to induce organ protection by a simple, non-invasive stimulus has facilitated the translation of RIC into the clinical setting. In patients, RIC can be induced by 3–4 cycles of inflation (ischemia) and deflation (reperfusion) of a standard blood pressure cuff placed on a limb. Following the original description of the method in 1997^[35] and its translation to humans in 2002^[29], multiple randomized clinical trials have shown that RIC affords organ protection in many clinical ischemia-reperfusion syndromes, including the kidney^[33,36], brain^[37], and heart^[38–41].

COOLING

Moderate hypothermia induced prior to reperfusion reduces infarct size in animal models^[42–44]. A clinical pilot study has suggested that patients admitted with anterior STEMI who are rapidly cooled to a body temperature below 35 °C by the combination of cold saline infusion together with an endovascular cooling catheter before primary PCI develop smaller infarcts^[45]. However, difficulties in applying the technique in the clinical setting without

delaying treatment together with inconsistent results cause controversy about the clinical value and applicability^[46], although a recent pooled analysis of two clinical trials indicate a potential beneficial effect^[47]. Most recently, the CHILL-MI study, using a similar cooling technique as in the initial pilot study, showed that while cooling did not have a general cardioprotective effect, it seems to reduce infarct size in patients with anterior STEMI admitted for primary PCI within four hours of symptom onset. In addition, cooling caused a significant reduction in heart failure events^[48]. A possible explanation for an overall lack of cardioprotective effect in the CHILL-MI study may be the fact that cooling below 35 °C was only achieved in 76% of the patients, and that sufficient cooling may be crucial for achieving cardioprotective effects.

PHARMACOLOGICAL CONDITIONING

The increasing insight into the mechanistic pathways involved in local and remote ischemic conditioning has encouraged identification of potential targets for pharmacological intervention against ischemia-reperfusion injury. A vast number of pharmacological agents have been shown to afford cardioprotection in experimental models, including adenosine^[49], erythropoietin^[50], rotigaptide^[51], statins^[52], atrial natriuretic peptide^[53], glucose-insulin-potassium^[54], P-selectin antagonist^[55], cyclosporine^[56], exenatide^[57] and metoprolol^[58]. A larger number of these agents have been tested in clinical studies (Table 1) with ambiguous results, the most promising being cyclosporine^[64], exenatide^[67] and metoprolol^[75], all of which seem to consistently provide cardioprotection in the clinical setting. For a comprehensive review, please see Kloner (2013)^[76]. However, an important limitation—and a potential explanation for the lack of success of pharmacological conditioning with some drugs, is that most agents act through a single signaling pathway in the complex and interactive system of protective mechanisms activated by ischemic conditioning and cooling^[13].

Cyclosporine

Cyclosporine, a widely used immunosuppressant drug, is believed to facilitate its cardioprotective effects by inhibition of mitochondrial permeability transition pore opening, thus preventing mitochondrial destruction^[77]. In a study by Piot *et al.*^[64], administration of cyclosporine at the time of reperfusion in STEMI patients treated with primary PCI, was associated with a reduction in infarct size measured by creatine kinase and troponin I release. In a subgroup analysis, a similar reduction in infarct size was demonstrated on day 5 with cardiac magnetic resonance imaging (CMR). In a follow-up study, Mewton *et al.*^[78] found that this infarct-sparing effect of cyclosporine was persistent at 6 mo. However, in a more recent study, no effect was shown of early cyclosporine administration as an adjunct to thrombolysis in STEMI patients in relation to infarct size, left ventricular function, heart failure or death^[65].

Table 1 Clinical studies using pharmacological adjunctive therapy in patients with acute myocardial infarction

	Intervention	n	Outcome
Adenosine			
Mahaffey <i>et al</i> ^[59] , 1999 (AMISTAD)	Infusion of adenosine for 3 h as adjunct to thrombolysis	236	Reduction in infarct size
Kloner <i>et al</i> ^[60] , 2006 (AMISTAD II)	Infusion of adenosine for 3 h	2118	No difference in death or heart failure
Atrial natriuretic peptide			
Kitakaze <i>et al</i> ^[61] , 2007 (J-WIND)	Infusion of atrial natriuretic peptide for 3 d	569	Reduction in CK, increase in LVEF
Atorvastatin			
Kim <i>et al</i> ^[62] , 2010 (STATIN-STEMI)	Oral atorvastatin 80 mg before primary PCI	171	No difference in death, revascularization or infarct size
Hahn <i>et al</i> ^[63] , 2011	Oral atorvastatin 80 mg before primary PCI	173	No difference in infarct size
Cyclosporine A			
Piot <i>et al</i> ^[64] , 2008	Infusion of cyclosporine before primary PCI	58	Reduction in infarct size
Ghaffari <i>et al</i> ^[65] , 2013	Infusion of cyclosporine as adjunct to thrombolysis	101	No difference in infarct size, death, heart failure or LVEF
Erythropoietin			
Voors <i>et al</i> ^[66] , 2010	Single dose erythropoietin	529	No difference in LVEF or infarct size
Exenatide			
Lønborg <i>et al</i> ^[67] , 2012	Infusion of exenatide for 6 h	105	Reduction in infarct size
Bernink <i>et al</i> ^[68] , 2012 (EXAMI)	Loading dose of exenatide before PCI followed by infusion for 72 h	39	No difference in left ventricular function or infarct size
Woo <i>et al</i> ^[69] , 2013	Subcutaneously and intravenous exenatide before primary PCI followed by twice daily subcutaneous injection for 2 d	58	Reduction in infarct size and improvement of LVEF
Glucose-insulin-potassium			
Mehta <i>et al</i> ^[70] , 2005 (CREATE-ECLA)	Infusion of GIK for 24 h	20201	No difference in mortality
Selker <i>et al</i> ^[71] , 2012 (IMMEDIATE)	Out-of-hospital infusion of glucose-insulin-potassium	357	Reduced mortality among patients with cardiac arrest
δ-protein kinase C			
Bates <i>et al</i> ^[72] , 2008	2 doses of KAI-9803	154	No difference in infarct size
Lincoff <i>et al</i> , 2014	Infusion of delcaseritib for 24 h	1083	No difference in infarct size
P-selectin antagonist			
Mertens <i>et al</i> ^[73] , 2006 (PSALM)	Infusion of recombinant P-selectin glycoprotein ligand-immunoglobulin as adjunct to thrombolysis	88	No difference in ST-segment resolution or LVEF
Tardif <i>et al</i> ^[74] , 2013 (SELECT-ACS)	Infusion of inclacumab before PCI in NSTEMI patients	322	Reduction in troponin I and creatine kinase
Metoprolol			
Ibanez <i>et al</i> ^[75] , 2013 (METOCARD-CNIC)	Infusion of metoprolol before primary PCI	220	Reduction in infarct size and improvement of LVEF

LVEF: Left ventricular ejection fraction; PCI: Percutaneous coronary intervention; CK: Creatine kinase; NSTEMI: Non-ST-elevation myocardial infarction.

Exenatide

Exenatide, a glucagon-like peptide-1 analog, is primarily used as an anti-diabetic drug for patients with type 2 diabetes. However, in addition to its beneficial metabolic effect, exenatide is believed to induce cardioprotection through activation of ischemia-reperfusion injury survival pathways^[79]. Lønborg *et al*^[67] found that in STEMI patients, a 6 h infusion of exenatide started prior to primary PCI was associated with increased myocardial salvage measured by CMR. This increase in myocardial salvage from exenatide infusion translated to a reduction in final infarct size, although reserved for patients with short system delay (< 132 min from first medical contact to first balloon inflation)^[80]. In a recent study by Woo *et al*^[69], subcutaneous injection together with intravenous infusion of exenatide as adjunct to primary PCI followed by twice daily subcutaneous injections of exenatide for another two days, was associated with both a reduction in infarct size and improvement of left ventricular function.

Metoprolol

Most randomized clinical trials investigating potential infarct sparing effects of betablockers in STEMI patients have been conducted in the pre-reperfusion era, and only a few studies have evaluated the cardioprotective effect of beta-blockage as an adjunct to thrombolysis or primary PCI. However, recently, the METOCARD-CNIC trial demonstrated that intravenous metoprolol administered to STEMI patients prior to primary PCI was associated with significantly smaller infarct size measured by CMR compared to primary PCI treatment alone. In addition, early metoprolol administration increased left ventricular function^[75].

IMPROVING THE OUTCOME OF MYOCARDIAL INFARCTION IN PATIENTS

The translation of cardioprotective strategies to counter the detrimental consequences of ischemia-reperfusion in-

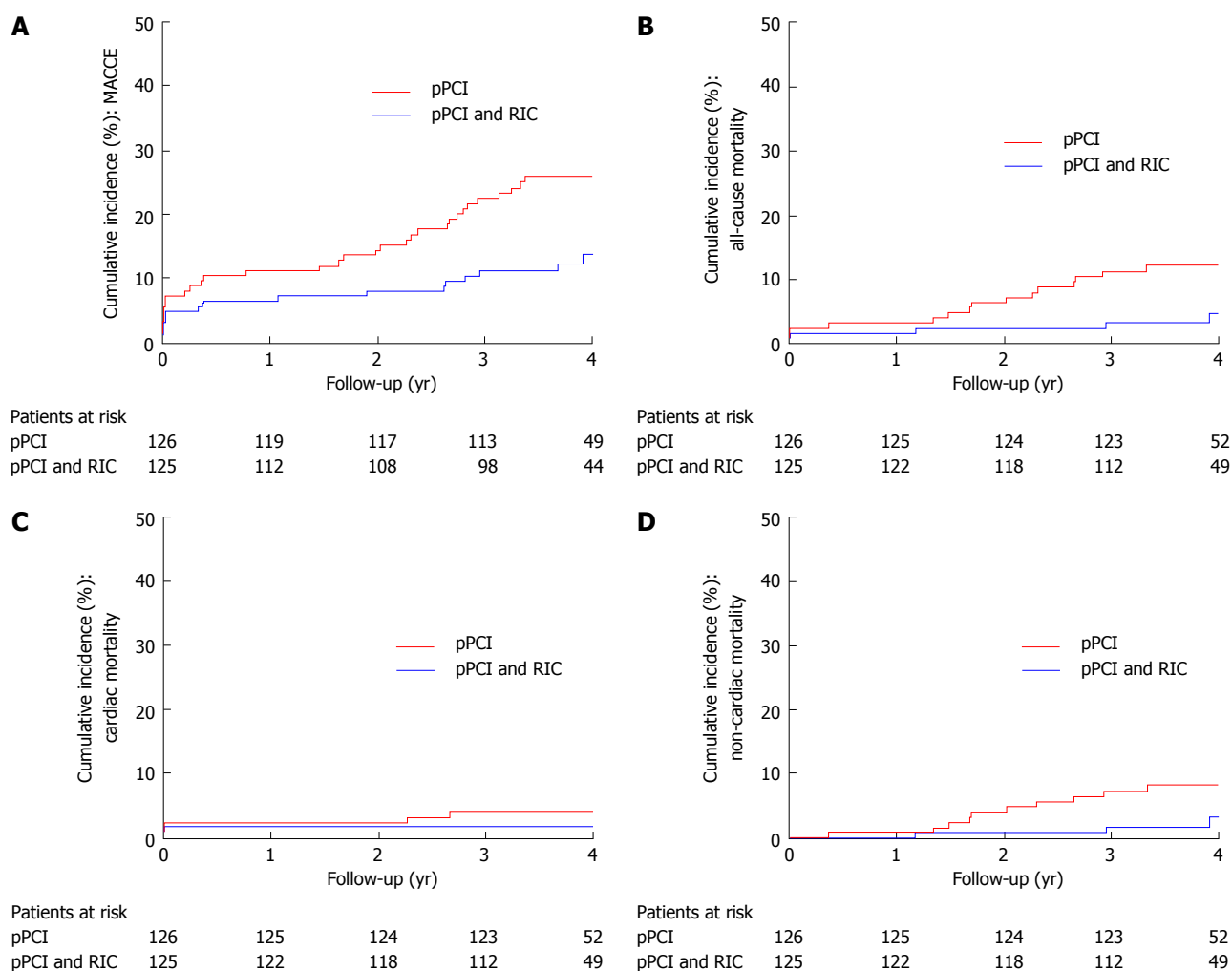


Figure 2 Effect of remote ischemic conditioning on long-term clinical outcome in patients with ST-elevation myocardial infarction treated with primary percutaneous coronary intervention. Cumulative incidence (%). A: Of major adverse cardiac and cerebrovascular events (MACCE) by year since randomization (per-protocol analysis). $P = 0.010$; B: Of all-cause mortality by year since randomization (per-protocol analysis). $P = 0.019$; C: Of cardiac mortality (%) by year since randomization (per-protocol analysis). $P = 0.248$; D: Of non-cardiac mortality (%) by year since randomization (per-protocol analysis). $P = 0.045$. Modified from Sloth *et al*^[89]. Eur Heart J (2014) 35: 168-175. pPCI: Primary percutaneous intervention; RIC: Remote ischemic conditioning.

jury is still in its infancy, and large-scale multicenter trials to show real-world clinical impact are lacking. However, recently published long-term clinical data on the use of RIC provide reason for optimism about a prognostic benefit of adjunctive therapy beyond opening the coronary artery.

REMOTE ISCHEMIC CONDITIONING IN PREDICTABLE ISCHEMIA

Predictable cardiac ischemia-reperfusion injury occurs in both elective PCI and CABG, and procedural tissue injury—as measured by biomarkers—is correlated to clinical outcome. Mid-scale clinical studies have shown that RIC applied prior to CABG^[39,81] and PCI^[38] reduces surrogate markers of myocardial injury, but until recently, the clinical relevance of these findings was questionable. However, two recent publications strongly suggest, that RIC should find a place as standard adjunctive therapy in elective PCI and CABG.

In a single center, randomized controlled trial, Davies

et al^[82] investigated the long-term clinical outcomes of 192 patients undergoing elective coronary angioplasty randomized to RIC or standard treatment. While their original study showed a significant reduction in troponin release in the RIC group^[38], the follow-up study revealed that this translated into a reduced major adverse cardiac and cerebrovascular events (MACCE) rate up to 6 years after the coronary intervention.

In another single center, double-blinded trial, Thielmann *et al*^[83] studied 329 low-risk patients undergoing elective isolated on-pump first-time CABG randomized to either standard CABG or CABG preceded by RIC. Besides reduced perioperative troponin I release as also shown previously by others^[84], the authors found a reduction in all-cause and cardiac mortality as well as MACCE in the intervention group during the follow-up period that was a mean of 1.5 year. During the follow-up period, MACCE occurred 23 times in the control group *vs* 8 times in the RIC group ($P = 0.011$). The authors observed 11 deaths in the control group and only 3 deaths in the RIC group ($P = 0.046$). The combined endpoint

(death, MACCE and repeat revascularization) yielded a HR of 0.38 (0.21-0.70) in favor of RIC. Interestingly, Thielmann *et al.*^[83] also found that RIC reduced the occurrence of sepsis, stroke and non-cardiac deaths, which adds to the speculation that RIC could confer systemic beneficial effects beyond the organ exposed to ischemia-reperfusion injury.

REMOTE ISCHEMIC CONDITIONING IN UNPREDICTABLE ISCHEMIA

In unpredictable ischemic events, like myocardial infarction and stroke, rapid restoration of blood flow to the ischemic territory has been the primary focus. Optimization of prehospital admission logistics to reduce any delay improves outcome^[85] and decreases mortality^[86]. While acute thrombolysis and primary PCI have improved outcome, recent studies show that further injury occurs early after reperfusion and can continue long afterwards^[87,88] emphasizing the need for therapies limiting clinical reperfusion injury in acute ischemic events.

In a study of 333 patients admitted with STEMI for primary PCI and randomized to either standard treatment or RIC performed in the ambulance during transportation to primary angioplasty, we showed, that RIC improves myocardial salvage index (0.75 in the RIC group *vs* 0.55 in the control group, $P = 0.033$) as measured by single-photon emission computed tomography^[40]. Recently, Sloth *et al.*^[89] published 4-year follow-up data on our original study, showing that the improved myocardial salvage translates into clinical prognostic benefit, as MACCE occurred for 17 (13.5%) patients in the RIC treated group compared with 32 (25.6%) patients in the control group, yielding a HR of 0.49 (95%CI: 0.27-0.89, $P = 0.018$). Furthermore, only 5 deaths (4%) occurred in the intervention group compared with 15 (12%) in the control group, yielding a HR of 0.32 (95%CI: 0.12-0.88, $P = 0.027$) (Figure 2)^[89]. Specific evaluation of death causes suggested a reduction in both cardiac and non-cardiac mortality, although only the latter was statistically significantly reduced (and most likely arose by chance). However, even when excluding non-cardiac deaths, MACCE was still reduced in the RIC group.

CONCLUSION

The globally increasing burden of cardiovascular disease calls for improved prevention and treatment. Acute and chronic coronary artery disease constitute the leading death cause in the World, and adjunctive therapies to limit the morbidity and mortality related to myocardial infarction may have major impact on global health. Pharmacological adjunctive therapy and rapid cooling decrease infarct size in some clinical studies but have yet to prove convincing clinical benefit. Remote ischemic conditioning-a low-cost, non-invasive and easily applicable adjunctive therapy-may confer prognostic benefit for patients undergoing coronary artery by-pass surgery and elective

and acute percutaneous coronary interventions. Large-scale studies with clinical endpoints, such as the ERICCA trial (ClinicalTrials.gov NCT01247545), the RIPHeart-study (ClinicalTrials.gov NCT01067703) and the CONDI 2 trial (ClinicalTrials.gov NCT01857414) are, however, needed to confirm the clinical effect, before RIC should be applied as standard adjunctive therapy. Similarly, as an adjunctive therapy to primary PCI the CIRCUS trial (ClinicalTrials.gov NCT01502774) will clarify the potential clinical benefit of cyclosporine A, and the DANAMI-3 trial (ClinicalTrials.gov NCT01435408) the potential clinical efficacy of ischemic postconditioning.

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WJC 6th Anniversary Special Issues (5): Myocardial infarction

Invasive strategy in patients with resuscitated cardiac arrest and ST elevation myocardial infarction

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Abstract

Coronary artery disease is the most frequent cause of sudden cardiac death. There is general consensus that immediate coronary angiography with percutaneous coronary intervention (PCI) should be performed in all conscious and unconscious patients with ST-elevation myocardial infarction in post-resuscitation electrocardiogram. In these patients acute coronary thrombotic lesion ("ACS" lesion) suitable for PCI is typically present in more than 90%. PCI in these patients is not only feasible and safe but highly effective and there is evidence of improved survival with good neurological outcome. PCI of the culprit lesion is the primary goal while PCI of stable obstructive lesions may be postponed unless post-resuscitation cardiogenic shock is present.

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Key words: Sudden cardiac arrest; ST-elevation myocardial infarction; Coronary angiography; Percutaneous coronary intervention

Core tip: There is general consensus that immediate coronary angiography with percutaneous coronary intervention (PCI) should be performed in all conscious and unconscious patients with ST-elevation myocardial

infarction in postresuscitation electrocardiogram. In these patients, acute coronary thrombotic lesion ("ACS" lesion) suitable for PCI is typically present in more than 90%. PCI in these patients is not only feasible and safe but highly effective and there is evidence of improved survival with good neurological outcome. PCI of the culprit lesion is the primary goal while PCI of stable obstructive lesions may be postponed unless postresuscitation cardiogenic shock is present.

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INTRODUCTION

Coronary artery disease has been documented in almost 80% of patients after resuscitated sudden cardiac arrest (CA)^[1,2]. In the past, most of these patients died either due to profound cardiac failure or post-resuscitation brain injury without any causative treatment^[3]. In year 2002 introduction of hypothermia, which was demonstrated to improve survival and neurological outcome of comatose patients, significantly changed the field of post-resuscitation treatment that became more intensive and cause-oriented^[4,5]. Besides, due to better pre-hospital "chain of survival" increasing numbers of patients after resuscitated cardiac arrest are being nowadays admitted^[6]. These include also patients with ST-elevation myocardial infarction (STEMI) in post-resuscitation electrocardiogram (ECG) requiring immediate coronary angiography (CAG) and percutaneous coronary intervention (PCI).

CAG

Despite the lack of randomized trials demonstrating ef-

Table 1 Non-randomized data on utilization of urgent coronary angiography and primary percutaneous coronary intervention in patients after resuscitated cardiac arrest^[1,7,9-48] *n* (%)

Author	Year	<i>n</i>	Comatose	STEMI	CA-PCI	PCI success	MIH	Survival	CPC 1 or 2	Survival comatose	CPC 1 or 2 comatose	Survival conscious
Kahn	1995	11	7 (64)	11/11 (100)	11 (100)	7/11 (64)	N	6/11 (55)	6/11 (55)	3/7 (43)	3/7 (43)	3/4 (75)
Spaulding	1997	84	NA	34/84 (40)	37 (44)	28/37 (76)	N	32/84 (38)	30/84 (36)	NA	NA	NA
Lin	1998	10	NA	10/10 (100)	10 (100)	10/10 (100)	N	9/10 (90)	NA	NA	NA	NA
Bulut	2000	10	NA	10/10 (100)	10 (100)	8/10 (80)	N	4/10 (40)	NA	NA	NA	NA
McCollough	2002	22	NA	22/22 (100)	22 (100)	22/22 (100)	N	9/22 (41)	NA	NA	NA	NA
Keelan	2003	15	13 (87)	15/15 (100)	15 (100)	14/15 (93)	N	11/15 (73)	9/15 (60)	NA	NA	NA
Bendz	2004	40	36 (90)	40/40 (100)	40 (100)	38/40 (95)	N	29/40 (73)	NA	NA	NA	NA
Quintero-Moran	2006	27	NA	27/27 (100)	27 (100)	23/27 (85)	NA	18/27 (67)	NA	NA	NA	NA
Sunde	2007	47	NA	NA	30 (64)	NA	Y	NA	NA	NA	NA	NA
Gorjup	2007	135	86 (64)	135 (100)	109 (81)	102/109 (94)	Y	90/135 (67)	74/135 (55)	44/86 (51)	25/86 (29)	49/49 (100)
Garot	2007	186	NA	186 (100)	186 (100)	161/186 (87)	Y	103/186 (70)	89/186 (48)	NA	NA	NA
Richling	2007	46	NA	46 (100)	46 (100)	NA	NA	24/46 (52)	22/46 (48)	NA	NA	NA
Markusohn	2007	25	18 (72)	25 (100)	25 (100)	22/25 (88)	Y	19/25 (76)	17/25 (68)	NA	NA	NA
Werling	2007	24	NA	NA	13 (54)	NA	NA	16/24 (67)	NA	NA	NA	NA
Hovdenes	2007	49	49 (100)	NA	36 (73)	NA	Y	41/49 (84)	34/49 (69)	41/49 (84)	34/49 (69)	NA
Valente	2008	31	31 (100)	31 (100)	31 (100)	NA	NA	23/31 (74)	NA	23/31 (74)	NA	NA
Mager	2008	21	NA	21 (100)	21 (100)	NA	NA	18/21 (86)	NA	NA	NA	NA
Wolfrum	2008	16	16 (100)	16 (100)	16 (100)	16/16 (100)	Y	12/16 (75)	NA	12/16 (75)	11/16 (69)	NA
Pleskot	2008	20	NA	NA	19 (95)	17/19 (89)	NA	NA	NA	NA	NA	NA
Peels	2008	44	NA	44 (100)	44 (100)	38/44 (86)	NA	22/44 (50)	NA	NA	NA	NA
Merchant	2008	30	NA	13 (43)	30 (20)	17/19 (89)	NA	22/30 (80)	NA	NA	NA	NA
Hosmane	2009	98	73 (74)	98 (100)	64 (65)	62/64 (97)	Y	63/98 (64)	57/98 (58)	39/73 (53)	33/73 (45)	24/25 (96)
Anyfantakis	2009	72	NA	23 (32)	27 (38)	24/27 (89)	NA	35/72 (49)	33/72 (46)	NA	NA	NA
Reynolds	2009	96	NA	42 (44)	NA	NA	Y	52/96 (54)	NA	NA	NA	NA
Lettieri	2009	99	NA	99 (100)	99 (100)	79/99 (80)	NA	77/99 (78)	72/99 (73)	NA	NA	NA
Pan	2010	49	NA	49 (100)	49 (100)	42/49 (86)	NA	31/49 (63)	NA	NA	NA	NA
Battista	2010	20	NA	10 (50)	20 (100)	NA	Y	8/20 (40)	6/20 (30)	NA	NA	NA
Dumas	2010	435	NA	134 (31)	202 (46)	177/202 (88)	Y	171/435 (39)	160/435 (37)	NA	NA	NA
Stub	2011	62	62 (100)	27 (44)	31 (50)	29/31 (94)	Y	NA	NA	NA	NA	NA
Tomte	2011	252	NA	NA	NA	NA	NA	140/252 (56)	108/212 (51)	113/171 (66)	73/171 (43)	41/41 (100)
Radsel	2011	212	171 (81)	158 (75)	165 (78)	150/165 (91)	Y	154/212 (73)	NA	NA	NA	NA
Mooney	2011	101	NA	68 (67)	56 (55)	NA	NA	NA	NA	NA	NA	NA
Cronier	2011	91	NA	50 (55)	46 (51)	43/46 (93)	Y	60/91 (66)	NA	NA	NA	NA
Moellmann	2011	65	NA	36 (55)	65 (100)	64/65 (98)	NA	46/65 (71)	NA	NA	NA	NA
Nanjayya	2012	35	35 (100)	31 (89)	21 (60)	NA	Y	20/35 (57)	14/35 (40)	20/35 (57)	14/35 (40)	NA
Bro-Jeppesen	2012	360	360 (100)	116 (32)	198 (55)	101/122 (83)	Y	219/360 (61)	207/360 (58)	219/360 (61)	207/360 (58)	NA
Zanutini	2012	93	93 (100)	32 (34)	NA	NA	Y	50/93 (54)	36/93 (39)	50/93 (54)	36/93 (39)	NA
Liu	2012	81	24 (30)	81 (100)	49 (60)	42/49 (86)	N	36/81 (44)	NA	NA	NA	NA
Zimmermann	2013	48	48 (100)	48 (100)	44 (92)	37/44 (84)	Y	32/48 (67)	16/48 (33)	32/48 (67)	16/48 (33)	NA
Hollenbeck	2013	269	269 (100)	0 (0)	122 (45)	NA	Y	151/269 (56)	NA	151/269 (56)	NA	NA
Velders	2013	224	108 (48)	224 (100)	217 (97)	NA	Y	183/218 (84)	168/218 (77)	NA	NA	NA
Skupaj	2013	3655	1499/1804 (83)	2012/3263 (62)	2253/3179 (71)	1373/1553 (88)	Y	2036/3384 (60)	1158/2241 (52)	747/1238 (60)	452/838 (54)	117/119 (98)

STEMI: ST-elevation myocardial infarction; PCI: Percutaneous coronary intervention; CA: Cardiac arrest; NA: Not available; MIH: Mild induced hypothermia

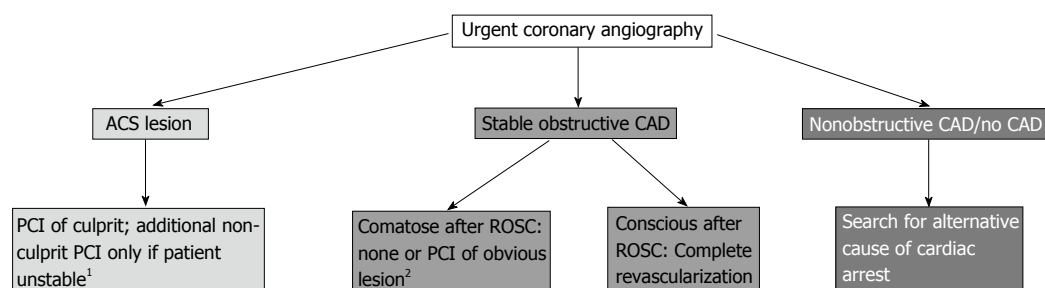


Figure 1 Revascularization strategy based on coronary angiography findings. ¹If ischemia or cardiogenic shock after successful culprit PCI; ²If considered responsible for cardiac arrest or beneficial for hemodynamic stability. ROSC: Return of spontaneous circulation; PCI: Percutaneous coronary intervention; CAD: Coronary artery disease.

fectiveness of immediate CAG and PCI in patients with resuscitated CA, we gradually increased the number of patients undergoing such immediate invasive coronary strategy. We extrapolated knowledge from randomized studies on acute coronary syndrome patients^[7] and generated our own experience on combination of immediate invasive coronary strategy mild induced hypothermia^[8,9]. After favorable experience with STEMI patients in post-resuscitation ECG, we applied the same protocol also to patients without STEMI in whom no obvious non-coronary cause of cardiac arrest was present. We were encouraged also by increasing number of independent peer-review experience by other investigators in more than 3500 patients cumulatively (Table 1). Patient selection and time to invasive procedure in these studies was different therefore results cannot be compared. Nevertheless we can appreciate that urgent PCI is feasible and highly effective in this population. There is also recent meta analysis of 10 observational studies showing immediate invasive coronary strategy to as independent predictor of survival (OR = 2.78; 95%CI: 1.89-4.10, $P < 0.001$)^[10].

Pubmed observational cohort studies on utilization of immediate CAG/PCI in patients with resuscitated sudden cardiac arrest (Table 1)^[1,8,11-49].

REPERFUSION STRATEGY

According to revascularization guidelines for STEMI without preceding CA^[50], CA-PCI should be primary directed towards “ACS lesions” for which we can assume direct cause-effect relationship with CA (Figure 1). The rationale is to reduce infarct size and improve hemodynamic and electrical stability. Patients who regain consciousness after return of spontaneous circulation have excellent prognosis (Table 1). Their survival is comparable or is even better that in general STEMI population without preceding CA. This may be partly explained by shorter ischemic times because of shorter patient delay. Index multi vessel and not only “culprit” PCI seems to be indicated only patients with post-resuscitation cardiogenic shock^[51]. We can speculate that complete revascularization improves left ventricular function, which may facilitate survival from post-resuscitation cardiogenic shock.

DISCUSSION

Nowadays, there is a question whether we should base our revascularization strategy for patients with STEMI in post-resuscitation ECG on non-randomized observational cohort studies. We believe, based on our experience and experience of others, that it would be very difficult to perform such prospective randomized trial. On the other hand we think such trial is needed for patients without STEMI in post-resuscitation ECG. However, regardless of this, we think patients with resuscitated cardiac arrest should be included in existing “STEMI networks” with direct transportation to the specialized “cardiac arrest centers” of excellence. Because of critical role of immediate CAG and PCI, interventional cardiologists should be an essential member of post-resuscitation team. However, when treating post CA patients we should avoid futility. In unfavorable settings of cardiac arrest (unwitnessed arrest, long delays to pre-hospital team arrival, no BLS, “non-shockable” first rhythm, long ACLS, recurrent arrest) or severe pre-arrest comorbidities, aggressive post-resuscitation treatment is not likely to result in quality survival.

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WJC 6th Anniversary Special Issues (5): Myocardial infarction

Impact of conditioning hyperglycemic on myocardial infarction rats: Cardiac cell survival factors

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Abstract

While clinical data have suggested that the diabetic heart is more susceptible to ischemic heart disease (IHD), animal data have so far pointed to a lower probability of IHD. Thus, the aim of this present review is to look at these conflicting results and discuss the protective mechanisms that conditioned hyperglycemia may confer to the heart against ischemic injury. Several mechanisms have been proposed to explain the cardioprotective action of high glucose exposure, namely, up-regulation of anti-apoptotic factor Bcl-2, inactivation of pro-apoptotic factor bad, and activation of pro-survival factors such as protein kinase B (Akt), vascular endothelial growth factor (VEGF), hypoxia inducible factor-1 α and protein kinase C- ϵ . Indeed, cytosolic increase in Ca²⁺ concentration, the mitochondrial permeability transition pore, plays a key role in the genesis of ischemic injury. Previous studies have shown that the diabetic heart decreased Na⁺/Ca²⁺ and Na⁺/H⁺ exchanger activity and as such it accumulates less Ca²⁺ in cardiomyocyte, thus preventing cardiac injury and the associated heart dysfunctions. In addition, the expression of VEGF

in diabetic animals leads to increased capillary density before myocardial infarction. Despite poor prognostic in the long-term, all these results suggest that diabetes mellitus and consequently hyperglycemia may indeed play a cardioprotective role against myocardial infarction in the short term.

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Key words: Conditioned hyperglycemia; Diabetes mellitus; Myocardial infarction; Cardioprotection; Survival factors

Core tip: Hyperglycemia or diabetes triggers a conditioned state that may protect the heart against ischemic injury and associated detrimental effects. These beneficial effects are present in short term diabetes and/or moderate hyperglycemia. The increase in glucose availability, the preferred energy substrate of the heart in stress condition, is likely to be one of the main cardioprotector mechanisms of hyperglycemia. However, other cardioprotective mechanisms seem to be involved, such as the release of cellular survival factors, ions preventing overload and angiogenesis. A fuller understanding of the mechanisms underlying conditioned hyperglycemia is then critical for the development of effective therapeutic strategies against ischemic heart disease.

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CONDITIONED HYPERGLYCEMIA AND MYOCARDIAL INFARCTION

Diabetes type 1 is a chronic disease characterized by hy-

perglycemia resulting from genetic and environmental factors. Complications of cardiac function are a leading cause of morbidity and mortality in type 1 diabetic patients^[1]. Diabetes induces cardiac dysfunction or diabetic cardiomyopathy, regardless of the presence or absence of vascular disease, coronary artery disease, arteriosclerosis and myocardial infarction^[2-4].

In hospital environments, glucose and insulin administration are induced in coronary artery bypass grafting patients. This therapy protects the myocardium and inhibits ischemia-induced adenosine monophosphate-activated protein kinase activation^[5]. However, intraoperative insulin resistance is associated with increased risk of complications, regardless of the patient's diabetic state^[6].

The increase in mortality in diabetic patients after myocardial infarction remains controversial. Intensive glucose control is widely used in patients with diabetes mellitus and stress-induced hyperglycemia. In this review study, we found that this strategy increases the risk of hypoglycemia, and dangerously increases catecholamine levels with hemodynamic response. Such significant changes may culminate in serious or even fatal cardiovascular events^[7].

Elevated admission glucose levels are common in patients with myocardial infarction and are strongly associated with increased mortality. Mortality of hyperglycemic patients was lower in the 1985 to 2008 period when compared to normoglycemic patients. Efforts to establish optimal treatment for these patients remain warranted^[8].

Accumulated evidence in clinical studies on diabetic cardiomyopathy suggests increased myocardial infarction and mortality in diabetic patients; however, experimental data regarding the increased resistance of diabetic animals to ischemic injury are quite controversial^[9]. Conversely, chronic hyperglycemia is associated with increased incidence of long-term cardiovascular complications, although its effect on acute hyperglycemic response and mortality after acute myocardial infarction remains unclear^[10].

One review study suggests that the diabetic heart may be more, equally, or even less susceptible to ischemia-reperfusion injury (novel cardioprotective strategy for the diabetic heart)^[11]. Our review study, however, aims at demonstrating the role of conditioned hyperglycemia as a protective mechanism of the heart after ischemic injury and in the preservation of cardiac function.

CELLULAR SURVIVAL FACTORS: CELL DEATH AND ANGIOGENESIS

Several studies have suggested that cardiomyocyte loss in ischemic cardiomyopathy may occur either by necrosis or by apoptosis, without significant inflammatory response^[12,13]. This loss has been found to contribute to the decline of the left ventricular function in humans^[14,15].

Indeed, experimental studies have shown that the chronic treatment of isolated cardiomyocytes with a high glucose content medium increased the rate of cell

death^[16]. In contrast, exposure to short periods of a high glucose medium or diabetes has been found to protect the heart against a variety of pathological insults, including ischemia, hypoxia, and calcium overload^[17-19]. Several mechanisms have been proposed to explain the cardioprotective role of high glucose exposure, such as up-regulation of antiapoptotic factor Bcl-2, inactivation of proapoptotic factor Bad, and activation of prosurvival factors^[17,20].

To investigate the mechanisms behind improved cardiac function (accompanied by a reduction in lesion area) in diabetic rats (30 d of hyperglycemia) undergoing myocardial infarction (15 d), we evaluated the gene expression regulating cardiac cellular survival factors: Bax, Fas, Bcl-2 and p53. In fact, gene expression was increased in diabetic animals after myocardial infarction, suggesting that the pro and anti apoptotic pathways can be activated simultaneously in this condition; this hypothesis was further strengthened by increased caspase-3 activity. These findings suggest an increased cell turnover acting to preserve cardiac function and reduce tissue injury^[21].

Cell survival factors can be activated by increased Bcl-2, as the up-regulation of Bcl-2 in some cells prevents excessive accumulation of calcium by mitochondria^[22], thus favoring cell survival. In this tissue, although calcium overload may be induced by ischemia, the association with hyperglycemia appears to reduce the activity of the $\text{Na}^+/\text{Ca}^{2+}$ exchanger^[23].

Lending support to these findings, a study showed a reduction in protein expression of the $\text{Na}^+/\text{Ca}^{2+}$ exchanger in diabetic infarcted hearts, which might contribute to mitochondrial disruption and contracture, inducing structural damage^[24]. In fact, the improvement in cardiac function in diabetic infarcted rats may be associated with the protective effect of Bcl-2, which abolishes the damage caused by the accumulation of calcium in the heart of diabetic rats.

Cytosolic Ca^{2+} overload during ischemia may be due to Ca^{2+} entry by reverse-mode of $\text{Na}^+/\text{Ca}^{2+}$ exchanger (NCX) secondary to the rise in Na^+ concentration. During ischemia, the anaerobic metabolism increases proton generation, which is extruded from the cell by Na^+/H^+ exchanger (NHE), resulting in increased cytosolic Na^+ concentration^[25]. This activates the reverse-mode of NCX exchanger, which in turn promotes an increase in Ca^{2+} concentration in the cardiomyocyte^[26]. Research has suggested that Na^+/H^+ exchange activity is decreased in diabetic hearts^[27]. Therefore, Ca^{2+} accumulation in the diabetic is lower than in the non-diabetic ischemic heart.

Several factors are related to cell survival: hypoxia inducible factor-1 α (HIF-1 α) is a transcription factor expressed in response to a decreased partial pressure of oxygen, and it is able to activate genes involved in angiogenesis, such as vascular endothelial growth factor (VEGF)^[28]. As a result of diabetic hyperglycemia, these survival factors were increased in diabetic animals before and after myocardial infarction^[21].

Interestingly, the expression of VEGF was also elevated before myocardial infarction in diabetic animals,

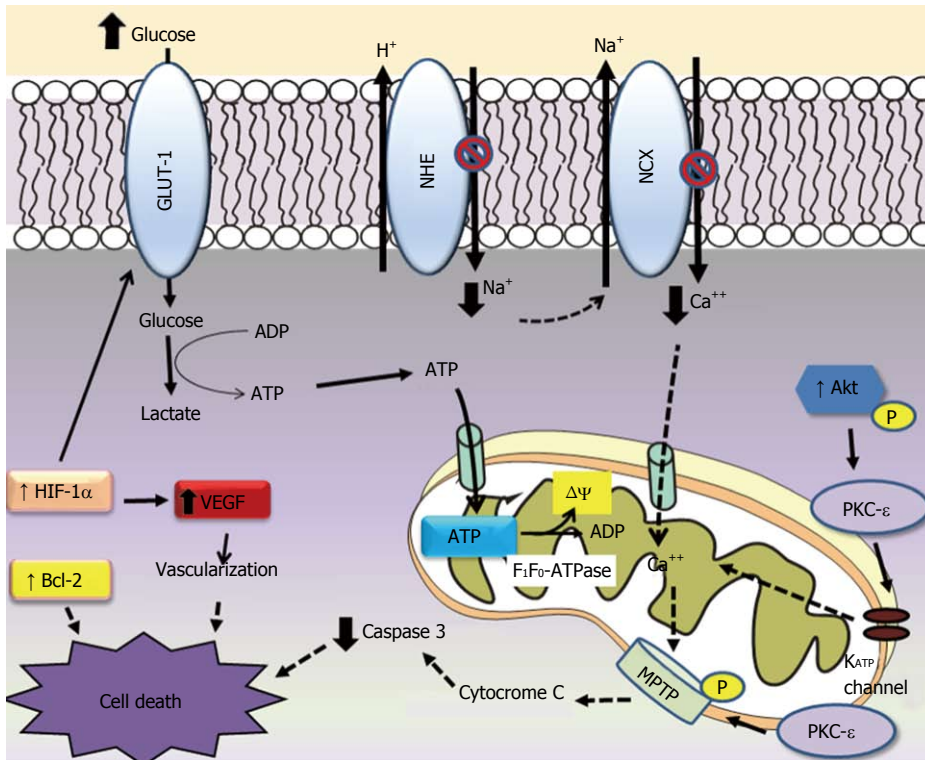


Figure 1 The process of apoptosis. GLUT-1: Glucose transporter type-1; NHE: Na^+/H^+ exchanger; NCX: $\text{Na}^+/\text{Ca}^{2+}$ exchanger; MPTP: Mitochondrial permeability transition pore; PKC- ϵ : Protein kinase C- ϵ ; VEGF: Vascular endothelial growth factor; HIF-1 α : Hypoxia inducible factor-1 α ; MPTP: Mitochondrial permeability transi-

and results were similar to the observed in interleukin 8 (IL-8) gene, *i.e.*, chemokine regulating neutrophil influx and activation with angiogenic propriety^[29-31]. IL-8 plays an important role in the recruitment of granulocytes in the infarcted myocardium, increasing cell adhesion (integrin) and activating the signaling pathways of cell survival mitogen-activated protein kinase and protein kinase C (PKC), which contribute to angiogenesis^[32]. Ooie *et al*^[33] have found that administration of streptozotocin for 12 wk in rats leads to increased tolerance to ischemic injury in an isolated heart model. These researchers also observed the translocation of protein kinase C- ϵ (PKC- ϵ) from the cytosol to the sarcolemmal membrane, where the protein is activated. PKC- ϵ is a K_{ATP} channel opener in both the sarcolemmal and mitochondrial membrane^[34]. Opening mitochondrial K_{ATP} channel during ischemia stabilizes mitochondrial potential, reduces mitochondrial Ca^{2+} overload, prevents ATP depletion, and the generation of reactive oxygen species^[34,35].

Mitochondrial permeability transition pore (MPTP) is a downstream of PKC- ϵ ^[36], which indicates that PKC interacts with MPTP, leading to phosphorylation of MPTP, and inhibits Ca^{2+} induced MPTP opening. Opening MPTP allows water and solutes to enter the mitochondria, increasing matrix volume and rupturing of the outer mitochondrial membrane. This results in the release of intermembrane cytochrome c, which can trigger apoptosis (Figure 1).

In this scenario, since hyperglycemia results in an increase of survival factors and induces angiogenesis, this may be interpreted as responses to repeated insults

which eventually determine an ischemic conditioning in diabetic rats. These responses are strongly associated with improved left ventricle (LV) function observed after ischemic injury, suggesting the presence of a physiological mechanism of protection against heart damage.

ROLE OF INFLAMMATORY CYTOKINES ON CARDIAC FUNCTION

Cardiac repair after myocardial infarction is dependent on the activation of tumor necrosis factor alpha (TNF- α), IL-1 β and IL-6 cytokines, which results in leukocyte recruitment to the infarcted area^[37]. In consequence, the immune imbalance between pro-inflammatory and anti-inflammatory properties can be modified in favor of more or less inflammatory factors, depending on the time course of the progression of heart failure. In this regard, changes in the concentration of TNF- α may have different effects on all the cell types involved in cardiac injury and repair, and in the suppression of cardiac contractility^[38] to improve cardiomyocyte apoptosis^[39].

In fact, Malfitano *et al*^[21] have found a reduction of TNF- α in diabetic rats after myocardial infarction. The signaling of IL-1 β is crucial for the activation of inflammatory and fibrogenic pathways in the healing of myocardial infarction, and it may play a role in the pathogenesis of post-infarction remodeling^[40]. Moreover, the induction of members of the IL-6 family leads to a rapid recruitment of mononuclear cells and cardiomyocyte ischemic myocardium^[41], thus indicating that the concentration of

IL-6 was increased only in infarcted rats, but remained unchanged in diabetic animals after ischemic injury.

These three pro-inflammatory cytokines are not only associated with the inflammatory response, but are also involved in heart failure, cardiomyopathy and LV remodeling, suggesting that the reduction of inflammatory factors may be one of the mechanisms responsible for improved heart function observed in this group. These findings corroborate a previous study of our group, in which it was demonstrated that hyperglycemia in mice and in cell culture is capable of suppressing the expression of pro-inflammatory mediators by apoptosis of neutrophils and lymphocytes^[42,43]. In fact, a high proportion of apoptotic lymphocytes in diabetic states strengthen the hypothesis that immune function is impaired in patients with poorly controlled diabetes^[42].

GLUCOSE METABOLISM IN CELL SURVIVAL

Another result which is in line with our findings is the increased expression of glucose transporter type-1 (GLUT-1) in diabetic rats after myocardial infarction. Indeed, previous studies have shown that the supply of glucose, with the regulation of GLUT-1, plays a critical role in cardioprotective response to myocardial ischemia^[21], with increased glucose supply during the acute ischemia^[44,45], and progression to heart failure^[46].

This is likely a result of increased availability and use of glucose, the preferred energy substrate of the heart in times of stress. Thus, the current clinical practice of tightly controlling blood glucose in patients having cardiac events may be detrimental to the heart in the acute setting^[47].

Much of the ATP generated by anaerobic glycolysis is consumed for the maintenance of ion gradient thought membranes. Part of the ATP generated is hydrolyzed by reverse mode of the mitochondrial F₁F₀-ATPase, which uses the energy to generate mitochondrial membrane potential ($\Delta\Psi$)^[48] (Figure 1).

CONCLUSION

Finally, the increase in survival pathways such as Bcl2, PKC- ϵ , Akt and in capillary density may effectively contribute to the reduction of ischemic injury and cardiac fibrosis (modulation of cardiac fibroblasts) in diabetic animals. This might be the key to a better heart function, as the increased GLUT-1 expression plays an important role in increasing glucose uptake in ischemic conditions. The clinical importance of the deficiency of glucose in the treatment of heart failure is not necessarily highlighted when blood glucose control is the pursued goal of treatment. In the DIGAMI II study reported on 1253 diabetic patients with acute myocardial infarction allocated to three treatment arms including acute insulin-glucose infusion followed by insulin-based long-term glucose control (group 1), insulin-glucose infusion followed by

standard glucose control (group 2), and routine metabolic management according to local practice (group 3) that neither all-cause mortality nor morbidity (stroke and non-fatal reinfarctions) differed between the three groups^[12].

The compensatory mechanism associated with the positive balance of regulatory genes related to program cell survival, reduction of inflammatory cytokines, and increased glucose use as energy substrate. Taken together, they promote greater plasticity and improved cellular resistance to ischemic injury in short term, suggesting an ischemic conditioning in hyperglycemia. These findings should be translated into more effective patient care strategies following ischemic events. Therefore, future studies should be conducted to further elucidate the mechanisms underlying conditioned hyperglycemia in cardioprotection after ischemia.

Possible cardioprotector mechanisms of conditioned hyperglycaemia or diabetes against ischemia and reperfusion injuries. Hyperglycaemia seems to be cardioprotective due to the increased glucose provision to heart during stress. In the ischaemia condition much of the ATP generated by glycolysis is breakdown by reverse mode of the mitochondrial F₁F₀-ATPase, which uses the energy to maintain mitochondrial potential ($\Delta\Psi$). Diabetic heart accumulates less Ca²⁺ due the inhibition NCX and NHE exchange activities. PKC- ϵ activity increases in diabetes, activating mitochondrial K_{ATP} channel and closing MPTP in the mitochondrial outer membrane. These effects reduce calcium overload, increasing ATP production and decreasing cytochrome C from mitochondria during ischemia. Hyperglycaemia increases anti apoptotic Bcl-2 protein and reduces caspase-3 activity. The contents of HIF-1 α mRNA and protein increase in diabetic heart. HIF-1 α target genes which in turn improve cellular oxygenation (VEGF) and glucose metabolism (GLUT-1).

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Metabolic, autonomic and immune markers for cardiovascular disease in posttraumatic stress disorder

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Abstract

Posttraumatic stress disorder (PTSD) has been associated with significantly greater incidence of heart disease. Numerous studies have indicated that health problems for individuals with PTSD occur earlier in life than in the general population. Multiple mechanistic pathways have been suggested to explain cardiovascular disease (CVD) risk in PTSD, including neurochemical, behavioral, and immunological changes. The present paper is a review of recent research that examines cardiovascular and immune risk profiles of individuals with PTSD. First, we address the relatively new evidence that the constellation of risk factors commonly experienced in PTSD fits the profile of metabolic syndrome. Next we examine the findings concerning hypertension/blood pressure in particular. The literature on sympathetic and parasympathetic responsivity in PTSD is reviewed. Last, we discuss recent findings concerning immune functioning in PTSD that may have a bearing on the high rates of CVD and other illnesses. Our primary goal is to synthesize

the existing literature by examining factors that overlap mechanistically to increase the risk of developing CVD in PTSD.

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Key words: Cardiovascular; Posttraumatic stress; Metabolic syndrome; Autonomic; Immune

Core tip: Research has documented a significantly increased cardiovascular disease (CVD) risk in posttraumatic stress disorder. The present paper is a review of recent research that examines cardiovascular and immune risk profiles of individuals with posttraumatic stress disorder (PTSD). First, we address the relatively new evidence that the risk factors commonly experienced in PTSD fit the profile of metabolic syndrome. Next we examine the findings concerning hypertension/blood pressure in particular. The literature on sympathetic and parasympathetic responsivity in PTSD is reviewed. Last, we discuss recent findings concerning immune functioning in PTSD that may have a bearing on the high rates of CVD and other illnesses.

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METABOLIC, AUTONOMIC AND IMMUNE MARKERS FOR CARDIOVASCULAR DISEASE IN POSTTRAUMATIC STRESS DISORDER

Posttraumatic stress disorder (PTSD), a disorder of

extreme stress/anxiety responses to a psychologically traumatic experience, has been associated with significantly greater incidence of heart disease^[1-4]. This effect has been demonstrated among combat Veterans^[1,5,6], firefighters^[7], and civilians^[2]. The characteristics associated with PTSD include re-experiencing symptoms such as intrusive thoughts and nightmares, avoidance behaviors, and arousal symptoms such as anger and hyper-vigilance. Lifetime prevalence of PTSD is about 8%, with higher rates among trauma victims and women. Numerous studies have indicated that health problems for individuals with PTSD occur earlier in life than in the general population^[6,8,9]. Further, there is limited evidence that the relationship of PTSD to physical health is independent of age, depression, or other comorbid anxiety disorders^[10]. Adult health problems may also be related to childhood trauma. In two large epidemiological studies, relationships were observed between childhood trauma and cardiovascular disease (CVD) evidenced as adults^[11,12], with up to 3 times greater risk of CVD. Multiple mechanistic pathways have been suggested to explain CVD risk in PTSD, including neurochemical^[13,14], metabolic^[15-17], and immunological changes^[18-24].

The present paper is a review of recent research that examines cardiovascular and immune risk profiles of individuals with PTSD. First, we address the relatively new evidence that the constellation of risk factors commonly experienced in PTSD fits the profile of metabolic syndrome^[25-28]. Next we examine the findings concerning hypertension/blood pressure (BP) in particular^[29-31]. The literature on sympathetic and parasympathetic responsivity in PTSD is reviewed. Last, we discuss recent findings concerning immune functioning in PTSD that may have a bearing on the high rates of CVD and other illnesses. Our primary goal is to synthesize the existing literature by examining factors that overlap mechanistically to increase the risk of developing CVD in PTSD.

METABOLIC SYNDROME AND PTSD

Most studies that have examined CVD risk factors in PTSD have not examined more than 1 or 2 risk variables, such as obesity or lipids. A study of police officers^[27] reinforced the importance of studying multiple CVD risk factors—this study revealed that those with the highest levels of PTSD symptoms (severe category) were 3 times more likely to exhibit 3 or more metabolic syndrome criteria [waist circumference, BP, high-density lipoprotein cholesterol, triglycerides, and glucose levels] than officers in the lowest PTSD symptom category (subclinical)].

The Violanti *et al.*^[27] findings are consistent with a recent study indicating Gulf War Veterans with higher severity of PTSD (measured on a continuum using the Clinician Administered Posttraumatic Stress Scale) were more likely to meet 3 or more of the CVD risk criteria for defining metabolic syndrome^[26]. Further analyses of these data by Heppner *et al.*^[32] indicated that antipsychotic medication use did not explain the increased risk for met-

abolic syndrome in severe PTSD. Similarly, among 245 low-socioeconomic-status subjects from general medical clinics in an inner-city hospital, significantly higher rates of metabolic syndrome were identified among patients with current PTSD, independent of antipsychotic medication use^[28].

Subsequent studies added to the literature providing evidence for the association of PTSD with metabolic syndrome. In one study, the prevalence of metabolic syndrome and its components were compared between patients with chronic war-related PTSD in Bosnia and Herzegovina vs patients without PTSD who underwent treatment for somatic problems^[33]. A significantly higher rate of metabolic syndrome was evident in patients with PTSD relative to the patients without PTSD, with hyperglycemia and abdominal obesity being more prevalent in patients with PTSD^[33]. Additionally, in a large retrospective database study of 207954 veterans^[25], metabolic syndrome was significantly higher in PTSD as compared to non-PTSD individuals. The results suggest PTSD accounted for 41% of the risk for metabolic syndrome^[25].

BLOOD PRESSURE AND PTSD

Early studies revealed elevated BP among combat veterans with PTSD^[34-36]. However, recent studies and meta-analytic reviews have reflected mixed findings^[29,30,37,38], raising doubt about the extent to which elevations in BP are consistently related to PTSD and might be a factor in CVD risk. Results of the meta-analyses by Buckley *et al.*^[29] and Pole^[30] suggested elevations in both resting systolic blood pressure (SBP) and resting diastolic blood pressure (DBP) for individuals with PTSD, when examining unweighted effect sizes. However, examination of weighted effect sizes produced much more circumscribed findings for BP in PTSD; the weighted effect sizes appeared to be conservative adjustments, as the mean effect sizes were reduced considerably relative to the unweighted means. In these meta-analyses, most studies of resting BP were fairly homogenous in terms of sample size, with only one study having a sample size greater than 115 ($n = 991$ for Keane *et al.*^[39]). This one very large study, which is weighted heavily for the meta-analyses, resulted in null effects for resting SBP and DBP. A potential methodological limitation in interpreting this large study is that only a single Dinamap reading was utilized for assessment of baseline BP (as opposed to multiple averaged readings and/or the gold standard sphygmomanometer-based casual BP assessments). In addition, the Keane *et al.*^[39] had a mean age of approximately 44 years—as most participants appeared to have a BP that was well within the normal range, it is possible that the BP assessment may have been affected by a limited range or floor effect.

Research conducted in our laboratory has supported relationships between PTSD and elevated BP. In a recently completed project, several CVD risk factors were assessed among relatively young women with PTSD (mean \pm SD, age = 30 ± 8 years), and compared with

two demographically similar groups with depression and no mental illness^[40]. Analyses revealed that SBP levels in the PTSD group were higher than in the no mental illness ($P < 0.001$) and depression ($P < 0.05$) groups. The DBP levels in the PTSD group were greater than the no mental illness group ($P < 0.05$), but were not significantly different than the depression group. This project utilized three standard sphygmomanometer-determined readings to calculate resting BP. The absolute levels of BP were generally in the normal range.

In another study we analyzed data from the United States National Comorbidity Survey to examine whether PTSD is significantly associated with hypertension, and whether this association is independent of depression^[31]. The study sample ranged in age from 15-54 years and was designed to be representative of the United States population. A total of 4008 respondents were identified who fit into one of four diagnostic groups: (1) history of PTSD diagnosis (lifetime) and no history of major depression ($n = 219$); (2) a lifetime history of both PTSD and major depression ($n = 210$); (3) a history of major depression (lifetime) and no PTSD ($n = 785$); and (4) no history of mental illness ($n = 2794$). The sample was 45% male. In this relatively young sample, the rate of hypertension was modest (7.8% overall). The group with a history of PTSD and no history of depression had the highest rate of hypertension (14.5%), and this rate was significantly higher than the rate in the no mental illness group (6.5%) and the group with history of depression and no PTSD (9.7%). These differences in hypertension rates were significant when controlling for the relationship between age and hypertension rate. The observation that the rate of hypertension between the PTSD no depression group and the PTSD plus depression group (13.9%) was not significantly different, suggested that the relationship of PTSD to high BP is independent of comorbid depression.

STRESS REACTIVITY AND PTSD

Exaggerated cardiovascular reactivity (CVR) in response to psychological stress is associated with markers for CVD such as hypertension, endothelial dysfunction, autonomic nervous system (ANS) dysregulation, and hypothalamic-pituitary-adrenal axis (HPA) alterations^[41-45]. Evidence of physiological reactivity in individuals with PTSD, during trauma reminders, points to CVR as one of the intervening variables between PTSD and the development of CVD^[46,47].

The literature provides evidence for the role of the sympathetic and parasympathetic nervous system dysregulation in PTSD. The roles of PTSD-related hyperarousal and re-experiencing symptoms in producing exaggerated CVR have been a central focus of PTSD/CVD research^[46]. Tucker *et al.*^[48] found greater autonomic reactivity in participants with PTSD than gender-matched trauma exposed controls. In this study^[48], SBP after trauma script delivery was the best measure for classifica-

tion of patients with PTSD (75% sensitivity) and trauma exposed controls (100% specificity).

Chronic autonomic activation leads to dysregulation of the HPA axis in PTSD, which may begin a cascade of physiological responses increasing allostatic load and promoting CVD^[42,49,50]. In response to acute stress, glucocorticoids (GC), primarily cortisol, are involved in both mobilization of defensive resources and in helping the body to return to homeostasis^[50]. Additionally, lowered cortisol levels shortly after traumatic events have been linked to increased risk of developing PTSD following a traumatic event^[51-54]. A recent meta-analysis^[53] of HPA function in PTSD identified significant differences in both basal cortisol and GC receptor sensitivity among individuals with PTSD relative to both trauma-exposed (TC) and non-TC controls (NTC). Specifically, individuals with PTSD showed reduced morning cortisol levels (compared with both TC and NTC), and enhanced GC sensitivity (compared to NTC) as measured by cortisol levels following the dexamethasone suppression test.

Implication of reduced parasympathetic control in individuals with PTSD is evidenced by the negative association between baroreceptor sensitivity and basal HR^[47,55]. Findings of lower HR variability among PTSD groups may provide evidence of autonomic dysregulation due to increased sympathetic hyperactivation and reduced parasympathetic activity^[55-58].

IMMUNE FUNCTIONING IN PTSD

Chronic alterations of neuroendocrine and inflammatory processes have been posited as one mechanism through which risk for CVD is elevated in PTSD. In addition to sympathetic nervous system (SNS) components such as epinephrine and norepinephrine, two interrelated stress-response systems-the HPA axis and the immune system-have been studied in relationship to traumatic stress and posttraumatic outcomes. Both the SNS and HPA axis modulate immune function through several mechanisms, including stimulating proliferation of T-cells and inducing the release of signaling proteins known as Interleukins (IL) or cytokines^[59]. Elevations of pro-inflammatory cytokines, such as IL-6, tumor necrosis factor- α , IL-1 β , and IL-2, as well as downstream acute-phase hepatic proteins such as C-reactive protein (CRP) and fibrinogen, are known to be involved in promoting inflammation, and chronic elevations have been linked to cardiovascular disease risk and other chronic diseases^[42,60,61]. A 2012 review of the literature^[62] indicated that, despite methodological and measurement differences, most studies reported positive associations between pro-inflammatory cytokine concentrations and PTSD symptomatology. Since this review, several studies have provided additional evidence of increased pro-inflammatory cytokines in PTSD^[63-66], although others have reported either no significant relationship^[21,67] or a negative association^[68,69] with PTSD symptoms. The findings related to CRP have been more equivocal, with

recent results ranging from decreased CRP^[70] or no difference^[71] to increased CRP in PTSD as compared with healthy controls^[38,72].

In addition to measuring basal cytokine levels, several recent studies have tested stimulated cytokine levels in PTSD either *in vivo*, through hydrocortisone administration^[18], or through *in vitro* cytokine production by immune cells, whether spontaneous, stimulated using a chemical such as phytohemagglutinin A or lipopolysaccharide, or suppressed using an exogenous GC such as dexamethasone^[20,21,68,73]. Promising new areas of research have also begun to identify genetic and epigenetic changes in DNA methylation^[73] and inflammatory pathways (*e.g.*, nuclear factor- κ B^[73,74]) that may be involved in the risk of PTSD and inflammation-related chronic disease.

Although PTSD seems to be linked to a variety of inflammatory biomarkers, limited preliminary evidence suggests that successful psychological and/or pharmacological treatment of PTSD may result in an abatement of systemic inflammatory responses. Tucker *et al*^[75] first described significant decreases in circulating pro-inflammatory IL-1 β and increases in anti-inflammatory soluble IL-2 receptors after treatment with one of two SSRI medications or placebo. However, another SSRI treatment study did not find any significant post-treatment changes in cerebrospinal fluid levels of IL-6^[76], despite achieving complete remission of PTSD symptoms. A cross-sectional study comparing women in recovery from PTSD to NTC and participants with current PTSD found elevated circulating IL-6 and CRP in current PTSD but identical levels for the recovery and NTC groups^[66]. A longitudinal case-study of one year of psychotherapy also found decreases in excreted IL-6 over time, which seemed to correspond with gradual symptom improvements^[77]. Additionally, following a four-week stress management intervention for survivors of childhood sexual abuse, Wilson^[78] found a modest but statistically significant increase in salivary secretory Immunoglobulin A, a secreted biomarker involved in viral and bacterial immunity^[79].

CONCLUSION

Considering the evidence reviewed in the present article, there appears to be considerable metabolic, autonomic and immune involvement in the elevated CVD risk among individuals with PTSD. There is a high level of agreement among studies that PTSD is positively associated with metabolic syndrome. Stress-related cellular dysfunction may contribute to metabolic syndrome in PTSD^[80]. Dysfunction related to stress-induced dysregulation of telomere/telomerase maintenance, mitochondria, and endoplasmic reticular stress may result in metabolic syndrome^[81-83]. Conceptualizing the CVD risk factors from the standpoint of metabolic syndrome allows one to fully appreciate the clinical significance of multiple interacting physiological risks in PTSD^[26,28]. In short, the impact of multiple risk factors is synergistic, resulting in a magnitude of risk greater than the sum of the individual risk factors.

Although findings concerning BP in PTSD are mixed, the overall direction of this relationship appears to be positive, with greater rates of hypertension in PTSD. Methodological factors in the study of resting BP in PTSD may have masked the extent of this problem. Additional studies across the range of BP levels (*i.e.*, normal, elevated, and high) may provide more insight into the extent of BP differences and prevalence of elevated BP in PTSD, as well as the mechanisms by which BP elevation occurs in early age.

The available evidence also suggests a positive relationship between PTSD and autonomic reactivity. Although further research is needed to fully elucidate the role of ANS stress reactivity in PTSD, recent advances suggest that sympathetic and parasympathetic dysfunction in PTSD may be evident through some reactivity paradigms^[56,57]. The burgeoning literature on immune functioning in PTSD is rapidly providing insights into additional mechanisms (*e.g.*, proinflammatory cytokines and other immune biomarkers) that assist in understanding the relationships of PTSD to illnesses such as CVD^[21,62,66]. In all, the available studies indicate a significant relationship between PTSD and immune dysfunction. With regard to future directions in the area of PTSD and CVD risks, further research on the role of ANS reactivity in PTSD-related CVD risk, as well as approaches to prevention and management of CVD risk factors in this population, would represent advanced directions in the field.

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Antioxidants, inflammation and cardiovascular disease

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Abstract

Multiple factors are involved in the etiology of cardiovascular disease (CVD). Pathological changes occur in a variety of cell types long before symptoms become apparent and diagnosis is made. Dysregulation of physiological functions are associated with the activation of immune cells, leading to local and finally systemic inflammation that is characterized by production of high levels of reactive oxygen species (ROS). Patients suffering from inflammatory diseases often present with diminished levels of antioxidants either due to insufficient dietary intake or, and even more likely, due to increased demand in situations of overwhelming ROS production by activated immune effector cells like macrophages. Antioxidants are suggested to beneficially interfere with diseases-related oxidative stress, however the interplay of endogenous and exogenous antioxidants with the overall redox system is complex. Moreover, molecular mechanisms underlying oxidative stress in CVD are not fully elucidated. Metabolic dybalances are suggested to play a major role in disease onset and progression. Several central signaling

pathways involved in the regulation of immunological, metabolic and endothelial function are regulated in a redox-sensitive manner. During cellular immune response, interferon γ -dependent pathways are activated such as tryptophan breakdown by the enzyme indoleamine 2,3-dioxygenase (IDO) in monocyte-derived macrophages, fibroblasts, endothelial and epithelial cells. Neopterin, a marker of oxidative stress and immune activation is produced by GTP-cyclohydrolase I in macrophages and dendritic cells. Nitric oxide synthase (NOS) is induced in several cell types to generate nitric oxide (NO). NO, despite its low reactivity, is a potent antioxidant involved in the regulation of the vasomotor tone and of immunomodulatory signaling pathways. NO inhibits the expression and function of IDO. Function of NOS requires the cofactor tetrahydrobiopterin (BH_4), which is produced in humans primarily by fibroblasts and endothelial cells. Highly toxic peroxynitrite ($ONOO^-$) is formed solely in the presence of superoxide anion (O_2^-). Neopterin and kynurenine to tryptophan ratio (Kyn/Trp), as an estimate of IDO enzyme activity, are robust markers of immune activation *in vitro* and *in vivo*. Both these diagnostic parameters are able to predict cardiovascular and overall mortality in patients at risk. Likewise, a significant association exists between increase of neopterin concentrations and Kyn/Trp ratio values and the lowering of plasma levels of vitamin-C, -E and -B. Vitamin-B deficiency is usually accompanied by increased plasma homocysteine. Additional determination of NO metabolites, BH_4 and plasma antioxidants in patients with CVD and related clinical settings can be helpful to improve the understanding of redox-regulation in health and disease and might provide a rationale for potential antioxidant therapies in CVD.

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Key words: Atherogenesis; Cardiovascular disease; Neopterin; Nitric oxide; Tetrahydrobiopterin; Tryptophan; Oxidative stress; Homocysteine; Vitamins; Antioxidative therapy

Core tip: Crosstalk between a number of pathways in

volved in the regulation of immune and endothelial homeostasis is strongly coordinated by redox processes. Underlying molecular mechanisms of atherogenesis include metabolic imbalances that are linked to the onset and progression of endothelial dysfunction and inflammation, finally leading to a status of heightened oxidative stress. Decrease of plasma antioxidants may develop secondarily due to an increased demand for oxidation-sensitive vitamins during inflammation. Antioxidant and vitamin supplementation therapy is controversially discussed and success might depend of an individual patient's demand.

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INTRODUCTION

Despite the availability of successful treatment strategies for dyslipidemia and hypertension, cardiovascular diseases (CVD) account for one third of all deaths worldwide, and prevalence still increases^[1,2].

CVD comprise a class of diseases that involve heart and systemic blood vessels^[3]. In coronary heart disease, cerebrovascular disease or peripheral arterial disease, impaired blood vessel function leads to an inadequate blood supply of organs. Deep vein thrombosis and pulmonary embolism are usually caused by blood clots in the leg veins.

Avoiding risk factors such as smoking, obesogenic lifestyle, *e.g.*, unhealthy diet, physical inactivity, high blood pressure, diabetes and dyslipidemia, is strongly recommended for disease prevention. Nevertheless, beside lifestyle, genetic, epigenetic and environmental factors may essentially influence the risk of CVD.

The multifactorial background makes it difficult to unravel initial pathological events, which are suggested to occur in a very early phase of disease, where symptoms are subclinical. Inflammation is considered to play a key role in both disease initiation and progression^[4]. Chronic inflammatory conditions attenuate endogenous antioxidant capacities due to continuous production of high levels of reactive oxygen species (ROS). Patients often represent with low blood levels of antioxidants^[5] and enhanced oxidative stress markers^[6]. This is usually due to increased demand in situations of overwhelming ROS production by activated immune effector cells like macrophages. Also insufficient nutritional intake may play a role. Uptake of exogenous antioxidants is suggested to beneficially interfere with diseases-related oxidative stress, however the interplay of endogenous and exogenous antioxidants with the overall redox system is complex.

The object of this review is to give an overview on immunobiochemical pathways activated in atherogen-

esis, which lead to oxidative stress-related pathological consequences. Understanding of the mechanisms will be helpful in the establishment of new preventive and therapeutic strategies.

MAIN FEATURES OF ATHEROGENESIS

Atherosclerosis is the most common pathological process that leads to CVD including myocardial infarction (MI), heart failure, stroke and claudication. A central event is the development of atherosclerotic plaques in the inner lining of arteries. Irritative inflammatory stimuli, hypertension, hyperglycemia and dyslipidaemia cause endothelial stress leading to expression of adhesion molecules and recruitment of leukocytes^[7].

Atherosclerotic plaques are characterized by necrotic cores, calcification, accumulation of modified lipids and foam cells, but also other cell types such as smooth muscle cells, vascular dendritic cells, T cells and endothelial cells are involved in lesion formation^[8]. The "oxidative modification hypothesis" of atherogenesis implies that low-density lipoprotein (LDL) oxidation is an early event in atherosclerosis^[9]. Cholesterol-containing LDL particles are retained in the artery wall and biochemically modified components of these particles in turn induce leukocyte adhesion but also intracellular cholesterol accumulation in invaded macrophages^[10]. Chronic inflammatory conditions are maintained due to the production of pro-inflammatory mediators through immune competent cells in the lesions^[11]. Activation of macrophages is a key factor in atherosclerotic plaque formation, fibrous cap disruption and thrombus formation.

While in the past atherosclerosis was viewed primarily as passive process of cholesterol accumulation, recent evidence indicates that it is a highly active process involving components of the vascular, immune, metabolic and endocrine system^[12]. Initial pathological changes occur in a variety of cell types long before symptoms become apparent and diagnosis is made^[13,14]. Of note, also in a large sample of cardiovascular disease-free adults, Chrysoschoou *et al*^[15] revealed an association of pre-hypertension with reduced serum antioxidant capacity and increased oxidized LDL probably indicating initial pathological changes.

Atherosclerotic plaque composition, endothelial erosion, intraplaque hemorrhage, adventitial and intraplaque neovascularization, rather than the percentage of stenosis, turned out to be critical predictors for both risk of plaque rupture and subsequent thrombogenicity^[12,16,17]. Disruption of a vulnerable or unstable plaque may lead to a complete occlusion, to plaque progression or result in an acute coronary syndrome, *i.e.*, acute MI (AMI), unstable angina and sudden cardiac death or stroke in case of carotid plaque destabilization.

OXIDATIVE STRESS AND IMMUNE ACTIVATION

Although substantial efforts have been made to dissect

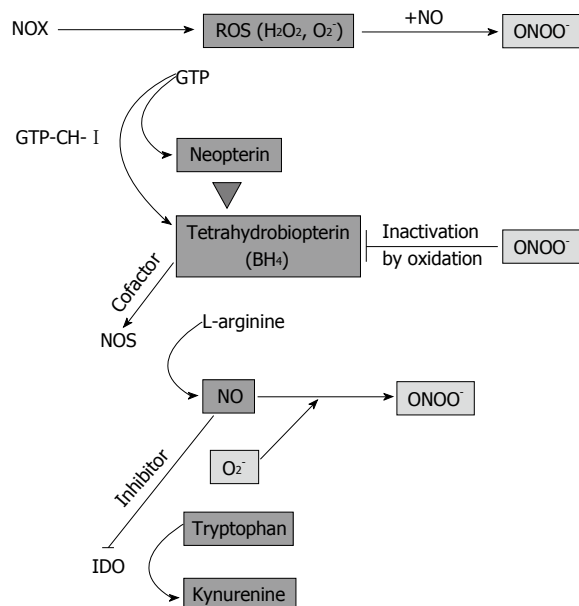


Figure 1 Regulatory circuits in inflammation and endothelial dysfunction. During inflammation, NADPH oxidase (NOX) produces high levels of reactive oxygen species (ROS). T cells and natural killer cells produce interferon- γ , which activates enzyme GTP-cyclohydrolase I (GTP-CH- I), indoleamine 2,3-dioxygenase (IDO) and inducible nitric oxide synthase (iNOS) in monocyte-derived macrophages (M) and dendritic cells (DC). In endothelial cells, endothelial NOS (eNOS) is constitutively expressed and GTP-CH- I produces tetrahydrobiopterin (BH₄), which is a NOS cofactor. BH₄ deficiency leads to NOS uncoupling and superoxide anion (O₂⁻) formation, which reacts with NO to form peroxynitrite (ONOO⁻). In a vicious cycle, ONOO⁻ oxidizes BH₄. In M/DC, GTP-CH- I synthesizes neopterin at expense of BH₄, which contributes to the low activity of iNOS in human M/DC. Furthermore, NO is a reversible inhibitor of the immunoregulatory enzyme IDO. IDO degrades the essential amino acid tryptophan to kynurenine.

molecular details of atherogenesis, a full understanding of the underlying mechanisms is still missing. However, activation of immune competent cells, leading to local and finally systemic inflammatory phenomena and the associated status of heightened oxidative stress are central events^[4].

Monocyte/macrophage accumulation at the lesion is a key factor in the pathology and involves several steps, such as monocyte recruitment by expression of adhesion molecules and chemotactic factors, induction of activation and differentiation processes as well as proliferation, and immobilization of macrophages in the inflamed plaque^[18]. Current data indicate that due to the presence of variable differentiation stimuli, different macrophage populations reside in the atherosclerotic plaque^[19]. Both M1 and M2 macrophages are present in atherosclerotic regions. Macrophage colony-stimulating factor (M-CSF), which is continuously present in circulation, induces predominantly M2-type macrophages with increased phagocytic activity, characterized by expression of interleukin (IL)-10, scavenger receptor A and mannose receptor^[18,19]. Granulocyte-macrophage CSF (GM-CSF) induces M1-polarized cells with antigen presentation capacities, which express tumor necrosis factor alpha (TNF α) and pro-inflammatory cytokines such as IL-1 β , IL-6, IL-8 and

IL-12 upon stimulation with interferon gamma (IFN- γ) or lipopolysaccharides (LPS)^[18,20]. While M1 macrophages were found to predominate in rupture-prone plaque regions, M2-type are located in the vascular adventitial tissue^[21]. However, also other macrophage phenotypes are suggested to contribute to the inflammatory process in atherosclerosis, such as the recently described platelet chemokine CXCL4-induced M4 cells^[22].

Immune reactions in atherosclerotic lesions are mainly T helper (Th1) type responses, as indicated by the dominance of pro-inflammatory and macrophage-stimulating cytokines found in advanced plaques^[11,23,24]. During Th1-type response, IFN- γ is probably the most important trigger for high ROS production in macrophages^[25] by phagocytic NADPH oxidase (NOX)^[26]. Main reactive species are hydrogen peroxide (H₂O₂), superoxide anion (O₂⁻), but also reactive nitrogen species such as peroxynitrite (ONOO⁻), nitrogen dioxide and trioxide^[27]. IFN- γ signaling initiates a variety of cellular defense mechanisms such as pro-inflammatory cytokine production *via* nuclear factor kappa B (NF- κ B) signaling, enhancement of antigen presentation^[28] and other important pathways, *e.g.*, neopterin formation *via* guanosine triphosphate (GTP)-cyclohydrolase I (GTP-CH- I) and indoleamine 2,3-dioxygenase (IDO)-mediated tryptophan breakdown^[29] (Figure 1).

Under normal conditions, low levels of ROS are mainly byproducts from electron transport chain reactions in the mitochondria^[30]. They are important regulators of several redox-sensitive pathways involved in the maintenance of cellular homeostasis^[31], and act by modifying molecules, enzymes and transcription factors as well by interfering with the endogenous antioxidant pool^[27,31,32]. Depletion of endogenous redox buffer systems in conditions with overwhelming oxidative stress is critical, not only due to triggering of immune responses but also through leading to endothelial and smooth muscle dysfunction, and thus to the progression of atherosclerosis^[33,34].

ROLE OF LIPOPROTEINS IN ATHEROSCLEROSIS

Proatherogenic oxidized LDL (oxLDL) accumulates in the vascular wall and contributes to the pathogenesis of vascular dysfunction early in the development of atherosclerosis. After incorporation *via* scavenger receptors of macrophages, oxLDL leads to their transformation into foam cells^[35]. Foam cells accumulate a variety of lipids in droplets in the cytoplasm and secrete extracellular matrix proteins that further support the retention of lipoproteins and attraction of immune cells, thus leading to an enlargement of the lesion^[10].

Oxidation of LDL is considered to occur primarily in the vascular wall^[36], but also circulating oxLDL was detected in CVD patients^[37]. Although the amount of circulating oxLDL is small compared to oxLDL present in vessels^[38], enhanced serum levels of oxLDL are predictive for endothelial dysfunction and coronary heart dis-

ease^[36-39]. The role of oxLDL as a relevant pro-atherogenic marker is further supported by the study of Meisinger *et al.*^[40], who found elevated oxLDL to be predictive for future coronary heart disease events in apparently healthy men. Oxidation of LDL contributes to the prooxidant environment in atherosclerotic lesions. OxLDL is a potent stimulus of vascular ROS formation, mainly through activation of NOX and uncoupling of endothelial nitric oxide (NO)-synthase (NOS) that promotes endothelial dysfunction^[36].

High-density lipoprotein (HDL) is another potential biomarker with anti-atherogenic properties due to its function in the reverse cholesterol transport and in decreasing lipoprotein oxidation^[41]. HDL is involved in several biological processes that counteract inflammation and oxidative stress, by beneficially influencing, *e.g.*, pancreatic beta-cell function, endothelial vasoreactivity, endothelial apoptosis, restorative processes and monocyte activation as well as adhesion molecules expression, thus being highly vasculoprotective^[42]. Paraonase-1, a calcium dependent enzyme, is located at the surface of HDL particles and contributes to the antioxidant and anti-inflammatory role of HDL^[43]. In particular, HDL-associated paraonase was shown to inhibit the formation of “minimally oxidized” LDL^[44]. Nevertheless, also other mechanisms are suggested to be involved in HDL-associated inhibition of LDL oxidation^[45].

Plasma HDL cholesterol (HDL-C) levels are inversely associated with CVD risk in preclinical and large epidemiologic studies. Low HDL-C level was identified as a robust predictor of lipid peroxidation irrespective of gender, age, obesity and inflammatory or metabolic biomarkers in the Styrian Juvenile Obesity/ Early DEteC-Tion of Atherosclerosis study employing 797 participants aged from 5 to 50 years^[46]. However, HDL is highly heterogeneous and the atheroprotective functions of the different HDL subpopulations are not completely understood. Furthermore, current data indicate that therapeutically increased HDL-C levels *per se* do not always correlate with enhanced HDL functions *in vivo*^[47,48].

Of note, accumulation of free, unesterified cholesterol can lead to crystal formation both *in vitro* and *in vivo*^[49]. Crystallized cholesterol in atherosclerotic plaques was shown to activate the NLR family, pyrin domain containing 3 (NLRP3) inflammasome complex by employing the complement system, thereby leading to the release of proinflammatory cytokine IL-1 β ^[50,51]. Cholesterol crystals were mainly found in advanced plaques, however the inflammatory responses caused by NLRP3 inflammasome activation might represent an important trigger in disease progression and could thus represent an important pharmaceutical target^[52].

NEOPTERIN FORMATION

Neopterin, a marker of immune system activation, is produced by GTP-CH- I in macrophages and dendritic cells (DC)^[53,54] and has emerged as an important independent and predictive marker in cardiovascular risk assessment^[6].

IFN- γ is the major stimulus for neopterin formation. Other cytokines have only limited stimulatory potential *in vitro* but some, *e.g.*, TNF α , can indirectly enhance IFN- γ induced neopterin formation^[55]. Of note, also pro-inflammatory compounds like LPS can elevate neopterin levels^[55]. The amount of neopterin secreted by human macrophages correlates with their ROS-generation capacity *in vitro*^[56] and neopterin concentration in body fluids is considered as an indicator for immune activation-associated oxidative stress^[57].

GTP-CH-1 catalyzes the conversion of guanosine triphosphate (GTP) to 7,8-dihydroneopterin triphosphate finally leading to the formation of neopterin, 7,8-dihydroneopterin and 5,6,7,8-tetrahydrobiopterin (BH₄)^[57]. Human monocyte-derived macrophages and DCs are the most important source of neopterin and its partially reduced derivative 7,8-dihydroneopterin, both present in relative constant ratio in human serum^[57], but not of BH₄, due to the relative deficiency of pyruvoyl-tetrahydropyrimidine synthase in this cell types^[58] (Figure 1). In contrast, cells from other animal species and other human cell types such as endothelial cells or fibroblasts preferentially produce BH₄, which is needed as a cofactor by several monooxygenases including NOS, phenylalanine hydroxylase or tyrosine hydroxylase^[59].

Elevated neopterin concentrations were reported to be associated with chronic immune activation in several diseases such as viral, bacterial and parasite infections, autoimmune or malignant tumor diseases and during rejection episodes in allograft recipients^[60-63]. Also patients with CVD present with increased neopterin concentrations, supporting the crucial involvement of chronic immune activation, in particular of macrophages, in atherogenesis. Several studies (Table 1) strengthened the impact of neopterin as an independent marker for CVD, with predictive value for coronary artery disease (CAD) progression^[6].

Of note, neopterin-positive macrophages were found in coronary atherectomy specimens from patients with stable angina pectoris and to a lesser extent in those with unstable angina pectoris, and the number of these macrophages correlated with T cell and neutrophil count in the lesions^[76]. Furthermore, neopterin was shown to induce an atherothrombotic phenotype in human coronary endothelial cells *in vitro* by promoting cellular adhesion molecules (intercellular adhesion molecule 1 and vascular cell adhesion molecule 1) and tissue factor (TF) expression mediated by activation of NF- κ B^[77]. These data suggest that neopterin is not only associated with the systemic inflammation process in atherosclerosis, but might also be of importance for the inflammatory process within the plaque and thus for plaque destabilisation^[6,76].

Neopterin concentrations correlate with IFN- γ -induced ROS production^[56]. In addition, neopterin has pro-oxidant properties itself by intensifying the effects of ROS as well as of reactive chlorine and nitrogen species^[78]. Of note, Herpfer *et al.*^[79] showed that neopterin is able to enhance ONOO⁻ as well as Cu(II)-mediated LDL oxidation, whereas 7,8-dihydroneopterin may protect

Table 1 Selected studies investigating neopterin concentrations in cardiovascular disease patients

Ref.	Condition	n	Result
Melichar <i>et al</i> ^[64] , 1994	AMI	13	Increased urinary neopterin
Anwaar <i>et al</i> ^[65] , 1999	Acute cerebral ischemia or transient ischemic attack, 1-yr follow-up	59 (57)	Increase of plasma neopterin after acute cerebral ischemia
Tatzber <i>et al</i> ^[66] , 1991	Different clinical stages of atherosclerosis	61	Elevated plasma neopterin in about 50% of hospitalized patients undergoing conservative or surgical therapy, higher neopterin levels were overrepresented in patients with higher Frederickson type
Weiss <i>et al</i> ^[67] , 1994	Cross-sectional community-based screening study (Ischemic Heart Disease and Stroke Prevention Study, Bruneck, Italy)	561 (total)	Serum neopterin correlated with the extent of carotid atherosclerosis
Schumacher <i>et al</i> ^[68] , 1997	AMI	21	Neopterin levels were highest in AMI patients but also elevated in those with CAD
Gurfinkel <i>et al</i> ^[69] , 1999	Stable CAD	62	
	Unstable angina pectoris (non-Q-wave AMI)	52 (26)	Serum neopterin correlated with score of atherosclerotic extension (angiography)
Zouridakis <i>et al</i> ^[70] , 2004	Chronic stable angina pectoris	124	CAD progression correlated with increased neopterin and high-sensitivity C-reactive protein as well endothelial activation markers
Avanzas <i>et al</i> ^[71] , 2005	Patients with chronic stable chest pain undergoing diagnostic coronary angiography, 1-yr follow-up	297	Elevated serum neopterin correlated with adverse coronary events during follow-up (17.2%)
Kaski <i>et al</i> ^[72] , 2008	NSTE ACS (unstable angina and NSTE MI), 6-mo follow-up	397 (147,250)	Baseline neopterin in unstable angina and NSTE MI comparable, increased neopterin was associated with adverse cardiac events
Johnston <i>et al</i> ^[73] , 2006	ACS (treatments: medication, uncoated or rapamycin-eluting coronary stents) and stable CAD	70 (35, 25, 10)	Serum neopterin correlated with thrombolysis in myocardial infarction; mean changes in serum neopterin higher in uncoated stent group
Barani <i>et al</i> ^[74] , 2006	Critical limb ischemia, 1-yr follow-up	36 (232)	Neopterin was elevated in patients with atrial fibrillation or flutter and with ischemic electrocardiogram changes which were at risk for adverse cardiac events
Ray <i>et al</i> ^[75] , 2007	ACS (PROVE IT-TIMI 22) 2-yr follow-up	3946	Increased neopterin was associated with increased risk of death and of acute coronary events after ACS

NSTE: Non-ST-segment elevation; PROVE IT-TIMI: PRavastatin or atorVastatin Evaluation Infection Therapy-Thrombolysis In Myocardial Infarction; AMI: Acute myocardial infarction; MI: Myocardial infarction; CAD: Coronary artery disease; ACS: Acute coronary syndrome. Table adapted and extended from Fuchs *et al*^[6].

LDL from oxidation under certain conditions^[79,80]. Neopterin may also enhance the effects of ONOO⁻ in the processes of protein nitration^[81]. This pro-oxidant property of neopterin indicates a potential involvement in the antimicrobial and antitumoral action of macrophages^[82]. The property of neopterin to interfere with and enhance the effects of various ROS might be of central relevance also in atherogenesis.

Inflammation-associated oxidative stress may lead to a rapid consumption of circulating antioxidants. In patients with CAD, higher neopterin concentrations were associated with a decline in levels of several antioxidant compounds and vitamins such as ascorbic acid, α -tocopherol, lycopene, lutein and zeaxanthin^[5].

TRYPTOPHAN BREAKDOWN

In parallel to neopterin formation, other IFN- γ -dependent pathways are activated during cellular immune response such as tryptophan breakdown by IDO. IDO catalyzes the rate-limiting step in the conversion of tryptophan (Trp) and other indole derivatives to kynurenine (Kyn)^[83] and is induced in monocyte-derived macrophages but also in fibroblast, endothelial and epithelial cells^[84,85] (Figure

1). Both expression and activity of the haeme-containing enzyme IDO is sensible to redox-regulation and IDO enzyme itself can exert antioxidant activity by scavenging of O₂⁻^[86,87]. The estimation of Kyn to Trp ratio (Kyn/Trp), expressed as μ mol kynurenine per mmol tryptophan, can be used as measure of IDO enzyme activity both *in vitro* and *in vivo*^[60,88]. Simultaneous measurement of immune activation markers such as neopterin, IFN- γ or soluble interleukin receptors, allow to relate circulating Trp levels with inflammation-induced IDO activity, as also hepatic tryptophan 2,3-dioxygenase (IDO) could degrade Trp. IDO, however, is regulated *via* tryptophan content and steroid hormones such as glucocorticoids^[89,90], while IDO is strongly induced in response to several pro-inflammatory stimuli such as IFN- γ , TNF α or LPS^[55,85].

Depletion of the essential amino acid Trp contributes to the development of an antiproliferative environment and represents an effective antimicrobial and antitumoral strategy^[91]. Also T cell proliferation depends on Trp availability, thus IDO activation is a metabolic checkpoint of immunoregulation^[92]. IDO activity is crucially involved in the control of T cell proliferation and in the generation of regulatory T cells, and thus in the suppression of autoimmune responses and promotion of tolerance^[92,93].

Metabolic control by reduction of Trp levels may slow down hematopoiesis in addition to other proinflammatory stimuli by affecting the growth and differentiation of erythroid progenitor cells. In line with this, in patients with inflammation-induced anemia, Kyn/Trp was found to inversely correlate with haemoglobin levels^[94,95].

Accelerated Trp breakdown was reported in patients with coronary heart disease^[96] and IDO activity correlated significantly with several risk factors for atherosclerosis in the Cardiovascular Risk in Young Finns Study^[97]. Niinsalo *et al.*^[98] reported that IDO activity positively correlated with carotid artery intima/media thickness, an early marker of atherosclerosis, although this association did not remain significant after adjustment with classical risk factors in this patient group.

In inflammatory diseases including CVD, a concurrent increase of neopterin production and tryptophan degradation is usually observed. The prognostic ability of neopterin is likely to relate to the association with IFN- γ in the atherogenic process^[6]. IDO-mediated tryptophan breakdown is suggested to be responsible for several additional aspects observed during disease progression^[29], *e.g.*, the development of depression. Because tryptophan is a precursor for the biosynthesis of serotonin, the lowered tryptophan availability under inflammatory conditions may limit serotonin formation and thus enhance the susceptibility for lowered mood and depression^[99]. Of note, development of depressive symptoms have been associated with increased CAD risk and poor prognosis^[100]. Estimation of Trp breakdown rate could contribute to a better understanding of the interplay between inflammation, metabolic syndrome, mood disturbance, and anemia, all previously described as significant predictors of an unfavorable outcome in patients with CVD^[101].

NITRIC OXIDE

NOS converts L-arginine into citrulline, thereby synthesizing NO. Free NO can migrate through cell membranes by diffusion, and although it relatively low reactivity, NO is a potent antioxidant molecule that can protect from ROS damage^[102]. However, NO is a free radical, and can undergo oxidation to nitrite and nitrate, react with O₂⁻ to form ONOO⁻, or bind to transition metals^[103]. NO signaling is strongly concentration dependent and although endogenous NO is essentially involved in many physiological processes and beneficial in a variety of circumstances, its reaction products may mediate nitrosative and oxidative stress. However, NO products can have also protective effects. In plasma, NO circulates primarily complexed in S-nitrosothiol species^[104] that are suggested to be a transport and buffer system that controls intercellular NO exchange. S-nitrosylation of the proteome is a unique form of posttranslational modification that can have significant consequences for protein function and cell phenotype. In particular in the cardiovascular system, S-nitrosothiols were shown to exert many actions, including promoting

vasodilation, inhibiting platelet aggregation, and regulating Ca(2+) channel function of myocytes^[105]. The impact of S-nitroso but also N-nitroso protein formation on the reduction of free NO under inflammatory conditions *in vivo* has still to be investigated^[106,107].

Endothelial and neuronal NOS are constitutively expressed and produce NO at low concentrations, while inducible NOS is activated, *e.g.*, in macrophages of several species in response to pro-inflammatory stimuli giving rise to higher NO output^[108]. Endothelial dysfunction, *e.g.*, vasodilation and/or platelet inhibition, a key feature of early atherosclerosis, is associated with the reduced availability of endothelium-derived NO^[109]. Defects in NO production, metabolism and response have been described to be responsible mechanisms.

In the presence of O₂⁻, ONOO⁻ formation may be a factor that limits NO bioavailability. Beside being strongly vasoconstrictory, ONOO⁻ has been shown to oxidize the NOS cofactor BH₄, thereby leading to eNOS uncoupling and O₂⁻ production^[110], thus starting a vicious cycle (Figure 1). Reduced vascular BH₄ levels were found in rat and mice models of atherosclerosis and diabetes^[111].

High NO output and generation of reactive nitrogen species *via* iNOS contribute to cytotoxic defense strategies in inflammation. However, although this has been reported for several species, including mice, until now, large output of NO by iNOS could not be equally demonstrated in human macrophages^[112,113]. Human macrophages produce neopterin at the expense of BH₄, and low BH₄ leads to NOS enzyme uncoupling. Furthermore, the pro-oxidant properties of neopterin may compensate for deficient NO and ONOO⁻ production^[114].

Of note, NO inhibits IDO expression and function by reversibly binding to the active site heme^[115]. Induction of IDO and NOS in IFN- γ -mediated inflammatory response is suggested to be functionally cross-regulated^[116]. The absence of NO-mediated immunoregulation may support enhanced IDO activity at the site of inflammation.

POTENTIAL ROLE OF TH2 RESPONSES IN CVD

Th1 responses are in general proinflammatory and known to be proatherogenic, while Th2 cells are usually involved in helminth and allergic responses. The role of Th2 cells in atherosclerosis seems to be very complex and even contradictory. A potential protective role of Th2 response is discussed in few studies^[117,118], while Ait-Oufella *et al.*^[24] assume a potential proatherogenic function of Th2 cells within the complex interaction theater of CD4⁺ T cell subsets in atherosclerosis. Thus, the exact role of the Th2 response remains to be elucidated based on an improved understanding of the complex interplay between Th1, Th2, and other T cell populations such as Th17 and Tregs within the atherosclerotic scenario^[18,24]. Overall, Th cell subset polarization in atherosclerosis is less distinct in humans compared to mice^[119].

High cholesterol diet of ApoE(-/-) mice with differ-

ent T cell subset polarization resulted in increased development of atherosclerosis in the aortic root and abdominal aorta in mice with predominantly Th1-like immune responses [ApoE(-/-) BL/6 mice] in comparison to animals with Th2 predominance [ApoE(-/-) BALB/c]^[120]. A potential of IL-4 to limit Th1 cell responses and reducing lesion size was observed in several murine atherosclerotic models^[121,122].

Only recently, Engelbertsen *et al*^[123] reported an association between Th2 immunity and reduced risk of MI, as high numbers of Th2 cells were associated with decreased mean common carotid intima-media thickness, reduced risk of AMI in women and IL-4 was independently associated with reduced risk of CVD. Although some limitations, as, *e.g.*, differences in lymphocyte number between healthy man and women or the use of long-term cryo-conserved cells, this study provides first hints for the clinical importance of an improved understanding of Th2-type responses in CVD. However, again in contrast to these positive, protective attributes, Shimizu *et al*^[124] suggested a role for Th2 cells and cytokines in the promotion of arterial aneurysm formation.

ANTIOXIDANTS IN CVD THERAPY

Oxidative stress triggers inflammation and endothelial disruption in atherogenesis. A number of studies showed that exogenous antioxidants can modulate endothelium-dependent vasodilation responses, endothelium-leukocyte interactions as well as balance between pro- and anti-thrombotic properties^[125]. Accordingly, antioxidant therapy was suggested to beneficially interfere with development and progression of atherosclerosis.

Th1/Th2 balance is crucially dependent on redox-events; while Th1 responses prevail at oxidative conditions, Th2 responses were shown to be supported by “antioxidative stress”^[126]. Thus, disequilibrium of Th1/Th2 cytokines may be involved in CVD as a mechanism of immunotoxicity. As Th1 and Th2 reactions crossregulate each other to balance immune responses^[127], suppression of Th1-type response by antioxidants would favour Th2-type reactions. Of note, several types of antioxidant were shown to reduce IFN- γ -stimulated tryptophan degradation and neopterin in peripheral blood mononuclear cells *in vitro*^[87,128].

A number of studies reported an inverse relationship between plasma antioxidants, or total antioxidant capacity and cardiovascular diseases^[5,15]. Low intake of antioxidants, in particular of vitamins, was suggested to be associated with an increased risk of CVD^[129,130]. Thus, the finding of an inverse correlation between concentrations of antioxidant compounds and vitamins and disease risk could relate to an increased requirement for antioxidant molecules during inflammatory diseases and insufficient supply with these compounds may further accelerate disease process. However, this assumption has not been conclusively proven in clinical trials and is still controversially discussed in the literature^[131-134]. Likewise,

equivocal effects of antioxidant supplementation with vitamin E, beta-carotene, alpha lipoic acid, coenzyme Q10, alone or in combination, on cardiovascular health were reported^[135].

Major effects were expected from vitamin E therapy. Due to its fat-solubility, vitamin E is part of cell membranes and lipoprotein particles, where it counteracts oxidation events. Vitamin E-mediated protection from oxidative stress and atherosclerotic plaque formation has been shown both *in vitro* and in mouse models. However, while in several clinical trials vitamin E supplementation lead to a reduction of risk of fatal and nonfatal AMI, others reported even a slight increase of mortality upon high dose vitamin E treatment^[136]. Thus, no final suggestion can be made about the impact of vitamin E supplementation and even recent metanalysis including a large trial number lead to inconsistent results^[137].

So far, although a general association of low vitamin levels and oxidative stress related conditions is established, no clear evidence for a beneficial effect of vitamin supplementation exists. The association between vitamin deficiency in patients and disease symptoms is suggested to result mainly from the inflammation-associated consumption of oxidation-sensitive vitamins^[29,132,138], which may lead to a variety of secondary effects.

Apart from being part of the antioxidant defense system, some vitamins act as enzyme cofactors. Low B vitamin availability (B6, B12 and folic acid) leads to impaired remethylation of homocysteine to methionine and thus to homocysteine accumulation, as they are essential cofactors in homocysteine-methionine metabolism. Increased homocysteine levels were found to be associated with arteriosclerotic outcomes and risk of stroke in elderly individuals^[139], and are considered as an independent risk marker for CVD^[140]. However, lowering homocysteine levels by B-vitamin supplementation failed to demonstrate beneficial effects in CVD^[141]. Also, in open-label study with demented patients on B vitamins, a decline of homocysteine has been observed, while neopterin levels were not affected^[142]. Recent data indicate that homocysteine accumulates secondarily due to heightened oxidative stress associated with immune activation^[143-145]. Thus, also the impact of the selected marker has to be critically evaluated when assessing the effect of vitamin supplementation.

A broader understanding of antioxidant action is clearly warranted. Beside their direct effects in the prevention of biomolecule oxidation by being oxidized themselves, several antioxidants mediate a variety of effects that are of longer duration, as they may induce signaling changes in the biological system^[146]. However, a variety of drugs may act also as antioxidants, thus antioxidant vitamins could interfere with pharmaco-relevant signaling pathways. This is of particular relevance for multi-target drugs such commonly used statins.

A major aim in the treatment of atherosclerosis is the prevention of LDL oxidation. Lipid-lowering compounds such as statins and niacin (vitamin B3, nicotinic

acid) are in use for a long time, alone or together, for cardiovascular protection in patients with coronary disease and low plasma levels of HDL^[147]. However, combination therapies with other antioxidant vitamins seemed even to counteract the beneficial effect of statin/niacin therapy^[147,148].

Statins are inhibitors of 3-hydroxy-3-methylglutaryl-co-enzyme A (HMG-CoA) reductase, and their lipid-lowering effects are suggested to reduce the risk of coronary heart disease^[149], although therapeutic efficacy is controversially discussed^[150].

The primary mechanism of statin action is suggested to be the reduction of LDL cholesterol, but several clinical trials indicate that statins exert pleiotropic effect that contribute to therapeutic efficacy. Statins act as effective antioxidants by inhibiting generation of ROS, but also by interfering with NOX and NOS, antioxidant enzymes, lipid peroxidation and LDL cholesterol oxidation^[151]. In *in vitro* studies with vascular smooth muscle and mononuclear cells, treatment with atorvastatin could reduce NF- κ B activation and expression of pro-inflammatory cytokines and chemokines^[152]. In human peripheral blood mononuclear cells and in monocytic cell lines, atorvastatin was shown to suppress stimulation-induced neopterin formation and tryptophan degradation, suggesting that both immunoreactivity of T cells and of monocyte-derived macrophages are down-regulated by this statin^[153]. Treatment with several statins could promote Th2 polarization of CD4+ T cells primed *in vitro* with anti-CD3 antibody and splenic antigen-presenting cells^[154]. These findings strongly suggest that statins contribute to the regulation of Th1/Th2 cell balance also *in vivo*. In endothelial cells, statins were shown to be involved in restorative processes by increasing NO-bio-availability and promoting re-endothelialization^[155]. Of note, lovastatin was able to prevent neopterin-induced activation of human coronary artery endothelial cells *in vitro* by interfering with NF- κ B activation and decreasing expression of cellular adhesion molecules and TF β ^[177]. Furthermore, lovastatin reduced C-reactive protein-induced NF- κ B activation in human umbilical vein endothelial cells^[156]. Beside NF- κ B, activation of inflammatory transcription factors activator protein 1 and hypoxia-inducible factor 1 α were shown to be down-regulated in human endothelial and vascular smooth muscle cells upon treatment with HMG-CoA reductase inhibitors^[157]. In line with the reported antioxidant and anti-inflammatory properties, statin use has been associated with lower neopterin levels in patients^[158,159].

The influence on redox-balance and Th1-type signalling pathways such as neopterin formation and tryptophan breakdown has been described for a variety of (potentially) cardioprotective antioxidant drugs and vitamins, *e.g.*, aspirin^[160], atorvastatin^[153], vitamins C and E^[161] and seems to be a common mechanism at least *in vitro*. Furthermore, circulating vitamin E was shown to increase upon statin therapy^[162,163]. Thus, due to interferences with common pathways, therapeutic efficacy might change when combining several antioxidant drugs and

supplements.

Furthermore, antioxidant composition may differ between patients, and estimation of antioxidant profiles before therapy could be useful to select candidate patients that would profit from antioxidant therapies^[164,165] and to avoid overdosage. Excessive antioxidant consumption may lead to adverse reactions ranging from favoring of Th2-type responses such as allergy and asthma to an increase of mortality^[166-168]. So far, for patients who respond well to statin/niacin therapy, additional supplementation might only be advantageous when nutritional deficiencies are still detectable, however this hypothesis has to be investigated in more detail.

Another question is, if moderate vitamin deficiencies cannot be better (and safer) regulated by changes of lifestyle factors, *e.g.*, by increasing the consumption of antioxidant-rich food.

NUTRITION, ANTIOXIDANTS AND CVD

The strong relationship between redox-status, immune response and metabolism is supported by the close association of metabolic diseases such as diabetes, obesity and metabolic syndrome with CVD^[169]. Tissues that are important in metabolism are suggested to have an evolutionary potential to mediate inflammatory responses^[170]. Metabolic and immune response pathways are closely cross-regulated to respond to the energetic demands necessary during immune activation. Several metabolic and immune cells show similarities on genetic and functional level, *e.g.*, pre-adipocytes can transdifferentiate into macrophages^[171] and activate similar transcriptional responses^[172].

In contrast to classical activation of the immune system, *e.g.*, by infection or tissue injury, inflammation may also be induced by metabolic triggers. So called metaflammation or para-inflammation is crucially involved in the development of chronic diseases such as diabetes, fatty liver disease and CVD^[172,173].

A variety of dietary factors are able to produce cardiometabolic imprints that predispose to disease development. *E.g.*, increased consumption of trans fatty acids (TFA) is supposed to activate pathways that are linked to insulin resistance syndrome. High TFA intake was found to be associated with harmful changes in serum lipids, systemic inflammation, endothelial function, and prospective observational studies demonstrated strong positive associations with the risk of MI, coronary heart disease death, and sudden death^[174]. Changes of traditional nutrition patterns, as it is the case, *e.g.*, in India, where "Westernization" led to an increase in uptake of sugar, salt, high fat dairy products, and TFA-rich food, are suggested to be at least partially responsible for an about 3-fold increase in the prevalence of CVD and diabetes in the latter part of the 20th century^[175].

But also excessive intake of antioxidants is a burden of modern life due to the omnipresence of preservatives, food colorants and vitamin supplements in the "Western diet". Although still nutritional deficiencies

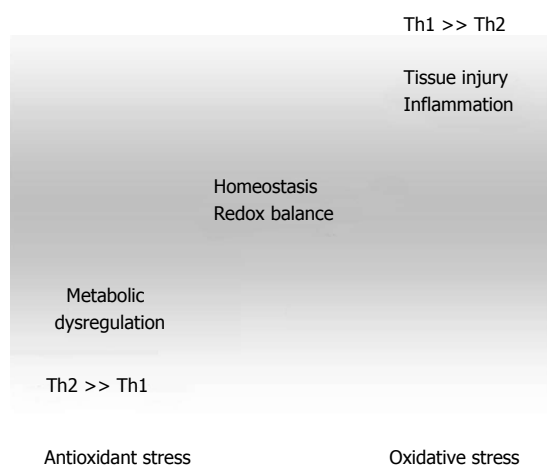


Figure 2 Dysregulation of redox- and Th1/Th2-balance in the course of atherogenesis. Excessive antioxidant intake in combination with other risk factors such as high caloric diet and low physical exercise lead to suppression of Th1-type immunity, thereby favoring Th2-associated development of allergies and asthma and promoting juvenile obesity. Factors such as high blood pressure and hyperlipidemia lead to shear stress and tissue injury. Inflammatory reactions are associated with high reactive oxygen species generation, which results in immunotoxicity due to oxidation of biomolecules (lipids, proteins, etc.).

may exist for some specific vitamins or other antioxidants, overall antioxidant stress may favour a Th2 environment by suppressing Th1 responses (Figure 2). In combination with high caloric diet and low physical activity, this may contribute to the development of obesity^[133]. Food additives such as sodium benzoate, propionic acid, sodium sulfite, sorbic acid and curcumin were shown to suppress Th1-type immune response *in vitro*^[176]. Antioxidant food additives also interfere with satiety saturation circuits, as they have shown to inhibit leptin release in cultured lipopolysaccharide-stimulated murine adipocytes in a dose- and time dependent manner^[177]. Lowering the amount of circulating leptin is suggested to contribute to a obesogenic environment, as the reduced satiety effect in turn could lead to compensatory antioxidant craving and thus even more food intake^[133]. Leptin is considered as a proinflammatory cytokine with proatherogenic features, as it increases monocyte chemoattractant protein-1 and endothelin-1 secretion by endothelial cells, enhances oxidative stress, promotes migration and proliferation of smooth muscle cells and increases platelet aggregation, thus facilitating thrombosis^[178]. In the initial phase of obesity-related inflammation, leptin is predictively associated with interleukin 6 plasma levels in juveniles^[179]. However, leptin resistance, which later develops during obesity, does also favor atherogenesis.

Obesity-related immune mediated systemic inflammation was found to be associated with the development of the metabolic syndrome and altered Trp metabolism. However, across lifespan from juvenility to adulthood, differences in the Trp breakdown rate were observed. While juvenile overweight/obese individuals showed a decreased to unaltered Kyn/Trp ratio in comparison to normal weight controls, obese adults had significantly

elevated Kyn serum levels and an increased Kyn/Trp ratio^[180]. Thus, while in younger patients Th2-type responses might be favored, potentially due to the high antioxidant intake, overwhelming inflammation with Th1-type cytokines may predispose for the development of atherosclerosis in adult age.

Epidemiological observations suggest that consumption of certain foods rich in bioactive compounds, *e.g.*, vitamins E and C, polyphenols and carotenoids such as lycopene and beta-carotene, and coenzyme Q10, is associated with decrease of atherosclerotic risk and such antioxidant-rich diet is supposed to be particularly effective in the early stages of atherosclerosis by preventing LDL oxidation and the oxidative lesion of endothelium^[181,182]. However, a balanced diet cannot always be translated into clinical benefit, despite its beneficial impact on human health.

There is accumulating evidence about the importance of maternal diet and early nutrition on different epigenetic mechanisms that promote the susceptibility to the development of metabolic diseases in adulthood, such as metabolic syndrome, insulin resistance, type 2 diabetes, obesity, dyslipidaemia, hypertension, and also CVD. Of note, both under- and overnutrition have been associated with adverse responses^[183,184]. Several studies indicate that impaired foetal growth, and/or *in utero* exposure to risk factors, especially maternal hypercholesterolaemia, may be relevant for the early onset of cardiovascular damage. Translational studies support this hypothesis; however, a direct causality in humans has not been ascertained^[185].

The influence of epigenetic mechanisms on the developmental induction of chronic diseases raises the possibility that nutritional or pharmaceutical interventions may be used to modify long-term cardio-metabolic disease risk and combat this rapid rise in chronic non-communicable diseases^[186].

CONCLUSION

Adaptive and innate immune responses are centrally involved in the chronic inflammatory process, which leads to destabilization of atherosclerotic lesions, these processes are tightly connected to metabolic factors, which are essentially influenced by life style and also the genetic/epigenetic frame. Inflammation-induced oxidative modifications contribute to all important clinical manifestations of CVD such as endothelial dysfunction and plaque disruption. However, due the poor performance of antioxidant strategies in limiting atherosclerosis and cardiovascular events, it remains to be answered if oxidative modification is causal for the initiation or is an injurious response to atherogenesis^[96]. Disease underlying interactions are too complex and the understanding is too fragmentary that clear, reliable therapeutic recommendations can be given^[101].

The strong interconnection of metabolic and inflammatory pathways suggests that metabolically induced inflammatory processes should be considered as early,

or even primary events^[171]. Many data support that there is a large time span between initial pathological changes and the onset of clinical manifestations. This time frame could be used for preventive strategies, however a better understanding of disease development and more sensitive detection methods would be a prerequisite.

A detailed knowledge on inflammatory and redox-regulated processes would also allow a better adaption of treatment regimes. Stable biochemical markers are necessary to control disease courses and treatment efficacy. In this context, *e.g.*, neopterin is a useful indicator of the immune activation status and oxidative stress^[6] and Kyn/Trp ratio accounts for aspects of immunoregulation *via* IDO and represents an important metabolic checkpoint. Normalization of tryptophan metabolism represents an important goal to improve the outcome of patients suffering from CVD, whereby treatments with IDO inhibitors such as 1-methyl tryptophan could be considered^[101]. However, IDO is well known for its immunosuppressive properties, and its inhibition by medications may also lead to adverse effects.

Also several antioxidant drugs, botanical extracts, phytocompounds and vitamins but also food-contained preservatives and colorants have been shown to negatively interfere with IDO^[87,166]. Both inhibition of enzymatic activity as well as downregulation of activatory signals may lead to a normalization of tryptophan breakdown ratio. Thus, nutrition might be considered as a major factor that influences tryptophan metabolism and underlying inflammation in a more gentle and balanced manner than medication.

Measurement of tryptophan and kynurenine concentrations, and calculation of the Kyn/Trp ratio are important predictors of an unfavourable outcome in patients with CVD. It will be important to investigate if these parameters can provide a basis for more successful and precise biologically grounded therapeutic protocols to further reduce cardiovascular morbidity and mortality^[101]. Combined measurements of multiple markers, such as additional determination of lipoproteins, NO metabolites, BH₄ and plasma antioxidants, will also be helpful to understand redox-regulation in health and disease and may allow to discriminate best between different clinical diagnostic categories and to evaluate treatment strategies.

In summary, a general evaluation of the effect of an “antioxidant therapy” is not possible at the moment. While vitamin supplementation might be beneficial under certain circumstances, a variety of studies indicate no or even adverse effects when administered alone and even more when used in combination with lipid-lowering agents. However, also for statin and niacin treatment a panel of adverse effects has been described^[187,188]. Although antioxidant supplementation may have some benefit to counteract secondary symptoms, their role in CAD seems to be of moderate importance^[145]. Surveillance of the antioxidant status before and during therapy would allow seek out patients that could benefit from vitamin supplementation^[164,165]. Impact of lifestyle factors such as nutrition and physical exercise, however, has turned out

as a major factor in CVD prevention and also in influencing treatment efficacy.

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Cardiomyopathies: Evolution of pathogenesis concepts and potential for new therapies

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Abstract

Cardiomyopathies are defined as diseases of the myocardium with associated structural and functional abnormalities. Knowledge of these pathologies for a long period was not clear in clinical practice due to uncertainties regarding definition, classification and clinical diagnosis. In recent decades, major advances have been made in the understanding of the molecular and genetic issues, pathophysiology, and clinical and radiological assessment of the diseases. Progress has been made also in management of several types of cardiomyopathy. Advances in the understanding of these diseases show that cardiomyopathies represent complex entities. Here, special attention is given to evolution of classification of cardiomyopathies, with the aim of assisting clinicians to look beyond schematic diagnostic labels in order to achieve more specific diagnosis. Knowledge of the genotype of cardiomyopathies has changed the pathophysiological understanding of their etiology and clinical course, and has become more important in clinical practice for diagnosis and prevention of cardiomyopathies. New approaches for clinical and prognostic assessment are provided based on contemporary molecular mechanisms of contribution in the pathogenesis of cardiomyopathies. The genotype-phenotype

complex approach for assessment improves the clinical evaluation and management strategies of these pathologies. The review covers also the important role of imaging methods, particularly echocardiography, and cardiac magnetic resonance imaging in the evaluation of different types of cardiomyopathies. In summary, this review provides complex presentation of current state of cardiomyopathies from genetics to management aspects for cardiovascular specialists.

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Key words: Dilated cardiomyopathy; Hypertrophic cardiomyopathy; Restrictive cardiomyopathy; Arrhythmic cardiomyopathy; Secondary cardiomyopathy

Core tip: Cardiomyopathies represent a different group of disorders in which myocardium is itself structurally and functionally abnormal. During recent decades, the genetics, pathophysiology and diagnosis of cardiomyopathy have advanced from the traditional methods of clinical presentation to new genetic and imaging techniques. Nevertheless, the differences in definition, classification, pathophysiological mechanisms and diagnosis are controversial issues in clinical practice. The purpose of this review is to present the current state of classification, genetics, diagnostic approaches and management in order to provide useful instructions for clinical practice.

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INTRODUCTION

Cardiomyopathies are defined as myocardial disorders in

Table 1 American Heart Association classification for cardiomyopathies

Primary cardiomyopathies	Genetic	HCM/ ARVC/LVNC/Conduction defects/Mitochondrial myopathies/ion channel disorders
	Mixed	DCM/restrictive
Secondary cardiomyopathies	Acquired	Inflammatory/Tako-Tsubo/Peripartum/Tachycardia induced/Infants of IDDM mothers
	Infiltrative	Amyloidosis, Gauchers, Hurler's, Hunter's
	Storage	Fabry's, Glycogen storage disease, Niemann-Pick disease, haemochromatosis
	Toxicity	Drugs, heavy metals
	Endomyocardial	EMF, Loeffler's endocarditis
	Inflammatory	Sarcoidosis
	Endocrine	Diabetes, hyperthyroidism, hypothyroidism, hyperparathyroidism
	Cardiofacial	Noonan's, lentiginosis
	Neuromuscular	Friedreich's ataxia, Duchenne-Becker muscular dystrophy, myotonic dystrophy
	Nutritional	Beriberi, scurvy, selenium
	Autoimmune	SLE, dermatomyositis, scleroderma
	Consequence of cancer therapy	Anthracyclines, radiation, cyclophosphamide,

ARVC: Arrhythmogenic right ventricular cardiomyopathy/dysplasia; DCM: Dilated cardiomyopathy; HCM: Hypertrophic cardiomyopathy; LVNC: Left ventricular non-compaction; EMF: Endomyocardial fibrosis.

which the myocardium is structurally and/or functionally abnormal in the absence of definite disease able to cause the myocardial pathology. Cardiomyopathies are classified traditionally according to morphological and functional criteria into four categories: dilated cardiomyopathy (DCM), hypertrophic cardiomyopathy (HCM), restrictive cardiomyopathy (RCM) and arrhythmogenic right ventricular (RV) cardiomyopathy/dysplasia (ARVC/D). DCM is the most common form of heart muscle disease, comprising approximately 60% of all cardiomyopathies and characterized by left ventricular (LV) dilation and systolic dysfunction. The dilated cardiomyopathy is often assumed as a common pathway of several cardiovascular pathologies.

EVOLUTION OF CLASSIFICATIONS

Cardiomyopathies are classified as either primary or secondary. Primary cardiomyopathies consist of disorders namely or predominantly confined to the heart muscle, which have genetic, nongenetic, or acquired causes. Secondary cardiomyopathies are disorders that have myocardial damage as a result of systemic or multi-organ disease^[1]. These cardiomyopathies can be primary myocardial disorders or develop as a secondary consequence of a variety of conditions, including myocardial ischemia, inflammation, infection, increased myocardial pressure or volume load and toxic agents.

In the 1980 World Health Organization (WHO) classification, cardiomyopathies were classified as "heart muscle diseases of unknown cause", reflecting a general lack of etiologic factors which may cause heart failure. The next WHO classification published in 1995 proposed "diseases of myocardium associated with cardiac dysfunction" and included for the first time ARVC/D, as well as primary RCM^[2,3].

A more recent definition and classification of cardiomyopathies was proposed by the American Heart Association (AHA) Scientific Statement Panel, which divides cardiomyopathies as follows: "Cardiomyopathies are a heterogeneous group of diseases of the myocardium as-

sociated with mechanical and/or electrical dysfunction, which usually (but not invariably) exhibit inappropriate ventricular hypertrophy or dilatation, due to a variety of etiologies that frequently are genetic. Cardiomyopathies are either confined to the heart or are part of generalized systemic disorders, and often lead to cardiovascular death or progressive heart failure-related disability"^[1].

So far as the classification of cardiomyopathies is difficult, because the etiology or pathophysiology is not always clarified, there is no agreement on classification approaches in regular clinical practice.

For promoting standard nomenclature, recent knowledge on underlying causes and pathophysiology of cardiomyopathies has been implemented in a cardiomyopathy classification system both on behalf of the AHA and European Society of Cardiology (ESC)^[4].

The AHA divides cardiomyopathies into two major groups based on predominant organ involvement. Primary cardiomyopathies (genetic, nongenetic, or acquired) are those solely or predominantly confined to heart muscle and are relatively less common. Secondary cardiomyopathies show pathological myocardial involvement as part of a several number of systemic pathologies (Table 1)^[5].

In 2013, the MOGE(S) classification for a phenotype-genotype nomenclature of cardiomyopathies was proposed by the World Heart Federation^[6]. This classification suggests a nosology that addresses five characteristics of cardiomyopathic disorders: morphofunctional state (M), organ involvement (O), genetic inheritance (G), etiologic annotation (E) and functional state (S) according to ACC/AHA A-D stage and New York Heart Association (NYHA) I-IV functional class. The description of five characteristics provides classification in MOGE(S) designation. The MOGE(S) classification has several advantages with regard to simultaneous maximal description of disease from clinical and genetic points. However, this classification does not fulfill the diagnostic criteria of cardiomyopathies in several clinical situations and may not be always applied in clinical practice, because of the lack of genetic testing in many clinical centers. On the other hand, the classification based on systematically genetic

testing and monitoring may cause overdiagnostic states without clinically evident signs of cardiomyopathies and absence of clinical phenotype. Further genetic research and development of multicenter registries are needed to clarify the clinical advantages and to make more practical of MOGE(S) classification of cardiomyopathies.

DCM

DCM represents the most common cardiomyopathy worldwide. It is a heart muscle disorder defined by the presence of a dilated and poorly functioning left or both ventricles. It can be primary (genetic, mixed or predominantly familial nongenetic, or acquired) or secondary (inflammatory, autoimmune, or thyrotoxic). This disease can be diagnosed in association with recognized cardiovascular disease; however, to qualify as DCM, the extent of myocardial dysfunction cannot be explained exclusively by abnormal loading conditions (hypertension or valve disease) or ischemic heart disease^[4,7]. A large number of cardiac and systemic diseases can cause systolic dysfunction and LV dilatation, but in the majority of cases no definite cause is found. This has led to the common terminology idiopathic dilated cardiomyopathy (IDC).

PREVALENCE

Prevalence in the general population remains undefined. This disorder develops at any age, in either sex, and in people of any ethnic origin^[8,9]. In adults, DCM arises more commonly in men than in women. In children, the yearly incidence is 0.57 cases per 100000, but is higher in boys than in girls (0.66 *vs* 0.47 cases per 100000, *P* < 0.006). Two-thirds of children are thought to have idiopathic disease^[4]. In adults, the prevalence is 1 in 2500 individuals, with an incidence of 7 per 100000 per year (but it could be underdiagnosed). The prevalence of DCM in the United States (adjusted for age) is 36 per 100000 of the population^[8]. The etiology includes genetic transmission (estimated at 30%-40%) identifying familial DCM, cytotoxic agents (*e.g.*, anthracycline derivatives), malnutrition (*e.g.*, protein deficiency), myocarditis (viral etiology), and autoimmune disease. In many cases, the disease is inherited, and is called familial dilated cardiomyopathy (FDC). The familial type might account for 20%-48% of all cases^[10].

FAMILIAL (GENETIC) DILATED CARDIOMYOPATHY

Prominent progress has been made in studies of the genetics of DCM. Most of the genes involved in the development of DCM encode structural elements of the cardiomyocytes, particularly dystrophy associated glycoprotein complex or components of the sarcomeric complex. Genetic predisposition may have a decisive role in the development of primary and secondary DCM. Currently, > 30 autosomal and 2-X-linked genes have been

shown to predispose to DCM and the number of these genes will continue to increase. There are sufficient data that with new diagnosis of IDC the clinical screening of first-degree family members will reveal familial (genetic) DCM in 20%-35% of those family members. Recent guidelines recommend that genetic testing should be provided in families in whom familial DCM is suspected for early diagnosis of cardiomyopathy in family members^[4].

The diagnosis of FDC is made when IDC is diagnosed in two closely related family members. About 20%-48% of DCM has been reported as familial, although with incomplete and age-dependent penetrance, and linked to a diverse group of > 20 loci and genes^[10]. Although genetically heterogeneous, the predominant mode of inheritance for DCM is autosomal dominant, with X-linked autosomal recessive and mitochondrial inheritance being less frequent. Thus, when taking a family history, specific attention should be given to a history of muscular dystrophy, features of mitochondrial disease (*e.g.*, familial diabetes, deafness, epilepsy, or maternal inheritance), and signs and symptoms of other inherited metabolic diseases^[10]. Several of the mutant genes linked to autosomal dominant DCM encode the same contractile sarcomeric proteins that are responsible for HCM, including α -cardiac actin; α -tropomyosin; cardiac troponin T, I and C; β - and α -myosin heavy chain; and myosin binding protein C. Z-disc protein-encoding genes, including muscle LIM protein, α -actinin-2, ZASP, and titin, also have been identified. DCM is also caused by a number of mutations in other genes encoding cytoskeletal/sarcomeric, nuclear envelope, sarcomere, and transcriptional coactivator proteins. The most common of these probably is the lamin A/C gene, also associated with conduction system disease, which encodes a nuclear envelope intermediate filament protein. Mutations in this gene also cause Emery-Dreifuss muscular dystrophy^[11-13]. Other DCM genes of this type include desmin, caveolin, and β - and α -sarcoglycan, as well as the mitochondrial respiratory chain gene^[1]. X-linked DCM is caused by the Duchenne muscular dystrophy (dystrophin) gene, whereas G4.5 (tafazzin), a mitochondrial protein of unknown function, causes Barth syndrome, which is an X-linked cardioskeletal myopathy^[10,13].

PATHOLOGY

Macroscopic examination

Macroscopic examination of heart reveals ventricular chamber dilation with thickened or normal thickness walls. Valvular changes are not typical, although dilation of valvular orifices may be present as secondary changes due to dilation of chambers. Coronary anatomy is most commonly normal, although the presence of nonocclusive atherosclerotic plaques may be present. Thrombi are found most frequently in ventricles and atrial appendages.

Histological examination

The most typical DCM pattern is the development of

interstitial and perivascular fibrosis of varying degree^[14]. Myocardial necrosis predominantly is present at subendocardium. Our study group investigated noninvasively using the Shirani method^[15] the degree of myocardial fibrosis in patients with IDC and ischemic dilatation cardiomyopathy. The percentage of volumic collagen fraction in the LV myocardium was significantly higher in DCM patients compared to those with ischemic cardiomyopathy. Increase of collagen fraction correlated with the degree of dilation of the left ventricle^[16].

Clinical manifestations

The most common clinical manifestations of DCM are congestive heart failure symptoms and thromboembolic complications. The disease commonly has a progressive course. The determination of time of manifestation is not easy, because the disease course for a long period is not symptomatic. Patients are admitted to hospital in cases with expressed heart failure symptoms. A careful history taking and physical examination with diagnostic studies are essential for differential diagnosis of DCM. More commonly, DCM manifests without any history and provoking factor. Cardiomegaly at radiological examination or on abnormal electrocardiography (ECG) may be the first findings in an asymptomatic patient. The left ventricle is dilated, and more spherical than usual with raised wall stress and depressed systolic function. As the disease progresses, definite symptoms of congestive heart failure present. Chest discomfort may occur in some cases, however this discomfort is not relieved by nitroglycerin. Physical examination may reveal gallop rhythm in decompensated patients. The jugular venous pulse is normal until right heart decompensation is present. The clinical course of DCM may be variable both with slow progression and rapidly progressive over several months. Cachexia and peripheral edema typically arise late in the course. Sudden death, presumably due to ventricular fibrillation may be the first manifestation. Some cases of DCM most probably develop due to viral myocarditis and these patients may have a history viral infection prior to deterioration of heart failure symptoms. An acute systemic febrile infectious disease (such as influenza) is followed by a latent period during which time the patient may be asymptomatic. It is reported also that in 20%-25% of patients with new-onset DCM may have cardiac recovery^[17].

Several clinical, laboratory and instrumental factors may have prognostic significance in DCM patients. These factors are symptomatic ventricular arrhythmias, persistent gallop rhythm, persistent jugular venous distention, systemic hypotension, persistently elevated B-type natriuretic peptide, left bundle branch block, pulmonary capillary wedge pressure > 20 mmHg, cardiac index < 2.5 L/min per square meter, severely reduced ejection fraction, restrictive diastolic filling pattern, and severe mitral regurgitation^[18].

ECG

ECG in patients with idiopathic DCM has no specific

diagnostic role, and abnormalities ranging from isolated T wave and ST segment changes to septal pathological Q waves, wide QRS complex in patients with LV fibrosis might be present. Prolongation of atrioventricular (AV) conduction, and bundle branch block can be observed. Sinus tachycardia and supraventricular arrhythmias are common, in particular atrial fibrillation. Approximately, 20%-30% of patients have nonsustained ventricular tachycardia and a small number present with sustained ventricular tachycardia. ECG is utilized as a first-line screening and diagnostic tool for detecting conditions associated with sudden death. Idiopathic DCM patients with a prolonged QRS have significantly worse survival than other patients^[19].

ECHOCARDIOGRAPHY

Echocardiography in DCM has characteristic patterns, although it is not possible to make differential diagnosis by echocardiography between idiopathic and other secondary LV dilation with dysfunction. M-mode echocardiography shows LV dilation with diffuse hypokinetic walls (Figure 1). Although cardiomyopathy is diffuse pathology, there may be segmental differences of the degree of hypokinesis revealed by two-dimensional echocardiography, which causes difficulties for differentiation from ischemic cardiomyopathy. Ventricular dilation usually is not accompanied by sufficient hypertrophy, which causes increase of volume-to-mass ratio^[20]. Doppler echocardiography shows frequently functional mitral and tricuspid regurgitation and a different degree of diastolic dysfunction, depending on severity of intracardial hemodynamic abnormalities.

CARDIAC CATHETERIZATION

Catheterization for exclusion of coronary artery disease is important for following management of DCM patients. Catheterization also may reveal increased LV end-diastolic pressure and pulmonary artery wedge pressure. Left ventriculography may show ventricular dilation with global hypokinesis.

CARDIAC MAGNETIC RESONANCE IMAGING AND DILATED CARDIOMYOPATHY

Cardiac magnetic resonance imaging (MRI) can differentiate ischemic from non-ischemic cardiomyopathies through use of late gadolinium imaging, even when the heart is globally dilated and dysfunctional (Figure 2). Infarction is characteristic in that it always causes subendocardial late gadolinium enhancement (LGE), which extends variably transmurally to the epicardium. It also follows a coronary territory distribution. The absence of LGE in a dysfunctional segment of myocardium implies the potential for recovery with time (stunning), medical treatment or revascularization (hibernation), biventricular pacing (dyssynchrony)^[21]. Nonischemic DCM may dem-

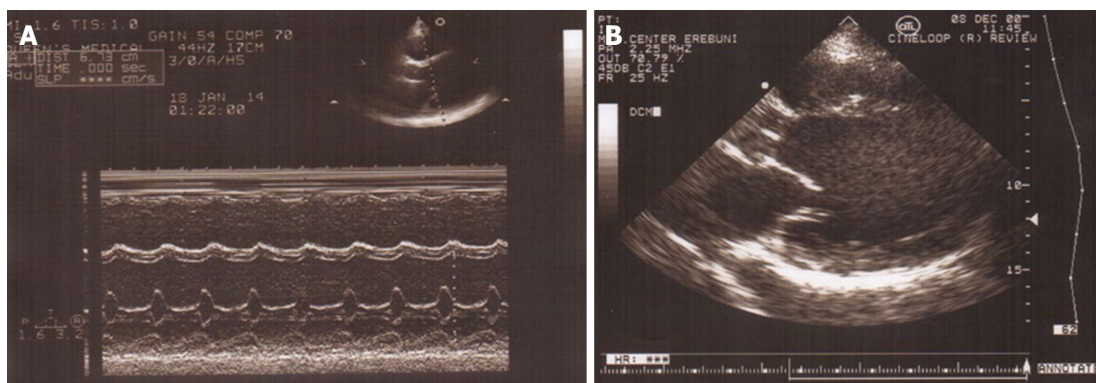


Figure 1 M mode and B mode echocardiogram of patient with idiopathic dilated cardiomyopathy. A: M mode echocardiogram shows dilated left ventricle with hypokinesis of interventricular septum and posterior wall; B: Parasternal long axis view of B mode echocardiogram showing remodeled left ventricular shape with loss of elliptical form.

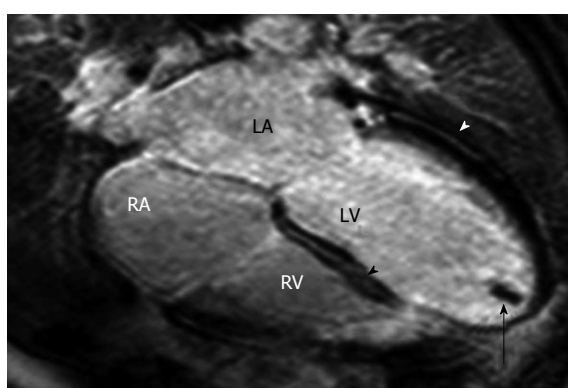


Figure 2 Dilated cardiomyopathy in a 36-year-old male soccer player with fatigue and a 3-5-d history of burning epigastric pain associated with nausea, vomiting, and early satiety^[105]. Horizontal long-axis late contrast-enhanced magnetic resonance imaging shows an apical thrombus (arrow) in the left ventricle (LV) and midwall enhancement in the lateral left ventricular wall (white arrowhead) and the interventricular septum (black arrowhead). RA: Right atrium; RV: Right ventricle; LA: Left atrium.

onstrate either no LGE or mid-wall LGE in areas not corresponding to a coronary territory. Additional features that can be detected using cardiac MRI include valvular regurgitation, apical thrombus, dyssynchrony with or without posterior scar, signs of decompensation, cardiac iron, LV hypertrophy (LVH), RV involvement and atrial size.

CHRONIC MYOCARDITIS AND DCM

The major long-term consequence of myocarditis is inflammatory dilated cardiomyopathy, but the pathways that lead to myocardial fibrosis are poorly understood.

The gold standard of diagnosing the underlying causes of myocarditis and inflammatory cardiomyopathy is the histological, immunohistological and polymerase chain reaction-based analysis of cardiac MRI-guided endomyocardial biopsy (EMB) specimens. Persistent viral infections and infection-associated or postinfectious inflammatory processes of the myocardium may be key pathological mechanisms of progression of myocarditis to cardiomyopathy.

ANTIVIRAL THERAPY APPROACH

Several recent studies have investigated endomyocardium-based etiological antiviral treatment of inflammatory cardiomyopathies.

Interferons serve as a natural defense against many viral infections. Their innate production is associated with clinical recovery from viral infection and subsequent sequelae, while exogenous administration is protective. Type I interferons are a promising choice for treatment of chronic viral myocarditis. Currently, there is no approved treatment for chronic viral heart disease, but data from open-label phase II studies have demonstrated that subgroups of patients, who had not improved upon regular heart failure medication, may have significant benefit even years after onset of chronic disease. In the study of a 6-mo interferon- β 1a therapy of patients with persistent enteroviral and adenoviral myocarditis, complete elimination of enteroviral and adenoviral genomes was demonstrated by follow-up biopsies taken 3 mo after termination of antiviral therapy. Virus clearance was paralleled by an improvement of mean LV function, a decrease in ventricular size, amelioration of heart failure symptoms, and a decrease of infiltrating inflammatory cells. No patient deteriorated and patients with severely affected LV dysfunction gained most benefit. Viral elimination after antiviral treatment suggests that early biopsy-based diagnosis and timely treatment may prevent disease progression and thereby improve the outcome of chronic viral cardiomyopathy. However there are limited data on efficacy of specific antiviral therapies and more studies are needed to identify patient cohorts who will benefit from targeted antiviral or immunosuppressive therapy. Treatment of myocarditis in current regular clinical practice remains supportive including the need for ventricular assist devices and heart transplantation^[22].

EMB

In recent years, EMB has become a useful diagnostic tool for the investigation and treatment of myocardial diseases. However, its routine use is criticized by some

authors for the lack of therapeutic usefulness^[23]. The techniques enable us to obtain multiple tissue samples from both ventricles with a low incidence of procedural complications. In addition to several clinical states such as after heart transplantation, specific myocardial diseases, the more frequent indication for EMB is suspected myocarditis in patients with progressive heart failure. In such cases, the correct analysis of tissue samples represents an important point to diagnosis. Although EMB provides suggestive findings in DCM, these findings may not always be revealed due to the technical difficulties of procedure and biopsy specimens may not contain pathological changes. The diagnostic performance of EMB is superior if the procedure is provided with a cardiac MRI-guided target area^[24]. Diagnostic findings that show absence of inflammation may assist in further management strategies for DCM. Thus, in selected cases, EMB represents a useful method for correct prognostic and therapeutic evaluation of DCM.

MANAGEMENT

There is no specific etiology-based therapy in DCM. The main principles of DCM treatment are general concepts of chronic heart failure treatment. Although conventional pharmacotherapy is not specific with regard to etiopathogenesis, it decreases mortality in such patients. Common treatment includes β -blockers, angiotensin-converting enzyme (ACE) inhibitors, spironolactone in patients with NYHA class II-IV heart failure. Diuretic therapy may have a beneficial effect on symptoms without a prominent effect on long-term outcome. β -Blockers and amiodarone can be used for management of supraventricular and ventricular arrhythmia. However, their long-term effect did not reduce mortality conditioned by sudden cardiac death (SCD)^[25]. An implantable cardioverter defibrillator (ICD) and biventricular pacemakers are indicated in appropriate patients with both idiopathic and secondary dilated cardiomyopathies with LV dysfunction for secondary prevention of SCD. ICD can be combined with cardiac resynchronization therapy in patients with prolonged QRS duration and LV dys-synchrony^[26]. However, the benefits of ICD were established in patients with systolic dysfunction of ischemic etiology^[25,27]. Individual studies in patients with nonischemic cardiomyopathy failed to show significant reduction of total mortality^[28-30], although a meta-analysis of five trials showed 31% mortality reduction^[31].

Surgical approaches to restore LV shape by reverse remodeling include LV reconstruction and implantation of external restraint devices. The aims of ventricular reconstruction procedures are to restore elliptical ventricular chamber to decrease wall stress, end systolic volume and mitral regurgitation^[32]. Most of these reconstruction procedures and trials have been estimated in patients with ischemic origin DCM.

The selected ventriculoplasty in combination with mitral annuloplasty is a useful option for patients with an extremely dilated left ventricle in IDC. Surgery should

be considered before inotropic dependency occurs when prior medical treatment has failed^[33].

In carefully selected patients, partial ventriculectomy combined with mitral valve reconstruction achieves short-term results comparable to those after heart transplantation^[34]. However, long-term results and multicenter evaluation are needed to define its place in the treatment of advanced heart failure. With studies directed to patient selection and surgical modification, ventriculoplasty will become a realistic option in the treatment of heart failure caused by nonischemic cardiomyopathy.

Stem cell therapy has shown moderate effects in clinical trials for ischemic cardiomyopathy, but it remains to be determined if these results are applicable to idiopathic DCM patients. There is a need for methodologically sound studies to elucidate underlying mechanisms and translate those into improved therapy for clinical practice. In a single center study with 110 patients with nonischemic DCM, intracoronary CD34⁺ stem cell transplantation was associated with improved ventricular function, exercise tolerance, and long-term survival^[35]. Higher intramyocardial homing in this study was associated with better stem cell therapy response.

To prove safety and efficacy of cell therapy for DCM, adequate randomized (placebo) controlled trials using different strategies are mandatory. The REGENERATE-DCM trial is the first ongoing randomized, double-blind, placebo-controlled trial worldwide to investigate the role of granulocyte-colony-stimulating factor and autologous bone-marrow-derived stem/progenitor cell therapy to improve cardiac function in patients with DCM^[36].

The 5-year survival averages 30%-40% and is improved by contemporary heart failure therapy, but not all patients respond well to therapy and some patients rapidly deteriorate no matter the therapeutic approach, and for them, heart transplantation remains the only option.

CARDIOMYOPATHIES WITH DILATED PHENOTYPE

Peripartum cardiomyopathy

Peripartum cardiomyopathy (PPCM) is a rare but potentially life-threatening condition that occurs in previously healthy women during the last month of pregnancy and up to 5-6 mo postpartum. The etiology and pathophysiology remain uncertain, although recent observations strongly suggest the specific role of prolactin cleavage secondary to unbalanced peri-/postpartum oxidative stress^[37]. PPCM is a diagnosis of exclusion, because it shares many clinical characteristics with other forms of systolic heart failure secondary to cardiomyopathy. The heart failure management requires a multidisciplinary approach during pregnancy, considering the possible adverse effects on the fetus. Some novel therapies, such as prolactin blockade, are proposed to either prevent or treat the patients with PPCM^[38]. A critical individual approach concerning the risks of subsequent pregnancy must be considered. As a result of its rare incidence, geographical

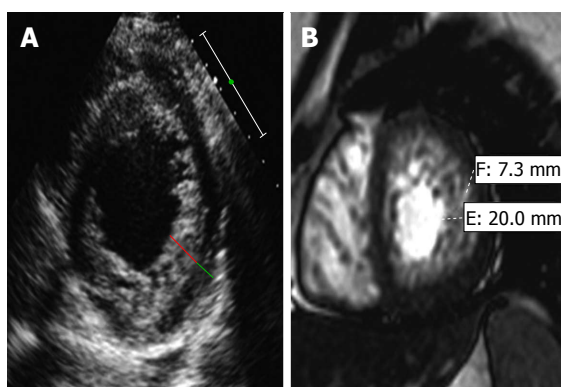


Figure 3 Non-compaction cardiomyopathy in two patients^[105]. A: Dilated cardiomyopathy in a 60-year-old man with new-onset congestive heart failure. Short-axis echocardiogram obtained in systole at the level of the left ventricle (LV) shows a two-layered myocardium with a noncompacted (red line) and compacted (green line) layer along the lateral, inferior, and anterior walls and a maximal end-systolic NC: C ratio > 2 ; B: Symptoms of New York Heart Association Class III heart failure and severely reduced ($\leq 35\%$) LV ejection fraction in a 35-year-old woman. Short-axis 2D SSFP cardiac magnetic resonance imaging obtained in end diastole shows thickening of the LV myocardium, with an NC: C ratio of 2.9. The patient underwent subsequent implantable cardioverter-defibrillator placement for primary prevention of sudden cardiac death.

differences, and heterogeneous presentation, PPCM continues to be incompletely characterized and understood. For all these reasons, PPCM remains a challenge in clinical practice, so future epidemiological trials and national registries are needed to learn more about the disease.

Classic criteria of PPCM include development of heart failure in the last month of pregnancy or within the first 5 mo postpartum, absence of an identifiable cause of heart failure, and absence of recognizable heart disease prior to the last month of pregnancy^[39].

LV non-compaction

LV non-compaction (LVNC) is a cardiomyopathy resulting from arrest of fetal development of the heart. This leads to altered myocardial architecture that is seen as a two-layered myocardium with a thin, compacted epicardial layer and a thick, noncompacted endocardial region. The noncompacted myocardial region is comprised of prominent trabeculations and deep intertrabecular recesses that directly communicate with the LV cavity. The condition may present without any associated cardiac malformation and is then labeled isolated LVNC. Non-compacted myocardium is also seen in conjunction with other cardiac abnormalities including cyanotic congenital heart disease, Ebstein's anomaly, and other cardiomyopathies. Clinical presentation in LVNC is seen with congestive heart failure, ventricular arrhythmia, and systemic thromboembolism. The condition is listed as an unclassified cardiomyopathy in the WHO and ESC classification of cardiomyopathies^[4] and as a primary genetic cardiomyopathy in the AHA classification^[5].

Both sporadic and familial forms are described.

The presence of significant non-compaction is estimated at 1:2000 in the general population. The condition

is, however, more prevalent in heart failure patients. More frequent use of cardiac imaging in clinical practice has increased recognition of this condition^[40].

Non-compaction myocardium clinically may represent from asymptomatic individuals to those with severe disease presenting with heart failure, ventricular arrhythmia, and systemic thromboembolism. Noncardiac features may include facial dysmorphism and neuromuscular disorders.

Echocardiography may reveal trabeculation in the LV wall. However in healthy persons this can be also found. To separate benign LV trabeculation from pathological LVNC following diagnostic criteria is proposed^[41].

Echo: Ratio of noncompacted to compacted myocardium in end-systole of $> 2:1$.

Cardiac MRI: Ratio of noncompacted to compacted myocardium in end-diastole of $> 2.3:1$. Cardiovascular imaging is important in the diagnosis of LV non-compaction. Cardiac MRI (Figure 3) has better resolution compared to echocardiography, which makes it a preferred imaging modality in such patients. Cardiac MRI is also reliable in distinguishing LVNC from other causes of LV apical deformity, including apical variant of hypertrophic cardiomyopathy, endomyocardial fibrosis (EMF) and apical thrombus^[42]. Pharmacological management of LVNC is mainly symptomatic and directed to relief of heart failure symptoms. Heart transplantation remains an option in patients with treatment-tolerant high functional class patients. Ventricular arrhythmia is not directly related to severity of LV dysfunction and a prophylactic ICD is recommended. Anticoagulation to prevent thromboembolic complications is recommended, particularly in patients with severe contractile dysfunction.

STRESS-INDUCED OR "TAKOTSUBO" CARDIOMYOPATHY

Stress-induced cardiomyopathy was termed Takotsubo cardiomyopathy by Japanese cardiologists in 1991^[43]. Advances in diagnostic imaging and emergency coronary angiography have contributed to increased recognition of stress-induced cardiomyopathy, and increasing numbers of reports have been published since then.

A history of intense emotional or physical stress and a typical pattern of LV contractile dysfunction on cardiac imaging are suggestive of the diagnosis. The most common abnormality on ECG is ST-segment elevation resembling ST segment elevation myocardial infarction^[44]. This cardiomyopathy is transient and reversible. Clinical presentation may be indistinguishable from acute coronary syndrome, invariably necessitating coronary angiography for exclusion of obstructive coronary artery disease. Prevalence is in 1%-2% of patients undergoing coronary angiography for acute coronary syndrome. Based on morphological features of the LV, presumed causative role of stress and catecholamine excess and transient nature of the contractile dysfunction, other

nomenclature used to describe this cardiomyopathy include ampulla cardiomyopathy, stress cardiomyopathy or catecholamine cardiotoxicity and transient LV apical ballooning syndrome^[45].

Distinct pattern of contractile abnormality is noted in the left ventricle. In the typical case the LV apex is dyskinetic and expanded and may be associated with hyperdynamic contractility of the basal LV segments. The shape of left ventricle in systole resembles a Japanese octopus trap (Takotsubo), which has a narrow neck and a wide base. The condition is associated with markedly elevated circulating catecholamine, which is assumed to be central in the pathophysiology of this condition though exact mechanism at the cellular level is not fully understood. In a report by Wittstein *et al*^[46], two to three times higher plasma catecholamine concentrations were found in 13 patients with transient LV apical ballooning syndrome compared with seven controls hospitalized for acute myocardial infarction with Killip class III heart failure. Preponderance of females afflicted by this condition is unclear.

Estrogen deficiency in the postmenopausal state may play a role^[47]. Of particular interest, in other conditions with elevated catecholamine levels like subarachnoid hemorrhage, segmental wall motion abnormality is also predominantly seen in women. A reverse pattern of contractile abnormality with apical sparing has also been reported. Cardiac MRI is helpful in diagnosing and monitoring clinical recovery. Absence of delayed hyperenhancement on cardiac MRI is particularly important in differentiating this condition from ischemic and other types of nonischemic cardiomyopathy and acute myocarditis: normal first-pass contrast enhanced rest myocardial perfusion, reversible myocardial edema in regions of contractile dysfunction, and absence of late gadolinium enhancement is strongly indicative of the diagnosis of Takotsubo cardiomyopathy. Resolution of contractile dysfunction, days to weeks after initial presentation, is confirmatory of the diagnosis.

DRUG-INDUCED CARDIOMYOPATHIES

Several drugs may cause acute and chronic cardiac systolic dysfunction with the development of myocardial remodeling. Many of drugs administered chronically are cardiotoxic and may trigger the development of cardiac injury even when used appropriately. ESC guidelines emphasize some specific drug groups, which are strongly related to development of heart failure^[48].

Anthracyclines are highly effective antineoplastic agents with wide application. However, one of the major complications in their long-term pharmacotherapy is cardiac dysfunction. Three distinct types of anthracycline-induced cardiotoxicity have been described^[49]. Acute or subacute injury can occur immediately after treatment with transient arrhythmias, pericarditis and myocarditis. These manifestations usually respond rapidly with interruption of anthracycline infusion. Long-term therapy may be associated with chronic cardiotoxicity resulting in cardiomyopathy. Late-onset anthracycline cardiotoxicity

may cause ventricular dysfunction and arrhythmias, which manifest years to decades after anthracycline treatment has been completed.

Echocardiography may serve as excellent diagnostic tool both for diagnosing and for screening, monitoring of patients on antineoplastic therapy.

A clinical study estimating the cumulative percentage of patients who developed doxorubicin-induced congestive heart failure found that cumulative dose of 400 mg/m² was 3%, increasing to 7% at 550 mg/m² and to 18% at 700 mg/m². Current anthracycline regimens typically contain less than the cumulative dose associated with increased risk of cardiomyopathy^[50,51].

Standard treatment for systolic heart failure is indicated for treatment for both asymptomatic and symptomatic cases, with ACE inhibitors, β -blockers, spironolactone.

Several agents have been studied to decrease cardiotoxicity in such patients. Dexrazoxane (also known as cardioxane) is the most investigated agent^[52,53]. It is the only approved cardioprotective agent in anthracycline chemotherapy, but there is no evidence for a difference in response rate or survival^[54]. Other agents such L-carnitine, coenzyme Q10, N-acetylcysteine, vitamin E, and trimetazidine, have been investigated as metabolic cardioprotective agents^[55-62]. Unfortunately, none of them showed prominent clinical efficacy in preventing anthracycline toxicity.

The alkylating agent cyclophosphamide is mainly cardiotoxic at high doses in bone marrow transplantation protocols^[63]. Cardiotoxicity is expressed from transient electrocardiographic changes and asymptomatic increases of serum levels of cardiac enzymes to severe cardiotoxicity such as exudative pericardial effusion, ventricular hypertrophy and fatal myopericarditis and (hemorrhagic) myocardial necrosis^[64].

ALCOHOLIC CARDIOMYOPATHY

Alcoholic cardiomyopathy represents one of the most common forms of secondary cardiomyopathies resembling IDC. The risk of development of alcoholic cardiomyopathy depends on both duration and doses of alcohol consumption. The clinical course and prognosis in alcoholic cardiomyopathy in withdrawal of alcohol consumption is better compared to those with idiopathic DCM^[65,66]. The diagnosis of alcoholic cardiomyopathy may have several difficulties with regard to widespread consumption of alcohol in many countries, including patients with idiopathic DCM and similarities of radiological patterns of myocardial remodeling in both idiopathic and alcoholic cardiomyopathy^[67].

ARRHYTHMOGENIC CARDIOMYOPATHY

Arrhythmogenic cardiomyopathy/RV dysplasia is the genetic form of cardiomyopathy characterized by fibrosis and fatty infiltration of RV myocardium and by manifestation of ventricular tachycardia/ventricular fibrillation. Lately, it has been shown that the disease is not confined

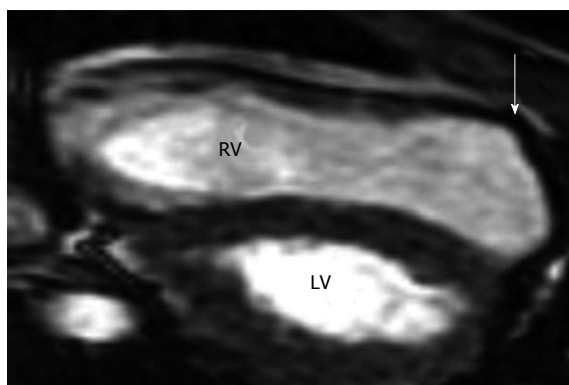


Figure 4 Arrhythmogenic right ventricle cardiomyopathy in a 17-year-old boy who experienced sudden cardiac death from sustained ventricular tachycardia during a soccer match and was revived with on-site defibrillation^[105]. Parasternal long-axis 2D echocardiograms obtained in end systole show a dilated right ventricle (RV) and regional dyskinesia at the RV outlet tract (arrow). LV: left ventricle.

only to the right ventricle as the name suggests, because the left ventricle may be affected in up to 75% of patients^[68]. This disease accounts for 20% of cases of SCD and mainly among young athletes dying suddenly, the prevalence of this cardiomyopathy is higher. In 30%-50% of cases arrhythmogenic cardiomyopathy represents family disease with autosomal-dominant inheritance of gene mutations encoding desmosomal proteins^[69]. Presenting symptoms range from palpitation to syncope and SCD. Myocardial electrical instability comprises the main clinical manifestation with ventricular ectopics and ventricular tachycardia. Biventricular or RV failure is less common and observed mainly in patients with long-term disease protected from SCD by ICD implantation.

Diagnosis of this condition may cause difficulties with nonspecific abnormalities on echocardiographic and angiographic examinations. EMB has a low sensitivity, because samples are usually taken from the septum; a region that is infrequently involved^[70]. ECG may have a diagnostic role with the following typical characteristics: wide QRS complexes in right chest leads, T wave inversion, and ϵ wave after QRS complex as a prototype of late ventricular potentials. The task force determined diagnostic criteria for arrhythmogenic cardiomyopathy, which involve data for cardiac MRI, ECG, positive family history, and arrhythmia clinics^[71].

Contrast-enhancement-cardiac MRI may help to guide targeted EMBs (Figure 4).

Predilection patterns with midwall contrast enhancement are found in the basal anterior region and/or the RV outflow tract. These patterns of fibrosis correlate with fibrofatty replacement of the myocardium at histological assessment and predict induction of ventricular tachycardia during electrophysiological studies^[69,71].

HYPERTROPHIC CARDIOMYOPATHY

Hypertrophic cardiomyopathy is a clinically heterogeneous autosomal dominant heart muscle disorder with inherited

etiology, primarily by mutations of genes encoding the cardiac sarcomere myofilament proteins. HCM prevalence is 0.2% and one-third of patients show no obstruction of LV outflow tract (LVOT), whereas two-thirds develop a significant gradient under resting conditions and/or on exertion^[72]. HCM was hardly diagnosed in the pre-echocardiographic era and abnormal electrocardiographs suggestive of LVH were attributed by clinicians to hypertensive heart disease. The etiology of HCM has similarly been sorted and HCM is an autosomal dominant genetic disorder, caused by mutations in at least 10 different genes, which code for sarcomeric proteins^[73]. Mutations in the β -myosin heavy chain gene, myosin binding protein C and troponin T account for 70%-80% of all cases. The total number of mutations is > 100 and new mutations are being discovered^[74]. These developments in the etiology of HCM resulted in a change of definition and HCM eventually was no longer a heart muscle disease of unknown cause.

GENETICS IN HCM

Sarcomere mutations are found in 60%-70% of adult and pediatric patients with a family history of HCM and in 30%-40% of apparently sporadic cases^[69]. Mutations in myosin heavy chain (MYH7) and myosin binding protein C (MYBPC3) are the most frequent and comprise up to 8% of cases of sarcomeric HCM. Several studies^[74] have demonstrated that cardiovascular deaths, progressive symptoms, and ventricular arrhythmias appear more prominent in HCM patients with sarcomeric mutations than in patients without mutations. Moreover, patients with more than one mutation have more severe symptomatology^[74]. However the phenotypic presentation and penetrance of mutations may be variable and dependent on several other factors such as presence of hypertension and age. The presence of LVH frequently cannot be diagnosed before adolescence. Thus, the interpretation of genetic testing should be complex including clinical assessment.

The clinical application of genetic testing depends on the confidence of the prediction of disease. Genetic testing must be conducted also as a family test, because its advantages are greatest in larger families with both disease presentations and healthy individuals.

PATHOLOGY IN HCM

HCM is characterized by asymmetrical or symmetrical hypertrophy of the left ventricle with increased LV mass. Asymmetrical hypertrophy is presented by comparing the thickness of the septum with the LV free wall and by presence of septal to free wall thickness ratio > 1.3. Asymmetric hypertrophy of interventricular septum is the most frequent form of HCM. Other presentations include symmetric, apical forms. RV involvement occurs in 17.6% of all cases of HCM, most frequently affecting the middle to apical portion of the right ventricle^[75,76].

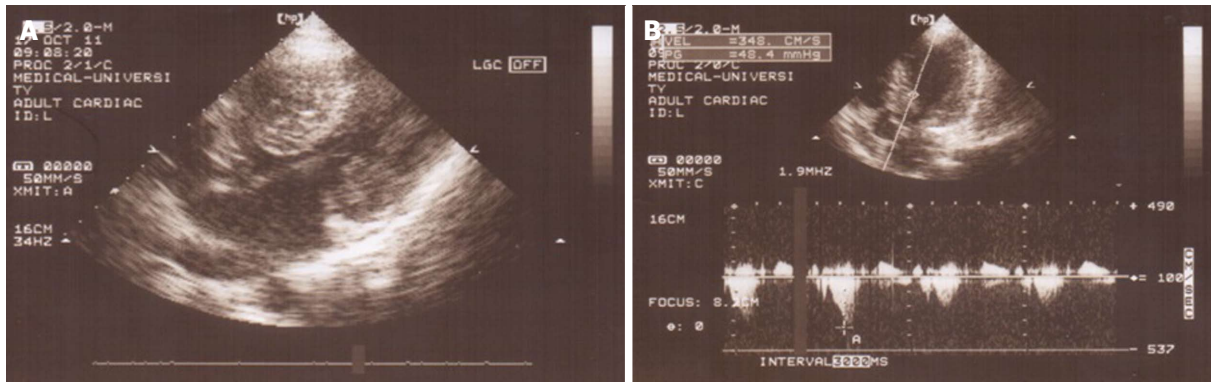


Figure 5 Patient with hypertrophic cardiomyopathy and subaortic stenosis. A: Parasternal long axis view showing expressed left ventricular (LV) hypertrophy at the region of the LV outflow tract; B: Doppler echocardiogram reveals the high subaortic gradient ($\Delta P = 48$ mmHg).

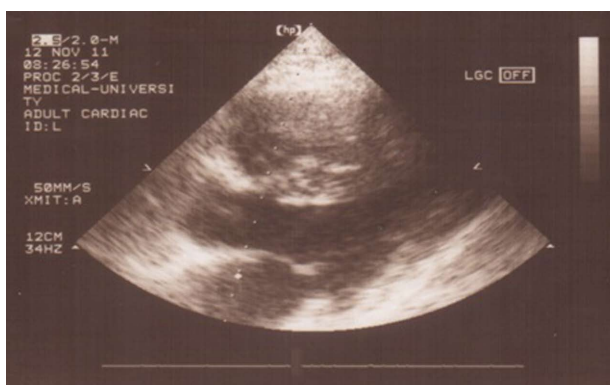


Figure 6 Echocardiogram of a 35-year-old patient with hypertrophic cardiomyopathy: massive hypertrophy of the interventricular septum with wall thickness 37 mm compared to posterior wall; hyperechogenic septal myocardium.

Pathological changes in HCM at the histological level are characterized by cardiomyocyte hypertrophy and disarray with bizarre enlarged nuclei, hyperchromasia and pleomorphism. Increased content of interstitial collagen volume may also be present^[77].

DIAGNOSIS OF HCM

Diagnosis relies on the electrographic and echocardiographic demonstration of hypertrophy patterns. LVH may be diffuse or more segmentally distributed (proximal and/or midportion of the interventricular septum, apex, anterior or lateral wall), but no single morphologic expression appears to be specific^[78].

In fact, differentiation of LVH secondary to HCM may be difficult from other diseases affecting the ventricles, for example, hypertrophy secondary to infiltrative diseases (e.g., amyloidosis), Fabry's disease^[79], glycogen storage disorders^[80], or systemic arterial hypertension. These diagnostic difficulties may rise with advanced age (Figures 5-8).

Besides LVH, LV outflow obstruction is one of the most common features of this disease. Asymmetric basal septal hypertrophy and the systolic anterior motion of the anterior leaflet of the mitral valve are the major con-

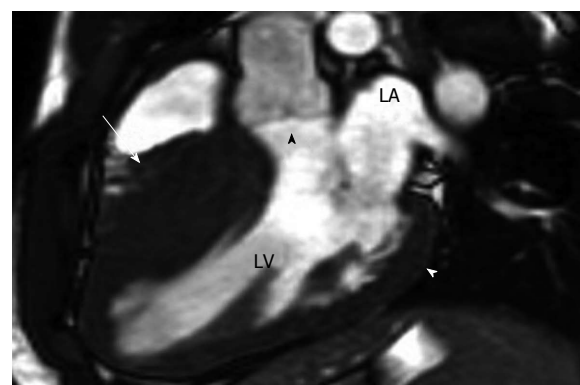


Figure 7 Hypertrophic cardiomyopathy^[105]. A: 2D SSFP cardiac magnetic resonance imaging, obtained in end diastole in the long-axis plane of the LV outflow tract (LVOT) in a 17-year-old boy with Hypertrophic cardiomyopathy found at family screening, shows marked asymmetric septal hypertrophy with a ratio of ventricular septal thickness (27 mm, arrow) to inferolateral wall thickness (9 mm, white arrowhead) of 3:1. Note that the hypertrophied septum encroaches on the LV lumen, causing mild narrowing of the LVOT (black arrowhead). LA: Left atrium; LV: Left ventricle.

tributors of LV outflow obstruction and the more or less significant accompanying mitral regurgitation^[81]. In a series of 320 consecutive HCM patients, this obstructive pathology at resting conditions (defined as a gradient ≥ 50 mmHg at rest) was found in 37% of patients^[82]. In the remaining patients, 52% developed dynamic outflow gradients during exercise or maneuvers which decrease afterload or increase contractility. Abnormal diastolic function is typical pattern of HCM. It may be present at early stages of HCM, even before morphological evidence of hypertrophy occurs^[83,84].

The clinical presentation of HCM patients shows remarkable diversity: some individuals experience none or minor symptoms, others may develop dyspnea at exercise or at rest, angina pectoris, palpitations, atrial fibrillation, dizziness, presyncope and syncope, fatigue or finally end-stage heart failure requiring cardiac transplantation^[85].

The changes on ECG are variable and include left axis deviation, occurrence of Q waves, a positive Sokolow index for hypertrophy, conduction abnormalities, ST-T depression or other abnormalities, negative T waves and giant T waves (particularly observed in Japanese

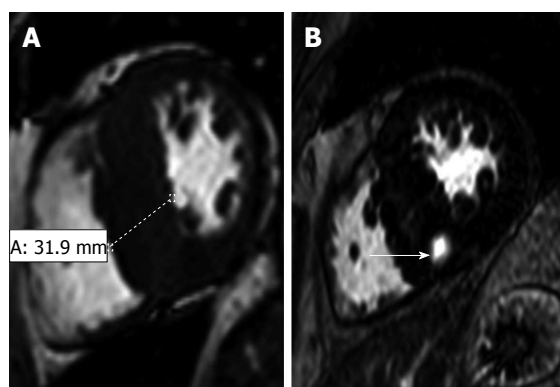


Figure 8 Hypertrophic cardiomyopathy in a 57-year-old man with a 2-year history of exertional dyspnea and chest discomfort who underwent implantable cardioverter-defibrillator placement for primary prevention of sudden cardiac death^[109]. A: Short-axis 2D SSFP magnetic resonance imaging (MRI) performed in end diastole shows asymmetric septal hypertrophy with a maximal thickness of 31.9 mm encroaching on the ventricular lumen; B: Short-axis late contrast-enhanced MRI shows a patchy nodular area of enhancement in the hypertrophied septum (arrow) that does not correspond to a coronary artery territory and, therefore, is distinctly different from an infarct scar.

patients with apical type of HCM^[86]. The ECG abnormalities may not parallel hypertrophy in all cases. Konno *et al*^[73] observed ECG abnormalities (in particular ST-T abnormalities) in about 54% of genetically affected, but nonhypertrophic patients at echocardiography. A normal ECG does not exclude the presence of HCM but suggests a mild manifestation of the disease^[87].

Risk stratification

Identification of high-risk HCM patients is important because of the need to implant an ICD. Several major risk factors of sudden death have been identified to date and these factors are: positive family history of premature SCD caused by HCM, documented nonsustained ventricular tachycardia, syncope at rest or during exercise, abnormal blood pressure response during exercise with increase in the systolic blood pressure of < 20 mmHg from the baseline value, and progressive fall in blood pressure during exercise or a fall in the systolic value by 20 mmHg after an initial increase, particularly in younger patients (< 40 years of age), expressed LVH with wall thicknesses > 30 mm^[88]. The highest rate of cases of SCD in adolescents was linked with pronounced hypertrophy^[88]. Potential additional risk factors include marked fibrosis on cardiac MRI, LV apical aneurysm, LVOT with gradient > 30 mmHg at rest, obstructive sleep apnea^[88].

MANAGEMENT OF HCM

Medical therapy

Many patients with LVOT gradients > 50 mmHg may still be asymptomatic, but most HCM patients have symptoms that need to be managed. β -Blockers represent the cornerstone of therapy and have proved effective in patients with angina or dyspnea on effort, particularly when associated with LVOT obstruction, and are often administered to decrease the frequency of non-

sustained ventricular arrhythmias. These beneficial effects are mediated by negative inotropic, chronotropic effects, improved ventricular relaxation, and increased time for diastolic filling. Despite these advantages, whether long-term treatment with β -blockers ultimately affects outcome in HCM patients remains undefined. By virtue of their efficacy in reducing LVOT obstruction and myocardial ischemia, current guidelines recommend β -blockers as first-line agents in symptomatic patients, both with and without resting obstruction. Two recent studies have consistently shown marked reduction or abolition in exercise-induced LVOT obstruction^[83]. In patients intolerant to β -blockers, verapamil may be a good alternative for treatment of HCM patients. Verapamil and diltiazem have been administered in symptomatic patients with non-obstructive HCM. HCM guidelines suggest caution in using calcium channel blockers in patients with significant LVOT obstruction and elevated pulmonary artery wedge pressure, due to their potentially adverse hemodynamic effects and risk of precipitating edema. The beneficial effects of calcium channel blockers are largely mediated by their negative inotropic and chronotropic effects, leading to prolonged LV filling time and improved redistribution of flow towards the subendocardial layers of the left ventricle. To date, there is no definite evidence that verapamil effectively improves functional capacity in HCM, although the drug has been used for decades to ameliorate quality of life in nonobstructive patients, and is considered standard treatment^[89]. Diltiazem was shown to improve LV diastolic parameters, either acutely or at mid-term administration^[84].

The class IA antiarrhythmic drug disopyramide has been used successfully to attenuate the pressure gradient and improve symptoms in patients with LVOT obstruction, generally in association with β -blockers. The beneficial effect of disopyramide is conditioned by negative inotropic effects, resulting in symptomatic improvement^[90]. Nevertheless, concerns regarding QTc prolongation and significant anticholinergic side effects may limit its long-term use.

Previously it was considered that amiodarone may have a protective role in HCM, with regard to ventricular arrhythmias. However, its efficacy in preventing sudden death is now considered not evident based on the fact that 20% of patients dying suddenly in one retrospective study were on active amiodarone treatment at the time of death^[91].

Several studies showed that approximately two-thirds of patients can be successfully managed by medical therapy with resulting symptoms limitation and decrease of LVOT gradient > 50^[89,91,92].

INTERVENTIONAL THERAPY AND SURGERY

Despite advances and efficacy of medical management of patients with HCM, many patients remain symptomatic and at high risk of SCD, which requires interven-

tional approaches to relieve LVOT obstruction. Alcohol septal ablation may be a suitable approach for patients with advanced age and high surgical risks. The procedure involves injecting 1-3 mL 96% ethanol into one of the septal branches supplying the hypertrophied myocardium, causing acute regional contractile dysfunction and leading to a thinning over the long term. This approach leads to reduction or elimination of the obstruction in 90% of cases. Mortality associated with the procedure is similar to that for myectomy (1%-2%) in experienced centers. High-grade AV block as a complication requiring implantation of a pacemaker is registered in experienced centers in 5% of cases^[93].

Septal myectomy using the Morrow procedure has been defined as the therapy standard for many years for patients with HCM, who cannot be adequately treated by pharmacotherapy. The procedure involves removal of a part of the hypertrophied basal septum or thinning of the remaining septum to 5-8 mm. A reduction or elimination of the gradient was achieved in > 90% of patients. The procedure is indicated in patients with symptoms corresponding to NYHA class III and gradient > 50 mmHg (rest or provocation). Perioperative mortality in experienced centers is 1%-2% and the rate of complete AV blocks postoperatively is 2%-5%^[94].

In patients with HCM, pacing the RV apex and apical septum can cause a decrease in the outflow tract gradient by decreasing the ventricular contractility, with a decrease in systolic movement of the basal septum to the LVOT. Continuous pacing with the development of LV enlargement may further decrease LVOT gradient. Dual chamber pacing has shown modest benefit in randomized controlled trials. It is mostly indicated in patients > 65 years of age, those who have indication for pacemaker or ICD implantation, and those who have a high risk of surgery^[95].

RESTRICTIVE CARDIOMYOPATHIES

Restrictive cardiomyopathy is a disease of the myocardium characterized by impaired ventricular filling and reduced diastolic volume of either or both ventricles, with normal or near-normal systolic function.

Unlike DCM and HCM, where the definition is morphological, the definition of restrictive cardiomyopathy is based on hemodynamic abnormalities. Myocardial relaxation abnormality with interstitial fibrosis and calcifications compose the fundamental abnormalities of restrictive cardiomyopathies. Restrictive filling is due to higher diastolic pressure and causes passive venous congestion. Cardiac output can be increased by an increase of heart rate, but becomes ineffective due to shortened filling time.

PREVALENCE

Restrictive cardiomyopathies form 5% of pediatric cardiomyopathies, but several types are more common in

certain populations. For example, EMF is a relatively common cause of heart failure in equatorial Africa^[96].

PATHOPHYSIOLOGY AND CLINICAL MANIFESTATIONS

These conditions result in impaired ventricular filling and primarily diastolic heart failure. They manifest with a clinical heart failure syndrome frequently indistinguishable from that caused by systolic dysfunction. AV block and symptomatic bradycardia can be seen, often indicating pacemaker insertion. Atrial fibrillation is poorly managed by conventional therapy.

Restrictive cardiomyopathies may be classified as primary (*e.g.*, EMF, Löffler's endocarditis, and idiopathic restrictive cardiomyopathy) or secondary. Causes of secondary restrictive cardiomyopathy include infiltrative diseases (*e.g.*, amyloidosis, sarcoidosis, and radiation carditis) and storage diseases (*e.g.*, hemochromatosis, glycogen storage disorders, and Fabry's disease). Fabry's disease, although rare, has assumed a new importance as effective therapy became possible.

Physical examination in restrictive cardiomyopathies may reveal congestive heart failure signs: peripheral edema, jugular vein distensions, and gallop rhythm. Echocardiographic typical signs of restrictive cardiomyopathy are normal ventricular dimensions with dilated atria as a feature of systemic venous congestion, normal or nearly normal systolic function. Myocardial calcifications are typical for EMF. Some patterns revealed by echocardiography may indicate etiology like granular sparkling of myocardium in amyloidosis (Figure 9), endocardial thickening and thrombus in eosinophilic endocardial disease and EMF.

Doppler features of restrictive cardiomyopathy are high early filling E/A wave ratio > 2, short isovolumic relaxation time < 60 ms, short deceleration time < 150 ms, and expressed pulmonary ravenous reversal flow^[97]. The treatment of restrictive cardiomyopathy patients is mainly symptomatic with diuretics and aldosterone antagonists. Severity of heart failure symptoms and absence of efficacy are the indications for cardiac transplantation^[98].

SPECIFIC TYPES OF RESTRICTIVE CARDIOMYOPATHIES

Amyloidosis

Amyloid heart disease is classified as primary, secondary, familial, or senile. Primary amyloid heart disease is caused by overproduction of amyloid light chain immunoglobulin from a monoclonal population of plasma cells, usually associated with multiple myeloma. Secondary amyloid heart disease is associated with chronic inflammatory conditions such as rheumatoid arthritis, tuberculosis, and familial Mediterranean fever^[99,100].

Familial and senile amyloid heart disease is related to the overproduction of transthyretin. Myocardial amyloid



Figure 9 Patient with secondary cardiac amyloidosis due to familial Mediterranean fever. Echocardiogram shows hypertrophic amyloid infiltration and increased hyperechogenic “granular sparkling” myocardium with increased myocardial wall thickness.

heart disease is confirmed by EMB (Figure 10). The presence of near-normal LV dimensions combined with increased myocardial wall thickness, particularly biventricular thickening, should arouse suspicion of an infiltrative cardiomyopathy, especially if accompanied by low-voltage QRS complexes on ECG. Unfortunately, there is no proven treatment for cardiac amyloidosis and the prognosis remains poor.

HEMOCHROMATOSIS

Hemochromatosis (“bronze diabetes”) is a disease that results in iron overload and deposition of iron in the sarcoplasmic reticulum of many organs, including the heart. Most commonly it has autosomal recessive type of Mendelian inheritance. Typically, this disorder has multi-system manifestations. Erythropoiesis remains normal, but progressive parenchymal iron deposition causes multi-organ insufficiencies. Excess of cellular iron leads to cellular death and fibrosis^[101]. The use of serum ferritin levels as a screen for this condition may be clinically important. Cardiac MRI can have diagnostic value to reveal cardiac involvement. Hemochromatosis may result in a restrictive or dilated cardiomyopathy, with characteristic histological features. Treatment is by repeated phlebotomy. Family screening is advised.

SARCOIDOSIS

Sarcoidosis is a systemic disease resulting in the formation of noncaseating granulomas that can infiltrate the myocardium. It is associated with restrictive cardiomyopathy in 5% of patients, but may later progress to DCM^[102]. It is difficult to diagnose unless there is other organ involvement (usually pulmonary). It may be suspected in patients with cardiomyopathy and lymphadenopathy, skin rashes, or splenomegaly. Cardiac sarcoidosis is associated with ventricular tachycardia and conduction abnormalities (especially complete heart block) that can cause syncope and SCD. EMB may show findings specific for sarcoidosis but, because of the patchy nature of the disease, biopsy

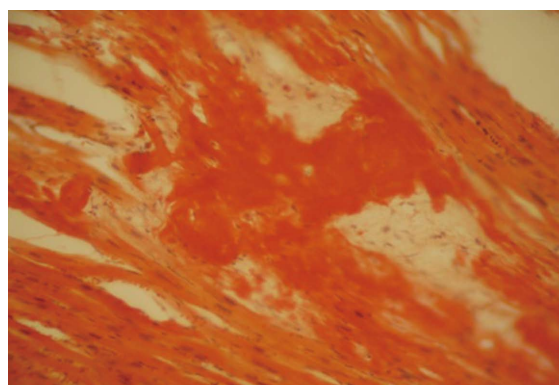


Figure 10 Amyloid deposits in myocardium in patient with secondary amyloidosis due to familial Mediterranean fever. Autopsy study with Congo-Red-positive extracellular deposits, causing disorder of myocardial organization.

may miss characteristic lesions, resulting in a low overall sensitivity. Cardiac granulomas may occasionally respond to steroids but turn to scar tissue^[103]. Sudden death cannot be prevented by steroids^[104]. Regular Holter monitoring is recommended to look for AV blocks, which should be treated with permanent pacemakers.

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Pulmonary arterial hypertension related to human immunodeficiency virus infection: A case series

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Abstract

AIM: To present 18 new cases of human immunodeficiency virus (HIV)-related pulmonary arterial hypertension (PAH) with presenting features, treatment options and follow-up data.

METHODS: This is a single-centre, retrospective, observational study that used prospectively collected data, conducted during a 14-year period on HIV-related PAH patients who were referred to a pulmonary hy-

pertension unit. All patients infected with HIV were consecutively admitted for an initial evaluation of PAH during the study period and included in our study. Right heart catheterisation was used for the diagnosis of PAH. Specific PAH treatment was started according to the physician's judgment and the recommendations for idiopathic PAH. The data collected included demographic characteristics, parameters related to both HIV infection and PAH and disease follow-up.

RESULTS: Eighteen patients were included. Intravenous drug use was the major risk factor for HIV infection. Risk factors for PAH, other than HIV infection, were present in 55.5% patients. The elapsed time between HIV infection and PAH diagnoses was 12.2 ± 6.9 years. At PAH diagnosis, 94.1% patients had a CD4 cell count > 200 cells/ μ L. Highly active antiretroviral therapy (present in 47.1% patients) was associated with an accelerated onset of PAH. Survival rates were 93.8%, 92.9% and 85.7% at one, two and three years, respectively. Concerning specific therapy, 33.3% of the patients were started on a prostacyclin analogue, and the rest were on oral drugs, mainly phosphodiesterase-5 inhibitors. During the follow-up period, specific therapy was de-escalated to oral drugs in all of the living patients.

CONCLUSION: The survival rates of HIV-related PAH patients were higher, most likely due to new aggressive specific therapy. The majority of patients were on oral specific therapy and clinically stable. Moreover, sildenafil appears to be a safe therapy for less severe HIV-related PAH.

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Key words: Human immunodeficiency virus infection; Pulmonary arterial hypertension; Treatment

Core tip: Human immunodeficiency virus (HIV)-related

pulmonary arterial hypertension (PAH) is a rare disease, and HIV-infected patients are seldom included in clinical trials. Therefore, case reports are crucial to better understand this disease and its response to specific therapies. In this retrospective, observational study, 18 HIV-related PAH patients were included. Highly active antiretroviral therapy was associated with an accelerated onset of PAH. The survival rates of HIV-related PAH patients were higher, most likely due to new aggressive specific therapy. The majority of patients were on specific oral therapy and were clinically stable. Furthermore, sildenafil appears to be a safe option for less severe disease.

Araújo I, Enjuanes-Grau C, Lopez-Guarch CJ, Narankiewicz D, Ruiz-Cano MJ, Velazquez-Martin T, Delgado J, Escibano P. Pulmonary arterial hypertension related to human immunodeficiency virus infection: A case series. *World J Cardiol* 2014; 6(6): 495-501 Available from: URL: <http://www.wjgnet.com/1949-8462/full/v6/i6/495.htm> DOI: <http://dx.doi.org/10.4330/wjc.v6.i6.495>

INTRODUCTION

Pulmonary arterial hypertension (PAH) is a progressive disease that is caused by the chronic obstruction of small pulmonary arteries, leading to right ventricular failure and potential death^[1]. Idiopathic and inherited forms have been described. However, this condition is associated with connective tissue diseases, portal hypertension, congenital heart disease, drugs, toxins and human immunodeficiency virus (HIV) infection^[2].

Before the introduction of highly active antiretroviral therapy (HAART), HIV-related PAH was underdiagnosed due to the patients' short survival, which was primarily caused by opportunistic infections. After the introduction of this novel antiretroviral therapy scheme, long-term cardiovascular complications, such as PAH, have emerged^[3].

The first case of HIV-related PAH was described in 1987 in an HIV-infected subject with haemophilia and membranoproliferative glomerulonephritis^[4]. Subsequently, several other cases have been reported. Nonetheless, HIV-related PAH is a rare disease: in 1991, prior to the introduction of HAART, the prevalence of HIV-related PAH was estimated to be 0.5% in developed countries^[5]. This rate is 25-fold higher than the prevalence of PAH in the general population^[6].

Recent studies have shown that prevalence has not changed in recent years. As described by Sitbon *et al*^[7], the prevalence is 0.46%, suggesting that HAART does not prevent HIV-related PAH. However, because most published studies do not include asymptomatic patients, the actual prevalence could be higher. In 2008, Reinsch *et al*^[8] found that the prevalence in asymptomatic patients is 4.8%, although the diagnosis of PAH was only based on echocardiographic parameters. HIV-related PAH is clinically

and histologically similar to idiopathic PAH^[3].

The aim of this study is to present 18 new cases of HIV-related PAH with presenting features, treatment options and follow-up data.

MATERIALS AND METHODS

This is a single-centre, retrospective, observational study using prospectively collected data that was conducted over a 14-year period between June 1998 and June 2012.

All HIV-infected patients consecutively admitted to the Pulmonary Hypertension Unit of Hospital 12 De Octubre for an initial evaluation of PAH during the study period were included in our study.

PAH was diagnosed with right heart catheterisation and defined by a resting mean pulmonary arterial pressure of more than 25 mmHg and a pulmonary capillary wedge pressure of less than 15 mmHg. Poor prognostic factors included a right atrium pressure (RAP) > 15 mmHg and a cardiac output ≤ 2.0 mL/min^[2,9].

No specific recommendations for the treatment of PAH-HIV have been made thus far; therefore, specific PAH treatment was initiated according to the physician's judgment and the recommendations for idiopathic PAH treatment. HAART is a combination of at least 3 antiretroviral drugs, such as 3 nucleoside reverse transcriptase inhibitors, 2 nucleoside reverse transcriptase inhibitors and 1 protease inhibitor or 2 nucleoside reverse transcriptase inhibitors and 1 non-nucleoside reverse transcriptase inhibitor.

All patients received nonspecific supportive therapy as recommended, unless such therapy was contraindicated or not necessary: oral anticoagulation to maintain an international normalised ratio of 2.0-3.0, long-term oxygen therapy if there was evidence of hypoxemia and diuretic therapy for right heart failure symptomatic control.

Baseline evaluation included an assessment of the NYHA functional class, 6-Minute Walk Distance (6MWD) and echocardiogram. A re-evaluation of right heart catheterisation was only performed if clinical worsening occurred. Follow-up was conducted indefinitely for alive patients or until death.

The data collected included demographic characteristics (age, gender), parameters related to both HIV infection and PAH and disease follow-up. The date of PAH diagnosis was used as the baseline for survival estimates.

Because patients had already consented to be included in the PAH national registry, no additional informed consent was needed for this sub-study.

Statistical analysis

Standard descriptive statistics were used. Variables such as New York heart association (NYHA) functional class and 6MWD were compared using the paired-sample *t*-test. Due to the small population size, univariate analysis was not possible.

All statistical tests were performed using SPSS for Windows (version 16.0: SPSS, Chicago, IL, United States).

Table 1 Patients' demographic and clinical characteristics at pulmonary hypertension diagnosis

Case No.	Age, yr	Gender	HIV risk factor	Duration of HIV infection previous to PAH, yr	CD4 count, cells/ μ L	HIV viral load, copies/mL	CDC stage	HAART	History of viral hepatitis	Other PAH risk factors	NYHA FC
1	25	F	IVDU	12	339	< 50	B3	No	Hep C	None	IV
2	39	F	IVDU	4	700	< 50	A1	No	Hep B + C	None	II
3	39	M	IVDU	11	460	< 50	B3	Yes	No	ASD	III
4	32	M	IVDU	12	500	< 50	B2	No	Hep C	ASD	III
5	43	M	UK	7	397	< 50	B3	Yes	No	Splenectomy without CTEPH	III
6	45	M	IVDU	8	332	< 50	B3	Yes	Hep B+C	Portal Hypertension	II
7	40	F	IVDU	22	517	< 50	C3	UK	Hep C	None	II
8	31	F	Hetero-sexual	1	444	< 50	A2	Yes	No	None	III
9	40	M	IVDU	22	900	3000	A1	No	Hep C	None	II
10	41	M	IVDU	21	772	308	A2	No	Hep C	None	II
11	40	M	IVDU	10	460	359810	A1	Yes	Hep C	Portal Hypertension	III
12	40	F	UK	5	46	114	C3	No	Hep C	Portal Hypertension	III
13	39	M	IVDU	10	1234	< 50	B1	Yes	Hep C	None	III
14	46	M	IVDU	14	411	< 50	A2	Yes	Hep C	Portal Hypertension	II
15	47	F	IVDU	14	800	< 50	A1	No	Hep C	ASD	III
16	47	M	IVDU	4	450	< 20	A2	Yes	Hep C	None	II
17	47	F	IVDU	23	760	< 20	C2	No	Hep B + C	Portal Hypertension	II
18	43	M	UK	19	NA	NA	A2	No	No	Portal Hypertension	III

ASD: Atrial septal defect; CDC: Centers for disease control; CTEPH: Chronic thromboembolic pulmonary hypertension; F: Female; M: Male; HAART: Highly active anti-retroviral therapy; HIV: Human immunodeficiency virus; IVDU: Intravenous drug use; NA: Not accessible; NYHA FC: New York heart association functional class; PAH: Pulmonary arterial hypertension; UK: Unknown.

RESULTS

Eighteen patients were admitted to our centre during the study period, and their baseline characteristics are listed in Table 1. Male gender was predominant (61.1%), and the mean age was 40.2 years (range 25-47 years).

Concerning HIV infection, intravenous drug use was the major risk factor for infection (77.8%). At PAH diagnosis, only 16.7% were in Centers for Disease Control and Prevention stage C. The mean CD4 cell count was 554 ± 267 cells/ μ L, with only one patient having a CD4 cell count < 200 cells/ μ L. The viral load was undetectable in 76.5% of the patients.

The mean time interval between HIV infection diagnosis and PAH diagnosis was 12.2 ± 6.9 years (range 1-23 years). Approximately half of the patients were on HAART; among those who were not on HAART, only three patients had an indication for HIV treatment before the diagnosis of PAH (one was not under treatment at all due to poor adherence, and the other two took only two drugs: a non-nucleoside reverse transcriptase inhibitor and a protease inhibitor). There is a statistically significant acceleration in the onset of PAH in patients on HAART ($P = 0.012$).

Concomitant viral hepatitis (either C or C and B) was present in 77.8% of the patients. In 55.5% of the patients, other risk factors for PAH were identified (Table 1), including portopulmonary hypertension, splenec-

tomy and congenital heart defects. An atrial septal defect (ASD) was present in three patients: two patients had the ostium secundum type with a bidirectional shunt and a diameter of 1.8 and 0.7 cm, and the other patient had Eisenmenger's syndrome due to a sinus venosus type ASD with a 3.0 cm diameter. At PAH diagnosis, 55.6% of the patients were in the NYHA functional classes III-IV. Shortness of breath was the most prevalent symptom (present in all patients), followed by chest pain (27.8%), syncope (22.2%) and peripheral oedema and ascites (5.6%).

Exercise capacity was assessed by the 6MWD (Table 2), with a mean achieved distance of 436 ± 113 m. All but one patient walked 300 m or more at diagnosis. There was an overall improvement in the test, but no significant difference was found among the patients with or without HAART ($P = 0.401$).

Hemodynamic parameters, as assessed by right heart catheterisation, showed a mean pulmonary artery pressure (mPAP) of 52.6 ± 12.2 mmHg (17.6% of patients had a mPAP between 35-40 mmHg, 23.5% were between 41-45 mmHg and 58.8% were > 45 mmHg), a RAP of 6.1 ± 3.8 mmHg (none of the patients were > 15 mmHg) and a cardiac output of 4.6 ± 1.4 mL/min (11.7% of the patients with a cardiac output ≤ 2.0 mL/min).

The mean follow-up period was 5.8 ± 4.2 years, with a minimum of 0.3 and a maximum of 11.8 years (Table 2). Overall, the patients had an improved NYHA functional class, with a reduction of approximately half a functional

Table 2 Patients' follow-up data

Case No.	Actual status	Period of follow-up, yr	Year of PAH diagnosis	Initial specific therapy	Last visit specific therapy	Initial 6MWT (m)	Final 6MWT (m)	Variation on NYHA FC
1	Dead (cause: heart failure)	2.8	1998	Epoprostenol	Epoprostenol	211	463	0
2	Alive	11.3	2001	Treprostinil	Sildenafil	NA	669	-1
3	Alive	10.8	2001	Sildenafil	Sildenafil + Ambrisentan	512	630	-1
4	Alive	9.9	2002	Sildenafil	Sildenafil + Ambrisentan + Iloprost	516	570	-2
5	Alive	11.3	2001	Treprostinil	Sildenafil	313	414	0
6	Dead (cause: liver disease)	0.3	2005	Sildenafil	Sildenafil	400	NA	NA
7	Alive	7.0	2005	Ambrisentan	Ambrisentan + Sildenafil	435	473	0
8	Missing	3.9	2006	Sildenafil	Sildenafil	300	511	-2
9	Alive	5.3	2006	Sildenafil	Sildenafil	455	546	0
10	Alive	4.5	2007	Sildenafil	Tadalafil	650	703	0
11	Alive	8.5	2003	Treprostinil	Tadalafil	510	570	-2
12	Alive	8.8	2003	Iloprost	Ambrisentan	NA	450	-1
13	Alive	11.8	2000	Treprostinil	Bosentan	327	489	-1
14	Missing	0.4	2005	Sildenafil	Sildenafil	500	NA	0
15	Alive	3.5	2008	Sildenafil + Bosentan	Sildenafil + Bosentan + Iloprost	350	420	0
16	Alive	1.6	2010	Tadalafil	Tadalafil	525	570	0
17	Alive	1.4	2011	Ambrisentan	Ambrisentan	439	423	0
18	Alive	0.5	2011	Sildenafil	Sildenafil	537	600	0

6MWT: 6 min walk test; NYHA FC: New York heart association functional class; NA: Not accessible; PAH: Pulmonary arterial hypertension.

class per patient ($P = 0.008$) and an improvement of 85 m on the 6MWD ($P = 0.002$). Functional class improvement was not dependent on HAART therapy ($P = 0.343$).

At PAH diagnosis, six (33.3%) patients were started on prostacyclin analogues. One patient was started on epoprostenol but died due to right heart failure. Recurrent infections of the Hickman catheter, which the patient used for drug abuse, might have played a role. At the last registered visit, the other five patients had clinically improved and reduced the specific therapy to oral drugs, such as phosphodiesterase-5 inhibitors and endothelin receptor antagonist (Table 2).

All but one of the remaining patients were started on specific oral monotherapy. On their most recent follow-up, these patients were on the same therapy, except for four patients who needed other specific drugs (two were started on dual combined therapy, and the other two were started on triple combined therapy). An improvement in NYHA functional class and 6MWD was observed in half and all of these patients, respectively. Specific oral therapy was well tolerated in all patients, without any major documented adverse reactions, except elevated liver enzymes in one patient on sildenafil, in whom the specific therapy was changed to tadalafil.

Concerning survival during the follow-up period, two patients died (11.1%), but only one death was related to PAH (right heart failure); this patient had one of the lowest CD4 cell counts (339 cells/ μ L). The other, as already discussed, had the worst NYHA functional class at PAH diagnosis; this death was related to chronic liver disease, and the patient died soon after PAH diagnosis. Two patients were lost to follow-up (Table 2). At 1, 2 and

3 years, the survival rates were 93.8%, 92.9% and 85.7%, respectively.

DISCUSSION

This study reports data on 18 HIV-infected patients diagnosed with PAH. HIV-infected patients are at a higher risk of developing PAH compared with the general population. Nevertheless, the global prevalence of this disease is low, and HIV-infected patients are rarely included in clinical trials because of the risk of interaction between PAH therapies and anti-retrovirals and the presence of multiple comorbidities in HIV-infected patients. Therefore, case reports and case series have become crucial to determine the characteristics of the disease and the efficacy of therapy. Despite our small number of patients, a major contribution with regard to survival rates and specific therapy can be made. In our study group, male gender was predominant, which is concordant with other authors and may reflect the high prevalence of men in the HIV population^[10-12]. However, in a recent cross-sectional study of 802 HIV-infected patients, 14 patients had symptomatic PAH, and women were more affected, with a male: female ratio of 1:1.4^[8]. Age at diagnosis did not differ from other studies that have reported a mean age ranging from 32 to 43 years^[6,10-14].

Intravenous drug use was the most prevalent risk factor among HIV-infected patients with PAH (77.8% of the patients). This high prevalence was also described in other studies^[10,12,13,15]. Nonetheless, patients with PAH related to HIV infection acquired *via* intravenous drug abuse have no clinical, functional or hemodynamic speci-

ficiencies, compared with patients with PAH related to HIV infection from any other route of transmission^[15].

The mean CD4 count at the time of PAH diagnosis was somewhat higher than those observed in other studies, with only one patient (5.8%) having a CD4 cell count < 200 cells/ μ L; the viral load was undetectable in the majority of patients. A CD4 cell count < 200 cells/ μ L was observed in 59.6% and 52% of patients in the studies of Zuber *et al.*^[12] and Nunes *et al.*^[15], respectively. This difference may reflect the efficacy of the actual antiretroviral therapy. Hence, HIV-related PAH occurs in the early and late stages of HIV infection and may not be related to viral load or immune status, partially demonstrating that HAART does not prevent PAH^[6,8,15].

The median time interval between the diagnoses of HIV disease and PAH, as described in literature, has ranged from 2.8 to 7.7 years^[6,10-12,15], which is much shorter than the time interval determined in our study (11.5 years). Degano *et al.*^[13] also described a more prolonged time interval (11 years), suggesting that HAART does not prevent but may delay the development of PAH in HIV-infected patients. However, in our study, HAART was found to accelerate the onset of PAH, and this finding has been corroborated by Reinsch *et al.*^[8] and Pellicelli *et al.*^[16]. This may be due to a closer monitoring of patients on HAART, enabling an earlier PAH diagnosis.

In our population, 55.5% of the patients had another PAH risk factor other than HIV infection, including atrial septal defect, splenectomy and portal hypertension, which differs from the results of other papers. In the study by Humbert *et al.*^[17], approximately 4% of PAH patients presented with two co-existing risk factors, mainly HIV infection with portal hypertension. Mesa *et al.*^[18] reported that 13% of the HIV-related PAH patients had coexistent liver disease. Other causes of PAH and chronic thromboembolic pulmonary hypertension were not reported in our patients and have been rarely reported in HIV-infected patients^[19].

The majority of the patients in our study were in a high NYHA functional class, which is consistent with other authors who have reported 71%-81% of patients in the NYHA classes III-IV at diagnosis^[15,17].

The survival rates were far better than those described in the literature. During the follow-up period of 5.8 ± 4.2 years, 12.5% patients died, and the survival rates at one, two and three years was 93.8%, 92.9% and 85.7%, respectively. In the study by Degano *et al.*^[13], the survival rates were closely related to our findings: 88%, 84%, 72% and 63% at one, two, three and five years, respectively, but others have reported lower survival rates^[14,15,20]. Mortality in patients with HIV-related PAH is usually due to right heart failure, rather than other complications of HIV infection, and PAH is considered an independent predictor of death in HIV-infected patients^[10,15]. This finding may relate to the fact that most of these individuals present in the later stages of PAH. In our study, the patient who died due to right heart failure had the worst NYHA functional class and showed no functional or hemodynamic improvement despite ag-

gressive therapy.

Apart from the effect on PAH development, HAART has been described to influence prognosis. In our population, the improvement in NYHA functional class did not differ between the groups, nor did exercise capacity, as measured by 6MWD. Concerning mortality, the patient who died due to right heart failure was not on HAART; the other patient who died was on HAART, but the cause of death was liver failure. HAART has been associated with an improvement in exercise capacity, NYHA functional class, right ventricular systolic pressure over right atrial pressure gradient and overall survival^[11-14,21,22]. However, there is also contradictory data stating that patients without HAART have no reduction in survival^[23]. No current trial has been designed to evaluate the effect of HAART on the progression of HIV-PAH, but due to the weight of scientific information favouring HAART, patients with HIV-related PAH should be treated with HAART, irrespective of their CD4 cell counts^[14]. This suggestion is also supported by our study.

An analysis of the cases of HIV-related PAH reported in the literature (from January 1987 to January 2009) showed a better outcome in patients treated with PAH-specific therapy than in those treated with just antiretroviral therapy^[24]. Regardless of the substantial progress in therapy over the last few years, no randomised study has established a drug of choice for the treatment of HIV-related PAH. The evidence for the use of bosentan and prostaglandin therapies comes from cohort studies, case-control studies or case series. Therefore, the treatment of HIV-related PAH relies on PAH-specific therapy and includes supportive treatments and disease-specific treatments.

In our population, six of the 18 patients were started on prostacyclin analogues. These were patients with worse functional status who were diagnosed between 1998 and 2003, when prostacyclin analogues were the only recommended specific therapy for PAH. Only one of these patients was on epoprostenol due to advanced disease. The other patients were started on either iloprost or treprostinil. The beneficial effects of this drug class have been demonstrated in patients with HIV-related PAH. Our patients on iloprost and treprostinil have shown an improvement in NYHA functional class, and treatment was de-escalated to oral drugs. De-escalation to specific oral therapy can be attempted in stable patients with good long-term progress. Favourable results have been noted when switching from prostacyclin and its analogues to bosentan, with the clinical stability and pulmonary pressure measurements being maintained^[25]. Similarly, transitioning from subcutaneous treprostinil to sildenafil was safely demonstrated in patients with PAH of varied aetiologies^[26].

Sildenafil was the most commonly used drug among our patients (61.1%), though tadalafil was also used (16.6%). In the majority of patients, the clinical results were satisfactory. However, the experience with phosphodiesterase-5 inhibitors in HIV-related PAH is preliminary, and no controlled studies exist. Beneficial effects derived

from case studies have been reported, including improvements in dyspnoea, NYHA functional class, exercise capacity and mPAP^[27-29]. However, because sildenafil is largely metabolised by cytochrome P450 3A4, there is a potential for drug interactions when it is co-administered with several antiretroviral therapies, particularly protease inhibitors. Therefore, sildenafil is rarely used. In a review of 154 case reports by Janda *et al.*^[11], phosphodiesterase-5 inhibitors were the least commonly used therapy and were only an option for patients who did not tolerate bosentan. Our study reinforces the benefits of sildenafil HIV-related PAH therapy, and few adverse events were reported.

This study has some limitations. This is a retrospective study conducted in a single centre, with possible biases. However, it would be ethically impossible to perform a prospective study designed to compare novel therapies such as prostacyclin analogues with less active treatments in a cohort of patients with HIV-related PAH. Because HIV-related PAH is a rare disease, few patients were included in this study, thus any analyses should be considered cautiously.

To summarise, this study adds important information to what has been reported in the literature. Survival rates of HIV-related PAH patients tend to be higher, which may be due to new aggressive specific therapies, such as prostanoids, but not to HAART. The majority of the patients were treated with specific oral therapy, even those primarily treated with prostacyclin analogues.

The onset and rapid progression of shortness of breath and other cardiopulmonary symptoms in HIV-infected individuals should suggest HIV-related PAH. A systematic cardiopulmonary evaluation and follow-up in specialised centres should be incorporated into the clinical management of HIV-infected patients to enhance quality of life, exercise capacity and survival through the delivery of HAART and specific therapy.

COMMENTS

Background

Pulmonary arterial hypertension (PAH) is a progressive disease that is caused by the chronic obstruction of small pulmonary arteries, leading to right ventricular failure and potential death. Idiopathic and inherited forms have been described.

Research frontiers

After the introduction of this novel antiretroviral therapy scheme, long-term cardiovascular complications, such as PAH, have emerged. The first case of human immunodeficiency virus (HIV)-related PAH was described in 1987 in an HIV-infected subject with haemophilia and membranoproliferative glomerulonephritis. Subsequently, several other cases have been reported. Nonetheless, HIV-related PAH is a rare disease: in 1991, prior to the introduction of highly active antiretroviral therapy (HAART), the prevalence of HIV-related PAH was estimated to be 0.5% in developed countries. This rate is 25-fold higher than the prevalence of PAH in the general population.

Innovations and breakthroughs

Recent studies have shown that prevalence has not changed in recent years. This study was designed to present 18 new cases of HIV-related PAH with presenting features, treatment options and follow-up data.

Applications

In this series, the survival rates of HIV-related PAH patients tended to be higher,

but this difference was not related to HAART. The majority of patients were treated with specific oral therapy, even in those who were primarily treated with prostacyclin analogues. The onset and rapid progression of shortness of breath and other cardiopulmonary symptoms in HIV-infected individuals can suggest HIV-related PAH, and its prompt identification and treatment can improve quality of life, exercise capacity and survival.

Term explanation

HAART: the use of multiple drugs that act on different viral targets to decrease the patient's total burden of HIV, to maintain the immune system's function and to prevent opportunistic infections. Prostacyclin analogues (epoprostenol, iloprost and treprostinil): drugs used in pulmonary arterial hypertension that reduce pulmonary pressure and improve right ventricular stroke work.

Peer review

This is an excellent review of 18 cases about PAH related to HIV infection. The authors have stated the differences with previous studies, including the time interval between the HIV and PAH diagnoses, PAH risk factors other than HIV infection, HAART, specific therapy and survival rates.

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Respiratory modulation of cardiac vagal tone in Lyme disease

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CONCLUSION: Respiratory modulation of cardiac vagal tone is impaired in Lyme disease, which suggests that Lyme disease may directly affect the vagus nerve or the brainstem.

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Key words: Cardiac vagal tone; Lyme disease

Core tip: Given that immune dysfunction, postural orthostatic tachycardia syndrome, fatigue, cognitive dysfunction, orthostatic palpitations, syncope, and stress, which may occur in Lyme disease, are associated with parasympathetic activity and reduced modulation of cardiac vagal tone, we hypothesized that modulation of cardiac vagal tone is impaired in this disease. This was confirmed in our study of 18 patients and 18 matched controls. Cardiac vagal tone is reflexly generated through arterial baroreceptor stimulation, by the afferents of the latter facilitating cardiac vagal motoneuron discharge relaying through interneurons in the nucleus tractus solitarius, implying that Lyme disease may directly affect the vagus or brainstem.

Abstract

AIM: To conduct the first systematic test of the hypothesis that modulation of cardiac vagal tone is impaired in Lyme disease.

METHODS: The response of cardiac vagal tone to respiratory modulation was measured in 18 serologically positive Lyme disease patients and in 18 controls.

RESULTS: The two groups were matched in respect of age, sex, body mass, mean arterial blood pressure, mean resting heart rate and mean resting cardiac vagal tone. The mean maximum cardiac vagal tone during deep breathing in the Lyme disease patients [11.2 (standard error 1.3)] was lower than in the matched controls [16.5 (standard error 1.7); $P = 0.02$].

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INTRODUCTION

Lyme disease or Lyme borreliosis is an arthropod-borne zoonosis caused by *Borrelia* spirochetes, the incidence of which has recently been increasing with the geographical spread of infected ticks and which was previously identified clinically in Europe as Garin-Bujadoux-Bannwarth syndrome and in the United States as Lyme arthritis^[1-3]. There is growing evidence for the role of the autonomic

nervous system in a wide range of diseases^[4] and autonomic instability has been reported in Lyme disease^[5] but has not, thus far, been systematically studied in this illness. It has recently been reported that a series of five female Lyme disease patients developed postural orthostatic tachycardia syndrome; they suffered from symptoms of fatigue, cognitive dysfunction, orthostatic palpitations and either near syncope or frank syncope^[6]. Again, a case report has been published of a 16-year-old female patient with clinical, radiological and scintigraphic features consistent with reflex sympathetic dystrophy associated with Lyme disease^[7].

Given that immune dysfunction, postural orthostatic tachycardia syndrome, fatigue, cognitive dysfunction, orthostatic palpitations, syncope, and stress, which may occur in Lyme disease^[6-11], are associated with parasympathetic activity and reduced modulation of cardiac vagal tone (or the related measure of heart rate variability)^[4,12-14], we hypothesized that modulation of cardiac vagal tone might be impaired in this illness. The aim of our study was to test this hypothesis by comparing the response of cardiac vagal tone to respiratory modulation in a sample of Lyme disease patients and matched controls. To the best of our knowledge, this was the first such study.

MATERIALS AND METHODS

The arterial blood pressure, resting cardiac rate, resting cardiac vagal tone, and the cardiac vagal tone following deep breathing were measured in 18 serologically positive Lyme disease patients who were undergoing routine clinical investigation, and in 18 normal controls; all subjects were asked to refrain from any caffeine-containing beverages from midnight before testing. For inclusion in this study, the Lyme disease patients, who were selected from outpatient attendees, were required to be IgM positive for Lyme disease and to be aged 18 years or over. The control subjects were identified as subjects who were not suffering from any autonomic nervous system dysfunction (dysautonomia) or from any condition that might directly or indirectly affect the autonomic nervous system, and were recruited from hospital staff, and from friends and family of staff members. The exclusion criteria for the normal controls included: under 18 years of age; subjects with dysautonomia; taking medications that affect the autonomic nervous system, such as stimulants, tricyclic antidepressants, anti-histaminergic medication, calcium-channel blockers, beta-adrenoceptor blocking drugs, beta agonists, monoamine oxidase inhibitors, levodopa, anti-psychotic drugs, clonidine and vasopressin; medical problems that affect the autonomic nervous system, such as neurodegenerative disorders, peripheral neuropathies, diabetes, connective tissue disease and infectious diseases. The clinical stage and presentation of the patients were early, presumed localized and without cardiac involvement (that is, without clinical evidence of Lyme carditis). As there has been no previous work in this area, it was not possible to calculate the value of beta, and therefore

calculate the statistical power, for this study. Written informed consent was obtained and a local research ethics committee approved the study. The study was carried out in accordance with the Declaration of Helsinki.

Resting cardiac rate and cardiac vagal tone were measured in real time using the NeuroScope Model 300BA (Brainstem Autonomic Function Monitor) (Medifit Instruments Ltd, London, United Kingdom) as described by Little *et al*^[15] and during a 10-s cycle of deep breathing as described by Julu *et al*^[16]. In particular, the non-invasive cardiac vagal tone was measured on a continuous, beat-to-beat basis and was defined as pulse-synchronized phase shifts in consecutive cardiac cycles; it is essentially a form of pulse interval variability which is quantified continuously from the electrocardiogram. The index of cardiac vagal tone was measured and quantified in arbitrary units of a linear vagal scale; the minimum value of this scale is zero, which corresponds to full atropinisation of human subjects.

Arterial blood pressure was measured using the Ohmeda 2300 Finapres (Ohmeda, Englewood, CO, United States).

Continuous variables for which data did not differ significantly from normality and for which the two groups did not have significantly different variances were compared between the Lyme disease and control groups using independent samples *t*-tests (equal variances), while the discrete nominal variable (sex) was compared between groups using Fisher's exact probability test. The software package IBM SPSS Statistics for Windows, Version 20.0 (IBM Corp, Armonk, NY, United States) was used for the statistical analyses.

RESULTS

The main findings are shown in Table 1. The two groups were matched in respect of age, sex, body mass, mean arterial blood pressure, mean resting heart rate, and mean resting cardiac vagal tone.

Details of the heart rate for each of the 18 patients before, during, and following the deep breathing procedure are provided in Table 2.

Corresponding details of the heart rate for each of the 18 control subjects before, during, and following the deep breathing are provided in Table 3.

The mean (\pm standard error) maximum cardiac vagal tone during deep breathing in the Lyme disease patients (11.2 ± 1.3) was significantly lower than that in the matched controls (16.5 ± 1.7 ; $P = 0.02$); these data are illustrated in Figure 1.

DISCUSSION

This study has demonstrated impairment of respiratory modulation of cardiac vagal tone in Lyme disease. This is an original finding which has not previously been described.

At the outset, it should be noted that our results demonstrate impaired respiratory modulation of cardiac vagal tone in Lyme disease; this is not the same as show-

Table 1 Main findings

	Lyme disease patients <i>n</i> = 18 mean (standard error)	Controls <i>n</i> = 18 mean (standard error)	<i>P</i> -value
Age, yr	35.6 (3.7)	44.7 (3.9)	0.10
Sex	7 males, 11 females	7 males, 11 females	1.00
Body mass	25.0 (1.2) kg	24.6 (0.80) kg	0.44
Arterial blood pressure	74.1 (3.9) mmHg	66.9 (4.4) mmHg	0.23
Resting cardiac rate	72.0 (3.1) min ⁻¹	63.7 (4.5) min ⁻¹	0.14
Resting cardiac vagal tone	4.7 (0.8)	5.7 (1.1)	0.46
Maximum cardiac vagal tone during deep breathing	11.2 (1.3)	16.5 (1.7)	0.02

Table 2 Heart rate data for the patients

Patient number	Heart rate at 20 beats before the deep breathing procedure	Heart rate 20 beats before the end of the deep breathing procedure	Heart rate two minutes after the deep breathing procedure
1	71.8	80.5	76.0
2	90.8	90.7	83.1
3	89.8	120.7	83.5
4	68.0	73.6	66.0
5	70.3	86.4	66.3
6	90.5	83.6	90.6
7	69.0	68.6	70.2
8	64.4	65.5	61.7
9	141.8	125.9	137.8
10	69.5	76.1	70.3
11	71.9	71.6	74.5
12	69.4	71.6	71.4
13	74.6	78.1	79.7
14	68.4	69.9	66.7
15	68.7	77.2	68.3
16	62.0	72.9	65.3
17	69.2	72.1	67.5
18	63.0	69.1	68.3

Table 3 Heart rate data for the controls

Patient number	Heart rate at 20 beats before the deep breathing procedure	Heart rate 20 beats before the end of the deep breathing procedure	Heart rate two minutes after the deep breathing procedure
1	86.8	88.7	90.9
2	52.8	70.2	52.0
3	67.0	74.9	69.5
4	73.7	83.7	75.8
5	62.9	63.9	54.3
6	65.0	73.4	61.8
7	65.2	69.2	65.6
8	73.8	78.0	76.0
9	64.5	70.6	53.8
10	66.6	66.7	64.2
11	63.4	72.6	66.7
12	62.9	69.8	63.1
13	75.4	73.5	79.0
14	78.8	81.8	72.1
15	70.6	81.2	66.4
16	76.0	70.9	74.9
17	88.0	92.3	81.8
18	75.9	74.8	68.3

ing changed cardiac vagal tone *per se*. Indeed, the resting cardiac vagal tone in the Lyme disease patients was found not to differ significantly from that in the matched control group. Therefore, in attempting to provide an explanation for our results, it will not suffice simply to look for causes of altered (*e.g.*, reduced) cardiac vagal tone in the

patient group.

The cause of the observed abnormalities might be vagal nerve changes resulting from Lyme disease. It is also worth bearing in mind that, since cardiac vagal tone is reflexly generated through arterial baroreceptor stimulation, by the afferents of the latter facilitating cardiac va-

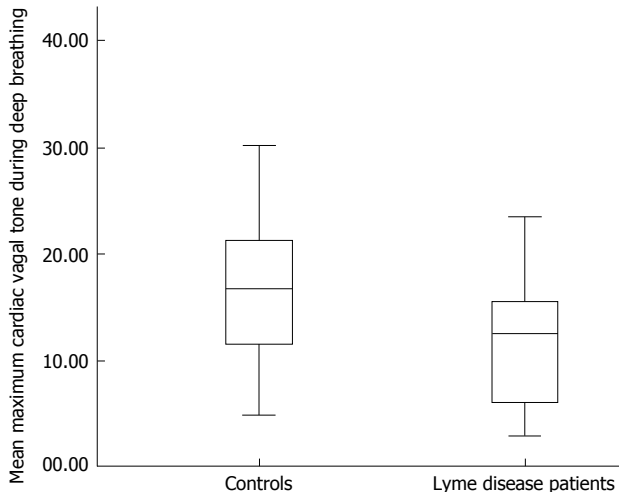


Figure 1 Boxplot of mean maximum cardiac vagal tone during deep breathing for the two groups.

gal motoneuron discharge relaying through interneurons in the nucleus tractus solitarius^[15,17,18], the results are also compatible with the possibility that Lyme disease might affect the brainstem. Indeed, given that the dorsal nucleus of the vagus nerve, the nucleus ambiguus, the nucleus tractus solitarius, and the spinal trigeminal nucleus, which give rise to or receive axons of the vagus nerve, are located in the medulla oblongata, these two possibilities are not mutually exclusive.

The causative *Borrelia* bacteria are able to undergo pleomorphic changes, including into a cystic form; indeed, it has been suggested that this may at least in part account for some cases of antibiotic resistance and recurrence of Lyme disease^[19]. It may be that this cystic form is often to be found in the brainstem in affected patients. However, this is unlikely to be an explanation here because this is believed to occur only in chronic Lyme neuroborreliosis.

It should be noted that there was no evidence that the patients were suffering from other disorders, such as Epstein-Barr viral infection, which might have caused false-positive serological results.

Finally, from Table 1 it can be seen that the mean resting cardiac rate in the controls (63.7 min^{-1}) was slightly (but not statistically significantly) lower than that in the patients (72.0 min^{-1}), while the mean resting cardiac vagal tone (5.7) was slightly (but not statistically significantly) higher than that in the patients (4.7). These findings might reflect the fact that the control group, in contrast to the Lyme patient group, were more physically fit; eight of the control subjects regularly engaged in exercise (sports, gymnasium attendance, or regular walking).

COMMENTS

Background

Lyme disease or Lyme borreliosis is an arthropod-borne zoonosis caused by *Borrelia* spirochetes, the incidence of which has recently been increasing with the geographical spread of infected ticks and which was previously identified clinically in Europe as Garin-Bujadoux-Bannwarth syndrome and in the United

States as Lyme arthritis.

Innovations and breakthroughs

Respiratory modulation of cardiac vagal tone is impaired in Lyme disease, which suggests that Lyme disease may directly affect the vagus nerve or the brainstem.

Applications

Cardiac vagal tone is reflexly generated through arterial baroreceptor stimulation, by the afferents of the latter facilitating cardiac vagal motoneuron discharge relaying through interneurons in the nucleus tractus solitarius, implying that Lyme disease may directly affect the vagus or brainstem.

Peer review

The topic is relatively new and there are few data about the topic of the study about (respiratory modulation of cardiac vagal tone in Lyme disease). This finding seems very interesting.

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Therapeutic equivalence in the treatment of hypertension: Can lercanidipine and nifedipine GITS be considered to be interchangeable?

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Abstract

AIM: To undertake a review of the evidence that nifedipine GITS and lercanidipine are therapeutically equivalent in the management of essential hypertension.

METHODS: A systematic review of the published literature was prompted by the findings of two meta-analyses which indicated that there was a lower incidence of peripheral (ankle) oedema with lercanidipine. However, neither meta-analysis gave detailed attention to comparative antihypertensive efficacy or cardiovascular protection. Accordingly, a systematic, detailed and critical review was undertaken of individual published papers. The review started with those studies incorporated into the 2 meta-analyses and then all other salient and directly relevant papers identified through the following search criteria: all randomized controlled trials in which the therapeutic profile and antihypertensive effects of lercanidipine were directly compared with those of nifedipine GITS (in hypertensive patients). The search

strategy was focused on the reports of clinical trials of lercanidipine *vs* nifedipine GITS, which were identified through a systematic search of PubMed (from 1966 to October 2012), Embase (from 1980 to October 2012) and the Cochrane library (from 1 October 2008 to end October 2013). The search combined terms related to lercanidipine *vs* nifedipine GITS (including MeSH search using calcium antagonists, calcium channel blockers and dihydropyridines).

RESULTS: With regard to blood pressure (BP) control and the consistency of BP control throughout 24-h, there is limited published evidence. However, two studies using 24 h ambulatory blood pressure monitoring clearly identified the dose-dependency of BP lowering with lercanidipine and its variably sustained 24-h efficacy. In contrast, there is evidence of a consistent antihypertensive effect throughout 24 h with nifedipine GITS. The incidence of the most common "side effect", *i.e.*, peripheral (ankle) oedema can be estimated as follows. For every 100 patients treated with lercanidipine, 2.5 will report oedema compared to 6 patients treated with nifedipine GITS. However, 98 or 99 patients will continue treatment with nifedipine GITS, compared with 99.5 patients on lercanidipine. Finally, with regard to outcome studies of cardiovascular (CV) morbidity and mortality, there is definitive outcome evidence for nifedipine GITS but there is no evidence that treatment with lercanidipine leads to reductions in CV morbidity and mortality.

CONCLUSION: There is no evidence in terms of long-term BP control and CV protection to justify the contention that lercanidipine is therapeutically equivalent to nifedipine GITS.

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Key words: Nifedipine GITS; Lercanidipine; Therapeutic

equivalence

Core tip: Even in this time of “evidence-based medicine”, there is a widespread presumption of “class effects” in therapeutic practice including that for antihypertensive drug treatments. Thus, guidelines tend to recommend treatment not with specific agents but with groups or classes such as “calcium channel blockers” on the presumption of the therapeutic equivalence or inter-changeability of different agents. This literature review focuses attention on the apparent therapeutic advantage of lercanidipine over nifedipine GITS on the basis of a lower incidence of the adverse effect of peripheral (ankle) oedema. Overall, however, the balance of evidence of efficacy favours nifedipine GITS.

Elliott HL, Meredith PA. Therapeutic equivalence in the treatment of hypertension: Can lercanidipine and nifedipine GITS be considered to be interchangeable? *World J Cardiol* 2014; 6(6): 507-513 Available from: URL: <http://www.wjgnet.com/1949-8462/full/v6/i6/507.htm> DOI: <http://dx.doi.org/10.4330/wjc.v6.i6.507>

INTRODUCTION

Hypertension treatment guidelines, particularly those in Europe, recommend a long-acting dihydropyridine calcium channel blocker (CCB) in the routine management of patients with hypertension, either as first line monotherapy or as a suitable combination partner for all other types of antihypertensive drug^[1,2]. In general, however, the guidelines do not nominate individual agents and there is an overall presumption of a “class” effect, *i.e.*, there is a presumption of therapeutic equivalence amongst all dihydropyridine CCBs licensed for once daily administration. The picture is further complicated by the mechanism harnessed to attain the suitability for once daily administration^[3]. There have been three alternative approaches: (1) An intrinsic, extended elimination half life, as with amlodipine; (2) An “apparent” prolongation of half life *via* a sophisticated, modified release formulation, as with nifedipine GITS (Gastro-Intestinal Therapeutic System); and (3) An increased duration of action *via* increased membrane-binding characteristics (attributed to a high membrane partition coefficient) despite a relatively short elimination half life, as with lercanidipine and lacidipine.

Since direct, comparative outcome studies within a drug class are rare, therapeutic equivalence is usually assumed through an amalgamation of different types of evidence: for example, members of the same chemical family with similar pharmacological characteristics; comparisons of published papers which separately evaluate the drugs in question; comparative studies of the drugs, usually in parallel group designs, for surrogate end-points and adverse drug reactions (ADRs).

With regard to ADRs, peripheral (ankle) oedema is a well-recognised, dose-dependent “side effect” associated with chronic treatment with long-acting dihydropyridine CCBs such as nifedipine GITS, lercanidipine and amlo-

dipine. There remains some debate, however, about the relative incidence of peripheral oedema with each of these individual agents and, in particular, the claims of a lesser incidence with lercanidipine^[4-11]. There also is considerable doubt as to whether or not the balance between antihypertensive efficacy and tolerability is superior with lercanidipine.

The fundamental remit of this paper is a critical review of the published information relating to the comparisons of two dihydropyridine CCBs, nifedipine (in its GITS formulation: Gastro-Intestinal Therapeutic System) and lercanidipine. Such information has been derived from a limited number of published direct, head-to-head comparisons and a small number of additional publications from which relevant comparative information can be derived.

The question of therapeutic equivalence and the inter-changeability of the two drugs have been addressed under three sub-headings: (1) The fundamental pharmacological response: in this case, blood pressure reduction; (2) The profile of adverse drug reactions: in this case, peripheral oedema; and (3) The long term treatment benefits: in this case, cardiovascular protection.

MATERIALS AND METHODS

This review was conducted in three phases: Phase 1-The starting point was a meta-analysis published in August 2009 as a systematic review of randomised, controlled, comparative clinical trials published during all years through to August 2008^[6]; Phase 2-The second stage was a critical review of a second, updated meta-analysis published in 2011^[7]; and Phase 3-The third component was a systematic, detailed and critical review of individual papers. First, those studies incorporated into the 2 meta-analyses. Then, in addition, all other salient and directly relevant papers identified through the following search criteria: all randomized controlled trials in which the therapeutic profile and antihypertensive effects of lercanidipine were directly compared with those of nifedipine GITS (in hypertensive patients). The search strategy was focused on the reports of clinical trials of lercanidipine *vs* nifedipine GITS, which were identified through a systematic search of PubMed (from 1966 to October 2012), Embase (from 1980 to October 2012) and the Cochrane library (from 1 October 2008 to end October 2013). The search combined terms related to lercanidipine *vs* nifedipine GITS (including MeSH search using calcium antagonists, calcium channel blockers and dihydropyridines).

The reference lists of original reports and meta-analyses of studies involving dihydropyridine calcium antagonists (retrieved through the electronic searches) were also scrutinised to identify studies that might not have been included in the computerized databases.

RESULTS

Phase 1

For the purposes of this meta-analysis, lercanidipine

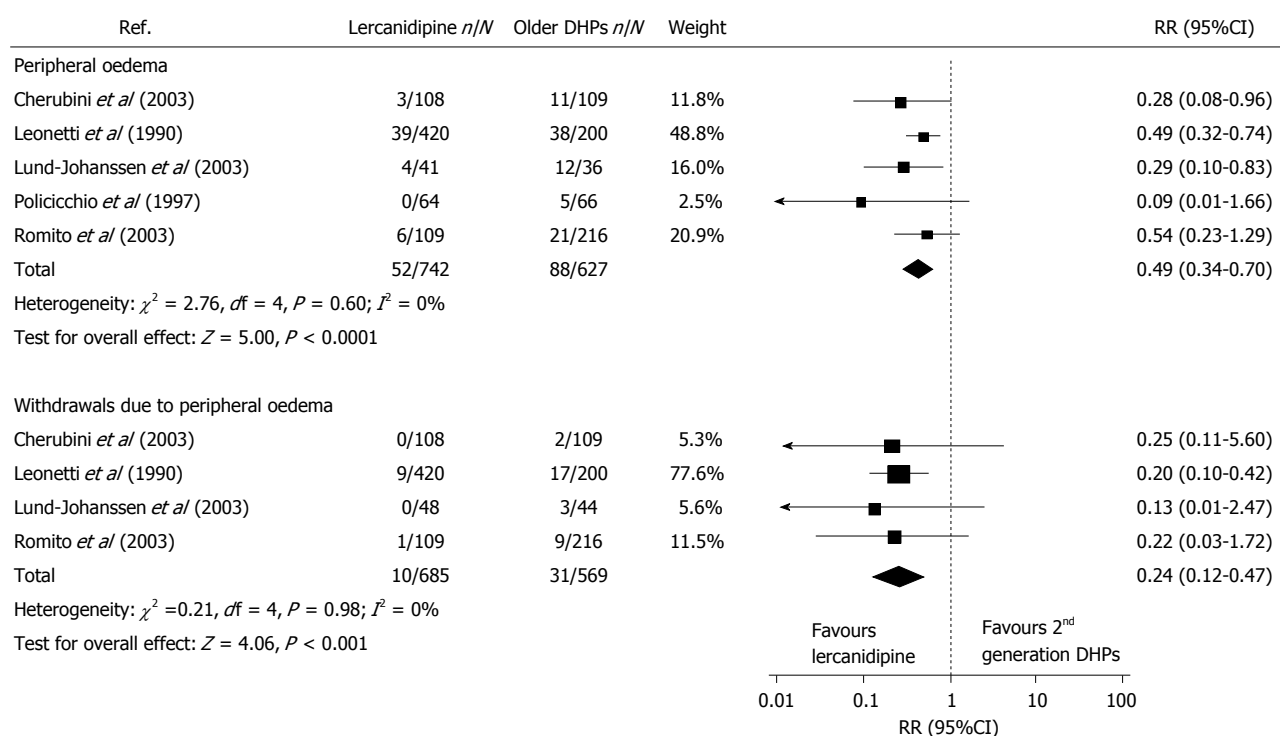


Figure 1 Incidence and withdrawals on account of peripheral oedema. Adapted and corrected from the first meta-analysis^[6].

was compared with a group of so-called “first generation dihydropyridine CCBs” (including nifedipine GITS and amlodipine)^[6]. The overall conclusion was that there was no significant difference between lercanidipine and these other competitor, “first generation CCBs” in terms of antihypertensive efficacy but there was a significant difference in favour of lercanidipine with respect to the incidence of, and withdrawal rates for, peripheral oedema (Figure 1).

Although three studies involving nifedipine GITS were cited in this paper, only 2 were included in the meta-analysis^[8-10]. It is important to note that within the statistical terms of the analysis itself, there were no significant differences between Nifedipine GITS and lercanidipine for the withdrawal rates for these 2 individual studies^[8,9] (Figure 1).

The 3 studies directly involving nifedipine GITS and lercanidipine are reviewed in greater detail below.

Phase 2

The second meta-analysis was more rigorous and more comprehensive but was essentially a repeat of the first analysis insofar as no new studies involving nifedipine GITS had been added^[7]. However, overall, it was a larger and more robust analysis by an independent group using stricter criteria.

In essence, the result was the same as for the first meta-analysis even although only 3 studies were incorporated for the comparison of lercanidipine and “older DHPs” (the same 2 studies with nifedipine GITS and a study involving amlodipine).

The conclusion was that, relative to “older DHPs”, lercanidipine was associated with a reduced incidence of

oedema: however, this component of the analysis was heavily influenced/weighted (78%) by the results of a study involving lercanidipine and amlodipine^[11]. Once again, within the structure of the meta-analysis, the same 2 individual studies with nifedipine GITS showed no statistically significant difference between nifedipine GITS and lercanidipine as far as the incidence of peripheral oedema was concerned (Figure 2)^[8,9].

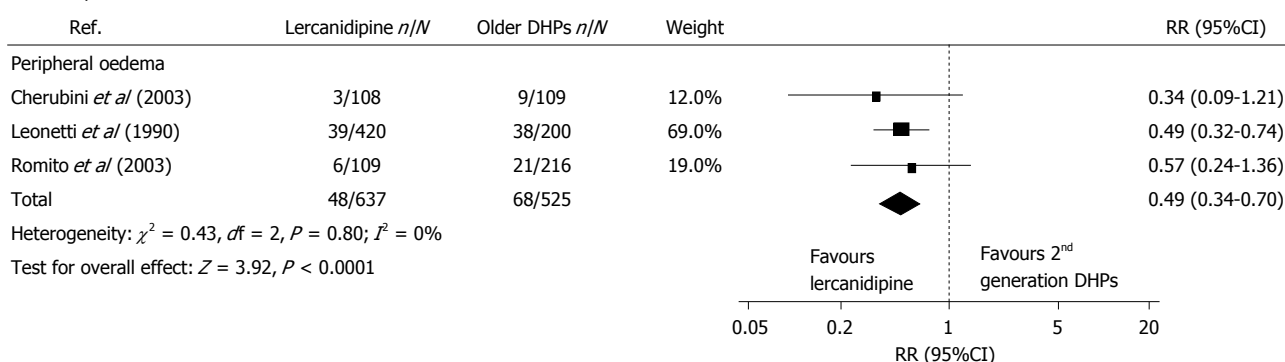
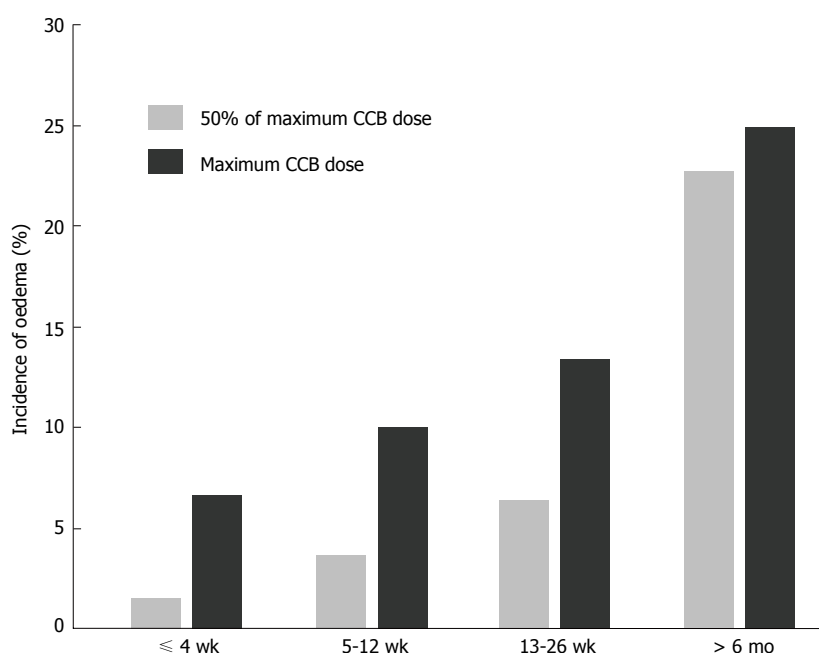
Additional features of clinical relevance and of practical importance in this second meta-analysis were as follows (Figure 3): (1) confirmation that the incidence of peripheral oedema is dose-dependent; (2) identification that the development of peripheral oedema is time-dependent, up to 6 mo treatment; and (3) awareness that the reduced incidence of peripheral oedema with “lipophilic DHPs” relative to “older DHPs” is not a unique feature of lercanidipine because lacidipine and manidipine were components of these analyses.

Phase 3-appraisal of individual studies

The comprehensive search of the literature databases revealed, in addition to the 3 studies cited in the first meta-analysis, a further 5 studies that met the pre-defined search criteria for the exploration of pertinent treatment issues.

Comparative studies: Romito *et al*^[9] reported a double blind, parallel group study of a total of 250 patients which compared lercanidipine (10 and 20 mg), felodipine (10 and 20 mg) and nifedipine GITS (30 and 60 mg) across an 8 wk treatment period. No significant differences in antihypertensive efficacy were reported.

The incidence of ADRs was significantly lower with

Lercanidipine *vs* older DHPsFigure 2 Incidence of peripheral oedema. Adapted from the second meta-analysis^[7].Figure 3 Dose and time-dependency of the development of peripheral oedema. Adapted from the second meta-analysis^[7].

both lercanidipine and nifedipine GITS: in particular, there were lower rates for ankle oedema with lercanidipine (5.5%) and nifedipine GITS (6.6%), relative to felodipine (13%). The incidence of ankle oedema was not significantly different for lercanidipine and nifedipine GITS.

Ankle oedema led to the withdrawal of 1 patient receiving lercanidipine ($n = 109$) compared to 4 patients receiving nifedipine GITS ($n = 106$) and 5 patients on felodipine ($n = 110$). These differences were not statistically significant.

Cherubini *et al*^[8] reported a double blind, randomised, parallel group study over 24 wk in elderly hypertensive patients comparing lacidipine (2 and 4 mg), lercanidipine (5 and 10 mg) and nifedipine GITS (30 and 60 mg).

The BP responder and normalisation rates were remarkably high with all 3 treatments, approximating to 100% in the case of nifedipine GITS, but not significantly different with the other 2 treatments. The incidence of oedema was lowest at 2.8% in the lercanidipine group

($n = 96$) compared to 7.5% with lacidipine ($n = 99$) and 10.1% with nifedipine GITS ($n = 97$) but this was not statistically significant. There were 2 withdrawals in the nifedipine group on account of oedema (out of 109 patients) and no withdrawals in the lercanidipine group.

There must be some concerns about the sensitivity of the BP methodology in this study because the BP responses were remarkably and unexpectedly high with all 3 drugs, especially considering that the doses of lacidipine and lercanidipine were relatively modest. With particular respect to lercanidipine, the consensus (in the published literature) is that 10 and 20 mg lercanidipine are the equivalent doses *vs* 30 and 60 mg nifedipine GITS. In fact, the 10/20 mg *vs* 30/60 mg comparability is specifically noted in the paper by Romito *et al*^[9].

Fogari *et al*^[10] designed specifically to assess indices of ankle volume and sub-cutaneous tissue pressure in patients randomly assigned in a double blind manner to 12 wk treatment with either lercanidipine (10 and 20 mg) or nifedipine GITS (30 and 60 mg).

There were no patient reports for peripheral oedema (hence the study was not incorporated into either of the published meta-analyses) and there were no patient withdrawals from either treatment group. There were statistically significant differences in ankle volume indices indicating a greater degree of ankle oedema with nifedipine GITS.

In summary, using a relatively sophisticated research methodology, this study demonstrated that nifedipine GITS had a greater propensity for the development of peripheral (ankle) oedema relative to lercanidipine. However, there were no clinical reports of any difference in incidence or withdrawal rates.

Other studies: Ambrosioni *et al.*^[12] reported the findings of 2 small studies exploring the antihypertensive efficacy of lercanidipine in doses of 5, 10 and 20 mg once daily in a total of 44 patients. Multiple 24-h ambulatory BP recordings were obtained and the following are the principal conclusions.

There was no statistically significant BP reduction with 5 mg lercanidipine but both single and multiple doses of 10 and 20 mg lercanidipine significantly reduced BP across 24 h. However, the BP reduction was not consistent across 24 h as assessed by the trough peak (TP) ratio. The TP ratios for the single dose study were not reported but, from one of the figures in the published paper, it can be estimated at about 39% with 10 mg and 44% with 20 mg; the corresponding values for multiple dosing were stated to be greater than 60%.

Omboni *et al.*^[13] reported a clinical study of more than 200 patients essentially confirmed the above findings: “At a dose of 10 mg lercanidipine had a significant and durable antihypertensive effect over 24 h but at 5 mg the effect was less consistent and did not last 24 h”. For 10 mg lercanidipine the TP ratio was reported at above 60% and from one of the figures in the published paper it appears to fall into the range 60%-75%.

Borghi *et al.*^[14] reported an open label, sequential treatment study lasting for a total of 8 wk and reliant upon a BP measurement obtained at a single time point (not defined in relation to drug administration).

A total of 125 patients were entered into the study because they were known to be experiencing “calcium antagonist-specific ADRs”, including peripheral oedema, whilst on treatment with amlodipine, felodipine, nifedipine GITS or nitrendipine. Patients were switched to lercanidipine and assessed after 4 wk treatment and then re-assigned to their original CCB and assessed again after a further 4 wk treatment.

In brief, no BP difference was detected (142/87 on lercanidipine and 141/87 mmHg on the other CCBs). Peripheral oedema was reported by 52% of patients after 4 wk of lercanidipine and by 87% of patients returned to their original CCB. The study did not report a direct comparison for the 28 patients treated with nifedipine GITS.

Once again, the BP methodology had little or no discriminatory power and the principal conclusion reflects a

comparison of lercanidipine against a group of “calcium antagonists”, with amlodipine accounting for more than half of the patients.

Barrios *et al.*^[15] reported an observational study, conventional clinic BP control was significantly better (but of borderline clinical significance) at 144.4/83.3 in 233 patients receiving lercanidipine 20 mg daily, compared to 145.0/84.5 mmHg in 104 patients receiving either amlodipine 10 mg or nifedipine GITS 60 mg daily. However, and in addition to other methodological concerns, there was no direct comparison involving nifedipine GITS, nor any data on the number of patients receiving GITS. Furthermore, approximately 50% of the patient population were receiving concomitant antihypertensive drugs, with approximately 30% receiving 2 additional antihypertensive drugs.

DISCUSSION

Any interpretation of the available published literature is potentially compromised by issues relating to dosage equivalence, methodology, study reliability, statistical power, investigator bias, funding/sponsorship *etc.* Nevertheless, the following is presented as an objective summary of the available evidence evaluating whether or not lercanidipine and nifedipine GITS can be considered to be therapeutically equivalent for the management of hypertension.

Antihypertensive efficacy

The initial report of antihypertensive equivalence reflected the achieved BPs at 24 h post-dose in the 3 comparative studies cited in the original meta-analysis^[6], *i.e.*, there were no statistically significant differences. However, this interpretation not only reflected a rather insensitive measure of overall BP control but also raised concerns because: (1) one of these studies was not designed as a BP comparison; and (2) a second study had clear methodological flaws because it assigned a responder rate of 86% for 5mg lercanidipine, a dose which 2 other studies found to be inadequately effective. Thus, there is a very “thin” evidence base for direct antihypertensive equivalence if reliance is placed upon conventional clinic BP measurements.

There obviously are other clinical reports which assessed the antihypertensive efficacy of lercanidipine but these were not direct, head-to-head comparisons. Overall, whilst equivalence (with nifedipine GITS) was inferred on the basis of results which were similar, these results cannot be directly compared in statistical terms because they were generated by different research groups, in different patient populations, using different methodologies, *etc.* There also are publications in which deductions are made in spite of confounding factors and the TOLERANCE study is an illustrative example^[15]. As discussed above, there was no direct comparison of lercanidipine and nifedipine GITS in this study, nor any data on the number of patients receiving GITS, and approximately 50% of the patient population were receiving at least one other antihypertensive drug.

In the absence of any other evidence, it might have proved difficult to challenge the conclusion of antihypertensive equivalence (which is actually based on one single, relatively robust, direct comparison!) but there were 2 studies employing 24 h ambulatory BP monitoring which explored the antihypertensive efficacy of lercanidipine in greater detail^[12,13]. Both studies identified the dose-dependency of the 24 h BP lowering effects with lercanidipine which, overall, displayed poorly sustained 24-h efficacy. Additionally these 2 papers incorporated measurements of trough: TP as part of their assessments of antihypertensive efficacy throughout 24 h. Whilst TP ratio as an index of antihypertensive efficacy is not without its limitations^[16], values of respectively 39% and 44% (estimated) following single 10 and 20 mg doses of lercanidipine and of “greater than 60%” for both doses during steady state treatment are not particularly high. In contrast, the published data with nifedipine GITS (by the same group, using the same methodology as for one of the lercanidipine studies) demonstrated that the drug elicits a consistent antihypertensive effect that is independent of dose and is characterised by a TP ratio approximating to 100%^[17].

In summary, it may be reasonably concluded that BP control throughout 24-h is more consistent and better sustained with nifedipine GITS than with lercanidipine during chronic treatment.

Peripheral (ankle) oedema

Despite the paucity of direct comparative studies, there is a reasonable volume of evidence to indicate that this “side effect” is less likely to occur with lercanidipine than with nifedipine GITS.

In the absence of definitive statistics, a reasonable approximation of the practical consequences of this differentiating characteristic is derived from the second meta-analysis which incorporated data from 99469 patients. In brief, for every 100 patients treated with lercanidipine, 2.5 will report peripheral oedema compared to 6 patients treated with nifedipine GITS: correspondingly, 0.5 patients will withdraw from lercanidipine treatment compared to 1.1 treated with nifedipine GITS. The corollary of this is that there will be 98 or 99 patients continuing treatment with nifedipine GITS, compared with 99.5 patients treated with lercanidipine.

As a footnote, however, there is the suggestion that this potentially advantageous feature is not unique to lercanidipine insofar as it may also be a feature of treatment with lacidipine and manidipine.

Cardiovascular protection

For nifedipine GITS there is definitive evidence of benefit in the treatment of hypertension and stable coronary artery disease^[18,19]. As there are no clinical outcome studies, there is no evidence that treatment with lercanidipine leads to reductions in cardiovascular (CV) morbidity and mortality.

In summary, the available evidence confirm the claims that lercanidipine has a lesser incidence of peripheral (ankle) oedema, relative to treatment with nifedipine

GITS. Whilst this may be factually accurate, it is a trivial difference in terms of clinical practice, particularly with respect to patient withdrawals, whereby 98 patients (out of 100) will continue treatment with nifedipine GITS. Set against this minor advantage and albeit with incomplete evidence, the antihypertensive efficacy of nifedipine GITS appears to be superior, particularly in respect of sustained 24-h BP control.

In conclusion, the ultimate aim of antihypertensive drug treatment (with CCBs and other classes of drugs) is sustained, long term BP control leading to a significant reduction in CV morbidity and mortality. There is no compelling evidence with lercanidipine to undermine the proven ability of nifedipine GITS to reduce death and CV events on the basis of an occasional, inconvenient but essentially innocuous adverse effect. Thus, there is no justification for assuming therapeutic equivalence between lercanidipine and nifedipine GITS and no grounds for considering that they are interchangeable if CV protection is the ultimate goal.

COMMENTS

Background

Drugs in the same “class” are often considered to be therapeutically equivalent and, therefore, inter-changeable. This review scrutinises the published literature to compare two antihypertensive drugs (lercanidipine and nifedipine GITS) and to assess whether or not there is good evidence that these drugs are therapeutically similar.

Research frontiers

Several new guidelines from international organisations have been recently published to advise on the treatment of hypertension but, as a general rule, no guidance is given on the choice of individual drugs. This critical review is intended for the prescribing clinician to allow him or her to make an informed evidence-based assessment which, in this case, addresses the comparison of two calcium channel blocking drugs.

Applications

The practical conclusion is that lercanidipine and nifedipine GITS cannot be considered to be inter-changeable because, although it appears less likely to cause peripheral (ankle) oedema, there is no direct evidence that lercanidipine can provide cardiovascular protection. In contrast, there is clear evidence of consistent 24-h blood pressure control and long-term cardiovascular protection with nifedipine GITS.

Peer review

This is an interesting paper. The authors have reviewed the role of lercanidipine in hypertension and compared it to nifedipine GITS in an extensive manner.

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Headache: An unusual presentation of acute myocardial infarction

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rule out the possibility of hemorrhage.

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INTRODUCTION

Atypical symptoms of myocardial infarction may delay the diagnosis, and therefore the proper management to rescue ischemic myocardium. Headache represents a rare symptom of myocardial ischemia^[1-5]. We report a patient with ST-segment elevation acute myocardial infarction who presented to the emergency department complaining of headache without chest discomfort.

CASE REPORT

An 86-year-old man with a history of hypertension and tobacco use presented to the emergency department complaining of recent onset severe occipital headache. The patient did not report any chest pain, dyspnea, or other typical symptoms of angina. On admission the patient was pale with tachycardia (100 beats/min), and, while his blood pressure was within normal range (100/60 mmHg). At auscultation, a mild systolic murmur was audible. The electrocardiogram (ECG) showed sinus bradycardia, ST-segment depression in leads V1-V5 and ST-segment elevation in posterior leads (V7-V9) (Figure 1). Transthoracic echocardiography revealed an impaired left ventricular ejection fraction (40%-45%) along with mild mitral valve regurgitation. Initial laboratory examinations showed elevated levels of high-sensitivity cardiac troponin T (250 ng/L). Due to his clinical presentation, a brain computed tomography (CT) imaging was im-

Abstract

Acute myocardial infarction should be diagnosed as early as possible for the appropriate management to salvage ischemic myocardium. Accurate diagnosis is typically based on the typical symptoms of angina. Headache is an unusual symptom in patients with acute myocardial infarction. We report a patient with ST-segment elevation acute myocardial infarction who presented to the emergency department complaining of severe occipital headache without chest discomfort.

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Key words: Headache; Angina; Myocardial infarction

Core tip: The association of headache with myocardial ischemia is unusual and is accompanied by chest discomfort. The only symptom of this patient was occipital headache and this is extremely rare. Owing to the rare occurrence of headache as a symptom of myocardial ischemia, diagnosis may be extremely difficult since a brain computed tomography imaging is important to

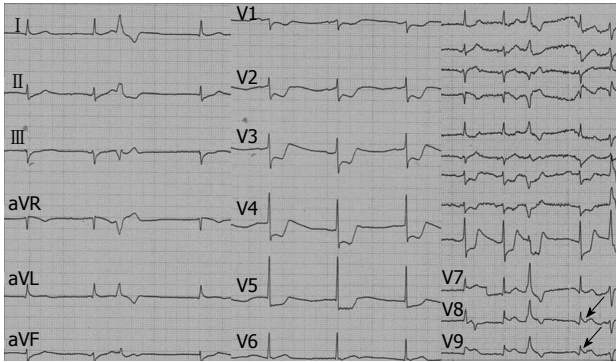


Figure 1 Electrocardiogram on admission demonstrating ST-segment depression in leads V1-V5 and ST-segment elevation in the posterior leads (V7-V9) (arrows).

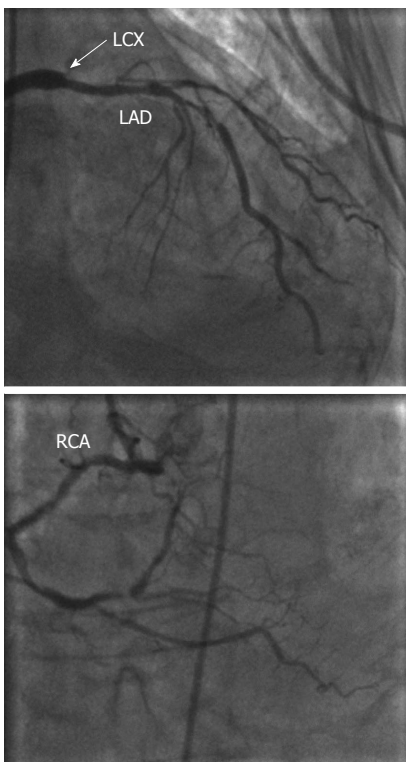


Figure 2 Coronary angiography showing total obstruction of the proximal left circumflex artery (arrow) and severe stenosis in left anterior descending artery and right coronary artery. LCX: Left circumflex artery; LAD: Left anterior descending artery; RCA: Right coronary artery.

mediately performed. The CT imaging was negative for intracerebral or subarachnoid hemorrhage. Following CT imaging, the patient prepared for cardiac catheterization and received aspirin (500 mg), clopidogrel (600 mg) and unfractionated heparin (70 U/kg). Coronary angiography was performed 60 min after admission and demonstrated a three-vessel coronary artery disease [the proximal left circumflex artery (LCX) was totally obstructed, the left anterior descending artery (LAD) displayed a severe stenosis and the right coronary artery was also severely diseased] (Figure 2). Proximal LAD lesion was directly stented, while the blood flow was restored in LCX artery revealing a severe stenosis of more than

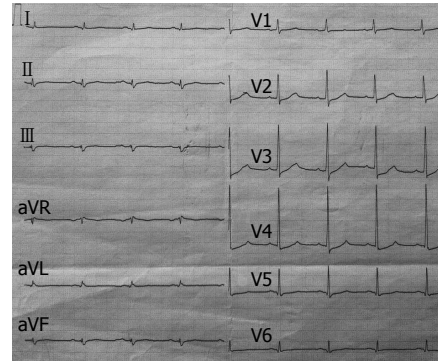


Figure 3 Electrocardiogram demonstrating resolution of the ST-segment depression in leads V1-V5 after revascularization.

90%. We attempted to insert the guidewire into the LCX but failed to cross the proximal part of LCX. Following revascularization, the patient was totally asymptomatic without headache, while the ECG was normalized (Figure 3). During the following days, the myocardial enzymes (CK-MB, hs-troponin T) followed the classic rise and fall kinetic pattern. He discharged 6 d later under dual anti-platelet (aspirin, clopidogrel), β -blocker and angiotensin converting enzyme inhibitor therapy.

DISCUSSION

Myocardial infarction should be diagnosed as early as possible for the appropriate management to salvage ischemic myocardium. Accurate diagnosis is based on both ECG and clinical presentation of the patient. Ischemia and myocardial infarction typically causes chest pain variously radiating elsewhere (shoulders, upper extremities and epigastrium). The association of headaches with myocardial ischemia is unusual and is accompanied by chest discomfort. The only symptom of this patient was occipital headache and this is extremely rare. Owing to the rare occurrence of headache as a symptom of myocardial ischemia, diagnosis may be extremely difficult since a brain CT imaging is important to rule out the possibility of hemorrhage.

The incidence of headache as a symptom of myocardial ischemia may be underestimated^[1-5]. Culic *et al*^[6] reported that headache is present (along with other symptoms) in 5.2% of patients with acute myocardial infarction. Moreover, in 3.4% of these patients headache was the primary complaint^[6]. Cardiac cephalalgia or headache angina is a recognized phenomenon, but the pathophysiological mechanism is still unclear^[7-8]. There is a connection between the central cardiac pathway and the cranial pain afferents. The cardiac sympathetic fibers originate from cervical lymph nodes which also innervate pain sensitive cranial structures^[9-10]. Furthermore, it is hypothesized that chemical mediators like bradykinin, serotonin and histamine can induce pain in shoulders, arms, neck and in this case headache. Another mechanism is based on the elevated intracranial pressure associated in the case of decreased cardiac output during myocardial

infarction and elevated venous pressure^[11,12]. Finally, increased levels of atrial and brain natriuretic peptides may be involved in intracranial pressure regulation^[13]. Even though the occurrence of headache as a sole manifestation of angina or myocardial infarction has been previously described, many clinicians ignore this unusual manifestation. The diagnosis of “cardiac headache” is difficult and requires a high degree of suspicion.

COMMENTS

Case characteristics

An 86-year-old man presented to the emergency department complaining of recent onset severe occipital headache.

Clinical diagnosis

The patient was pale with tachycardia and electrocardiogram (ECG) signs suggestive of myocardial infarction.

Differential diagnosis

The differential diagnosis included intracerebral or subarachnoid hemorrhage and myocardial infarction.

Laboratory diagnosis

Elevated levels of high-sensitivity cardiac troponin T were initially recorded.

Imaging diagnosis

Brain computed tomography imaging excluded intracerebral or subarachnoid hemorrhage, while coronary angiography demonstrated a three-vessel coronary artery disease.

Treatment

Proximal left anterior descending artery lesion was directly stented, while the blood flow was restored in left circumflex artery revealing a severe stenosis of more than 90%.

Experiences and lessons

Careful ECG interpretation in the setting of acute headache is of major importance.

Peer review

Asvestas *et al* report a rare case of a patient who presented with headache as the sole symptom of an acute myocardial infarction. The mechanisms by which headache is linked to ischemic vascular disease remain uncertain and are likely to be complex. The paper is generally well-written and interesting.

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GENERAL INFORMATION

World Journal of Cardiology (*World J Cardiol*, *WJC*, online ISSN 1949-8462, DOI: 10.4330) is a peer-reviewed open access (OA) academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

Aim and scope

WJC covers topics concerning arrhythmia, heart failure, vascular disease, stroke, hypertension, prevention and epidemiology, dyslipidemia and metabolic disorders, cardiac imaging, pediatrics, nursing, and health promotion. Priority publication will be given to articles concerning diagnosis and treatment of cardiology diseases. The following aspects are covered: Clinical diagnosis, laboratory diagnosis, differential diagnosis, imaging tests, pathological diagnosis, molecular biological diagnosis, immunological diagnosis, genetic diagnosis, functional diagnostics, and physical diagnosis; and comprehensive therapy, drug therapy, surgical therapy, interventional treatment, minimally invasive therapy, and robot-assisted therapy.

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The columns in the issues of *WJC* will include: (1) Editorial: The editorial board members are invited to make comments on an important topic in their field in terms of its current research status and future directions to lead the development of this discipline; (2) Frontier: The editorial board members are invited to select a highly cited cutting-edge original paper of his/her own to summarize major findings, the problems that have been resolved and remain to be resolved, and future research directions to help readers understand his/her important academic point of view and future research directions in the field; (3) Diagnostic Advances: The editorial board members are invited to write high-quality diagnostic advances in their field to improve the diagnostic skills of readers. The topic covers general clinical diagnosis, differential diagnosis, pathological diagnosis, laboratory diagnosis, imaging diagnosis, endoscopic diagnosis, biotechnological diagnosis, functional diagnosis, and physical diagnosis; (4) Therapeutics Advances: The editorial board members are invited to write high-quality therapeutic advances in their field to help improve the therapeutic skills of readers. The topic covers medication therapy, psychotherapy, physical therapy, replacement therapy, interventional therapy, minimally invasive therapy, endoscopic therapy, transplantation therapy, and surgical therapy; (5) Field of Vision: The editorial board members are invited to write commentaries on classic articles, hot topic articles, or latest articles to keep readers at the forefront of research and increase their levels of clinical research. Classic articles refer to papers that are included in Web of Knowledge and have received a large number of citations (ranking in the top 1%) after being published for more than years, reflecting the quality and impact of papers. Hot topic articles refer

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- 3 **Tian D**, Araki H, Stahl E, Bergelson J, Kreitman M. Signature of balancing selection in Arabidopsis. *Proc Natl Acad Sci USA* 2006; In press

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- 6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

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- 9 Outreach: Bringing HIV-positive individuals into care. *HRS-A Careaction* 2002; 1-6 [PMID: 12154804]

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- 15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: <http://www.cdc.gov/ncidod/eid/index.htm>

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- 16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee.

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