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Contents

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CASE REPORT

ABOUT COVER

AIM AND SCOPE

World Journal of Cardiology (*World J Cardiol*, *WJC*, online ISSN 1949-8462, DOI: 10.4330) is a peer-reviewed open access journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

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.

We encourage authors to submit their manuscripts to *WJC*. We will give priority to manuscripts that are supported by major national and international foundations and those that are of great basic and clinical significance.

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CASE REPORT

Transcatheter aortic valve replacement in membranous interventricular septum aneurysm with left ventricular outflow tract extension

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Author contributions: Banga S reviewed the literature and wrote the manuscript; Barzallo MA and Mungee S operated the patient and revised the manuscript; Nighswonger CL helped in getting consent from the patient and image collection.

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Abstract

We report a challenging case of a 81-year-old male with history of severe calcific aortic valve stenosis and aneurysmal membranous interventricular septum. The presence of anomalies in the sub-annular area can lead to valve malpositioning and its consequences. Transcatheter aortic valve implantation (TAVR) in patients with aneurysm of the perimembranous interventricular septum extending into the left ventricular outflow tract has not been previously reported. This case describes a successful transfemoral TAVR with an Edwards SAPIEN XT valve (Edwards Lifesciences, Irvine, CA, United States) with such anomaly.

Key words: Transcatheter aortic valve replacement; Aneurysmal membranous interventricular septum

Core tip: Congenital perimembranous ventricular septal aneurysm is reported to be rare and its co-occurrence with severe calcific aortic stenosis is even rarest. This unique case establishes that the transcatheter aortic valve replacement can be done in patients with aneurysmal perimembranous interventricular septum. This was achieved in our case by implanting the prosthetic valve more distally into the left ventricular outflow tract requiring apposition of the Edwards SAPIEN XT skirt at

annulus with most of the valvular metallic frame in supra-annular position.

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INTRODUCTION

Extension of aneurysm in the left ventricular outflow tract (LVOT) from the perimembranous interventricular septum is a unique challenge with transcatheter aortic valve implantation (TAVR). The valve position in TAVR across the aortic annulus needs to be adequate for the proper deployment of the prosthetic valve. Presence of subvalvular aneurysm poses a challenge in effective valve deployment since there is always a possibility of serious negative outcome. The sub-annular, annular and supra-annular assessment of the landing zone is usually done using multi-imaging modality including transesophageal echocardiography (TEE) and multi-detector computer tomography (MDCT) .We describe a patient with perimembranous interventricular septum aneurysm extending into the LVOT requiring apposition of the Edwards SAPIEN XT skirt at annulus with most of the valvular metallic frame in supra-annular position.

CASE REPORT

An 81-year-old male patient with post coronary artery bypass graft (CABG), pacemaker for 2:1 AV block and moderate chronic obstructive lung disease (COPD), history of TIA was planned for the TAVR for symptomatic severe aortic stenosis in view of high risk for open aortic valve replacement (Society of Thoracic Surgeons score of 8-12). He presented with recent worsening of shortness of breath. The high STS score in this patient was determined based on multiple factors which are part of the scoring criteria including presence of aortic insufficiency, previous CAD, Moderate COPD per PFT results, prior sternotomy/CABG. TEE showed a perimembranous ventricular septal aneurysm with LVOT extension and severe calcific stenotic aortic valve (AVA of 0.9 cm^2) with moderate aortic regurgitation (Figure 1A). Pre-procedural CT findings confirmed the focal septal aneurysm below the aortic annulus in the transverse section (Figure 1B) and in the coronal section (Figure 1C). The aneurysm extended from 0.2 mm below the annulus to 14.5 mm along the septum on 3-D reconstructed CT image (Figure 1D). Distances from the aortic annulus to left main and right coronary ostium were 12.9 mm and 18.9 mm respectively (Figure 1E and F). The aortic annular measurements included: maximum and minimum diameter in the cross-sectional view of 29 mm and 25.5 mm respectively (average diameter of 27.3 mm); perimeter of 87.2 mm and annular area of 594.3 mm^2. Figure 2A and B demonstrate the sub-annular area of 571.8 mm^2 at the level of aneurysm in membranous septum. The aortic annular cross-sectional area on multi-planar reformatted en-face view was 602 mm^2 (40% phase), suggesting a 29 mm Edwards SAPIEN XT valve.

A 29 mm balloon-expandable transcatheter valve was positioned across the aortic annulus using the NovaFlex delivery system (Edwards Lifesciences, Irvine, CA, United States) after appropriate valve orientation by transfemoral approach. The Edwards SAPIEN XT prosthetic valve comes with the total frame height of 19.1 mm and skirt height of 12 mm. The valve was positioned at supra-annular position with 80% aortic and 20% ventricular ratio at the level of leaflet insertion of the native valve, given the presence of septal aneurysm with LVOT extension (Figure 3A). Appropriate valve deployment was achieved. No paravalvular aortic regurgitation with patent coronaries was noticed post-valve deployment (Figure 3B). The patient tolerated the procedure well and was discharged two days after procedure. At 8 week follow-up, patient had improved symptoms with repeat Cardiac CT scan showing stable prosthetic valve and no change in the perimembranous aneurysm (Figure 3C).

DISCUSSION

Congenital perimembranous ventricular septal aneurysms are not uncommon. Incidence of interventricular membranous septum aneurysm is reported to occur in 0.3 % of patients with congenital heart disease[1]. Etiology includes idiopathic or may be related to healed ventricular septal defect[1,2]. But there are few reports that relate the development to a previous episode of infection or trauma[3]. These aneurysms can be classified as true, false and pseudo-aneurysm[4]. Those with a wide base and regular contours are true while those with a narrow base and irregular shape are termed as false. A pseudo-aneurysm is complication of ischemic insults or transaortic septal myotomy[4]. Patients with interventricular septum aneurysm are often asymptomatic; if symptoms develop they are usually related to an associated complication. Like other aneurysms this anomaly predisposes patients to arrhythmogenic and thrombogenic events. Different modalities including conventional ventriculography, echocardiogram, cardiac MRI and MDCT are used for diagnosis. Morphological and functional assessment can be done with cardiac MRI or MDCT[4]. Both cardiac MRI and MDCT can also be used after surgery to determine the integrity of the patch and also to identify any residual defect but CT gives radiation exposure[4] .

Surgical intervention is rarely indicated except when concurrent heart diseases, hemodynamic abnormalities, and aneurysm-related complications are detected. Presence of thrombus may justify anticoagulation treatment[5]. Failure of anticoagulation therapy is an

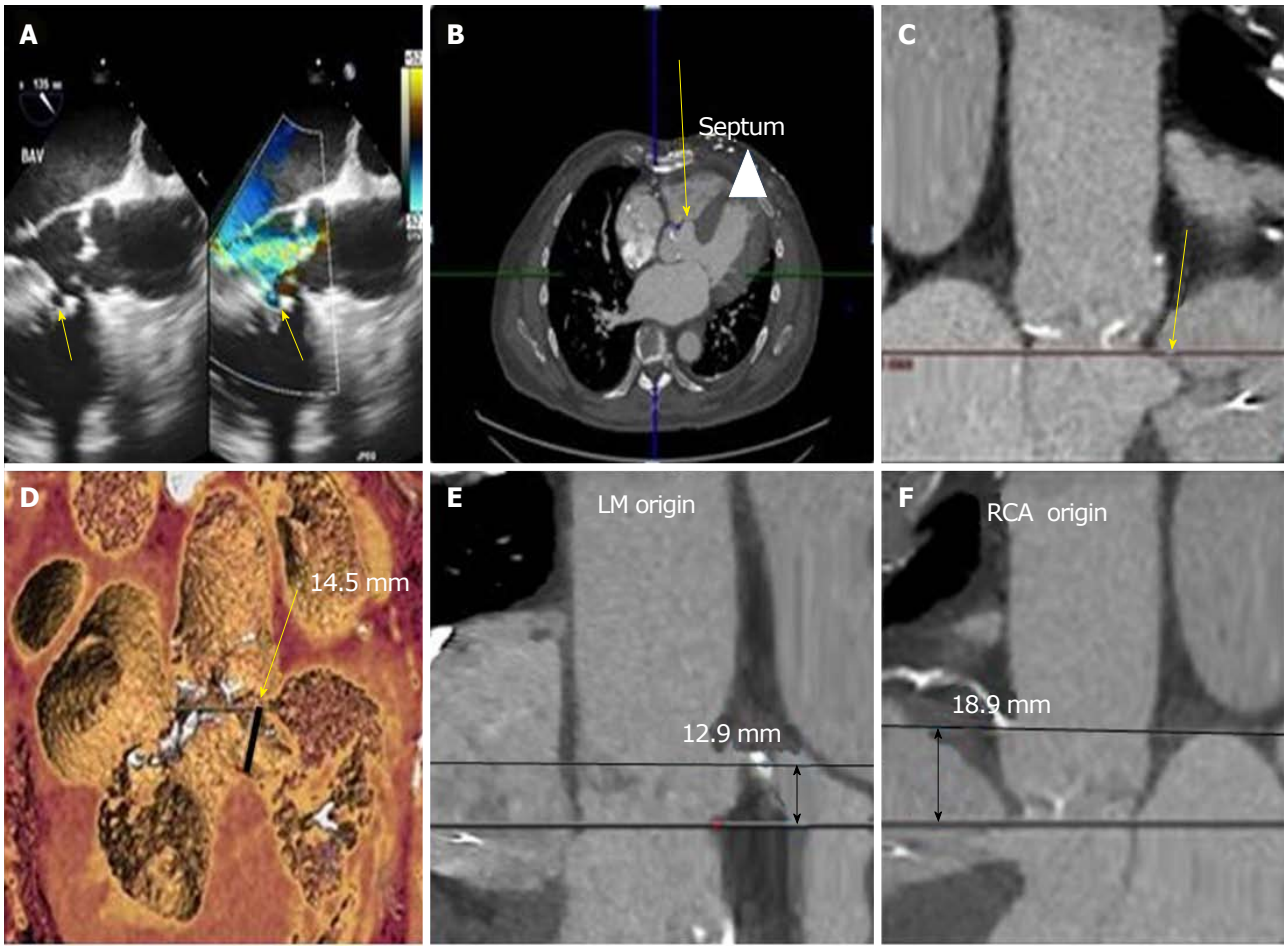

Figure 1 Assessment of the calcific aortic valve and interventricular septal aneurysm prior to transcatheter aortic valve replacement. A: Transesophageal echocardiography shows a perimembranous ventricular septal aneurysm (arrow) and severe calcific stenotic aortic valve with moderate aortic regurgitation; B: Cardiac computer tomography (CT) findings confirmed the focal interventricular septal aneurysm (arrow) below the aortic annulus in the transverse view along the membranous septum with left ventricular outflow tract extension (arrowhead); C: Cardiac CT in coronal view showing interventricular septal aneurysm (arrow) below the annulus; D: The dimension at the neck of septal aneurysm (arrow) was 14.5 mm on 3-D reconstructed CT image; E and F: The aortic annulus to left main ostium distance was 12.9 mm and annulus to right coronary ostium distance was 18.9 mm.

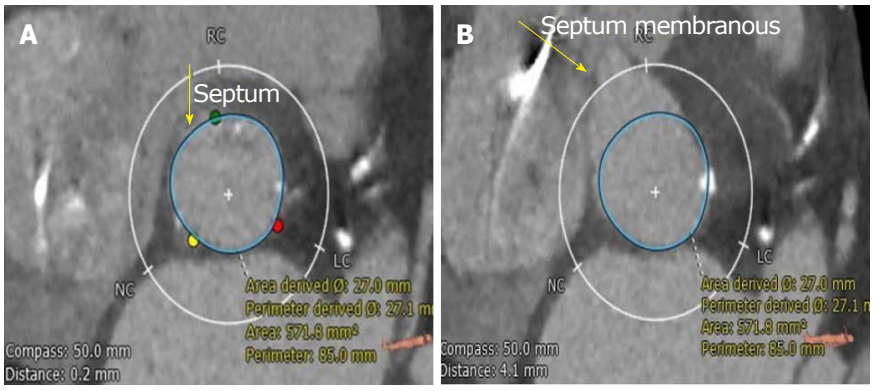

Figure 2 Measurements below and at the level of aortic annulus. A: The aortic measurements included area of 571.8 mm[2]; B: Perimeter of 85 mm at 0.2 mm below the level of annulus, and also at 4.1 mm below the annulus and at level of aneurysm.

indication for surgical resection even in the absence of echocardiographic evidence of thrombus[5]. So periodic echocardiographic examination is recommended by some clinicians. Direct surgical ablation has shown satisfactory outcomes in patients with life threatening ventricular arrhythmias. Failure to precisely localize conduction system at the operation can lead to the development of complete heart block[6]. Although surgical option is available, most of them are left as such if they do not complicate. In our patient there was

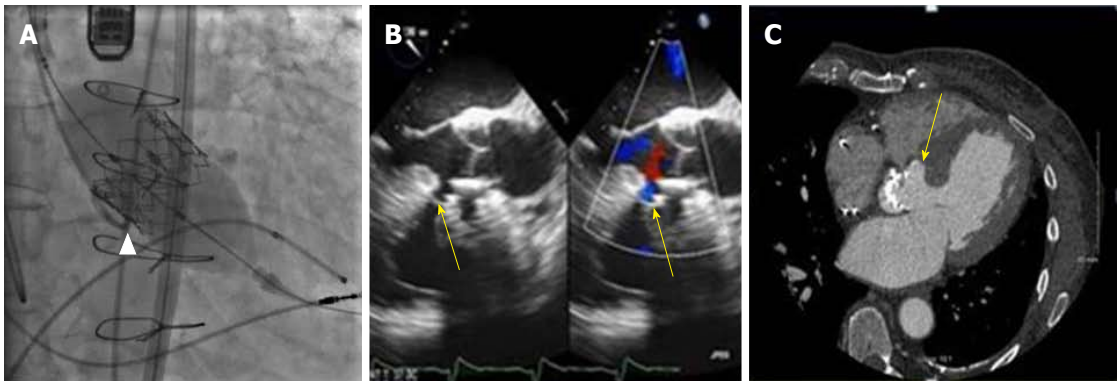

Figure 3 Post deployment assessment of the 29 mm Edwards SAPIEN XT valve at aortic position. A: Deployment of the 29 mm Edwards SAPIEN XT valve at the level of tip of pig tail catheter; B: Immediately after deployment of 29 mm Edwards SAPIEN XT valve, TEE shows color doppler signals in interventricular septal aneurysm (arrows); C: Follow up cardiac computer tomography showed stable prosthetic valve and interventricular septal aneurysm (arrow).

never a need to address it in the past. But as the patient was undergoing TAVR, the interventricular septum was assessed using imaging modalities.

Cardiac MDCT may be the optimal imaging modality to characterize not only the size and location of septal aneurysm[7,8], but also for pre-procedural TAVR planning. Proper assessment of the landing zone including the sub-valvular area below the aortic annulus and along the LVOT is essential. It has been seen that most favorable results are obtained during deployment when full coverage of the aortic leaflets is obtained with secure anchoring at and below the level of the insertion of the native valve leaflets. Based on these observations, the conventional recommendation is to implant the device with 50% above and 50% below native leaflet insertion[9]. But multiple positions have been documented in the literature showing variable ventricular device fractions below the anatomical annulus ranging from low to high[9]. Deployment of the Edwards SAPIEN XT prosthetic valve either getting positioned in a more sub-annular or more supra-annular location is quiet common. Most of the deployments are more supra-annular with varying aortic to ventricular ratio from 60:40 to 90:10.

The real-time imaging in the catheterization lab is inadequate for judgement of the level of leaflet insertion of the native valves. Therefore, the virtual basal ring, which is the anatomical annulus, is taken as the line of implantation during deployment. Malposition of valve can result in valve migration and resulting more severe para-valvular leak or embolization in high supra-annular placement *vs* more chances of AV conduction blocks in sub-annular placement[10]. Other complications including post TAVR shunts have also been reported[11]. Careful placement of the prosthetic valve in a more aortic position like in our case can be the solution despite the presence of aneurysm at the sub-aortic level. This placement does not affect the outcome provided the balloon-expandable valve is strategically placed more aortic than usual position, allowing the transcatheter valve skirt to completely cover the annulus reducing chances of paravalvular leak, as seen in our patient. Now Edward SAPIEN 3 is available which is a new fourth generation valve in the balloon-expandable Sapien series of devices and is easy to deploy due to its ultra-low delivery profile. At that time, the operators had good experience with Edward SAPIEN XT, and the new generation valve was under research. As per our knowledge, the present case is the first report of the utilization of TAVR procedure in a patient with interventricular septal aneurysm and need of higher aortic positioning with an Edward SAPIEN XT valve.

This case emphasizes the feasibility of doing TAVR in patients with interventricular septal aneurysm with LVOT extension. The present case also demonstrates the advantage of careful planning and strategic deployment of the TAVR prosthetic valve in patients with the above anomaly.

ARTICLE HIGHLIGHTS

Case characteristics

Patient with severe calcific aortic stenosis presented with worsening symptom of shortness of breath.

Clinical diagnosis

Patient was diagnosed as symptomatic severe aortic stenosis clinically.

Differential diagnosis

Left ventricular outflow tract obstruction, sub-valvular aortic stenosis and supra-valvular aortic stenosis are the differentials.

Laboratory diagnosis

ECG showed intermittent paced rhythm due to pacemaker and chest x-ray showed sternal wires due to previous coronary artery bypass graft.

Imaging diagnosis

Echocardiography and computer tomography showed severe calcific aortic stenosis with perimembranous interventricular septum aneurysm extending into left ventricular outflow tract.

Pathological diagnosis

Patient had congenital heart defect which included interventricular septum aneurysm extending into left ventricular outflow tract with acquired severe calcific stenosis of tri-leaflet aortic valve.

Treatment

The patient was treated with transcatheter aortic valve replacement .This was achieved in our case by implanting the prosthetic valve more distally into the left ventricular outflow tract (LVOT) requiring apposition of the Edwards SAPIEN XT skirt at annulus with most of the valvular metallic frame in supra-annular position.

Related reports

During transcatheter aortic valve replacement, normally the conventional recommendation is to implant the device with 50% above and 50% below native leaflet insertion .We had 80% aortic and 20% ventricular ratio of the device at the level of leaflet insertion of the native valve.

Term explanation

LVOT denotes left ventricular outflow tract obstruction and TAVR denotes transcatheter aortic valve replacement.

Experiences and lessons

The transcatheter aortic valve replacement can be done in patients having high surgical risk with perimembranous interventricuar septum aneurysm by implanting the device more distally into the LVOT.

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MINIREVIEWS

ABOUT COVER

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AIM AND SCOPE

World Journal of Cardiology (*World J Cardiol*, *WJC*, online ISSN 1949-8462, DOI: 10.4330) is a peer-reviewed open access journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

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MINIREVIEWS

Red blood cell distribution width in heart failure: A narrative review

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Abstract

The red blood cell distribution width (RDW) is a simple, rapid, inexpensive and straightforward hematological parameter, reflecting the degree of anisocytosis *in vivo*. The currently available scientific evidence suggests that RDW assessment not only predicts the risk of adverse outcomes (cardiovascular and all-cause mortality, hospitalization for acute decompensation or worsened left ventricular function) in patients with acute and chronic heart failure (HF), but is also a significant and independent predictor of developing HF in patients free of this condition. Regarding the biological interplay between impaired hematopoiesis and cardiac dysfunction, many of the different conditions associated with increased heterogeneity of erythrocyte volume (*i.e.*, ageing, inflammation, oxidative stress, nutritional deficiencies and impaired renal function), may be concomitantly present in patients with HF, whilst anisocytosis may also directly contribute to the development and worsening of HF. In conclusion, the longitudinal assessment of RDW changes over time may be considered an efficient measure to help predicting the risk of both development and progression of HF.

Key words: Heart failure; Heart disease; Mortality; Erythrocytes; Red blood cell distribution width

Core tip: The red blood cell distribution width is a simple, rapid, inexpensive and straightforward hematological parameter, reliably reflecting the degree of anisocytosis *in vivo*. The current epidemiological and biological

evidence suggests that longitudinal assessment of red blood cell distribution width over time may be considered an efficient measure to help predicting the risk of both development and progression of heart failure.

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INTRODUCTION

Heart failure definition, etiology and epidemiology

As a complex clinical syndrome, heart failure (HF) is characterized by certain symptoms and signs such as dyspnea and fatigue, which impair exercise tolerance, fluid retention, and may provoke pulmonary and/or splanchnic congestion, ankle swelling, peripheral edema, elevated jugular venous pressure, and pulmonary crackles[1,2]. These are principally due to structural and/or functional cardiac abnormalities, which result in an impaired cardiac output and/or elevated intracardiac pressures[1]. The classification of the different types of HF is based on left ventricle ejection fraction (LVEF) as follows: (1) HF with preserved LVEF (HFpEF), *i.e.*, patients with normal LVEF (≥ 50%); (2) HF with reduced EF (HFrEF), *i.e.*, patients with reduced LVEF (< 40%); (3) HF with midrange EF (HFmrEF), *i.e.*, patients with an LVEF in the range of 40%-49%[1].

The etiology of HF is varied, including a wide range of pathologies both cardiovascular and non-cardiovascular. Many patients will suffer different diseases at the same time, which ultimately trigger the HF. Nonetheless, a history of ischemic heart disease (IHD) and myocardial infarction or revascularization is very common among patients with HF[1]. Thus, among the most important causes of death in patients with HF are cardiovascular diseases, mainly sudden death and worsening HF[3,4]. It seems that HFpEF and HFrEF have different etiological profiles, since patients with HFpEF are more often older, women and have a history of hypertension and atrial fibrillation (AF). However, a history of myocardial infarction is uncommonly found in HFpEF patients[5].

The prevalence of HF in developed countries is considered to be around 1%-2% of the adult general population[1]. The incidence increases with age, up to ≥ 10% among people > 70 years of age[6]. For instance, 20% of American population ≥ 40 years of age will develop HF[7] and nearly 5.1 million people in the United States already have clinical signs and symptoms of HF, with a prevalence that seems to be constantly increasing[8], so that approximately 33% of men and 28% of women ≥ 55 years will develop HF worldwide[9]. Using the conventional definition, the percentage of patients with HFpEF ranges from 22% to 73%[1]. Likewise, the incidence of HF may be decreasing, more for HFrEF than for HFpEF[10,11]. Inequalities in the epidemiology of HF have been also reported. A high risk of developing HF has been reported in black populations[12], whilst the incidence seems the lowest among white women[13] and the highest among black men[14], with a higher 5-year mortality[15]. Non-Hispanic black males have a higher prevalence (4.5%) than females (3.8%), whilst non-Hispanic white males also have a higher prevalence (2.7%) than females (1.8%)[8].

Many prognostic biomarkers of death and/or hospitalization in patients with HF have been studied and identified[1]. Unfortunately, their clinical uses remains limited due to the challenges in stratifying the risk of HF patients. Furthermore, multiple prognostic risk scores have been developed in HF[4,16,17], and may be helpful to predict death in these patients. However, they are less useful to predict HF hospitalizations[16,17]. In fact, several studies only reported a moderate accuracy of these models to predict mortality, whilst they were basically less accurate for predicting hospitalization[16,17].

ANISOCYTOSIS

The erythrocytes, also known as red blood cells (RBCs), are non-nuclear corpuscular elements of blood produced in the bone from erythroid colony-forming unit-erythroid (CFU-E) progenitors, which undergo a complex process of maturation (also known as erythropoiesis) into proerythroblasts, erythroblasts, reticulocytes and, finally, into mature erythrocytes[18]. The ensuing conversion of erythroblasts into reticulocytes and erythrocytes is accompanied by the loss of the nucleus, which makes erythrocytes virtually terminal elements (Figure 1).

The entire process of erythropoiesis is regulated by several transcription factors, chromatin modifiers, cytokines, and hormones, the most important of which is erythropoietin (Epo), which not only stimulates the proliferation and differentiation of hematopoietic precursors but is also essential for survival of newly generated RBCs[18]. Physiological erythropoiesis mainly occurs in the bone marrow, so that proerythroblasts and erythroblasts (in their different stages of maturation, *i.e.*, basophilic, polychromatophilic and orthochromatic) are normally absent in the bloodstream, whilst the number of reticulocytes is typically < 1% of the total RBC population[19]. The leading function of RBCs is carrying oxygen throughout the bloodstream, from the lungs to the peripheral tissues, mainly bound to hemoglobin, the most important protein contained within the erythrocytes. The total number of mature RBCs in adult human blood is usually comprised between 4.7×10^{12}/L-6.1×10^{12}/L in men and 4.2×10^{12}/L-5.4×10^{12}/L in women, respectively, with a mean survival time in blood of approximately 100-120 d. A reduction of RBC number below these conventional thresholds is known as "anemia", which is usually diagnosed when the level of hemoglobin in blood falls below 130 g/L in men and 120 g/L in women, respectively[18].

A typical mature erythrocyte appears as a disc-shaped

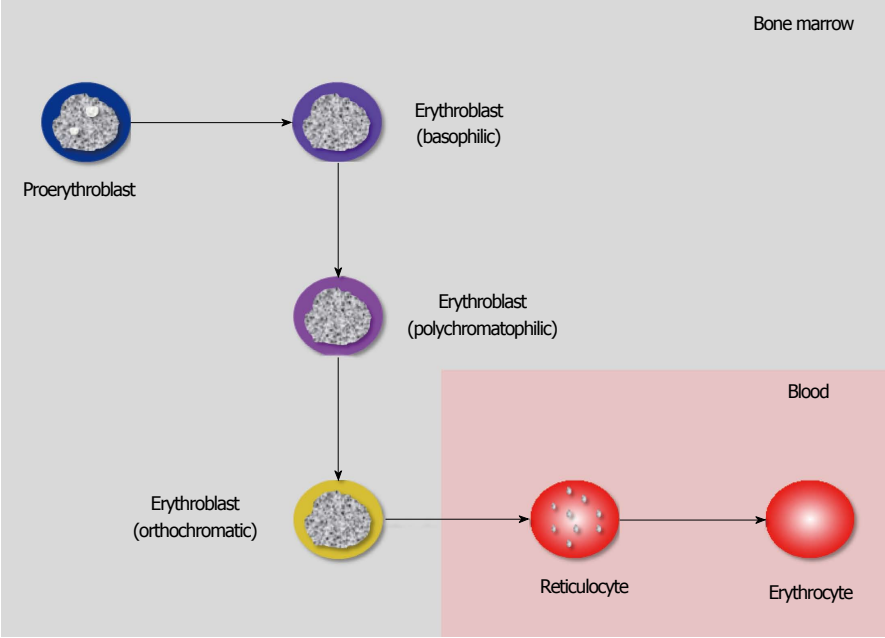

Figure 1 Physiological erythropoiesis.

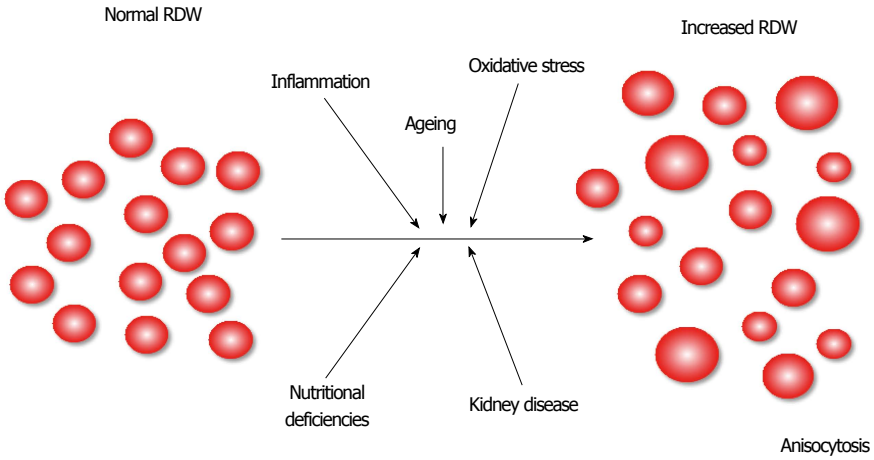

Figure 2 Pathophysiological mechanisms causing anisocytosis. RDW: Red blood cell distribution width.

element with a pale-staining central area, a diameter comprised between 6-8 μm and a total volume (also known as mean corpuscular volume (MCV)] comprised between 80-100 fL. RBC with abnormal volumes, either reduced or increased, are conventionally called microcytic or macrocytic, respectively[19]. RBCs display a physiological size heterogeneity in adult human blood, which is usually measured in terms of RBC distribution width (RDW). This simple and straightforward parameter can thus be expressed both in absolute value, as the standard deviation (SD) of erythrocyte volumes (RDW-SD), or as the coefficient of variation (RDW-CV) of erythrocyte volumes [*i.e.*, (RDW-SD)/ (MCV)*100]. The normal range of RDW-CV is 11.5-14.5% but often varies according to the technique used for its assessment by the different commercially available hematological analyzers[20]. Although a decreased RDW value is very uncommon and has no clinically significance[21], an increase of this parameter is called anisocytosis and has many important consequences on the future risk of adverse cardiovascular events and mortality in the general population[22], as well as in patients with HF or in those at risk of developing HF[23], as more comprehensively discussed in the next sections of this article.

Anisocytosis can hence be essentially defined as a DW value exceeding the analyzer-dependent threshold[24]. More practically, it can be defined as the presence of erythrocytes with a large size heterogeneity in peripheral venous blood, as simplified in Figure 2. The partial or complete derangement of many biological pathways, mainly including aging, inflammation, oxidative stress, nutritional deficiencies, and impaired renal function, has been straightforwardly associated with disrupted erythropoiesis resulting in variable degrees of

Table 1 Differential diagnosis of anemia based on mean corpuscular volume and red blood cell distribution width

Conditions	MCV	RDW
Chronic diseases anemia	↓	N
Heterozygous thalassemia	↓	N
Iron deficiency	↓	↑
β-thalassemia	↓	↑
Sickle cell trait	↓	N
Haemolytic anemia	N/↓	↑
Hereditary spherocytosis	N/↓	↑
Sickle cell disease	N	↑
Haemorrhage	N	N
Blood transfusions	N	↑
Chronic liver disease	N/↑	↑
Aplastic anemia	↑	N
Folate deficiency	↑	↑
Vitamin B12 deficiency	↑	↑
Myelodysplastic syndrome	↑	↑

MCV: Mean corpuscular volume; RDW: Red blood cell distribution width; N: Normal; ↓: Decreased; ↑: Increased.

anisocytosis (Table 1)[25]. Therefore, the aim of this article is to provide an overview of the epidemiological and biological evidence linking anisocytosis and HF.

ANISOCYTOSIS AND HEART FAILURE

Baseline assessment of anisocytosis in HF patients

The very first large prospective study which explored the clinical significance of measuring RDW in patients with HF was published in 2007 by Felker *et al*[26]. Briefly, the authors measured RDW values at enrollment in 2679 chronic HF patients recruited from the North American Candesartan in HF: Assessment of Reduction in Mortality and Morbidity (CHARM) study (validation cohort), who were followed-up for at least 2 years for collecting data on death or hospitalization for managing worsened HF. The data obtained in this cohort were then validated in a replication dataset consisting of additional 2140 HF patients enrolled from the Duke Databank in 1969, and with follow-up data completely available for more than 96% patients. In the final multivariable analysis, including all significant clinical and laboratory parameters, each 1 SD increase of RDW in the CHARM Cohort was associated with 17% higher risk of cardiovascular death or hospitalization for HF [hazard ratio (HR), 1.17; 95% confidence interval (95%CI), 1.10-1.25] and 12% higher risk (HR = 1.12; 95%CI: 1.03-1.20) of all-cause mortality. In the validation cohort, each 1 SD increase of RDW was also associated as with 29% enhanced risk (HR = 1.29; 95%CI: 1.16-1.43) of all-cause mortality.

The following year, Tonelli *et al*[27] published the results of another large prospective study, based on 4111 participants of the Cholesterol and Recurrent Events study, free of HF at baseline, who had their RDW value measured at enrollment and were then followed-up for a median period of approximately 60 mo. In a multivariable model adjusted for all significant clinical and laboratory parameters, each 1% increase in RDW value was associated with 14% increased all-cause mortality (HR = 1.14; 95%CI: 1.05-1.24). Importantly, each 1% increase in RDW value was also associated with 15% higher risk (HR = 1.15; 95%CI: 1.05-1.26) of developing symptomatic HF on follow-up.

These earlier findings were then replicated in a vast number of prospective, retrospective and cross-sectional studies, which were meta-analyzed by Huang *et al*[28], Shao *et al*[29] and, more recently, by Hou *et al*[30] (Table 2).

More specifically, in the meta-analysis by Huang and collaborators[28], each 1% increase in RDW value was associated with 10% enhanced risk of future mortality events (HR = 1.10; 95%CI: 1.07-1.13) in patients with HF. No substantial difference was observed between retrospective (n = 4; HR, 1.09 and 95%CI: 1.02-1.17) and prospective (n = 5; HR = 1.10 and 95%CI: 1.05-1.15) studies, whilst a greater risk was observed in studies with follow-up >2 years (n = 5; HR = 1.13 and 95%CI: 1.09-1.16) than in those with shorter follow-up (n = 4; HR = 1.04; 95%CI: 1.02-1.06). In the ensuing meta-analysis of Shao *et al*[29], each 1% increase in RDW value was associated with 19% enhanced risk of major adverse cardiovascular events (HR = 1.19; 95%CI: 1.08-1.30), with 12% higher risk of death (HR = 1.12; 95%CI: 1.08-1.16), as well as with 9% higher risk of hospitalization (HR = 1.09, 95%CI: 1.03-1.16) in patients with HF. Notably, the association between RDW value and death was found slightly stronger in patients with chronic HF (HR = 1.13, 95%CI: 1.08-1.18) than in those with acute HF (HR = 1.09; 95%CI: 1.04-1.15). More recently, the meta-analysis of Hou *et al*[30] showed that each 1% increase in RDW value was associated with 11% higher risk of death (HR = 1.11; 95%CI: 1.04-1.14) in patients with HF, whilst each 1% increase in RDW value was associated with 11% higher risk of HF in patients with preexisting cardiovascular disease (HR = 1.11; 95%CI: 1.05-1.17).

Dynamic changes of anisocytosis in heart failure patients

Although the notion that baseline RDW assessment may help to predict both unfavorable outcomes in patients with acute or chronic HF as well as the risk of developing HF in patients without this condition seems now quite straightforward (Table 2), an alternative concept is strongly emerging, indicating that serial assessment of RDW over time may be more clinically meaningful and informative than the admission value (Table 3).

The first study which assessed the significance of longitudinal RDW changes in patients with HF was published by Cauthen *et al*[31]. The authors retrospectively analyzed data from 6159 ambulatory chronic HF patients, with the aim of exploring the potential association between clinical outcomes and RDW changes over a 1-year follow-up period. Although each 1% increase in baseline RDW value was independently associated with 9% enhanced risk of 1-year all-cause mortality [relative risk (RR) = 1.09; 95%CI: 1.01-1.17], this association

Table 2 Meta-analyses exploring the association between baseline red blood cell distribution width value and heart failure

Ref.	Variable	Outcome measure	Baseline RDW
Huang *et al*[28], 2014	1% increase in RDW value	Risk of future death in patients with HF	HR, 1.10 (95%CI: 1.07-1.13)
		Risk of hospitalization in patients with HF	HR, 1.09 (95%CI: 1.03-1.16)
Shao *et al*[29], 2015	1% increase in RDW value	Risk of future MACE in patients with HF	HR, 1.19 (95%CI: 1.08-1.30)
		Risk of future death in patients with HF	HR, 1.12 (95%CI: 1.08-1.16)
Hou *et al*[30], 2017	1% increase in RDW value	General risk of HF	HR, 1.11 (95%CI: 1.05-1.17)
			HR, 1.11 (95%CI: 1.04-1.14)

HF: Heart failure; HR: Hazard ratio; MACE: Major adverse cardiovascular events; RDW: Red blood cell distribution width.

Table 3 Studies exploring the association between serial red blood cell distribution width changes and heart failure

Ref.	Study design	Outcome measure	Variable	Baseline RDW	Longitudinal RDW change
Cauthen *et al*[31], 2012	Retrospective, 6159 patients with chronic HF	1-year all-cause mortality	1% increase in RDW at diagnosis or during 1 year of follow-up	RR, 1.09 (95%CI: 1.01-1.17)	RR, 1.21 (95%CI: 1.08-1.34)
Makhoul *et al*[32], 2013	Prospective, 614 patients with acute decompensated HF followed-up during hospital stay	All-cause mortality during hospital stay	1% increase in RDW value at admission or during hospital stay	HR, 1.15 (95%CI: 1.08-1.21)	HR, 1.23 (95%CI: 1.09-1.38)
Núñez *et al*[33], 2014	Prospective, 1702 patients with HF followed-up for 18 mo	All-cause mortality during follow-up	RDW ⩾ 15% at admission or during follow-up	Anemic patients: HR, 1.04 (95%CI: 1.00-1.07) Non-anemic patients: HR, 1.11 (95%CI: 1.05-1.19)	Anemic patients: HR, 1.08 (95%CI: 1.04-1.13) Non-anemic patients: HR, 1.31 (95%CI: 1.22-1.42)
Ferreira *et al*[35], 2016	Retrospective, 502 patients with acute decompensated HF	Hospitalization for acute decompensated HF or 180-d cardiovascular death	RDW ⩾ 15% at admission and delta RDW > 0 at discharge	OR, 1.29 (95%CI: 0.71-2.33)	OR, 2.47 (95%CI: 1.35-4.51)
Muhlestein *et al*[34], 2016	Prospective, 6414 patients with HF followed-up during hospital stay	30-d all-cause mortality	1% increase in RDW value at admission and during hospital stay	HR, 1.09 (95%CI: 1.07-1.12)	HR, 1.09 (95%CI: 1.03-1.16)
Uemura *et al*[36], 2016	Prospective, 229 patients with acute decompensated HF followed-up followed for 692 d	All-cause mortality during follow-up	RDW ⩾ 14.5% at admission and positive change of RDW at discharge	HR, 1.08 (95%CI: 0.99-1.19)	HR, 1.19 (95%CI: 1.01-1.41)
Turcato *et al*[37], 2017	Retrospective, 588 patients with acute decompensated HF	30-d all caused mortality	ΔRDW > 0.4% at 48 and 96 h	-	OR, 3.04 (95%CI: 1.56-5.94) and 3.65 (95%CI: 2.02-6.15)

HF: Heart failure; HR: Hazard ratio; OR: Odds ratio; RDW: Red blood cell distribution width; RR: Relative risk.

was found to be much stronger considering longitudinal RDW variations (RR for each 1% increase in RDW during follow-up, 1.12; 95%CI: 1.08-1.34).

In the study performed in 2013 by Makhoul *et al*[32], the population consisted of a total number of 614 patients with acute decompensation of HF, who had RDW measured at baseline and throughout hospital stay, and who were then followed-up for 1 year. Interestingly, each 1% increase in RDW value measured at baseline was independently associated with a 15% higher risk (HR = 1.15; 95%CI: 1.08-1.21) of all-cause mortality, but this association was even stronger using longitudinal changes of RDW, since each 1% increase in RDW value during hospital stay was associated with 23% higher risk (HR = 1.23; 95%CI: 1.09-1.38) of all-cause mortality.

In 2014, Núñez *et al*[33] also studied 1702 patients discharged after being diagnosed with acute HF, and who had their RDW assessed during a median follow-up period of 18 mo. The baseline RDW value was found to be independently associated with all-cause mortality both in anemic (HR = 1.04; 95%CI: 1.00-1.07) and non-anemic patients (HR = 1.11; 95%CI: 1.05-1.19), but an even stronger association was found between the last longitudinally updated RDW (*i.e.*, the mean of RDW values measured during follow-up) and death, both in anemic (HR = 1.08; 95%CI: 1.04-1.13) and non-anemic (1.31; 95%CI: 1.22-1.42) patients.

In an ensuing article, Muhlestein *et al*[34] published the results of a prospective study based on 6414 patients hospitalized for HF, who had RDW measured within 24 h from admission and at least one more time during hospitalization. As predictable, each 1% increase in RDW measured at baseline was independently

associated with a 9% higher risk of 30-d all-cause mortality (HR = 1.09; 95%CI: 1.07-1.12), but a similar risk was also observed for each 1% increase in RDW during hospitalization (HR = 1.09; 95%CI: 1.03-1.16). Interestingly, the risk of 30-d all-cause death was considerably magnified (*i.e.*, HR, 2.02) when data of both the baseline value and longitudinal changes of RDW were combined in the predictive model.

Ferreira *et al*[35] carried out a retrospective study based on 2 independent cohorts of patients admitted to the emergency department with acute decompensation of HF, the first (*i.e.*, the derivation cohort) consisting of 170 patients and the second (*i.e.*, the validation cohort) consisting of 332 patients. RDW was measured at admission and at hospital discharge, with calculation of the ratio between these two values (*i.e.*, ΔRDW). In the final model, a RDW value >15% at admission was independently associated with a 29% higher risk [odds ratio (OR), 1.29; 95%CI: 0.71-2.33] of composite outcome (hospitalization for acute decompensated HF or 180-d cardiovascular death), whilst such risk was found to be substantially higher for patients with ΔRDW > 0 (OR = 2.47; 95%CI: 1.35-4.51). Even more importantly, the combination of RDW value > 15% at admission and ΔRDW > 0 yielded a substantially higher risk of composite outcome than the two measures alone (OR = 3.40; 95%CI: 1.63-7.08).

Uemura *et al*[36] studied 229 patients hospitalized for acute decompensated HF, who had their RDW measured at admission and at hospital discharge, and who were then followed-up for a median period of 692 d. Although an increased baseline value of RDW at admission (*i.e.,* $\geqslant$ 14.5%) was slightly but non-significantly associated with all-cause mortality (HR, 1.08; 95%CI: 0.99-1.19), patients exhibiting a positive change (*i.e.*, an increase) of RDW between admission and discharge had a 19% higher risk of all-cause mortality on follow-up (HR = 1.19; 95%CI: 1.01-1.41).

More recently, Turcato *et al*[37] carried out a retrospective study including 588 patients hospitalized for acute decompensation of HF. RDW values were measured at admission and also after 48 h and 96 h of hospitalization. Interestingly, a ΔRDW > 0.4% calculated between the value at admission and those obtained after 48 h and 96 h of hospital stay was independently associated with a over 3-fold higher risk of 30-d mortality (OR of 48 h ΔRDW, 3.04; 95%CI: 1.56-5.94 and OR of 96 h ΔRDW, 3.65; 95%CI: 2.02-6.15).

Finally, Xanthopoulos *et al*[38] studied 218 patients who were admitted to the emergency department for acute HF, and who had their RDW measured at admission, at discharge and at 4, 8 and 12 mo afterward. Follow-up for all-cause mortality or rehospitalization was 12 mo. Each 1% increase in RDW value at admission was independently associated with the composite endpoint both in non-diabetic (HR = 1.14; 95%CI: 1.01-1.29) and diabetic (1.35; 95%CI: 1.12-1.62) patients. Notably, the longitudinal changes of RDW showed a significant interaction with diabetes (β coefficient, -0.002; *P* = 0.042), thus highlighting that metabolic imbalances may actually have an impact on longitudinal changes of RDW. According to these findings, anisocytosis may hence be considered not only a bystander but also a potential underlying biological mechanism explaining the adverse long-term effects of diabetes on the risk of hospitalization and mortality in patients with HF[39].

THE BIOLOGICAL INTERPLAY BETWEEN ANISOCYTOSIS AND HEART FAILURE

Regarding the physiopathological interplay between anisocytosis and HF, many of the different conditions impairing hematopoiesis, and thus potentially leading to a larger size heterogeneity of RBC volumes (Figure 2), may be concomitantly present in patients with HF.

Convincing evidence has accumulated that both cell- and cytokine-mediated inflammatory pathways actively contribute to development and progression of HF[40]. An important interplay has also been recognized between inflammation and anisocytosis since inflammation is frequently associated with bone marrow dysfunction and an increase of circulating premature erythrocytes[41]. As regards oxidative stress, an excess production of reactive oxygen species (ROS) has been associated with both adverse cardiac remodeling[42] and deranged hematopoiesis, ultimately leading to anisocytosis[43]. Nutritional deficiencies are commonplace in many forms of anemia characterized by different degrees of anisocytosis[44], but they are also deeply involved in onset and progression of HF[45]. The progressive impairment of renal function is one of the leading causes of anemia and anisocytosis, especially in the elderly[46], but is also an important determinant of adverse outcomes in patients with HF[47]. Lastly, anisocytosis gradually increases with aging as a result of multiple metabolic dysfunctions[48], but advanced age is also a strong contributing factor for cardiac dysfunction[49]. Therefore, the current evidence suggests that anisocytosis and HF may share many pathogenetic mechanisms, which may explain why both conditions may develop and progress in parallel, thus making RDW a reliable marker of cardiac dysfunction.

Nevertheless, anisocytosis may also play a direct role in the onset and progressive worsening of HF. The erythrocyte size heterogeneity mirrors a reduced (often severely impaired) function of this essential corpuscular blood elements. In conditions of high anisocytosis, RBCs are often characterized by lower deformability and decreased oxygen-carrier capacity, thus contributing to reduced oxygenation of many peripheral tissues and cells (including cardiomyocytes), whilst abnormal erythrocytes may also actively participate in the pathogenesis of cardiac fibrosis through promotion or amplification of inflammation, cardiomyocyte stress and apoptosis[20].

CONCLUSION

The RDW is a simple, rapid, inexpensive and straightforward hematological parameter, which is now automatically generated by all commercially available hematological analyzers together with the complete blood cells count (CBC). Increased RDW values in venous blood samples truly mirror the degree of anisocytosis *in vivo*, and can hence be used for diagnostic, prognostic and even therapeutic decisions in many acute and chronic pathological conditions[50].

The currently available scientific evidence convincingly suggests that RDW measurement not only predicts the risk of adverse outcomes (cardiovascular and all-cause mortality, hospitalization for acute decompensation or cardiac dysfunction) in patients with HF but is also a significant and independent predictor of developing HF in patients free of this condition at the time of baseline assessment (Table 2). Nevertheless, the longitudinal assessment of RDW changes over time (*i.e.*, during a hospital stay or shortly afterward) may be an even more effective measure than the baseline value for predicting adverse outcomes in patients with chronic, acute and even acutely decompensated HF (Table 3). The longitudinal assessment of RDW has another important advantage, emerging from its insensitivity to the analyzer used for its measurement. In fact, longitudinal changes either assessed as differences or ratios between the first and the following measurements, may help overcoming the still unresolved issue of poor harmonization of RDW measures[24], which still hampers the identification of an universally valid diagnostic or predictive threshold. It is also noteworthy in the two studies combining RDW values at admission and their subsequent variations during follow-up[34,35], the diagnostic efficiency of this combination was found to be much better than either measure alone for predicting adverse outcomes in HF patients.

In conclusion, we suggest that the serial measurement of RDW, and especially the combination of admission value with subsequent changes during in-hospital or home care, may be seen as an affordable and efficient tool to help assessing the prognosis of patients with HF and for reliably predicting the risk of adverse events.

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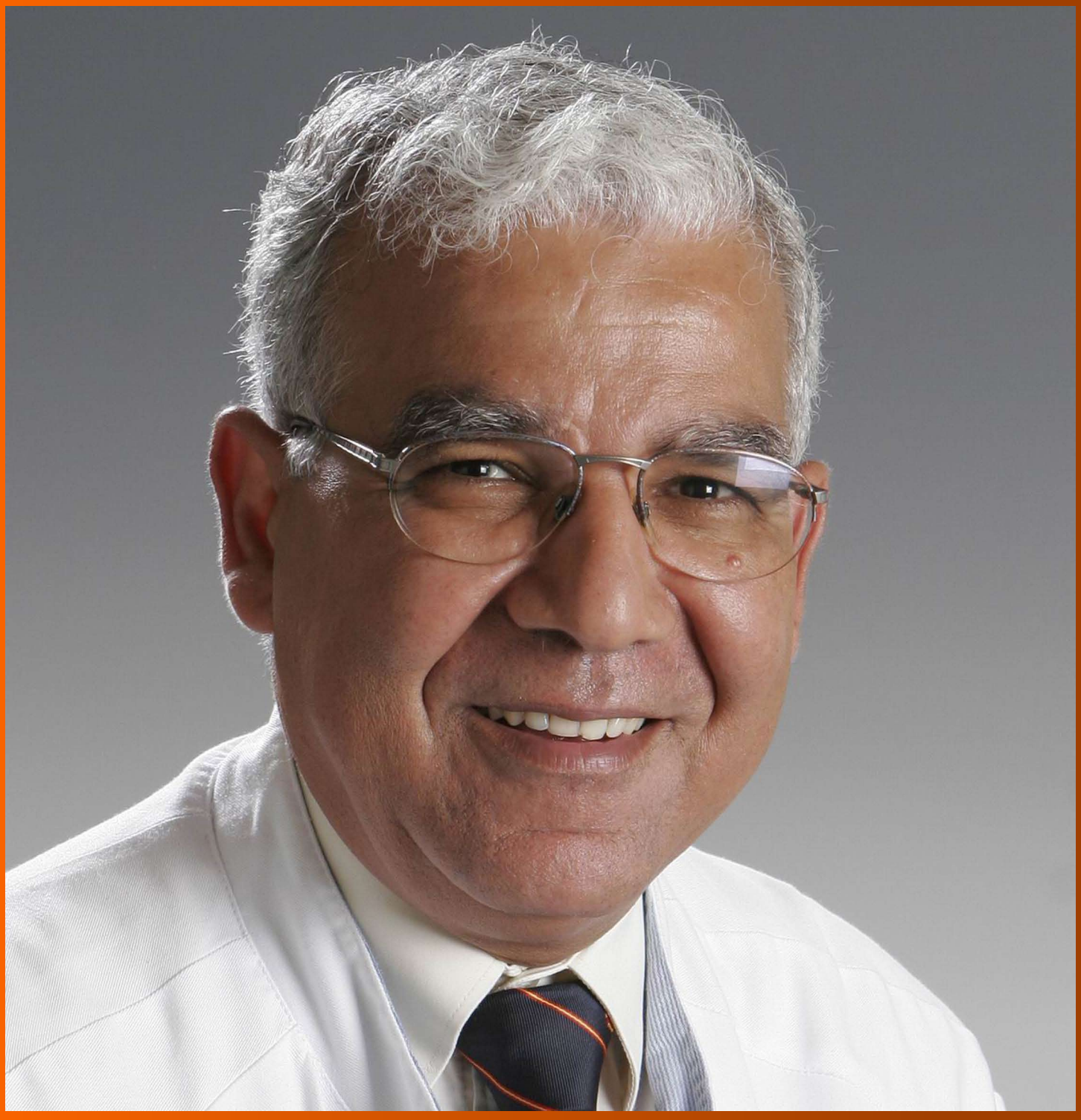

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CASE REPORT

Increased frequency of angina attacks caused by switching a brand-name vasodilator to a generic vasodilator in patients with vasospastic angina: Two case reports

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Abstract

It is well known that calcium channel blockers (CCBs) are the first line of therapy for vasospastic angina (VSA). Here, we report two cases of VSA with an increase in the frequency of angina attacks after switching from a brand-name to a generic CCB. In both cases, angina recurred upon switching from a brand-name CCB to a generic CCB during follow-up. The patients' condition improved upon switching back to the original CCB. Both cases involved a high severity of VSA, based on the results of spasm provocation testing. These findings suggest that, in some patients with severe VSA, the frequency of angina attacks increases when switching from a brand-name CCB to a generic CCB. Cardiologists should consider this factor when prescribing drugs for angina.

Key words: Vasospastic angina; Acetylcholine; Brand-name drugs; Generic drugs; Refractory chest pain

Core tip: Calcium-channel blockers (CCBs) are the first line of therapy for vasospastic angina (VSA). Here, we report two cases of VSA with an increase in the frequency of angina attacks after switching from a brand-name to a generic CCB. Switching back to the original CCB improved the patients' condition in

both cases. Both cases involved highly severe VSA. It is important for cardiologists to check whether VSA patients who have refractory angina attacks while taking a CCB are taking a brand-name or generic CCB.

Goto-Semba R, Fujii Y, Ueda T, Oshita C, Teragawa H. Increased frequency of angina attacks caused by switching a brand-name vasodilator to a generic vasodilator in patients with vasospastic angina: Two case reports. *World J Cardiol* 2018; 10(3): 15-20 Available from: URL: http://www.wjgnet.com/1949-8462/full/v10/i3/15.htm DOI: http://dx.doi.org/10.4330/wjc.v10.i3.15

INTRODUCTION

Vasospastic angina (VSA) is caused by myocardial ischemia due to sudden excessive vasoconstriction of the epicardial coronary arteries[1,2]. It has been demonstrated that coronary spasm causes not only unstable angina but also exertional angina, acute coronary syndrome, and acute sudden death[1,2]. In every patient, it is important to assess whether coronary spasm is associated with the patients' symptoms or with their pathology. VSA is generally diagnosed on the basis of a combination of characteristic chest symptoms and transient ST-T segment changes on the electrocardiogram (ECG)[3]. However, our personal experience is that in many patients, the diagnosis of VSA cannot be made based on these findings. In such cases, the spasm provocation test (SPT) has been very effective in making a correct diagnosis of VSA[4,5]. The treatment for VSA is based on life-style management and drug therapy. The use of calcium-channel blockers (CCBs) to prevent VSA is recommended as the first line of therapy[3].

Generic drugs are identical to, but substantially less expensive than their brand-name counterparts with respect to the dosage, strength, route of administration, quality, performance characteristics, and intended use[6]. Thus, the use of generic drugs can help reduce overall medical expenses, and their market share is expanding even in Japan. In general, the effects of brand-name and generic drugs are identical[6,7]. However, the effects may not be applicable for all patients and may differ according to the patients' disease severity and/or subtype.

Here, we present two cases of VSA with increase in the frequency of angina attacks after switching from a brand-name CCB to a generic CCB.

CASE REPORT

Case 1

A 70-year-old woman experienced chest pain at rest. She was admitted to our institution to undergo coronary angiography (CAG) because her cardiac CT scan indicated coronary artery stenosis. On admission, her vitals were stable. Blood testing revealed hyperlipidemia. ECG, echocardiography, and chest radiography showed no specific findings. CAG showed no significant coronary stenosis, and subsequent SPT using acetylcholine (ACh) revealed bilateral spasm at the distal segment of the right coronary artery (RCA) at a dose of 50 μg of ACh, and a focal spasm at the mid-segment of the left anterior descending (LAD) coronary artery at a dose of 30 μg of ACh. Intracoronary infusions of nitroglycerin relieved the bilateral coronary spasms (Figure 1). She was diagnosed with VSA and was prescribed diltiazem hydrochloride (100 mg capsule, BID) and pitavastatin calcium hydrate (2 mg tablet, QD). After 10 mo, isosorbide dinitrate patches (40 mg patch, QD) were added because her chest pain recurred four times a month. After that, however, she felt discomfort due to dermal isosorbide dinitrate, so the patches were discontinued and she was switched from diltiazem hydrochloride to benidipine hydrochloride (4 mg tablet, BID), which improved her anginal symptoms. After 4 mo, she switched from benidipine hydrochloride to a generic CCB. At that time, she began to have angina attacks four to five times a month. Therefore, we switched her back to the brand-name CCB, and she has not experienced chest pain since (Table 1).

Case 2

A 50-year-old man, who had previously undergone percutaneous coronary artery stenting for unstable angina and was also diagnosed as having VSA, was treated with many kinds of vasodilators. He was admitted to our institution to undergo CAG due to increased frequency of chest pain at night and during early mornings, with an overall frequency of three or four times per week over several months. His coronary risk factors included smoking (40/d × 30 years) and hypercholesterolemia. On admission, his vitals were stable. ECG, chest radiography, and echocardiography showed no specific findings. CAG showed no significant coronary stenosis, including stented segments. SPT, performed when taking vasodilators, revealed diffuse spasms in the three major coronary arteries (at doses of 30 μg of ACh for the RCA and 50 μg of ACh for the left coronary artery). Intracoronary infusions of nitroglycerin relieved the bilateral coronary spasms (Figure 2). We questioned him in detail about his past medications to determine treatment options. He had been on medication [isosorbide dinitrate (20 mg tablet, BID and 40 mg patch, QD), diltiazem hydrochloride (100 mg tablet, BID), verapamil hydrochloride (80 mg tablet, at bedtime), sarpogrelate hydrochloride (100 mg tablet, BID), ezetimibe (10 mg tablet, QD), aspirin (100 mg tablet, QD), rosuvastatin calcium (20 mg tablet, QD), ethyl icosapentate (900 mg capsule, BID), and nitroglycerin (0.3 mg tablet, prn)] before admission, but the frequency of angina attacks had been increasing ever since he switched from a brand-name CCB to a generic CCB several months earlier. After we switched back from the generic CCB to the brand-name CCB, the frequency of angina attacks decreased to once per

Table 1 Time course of frequency of chest pain and cardiovascular drug regimen in Case 1

Time course	Frequency of chest pain	Cardiovascular drug regimen
Discharge	None	Diltiazem hydrochloride (brand-name) 100 mg capsule, BID Pitavastatin calcium (brand-name) 2 mg tablet, QD
10 mo later	4/mo	Diltiazem hydrochloride (brand-name) 100 mg capsule, BID Pitavastatin calcium (brand-name) 2 mg tablet, QD Isosorbide dinitrate (brand-name) 40 mg tape, QD
11 mo later	None, but nausea (+)	Benidipine hydrochloride (brand-name) 4 mg tablet, QD Pitavastatin calcium (brand-name) 2mg tablet, QD
12 mo later	None	Benidipine hydrochloride (brand-name) 4 mg tablet, QD Pitavastatin calcium (brand-name) 2 mg tablet, QD
14 mo later	None	Benidipine hydrochloride (generic) 4 mg tablet, QD Pitavastatin calcium (brand-name) 2 mg tablet, QD
15 mo later	4-5/mo	Benidipine hydrochloride (brand-name) 4 mg tablet, QD Pitavastatin calcium (brand-name) 2 mg tablet, QD
Thereafter	None	Benidipine hydrochloride (brand-name) 4 mg tablet, QD Pitavastatin calcium (brand-name) 2 mg tablet, QD

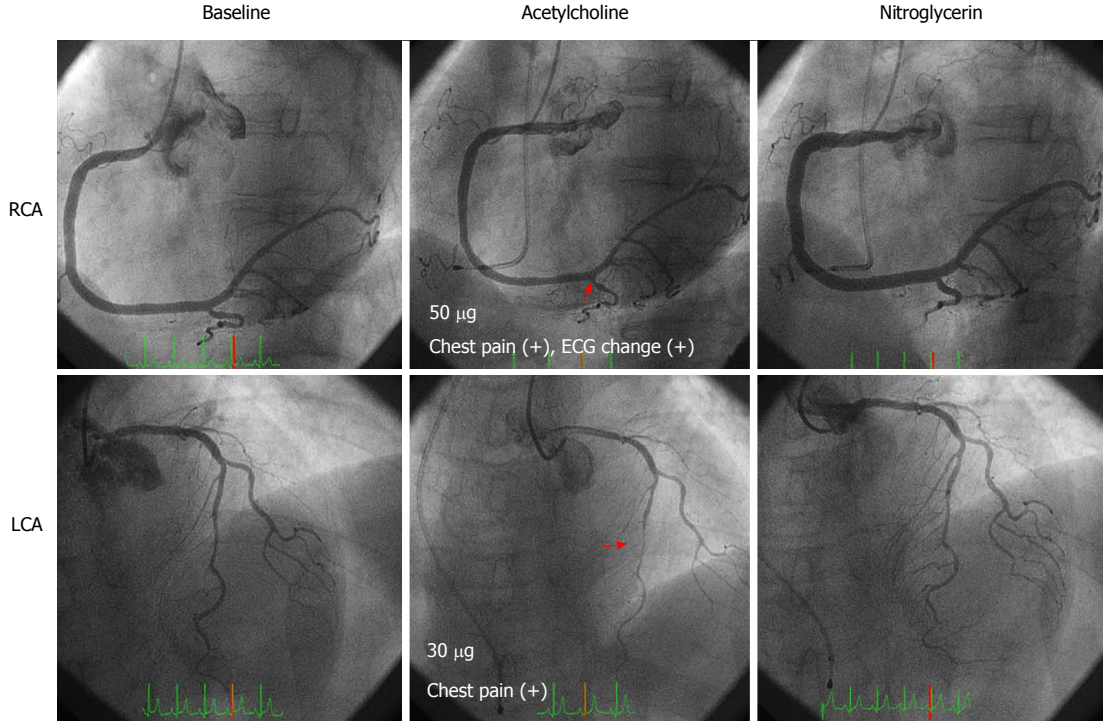

Figure 1 Coronary angiography and spasm provocation test (SPT) for Case 1. Coronary angiograms show angiographically normal coronary arteries (left upper and lower panels). During the SPT, coronary spasms occurred at the distal segment of the right coronary artery (RCA) at 50 μg of ACh (middle upper panel) and at the mid-segment of the left anterior descending coronary artery (LAD) at 30 μg of ACh (middle lower panel). These coronary spasms resolved after an injection of nitroglycerin (right upper and lower panels). Spastic segments are indicated by arrows.

week (Table 2).

DISCUSSION

We describe two cases of VSA with an increase in the frequency of angina attacks after switching from a brand-name CCB to a generic CCB. In both cases of VSA, chest pain was under control to some extent while taking the brand-name CCB. However, switching to a generic CCB increased the frequency of angina attacks. Switching back to the brand-name CCB regimen reduced the frequency of angina attacks. These cases suggest that switching of coronary vasodilators from a brand-name drug to a generic drug has could worsen anginal symptoms in some patients with VSA.

One advantage of using generic drugs is the reduction in medical expenditure because of their low cost. However, brand-name drugs and generic drugs differ in terms of their dosage, additives, and production methods. A comparative study of the amount of CCB-related substances identified in a purity test reported that a generic CCB contains twice as much analog of the active ingredient than a brand-name CCB[8]. On the other hand, according to meta-analyses, generic and

Table 2 Time course of frequency of chest pain and cardiovascular drug regimen in Case 2

Time course	Frequency of chest pain	Cardiovascular drug regimen
Several months ago		Diltiazem hydrochloride (brand-name) 100 mg capsule, BID Isosorbide dinitrate (brand-name) 20 mg capsule, BID Isosorbide dinitrate (brand-name) 40 mg tape, QD Verapamil hydrochloride (brand-name) 80 mg tablet, at bedtime Sarpogrelate hydrochloride (generic) 100mg tablet, BID Rousvastatin calcium (brand-name) 20 mg tablet, QD Ezetimibe (brand-name) 10 mg tablet, QD Ethil isosapentate (generic) 900 mg capsule, QD
	1/wk	
Several months ago, admission		Diltiazem hydrochloride (generic) 100 mg capsule, BID Isosorbide dinitrate (brand-name) 20 mg capsule, BID Isosorbide dinitrate (brand-name) 40 mg tape, QD Verapamil hydrochloride (brand-name) 80 mg tablet, at bedtime Sarpogrelate hydrochloride (generic) 100 mg tablet, BID Rousvastatin calcium (brand-name) 20 mg tablet, QD Ezetimibe (brand-name) 10 mg tablet, QD Ethil isosapentate (generic) 900 mg capsule, QD
	3-4/wk	
Thereafter		Diltiazem hydrochloride (brand-name) 100 mg capsule, BID Isosorbide dinitrate (brand-name) 20 mg capsule, BID Isosorbide dinitrate (brand-name) 40 mg tape, QD Verapamil hydrochloride (brand-name) 80 mg tablet, at bedtime Sarpogrelate hydrochloride (generic) 100 mg tablet, BID Rousvastatin calcium (brand-name) 20 mg tablet, QD Ezetimibe (brand-name) 10 mg tablet, QD
	1/wk	Ethil isosapentate (generic) 900 mg capsule, QD

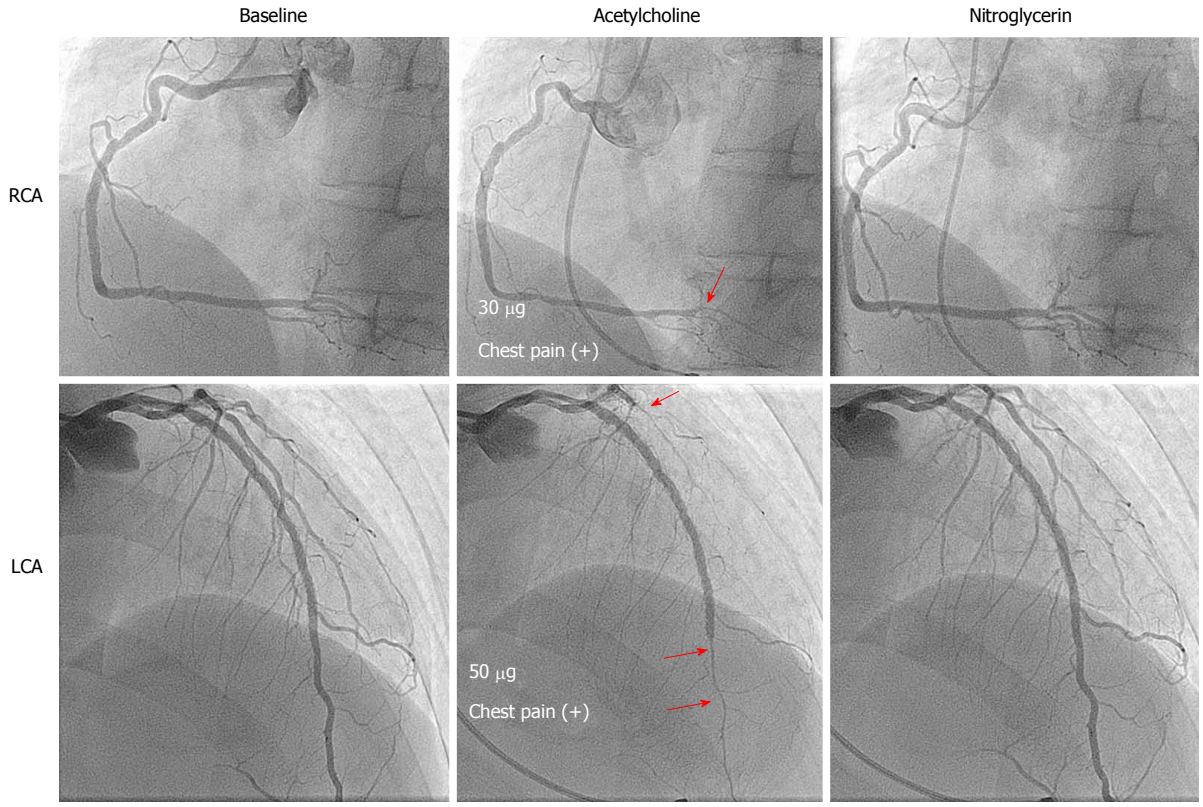

Figure 2 Coronary angiography and SPT for Case 2. Coronary angiograms show no significant coronary stenosis of either the RCA (left upper panel) or the left circumflex artery (LCA, left lower panel). The SPT performed during treatment with several vasodilator showed coronary spasms at the distal segments of the RCA at a dose of 30 μg ACh (middle upper panel), distal to the stented segment of the LAD and at the diffuse segment of the LCA (middle lower panel). These coronary spasms resolved immediately after an injection of nitroglycerin (right upper and lower panels). Spastic segments are indicated by arrows.

brand-name drugs used in cardiovascular disease are clinically equivalent: there is no evidence supporting the superiority of brand-name drugs over generic drugs[6,7]. Specifically, the difference in the effects of brand-

name and generic vasodilators used for cardiovascular diseases, especially for VAS, is not known.

Variation in the severity of VSA is seasonal, and it cannot be denied that the worsening and improvement of angina attacks in these two cases may be because of the natural course of VSA symptoms. However, we think that the dramatic changes in the frequency of angina attacks immediately after switching of CCBs-between generic and brand-name drugs-was because of the lower efficacy of the generic CCBs used. Although similar effects can be expected in the majority of patients treated for VSA with either generic or brand-name drugs, it is possible that the effects of these two drugs differ based on patients' disease severity and/or the nature of their disease. Our two cases of VSA demonstrated a positive SPT including multi-vessel spasms and spasm provocation induced by low doses of ACh, which is characteristic of intractable VSA[9]. In addition, the patient described in case 2 had a positive SPT even while on a treatment regimen that included several vasodilators, demonstrating highly severe VSA. Accordingly, even a minor change in the effect of CCBs when switching between brand-name drugs and generic drugs may influence the VSA attack threshold. Thus, switching from a brand-name drug to a generic drug may worsen angina attacks in patients with highly severe VSA.

CCBs are generally recommended as the first line of therapy to prevent angina attacks in VSA patients, and some patients have angina attacks even while taking CCB medications[3]. In such cases, we follow several courses of action. First, we must consider the type of CCB, because CCBs may differ in their ability to prevent angina attacks[10,11]. Second, we must consider the dosing regimen, such as whether a submaximal or maximal dose or medication once or twice a day would be appropriate. We sometimes encounter patients on a once-a-day CCB regimen who have angina attacks just before they are due to take their medication. Third, we must consider the medication timing. In general, angina attacks often occur between midnight and the early morning[1,2]. Thus, taking a CCB at bedtime is usually recommended. However, for some VSA patients, taking a CCB at the time of rising may be effective. In addition, we may add another vasodilator such as long-acting nitrates, nicorandil and other types of CCBs (dihydropyridine CCB *vs* non-dihydropyridine CCB)[12]. Finally, as shown in the present case reports, we must check whether the prescribed vasodilators are brand-name vasodilators or not. This may also prevent a redundant increase in the numbers of vasodilators prescribed to such patients.

There were several limitations in the present case reports. We did not observe any ST-T changes on ECG during anginal attacks. Furthermore, we did not perform a repeat coronary angiography and spasm provocation test to confirm the effect of brand-name *vs* generic coronary vasodilators. Thus, the severity of anginal symptoms was based only on self-assessment.

In conclusion, switching of CCBs from brand-name drugs to generic ones may worsen angina attacks in some patients with VSA. Therefore, when treating VSA patients with medication-refractory anginal symptoms, it is important that cardiologists confirm the type (brand-name or generic) of vasodilator drugs used.

ARTICLE HIGHLIGHTS

Case characteristics

The frequency of angina attacks increased after switching a brand-name vasodilator to a generic vasodilator in two patients with vasospastic angina (VSA).

Clinical diagnosis

VSA.

Differential diagnosis

Organic coronary stenosis, microvascular angina, chest pain syndrome and gastroesophageal reflux disease.

Laboratory diagnosis

Both patients had dyslipidemia, but the laboratory tests for lipid levels were within normal limits because they were being treated for dyslipidemia.

Imaging diagnosis

Coronary angiography and the spasm provocation test showed bilateral coronary spasm in both cases. These findings are indicative of severe VSA.

Treatment

After switching back from the generic vasodilators to the brand-name vasodilators, the frequency of angina attacks decreased to baseline in both patients.

Related reports

According to meta-analyses, the clinical effects of generic and brand-name drugs used in cardiovascular disease are similar, but it is unclear whether this is the case for patients with higher severity of VSA.

Term explanation

VSA is characterized by the transient vasoconstriction of the epicardial coronary artery, leading to myocardial ischemia. VSA causes not only rest angina but also exertional angina, acute coronary syndrome and ischemic cardiac arrest.

Experience and lessons

Generic vasodilators may not sufficiently prevent angina attacks in patients with a high severity of VSA. Thus, when treating VSA patients with medication-refractory anginal symptoms, it is important that cardiologists confirm the type (brand-name or generic) of vasodilator drugs used.

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ORIGINAL ARTICLE

Retrospective Study

Outcomes after asystole events occurring during wearable defibrillator-cardioverter use

Jackson J Liang, Nicole R Bianco, Daniele Muser, Andres Enriquez, Pasquale Santangeli, Benjamin A D'Souza

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Author contributions: Liang JJ, Bianco NR, and D'Souza BA designed the study, performed the analyses and wrote the initial manuscript draft; Muser D, Enriquez A and Santangeli P assisted with the writing of the manuscript and provided critical editing of the manuscript.

Institutional review board statement: The institutional review board at the University of Pennsylvania exempted this study from review.

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Conflict-of-interest statement: Nicole R Bianco is a research scientist at ZOLL Medical Corporation; Benjamin A D'Souza has received compensation (< $10000) for speaking for ZOLL Medical Corporation. The other authors report no conflicts of interest. The other authors report no potential conflicts of interest relevant to this article.

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Abstract

AIM

To examine whether wearable cardioverter defibrillator (WCD) alarms for asystole improve patient outcomes and survival.

METHODS

All asystole episodes recorded by the WCD in 2013 were retrospectively analyzed from a database of device and medical record documentation and customer call reports. Events were classified as asystole episodes if initial presenting arrhythmia was asystole (< 10 beats/minor $\geqslant$ 5 s pause). Survival was defined as recovery at the scene or arrival to a medical facility alive, or not requiring immediate medical attention. Episodes occurring in hospitals, nursing homes, or ambulances were considered to be under medical care. Serious asystole episodes were defined as resulting in unconsciousness, hospital transfer, or death.

RESULTS

Of the total 51933 patients having worn the WCD in

2013, there were 257 patients (0.5%) who had asystole episodes and comprised the study cohort. Among the 257 patients (74% male, median age 69 years), there were 264 asystole episodes. Overall patient survival was 42%. Most asystoles were considered "serious" (*n* = 201 in 201 patients, 76%), with a 26% survival rate. All 56 patients with "non-serious" asystole episodes survived. Being under medical care was associated with worse survival of serious asystoles. Among acute survivors, 20% later died during WCD use (a median 4 days post asystole episode). Of the 86 living patients at the end of WCD use period, 48 (56%) received ICD/pacemaker and 17 (20%) improved their condition.

CONCLUSION

Survival rates after asystole in patients with WCD are higher than historically reported survival rates. Those under medical care at time of asystole exhibited lower survival.

Key words: Asystole; Bradycardia; Cardiac arrest; Defibrillator; LifeVest

Core tip: Survival rates after asystole, including serious episodes, in patients being treated with wearable cardioverter-defibrillators is higher than historically reported survival rates in the emergency medicine literature. Wearable cardioverter-defibrillators may improve outcomes by alarming and alerting bystanders to assist patients with asystole events.

Liang JJ, Bianco NR, Muser D, Enriquez A, Santangeli P, D'Souza BA. Outcomes after asystole events occurring during wearable defibrillator-cardioverter use. *World J Cardiol* 2018; 10(4): 21-25 Available from: URL: http://www.wjgnet.com/1949-8462/full/v10/i4/21.htm DOI: http://dx.doi.org/10.4330/wjc.v10.i4.21

INTRODUCTION

Survival to hospital discharge for out-of-hospital cardiac arrest (OHCA) victims found to be in bradycardia or asystole is low (2%). The wearable cardioverter-defibrillator (WCD) has been increasingly utilized to detect and treat potentially fatal ventricular arrhythmias in high-risk patients with cardiomyopathy and low left ventricular ejection fraction (LVEF). Most life-threatening arrhythmias recorded by the WCD are ventricular arrhythmias (VA) such as ventricular tachycardia (VT) and ventricular fibrillation (VF). The WCD can deliver treatment shocks to terminate these tachyarrhythmias. However, a significant percentage of recorded episodes with WCD have been asystole or severe bradycardia episodes; 24.5% of SCAs in the study by Chung *et al*[1]. The WCD does not have antibradycardia pacing capabilities, but does alarm and instruct bystanders to call for help and perform CPR.

Patients with OHCA due to bradycardia or asystole are less likely than those with VT or VF to arrive to the hospital alive and survive to discharge[2,3]. Shorter time intervals between collapse to initiation of bystander cardiopulmonary resuscitation (CPR) and notification of emergency medical services (EMS) are associated with improved overall survival as well as neurologically favorable survival[4-9]. Since the WCD alerts for asystole, it may contribute to improved outcomes in patients who suffer from severe bradycardia or asystolic cardiac arrest by alerting bystanders to perform CPR and contact EMS. We examined the incidence of WCD alerts related to outcomes in patients with asystole and/or severe bradycardia.

MATERIALS AND METHODS

Patient population and definitions

All patients prescribed a WCD between January 1, 2013 and December 31, 2013 were analyzed using a corporate database (ZOLL LifeVest). This database includes indications for WCD prescription, baseline demographics (age and gender), complaints, and all device-recorded events. All patients signed consent to use their data and all data were de-identified.

An "asystole episode" was defined as bradycardia with heart rate < 10 beats/min, or having a pause lasting ⩾ 5 s. To identify patients with asystole episodes, the database was retrospectively screened to identify all episodes of primary asystole ECG recordings. Episodes of post-shock asystole or asystole following untreated VT episodes were excluded from the study. All episodes were manually adjudicated to ensure that a true asystole event had occurred. For the purposes of this study, a "serious asystole episode" was defined as any life-threatening asystole episode which either required hospitalization or led to unconsciousness or death. "Acute survival" was defined as recovery at the scene or arrival to a medical facility alive, or not requiring immediate medical attention. For the purposes of this study, asystole episodes occurring in a "health care setting" were defined as any events in a hospital, nursing home, or ambulance. Survival was determined by customer call reports at the end of WCD use, or by a mortality search of the Social Security death index if the customer call report at the end of WCD use did not indicate death (data available to 2/28/2014).

Statistical analysis

Descriptive statistics were utilized to describe this population based on data collected at the time of referral for WCD prescription or during use. All continuous values were reported as mean ± SD, or median and range for skewed distributions. Categorical values were expressed as absolute numbers and percentages. To test for differences in the proportions

Table 1 Patient demographics at the start of wearable cardioverter defibrillator use

Parameter	All (n = 257)	Not serious (n = 56)	Serious (n = 201)
Age, yr (median, range)	69 (25-90)	69 (25-82)	69 (39-90)
Sex			
Male (%)	191 (74.3)	41 (73.2)	150 (74.6)
Female	65 (25.3)	15 (26.8)	50 (24.9)
NA	1 (0.4)	0 (0)	1 (0.5)
LVEF % (median, range) (n = 241 reported)	25 (10-65)	25 (10-65)	27.5 (10-60)
Primary indication, n (%)			
MI/NICM	198 (77.0)	43 (76.8)	155 (77.1)
ICD Explant	22 (8.6)	6 (10.7)	16 (8.0)
VT/SCA	35 (13.6)	7 (12.5)	28 (13.9)
Genetic risk	1 (0.4)	0 (0)	1 (0.5)
NA	1 (0.4)	0 (0)	1 (0.5)
History of diabetes mellitus			
Yes	128 (49.8)	18 (32.1)	110 (54.7)[c]
No	111 (43.2)	38 (67.9)	73 (36.3)
NA	18 (7.0)	0 (0)	18 (9.0)
History of ESRD/HD			
Yes	34 (13.2)	5 (8.9)	29 (14.4)
No	204 (79.4)	51 (9.1)	153 (76.1)
NA	19 (7.4)	0 (0)	19 (9.5)
History of arrhythmias[1]	237	54	183
Patients reported			
Any arrhythmia listed below	169 (71.3)	41 (75.9)	128 (69.9)
Sustained VT/VF	68 (28.7)	19 (35.2)	49 (26.8)
Bundle branch block	49 (20.7)	18 (33.3)[b]	31 (16.9)
AFib/Aflutter/SVT/AT	98 (41.4)	23 (42.6)	75 (41.0)
Bradycardia/Heart Block/PEA	31 (13.1)	6 (11.1)	25 (13.7)

[1]Percentages were calculated based on patients with information. [b]$P < 0.05$ as no serious group compared to serious group using Fisher's exact test, P-value are calculated based on patients with information; [c]$P < 0.001$ as no serious group compared to non-serious group using Fisher's exact test. AFib: Atrial fibrillation; Aflutter: Atrial flutter; SVT: Supraventricular tachycardia; AT: Atrial tachycardia; PEA: Pulseless electrical activity; NA: Not reported.

of clinical variables between serious and non-serious asystole episodes, Fisher's exact test was used. Univariate logistical regression analysis was used to identify potential variables associated with survival of serious asystole episodes, where a P value of 0.05 was considered statistically significant.

RESULTS

Of the total 51933 patients having worn the WCD in 2013, there were 257 patients (0.5%) who had isolated asystole episodes and comprised the study cohort (Supplemental Figure). The cohort wore the WCD for 40.8 total patient-years during which a total of 264 asystole episodes occurred (one asystole episode in 251 patients, 2 asystole episodes in 5 patients, 3 asystole episodes in 1 patient). The cohort was 74% male and had a median age of 69 years. Over three-fourths of WCD prescriptions were for recent myocardial infarction (MI) or non-ischemic cardiomyopathy (NICM). Table 1 summarizes the baseline characteristics. A greater proportion of patients having a serious event had a history of diabetes mellitus ($P < 0.001$), while more patients with non-serious asystole episodes had a history of a bundle branch block ($P < 0.05$).

Overall survival for patients with asystole episodes was 42%. The majority of patients had asystole episodes that were considered serious (201; 78%). The rate of acute survival in patients with serious asystole episodes was 26%, while all 56 patients with non-serious asystole episodes survived. Further analysis for patients with serious asystole episodes suggested that survival was worse when the location was in a healthcare setting (Supplemental Table).

For the 108 patients that survived the acute event, twenty-two (20%) of them later died (median 4 d post-asystole episode), while 86 (80%) survived post-WCD use. Information regarding reason for WCD discontinuation is shown in Table 2. Overall, 44% of patients were implanted with an ICD or pacemaker a median of four days after the asystole episode.

DISCUSSION

This study examines the outcomes of asystole and severe bradycardia during WCD use among patients who were prescribed the device to prevent sudden death due to ventricular arrhythmias. In this population, asystole episodes were infrequent, occurring in 0.5% of patients treated with WCD during the time period. Over three quarters of these asystole episodes were serious enough to result in unconsciousness, hospitalization, or death. Survival rates after asystole episodes and serious asystole episodes were 44% and 26% respectively. These rates are significantly higher than those reported in the literature for non-shockable cardiac arrest.

Table 2 Wearable cardioverter defibrillator discontinuation among acute survivors

Reason	Patients [*n* = 108, *n* (%)]	Days post-asystole (median, range)
Received ICD or pacemaker	48 (44.4)	4 (0-175)
Condition improved	17 (15.7)	39 (3-525)
Condition deteriorated	10 (9.3)	4 (0-44)
Patient decision	5 (4.6)	73 (12-80)
Unknown/other	5 (4.6)	33 (0-96)
Died	22 (20.4)	4 (0-44)
Still wearing	1 (0.9)	NA

Due to the increased incidence of life-threatening ventricular arrhythmias in patients with cardiomyopathy and low ejection fraction, a WCD is often recommended for patients who are not immediate candidates for ICD therapy[10]. These patients may possess a history of palpitations or syncope which may cause concern for sustained VAs. However, it is important to recognize that in such patients with structural heart disease there is also a high incidence of conduction disease; furthermore, conduction disease may be exacerbated by the concomitant use of medications such as beta-blockers, digoxin, or antiarrhythmic drugs (*i.e.*, amiodarone, sotalol, dofetilide, *etc.*).

The WCD appears to serve as an effective monitoring device for severe bradycardic events. While the WCD has been shown to prevent sudden cardiac death due to VAs in certain patients[1,11-16], our study suggests that it may also provide an additional benefit in improving outcomes in patients who suffer from bradycardic conditions both in the acute setting as well as long-term by helping to determine which patients qualify for permanent pacemaker devices. Of the 86 patients surviving to WCD discontinuation, 48 (56%) of them were implanted with an ICD or pacemaker, a median of four days after the asystole episode. Although the device does not provide antibradycardia treatment, it does aid patients by alerting bystanders with an audible tone, thus potentially decreasing time to CPR and EMS notification. Shorter time to CPR and EMS arrival have been repeatedly shown to correlate with improved survival and neurologic outcome after cardiac arrests[8]. Just as pacemakers or rhythm monitors may detect sustained ventricular arrhythmias which would meet indications for ICD implantation or upgrade, the WCD may detect symptomatic bradycardic rhythms which would lead to permanent pacemaker or ICD implantation.

Limitations

This was an observational retrospective study and data was derived from the manufacturer's database. While rhythm strips for each recorded event was adjudicated to assure that a bradycardic/asystolic event meeting criteria for device detection had occurred, the clinical details surrounding the asystole episodes for each patient were limited. The WCD database included a limited amount of patient information, and information regarding patient comorbidities, medical therapy, and outcomes. For example, the fact that the overall survival rates among patients with serious episodes was lower in patients whose event occurred in a location under medical care (*i.e.*, hospital, emergency room, dialysis center, rehabilitation center, or long-term care nursing facility) could be due to the fact that patients already under medical care may have had more comorbidities than those whose serious asystole episode occurred outside of a medical facility. Thus our findings, while interesting, should be considered hypothesis-generating.

In conclusion, while the current indication for WCDs in high-risk patients is to detect and treat VAs, patients with reduced LVEF are also at increased risk of having severe bradycardic events. The WCD may improve survival in patients with severe bradycardic/asystolic episodes by alerting bystanders to notify EMS and to perform early CPR, as well as to detect episodes leading to appropriate permanent device implantation.

ARTICLE HIGHLIGHTS

Research background

Outcomes in patients with asystole and severe bradycardic events is poor. The wearable cardioverter defibrillator (WCD) can deliver shocks to terminate ventricular tachycardia and fibrillation, and also alarms for asystole and severe bradycardia events which can alert bystanders to help.

Research motivation

Minimal data exists on whether WCD improves outcomes and survival in patients with asystole and severe bradycardia events.

Research objectives

This study aimed to examine whether WCD alarms for asystole improve patient outcomes and survival.

Research methods

Retrospective analysis all asystole episodes documented in the WCD registry during the year of 2013 and examination of outcomes and survival.

Research results

There were 264 asystole episodes in 257 patients and 76% of these events were considered "serious". Overall patient survival after asystole or severe bradycardia events was 42%, and survival after "serious" asystole events was 26%. Among acute survivors, 20% later died during WCD use. Of the 86 living patients at the end of WCD use period, 48 (56%) received ICD/pacemaker and 17 (20%) improved their condition.

Research conclusions

While the current indication for WCDs in high-risk patients is to detect and treat ventricular arrhythmias, patients with reduced LVEF are also at increased risk of having severe bradycardic events. The WCD may improve survival in patients with severe bradycardic/asystolic episodes by alerting bystanders to notify emergency medical services and to perform early cardiopulmonary resuscitation, as well as to detect episodes leading to appropriate permanent device implantation.

Research perspectives

Future large prospective studies examining outcomes of WCD for asystole and severe bradycardia events are necessary to confirm a survival benefit with the device.

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ORIGINAL ARTICLE

Retrospective Study

Preventive fraction of physical fitness on risk factors in cardiac patients: Retrospective epidemiological study

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Institutional review board statement: The study was reviewed and approved by the clinic of Saint Orens according to the rules of the country. Institutional Review Board, law n°2004-806; August 9, 2004.

Informed consent statement: All participants, and this investigation was conducted in accordance to the World Medical Association Declaration of Helsinki, and depended on country rules (law n°2004-806; August 9th 2004). Also, the analysis used clinical data without storage of patient identifiers that were obtained after each patient agreed to treatment by written consent.

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Abstract

AIM

To quantify the preventive fraction of physical fitness on the risk factors in patients with cardiovascular diseases (CVDs).

METHODS

A total of 249 subjects (205 men and 44 women) suffering from CVD were categorized into four groups, according to their percentage of physical fitness. We calculated the odds ratio to obtain the preventive fraction in order to evaluate the impact of the physical fitness level on the risk factors (*i.e.*, abdominal obesity, depression, diabetes, dyslipidemia, hypertension, obesity, overweight and smoking).

RESULTS
It is observed that a normal physical fitness level is sufficient to induce a preventive action on abdominal obesity (38%), diabetes (12%), hypertension (33%), obesity (12%) and overweight (11%). Also, the preventive fraction increases with the level of physical fitness, in particular for hypertension (36%) and overweight (16%). A high physical fitness level does not necessarily induce a preventive action in most risk factors, excluding depression.

CONCLUSION
This is the first study which demonstrates that reaching a normal physical fitness level is enough to induce a protection for some risk factors, despite having a CVD.

Key words: Physical fitness; Cardiovascular diseases; Risk factors; Preventive fraction; Epidemiological study

Core tip: The effect of physical fitness on the risk factors in patients who have developed a cardiovascular disease remains an open question. This retrospective study aims to measure the preventive fraction of the risk factors observed at different level of the physical fitness. Our work provides new insights on the aggregate role of physical fitness in the development of risk factors in patients with cardiovascular diseases. These results may interest the readership and the journal due to its novelty and of its possible therapeutic use.

Caru M, Kern L, Bousquet M, Curnier D. Preventive fraction of physical fitness on risk factors in cardiac patients: Retrospective epidemiological study. *World J Cardiol* 2018; 10(4): 26-34 Available from: URL: http://www.wjgnet.com/1949-8462/full/v10/i4/26.htm DOI: http://dx.doi.org/10.4330/wjc.v10.i4.26

INTRODUCTION

Cardiovascular diseases (CVDs) remain the main cause of death in the world with about 17.5 million deaths[1]. Over the past few years, more and more people in the world develop CVDs; the American Heart Association (AHA) estimated that one in three Americans has a cardiac pathology[2]. As a matter of fact, in 2014, Nichols *et al*[3] observe that almost half of the deaths in Europe are attributable to CVDs, touching approximately 1.9 million men and 2.2 million women.

The development of different risk factors[4] (*i.e.*, abdominal obesity, depression, diabetes, dyslipidemia, hypertension, obesity, overweight, smoking) and physical inactivity promote CVDs. Physical inactivity, which is the fourth cardiovascular risk factor, has deleterious effects on general and cardiovascular health[5]. It is responsible for 5.3 million deaths[6] and it may be responsible for 12% of the risk factors of CVDs[7]. CVDs are usually associated with a high level of risk factors[8]. Thus, the practice of physical activities allows to decrease the risk of CVDs[9] and has a protective role against metabolic risk factors[10]. In point of fact, non limited to CVDs, physical activity can be considered a non-pharmacologic treatment both in human for other diseases such as musculoskeletal diseases[11,12] and immunology diseases[13,14].

Cardiac rehabilitation *vs* a conventional therapy[15] induces a reduction of 20% to 32% of all-cause mortality[16]. The goal of cardiac rehabilitation for CVDs is to improve their physical fitness[17] and to reduce CVDs in accordance with current guidelines[18]. We know that the level of physical fitness has an impact on mortality[19] and that the practice of physical activity has benefits on the risk factors after cardiovascular rehabilitation programs[16]. However, we do not know the preventive action of physical fitness on the risk factors in patients who have developed CVDs.

Consequently, the aims of this work are, on the one hand, to observe the distribution of risk factors according to physical fitness and, on the other hand, to study the impact of physical fitness on the preventive fraction of the risk factors in a population of cardiac subjects. We hypothesize that a normal physical fitness level in CVD patients is enough to induce a preventive action on cardiovascular risk factors.

MATERIALS AND METHODS

Study population

In this retrospective epidemiological study, all data were collected in May, 2008 from subjects with CVDs admitted in a cardiac rehabilitation center. Inclusion criteria were participants with coronary, infarct, heart failure or valvulopathy, and the exclusion criteria were participants under 18 years old and with lung disease as primary pathologies. Informed consent was obtained from all participants, and this investigation was conducted in accordance to the World Medical Association Declaration of Helsinki, and depended on country rules (law n°2004-806; August 9, 2004).

Assessment of the physical fitness

At their admission to the cardiac rehabilitation program, all the subject were evaluated for risk factors and physical fitness. Physical fitness of subjects was evaluated from an exercise stress test on ergocycle, conducted by physicians, physiotherapists and exercise physiologist, in accordance with the current recommendations of AHA[20]. In order to evaluate the physical fitness of subjects, the maximum oxygen consumption ($V \cdot O_2$peak) was calculated using equations published by Wasserman and Hansen normalizing $V \cdot O_2$peak depending age, gender, weight and height[21,22]. The percentage of physical fitness is the ratio between $V \cdot O_2$peak measured and $V \cdot O_2$peak predicted. It has been calculated using the following

equation: % predicted
$V \cdot O_2$peak = measured $V \cdot O_2$peak ($mL \cdot kg^{-1} \cdot min^{-1}$)/ predicted $V \cdot O_2$peak ($mL \cdot kg^{-1} \cdot min^{-1}$) × 100

Assessment of the risk factors

Cardiovascular risk factors were defined by the following standards[23,24] at the time of the study and were analysed from recent medical records (less than 2 mo) of patients or evaluated at the entrance on the program. Abdominal obesity was defined if the values of the abdominal circumference were ⩾ 102 cm for the male and ⩾ 88 cm for the female. Diabetes was defined if a subject had a high fasting glucose (> 126 mg/dL or > 7.0 mmol/L), a high non-fasting glucose (> 198 mg/dL or > 11.0 mmol/L), a high glycated hemoglobin (HbA1C > 7%), a diagnosis of diabetes by a physician, a self-reported use of oral hypoglycemic treatment or insulin. Dyslipidemia was defined if a subject had a high total serum cholesterol level (> 250 mg/dL or > 6.5 mmol/L), a high LDL-cholesterol (> 155 mg/dL or > 4.0 mmol/L), a low HDL-cholesterol (for the male: < 40 mg/dL or < 1.0 mmol/L and for the female: < 48 mg/dL or < 1.2 mmol/L), a self-reported use of a treatment for abnormally high levels of cholesterol or a diagnosis of dyslipidemia by the physician. Hypertension was defined if a subject had a high blood pressure (⩾ 140/90 mmHg at rest), a self-reported use of treatment for hypertension, or a diagnosis of hypertension by the physician. Overweight was defined if the subject had a body mass index (BMI) between 25 and 30 and obesity was defined if the subject had a BMI upper than 30. Depression was defined by a self-reported use of a treatment or diagnosis of depression by a physician. The risk factor associated with smoking was allocated into two categories. Participants classified as "smokers" had the characteristic of being active smokers, having an almost daily consumption or consuming a cigarette for the last time in the six months before the testing procedure. Participants "non-smokers" had the characteristic of never having smoked or the cessation of cigarette smoking more than six months before the testing procedure.

Preventive fraction

The preventive fraction is a ratio used in epidemiological studies to assess the impact of an exposure factor (physical activity) on a disease (risk factors)[25,26]. Assuming that the exposure factor (physical activity) is represented by its consequence (physical fitness)[27]. It is an important evaluation tool, which allows knowing the preventive action of the physical fitness levels on the risk factors studied. The PF is derived from odds ratio (OR), indeed, the OR is a measure of association between the physical fitness level and the risk factors. Thus, the preventive fraction can be calculated when OR is under one, as PF = (1-OR). It can then be expressed in percentage with the following equation: PF (%) = (1-OR) × 100. This provides a percentage of risk factors reduction in the exposed group that can be attributed to the beneficial exposure of physical fitness level of the subjects[25].

Statistical analysis

The final data analysis has allowed to obtaining, for each subject, a physical fitness levels in the aim to normalize the data and to obtain a classification by physical fitness levels (*i.e.*, high, normal, low and poor). The higher the percentage was, the higher the physical fitness level was, and inversely. We considered the subjects with a normal physical fitness as being physically active before their CVDs and conversely for the subjects with a poor physical fitness[28].

Statistical analysis was performed using R (R Foundation for Statistical Computing, Vienna, Austria). Quantitative variables were represented by their mean and median and their dispersion was evaluated by the standard deviation. Qualitative variables were represented by their frequency. To compare two means, a two-tailed Student *t*-test was performed with a significance level of 5%. Comparisons of two percentages were performed through a χ^2 test with a threshold at 5%. The Fisher exact test (performed using univariate analysis) was used when the conditions for applying the χ^2 test were not met. We carried an analysis of variance (ANOVA) at one factor, for the multiple comparisons of the means. The χ^2 tests were applied to contingency tables, comparing multiple categorical variables. The α risk was controlled by Holm method in the analysis of variance and by the Tukey's HSD for the χ^2 tests. The OR, related to the risk factors, were obtained using the logistic regression. The selection of logistic regression models was made by minimizing the Akaike criterion. The PF was obtained from the OR when OR < 1.

RESULTS

Characteristics of all participants (n = 249) are shown in Table 1. In each model, the subjects were divided into two groups (Table 2) according to their physical fitness level. This distribution allowed to assigning the subjects in the model[a], from group 1 with a normal physical fitness level (⩾ 80% predicted $V \cdot O_2$peak) to group 2 with a poor physical fitness level (< 80% predicted $V \cdot O_2$peak). In the model[b], the subjects were assigned to a group 1 with the high physical fitness level (⩾ 100% predicted $V \cdot O_2$peak) to group 2 with the low physical fitness level (< 100% predicted $V \cdot O_2$peak). We observed in Figure 1 that subjects with a high physical fitness level were less exposed to different risk factors, compared to those with a low physical fitness level. According to our study design we observed (Table 2) that the $V \cdot O_2$peak during exercise stress test of the subjects, in the model[a] and model[b], was higher for subjects in group 1 than in group 2. The $V \cdot O_2$peak in the group 1^b was higher than the one in the group 1^a during exercise stress test because, only the subjects

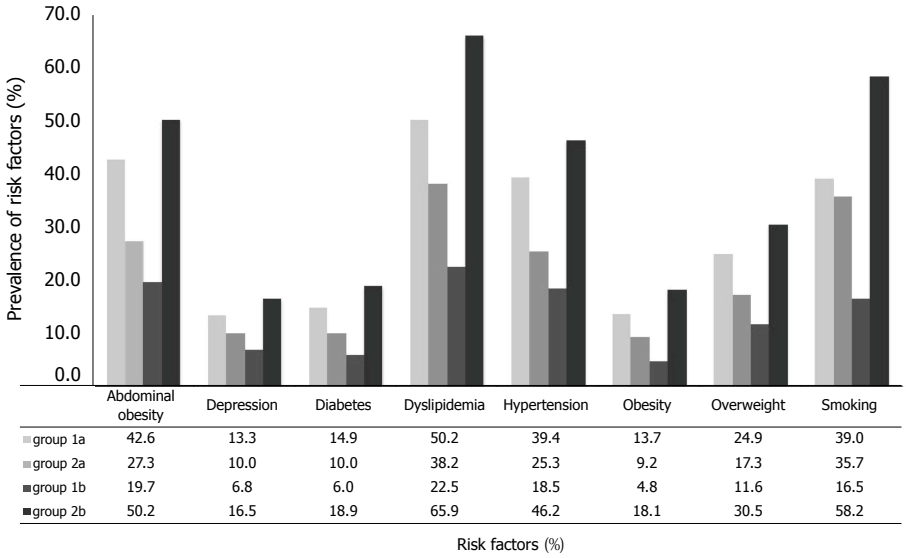

Figure 1 Distribution of the risk factors by the physical fitness level. From left to right for each risk factor: the first column (very clear gray) represents the group 1[a] (normal physical fitness), the second column (light gray) represents the group 2[a] (poor physical fitness), the third column (dark gray) represents the group 1[b] (highest physical fitness) and the fourth column (black) represents the group 2[b] (lowest physical fitness).

Table 1 Characteristics of the included subjects (n = 249) in this studies n%

Variables	mean ± SD
Gender (males/females)	205/44
Age, yr	61.8 ± 11.4
Weight, kg	78.7 ± 15.7
Height, cm	169.9 ± 8.5
Body Mass Index, kg.m^{-2}	27.2 ± 4.6
P_{max} during exercise stress test, W	108.6 ± 35.7
P_{max} predicted, W	167.5 ± 48.2
V·O$_2$ peak during exercise stress test, mL/kg·min	22.1 ± 4.8
V·O$_2$ peak predicted	25.2 ± 5.1
METs peak during exercise stress test, mL/kg·min	6.3 ± 1.4
Physical fitness, % predicted V·O$_2$ peak	89.6 ± 20.5
Risk factors	**Prevalence, n (%)**
Abdominal obesity	174 (69.9)
Depression	58 (23.3)
Diabetes	62 (24.9)
Dyslipidemia	220 (88.4)
Hypertension	161 (64.7)
Obesity	57 (22.9)
Overweight	105 (42.2)
Smoking	186 (74.7)

P_{max}: Maximal power; V·O$_2$: Maximal oxygen consumption; METs: Metabolic equivalents of task.

which had the highest physical fitness were assigned to the group 1[b]. In Group 1[a], the subjects had a V·O$_2$peak during exercise stress test (23.6 ± 5.1 mL·kg^{-1}·min^{-1}) similar to the V·O$_2$peak predicted (23.4 ± 4.7 mL·kg^{-1}·min^{-1}), whereas in group 1[b], the V·O$_2$peak during exercise stress test (25.5 ± 5.5 mL·kg^{-1}·min^{-1}) is much higher than the V·O$_2$peak predicted (22.4 ± 4.6 mL·kg^{-1}·min^{-1}). In group 2[a] and group 2[b], V·O$_2$peak during exercise stress test (20.0 ± 3.5 mL·kg^{-1}·min^{-1} and 20.9 ± 4.0mL·kg^{-1}·min^{-1}, respectively) were lower than V·O$_2$peak predicted (27.8 ± 4.6 mL·kg^{-1}·min^{-1} and 26.2 ± 4.9 mL·kg^{-1}·min^{-1}, respectively).

The OR was calculated to obtain the PF of the cardiovascular risk factors in order to assess the effect of the exposure factor. Upon univariate analysis (Table 3), in the model[a], PF was calculated for age (6%), abdominal obesity (38%), diabetes (12%), hypertension (33%), obesity (12%) and overweight (11%). In the model[b], PF was calculated for the age (5%), abdominal obesity (37%), depression (22%), hypertension (36%) and overweight (16%). In both models, PF was not calculated for dyslipidemia and smoking because OR > 1.

DISCUSSION

Our main results validate the hypothesis whereby a normal physical fitness level provides a preventive action on cardiovascular risk factors despite people having already developed a CVD. The findings add new insights with previously published reports[29] and allow the identification of a prophylactic effect of the physical fitness on cardiovascular risk factors studied despite presenting the diagnosis of heart disease.

The presence of risk factors for the patient does not necessarily imply a direct relationship between cause and effect because some people could have a CVD inheritance. Moreover, it is not necessary to have risk factors to develop a CVD, the genetic heritage of the person might be the cause[30]. The overall percentage of the risk factors prevalence seems to be higher in our population compared to previous studies, nevertheless, it follows the trend according to the exposure of patients to differents cardiovascular risk factors[31,32]. Several epidemiological studies demonstrated that low physical activity levels are associated with a higher

Table 2 Characteristics of subjects for each of models

Variables (units)	Model[a]		*P* value	Model[b]		*P* value
	Group 1[a] (*n* = 143)	Group 2[a] (*n* = 106)		Group 1[b] (*n* = 64)	Group 2[b] (*n* = 185)	
Gender (males/females)	101/42	104/2	-	39 / 25	166 / 19	-
Age (yr)	64.7 ± 11.0	58.0 ± 10.8	0.001	66.2 ± 11.7	60.3 ± 10.9	0.001
Weight (kg)	77.2 ± 14.8	80.7 ± 16.6	0.090	75.0 ± 15.1	80.0 ± 15.7	0.030
Height (cm)	167.8 ± 9.1	172.7 ± 6.8	0.001	166.3 ± 8.1	171.2 ± 8.3	0.001
Body Mass Index (kg/m^2)	27.8 ± 4.2	27.0 ± 5.0	0.500	27.0 ± 4.3	27.2 ± 4.7	0.700
P_{max} during exercise stress test (W)	118.0 ± 39.1	95.8 ± 25.7	0.001	128.3 ± 45.0	101.7 ± 29.1	0.001
P_{max} predicted (W)	150.8 ± 46.9	190.0 ± 40.3	0.001	139.5 ± 49.9	177.2 ± 43.7	0.001
V·O$_2$ peak during exercise stress test (mL/kg/min)	23.6 ± 5.1	20.0 ± 3.5	0.001	25.5 ± 5.5	20.9 ± 4.0	0.001
V·O$_2$ peak predicted (mL/kg/min)	23.4 ± 4.7	27.8 ± 4.6	0.001	22.4 ± 4.6	26.2 ± 4.9	0.001
METs peak during exercise stress test	6.8 ± 1.5	5.7 ± 1.0	0.001	7.3 ± 1.6	6.0 ± 1.1	0.001
Physical fitness (% predicted V·O$_2$ peak)	102.2 ± 17.6	72.6 ± 8.1	0.001	115.2 ± 19.2	80.8 ± 11.7	0.001

Model[a]-group 1[a]: Patients with a normal physical fitness level; Model[a]-group 2[a]: Patients with a poor physical fitness level; Modelb-group 1b: Patients with a high physical fitness level; Model[b]-group 2[b]: Patients with a low physical fitness level. P_{max}: Maximal power; V·O$_2$: Maximal oxygen consumption; METs : Metabolic equivalents of task.

Table 3 Measures-univariate and multivariate on subjects with cardiovascular risk factors

Variables	Univariate analysis			Multivariate analysis		
	OR (95%CI)	*P* value	PF (95%CI)	OR (95%CI)	*P* value	PF (95%CI)
Model[a]						
Age	0.94 (0.92; 0.96)	< 0.001	0.06 (0.04; 0.08)	0.93 (0.90; 0.96)	< 0.001	0.07 (0.04; 0.10)
Abdominal obesity	0.62 (0.36; 1.07)	0.09	0.38 (-0.07; 0.64)	-		
Depression	1.02 (0.56; 1.85)	0.92	-	-		
Diabetes	0.88 (0.48; 1.57)	0.68	0.12 (-0.57; 0.52)	-		
Dyslipidemia	1.24 (0.56; 2.83)	0.59	-	-		
Hypertension	0.67 (0.39; 1.13)	0.13	0.33 (-0.13; 0.61)	-		
Obesity	0.88 (0.48; 1.61)	0.70	0.12 (-0.60; 0.52)	-		
Overweight	0.89 (0.53; 1.48)	0.65	0.11 (-0.48; 0.47)	0.64 (0.35; 1.14)	0.130	0.36 (-0.14; 0.65)
Smoking	2.48 (1.34; 4.74)	< 0.010	-	-		
Model[b]						
Age	0.95 (0.92; 0.97)	< 0.001	0.05 (0.03; 0.08)	0.95 (0.92; 0.98)	0.001	0.05 (0.02; 0.08)
Abdominal obesity	0.63 (0.32; 1.20)	0.17	0.37 (-0.20; 0.68)	-		
Depression	0.78 (0.41; 1.54)	0.47	0.22 (-0.54; 0.59)	-		
Diabetes	1.11 (0.58; 2.22)	0.75	-	-		
Dyslipidemia	1.11 (0.44; 2.57)	0.80	-	-		
Hypertension	0.64 (0.33; 1.18)	0.16	0.36 (-0.18; 0.67)	-		
Obesity	1.39 (0.70; 2.94)	0.36	-	3.40 (1.06; 11.83)	0.040	-2.4 (-10.83; -0.06)
Overweight	0.84 (0.47; 1.49)	0.55	0.16 (-0.49; 0.53)	-		
Smoking	2.03 (1.08; 3.76)	0.02	-	-		

-: This variable was eliminated from the selection of logistic regression models in minimizing the Akaike criterion. Model[a]: Patients with a normal physical fitness level; Model[b] : Patients with a high physical fitness level; OR: Odds ratio; PF: Preventive fraction.

prevalence of most CVDs risk factors[29]. Our group 2[b], composed of patients with the lowest physical fitness level, confirms this observation. It is shown that a low physical fitness level is associated with an important risk factor and with increased mortality for both men and women[33]. The physical fitness level declines with the age, even more, if a regular physical activity is not preserved. Contrary to what is observed in the literature[34], our study show that the subjects in the group 1[a] with a normal physical fitness level (20% below the predicted) and in the group 1[b] with a high physical fitness level were the oldest (64.7 ± 11.0 years old and 66.2 ± 11.7 years old, respectively).

The subjects physically or professionally active before their cardiac events, no matter their age, will be able to have a better physical fitness level than those who were physically inactive. Within this context, our study observed positive results for the patients admitted into a cardiac rehabilitation center. Indeed, getting a physical fitness level close to the baseline level (even 20% below the predicted fitness) induces a preventive action on the cardiovascular risk factors. In the group 1[a], we observed a positive action of the physical fitness level on five of our eight risk factors studied (*i.e.*, abdominal obesity, diabetes, hypertension, obesity and overweight). A correlation between physical activity and physical fitness level demonstrates that it is the practice of physical activity that could reduce many risk factors[33]. Kodama *et al*[35] have confirmed that the physical fitness level is associated

with a weakening in CVDs. The subjects who are exposed to a high physical fitness level (group 1^b) are susceptible to get a higher preventive action on hypertension than group 1^a (PF = 36% and PF = 33%, respectively). It is argued that improving physical fitness, through the physical activity, has an effect on hypertension by reducing blood pressure[36]. Physical activity is also important in the fight against the weight gain and the development of fat and abdominal obesity which are favorable to the appearance of hypertension[37]. Thus, our results show a preventive action of the normal and high physical fitness level groups on the abdominal obesity. This preventive action is in favor of the group 1^a (PF = 38%), comparatively to the group 1^b (PF = 37%). In a recent study, it has been shown that the excess of abdominal fat would be associated with a higher risk of cardiovascular mortality than overweight or obesity[38]. Physical activity is known to decrease the risk of cardiovascular mortality in patients with obesity[39]. In our study, it is clearly identified that a normal physical fitness level induces a preventive action on the obesity (PF = 12%) since the group 1^b has not observed a benefit action of the exposure factor on this risk factor. We observe the same result for diabetes risk factor. Indeed, the group with a normal physical fitness level induces a preventive action for diabetes (PF = 12%), which was not observed for the subjects with a high physical fitness level. Reaching moderate or high physical activity levels reduce the risk of CVDs mortality in type 2 diabetics patients[40] by improving glucose metabolism and insulin sensitivity[37]. A moderate exercise program can also reduce the diabetes risk and percentage of body fat[41]. It is especially important in the prevention of cardiovascular risk factors because the subjects who suffer overweight have a high risk of developing diabetes[42]. Our results demonstrate that the subjects who have a normal physical fitness level induce a preventive action of 11% on the overweight risk factor. A 5% difference, in favor of group 1^b with a high physical fitness level (PF = 16%), was observed for overweight. The logistic regression models in the multivariate analysis have shown that the group 1^a, composed of subjects with a normal physical fitness level, induced a preventive action of 36% on the overweight. These findings strengthen our hypothesis and highlight the importance of having a normal physical fitness level, without necessarily being a patient with a high physical fitness level.

Yet, only the group 1^b with a high physical fitness level induce a preventive action on the depression risk factor (PF = 22%). We have not observed a preventive action on the depression in the patients with a normal physical fitness level. The subjects with a low self-reported physical activity levels are associated with an increased prevalence of depressive symptoms[43]. The patients with CVDs and with depression are likely to have recurrent heart problems[44,45]. According to Gary *et al*[46] the patients who are facing a cardiac complication recognize a depressive episode afterward. Furthermore, our results demonstrate the importance of having a high physical fitness level, before and after a cardiac event, to induce a preventive action on the depression. Finally, our findings have not observed a preventive action for smoking, this is consistent with the statement of Marín Armero *et al*[47] who suggest that the best way to stop smoking is to combine smoking cessation with a psychological program. Smoking may induce changes in the serum lipoprotein profiles causing an increase in total cholesterol[48], which might explain that no positive effect of the physical fitness levels were observed for dyslipidemia.

This study is based in retrospective data, which may represent some limitations. Retrospective studies have disadvantages because peoples who were responsible for the data collections might have made classification errors or information bias. This is why we have worked closely with the cardiologist of the cardiac rehabilitation center whose data were from. Also, as pharmacological treatments could have been optimized since the data collection it could be argued that results would have been different and that the positive impact of physical training would be attenuated. Over a long period (from 1988 until now), since the firsts meta-analysis by Oldridge *et al*[49] and O'Connors *et al*[50] and despite the increasing development of new medication, the result of exercise on mortality reduction in CVDs is quite constant[16]. The works of Bouchard et Shepard shows that a part of physical fitness can be genetically determined and not related to environment (by physical activity practice)[51]. Finally, treatments were not introduced in the study as recruitment were made from University hospital with patients arriving with optimized treatment so inducing a low deviation between subject, furthermore due to the small number of the subjects for such a study we did not separate the different pathologies in the analysis and consider CVD's as a whole group.

It is established that the exercise capacity is an important prognostic factor in patients with CVD[28]. There is evidence of an inverse relationship between the physical activity and CVDs; our study reinforces these statements. Regular physical activity is a practice accessible to all patients with CVDs, but it may be difficult to adhere to an aerobic-based exercise program, due to external constraints. Our study suggests that even if the recommendations of ACSM[52] (allowing to reach 100% of the theoretical physical fitness) are not met, a normal physical fitness level, even 20% below the predicted fitness, is enough to reduce some of the risk factors studied. This is in concordance with the recommendations of European Society of Cardiology[53] which supports that the subjects with a physical fitness level, even 25% below the predicted fitness, will face long-term health issues. The practice of physical activity should be maintained throughout life to preserve these training effects[19].

In summary, this study demonstrated that a normal

physical fitness level induces a preventive action for most risk factors studied and that a high level of physical fitness does not necessarily lead to a better preventive fraction. Our work provides new insights on the aggregate role of physical fitness in the development of cardiovasculars risk factors.

ARTICLE HIGHLIGHTS

Research background

Cardiovascular diseases (CVDs) remain the main cause of death in the world with about 17.5 million deaths. CVDs are usually associated with a high level of risk factors. The practice of physical activity has benefits on the risk factors, however, we do not know the preventive action of physical fitness on the risk factors in patients who have developed CVDs. Thus, this study aims to quantify the preventive fraction of physical fitness on the risk factors in patients with CVDs.

Research motivation

The effect of physical fitness on the risk factors in patients who have developed a cardiovascular disease remains an open question. Regular physical activity is a practice accessible to all patients with CVDs, but it may be difficult to adhere to an aerobic-based exercise program, due to external constraints.

Research objectives

Quantifying the preventive fraction of physical fitness on the risk factors in patients with CVDs is very important. The aggregate role of physical fitness in the development of cardiovascular risk factors needs to be better documented. Our work provides new insights on this research field.

Research methods

A total of 249 subjects (205 men and 44 women) suffering from a CVD were categorized into four groups, according to their percentage of physical fitness. The physical fitness of subjects was evaluated from an exercise stress test on an ergocycle. We calculated the odds ratio to obtain the preventive fraction in order to evaluate the impact of the physical fitness level on the risk factors (*i.e.*, abdominal obesity, depression, diabetes, dyslipidemia, hypertension, obesity, overweight and smoking). The preventive fraction is a ratio used in epidemiological studies to assess the impact of an exposure factor (physical fitness) on a disease (risk factors). It is an important evaluation tool that allows knowing the preventive action of the physical fitness levels on the risk factors studied.

Research results

It is observed that a normal physical fitness level is sufficient to induce a preventive action on abdominal obesity (38%), diabetes (12%), hypertension (33%), obesity (12%) and overweight (11%). Also, the preventive fraction increases with the level of physical fitness, in particular for hypertension (36%) and overweight (16%). A high physical fitness level does not necessarily induce a preventive action in most risk factors, excluding depression. Our study suggests that even if the recommendations of ACSM (allowing to reach 100% of the theoretical physical fitness) are not met, a normal physical fitness level, even 20% below the predicted fitness, is enough to reduce some of the risk factors studied.

Research conclusions

This study demonstrates that a normal physical fitness level induces a preventive action for most risk factors studied. A high level of physical fitness does not necessarily lead to a better preventive fraction. CVDs remain the main cause of death in the world with about 17.5 million deaths. It is observed that almost half of the deaths in Europe are attributable to CVDs, touching approximately 1.9 million men and 2.2 million women. The development of different risk factors (*i.e.*, abdominal obesity, depression, diabetes, dyslipidemia, hypertension, obesity, overweight, smoking) and physical inactivity promote CVDs. The practice of physical activities allows to decrease the risk of CVDs and has a protective role against metabolic risk factors.

Research perspectives

There is evidence of an inverse relationship between the physical activity and CVDs; our study reinforces these statements. However, it may be difficult to adhere to an aerobic-based exercise program, due to external constraints. Our study suggests that a normal physical fitness level, even 20% below the predicted fitness, is enough to reduce some of the risk factors studied. The practice of physical activity should be maintained throughout life to preserve these training effects. The future research should include the pharmacological treatments.

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EDITORIAL

Prognostic utility of global longitudinal strain in myocardial infarction

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Abstract

Cardiovascular magnetic resonance (CMR) represents the reference standard for cardiac morphology and function assessment. Since introduction in 2009, CMR feature tracking (CMR-FT) has become a frequently used tool in the assessment of myocardial deformation and wall motion on the basis of routinely acquired b-SSFP cine images. Extensive validation has led to excellent intra- and inter-observer as well as inter-study reproducibility. CMR-FT derived myocardial deformation indices such as left ventricular (LV) strain have been shown to be impaired in cardiac diseases such as cardiomyopathies as well as myocardial infarction. Although LV ejection fraction (LVEF) is the routinely and frequently utilized parameter for systolic myocardial function assessment and major adverse clinical event (MACE) prediction, it fails to assess regional differences. Recently, LV strain has emerged as a superior measure for risk assessment and MACE prediction as compared to the established markers *e.g.*, LVEF. This editorial aims to elucidate current discussions in the field of strain assessment in myocardial infarction in the light of recent data from a large prospective multicentre CMR study.

Key words: Feature tracking; Myocardial infarction; Cardiovascular magnetic resonance; Cardiomyopathy; Prognosis

Core tip: Cardiovascular magnetic resonance feature-tracking bears the potential for superior risk evaluation

in infarct patients beyond established risk factors such as left ventricular ejection fraction. However, further clinical trials are inevitably needed to establish vendor independent thresholds for clinical routine use in various cardiac diseases.

Schuster A, Backhaus SJ, Stiermaier T, Eitel I. Prognostic utility of global longitudinal strain in myocardial infarction. *World J Cardiol* 2018; 10(5): 35-37 Available from: URL: http://www.wjgnet.com/1949-8462/full/v10/i5/35.htm DOI: http://dx.doi.org/10.4330/wjc.v10.i5.35

PROGNOSTIC UTILITY OF GLOBAL LONGITUDINAL STRAIN IN MYOCARDIAL INFARCTION

Since introduction in 2009, cardiovascular magnetic resonance feature tracking (CMR-FT) has been applied in research extensively, and its clinical utility has remarkably increased[1-8]. Whilst there is evidence to suggest that some of the CMR-FT indices including global longitudinal strain (GLS) carry independent prognostic implications in dilated and chronic ischaemic cardiomyopathy as well as tetralogy of Fallot[9-11] evidence in myocardial infarction has only recently become available and shows some degree of controversy[12,13]. Gavara *et al*[13] demonstrated the association of CMR-FT derived left ventricular GLS with major adverse cardiac events (MACE). However they failed to demonstrate an additional prognostic value over established CMR parameters in a retrospective collective of 323 STEMI patients. It is important to note that these results are expanded with recent prospective data by Eitel *et al*[12]. Both studies agree on the distinct relationship of myocardial deformation indices with MACE and demonstrate GLS to be the most robust parameter to predict reinfarction, heart failure and cardiac deaths[12,13]. However, the study by Eitel *et al*[12] suggests an incremental prognostic role of CMR-FT derived GLS over and above classical CMR markers of prognosis irrespectively of clinical risk factors in 1235 acute myocardial infarction (AMI) patients (including STEMI and NSTEMI)[12].

Several factors need to be considered that may potentially account for this discrepancy: (1) Even though CMR-FT algorithms are generally based on optical flow technology[1] there are inherent differences in the way strain is being calculated. Whilst the technique used by Gavara *et al*[13] is based on the assessment of several myocardial layers between endo and epicardium the technique used by Eitel *et al*[12] is predominantly based on endocardial boundary tracking[1]. In fact, there is evidence to suggest that small numerical strain differences between both techniques occur in healthy volunteers[14]; (2) since it is well known that 2D deformation imaging techniques are limited in reproducibility on a segmental level mainly because of through plane motion with subsequent fading of features during systole[1], it is interesting to speculate whether the calculation of global strain values from the averages of 16 segmental peak strains as performed by Gavara *et al*[13] is less accurate than their calculation from averaged global strain curves as performed with alternative CMR-FT software which was utilized in the study by Eitel *et al*[12]; (3) as opposed to the methodology used by Gavara *et al*[13] the technique used by Eitel *et al*[12] is based on the average of three repeated measurements to further reduce variability[13-15]; and (4) the differences in sample size and study design may have resulted in greater statistical power in the prospective trial by Eitel *et al*[12] explaining the demonstration of additional clinical value of GLS. Notwithstanding these considerations, further refinements of the underlying technology and additional prospective clinical trials defining the relative diagnostic and prognostic yields of these techniques in identical patient collectives are warranted to establish interchangeability of different CMR-FT techniques in risk stratification in various diseases[9-15]. Taken together, considering recent evidence to suggest a significant role in risk stratification[9-12] and presuming that these findings are confirmed in further prospective trials alongside with the achievement of the latter technology refinements, CMR-FT risk stratification may establish itself within routine CMR imaging following AMI and other cardiac pathologies.

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FIELD OF VISION

More to the picture of the psychological impact of endocarditis and thoracic aortic pathology

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Abstract

Over the years there has been substantial advanced in the diagnosis and surgical management of complex thoracic aortic disease and complex endocarditis. As these therapies are being offered to a growing segment of patients-and more and more patients are felt to potentially benefit from such therapies, the long-term consequences of these interventions is sometimes poorly understood. While traditional medical complications, such as stroke, renal failure, respiratory failure, and even death are often the focus of outcomes studies, little is known on the impact of these diseases and therapies on mental health. This commentary emphasizes the importance of better understanding the psychologic impact of endocarditis and thoracic aortic pathology as reviewed by Dr. Bagnasco.

Key words: Endocarditis; Thoracic aorta; Mental health; Anxiety; Depression

Core tip: Dr. Bagnasco's review emphasizes the importance of considering the psychologic implications of the diagnosis and therapies associated with thoracic aortic pathology and endocarditis.

Ginesi M, Firstenberg MS. More to the picture of the psychological impact of endocarditis and thoracic aortic pathology. *World J Cardiol* 2018; 10(6): 38-40 Available from: URL: http://www.wjgnet.com/1949-8462/full/v10/i6/38.htm DOI: http://dx.doi.org/10.4330/wjc.v10.i6.38

COMMENTARY ON HOT TOPICS

The article, "Infective endocarditis and thoracic aortic disease: a review on forgotten psychological issues" by Marianna Bagnasco provides a very good overview of the studies related to the psychological and quality of life outcomes related to infective endocarditis and

thoracic aortic disease[1]. However there are a few points that could be addressed when interpreting this dataset. First, while most of these papers use the same or similar validated methods of comparing post-operative quality of life or anxiety and depression, these measures compare patients to age and sex matched general population controls, rather than the patient's own pre-operative condition. Patients may have a significant amount of anxiety regarding the diagnosis of thoracic aortic aneurysm that might be significantly lessened after surgery, even if still elevated compared to the general population. Likewise, a patient who already has a prosthetic valve - or other baseline comorbidities or social issues (such as intravenous substance abuse) - who develops endocarditis, might already has a diminished quality of life that is further diminished by contracting infective endocarditis But, the extent to which their baseline quality of life is diminished is difficult to tell if not compared to their pre-operative condition. This is of significant concern when evaluating these patients and managing this population as none of these studies compares patients' quality of life outcomes to those prior to surgery, nor to matched controls that did not undergo surgery - all of which data that might be inherently impossible to ever accurately obtain. The only study that even hints at this is by Verhagen *et al*[2], in which patients' employment and symptom status prior to infective endocarditis treatment is considered.

With the thoracic aortic disease group, this is less of a concern because the majority of those studies conclude that the risk to quality of life is acceptable given that post-operative scores are within normal ranges or only slightly reduced from the general population. Assuming that not proceeding with surgery incurs a significant health risk, this is determined to be an acceptable risk. When comparing anxiety and depression however, it would be helpful to know where these patients were pre-operatively - again data that might be impossible to ever adequately determine given the nature of aortic pathologies. The infective endocarditis group is more problematic given that all the studies except one demonstrate a decreased quality of life that may not have been present pre-operatively given the acuity of disease. However, none of these studies provide guidance on how this problem should be approached given that proceeding with surgery decreases mortality. Clearly, there are problems that need further studies in this area.

Another point to take away from this review is that the type of thoracic aortic operation does not greatly influence quality of life or anxiety/depression outcomes, although, there are some notable exceptions. In general, Dr. Bagnasco emphasizes that the type of procedure used for thoracic repair, urgency or emergency, open or endovascular, biologic or mechanical repair had no significant effect on quality of life outcomes. The only exception is in the context of valve surgery where Aicher and colleagues indicate that pulmonary allografts and aortic valve repair had better quality of life outcomes than mechanical valve replacement, though no difference was seen in anxiety or depression[3]. The other exceptions were the two studies by Immer *et al*[4,5], that indicated that continuous cerebral perfusion and selective antegrade cerebral perfusion were associated with improved quality of life when compared to deep hypothermic circulatory arrest with pentothal alone. In these two cases the results are not surprising, the interventions were neuroprotective and thus the patients had less neurologic morbidity and improved quality of life.

Lastly, this review suggests what further directions can be taken to more thoroughly explore the effect these diseases have on quality of life. While the authors of this review do hint that increased anxiety and depression may inhibit or complicate recovery, none of these studies actually quantify whether patients with increase anxiety or depression have increased complications or prolonged post-operative recoveries. Also, as previously mentioned, these studies quantify risk to quality of life or increased anxiety and depression, but few of them suggest what to do regarding the management of the anxiety and depression when it arises. Many clinicians find treating a patient with a multidisciplinary team including a psychologist or counselor to improve patient outcomes, for example in a situation where a new diagnosis or a traumatic event changes a patient's course significantly. Further studies might include comparing outcomes of patients treated using multidisciplinary team - including psychological services. Whether improved patient outcomes and a decreased long-term burden of altered quality of life, anxiety, and depression can be demonstrated should clearly be a focus of further research. Without a doubt, we must do better in understanding the psychological factors that impact outcomes once the patient leaves the hospital.

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META-ANALYSIS

Patent foramen ovale closure reduces recurrent stroke risk in cryptogenic stroke: A systematic review and meta-analysis of randomized controlled trials

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Abstract

AIM

To investigate if patent foramen ovale (PFO) closure device reduces the risk of recurrent stroke in patients with cryptogenic stroke.

METHODS

We searched five databases - PubMed, EMBASE, Cochrane, CINAHL and Web-of-Science and clinicaltrials.gov from January 2000 to September 2017 for randomized trials comparing PFO closure to medical therapy in cryptogenic stroke. Heterogeneity was determined using Cochrane's Q statistics. Random effects model was used.

RESULTS

Five randomized controlled trials with 3440 patients were included in the analysis. Mean follow-up was 50 ± 20 mo. PFO closure was associated with a 41% reduction in incidence of recurrent strokes when compared to medical therapy alone in patients with cryptogenic stroke [risk ratio (RR): 0.59, 95%CI: 0.40-0.87, P = 0.008]. Atrial fibrillation was higher with device closure when compared to medical therapy alone (RR: 4.97, 95%CI: 2.22-11.11, P < 0.001). There was no difference between the two groups with respect to all-cause mortality, major bleeding or adverse events.

CONCLUSION

PFO device closure in appropriately selected patients with moderate to severe right-to-left shunt and/or atrial septal aneurysm shows benefit with respect to recurrent strokes, particularly in younger patients. Further studies are essential to evaluate the impact of higher incidence of atrial fibrillation seen with the PFO closure device on long-term mortality and stroke rates.

Key words: Patent foramen ovale; Cryptogenic stroke; Meta-analysis

Core tip: The American Association of Neurology guidelines focused update recommended against routine patent foramen ovale (PFO) closure in patients with cryptogenic stroke; but two recent randomized trials showed a significant reduction in recurrent stroke events in patients who had a PFO closure device when compared to patients on medical therapy alone. We therefore, performed a systematic review & meta-analysis of five available randomized controlled clinical trials that addressed the efficacy of PFO closure in patients with cryptogenic stroke. Our analysis shows PFO closure device in appropriately selected patient population is associated with reduction in recurrent stroke events but at the cost of increase in incidence of atrial fibrillation.

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INTRODUCTION

The prevalence of patent foramen ovale (PFO) in the general population is approximately 15%-25%[1-3]. Cryptogenic stroke accounts for 25% of the strokes in the United States[4,5]. Although PFO is strongly associated with cryptogenic stroke, the incidence of PFO is approximately only 40%-60% in patients with cryptogenic stroke suggesting all cryptogenic strokes are not essentially secondary to a PFO[6,7]. The issue with selecting patients for PFO closure is that in patients with PFO, the overall incidence of recurrence of PFO related cryptogenic strokes is much lower than the incidence of non-PFO related strokes[8,9]. In the PFO related cryptogenic stroke population, one third of the recurrent stroke risk is not related to the PFO itself and closure of PFO would not prevent the risk of recurrent stroke in this population[10,11]. Previously published randomized controlled trials (RCTs) evaluated device closure of PFO as compared to medical therapy but results were limited by very low event rates, lack of appropriate patient selection and large dropout rates at follow up[12,13]. Considering this, we performed a systematic review and meta-analysis of all the published trials including the three recent RCTs[14-16] to compare device closure to medical therapy for PFO in patients with cryptogenic stroke.

MATERIALS AND METHODS

Search strategy

We performed a search of five databases-EMBASE, PubMed, Cochrane, WOS and CINAHL for RCTs between January 2000 and September 2017 using the following: "cerebrovascular disease", "patent foramen ovale", "atrial septal defect", "cryptogenic strokes", "anti coagulation therapy", "anti platelet therapy" and their various combinations. Our search was limited to English language and we included adult population only. We also searched clinicaltrials.gov and performed a secondary search of the references of the relevant articles. The methodology has been validated and published in previous studies[17].

Study selection

Studies need to meet the following criteria to be eligible for inclusion: (1) RCT; (2) age > 18 years of age; (3) compare PFO device closure to medical therapy in patients with cryptogenic stroke; and (4) report the estimate of relative-risk (RR) with a 95% confidence interval (CI), or any other equivalent measures of RR including odds ratio, hazard ratio or provide other forms of data from which effect size could be calculated. After relevant exclusions, the final study population was extracted from five studies. Our search strategy is shown in Supplementary Figure 1.

Data extraction

Two reviewers independently reviewed the abstracts, titles of the individual studies and selected full-length articles identified by the above-mentioned search strategy to include/exclude studies. The reviewers also independently extracted and abstracted the data from these studies including design, methods, study characteristics, and other relevant outcomes. Any discrepancy between the first and second authors was resolved by consensus or by consulting with the third author.

Patient selection

Our study included patients with cryptogenic stroke and PFO, who received either PFO device closure or medical therapy (anti platelet therapy). Age criteria of the individual trials are shown in Table 1. Trials enrolled patients with cryptogenic stroke in the 3 to 6 mo prior to randomization. While CLOSE[14], REDUCE[15] and RESPECT[16] only included cryptogenic ischemic strokes, CLOSURE I[12] and PC[13] included transient ischemic attacks (TIAs) as well.

Outcomes

Our primary outcome of interest was incidence of recurrent ischemic stroke. Secondary outcomes included incidence of atrial fibrillation, all-cause mortality, major bleeding and adverse events. We also compared TIA events between the device closure and the medical therapy group and reported outcomes from the available studies.

Statistical analysis

Random effects model was used to pool categorical data. Analysis of risk ratio (RR) with 95%CI limits was performed. Cochrane's Q statistics was used to assess heterogeneity of the included studies for outcomes of

Table 1 Baseline characteristics

Variables	Treatment groups	CLOSE (mean ± SD) or *N*	CLOSURE I (mean ± SD) or *N*	PC (mean ± SD) or *N*	REDUCE (mean ± SD) or *N*	RESPECT (mean ± SD) or *N*
Age (yr)	PFO Closure	42.9 ± 10.1	46.3 ± 9.6	44.3 ± 10.2	45.4 ± 9.3	45.7 ± 9.7
	Medical therapy	43.8 ± 10.5	45.7 ± 9.1	44.6 ± 10.1	44.8 ± 9.6	46.2 ± 10
Age range (yr)	PFO Closure	16-60	18-60	< 60	18-59	18-60
	Medical therapy	16-60	18-60	< 60	18-59	18-60
Male	PFO Closure	137	233	92	261	268
	Medical therapy	142	238	114	138	268
Smoker	PFO Closure	68	96	52	63	75
	Medical therapy	69	104	47	25	55
Hypertension	PFO Closure	27	151	49	112	160
	Medical therapy	24	131	58	58	163
Hyper lipidemia	PFO Closure	30	212	50	-	196
	Medical therapy	36	189	62	-	195
Diabetes mellitus	PFO Closure	3	-	5	18	33
	Medical therapy	9	-	6	10	41
CAD	PFO Closure	-	6	4	-	19
	Medical therapy	-	4	4	-	9
Family hx of CAD or stroke	PFO Closure	-	247	53	-	136
	Medical therapy	-	257	40	-	109
CHF	PFO Closure	-	2	-		3
	Medical therapy	-	0	-		0
MI	PFO Closure	0	7	3	-	5
	Medical therapy	0	5	1	-	2
Cardiac catheterization	PFO Closure	-	23	-	-	-
	Medical therapy	-	17	-	-	-
Valvular disease	PFO Closure	-	49	8	-	-
	Medical therapy	-	45	5	-	-
Arrhythmia	PFO Closure	-	26	-	-	-
	Medical therapy	-	19	-	-	-
PTCA	PFO Closure	-	6	-	-	-
	Medical therapy	-	2	-	-	-
PVD	PFO Closure	-	5	3	-	5
	Medical therapy	-	7	2	-	1
Stokes-adams syndrome	PFO Closure	-	4	-	-	-
	Medical therapy	-	3	-	-	-
DVT or PE	PFO Closure	5	0	-	-	-
	Medical therapy	4	4	-	-	-
Migraine	PFO Closure	67	-	47	-	195
	Medical therapy	78	-	38	-	186
Pericarditis	PFO Closure	-	2	-	-	-
	Medical therapy	-	3	-	-	-
Cardio myopathy	PFO Closure	-	1	-	-	-
	Medical therapy	-	0	-	-	-
Index cryptogenic stroke	PFO Closure	238	324	165	441	-
	Medical therapy	235	329	163	223	-
Index TIA	PFO Closure	-	122	33	-	-
	Medical therapy	-	132	42	-	-
TEE with moderate-severe shunt	PFO Closure	-	250	135	348	385
	Medical therapy	-	231	112	173	352
Atrial septal aneurysm > 10 mm	PFO Closure	-	158	47	86	180
	Medical therapy	-	165	45	-	169
> 1 previous TIA or stroke	PFO Closure	10	-	76	68	111
	Medical therapy	7	-	79	24	112

CAD: Coronary artery disease; CHF: Congestive heart failure; DVT: Deep vein thrombosis; MI: Myocardial infarction; PE: Pulmonary embolism; PFO: Patent foramen ovale; TEE: Transesophageal echocardiogram; TIA: Transient ischemic attack.

interest. I^2 values of < 25%, 25%-50%, and 50%-75% represented low, moderate and high heterogeneity respectively. Publication bias was visually assessed by using funnel plot. Whenever necessary, we included an exclusion-sensitivity analysis to minimize heterogeneity. We performed meta-regression when necessary study the impact of moderator variables on outcomes of interest. A *P*-value of < 0.05 was considered to be statistically significant. Analyses were performed by Mahesh Anantha-Narayanan using the software Comprehensive Meta-analysis (version 3.3)[18].

RESULTS

Study characteristics

Five RCTs were included[12-16] in the final analysis. Table

Table 2 Details of the included randomized controlled trials

Study name	Type of study	Devices used	Follow-up (median or mean), (mo)	PFO closure device	Medical therapy	Primary composite end point
CLOSE	Randomized multicenter	Amplatz PFO Occluder or Cribriform; Starflex; CardioSeal; Intrasept PFO; PFOStar; Helex; Premere; PFO occluder OCCLUTECH; PFO occluder GORE (GSO)	64	238	235	Fatal or nonfatal stroke
CLOSURE I	Prospective, multicenter, randomized, open-label, two-group superiority trial	STARFlex device (NMT Medical)	22	447	462	Composite of stroke or TIA during 2 yr of follow-up, death from any cause during the first 30 d, and death from neurologic causes between 31 d and 2 yr
PC	Multicenter, multinational, randomized, clinical trial	Amplatzer PFO Occluder (St. Jude Medical)	54	204	210	Composite of death, nonfatal stroke, TIA, or peripheral embolism
REDUCE	Multinational, randomized, clinical trial	Gore Helex or Gore Cardioform (WL Gore and Associates) septal occluders	38	441	223	Freedom from recurrent clinical ischemic stroke through at least 24 mo and incidence of new brain infarct
RESPECT	Prospective, multicenter, controlled, randomized, open-label clinical trial	Amplatzer PFO Occluder	71	499	481	Recurrent nonfatal ischemic stroke, fatal ischemic stroke, or early death

CLOSE: Patent Foramen Ovale Closure or Anticoagulants *vs* Antiplatelet Therapy to Prevent Stroke Recurrence; CLOSURE I: Evaluation of the STARFlex Septal Closure System in Patients with a Stroke and/or Transient Ischemic Attack due to Presumed Paradoxical Embolism through a Patent Foramen Ovale; PC: Percutaneous Closure of Patent Foramen Ovale Using the Amplatzer PFO Occluder with Medical Treatment in Patients with Cryptogenic Embolism; REDUCE: GORE® HELEX® Septal Occluder/GORE® CARDIOFORM Septal Occluder and Antiplatelet Medical Management for Reduction of Recurrent Stroke or Imaging-Confirmed TIA in Patients With Patent Foramen Ovale (PFO); RESPECT: Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment; PFO: Patent foramen ovale; TIA: Transient ischemic attack.

1 shows the baseline characteristics of the included studies and patients groups used in the analysis.

Patients

The overall study population consisted of 3440 patients extracted from 5 RCTs and 1991 were males. Mean follow up time was 50 ± 20 mo. Mean age of the entire cohort was 45 ± 1.1 years. In CLOSE, 238 patients were assigned to the PFO closure group, 187 patients were assigned to the anti-coagulation group and 409 patients received anti-platelet therapy alone. Details of the included trials are listed in Table 2.

Recurrent ischemic stroke - PFO closure vs medical therapy

Risk of recurrent ischemic stroke was 41% lower in patients who received PFO device closure when compared to patients who received medical therapy alone (RR: 0.59, 95%CI: 0.40-0.87, $P = 0.008$) (Figure 1). Sensitivity analysis with exclusion of the study with the maximum strength[12] did not alter the results (RR: 0.51, 95%CI: 0.33-0.81, $P = 0.004$). Funnel plot showed very minimal bias (Supplementary Figure 2) and heterogeneity within the included studies was found to be moderate ($I^2 = 30$). A meta-regression of incidence of recurrent stroke on follow-up time was insignificant (Supplementary Figure 3) ($P = 0.408$). Incidence of TIA was not different between PFO closure and medical therapy (RR: 0.78, 95%CI: 0.48-1.25, $P = 0.301$).

Atrial fibrillation - PFO closure vs medical therapy

Atrial fibrillation was significantly higher in the PFO closure group when compared to group that received medical therapy (RR: 4.97, 95% CI: 2.22-11.11, $P < 0.001$) (Figure 2). Sensitivity analysis with exclusion of study with maximum strength[12] did not change the results (RR: 7.57, 95%CI: 3.42-16.72, $P < 0.001$). Heterogeneity within the

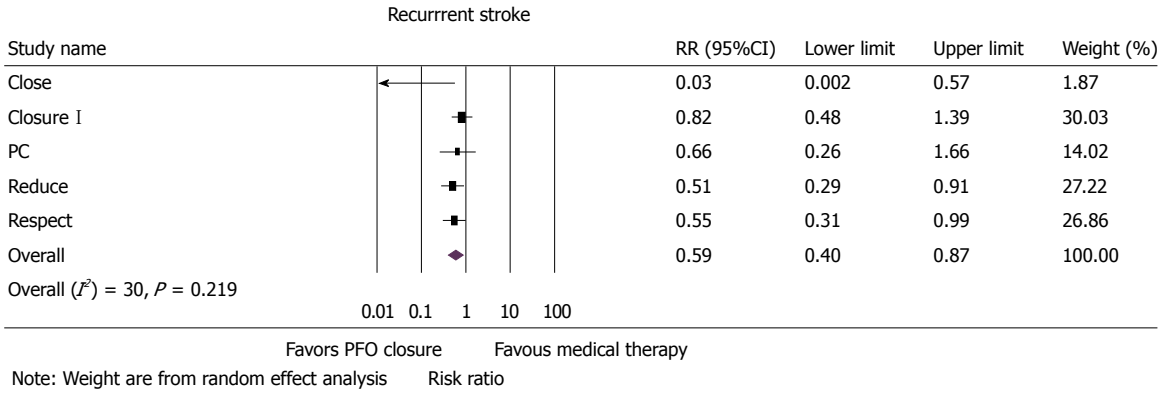

Figure 1 Forest plot and pooled analysis for recurrent ischemic stroke (*n* = 3440) in cryptogenic stroke patients (patent foramen ovale closure *vs* medical therapy alone). RR: Relative risk.

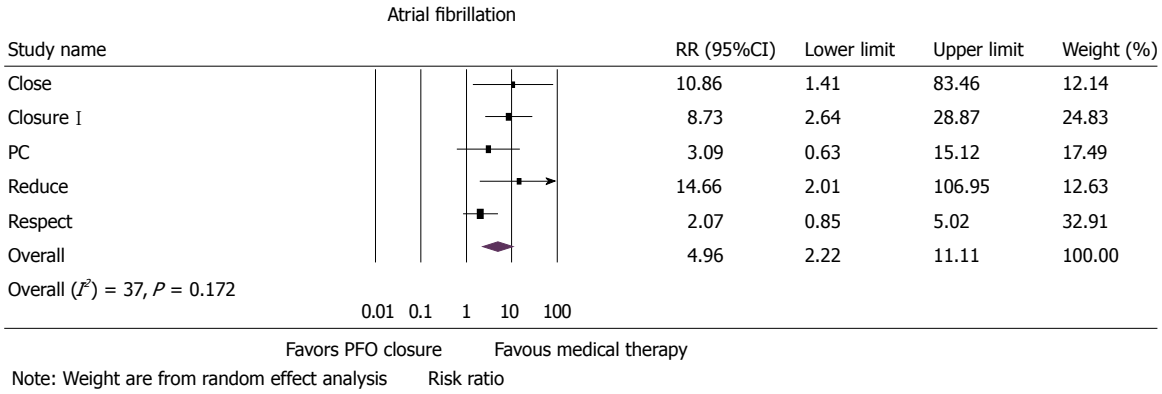

Figure 2 Forest plot and pooled analysis for atrial fibrillation (*n* = 3391) in cryptogenic stroke patients (patent foramen ovale closure *vs* medical therapy alone). RR: Relative risk.

included studies was moderate (I^2 = 37).

All-cause mortality- PFO closure vs medical therapy

All-cause mortality was similar between the groups (RR: 1.09, 95%CI: 0.47-2.53, P = 0.839) (Supplementary Figure 4). Sensitivity analysis performed with exclusion of study with maximum strength[16] did not change the results (RR: 1.04, 95%CI: 0.27-4.02, P = 0.952). Heterogeneity of the included studies was low (I^2 = 0).

Major bleeding- PFO closure vs medical therapy

Major bleeding events were similar between PFO closure and medical therapy groups (RR: 0.76, 95%CI: 0.36-1.58, P = 0.466) (Supplementary Figure 5). Sensitivity analysis performed with exclusion of study with the maximum strength[15] did not alter the results (RR: 0.75, 95%CI: 0.27-2.11, P = 0.587). Heterogeneity within the included studies was moderate (I^2 = 28).

Adverse events- PFO closure vs medical therapy

Rate of adverse events did not differ between the PFO device closure and the medical therapy groups (RR: 0.94, 95%CI: 0.83-1.07, P = 0.343) (Supplementary Figure 6). Sensitivity analysis excluding the study with maximum strength[13] did not affect the results (RR: 0.90, 95%CI: 0.74-1.10, P = 0.299). Heterogeneity of the included studies was low (I^2 = 0).

DISCUSSION

Results from our current meta-analysis show that PFO device closure reduces the risk of recurrent stroke in appropriately selected patients with cryptogenic stroke. There was a higher incidence of atrial fibrillation associated with PFO closure but there was no significant difference in all-cause mortality, major bleeding or adverse events between the groups.

The usage of PFO closure devices, especially the Amplatzer device, increased steadily since 1998 until 2006 when the device was voluntarily withdrawn by the dealer[19]. The device did not qualify for Humanitarian device exemption (HDE) related to its increased usage without supporting evidence[19]. The American Association of Neurology issued a practice update in August 2016 recommending against the routine use of PFO closure devices in cryptogenic stroke patients[20]. Following this update, the Amplatzer closure device regained its approval for use in patients with PFO by the Center for Devices and Radiological Health of the Food and Drug Administration. The approval comes with an

advisory stating that the decision to implant the device should be determined by a cardiologist and a neurologist after excluding the other common etiologies of stroke.

Guidelines for PFO closure in cryptogenic stroke patients come from two major RCTs[12,13] along with the 2 year follow-up data of the third RCT, the RESPECT trial[21]. CLOSURE I compared STARFlex device to medical therapy in patients with cryptogenic stroke. The trial reported no difference in recurrent stroke events between PFO device closure and medical therapy[12]. Also, there were significantly higher numbers of device related procedural complications. Interpretation of results from the trial was limited by lower number of events when compared to number of patients lost at follow up. Following this came PC[13] and RESPECT[21] that compared Amplatzer closure device with medical therapy for prevention of cryptogenic stroke. Though results from the individual trials did not report any meaningful difference with respect to recurrent ischemic strokes, previous meta analyses and pooled analysis including these trials showed a significant reduction in incidence of recurrent ischemic stroke events with the use of Amplatzer device[22,23]. Combined analysis also showed significantly higher rates of atrial fibrillation in PFO device closure group[22,23]. Recently the long-term follow-up data from RESPECT showed a significant reduction in recurrent ischemic stroke events in the PFO device closure group compared to medical therapy[16] as well as the two other major RCTs - CLOSE and REDUCE.

It is worthwhile discussing the inclusion criteria of the previously published trials. CLOSURE I, PC and RESPECT included patients with any PFO size with or without atrial septal aneurysm. In these initial trials, there was an overall higher dropout rate for the very low event rate at follow up. Notably, there were issues with patient selection. For example, patients with small PFO and patients with concomitant atrial fibrillation were included in these trials. In these patients, atrial fibrillation and concomitant coronary disease increases the risk of arterial stroke and these patients may not essentially benefit from PFO closure.

The CLOSE, REDUCE and RESPECT trials recently reported long term outcomes in patients with large sized PFO or patients with atrial septal aneurysm. Whereas REDUCE used GORE Helex or GORE Cardioform device, CLOSE included multiple devices as listed in Table 2. CLOSE showed a significant reduction in recurrent ischemic stroke events in patients with PFO closure device when compared to medical therapy alone. The trial also compared anti platelet to anti-coagulation therapy and reported no meaningful difference in recurrent ischemic strokes between the two groups. We did not have similar data from the other trials to compare efficacy of anti-coagulation therapy to anti-platelet therapy. REDUCE showed a 77% reduction in the incidence of recurrent ischemic strokes with PFO closure therapy. The trial also showed a 49% reduction in new brain infarcts on MRI. CLOSE and REDUCE differ significantly from the previously published RCTs as these trials employed very strict exclusion criteria to exclude patients with other source of emboli including patients with atrial fibrillation, coronary artery disease and small vessel disease. CLOSE only studied patients with a large PFO or an atrial septal aneurysm whereas REDUCE included patients mostly with moderate to severe right-to-left shunt. Also, the definitions employed were considerably strict to avoid including symptoms that could mimic a TIA.

Another interesting result in CLOSE was the higher incidence of recurrent ischemic strokes in patients with concurrent PFO and atrial septal aneurysm when compared to patients with a PFO alone suggesting that aneurysmal atrial septum is associated with higher risk of recurrent strokes. We could not analyze this effect as shunt sizes were not reported in the other studies. The diagnosis of PFO can be challenging in some patients. The presence of an eustachian valve (EV) can potentially lead to a false negative arm based echocardiographic bubble study in the presence of PFO as the valve redirects contrast free blood from inferior vena cava to atrial septum, thereby preventing the contrast rich superior vena cava blood from reaching the left side. Previous investigators demonstrated that the detection of atrial septal defect was enhanced when contrast agent was delivered into inferior vena cava rather than the superior vena cava[24-26]. CLOSE investigators recommended looking for an EV during TEE but none of the included trials compared superior *vs* inferior vena caval injection techniques.

The strength of our meta-analysis is the inclusion of only RCTs to avoid potential patient selection bias. The previous RCTs including RESPECT, CLOSURE I and PC suffered slow recruitment which could introduce a potential recruitment bias. Previous studies included patients with small to medium PFOs and combining these trials with the REDUCE and CLOSE trial with strict inclusion criteria for PFO may create bias. Trials did not differentiate between cryptogenic and non-cryptogenic strokes at follow up. Also, studies did not have a long term atrial fibrillation follow up data. The variable definitions used across the studies for major bleeding may create bias. We did not have patient level data to assess outcomes for sub-groups with different shunt sizes. Studies used different PFO closure devices (Amplatzer in PC and RESPECT, GORE Helex/Cardioform in REDUCE, STARFLEX in CLOSURE I whereas CLOSE used multiple closure devices) and so we did not have enough power to compare outcomes between various PFO closure devices. Studies reporting device complications were limited in number making it difficult to draw strong conclusions. Finally, publication bias is a limitation of any meta-analysis.

In summary, this systematic review and meta-analysis of the published RCTs supports PFO device closure in selected patients with cryptogenic stroke, especially with moderate and large sized shunt and/or with atrial septal aneurysm. PFO closure is associated

with a lower incidence of recurrent ischemic strokes but carries a higher risk of atrial fibrillation. Further RCTs to study the long-term effect of atrial fibrillation on recurrent stroke events are essential.

ARTICLE HIGHLIGHTS

Research background

Cryptogenic stroke accounts for one-fourth of the ischemic strokes and the presumed mechanism is venous thromboembolisms entering systemic circulation via patent foramen ovale (PFO). Percutaneous device closure of PFO has been shown to reduce stroke rates but there is lack of evidence on whether percutaneous closure of PFO is better when compared to medical therapy with antiplatelet and/or anticoagulation. Previously published randomized controlled trials (RCTs) comparing PFO closure to medical therapy lacked appropriate patient selection and had large dropout rates at follow up. Based on this available data, the American Association of Neurology (AAN) guidelines recommended against PFO device closure

Research motivation

Though current guidelines do not support PFO device closure, two recently published RCTs showed reduction in incidence of recurrent strokes with PFO closure in appropriately selected patient population with cryptogenic stroke. We therefore performed a systematic review and meta-analysis to evaluate if PFO closure is superior to medical therapy alone including all published RCTs to date.

Research objectives

The purpose of the study is to analyze if PFO closure device is superior to medical therapy alone to prevent recurrent strokes in appropriately selected patient population with cryptogenic stroke.

Research methods

We searched five databases for studies comparing PFO device closure to medical therapy in patients with cryptogenic stroke. To qualify for inclusion, trials must have a randomized design, include patients > 18 years of age and compare PFO closure to medical therapy in patients with cryptogenic stroke. We obtained a total of five randomized controlled trials for inclusion and performed a meta-analysis. Our primary outcome was incidence of recurrent ischemic stroke. We also looked at secondary outcomes including incidence of atrial fibrillation, all-cause mortality, major bleeding and adverse events.

Research results

PFO device closure in appropriately selected patient population with cryptogenic stroke is superior to medical therapy alone in reducing incidence of recurrent strokes. There was no difference between the PFO device closure and the medical therapy groups in terms of overall mortality, major bleeding and adverse events but there was a significant increase in incidence of atrial fibrillation in the closure device group.

Research conclusions

Our current meta-analysis including all published randomized controlled trials comparing PFO closure device to medical therapy alone supports PFO device closure in appropriately selected patient population. PFO closure in younger patients with moderate to large PFO and with atrial septal aneurysm is clearly associated with reduction in incidence of recurrent strokes without increasing mortality, major bleeding or adverse events. There is an increase in atrial fibrillation with PFO closure compared to medical therapy alone but this was mostly in the immediate post-operative period.

Research perspectives

From this meta-analysis, it could be seen that PFO closure device reduces risk of recurrent stroke in appropriately selected patient population with cryptogenic stroke. PFO closure is associated with increase in atrial fibrillation but this could likely be an organic phenomenon related to atrial irritation from the device itself. Further studies are essential to address whether this increase in atrial fibrillation rates with PFO closure device is associated with adverse outcomes on long term follow up.

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EDITORIAL

Preventing pediatric cardiothoracic trauma: Role of policy and legislation

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Abstract

Data from the last 50 years suggest that pediatric patients typically suffer cardiothoracic injuries following blunt traumatic force (70%) in the setting of either motor vehicle crashes (53.5%) or vehicle-pedestrian accidents (18.2%). Penetrating trauma accounts for 30% of pediatric cardiothoracic injuries, half of which are gunshot wounds. Graduated driver licensing programs, gun-control legislation, off-road vehicle regulation, initiatives such as "Prevent the Bleed", as well as professional society recommendations are key in preventing pediatric cardiothoracic injuries.

Key words: Pediatric trauma; Blunt cardiac trauma; Penetrating cardiac trauma; Injury; Children; Policy; Legislation

Core tip: Graduated driver licensing programs, gun-control legislation, off-road vehicle regulation, initiatives such as "Prevent the Bleed", as well as professional society recommendations are key in preventing pediatric cardiothoracic injuries.

Mylonas KS, Hemmati P, Tsilimigras DI, Texakalidis P, Economopoulos KP. Preventing pediatric cardiothoracic trauma: Role of policy and legislation. *World J Cardiol* 2018; 10(7): 49-51 Available from: URL: http://www.wjgnet.com/1949-8462/full/v10/i7/49.htm DOI: http://dx.doi.org/10.4330/wjc.v10.i7.49

INTRODUCTION

Trauma is a leading cause of pediatric mortality in the developed world and can have substantial physical and psychological sequalae in surviving victims[1]. Cardiothoracic injury is the second most commonly reported trauma-associated cause of fatality after head trauma[2,3]. Although isolated cardiothoracic injury is typically non-lethal, mortality rates can be as high as 20%-40% in multi-system trauma patients[4]. Our group recently analyzed epidemiological and outcomes data on a total of 1062 pediatric cardiac trauma patients that were treated at United States centers in the last 50 years[5]. In this editorial, we explore various policy interventions directed at reducing the incidence, morbidity, and mortality of cardiothoracic trauma in children.

Pediatric patients typically suffer cardiothoracic injuries following blunt traumatic force (70%) in the setting of either motor vehicle crashes (MVCs) (53.5%) or vehicle-pedestrian accidents (18.2%)[5,6]. A National Trauma Data Bank analysis revealed that teenagers are at a higher risk of suffering blunt cardiothoracic injury[7], at least partly due to sociobehavioral factors. In several states, teenagers can get a learner's permit before age 16 and a driver's license by age 16. Also, a number of risk factors predisposing to MVCs, such as reckless driving, cell phone use while driving, and driving while intoxicated (DWI) are frequently seen amongst adolescents[8-10].

Therefore, preventing MVCs is essential in diminishing pediatric cardiothoracic trauma rates. Graduated driver licensing (GDL) has been legislated in an effort to reduce MVC rates and is predicated on the concept of slowly and safely exposing young drivers to higher-risk driving conditions[11,12]. Traditionally GDL programs begin with restricted to supervised driving, followed by unsupervised driving under settings that involve intermediate risk, and ultimately lead to full licensure[12]. According to data from the Fatality Analysis Reporting System, National Automotive Sampling System General Estimates System, Census Bureau, and National Household Travel Surveys, per capita fatal and police-reported MVC rates in 2012 were higher for middle-aged drivers than for adolescent over 16 years old. Fatal DWIs also decreased for teenagers after introducing GDL programs[13]. In addition, implementing school-based pedestrian safety intervention programs has been shown to reduce the incidence of pediatric pedestrian collisions[14,15].

Off-road vehicles (ORVs) have also been associated with pediatric cardiothoracic trauma among various other types of injury[16-18]. The Eastern Association for the Surgery of Trauma supports the enactment and implementation of legislature as a way of reducing ORV-related injuries[17]. A landmark act regulating the use of ORVs was "Sean's Law" which amended Massachusetts General Laws Chapter 90b (Sections 21-35). After the enforcement of "Sean's Law", the rate of emergency department discharges in Massachusetts declined by over 30% in children under the age of 10, 50% in 10- to 13-year-old, and nearly 40% in 14- to 17-year-old[16].

Our recent analysis also suggests that penetrating trauma accounts for 30% of pediatric cardiothoracic injuries, half of which are gunshot wounds (GSWs)[5]. Of note, in recent years, GSW-related mortality rates in United States adolescents exceeded deaths from MVCs[19]. In an attempt to reduce firearm injuries in children, both the American Academy of Pediatrics (AAP) and the American Pediatric Surgical Association support firearm-control legislation[20,21]. The AAP also endorses all efforts to identify adolescents at high risk for becoming GSW victims, including those with a history of family or peer violence, substance abuse, depression, previous suicide attempts, or carrying of weapons[20]. Child health care professionals are encouraged to engage in discussions with parents regarding making a gun-safe environment at home by either implementing safe storage techniques (ammunition and firearm stored separately and locked) or by removing firearms from the family's house altogether[20,22]. Similarly, the American College of Surgeons (ACS) Committee on Trauma advocates towards firearm safety features such as proof locks and "smart gun" technology[23].

CONCLUSION

Data from the last 50 years suggest that, in the United States, the vast majority of pediatric cardiothoracic injuries occur due to MVCs and GSWs[5]. Although public education programs such as the ACS's "Stop the Bleed" (teaching bystanders how to respond to life-threatening arterial hemorrhage) will save lives after traumatic wounds, we feel that advocating for methods that would prevent these injuries in the first place is equally, if not more, important[24]. Gun-control and ORV legislation, GDL programs, initiatives such as "Prevent the Bleed", as well as professional society recommendations are applicable in pediatric cardiothoracic trauma and can prevent these injuries[25].

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REVIEW

Novel approaches for the treatment of ventricular tachycardia

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Abstract

Ventricular tachycardia (VT) is a crucial cause of sudden cardiac death (SCD) and a primary cause of mortality and morbidity in patients with structural cardiac disease. VT includes clinical disorders varying from benign to life-threatening. Most life-threatening episodes are correlated with coronary artery disease, but the risk of SCD varies in certain populations, with various underlying heart conditions, specific family history, and genetic variants. The targets of VT management are symptom alleviation, improved quality of life, reduced implantable cardioverter defibrillator shocks, prevention of reduction of left ventricular function, reduced risk of SCD, and improved overall survival. Antiarrhythmic drug therapy and endocardial catheter ablation remains the cornerstone of guideline-endorsed VT treatment strategies in patients with structural cardiac abnormalities. Novel strategies such as epicardial ablation, surgical cryoablation, transcoronary alcohol ablation, pre-procedural imaging, and stereotactic ablative radiotherapy are an appealing area of res-

earch. In this review, we gathered all recent advances in innovative therapies as well as experimental evidence focusing on different aspects of VT treatment that could be significant for future favorable clinical applications.

Key words: Ventricular tachycardia; Catheter ablation; Epicardial; Sudden cardiac death; Novel techniques; Substrate

Core tip: Antiarrhythmic drug therapy and endocardial catheter ablation remains the cornerstone of ventricular tachycardia (VT) treatment management, but both treatments have limited efficacy and important adverse effects. Catheter ablation for cardiomyopathic (scar-related) VT is associated with recurrence rates as high as 50% at 6 mo. Implantable cardioverter defibrillator provides a safety net; however, there is an increased need for more effective and safer methods to decrease VT recurrence episodes. We sought to review current literature in order to summarize data on innovative techniques for VT treatment.

Spartalis M, Spartalis E, Tzatzaki E, Tsilimigras DI, Moris D, Kontogiannis C, Livanis E, Iliopoulos DC, Voudris V, Theodorakis GN. Novel approaches for the treatment of ventricular tachycardia. *World J Cardiol* 2018; 10(7): 52-59 Available from: URL: http://www.wjgnet.com/1949-8462/full/v10/i7/52.htm DOI: http://dx.doi.org/10.4330/wjc.v10.i7.52

INTRODUCTION

Sudden cardiac death (SCD) is a vital public health issue, accountable for almost 50% of all cardiovascular deaths[1]. In the last three decades, SCD was the leading cause for almost 230000 to 350000 deaths per annum in the United States[1]. Ventricular arrhythmias account for 25% to 36% of witnessed sudden cardiac arrests (SCA) at home and 38% to 79% of witnessed SCA in public[2].

Ischemic heart disease, structural disorders, various forms of cardiomyopathy associated with myocardial fibrosis, cardiac channelopathies, myocarditis, congenital heart diseases, and other genetic rare disorders are associated with ventricular arrhythmias[1].

Even though treatment for heart failure lowers mortality and SCD, it was unsuccessful in lessening ventricular tachycardia (VT) recurrences[3]. Implantable cardioverter defibrillators (ICD) are very effective in eliminating VT episodes and in lowering the possibility of SCD, but they are not useful for arrhythmia prevention[4]. When the VT substrate manifests, anti-arrhythmic drug treatment or catheter ablation are the current choices to reduce VT episodes[5]. Catheter ablation and antiarrhythmic drug therapy though, are also limited by incomplete efficacy, unfavorable side effects, and procedural risk[5]. In this review, we outline the current advances in VT treatment options and describe the imaging modalities, progress, and novel strategies.

LITERATURE SEARCH

We have collected all experimental and clinical investigations focused on new aspects that could be essential for tailoring VT therapy according to underlying etiology, in order to achieve higher efficacy. The MEDLINE database was screened for studies with the medical term "ventricular tachycardia" and keywords "treatment", or "ablation", or "management". We restricted our search to English literature.

NOVEL VT THERAPIES

Epicardial catheter ablation

Endocardial catheter ablation and antiarrhythmic drug treatment are currently the mainstays of VT treatment[1,3]. However, the procedural success rates of VT are quite variable due to the heterogeneous substrates that reflect the variety of pathophysiological processes[6,7]. The success rate of endocardial ablation in patients with outflow tract VT is 84%, in patients with papillary muscle VT is 60%, and in patients with idiopathic left ventricular VT is 70%[6]. Moreover, the VT recurrence rates of endocardial ablation in ischemic cardiomyopathy patients are between 23% and 49% and in dilated cardiomyopathy patients between 46% and 61%[7]. Non-ischemic cardiomyopathy patients have worse outcomes than ischemic cardiomyopathy patients due to scar patterns with epicardial and intramural sites[7].

Epicardial ablation has emerged as a potential alternative ablation strategy in order to increase the success rate in complex substrates and to eliminate VT in patients with different cardiomyopathies and more recently in patients with Brugada syndrome[8-11]. Percutaneous approach to the pericardial area facilitates epicardial ablation when the VT substrate is situated in the subepicardium[8] (Figure 1). Adjacency to coronary circulation and the phrenic nerve may hinder the procedure in certain situations[9]. In patients with previous heart surgery or previous epicardial ablation attempts, percutaneous access may not be possible and as such, video-assisted thoracoscopy may be a good and minimally invasive alternative to open surgery[12].

Epicardial ablation is a safe procedure with low complication rates[13]. Pericardial effusion is the most common complication[13]. Damage to subdiaphragmatic organs and hemorrhage from diaphragmatic vessels have also been reported[13].

Della Bella *et al*[14] evaluated the possible benefit of endo-epicardial catheter ablation for the management of VT in 528 patients with any form of structural cardiac disorder (Figure 2). Endo-epicardial catheter ablation resulted in a VT recurrence rate of 34.1%, in comparison

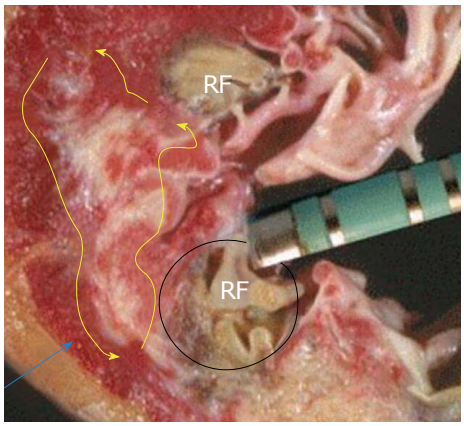

Figure 1 Arrhythmia substrate is deep (blue arrow), but the radiofrequency ablation lesions are not that deep. RF: Radiofrequency.

to a rate of up to 50% with the standard endocardial approach[14].

Intramyocardial infusion-needle catheter ablation

Transcoronary alcohol ablation has emerged to approach deep intramyocardial substrate in patients not amenable to endo-epicardial catheter ablation (mechanical valve, thrombus, significant comorbidities)[15,16]. Transcoronary alcohol ablation requires the injected dose of sterile pure ethanol with proximal balloon expansion to a culprit vessel with a target of abolishing perfusion[15,16] (Figure 3). This method can prevent recurrent VT, VT storm and can control incessant VT[15,16]. The exact recognition of the target vessel and the existence of collaterals may hinder the adoption of the method[15-17].

Kim *et al*[15] introduced the novel use of cardioplegia as a mapping technique in order to identify the critical VT isthmus to facilitate effective transcoronary ethanol ablation and avoid irreversible myocardial injury. Furthermore, Sapp *et al*[17] showed that intramyocardial needle mapping and ablation with saline infusion could create deep injuries and is a practical and efficient method. Intracoronary wire mapping and coil embolization have also been utilized just as alcohol ablation to target VT arising from intraventricular septum[18]. After intracoronary wire mapping and recognition of a culprit vessel, coils are directed to embolize the branch, eliminating the desired target perfusion[18].

Bipolar ablation

Bipolar ablation between two ablation catheters located on either position of the septum from both ventricles improves lesion transmurality because it depends less on catheter contact and alignment[19,20] (Figure 4). Bipolar ablation has the theoretical benefit of producing more powerful energy and providing deeper lesions, in comparison to two separate unipolar catheters[19,20]. Sakamoto *et al*[20] recently successfully eliminated the critical VT circuit in a patient with an arrhythmogenic substrate (cardiac sarcoidosis), utilizing bipolar ablation.

Cardiac sympathetic denervation

Accumulated evidence strongly suggests a role of sympathetic neuromodulation in controlling refractory VT[19-24]. Cardiac sympathetic denervation surgery has been proven to be useful for the management of congenital long QT syndrome and catecholaminergic polymorphic VT[21]. The procedure requires extraction of the lower fraction of the stellate ganglion and T2-T4 sympathetic thoracic ganglia[21]. Complications regarding the procedure were infrequent, with 4% developing acute ptosis or Horner syndrome[21]. Vaseghi *et al*[21] showed that cardiac sympathetic denervation has greater shock free survival as well as a considerable decline in shock burden in patients with recurrent VT or VT storm, regardless of antiarrhythmic drug therapy and catheter ablation. In addition, bilateral cardiac sympathetic denervation appeared to be more efficacious than left-sided denervation[21,22].

Augmented sympathetic activity leads to early and delayed afterdepolarization, enhances diffuse repolarization, leading to ventricular electrical susceptibility and increases the possibility of malignant VT[23]. Stellate ganglionectomy lengthens the ventricular refractory period and raises the VF threshold, decreasing VT or VF inducibility in the context of myocardial infarction[23,24]. Locally invasive sympathetic ganglion block could select individuals with greater possibilities of long-term clinical benefits prior to sympathetic denervation[23,24].

Renal sympathetic denervation

Enhanced sympathetic tone shortens the ventricular effective refractory period, enhances automaticity, and lowers the threshold for ventricular arrhythmias[25-27]. Feyz *et al*[25] performed bilateral renal denervation in a patient with polymorphic VT with excellent results. Aksu *et al*[27] also showed that catheter-based renal denervation was successful in a patient with an electrical storm due to catecholaminergic polymorphic VT. However, the microanatomy of human renal vessels has great variability. Accessory renal vessels that bifurcated early can also influence the result negatively, and there is still the absence of procedural endpoint during the technique[26].

As a result, renal sympathetic denervation is not currently recognized as an ideal or approved VT treatment method[25-27]. However, certain ventricular arrhythmias do not terminate after catheter ablation, thus making renal sympathetic denervation a possible option for patients in whom other ablative approaches were ineffective[25,27].

Stereotactic radioablative therapies

Despite catheter-oriented ablation, which applies radiofrequency or freezing to damage tissues, radiotherapy is based on photons from X-rays or gamma rays to injure the desired target, mainly cancer. Through novel distribution methods such as intensity-modulated radiotherapy, a dosage of radiotherapy can be precisely and accurately directed to the desired site, while diminishing

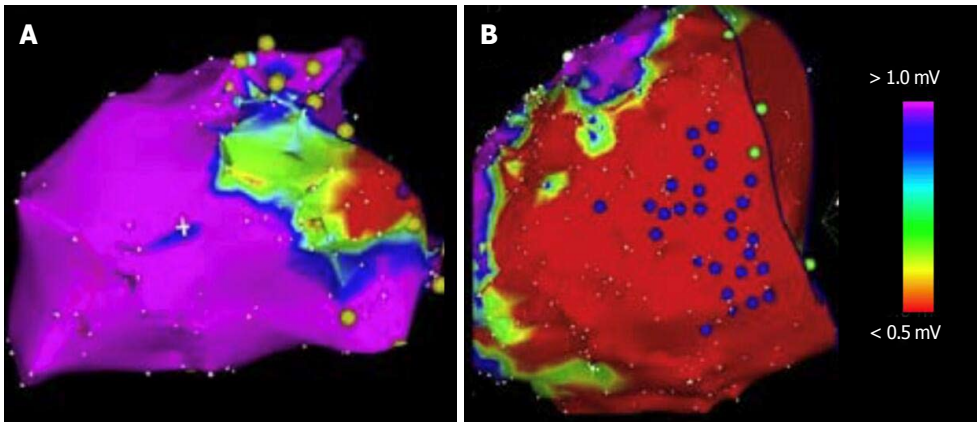

Figure 2 Endocardial and epicardial voltage mapping. A: The voltage map of the endocardium shows an area of scar. The map is color-coded to represent bipolar electro-gram voltage (red: Dense scar, 0.5 mV; purple: Normal tissue, 1.5 mV, intervening colors represent voltage values in between); B: The voltage map of the epicardium shows a larger area of scar.

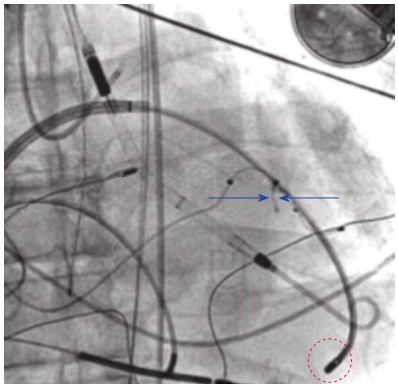

Figure 3 Transcoronary alcohol ablation. Coronary angiography of the left anterior descending artery shows a septal perforator with a course to the site of earliest activity. A balloon catheter occludes this branch and ethanol is infused (blue arrows). The ablation catheter is placed at the region of earliest activity (red circle).

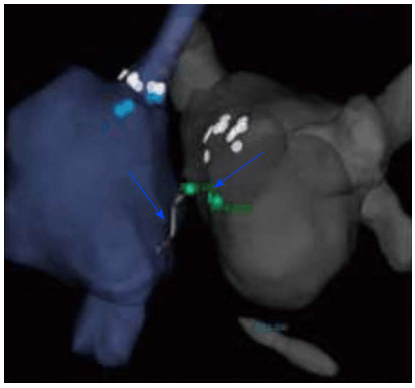

Figure 4 Bipolar ablation. Bipolar radiofrequency ablation between the right and left ventricular septum using two catheters.

dosage to adjoining healthy tissues[28,29].

Ablative radiotherapy is generally a noninvasive, outpatient method, which does not involve anesthesia[28,29]. Potential risks consist of damage to tissue next to the ablated site, such as brain edema for intracranial lesions, pneumonitis for chest therapies, myelopathy for spinal carcinomas, or bowel perforation for abdominal locations[28,29]. In comparison to radiofrequency or cryoenergy, the damage from ablative radiotherapy progresses over days to months, needing time for the total tissue damage to be shown[28,29].

The first patient was treated on a robotic radiosurgery system (CyberKnife®, Accuray, Sunnyvale, CA, United States) in 2012[28]. The follow-up revealed no definite acute or late adverse effects, and a seven-month reduction burden in VT on standard antiarrhythmic drug therapy, suggesting a potential transient benefit of this method[28].

Cuculich *et al*[29] investigated five patients with increased-risk, refractory VT. The authors focused on arrhythmogenic scar sites by merging anatomical imaging with noninvasive electrocardiographic imaging during VT that was produced using an ICD[29]. Patients were treated with a single dose of 25 Gy while awake, using a noninvasive distribution of accurate ablative radiation with stereotactic body radiation treatment[29]. Cuculich *et al*[29] reported a reduction in events of VT in all five patients.

Cryoablation

Catheter radiofrequency ablation of VT originating from the left ventricle's papillary muscles has been linked to conflicting outcomes[30,31]. Rivera *et al*[31] investigated twenty-one patients with drug-refractory VT, who underwent catheter cryoablation or radiofrequency ablation. Cryoablation was correlated with greater success rates and smaller recurrence rates than radiofrequency procedures, superior catheter support, and smaller frequency of polymorphic arrhythmias[31]. Marai *et al*[30] recently used cryoablation guided by intracardiac echocardiography, 3-dimensional mapping system, and image integration to treat a patient with refractory VT originating from papillary muscle with excellent results.

Surgical therapy for VT

Catheter ablation provides efficient outcomes for su-

stained monomorphic VT, but certain situations, such as the existence of mural thrombus and heavy calcification, can lead to adverse results[32,33]. Higuchi *et al*[33] successfully treated a 67-year-old patient with sustained monomorphic VT due to ventricular scar and resistant to endocardial radiofrequency ablation, by left ventricular reconstruction with cryoablation. Li *et al*[34] conducted a retrospective investigation of 38 consecutive surgical epicardial VT ablation procedures and compared the results with those of a propensity-matched percutaneous epicardial access control group. Surgical epicardial access after heart surgery for VT ablation showed no statistical difference in long-term results in comparison to the percutaneous epicardial group[34].

Recently, Berte *et al*[35] presented the first animal survey utilizing a more potent cryoablation system that can generate larger, transmural ventricular lesions from both the endocardium and the epicardium. Surgical cryoablation in sheep had no acute macroscopic vascular or extracardiac damage and resulted in 100% successful lesions at necropsy[35].

In some patients with non-ischemic cardiomyopathy and VT refractory to standard therapy or undergoing cardiac surgery, surgical ablation may be an alternative option for potentially reducing the burden of ICD shocks during long-term follow-up[36]. Liang *et al*[36] showed that detailed arrhythmogenic substrate in the electrophysiology lab before surgery, in conjunction with a direct scar and radiofrequency ablation lesions visualization in the operating room, is crucial for guiding surgical ablation.

Extracorporeal life support for refractory VT

Extracorporeal life support is a highly efficient bridging treatment in patients with refractory VT associated with cardiogenic shock[37]. Extracorporeal life support allows the usage of negative inotropic antiarrhythmic drug therapy, leads to the weaning of catecholamine delivery, thus resolving the dangerous period of the catecholamine driven electrical storm[37]. The utilization of extracorporeal life support maintains hemodynamic support during an ablation procedure, while mapping and induction of VT are commenced and provides sufficient vital organ perfusion in patients with refractory VT[37]. Current literature suggests the usage of extracorporeal life support, as it has proven to be a safe, practical and efficient therapeutic solution when traditional treatments have failed[37].

Steroid pulse therapy

Okabe *et al*[38] successfully treated a patient with cardiac sarcoidosis associated with VT using steroid pulse therapy.

Gene therapy

Catecholaminergic polymorphic VT (CPVT) is a rare cardiac ion channelopathy induced by anomalies in proteins that regulate Ca^{2+} transport in heart cells that can lead to SCD[39,40]. CPVT is associated with mutations in the gene encoding the cardiac RyR2, a cardiac ryanodine receptor protein which is involved in calcium homeostasis and mutations in the gene that encodes calsequestrin (CASQ2), a protein that interacts with RyR2[39-41].

Denegri *et al*[42] showed that viral gene transfer of wild-type CASQ2 into the heart of mice prevented and reverted severe manifestations of CPVT. Furthermore, Lodola *et al*[43] infected induced pluripotent stem cells with an adeno-associated viral vector serotype 9 (AAV9) encoding the human CASQ2 gene and noticed a significant decline in the percentage of delayed afterdepolarizations. Li *et al*[44] used tetracaine, a local anesthetic drug with known RyR2 inhibiting action, in mice and showed that the drug efficiently halted the induction of VT in a mouse model of CPVT.

INNOVATIVE MODALITIES FOR VT AND FUTURE CLINICAL APPLICATIONS

Endo-epicardial ablation reduces VT recurrences, but not all patients have a VT substrate[45]. Contrast-enhanced magnetic resonance imaging (ceMRI) is utilized to identify VT substrate after myocardial infarction[45]. Arena *et al*[45] showed that ceMRI-based endo-epicardial signal intensity mapping in a porcine model allowed characterization of the epicardial VT substrate.

Klein *et al*[46] used 3D meta-iodobenzylguanidine (MIBG) imaging to guide VT ablation. MIBG innervation defects are greater than scars produced from bipolar voltage maps, and the investigation showed that 36% of successful ablative locations were situated in sections of irregular innervation and normal voltage, suggesting that innervation maps may identify additional VT ablation sites[46].

Zhang *et al*[47] investigated non-invasive high-resolution mapping and electrocardiographic imaging to provide epicardial substrate information. Electrocardiographic imaging identified scar electrophysiologic substrates in ischemic cardiomyopathy patients[47].

Cardiac ripple mapping for slow conducting channels is an innovative technique to integrate voltage and activation mapping[48,49]. Cardiac ripple mapping allows the concurrent vision of voltage and activation data and facilitates recognition of slow conduction channels within scar areas in the myocardium that could be probable VT ablation sites[48,49]. Table 1 summarizes the studies investigating novel approaches for the treatment of VT.

CONCLUSION

The management of patients with VT can be demanding. ICD implant led to a considerable difference in the survival of subjects with VT, but the estimate of subjects with recurrent ICD shocks is still a growing issue. Antiarrhythmic drug treatment has reduced effectiveness and is correlated with serious adverse effects. Catheter ablation remains the cornerstone in

Table 1 Summary of studies investigating novel approaches for the treatment of ventricular tachycardia

Ref.	Type of study	No. of subjects	Focus of study	Complications
Della Bella *et al*[14]	Clinical	528	Endo-epicardial Ablation	Pericardial effusion, tamponade
Kim *et al*[15]	Clinical	1	Cardioplegia/Transcoronary alcohol ablation	Atrioventricular block, extensive myocardial damage, perforation
Sapp *et al*[17]	Clinical	8	Intramyocardial infusion-needle catheter ablation	Atrioventricular block, perforation, tamponade
Tholakanahalli *et al*[18]	Clinical	2	Intracoronary wire mapping and coil embolization	Atrioventricular block, coronary injury, embolization of unintended branches
Vaseghi *et al*[21]	Clinical	121	Cardiac sympathetic denervation	Hemothorax, pneumothorax, ptosis or Horner syndrome
Cuculich *et al*[29]	Clinical	5	Stereotactic radioablation therapy	Fatigue
Rivera *et al*[31]	Clinical	21	Cryoablation	-
Li *et al*[34]	Clinical	38	Surgical epicardial ablation	Ventricle laceration
Berte *et al*[35]	Experimental	5 (sheep)	Surgical cryoablation	-
Liang *et al*[36]	Clinical	20	Surgical cryoablation	-
Denegri *et al*[42]	Experimental	25 (mice)	Viral gene transfer of wild-type CASQ2	-
Li *et al*[44]	Experimental	9 (mice)	Tetracaine derivatives (RyR2 inhibitors)	-
Arenal *et al*[45]	Experimental	31 (pigs)	MRI-based signal intensity mapping for epicardial substrate	Coronary occlusion
Klein *et al*[46]	Clinical	15	3D meta-iodobenzyl-guanidine innervation maps to assess substrate and successful ablation sites	-
Zhang *et al*[47]	Clinical	32	Non-invasive high-resolution endocardial and epicardial mapping and electro-cardiographic imaging	-
Luther *et al*[48]	Clinical	15	Cardiac ripple mapping for slow conducting channels	-
Jamil-Copley *et al*[49]	Clinical	21	Cardiac ripple mapping for slow conducting channels	-

the treatment of VT and efficiently lowers recurrent VT episodes but carries upfront procedural danger. Novel methods could enhance its future effectiveness. The final management strategy should be individualized utilizing clinical and imaging assessment, patient views and intentions, futility concerns, and operator's catheter ablation experience.

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CORRECTION

Correction to "Clinical outcomes of combined flow-pressure drop measurements using newly developed diagnostic endpoint: Pressure drop coefficient in patients with coronary artery dysfunction"

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Correction 1

The percentage value of 8.57%, in page 284, line 10 and in page 287, lines 4 and 8, is a typo[1]. It should read as 5.7%, which corresponds to 2/35, as correctly reported within the parentheses.

Correction 2

Figure 1A in page 287 reflects the correct percentage, which is 5.7%.

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REVIEW

Newer echocardiographic techniques for aortic-valve imaging: Clinical aids today, clinical practice tomorrow

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Abstract

Increasing life expectancy is expected to lead to a corresponding increase in the prevalence of aortic valve disease (AVD). Further, the number of indications for transcatheter aortic valve replacement (TAVR) as a treatment option for AVD is expanding, with a growing role for echocardiography in its management. In this review we summarize the current literature on some newer echocardiographic modalities and the parameters they generate, with a particular focus on their prognostic and clinical value beyond conventional methods in the management of aortic stenosis, TAVR, and aortic regurgitation. Speckle tracking and 3D echocardiography are now increasingly being used in the management of AVD. For instance, global longitudinal strain, the best-studied speckle tracking echocardiographic parameter, can detect subtle subclinical cardiac dysfunction in patients with AVD that is not apparent using traditional echocardiographic techniques. The emerging technique of 3D full volume color Doppler echocardiography provides more accurate measurement of the severity of aortic regurgitation than 2D-proximal isovelocity surface area. These novel techniques are promising for evaluating and risk stratifying patients to optimize surgical interventions, predict recovery, and improve clinical outcomes.

Key words: Aortic stenosis; Aortic regurgitation; Speckle tracking echocardiography; Strain; Torsion; Transcatheter aortic valve replacement; Low flow low gradient aortic stenosis; 3D echocardiography

Core tip: Reduced strain is now established for early diagnosis, prognosis, and risk stratification, predicting post-op recovery and showing associations with mortality. Decreased global longitudinal strain (GLS) is a robust parameter to diagnose subclinical left ventricular dys-

function before the left ventricular ejection fraction deteriorates and the patient develops symptoms. GLS also correlates with disease severity and helps to identify patients with excess risk of cardiovascular events and death who are likely to benefit from earlier surgical intervention. The high accuracy and reproducibly of 3D echocardiography has made the precise assessment of volume and AR possible and, therefore, the early recognition of its severity.

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INTRODUCTION

The prevalence of aortic valve disease (AVD) continues to rise in line with increasing life expectancy. Aortic stenosis (AS) is the most common valvular heart disease, affecting 12.4% of patients over 75 years in North America and Europe[1], while the incidence of aortic regurgitation (AR) increases with age and affects 4%-5% of the population overall[2]. The introduction of minimally invasive techniques such as transcatheter aortic valve replacement (TAVR) has revolutionized the management of AVD. Current AVD management mainly represents a "horse has bolted" approach since symptoms have already developed or the left ventricle is damaged, and consequently the medical and socio-economic impact is greater than if the disease was managed earlier in its course or prevented. Here we discuss the role of newer echocardiographic techniques in the management of AS and AR. For each, we first discuss the current guidelines before outlining the modalities that are expected to change clinical practice in the future.

AORTIC STENOSIS

In developed countries, AS is most commonly caused by calcific degenerative valve disease, with congenitally abnormal valves (commonly bicuspid) with superimposed calcification and rheumatic valve disease being less common causes[3]. With advances in technologies, AS is increasingly recognized as a complex disease with different patient subgroups and pathophysiologies. In order to individualize treatment, accurate and timely sub classification is important.

Current guidelines and classification

According to American College of Cardiology (ACC)/American Heart Association (AHA) 2014 guidelines[3], severe AS is defined as a peak aortic velocity of > 4 m/s, which corresponds to a mean aortic valve gradient of > 40 mmHg and calculated valve area of 1.0 cm^2 or less[3]. Valvular heart disease guidelines from major societies like the ACC/AHA (2014)[3], European Society of Cardiology (ESC; 2012)[4], and Canadian Cardiovascular Society (2004)[5] recommend aortic valve replacement (AVR) as a class I indication in symptomatic patients with severe AS, asymptomatic patients with severe AS and left ventricular ejection fraction (LVEF) < 50%, and asymptomatic patients with severe AS who are undergoing other cardiac surgery.

Aortic stenosis leads to pressure overload in the left ventricle (LV). To maintain cardiac output, there is compensatory LV hypertrophy, which, although seemingly beneficial, is in fact maladaptive and results in cardiac fibrosis, heart failure, and ultimately increased mortality[6]. Over the last decade, new perspectives on the pathophysiology of AS have resulted in a new, four flow gradient pattern classification system that challenges the previous misconception that patients with AS and normal ejection fraction (EF) inevitably have normal flow. Patients are first divided based on left ventricular flow state-normal flow (NF) *vs* low flow (LF), where low flow is defined as LV stroke volume of < 35 mL/m^2[7], and then based on pressure gradient-low gradient (LG) *vs* high gradient (HG), where low gradient is defined as mean trans-aortic pressure gradient of < 40 mmHg. This makes the four categories NF/LG, NF/HG, LF/LG, and LF/HG[7-10], as shown in Table 1.

The LF/LG subgroup occurs in patients with low forward stroke volume and is associated with a worse prognosis and higher mortality than patients with high gradient severe AS[11]. Despite this, this group was noted to undergo the lowest rates of surgical intervention of the four categories[8]. Prognostic stratification using the above categories is therefore essential to prevent delay in timely intervention.

It is also important to distinguish pseudo-AS from true AS in the LF/LG subgroup. Pseudo-AS is seen in patients with mild to moderate AS due to incorrect calculation of lower aortic valve area (AVA) from poor forward flow causing incomplete valve opening, an inherent pitfall in the continuity equation. Therefore, ACC/AHA guidelines for assessing valvular heart disease recommend low dose (up to 20 mg/kg per minute) dobutamine stress echocardiography (DSE) to distinguish true from pseudo-AS in patients with LF/LG AS and decreased LVEF (< 40%)[3]. In pseudo-AS, gradient increases will correspond to proportionate increases in AVA, whereas in true AS, the AVA will remain diminished (AVA $\leqslant$ 1 cm^2) even with progressive dobutamine dosage. An absence of contractile reserve, *i.e.*, a failure to increase stroke volume by 20%, also indicates a worse prognosis. However, DSE's high dependence on flow response results in high inter-patient variability, especially in those with restrictive physiology. Mal-alignment of the Doppler signal, erroneous measurement of LVOT diameter, poor quality images due to severe calcification in and around the AV, and extremes of body

Table 1 Prevalence[8,9], prognosis[10] and percentage of patients undergoing surgery[8] for severe aortic stenosis and preserved ejection fraction

	High gradient (mean > 40 mmHg)	Low gradient (mean < 40 mmHg)
Normal flow (SV > 35 mL/m^2)		
Prevalence	30%-62.7%	15.3%-38%
Prognosis (2 yr survival rates)	44% ± 6%	83% ± 6% (best prognosis)
% Undergoing surgery	80% (highest rates of surgery)	53%
Low flow (SV < 35 mL/m^2)		
Prevalence	8%-13.2%	8.8%-24%
Prognosis (2 yr survival rates)	30% ± 12%	27% ± 13%-worst prognosis
% Undergoing surgery	68%	36%-lowest rates of surgery

Table 2 Definitions of basic strain parameters

Parameter	Definition
Strain	Change in myocardial fiber length relative to its resting phase
Global longitudinal strain	Percentage change in LV fiber length in the longitudinal axis
Global circumferential strain	Percentage change in LV circumference in the short axis view
Global radial strain	Percentage change in LV wall thickness in the short axis view
Strain rate	Rate at which change in myocardial fiber length relative to its resting phase occurs
Twist/Torsion/Rotation	Myofiber geometry in the LV myocardium changes from a right-handed helix in the subendocardium to a left-handed helix in the subepicardium, and this results in twisting during systole with the apex rotating counterclockwise and the base in a clockwise direction

LV: Left ventricle.

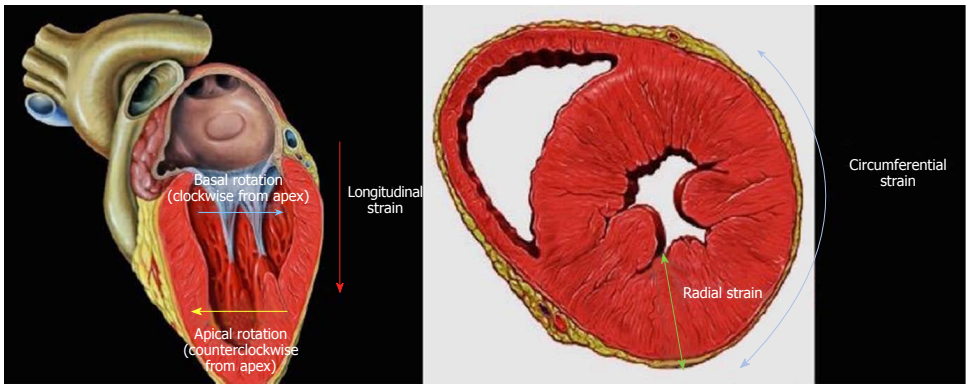

Figure 1 The different planes of strain.

size (*i.e.*, very low body surface area or morbidly obese patients) challenge the reliability of DSE.

Impaired LVEF in AS is associated with higher operative mortality[12], worse long-term prognosis[13], and less than 50% of patients recover to normal LVEF following AV replacement[12]. Even in the presence of symptoms, the majority of patients with severe AS have a normal EF[14]. Therefore, more sensitive parameters have been developed to identify patients likely to benefit from surgical treatment despite a preserved EF.

Speckle tracking echocardiography

Impaired myocardial contractility often precedes the observable decrease in LVEF[6]. Early markers and predictors of myocardial dysfunction would therefore be highly desirable to recognize the subset of patients that would benefit from early intervention. A newer technique for strain imaging called speckle-tracking echocardiography (STE) is highly reproducible, angle-independent, and more sensitive for detecting global and regional LV wall function than routine echocardiographic indices like tissue Doppler imaging and conventional imaging techniques like multi-slice computed tomography (MSCT) and cardiac MRI (cMR)[15,16].

LV strain essentially assesses changes in myocardial fiber length relative to their resting phase. Strain rate indicates the speed at which this deformation occurs. An echocardiographic image is a grayscale image derived from the speckles produced by ultrasound waves scattered by body tissue. STE measures myocardial deformation (strain) based on speckle displacement and assesses the parameters of strain, strain rate, twist/torsion, and rotation (see definitions, Table 2 and Figure 1). We summarize current clinical data supporting the use of STE parameters in the prognostication and management of AS below.

Longitudinal strain: Longitudinal strain refers to the percentage change in LV fiber length in the longitudinal axis. Global longitudinal strain (GLS) is the most studied parameter to date, and it reflects contraction of longitudinally arranged subendocardial fibers. Severe AS hinders myocardial perfusion, particularly in the subendocardium, due to higher wall stress and impaired coronary blood flow[17]. Hence, decreased longitudinal shortening is the first impairment seen in patients with AS[18]. As the severity of AS increases, GLS decreases[19].

As the ventricle is non-spheroidal, pressure increases lead to the basal and mid LV segments being exposed to higher wall stress than the apical segments[20] according to Laplace's law, as the heart base has a larger curvature and flatter contour compared to the middle and apical segments[21,22]. As would be expected, these segments respond better after unloading with AVR compared to the apical segments.

In a retrospective study of 395 patients with moderate to severe AS and preserved EF, GLS was an independent predictor of mortality[23]; this was subsequently confirmed in a prospective study of 142 patients[24]. GLS also shows incremental prognostic benefit over traditional parameters like AV gradient, stroke volume index[8,25], and valvuloarterial impedance[26,27]. Therefore, GLS can be used to detect subtle subclinical dysfunction that may not be apparent using current standard echocardiographic parameters. Lee *et al*[28] reported a higher percentage of two-year cardiac events (re-admission for heart failure or death) in asymptomatic severe AS patients with impaired GLS (-16.5%; 77% sensitivity and 67% specificity) who were managed conservatively. This suggests that incorporating GLS into current risk models might further optimize timing for AVR. In two prospective studies with severe AS and preserved EF (103 patients[29] and 340 patients[9], respectively), GLS was noted to be particularly worse in patients with LF AS compared to patients with NF AS, again supporting the hypothesis that the low flow state represents a more advanced form of the disease.

In asymptomatic moderate and severe AS patients with preserved LVEF, reduced GLS worse than -15% was a significant risk factor for cardiac hospitalization, AVR, cardiovascular death[30,31], all-cause mortality at one year[24], and, interestingly, increased risk of post-operative atrial fibrillation independent of left atrial size and age[32]. Other studies have established that regional deformation analysis is also important, with an additional parameter called basal longitudinal strain (BLS) less than -13% associated with adverse outcomes including heart failure, MI, all-cause mortality, and symptomatic status in asymptomatic severe AS. In fact, BLS has the strongest association with symptomatic status of all the longitudinal strain parameters[33]. Kempny *et al*[34] studied 101 patients undergoing TAVR and showed that pre-echocardiographic assessment of GLS is associated with post-operative symptom improvement.

Circumferential strain: The percentage change in LV circumference in the short axis view is called circumferential strain, which reflects contraction of the circumferentially arranged mid-layer fibers. Following a decrease in longitudinal strain, circumferential fibers compensate for the loss in longitudinal function. Hence, impairment of both longitudinal and circumferential strain suggests more extensive myocardial damage. Global circumferential strain (GCS) is considered an important prognostic factor in patients with symptomatic AS, and conservatively treated patients with impaired GCS have higher two-year all cause mortality and re-admission for heart failure than those who do not[28].

Radial strain: The percentage change in wall thickness in the short axis view is known as the radial strain. As noted above, impaired subendocardial perfusion is an early feature of AS due to increased wall stress and impaired coronary blood flow. Impaired endocardial radial strain is observed in patients with AS and preserved LVEF and correlates with AS severity; epicardial radial strain is, however, preserved[35]. Hyodo *et al*[36] suggested the use of a novel parameter called the bilayer ratio (subendocardial to subepicardial strain ratio), the value of which decreases as the severity of AS increases given the decrease in subendocardial thickness due to ischemia and compensatory increase in subepicardial thickness. This was deemed to be superior to longitudinal strain, which only takes the subendocardium into account.

Twist/torsion and rotation: Myofiber geometry in the LV myocardium changes from a right-handed helix in the subendocardium to a left-handed helix in the subepicardium. This configuration results in twisting during systole, with the apex rotating counterclockwise and the base in a clockwise direction. When both layers contract simultaneously, a larger radius of rotation for the outer epicardial myofiber layer results in mechanical predominance of the epicardial fibers in the overall direction of rotation. LV twist is proportionate to the severity of AS[37], which is thought to be a consequence of subendocardial dysfunction reducing inhibition of longitudinal muscle fibers. Conversely, untwisting rate is delayed and decreased[38].

Santoro *et al*[39] also observed an increase in LV twist in LV hypertrophy with preserved EF and suggested it as a marker of early systolic dysfunction. The LV twist to circumferential shortening ratio (TSR) is also considered a reliable marker of subendocardial dysfunction[40], and van Dalen *et al*[37] demonstrated an increase in TSR in AS. Apical rotation (ApRot) is also known to increase in severe AS[38,39]. Some studies have shown that ApRot is positively associated with the presence of symptoms[41], while others[42] have found that patients with low ApRot have higher rates of syncopal events, a similar rate of overall symptoms, and that increased ApRot is an independent predictor of mortality in severe AS with preserved EF. Asymptomatic patients with

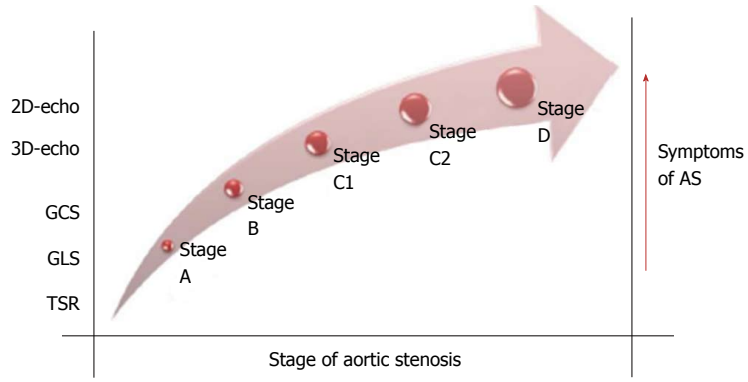

Figure 2 Ratio of left ventricle twist to circumferential shortening. GLS: Global longitudinal strain; GCS: Global circumferential strain; TSR: The LV twist to circumferential shortening ratio; AS: Aortic stenosis.

severe AS and increased ApRot have similar survival to symptomatic patients, but the measurement is useful for identifying patients who might benefit from early evaluation for aortic valve replacement (AVR)[42].

3D strain

The widespread emergence of 3D echocardiography has also introduced the possibility of measuring 3D strain (3D-STE). 2D-STE assumes geometric LV morphology, needs multiple, high-quality image acquisition, and there is the possibility of mistracking speckles that move out of the scanning plane. 3D-STE, using the block-matching method in full-volume datasets, has been developed to overcome these shortcomings, and it tracks the 3D motion of the acoustic speckles but is independent of speckles moving out of the scanning plane and free of geometric presumptions. 3D-STE represents a more accurate model than 2D-STE because all strain parameters are simultaneously obtained from one volume image[43] in contrast to 2D-STE, in which the long and short axes are measured at different points in time.

As expected, compared to LVEF, 3D-STE is a more sensitive and accurate assessment of early LV dysfunction[44]. In a study of 104 asymptomatic patients with severe AS and preserved EF, 3D-GLS, 3D-GRS, and 2D-GLS were all found to be useful predictors of major adverse cardiac events (MACE). 3D-GLS was also an independent predictor of MACE after correcting for LV mass index and mean pressure gradient[45]. However, poor temporal resolution and the need for a high frame rate hamper its current widespread use. Further prospective studies utilizing a 3D-GLS-guided approach are imperative to assess its role in predicting adverse cardiovascular outcomes.

Treatment of AS: The role for newer imaging modalities

In addition to playing a role in early diagnostics and patient stratification, newer imaging modalities like MSCT, cMR, and 3D trans-esophageal echocardiography are increasingly being used as part of the treatment of AS. AS is only treatable by valve replacement, traditionally surgically (SAVR) but now also with balloon-expandable or self-expanding valves *via* TAVR. With the recent United States Food and Drug Administration (FDA) approval of the Sapien XT and Sapien 3 transcatheter heart valves in patients at intermediate risk for open-heart surgery, TAVR will increasingly be used beyond only high-risk and inoperable cases. Pre-procedural, intra-procedural, and post-procedural echocardiography are recommended as part of TAVR evaluation[46]. These are described in detail below (Figure 2).

Pre-TAVR, transthoracic echocardiography (TTE) helps to determine the degree of stenosis, valvular cusp size, motion, the location and amount of calcification, the aortic root and annular anatomy, mitral valve pathology, the presence of a bulging inter-ventricular septum at the level of the aortic root, baseline LV and RV function, and pulmonary artery pressure[6]. With modern echocardiograms, Doppler echocardiographic interrogation of aortic valve gradients is superior and preferred to other imaging modalities, although misalignment of the Doppler signal with the AS jet of over 20 degrees and the pressure recovery phenomenon in the ascending aorta diameter < 30 mm are known limitations.

The effective orifice area is determined using the left ventricular outflow tract (LVOT) diameter on TTE or transesophageal echocardiography (TEE). It is important to measure this 1-2 mm apical to the aortic annulus, and a difference of > 2 mm between the aortic annulus and LVOT should prompt repeat measurement[6]. A basal inter-ventricular septal bulge may also lead to inaccurate measurements and superior displacement of the deployed valve, so this also needs pre-operative determination[6]. On the other hand, a thin septum is also important to recognize pre-operatively to avoid post-operative ventricular septal rupture.

It is well established that multi-slice computer tomography (MSCT) overestimates the LVOT by 20% and 3D echocardiogram underestimates by 20% given the elliptical shape of the LVOT. Aortic valve area (AVA) measured by CT for severe AS needs a higher cut-off (1.2 cm^2) compared to AVA measured by echocardiography (1 cm^2)[47]. It is challenging to obtain the appropriate cross-sectional view by 2D-TEE

due to the movement of the aortic annulus along the long axis and its tilting movement during the cardiac cycle. Volumetric 3D-TEE overcomes this problem by incorporating the entire AV valve. As anticipated, in a prospective study of 60 patients, Nakai *et al*[48] showed that 3D-TEE is more accurate that 2D-TEE for calculating the AVA. Further, 3D-TEE provides a more accurate reconstruction of the aortic root and better measurement of the distance between the annulus and coronary ostia, most importantly the left coronary ostium.

One of the most important roles for echocardiography is to assist in choosing the appropriate size of prosthetic heart valve. Undersizing of the prosthetic causes para-valvular aortic regurgitation (PVR), while oversizing of artificial valves, especially in the setting of a calcified LVOT, is associated with higher risk of aortic rupture and periaortic hematoma as the native calcific valves are retained behind the artificial valve. Measurement of LVOT diameter by TTE has long been used and validated for calculation of the aortic valve area and AS severity, but TTE measurements should not be relied upon to decide the prosthetic valve size. There is an ongoing discussion about which method is most accurate and reproducible for valve sizing; Tsang *et al*[49] compared cMR, MSCT, and 3D-TEE *in vivo* and *in vitro* and showed that cMR was most accurate and reproducible. Several studies have suggested that MSCT is superior to 3D-TEE[49,50], while others[51] have noted good agreement between annulus perimeter and the area measured by 3D-TEE and MSCT. Altiok *et al*[52] also showed highly consistent measurements of sagittal and coronal diameters on 3D-TEE and MSCT.

The distribution and extent of calcification should also be determined preoperatively by echocardiography as it is a useful predictor of procedural success. It is also crucial to identify patients with obliteration of the sinus of Valsalva (SOV) or smaller or shorter SOV height, as these patients require shorter prosthetic valves. 3D-TEE has also emerged as a valuable tool (comparable to MSCT) for accurately measuring left main coronary artery to annulus distance and length of coronary cusp[53].

Intra-TAVR, fluoroscopy is advocated by the 2012 ACCF/AATS/SCAI/STS expert consensus document[54] on TAVR regardless of type of access. However, in a prospective study of 100 patients undergoing transapical transcatheter aortic valve implantation, Bagur *et al*[55] noted similar acute and 30-d outcomes for patients managed intra-operatively with angiography and TEE. Current American and European guidelines advocate the use of 2D and 3D-TEE support during TAVR.

The first step of the TAVR procedure is to place the pacing wire in the right ventricle, with echocardiography used to confirm its position and exclude perforation of the ventricle or pericardial effusion. Next, a stiff wire is placed into the left ventricle, with echocardiography ensuring its stability at the apex and lack of entanglement with mitral apparatus and again excluding perforation and pericardial effusion. The aortic root must be continually visualized during balloon aortic valvuloplasty, after which coronary artery patency is established, LV wall motion assessed, and position of the calcified coronary leaflets noted. The TAVR valve is then introduced. It is important to ensure that the native leaflets are covered by the TAVR valve. In trans-apical valve placement, the puncture site is visualized. It is also important to ensure angulation of the valve away from the inter-ventricular septum and the right ventricle.

TEE during TAVR is usually performed under general anesthesia, which requires intubation and hence increases the patient's risk profile. TTE seems to be a reasonable alternative to TEE but factors against TTE include relatively poor image quality, inability to position the patient, and potential compromise of operative field sterility with the trans-apical or trans-aortic approach. Intracardiac echocardiography (ICE) can overcome some of these issues, and ICE has been used in the closure of inter-atrial defects and in some electrophysiological interventions. For TAVR monitoring, the ICE catheter is introduced through the femoral vein and advanced to the superior cavo-right atrial junction. Apart from TR jet velocity, ICE allows placement of guide wires and catheters carrying the valve, valve deployment, and continuous monitoring for pericardial effusion. However, it has yet to be optimized for accurately assessing paravalvular regurgitation (PVR) given its narrow sector angle and poor resolution. Further, ICE requires venous access, which carries a risk of hematoma and bleeding complications. Since the ICE catheter shares the same RV space, there is a risk of dislodging the pacemaker leads used for rapid pacing during valve deployment[56]. 3D-ICE imaging currently has a limited field of view of only 22°, making the measurement of annular size difficult.

Post-TAVR, valve deployment, position, shape, and leaflet motion must be confirmed. Then, hemodynamic measurements need to be performed to assess valve function. Effective orifice area, Doppler velocity index, and mean and peak trans-valvular gradients should be measured. Effective orifice area is determined using the LVOT diameter, which is measured from the outer to outer stent diameter at the lower edge or inner to inner stent diameter at the upper edge if the valve is low. LV and RV function and pulmonary artery pressures are also noted as a part of the post-operative evaluation.

TEE and TTE are routinely used in clinical practice to detect immediate post-operative complications like malposition, valvular regurgitation or PVR, mitral valve damage, aorta to right atrium fistulae, cardiac shunts secondary to inter-ventricular septal damage, pericardial effusion, and cardiac tamponade following free wall or annular rupture, coronary artery patency, and left ventricular wall akinesis due to inadvertent coronary ostial closure. More than a moderate degree of PVR is clearly associated with increased short- and long-term mortality[57]; however, data on mild PVR and outcomes are conflicting. The exact incidence of PVR varies widely across studies due to the differences in

the parameters and criteria used to grade PVR; different schemes used to classify PVR severity; and a lack of standard assessments for PVR. To address this issue, a classification of PVR has recently been proposed that divides severity into five categories: trace, mild, mild-to-moderate; moderate; moderate-to-severe, and severe[25].

Doppler is the gold standard for evaluating PVR. Both TTE and TEE may be required, as the PVR jets located posteriorly and anteriorly are often shadowed in TTE and TEE views, respectively, as a result of the shadowing caused by native aortic valve calcifications and the prosthetic stent. It is always important to use color Doppler with echocardiography in both the long and short axis views. Further, jets must be quantified in terms of number, width, path, and convergence. The 2012 Valve Academic Research Consortium (VARC) 2 defines moderate PVR as the circumferential extent of the PVR estimated in the parasternal short axis at 10%-30% and severe PVR at > 30%[58]. Tiny para-valvular jets usually regress spontaneously over a period of 10-15 min[59], as do those appearing with self-expandable balloon aortic valves as the frame expands[59]. Therefore, it is important to wait for a while before intervening. With multiple jets, eccentricity, presence of calcification, and changing loading conditions, the accurate assessment of PVR severity can be difficult using conventional echo methods. 3D-TTE has been shown to be superior for assessing PVR utilizing 3D vena contracta and 3D regurgitant volumes[60].

TTE can be used to determine prosthesis location in the long axis view compared to LVOT location. In the short axis view, TTE can determine if the proper circular shape has been assumed. There is a now a trend toward using only TTE in appropriately selected patients. In a retrospective study of 111 patients, Sengupta *et al*[61] demonstrated a significant difference in the procedural time with non-inferiority in terms of procedural success, extent of PVR, additional valve implantation, and complications such as peri-procedural stroke rate or death. However, prospective data supporting TTE use during TAVR are still lacking.

Echocardiography should be performed prior to discharge (and after 30 d) to establish a new baseline of replaced valve function including mean transaortic gradient, valve area, and PVR. As data on the long-term functioning of TAVR are not robust, annual TTE follow up to assess valvular and ventricular function should be undertaken.

Post TAVR cardiac remodeling – the role for imaging

Several studies have reported reverse remodeling (improvement in strain parameters) in the minutes, 72 h, and month following TAVR[36,62-64]. In a prospective study, Swan *et al*[65] demonstrated immediate improvement (within minutes) in circumferential and radial strain following TAVR. Kim *et al*[66] conducted a multilayer strain study and demonstrated a significant improvement in longitudinal but not circumferential strain following TAVR as early as one week. A study of 68 LF LG severe AS patients showed significant improvements in GLS at 6 and 12 months after TAVR[67]. Interestingly, post TAVR changes in strain pattern do not appear to be influenced by pacemaker-induced rhythm or post-procedure new left bundle branch block[64]. Kempny *et al*[34] reported a correlation between improvement in longitudinal strain and symptomatic improvement following TAVR, while Løgstrup *et al*[68] (*n* = 100, mean EuroScore: 10.5 ± 2.8) noted a correlation between improvement in GLS and decrease in mortality rate following TAVR. Poulin *et al*[69] (*n* = 102 patients) reported that improvements in longitudinal systolic and diastolic deformation were significantly lower in patients with prosthesis-patient mismatch at follow-up.

AORTIC REGURGITATION

The most common causes of AR in developed countries are aortic root dilation, calcific valve disease, and bicuspid aortic valve, with rheumatic AR the less common etiology. Less common causes include infective endocarditis and aortic dissection. The inability of valve leaflets to remain coapted during diastole leads to blood flow back into the left ventricle. This leads to increase in end-diastolic volume and elevated wall stress, eventually leading to compensatory eccentric hypertrophy from volume overload. In contrast to AS (where both pressure and volume overload occurs), this eccentric LV change predominantly affects the circumferentially arranged fibers leading to more severe impairment in GCS as compared to GLS.

Current recommendations

ACC/AHA 2014 guidelines define severe AR as a Doppler jet width ⩾ 65% of LVOT, vena contracta > 0.6 cm, regurgitant volume ⩾ 60 mL/beat, regurgitant fraction of ⩾ 50%, and effective orifice area of ⩾ 0.3 cm^2[3]. Guidelines from the ACC/AHA (2014)[3], European Society of Cardiology (ESC; 2012)[4], and Canadian Cardiovascular Society (2004)[5] on the management of valvular heart disease recommend AVR as a class Ⅰ indication in symptomatic patients with severe AR, asymptomatic patients with severe AR and LVEF of < 50%, and patients with severe AR who are undergoing other cardiac surgery. AVR is also recommended as a Class Ⅱa indication for patients with severe AR, normal LVEF ⩾ 50% but severe LV dilation [LV end-systolic diameter (LVESD) of > 50 mm], or indexed LVESD of > 25 mm/m^2. It is also reasonable to pursue AVR in patients with moderate AR undergoing cardiac surgery. However, severe dilation and decreased LVEF represent the late stage of the disease, and other parameters to identify subtle LV dysfunction early in the course of disease are desired.

Speckle tracking echocardiography in AR

STE has also been used in the assessment of AR.

Stefani *et al*[70] examined 60 patients including young athletes with bicuspid aortic valves and mild AR with matched controls and found a reduced longitudinal peak systolic strain in LV basal segments. A single center retrospective study of 314 patients with chronic moderate to severe AR noted that global longitudinal strain was independently predictive of mortality (at a threshold of -12.5%)[71]. Di Salvo *et al*[72] showed that patients with moderate to severe AR with a progressive pattern and symptom development had significantly reduced longitudinal strain compared to those with stable disease (-17.8% ± 3.9% *vs* -22.7% ± 2.7%, P = 0.001) despite having similar LVEFs. In a longitudinal study of 64 patients with moderate to severe AR, Olsen *et al*[73] noted that patients with reduced GLS, strain rate, and early diastolic strain were more likely to have progressive disease (symptom development or worsening LVEF) in patients managed conservatively and also poorer outcomes following surgery. In a study of 90 patients, Iida *et al*[74] demonstrated that the LVEF may continue to be normal despite a significant lowering of longitudinal strain due to compensatory increases in wall thickening in the subepicardium.

Gabriel *et al*[75] reported a correlation between reduced longitudinal strain rate and subclinical LV dysfunction on exercise echocardiography in patients with moderate to severe AR. Similarly, Marciniak *et al*[76] also found that longitudinal and radial strain rates were a sensitive indicator of subclinical dysfunction in severe AR. Interestingly, Onishi *et al*[77] noted that LV radial systolic strain rate was predictive of LVEF post surgery. In moderate to severe AR with preserved EF, Ewe *et al*[78] noted impairment in all three strains (longitudinal, circumferential, and radial) in symptomatic compared to asymptomatic patients. Also, impaired baseline GLS (per 1% decrease, HR = 1.21, P = 0.04) or GCS (per 1% decrease, HR= 1.22, P = 0.04) was predictive of the need for surgery in asymptomatic patients. Li *et al*[44] noted that circumferential strain is a more sensitive marker for AR/volume overload compared to longitudinal strain for AS/pressure overload. Similarly, Broch *et al*[79] showed that in asymptomatic patients with moderate to severe AR and preserved LVEF, GCS was higher and thought to contribute to reduced GLS.

Decreased LV apical rotation and torsion have been detected in moderate to severe AR with preserved EF compared to normal healthy subjects[80], while others[81] have noted lower LV torsion in the severe AR group compared to the moderate AR group but no difference in the apical rotation compared to moderate AR and control patients. Finally, in a prospective study by Chen *et al*[82] for severe AR and reduced EF, there were significant improvements in GLS and GCS at three months following AVR when measured using 3D-STE.

3D echocardiography

Although many different 2D echocardiography parameters can be used to quantify AR, it is still challenging. Not only are there subtle differences in the scan plane with altered size of the vena contracta jet, but also its shape is not always circular but sometimes irregular or ellipsoid. 3D-echocardiography can be used to directly measure the vena contracta area (3D-VCA). Sato *et al*[83] showed that the 3D-VCA was 32 mm^2 in severe AR (sensitivity: 89%; specificity: 98%). 2D-derived proximal isovelocity surface area (PISA) and regurgitant volume (Rvol) suffer from geometric assumptions, angle correction, and problems with assessing multiple jets. Choi *et al*[84] reported 3D full volume color Doppler echocardiography to be more accurate then 2D-PISA for assessment of all AR grades, especially with eccentric or multiple jets. Perez de Isla *et al*[85] reported that 3D color Doppler echocardiography was both accurate and reproducible for AR evaluation with a high correlation with gold standard cMR. Real-time 3D-TEE was also able to reveal specific anatomical differences between type Ⅰ (annular dilation) and type Ⅱ (prolapsed) AR[86].

CLINICAL APPLICATION OF EARLY DIAGNOSTICS

Reduced strain is now established for early diagnosis, prognosis, and risk stratification, predicting post-op recovery and showing associations with mortality. Decreased GLS is a robust parameter to diagnose subclinical LV dysfunction before the LVEF deteriorates and the patient develops symptoms. GLS also correlates with disease severity and helps to identify patients with excess risk of cardiovascular events and death who are likely to benefit from earlier surgical intervention. The high accuracy and reproducibly of 3D echocardiography has made the precise assessment of volume and AR possible and, therefore, the early recognition of its severity.

CONCLUSION

Newer echocardiographic techniques have significantly enhanced our understanding of the pathophysiology of aortic valve diseases and are being increasingly employed to assess disease severity and to risk-stratify patients. Early detection of LV dysfunction is paramount in these patients to allow timely intervention before irreversible impairment occurs. Novel non-invasive imaging techniques such as speckle tracking echocardiography and 3D imaging have shown promise in the quantification of subclinical myocardial damage *in vivo*. With development of higher processing power echocardiograms, newer generation probes, and with increasing familiarity and experience with these techniques, these are likely to become the new norm.

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REVIEW

Myocardial reperfusion injury and oxidative stress: Therapeutic opportunities

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Abstract

Acute myocardial infarction (AMI) is the leading cause of death worldwide. Its associated mortality, morbidity and complications have significantly decreased with the development of interventional cardiology and percutaneous coronary angioplasty (PCA) treatment, which quickly and effectively restore the blood flow to the area previously subjected to ischemia. Paradoxically, the restoration of blood flow to the ischemic zone leads to a massive production of reactive oxygen species (ROS) which generate rapid and severe damage to biomolecules, generating a phenomenon called myocardial reperfusion injury (MRI). In the clinical setting, MRI is associated with multiple complications such as lethal reperfusion, no-reflow, myocardial stunning, and reperfusion arrhythmias. Despite significant advances in the understanding of the mechanisms accounting for the myocardial ischemia reperfusion injury, it remains an unsolved problem. Although promising results have been obtained in experimental studies (mainly in animal models), these benefits have not been translated into clinical settings. Thus, clinical trials have failed to find benefits from any therapy to prevent MRI. There is major evidence with respect to the contribution of oxidative stress to MRI in cardiovascular diseases. The lack of consistency between basic studies and clinical trials is not solely based on the diversity inherent in epidemiology but is also a result of the methodological weaknesses of some studies. It is quite possible that pharmacological issues, such as doses, active ingredients, bioavailability, routes of administration, co-therapies, startup time of the drug intervention,

and its continuity may also have some responsibility for the lack of consistency between different studies. Furthermore, the administration of high ascorbate doses prior to reperfusion appears to be a safe and rational therapy against the development of oxidative damage associated with myocardial reperfusion. In addition, the association with N-acetylcysteine (a glutathione donor) and deferoxamine (an iron chelator) could improve the antioxidant cardioprotection by ascorbate, making it even more effective in preventing myocardial reperfusion damage associated with PCA following AMI.

Key words: Acute myocardial infarction; Repefusion injury; Oxidative stress; Ascorbate; N-acetylcysteine; Deferoxamine

Core tip: Acute myocardial infarction is the leading cause of death in the world. At least half of the resulting myocardial damage is associated with myocardial reperfusion. Myocardial reperfusion injury is associated with reactive oxygen species production and iron mobilization. Treatment with antioxidants such as ascorbate, N-acetylcysteine, and an iron chelator such as deferoxamine, could prevent the development of this damage.

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INTRODUCTION

Acute myocardial infarction (AMI) is the leading cause of death worldwide, and it is associated with high morbidity and mortality. The AMI complications have significantly decreased with the development of interventional cardiology and percutaneous coronary angioplasty (PCA) treatment, which quickly and effectively restore the blood flow to the area previously subjected to ischemia[1]. Paradoxically, the restoration of blood flow to the ischemic zone leads to a massive production of reactive oxygen species (ROS), which generate rapid and severe damage to biomolecules, in a phenomenon called myocardial reperfusion injury (MRI)[2,3]. Sources of ROS in reperfusion include the predominant contribution of NADPH oxidases, which are present in many cell types in myocardial tissue. Other sources are xanthine oxidase, uncoupled eNOS and the mitochondrion[4]. In the clinical setting, MRI is associated with multiple complications such as lethal reperfusion, no-reflow phenomenon, myocardial stunning, and reperfusion arrhythmias (Figure 1).

Despite significant advances in the understanding of the mechanisms accounting for MRI, it remains an unsolved problem. Although promising results have been obtained in experimental studies (mainly in animal models) these benefits have not been translated into clinical settings. Clinical trials have failed to find benefits from any therapy to prevent MRI, demonstrating a clear dissociation between the bench and the bedside[5].

Prevention of MRI in the clinical setting has intrinsic difficulties in its approach. First, any therapy oriented to MRI prevention must be administered prior to myocardial reperfusion (in other words, prior to PCA). In addition, it should be applied in doses high enough to counterbalance the rapid and massive ROS production following reperfusion. Moreover, there are many different visions regarding the best biomarker to define MRI in patients, and so clinical trials express their results with different outcomes (such as clinical outcomes, serum cardiac biomarkers, echocardiographic parameters, cardiac magnetic resonance, among many others) which makes the analyses even more difficult. All these elements have made it difficult to develop an effective therapy to prevent MRI in AMI patients. The present review focuses on the cellular and molecular mechanisms of oxidative-stress induced MRI during AMI, and the key points to develop an appropriate strategy to reduce oxidative damage derived from myocardial reperfusion.

PATHOPHYSIOLOGY

MRI is a clinical problem associated with procedures such as thrombolysis, angioplasty, and coronary bypass surgery, which are commonly used to re-establish the blood flow and minimize the damage to the heart due to severe myocardial ischemia[3]. There are three main hypotheses which have been proposed to explain the pathogenesis of ischemia reperfusion (IR) injury: oxidative stress, iron mobilization, and Ca^{2+}-overload[6,7]. All of these mechanisms are most likely related, but it is not known whether they operate simultaneously or one precedes the other (Figure 2).

Oxidative stress

The level of myocardial tissue oxygenation increases following restoration of blood flow, which is initiated with a burst of ROS generation[8]; these ROS are the major initiators of myocardial damage in MRI[3]. Increased ROS production is mainly due to the activation of xanthine oxidase in endothelial cells, mitochondrial electron transport chain reactions in cardiomyocytes, and NADPH oxidase in inflammatory cells[9] (Figure 1).

Oxidative stress occurs when there is an imbalance between the generation of ROS and the antioxidant defense systems in the body so that the latter becomes overwhelmed[10]. ROS include hydrogen peroxide (H_2O_2), the superoxide radical anion, the hydroxyl radical ($OH^{\bullet}$), and peroxynitrite anion ($ONOO^-$), and they have all been shown to increase with reperfusion[11] (Figure 2). As a result of lipid peroxidation, oxidation of DNA and proteins and membrane damage may take place.

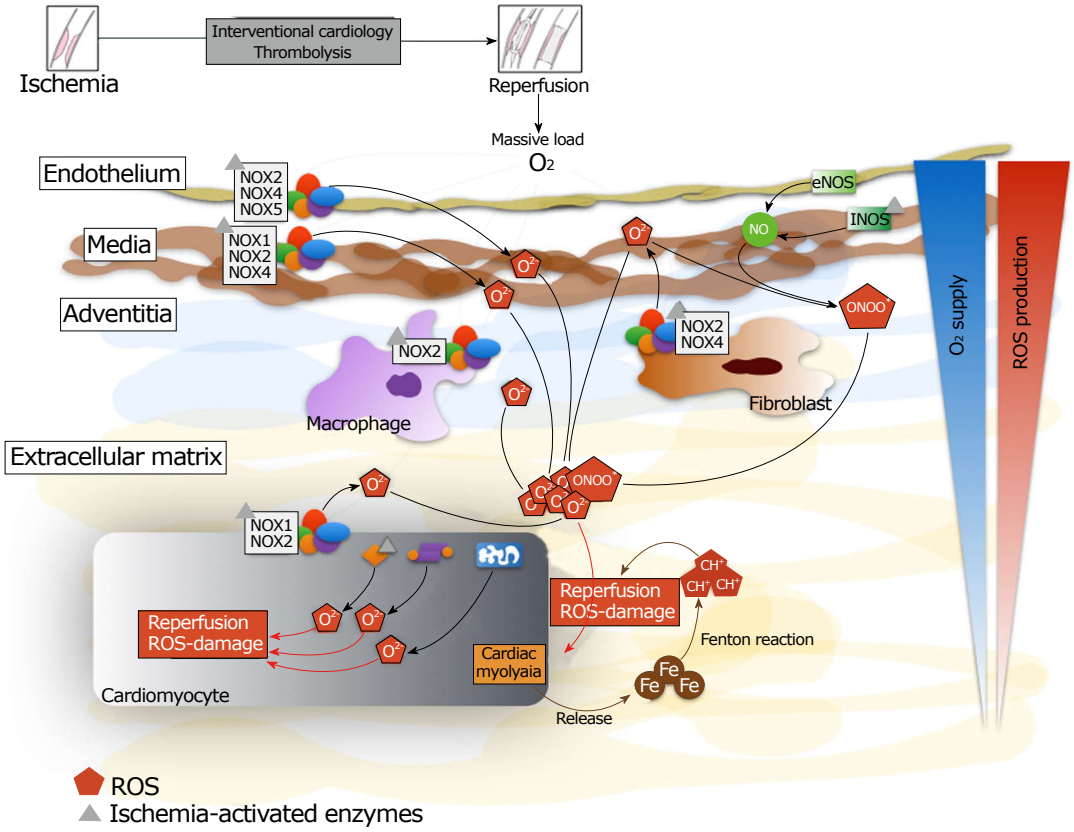

Figure 1 Generation of reactive oxygen species and mobilization of iron after myocardial reperfusion. There is a massive production of reactive oxygen species and iron mobilization by the different cellular types of the myocardial tissue. The iron reacts with superoxide anion to produce hydroxyl radical by the Fenton reaction. Inside cardiomyocyte, there is intracellular production of reactive oxygen species through NADPH oxidase, eNOS uncoupled, xanthine oxidase and mitochondrion. NOX: NADPH oxidase; ROS: Reactive oxygen species; Fe: Iron; eNOS: Endothelial nieric oxide synthases.

This leads to alterations in membrane permeability and to modifications of protein structure and functional changes[12].

ROS sources: In pathophysiological conditions, there are many sources of ROS in myocardial tissue. The most important sources are NADPH oxidases (NOX), uncoupled eNOS, xanthine oxidases and the mitochondrion. NOX catalyzes the one electron reduction of O_2 to generate super-oxide radical anion ($O_2^{\bullet -}$), using NADPH as the source of electrons. This enzyme is largely present in the activated neutrophil, wherein it generates large amounts of toxic $O_2^{\bullet -}$ and other ROS important in bactericidal function[13]. Pathogenic roles of NOX-derived ROS are also verified in human IR injury *in vivo*[14]. It was recently reported that in isolated perfused murine hearts that *NOX1* and/or *NOX2* gene knock-out significantly attenuated MRI (by up to 50% of the final infarct size)[15], thus demonstrating the crucial importance of this enzyme in MRI.

The NO synthases (NOS) are a family of enzymes that convert the amino acid L-arginine to L-citrulline and NO. Endothelial NOS (eNOS) plays a major role in the regulation of vascular function. The eNOS may become uncoupled in the absence of the NOS substrate L-arginine or the cofactor BH4. Uncoupled eNOS results in the production of $O_2^{\bullet -}$ instead of NO[16-18]. This perpetuates a vicious cycle because peroxynitrite, the reaction product of superoxide and NO, leads to further eNOS uncoupling[19]. Furthermore, eNOS uncoupling may play a major role in MRI by increasing ROS production and limiting NO availability[20].

Xanthine oxidase is predominantly present in the vascular endothelium in the normal heart and generates $O2^{\bullet -}$, H_2O_2, and $OH^{\bullet}$ as byproducts of its normal metabolic action[21]. Under pathological conditions, such as tissue ischemia, xanthine dehydrogenase can be converted to Xanthine oxidase. In IR this enzyme catalyzes the formation of uric acid with the coproduction of $O2^{\bullet -}$[22]. Superoxide release results in the recruitment and activation of neutrophils and their adherence to endothelial cells, which stimulates the formation of xanthine oxidase in the endothelium, with further $O2^{\bullet -}$ production[23]

Mitochondria are cellular organelles involved in energy production, so any injury that they may suffer could cause impairment of cellular energy that could lead, depending on the intensity of the injury, to apoptosis or different levels of cellular damage. During ischemia, due

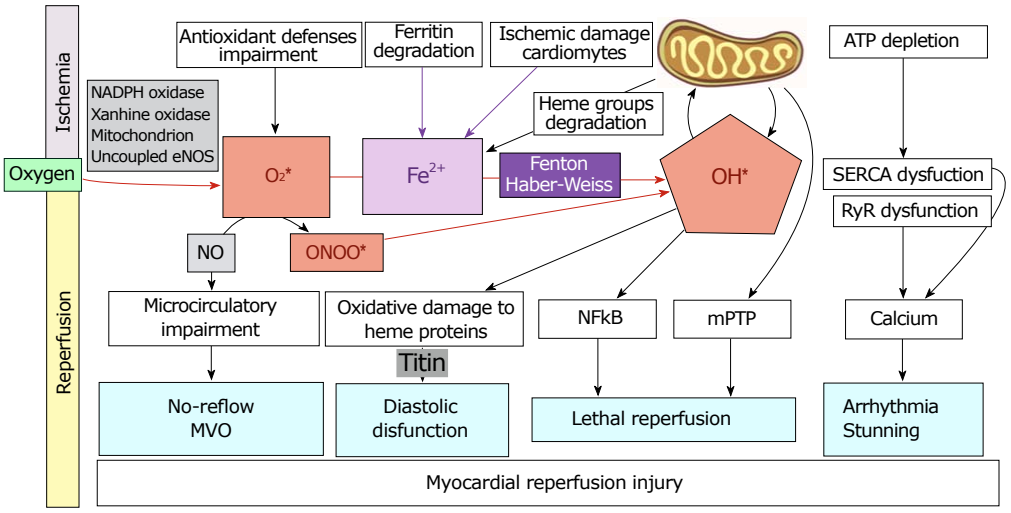

Figure 2 Role of reactive oxygen species and iron mobilization in myocardial reperfusion injury and its clinical implications. MVO: Microvascular obstruction; ONOO*: Peroxynitrite; NO: Nitric oxide; OH *: Radical hydroxyl; Fe: Iron; RyR: Ryanodine receptor channel; SERCA: Sarco/endoplasmic reticulum Ca^{2+}-ATPase.

to the lack of oxygen, the electron transport chain cannot function correctly and therefore ROS are produced at high levels. Additionally, ROS may cause oxidative damage of mitochondrial DNA, impairing mitochondrial function. This damage performs a positive feedback on ROS production that, at the same time, perpetuates mitochondrial damage and ROS synthesis. Oxidative injury to the mitochondrial membrane can also occur, resulting in membrane depolarization and the uncoupling of oxidative phosphorylation, with altered cellular respiration[24]. This can ultimately lead to mitochondrial damage, with release of cytochrome c, activation of caspases, and apoptosis[25].

RNS sources: The ROS are not solely responsible for free radical damage. Reactive nitrogen species (RNS), mainly peroxynitrite anions (ONOO-), also generate RNS-damage, thus producing nitrosative stress. Peroxynitrite results from the interaction between NO and the superoxide anion[4], and NO is synthesized mainly by nitric oxide synthases which have two isoforms in the cardiomyocyte: endothelial (eNOS) and inducible (iNOS). Oxidative and nitrosative damage causes the uncoupling of both NOS isoforms, resulting in the enhanced synthesis of $O2^{\bullet-}$[4].

Evidence supports the view that nitrosative stress plays an important role in the pathogenesis of MRI. While NO itself is not harmful, some of the reaction products (mainly $OH^{\bullet}$) resulting from high ONOO- formation in the cell are highly cytotoxic substances[26]. The production of $O2^{\bullet-}$ is increased during reperfusion, which interacts with NO and leads to the formation of ONOO-, thus triggering the previously described phenomenon[27]. Peroxynitrite not only causes structural damage by attacking macromolecules, but it also leads to myocardial functional impairment[28]. The general view about the mechanisms that lead to nitrosative stress is that IR can induce iNOS expression and that the resulting high concentrations of NO can lead to cardiac injury[26]. The drop in NO concentration occurring during cardiac IR plays an important role in triggering the transcription nuclear factor kappaB (NF-κB) leading to activation and successive induction of iNOS expression during the reperfusion phase[29-31]. Figure 1 shows a diagram of ROS and RNS sources in myocardial tissue.

Iron mobilization

It has been postulated that iron homeostasis could play an important role in the development of MRI in the cardiomyocytes[32,33]. Free iron is deleterious for cells; thus generally it is bound to proteins forming complexes[34]. During ischemia, iron metabolism is impaired, and it is released as free iron. This catalytic free iron can generate ROS through the Fenton reaction, catalyzing the production of ·OH from H_2O_2 and $O_2^{\bullet-}$[35]. It has been reported that susceptibility to injury from H_2O_2 in rat hearts is associated with the magnitude of the intracellular low molecular weight iron pool[36]. Some metals with redox properties have a well-documented role in the development of MRI[37,38]. Following reperfusion, both iron and copper are released to the coronary circulation[32] which can contribute to ROS generation (Figure 2). In patients with thalassemia the iron overload is related to arrhythmias and congestive heart failure, which is the main cause of death among these patients[39]. Iron chelation therapy has significantly improved the survival of patients with thalassemia[40], because iron chelators are effective and safe drugs to treat the iron poisoning[41].

Calcium homeostasis

Oxidative stress modifies phospholipids and proteins leading to lipid peroxidation and thiol-group oxidation; these changes are considered to alter membrane

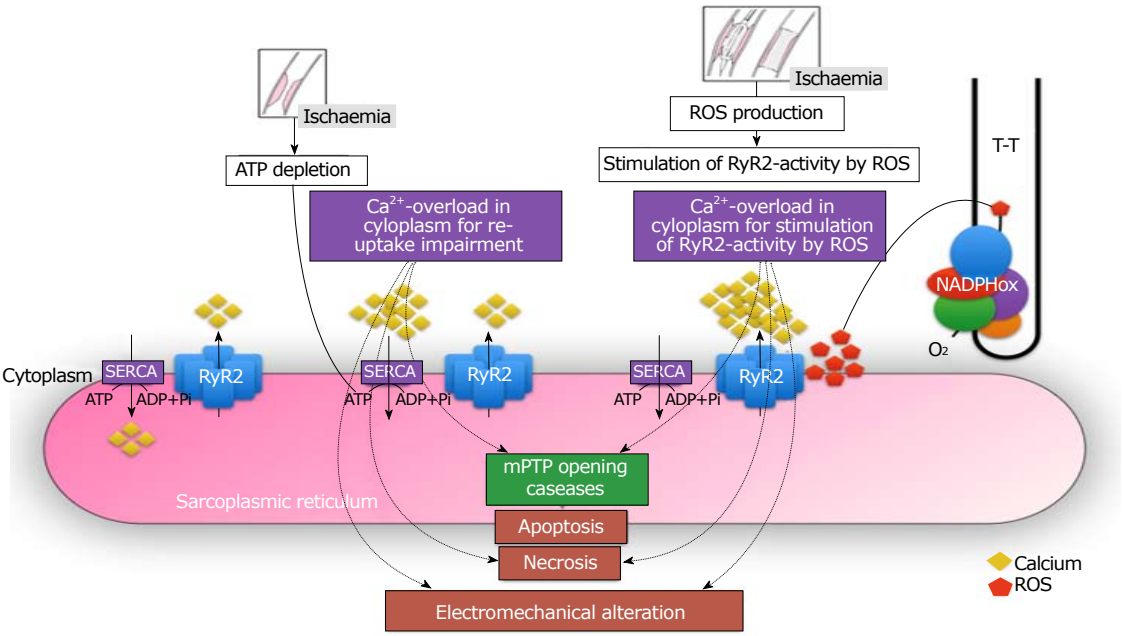

Figure 3 Central role of calcium in the electro-mechanical dissociation of cardiomyocyte after myocardial reperfusion. RyR: Ryanodine receptor channel; SERCA: Sarco / endoplasmic reticulum Ca^{2+}-ATPase; mPTP: Mitochondrial permeability transition pore; Ca: Calcium; ROS: Reactive oxygen species.

permeability and configuration in addition to producing functional modifications of various cellular proteins[42]. Oxidative stress may result in cellular defects including a depression in the sarcolemma Ca^{2+}-pump ATPase that leads to a decreased Ca^{2+}-efflux, and a depression in (Na + K)-ATPase activity that, in turn, leads to an increased Ca^{2+}-influx[43]. Oxidative stress has also been reported to depress the sarcoplasmic reticulum Ca^{2+}-pump ATPase (SERCA) and thus inhibit Ca^{2+} sequestration from the cytoplasm in cardiomyocytes[44]. The depression in Ca^{2+}-regulatory mechanism by ROS ultimately results in intracellular Ca^{2+} ($[Ca^{2+}]i$) overload and cell death. In addition, an increase in $[Ca^{2+}]i$ during ischemia induces the conversion of xanthine dehydrogenase to xanthine oxidase and subsequently results in increased production of $O_2^{\bullet-}$[44].

Recently it has been shown that the function of the channel ryanodine receptor (RyR) is controlled by ROS[45]. It has been demonstrated that NADPH oxidase and the RyR channel could be located adjacent to each other in the T-tubules of cardiomyocytes[46]. Thus, the increase in ROS production after myocardial reperfusion could lead to an increase in RyR channel function, resulting in an intracellular calcium overload, thereby causing activation of pro-apoptotic intracellular pathways, necrosis, and electromechanical alteration. All these mechanisms are summarized in Figure 3.

Redox-sensitive signaling pathways: Not only do ROS exert their actions by directly modifying organic molecules, but ROS are also involved in the regulation of the expression of several genes[47]. NF-κB and AP-1, both of which can experience ROS-mediated activation, stimulate the transcription of several protein mediators, for example, proinflammatory cytokines that activate several cell death pathways[48]. The role of cytokines, chemokines, leukocytes, and acute-phase proteins such as high-sensitivity C-reactive protein in the pathogenesis of MRI has been reported in several studies[49,50]. Oxidative stress, ROS and inflammation are linked in a way that is very difficult to dissect. These phenomena have important molecular bridges that are activated in the presence of ROS[51], leading to the activation of multiple mechanisms that cause heart tissue remodeling and therefore enhance the susceptibility to rhythm disorders. Among those molecules, the most studied has been the transcriptional factor NF-κB, a factor that responds to changes of the cellular oxidative state, ischemia-reperfusion, and inflammatory molecules[52]. When NF-κB is activated, for example in the presence of ROS by phosphorylation of its inhibitory cofactor (Iκ-B), it bonds to a DNA response element and promotes the transcription of genes involved in inflammatory and pro-fibrotic response, for example IL-6, which transforms growth factors TGF-β and TNF-α[53]. Those molecules act in various tissues, but particularly in the heart, producing extracellular matrix remodeling and fibrosis (structural remodeling), which changes the electrophysiological properties of the heart. Several studies have associated NF-κB activation with cardiac dysfunction, ventricular hypertrophy, and maladaptive cardiac growth[54] (Figure 2).

Exposure to low-to-moderate ROS levels should trigger a survival response and reinforce ROS scavengers of the antioxidant defense system to elicit a cardioprotective effect for myocardial reperfusion. The molecular mechanism responsible for this adaptive change involves enhanced antioxidant activity achieved

by up-regulating several housekeeping genes partly under the control of Nrf2 (nuclear factor-erythroid 2-related factor 2); Nrf2 is normally sequestered in the cytosol by Keap[55]. Upon oxidative stimulation, Nrf2 oxidizes or covalently modifies Keap1 thiol groups, which dissociate from Keap1 and undergo nuclear translocation. In the nucleus, Nrf2 binds to antioxidant response elements in target gene promoters[56], which increase the expression of antioxidant enzymes. It has been demonstrated that the constitutive levels/activities of a number of important antioxidants and phase 2 enzymes, such as CAT, GSH-Px, glutathione reductase, glutathione transferase, NADPH-quinone oxidoreductase 1, and heme oxygenase-1 in primary cardiomyocytes are dependent on Nrf2 status. In addition, Nrf2 diminishes the susceptibility of cardiomyocytes to injury elicited by oxidants and electrophilic species[57], making the Nrf2 signaling pathway an important mechanism for myocardial cytoprotection. It is of interest to note that ROS levels could be responsible for the activation of NF-κB and/or Nrf2 pathways.

Clinical implications: Myocardial damage caused by ischemia-reperfusion events are mainly associated with four clinical conditions: lethal reperfusion, myocardial stunning, no-reflow phenomenon, and reperfusion arrhythmias (Figure 2).

Lethal reperfusion is a paradoxical type of MRI caused by the restoration of coronary blood flow after an ischemic episode. It is defined as the death of cardiomyocytes that were viable immediately before myocardial reperfusion. Its main manifestation is as an increased infarct size due to reperfusion, a condition mainly associated with AMI[3]. In the late fifties, it was suggested that myocardial reperfusion contributes part of the histological damage associated with ischemia-reperfusion models. However, for decades it was very complex to determine the precise evolution of necrosis along the transition from ischemia to reperfusion in myocardial tissue[58]. Nowadays, the harmful effects of myocardial reperfusion damage, also known as lethal reperfusion injury, are considered to involve myocardial cell death derived from the restoration of blood flow subsequent to an ischemic process, and to act through mechanisms strongly associated with oxidative stress[3].

Reperfusion arrhythmias clinically represent a major comorbidity of AMI with an 88.7% occurrence rate in certain small clinical trials with continuous monitoring[59]. In addition, postoperative atrial fibrillation (POAF), the most common reperfusion arrhythmia associated with cardiac surgeries, has an incidence ranging between 20%-40%[60]. Myocardial stunning, despite being a reversible damage, is the cause of an impaired ventricular function that leads to increased morbidity. It is derived from a short-term ischemia-reperfusion process that was first reported in the early 1930s[61]. Myocardial stunning is present to a greater or lesser extent in all survivors of AMI. In the late 1980s evidence began to appear suggesting an important role of oxidative stress in the development of myocardial stunning, proposing that the main injury pathway could be an altered calcium homeostasis associated with sarcoplasmic reticulum damage[62]. More recently, clinical studies have strengthened this hypothesis[63], and it has been reported in animal models that interventions aimed to improve antioxidant defenses attenuate myocardial stunning[64,65].

The no-reflow phenomenon is an impaired myocardial perfusion of a specific segment of the coronary system that is not associated with an angiographic occlusion of the respective vessel[66]. Vascular and endothelial damage can occur after the reperfusion of previously blocked coronary circulation. It can be exhibited as a microvascular dysfunction after restoring the flow during either angioplasty or thrombolysis, thus leading to the development of the no-reflow phenomenon[67]. The presence of coronary microvascular dysfunction and this phenomenon are associated with larger infarct size, lower left ventricular ejection fraction, adverse left ventricular remodeling in the remote stage of myocardial infarction, and increased incidences of heart failure and death, compared with patients without no-reflow phenomenon[68]. Some studies using animal models showed that antioxidant strategies are able to reduce this phenomenon[69-71], and this data is consistent with a small clinical trial finding that antioxidant depletion is associated with no-reflow phenomenon in AMI[72]. In addition, recent research in rabbits shows that the suppression of the oxidative stress-sensitive transcription factor NF-κB, a key mediator of inflammation in cardiovascular systems, reduces myocardial no-reflow phenomenon[73].

Recently, our group has reported major clinical benefits with the use of antioxidants in pathologies associated with myocardial reperfusion, such as POAF and AMI. With regard to POAF, we documented a significant decrease in the incidence of this arrhythmia in patients undergoing cardiac surgery with extracorporeal circulation after administration of ascorbate, alpha-tocopherol, and omega-3 polyunsaturated fatty acids, which was accompanied by a significant decrease in oxidative stress biomarkers in auricular tissue and peripheral blood[60].

ROLE OF ANTIOXIDANTS

Despite a molecular basis and *in vitro* evidence supporting the use of antioxidants to prevent MRI, clinical evidence continues to be controversial. In the clinical setting, impaired micro-circulatory reperfusion was improved by ascorbate infusion in patients undergoing elective PCA[74]. Similar results were recently reported by our group[75]. These results suggest a positive role of antioxidants in counteracting the deleterious effects of oxidative stress on microvascular function. On the other hand, the ROS scavenger edaravone when administered to patients with AMI immediately prior to reperfusion, significantly reduced infarct size and

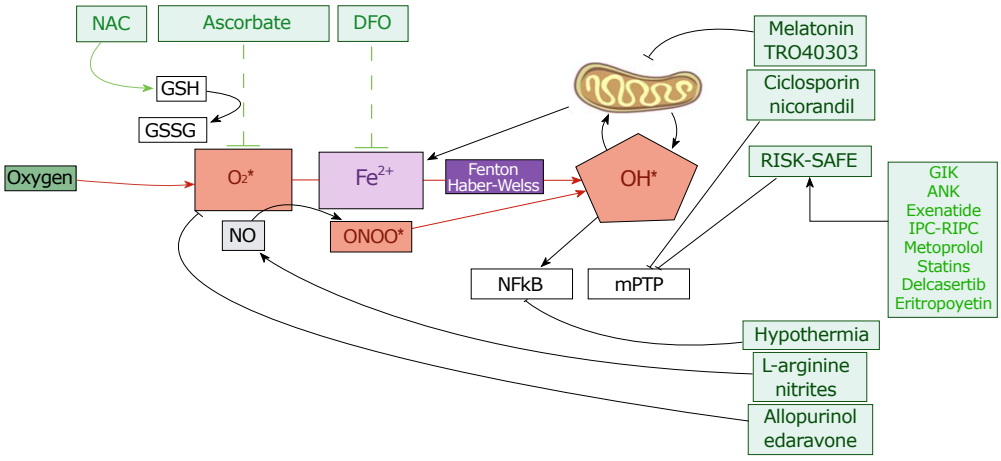

Figure 4 Experimental, pharmacological and clinical approaches to prevent myocardial reperfusion injury at cellular level. RISK: Reperfusion injury salvage kinase pathway; SAFE: Survivor activating factor enhancement pathway; GSH: Reduced glutathione; GSSG: Oxidized glutathione; NAC: N-acetylcysteine; DFO: deferoxamine; ONOO*: Peroxynitrite; NO: Nitric oxide; OH *: Radical hydroxyl; mPTP: Mitochondrial permeability transition pore.

reperfusion arrhythmias[76,77]. Also some experimental studies reported that the use of deferoxamine (DFO) and N-acetylcysteine (NAC) could improve microvascular dysfunction[78,79].

Carotenoids represent another potential pharmacological alternative in the management of MRI[80]. Carotenoids are a widely distributed group of fat-soluble pigments which exert antioxidant, anti-inflammatory, and antiproliferative properties[81]. Several experimental data support potential role of carotenoids in this pathological condition: Tong *et al*[81] demonstrated that pretreatment with lycopene reduced cardiomyocyte death induced by ischemia/reoxygenation *in vitro*, and also reduced myocardial infarct size in an *in vivo* model of AMI[82]. Another carotenoid, crocetin, protected against myocardial reperfusion injury *in vivo* by inhibiting ROS production, reducing eNOS expression and myocardium apoptosis[82]. All-trans retinoic acid presented also protective activity against reperfusion injury both *in vitro* and *in vivo*, probably by down-regulating MAPK signaling[84]. Despite the fact that carotenoids have been useful in preventing MRI in experimental studies and have arisen as a promising pharmacological alternative, further clinical studies and randomized clinical trials are required.

In the following paragraphs we will discuss a new hypothesis for the prevention of MRI through the combined use of ascorbate, NAC, and DFO prior to reperfusion in order to strengthen antioxidant defense systems and so prevent oxidative damage (Figure 4).

Ascorbate

The basis of this hypothesis is to achieve high plasma levels of ascorbate prior to reperfusion in order to strengthen the antioxidant defense system of myocardial tissue. Thus, when oxygen suddenly arrives to the previously ischemia-damaged myocardial tissue-which is the primary substrate for the production of the highly reactive superoxide anion radical-ascorbate may efficiently reduce ROS and prevent oxidative damage[5,8]. To support this hypothesis, we will discuss the main actions of this antioxidant and its pharmacokinetic properties.

Ascorbate is an essential antioxidant that performs its roles in different cell locations by acting in water-soluble components[85,86]. The most studied mechanism in which ascorbate acts is partly based on its ability to directly reduce ROS[87-89]. Besides its ROS scavenger actions, ascorbate exerts a complex modulation of numerous enzymes involved in ROS production, endothelial dysfunction, platelet aggregation, and smooth muscle cell tone[90-92]. The four most important mechanisms in which ascorbate modulates the endothelial function are NADPH down-regulation, and the up-regulation of eNOS, phospholipase A2, and antioxidant enzymes. NADPH oxidase, the most important superoxide source in the cardiovascular system, can be directly down-regulated by ascorbate[91,92]. The mechanism behind this effect has not been completely elucidated. It has been reported that ascorbate could be involved in the transcriptional and post-transcriptional modulation of NADPH oxidase[89,93] as well as in its synthesis[94]. In the presence of oxidative stress, eNOS is mostly in its uncoupled form which leads to endothelial dysfunction. In this context, ascorbate has been shown to increase eNOS activity, by preventing the oxidation of tetrahydrobiopterin and by inhibiting the p47phox subunit expression[95]. Therefore, ascorbate increases NO synthesis, reduces ROS formation and contributes to vascular tone regulation[96-98]. In relation to the up-regulation of antioxidant enzymes, some studies have demonstrated a positive correlation between antioxidant vitamin and antioxidant enzyme activity, particularly SOD. The mechanisms underlying these findings are not well explained, but it is plausible to hypothesize the existence of transcriptional and post-transcriptional events involved in the up-regulation of those antioxidant enzymes[92].

Table 1 Clinical trials

	Study details	Country	*n* Intervention		Main findings	Ref.
AA	Ascorbate previous to elective coronary angioplasty	Italy	28	28	Decrease in oxidative stress and improves reperfusion parameters	[74]
	Ascorbate previous to primary coronary angioplasty in patients with AMI	Chile	53	46	Improve ventricular function and reperfusion No differences in infarct size	[75]
NAC	N-acetylcysteine previous and after primary coronary angioplasty in patients with AMI	Germany	126	126	Decrease in oxidative stress No differences in infarct size	[105]
	N-acetylcysteine and nitroglycerine previous to primary coronary angioplasty in patients with AMI	Australia	67	65	Decrease in infarct size and cardiac damage biomarkers	[116]
DFO	Deferoxamine previous and after coronary angioplasty in patients with AMI	Australia	28	32	Decrease in oxidative stress No differences in infarct size	[114]

Main clinical studies that have used ascorbate, N-acetylcysteine or deferoxamine to prevent reperfusion injury in patients affected by acute myocardial infarction and treated with coronary angioplasty. AA: Ascorbate; NAC: N-acetylcysteine; DFO: Deferoxamine; IR: Ischemia reperfusion; AMI: Acute myocardial infarction.

Ascorbate counteracts and prevents the oxidation of lipids, proteins, and DNA, subsequently protecting their structure and biological function. Together with glutathione, ascorbate constitutes a primary line of defense against ROS[99]. Ascorbate, in aqueous compartments, can recycle α-tocopherol in membranes by reducing the α-tocopheroxyl radical back to α-tocopherol[100]. Accordingly, ascorbate has been shown to recycle α-tocopherol in lipid bilayers[101] and erythrocytes[95].

Ascorbate scavenging is concentration-dependent and requires intravenous administration. This is necessary because ascorbate concentration in plasma is tightly controlled and an excess of ascorbate is excreted as a function of dosage. In fact, even with supplementation approaching maximally tolerated doses, ascorbate plasma concentrations are always < 250 μmol/L. By contrast, intravenously injected ascorbate can safely lead to concentrations of 25-30 mmol/L[102]. It is of interest to mention that intra-arterial administration of high doses of ascorbate has been demonstrated to abolish both *in vivo* and *in vitro* effects of the superoxide anion with respect to the impairment of vascular endothelial function in patients with essential hypertension[103]. Unfortunately, oral doses are not enough to scavenge superoxide anions, thus a beneficial effect should not be expected.

Our group recently developed a randomized clinical trial in patients with AMI undergoing PCA, where massive doses of ascorbate (or placebo) were administered prior to PCA. Patients treated with ascorbate prior to myocardial reperfusion showed a better recovery of ejection fraction at 2-3 mo (measured by cardiac magnetic resonance) and significantly higher myocardial perfusion after PCA (*TIMI*-myocardial perfusion grade) than placebo patients, with no differences in infarct size[75] (Table 1).

N-acetyl-L-cysteine

Ascorbate consumes glutathione (GSH) to exert its antioxidant activity. High doses of ascorbate might be associated with a decrease in cellular GSH reserves[5]. For this reason, N-acetyl-L-cysteine (NAC) - a known GSH-donor-may also have synergistic effects with high doses of ascorbate. In the following paragraphs, we will discuss the potential role of NAC in preventing MRI.

Despite numerous studies and a prolonged track record of clinical trials, the effects of NAC are clouded in controversy and its pharmacological mechanism has not yet been fully clarified. However, there is plenty of evidence regarding its mechanism of action. First of all, NAC's main feature, and also the most studied one, is its capacity to act as a precursor for synthesis of GSH, thus replenishing GSH that has become depleted through the use of this peptide in detoxification routes[104]. However, it is vital to think of NAC as a pro-drug, because actions that are driven by this drug are dependent on its successful conversion to the antioxidant and detoxifying agent, GSH. Another frequently mentioned property of NAC is its intrinsic antioxidant activity. Nevertheless, the evidence regarding the antioxidant potential of NAC suggests that it does not have a noteworthy direct antioxidant activity[105].

NAC acts indirectly through chelation of metal ions such as catalytic iron[106,107] giving it the capability of mediating Fenton's reaction, thus ameliorating the possibility of the formation of hydroxyl radicals. This property is due to the fact that NAC forms conjugates with some metals. However, the importance of this mechanism in driving any protective effects compared to intracellular GSH replenishing is still unclear. Current evidence agrees on the capability of NAC to act as an inhibitor of NF-κB[108], a transcription factor that plays a critical role in inflammation, immunity, cell proliferation, differentiation, and survival. In conclusion, molecular mechanisms by which NAC exerts its diverse effects are complex and still unclear. Although it has been shown that NAC interacts with numerous biochemical pathways, its main mechanism involves serving as a precursor of cysteine and replenishing cellular GSH levels[104].

NAC has been widely used in different experimental and clinical settings to counteract oxidative stress. It has been demonstrated that NAC in combination with nitroglycerin and streptokinase is associated with significantly less oxidative stress and improved preservation of left ventricular function[109]. However, it has also been reported that a high-dose of NAC prior to PCA, although it reduces oxidative stress, does not provide an additional advantage in the prevention of MRI[110]. Additionally, an interesting study published in 2006 shows that administration of NAC in combination with streptokinase significantly diminishes oxidative stress and improves left ventricular function in patients with AMI[111]. A recent study using a rat model of myocardial ischemia-reperfusion injury demonstrates that treatment with continuous infusion of NAC (150 mg/kg per hour) starting 30 min before occlusion and lasting for 2 h (or until 1 h after the start of reperfusion) produces a significant limitation of the infarct and allows the recovery of the decreased total glutathione when compared to control[112]. Recently has been published the NACIAM trial by Pasupathy *et al*[113], that demonstrated a protective effect with the use of high doses of NAC in combination with a nitric oxide donor in patients with AMI (Table 1). This important study shows that NAC has a powerful protective effect when used in combination and previous to myocardial reperfusion. In summary, due to the known antioxidant and cardioprotective effect and its role as GSH-donor, it is plausible to suggest that NAC might have a synergistic effect with high doses of ascorbate and deferoxamine to prevent MRI.

Deferoxamine

Given the known role of iron in the lethal reperfusion, iron chelators have been tested to ameliorate this injury. One of the most frequently used drugs for this purpose is DFO. The first reports of its use to improve cardiac function in myocardium iron overload by directly removing iron from the myocardium[114] date from 1980s[115]. In animal models of AMI, the use of DFO has exhibited positive results. Some studies performed in dogs reported a decrease in the infarct size when they used DFO during the reperfusion, suggesting that iron-catalyzed production of ROS contributes to cardiomyocyte necrosis in the setting of MRI[116,117]. Studies have described improved recovery of myocardial function after ischemia, by using iron chelation[36,118]. The results obtained from animal models of MRI have suggested the use of iron chelators in the human model with partial results to date. Paraskevaidis *et al*[119] suggested DFO infusion was able to reduce myocardial stunning after elective coronary artery bypass grafting and to improve long-term ejection fraction. In a recent clinical study, Chan *et al*[120] randomized patients with STEMI to intravenous deferoxamine before coronary angioplasty and then for 12 h *vs* placebo (Table 1). The serum iron levels and lipid peroxidation biomarkers were reduced in the DFO-group without differences in the infarct size. The role of iron and ascorbate in the MRI has become of increasing interest in the last few years. It has been demonstrated that the combined use of DFO and ascorbate prevent reperfusion arrhythmias[121].

As has been previously discussed, cumulated evidence from both experimental and clinical studies leads us to support the view that a novel combined antioxidant strategy could limit MRI and its consequences. This novel hypothesis is based on the combined use of antioxidants prior to the reperfusion therapy in order to limit the oxidative challenge during reperfusion. The key points of this novel intervention are: (1) To achieve high plasma concentrations of ascorbate through massive intravenous doses to counteract the ROS and RNS production; (2) the use of NAC to prevent GSH depletion; and (3) the use of DFO to diminish the catalytic free iron levels in order to prevent the ROS production by the Fenton reaction.

Accordingly, in our laboratory recent studies of the murine Langendorff model have been conducted to determine the effect of antioxidants in MRI. We are now studying the effect of ascorbate, NAC, and DFO used alone and in association. Under these conditions, we expect a lower vulnerability of the myocardial tissue to the reperfusion injury associated with oxidative stress. This protective effect could be expressed by a lower infarct size, reduced post-reperfusion arrhythmias and myocardial stunning occurrence, and improved microvascular function. Finally, at present, there is no evidence available from any trial that has applied this antioxidant protocol to diminish MRI. Table 1 shows a summary of the main clinical studies that have used antioxidants to prevent MRI in patients with AMI.

CONCLUSION

There is major evidence with respect to the contribution of oxidative stress to MRI in cardiovascular diseases. Despite the many significant advances in the understanding of the mechanisms of MRI, it remains an unsolved problem. There is a lack of consistency between basic studies and clinical trials aimed to reduce MRI through antioxidant therapies. Although promising results have been obtained in experimental studies (mainly in animal models), these benefits have not been translated into clinical settings. It is noteworthy that the administration of high ascorbate doses prior to reperfusion and also NAC administration appear to be safe and rational therapies against the development of oxidative damage associated with myocardial reperfusion. Furthermore, ascorbate association with NAC and DFO could improve the beneficial effect of ascorbate, making it even more effective in preventing myocardial reperfusion damage associated with PCA following AMI.

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MINIREVIEWS

Established and novel pathophysiological mechanisms of pericardial injury and constrictive pericarditis

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Abstract

This review article aims to: (1) discern from the literature the immune and inflammatory processes occurring in the pericardium following injury; and (2) to delve into the molecular mechanisms which may play a role in the progression to constrictive pericarditis. Pericarditis arises as a result of a wide spectrum of pathologies of both infectious and non-infectious aetiology, which lead to various degrees of fibrogenesis. Current understanding of the sequence of molecular events leading to pathological manifestations of constrictive pericarditis is poor. The identification of key mechanisms and pathways common to most fibrotic events in the pericardium can aid in the design and development of novel interventions for the prevention and management of constriction. We have identified through this review various cellular events and signalling cascades which are likely to contribute to the pathological fibrotic phenotype. An initial classical pattern of inflammation arises as a result of insult to the pericardium and can exacerbate into an exaggerated or prolonged inflammatory state. Whilst the implication of major drivers of inflammation and fibrosis such as tumour necrosis factor and transforming growth factor β were foreseeable, the identification of pericardial deregulation of other mediators (basic fibroblast growth factor, galectin-3 and the tetrapeptide Ac-SDKP) provides important avenues for further research.

Key words: Inflammatory pericarditis; Autoimmune disease; Tuberculous pericarditis; Fibrosis mechanism; Constrictive pericarditis

Core tip: Constrictive pericarditis arises as a complication of pericarditis from a wide range of aetiologies. A comprehensive understanding of the fibrotic process eventually leading to pathological symptoms is currently lacking.Through this review of the literature, we have identified various molecular mediators which are likely to play a role in the establishment of constriction and which warrant further studies.

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INTRODUCTION

Pericarditis describes the clinical syndrome that occurs in response to injury of the pericardium. Following an episode of pericarditis, the natural history of the disease is variable and unpredictable. In a significant proportion of patients there is progression from acutely inflamed pericardium to chronic thickening, fibrosis, and fusion of the two pericardial layers with often dire consequences for patients. The molecular mechanisms involved in the inflammatory and immune mediated injury during pericarditis and the mechanisms involved in progression to constrictive pericarditis are poorly understood[1]. Such an understanding may be important to the design and development of interventions which are able to interrupt and prevent maladaptive and deleterious pericardial responses.

We conducted a comprehensive review of the available literature to summarize what is currently known about (1) immune and inflammation-mediated pericardial injury in a range of different causes of pericarditis; and (2) the molecular mechanisms involved in both pericarditis and subsequent post inflammatory progression to fibrosis and constrictive pericarditis.

SEARCH STRATEGY

The literature search was conducted in Pubmed, Embase, ScienceDirect and Google Scholar to identify journal articles for the review that had been published up to July 2017. In order to identify papers describing inflammatory and fibrotic processes occurring in the different types of pericarditis, the following search terms were used: "Pericarditis"and ("inflammation" or "fibrosis" or "constrictive" or "constriction"). The search was repeated for the common types of pericarditis described using the following search terms in the search criteria described above: "(uraemic or uremic)", "tuberculous", "malignant", "radiation", "autoimmune", "viral", "infectious", "post surgery" and "myocardial infarction"[2]. Literature regarding different animal models of pericarditis was obtained using the search terms: "animal model" and "pericarditis". Papers were then filtered according to their titles and content for the identification of relevant literature.

NORMAL PERICARDIUM

The pericardium is double layered flask-like sac which encloses the heart through its attachments to the great vessels, namely the vena cava, aorta, and pulmonary artery and vein. It is lined on the outside by the parietal pericardium, which is a fibrous layer of connective tissue rich in elastic fibres and collagenous fibres. This fibrosa is supplied by a network of blood and lymphatic vessels that contains macrophages and fibroblasts. The inner visceral pericardium is a single serous layer composed of flat, irregular, ciliated mesothelial cells resting on a thin basement membrane and separated from the fibrous layer by a thin sub-mesothelial space[3,4]. These two layers of the pericardium are 1-2 mm thick and give rise to a cavity which contains on average 15 to 35 mL of pericardial fluid, under normal physiological conditions[5]. Pericardial fluid is formed from ultrafiltration of plasma and comprises largely globular proteins, phospholipids and surfactant-like prostaglandins[6].

PATHOPHYSIOLOGICAL RESPONSE OF THE PERICARDIUM TO INJURY

Pericarditis

The pathophysiological response of the pericardium to injury is characterized by intense inflammation with or without effusion, and the clinical syndrome of pericarditis. Pericarditis is a common disorder[7] that can result from both an infectious and non-infectious aetiology and presents clinically as pericarditis with and without effusion. Causes of pericarditis include viral, bacterial, fungal, uraemic, post-acute myocardial infarction, neoplastic, post-cardiac surgery, following mediastinal irradiation and as a consequence of systemic autoimmune diseases[2]. The major complications of pericarditis are cardiac tamponade with and without hemodynamic instability in the short term, constrictive pericarditis in the long term and death[5]. The latter is usually the consequence of chronic inflammation, thickening, adhesion, fibrosis and obliteration of the pericardial space.

CLINICAL MODELS OF POST INFLAMMATORY PERICARDITIS

Uraemic pericarditis

Uraemic pericarditis is a complication of acute and chronic renal failure, which can arise prior to, and on dialysis treatment. The condition was prevalent before the widespread use of dialysis and was commonly associated with a poor prognosis and high mortality.

Currently, with modern dialysis, it has a highly improved prognosis and survival rate[8]. The mechanism of the development of pericarditis in uraemic disease is poorly understood. Although pericarditis is more frequent in cases of severe uraemia, there is no correlation between blood urea and creatinine levels and the appearance of pericarditis[9]. Uraemic pericarditis is usually exudative with protein and large numbers of mononuclear cells in the pericardial fluid[10]. Serous or haemorrhagic effusions are common and typically evolve into a fibrinous state. This fibrotic state often manifests as a rough granular surface with irregular, scattered adhesions between parietal and visceral pericardium in a "bread and butter" pattern[8,11]. However, densely adherent pericarditis and gross pericardial thickening with organizing fibrinous pericarditis have been found at autopsy in cases of uraemic disease[12].

Radiation pericarditis

Radiation pericarditis occurs as a complication of radiation therapy of malignant mediastinal tissues and organs, most commonly breast cancer or mediastinal Hodgkin's disease. Radiation pericarditis was a common adverse outcome when large areas of the heart were exposed to high doses of radiation therapy, but the advent of chemo- and immuno- therapy has decreased the incidence of the condition[13]. Both acute and late post radiation pericardial injuries have been described. Acutely, radiation toxicity can cause micro-vascular damage and episodic pericardial ischemia, which in turn leads to permeable neovascularization and fibrous deposition. Later, activated fibroblasts express increasing type Ⅰ collagen levels, with subsequent focal massive hyalinization, adhesions of the epicardium and thickening pericardium[14,15]. There is also evidence of impaired drainage of extracellular fluid from the pericardium, a chronic fibrinous exudative pericarditis and vascular and lymphatic fibrosis[16].

The degree of inflammation and thickening in radiation pericarditis corresponds to the X-ray exposure, with marked thickening observed more at the site of irradiation. This suggests a cellular injury and necrosis induced inflammatory response as a result of the acute radiation of actively proliferating cells, potentially mesothelial cells of the pericardium. On a molecular level, increased collagen synthesis and the pathological remodelling of the pericardium post radiation have been associated with the activation of various growth factors and cytokines including transforming growth factor β (TGF-β) and connective tissue growth factor (CTGF)[17].

Autoimmune disease pericarditis

Pericardial involvement can arise in various autoimmune diseases, most commonly systemic lupus erythematosus (SLE), rheumatoid arthritis (RA) and systemic sclerosis (SSc)[2].

SLE is a chronic inflammatory disease with a broad range of clinical manifestations and a variable disease course. The exact aetiology of SLE is still unclear, but it is likely to be mediated by antibodies and immune complexes (IC) which typically contribute to the clinical manifestation of SLE. Immune complexes can result in complement activation and inflammation and they have been detected in the pericardial fluid in SLE[18]. While pericarditis is the most common cardiac manifestation of SLE, constrictive pericarditis is a rare occurrence[19].

RA is a chronic inflammatory disorder that primarily affects joints. Symptomatic pericarditis arises in less than 10% of patients with severe disease and is often associated with a poor prognosis[20]. The pericardial involvement is usually a diffuse pericardial effusion, sometimes associated with leukocyte infiltration and often positive for rheumatoid factor and immune complexes. Constrictive pericarditis is not common in RA and can arise despite second-line therapy. Thickened pericardia with collagenous fibrous tissue and organising fibrin, fibrinous exudate and leukocyte infiltration have been described[21]. Asymptomatic pericardial effusions occur in upto 30%-50% of patients with RA and represents the most common cardiac manifestation of the disease.

Systemic sclerosis is a systemic autoimmune disease characterized by aberrant fibroblast activity resulting in dense fibrosis of visceral organs and skin. Pericardial manifestations include pericardial effusions, fibrous pericarditis, pericardial adhesions or constrictive pericarditis. Clinical manifestations of pericardial pathology are apparent in over 5%-16% of cases. The pathogenesis of pericardial effusions in SSc is believed to differ from the inflammatory pathway triggered by auto-antibodies and immune complexes of SLE and RA as evidenced by the "non-inflammatory" profile of the pericardial fluid. Instead, the release of basic fibroblast growth factor (bFGF) and histamine by mast cells may contribute to the pathophysiological manifestations[22,23].

The inflammatory basis of autoimmune pericarditis, centered around the role of the inflammasome, has recently been reviewed by Xu *et al*[24].

Post myocardial infarction pericarditis

Pericarditis is a common sequelae of transmural myocardial infarction (MI) and arises "early" as pericarditis epistenocardica or as a "delayed" presentation in the form of Dressler syndrome[25].

The acute form of pericarditis is often diagnosed 1-4 d post MI[26] and is sometimes accompanied by a pericardial effusion. Vascular injury and myocardial necrosis have been associated with increased incidence of pericarditis, suggesting an inflammatory response to injury[27,28]. Fibrous deposits and adhesions often develop in the visceral and parietal pericardium covering the area of infarction but may also involve wider and more diffuse pericardial surfaces[29].

Dressler syndrome (DS) commonly arises around

two weeks post MI. It is an uncommon presentation since the advent of early reperfusion therapy with thrombolytic therapy and primary percutaneous intervention, and with the widespread use of heparin. DS is presumably a recurrent immune-inflammatory syndrome arising from the release of auto-myocardial antigens from necrosis of myocardial tissues. The formation of immune complexes are believed to trigger a hypersensitivity reaction from molecular mimicry and cross-reactions[25,30]. Indeed, the presence of increased anti-myocardial antibodies following myocardial injury has been previously suggested and supports a possible autoimmune pathogenesis[31].

Post cardiac surgery pericarditis

Pericarditis can present as a midterm or late complication of cardiac surgery. Post surgery pericarditis often bears restrictive haemodynamic characteristics despite an open pericardium and can occur as early as 2 wk following surgery[32]. Adhesions and fibrous patches in the pericardium lead to constrictive pericarditis and cause symptoms of dyspnoea, and signs of congestive cardiac failure. Whilst the exact mechanism for the development of pericardial fibrosis following surgery is obscure, the presence of blood in the pericardial cavity may play a role, with failure to drain bloody effusions being a risk factor for the development of fibrosis. Blood in the pericardium may result in irritation of the serosal layer and inflammation[33]. However, pericardial fibrosis in the absence of bloody effusions after surgery has also been documented[34].

Post infectious pericarditis

A range of infectious organisms can affect the pericardium, but the most common causes are viruses (coxsakie viruses, influenza virus and enteric cytopathogenic human orphan virus, among others) and bacteria (*Staphylococcus* and *Streptococcus, Haemophilus,* and *M. tuberculosis*).

Bacterial (purulent) pericarditis which is a life threatening condition is characterised by gross pus in the pericardium or microscopically purulent effusion[35]. It is an uncommon occurrence in the developed world, due to widespread antibiotic usage. However, tuberculous pericarditis is a leading cause of pericarditis in Sub Saharan Africa and is discussed separately below[36].

Viral pericarditis, on the other hand, is a common manifestation and is often self-limiting, in that only a small number of patients develop fibrous complications. Viral antigens lead to an inflammatory response of lymphocytic predominance which often results in effusions. Cytotoxic and T and/or B cell-driven immune-mediated mechanisms of inflammation have been described in different types of viral infections[1]. Increased levels of IL-6 and IL-8 have also been described in both serum and pericardial fluid in viral pericarditis, with a marked local increase in the pericardial cavity[37,38]. An increase in pericardial TNF-α levels has also been measured in the pericardial fluid by Ristić *et al*[37], whilst TGF-β levels were only elevated in serum. However, conflicting Interferon-γ (IFN-γ) deregulation has been reported by the two studies, with a strongly elevated levels described by Pankuweit *et al*[38], whilst no differences were reported by Ristić *et al*[37]. This is probably due to the small sample size used in the latter study. Further, Karatolios *et al*[39] measured increased pericardial and serum levels of vascular endothelial growth factor (VEGF) in viral pericarditis as well as decreased bFGF levels in the pericardial fluid. Elevated serum cardiac troponin Ⅰ (cTn Ⅰ) levels have been observed in viral pericarditis and have been associated with ST-segment elevation, and pericardial effusion. Whilst, this increase is often more pronounced with increased myocardial inflammation, it did not affect the prognosis and the development of tamponade and fibrosis[40].

Tuberculous pericarditis

Tuberculous (TB) pericarditis accounts for roughly 4% of cases of acute pericarditis in the developed world. However, in developing countries with a high prevalence of tuberculosis, around 70% of cases of large pericardial effusion are attributable to TB[41,42]. Further, HIV co-infection has not only increased the number of TB pericarditis cases, but has also changed its clinical manifestations and therapeutic considerations[43].

The spread of Mycobacterium tuberculosis (MTb) to the pericardium occurs either through retrograde lymphatic spread or through haematogenous spread from primary sites of infection[36,44]. The inflammatory process in TB pericarditis follows a sequence of pathological events. An early fibrinous exudate is formed with leucocytosis, and early granuloma formation as a response to the high mycobacterial abundance, followed by a sero-sanguineous effusion with a predominantly lymphocytic exudate. The effusion gradually recedes whilst the granulomatous architecture is organised to restrict mycobacterial spread. Fibrin, collagen and extracellular matrix (ECM) deposition lead to pericardial thickening and fibrosis[36].

Infection of the pericardium with the bacilli elicits an immune response, stimulating lymphocytes to release cytokines which activate macrophages and influence granuloma formation. This initial reaction presents pathologically with polymorphonuclear leucocytosis and granuloma formation[45]. Marked elevations of IL-10 and IFN-γ accompanied by low levels of bioactive TGF-β levels in tuberculous pericardial fluid suggest a Th-1 mediated delayed type hypersensitivity response to the pathogen[46]. Similarly, Reuter *et al*[47] measured significantly increased IFN-γ levels in the pericardial fluid and observed large numbers of mesothelial cells in tuberculous pericardial aspirates.

A role for complement fixing antimyolemmal antibodies has also been suggested in the development of exudative tuberculous pericarditis through cardiocyte cytolysis[48]. More recently, it was shown that the tetrapeptide N-acetyl-seryl-aspartyl-lysyl-proline (Ac-

SDKP) and galectin-3 could be detected in tuberculous pericardial fluid. The reduction in Ac-SDKP levels in TB pericardial effusion has been suggested to contribute to the development of fibrosis associated with TB pericarditis[49].

Elevated pericardial adenosine deaminase (ADA) activity and lysozyme levels have also been associated with TB pericarditis, and are of significant value in the diagnosis of TB pericarditis[47]. High ADA levels are also prognostic for the development of constrictive pericarditis[50].

Malignant pericarditis

Both primary (mesotheliomas, sarcomas, fibromas) and secondary (carcinoma, lymphoma, and carcinoid) neoplasms can be accompanied by pericardial inflammation. However, neoplastic pericarditis arises mostly from secondary disorders as a result of tumour spread and metastasis through lymphatic and haematogenous spread[51]. Effusions are common in neoplastic pericarditis and can be bloody. Malignant cells can also be present in the pericardium but almost 50% of symptomatic pericarditis cases have negative cytological results for malignant cells[52]. However, malignancies are commonly widespread when pericardial symptoms become apparent and malignant invasion of the heart and the deposition of fibrous tissue often lead to constriction[53]. Sub-acute inflammation with lymphocytic accumulation and mesothelial hyperplasia has been described in primary pericardial mesothelioma[54].

Ristić *et al*[37] measured elevated serum and pericardial levels of IL-6 and TGF-β in malignant pericarditis as compared to bypass surgery controls. TNF-α and IFN-γ levels were however not affected. A study by Pankuweit *et al*[38], found that IFN-γ levels in effusions were found to be slightly lower than in the serum. In accordance with Ristić *et al*[38] IL-6 and IL-8 levels were markedly increased in pericardial fluid as compared to the serum, suggesting a local initiation of the inflammatory response. Cardiac embryonic antigen is useful in the diagnosis of malignant pericarditis and levels above 5 ng/mL are found in the majority of cases[55].

ANIMAL MODELS OF PERICARDITIS

Several animal models of pericarditis have been described whereby the onset of inflammation was triggered by diverse mechanisms. A severe inflammatory reaction has been described in the pericardium of sheep injected with a bacterial toxin and Freund's adjuvant. A cellular mesothelial response was observed with changes to the morphology and disturbance to the architecture, followed by detachment from neighbouring cells and desquamation. An accompanying increase in vascular permeability resulted in the accumulation of large numbers of inflammatory cells and the exudation of fibrin. An increased collagen turnover was apparent after 6 d and the appearance of adhesions occurred as early as 2 wk post injection[56].

Coxsackie B viruses are known to cause perimyocarditis, an acute inflammation of the pericardium and the underlying myocardium[57]. In Coxsackie B3 induced perimyocarditis in mice, an early onset of myocardial injury and necrosis has been observed, followed by marked pericardial fibrosis[58]. In this particular study, the sub-epicardial myocardial tissues appeared to mostly contribute to the fibrotic process, with infiltration by macrophages, lymphocytes and polymorphonuclear leukocytes observed in the myocardial layer. However, in Coxsackie B4 pericarditis in mice, fibrotic lesions occurred independently of, or in conjunction with adjacent myocardial lesions. Similar patterns of inflammation were observed in the mesothelial cells with necrosis, cellular infiltration, inflammatory cell infiltration and fibrinous exudate. The inflammatory processes are likely to be as a result of infection of mesothelial cells by the virus, since viral antigens have been detected in the mesothelial cells[59]. Interleukin-33 (IL-33) induced eosinophilic pericarditis has also been implicated in Coxsackie B infection[60].

IFN-γ and TGF-β knockout (KO) mice bear gross histological and haemodynamic characteristics of pericarditis. Pericarditis in the IFN-γ mice presented as a thick and stiff pericardium which formed adhesions to surrounding structures. Mesothelial hyperplasia in the pericardium was accompanied by a morphological change to a cuboidal shape. In addition to the predominant mononuclear cell infiltration, the pericardial inflammatory infiltrate of the IFN-γ KO mice had marked eosinophilia. Similarly, cardiac myocytes bordering areas of inflammation in the TGF-β KO mice presented with eosinophilic inclusions and contained large nucleoli[61,62].

THE FIBROTIC PROCESS AND CONSTRICTIVE PERICARDITIS

Constrictive pericarditis

Constrictive pericarditis is a clinical syndrome, characterised by a thickened and non-compliant pericardium, which restricts cardiac filling[63]. The most apparent pathological features of constrictive pericarditis are inflammation and fibrotic thickening of the thin and elastic parietal and visceral pericardial linings. The pericardium commonly bears areas of inflammation of the serosa, scarring, and fibro-calcification[63].

Constrictive pericarditis may result from severe acute inflammation or recurrent less severe inflammatory events over a highly variable time course from the period of injury[64]. While the predictors of progression to constriction following acute pericarditis are poorly understood the incidence of constrictive pericarditis is significantly dependent on the aetiology of the pericarditis. Whilst idiopathic and viral pericarditis have a low incidence of constrictive complications (0.8/1000 person-years), tuberculous (31.7/1000 person-years) and purulent pericarditis (52.74/1000 person-years) are associated with the highest rates of progression to

Table 1 Summary of Inflammatory and fibrotic cytokines and growth factors (detected in pericardial fluid) likely to modulate the pathophysiological processes leading to chronic fibrosis in the pericardium

Inflammatory/ fibrotic mediator	Major roles in Inflammation and fibrosis	References
TGF-β	Anti-inflammatory mediator ECM deposition and remodelling	[17,37,46,61]
CTGF	Myofibroblast activation ECM deposition and remodelling	[17]
TNF-α	Inducer and regulator of inflammation Macrophage and Natual Killer cell recruitment	[37,38]
IL-6	Late role in inflammatory cascade Adaptive Immune system activation	[37,38]
IL-8	Later role in inflammatory cascade Neutrophil cell recruitment	[37,38]
IL-10	Inflammatory mediator	[46]
IFN-γ	Immune response modulation Macrophage and Natual Killer cell activation Anti-fibrotic	[37-39,46,62]
VEGF	Angiogenesis and fibrosis promotion Fibrosis resolution	[39]
bFGF	ECM deposition	[23,39]
Ac-SDKP	Major role in the inhibition of fibrosis	[49]
Galectin-3	Myofibroblast activation ECM deposition	[49]

TGF-β: Growth factor β; CTGF: Connective tissue growth factor; TNF-α: Tumor necrosis factor-α; IFN-γ: Interferon-γ; VEGF: Vascular endothelial growth factor; bFGF: Basic fibroblast growth factor; ECM: Extracellular matrix.

pericardial constriction[7].

Molecular mechanisms of fibrosis

Although the molecular processes leading to fibrogenesis are likely to be unique for different pathologies, some key mechanisms and pathways are common to most fibrotic events[65]. The fibrotic cascade of events is triggered upon insult to epithelial or endothelial cells which results in the activation of the coagulation cascade. The initial inflammatory response is characterised by the release of various pro-inflammatory cytokines, including tumour necrosis factor-α, TNF-α[66,67]. TNF-α is a pleiotropic cytokine with a central role in the activation and recruitment of immune cells and the regulation of pro-inflammatory cytokine production[68]. Activated leukocytes then proceed to release pro-fibrotic cytokines such as IL-13 and TGF-β which drive EMT and ECM component production. TGF-β, is a key mediator of the fibrotic response and it acts *via* canonical (Smad-dependent) and non-canonical (non-Smad-based) signalling pathways to coordinate an ECM accumulation through increased synthesis as well as a decreased degradation of ECM components[69-71].

Molecular mechanisms of pericardial fibrosis

Molecular mechanisms of pericardial constriction remain to be fully elucidated but are likely to follow a classical pattern of pericardial inflammation mediated by various cytokines (Table 1), including TNF-α, followed by abnormal healing with an exaggerated TGF-β mediated profibrotic response leading to pericardial fibrosis. Both experimental mice models of acute pericarditis and pericardial fluid from patients with tuberculous effusive constrictive pericarditis (associated with a high incidence of pericarditis), demonstrate a mixed picture of both pro-inflammatory IFN-γ, and anti inflammatory cytokines IL-8, and IL-10[72], but their exact roles are as yet unclear.

Patterns of inflammation and fibrosis in the pericardium suggest that both myocardial and pericardial cells play a role in the pathogenesis of pericarditis and constriction. A change in mesothelial cell morphology has been consistently described in various forms of pericarditis. Further, a loss of the mesothelial cell architecture, as well as mesothelial desquamation often accompanies constrictive pericarditis (Figure 1). The transition from a "flat" to a "cuboidal" shape has been associated with an "activation" of mesothelial cells and a distinct enzymatic profile of the cells with functions being geared towards oxidative stress and inflammatory responses[73,74]. Activated mesothelial cells secrete chemokines and adhesion molecules to aid in the recruitment and migration of leukocytes across the mesothelium. They are also known to mediate the inflammatory process and produce ECM components[75]. Further, mesothelial cells can undergo phenotypic changes similar to epithelial-to-mesenchymal transition to adopt fibroblast-like morphology and function in the healing serosa[4,76]. The active regulation of both pro- and anti-inflammatory mediators by mesothelial cells suggests a key role for the cells in maintaining pericardial homeostasis and also in the pathogenesis of pericardial fibrosis. Pericardial interstitial cells (PICs) have also been implicated in the production of ECM and calcification in the pericardium[77].

PICs have a comparable immune-phenotype to

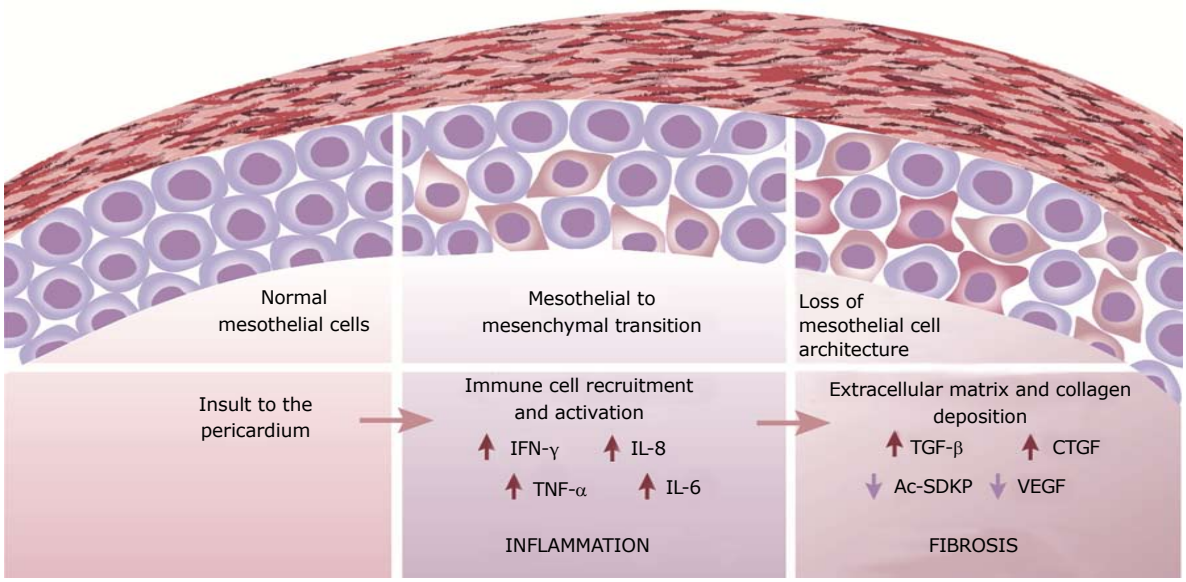

Figure 1 Molecular mediators involved in the inflammatory and fibrotic processes arising in constrictive pericarditis. Ac-SDKP: N-acetyl-seryl-aspartyl-lysyl-proline; TGF-β: Growth factor β; TNF-α: Tumor necrosis factor-α; CTGF: Connective tissue growth factor; IFN-γ: Interferon-γ; VEGF: Vascular endothelial growth factor.

mesenchymal stem cells. PICs cultured from fibro-calcific human samples could be differentiated into myofibroblasts and osteoblasts which are central to the development of fibrosis and the production of extra-osseous calcification. TGF-β and bone morphogenetic protein 2 (BMP-2) were associated with the trans-differentiation process. TGF-β increased PIC mRNA expression of collagens Ⅰ and Ⅲ whilst decreasing the matrix metalloprotease-2 and -9 mRNA levels which are important for elastin degradation, thus regulating the fibrotic process by modulating fibrosis related gene expression[77].

TGF-β is a master regulator of extracellular matrix component expression and the development of fibrosis. Increased pericardial fluid and serum levels of TGF-β have been described in various forms of pericarditis and have been associated with increased collagen synthesis. It is thus safe to say that TGF-β might play a key role in the development of fibrosis in the pericardium. Interestingly, Ristic *et al*[37] did not detect any increase in TGF-β levels in viral pericardial fluid and this could account for the low proportion of constrictive pericarditis arising in this group.

Ac-SDKP, which is known to decrease TGF-β signalling by decreasing TGF-β transcription and the phosphorylation of Smad2 and Smad3 and their translocation to the nucleus[78-81], may play a role in the pathway to pericardial fibrosis. Patients with TB pericarditis, have been found to have diminished Ac-SDKP levels compared to particpants without pericarditis undergoing cardiac sugery[49]. Lowered Ac-SDKP levels could arise from an increase in angiotensin converting enzyme (ACE) activity, which is known to degrade Ac-SDKP[82,83]. An increase in ACE serum levels has been reported in granulomatous conditions including Mtb infection, and is believed to arise from an overflow of ACE production by the macrophages and phagocytes in the granulomatous lesions into the circulation. Thus increased ACE levels, resulting in increased enzymatic cleavage of Ac-SDKP and a subsequent dampening in its anti-fibrotic potential, could potentially contribute to the pathogenesis of constriction.

Finally, an increase in CTGF was associated with ECM deposition and pericardial remodelling[17]. This is not surprising as CTGF expression is known to be induced by TGF-β in cardiac fibroblasts and cardiac myocytes, whereby it contributes to the expression of fibronectin, collagen type Ⅰ and plasminogen activator inhibitor-1[84]. Interestingly a decrease in VEGF was observed in viral pericarditis which rarely results in a constrictive pericarditis. Whilst VEGF mediated angiogenesis is known to be important for the promotion of fibrosis, it also plays a role in fibrosis resolution[85]. Indeed, an angio-fibrotic switch of VEGF and CTGF has been described in proliferative diabetic retinopathy, whereby the VEGF to CTGF ratio closely dictates the progression to fibrosi[86,87]. CTGF has also been shown to bind to VEGF and to inhibit its angiogenic functions[88]. Hence, it is possible that such CTGF-VEGF interplay is also involved in the progression to fibrosis in the pericardium. This would further explain the high VEGF levels coinciding with low levels of bFGF in viral pericardial fluid.

CONCLUSION

In this review, we have highlighted that the pericardium is subjected to noxious injury from a wide spectrum of infections and non infections causes and that the pathogenesis of pericarditis in each instance may differ in significant ways. Importantly the progression from

pericarditis, to the development of pericardial fibrosis varies significantly by etiology. A classical pattern of inflammation in the pericardium mediated by various cytokines is likely to occur as a result of most types of insult. However, the unfolding of events leading to the development of fibrosis post-inflammation is harder to accurately predict. Nevertheless, this review has allowed us to postulate various cellular events and signalling cascades which are likely to contribute, albeit to different extents in varying types of pericarditis, to the pathological fibrotic phenotype. Whilst the role of common players such as TGF-β and TNF-α in the inflammatory process can be quite easily predicted, their complex range of functions makes them unattractive targets in the management and treatment of constrictive pericarditis. However, the identification of other pro-and anti-fibrotic mediators such as Galectin-3, Ac-SDKP and bFGF, with a narrower range of functions could represent new avenues for the treatment of pericarditis. Research aimed at developing a better understanding of molecular mechanisms involved in the progression of pericarditis to fibrosis may be able to (1) identify high risk patients for progression to constrictive pericarditis through novel markers of fibrosis; and (2) identify novel targets for therapy to interrupt the progression to fibrosis and prevent the development of constrictive pericarditis.

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ORIGINAL ARTICLE

Basic Study

NBCe1 Na^+-$HCO3^-$ cotransporter ablation causes reduced apoptosis following cardiac ischemia-reperfusion injury *in vivo*

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Author contributions: Shull GE, Vairamani K, Wang Y and Lorenz JN designed and coordinated the research; Shull GE and Vairamani K wrote the paper; Wang Y, Vairamani K and Huang W performed the ischemia reperfusion studies; Lorenz JN performed the cardiovascular physiology studies; Medvedovic M, Vairamani K and Shull GE performed the RNA Seq analysis; Prasad V and Chen Y established the animal model and provided important critiques of the study; all authors approved the final version of the manuscript.

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Abstract

AIM

To investigate the hypothesis that cardiomyocyte-specific loss of the electrogenic NBCe1 Na^+-HCO_3^- cotransporter is cardioprotective during *in vivo* ischemia-reperfusion (IR) injury.

METHODS

An NBCe1 (*Slc4a4* gene) conditional knockout mouse (KO) model was prepared by gene targeting. Cardiovascular performance of wildtype (WT) and cardiac-specific NBCe1 KO mice was analyzed by intraventricular pressure measurements, and changes in cardiac gene expression were determined by RNA Seq analysis. Response to *in vivo* IR injury was analyzed after 30 min occlusion of the left anterior descending artery followed by 3 h of reperfusion.

RESULTS

Loss of NBCe1 in cardiac myocytes did not impair cardiac contractility or relaxation under basal conditions or in response to β-adrenergic stimulation, and caused only limited changes in gene expression patterns, such as those for electrical excitability. However, following ischemia and reperfusion, KO heart sections exhibited significantly fewer apoptotic nuclei than WT sections.

CONCLUSION

These studies indicate that cardiac-specific loss of NBCe1 does not impair cardiovascular performance, causes only minimal changes in gene expression patterns, and protects against IR injury *in vivo* .

Key words: Deep sequencing; Ischemic; Apoptosis; *Slc4a4*; NBCe1

Core tip: The NBCe1 Na^+-HCO_3^- cotransporter and NHE1 Na^+/H^+ exchanger both mediate Na^+-loading and intracellular pH regulation in cardiomyocytes. Inhibition of NHE1 protects against ischemia-reperfusion (IR) injury, and evidence suggests that loss of NBCe1 activity could also be cardioprotective. We have developed a conditional NBCe1 knockout mouse model and have used it to determine the effects of NBCe1 ablation in cardiac muscle. These studies demonstrate that loss of NBCe1 does not impair cardiac performance. However, cardiomyocyte apoptosis following IR injury *in vivo* is much lower in hearts that lack NBCe1, thus indicating that loss of NBCe1 is cardioprotective.

Vairamani K, Prasad V, Wang Y, Huang W, Chen Y, Medvedovic M, Lorenz JN, Shull GE. NBCe1 Na^+-HCO_3^- cotransporter ablation causes reduced apoptosis following cardiac ischemia-reperfusion injury *in vivo*. *World J Cardiol* 2018; 10(9): 97-109 Available from: URL: http://www.wjgnet.com/1949-8462/full/v10/i9/97.htm DOI: http://dx.doi.org/10.4330/wjc.v10.i9.97

INTRODUCTION

Regulation of intracellular pH (pH_i) in cardiac myocytes is critical for cardiac function[1-4]. Cardiomyocytes express a sarcolemmal Na^+/H^+ exchanger (NHE1), two Na^+-HCO_3^- cotransporters, and a number of Na^+-independent electroneutral Cl^-/HCO_3^- exchangers[1,2,5]. The Cl^-/HCO_3^- exchangers extrude HCO_3^- in exchange for Cl^- and therefore serve as acid-loading mechanisms[1,2]. In addition, they facilitate Na^+-loading by operating in concert with the Na^+-dependent acid extruders[6] and have the potential to contribute to CO_2 disposal[7]. The sarcolemmal Na^+/H^+ exchanger and Na^+-HCO_3^- cotransporters are activated by intracellular acidification and serve to alkalinize the cell by extruding H^+ or bringing in HCO_3^-[1,2]. Because their acid-base transport activities are coupled with uptake of Na^+, these transporters stimulate Ca^{2+}-loading via effects on the Na^+/Ca^{2+} exchanger[4], which in turn can affect contractility[8].

The effects of NHE1 activity on Na^+- and Ca^{2+}-loading and on ischemia-reperfusion (IR) injury in heart, using both inhibitors[9-13] and a gene-targeted mouse model[14], are well established. The cardiac functions of the Na^+-HCO_3^- cotransporters and their relevance to disease processes are less understood. Two Na^+/HCO_3^- cotransporters, one electrogenic (NBCe1) and one electroneutral (NBCn1), are expressed in mammalian hearts. Based on RNA seq data[5,7], NBCe1 mRNA expression in mouse heart is about double that of NBCn1 and data available in the EMBL-EBI Expression Atlas (https://www.ebi.ac.uk/gxa/home) shows that this is also the case in the human heart. NBCe1 has been localized to the lateral sarcolemma, intercalated disc, and t-tubules of cardiomyocytes[1], and it has been suggested that the presence of NBCe1 in the t-tubule may contribute to electrical events involved in excitation-contraction coupling[1]. Inhibition of NBCe1 has been shown to reduce infarct size and improve ventricular function during reperfusion of the isolated rodent heart[15,16], and the expression of NBCe1 is elevated in hearts of human patients with heart failure[15]. In a rat model of pressure overload hypertrophy,

both NBCe1 and NBCn1 mRNAs were elevated[17]. These observations suggest that increased Na^+-HCO_3^- cotransport activity may be a contributing factor during pathological conditions like heart failure, myocardial infarction, and ischemic injury.

Mice with a targeted global disruption of the *Slc4a4* gene exhibit severe metabolic acidosis, absorptive and secretory defects, growth retardation, hyperaldosteronism, splenomegaly, and abnormal dentition, and they die before weaning[18]. Because of the severe phenotype it was not possible to examine the cardiac functions of NBCe1 using the global KO. The studies performed to assess cardio-protective effects of inhibiting NBCe1 in the heart have been performed using an anti-NBCe1 antibody[15,16] or the compound S0859, reported to be a common inhibitor of all NBCs[16]. To better understand the functions of NBCe1 in heart, we generated cardiomyocyte-specific conditional NBCe1 KO mice. The cardiovascular functions of WT and KO mice were analyzed *in vivo* under basal conditions and in response to β-adrenergic stimulation. To determine if the loss of NBCe1 is protective against IR injury *in vivo*, WT and NBCe1 KO mice were subjected to ligation of the left anterior descending artery followed by a period of reperfusion.

MATERIALS AND METHODS

Generation of a conditional NBCe1 knockout mouse model

Design and construction of the targeting vector, gene targeting of embryonic stem (ES) cells, and subsequent steps needed to generate mice carrying a floxed allele of NBCe1 were performed by the Animal Models Core Facility of the University of Cincinnati. The targeting construct was prepared with LoxP sites flanking coding exon 12 for transcripts ENSMUST00000148750 and ENSMUST00000156238 of the *Slc4a4* gene, both of which have an upstream non-coding exon. It should be noted that there are multiple transcripts for the *Slc4a4* gene and that the numbering of exons differs in some transcripts. However, because the targeted exon is an essential exon in all transcripts, the model can be used for conditional deletion of *Slc4a4* transcripts in any tissue. The targeted exon is 134 nucleotides in length, begins with the codons for the amino acid sequence GVLESFLGT and ends with the codons for the amino acid sequence FERLLFNFS. Because it also contains two nucleotides of the next codon, deletion of this exon causes any transcripts that might be produced to go out of frame, thus eliminating all codons following that for amino acid 499, which include sequences that encode the transmembrane domains necessary for ion transport.

To prepare the targeting construct, LoxP sites were inserted at the ends of a 1.2 kb genomic DNA fragment containing exon 12. The proximal LoxP site was 709 nucleotides upstream of exon 12, and the distal LoxP site was 393 nucleotides downstream of exon 12. A neomycin resistance gene (neo), which allowed for positive selection of ES cells, was inserted just inside the distal LoxP site and was flanked by flippase recognition target (FRT) sites, which allowed its removal at a later step. The 5′ arm of the targeting construct was a 3.4 kb fragment from sequences in intron 11 that immediately preceded the insertion site of the proximal LoxP site, and the 3′ arm was a 2.3 kb fragment from intron 12 that immediately followed the insertion site of the distal LoxP site. Each of the genomic fragments used to prepare the construct were amplified by polymerase chain reaction (PCR) from mouse genomic DNA. A thymidine kinase gene was included after the 3′ arm in order to allow negative selection of ES cells. The targeting construct was electroporated into ES cells derived from 129/SvJ mice and targeted ES cells were identified by long-range PCR and used to generate chimeric mice. When germline transmission of the targeted allele was achieved, the mice were bred with C57Bl6 mice expressing FLP recombinase to remove the Neo gene. For cardiac myocyte-specific deletion of *Slc4a4* exon 12, the mice were bred with a C57Bl6 mouse carrying the Cre recombinase gene driven by the β-myosin promoter, which is an effective strategy for Cre-mediated recombination beginning during embryonic development in cardiac myocytes[19].

All procedures using animals conformed to guidelines published by the National Institutes of Health (Guide for the Care and Use of Laboratory Animals) and were approved by the Institutional Animal Care and Use Committee at the University of Cincinnati. Mice were used in this study, as it is the best mammalian model for preparing genetic modifications and appropriate techniques are available for analysis of cardiovascular performance and response to *in vivo* IR injury. All appropriate measures were taken to minimize pain or discomfort. Mice were maintained in a specific pathogen free, temperature controlled barrier facility, with a 12 h light-dark cycle, and access to food and water ad libitum.

Genotype analysis

PCR genotyping of mice carrying the floxed allele was performed using DNA from tail biopsies and the following primers: Forward primer: 5′-TGGTGGC TTAAATTGCAAATGGC-3′; Reverse primer: 5′-CATAAC CCACTAAGTCCAGTACG-3′. These primers flank the proximal LoxP site and yield a 176-base pair PCR product for the wild-type *Slc4a4* allele, and a 223-base pair PCR product for the floxed allele, with the increase in size being due to the LoxP site. An additional PCR reaction was performed to determine the presence or absence of the *Cre* transgene.

Quantitative PCR analysis of the degree of knockdown of functional NBCe1 mRNA

To determine the degree of knockdown of NBCe1 mRNA

in KO (*Slc4a4*$^{flx/flx(Cre)}$) relative to WT (*Slc4a4*$^{flx/flx}$) hearts, quantitative reverse transcriptase-PCR analysis (qRT-PCR) was performed using an ABI 7300 Real Time PCR system as described previously[7]. cDNA was prepared from mRNA isolated from whole heart of 4 mo old male mice (n = 6 for each genotype) and was PCR amplified using a forward primer (5'-TTCAGGCTCTCTCTGCGATT-3') from coding exon 11 and reverse primer from coding exon 12 (5'-CTCAAGATGGTAAGCGGTTGA-3').

Analysis of left ventricular function and blood pressure

Cardiovascular performance was determined using intraventricular and intra-arterial pressure measurements as described previously[20,21]. The mice (2-3 mo old; n = 4 male and 4 female *Slc4a4*$^{flx/flx}$ and 8 *Slc4a4*$^{flx/flx(Cre)}$) were anesthetized with a mixture of ketamine and inactin, surgically instrumented, and their body temperatures maintained using a thermally controlled surgical stage. A high fidelity pressure transducer (Millar Instruments, Houston, TX) was introduced into the left ventricle through the right carotid artery to measure left ventricular pressure, and blood pressure was recorded *via* a fluid filled catheter in the right femoral artery. A catheter in the right femoral vein was used for infusion of dobutamine, a β-adrenergic agonist.

RNA Seq analysis

Total RNA was isolated from whole hearts of 4 mo old male *Slc4a4*$^{flx/flx}$ and *Slc4a4*$^{flx/flx(Cre)}$ mice (n = 6 of each genotype). RNA Seq analysis was performed in the University of Cincinnati Genomics and Sequencing Core using the Illumina HiSeq 1000 platform, and sequence reads were aligned to the reference mouse genome using TopHat aligner[22]. Statistical analysis was performed using the negative-binomial model of read counts as carried out in the DeSeq Bioconductor package[23]. mRNA expression data are presented as Reads Per Kilobase per Million mapped reads (RPKM), which normalizes for the size of the mRNA and allows direct comparisons of transcript abundance.

Gene Ontology analysis

For Gene Ontology (GO) analyses, we used the GOrilla program[24] (http://cbl-gorilla.cs.technion.ac.il/). As discussed previously[7,25], two analysis options are available: (1) Two Unranked Lists, in which a target list of genes with a specific range of P values is compared against the list of all genes analyzed; and (2) a Single Rank List, with the entire gene set ranked according to P values, thereby avoiding the use of an arbitrary cutoff of P values. Both analyses were performed. However, because of the low number of genes with highly significant changes, we relied primarily on the Two List analysis, in which significance and enrichment are calculated based on the number of genes in each GO category that appear in the target list and background list. Enrichment is defined as = (b/n)/(B/N), where b is the number of genes in the intersection, n is the number of genes in the top of the user's input list or in the target set when appropriate, B is the total number of genes associated with a specific GO term, and N is the total number of genes. The program calculates statistical probabilities using the hypergeometric distribution[24]. In addition to a P value, the program provides an FDR q-value, which considers the total number of GO categories and corrects for the false discovery rate (FDR).

In vivo myocardial ischemia-reperfusion injury

Surgery to induce IR injury was performed on 4-5 mo old male mice (n = 4 for each genotype) as described previously[26]. Mice were anesthetized with ketamine-inactin and were mechanically ventilated using a rodent ventilator (Model 845, Harvard Apparatus) connected to an endotracheal tube. The heart was exposed by a left side limited thoracotomy and a 6-0 silk suture was passed beneath the left anterior descending artery (LAD) with a tapered needle[26]. A loose double knot was made with the suture and a 5 mm long piece of PE-10 tubing was placed through the loop. The loop was tightened around the artery and tubing to occlude blood flow. After 30 min, the knot was untied and the tubing was removed. The chest cavity was closed with continuous 4-0 silk sutures and the heart was reperfused for 3 h. The mice were euthanized and the chest cavity was opened to isolate the heart. The aorta was cannulated and perfused initially with PBS containing Heparin (10 units Heparin per ml) followed by a modified Krebs-Henseleit buffer (pH 7.4) containing 110 mmol/L NaCl, 16 mmol/L KCl, 16 mmol/L $MgCl_2$, 1.2 mmol/L $CaCl_2$, and 10 mmol/L $NaHCO_3$. Finally, the isolated heart was perfused with 10% buffered formalin and left in 10% buffered formalin for 48 h. The left ventricle was embedded in paraffin and sectioned, with great care taken to identify the exact location of the sections relative to the LAD occlusion site.

TUNEL assay

Cardiomyocyte death by apoptosis in hearts from mice subjected to IR injury (described above) was analyzed using the In Situ Cell Death Detection Kit, TMR red from Roche. Sections that were carefully oriented relative to the occlusion site were deparaffinized, hydrated and pretreated with proteinase K (20 μg/mL in 10 mmol/L tris/HCl, pH 7.4) for 30 min at 37 ℃. The sections were then incubated with the TUNEL mixture for 60 min at 37 ℃. The sections were rinsed with PBS and counterstained with 1:200 dilution of α-Sarcomeric actin antibody (Sigma, A2172) for 60 min at 37 ℃. The section was then rinsed and stained with 1:200 dilution of Fluorescein (FITC) anti-mouse secondary antibody (Jackson Immunoresearch, 115-095-146) for 60 min at 37 ℃. The sections were mounted with ProLong gold antifade mountant with DAPI from Life technologies. Images were taken under 40 × objective on a Olympus BX41 microscope equipped with a digital camera and MagnaFireTM software.

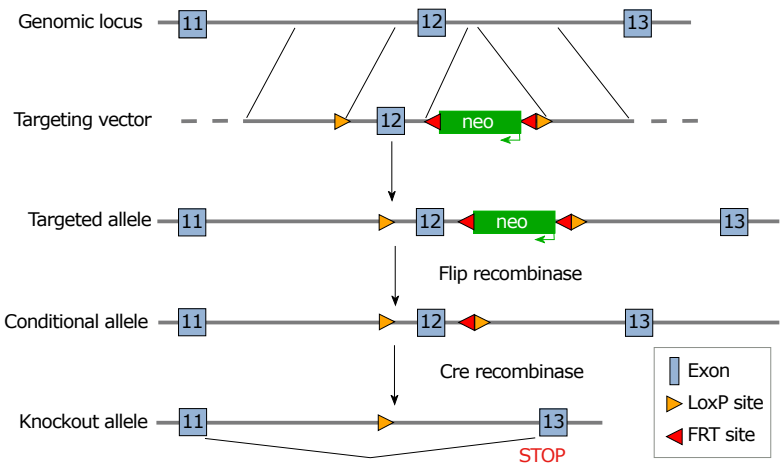

Figure 1 Targeting strategy for generation of *Slc4a4* cardiac myocyte conditional KO mice. The targeting construct contained the neomycin resistance gene (neo) to allow selection of ES cells after homologous recombination. The neo gene was flanked with flippase recognition target (FRT) sites, which allowed removal of neo when mice carrying the targeted allele were bred with transgenic mice expressing Flip recombinase. After confirming the deletion of neo, mice carrying the floxed allele were bred with mice expressing Cre recombinase controlled by the β-MHC promoter, which mediates the deletion of exon 12 of *Slc4a4* in cardiac myocytes.

Statistical analysis

Values are presented as means ± SEM. Individual comparisons were made using a two-tailed Student's *t*-test, and a *P* value < 0.05 was considered significant. For group comparisons, a mixed factor analysis of variance with repeated measures on the second factor was used. Statistical analyses of RNA Seq data and GO data are described in the respective sections above. Statistical methods were reviewed by coauthor Dr. Mario Medvedovic, Director of the Division of Biostatistics and Bioinformatics in the Department of Environmental Health.

RESULTS

Generation of a mouse model with cardiomyocyte-specific deletion of NBCe1 mRNA

A targeting construct in which coding exon 12 of the *Slc4a4* gene was flanked with LoxP sites was prepared (Figure 1) and electroporated into ES cells, which were then subjected to a positive-negative selection procedure. Cells carrying the floxed allele were injected into blastocyts and used to generate chimeric animals. After achieving germline transmission of the targeted allele, the neo gene was deleted by breeding the mice with a transgenic mouse expressing Flip recombinase.

To delete *Slc4a4* in cardiac myocytes, the *Slc4a4*$^{flx/flx}$ mouse was crossed with a transgenic mouse expressing Cre recombinase driven by the β-myosin heavy chain (β-MHC) promoter[19] to obtain *Slc4a4*$^{flx/+(Cre)}$ and *Slc4a4*$^{flx/+}$ mice. Further breeding was performed to obtain *Slc4a4*$^{flx/flx(Cre)}$ (KO) and *Slc4a4*$^{flx/flx}$ (WT) mice, which were mated to obtain experimental pairs. This allowed mice of both genotypes being used for experiments to be housed in the same cages, with sibling pairs often used for experiments. Male and female KO mice appeared normal, and WT and KO mice were indistinguishable in body weight, appearance, and behavior. Also, there was no significant difference in the heart weight: body weight ratios (WT: 4.38 ± 0.15 mg/g; KO: 4.56 ± 0.11 mg/g; *n* = 4 male and 4 female of each genotype at 4 mo of age).

Genotypes were determined by PCR analysis of tail DNA, which yielded a 176-base pair product for the WT allele and a 223-base pair product for the floxed allele (Figure 2A); a separate reaction was performed to test for the presence or absence of the Cre gene. The knockdown of *Slc4a4* mRNA in the heart was confirmed by qRT-PCR analysis of whole heart mRNA using primers from coding exons 11 and 12. This allowed a quantitative assessment of the percentage of NBCe1 transcripts that lack coding exon 12. Loss of this exon causes the sequences following codon 499, which encode most of the transmembrane domains, to be out of frame. As shown in Figure 2B, the amount of NBCe1 mRNA containing exon 12 was reduced by approximately 70% in whole hearts of *Slc4a4*$^{flx/flx(Cre)}$ mice relative to those of *Slc4a4*$^{flx/flx}$ mice. It should be noted that expression of NBCe1 is not restricted to cardiac myocytes, and has been shown to be expressed in both vascular and nerve tissues[27]. Thus, the reduction in functional NBCe1 mRNA in cardiac myocytes is likely to be greater than that indicated by qRT-PCR analysis of whole heart mRNA.

Cardiovascular performance in NBCe1 KO and WT mice under basal conditions and in response to β-adrenergic stimulation

Cardiovascular performance *in vivo* was analyzed under basal conditions and in response to β-adrenergic stimulation using dobutamine. Anesthetized and surgically instrumented mice were analyzed using a pressure transducer in the left ventricle to measure intraventricular pressures and a catheter in the right femoral artery to measure blood pressure and heart rate. There was no difference in heart rate (HR),

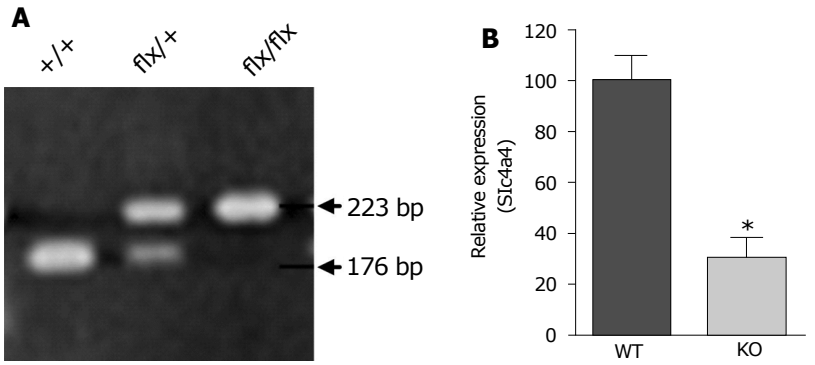

Figure 2 Polymerase chain reaction genotyping and quantitative reverse transcriptase-polymerase chain reaction of NBCe1 mRNA. A: PCR analysis of DNA from tail biopsies, using primers flanking the proximal LoxP site, showing bands for the alleles in *Slc4a4*$^{+/+}$, *Slc4a4*$^{flx/+}$ and *Slc4a4*$^{flx/flx}$ mice. The larger size of the band for the floxed allele is due to the presence of the LoxP site; B: Quantitative RT-PCR analysis of cDNA prepared from whole heart RNA (n = 6 for each genotype) showing a reduction of Slc4a4 mRNA in hearts of KO (*Slc4a4*$^{flx/flx(Cre)}$) relative to WT (*Slc4a4*$^{flx/flx}$ without *Cre*) mice. PCR: Polymerase chain reaction.

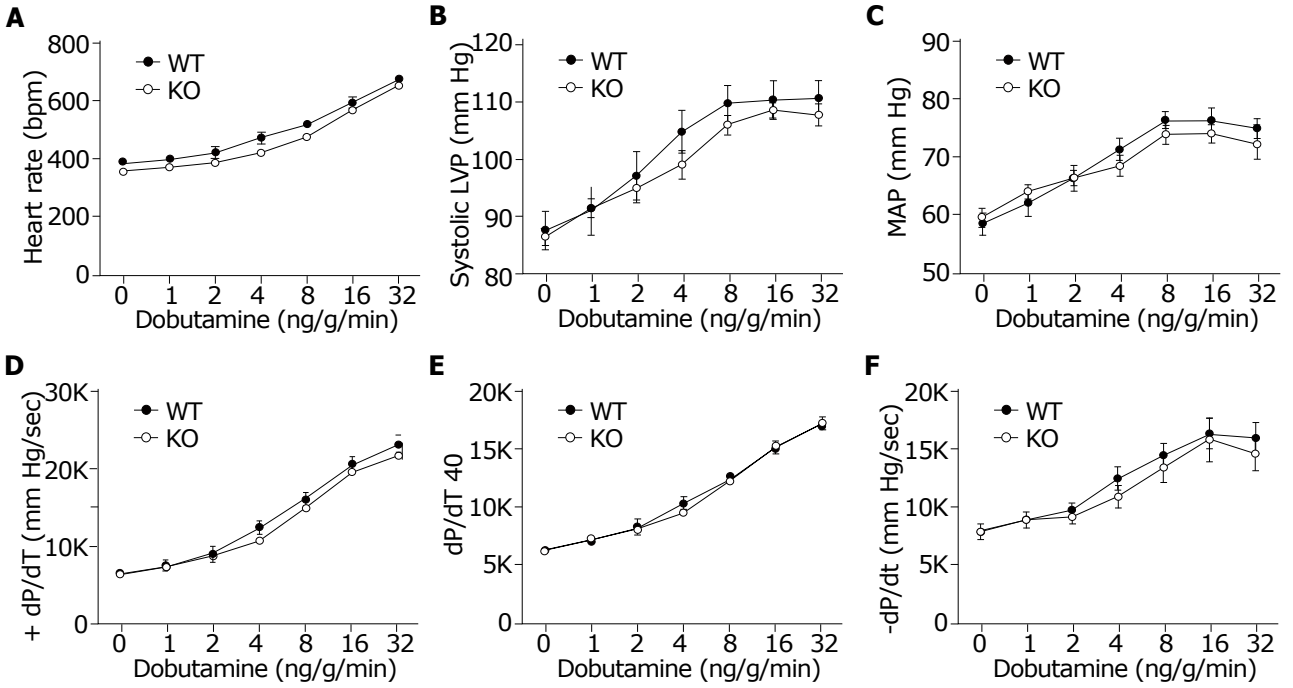

Figure 3 Cardiovascular performance in WT and KO mice. Intraventricular and intra-arterial pressure measurements were recorded using transducers in the left ventricle and right femoral artery of anesthetized 2-3 mo old WT (*Slc4a4*$^{flx/flx}$) and KO (*Slc4a4*$^{flx/flx(Cre)}$) mice under both basal conditions and in response to β-adrenergic stimulation (intravenous infusion of increasing doses of dobutamine). A: Heart rate; B: Systolic left ventricular pressure; C: Mean arterial pressure; D: Positive dP/dt in mm Hg/sec; E: Positive dP/dt at 40 mm Hg; F: Negative dP/dt in mm Hg/sec is shown for WT and KO mice. n = 8 WT (4 female, 4 male) and 8 KO (4 female, 4 male) mice.

systolic ventricular pressure, or mean arterial pressure (Figure 3A, 3B and 3C) between WT (*Slc4a4*$^{flx/flx}$) and KO (*Slc4a4*$^{flx/flx(Cre)}$) mice under basal conditions or in response to β-adrenergic stimulation. Left ventricular contractility (+dP/dT and +dP/dt$_{40}$) and relaxation (-dP/dt) (Figure 3D, 3E and 3F) were essentially the same in WT and KO mice, indicating normal cardiac function in NBCe1-deficient mice.

RNA sequencing of mRNA from NBCe1 KO and WT hearts

To identify patterns of differential gene expression changes in response to the loss of NBCe1 in cardiac myocytes, we performed RNA Seq analysis using mRNA from hearts of WT and KO mice. Between WT and KO hearts, there were 452 differentially expressed genes with $P < 0.05$. However, only a few of these genes had a highly significant FDR value. Many of the genes that fell within the range of $P < 0.05$ were expressed at very low levels or were absent in some samples. The genes that were expressed at low levels included sixteen major urinary proteins (Mups) and six cytochrome P450s, which were sharply induced in the KO. After removal of those genes with very low expression, the remaining 347 genes were subjected to GO analyses.

Because it has been proposed that the electrogenic

Table 1 Enriched Gene Ontology categories in NBCe1 cardiac conditional KO mice

GO category	*P*-value	Q-value	Enrichment	(N, B, n, b)
GO categories dealing with ion homeostasis				
GO:0006873 Cellular ion homeostasis	1.13E-4	5.68E-1	2.45	(21545, 579, 334, 22)
GO:0051453 Regulation of intracellular pH	1.92E-4	5.80E-1	5.86	(21545, 77, 334, 7)
GO:0030003 Cellular cation homeostasis	2.12E-4	4.58E-1	2.4	(21545, 564, 334, 21)
GO categories dealing with apoptosis				
GO:0043652 Engulfment of apoptotic cell	4.09E-4	4.42E-1	19.35	(21545, 10, 334, 3)
GO:1901030 Mitochondrial membrane permeabilization involved in apoptotic signaling	4.09E-4	4.12E-1	19.35	(21545, 10, 334, 3)
GO categories dealing with membrane compartments				
GO:0005783 Endoplasmic reticulum	2.82E-6	1.06E-3	2.03	(21545, 1493, 334, 47)
GO:0030315 T-tubule	3.45E-5	7.18E-3	7.65	(21545, 59, 334, 7)
GO:0016529 Sarcoplasmic reticulum	3.00E-4	3.30E-2	6.56	(21545, 59, 334, 6)
GO:0042383 Sarcolemma	4.84E-4	4.77E-2	4.41	(21545, 117, 334, 8)

GO categories were identified using the Two unranked list option of the GOrilla Gene Ontology program[24]. N is the total number of genes, B is the total number of genes associated with a specific GO term, n is the number of genes in the target set, b is the number of genes in the intersection. Enrichment = (b/n)/(B/N). Differential mRNA expression data were generated by RNA Seq analysis of hearts from 6 adult male mice for the NBCe1 KO (*Slc4a4*$^{flx/flx(Cre)}$) and NBCe1 WT (*Slc4a4*$^{flx/flx}$) genotypes.

activity of NBCe1 and its expression in t-tubules is likely to affect electrical activity of cardiac myocytes[1], we anticipated that there might be changes in genes involved in membrane excitability and cardiac conduction. In addition, because it has been suggested that NBCe1 activity can serve as a major mechanism for Na^+-loading, with subsequent effects on Ca^{2+}-handling and contractility[4,8], we were interested in whether the loss of NBCe1 might affect expression of genes encoding myofibrillar proteins, Ca^{2+}-handling proteins, and proteins that affect Na^+-loading.

As shown in Table 1, changes in Biological Function GO categories for cellular ion homeostasis, including subcategories for intracellular pH and cation homeostasis, were indicated, but the changes were modest and their statistical significance was poor (low FDR). Two Biological Function GO categories relating to apoptosis were identified, and their statistical significance was poor. However, when GO analysis was run using the single rank option for GOrilla GO analysis (see materials and methods), additional genes were identified for GO:0043652 (Engulfment of Apoptotic Cell) and an acceptable FDR value for this GO category was attained. There were no significant Molecular Function GO categories, but among Cellular Component GO categories there were a number dealing with membrane compartments (Table 1). These included GO categories for the endoplasmic and sarcoplasmic reticulum, t-tubules, and sarcolemma.

Genes for channels, pumps, and transporters that exhibited differential expression are shown in Table 2. Among K^+ channels, modest upregulation of *Kcnj2* and *Kcnj11* (both in the t-tubule GO category) was observed along with higher upregulation of *Kcna4* (K_v1.4; 1.50-fold increase), which is expressed in t-tubules and sarcolemma[28], and *Kcnk2* (TREK-1; 1.65x), which is expressed in intercalated discs[29]. Among Ca^{2+} channels, *Cacna1s* (Cav1.1; L-type α1S) was upregulated and *Cacnb1* (a beta subunit) was downregulated. Both Ca^{2+} channel subunits are in the t-tubule. However, they are major components of the skeletal muscle Ca^{2+} channel and are expressed at much lower levels in heart. The only other gene for a Ca^{2+}-handling protein that was changed was *Atp2a1*, the skeletal muscle sarcoplasmic reticulum (SR) Ca^{2+} pump, which is expressed at very low levels in heart.

Slc9a1 mRNA, encoding the NHE1 Na^+/H^+ exchanger, was slightly upregulated, and *Slc9a9*, an organellar Na^+/H^+ exchanger, was also upregulated. Other H^+-coupled transporters with altered expression (Table 2) were transporters for peptides (*Slc15a1, Slc15a2*), amino acids (*Slc36a1*), and lactate (*Slc16a3*). Additional transporters included two amino acid transporters (*Slc1a5 and Slc7a1*), an iron transporter (*Slc40a1*), and a zinc transporter (*Slc39a13*). The expression of NBCn1 (*Slc4a7*), the only other Na^+-HCO_3^- cotransporter expressed in heart, was not significantly changed (RPKM values: 6.67 ± 0.42 in WT; 6.99 ± 0.15 in KO).

Differentially expressed genes for proteins involved in apoptosis are shown in Table 3. Some of these were identified because of their inclusion in the apoptosis GO categories shown in Table 1 (*Xkr8*, *Rac3*, *Thbs1*, *Zfp13*, *Sh3glb1*, and *Siva1*). Others were identified based on literature searches and a P value ⩽ 0.01 (*Msrb3*, *Xlrl*, *Ier5*, *Hint1*, *and Stmn1*).

Reduced apoptosis in NBCe1 KO hearts in response to in vivo ischemia-reperfusion

To determine whether ablation of NBCe1 would provide protection against IR injury, WT and KO hearts were subjected to 30 min of ischemia by temporary ligation of the left anterior descending (LAD) artery, followed by 3 h of reperfusion. TUNEL staining was performed to detect apoptotic cell death and to quantify apoptotic nuclei in WT and KO heart sections. Apoptotic nuclei were detected primarily in the left ventricular free wall in both WT and KO heart sections (Figure 4A). However, there were significantly fewer apoptotic nuclei (Figure

Table 2 Ion channel and transporter genes altered in NBCe1-null hearts

Gene symbol	Description	Fold change	*P* value
Kcnj2	Inwardly-rectifying K^+ channel J2	1.18	0.02
Kcnj11	Inwardly-rectifying K^+ channel J11	1.14	0.03
Kcnk2	K^+ channel K2; TREK-1	1.65	0
Kcna4	K^+ channel, shaker-related 4; Kv1.4	1.50	0.05
Cacna1s	L type Ca^{2+} channel, alpha 1S subunit	1.44	0
Cacnb1	Ca^{2+} channel, beta 1 subunit	0.51	0
Atp2a1	Skeletal muscle SR Ca^{2+} pump	1.82	0.04
Slc9a1	Sarcolemmal Na^+/H^+ Exchanger	1.18	0.05
Slc9a9	Organellar Na^+/H^+ Exchanger	1.44	0.03
Slc16a3	Monocarboxylic acid transporter,	1.92	0.04
Slc1a5	Neutral amino acid transporter	0.81	0.04
Slc7a1	Cationic amino acid transporter, y+ system	1.24	0
Slc15a2	Proton/peptide transporter	1.87	0.01
Slc15a1	Oligopeptide transporter	0.56	0.03
Slc40a1	Iron transporter; ferroportin	0.86	0.02
Slc39a13	Zinc transporter	1.23	0.03
Slc36a1	Proton/amino acid symporter	0.83	0.05

Differential mRNA expression is presented as fold-changes in NBCe1-null hearts ($Slc4a4^{flx/flx(Cre)}$) relative to WT ($Slc4a4^{flx/flx}$) hearts.

Table 3 Differential expression of apoptosis genes in NBCe1-null hearts

Gene symbol	Description	Fold change	*P* value
Xkr8	X Kell Blood Group Precursor Related 8	0.61	0.015
Rac3	RAS-Related C3 Botulinum Substrate 3	0.36	0.016
Thbs1	Thrombospondin 1	0.79	0.020
Zfp13	Zinc Finger Protein 13	0.46	0.023
Sh3glb1	SH3-Domain GRB2-like B1 (Endophilin)	1.13	0.024
Siva1	SIVA1, Apoptosis-Inducing Factor	0.66	0.030
Msrb3	Methionine Sulfoxide Reductase B3	1.19	0.002
Xlrl	Xlr-like	1.77	0.003
Ier5	Immediate Early Response 5	0.80	0.005
Hint1	Histidine Triad Nucleotide Binding Protein 1	0.84	0.010
Stmn1	Stathmin 1	1.37	0.010

Differential mRNA expression is presented as fold-changes in NBCe1-null hearts ($Slc4a4^{flx/flx(Cre)}$) relative to WT ($Slc4a4^{flx/flx}$) hearts. The first six genes on this list were identified based on inclusion in the two apoptosis GO categories identified in Table 1.

4B) in KO (40.6 ± 6.4 apoptotic nuclei per mm^2) than in WT (142.0 ± 13.6 apoptotic nuclei per mm^2) heart sections.

DISCUSSION

On the basis of functional studies and expression data it is clear that NBCe1 serves as a major uptake mechanism for both Na^+ and HCO_3^- in cardiac myocytes[1,4]. Na^+-loading can affect both cardiac contractility and response to IR injury[4,8,15,16], and there is evidence that HCO_3^- has a major effect on contractility, both in isolated myocytes[5] and in the isolated work-performing heart[30]. Also, because NBCe1 is electrogenic and expressed in t-tubules, lateral sarcolemma, and intercalated discs[1], it has the potential to affect membrane potential and electrical activity of the myocyte. To begin testing the cardiovascular functions of NBCe1 we developed a mouse model carrying a floxed allele for NBCe1 and analyzed the effects of cardiomyocyte-specific ablation on cardiovascular performance and *in vivo* IR injury. In addition, we performed RNA Seq analysis to determine whether remodeling of cardiac systems occurs at the level of mRNA expression patterns in response to the loss of NBCe1.

The loss of NBCe1 did not impair cardiovascular performance, and heart weights did not differ between the two genotypes. NBCe1 mutant mice exhibited normal heart rates, blood pressures, and basal contraction and relaxation, and when they were treated with a β-adrenergic agonist, they exhibited normal increases in contraction and relaxation. The lack of any apparent detrimental effects supports the notion that inhibition of cardiac NBCe1 activity could be used for cardioprotection. These results also suggest that uptake of HCO_3^- by NBCe1 is not required for the stimulation of contraction observed in isolated myocytes and hearts in the presence of HCO_3^-[5,30], although it is possible that the high rate of HCO_3^- production from metabolically produced CO_2 *in vivo* prevents any deficit in intracellular HCO_3^- levels. Alternatively, reduced HCO_3^--efflux *via* Cl^-/HCO_3^- exchange or increased uptake *via* NBCn1 may be sufficient to maintain intracellular HCO_3^- homeostasis *in vivo* when NBCe1 was ablated. Also,

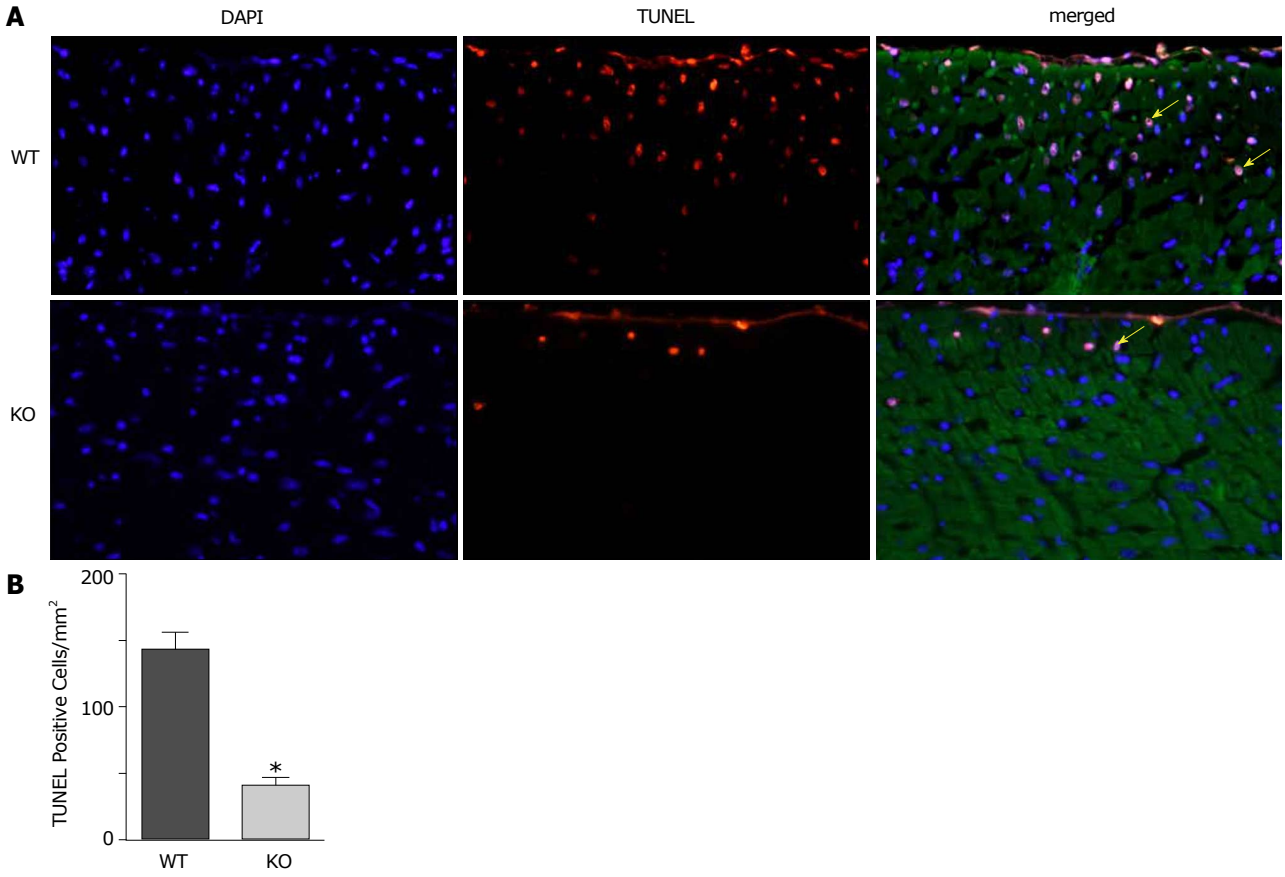

Figure 4 TUNEL staining to quantify apoptosis in WT and KO heart sections after ischemia and reperfusion. Mice were subjected to 30 min of ischemia by occlusion of the LAD, followed by 3 h of reperfusion, and heart sections were processed to analyze apoptosis. A: Representative images from WT and KO heart sections, taken from a region approximately 1 mm distal to the occlusion site, showing nuclei stained with DAPI (blue), TUNEL (red) and sarcomeric actin (green). Yellow arrows point to apoptotic nuclei (pink); B: Quantification of apoptotic nuclei. n = 4 mice of each genotype, $P \leqslant 0.05$.

the NHE1 Na^+/H^+ exchanger was slightly upregulated at the mRNA level and provides a powerful alternative mechanism of Na^+-loading and pH_i regulation. It should be noted that genetic ablation of NHE1 also caused no impairment of cardiovascular performance[31], and it had beneficial effects on cardiac energy metabolism, including increased glucose utilization and metabolic flexibility[31]. Interestingly, NBCe1 activity is involved in acute stimulation of glycolysis in astrocytes in response to membrane depolarization[32]. Thus, one could speculate that the increased glucose utilization observed in hearts of NHE1-null mice[31] might be due in part to a compensatory increase in NBCe1 activity.

Because they have opposing activities with respect to HCO_3^- fluxes, it is of interest to compare the results of ablating NBCe1, the predominant HCO_3^--uptake mechanism in heart, with the results of ablating the AE3 (*Slc4a3*) Cl^-/HCO_3^- exchanger. Both the very high mRNA expression levels of AE3[7] and its predominant role in recovery of myocytes from an alkaline load[33] demonstrate that it is the predominant HCO_3^--extrusion mechanism in the heart. In humans, heterozygous mutations in AE3 contribute to heart disease[34]. In mice, the loss of AE3 caused a mild impairment of force-frequency responses[35] and exacerbated heart disease caused by other genetic defects[21,36]. However, AE3-null mice exhibited normal cardiac contraction and relaxation under both basal conditions and after β-adrenergic stimulation[33]. Nevertheless, RNA Seq analysis indicated that AE3-null hearts undergo major remodeling of cardiac gene expression patterns involved in hypoxia responses and angiogenesis, energy metabolism, sarcomere function, and membrane excitability and electrical conduction[7].

Unlike the results of the AE3 RNA Seq study, RNA Seq analysis of NBCe1-null hearts revealed little evidence of cardiac remodeling at the mRNA level. For example, altered expression of genes involved in sarcomere function were very prominent in AE3 null-hearts[7], but no such changes were observed in NBCe1-null hearts, which is consistent with the normal contractility and β-adrenergic responses. Similarly, changes in energy metabolism genes were extensive in AE3-null hearts, but were not observed in NBCe1-null hearts, despite the known stimulatory effect of NBCe1 activity on glycolysis in astrocytes[32]. We also observed no changes in hypoxia response and angiogenesis genes, which were prominent in AE3-null hearts. However, there were several interesting changes related to membrane excitability.

One of the predictions by other investigators[1] was that the electrogenic activity of NBCe1 in the sarcolemma, t-tubules, and intercalated discs, with inward transport of one Na^+ and two HCO_3^- ions during depolarization, would affect membrane excitability. The changes in genes involved in membrane excitability and electrical conduction were extensive in AE3-null hearts, and included voltage-sensitive Na^+, K^+, and Ca^{2+} channels, and gap junction proteins involved in electrical coupling between myocytes. Few such changes were observed in NBCe1-null hearts. However, a number of K^+ channel genes were upregulated. These included *Kcna4*, encoding Kv1.4, and *Kcnk2*, encoding TREK-1. Kv1.4 is co-expressed with NBCe1 in t-tubules and the sarcolemma[28]. It mediates transient outward currents during the initial phase of depolarization[37] and might therefore counteract the lengthening of the action potential expected with a reduction in NBCe1 activity[38]. TREK-1 is expressed in intercalated discs[29] and plays an important role in regulating excitability of the sinoatrial node[39]. Thus, increased expression and activity of TREK-1 has the potential to counteract the electrical effects of the loss of NBCe1 activity in intercalated discs.

Although there were changes in two voltagesensitive Ca^{2+} channel subunits in t-tubules (*Cacna1s*, an α subunit expressed at low levels; *Cacnb1*, a β subunit, expressed at very low levels), both are primarily skeletal muscle isoforms. In contrast, *Cacna1c*, which encodes the major L-type Ca^{2+} channel in cardiac muscle (Cav1.2), was not changed (RPKM values: 26.8 ± 0.8 in WT; 26.2 ± 0.6 in KO). The only other gene for a Ca^{2+}-handling protein that was changed was *Atp2a1*, the skeletal muscle sarcoplasmic reticulum Ca^{2+} pump. However, *Atp2a1* is expressed at exceedingly low levels in heart (< 1 RPKM in WT), whereas *Atp2a2*, the cardiac Ca^{2+} pump was expressed at very high levels and was not changed (RPKM values: 2185 ± 47 in WT; 2183 ± 23 in KO). The major Na^+/Ca^{2+} exchanger (NCX1, *Slc8a1*) also was not significantly changed (RPKM values: 25.0 ± 0.6 in WT; 27.3 ± 0.7 in KO). These data provide little support for remodeling of Ca^{2+}-handling systems at the mRNA level.

A major objective was to determine whether genetic ablation of NBCe1 is cardioprotective during IR injury. The role of NHE1 in cardiac IR injury has been extensively studied using both inhibitors and genetic approaches[9-14], and it is generally accepted that the mechanism of protection involves reductions in Na^+-loading, Ca^{2+}-loading, and the rate of pH_i recovery during reperfusion. Since NBCe1, like NHE1, mediates both Na^+-loading and recovery from an acid load[40], a number of investigators have noted that NBCe1 activity could potentially contribute to IR injury. In fact, two groups have shown that inhibition of NBCe1 during reperfusion of mouse or rat hearts that were subjected to ischemia provides some protection against IR injury[15,16]. These results using isolated heart preparations support a role for NBCe1 in IR injury that is similar to that of NHE1 and indicate that a reduction in its activity can be cardioprotective.

Previous studies have shown that apoptotic cell death occurs mainly during reperfusion of ischemic tissue[41-43]. An increase in intracellular Ca^{2+} results in opening of the mitochondrial permeability transition pore[44], which then leads to apoptosis. In the current study, after WT and KO mice were subjected to 30 min of LAD occlusion and 3 h of reperfusion, apoptotic cell death and apoptotic nuclei were detected and quantified in heart sections taken from just below the point of occlusion. The significant reduction in the numbers of apoptotic nuclei in NBCe1 KO hearts following cardiac IR injury *in vivo* indicates that reduced NBCe1 activity is cardioprotective. Thus, both the studies using isolated hearts[15,16] and the current studies showing reduced apoptosis following *in vivo* IR injury support the hypothesis that a reduction in NBCe1 activity is cardioprotective. Given the severe effects of global NBCe1 ablation[18], only partial inhibition of NBCe1 is likely to be acceptable as part of a treatment strategy, however, it is possible that an NBCe1 inhibitor could be used in combination with other treatments.

As discussed above, the primary mechanism of NBCe1-mediated cardioprotection is likely to be the reductions in Na^+-loading, Ca^{2+}-loading, and the rate of pHi recovery during reperfusion. However, because a genetic ablation strategy was employed, rather than acute inhibition of NBCe1, it is possible that the long-term absence of NBCe1 has elicited remodeling that contributes to cardioprotection. This possibility is supported by the observation that genetic ablation of NHE1 reduces oxidative stress in the heart, high-fat diet-induced myocardial stress[31], and fatty liver disease[45], which are clear indications of long-term remodeling. A potentially interesting set of changes observed in the RNA Seq data were those involving genes with functions in apoptosis. The q-values for the apoptosis GO categories (Table 1) were not highly significant and these findings must therefore be considered with caution. Nevertheless, the observation provides suggestive evidence that ablation of the NBCe1 gene using the β-myosin promoter, which would be largely complete by birth, may cause changes in gene expression that tend to protect against apoptosis. For example, Siva1 (apoptosis-inducing factor) normally interacts with and inhibits Stathmin, thus promoting apoptosis[46,47]. Thus, down-regulation of Siva1 (0.66-fold, RPKM: 4.8 ± 0.3 in WT; 3.2 ± 0.2 in KO) and upregulation of Stathmin (1.37-fold, RPKM: 9.6 ± 0.5 in WT; 13.2 ± 1.2 in KO) would be expected to reduce apoptosis. Another interesting example is Xlrl, which was upregulated (1.77-fold, RPKM: 1.96 ± 0.34 in WT; 3.49 ± 0.17 in KO). Little is known about this gene, but Xlrl is almost identical to Xlr (95% amino acid identity and no gaps over their entire length of 208 amino acids), which protects against apoptosis[48]. Xlr was also upregulated (1.36-fold), but its levels of expression were lower.

The current study has a number of limitations. First, our mice were on a mixed 129/Svj and C57Bl6 background, rather than on a highly inbred background. The lack of a highly inbred background was likely

responsible for the relatively high variability in our RNA Seq data compared to the very low variability that we observed when performing RNA Seq analysis using mRNA from hearts of AE3-null and WT mice on a highly inbred background[7]. With much lower variability, it would have been possible to detect more subtle patterns of changes in gene expression. However, it was clear from the data that there were no extensive changes in gene expression patterns for sarcomeric or metabolic genes, and that the changes in ion channel genes were not extensive.

A second limitation is that the 30 min period of ischemia and 3 h of reperfusion were chosen to maximize our ability to detect apoptotic cell death, which plays a major role in ischemic injury. However, this protocol is not optimal for analysis of necrotic cell death, for detecting differences in cardiac function between WT and KO mice, or for detecting markers of myocardial infarction such as serum troponin levels. For such studies, a longer period of ischemia or a myocardial infarction model, with permanent occlusion of the LAD and long-term follow-up, would be necessary. In myocardial infarction studies it would also be useful to determine whether NBCe1 heterozygosity could provide some degree of cardioprotection, since any cardiac therapy using complete pharmacological inhibition of NBCe1 would have a severe impact on kidney function. Even limited cardioprotection caused by partial inhibition could be useful, however, as it might be possible to combine partial inhibition of NBCe1 with partial inhibition of the NHE1 Na^+/H^+ exchanger, which appear to act *via* similar mechanisms (see introduction).

An additional potential limitation was that our WT controls were *Slc4a4*$^{flx/flx}$ mice rather than *Slc4a4*$^{+/+(Cre+)}$ mice. A study published after we had performed our RNA Seq analysis reported that prolonged Cre expression driven by the α-myosin heavy chain promoter can be cardiotoxic[49]. However, we used a Cre transgene driven by the β-myosin promoter[19], which is expressed at much lower levels than the α-myosin promoter after birth. As an indication of cardiotoxicity, long-term expression of Cre via the α-myosin promoter caused approximately 7-fold increase in expression of atrial natriuretic factor mRNA and approximately 2.5-fold increase in expression of β-myosin mRNA[48]. However, these genes were not changed in the NBCe1 KO carrying Cre driven by the β-myosin promoter. Of greater relevance, 6 mo old mice expressing Cre *via* the α-myosin promoter exhibited an approximately 3-fold increase in apoptosis. In our own studies, however, only the NBCe1 cardiac-specific KO mice were carrying the Cre transgene, and they exhibited significantly less apoptosis than the *Slc4a4*$^{flox/flox}$ controls. These results clearly indicated a cardioprotective effect of NBCe1 ablation, despite the presence of Cre.

In summary, we have developed a conditional knockout mouse model for *Slc4a4* and have used it to test the effects of cardiac-specific ablation of NBCe1 in heart. The results show that loss of NBCe1 does not impair cardiovascular performance and that it significantly reduces the incidence of apoptosis following *in vivo* IR injury. These results are consistent with the results of previous studies using the isolated heart[15,16] and support the view that inhibition of NBCe1 during reperfusion has the potential to serve as a component of a cardioprotective treatment strategy.

ARTICLE HIGHLIGHTS

Research background

There is a strong rationale for the hypothesis that inhibition of NBCe1-mediated Na^+-HCO_3^- cotransport activity protects against cardiac ischemia-reperfusion injury. This suggests that inhibition of NBCe1 could become part of a cardioprotective strategy.

Research motivation

Previous studies have been performed using the isolated heart, but there are no *in vivo* studies supporting the hypothesis that loss of NBCe1 activity is cardioprotective. Such studies are critical if NBCe1 inhibition is to be developed as a therapeutic strategy.

Research objectives

The objective of this study was to test whether loss of NBCe1 in the heart would protect against cardiac ischemia-reperfusion injury *in vivo*.

Research methods

Gene targeting was used to develop a conditional knockout mouse model in which the NBCe1 gene was ablated in cardiomyocytes. Hemodynamic measurements were performed to assess the effects of cardiac-specific NBCe1 ablation on cardiovascular performance, RNA Seq analysis was used to study changes in the cardiac transcriptome, and histological techniques were used to analyze cardiomyocyte apoptosis in response to ischemia-reperfusion injury.

Research results

NBCe1 ablation did not impair cardiovascular performance and caused only limited changes in the cardiac transcriptome. However, it caused a significant reduction in apoptosis following *in vivo* cardiac ischemia-reperfusion injury.

Research conclusions

Loss of NBCe1 in heart does not cause any apparent adverse effects, but does have a cardioprotective effect following ischemia and reperfusion *in vivo*.

Research perspectives

Future studies should focus on whether NBCe1 ablation is cardioprotective following myocardial infarction and whether partial inhibition of NBCe1 can be combined with other treatments that reduce Na^+ and Ca^{2+} loading.

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ORIGINAL ARTICLE

Clinical Trials Study

Accuracy of myocardial viability imaging by cardiac MRI and PET depending on left ventricular function

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Abstract

AIM

To compare myocardial viability assessment accuracy of cardiac magnetic resonance imaging (CMR) compared to [^{18}F]-fluorodeoxyglucose (FDG)- positron emission tomography (PET) depending on left ventricular (LV) function.

METHODS

One-hundred-five patients with known obstructive coronary artery disease (CAD) and anticipated coronary revascularization were included in the study and examined by CMR on a 1.5T scanner. The CMR protocol consisted of cine-sequences for function analysis and late gadolinium enhancement (LGE) imaging for viability

assessment in 8 mm long and contiguous short axis slices. All patients underwent PET using [^{18}F]-FDG. Myocardial scars were rated in both CMR and PET on a segmental basis by a 4-point-scale: Score 1 = no LGE, normal FDG-uptake; score 2 = LGE enhancement < 50% of wall thickness, reduced FDG-uptake (⩾ 50% of maximum); score 3 = LGE ⩾ 50%, reduced FDG-uptake (< 50% of maximum); score 4 = transmural LGE, no FDG-uptake. Segments with score 1 and 2 were categorized "viable", scores 3 and 4 were categorized as "non-viable". Patients were divided into three groups based on LV function as determined by CMR: Ejection fraction (EF), < 30%: *n* = 45; EF: 30%-50%: *n* = 44; EF > 50%: *n* = 16). On a segmental basis, the accuracy of CMR in detecting myocardial scar was compared to PET in the total collective and in the three different patient groups.

RESULTS

CMR and PET data of all 105 patients were sufficient for evaluation and 5508 segments were compared in total. In all patients, CMR detected significantly more scars (score 2-4) than PET: 45% *vs* 40% of all segments (P < 0.0001). In the different LV function groups, CMR found more scar segments than PET in subjects with EF< 30% (55% *vs* 46%; P < 0.0001) and EF 30%-50% (44% *vs* 40%; P < 0.005). However, CMR revealed less scars than PET in patients with EF > 50% (15% *vs* 23%; P < 0.0001). In terms of functional improvement estimation, *i.e.*, expected improvement after revascularization, CMR identified "viable" segments (score 1 and 2) in 72% of segments across all groups, PET in 80% (P < 0.0001). Also in all LV function subgroups, CMR judged less segments viable than PET: EF < 30%, 66% *vs* 75%; EF = 30%-50%, 72% *vs* 80%; EF > 50%, 91% *vs* 94%.

CONCLUSION

CMR and PET reveal different diagnostic accuracy in myocardial viability assessment depending on LV function state. CMR, in general, is less optimistic in functional recovery prediction.

Key words: Magnetic resonance imaging; Positron-emission tomography; Myocardial infarction; Coronary artery disease; Myocardium; Ventricular dysfunction

Core tip: Both cardiac magnetic resonance imaging (CMR) and [^{18}F]-fluorodeoxyglucose-positron emission tomography (PET) are considered standard methods and reliable in myocardial viability imaging in coronary artery disease. However, CMR in general detects more scar and is, therefore, less optimistic in functional recovery prediction. Moreover, CMR and PET reveal different diagnostic accuracy depending on left ventricular (LV) function state: Particularly in severe and moderate LV function impairment, where revascularization is performed to improve function, CMR detects more scar and less viable myocardium - most probably due to higher spatial resolution. This aspect has not been reported, yet. Irrespective of LV function, PET might overestimate the improvement of regional and global function after revascularization.

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INTRODUCTION

Left ventricular (LV) dysfunction due to myocardial ischemia is one of the most common manifestations in chronic coronary artery disease (CAD), but does not necessarily represent non-viable, irreversibly injured tissue[1-4]. Although large multicenter studies such as the positron-emission-tomography (PET) and recovery following revascularization PARR-2 trial[5,6] or the surgical treatment for ischemic heart failure STICH-trial have been performed, even today there is no general consensus as to when assigning patients to either optimized medical treatment alone or to a combination of medical treatment plus revascularization procedures [(percutaneous coronary intervention or coronary artery bypass graft (CABG) surgery)][7-12]. Arriving at the optimal management strategy for these patients is a complex multifactorial process that includes not only viability but also processes such as ischemia and remodeling[4,7, 8,13-15].

Currently, several imaging modalities are used for the evaluation of myocardial viability, each of them assessing different myocardial features: *e.g.*, low-dose dobutamine stress echocardiography (DSE), nuclear techniques such as PET or single-photon-emission-computed-tomography (SPECT) as well as cardiac magnetic resonance imaging (CMR). Traditionally, nuclear techniques were regarded as gold standard for viability testing owing to their high sensitivity and negative predictive value (NPV) [*e.g.*, fluorodeoxyglucose (FDG)-PET 92% and 87%, respectively][7,12,16,17]. For this purpose mainly three tracers are used evaluating cell membrane integrity, perfusion and intact mitochondria ([^{201}Tl] thallium- or [^{99m}Tc] technetium-SPECT)[18] or maintained metabolism ([^{18}F] FDG-PET)[2].

With recent advances of the hard and software, especially the introduction of non-breath-hold sequences and arrhythmia rejection protocols[19,20], CMR has become a versatile alternative to nuclear imaging, coming along with an excellent spatial resolution[17]. While late gadolinium enhancement (LGE) allows visualization of the transmural extent of the scar by achieving signal intensity differences of nearly 500% between irreversibly injured and viable myocardium[14,18,21],

dobutamine stress CMR analyzes contractile reserve of dysfunctional myocardium similar to DSE[2,7]. Although the low specificity of LGE-CMR is well known, which is mainly attributable to the variable functional recovery in segments with LGE covering 25%-75% of the wall[1,14,22], its general high diagnostic accuracy for detecting myocardial scars has been proven in different studies[2,7,14,22-25]. However, so far, the value of CMR and PET has not been defined considering different LV function states. The aim of this study therefore was to evaluate the diagnostic accuracy of LGE-CMR viability assessment and PET and to compare them in patient groups with different LV functions.

MATERIALS AND METHODS

Study population

The local institutional review board (Ethics Committee of the Medical Faculty, University Essen) approved the study protocol and informed written consent has been given by all participants.

Within 30 mo, 105 patients (87 men, 18 women; mean age, 61 ± 11 years) with known obstructive CAD as proven by catheter coronary angiography and indication for CABG surgery were enrolled in the study. All of them underwent nuclear myocardial viability testing for clinical indication. After completion of the nuclear imaging contrast-enhanced CMR was performed; all imaging examinations took place within 6 ± 4 d before scheduled CABG surgery.

CMR: Study protocol

CMR scans were performed on a 1.5T scanner (Magnetom Sonata, Siemens Medical Solutions, Erlangen, Germany). Patients were examined in supine position. The spine array coil (two elements) and a body flex phased array coil (two elements) were combined for signal reception.

The CMR protocol consisted of a LV functional study by an electrocardiography (ECG)-triggered breath-hold segmented steady-state free precession (SSFP) cine sequence [repetition time (TR)/echo time (TE), 3.0/1.5 ms; flip angle, 60°; bandwidth, 975 Hertz per pixel]. Slice thickness was 8 mm. At first, three standard long axis views were acquired (four-chamber view, two-chamber view, LV three-chamber view); thereafter, the entire LV was covered by contiguous short axis slices without interslice gap. LGE images were acquired after administration of 0.2 mmol/kg bw Gadolinium-DTPA (Magnevist™, Bayer AG, Leverkusen, Germany) at a flow rate of 2 mL/s. Again, three long and all short axis slices were scanned utilizing an established ECG-triggered segmented 2D inversion-recovery gradient-recalled echo sequence (TR/TE, 8/4 ms; flip angle, 25°) during breath-hold[21]. LGE images were acquired 8 to 15 min after contrast media injection. To null the signal of normal myocardium the inversion time (TI, non-selective inversion pulse) had to be manually adjusted between 200 and 260 ms. The rectangular field-of-view (FOV) provided an in-plane resolution of 1.6 × 1.3 mm^2 for all sequences.

CMR: Image analysis

Two experienced radiologists, who were blinded to nuclear study results, analyzed all CMR data in a consensus reading. SSFP images were reviewed as cine-loops on an interactive workstation. LV volumetry was done using the ARGUS™ software (Siemens Medical Systems, Erlangen, Germany) by manual drawing of the endocardial contours on all short axes in end-diastolic and end-systolic phase including the papillary muscles to the LV lumen[26]. End-diastolic volumes (EDV) and end-systolic volumes (ESV) were measured by slice summation; ejection fraction (EF) was calculated using the equation: EF = (EDV - ESV)/EDV.

For quantification of myocardial viability, all short axis images were segmented using a 6-segment model. The LGE extent was assessed and quantified in each short axis segment by the 4-point scoring system given in Table 1. As recommended in the guidelines, a cutoff value of 50%-transmurality was set to discriminate myocardium with a chance to functionally recover after revascularization ("viable", score 1 and 2) from myocardium without beneficial functional prognosis ("non-viable", score 3 and 4)[15,27] .

Nuclear studies: Imaging protocol

The PET study was done under fasting conditions (at least 4 h) and after oral administration of two doses of acipimox 500 mg (Olbemox™, Pharmacia, Erlangen, Germany) and 75 g of glucose. Imaging was performed using a high-resolution PET camera (Siemens ECAT HR+, Erlangen, Germany). Forty minutes after intravenous application of [^{18}F]-FDG (370 MBq) PET data was acquired in a 2-dimensional fashion: (1) transmission scan (duration, 10 min) 60 min after injection; (2) emission scan (duration, 30 min). After attenuation and scatter correction the emission data was reconstructed in an iterative fashion (OSEM algorithm, 2 iterations, 32 subsets, Gauss filter FWHM 6 mm). Furthermore, the 2-dimensional data stack was reformatted into a 3-dimensional volume to create 8 mm long and short axis slices corresponding to the acquired MR data.

Nuclear studies: Image analysis

As with CMR data, myocardial FDG-uptake was evaluated using the same 4-point scale (Table 1) for each myocardial segment. Preserved or increased glucose utilization and subsequent FDG-uptake indicated cell survival, while reduced FDG-uptake defined myocardial scar.

Comparison and statistical analysis

For statistical analyses SPSS Statistics software (version 22, IBM Corp., Amonk, NY, United States) was

Table 1 Scoring system for evaluation of myocardial viability in cardiac magnetic resonance imaging and positron emission tomography

Score	CMR	PET
1	No enhancement	Normal FDG uptake
2	Enhancement < 50% of wall thickness	Reduced FDG uptake, ⩾ 50% of maximum
3	Enhancement ⩾ 50% of wall thickness	Reduced FDG uptake, < 50% of maximum
4	Transmural enhancement	No FDG uptake

Based on the data by Kim *et al*[22], score 1 and 2 represent viable myocardium, while score 3 and 4 are regarded as non-viable tissue ("scar") in view of expected functional improvement after revascularization. Per definition, reduced or completely missing viability encompassed decreased or no FDG-uptake. CMR: Cardiac magnetic resonance imaging; PET: Positron emission tomography; FDG: Fluorodeoxyglucose.

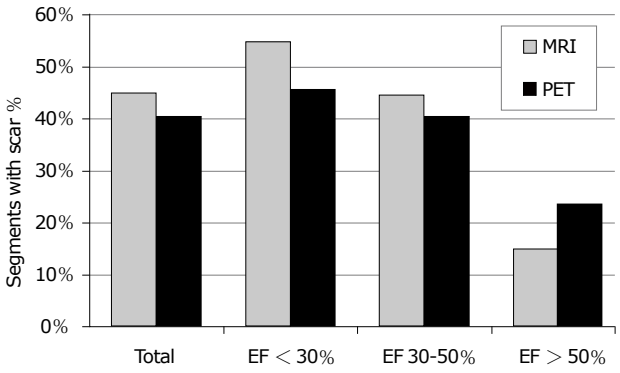

Figure 1 Histogram showing the frequency of scar detection in cardiac magnetic resonance imaging (grey bars) and positron emission tomography (black bars). In total, cardiac magnetic resonance imaging (CMR) found scars in 45% of all segments compared to PET in 40%. CMR depicted significantly more scars in patients with severely (EF < 30%) and moderately (EF, 30%-50%) impaired left ventricular function. However, PET suggested more scars in EF > 50% group. PET: Positron emission tomography; EF: Ejection fraction.

used. Statistical significance was assumed with $P < 0.05$. Moreover, Bonferroni correction was performed, yielding an adapted level of significance of $P = 0.008$.

At first, 3 different patient groups were composed based on the global LV function as assessed by CMR: (1) severely impaired LV function (EF < 30%); (2) moderately decreased LV function (EF 30%-50%); and (3) non-compromised LV function (EF > 50%). After that, CMR viability scores were compared segment-based to PET scores in two ways: first, normal segments (score 1) and segments with any kind of scar (score 2-4) were analyzed. Secondly, according to data published by Kim *et al*[22], evaluation of segments with no or little scar (scores 1 and 2, "viable"), which are expected to improve after revascularization, were compared to segments with score 3 and 4 ("non-viable"). In each case, sensitivity, specificity, positive predictive value (PPV), NPV, and accuracy were evaluated in contingency tables for CMR as test variable compared to PET. Diagnostic accuracy of CMR and PET were compared for the three LV function groups separately. Parametric data is expressed as mean ± SD. Two-tailed Fisher's exact test was applied to compare frequencies of scar detection (scores 2-4) and functional recovery estimation (scores 1 and 2) between CMR and PET. Cohen's Kappa was calculated for the agreement of CMR and PET in detecting scar and functional recovery estimation.

RESULTS

All patients successfully finished the study protocol, therefore complete data sets of 105 subjects underwent analysis. Depending on the long axis diameter, the LV was covered in CMR by 8 to 14 short axis slices. The 3D PET data set was then separated accordingly into the same number of slices yielding a total of 5508 segments. Mean CMR volumetric measures were: EDV, 198 ± 69 mL (range, 63-386 mL) and ESV, 137 ± 66 mL (range, 24-316 mL), resulting in a mean EF of 34% ± 14% (range, 9%-78%). Forty-five patients had an EF < 30%, 44 patients 30%-50%, and 16 patients > 50%.

Scar assessment by CMR and PET depending on LV function

As demonstrated by Figure 1, CMR detected myocardial scars (score 2-4) in 45% of all segments, while PET depicted scars in 40% of all segments ($P < 0.0001$). Inter-observer agreement (Cohen's Kappa) between CMR and PET in scar detection was 0.39 (fair to moderate). Analysis of the different patient groups revealed that CMR found more scars than PET in subjects with EF < 30% (55% *vs* 46%; $P < 0.0001$) and EF 30%-50% (44% *vs* 40%; $P < 0.005$). However, CMR revealed less scars than PET in patients with EF > 50% (15% *vs* 23%; $P < 0.0001$). Statistical values (sensitivity, specificity, PPV, NPV, and accuracy) within the 3 different patient groups are summarized in Table 2. Viable segments which can be expected to improve after revascularization (score 1 and 2) were detected by CMR in 72% (3949/5508) compared to non-viable segments (score 3 and 4) in 28% (1559/5508). For PET, viability of segments was declared in 80% (4396/5508) and non-viability in 20% (1112/5508). CMR and PET significantly differed in depicting viable and non-viable segments ($P < 0.0001$). Inter-observer agreement (Cohen's Kappa) between CMR and PET in functional recovery estimation was 0.48 (moderate). Analysis of the different patient groups Analysis of the different subgroups revealed that CMR judged segments as

Table 2 Myocardial scar detection by cardiac magnetic resonance imaging (contingency table)

	Sensitivity	Specificity	PPV	NPV	Accuracy
All patients	69%	71%	62%	77%	70%
EF< 30%	79%	66%	66%	79%	72%
EF 30%-50%	64%	69%	58%	74%	67%
EF > 50%	25%	89%	41%	79%	74%

Detection of myocardial scar (score 2-4) by cardiac magnetic resonance imaging (CMR) as test parameter compared to positron emission tomography (PET). Analysis was done for the whole patient collective as well as in the three patient subgroups with different ejection fraction (EF). In patients with moderately or severely compromised EF CMR outperformed PET. NPV: Negative predictive value; PPV: Positive predictive value.

Table 3 Functional recovery as detected by cardiac magnetic resonance imaging shown as contingency table

	Sensitivity	Specificity	PPV	NPV	Accuracy
All patients	72%	83%	51%	92%	81%
EF < 30%	74%	79%	55%	90%	78%
EF 30%-50%	73%	82%	50%	93%	81%
EF > 50%	30%	92%	19%	95%	89%

The contingency table shows the detection of tissue with potential functional recovery (score 1 and 2) by cardiac magnetic resonance imaging (CMR) as test variable compared to positron emission tomography (PET). Calculation was performed for the whole patient collective as well as separately for the three patient subgroups with different EF. Except for patients with not compromised left ventricular function sensitivity, specificity, PPV, NPV and accuracy were higher in CMR. EF: Ejection fraction; NPV: Negative predictive value; PPV: Positive predictive value.

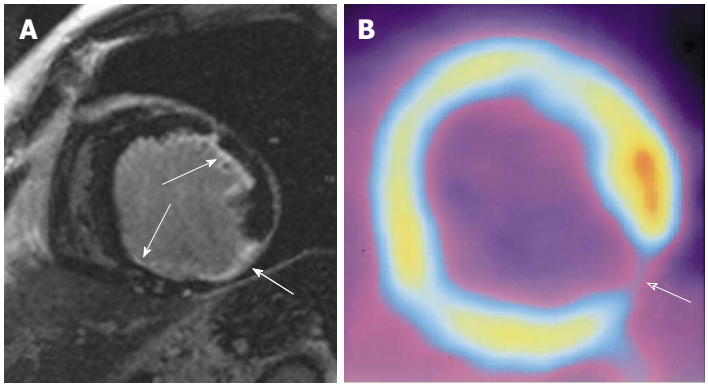

Figure 2 A sixty-seven-year-old man with severe coronary artery disease and history of myocardial infarction. A: Short axis inversion-recovery gradient-recalled echo cardiac magnetic resonance imaging (CMR) image of the mid- to apical-portion of the left ventricular shows a small area of transmural late gadolinium enhancement (LGE) in the inferolateral wall (broad arrow). CMR viability scores: Anterior: 2; anterolateral: 2; inferolateral: 4, inferior: 2; B: The positron emission tomography (PET) image of the corresponding slice reveals an uptake defect (broad arrow) in the same segment suggesting a transmural scar. PET viability scores: anterior: 2; inferolateral: 4. Small subendocardial scars with LGE in CMR (A) in the anterolateral and inferior wall (small arrows) were overseen in PET.

viable in 66% in patients with severely compromised LV function, in 72% in subjects with moderately reduced LV function and in 91% in patients with non-compromised LV function. For PET, these values were 75%, 80%, and 94% respectively. Comparison of CMR and PET showed that CMR declared significantly less segments as viable than PET in patients with severely or moderately reduced LV function (for all, $P < 0.0001$). In patients with uncompromised LV function no statistical significance was evident between both modalities after Bonferroni correction ($P = 0.03$).

Table 3 provides statistical values for CMR in the estimation of functional recovery (MRI score 1 and 2) compared to PET. Comparison of Tables 2 and 3 reveals that overall performance of CMR was better in Table 3, when small scars (< 50% transmurality) were excluded. Figure 2 gives an example of a transmural scar detected both by CMR and PET as well as of small subendocardial scars that were found by CMR but overseen in PET. Figure 3 shows diagrams of the volumetric measures in relation to the total extent of scar (mean scar score).

DISCUSSION

Results from myocardial viability testing play an important role in clinical decision making especially in patients with impaired myocardial function, who might require invasive treatment. Albeit several studies reported on patients who benefited from restoration of blood flow despite pre-interventional proof of non-viable tissue and without post-operative functional

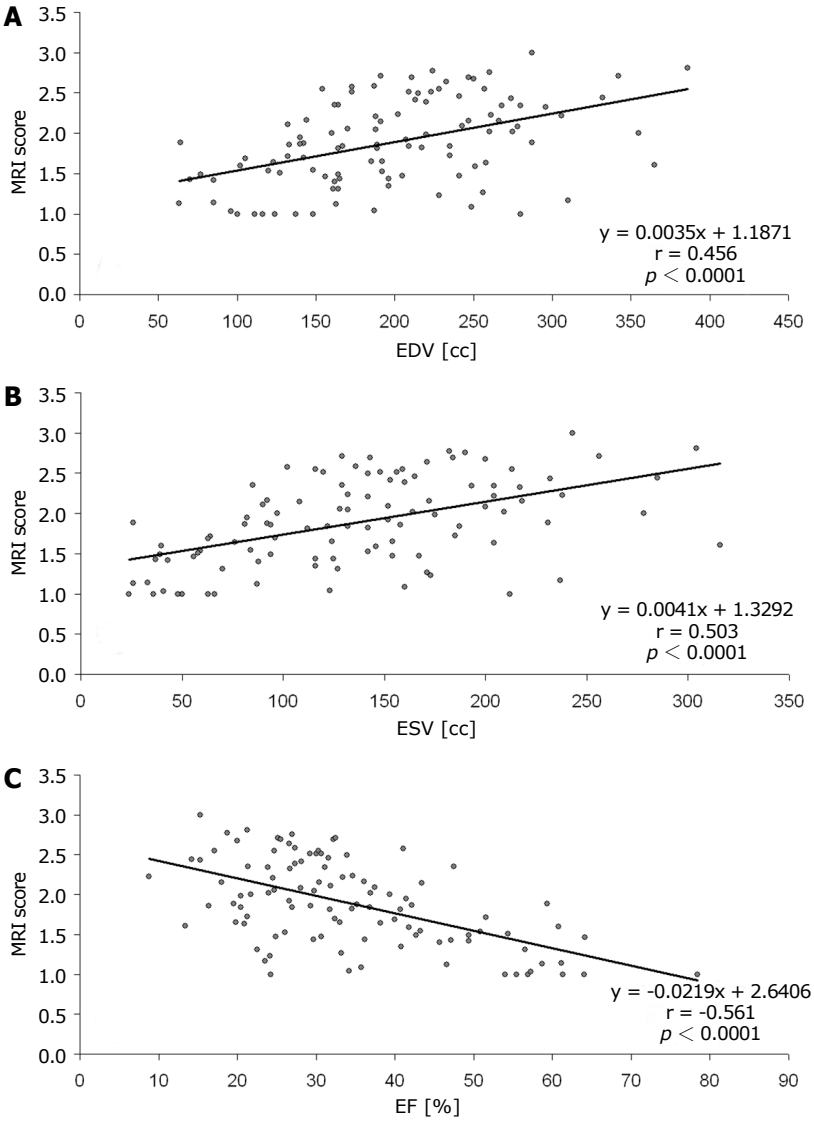

Figure 3 Correlation of left ventricular volumes and function to the MRI-derived extent of myocardial scar (summarized as mean magnetic resonance imaging score per patient). A: End-diastolic volumes (EDV); B: End-systolic volumes (ESV); C: Ejection fraction (EF).

recovery consequently[11,28,29], general consensus exists that information on the transmural extent of myocardial scar is of importance because it holds a close relationship with recovery of segmental function at follow-up[3]. We, therefore, sought to evaluate the diagnostic accuracy of LGE-CMR viability assessment and PET in patient groups with different LV functions. The main findings were: (1) in subjects with severely or moderately reduced LV function, CMR detects considerably more myocardial scars than PET; (2) scars, which are only seen in PET in patients with non-compromised LV function are probably false-positive results or artifacts; and (3) in patients with impaired LV function (EF < 50%), CMR demonstrates more non-viable myocardium compared to PET and is generally less optimistic concerning functional recovery after revascularization procedures.

Within the last decade CMR has more and more replaced nuclear imaging techniques in myocardial viability assessment. In particular, CMR seems to be useful in identifying patients, who most likely will not benefit from coronary revascularization[11]. Kühl *et al*[11] demonstrated that none of the segments which were classified as viable by PET/SPECT and nonviable by CMR showed functional recovery 6 mo after revascularization procedures, while 42% of segments described as viable by CMR and non-viable by PET/SPECT still improved[7].

To our knowledge, the present study is the first to compare CMR and PET differentiated in groups depending on LVEF. In patients with severely or moderately reduced LVEF, our study revealed a high sensitivity, specificity and NPV, indicating that CMR is good in detecting myocardial scars. Especially, the high NPV is of great importance in decision-making: if CMR indicates non-viable tissue, low likelihood for functional improvement after revascularization would be expected,

which might prevent patients from unnecessary invasive procedures and potential peri-interventional risks. Moreover, CMR demonstrated considerably more nonviable myocardial tissue than PET with better sensitivity, PPV, NPV and accuracy (excluding small scars with < 50% transmural extent, score 2; Tables 2 and 3). One reason for that most probably is the significantly higher spatial resolution of CMR compared to PET, which is of benefit in finding subendocardial scars and in analyzing the thinned myocardial walls in subjects with severely reduced LVEF. Another explanation might be related to the fact that FDG-uptake represents viability, so that small amounts of viable cells lead to visible FDG-uptake indicating viability[11,29,30], although structural changes may already be present (*e.g*., expansion of extracellular spaces), leading to altered gadolinium kinetics. In addition to that, PET evaluates myocardial viability semiquantitatively: FDG-uptake in a given segment is expressed relative to the segment with maximum FDG-uptake. As a consequence, in thinned myocardium already small rims of reduced FDG-uptake may decrease relative percentage of FDG-uptake to below the threshold value set for viability, albeit viable tissue exists[11], resulting in false-negative evaluation of myocardial viability.

PET detected more scars in subjects with noncompromised LVEF (> 50%), similar to what Klein *et al*[30] described in their study. These surplus segments seen in PET only are most likely false-positive results or artifacts: As LVEF is only marginally or not impaired, only small amounts of non-viable subendocardial tissue are expected. Larger scars would have had more impact on myocardial function. However, a considerable number of non-viable cells is needed for detectable reduction of the relative FDG-uptake below the threshold-value considered for viability, which seems less probable in small scars[31-33]. Owing to the lower spatial resolution of PET it appears unlikely that these small scars were depicted by PET with higher sensitivity than by CMR[3,17]. This is further underlined by studies describing that more than half of the small subendocardial scars depicted by CMR cannot be delineated in PET[30]. Moreover, a minimum of 2 g irreversibly injured myocardium can be detected by LGE-CMR compared to a minimum tissue of 10 g required in PET[33]. Because of that recent studies have denominated LGE-CMR as method of choice for small subendocardial unrecognized myocardial infarction scars[34,35]. Other shortcomings of PET are its radiation exposure, the long examination time and the allocation of appropriate tracers[11]. CMR has evolved as a valuable alternative to PET for evaluation of viable and infarcted myocardium by different techniques (morphology, edema, function, perfusion and scar) in a single examination[2]. Estimated examination time for a complete CMR work-up is 30-60 min. Whether the recently emerging combination of PET and CMR (PET/CMR-hybrid) might be an alternative to CMR alone in assessment of myocardial viability will be the task of future studies[36,37].

We are aware of the following limitations of our study: First, the possibility of anatomical misalignment between different imaging modalities cannot be excluded. Within the last years, hybrid PET/CT-systems had increasingly replaced single PET-scanners. However, as published in a review by Anagnostopoulos *et al*[38] the impact of PET/CT-imaging on clinical outcomes in patients suffering from CAD is still unclear. They therefore recommended that until further studies are performed anatomical or functional imaging should be done sequentially by cardiac CT or PET depending on the pre-test probability of CAD[38]. In patients with higher probability PET should be the first line modality as its ability to guide patient management decisions regarding revascularization or medical treatment has been shown[39]. Therefore, we think that our results can be regarded representative, even though we are aware of the limitations of comparing semi-quantitative assessment of radiotracer uptake in PET as comparator for evaluating LGE-CMR. Furthermore, we defined myocardial scar as area with decreased FDG-uptake, even though reduced FDG-uptake might also be caused by stunned myocardium. The most appropriate approach would have been to perform both a functional and perfusion scan, in which stunned myocardium would have been detected as area with reduced FDP-uptake but normal perfusion (perfusion-metabolism reverse mismatch)[33]. However, for the given clinical indication in our patients the functional scan was sufficient and therefore no perfusion data was available. Another technical limitation might be that we did not use a glucose-insulin clamp to standardize the glucose metabolism within the whole myocardium. Like others[36,37], in our institution PET imaging is done under fasting condition and oral administration of two doses of acipimox and 75 g glucose prior to FDG application. Therefore, we believe the number of false-negative segments to be negligible. However, the lack of clinical approval of acipimox in the United States hampers representativeness of our data abroad. Moreover, no correction technique was applied for PET. And finally, a detailed segment-to-segment attenuation comparison was only partly done in our study, but would have been of interest to get deeper information on exact differences between PET and CMR regarding scar detection, *e.g.*, considering the location of scar keeping in mind that the exact delineation of the inferior LV segments is often impaired in PET[30,40]. This has to be investigated by further studies.

In conclusion, our study demonstrates differences in diagnostic accuracy of CMR and PET differentiating between patient groups according to LV ejection fraction. Advantages of CMR compared to PET were found in detecting scars and non-viable tissue in subjects with severely or moderately reduced LVEF. CMR is generally less optimistic concerning functional recovery after revascularization procedures, which is of

great importance in clinical decision-making.

ARTICLE HIGHLIGHTS

Research background

Cardiac magnetic resonance imaging (CMR) and positron emission tomography (PET) have been established for myocardial viability imaging in coronary artery disease (CAD). However, differences in accuracy have been reported. It has been shown that CMR provides higher sensitivity in detecting small scars due to the significantly higher spatial resolution. So far, no data are available on differences in diagnostic accuracy depending on left ventricular (LV) function although it might be suggested that LV volumes and wall thickness, for example, might have an impact on the sensitivity.

Research motivation

The above mentioned missing data have been collected in our large study and have now been made available. This study might help to better understand the advantages and disadvantages of the two different methods.

Research objectives

The primary objective of this research was to compare contrast-enhanced CMR and fluorodeoxyglucose-PET for the evaluation of myocardial viability in known CAD under different LV function conditions.

Research methods

One-hundred-five CAD patients were examined by CMR and PET. Myocardial scars were rated in both CMR and PET on a segmental basis in each 8 mm thick short axis slice concerning presence and extent of myocardial scar after myocardial infarction. For each of the evaluated 5518 segments, direct comparison was performed and three patient groups with different LV function were analyzed. In particular two aspects, diagnostic accuracy has been evaluated: (1) scar detection; and (2) functional improvement estimation by the two methods.

Research results

As expected, CMR has a higher sensitivity for scar detection and, therefore, is less optimistic than PET in the prediction of functional recovery after revascularization. In the different LV function groups, CMR found more scar segments than PET in subjects with EF < 30% and EF 30%-50% (44% *vs* 40 %; $P < 0.005$), whereas CMR revealed less scars than PET in patients with EF > 50%.

Research conclusions

There are differences in the diagnostic accuracy between both modalities that have not been described, yet. This new knowledge helps to understand the strengths and weaknesses of the two modalities. One should keep in mind that particularly in severely impaired LV function - where viability really matters - CMR is able to detect more scars. In those cases, using CMR instead of PET could prevent unnecessary revascularizations and accompanying complications.

Research perspectives

This study could initiate more research on particular myocardial viability imaging aspects to better sort outpatient conditions that influence the accuracy of available techniques.

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LETTERS TO THE EDITOR

Snugger method - The Oldenburg modification of perceval implantation technique

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Abstract

We present a modified implantation technique of the Perceval® sutureless aortic valve (LivaNova, London, United Kingdom) that involves the usage of snuggers for the guiding sutures during valve deployment. Both limbs of each guiding suture are pulled through an elastic tube, which is fixed with a Pean clamp, which tightens the sutures and fixes the prosthesis to the aortic annulus during valve deployment. This method proved safe and useful in over 120 cases. Valve implantation was facilitated and the need for manipulation by the assistant or the nurse was eliminated.

Key words: Aortic valve; Surgical; Perceval; Snugger; Sutureless aortic valve

Core tip: In this article, we are presenting a modified implantation technique of the Perceval sutureless aortic valve prosthesis to enhance proper positioning of the prosthesis and aid the reproducibility of the implantation procedure. The modification involves using snuggers to fix the valve prosthesis to the aortic annulus during deployment.

Mashhour A, Zhigalov K, Szczechowicz M, Mkalaluh S, Easo J, Eichstaedt H, Borodin D, Ennker J, Weymann A. Snugger

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TO THE EDITOR

Introduction

Surgery of the aortic valve replacement (AVR) is still recommended in certain patients with aortic valve disease. Two approaches have become quite popular; surgical and trans-catheter aortic valve replacement (SAVR and TAVR, respectively), whereby TAVR is mostly reserved for elderly patients with higher surgical risk[1,2]. Although not considered in the current guidelines, the sutureless variety of SAVR has been proven to reduce the overall surgical risk by significantly reducing operative and cross-clamp times, while demonstrating lower incidence of known complications of TAVR with comparable or even better results, especially in intermediate-risk patients[3-5].

The Perceval valve (Sorin Group Italia Srl, Saluggia, Italy) is a self-anchoring, self-expanding, sutureless, surgical aortic bioprosthesis. The valve leaflets are mounted to an elastic nickel-titanium alloy stent[3]. The stent anchors the valve *via* six sinusoidal posts to the aortic root at the sinuses of Valsalva, while the valve prosthesis seals the left ventricular outflow tract (LVOT) through an intra-annular and a supra-annular sealing ring. Correctly positioned, the leaflets of the valve prosthesis are aligned with those of the native aortic valve and the inflow ring of the prosthesis lies at the level of the insertion plane of the native leaflets[6]. The intra-annular ring of the Perceval valve prosthesis is supplied with three eyelets to pass guiding sutures which are previously made at the hinge points of the native aortic valve leaflets.

The valve prosthesis is then inserted into the aortic root over these guiding sutures and deployed "hand-held" in position. We describe a modification of this technique, where the prosthesis is virtually "fixed" onto the aortic annulus during deployment, which guarantees correct positioning of the prosthesis and aid the reproducibility of the implantation procedure.

Implantation technique according to the manufacturer (Sorin group)

The aortotomy should be in a transverse manner at least 3.5 cm above the aortic annulus to facilitate aortic closures. The native aortic valve is excised as with other SAVR prostheses. Although a complete decalcification of the aortic annulus is not necessary, a regular annular profile is essential for proper sealing. Sizing of the aortic annulus should be performed using the dedicated sizers. Now, the prepared prosthesis can be put in place. To ensure correct placement and alignment, a suture is made at hinge point of each leaflet perpendicular to the annulus, so that the three sutures are approximately 120° equidistant. The suture points should be 2-3 mm afar from each side of the insertion plane of the leaflets. After each suture is taken, the needle should be cut off and both ends of the thread secured with a clamp.

Each of the guiding sutures is then passed through one of the eyelets of the prosthesis. After that, the valve prosthesis is parachuted into the aorta sliding on the guiding threads which are kept straight with a gentle pull maintaining alignment with the aorta. Correct position of the prosthesis is reached when it is descended until it is stopped at the insertion points of the threads and the commissural struts of the prosthesis are aligned with the native commissures.

The valve is then released in two steps. First, the inflow section is released by rotating the control button on the delivery device until a click is heard and felt. At this stage, it is important to ensure that the sinusoidal struts correspond to the sinuses of Valsalva and that the stent of the prosthesis does not obstruct the coronary ostia. Second, the outflow section is released by withdrawing the sliding sheath off the holder avoiding rotational movement. It is important to keep the holder in an axial position to aorta all the time.

After visual assessment of the correct position and alignment of the prosthesis, patency of the coronary ostia and that no annulus is visible below and above the valve inflow ring, the inflow ring should be postdilated (4 atmospheric pressure for 30 s) using a dedicated catheter. While the postdilation balloon is inflated, warm sterile saline is poured within the aortic root to ensure optimal valve sealing and optimized anchoring. The guiding sutures are removed and the aortotomy is closed as usual taking care not to capture the stent of the prosthesis within the closure suture.

How we do it

Preparations of the prosthesis and the aortic root as well as the sizing procedure and prosthesis selection are similar to the method described above. The guiding sutures are also placed as described. We use 3/0 double-armed poly-propylene sutures. The suture is made with one needle from the LVOT side to the aorta side of the hinge point of each leaflet leaving 2-3 mm on each side as recommended above. The other needle is passed through the eyelet of the Perceval prosthesis before both needles are cut off.

Now, instead of directly securing the thread with a clamp, both ends are passed through an elastic tube making a snugger. While holding the prosthesis holder in place and axial to the aortic root, the snuggers are tightened. While tightening each snugger, both ends of the thread are pulled upwards. This "pull" is partially opposed by a light downward pressure on the prosthesis in the direction of the insertion of the guiding suture. The snugger is then pulled tight and secured with a Pean clamp (Figure 1).

This is repeated with the other two guiding sutures.

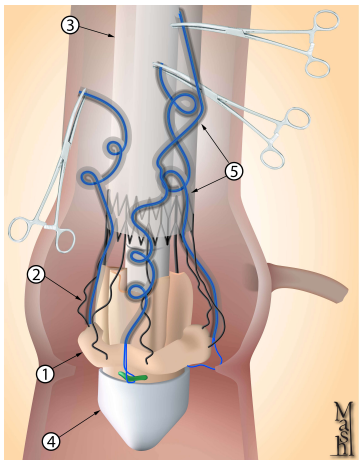

Figure 1 Graphic presentation of the prosthesis in place after tightening the snares and securing with clamps. 1 represents valve prosthesis; 2 represents valve stent; 3 represents shaft of the dual holder device; 4 represents tip of the dual holder device; 5 represents the snares.

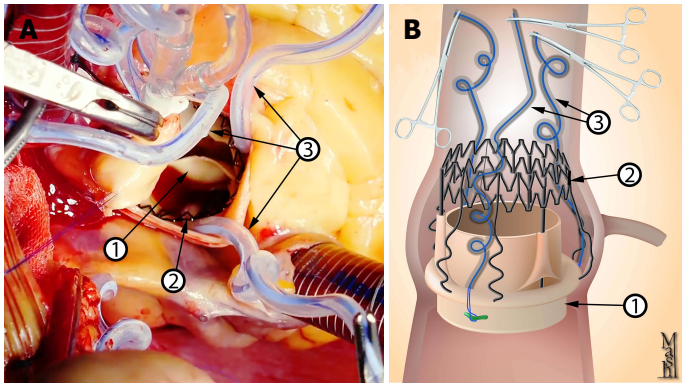

Figure 2 Intraoperative picture. A: Graphic presentation of the prosthesis after deployment; B: Prosthesis. Notice that the snare should not lie between the ring of the prosthesis and the annulus of the aorta. 1 represents valve prosthesis; 2 represents valve stent; 3 represents the snares.

The assistant should retract the aortic wall slightly open, so that the descent of the elastic tube into the tightened position is done under direct vision. It is important that the snuggers are tight enough; however, care should be taken that the elastic tube ends above the sealing ring of the inflow stent of the prosthesis and not trapped between the ring and the aortic annulus (Figure 2), as this could lead to incomplete deployment of the prosthesis, difficult withdrawal of the elastic tube and, potentially, dislodgement of the prosthesis during withdrawal of the elastic tube.

Next, the prosthesis is deployed in the same fashion described above. In this step, the assistant can help stabilize the prosthesis and hold the aorta open to aid visualization. Checking for correct positioning *etc.* as well as postdilation and irrigation with warm saline are also performed as described above.

Now, the snuggers a loosened and the elastic tubes are withdrawn. This should be done slowly and under direct vision taking care not to dislodge the prosthesis. The threads are then pulled out carefully. The prosthesis is checked again for proper anchoring and correct seat, and the aortotomy is closed.

Comment

As rapid-deployment prosthesis, one of the main benefits of the Perceval prosthesis is reducing operative and cross-clamp times through simplifying the surgical implantation technique. However, absolute stability is required during valve deployment to ensure proper seating of the prosthesis within the aortic root. Otherwise, valve malposition could occur[7].

On the contrary, in the technique described in this work, after tightening the snuggers, the prosthesis and the aortic annulus are fixed together eliminating the need for extra manipulations by the assistant or the nurse, so that the surgeon can self-sufficiently deploy the valve with one hand holding the delivery device and the other hand rotating the control button to release the valve.

Moreover, while tightening each snugger, the surgeon should pay attention to this one guiding suture; a step which is repeated with each suture at a time. On the contrary, the standard technique recommended by the manufacturer requires ensuring that the prosthesis is seated in the right position in respect to the three guiding sutures simultaneously.

According to the manufacturer's recommendations, traction sutures should be released prior to the deployment of the valve. We did not consider this step necessary as the snuggers would literally fix the valve prosthesis to the aortic annulus at three points forcing it into planarity and thus eliminating any distorting leverage exerted by the traction sutures. The continued presence of the traction sutures allows better visualization of the aortic annulus during prosthesis deployment.

In the manufacturer's recommendations, in case of a hypoplastic coronary ostium, the first guiding suture should be in the corresponding sinus. We did not encounter this in our case series. We also did not find any reports on the use of Perceval prosthesis in cases with a hypoplastic coronary ostium. Indeed, this should not be problematic. Nevertheless, the modification proposed in this work would add more security to the implantation, as the snuggers push the prosthesis down as far as possible, guaranteeing freedom of the hypoplastic ostium.

The use of snuggers, was reported once to facilitate a total endoscopic AVR[8]. However, to our knowledge, the use of snuggers to fixate the Perceval prosthesis during deployment in the way described in this work has not been described before. Until now, we have used this modification in over 120 patients with 100% primary success and excellent postoperative results.

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EDITORIAL

T-cells in myocardial infarction: Culprit instigators or mere effectors?

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Abstract

Immune system activation and dysfunction characterize the early phase of reperfusion after a myocardial infarction (MI). Despite initially neglected, adaptive immunity has been recently showed to play an important role in this setting. In fact, the immune system can recognize sequestered antigens released by the necrotic tissue, initiating a deleterious autoimmune vicious circle leading to worse outcome. In their recent work, Angelini *et al* shed the light on a new feature of post-MI which involves two "old players" of post-ischemic myocardial injury: CD31 and matrix metalloproteinase (MMP)-9. Specifically, the authors showed that an enhancement of MMP-9 release could determine the cleavage of inhibitory CD31 from CD4+ T-cells surface in patients with Acute Coronary Syndromes (ACS). These findings open the room for new studies investigating the role of MMP9 in other pathological processes associated with a reduction of CD31 functionality, such as plaque instability and rupture. Of interest, in the case of a causative role for CD31 shedding in ACS would be confirmed, there might be a potential role for the administration of CD31 protein or analogue compounds to blunt post-ischemic cardiac inflammation and improve ACS outcome.

Key words: Matrix metalloproteinase; Lymphocytes; Autoimmunity; Inflammation; Myocardial infarction; Adaptive immunity

Core tip: CD31 and matrix metalloproteinases (MMP)-9 are known mediators that are upregulated during reperfusion after cardiac ischemia. By inhibiting T-cell

receptor-dependent lymphocyte activation, the functional CD31 could reduce post-ischemic inflammatory response; while MMP-9 is deeply involved in inflammatory cell recruitment and myocardial remodeling. A recent paper published in European Heart Journal linked these mediators by showing CD31 cleavage to be MMP-9 dependent in patients with acute coronary syndromes (ACS). Whether this process is causative of ACS or rather its effect still needs to be clarified.

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INTRODUCTION

Acute Coronary Syndromes (ACS)-including unstable angina and myocardial infarction (MI) are the most detrimental atherosclerosis-related complications being the leading causes of mortality worldwide and a considerable source of morbidity[1]. Although outstanding leap forwards of primary and secondary prevention measures, the issue of the residual risk for ischemic complication is still unsolved[2]. Also, it is now well-recognized that after a prompt reperfusion, as it is the case of vast majority of patients suffering from MI, the ischemic hearts need to face an additional damage directly induced by the re-establishment of blood flow itself[3]. The role of innate immunity in the determination of both residual risk and ischemia/reperfusion injury has been studied from decades and is now better established[4-6]. The adaptive immune system (*i.e.*, T-cells and B-cells) have only recently come into focus. Indeed, lymphocytes' ability to react only against specific non-self-antigens, as opposed to the reactivity against non-specific danger signal showed by innate immunity, excluded these mediators from the list of "guilty" parties for a long time. Only recently, the recognition of a role for the release of sequestered antigens from the necrotic tissue in the progressive diversification of autoreactive lymphocytes (*i.e.*, epitope spreading) shed the light on the potential involvement of adaptive auto-reactivity in the determination of post-MI outcome[7]. After an ACS, the necrotic heart tissue releases several danger-associated molecular patterns (DAMPs) together with cardiac intracellular proteins[8,9]. In this highly inflamed micro-environment, cardiac antigens can be recognized by autoreactive lymphocyte clones and trigger autoimmunity processes. Afterward, the same immune-mediated tissue injury supplies the amount of autoantigens necessary to maintain the auto-reactivity thus sustaining the dysfunctional immune cardiac process[9]. This editorial refers to the outstanding research article entitled "matrix metalloproteinases-9 might affect adaptive immunity in non-ST segment elevation ACS by increasing CD31 cleavage on CD4+ cells", recently published by Angelini *et al*[10] in European Heart Journal.

T-CELLS AND ACS

Although several studies have implicated T-cells in the pathophysiology of ACS, the knowledge about their specific role is still elusive. Considering the heterogeneity of T-cell subsets and the quickly evolving local and systemic environment after ACS, a tight regulation of rapidly changing T-cell phenotypes with regulator or effector functions is likely[11]. Experimental evidence highlights infiltrating T-cells as effector lymphocytes which have been antigen-restricted and primed in the heart-draining lymph nodes. Of interest, after ACS, particular subsets of pro-inflammatory CD28- CD4+ and Th17 lymphocytes are released in the blood stream and produce large amounts of interferon-γ and IL-17: Detrimental cytokines with known ability to increase cardiomyocyte death, fibroblast proliferation and pro-fibrotic gene expression[12-14]. Not only detrimental T-cells with effector functions are increased after ACS but they also display dysfunctional features. Indeed, they overexpress CD40 ligand in this way being more easily activated by antigen presenting cells[15]. Furthermore, a direct cytotoxic effect of infiltrating autoreactive CD8+ T-lymphocytes with specificity towards cardiac myosin has been described[16]. To further potentiate the detrimental role of T lymphocytes in the setting of MI, the raise of pro-inflammatory lymphocyte subsets is accompanied by a reciprocal reduction in CD4+CD25+Foxp3+ regulatory T-lymphocytes with a beneficial cardiac protective role[17].

MMP-9 AND CD31: A DANGEROUS ASSOCIATION

Post-transcriptional CD31 modifications showed capacity to affect normal T-lymphocyte function. Indeed, CD31 (also known as platelet endothelial cell adhesion molecule-1) was shown to regulate T lymphocyte activity through the inhibition of T cell receptor (TCR) signalling[18]. Of interest, CD31 extracellular domain is shed from the lymphocyte surface during ACS and this contributes to the over activation of adaptive immunity[19]. In their recent article, Angelini *et al*[10] added one more piece to this puzzle by showing matrix metalloproteinase (MMP)-9 to be involved in CD31 cleavage in lymphocytes from ACS patients. Firstly, they confirm CD31 shedding to be a specific feature of lymphocytes in ACS, as compared to samples from healthy subjects but also patients with stable angina (SA). Then, the authors demonstrated *in vitro* that down-regulation of the functional CD31 domain in ACS is associated with TCR activation and is led by post-transcriptional mechanisms since post-stimulation levels of CD31 mRNA were similar in ACS and SA cells. Finally, after observing CD31 to be a possible substrate for MMP-9 by using an dedicated software predicting novel substrates and their cleavage sites, the auth-

ors show lymphocytes from ACS patients to produce higher enzyme levels after stimulation and CD31 active domain to be preserved by MMP-9 inhibition. Based on these results, the authors propose a new sequence of events that might characterize ACS onset in which the increased release of MMP-9 causes CD31 cleavage, thus affecting TCR-dependent T-cell activation and causing T-cell hyperactivity[10].

PERSPECTIVES

Angelini *et al*[10] added knowledge to the field of dysfunctional adaptive immunity in ACS. At the same time, they raise new appealing questions. In particular, CD31 is known to mediate also endothelial-endothelial interactions, thus allowing the constitution of the continuous and protective intimal cell monolayer[20]. Now, further investigations are advisable to assess whether the inflammation-induced overproduction of MMP-9[21] could reduce these interactions and potentially contribute to endothelial erosion and plaque instability. Under this point of view, CD31 was previously described to target macrophage activation, as well as cytokine and chemokine release within atherosclerotic plaques and aneurysmal peri-aorta[22]. Also, it would be of interest to show CD31 modifications in lymphocytes to take act before ACS onset. In general, this is a very common weakness of studies focused on cellular phenotype during ACS due to the requirement of intact cells for fluorescent-activated sorting which does not allow sample storage before the dosage. Animal studies could help in assessing this causal connection.

Given the fact that CD31 protein or analog molecules are already available[23], answering these questions could point out CD31 replacement as a potential therapeutic approach to blunt inflammation and modulate tissue damage in acute cardiovascular diseases (such as MI and stroke) that are characterized by an impaired adaptive immunity.

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REVIEW

Overview of coronary artery variants, aberrations and anomalies

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Abstract

Coronary artery anomalies and variants are relatively uncommon congenital disorders of the coronary artery anatomy and constitute the second most common cause of sudden cardiac death in young competitive athletes. The rapid advancement of imaging techniques, including computed tomography, magnetic resonance imaging, intravascular ultrasound and optical coherence tomography, have provided us with a wealth of new information on the subject. Anomalous origin of a coronary artery from the contralateral sinus is the anomaly most frequently associated with sudden cardiac death, in particular if the anomalous coronary artery has a course between the aorta and the pulmonary artery. However, other coronary anomalies, like anomalous origin of the left coronary artery from the pulmonary artery, atresia of the left main stem and coronary fistulae, have also been implicated in cases of sudden cardiac death. Patients are usually asymptomatic, and in most of the cases, coronary anomalies are discovered incidentally during coronary angiography or on autopsy following sudden cardiac death. However, in some cases, symptoms like angina, syncope, heart failure and myocardial infarction may occur. The aims of this article are to present a

brief overview of the diverse coronary variants and anomalies, focusing especially on anatomical features, clinical manifestations, risk of sudden cardiac death and pathophysiologic mechanism of symptoms, as well as to provide valuable information regarding diagnostic workup, follow-up, therapeutic choices and timing of surgical treatment.

Key words: Ectopic coronary arteries; Coronary artery anomalies; Coronary fistulae; Coronary artery variants; Myocardial bridging; Coronary artery anatomy; Sudden cardiac death

Core tip: Coronary artery anomalies and variants are a diverse group of congenital disorders of the coronary artery anatomy with a wide variety of clinical manifestations. Though relatively uncommon and usually discovered incidentally during coronary angiography, they have garnered interest because they are the second most common cause of sudden cardiac death in young competitive athletes. Though by no means entirely exhaustive, this overview aims to act as a guide for the practicing cardiologist along the complex web of these disorders and may facilitate the assessment, investigation, follow-up and treatment of patients diagnosed with or suspected of having a coronary artery anomaly.

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INTRODUCTION

Coronary artery anomalies and variants are a diverse group of congenital disorders of the coronary artery anatomy with a wide variety of clinical manifestations. Though relatively uncommon and usually discovered incidentally during coronary angiography, they have attracted interest as they constitute the second most frequent cause of sudden death in young adults participating in competitive sports[1,2]. Though by no means entirely exhaustive, this overview aims to act as a guide for the practicing cardiologist along the complex web of these disorders and may facilitate the assessment, investigation, follow-up and treatment of patients diagnosed with or suspected of having a coronary artery anomaly. The majority of the figures presented are from our personal dataset.

It is important to have definite morphological criteria to describe normal coronary arteries. Angelini[3] has suggested criteria of normality of coronary anatomy, using several morphological features of the coronary arteries, such as number of ostia, location, course and branches. We also need to distinguish between normal variants of coronary anatomy and proper coronary anomalies. Anatomical features of the coronary arteries should be considered variants rather than congenital anomalies when they are prevalent in more than 1% of general population[4,5].

NORMAL CORONARY ANATOMY

Before venturing to explore the various coronary anatomy variations and anomalies, it is worth going through a brief overview of normal coronary anatomy. Normally there are two main coronary arteries, which stem from the sinuses of Valsalva and descend towards the cardiac apex. The left main stem (LMS) originates from the left sinus of Valsalva and crosses between the main pulmonary artery and the left atrial appendage. LMS has an average length of 2-4 cm and normally bifurcates into the left anterior descending artery (LAD) and the left circumflex artery (LCX). The right coronary artery (RCA) stems from the right sinus of Valsalva. The LAD descends towards the apex of the heart in the epicardial fat across the anterior interventricular sulcus. Its length varies between 10 and 13 cm and gives rise to diagonal and septal branches. It supplies the anterior wall, the apex and a significant portion of the interventricular septum. The LCX has a length of 5-8 cm and crosses the coronary sulcus on the diaphragmatic cardiac surface. It gives rise to the obtuse marginal branches and supplies mostly the lateral wall of the left ventricle. The RCA passes to the right between the pulmonary artery and the right auricle, descends across the right atrioventricular sulcus and continues posteriorly after the acute margin of the heart. Normal length is 12-14 cm. During its course, it may give rise to several branches, like the conus branch, sinoatrial branch, right ventricular branch, atrioventricular nodal branch, posterior descending branch (PDA) and posterolateral branch. It can broadly be considered as the artery that supplies the right side of the heart[1,6]. According to Angelini[3], the coronary anatomy falls within the spectrum of normality when: (1) there are two to four coronary ostia located at the upper midsection of the anterior aspect of the right and left sinuses of Valsalva. This is because sometimes the LAD and LCX may have separate origins from the left sinus, whereas the RCA and the conus branch may have separate origins from the right sinus; (2) a proximal stem bifurcating into major arteries is present only in the left coronary system (LMS bifurcating into LAD and LCX); (3) coronary arteries originate from the aortic wall with an angle of 45°-90°, follow an extramural (subepicardial) course, provide adequate branches for the perfusion of myocardium and terminate at the capillary bed distally; and (4) RCA perfuses the right ventricular free wall, LAD perfuses the anteroseptal wall and the obtuse marginal branch of LCX perfuses the free wall of the left ventricle (essential perfusion territories).

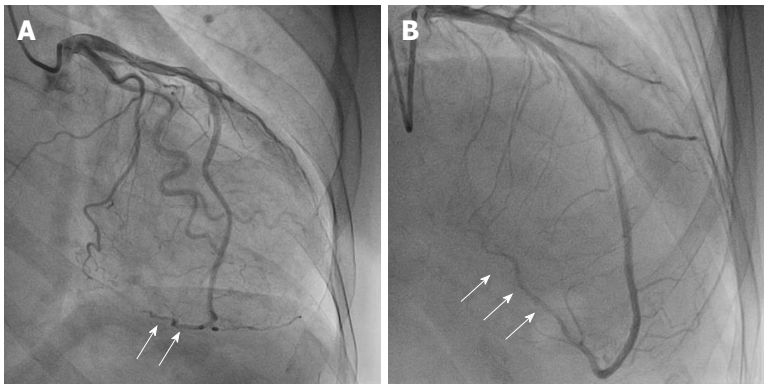

Figure 1 Wrap-around left anterior descending artery. A, B: Angiographic views of a large left anterior descending artery that wraps around the apex of the heart and supplies blood to part of the inferior wall (arrows) in anteroposterior caudal (A) and cranial view (B). From the authors' personal dataset.

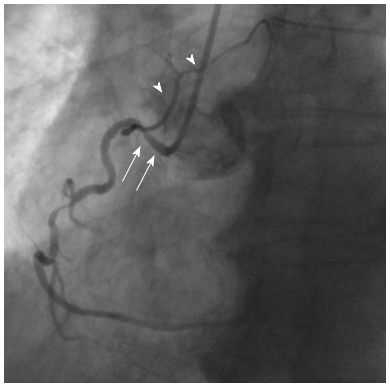

Figure 2 Shepherd's crook right coronary artery. Arrows show the prominent ascending course of proximal right coronary artery segment and an equally prominent, almost 180° switchback turn (left anterior oblique view). Arrowheads show the sinoatrial branch. From the authors' personal dataset.

CORONARY ARTERY VARIANTS

Based on the 1% rule mentioned above, frequent variations of the coronary arteries like those involving coronary dominance, take-off and course, supply of the inferior wall, the sinoatrial and atrioventricular nodes as well as the presence of a separate conus branch, a ramus intermedius branch and myocardial bridging fall within the limits of normality. The PDA usually arises from the RCA, in which case we have right coronary dominance (in 70% of the population); however, it may also arise form the LCX (left dominance - 10% of cases) or both (co-dominance - 20%)[7].

Supply of the inferior wall may also present several variations. The PDA may be very small or have an early take-off. In the case of a small PDA, perfusion of the inferior wall is usually provided by RCA, LCX and obtuse marginal branches. Occasionally LAD may be a very long vessel that goes beyond the apex of the heart and reaches the inferior interventricular groove, thus perfusing the apical inferior wall of the heart (wraparound LAD) (Figure 1)[8].

The sinoatrial branch supplies the sinoatrial node and usually arises from the proximal RCA in 60% of cases (Figure 2). However, it may also arise from the proximal LCX or more rarely from the distal segment of either of these vessels[9]. The atrioventricular nodal branch that provides blood to the atrioventricular node usually arises from the distal segment of whichever artery is dominant, RCA (more frequently) or LCX[7].

Another frequent normal variant is the presence of a ramus intermedius branch. In this case, the LMS trifurcates into three branches instead of two as usual, the LAD, the LCX and the ramus intermedius branch. This branch usually takes the route of a diagonal or obtuse marginal branch and supplies the lateral and inferior walls of the heart[10].

Other normal variants include an acute take-off of the LCX, in which case there is an angle < 45° between the LMS and the LCX, probably caused by a distal point of origin of the LCX[11]. A "shepherd's crook" RCA, in which the RCA follows a tortuous and high course with a prominent ascending course of its proximal segment and an equally prominent, almost 180° switchback turn (Figure 2), may comprise a technical challenge in interventional cardiology due to the poor support provided by the guiding catheters[7]. Other variants include separate origin of the conus branch directly from the right sinus of Valsalva[12], presence of a descending septal branch originating from the RCA that supplies part of the basal interventricular septum (Figure 3) and high take-off of a coronary ostium (5 mm or more above the aortic sinotubular junction), in which case the affected coronary artery (usually the RCA) takes an intramural course within the wall of the ascending aorta and is then externalized at its normal origin site[7,13-15].

All aforementioned variants are clinically benign and pose no threat to patients. Usually they are incidental findings during coronary angiography performed for other reasons and do not require any diagnostic work-up, further investigation or treatment. At most, some of them, like the shepherd's crook RCA, may present technical challenges during coronary intervention for other issues, due to difficulty in engaging angiographic catheters and guides. In addition, a descending septal branch, which originates from the RCA and supplies part of the interventricular septum, may be used as a target

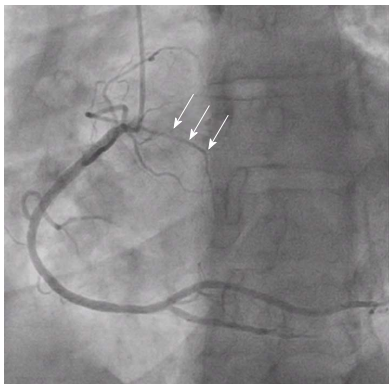

Figure 3 Descending septal branch. A branch of proximal right coronary artery (arrows) providing blood to part of the basal interventricular septum (left anterior oblique view with shallow cranial angulation). This branch may occasionally have a separate origin from the right sinus of Valsalva. From the authors' personal dataset.

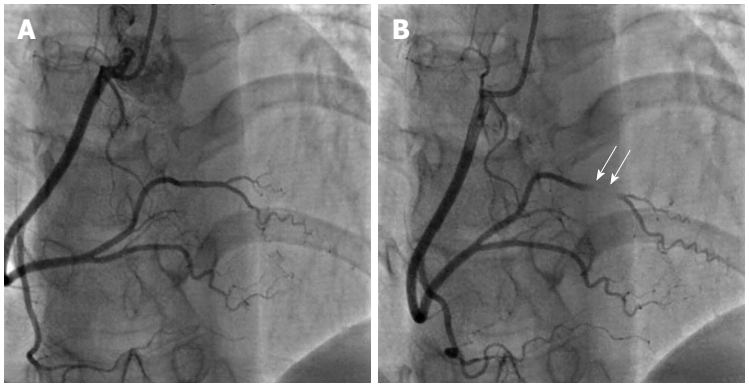

Figure 4 Myocardial bridging. A: Anteroposterior view with cranial angulation shows normal appearance of right coronary artery in diastole; B: Complete obliteration of a short segment of the posterolateral branch in systole (arrows) due to myocardial bridging. From the authors' personal dataset.

for alcohol septal ablation in symptomatic patients with hypertrophic obstructive cardiomyopathy whose basal septum is supplied by this branch of the RCA. In addition, a descending septal branch from the RCA may be an important source of collateral retrograde filling of a proximally occluded LAD.

MYOCARDIAL BRIDGING: ANOMALY OR VARIANT?

There is some confusion whether myocardial bridges constitute an anomaly or a normal variation. The prevalence of myocardial bridging varies between 0.15%-25% angiographically and 5%-86% at autopsy, and therefore its frequency in the general population suggests that it should be considered a normal variant[1,3,5,16]. A myocardial bridge is defined as an atypical course of a coronary artery intramyocardially, which may result in compression of the vessel during systole (Figure 4). It must be pointed out that myocardial bridging is a fixed defect that is entirely different to the dynamic phenomenon of coronary artery spasm. Coronary spasm entails intense vasoconstriction of an epicardial coronary artery due to hyper-reactivity of vascular smooth muscle cells and occasionally some degree of endothelial dysfunction in the presence of vasoconstrictor stimuli, leading to occlusion or near occlusion of the vessel and symptoms of Prinzmetal angina or acute coronary syndrome. Myocardial bridging usually involves the proximal and mid segment of the LAD and the length of the intramyocardial segment ranges between 10 and 50 mm. Patients with myocardial bridging are usually asymptomatic and the condition is considered benign[17]. However, there have been reports of rare cases of myocardial bridging related to ischemia and atypical angina. Possible causes are endothelial dysfunction, a delay in the diastolic reopening of the intramyocardial segment of the artery that was compressed during systole and a deeper intramyocardial course of the bridge, as opposed to the more benign superficial myocardial bridges[18-20]. Endothelial dysfunction is frequent in cases of myocardial bridging and may be revealed by functional studies, like intracoronary acetylcholine challenge. Any kind of percutaneous intervention on myocardial bridges is not supported at present due to the risks involved (restenosis, crushing and fracture of the stent)[4,21].

The presence of myocardial bridging in patients with hypertrophic cardiomyopathy (HCM) is a point of contention both in terms of clinical significance and

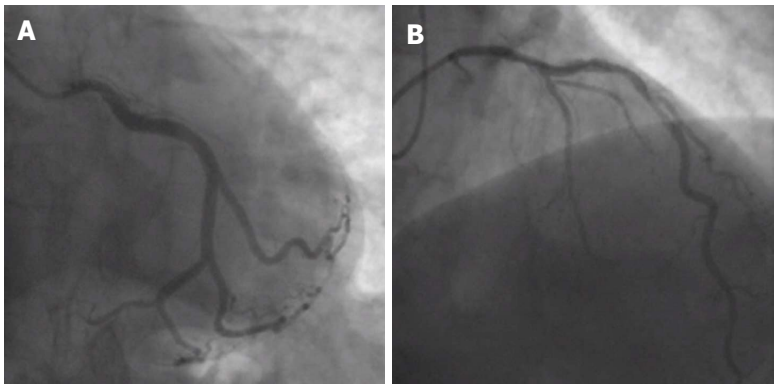

Figure 5 Absence of left main stem. A, B: Separate ostia of left circumflex artery (A, anteroposterior caudal view) and left anterior descending artery (B, shallow right anterior oblique view with cranial angulation) indicating a congenital absence of left main stem. From the authors' personal dataset.

therapeutic management. Myocardial bridging is much more frequent in patients with HCM compared to the general population, with a prevalence of up to 30%[22]. In HCM patients, myocardial bridging tends to be of the deep intramyocardial course of the LAD variety, but it does not seem to affect the prognosis and risk of sudden death in adults[22-24]. Therefore, in adult asymptomatic patients with HCM, myocardial bridging appears to be a benign condition that does not warrant any treatment. However, the issue remains open regarding younger and/or symptomatic patients with HCM. Myocardial bridging has not been ruled out as a possible cause of ischemia and sudden death in younger individuals with HCM and may be associated with angina symptoms in adult patients. Provided there is a positive test for functional ischemia in the LAD territory, treatment with stent implantation, coronary artery bypass surgery or surgical unroofing *via* supra-arterial myotomy may improve quality of life in adult symptomatic patients with HCM and documented myocardial bridging, as well as reduce risk of sudden cardiac death and alleviate symptoms in younger patients[23].

CLASSIFICATION OF CORONARY ARTERY ANOMALIES

Several classification schemes have been proposed for coronary artery anomalies. Based on clinical significance some authors categorize them as major and minor. Based on functional relevance they can be classified as: (1) anomalies that are associated with definite ischemia (for example, anomalous origin of the LMS from the pulmonary artery or atresia of a coronary artery); (2) anomalies that are not associated with ischemia (for example, separate ostia of LAD and LCX with absence of LMS, split LAD or split RCA); and (3) anomalies with exceptional ischemia (like anomalous origin of coronary artery from the contralateral sinus and coronary fistulae). However, the most detailed and accurate classification has been proposed by Angelini[3] and is based on anatomical features. According to this classification, coronary anomalies can be characterized as: (1) anomalies of origination and course of coronaries (separate ostia of LAD and LCX, anomalous location of coronary ostia within the aortic root, outside the sinuses of Valsalva or at the contralateral sinus, single coronary artery); (2) anomalies of intrinsic coronary anatomy (split RCA/LAD, ostial stenosis/atresia, ectasia, hypoplasia, intramural course/bridging, absent coronary artery, ectopic origin of first septal branch, ectopic origin of PDA from the LAD or a septal branch); (3) anomalies of coronary termination (mainly fistulas); and (4) anomalous collateral vessels.

Table 1 summarizes the most common variations, aberrations and anomalies for coronary anatomy, based on anomalies of origin, course, intrinsic coronary anatomy and termination.

ANOMALIES OF ORIGINATION AND COURSE

Absence of LMS

Absence of the LMS (separate ostia of LAD and LCX) is the most common coronary anomaly, with an incidence ranging between 0.41%-0.67% (Figure 5). It is a benign anomaly that causes no hemodynamic impairment or ischemic consequences[15,25].

Anomalous location of coronary ostia

A coronary ostium may have an anomalous origin but may be still located within the proper coronary sinus; in those cases, the coronary ostium may originate from a higher position or a lower position compared to the normal site of origin, or may stem from the commissural level. On the other hand, when the anomalous coronary ostium is located outside the proper coronary sinuses, it can present in a wide variety of locations, like the non-coronary sinus of Valsalva, the ventricles and ectopic sites in the aorta or the large arteries (ascending or descending aorta, anonymous artery, carotid arteries), or even smaller arteries (bronchial arteries, internal thoracic artery, *etc*). Anomalous origin of a coronary artery from the contralateral sinus of Valsalva is particularly interesting from a clinical point of view,

Table 1 Classification of coronary artery variants, aberrations and anomalies

Variations/anomalies of origin and course
1 Separate ostia of LAD and LCX (absent left main stem)
2 Separate ostium of conus branch
3 Anomalous location of coronary ostium
Within sinuses of Valsalva
High, low or commissural
From posterior ("non-coronary") sinus
Outside sinuses of Valsalva
Ascending aorta, aortic arch, innominate artery
Descending aorta
Bronchial arteries
Pulmonary arteries
Anomalous origin from contralateral sinus
4 Single coronary artery
Variations/anomalies of intrinsic coronary anatomy
1 Trifurcation of left main (presence of ramus branch)
2 Wrap-around LAD (supplying apical inferior wall)
3 Descending septal branch from RCA (supplying basal septum)
4 Split RCA
5 Split LAD
6 Hypoplasia of coronary artery
7 Atresia of coronary artery
8 Ectasia of coronary arteries
9 Myocardial bridging
Anomalies of coronary termination
1 Fistulas
2 Small number of arteriolar/capillary ramifications

LAD: Left anterior descending artery; LCX: Left circumflex artery; RCA: Right coronary artery.

because these anomalies can be associated with sudden cardiac death, especially when the anomalous coronary artery crosses interarterially between the aorta and the pulmonary artery[26-30].

Anomalous origin of coronary ostium from contralateral sinus

A coronary artery that originates from the contralateral sinus of Valsalva can follow five potential paths towards its perfusion territory: (1) pre-pulmonic, anterior to the right ventricular outflow tract (usually benign, though rarely associated with angina); (2) retro-aortic, posterior to the aortic root (no hemodynamic consequences); (3) trans-septal, with a subpulmonic intramyocardial course; (4) retro-cardiac, behind the mitral and tricuspid valves, in the posterior atrioventricular groove; and (5) inter-arterial, between the aorta and the pulmonary artery[1-3].

The inter-arterial path has clinical significance, as it has been associated with an increased risk of sudden cardiac death, especially in young athletes[1-4,31,32]. The causes are not clear and several explanations have been proposed. In some cases, autopsy findings have shown an acute angle in the take-off of the anomalous coronary artery with a slit-like lumen and a proximal course between the aorta and the pulmonary trunk[2]. In other cases, histological examination has also shown an intramural course of the anomalous coronary within the aortic wall. It has been proposed that the acute angulation and slit-like ostium of the anomalous coronary vessel predispose to myocardial ischemia. Exercise-induced expansion of the aortic root and the pulmonary trunk compresses and exacerbates the slit-like ostium, resulting in further ischemia[4,6,33,34]. A scissors-like mechanism that compresses the anomalous coronary between the aorta and the pulmonary artery has also been suggested[3,35]. Intravascular ultrasound studies have demonstrated an intramural proximal intussusception of the ectopic artery at the aortic wall for a variable distance[36,37]. The intussuscepted segment of the vessel is smaller in circumference compared to its more distal segment (circumferential hypoplasia), and its cross-section is ovoid instead of circular. These parameters lead to a lateral luminal compression that is present throughout the whole of the cardiac cycle but even more pronounced during systole[3,37]. Furthermore, the intramural segment has thin inner and outer aortic wall layers. Therefore, the section of the aorta that is penetrated by the ectopic artery is a localized weak spot, prone to more extensive distensibility, which can further exacerbate stenosis and ischemia[37].

Ectopic RCA originating from the left sinus of Valsalva has a frequency of 0.03%-0.92% (Figure 6), and ectopic LAD arising from the RSV has a frequency of 0.03% (Figure 7)[1]. Both of these anomalies may be associated with an intramural inter-arterial course, in which case there is an increased risk of sudden cardiac death. Ectopic origin of the LCX from the right sinus of Valsalva (Figure 8) or from the proximal RCA is the second most common coronary artery anomaly, with a frequency of 0.37%[1,14,38,39], but it is considered benign and the course of the ectopic LCX is usually retroaortic or retrocardiac[4,15].

It must be noted that anomalous origin of a coronary artery from an opposite sinus of Valsalva is related with sudden death mostly in young athletes < 35 years old but less frequently in older patients. Symptoms like angina, syncope, heart failure and myocardial infarction may appear in both age groups but are seen more frequently in older patients. It has been proposed that stiffening of the aortic wall in older adults is the reason why sudden death is less frequent in this age group[3,40]. Diagnosis of anomalous origin of a coronary artery from the contralateral sinus is often difficult, since most of the times patients are asymptomatic prior to sudden cardiac death. However, there have been some reports of premonitory symptoms like syncope or chest pain prior to sudden death[2,41,42]. Diagnostic workup in patients with the above symptoms (especially young athletes) must include electrocardiography, Holter monitoring and focused expert echocardiography. If at least two normally located coronary ostia can be identified with echocardiography, no further investigations are needed[3]. However, if echocardiographic findings are inconclusive, further imaging with computed tomography or magnetic resonance imaging is recommended[3,43-45]. Treadmill evaluation is unfortunately hampered by a high incidence of false positive and false negative

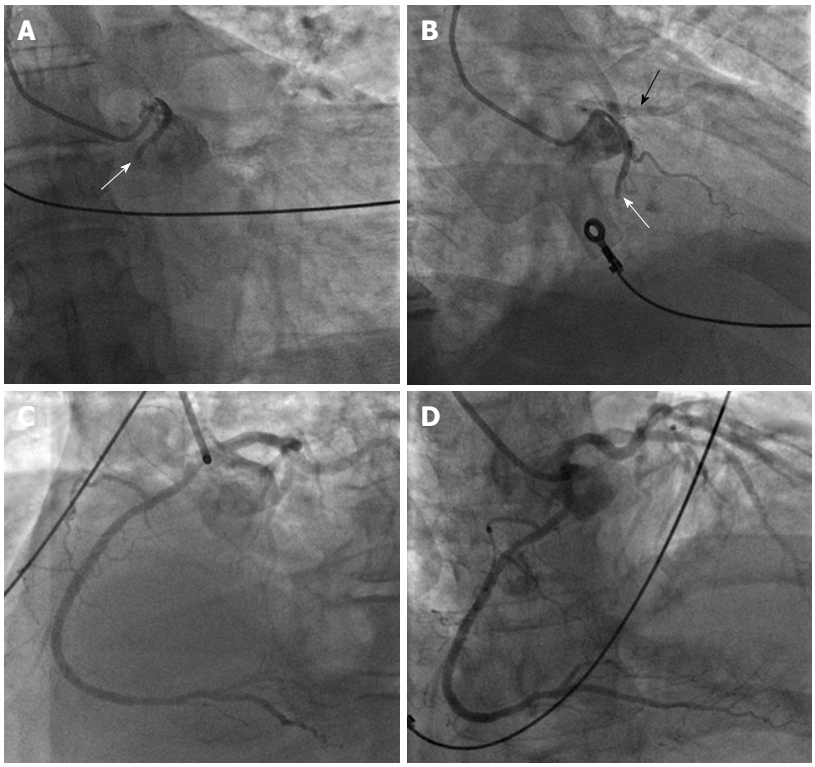

Figure 6 Ectopic right coronary artery originating from the left sinus of Valsalva. A, B: Proximal occlusion of anomalous right coronary artery (RCA) (white arrows) with origin from the left sinus of Valsalva in a patient with inferior wall ST elevation myocardial infarction (A: anteroposterior caudal view; B: right anterior oblique view). The black arrow in panel B shows a patent proximal left anterior descending artery in non-selective angiography of the left coronary artery (LCA); C, D: Left anterior oblique view with cranial angulation (C) and anteroposterior cranial view (D) show the LCA and an excellent final angiographic of the anomalous RCA after successful primary percutaneous coronary intervention. From the authors' personal data and from Ref.[73] (modified with permission).

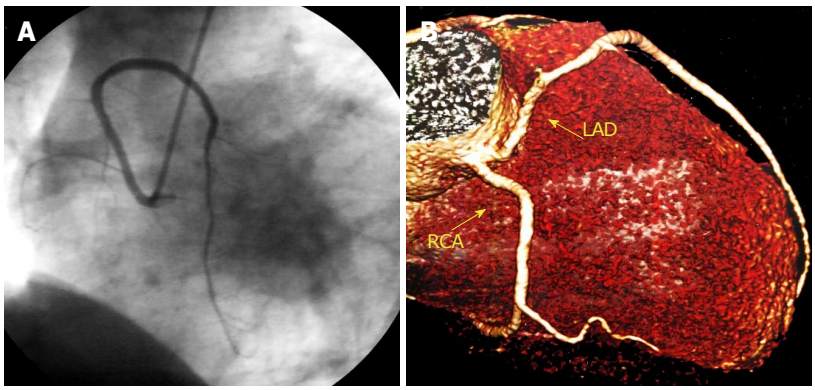

Figure 7 Ectopic left anterior descending artery originating from the right sinus of Valsalva. A: Left anterior oblique view with cranial angulation of the left anterior descending artery (LAD) originating from the right Valsalva sinus in coronary angiogram; B: Reconstructed image from computed tomography coronary angiogram showing both LAD and right coronary artery arising from the right sinus of Valsalva. From the authors' personal dataset. LAD: Left anterior descending; RCA: Right coronary artery.

results[2,37,46]. If the anomaly is confirmed, patients should undergo nuclear stress testing to evaluate exercise-induced ischemia and to establish a baseline for follow-up. Coronary angiography may reveal additional obstructive coronary disease, and intracoronary imaging establishes the severity of the condition[3,4]. Intravascular ultrasound and/or optical coherence tomography findings that determine the severity of an anomalous origin of a coronary artery from an opposite sinus include the length of the intramural segment, the hypoplasia index that quantifies the severity of the circumferential hypoplasia (ratio of the circumference of the intramural segment vs the circumference of the more distal epicardial segment of the vessel), the vessel asymmetry score (ratio of transverse to longitudinal diameter in a cross-sectional image from intravascular ultrasound) and the systolic vs diastolic cross-sectional area of stenosis during a cardiac cycle at rest and during simulated exercise with infusion of saline, atropine and dobutamine (SAD test)[4,47]. When an anomalous left coronary artery (LCA) with origin from the right sinus of Valsalva is diagnosed incidentally during coronary angiography, specific

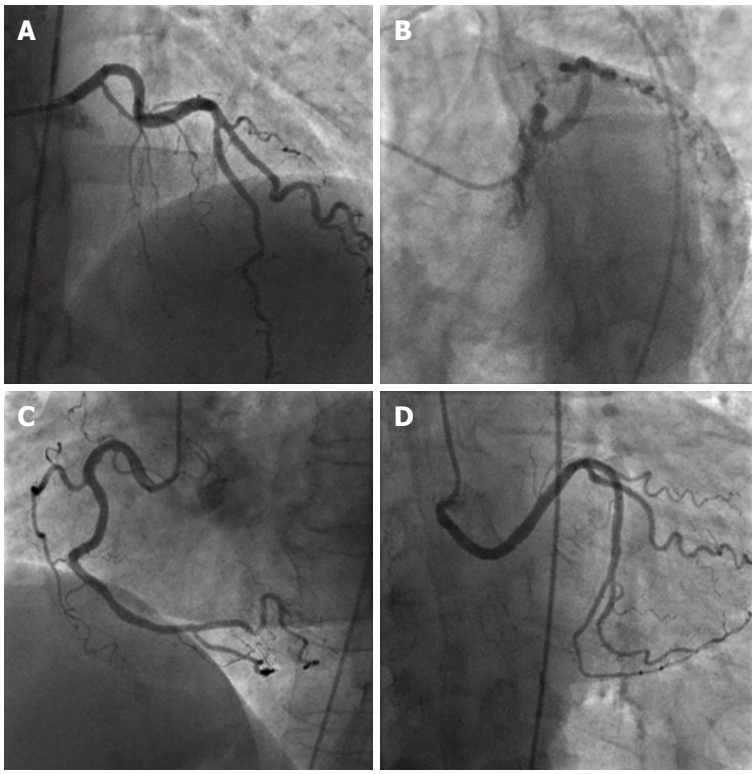

Figure 8 Ectopic left circumflex artery originating from the right sinus of Valsalva. A, B: Left coronary artery providing left anterior descending artery, with absence of left circumflex artery (LCX) (A: anteroposterior cranial view; B: left anterior oblique view with caudal angulation); C, D: Separate origin of right coronary artery (C, left anterior oblique view) and aberrant LCX from the right sinus of Valsava (D, anteroposterior caudal view). From the authors' personal dataset.

angiographic anatomical findings help differentiate between the inter-arterial and the more benign trans-septal varieties of this anomaly, since in the trans-septal origin the LMS gives rise to the first septal branch, presents a mild concentric myocardial bridge effect at the distal segment and connects with mid-LAD[4]. However, computed tomography remains the most accurate method to characterize the course of ectopic coronary arteries.

Asymptomatic patients with anomalous RCA arising from the left sinus of Valsalva with a negative nuclear stress test need regular follow-up only. Symptomatic patients and asymptomatic patients with a positive nuclear stress test must be further assessed with intra-coronary imaging with intravascular ultrasound or optical coherence tomography, and if a significant stenosis or high risk features are found, percutaneous coronary intervention with stent[3,36,48] or surgical repair should be offered. Patients with anomalous LMS arising from the right sinus of Valsalva should undergo surgical repair regardless of symptoms, if younger than 35 years old. Older patients should undergo surgery if they develop symptoms or if they have a positive nuclear stress test[4]. Surgical options include osteoplasty (creation of a new ostium at the end of the ectopic artery's intramural segment), direct reimplantation of the ectopic artery at the aortic root (a challenging procedure) and unroofing of the intramural segment (excising of the common wall located between the aorta and the anomalous coronary)[4,33,49-51]. Currently, unroofing is the most favored of these procedures. Bypass surgery with an internal mammary artery is not preferred, because of the high risk of regression of the graft lumen due to competitive flow[4,52,53].

Anomalous origin of coronary arteries outside the aortic root

The most dramatic clinical appearance in this group of congenital coronary anomalies occurs when the ectopic coronary arises from the pulmonary artery. The RCA originates from the pulmonary artery in 0.002% of the general population. In this anomaly, blood flows from the LCA to the RCA *via* collaterals and further back into the pulmonary artery. Most patients with this anomaly are asymptomatic; however, sudden cardiac death, heart failure and syncope have been occasionally reported[1,15,25].

Anomalous origin of the LCA from the pulmonary artery (ALCAPA) is called Bland-White-Garland syndrome and has a low prevalence of 0.008%. The RCA is dilated and provides extensive collaterals to LCA. This condition may coexist with aortic coarctation and a patent ductus arteriosus. Most patients (about 85%) develop symptoms of myocardial ischemia and heart failure in infancy (Figure 9) and die within the first year of life. However, a minority of patients may remain asymptomatic and survive into adulthood, probably because of adequate blood flow to the LCA territory from the RCA collaterals (Figure 10). Treatment is surgical and reimplantation of the LMS onto the aorta is

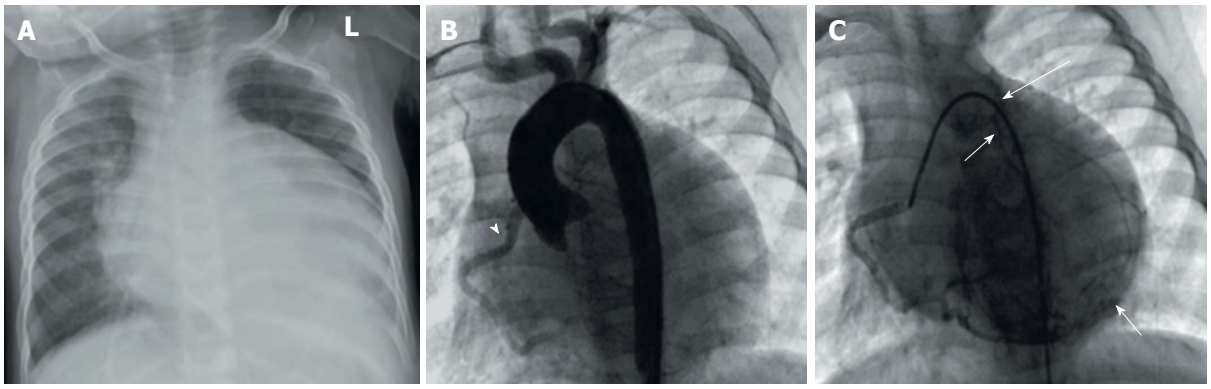

Figure 9 Anomalous origin of the left coronary artery from the pulmonary artery in infant. A: Cardiomegaly in chest X-ray; B: Aortogram showing only right coronary artery (RCA) originating from the aortic sinuses (arrowhead) but no left coronary artery; C: Selective angiography of RCA shows extensive collaterals from the RCA backfilling the left system and the pulmonary artery (arrows). Reproduced from ref. [74].

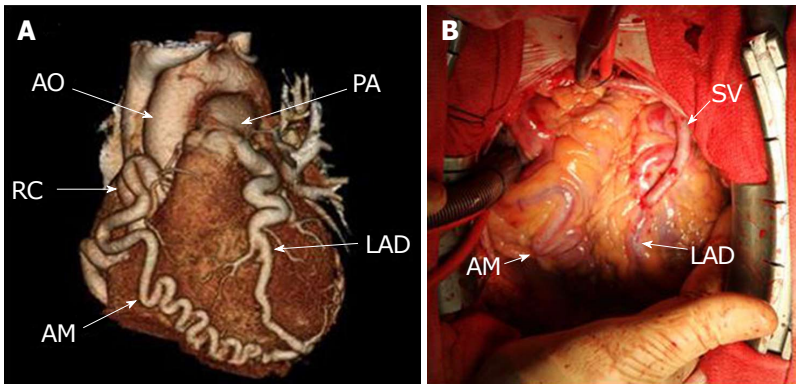

Figure 10 Anomalous origin of the left coronary artery from the pulmonary artery in adult. A: Three-dimensional reconstruction of computed tomography images showing prominent collaterals from right coronary artery to the left anterior descending artery (LAD), while LAD originates from the pulmonary artery; B: Coronary bypass grafting with a saphenous vein graft to the LAD. Reproduced from ref. [75]. SV: Saphenous vein; RC: Right coronary; LAD: Left anterior descending.

the preferred method. However, the procedure is more technically challenging in adults due to the frailty of the coronary artery. Ligation of the LCA ostium and coronary artery bypass grafting with venous or arterial grafts is a viable alternative in these cases (Figure 10)[14,15,25,54,55]. The LAD arises from the pulmonary artery extremely rarely in 0.0008% of the general population and is associated with myocardial ischemia and sudden cardiac death[1,15,38]. There have also been reports of all coronary arteries originating from the pulmonary artery. Patients die within the first month of life, and the condition frequently coexists with patent ductus arteriosus and other major congenital cardiac anomalies[25,56]. Finally, cases of accessory coronary arteries arising from the pulmonary artery have been documented. The most frequent artery involved is the conus branch, and this anomaly has no clinical significance[1,25].

Single coronary artery

There have been several reports of presence of a single coronary artery with a variety of anatomies. A single coronary artery may originate either from the left or the right Valsalva sinus and may sometimes coexist with other congenital anomalies[1]. Lipton *et al*[57] proposed an anatomical classification of single coronary arteries based on location of the ostium (R: right Valsalva sinus, L: left Valsalva sinus), anatomical distribution (Ⅰ: single coronary artery following course of normal left or RCA, Ⅱ: a coronary artery with abnormal origin from the proximal segment of the other coronary artery, Ⅲ: single coronary artery with a origin from the right Valsalva sinus, with the LAD and LCX originating separately from the common trunk) and course of the transverse trunk (A: anterior course to the great vessels, B: between the aorta and the pulmonary artery, P: posterior course, S: septal course, C: combined type).

When the single coronary artery has an origin from the left sinus, the RCA may originate from the proximal or mid segment of the LAD and follows a course anterior to the pulmonary artery or between the aorta and the pulmonary artery towards the right atrioventricular groove (Figure 11). The prevalence of this anomaly is around 0.024%-0.066% in the general population[1,58,59]. This anomaly is usually benign, provided that the course of the anomalous RCA is not inter-arterial. If, however, the anomalous RCA crosses between the aorta and the pulmonary artery, myocardial ischemia and sudden cardiac death may occur[29,58,60,61]. Rarely, the RCA may be supplied by the distal LCX (Figure 12).

When the single coronary artery originates from

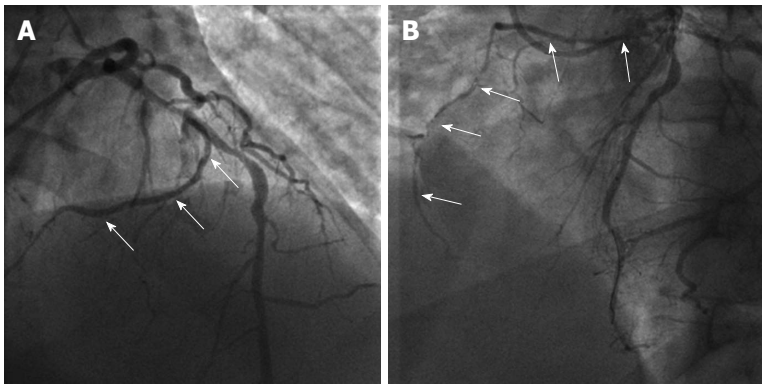

Figure 11 Single coronary artery from the left sinus. A, B: Angiographic images showing the origin (arrows in A, anteroposterior cranial view) and course (arrows in B, left anterior oblique view) of the right coronary artery from the mid segment of left anterior descending artery. From the authors' personal dataset and from Ref. [76] (modified with permission).

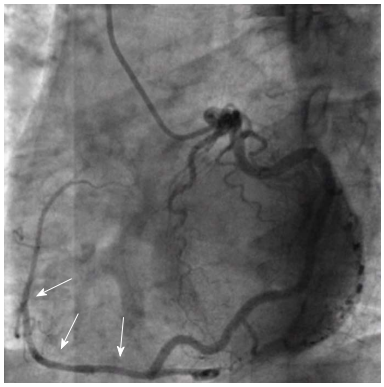

Figure 12 Single coronary artery from the left sinus. Angiographic images showing the origin and course (arrows) of the aberrant right coronary artery from the distal segment of left circumflex artery (left anterior oblique view). From the authors' personal dataset.

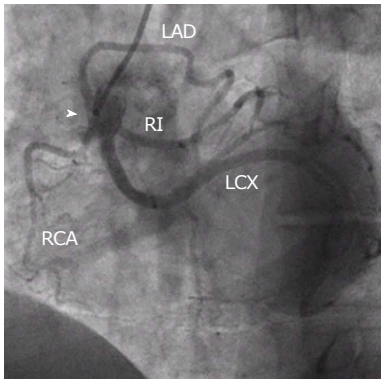

Figure 13 Single coronary artery originating from the right sinus. Common trunk from the right sinus (arrowhead) providing right coronary artery, left anterior descending artery, left circunflex artery and ramus intermedius. From the authors' personal dataset. RCA: Right coronary artery; LAD: Left anterior descending; LCX: Left circunflex artery; RI: Ramus intermedius.

the right sinus (Figure 13), the LCA follows an anterior or inter-arterial path towards its perfusion territory. Prevalence is around 0.02%-0.05%, and this condition is associated with sudden cardiac death more frequently than an anomalous single coronary artery originating from the left sinus. The anterior variant is usually - but not always - benign, whereas the inter-arterial variant is the potentially most threatening one[1,15,62].

ANOMALIES OF INTRINSIC CORONARY ANATOMY

Split RCA

A split RCA is the most common type of coronary artery anomaly, with a frequency around 1% in the general population. It is a benign anomaly in which the RCA has a split PDA (Figure 14). The split RCA is divided early into an anterior and posterior branch. The anterior branch runs through the free wall of the right ventricle and supplies a PDA that follows the distal posterior interventricular groove, whereas the posterior branch follows the right atrioventricular groove and leads to a PDA that runs through the proximal segment of the posterior interventricular groove[1,63-65].

Split LAD

There have been reported four types of split LAD. In types 1-3, the LAD branches into two subdivisions, a short one that terminates high in the anterior interventricular groove and a longer one that branches off the proper LAD, descends on the left (type 1) or the right (type 2) ventricular side of the anterior interventricular groove or intramyocardially (type 3) and finally reenters the anterior interventricular groove distally. Sometimes in type 3 the intramyocardial LAD never emerges but instead provides septal branches to the apical septum. Type 4 is an entirely different entity, in which a short LAD originates from the LMS and terminates high in the anterior interventricular groove, while a duplicated LAD arises from the RCA and follows a pre-pulmonic, septal or inter-arterial course towards the distal anterior interventricular groove. This anomaly is relatively benign; however, it may complicate significantly surgical intervention[7,66,67].

Atresia of LMS

True atresia of the LMS is an extremely rare congenital

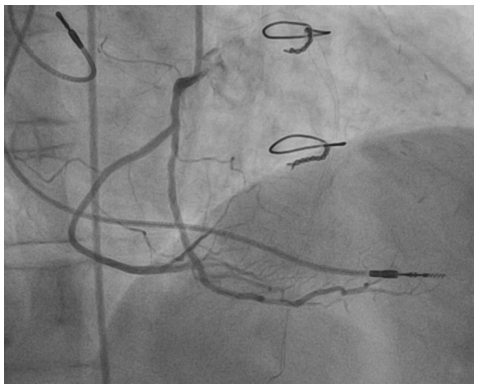

Figure 14 Split right coronary artery. Right coronary artery is divided early into two branches, both of which supply posterior descending arteries. From the authors' personal dataset.

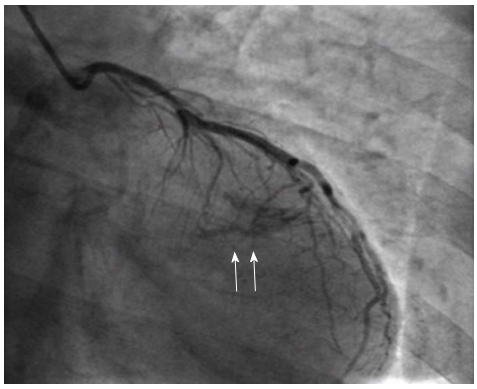

Figure 15 Coronary fistula. Opacification of the left ventricle during injection of the left coronary artery (arrows) indicate the presence of a fistula. From the authors' personal dataset.

disorder in which there is neither left coronary ostium nor LMS. The LAD and the LCX connect but end blindly proximally. The left system receives blood retrogradely *via* collaterals from the RCA, but in most cases blood flow is inadequate for the needs of the perfusion territory, resulting in symptoms of myocardial ischemia and an increased risk of sudden cardiac death. This condition often coexists with supravalvular aortic stenosis and other congenital cardiac defects. Patients usually become symptomatic during infancy or early childhood, but there have been reports of patients who remained asymptomatic during childhood and young adulthood and developed symptoms later in life. Due to poor prognosis, atresia of the LMS requires surgical intervention with coronary artery bypass grafting and an internal mammary artery graft to the LAD in adults, whereas in children surgical reconstruction of the LMS with a baffle of ascending aorta may be preferable[1,68].

Hypoplasia of coronary arteries

Congenital hypoplasia of coronary arteries presents as a narrowed luminal diameter (less than 1.5 mm) in one or two of the three main coronary arteries with no compensatory branches. Limitations to blood flow caused by the narrow lumen lead to symptoms of myocardial ischemia and sudden cardiac death. Most frequent variants in reported cases are hypoplasia of both LCX and RCA and hypoplasia of the LAD. Treatment options are extremely limited. Transmyocardial revascularization and implantable cardioverter-defibrillator have been suggested in the literature[13,69-71].

ANOMALIES OF CORONARY TERMINATION

Coronary fistulae are defined as abnormal connections between the termination of a coronary artery or its branches and a low-pressure vascular space, like a cardiac chamber or a great vessel (Figure 15). They may present as small discrete fistulae or more complex arteriovenous malformations. Reported prevalence is 0.3%-0.87% in the general population. Most patients are asymptomatic; however, there have been reports of symptoms of myocardial ischemia, heart failure, arrhythmia and sudden cardiac death, pulmonary hypertension, rupture and endocarditis, usually after the age of 50.

Several mechanisms for the causes of these symptoms have been proposed. Fistulae draining into the right heart chambers (60% of cases) function as left to right shunts and may cause right ventricular volume overload. Termination in a low pressure space causes enlargement and tortuosity of the fistulous coronary artery that leads to vascular wall degeneration, aneurysmatic dilatation and predisposition to rupture. Furthermore, the dilatation of the involved coronary artery may cause distortion of the aortic root and aortic valve disruption and regurgitation. Myocardial ischemia may result from two separate mechanisms: (1) a persistent or episodic steal of blood flow from the normal coronary branches to the competing fistulous low-pressure tract; and (2) stenosis and obstruction of side branches secondary to thrombus formation related to ulceration and atherosclerosis in the aneurysmal coronary artery. Indications for closing a coronary fistula are not well established. Symptomatic patients should definitely be treated as well as patients with a pulmonary to systemic flow ratio that exceeds 1.5 and patients with severe aneurysmal degeneration. Available options are surgical closure at the drainage site or catheter-based repair with catheter occlusion devices. It is generally recommended to intervene before adulthood, since negative postoperative remodeling of the fistulous artery is much more common in children compared to adults[4,15,17,37,38].

Furthermore, we have recently described a fistulous tract from the left ventricle to the Thebesian venous network of the myocardium[72]. Thebesian veins are small valveless veins in the walls of all four heart chambers that act as an alternative channel of nutrition to the myocardium or as venous drainage conduits. They are more prevalent in the right heart chambers, but they can also appear in the left ventricle. We described the case of inadvertent angiography of a large

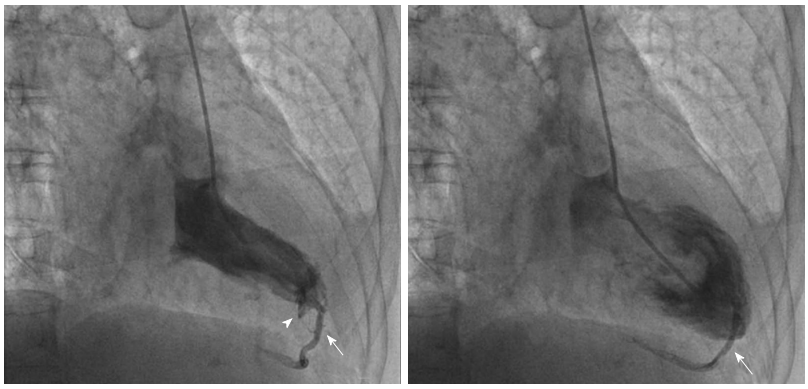

Figure 16 Inadvertent cardiac phlebography through the Thebesian network. A, B: Right anterior oblique views in systole (A) and diastole (B) during left ventriculography show a minor subendocardial staining (arrowhead) and opacification of a posterior interventricular vein (arrows), due to opening of a 'functional' fistula between the left ventricle and the cardiac vein through the Thebesian network. From the authors' personal dataset and from Ref. [72] (with permission).

posterior interventricular cardiac vein during a left ventriculogram. This happened because the end-hole of the angiographic catheter inadvertently engaged the endocardial opening of a small Thebesian vein, leading to retrograde opacification of the cardiac vein through the Thebesian network (Figure 16)[72].

CONCLUSION

It becomes apparent that the term "coronary artery anomalies" covers a very wide spectrum of anatomical entities with diverse clinical manifestations and varying degrees of severity. Coronary artery variants have a prevalence of at least 1% in the general population and are mostly clinically benign. On the other hand, coronary artery anomalies are much more uncommon, and their clinical significance varies from benign without ischemic consequences to ischemia-related symptoms and arrhythmias leading to an increased risk of sudden cardiac death. Anomalous origin of a coronary ostium from the contralateral sinus is the anomaly most frequently associated with sudden cardiac death, in particular in the case of anomalous LCA from the right sinus or if the anomalous coronary artery has a course between the aorta and the pulmonary artery or other high-risk features. Other coronary anomalies, like anomalous origin of the LCA from the pulmonary artery or atresia of the LMS, have also been associated with extensive ischemia and high risk of sudden cardiac death early in infancy or in early adulthood. Accurate diagnosis, risk-assessment and appropriate choice of treatment are of utmost importance, since coronary artery anomalies constitute the second most common cause of sudden cardiac death in young competitive athletes. The rapid advancement of imaging techniques, including intravascular ultrasound, optical coherence, computed tomography and magnetic resonance imaging, have provided us with a wealth of new information on the subject as well as more accurate diagnostic criteria regarding the severity of these conditions that allow risk-stratification for sudden cardiac death and provide guidelines for optimal treatment. Consultation of focused experts by individual cardiologists in cases of suspected or diagnosed coronary artery anomalies and systematic referral of diagnosed patients to specialized centers play a significant role in timely diagnosis, appropriate management and successful prevention of sudden cardiac death.

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MINIREVIEWS

Chronic ischemic mitral valve regurgitation and surgical perspectives

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Abstract

Chronic ischemic mitral valve regurgitation is a result of disturbed left ventricular geometry secondary to myocardial ischemia in the absence of intrinsic mitral valve pathology. It is a common complication after myocardial infarction, and patients who have ischemic mitral regurgitation (IMR) have a worse prognosis compared to patients who have ischemic heart disease alone, and this is directly related to the severity of IMR. Medical therapy has limited efficacy, and surgical options including various repair techniques and valve replacement had been tried with variable success. Still there is intense debate among surgeons whether to interfere with moderate degree IMR at the time of coronary artery revascularization.

Key words: Mitral regurgitation; Myocardial infarction; Ring annuloplasty; Valve replacement

Core tip: Chronic ischemic mitral valve regurgitation is a valvular dysfunction secondary to myocardial infarction. Debates among surgeons surround the decision to intervene and the type of intervention in moderate degree ischemic regurgitation. A comprehensive approach addressing the whole pathology of myocardial ischemia and ventricular dysfunction may be of value.

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INTRODUCTION

Chronic ischemic mitral regurgitation (IMR) is a complication that is determined by the extent and severity of myocardial infarction as well as ventricular dyssynchrony and afterload[1]. In contrast to primary mitral valve regurgitation caused by structural valve abnormality in which there is an increasing agreement among surgeons for therapeutic options, IMR management options are still a matter of debate among clinicians[2].

An increasing consensus among authors indicates that a severe form of IMR should be corrected, however surgical intervention with moderate forms of IMR at the time of coronary revascularization is still a matter of debate[3]. There has been an evolution in surgical techniques of mitral valve repair over the years, however the continuous left ventricular remodeling process resulting in recurrence of the valve incompetence remained a major drawback of this approach[4]. Mitral valve replacement preserving the subvalvular apparatus demonstrated a more durable valve competence and comparable left ventricular reverse remodeling and survival at a two year follow up period in comparison with mitral valve repair[5].

DEFINITION AND BURDEN OF ISCHEMIC MITRAL VALVE REGURGITATION

IMR is defined classically as mitral valve regurgitation due to a previous myocardial infarction[1]. Based on this definition, left ventricular remodeling consequences are considered integral parts leading to the development of IMR following myocardial infarction. Therefore, IMR is a complication of myocardial infarction due to structural left ventricular dysfunction in the presence of normal intrinsic mitral valve structure[6]. This definition takes into consideration both the history of myocardial infarction as well as the resulting left ventricular abnormalities together. IMR is not a mitral valve disease per say, but a consequence of the disturbed closing and tethering forces related to the papillary muscle mechanics as a result of left ventricular remodeling following myocardial infarction[6]. Other mitral valve pathologies may coexist with a previous history of myocardial infarction like rheumatic or myxomatous mitral valve disease. These do not indicate an ischemic mitral valve disease, therefore the description of the mitral valve regurgitation depends on the mitral valve structure and the left ventricular structural dysfunction. Carpentier classification in 1983 characterized the pathophysiology of IMR to either 1. Mitral leaflet motion restriction in systole, type ⅢⅠb or 2. Isolated mitral annular dilatation, type Ⅰa[7].

IMR is a significant clinical problem that affects 1.6-2.8 million people in the United States and it may happen in 10%-20% of patients with ischemic heart disease[5,8]. With the new technologies implemented in the current era of coronary artery interventions and the aging population, one can expect that the incidence of IMR will increase, which had been demonstrated to have a significant negative impact on patient survival and the development of heart failure[9].

Grigioni *et al*[9] demonstrated in patients with Q wave after myocardial infarction that the prevalence of adverse events had been linked directly to the presence and degree of severity of IMR. When patients are matched in their base line characteristics those who had a severe degree of IMR (ERO > 20 mm) are six times more likely to have heart failure compared to patients without IMR regardless of the symptomatology status (RR 6.4, 95%CI: 2.9 to 14.3; $P < 0.0001$). Therefore, detecting and quantifying IMR is highly crucial in planning a treatment strategy following myocardial infarction.

CHOICE OF SURGICAL INTERVENTION IN SEVERE IMR, REPAIR *VS* REPLACEMENT

There is an agreement among clinicians that severe IMR should be surgically treated, however treatment of moderate IMR is still a matter of debate[10]. Many changes have occurred in surgical approaches over the past years. Initially, mitral valve replacement with excision of the mitral valve apparatus was the primary choice because it restores the competency of the valve. The drawback of this approach is the impaired left ventricular function and geometry due to excision of the subvalvular apparatus[8]. Mitral valve repair using ring annuloplasty was another solution because it preserves the subvalvular apparatus and theoretically preserves the mitral valve competency. Proponents of this therapeutic modality take in consideration the unique shape of the mitral annular configuration in determining the mitral competence by decreasing the leaflet stress during systole[11]. This approach does work for type Ⅰ IMR, however it incompletely corrects type ⅢⅠb dysfunction. The ideal solution is to adopt a comprehensive approach that will take all the aspects of the disease in consideration. Physiological changes are asymmetric in the left ventricle geometry as well as the annulus, so new advances had been designed even in the ring technology to reshape the annulus taking in consideration the saddle pattern of the mitral annular configuration[12].

Whether to replace or repair severe chronic ischemic mitral valve regurgitation has been a subject of intense debate. The tradeoff between the durability of mitral valve repair is correcting a regurgitant valve *vs* an adverse consequence of prosthetic valve insertion. It was observed that patients, who had severe ischemic mitral valve regurgitation demonstrated a comparable

degree of left ventricular reverse remodeling between mitral valve repair and replacement at one year follow up[5]. However, the rates of recurrent mitral valve regurgitation amongst the survivors of the repair cohort were 32.6% at one year and 46% at the two year follow up[5]. Other forms of surgical options addressing the left ventricular geometrical changes had been tried with variable success rates. Fattouch *et al*[13] reported a durable mitral valve repair with less than 3% recurrence rate of moderate mitral valve regurgitation by adopting papillary muscle relocation, non-restrictive mitral annuloplasty, and myocardial revascularization in patients with severe IMR.

Lorusso *et al*[14] demonstrated that there was a comparable incidence of adverse outcomes between the repair and replacement matched groups in the short and long term follow up periods in patients with severe ischemic mitral valve regurgitation. However, mitral valve repair remained the strongest predictor for the need for mitral valve re-operation[14].

MODERATE IMR AT THE TIME OF CORONARY ARTERY BYPASS GRAFT

There is general agreement among clinicians that significant IMR should be addressed at the time of coronary artery bypass graft (CABG). However, the drawback of this approach is that a combined procedure may increase the risk of surgery on a sick heart and doing coronary revascularization alone may improve ventricular status. Whether to treat moderate IMR at the time of CABG has been a real debate in the field of cardiology and cardiac surgery. This led to the conduction of four randomized controlled trials, which are the only ones published until now addressing this subject[3,15-17].

Fattouch *et al*[3] concluded that a mitral valve intervention for significant functional mitral valve regurgitation at the time of CABG might improve the degree of functional mitral regurgitation, the New York Heart association functional class, and left ventricular ejection fraction. Chan *et al*[16] observed similar results as Fattouch *et al*. They demonstrated that there was an improvement in the degree of functional mitral regurgitation, reverse left ventricular remodeling, and functional capacity when mitral valve repair was added to coronary artery revascularization in the presence of moderate IMR.

A more recent conducted trial by Bouchard *et al*[15] demonstrated that there was no obvious clinical benefits of adding mitral valve intervention at the time of CABG after one year follow up, despite the tempting value early in the post-operative period. However, the major drawback of this trial is that it included only 31 patients in both cohorts. Smith *et al*[17] demonstrated that there was some degree of improvement of the mitral valve grade in association with mitral valve repair at the time of CABG. However, the incidence of adverse events was increased.

Evidence from observational studies also has been a matter of debate. Aklog *et al*[18] demonstrated that there was clear superiority in performing mitral valve repair for moderate IMR at the time of CABG compared to revascularization alone in correcting mitral valve incompetence. Kang *et al*[19] demonstrated in their study that the addition of mitral valve intervention might increase operative mortality compared to patients who have CABG alone.

With these conflicting results in the randomized controlled trials addressing this issue, Altarabsheh *et al*[20] published a systemic review and meta-analysis in 2017 that included the four randomized trials and seven relevant observational studies with a total of 1447 patients. They clearly demonstrated that the addition of mitral valve repair for moderate IMR at the time of CABG did not have survival or functional improvement at the five year follow up despite the fact that it may improve the degree of mitral valve competence.

CONCLUSION

IMR remains a significant complication of myocardial infarction and continued to have therapeutic challenges. Complex mechanisms involving mitral annulus and subvalvular apparatus play a role, and ideal surgical repair should take the whole pathology in consideration. Future repair techniques, which address disturbed left ventricular mechanics, may be of value, and currently mitral valve replacement preserving the subvalvular apparatus is a valid surgical option. Moderate IMR could be addressed by coronary revascularization alone at the time of CABG.

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ORIGINAL ARTICLE

Observational Study

Successful endovascular treatment in patients with acute thromboembolic ischemia of the lower limb including the crural arteries

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Abstract

AIM

To examine the efficacy and safety of the 6 French (6F) Rotarex®S catheter system in patients with acute limb ischemia (ALI) involving thromboembolic occlusion of the proximal and mid-crural vessels.

METHODS

The files of patients in our department with ALI between 2015 and 2017 were examined. In seven patients, the Rotarex®S catheter was used in the proximal segment of the crural arteries. Data related to the clinical examination, Doppler sonography, angiography and follow-up from these patients were further used for analysis.

RESULTS
Two patients (29%) had thrombotic occlusion of the common femoral artery, and the remaining five exhibited thrombosis of the superficial femoral artery and popliteal artery. Mechanical thrombectomy was performed in all cases using a 6F Rotarex®S catheter. Additional Rotarex®S catheter thrombectomy due to remaining thrombus formation with no reflow was performed in the anterior tibial artery in two of seven cases (29%), in the tibiofibular tract and posterior tibial artery in two of seven cases (29%) and in the tibiofibular tract and fibular artery in the remaining three of seven cases (43%). Ischemic symptoms resolved promptly in all, and none of the patients experienced a procedural complication, such as crural vessel dissection, perforation or thrombus embolization.

CONCLUSION
Mechanical debulking using the 6F Rotarex®S catheter system may be a safe and effective treatment option in case of thrombotic or thromboembolic occlusion of the proximal and mid-portion of crural arteries.

Key words: Thrombus aspiration; Rotarex®S mechanical debulking catheter; Crural arteries; Lower limb; Critical limb ischemia; Acute occlusion; Duplex sonography

Core tip: Herein, we report on seven consecutive patients with acute limb ischemia, who were treated by an endovascular approach, using the 6 French (6F) Rotarex® S catheter system for local mechanical thrombectomy. The procedures were effective in all cases, restoring flow and abolishing ischemic symptoms without causing any complications. Thus, mechanical debulking using the 6F Rotarex®S catheter system may be a safe and effective treatment option in the case of thrombotic occlusion of the proximal and mid-portion of crural arteries, obviating the need for local thrombolysis, which is associated with an increased risk for major bleeding.

Giusca S, Raupp D, Dreyer D, Eisenbach C, Korosoglou G. Successful endovascular treatment in patients with acute thromboembolic ischemia of the lower limb including the crural arteries. *World J Cardiol* 2018; 10(10): 145-152 Available from: URL: http://www.wjgnet.com/1949-8462/full/v10/i10/145.htm DOI: http://dx.doi.org/10.4330/wjc.v10.i10.145

INTRODUCTION

Acute limb ischemia (ALI) constitutes a medical emergency defined as a severely reduced perfusion of the leg resulting from a total or subtotal arterial occlusion, with symptoms debuting < 14 d prior to presentation. It has an incidence of around 140/million/year and a prevalence of 1%-3%[1,2]. Depending on the severity of symptoms, patients can be grouped according to the Rutherford classification of lower extremity ischemia[3]. Although significant advances have been made in the treatment of ALI, most of the studies still report an amputation rate of 10%-30% at 30 d[4-6]. Patients with thromboembolic ALI are especially at high risk for major amputation and death due to sepsis and multi-organ dysfunction. Such patients are usually older than 75 years and show further co-morbidities, including atrial fibrillation and history of heart failure[7].

Previous studies demonstrated the superiority of catheter-directed thrombolysis (CDT) compared to surgical treatment in regard to amputation-free survival in patients presenting with ALI[6,8]. However, this technique has its clear limitations in patients with an increased bleeding risk. Therefore, percutaneous mechanical thrombectomy systems have emerged in the last years as a valid therapeutic option in patients with ALI[9]. One such system, the Rotarex®S mechanical debulking catheter (Straub Medical, Wangs, Switzerland) is based on mechanical fragmentation and simultaneous aspiration of occlusion material, thus transporting the debris out of the patient. Several studies have shown a very high success rate of Rotarex®S alone or in combination with drug-coated balloons in terms of establishing vessel patency in patients with ALI[5]. However, operators should be cautious when using the 6 French (6F) Rotarex®S catheter in arteries below-the-knee because this catheter system is limited to vessel diameters of ⩾ 3mm and might cause dissection or perforation when used in smaller diameter arteries. Herein, we present the clinical safety and effectiveness of the 6F Rotarex®S system in a miniseries of seven patients with acute lower limb ischemia affecting their crural arteries.

MATERIALS AND METHODS

The files of 102 patients with thrombotic occlusions of the lower extremities between January 2015 and December 2017 at the Department of Cardiology and Vascular Medicine, Academic Teaching Hospital Weinheim were examined. In seven patients, the Rotarex®S catheter was used in the proximal segment of the crural arteries, and the data from these patients were further used for the analysis. In the remaining 95 patients, the Rotarex®S catheter was used for mechanical thrombectomy in iliac and femoropopliteal arteries. The study was approved by the local ethics committee of the University Hospital Heidelberg (S-100/2017). Retrospective data were collected in accordance with the Declaration of Helsinki.

Interventional treatment

All patients received a bolus of 2500 U of heparin after placement of a 6F sheath introducer in the femoral artery. During interventional treatment, all patients also received heparin to reach an activated clotting time of > 300 s. If necessary, patients also received 500 mg

Table 1 Baseline characteristics of our seven patients

	Patient A	Patient B	Patient C	Patient D	Patient E	Patient F	Patient G	All patients
Sex	Male	Male	Male	Male	Male	Male	Male	All male (100%)
Age (yr)	89	72	55	67	85	67	80	74 ± 11
Cardiovascular risk factors	Hypertension Hyperlipidemia Type 2 DM	Hypertension Hyperlipidemia Type 2 DM	Hypertension Hyperlipidemia Type 2 DM Smoking	Hypertension Hyperlipidemia Smoking	Hypertension Hyperlipidemia Type 2 DM	Hypertension Hyperlipidemia Smoking	Hypertension Hyperlipidemia	Hypertension (100%) Hyperlipidemia (100%) Type 2 DM (57%) Smoking (43%)
PAD history	No	Surgical endatherectomy of the left common femoral artery 2012	No	Prior Angioplasty and stent placement in the left popliteal artery 2015	No	Prior Angioplasty and stent placement in the left popliteal artery 2016	No	3/7 (43%)
LV function	Moderately reduced	Normal	Normal	Normal	Severely reduced	Mildly reduced	Normal	Reduced in 3/7 (43%)
Symptoms onset	For 12 h	For 16 h	For 2 h	For 12 h	For 36 h	For 6 h	For 36 h	17 ± 13
CAD history	3 vessel CAD	3 vessel CAD	No	3 vessel CAD	3 vessel CAD	3 vessel CAD GABG 2005	3 vessel CAD	6/7 (86%)
Baseline medication	Aspirin ß-blocker ACE inhibitor Statin Diuretics	Aspirin ß-blocker ACE inhibitor Statin	Aspirin ACE inhibitor Statin	Aspirin ß-blocker ACE inhibitor Statin Diuretics	Aspirin ß-blocker ACE inhibitor Statin Diuretics	Aspirin ß-blocker ACE inhibitor Statin Diuretics	Aspirin ß-blocker ACE inhibitor Statin	Aspirin (100%) ß-blocker (86%) ACE inhibitor 100%) Statin (100%) Diuretics (57%)
Other comorbidities	Reduced renal function with estimated GFR of -40 mL/min/1.73 m² Atrial fibrillation Heart failure NYHA Ⅲ	Reduced renal function with estimated GFR of -50 mL/min/1.73 m² Atrial fibrillation	None	Reduced renal function with estimated GFR of -45 mL/min/1.73 m² Atrial fibrillation	Reduced renal function with estimated GFR of -55 mL/min/1.73 m² Atrial fibrillation Heart failure NYHA Ⅲ	Reduced renal function with estimated GFR of -50 mL/min/1.73 m²	Reduced renal function with estimated GFR of -40 mL/min/1.73 m² Atrial fibrillation Heart failure NYHA Ⅱ	Reduced renal function (86%) Atrial fibrillation (71%) Heart failure (43%)

ACE: Angiotensin converting enzyme; LV: Left ventricular; CAD: Coronary artery Disease; PAD: Peripheral artery disease; NYHA: New York Heart Association; GFR: Glomerular filtration rate.

aspirin during and 300 mg clopidogrel during or after the interventional procedure. If additional thrombolysis was deemed necessary, a bolus of 10 mg recombinant tissue plasminogen activator (rtPA) was administrated after placement of the dedicated thrombolysis catheter (Unifuse catheter, AngioDynamics, Netherlands). Postprocedural rtPA was continuously administered at an infusion rate of 1 mg/h for 6-18 h, adding heparin to achieve partial thromboplastin time of 50-60 s.

Statistical analysis

Continuous variables are presented as numbers, providing the corresponding range of each variable. Categorical variables are represented as percentages. Measures of the vessel diameters were conducted using ImageJ software (version 1.50, NIH, Bethesda, MD, United States).

RESULTS

Demographic characteristics and procedural data

We present a mini-series of seven patients (Patient A-G). Baseline characteristics of our patients are provided in Table 1. Patients were referred to our department with symptoms of ALI with new onset of pain, paleness and pulselessness during the last 17 ± 13 h. Duplex sonography revealed thrombotic occlusion of the common femoral

Table 2 Duplex sonography and digital subtraction angiography findings of our patients

	Patient A	Patient B	Patient C	Patient D	Patient E	Patient F	Patient G
Duplex sonography findings	Thrombotic CFA occlusion	Thrombotic CFA occlusion	Thrombotic occlusion of the distal SFA	Thrombotic occlusion of the popliteal artery	Thrombotic occlusion of the distal SFA	Thrombotic occlusion of the distal SFA	Thrombotic occlusion of the popliteal artery
DSA findings	Thrombotic CFA occlusion	Thrombotic CFA occlusion	Thrombotic occlusion of the distal SFA and of the popliteal artery	Thrombotic occlusion of the popliteal artery	Thrombotic occlusion of the distal SFA and of the popliteal artery	Thrombotic occlusion of the distal SFA and of the popliteal artery	Thrombotic occlusion of the popliteal artery
Treated crural vessels	Proximal and mid tibial anterior artery	Proximal and mid tibial anterior artery	Proximal and mid posterior tibial artery	Tibiofibular tract and posterior tibial artery	Tibiofibular tract and fibular artery	Tibiofibular tract	Tibiofibular tract and fibular artery
Rotarex catheter	6F	6F	6F	6F	6F	6F	6F
Local lysis	Yes	No	No	Yes	Yes	Yes	Yes
Second look DSA	Yes	No	No	Yes	Yes	Yes	Yes

CFA: Common femoral artery; SFA: Superficial femoral artery; DSA: Digital subtraction angiography; 6F: 6 French.

Table 3 Overview of the diameters of the crural vessels, where 6 French Rotarex®S catheter thrombectomy was performed

	Proximal anterior tibial artery	Mid anterior tibial artery
Patient A	3.2 mm*	2.8 mm
Patient B	3.4 mm Proximal posterior tibial artery	2.7 mm Mid posterior tibial artery
Patient C	3.5 mm Tibiofibular tract	3.0 mm Proximal posterior tibial artery
Patient D	3.5 mm Tibiofibular tract	3.0 mm Proximal fibular artery
Patient E	4.0 mm Tibiofibular tract	2.5 mm
Patient F	3.5 mm Tibiofibular tract	Proximal fibular artery
Patient G	4 mm	3.5 mm

* Proximal anterior tibial artery within moderate stenosis = 2.1 mm

artery (CFA) in two of seven cases (29%), and of the distal superficial femoral artery (SFA) and of the popliteal artery in the remaining five of seven cases (71%). The localization of arterial occlusion was confirmed in all cases by digital subtraction angiography. Mechanical thrombectomy was performed in all cases using a 6F Rotarex®S catheter and was combined by local lysis in five of seven cases (71%). Rotarex®S catheter thrombectomy was performed in the CFA and in the SFA in two of seven cases (29%), and in the SFA and in the popliteal artery in the remaining five of seven cases (71%). Additional Rotarex®S catheter thrombectomy due to remaining thrombus formation with no reflow in the crural arteries was performed in the anterior tibial artery in two of seven cases (29%), in the tibiofibular tract and posterior tibial artery in two of seven cases (29%) and in the tibiofibular tract and fibular artery in the remaining three of seven cases (43%)(Table 2).

Efficacy and safety data

In all seven cases, 6F Rotarex®S catheter thrombectomy resulted in vessel patency, whereas no vessel dissections or perforations were observed. Compared to the remaining 95 patients who received Rotarex®S catheter thrombectomy in iliac and femoropopliteal vessels, it should be noted that Rotarex®S efficacy was present in 93 of 95 cases (98%), whereas vessel dissection or perforation was observed in two of 95 cases (2%), which in both cases was treated using an endovascular approach by prolonged balloon inflation and by placement of a stent, respectively.

Size of the treated crural arteries

The size of the proximal crural arteries varied between 3.2 and 4.0 mm, whereas the size of the mid-portion of the crural arteries varied between 2.5 and 3.5 mm. An overview of the diameters of the proximal and mid-portions of the crural arteries of our patients, where mechanical thrombectomy was performed, can be appreciated in Table 3.

Post-procedural data

Ischemic symptoms promptly resolved in all patients after the index procedure. Duplex sonography on the following day exhibited patency of all of the treated crural arteries. In addition, further clinical course was

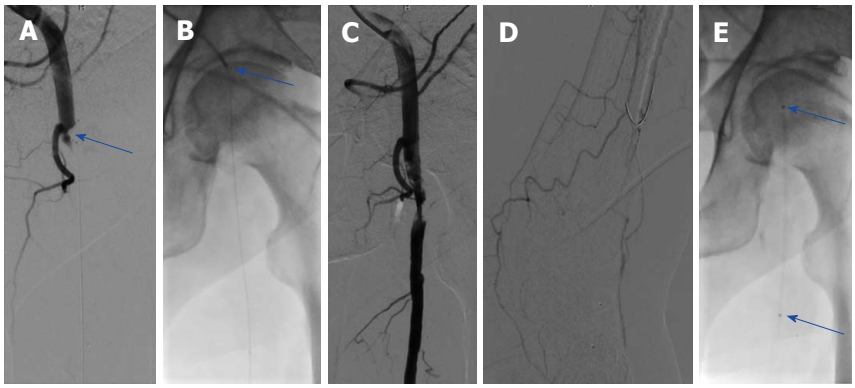

Figure 1 The angiography of patient A. A: Thrombotic occlusion of the common femoral artery (CFA) (blue arrow); B: Mechanical debulking using the Rotarex®S catheter (arrow); C,D: Anterograde flow was restored in the CFA after debulking with reduced flow in the foot arteries; E: Local thrombolysis was performed using a dedicated Unifuse catheter (arrow).

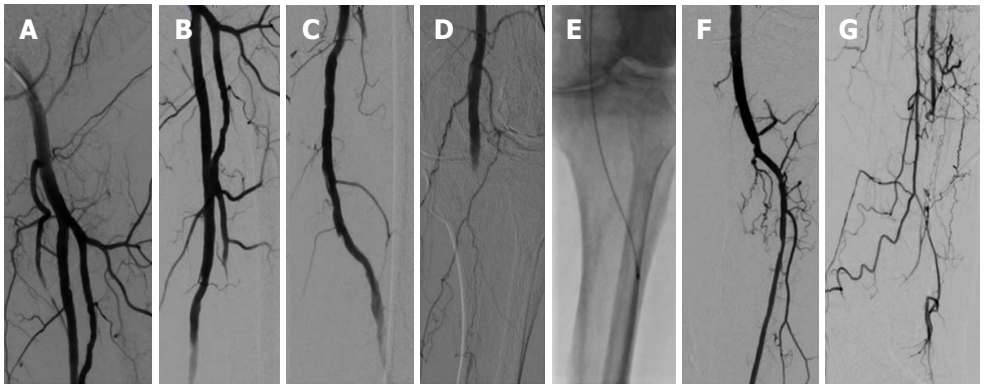

Figure 2 The angiography of patient A. The following day, a complete resolution of thrombus material was found in the common femoral artery. A-D: Superficial femoral artery and deep femoral artery (A-C) with new occlusion of the popliteal artery (D); E: Repeated Rotarex® debulking in the popliteal artery and continued to the proximal and median parts of the anterior tibial artery; F,G: Restoration of flow of the anterior tibial artery and of the foot.

uneventful in all seven patients, who were discharged within three days after mechanical thrombectomy. Five of seven (71%) patients were diagnosed with atrial fibrillation and were put on triple anticoagulation with 100 mg aspirin, 75 mg clopidogrel and oral anticoagulation for 4 wk, and were then continued with oral anticoagulation. The remaining two patients were treated with 100 mg aspirin and 75 mg clopidogrel for 3 mo and were then put on 100 mg aspirin daily. Representative images of our patients (Patient A-C) can be appreciated in Figures 1-4.

DISCUSSION

ALI is a serious medical condition that requires rapid diagnosis and prompt initiation of appropriate treatment. Depending on the clinical presentation and anatomy of the lesion, either an endovascular approach or a surgical therapy may be chosen. CDT is the classical method employed in the treatment of ALI. Mechanical thrombectomy techniques, on the other hand, represent a relatively new treatment in patients with ALI. Various devices using different mechanisms of action, (*i.e.*, fragmentation, aspiration or rheolytic thrombectomy) were shown to be useful alone or associated with the use of additional thrombolytics or local thrombolysis (combined mechanical and pharmacologic thrombectomy) for the management of patients with ALI. The main advantage of mechanical thrombectomy consists of the reduction of thrombotic burden, which reduces or even avoids the need for local thrombolysis. This is of major importance, particularly in patients with contraindication to thrombolysis due to high bleeding risks.

Many mechanical thrombectomy devices are currently used for the endovascular treatment of ALI. The ThromCat XT catheter device consists of an atraumatic tip and a flexible steel helix and can provide an effective aspiration capacity of 0.63 mL/s even in vessels with relative large diameters[10]. However, due to the small aspiration ports of this catheter system, it is limited to the treatment of fresh arterial occlusions, as it is difficult for the system to aspirate partially organized thrombotic material. The AngioJet (Possis Medical, Minneapolis, Minnesota, United States) on the other hand, is a combined pharmacologic and mechanical thrombectomy system, which is dedicated to peripheral interventions and uses active aspiration and Power Pulse™ lytic

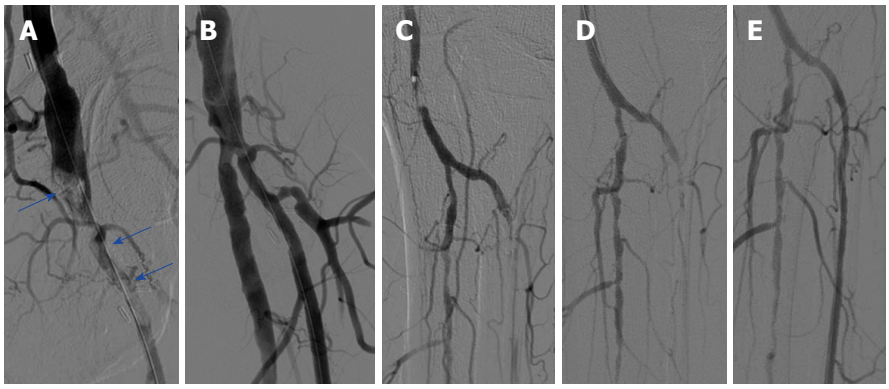

Figure 3 The angiography of patient B. A: Thrombotic occlusion of the common femoral artery and profound femoral artery (blue arrows); B: Good angiographic reflow after repeated treatment with the 6F Rotarex®S mechanical debulking catheter; C: Thrombus formation in the popliteal and in the anterior tibial artery; D: No flow restoration in the anterior tibial artery after treatment with the 6F Rotarex®S in the popliteal artery; E: Flow restoration after deploying the Rotarex®S in the anterior tibial artery.

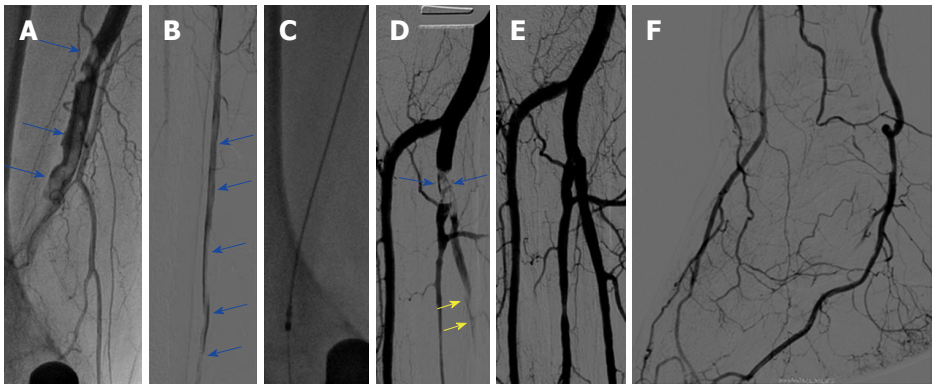

Figure 4 The angiography of patient C. A: Thrombotic occlusion of the right popliteal artery (blue arrows); B: Further thrombus formation in the right posterior tibial artery (blue arrows); C: Rotarex®S catheter in the popliteal artery; D: Remaining thrombus formation in the tibiofibular trunk and in the posterior tibial artery (arrows); E,F: Flow restoration in the foot after using the Rotarex®S in the proximal and median segments of the posterior tibial artery.

delivery to remove the thrombus and restore blood flow[11]. It should be noted that only observational, non-randomized data are available for such devices, including the Rotarex®S system, whereas no direct comparisons for different thrombectomy devices have been reported so far.

The Rotarex®S system is a purely mechanical endovascular thrombectomy device (Straub Medical AG, Switzerland)[12,13]. The system consists of an external drive system, which is connected to the Rotarex®S catheter *via* a magnetic clutch. Inside the catheter tube, a helix transmits the rotation from the drive system to the catheter head, which can rotate with up to 60000 rpm, thus creating a powerful vortex to debulk all detachable occlusion material from the vessel. The fragmented debris is subsequently aspirated through side slits in the catheter head. The inner helix simultaneously creates a strong suction force, following the Archimedes principle, and finally transports the fragmented material into an external collecting bag. The Rotarex®S catheter is currently available in three sizes, including 6F, 8F and 10F, and is inserted over a dedicated 0.018 guidewire. The aspiration efficacy is approximately 0.75 mL/s for the 6F system, which can be safely used in vessels with a diameter of $\geqslant$ 3 mm to 5 mm.

Several studies have demonstrated the efficacy of this system in the treatment of patients with ALI[14-18]. In this regard, a high success rate of > 98% was reported in a recent study, which elegantly demonstrated that purely mechanical thrombectomy by the Rotarex®S system was safer and more effective than thrombolysis, which was associated with higher rates of major bleedings, longer hospitalization durations and higher costs[19]. Potential complications associated with the Rotarex®S endovascular system is peripheral embolization of thrombotic debris in peripheral foot arteries (in most of the cases after additional balloon angioplasty and not directly related to Rotarex®S thrombectomy) and vessel dissection or perforation in smaller vessels. Particularly in vessels smaller than 3 mm in diameter, perforation may occur due to complete filling of the vessel by the catheter, which may eventually suck the vessel wall into the side windows of the catheter head. Although such complications can in most cases be treated by prolonged balloon inflation or by stent placement without requiring surgical action[16,20], the use of the 6F Rotarex®S system

is not currently generally recommended for crural arteries in the current literature[21]. In this regard, the use of the Rotarex®S has been reported only in a relatively small number of patients with ALI involving below the knee vessels (n = 4 in the study of Stanek *et al*[18]).

To the best of our knowledge the present study is the first in the current literature, which in detail describes the efficacy and safety of the 6F Rotarex®S system in a miniseries of seven patients, who were all treated for ALI in the proximal or mid-part of relatively big crural arteries with good angiographic and clinical results. Although no vascular complications in terms of dissection or perforation occurred in the crural arteries, the use of the 6F Rotarex®S debulking system should be performed with caution in crural arteries.

In conclusion, mechanical debulking using the 6F Rotarex®S catheter system may be a safe and effective treatment option in case of thrombotic or thrombo-embolic occlusion of the proximal and mid portion of crural arteries in patients presenting with ALI, especially when local thrombolysis needs to be avoided due to increased bleeding risk.

ARTICLE HIGHLIGHTS

Research background

Endovascular treatment of acute limb ischemia (ALI) is increasingly gaining importance in older and multimorbid patients, compared to conventional surgical techniques. The Rotarex®S debulking system is one such endovascular device, which can be used for catheter-assisted thrombectomy in ALI. However, the use of the 6 French (6F) Rotarex®S system is not generally recommended for crural arteries in the current literature.

Research motivation

Limited data exist to date on the efficacy and safety of the 6F Rotarex®S system for thrombectomy in crural arteries.

Research objectives

Our study aimed to examine whether the 6F Rotarex®S system can be used effectively and safely for endovascular thrombectomy of crural arteries in patients with ALI.

Research methods

Retrospective analysis of all patients who were referred to our department for endovascular thrombectomy dues to ALI between January 2015 and December 2017.

Research results

We identified seven patients who underwent endovascular Rotarex®S catheter thrombectomy in crural arteries due to remaining thrombus formation with no reflow. In two cases, thrombectomy was performed in the anterior tibial artery, in another two cases, in the posterior tibial artery and in the remaining three cases, in the fibular artery. In all seven cases, treatment resulted in restoration of the blood flow to the foot arteries, resolving ischemic symptoms. Vessel dissection or perforation did not occur in any of the seven cases..

Research conclusions

Endovascular thrombectomy using the 6F Rotarex®S catheter system may be safe and effective for the treatment of thrombotic occlusion of the proximal and mid portion of crural arteries. In particular, patients with high bleeding risk may profit from such a "mechanical only" treatment option without the need for additional thrombolysis.

Research perspectives

Larger prospective trials are necessary in the future to examine the efficacy and safety of the 6F Rotarex®S catheter system in smaller arteries of the lower limb.

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ORIGINAL ARTICLE

Observational Study

Incidental congenital coronary artery vascular fistulas in adults: Evaluation with adenosine-^{13}N-ammonia PET-CT

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Author contributions: All authors contributed to this paper; concept and design by Said SAM and Basalus MWZ; data acquisition by Moons AHM, Schroeder-Tanka JM and Nijhuis RLG; analysis of nuclear studies Agool A, Wagenaar NRL and Slart RHJA; Slart RHJA performed critical revision of manuscript; all authors have approved the final version of the paper.

Institutional review board statement: The study was reviewed and approved by the local medical ethical committee of the Eastern region, Enschede, The Netherlands (ID METC: K18-14, METC/18082.sai).

Informed consent statement: The study was reviewed and approved by the local medical ethical committee and the requirement to obtain informed consent was waived due to the retrospective nature of the report, the Eastern region, Enschede, The Netherlands (ID METC: K18-14, METC/18082.sai).

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Abstract

AIM

To assess the functionality of congenital coronary artery fistulas (CAFs) using adenosine stress ^{13}N-ammonia positron emission tomography computed tomography (PET-CT).

METHODS

Congenital CAFs were incidentally detected during coronary angiography (CAG) procedures in 11 adult patients (six males and five females) with a mean age of 64.3 years (range 41-81). Patients were collected from three institutes in the Netherlands. The characteristics of the fistulas (origin, pathway and termination), multiplicity of the origins and pathways of the fistulous vessels were assessed by CAG. Five patients underwent adenosine pharmacologic stress ^{13}N-ammonia PET-CT to assess myocardial perfusion and the functional behavior of the fistula.

RESULTS

Eleven patients with 12 CAFs, 10 unilateral and one bilateral, originating from the left anterior descending coronary artery (n = 8), right coronary artery (n = 2) and circumflex (n = 2). All fistulas were of the vascular type, terminating into either the pulmonary artery (n = 11) or coronary sinus (n = 1). The CAG delineated the characteristics of the fistula (origin, pathway and termination). Multiplicity of the origins and pathways of the fistulous vessels were common in most fistulas (8/12, 67% and 9/12, 75%, respectively). Multiplicity was common among the different fistula components (23/36, 64%). Adenosine pharmacologic stress ^{13}N-ammonia PET-CT revealed normal myocardial perfusion and ejection fraction in all but one patient, who showed a reduced ejection fraction.

CONCLUSION

PET-CT may be helpful for assessing the functional status of congenital CAFs in selected patients regarding clinical decision-making. Studies with a larger patient series are warranted.

Key words: Coronary angiography; Coronary-pulmonary artery fistulas; Adenosine ammonia positron emission tomography computed tomography; Coronary vascular fistulas; Congenital coronary artery fistulas

Core tip: Congenital coronary artery fistulas are usually detected as a coincidental finding during non-invasive and invasive diagnostic modalities for the assessment of coronary artery disease. Positron emission tomography computed tomography (PET-CT) is not frequently applied for functional assessment. In the current study, five patients underwent adenosine ^{13}N-ammonia PET-CT to assess myocardial perfusion and the functional behavior of the fistula. PET-CT revealed normal myocardial perfusion and ejection fraction in all but one patient, who showed a reduced ejection fraction. Combined with semi-quantitative results, patients with normal flow, revealed by PET-CT, could be treated medically, thereby avoiding the need for transcutaneous or surgical occlusion of the fistulas.

Said SAM, Agool A, Moons AHM, Basalus MWZ, Wagenaar NRL, Nijhuis RLG, Schroeder-Tanka JM, Slart RHJA. Incidental congenital coronary artery vascular fistulas in adults: Evaluation with adenosine-^{13}N-ammonia PET-CT. *World J Cardiol* 2018; 10(10): 153-164 Available from: URL: http://www.wjgnet.com/1949-8462/full/v10/i10/153.htm DOI: http://dx.doi.org/10.4330/wjc.v10.i10.153

INTRODUCTION

Congenital coronary artery fistulas (CAFs) are most often incidentally found during coronary angiography (CAG)[1], computed tomography coronary angiography (CTCA)[2] and transthoracic echocardiography (TTE)[3-5]. Coronary artery vascular and cameral fistulas are not only seen in humans, but are also occasionally observed in other mammals[6]. CAFs are classified as anomalies of termination[7]. Several diagnostic modalities are available for the morphological and functional detection of CAFs, including physical examination (presence of a continuous murmur), non-invasive methods such as echocardiography[8,9], myocardial perfusion imaging (MPI)[10,11], CTCA[3,9,12] and cardiovascular magnetic resonance imaging (MRI)[13], invasive techniques such as right heart catheterization, CAG and fractional flow reserve (FFR)[1,14-18], and incidental detection during positron emission tomography computed tomography (PET-CT)[19,20]. Exercise and pharmacological PET-CT is commonly applied for the assessment of myocardial perfusion and ischemia, and for the diagnosis and risk stratification of ischemic coronary artery disease (CAD)[21,22]. Adenosine ^{13}N-ammonia PET-CT is useful for assessing coronary flow reserve and myocardial perfusion for risk stratification in patients with CAD[23], the results of which influence patient management strategies[24]. Myocardial ischemia can also be detected using single-photon emission computed tomography (SPECT) in patients with congenital CAFs[15]. It is unclear whether congenital fistulas are associated with reduced myocardial perfusion, which is sometimes associated with impaired left ventricular function. Indications for surgical intervention or percutaneous therapeutic embolization are based on the patient's clinical presentation and on imaging findings. The aim of the present study was to evaluate the value of adenosine pharmacological stress ^{13}N-ammonia PET-CT in a selected population of patients with incidentally identified congenital CAFs.

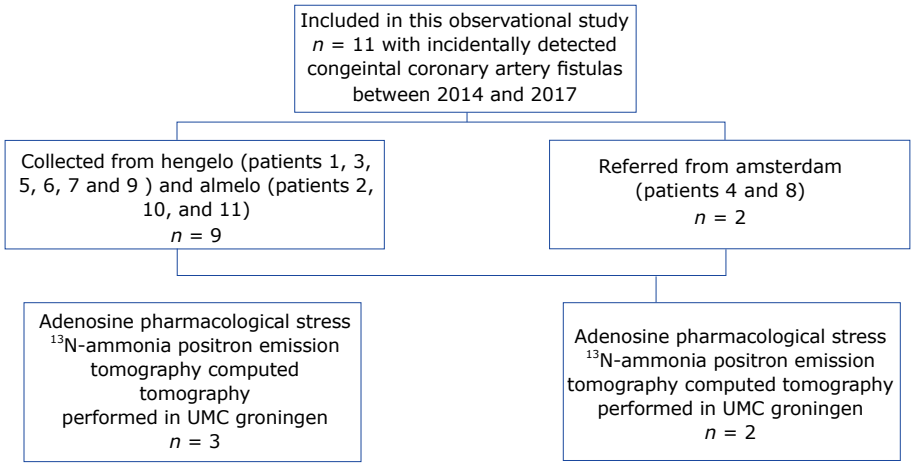

Figure 1 Flowchart of the study patients who were collected from 3 different non-academic Dutch institutes.

MATERIALS AND METHODS

Study subjects

We collected 11 patients (six males and five females; mean age of 64.3 years, range 41-81 years) with CAFs which were incidentally detected during routine CAG between 2014 and 2017. The FFR was not determined due to a lack of facilities. The patients were collected from three centers in the Netherlands as follows: Amsterdam, patients 4 and 8; Hengelo, patients 1, 3, 5, 6, 7 and 9; and Almelo, patients 2, 10 and 11 (Figure 1). Patient data was obtained from the databases of three Dutch cardiac catheterization laboratories (Slotervaart Hospital, Amsterdam; Onze Lieve Vrouwe Gasthuis, Amsterdam; and Hospital Group Twente, Almelo-Hengelo).

All patients underwent electrocardiography (ECG) and TTE. Five patients were further analyzed by adenosine stress/rest ^{13}N-ammonia PET-CT to quantify myocardial blood flow (MBF), myocardial perfusion and coronary flow reserve. Further studies to clarify the clinical presentation and fistula characteristics were performed at the clinician's discretion. Stress and rest MPI SPECT (Symbia S, Siemens Medical Solutions, Erlangen, Germany) were performed in one patient (patient 7), CTCA and MRI were performed in two patients (patients 2 and 4), and shunt calculation by the oximetric method was performed in four patients (patients 3, 4, 7 and 8).

The ECG-gated PET images were acquired using a whole-body 64-slice PET-CT scanner (Biograph True Point; Siemens Medical Solutions). The PET data were acquired in 3D list mode. Patients were studied after an overnight fast, and all refrained from caffeine-containing beverages or theophylline-containing medications for 24 h before the study. Myocardial perfusion was assessed at rest and during vasodilator stress induced by adenosine, using ^{13}N-ammonia as the perfusion radiotracer. Two CT-based transmission scans (120 kVp; 20–30 mA; helical scan mode with a pitch of 1.35) were obtained before and after the resting perfusion studies, performed with normal breathing to correct for photon attenuation of PET. The procedure involved the intravenous administration of 400 MBq of ^{13}N-ammonia during rest and 400 MBq of ^{13}N-ammonia during adenosine-induced pharmacological stress.

The PET and SPECT images were interpreted semi-quantitatively using the standard American Heart Association 5-point scoring system[25], and traditional metrics including summed difference score, summed stress score and summed rest score (SRS) were calculated. The SRS (in a fixed perfusion defect) was considered to be a measure of the extent and severity of a previous myocardial infarction (MI). Quantitative MBF values (mL/g per minute) at rest and under stress were computed for each sample on the polar map, as described previously[21], using a three-tissue compartment pharmacokinetic model for ^{13}N-ammonia[26]. Myocardial perfusion reserve (MPR) was calculated as the ratio between stress MBF and rest MBF (making it a unitless variable). The resting MBF was corrected for the rate-pressure product. The global MPR and stress MBF were calculated for the whole left ventricular region (defined by the left ventricle long-axis plane), representing the parameters of interest for our analysis.

The ECG-gated images were analyzed using the QGS software package (Cedars-Sinai, Los Angeles, CA, United States)[27]. Short-axis images were processed, and ventricular edges and cavity volumes were calculated for each of the eight re-binned dynamic frames that were reconstructed for the average cardiac cycle. The algorithm for determining edges and calculating volume has been described previously.

Ethical considerations

The study was reviewed and approved by the local medical ethical committee of the eastern region, Enschede, the Netherlands (ID METC: K18-14, METC /18082.sai). As the patients' personal information was protected, and therefore could not be identified and anonymized, it was exempt from consent by the local medical ethical

Table 1 Symptoms, clinical presentation and physical findings of adult subjects with congenital coronary artery fistula

Case	Fistula origin and termination	Symptoms and clinical presentation	Previous history and risk factors	Physical findings	BMI	Intervention
1	RCA and LAD to PA	Chest pain NSTEMI/PMI (CK 390 U/L)	Tubular adenoma of sigmoid, celiac disease	Normal	32.7	None
2	LAD to PA	Chest pain NSTEMI (CK 573 U/L)	Old IMI Asthma	Normal	25.9	CABG and surgical closure of the fistula
3	LCx to PA	Chest pain Dyspnea on exertion	Blanco	Normal	26.6	Coiling of the fistula and PCI of LAD
4	RCA to CS	Dyspnea on exertion	Diaphragmatic hernia, asthma and hypertension	Systolic ejection murmur grade 2/6 2 d ICS	28.2	None
5	LAD to PA	Non-sustained VT	DM, COPD, hypertension, hypothyroidism	Systolic ejection murmur grade 2/6 2 d ICS	33.4	PCI of OM branch and FFR of LAD. Coiling of the fistula
6	LAD to PA	Dyspnea on exertion	COPD Severe mitral valve regurgitation	Apical mitral regurgitation murmur grade 2/6	25.5	Mitral valve plasty
7	LAD to PA	Chest pain	Celiac disease	Normal	24.2	
8	LAD to PA	Angina pectoris	Hypercholesterolemia Positive family history for CAD	Systolic ejection murmur grade 2/6 2 d ICS	21.1	PCI of LAD
9	LCx to PA	Palpitation PAF and non-sustained VT Hypertension	Ischemic CVA	Normal	24.8	None
10	LAD to PA	Angina pectoris	NSTEMI 2010 (CK 328 U/L). PCI of RCA 2012	Normal	24.2	Coiling of the fistula
11	LAD to PA	Chest pain	Hypertension, hypercholesterolemia Positive family history for CAD Smoker	Normal	29.1	None

BMI: Body mass index; CABG: Coronary artery bypass grafting; CAD: Coronary artery disease; CK: Creatinine kinase; COPD: Chronic obstructive pulmonary disease; CS: Coronary sinus; CVA: Cerebral vascular disease; DM: Diabetes mellitus; FFR: Fractional flow reserve; ICS: Intercostal space; IMI: Inferior wall myocardial infarction; LAD: Left anterior descending coronary artery; LCx: Left circumflex coronary artery; NSTEMI: Non-ST elevation myocardial infarction; OM: Obtuse marginal branch; PA: Pulmonary artery; PAF: Paroxysmal atrial fibrillation; PCI: Percutaneous coronary intervention; PMI: Posterior myocardial infarction; RCA: Right coronary artery; VT: Ventricular tachycardia.

committee.

Statistical analysis

Categorical data are expressed as numbers with percentages, and continuous data are expressed as means with a range.

RESULTS

This retrospective case series included 11 (Figure 1) patients with 12 congenital coronary vascular fistulas (CVFs). Of those patients, five underwent adenosine pharmacologic stress ^{13}N-ammonia PET-CT to assess myocardial perfusion and functionality of the fistula.

Clinical presentations and features (Table 1) included limited posterior MI (patient 1), angina pectoris and chest pain (n = 6), dyspnea on exertion (n = 3) and asymptomatic abnormal resting ECG (n = 1). One patient (patient 9) presented with palpitation, transient ischemic attack, paroxysmal atrial fibrillation and non-sustained ventricular tachycardia. Previous MI was reported in two patients (patients 2 and 10). Patient 5 had exercise-induced non-sustained ventricular tachycardia. Physical examination was unremarkable in seven patients. Apical systolic murmur was heard in one patient, and systolic ejection murmur was heard in the second intercostal space in three patients.

In regard to the ECG, sinus rhythm was present in 10 patients and permanent atrial fibrillation was found in one patient. We also observed tall R-waves in precordial lead 2 (n = 1), signs of previous inferior MI (n = 1), non-specific repolarization abnormalities (n = 4), left bundle branch block (n = 1), left axis deviation (n = 1) and 1st degree atrioventricular delay (n = 1).

Echocardiography revealed normal findings in four patients, inferolateral hypokinesia in one patient, anteroseptal akinesia in one patient, mild aortic valvular stenosis with moderate aortic regurgitation (AR) in one patient, mild AR in one patient, mild mitral regurgitation (MR) in three patients, moderate to severe MR in one patient, and mild tricuspid regurgitation in three patients. Right ventricular systolic pressure was normal in all patients. Dilated coronary sinus (CS) was found in one patient (patient 4). One patient underwent

Table 2 Angiographic characteristics of fistula components

Case	Fistula origin and termination	Yr of detection	Angiographic characteristics of fistula components								
			LCx			RCA			LAD		
			O	P	T	O	P	T	O	P	T
1	RCA and LAD to PA	2014				M	MT	M	S	MT	S
2	LAD to PA	2015							M	MT	M
3	LCx to PA	2015	S	ST	S						
4	RCA to CS	2015				S	ST	S			
5	LAD to PA	2016							S	ST	S
6	LAD to PA	2016							M	M	M
7	LAD to PA	2016							M	MT	M
8	LAD to PA	2015							M	MT	S
9	LCx to PA	2016	M	MT	M						
10	LAD to PA	2017							M	M	M
11	LAD to PA	2017							M	MT	S

CS: Coronary sinus; LAD: Left anterior descending coronary artery; LCx: Left circumflex coronary artery; RCA: Right coronary artery; PA: Pulmonary artery; M: Multiple; MT: Multiple and tortuous; S: Single; ST: Single and tortuous; T: Termination; O: Origin; P: Pathway.

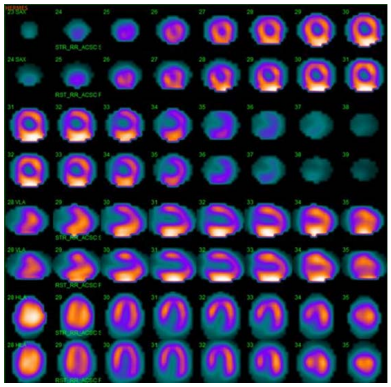

Figure 2 ^{99m}Tc-sestamibi single-photon emission computed tomography scintigraphy, demonstrating normal myocardial perfusion and a normal left ventricular ejection fraction.

^{99m}Tc-sestamibi SPECT scintigraphy (patient 7), which revealed normal myocardial perfusion (Figure 2) and a normal left ventricular ejection fraction (LVEF) of 0.67. Two patients underwent CTCA (patient 2, patient 4), which confirmed the diagnosis of coronary artery vascular fistulas.

Cardiovascular MRI was performed in two patients (patients 2 and 4), which revealed moderate left ventricular hypertrophy and signs of healed MI in three flow territories (patient 2). Shunt calculation by oximetry was performed in four patients (patients 3, 4, 7 and 8) who showed left-to-right shunt ratios of 1.75:1, 1.3:1, 1.1:1 and 2.0:1, respectively, with a mean of 1.53:1 (range 1.1-2.0).

CAG was used to delineate the characteristics of the fistula (origin, pathway and termination; Figures 3-10 and Table 2). The multiplicity of the origin of the fistulous vessels and the pathway were plural in most fistulas (8/12, 67% and 9/12, 75%, respectively). The termination was equally distributed between single (6/12, 50%) and multiple (6/12, 50%) fistulous vessels. Multiplicity was common among the different fistula components (23/36, 64%). Tortuosity of the pathway was found in eight fistulas (8/12, 67%).

There were 10 unilateral (Figure 4) and one bilateral (Figure 3A and B) fistulas. All fistulas were of the coronary vascular type, terminating into the pulmonary artery (PA, *n* = 11; Figure 5) or the coronary sinus (*n* = 1; Figure 6), and originating from the left anterior descending coronary artery (LAD; *n* = 8; Figure 7), right coronary artery (RCA; *n* = 2; Figures 3B and 6) or left circumflex coronary artery (LCx; n = 2; Figures 5 and 10). The characteristics of the fistula (origin, pathway and termination) showed multiple origins of fistulous vessels and pathways in most fistulas (8/12, 67% and 9/12, 75%, respectively; Figure 9). Multiplicity was common among the different fistula components (22/36, 61%; Figures 3B, 4 and 10). In contrast, single (7/12, 58%) termination of the fistulous vessels was more common than multiple (5/12, 42%) termination of fistulous vessels.

Dilated RCA was found in one patient (patient 4; Figure 6A), while large and small aneurysmal formation was present in two patients (patients 2 and 6, respectively; Figures 4 and 8). The FFR was not measured. The ECG-gated imaging of adenosine stress/rest ^{13}N-ammonia PET-CT (Table 3) demonstrated homogenous distribution of perfusion in two patients, who showed no perfusion defects (patients 3 and 11). One patient showed diffuse, reversible reductions in perfusion in the apical and antero-septal regions, and partly in the basal anterior segment (patient 4) (Figure 11). In another patient, perfusion of the LAD area was slightly lower than the inferior segment, but it was equal to that of the lateral wall (patient 7). Normal perfusion with reduced LVEF (rest 33% and stress 39%) was probably underestimated in one patient (patient 8). In the five patients, the mean global stress/rest ratio for MPR was 2.9 (range 2.33-3.90). The mean regional stress/rest ratio was 3.0 for the LAD (range 2.35-4.50), 2.9 for the RCA (range 2.49-3.60) and 2.8 for the LCx (range 2.36-3.20). Blood flow through the LAD was slightly higher than flow through the RCA and LCx.

Table 3 Pharmacological adenosine stress/rest ^{13}N-ammonia positron emission tomography computed tomography in 5 patients with unilateral coronary vascular fistulas

Case	CAF	Stress/rest perfusion segments				LVEF (%)		Semi-quantitative findings	CAD	Prior procedure	Management of CAF
		LCx	RCA	LAD	Global	Rest	Stress				
3	LCx-PA	2.74	2.49	2.56	2.59	52	57	No perfusion defects	1-VD	PCI-LAD	PTE
4	RCA-CS	2.65	2.7	2.71	2.69	65	65	Diffuse reversible reduction of perfusion in the apical, antero-septal and partially in basal anterior segment	None	None	CMM
7	LAD-PA	2.36	2.55	2.35	2.33	60	65	Perfusion of LAD area is less than inferior segment	None	None	CMM
8	LAD-PA	3.02	2.91	2.94	2.95	33	39	Normal perfusion with reduced LVEF	1-VD	PCI-LAD	CMM
11	LAD-PA	3.2	3.6	4.5	3.9	65	65	No perfusion defects	None	None	CMM

CAD: Coronary artery disease; CAF: Coronary artery fistula; CMM: Conservative medical management; CS: Coronary sinus; LAD: Left anterior descending coronary artery; LCx: Left circumflex coronary artery; LVEF: Left ventricular ejection fraction; PA: Pulmonary artery; PCI: Percutaneous coronary intervention; PTE: Percutaneous transcatheter embolization; RCA: Right coronary artery; VD: Vessel disease.

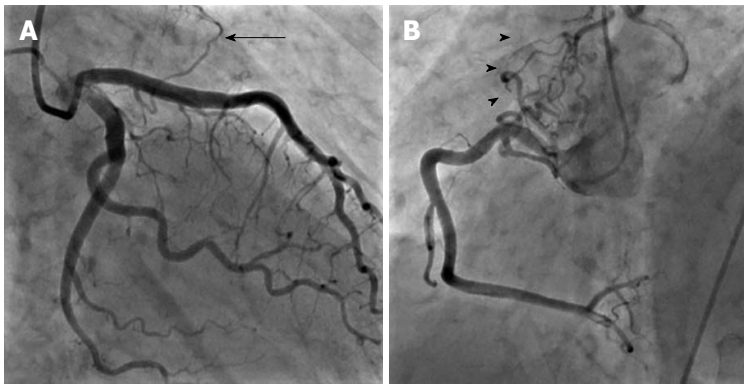

Figure 3 Bilateral fistulas. A: Balateral fistulas from the left anterior descending coronary artery to the pulmonary artery with single origin, multiple pathway and single termination (arrow); B: Balateral fistulas from the right coronary artery to the PA with multiple origin, pathway and termination (arrowheads).

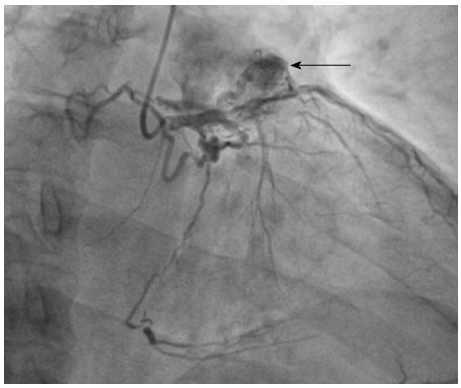

Figure 4 Fistula from the proximal left anterior descending coronary artery to pulmonary artery with multiple origin, pathway and termination associated with large aneurysmal formation (arrow).

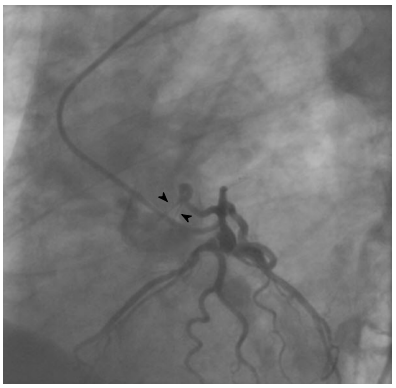

Figure 5 Fistula from the proximal left circumflex artery ending into the pulmonary artery characterized with single origin, pathway and termination emptying with double jets (arrowheads) ending into the pulmonary artery.

Absolute flow quantification in one patient (patient 3) yielded normal myocardial perfusion with high flow in the LCx, which was the fistula-related vessel, when compared to RCA and LAD flow, confirming successful percutaneous transcatheter embolization (PTE) closure of the fistulous vessel. On the other hand, semi-quantitative analysis revealed normal perfusion in two patients and a diffuse reduction in perfusion in the other two patients. When combined with the semi-quantitative results, findings of normal flow by PET-CT indicate that conservative medical management (CMM) can be used as a management option for fistulous

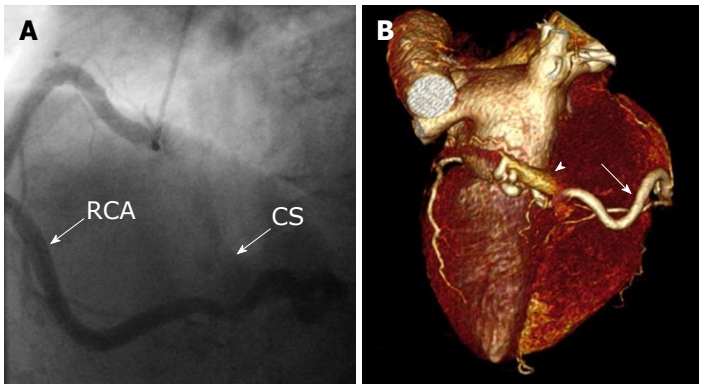

Figure 6 Unilateral fistula and computed tomography coronary angiography. A: Unilateral fistula originating from the right coronary artery (RCA) terminating into the coronary sinus (CS) with single origin, pathway and termination with dilated RCA and enlarged CS; B: Computed tomography coronary angiography: Coronary artery fistula originating from the distal segment of RCA (arrow) and terminating into the coronary sinus. Volume-rendered three-dimensional image reconstruction demonstrating fistulous vessel located posterior connected with the CS (arrowhead). RAC: Right coronary artery; CS: Coronary sinus.

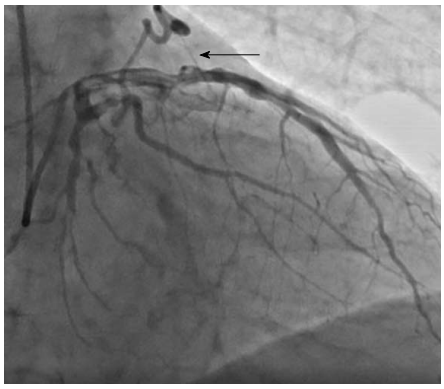

Figure 7 A fistulous connection between the left anterior descending coronary artery and pulmonary artery with single origin, pathway and termination with a single jet ending into the pulmonary artery (arrow).

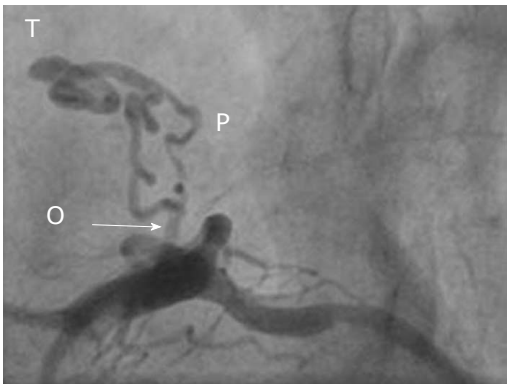

Figure 9 Left lateral frame demonstrating a fistula with multiple origin (arrow) and pathway from the proximal left anterior descending coronary artery ending to the pulmonary artery with a single termination. O: Origin; P: Pathway; T: Termination.

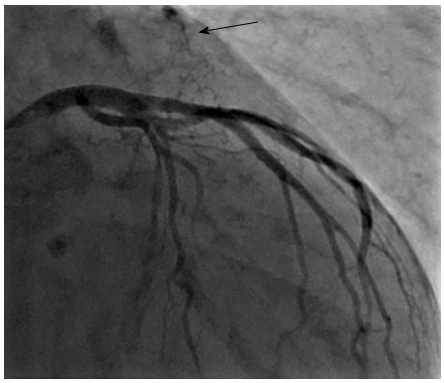

Figure 8 Right anterior oblique view shows the fistulous vessel between the left anterior descending coronary artery and the pulmonary artery with multiple origin, pathway and termination with small aneurysmal formation (arrow).

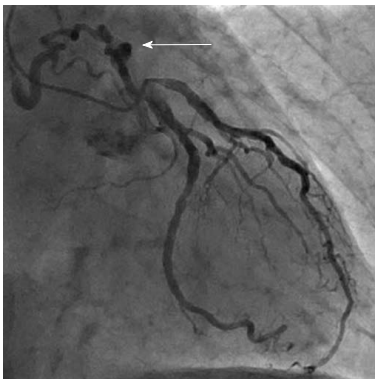

Figure 10 Left anterior oblique view shows a fistula between proximal left circumflex coronary artery (arrow) with multiple origin, pathway and termination with outflow to the pulmonary artery.

vessels, thereby avoiding the need for occlusion of the fistula.

The interventions included leaving a small fistula without percutaneous or surgical intervention; surgical ligation (SL) of the fistula in combination with CABG (patient 2); percutaneous closure of the fistulous tract (LCx to PA) and percutaneous coronary intervention (PCI) of the LAD due to chest pain and dyspnea upon exertion (patient 3); PCI of the OM branch of the LCx and coiling of the fistula (LAD to PA) in a patient (patient 5) with non-sustained ventricular tachycardia; and transcutaneous obliteration of the fistula secondary to

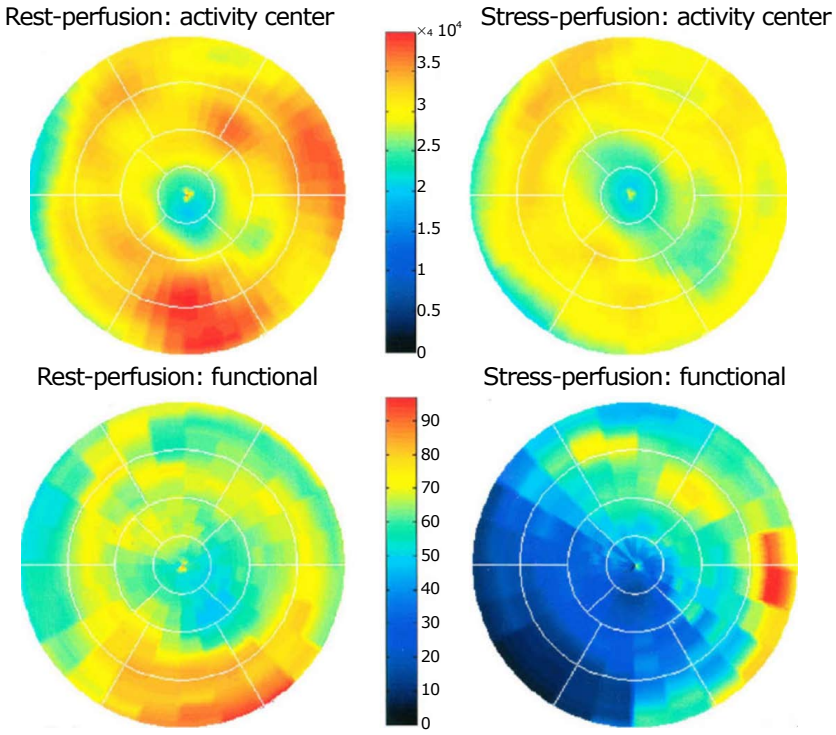

Figure 11 Positron emission tomography computed tomography scanning demonstrating normal findings on the rest ^{13}N-ammonia polar map (left panel) and normal perfusion on adenosine ^{13}N-ammonia polar map (right panel). Myocardial perfusion was assessed at rest and during vasodilator pharmacological stress induced by adenosine, using 400 MBq of ^{13}N-ammonia as the perfusion radiotracer.

angina pectoris (patient 10).

Treatment and management of the fistula included CMM in seven patients, PTE in three patients and SL combined with coronary artery bypass grafting (CABG) in one patient. Of the patients who underwent adenosine stress/rest ^{13}N-ammonia PET-CT, PTE was performed in only one patient (patient 3). This patient showed high flow in the LCx, which was the fistula-related vessel, and PTE was successfully performed with angiographic documentation. In the other four patients (patients 4, 7, 8 and 11), PET-CT showed no flow restrictions, indicating CMM and avoiding the need for fistula closure.

Five patients had known CAD (one vessel disease in four patients and three vessel diseases in one patient). Of these patients, three underwent PCI procedures, one patient was managed with optimal medical treatment, and one patient underwent CABG in combination with fistula ligation.

DISCUSSION

In this study, we describe congenital CAFs that were incidentally found in 11 adult patients during routine CAG. To investigate the functional characteristics of these fistulas, PET-CT was performed at rest and after adenosine pharmacological stress in five subjects. To date, the role of PET-CT has not been extensively studied in adult patients with congenital CAFs.

Congenital CAFs are usually asymptomatic in many adult patients and are usually incidentally detected during routine CAG for suspected CAD. Over the past century, congenital CAFs associated with continuous cardiac murmur have often been confused with patent ductus arteriosus Botalli[28,29]. More recently, congenital CAFs have been misdiagnosed as a right atrial myxoma[30].

Coronary artery vascular and cameral fistulas are increasingly found during echocardiography[3,31,32], CTCA[2,33] and diagnostic CAG procedures[1]. One study reported the diagnosis of a small coronary-pulmonary fistula (CPF) by echocardiography in asymptomatic dizygotic twin infant brothers[31], suggesting a possible genetic cause of CAFs. Invasive CAG is considered the gold standard for the detection and diagnosis of congenital CAFs; however, non-invasive imaging techniques such as contrast echocardiography[34], 2D and color Doppler echocardiography, cardiovascular MRI and CTCA provide valuable complementary data for the visualization of fistula components (origin, pathway and termination sites) that are not visible on the CAG[20,35-37].

FFR

The value of FFR has been emphasized by several authors. Ouyang *et al*[38] reported deferral of treatment of the fistula-related artery and tandem intermediate stenosis in a patient with a huge CAF originating from the LAD and draining into the PA based on the findings of FFR. In the case of an adult subject assessed by both FFR and intravascular ultrasound, PCI was performed

for significant stenosis of the LAD, which was the fistula-related artery (LAD-PA), but the congenital fistula remained untouched due to the absence of myocardial ischemia[18]. In congenital CAFs, the steal phenomenon has been demonstrated by FFR[17]. Few reports have been published regarding the functional assessment of congenital CAFs (left main PA) in which FFR was used to guide clinical decision-making for intervention. In one of these reports, normal FFR was observed for a patient with concomitant moderate coronary artery stenosis, which led to the deferral of surgical or transcutaneous interventions[39]. Furthermore, Hollenbeck *et al*[40] demonstrated ischemic changes due to the combination of a moderate LAD stenosis and CVF, which was relieved by PCI. Oh *et al*[41] assessed the hemodynamic significance of congenital multiple microfistulas and coronary cameral fistulas by FFR, which ruled out ischemia. In 2014, Sasi *et al*[42] assessed CAF using coronary flow reserve (CFR) and FFR. The LCx FFR and CFR were 0.97 and 2.33, respectively, and the LAD FFR of 0.86 was associated with a CFR of 1.56. This patient was treated medically. In 2016, Ito *et al*[43] successfully performed FFR-guided PCI of an intermediate LAD stenosis associated with CAFs, and the fistula was treated conservatively. Bi-directional flow in the fistula may occur in the left ventricle[44] and the right ventricle[45]; however, none of our patients demonstrated bi-directional fistulous flow.

Radionuclide examinations and MPI

In the 1990s, myocardial perfusion scintigraphy SPECT using Tl-201 was performed in some patients to determine fistula-related ischemia. A report by Gupta *et al*[46] in 1991, followed by Glynn *et al*[47] in 1994, reported the first case studies documenting the use of thallium-201 perfusion imaging for physiological assessment of CAF (LAD-PA) and as the cause of an exercise-induced reversible thallium-201 perfusion defect in an adult patient[46,47]. The pharmacological stress MPI SPECT technique may indicate segmental perfusion defects in patients with congenital CPF in the absence of CAD[11]. In a patient series evaluated by Lee *et al*[11], 35% of patients with congenital CPF without CAD developed perfusion defects, but the findings were only clinically relevant in 12%.

Adenosine stress-induced ^{13}N-ammonia PET-CT uptake in the myocardium is related to perfusion and may offer better assessment of myocardial ischemia. Adenosine stress ^{13}N-ammonia PET-CT has several advantages over SPECT, such as higher spatial resolution and sensitivity, absolute quantification, better counting efficiency and improved attenuation correction[11,24]. In 2011, a report described the application of adenosine ^{13}N-ammonia PET-CT in congenital CAFs for the first time[19].

Adenosine ^{13}N-ammonia PET-CT scanning is routinely applied to assess the functional status and quantify flow in patients with CAD[26,48], which could also be used in subjects with congenital coronary artery anomalies of origin (*i.e.*, single coronary artery[49]) and termination (*i.e.*, CAFs[19]).

Quantification of myocardial perfusion facilitates the high-performance detection and localization of perfusion abnormalities. In the same patient with CAF, PET-CT was reported to show greater areas of ischemic change than ^{99m}Tc-sestamibi scintigraphy[50]. In a comparative study by Kong *et al*[20], adenosine stress ^{13}N-ammonia PET-CT imaging was shown to have higher diagnostic sensitivity (91% *vs* 65%) and specificity (89% *vs* 82%) compared with SPECT using Tc-99m sestamibi, providing better assessment of myocardial perfusion. Thus, MPI may guide decisions regarding which patients will benefit from invasive treatment. Adenosine ^{13}N-ammonia PET-CT may prove to be valuable in clinical decision-making for whether to close the fistulous communication based on the presence or absence of distribution abnormalities[51]. Successful SL of the fistula and reconstruction of the CS was performed in an adult male with a congenital RCA-CS fistula, which was associated with aneurysmal dilatation of the CS and stenosis of the CS ostium[3]. In the patient series reported by Zhang *et al*[52], SL of isolated congenital CAFs was related to lower morbidity and mortality associated with residual shunt in 8/47 (17%) patients, two of whom required PTE. Based on the findings of adenosine ^{13}N-ammonia PET-CT in our five patients, transcutaneous or surgical intervention was avoided in four subjects. In the current series, treatment and management of the fistula included CMM in seven patients, PTE in three patients and SL in one patient.

In conclusion, adenosine ^{13}N-ammonia PET-CT is a useful technique that provides additional information for diagnosis and decision-making related to the management of incidentally detected congenital CAFs. The technique may also be useful for determining the functional status of the fistula and may add some clues for clinical decision-making in adult patients with congenital CAFs. Further prospective studies with a large number of patients are warranted.

Limitations of the study

Firstly, the study was retrospective in nature, with patients collected from different cardiac catheterization laboratories in the Netherlands. Secondly, this study contained a small sample size, involving a limited number of patients collected from three centers which used different diagnostic modalities. There is increasing need for a prospective international registry.

ARTICLE HIGHLIGHTS

Research background

Congenital coronary artery fistulas (CAFs) are uncommon coronary artery vascular anomalies which are often incidentally found during coronary angiography (CAG) performed for suspected atherosclerotic coronary artery disease (CAD). Moreover, most asymptomatic patients are diagnosed with CAFs during evaluation for cardiac murmur. Nowadays, congenital

CAFs are increasingly detected due to the widespread use of non-invasive techniques such as echocardiography and computed tomography coronary angiography (CTCA). Functional assessment and determination of the clinical significance of CAFs is of great importance for therapeutic decision-making. The choice of treatment strategy depends on the size and location of the fistula, the magnitude of left-to-right shunt and the characteristics of the fistulous tract. Many diagnostic modalities are currently used to evaluate the functional characteristics of the fistula, including non-invasive methods such as Doppler echocardiography, CTCA and radionuclide angiography, and invasive methods such as right heart catheterization and fractional flow reserve (FFR), among others. In the current study, the role of positron emission tomography computed tomography (PET-CT) is described in an observational setting. We aimed to determine the impact of the fistula on the clinical status of the patient, in addition to whether PET-CT can be used to assess the functional status of the fistula. This information was used to determine the best therapeutic strategy, which included monitoring, conservative medical management (CMM), transcutaneous catheter embolization or surgical ligation (SL). In general, echocardiography represents the first diagnostic imaging approach, but it may be limited by an inappropriate acoustic window. Modern echocardiography equipment has greater sensitivity, which explains why congenital CAFs are frequently diagnosed by this method. Echocardiography can be used to diagnose and evaluate the hemodynamic significance, anatomy and physiopathology of CAFs. CTCA is a widely used technique that can be used for morphological and functional analyses, as well as for perfusion studies of CAFs. CTCA allows for comprehensive cardiac evaluation, providing morphological and functional data on coronary circulation and myocardial perfusion status, as well as anatomical images. Electrocardiography (ECG)-gated cardiovascular computed tomography may play an important role in the evaluation of the origin, pathway, termination and morphology of the fistula in relation to the adjacent anatomical structures, as well as cardiac morphology and contractility. Cardiovascular magnetic resonance does not use ionic radiation and plays a crucial role in determining myocardial wall viability, characterizing the myocardial tissue and its morphology, as well as providing detailed data related to cardiac function, estimated blood flow within the fistula and the anatomical characteristics. Myocardial perfusion imaging (MPI) is used to identify abnormalities in cardiac and pulmonary circulation, providing the Qp: Qs ratio is required to diagnose and quantify left-to-right shunt, and to assess myocardial perfusion defects that occur as a result of segmental hypoperfusion caused by the fistula-bearing vessel. Myocardial perfusion single-photon emission computed tomography (SPECT) is used to detect myocardial ischemia and to stratify the risk of experiencing a cardiac event in patients with CAFs. The hemodynamic significance of this modality remains unclear. The closure technique for congenital CAFs will be chosen after thorough diagnostic imaging and functional investigation has been performed to assess the hemodynamic and functional significance of the fistula, its anatomical morphology, and its impact on the clinical status of the patient.

Research motivation

The aim of this study was to review and present the current data on non-invasive and invasive diagnostic methods used to evaluate the anatomical morphology and functional significance of CAFs. Medical imaging is important for assessing the location and size of CAFs.

Research objectives

We assessed the hemodynamic impact of CAFs using ^{13}N-ammonia PET-CT imaging under pharmacological adenosine-induced stress and at rest. Future research in a larger group of symptomatic and asymptomatic patients with a greater magnitude of left-to-right shunt is warranted.

Research methods

This was an observational study of 11 subjects with congenital CAFs that had been incidentally found during CAG performed for suspected atherosclerotic CAD. In all patients, physical examination, ECG, echocardiography, chest X-ray and laboratory investigation were performed. The patients were collected from three non-academic hospitals in the West and East regions of the Netherlands. FFR was not measured due to a lack of interventional cardiology facilities in these non-interventional hospitals. Different fistula characteristics were delineated using coronary angiographic imaging techniques. Five subjects underwent pharmacological adenosine stress/rest ^{13}N-ammonia PET-CT to assess the hemodynamic impact of the fistula. PET-CT was performed in a different academic center. PET-CT is considered a superior diagnostic modality as it provides data on the metabolic status of the myocardial tissue.

Research results

The patients involved in this study had a variety of clinical presentations, including limited posterior non-ST-elevation myocardial infarction (MI), angina pectoris and chest pain (n = 6), dyspnea upon exertion (n = 3), and an asymptomatic presentation with abnormal resting electrocardiogram (n = 1). One patient presented with palpitation, ischemic cerebrovascular accident, paroxysmal atrial fibrillation and non-sustained ventricular tachycardia. Another patient presented with exercise-induced non-sustained ventricular tachycardia. Previous MI was reported in two patients. The physical examination was unremarkable in seven patients. Apical systolic murmur was heard in one patient, and systolic ejection murmur was heard in the second intercostal space in three other patients. Although continuous cardiac murmur is usually present in patients with CAF, no continuous murmur was heard in the current group of patients. In this case series, the body mass index of subjects ranged between 21.1 to 33.4 kg/m^2, with four patients classified as normal weight, five as overweight and two as obese. The electrocardiogram demonstrated sinus rhythm in 10 patients and permanent atrial fibrillation in one patient. Echocardiography revealed dilated coronary sinus in one patient. None of the patients showed pulmonary hypertension, with normal results for right ventricular systolic pressure. There were 10 single-sided and one double-sided fistulas. All fistulas were of the coronary vascular type, terminating into the pulmonary artery (n = 11) or coronary sinus (n = 1), and originating from the LAD (n = 8), right coronary artery (RCA, n = 2) or left circumflex coronary artery (LCx, n = 2). In regard to the characteristics of the fistula (origin, pathway and termination), the origin and pathway of the fistulous vessels was plural in most fistulas (8/12, 67% and 9/12, 75%, respectively). Multiplicity was common among the different fistula components (22/36, 61%). In contrast, single (7/12, 58%) termination of the fistulous vessels was more common than multiple (5/12, 42%) termination of fistulous vessels. The termination was equally distributed between single (6/12, 50%) and multiple (6/12, 50%) fistulous vessels. Multiplicity was common among the different fistula components (23/36, 64%). Tortuosity of the pathway was found in eight fistulas (8/12, 67%). A dilated RCA was found in one patient, and large and small aneurysmal formation was present in two patients. The presence of tortuosity and multiplicity of the fistulous tract meant that percutaneous intervention would be very challenging. In patient 2, who had symptomatic significant CAD, SL of the fistula was performed in combination with coronary artery bypass grafting. The characteristics of the fistula components in this patient were multiple origin and termination with multiple-tortuous pathways, which meant the percutaneous approach could not be used. In four patients (patients 4, 7, 8 and 11), PET-CT showed no flow restrictions. Thus, CMM could be implemented, avoiding the need for fistula closure either transcutaneous or surgically. The adenosine stress/rest ^{13}N-ammonia PET-CT performed in five subjects demonstrated homogenous distribution of perfusion in two patients, and no perfusion defects in two patients. One patient showed diffuse, reversible reduction in perfusion in the apical and antero-septal regions, and also partly in the basal anterior segment. In another patient, perfusion of the left anterior descending coronary artery (LAD) area was slightly lower than the inferior segment, but it was equal to the lateral wall. Normal perfusion with reduced left ventricular ejection fraction (rest 33%, stress 39%) was probably underestimated in one patient. In these five patients, the mean global stress/rest ratio was 2.9 (range 2.33-3.90). The mean regional stress/rest ratio was 3.0 for the LAD (range 2.35-4.50), 2.9 for the RCA (range 2.49-3.60) and 2.8 for the LCx (range 2.36-3.20). Blood flow through the LAD was slightly higher than through the RCA and LCx. Absolute flow quantification revealed normal myocardial perfusion with high flow in the LCx, which was the fistula-related vessel, compared to the flow of the RCA and the LAD, indicating successful PTE closure procedure of the fistulous vessel. On the other hand, semi-quantitative analysis revealed normal perfusion in two patients and a reduction in diffuse perfusion in the other two patients.

Research conclusions

The hemodynamic characteristics of incidentally found CAFs are of great importance to guide decision-making for whether to treat patients or perform periodic monitoring. Pharmacological adenosine stress/rest ^{13}N-ammonia PET-CT in patients with incidentally found congenital CAFs provided adequate

and clear information regarding the hemodynamic burden of the fistula in this small patient population. For better diagnosis of incidentally found congenital CAFs, pharmacological adenosine stress/rest ^{13}N-ammonia PET-CT should be performed as part of the diagnostic imaging work-up. However, this needs to be confirmed in a large, prospective, international study or registry. In the current study, pharmacological adenosine stress/rest ^{13}N-ammonia PET-CT was performed in a limited number of adult patients with incidentally found congenital CAFs. This test is achievable in patients with congenital CAFs. That pharmacological adenosine stress-rest ^{13}N-ammonia PET-CT in incidentally found congenital CAFs is currently, in this patient population, can provide adequate and clear answer regarding the hemodynamic burden of the fistula and guiding the clinical decision making. For patients with CAFs, multiple imaging modalities are required to assess the anatomical morphology, hemodynamic significance and behavior of the fistula in order to assist in the choice of therapeutic strategy. Angiographic characterization of the individual fistula components (origin, pathway and termination) may help guide the selection of closure technique, either percutaneously or surgically.

Research perspectives

Further studies on a larger number of patients with congenital CAFs (small or large, symptomatic or asymptomatic, treated or untreated) are required to determine the prospective incidence and other characteristics, such as history and long-term outcomes. In 2018-2019, we are planning to initiate an international registry on CAFs (Euro-CAF Survey) to address the diagnostic and therapeutic issues.

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SYSTEMATIC REVIEW

Undiscovered pathology of transient scaffolding remains a driver of failures in clinical trials

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Abstract

AIM

To statistically examine the released clinical trials and meta-analyses of polymeric bioresorbable scaffolds resuming the main accomplishments in the field with a translation to the routine clinical practice.

METHODS

The statistical power in clinical trials such as ABSORB Japan, ABSORB China, EVERBIO II, AIDA, and few meta-analyses by the post hoc odds ratio-based sample size calculation, and the patterns of artery remodeling published in papers from ABSORB A and B trials were evaluated.

RESULTS

The phenomenal admiration from the first ABSORB studies in 2006-2013 was replaced by the tremendous disappointment in 2014-2017 due to reported relatively higher rates of target lesion failure (a mean prevalence of 9.16%) and device thrombosis (2.38%) in randomized controlled trials. Otherwise, bioresorbable vascular scaffold (BVS) performs as well as the metallic drug-eluting stent (DES) with a trend toward some benefits for cardiac mortality [risk ratio (RR), 0.58-0.94, $P > 0.05$]. The underpowered design was confirmed for some studies such as ABSORB Japan, ABSORB China, EVERBIO Ⅱ, AIDA trials, and meta-analyses of Polimeni, Collet, and Mahmoud with some unintentional bias (judged by the asymmetrical Funnel plot). Scaffold thrombosis rates with Absorb BRS were comparable with DES performed with a so-called strategy of the BVS implantation with optimized pre-dilation (P), sizing (S) and post-dilation (P) (PSP) implantation (RR, PSP *vs* no PSP 0.37) achieving 0.35 per 100 patient-years, which is comparable to the RR 0.49 with bare-metal stents and the RR 1.06 with everolimus DES. Both ABSORB Ⅱ and ABSORB Ⅲ trials were powered enough for a five-year follow-up, but the results were not entirely conclusive due to the mostly non-significant fashion of data. The powered meta-analyses were built mostly on statistically poor findings.

CONCLUSION

The misunderstanding of the pathology of transient

scaffolding drives the failures of the clinical trials. More bench studies of the vascular response are required. Several next-generation BVS including multifunctional electronic scaffold grant cardiology with a huge promise to make BVS technology great again.

Key words: Bioresorbable scaffold; Device thrombosis; Clinical outcomes; Statistics; Intravascular imaging; Arterial remodeling; Transient scaffolding

Core tip: The high rates of target lesion failure and device thrombosis in randomized controlled trials caused confusion in the international interventional community with a decline of the technology in routine practice. The provided statistical analysis confirms the underpowered design of some clinical studies and meta-analyses of bioresorbable scaffolds. The misunderstanding of the pathobiology of the transient scaffolding drives the failures of the clinical trials. More bench studies of the vascular response are required to verify the leading mechanism of the device failure. Several next-generation scaffolds including multifunctional electronic scaffold grant cardiology with a huge promise to make this technology great again.

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INTRODUCTION

The groundbreaking news of September 8, 2017 delivered by Abbott Vascular (Santa Clara, CA; https://www.vascular.abbott/) outlined that "due to low commercial sales, Abbott will stop selling the first-generation Absorb bioresorbable vascular scaffold (BVS)". The reassuring point was that Abbott will continue work on a next-generation 99 μm bioresorbable device. This was the end of the device thrombosis story that reached its climax this year when the United States Food and Drug Administration (FDA) on March 18, 2017 (and then on October 31, 2017 after release of ABSORB Ⅱ 4-year, ABSORB Ⅲ 3-year, and ABSORB Ⅳ 30-d results at TCT 2017 in Denver, CO, United States) informed[1] health care providers who are managing patients with Absorb GT1 BVS that there is a high rate of major adverse cardiac events (MACE) or correctly target lesion failure (TLF) registered in patients receiving BVS when compared to metallic XIENCE drug-eluting stent (DES). This alert was initially provoked by the release of the two-year data from the ABSORB Ⅲ trial (a paper was not published yet) showing[2] an 11% rate of MACE in patients treated with BVS (n = 1322) at two years compared with 7.9% (n = 686) in XIENCE DES (P = 0.03). This study also demonstrated a 1.9% rate of scaffold thrombosis (ST) within the BVS *vs* 0.8% within the XIENCE stent at two years (P > 0.05, NS). These observed higher MACE rates in BVS patients were more likely when the device was implanted in small heart vessels (< 2.25 mm). Almost immediately after the United States, the European Union restricted BVS[3] to the sites of clinical registries (valid as of May 31, 2017). The CE Mark of approval remains in place, but only centers participating in formal registries (about 12 registries across Europe covering 114 hospitals) should be using BVS for now. Furthermore, the Australian Therapeutic Goods Administration (TGA) on May 2, 2017[4] issued a hazard alert as well and recalled all BVS from medical centers not studying the device. These reactions[5-15] of the healthcare authorities amid few recently published meta-analyses[16-25] wreck confusion[26-37] among physicians[38-45] about when and if they will ever be using the device again, jeopardizing the future of BVS and further development of bioresorbable devices. Notwithstanding, did we clear the situation with causes of these trends toward increased MACE and ST in the case of BVS? What is going on with cardiac mortality after BVS? Can we trust these data? Can we propose a solution and optimize our approaches for BVS implantation to prevent these complications and secure the technology? Do we understand the pathology of transient scaffolding? Should we first complete the bench studies and clear the vascular pathobiology of the BVS implantation?

Certainly, we face a real phenomenon of the elevated TLF and ST after implantation of BVS, which is very confusing and disappointing for physicians even for the fathers of technology such as Professor Patrick W Serruys, MD, PhD (Erasmus MC, Rotterdam, The Netherlands; Imperial College, London, United Kingdom) who said that "It's not what we were expecting…That's the reality!...Of course, we're still in the first generation…" (a report to TCTMD on Oct 30, 2016 at TCT2016, Washington, DC, United States). We must mind the fact that this is a first-generation technology, and as Professor Gregg Stone, MD (Columbia University, NY, United States) said once, "If science stopped with every challenge for first gen devices, we would have no PCI devices!" (Twitter, @GreggWStone, Apr 16th, 2017). Meanwhile, the Colombo's concept of the plastic jacket (a team of Professor Antonio Colombo, MD, San Raffaele Scientific Institute, Milan, Italy)[10], recently reported positive results of the European registries (German GABI-R, Italian IT-DISAPPEARS, Italian RAI, Swedish SCAAR, British Absorb United Kingdom, and French France Absorb) and Asian randomized controlled trials (RCT)[11] (ABSORB China, ABSORB Japan) are very reassuring and promising with relatively low rates of both TLF (3.9%-9.9% by one year) and ST (< 1.7%) even in complex lesions due to optimized accurate technique of the implantation (a high-pressure post-dilation in some

registries was performed in 96.8% of cases with full PSP strategy in > 65.8% of lesions).

The running fourth industrial revolution[23-38] supports us with the remarkable idea of the transient scaffolding[39-51] and a dream of the vascular restoration therapy[25] of coronary atherosclerosis that has a potential to revolutionize cardiology providing physicians with a tackle for both to revitalize a circulation[20-36] in the coronary pool tailoring atheroregression[37-52]. Since 2006 the multimodality imaging studies of ABSORB[31] and ABSORB B[53-56] clinical trials that examined BVS have crashed to perform significant regression of atherosclerosis but with a trend toward absolute reduction of the percent atheroma volume (PAV) at 60 mo (at least -2.62%), which claims further research efforts.

The goal of this systematic review was to evaluate the accomplishments of the clinical trials, and patterns of pathology with trends of the artery remodeling in patients who underwent transient scaffolding with polymeric BVS within 60 mo after implantation with the grey-scale (GS) and virtual histology (VH) intravascular ultrasound (IVUS) imaging, quantitative coronary angiography (QCA), multislice computed tomography (MSCT) angiography, and optical coherence tomography (OCT). This review must answer the question about both the reasons for unsuccessful experience in clinical trials and the potential of BVS for regression of atherosclerosis with its further introduction into the routine clinical practice.

MATERIALS AND METHODS

The available sources of the information published in PubMed/MEDLINE (primary electronic database), Google Scholar, ResearchGate, ClinicalTrials.Gov, and SCOPUS with the key words BVS, BRS, regression of atherosclerosis, imaging, artery remodeling, and atherosclerosis through the last 20 years with a focus on polymeric BVS and particularly ABSORB trials were investigated. The estimated observations comprised mean and/or median numbers of the variables reported by the authors of the original papers without access to the detailed patient-by-patient matrix of the evaluated studies. This systematic review (without meta-analysis) was accomplished by two reviewers who independently analyzed abstracts, extract data, and calculate the risk of bias. The received data have a different quality and potential of comparability but provide the most recent information. The risk of bias of each included trial was tested with the Cochrane Collaboration's tool and elaborated with the information about expert imaging analysis and a methodology of the statistical estimation.

We have selected some trials for the further in-depth analysis including special subanalysis of the published results from ABSORB A and B trials. The study design of ABSORB A (NCT00300131) and B (NCT00856856) trials with a description of the study population, study device, study procedure, and definitions[31-43] were previously reported[44-56]. Briefly, the Absorb BVS device (Abbott Vascular, Santa Clara, CA, United States) was examined in the single-group, prospective, open-label study (A), with safety and imaging endpoints, 30 patients were enrolled at four participating sites between March 7, and July 18, 2006. The BVS was tested in 101 patients of the ABSORB Cohort B study, which was subdivided into two subgroups of patients: the first group (B1) underwent invasive imaging with QCA, IVUS grey-scale, and OCT at 6, 24, and 60 mo (n = 45), whereas the second group (B2) underwent invasive imaging at 12, 36, and 60 mo (n = 56).

Statistical analysis

For binary variables, percentages were calculated. Continuous variables are performed as the mean and standard deviation (SD) with a median (m) and 95% confidential interval (CI). The overall comparison of serial measurement was assessed by applying the Friedman test, and pairwise comparisons between post-procedure, and follow-up was calculated by a Wilcoxon signed-rank test adjusted by the Bonferroni method. The unpaired t-test was applied in cases when the matrix of datasets was unavailable. To assess the changes of imaging variables over time, the longitudinal repeated measurement analysis using a mixed effect model with five follow-up visits (at post-procedure, 6 mo, 1 year, 2 years, and 3 years) was performed in the SAS procedure PROC MIXED by pooling two cohorts (B1 and B2), as these two groups of patients were comparable in baseline characteristics. Compound symmetry covariance structure was used in the mixed model. In fact, there is no additional random effect beyond the residual error in this analysis. As no formal hypothesis examination was scheduled for assessing the success of the study, no statistical adjustment was proceeded. P values presented are exploratory analyses only and should therefore be interpreted cautiously. The estimated P value for the plaque burden (PB) in the ABSORB cohort A and B trials was adjusted by the maximum P value calculated originally for numerator or denominator at the formula of the PAV due to unavailability of the datasets with a frame-by-frame and patient-by-patient analysis. The P value was interpreted as non-significant (NS, > 0.05) in the case if historically assessed P value of either numerator or denominator was above 0.05. Statistical analysis was completed with SPSS 20.0 software (SPSS Inc., Chicago, IL, United States).

RESULTS

Determination of whether recent trials were underpowered

Current RCTs are being conducted with an underpowered design. In our previous analysis[12], we concluded that the meta-analyses were built on the non-significant data. Only a combo analysis of ABSORB Ⅲ and ABSORB IV has a chance to clear those trends with ST in the near future (one-year results of ABSORB IV trial are expected before Spring 2018). We intentionally conducted the brief analysis (Table 1) in order to cal-

Table 1 The results of post hoc odds-ratio-based sample size calculations for randomized controlled trials and meta-analyses of the bioresorbable vascular scaffold

Trial	No. patients with BVS (ad hoc sample size)	No. patients with metallic DES (ad hoc sample size)	TLF, RR (BVS/DES), *P* value: Total TLF	TLF, rate in BVS patients	Cardiac death	TV-MI	ID-TLR	ST (definite/probable), RR, *P* value	ST (definite/probable), rate in BVS patients	Estimated (*post hoc*) minimal sample size for groups BVS:DES (by TLF), (eOR)	Estimated (*post hoc*) minimal sample size for groups BVS:DES (by ST), (eOR)	Post-dilation, percent of patients	Full PSP, estimated maximum, percent of patients	Small vessels, QCA RVD (< 2.25 mm), percent of patients
BVS randomized controlled trials														
ABSORB Ⅱ, by 3 yr[31]	335	166	2.11[S] *P* = 0.04	10.5%	0.5 *P* = 0.40	5.20[S] *P* = 0.01	1.65 *P* = 0.56	Nul *P* = 0.03	2.8%	324:162 eOR= 2.23	NA	Approximately 60%	NA	NA
ABSORB Ⅱ, by 4 yr[UD][42]	289	139	2.04[S] *P* = 0.05	11.1%	NA	NA	NA	NA	3.0%	293:141[UD] eOR= 2.04	NA	NA	NA	NA
ABSORB Ⅲ, by 1 yr (13 mo)[2]	1313	677	1.28 *P* = 0.16	7.8%[2]	4.12 *P* = 0.29	1.31 *P* = 0.18	1.21 *P* = 0.5	2.08 *P* = 0.13	1.5%	1236:637 eOR = 1.31	1285:666 eOR= 2.09	66%	66%	19%
ABSORB Ⅲ, by 2 yr (25 mo)[2]	1322	686	1.39[S] *P* = 0.03	11.0%	1.83 *P* = NS	1.49[S] *P* = 0.04	1.23 P = NS	2.38 *P* = NS	1.9%	1291:669 eOR= 1.45	1215:630 eOR= 2.52	66%	66%	19%
ABSORB Ⅲ, by 3 yr[UD][43]	1322	686	1.31 *P* = 0.06	13.4%	1.17 *P* = 0.71	1.47[S] *P* = 0.03	1.23 *P* = 0.27	3.12[S] *P* = 0.01	2.3%	1262:655 eOR= 1.23	1375:714[UD] eOR= 3.16	NA	NA	18.8%
ABSORB Ⅳ, by 1 yr (13 mo)[2]	1273 (1500)[1]	1273 (1500)[1]	NA	NA	NA	NA	NA	NA	0.5%	NA	NA	83%	83%	4%
ABSORB Japan, by 3 yr[UD][11]	258	128	1.62 *P* = 0.23	8.9%	Nul *P* = 1.00	1.74 *P* = 0.31	1.79 *P* = 0.23	2.25 *P* = 0.35	3.6%	260:130[UD] eOR= 1.69	248:124 eOR= 2.28	Approximately 80% (low pressure)	NA	NA
ABSORB China, by 3 yr[UD][11,37]	234	229	1.17 *P* = 0.71	5.5%	0.33 *P* = 0.31	2.97 *P* = 0.16	1.64 *P* = 0.33	Nul *P* = 0.16	0.9%	231:231[UD] eOR= 1.19	NA	16.9%	13.5%	18.1%
EVERBIO Ⅱ, by 9 mo[UD][28]	78	160	1.33 *P* = 0.60	12%	Nul *P* = 0.33	NA	1.11 *P* = 0.83	Nul *P* = 0.33	1%	83:170[UD] eOR= 1.26	NA	34%	34%	NA
AIDA, by 2 yr[UD][29]	924	921	1.17 *P*= 0.31	10.3%	0.78 P = 0.43	1.60[S] *P* = 0.04	1.33 *P* = 0.15	3.87[S] *P* < 0.001	3.5%	941:941[UD] eOR= 1.17	898:898 eOR= 4.09	74%	74%	19%
DES trials and BVS registry comparators														
RESOLUTE All-Comers, by 1 yr[UD][13]	1140	1152	1.01 *P* = 0.94	8.3%[2]	1.75 *P* = 0.08	0.98 *P* = 0.92	0.87 *P* = 0.50	2.29 *P* = NS	1.6%	1132:1132 eOR= 1.00	1152:1152[UD] eOR= 2.26	NA	NA	NA
RESOLUTE All-Comers, by 5 yr[UD][13]	1140	1152	1.05 *P* = 0.61	17.0%	1.14 *P* = 0.48	1 *P* = 1.00	1.09 *P* = 1.58	1.41 *P* = 0.24	2.4%	2632:2632[UD] eOR= 0.43	1133:1133 eOR= 2.03	NA	NA	NA
SCAAR Registry, by 2 yr[UD][11]	810	67099	NA	NA	NA	NA	NA	2.5 *P* = 0.006	1.5%[2]	NA	826:68308[UD] eOR= 2.47	NA	NA	Nul
Recent meta-analyses of BVS														
Polimeni *et al*[6], at 2 yr[3UD]	3079	2140	1.33[S] *P* = 0.01	9.4%	0.94 *P* = 0.80	1.66[S] *P* < 0.01	1.32 *P* = 0.05	3.22[S] *P* < 0.0001	2.3%	2708:1881 eOR= NA	3214:2234[UD] eOR= NA	> 61%	61%	NA
Collet *et al*[7], at 2 yr[3UD]	996	696	1.48 *P* = 0.09	8.2%	0.69 *P* = 0.35	2.25 *P* = 0.09	1.89[S] *P* = 0.02	2.93[S] *P* = 0.01	2.2%	616:437 eOR= NA	2759:1930[UD] eOR= NA	NA	NA	NA
Ha *et al*[8], mostly at 2 yr[3]	1379	1095	1.31 *P* = 0.12	7.7%	0.58 *P* = 0.23	2.59[S] *P* = 0.02	1.70[S] *P* = 0.04	2.35[S] *P* = 0.02	2.6%	1233:987 eOR= NA	1374:1082 eOR= NA	> 36%	36%	NA

Mahmoud *et al*[5], at 2 yr[UD]	3166	2226	1.32[S] *P* < 0.01	10.90%	0.75 *P* = 0.21	1.65[S] *P* < 0.001	1.39[S] *P* = 0.01	3.22[S] *P* < 0.0001	2.40%	3206:2258[UD] eOR= 1.4	3174:2235[UD] eOR= 3.58	> 34%	34%	NA
Sorrentino *et al*[9], mostly at 2 yr	3261	2322	1.32[S] *P* < 0.01	9.60%	0.89 *P* = 0.63	1.62[S] *P* < 0.001	1.40[S] *P* = 0.007	3.15[S] *P* < 0.0001	2.40%	3118:2227 eOR= 1.38	3241:2315 eOR= 3.49	> 34%	34%	NA
Ali *et al*[35], at 2 yr[5]	3261	2322	1.29[S] *P* < 0.01	9.40%	0.9 *P* = 0.90	1.64[S] *P* < 0.001	1.39[S] *P* = 0.009	2.99[S] *P* < 0.0001	2.30%	3054:2183 eOR= 1.32	3207:2296 eOR= 3.32	67%	56%	< 51.8%
Zhang *et al*[36], at > 1 yr[3UD]	3237	2303	1.37[S] *P* < 0.01	9.96% (7.3%)[4]	0.92 *P* = 0.711	1.63[S] *P* < 0.001	1.31[S] *P* = 0.027	3.40[S] *P* < 0.001	2.5% (1.8%)[4]	2968:2116 eOR= NA	3470:2469[UD] eOR= NA	NA	NA	NA
Ali *et al*[39], at 3 yr[5UD]	2096	1189	1.37[S] *P* = 0.01	11.70%	0.9 *P* = 0.77	1.68[S] *P* = 0.001	1.41[S] *P* = 0.03	2.83[S] *P* = 0.01	2.40%	2083:1177[UD] eOR= 1.5	2068:1162 eOR= 4.1	NA	NA	NA
Kang *et al*[45], at > 2 yr[3UD]	3179	2239	1.39[S] *P* < 0.001	12.50%	0.86 *P* = 0.49	1.67[S] *P* < 0.001	1.46[S] *P* = 0.004	3.59[S] *P* < 0.001	2.60%	2957:2083 eOR= NA	3297:2322[UD] eOR= NA	NA	NA	NA

[1]Enrollment is not completed yet (2546/3000 subjects in ABSORB IV trial were allocated in March 2017; presented data are preliminary); [2]Primary end-point; [3]Odds ratio (OR) was provided by the author instead of RR (estimated OR was calculated from the data provided by the author in the article if applicable); [4]Pooled incidence of definite or probable stent thrombosis at longest follow-up in patients receiving BVS[36]; [5]D + L, DerSimonian and Laird random-effect model. The OR, confidence level and relevant sample size were determined with a validated online calculator of Select Statistical Services (https://select-statistics.co.uk/calculators/confidence-interval-calculator-odds-ratio/; https://select-statistics.co.uk/calculators/sample-size-calculator-odds-ratio/; Exeter, United Kingdom) with a 95%CI, estimated relative precision (calculated as a percentage by which the lower limit for the confidence interval is less than the estimated odds ratio) and the known prevalence of the variables. The estimated odds ratio (eOR), which was calculated from the data that were provided by the author in the original article, represents the odds that an outcome will occur given a particular exposure, compared to the odds of the outcome occurring in the absence of that exposure. Either P value or OR presented inside the cells below the numbers. Cells with "S" depict data with a statistically significant *P* value ($P < 0.05$, addressing the question of whether the intervention effect is precisely nil). Cells with "UD" indicate variables with underpowered design by sample size (when the estimated post hoc sample size is bigger than ad hoc one). If not mentioned, the data from meta-analyses presented are from the Fixed effects model.

culate a posthoc sample size by the odds ratio (OR) and estimate the statistical power for each available RCT comparing BVS with DES. The documented high resemblance between ad hoc and post hoc sample size calculations confirms the presence of bias due to the very confusing tailored fashion of their appearance. The OR-based sample size calculation that we used in our analysis is one of the most simple and reliable. It is sensitive to a relative precision, a prevalence, an OR, and a presence to absence ratio. Both ABSORB Ⅱ and ABSORB Ⅲ were specifically designed and powered for a five-year supervision. However, RESOLUTE All-Comers[13] became dramatically underpowered beyond the primary end-point by the five-year follow-up. Both ABSORB China and ABSORB Japan were not powered enough either. ABSORB China lost statistical power by the second year of the trial, and ABSORB Japan lost statistical power at three years. Regretfully, EVERBIO Ⅱ and AIDA RCTs, available registries with DES, and few meta-analyses[6,7,36], were not optimally powered either (Table 1). Regretfully, ABSORB Ⅱ[42] and ABSORB Ⅲ[43] became underpowered by four years and three years, respectively. Moreover, in cases with truly powered research, all the outcomes with *P* values > 0.05 must be interpreted as false, which means that we can only trust the higher rates of TLF driven by the target vessel myocardial infarction (TV-MI).

Determination of bias

Results of the recently published (Mahmoud *et al*[5]) meta-analysis (six RCTs with 5392 patients including ABSORB Ⅲ, ABSORB China, ABSORB Japan, AIDA, ABSORB Ⅱ, EVERBIO Ⅱ; mean follow-up was 25 mo) were rather ambiguous. BVS had a higher rate of TLF [risk ratio (RR), 1.32, $P = 0.002$] with the worst results in ABSORB Ⅱ (34/335 *vs* 8/166) compared with metallic DES run by the higher rates of TV-MI (RR, 1.65, $P < 0.0001$) and ischemia-driven target lesion revascularization (ID-TLR; RR, 1.39, $P = 0.01$). The risk of definite or probable ST (RR, 3.22, $P < 0.0001$) and very late ST (> one year; RR, 4.78, $P = 0.004$) was higher with BVS. This is a very tricky meta-analysis with a sophisticated statistical adjustment, which is totally undermining benefits of BVS for cardiac (RR, 0.75; $P = 0.21$) and all-cause mortality (RR, 0.79, $P = 0.36$). The better outcomes with BVS were observed in ABSORB China (cardiac mortality RR = 0.33, all-cause mortality RR = 0.17) and ABSORB Ⅱ (cardiac mortality RR = 0.50, all-cause mortality RR = 0.66). The worst performance of BVS was documented in ABSORB Japan. Six meta-analyses from the teams of Collet *et al*[7], Ha *et al*[8], Sorrentino *et al*[9], Ali *et al*[35,39], Zhang *et al*[36], and Kang *et al*[45] released in 2017 with the latest findings demonstrate very similar numbers. The high-quality seven-study meta-analysis of Ali *et al*[35,39] demonstrated the inferiority of Absorb BVS *vs* metallic DES in randomized trials where BVS consorted with elevated rates of composite device-oriented and

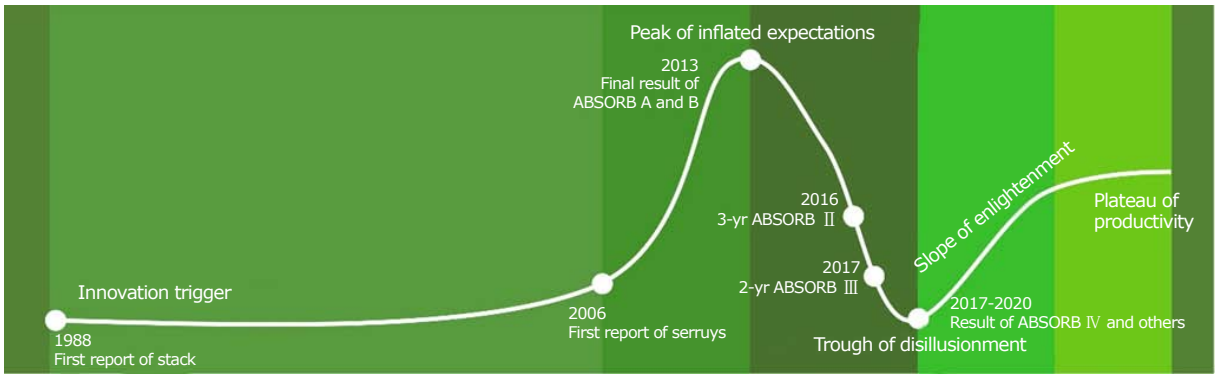

Figure 1 Performance of bioresorbable vascular scaffolds in the market. A schematic representation of the Gartner Hype Cycle for the bioresorbable vascular scaffold.

patient-oriented adverse events at both two- and three-year follow-up compared with DES, with a certain risk of adverse events between one and three years. The pooled meta-analysis of Zhang *et al*[36] with the longest follow-up findings from both observational and randomized trials exposed the incidence of definite or probable ST after BVS of 1.8% (95%CI: 1.5% to 2.2%, n = 21884), and the incidence of TLF of 7.3% (CI: 5.9% to 8.8%, n = 19998).

BVS is as good as DES by the rates of cardiac mortality with a trend toward more benefits from BVS for survival. Statistically, it is quite a challenging scenario to draw any conclusions from the data with no strong evidence that the intervention has an effect (with $P > 0.05$). The best evidence synthesis with only methodologically sound studies must be included in a meta-analysis to avoid any kind of bias. If the RCTs alone failed to demonstrate statistically significant data for ST, sources of bias by the method in such a meta-analysis of the weak studies cannot be controlled. Clinically, it is of paramount importance to detect any number of severe adverse events associated with the intervention in order to protect patients, but we must be honest with the correct interpretation of the findings and further conclusions.

Our previous analysis[12] with a Funnel plot of the existing observational and randomized trials demonstrated that there is an unintentional bias with a lack of data from patients with metallic DES in order to compare and judge BVS properly. The meta-analysis of Polimeni *et al*[6] (five RCTs with 5219 patients) and Sorrentino *et al*[9] (seven RCTs with 5583 patients) observed similar trends of clinical outcomes and another Funnel plot analysis. Unfortunately, the authors ignored clear asymmetry in the Funnel plots especially in the case of TV-MI, cardiac death, and ST where we can exclude a publication bias (due to negative Egger or Harbord test with $P > 0.05$). There are at least three studies with small sample sizes, which means it produces less precise estimated effects[14]. The ultimate assessment is very subjective but difficult because the number of trials is not large (less than ten). This "asymmetrical" bias can occur because of the poor methodological design in the trials, which is typical for a relatively small sample size trial because it can lead to spuriously inflated estimated treatment effects. It is challenging to specify the nature of the bias, and the only way to overcome it is to conduct a well-powered statistically harmonized RCT.

A tailored strategy

The story of BVS looks like a curve of the Gartner Hype Cycle[34] (Figure 1). The innovation trigger of BVS technology began in 1988 when the team of Professor Richard S Stack from Duke University (Durham, NC) first reported in the American Journal of Cardiology about a PLLA bioabsorbable stent. There were no usable products, but it brought us to the next stage[34], Gartner's peak of inflated expectations. This stage started in 2006 with the first publication in the Journal of Catheterization and Cardiovascular Interventions from the team of Professor Patrick W Serruys from Erasmus MC (Rotterdam, The Netherlands). The third scientific compendium of 2013 included 72 articles (mostly pre-clinical studies, clinical ABSORB cohorts A and B trial, ABSORB EXTEND) covering all the challenging options related to transient scaffolding. This was a stage according to Gartner when early publicity was producing a number of success stories accompanied by scores and minor failures. The story became different with a new stage of the so-called trough of disillusionment in 2013 when the first paper with a design of ABSORB Ⅱ trial was released in the American Heart Journal. The three-year (TCT 2016, Washington, DC) and four-year (TCT 2017, Denver, CO) results of ABSORB Ⅱ, and then the two-year (ACC 2017, Washington, DC) and three-year (TCT 2017, Denver, CO) reports of ABSORB Ⅲ trial destroyed all the previous illusions warning about concerns of a higher prevalence of TLF and ST in BVS patients. It is standard at this stage to continue investments to improve the products to the satisfaction of early adopters. In the future, a slope of enlightenment with more clearance about how technology can be beneficial and become more widely understood. Likely, the results of the ABSORB IV trial and further meta-analyses will resolve the situation with trends during 2017-2020. We predict that the second- and third-generation BVS (with thinner struts below 100

μm) will result in a plateau of productivity and finally the adoption of the technology.

Device thrombosis in interventional studies: Preparation is the only solution

ST rates with Absorb BRS were comparable with DES[44] performed with a lesion preparation or so-called PSP implantation[24] (RR, PSP *vs* no PSP 0.37) achieving 0.35 per 100 patient-years, which is comparable to the RR 0.49 with bare-metal stents, the RR 1.06 with everolimus DES, the RR 0.44 with paclitaxel DES, the RR 0.60 with sirolimus DES, and the RR 0.70 with zotarolimus DES.

From clinical outcomes to arterial remodeling: A pooled analysis of plaque burden in selected ABSORB A and B trials

The pathobiological mechanism responsible for failures of BVS in clinical trials and to assess patterns of the arterial remodeling have been investigated. A total of 30 patients were enrolled in the ABSORB A trial (a revision 1.0 of BVS) between March 7 and July 28, 2006[31,57], and 101 patients were assigned to the ABSORB Cohort B study (a revision 1.1 of BVS) from March 19 to November 6, 2009[53,55,56]. Baseline characteristics were published elsewhere. The main clinical outcomes and adverse events were previously reported[31,53,55-57].

Figure 2 and Table 2 show the pooled data of PB and mean plaque area (MPA) collected with IVUS and MSCT. Between 6 and 60 mo of follow-up, there were 25 (A), 21 (B1), and 30 (B2) serial IVUS measurements. At five years, 18 patients took MSCT as an optional investigation that was performed at three of four centers. Quantitative analysis of the scaffolded segment was feasible in all patients. The insignificant increase of PB was documented in ABSORB cohort A and B1 trials at 6, 24, and 60 mo (if applicable). The absolute growth of PB was +7.52% (*P* value is not applicable, NA; *n* = 25) at 6 mo (a +13.72% relative increase), and +1.63% (*P* value is NA) at 24 mo (a relative +2.97% from baseline) in ABSORB A trial (*n* = 29), and +2.47% (*P* < 0.02, *n* = 33) at 6 mo (a +4.62% relative increase), +1.89% (NA, *n* = 33) at 24 mo (+3.53%) with a - 2.46% (estimated *P* value < 0.06, *n* = 21) reduction at 60 mo (a -4.59% relative decrease) in ABSORB cohort B1 trial (*n* = 45). A +1.60% increase of PB (*P* value is NA, *n* = 45) registered at 12 mo (a +2.94% relative increase) with a further -1.10% reduction at 36 mo (a -2.02% relative decrease from baseline, *P* = 0.05, *n* = 45), and a -2.62% decrease at 60 mo (a -4.88% relative decrease, estimated *P* value < 0.22, *n* = 30) in ABSORB cohort B2 trial (*n* = 56).

In order to evaluate the quality of the data, the accuracy of the imaging modalities in ABSORB cohort B1 trial was estimated. The length of the scaffolded region was measured in patients who underwent QCA, IVUS, VH-IVUS, MSCT, and OCT and then compared with the nominal size of the scaffold, which was equal to 18 mm in all cases (Figure 3). The accuracy (a trueness by ISO 57251) was highest for OCT imaging (96.6%) with very good precision (estimated by 95%CI of a trueness; the length of the scaffold was correct in 13.1% of cases). The lowest accuracy assessed in MSCT analysis with a 62.0% trueness and poor precision (the length was overestimated in 93.2% of observations). The moderate accuracy with relatively poor precision attested for QCA (82.7%, totally underestimated), IVUS, and VH-IVUS (82.9% and 84.3%, respectively, the length was mostly overestimated).

Plaque burden and lesion composition in ABSORB cohort B1 trial

The GS IVUS analysis of 32 patients (72.73% of the cohort) with serial imaging examination established the statistically significant increase in PB at 6 mo (a +2.73% absolute increase, *P* = 0.05) with a further light decrease between 6 mo and 2 years (a +2.54% absolute increase from baseline, *P* = 0.08) with similar dynamic edges (Table 2 and Figure 4). Eight patients proved a -2.67% absolute abatement of PB at 24 mo (*P* = 0.28). The VH-IVUS assessments (Figure 4) substantiated a 0.12-fold increase in the number of VH-thin-cap fibroatheromas (VH-TCFA) from post-procedure to 24-mo follow-up as a manifestation of the natural history of atherosclerosis and significant area enlargement of the fibrous tissue (+48.52%, *P* = 0.02, *n* = 32) in the lesions without any powered (*P* > 0.05) distinction of the other plaque components. The patients with reduction of PB (*n* = 8) had a composition of the lesion at the scaffold region pre-procedure (one observation) with less pronounced depositions of calcium (*P* > 0.05) and a higher value of fibrous tissue (*P* > 0.05), which was very similar to the composition of the lesions that were documented in both edges (*P* > 0.05) compared to 24 patients (three observations) with increased PB at 24 mo. Post-procedure, the general tendency for reduction of the dense calcium was shown (*P* = 0.10) in all observations, which was related to the degradation of the scaffold that sometimes imitates calcium in VH-IVUS. A -0.11-fold decrease in the number of VH-TCFA per patient with a trend toward change of the percentages of necrotic core (a -11.10% relative decrease, *P* = 0.13) and fibrous tissue (a +20.12% relative increase, *P* = 0.11) with a significant increase of fibro-fatty tissue (a 0.91-fold increase, *P* = 0.04) at 24 mo was argued in observations (*P* = 8) to be "regression of atherosclerosis".

Currently, it is unclear whether the plaque regression is a true phenomenon due to the disappearance of the scaffold, which is ultimately replaced by connective tissue[56]. The documented trend toward a reversal of atherosclerosis, lumen enlargement, and progressive hyaline arteriosclerosis[58] (mediating so-called OCT-phenomenon of the "golden tubes"[59]) after placement of BVS resembles the previously delineated histologic findings in animals[59-62] and human autopsies[63].

The curve of the PB draws a four-phase regression of

Table 2 Serial imaging analysis of the artery remodeling in ABSORB cohort A and B trials

Variable	Post-procedure (baseline)	6 mo	12 mo	24 mo	36 mo	60 mo	Friedman *P* value
Intravascular ultrasound, 60-mo results of ABSORB cohort B (B1, *n* = 21, and B2, *n* = 30) trial							
Mean vessel area in mm^2, mean ± SD (*n*), BL-to-FUP *P* value	14.56 ± 3.82 (21)	14.92 ± 3.78 (21), 0.3925		15.88 ± 4.02 (21), 0.0014[S]		15.28 ± 4.53 (21), 2.1371	0.0193[S]
	13.61 ± 2.40 (30)		14.15 ± 2.61 (30), 0.2140		14.25 ± 2.57 (30), 0.0788	13.23 ± 2.70 (28), 0.2701	0.0337[S]
Mean lumen area in mm^2, mean ± SD (*n*), BL-to-FUP *P* value	6.75 ± 1.19 (21)	6.59 ± 1.20 (21), 0.0610		7.24 ± 1.91 (21), 0.1995		7.46 ± 2.45 (21), 0.0851	0.0626
	6.31 ± 0.86 (30)		6.31 ± 1.01 (30), 0.5131		6.70 ± 1.48 (30), 0.0858	6.48 ± 1.50 (30), 0.5666	0.2221
Plaque burden in %, mean ± estimated SD (*n*)[1], BL-to-FUP *P* value	53.64 ± 14.08 (21)	55.83 ± 14.15 (21), < 0.39[2]		54.41 ± 14.35 (21), < 0.20[2]		51.18 ± 16.81 (21), < 2.14[2]	< 0.06[2]
	53.64 ± 9.46 (30)		55.41 ± 10.22 (30), < 0.51[2]		52.98 ± 11.70 (30), < 0.09[2]	51.02 ± 11.81 (30), < 0.56[2]	< 0.22[2]
Mean plaque area in mm^2, mean ± SD (*n*), BL-to-FUP *P* value	7.81 ± 2.98 (21)	8.33 ± 2.88 (21), 0.0660		8.64 ± 2.85 (21), 0.0004[S]		7.75 ± 2.62 (21), 4.4007	0.0025[S]
	7.30 ± 1.85 (30)		7.84 ± 1.92 (30), 0.0220[S]		7.55 ± 1.58 (30), 0.8121	6.79 ± 1.90 (28), 0.0108[S]	< 0.0001[S]
Intravascular ultrasound, 36-mo results of ABSORB cohort B (B1, *n* = 33, and B2, *n* = 45) trial							
Mean vessel area in mm^2, mean ± SD (*n*), BL-to-FUP *P* value	14.04 ± 3.80 (33)	14.44 ± 3.82 (33), 0.008[S]		15.35 ± 4.05 (33), < 0.001[S]		NA	NA
	13.79 ± 2.37 (45)		14.43 ± 2.64 (45), 0.03[S]		14.58 ± 2.67 (45), 0.002[S]	NA	0.18
Mean lumen area in mm^2, mean ± SD (*n*), BL-to-FUP *P* value	6.53 ± 1.24 (33)	6.36 ± 1.18 (33), 0.02[S]		6.85 ± 1.78 (33),0.35		NA	NA
	6.29 ± 0.90 (45)		6.35 ± 1.17 (45), NS		6.81 ± 1.62 (45), 0.05[S]	NA	0.007[S]
Plaque burden in %, mean ± estimated SD (*n*)[1], BL-to-FUP *P* value	53.49 ± 14.48 (33)	55.96 ± 14.80 (33), < 0.02[S]		55.37 ± 14.61 (33), < 0.35		NA	NA
	54.39 ± 9.35 (45)		55.99 ± 10.32 (45), NS		53.29 ± 12.68 (45), < 0.05[S]	NA	NA
Mean plaque area in mm^2, mean ± SD (*n*), BL-to-FUP *P* value	7.52 ± 2.84 (33)	8.08 ± 2.87 (33), < 0.001[S]		8.49 ± 2.89 (33), < 0.001[S]		NA	NA
	7.50 ± 1.82 (45)		8.08 ± 1.94 (45), < 0.001[S]		7.77 ± 1.73 (45), NS	NA	0.004
Intravascular ultrasound, 24-mo (*n* = 25), and MSCT, 60 mo (*n* = 18), results of ABSORB cohort A trial							
Mean vessel area in mm^2, mean ± SD (*n*), BL-to-FUP *P* value	13.49 ± 3.74 (25)	13.79 ± 3.84 (25), 0.98	NA	12.75 ± 3.43 (19), 0.68	NA	NA	NA
	NA	NA	NA	13.17 (18) (18 mo baseline)	NA	11.93 (18), 0.26	NA
Mean lumen area in mm^2, mean ± SD (*n*), BL-to-FUP *P* value	6.04 ± 1.12 (25)	5.19 ± 1.33 (25), < 0.0001[S]	NA	5.47 ± 2.11 (19), 0.12	NA	NA	NA
	NA	NA	NA	4.47 (18) (18 mo baseline)	NA	4.29 (18), 0.11	NA
Plaque burden in %, mean ± estimated SD (*n*)[1], BL-to-FUP *P* value	55.23 ± 15.31 (25)	62.36 ± 17.37 (25), < 0.98	NA	57.10 ± 22.02 (19), < 0.68	NA	NA	NA
	NA	NA	NA	66.06 (18) (18 mo baseline)	NA	64.04 (18), < 0.26	NA
Mean plaque area in mm^2, mean ± SD (*n*), BL-to-FUP *P* value	7.44 ± 2.83 (25)	8.60 ± 2.85 (25), < 0.0001[S]	NA	7.10 ± 2.02 (19), 0.80	NA	NA	NA
	NA	NA	NA	8.23 (18) (18 mo baseline)	NA	7.10 (18), 0.23	NA

Numbers are expressed in mean ± SD or *n*. [1]The SD cannot be directly calculated due to unavailability of the patient-by-patient matrix of the ABSORB trial, and presented as either a 5% deviation or adjusted by the maximum deviation for both numerator and denominator; [2]The *P* value cannot be directly calculated due to unavailability of the patient-by-patient matrix of ABSORB trial, and performed as an estimated *P* value adjusted by the maximum *P* value in either numerator or denominator. The cells with "S" performed statistically significant changes ($P < 0.05$) of the variables. NS: Non-significant (*P* value > 0.05); NA: Non-available or not applicable.

atherosclerosis. First, the polymeric struts are covered by a fibromuscular neointima (first 6-12 mo, or "reactive" phase) with an inflammatory "swelling" (a foreign body reaction, including multinucleated giant cells, macrophages, and lymphocytes) of the artery wall (slowly shrinking inflammatory infiltrate with macrophages and lymphocytes mostly observed between 12 and 36 mo, maximum of 42 mo)[60,61]. The increase of the necrotic area post-procedure in VH-IVUS definitely consorted with the fibrinoid necrosis in the scaffolded lesion, but this fact demands a special investigation to discern the hyalinosis whereas the association of the necrotic core

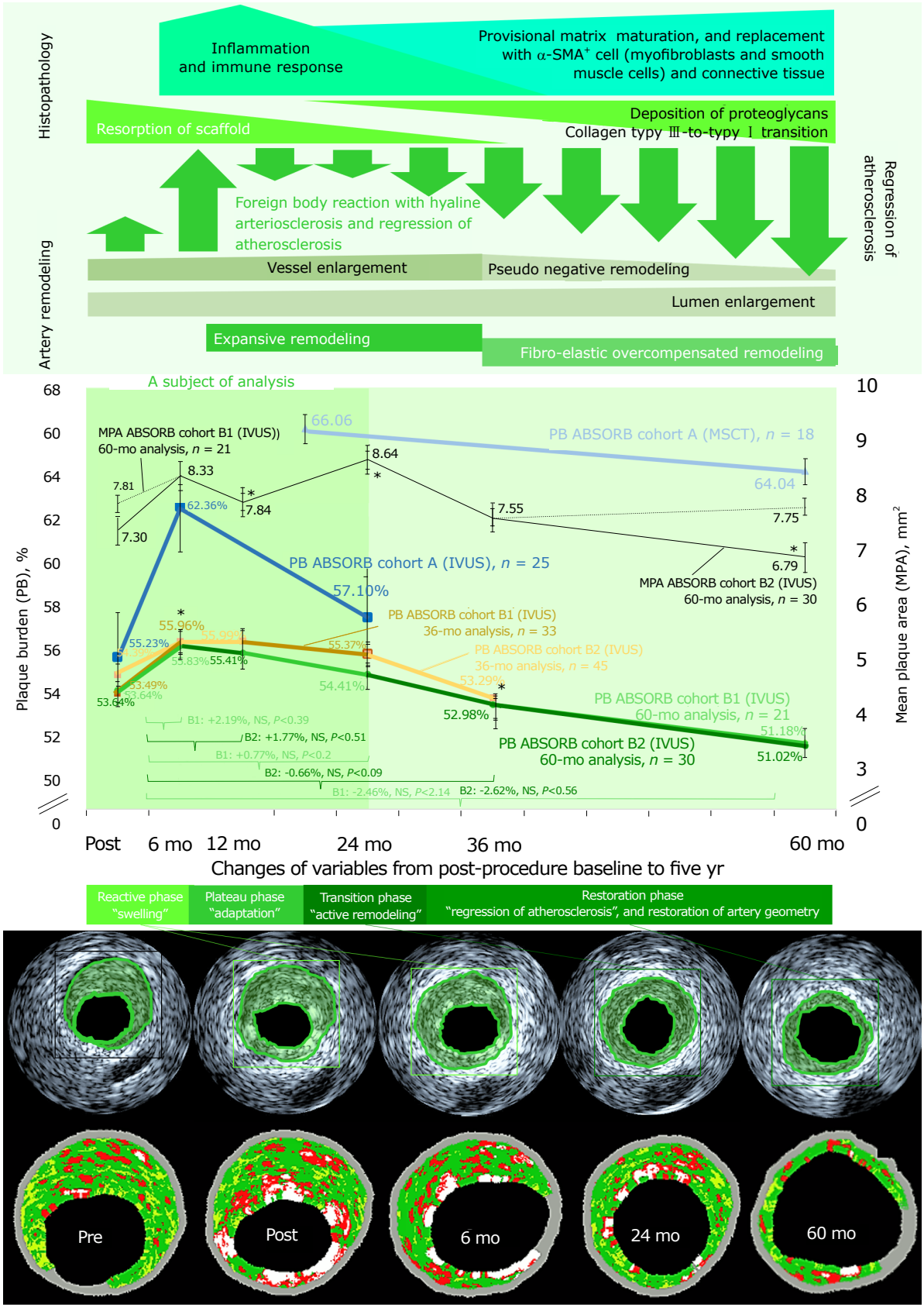

Figure 2 Plaque burden in patients of ABSORB cohort A and B trials at 60 mo. The top panel outlines the acute/subacute and chronic inflammatory/immune response to the implantation of the BVS, which is ongoing during the first 24-36 mo. The middle panel renders a pooled analysis of the plaque burden (PB) and mean plaque area (MPA) in the selected ABSORB phase Ⅰ/Ⅱ trials and different multimodality imaging analyses through the five years of the study. The bottom panel shows an example of the grey scale- and virtual histology-IVUS analyses in the five-year time-frame of the ABSORB trial highlighting a clear reduction of the plaque area and artery remodeling with the lumen enlargement and positive expansive remodeling of the vessel at least until 24 mo with the further constrictive-like remodeling. The figure was adapted from reference [34].

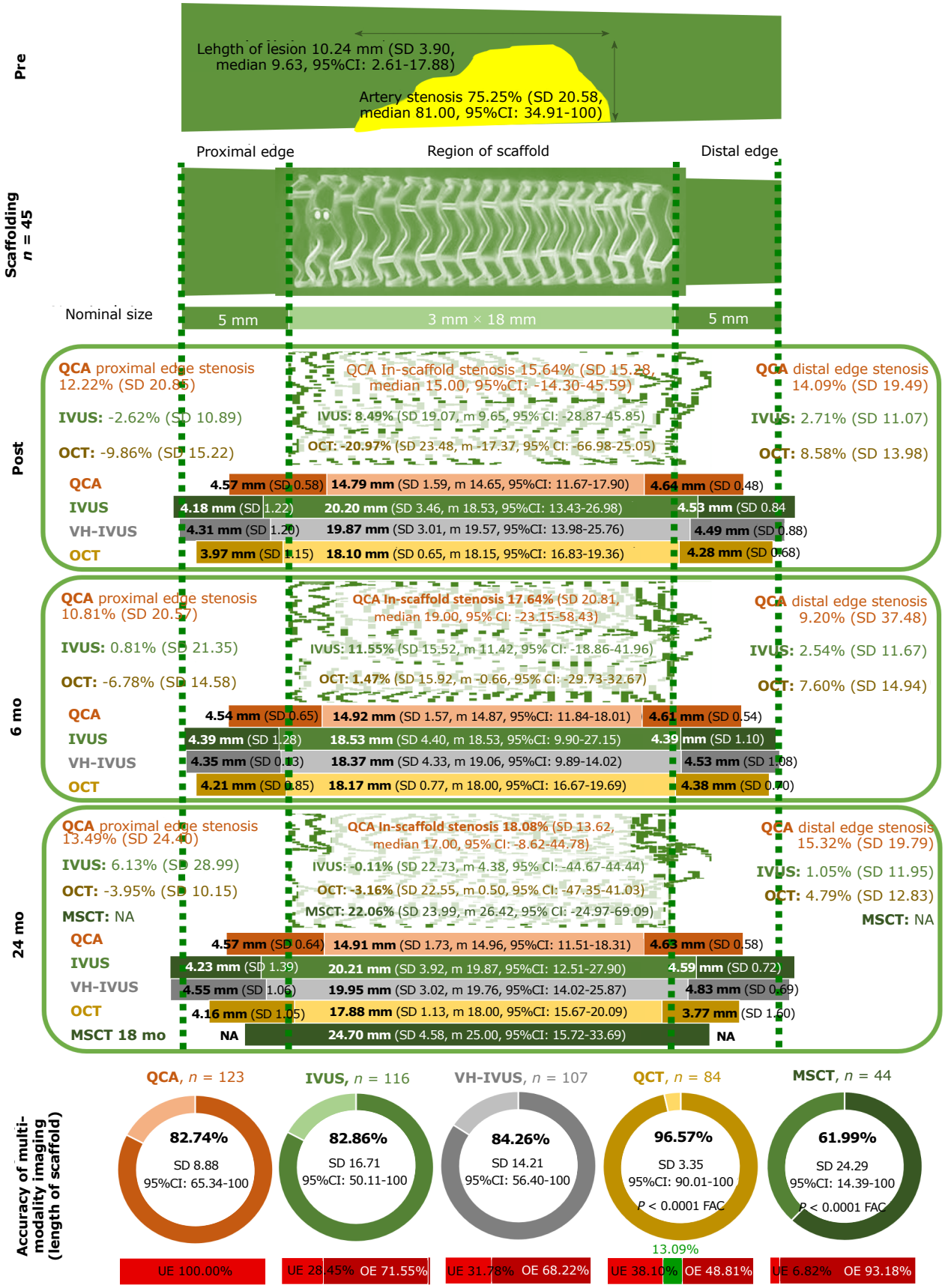

Figure 3 The accuracy of multimodality imaging analysis. The analysis of accuracy (trueness and precision) administered with quantitative coronary angiography, intravascular ultrasound, virtual histology-IVUS, multislice computed tomography, and optical coherence tomography by the nominal length of the scaffold, which was 18 mm in all cases. The panel defines the spread-out-vessel graphics (axial resolution of 200 μm) with the appearance of the scaffolded and edge regions pre- and post-procedure at 6 mo and 24 mo. The figure was adapted from ref. [34]. UE: Underestimated (observations with the length of the scaffolded region less than 18 mm); OE: overestimated (the examined scaffolded region was more than 18 mm). QCA: quantitative coronary angiography; IVUS: intravascular ultrasound; VH-IVUS: virtual histology-intravascular ultrasound; OCT: optical coherence tomography; MSCT: multislice computed tomography.

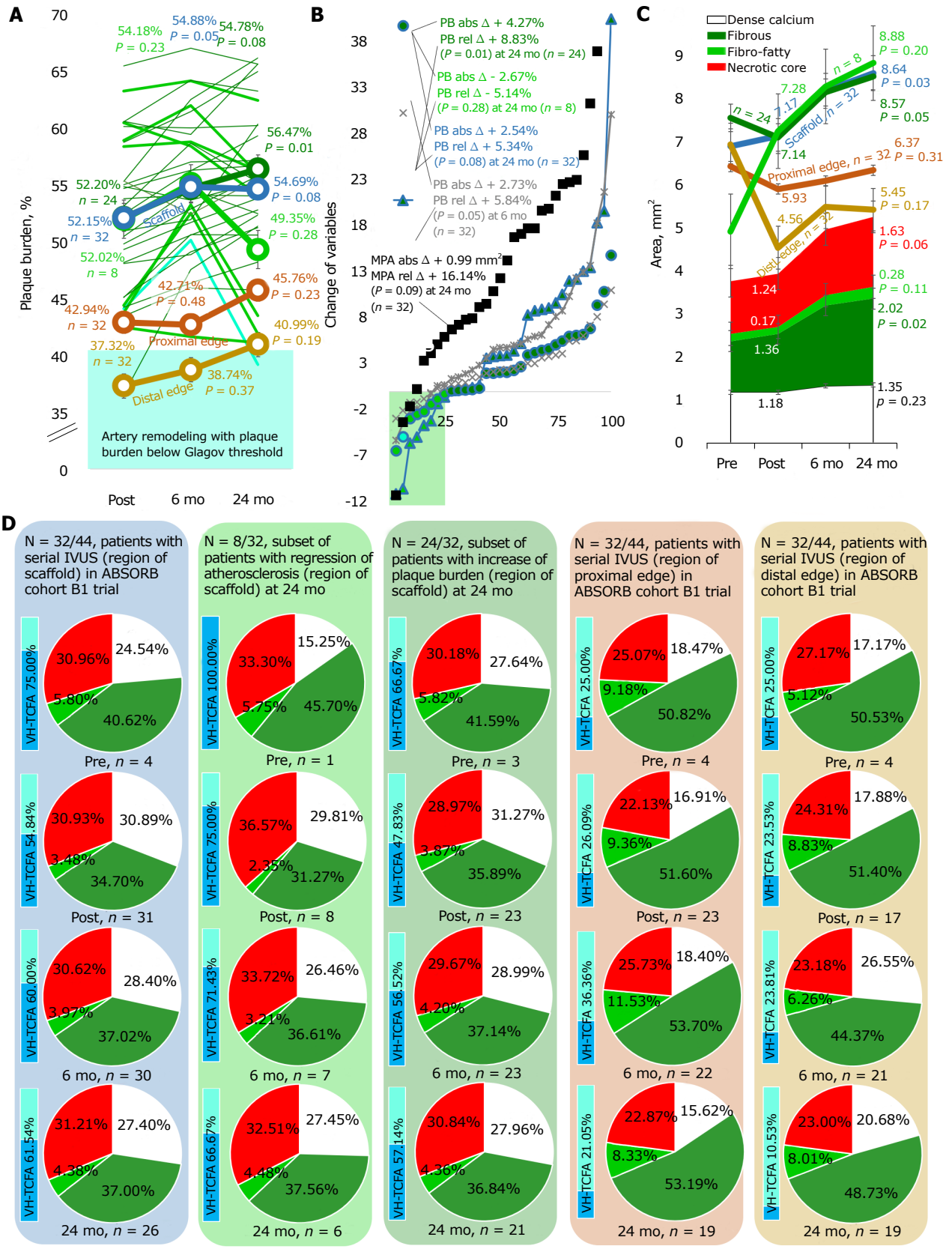

Figure 4 The artery remodeling in ABSORB cohort B1 trial. A, B: The plaque burden (%) in 44 patients of cohort B1 trial (panel A with the changes at panel B); C, D: The proportion between the lesion components, which was computed by virtual histology-intravascular ultrasound imposed for each patient, but the percentage of each plaque component did not differ significantly between baseline and 24 mo. The depicted results mounted as the mean of the estimated proportions. The figure was adapted from ref. [34]. *n*: Number of patients; MPA: Mean plaque area; abs: Absolute; rel: Relative; VH-TCFA: Virtual histology-thin-cap fibroatheroma; PB: plaque burden; VH-IVUS: virtual histology-intravascular ultrasound.

is based on the value of the cholesterol deposits (VH-IVUS fibro-fatty component). Second, struts and artery are of stable morphology through 18 mo (a "plateau phase" with an adaptation of the artery wall to the altered hemodynamics/shear stress and a foreign body in the grip of inflammation and a "frame" of the scaffold). Third, the struts become replaced by proteoglycan matrix (arterial hyalinosis)[58] at 24 mo (a "transition" phase with an active compensatory artery remodeling that starts at 12 mo with a peak at 18 mo)[60,61], which corresponds to resorption of BVS (morphological changes in the scaffold resorption sites begin at 18 mo) with a light calcification of the vessel wall and increasing eosinophilia (30 mo). These changes are linked to the absorption and inspissation of proteins (presence of proteinaceous material including albumin being a manifestation of the Vroman effect[64,65]). The precipitation of calcium phosphate might be the result of a benign, localized drop in pH caused by acidic polymer degradants at the strut-tissue interface. Fourth, the strut sites are eventually composed of a provisional matrix (mostly, proteoglycan) that matures from collagen type Ⅲ integration (36 mo) to eventual replacement by α-SMA$^+$ cells (myofibroblasts and smooth muscle cells) and collagen type I at 42 to 48 mo (hyaline-associated arteriosclerosis with an excess of the dense connective tissue at the sites of the struts replacement, which looks like a fibrous tissue at VH-IVUS), demonstrating an augmenting integration of scaffold into the arterial tissue (a "restoration" phase). Strictly speaking, the process of "bioresorption" finishes by 24 mo with the consequent "integration" of the struts within the arterial wall. The debris of the scaffold can be pinpointed until 36 mo. The drawbacks (increased stenosis and greater neointimal thickness) of the BVS seen at early time points were no longer pertinent at 36 mo[61]. Meanwhile, the MPA in IVUS exhibits a biphasic change with an increase until 12-24 mo and a plaque reduction until 24-36 mo[55],which is relevant to the above-mentioned findings, but different from the dynamics of PB.

The process of the PB reduction or "regression of atherosclerosis" starts at 12 mo and turns substantial with a relatively slow pace after 36 mo. However, the histopathologic signs of the excessive extracellular matrix production (including VH-IVUS signs of the fibrous metamorphosis in the lesion) with the "hardening" hyaline arteriosclerosis cause debate for a potential of the transient scaffolding for the "restoration" of the artery wall. Frankly, a hyaline deposition in the middle-size arteries is typical for aging and very benign in elderly patients[22,23]. The nature and structure of hyaline (nonfibrillar glycoprotein) in the case of the transient scaffolding is not entirely clear. However, the accumulation of the extracellular matrix in tissue might be evidence for a reversal of atherogenesis. Moreover, such a phenomenon with a lumen enlargement (as a result of the transient scaffolding) could be the only way to settle on atherosclerosis protecting the arteries, which necessitates further long-term studies.

The scaffold-induced hyaline arteriosclerosis managed by the complex immune response is typical for the foreign body (biomaterial-induced) reaction[60,61,64,65]. The mTOR-inhibition with everolimus devaluates the immune response to the scaffold. However, in human autopsies[62], macrophage and granulocyte activation where the limus drugs are not effective enough are observed. The complement system, a major host defense system, conserves clotting and inflammation, which is the most critical for the rate of ST and any adverse events[64,65]. Such an immune hurricane amid the post-intervention healing of the vessel wall has a potential to catalyze specific artery remodeling with a lumen enlargement, certain atheroprotective patterns, and hyaline arteriosclerosis as an outcome of the foreign body reaction to BVS partly adjusted with mTOR-inhibition.

The decrease in the number of TCFA lesions in the tested cohort of patients with "regression of atherosclerosis" is further evidence of the BVS benefits promising the prevention of MACE merely because it is known[59,66,67] that VH-IVUS can identify plaques at increased risk of subsequent events, and VH-TCFA are strongly linked with MACE (VIVA trial, 2011). Historically BVS (since 2006 in at least five studies: ABSORB Ⅱ, ABSORB-Japan, ABSORB-China, ABSORB Ⅲ, and ABSORB-Extend) substantiated the excellent clinical profile[20-54] with the proper safety (relatively low rate of TLF) that with the reduction of PB is able to significantly shift the management of atherosclerosis.

The benign adaptive artery remodeling with the lumen enlargement and vessel wall thinning of atherogenesis (the ABSORB B trial confirmed the strong trend toward reduction of PB through 60 mo without signs of the "natural" progression of atherosclerosis) with a potential to become a magic bullet in order to ultimately overpower atherosclerosis.

The window of external elastic membrane enlargement and Glagov-Pasterkamp artery remodeling in ABSORB trials

The multiple linear and polynomial regression analysis of the different degrees (Figure 5) in both scaffold (Figure 5A) and edge (Figure 5B) regions (290 observations) in ABSORB cohort B1 trial authenticated the existence of the window of external elastic membrane (EEM) enlargement with the boundaries between 30.26% and 50.01% where EEM slows down without compromised lumen geometry. The number of observations with PB below 30.26% was not high enough to ultimately clarify the lower limit (P = 0.06), but box-and-whisker analysis certified the statistically significant difference between three distributions above 30.26%, in particular between 30.26%-40.00% and 40.00%-50.01% (P = 0.02), which denotes that the Glagov threshold of a 40% PB is a real phenomenon but with the broader boundaries when lumen becomes narrow if PB achieves 50.01% (P < 0.02). These findings were corroborated at the analysis of associations between IVUS PB and artery stenosis. The

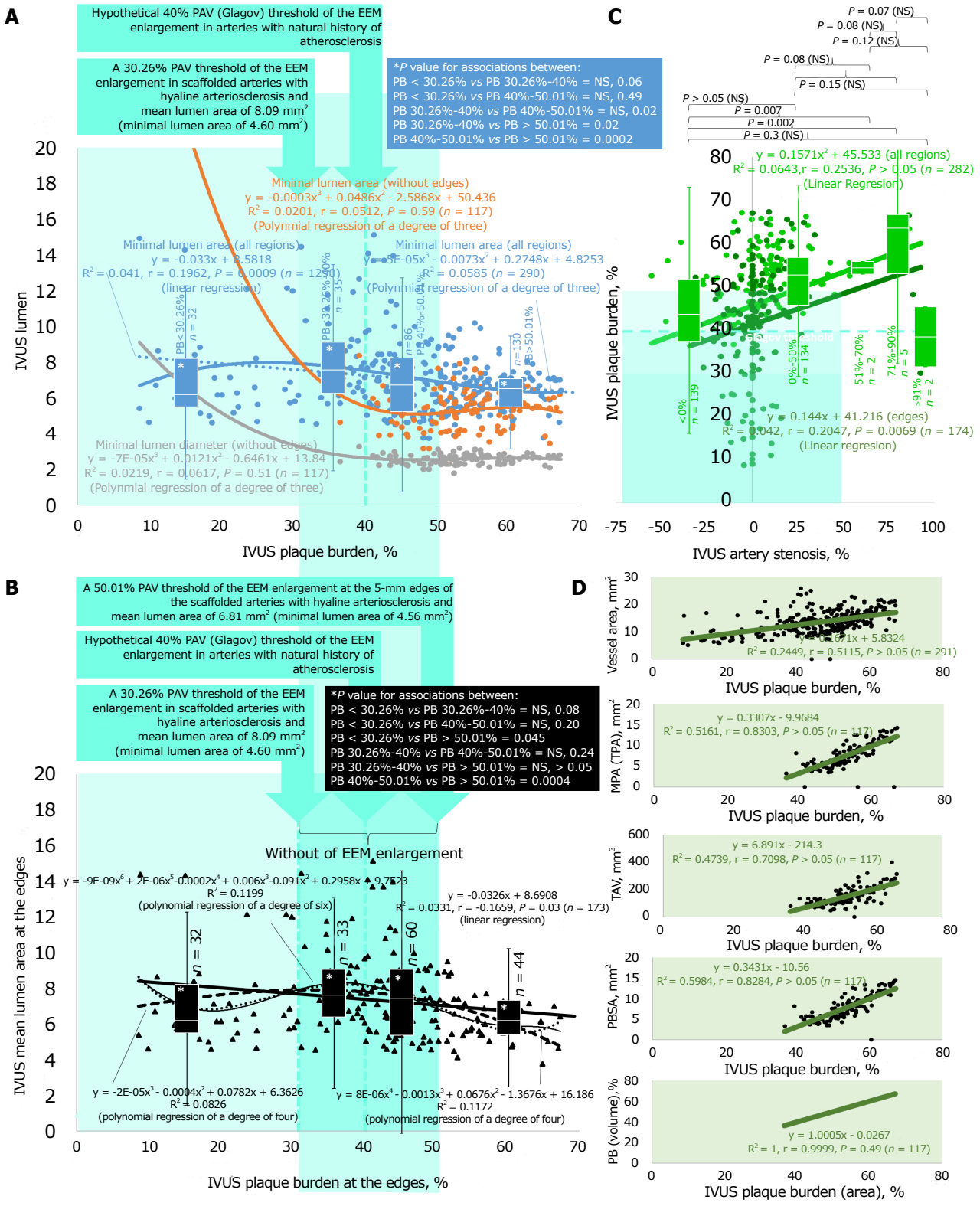

Figure 5 The external elastic membrane enlargement and Glagovian artery remodeling. A, B: Character regression analysis of the associations between plaque burden (PB) and lumen geometry verified by intravascular ultrasound (IVUS). The linear and polynomial regression of the different degrees at the regions of scaffold and edges bared two boundaries (30.26% and 50.01%) of the phenomenon of the external elastic membrane (EEM) enlargement (shown with a vertical stripe). The further box-and-whisker analysis was from four PB distributions (PB < 30.26%, PB 30.26%-40%, PB 40%-50.01%, and PB > 50.01%) to assess patterns of the Glagovian artery remodeling; C, D: The comparison of PB with artery stenosis (adjusted by the mean reference area) with a five-distribution box-and-whisker analysis (artery stenosis < 0%, 0%-50%, 51%-70%, 71%-90%, and > 91%); The upper boundary of the window of the EEM enlargement where artery stenosis was no more than 45% (C). The associations between IVUS PB and other variables characterizing the lesion geometry were estimated (D). The *P* value was calculated for comparison of one or two variables in order to either examine the means of two groups (paired or unpaired *t* test) or test statistical consistency for regression. The figure was adapted from ref. [34]. *n*: Number of observations; PAV: Percent atheroma volume; R2: Coefficient of determination; r: Pearson correlation (for linear regression); IQR: Interquartile range; NS: Non-significant (*P* > 0.05); PBSA: Plaque behind stent area; TAV: Total atheroma volume; MPA: Mean plaque area.

artery stenosis was below 0% until the threshold of a 45.76% PB in all regions (including scaffold and edges), and a 40.34% PB in edges (beyond the scaffold). The upper boundary of a 50.01% PB was associated with a 33.85% IVUS artery stenosis in all regions and a 45.09% in edges that is relevant to data of the box-and-whisker analysis that did not reveal any significant difference in PB if match artery stenosis was below 0% and 0%-50%. The VH-IVUS examination (Figure 6, top right panel) of PB supported a 32.07%-49.13% window of EEM enlargement for all regions ($P > 0.05$ for all comparisons, FAC) *vs* a 32.07%-54.86% window for 12 observations in naïve pre-procedure arteries ($P > 0.05$, FAC).

Eight BVS patients in the ABSORB B1 trial had a 2.67% decrease of PB at 24 mo ($P = 0.28$). The phenomenon of the window of EEM enlargement with a PB of 30.26%-54.86% was disclosed in the population, but only one patient had a PB reduction below a 40% Glagovian threshold. At 24 mo, 15/32 patients achieved PB within a window of EEM enlargement a *vs* 19 patients at baseline without cases below a lower end of the interval. Implantation of BVS in ABSORB Ⅱ trial[17,68,69] was defined by more pronounced sub- and decompensated arterial remodeling when compared with stenting (Figure 7). There was documented positive remodeling with lumen enlargement and plaque decrease (OR, 0.23, 95%CI: 0.14, 0.38, $P < 0.02$) with more stable arterial geometry in the metallic jacket, subcompensated expansive remodeling (OR, 3.13, 95%CI: 1.74, 5.65, NS), and constrictive remodeling (OR, 3.24, 95%CI: 1.67, 6.28, NS). Transient scaffolding was labeled by tremendous regression of atherosclerosis in 6.9% of BVS patients *vs* 1.5% after stenting (OR, 4.95, 95%CI: 1.13, 21.77, $P = 0.02$) when compared with DES XIENCE.

The evaluated patterns of the Glagovian artery remodeling[50,51] play a role in the estimation of the existing CV risks in real clinical practice. A large PB of > 70% is related to higher risk of MACE being a predictor of events. Half of these events were related to nonculprit lesions (PROSPECT trial, 2011)[22,23]. The knowledge about the window of the EEM enlargement ("Glagov threshold"[23,50,51]) might be pivotal in the selection of the optimal strategy as a target for the reduction of PB. The decrease of PAV below that threshold or upper boundary bonds the restoration of the artery geometry and local circulation amid atheroprotective reorganization of the lesion and benign progressive hyalinosis. This was validated in 4/8 patients (one patient committed PB reduction below a 40% PB) of the ABSORB cohort B1 trial with a reversed atherogenesis at 24 mo with a similar trend in the entire population of the ABSORB B trial at 60 mo. Meanwhile, the PB in the Cath Lab might be assessed with the moderate accuracy by IVUS or VH-IVUS (to evaluate a composition of the lesion) and poor accuracy by MSCT[57]. However, accuracy analysis in the study was impaired by the progress of bioresorption with discontinuation and dismantling[16] of the scaffold as well as technical difficulties of the imaging[19-35], which were released previously[36-52,59].

Associations between components of lesion and artery geometry in ABSORB cohort B1 trial

The PB by the artery dimensions can be evaluated by correlation (Pearson's R^2 and r) between PAV, artery stenosis, lumen area and others (Figure 5C and D, and Figure 6) with the available multi-modality imaging tools. A low heterogeneity of data was appropriate for assessment of correlation and regression ($P > 0.05$ if not mentioned) to see how two variables vary together. The moderate correlation was validated ($P > 0.05$, FAC) for associations between PB and artery stenosis ($r = 0.25$ in all regions; $r = 0.20$ in edges, $P = 0.007$), vessel area ($r = 0.51$), and total atheroma volume (TAV) ($r = 0.71$) with high correlation between PB, plaque behind stent area (PBSA) ($r = 0.83$), and MPA ($r = 0.83$). There was no difference ($P > 0.05$ FAC) between PB calculated by either area or volume in IVUS ($R^2 = r = 1.0$) with the minimal distinction between PB measured by IVUS and VH-IVUS ($r = 0.94$). MSCT was less accurate (Figure 6, top left panel) and overestimated PB when compared to IVUS ($r = 0.22$, $P = 0.08$).

To test comparability of the imaging modalities (Figure 6, middle panel), the variables were performed in IVUS with QCA, VH-IVUS, and OCT at the post-procedure baseline, 6 mo, and 24 mo. Then they were compared with the MSCT measurements at 18 mo, which were received at the inflammatory phase of the BVS resorption and resemble those at 24 mo. The IVUS mean lumen area (MLA) had the highest correlation (Figure 6, middle panel) with VH-IVUS ($r = 0.94$), moderate with QCA ($r = 0.62$) and MSCT ($r = 0.40$, $P = 0.003$), and lowest surprisingly with OCT ($r = 0.04$) with similar associations for artery stenosis ($P > 0.05$, FAC, if not mentioned). Measuring a degree of the association between IVUS PB and the lumen area, which was evaluated with other imaging modalities, we revealed a moderate correlation with MSCT ($r = 0.38$, $P = 0.005$), but not with others ($r < 0.12$, $P > 0.05$).

The estimation of the lesion's components (Figure 6, bottom panel) verified a trend toward correlation between VH-IVUS PB and the size of necrotic core ($r = 0.78$) as well as deposits of dense calcium ($r = 0.75$, $P > 0.05$ FAC). However, MLA had the highest but moderate correlation with fibrous ($r = 0.25$, $P = 0.0001$) and fibro-fatty tissue ($r = 0.42$, $P > 0.05$). The strongest association between different components vindicated for necrotic core and calcium ($r = 0.85$, $P > 0.05$), fibrous and fibro-fatty tissue ($r = 0.75$, $P > 0.05$), necrotic core and fibrous tissue ($r = 0.63$, $P > 0.05$), and necrotic core and fibro-fatty tissue ($r = 0.20$, $P = 0.004$).

DISCUSSION

Impact of the findings on daily practice

The most critical point for the first-generation BVS remains unpredictable prognosis. The modern-day transient scaffolding means a 36-48-mo biodegrada-

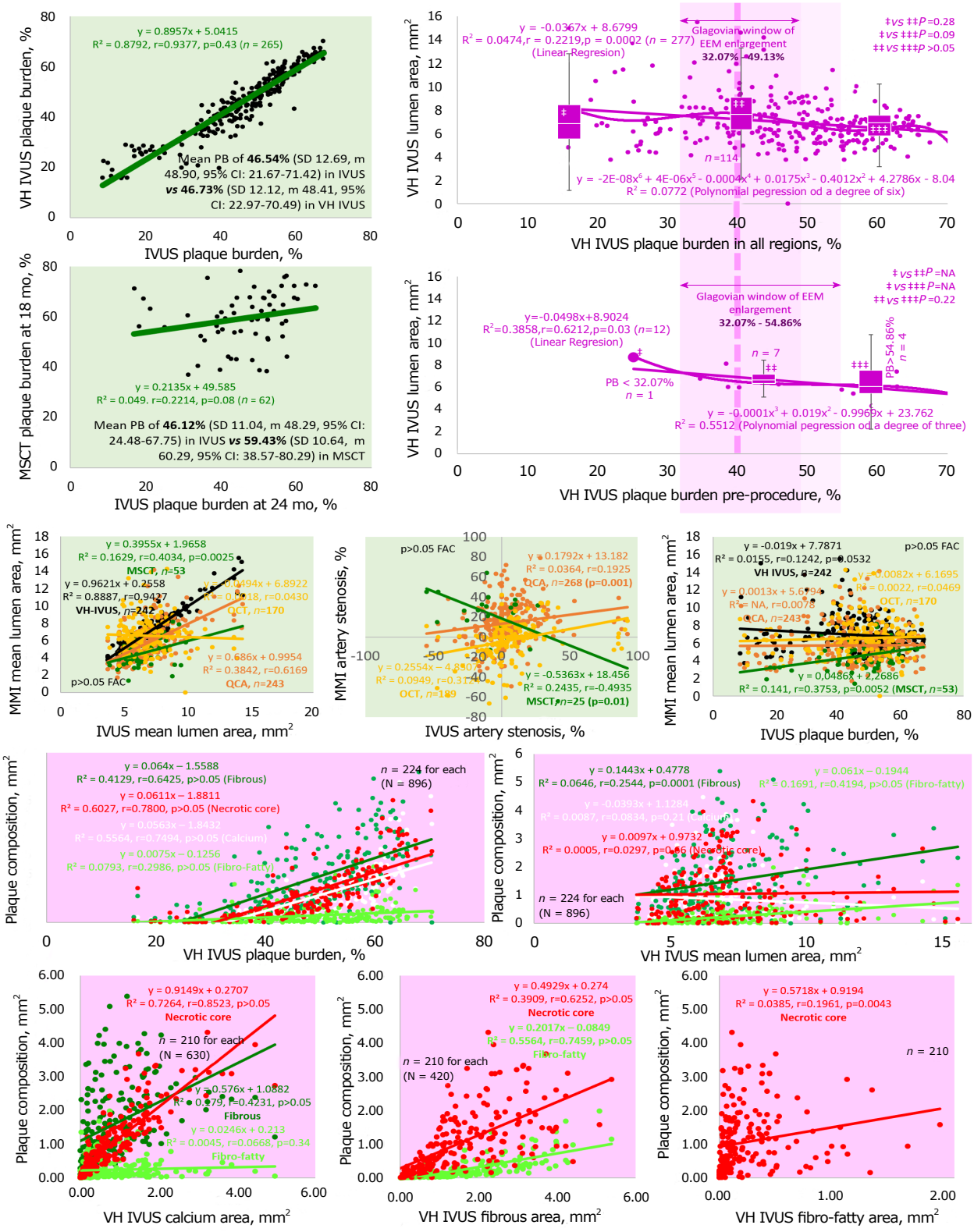

Figure 6 The association between the components of the lesion and artery layers. The correlation between plaque burden (PB) assessed by intravascular ultrasound (IVUS) and virtual histology (VH)-IVUS was strong with relatively weak association with PB evaluated by multislice computed tomography (MSCT) (top left panel). The three-distribution (PB < 32.07%, PB 32.07%-49.13%, and PB > 49.13%) box-and-whisker analysis (top right panel separately for all regions and pre-procedure) of the VH-IVUS-examined correlation between PB and lumen area vindicated existence of the window of the external elastic membrane (EEM) enlargement between 32.07% and 49.13%. The pre-procedure evaluation in naïve arteries with a broader size of the window between 32.07% and 54.86%. The middle and bottom panels set out correlations between plaque burden, lumen, vessel wall dimensions, and components of the lesion examined by the various imaging modalities. The *P* value was calculated for comparison of one or two variables in order to either estimate the means of two groups (paired or unpaired *t* test) or appreciate statistical consistency for regression. The figure was adapted from ref. [34]. *n*: Number of observations; N: Total number of observations at the screened population; R2: Coefficient of determination; r: Pearson correlation (for linear regression); IQR: Interquartile range; NS: Non-significant ($P > 0.05$); NA: Not applicable.

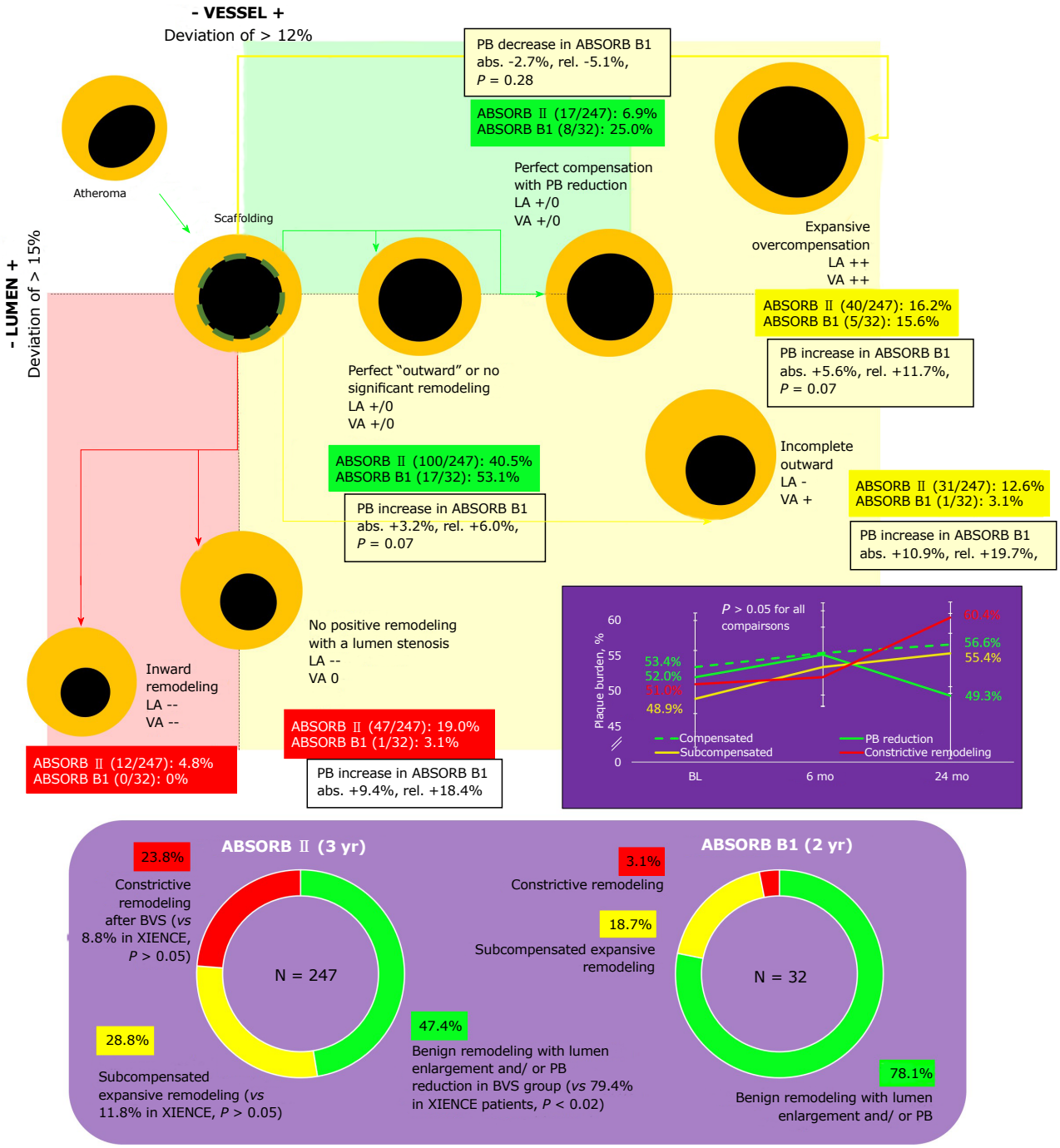

Figure 7 Arterial remodeling in coronary arteries after transient scaffolding with Absorb bioresorbable vascular scaffold. Patterns of Pasterkamp remodeling demonstrated at the top panel with a percent of patients in RCT ABSORB II and observational ABSORB B1 trials with a plaque burden (PB) change in ABSORB cohort B1 trial. The bottom panel demonstrates a percentage of the different types of the arterial remodeling in Absorb bioresorbable vascular scaffold patients. The middle dark purple panel shows dynamics of PB in patients of ABSORB cohort B1 trial. Mean PB in subsets failed to achieve Glagovian threshold of a 40% PB in all scenarios. $P < 0.05$ if compared with XIENCE.

tion with compromised local shear stress[15], a risk of malapposition, uncovered struts, fractures, and discontinuation[16]. The immune and inflammatory response, hyaline arteriosclerosis (sometimes with abundance of the connective tissue which appears as an OCT-phenomenon of the "golden tubes")[17,34,35], and a foreign body-like reaction drive the biological retaliation of the vessel to the implanted scaffold with a pronounced risk of thrombosis and decompensated artery remodeling. At least 19% of the lesions after BVS develop progressive atherosclerosis but without a clear impact on clinical outcomes[17,34,35].

Lower affordability (with budget constraints especially in case of PSP scenario with advanced multimodality imaging), poor availability of BVS sizes, clinical concerns, and awareness due to confusing results from RCT tremendously restrict a broad utilization of BVS in real-world cardiology despite the phenomenal success

of BVS in the first observational studies (ABSORB A, ABSORB B, and others since 2006).

Attributes of BVS trials

BVS has a good clinical and research profile with a tremendous number of patients[5-9,17,19-21]. More than 150000 patients were treated, and more than 30000 patients were studied in 12 RCTs and 20 registries in more than 100 countries. The procedural success was tested in REPARA and GABI-R trials. Healing success comparable to the most advanced modern-day DES was confirmed in TROFI, Ⅱ, and ESTROFA-BVS trials. Effectiveness and safety comparable to DES was documented in ABSORB Ⅲ, ABSORB Japan, ABSORB China, ABSORB FIRST, and GHOST-EU trials. Event rates comparable to DES were observed in ABSORB II and ASSURE trials. Low long-term event rates were shown in the ABSORB EXTEND trial. Stable lumen area (OCT-documented compensated lumen enlargement) including a partial restoration of the vasomotor function was performed in the ABSORB cohort B trial[17,23,25]. A phenomenon of the vessel wall thinning was also shown. This is a kind of regression of atherosclerosis below a threshold of the 40% PB in accordance with the concepts of artery remodeling developed by Glagov and Pasterkamp[17,22,23]. Only 23.1% of patients had expansive remodeling of the artery with lumen enlargement and plaque decrease[11,17,24].

Transient scaffolding is challenging because the scaffold failure remains an Achilles' heel of the technology. It is mostly associated with extensive malapposition and further secondary evaginations (9%), late discontinuity (8%), peri-strut low intensity area (5%), uncovered strut with delayed endothelialization (4%), under-deployment (4%), incomplete lesion coverage (4%), recoil with a decrease of radial strength including scaffold fracture and collapse, acute disruption of struts and overlapping struts (3%), restenosis (2%), neoatherosclerosis with severe inflammation (1%), bifurcation concerns (1%), and non-specific imaging findings including acute and chronic inflammatory responses, and increased thrombogenicity (1%)[26,27]. These points require some clinical awareness despite confusing statistics (an underpowered fashion at least for some variables in RCTs such as ABSORB China and Japan, EVERBIO II[28], and AIDA[29] and no optimized design of a few meta-analyses with a lack of statistical power from the teams of Polimeni, Collet, Mahmoud, Ali, Zhang, and Kang; Table 1) and relevant efforts to prevent the aforementioned complications.

Concerns from the European task force

There are several concerns to consider in real clinical practice with BVS (according to the ESC-EAPCI Task Force, not yet published, announced in May 2017 at EuroPCR, Paris, France)[30] and therefore must overcome to protect patients and harmonize intervention remain: (1) optimization of the implantation by the PSP scheme (pre-dilation with a residual stenosis < 30% (under IVUS imaging ideally), correct sizing (excluding patients with a vessel size < 2.25 mm and > 3.5 mm), post-dilation (balloon diameter/scaffold diameter = 1:1; balloon diameter < scaffold diameter + 0.5 mm) with a non-compliant balloon pressure > 18 atm (under OCT imaging ideally) to prevent malapposition and injury of BVS); (2) fractures and discontinuations (could be managed by the harmonized implantation); (3) duration of the anti-thrombotic therapy (> 18 mo) until the disappearance of the uncovered struts, which means hypothetically that some protection (for instance, with a prophylactic dose of oral anticoagulants) is necessary even for 48 mo[6]; and (4) optimal sites of intervention avoiding complex lesions (left main, bifurcations, long lesions, chronic total occlusions, calcification) and small vessels (< 2.25 mm)[7] excluding CHIP patients (at least for the moment due to absence of the strong evidence for any clinical benefit of the strategy). However, according to the ESC/EAPCI Task Force report[30] and an academic collaboration analysis[40], pre-dilation in ABSORB studies (ABSORB Ⅱ[31], ABSORB Ⅲ[2], ABSORB China, ABSORB Japan, ABSORB EXTEND[11]; pooled 2973 patients) was performed in 99.8% of cases, but high-pressure post-dilation in only 12.7%. Taking into account a number of patients (82.3%)[40] with optimal sizing (2.25 mm < RVD < 3.5 mm), a percentage of cases with full PSP were not higher than 10.4%[30], which means it is difficult to judge clinical outcomes in these RCTs.

Accomplishments of the ABSORB trials

The serial multi-imaging approach of the prospective, single-group, open-label study displayed that the transient scaffolding with BVS can beget a reduction of PB below the baseline in coronary arteries at 24 mo. Atherosclerosis was first described when Leonardo da Vinci autopsied a centenarian man. Leonardo theorized that the cause of the degeneration of the vessels were very close to the understanding of the role of cholesterol in atherosclerosis[46]. However, it was not described again until 1904 when Marchand first introduced the term, and in 1912 when Anichkov *et al*[47] effectuated lesions by adding pure cholesterol to rabbit food.

The latter part of the century was spent understanding the pathology and the reversal of atherosclerosis[47]. The first interventional study was published by Friedman *et al*[48] in 1957. Then the angiographic paradox was studied in the 1960s[49,50]. The first retrospective analysis with statins that found the benefits of low-density lipoprotein-cholesterol (LDL-C) in reducing coronary calcium-volume score was reported in 1998[51] with a series of further intravascular imaging studies of the lipid-lowering strategies[19,22] manifesting the strides of the third industrial revolution in biomedicine with a maximum 1.22% absolute reduction of PB under intensive statin therapy (ASTEROID trial, 2006; SATURN, 2011; IBIS-4, 2015; and STABLE, 2016)[22]. Four Japanese trials (ESTABLISH, 2004; JAPAN-ACS, 2009; COSMOS, 2009;

and TWINS, 2009) demonstrated a dramatic 10.4% absolute reduction of PAV. However, statin therapy did not reduce mortality[22,66-69]. Unfortunately, statin trials such as REVERSAL (2004), CAMELOT (2004), A-PLUS (2004), ACTIVATE (2006), PERISCOPE (2008), ILLUSTRATE (2007), STRADIVARIUS (2008), IBIS-2 (2008), TOGETHAR (2010), and YELLOW (2013) did not successfully reduce atherosclerosis[22]. Novel lipid-lowering agents (combination of ezetimibe and statins) in ZEUS (2014) and PRECISE-IVUS (2015) showed a 2.39% decrease of PB, but results of the trials testing the PCSK9 (proprotein convertase subtilisin kexin 9) inhibitors are not yet available[22].

Fully bioresorbable BVS is a novel approach for the treatment of coronary stenosis that supplies a transient vessel support with drug delivery advocating the increases of the fourth industrial revolution with the potential to pave the way for a reduction in atherosclerosis[19-25].

Limitations

The analyzed ABSORB and some other BVS studies, with a small number of patients and moderate accuracy were unpowered to detect changes in the imaging endpoints from baseline to follow-up. It is infeasible to determine the impact of both transient scaffolding and statin therapy on atherosclerosis in the absence of any baseline or follow-up data with LDL-C. More than 60% of patients enrolled in ABSORB A and B trials have had hyperlipidemia-requiring medication, but the levels of LDL-C were never reported, which does not allow us to estimate a contribution of statin drugs or other interventions to the size of the coronary atherosclerotic lesions.

Future perspective

Unfortunately, all BVS in development today are of the same first generation. Due to smaller struts, which are the key and the only point of the modern-day innovators that can optimize re-endothelialization and prevent the phenomenon of the uncovered struts attenuating biological response and slightly reducing the rate of complications. Notwithstanding, it is not solving mechanical concerns including options of integrity, radial strength, durability, duration of bioresorption, and implantation-associated troubles causing malapposition and ST. Both the optimization of the BVS implantation[24,44,68] and introduction of drug-coated balloons[38] after the implantation have the potential to dramatically harmonize short- and long-term outcomes. Recently published results of the BIOFLOW V randomized trial[32] demonstrated superiority of the ultrathin (60 μm) bioresorbable polymer sirolimus-eluting stent over the durable polymer everolimus-eluting stent, which means that this direction is quite promising. These findings are totally relevant to the BIONICS study (not yet published, TCT 2016 in Washington, DC, United States) of the ridaforolimus-eluting cobalt-chromium stent with the narrowest struts made of a combination of 40 μm struts with 72 μm supportive struts (a rate of ST was low at 0.4%). At least two BVS with thinner struts below 100 μm are in translational development today as well as early phase clinical trials (a courtesy of Amaranth Medical and Abbott Vascular on October 31, 2017 at TCT 2017 in Denver, CO, United States). Meanwhile, the biology and pathology of the transient scaffolding (including specific options of acute fracture, chronic recoil, and late intraluminal scaffold dismantling) remain largely unknown. That is why we cannot expect any breakthrough in this field until success in translational research including biology and pathology of arterial remodeling, immune response, foreign body reaction, and inflammatory feedback of the coronary, adventitial and perivascular adipose tissue (the last one is feasible with a PET/CT). The absence of the broad financial support for in-depth science and an expectant strategy of the industry including a pressure over editors and editorial content at the leading journals[41] compromise scientific findings and discourage progress in the field. A decision of Boston Scientific that halted the project of the Renuvia scaffold in July 2017 (courtesy of TCTMD, August 1, 2017) 3 mo prior to the release of the positive clinical outcomes at TCT 2017 jeopardized the future of the bioresorbable medical device technology. Potentially, the development of new polymers, exploration of the polymer biodegradation, and examination of the vascular biology and pathology of the transient scaffolding as well as immune response to the BVS implantation could shift BVS to a new level. The possibilities for BVS are exciting with the development of an electronic multi-tasking BVS[33] that has the potential to revolutionize this technology with an optimized mechanical profile and applied nanotechnologies able to measure blood flow (including shear stress) and temperature, release drugs, and dissolve when it is necessary.

Furthermore, large-scale randomized trials are necessary to evaluate associations between documented patterns of the artery remodeling (lumen enlargement with a PB reduction) within the Glagovian concept of atherogenesis and long-term clinical outcomes (including adverse events, in particular, MACE, restenosis, device thrombosis, complications of the device discontinuation, *etc*) of the transient scaffolding. The histopathological study of the hyaline arteriosclerosis in the middle-size coronary arteries could shed light on the physiology of transient scaffolding, clinical importance, and prognosis of patients who underwent implantation of BVS.

The pathology of transient scaffolding remains largely unknown. What is known has prevented further development of the technology because the controversial results are confusing, and therefore it has destroyed optimization of clinical approaches. The current study uncovered some of the flaws of the clinical trials. Many of these observations are clinically relevant and have to potential to advance the strategies for both imaging and treatment of progressive atherosclerosis.

ARTICLE HIGHLIGHTS

Research background

Bioresorbable vascular scaffold (BVS) initially had incredible success in the first ABSORB studies in 2006-2013, but was consequently deemed a failure due to reported relatively higher rates of target lesion failure (TLF) and device thrombosis in randomized controlled trials. However, BVS performs as well as the metallic drug-eluting stent (DES) with a trend toward some benefits for cardiac mortality.

Research motivation

The exploration of the insights in statistics of the relevant studies has a potential to discover the main obstacles of the BVS research and development preventing major cardiovascular events and therefore improving clinical outcomes adapting the technology in routine clinical practice.

Research objectives

The overarching objective was to supplant the perils of the current standard of care with the polymeric bioresorbable scaffolds.

Research methods

We evaluated the statistical power in clinical trials such as ABSORB Japan, ABSORB China, EVERBIO Ⅱ, AIDA, and meta-analyses by the post hoc OR-based sample size calculation, and the patterns of artery remodeling published in papers from ABSORB A and B trials.

Research results

The underpowered design was confirmed for some studies such as ABSORB Japan, ABSORB China, EVERBIO Ⅱ, AIDA trials, and meta-analyses of Polimeni, Collet, and Mahmoud with some unintentional bias (judged by the asymmetrical Funnel plot). ST rates with Absorb BRS were comparable with DES performed with a strategy of the BVS implantation with optimized pre-dilation (P), sizing (S), and post-dilation (P) (PSP) implantation achieving 0.35 per 100 patient-years, which is comparable to the RR 0.49 with bare-metal stents and the RR 1.06 with everolimus DES. Both ABSORB Ⅱ and ABSORB Ⅲ trials were powered enough for a five-year follow-up, but the results were not entirely conclusive due to the mostly non-significant fashion of data. The powered meta-analyses were built mostly on statistically poor findings.

Research conclusions

The misunderstanding of the pathology of transient scaffolding drives the failures of the clinical trials. More bench studies of the vascular response are required. Several next-generation BVS including multifunctional electronic scaffold grant cardiology with a huge promise to make BVS technology great again.

Research perspectives

The biology of transient scaffolding remains mostly unknown. The thin-strut scaffolds and stents with advanced mechanical features are able to partly solve the problem of device thrombosis. Nevertheless, the unclear mechanism of related complications challenges the further development of the technology. Future research must be focused on both bench and bedside studies of vascular biology and pathology of the transient scaffolding in order to understand which mechanism is a leading source of the troubles that we face in routine clinical practice with bioresorbable scaffolds.

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CASE REPORT

Takotsubo syndrome - different presentations for a single disease: A case report and review of literature

Alberto Fuensalida, Maurice Cortés, Luigi Gabrielli, Manuel Méndez, Alejandro Martínez, Gonzalo Martínez

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Abstract

We report three cases of Takotsubo syndrome (TS) with atypical myocardial involvement. All three cases were triggered by physical or mental stress, resulting in transient myocardial compromise. However, the clinical presentation, localization and extent of myocardial damage varied in each case, ranging from low-risk acute chest pain to cardiogenic shock with low ejection fraction and dynamic obstruction of the left ventricular outflow tract. These cases outline the range of possible presentations of this rare entity and illustrate atypical forms of TS.

Key words: Coronary angiography; Acute coronary syndrome; Stress cardiomyopathy; Takotsubo syndrome

Core tip: Although less frequent, atypical presentations of Takotsubo syndrome - different from the classical apical ballooning - need prompt recognition by physicians. In addition to being a diagnostic challenge, this malady can present with severe complications, such as cardiogenic shock, arrhythmias and others. Herein, we show the presentation and management of atypical cases, with emphasis on their clinical recognition.

Fuensalida A, Cortés M, Gabrielli L, Méndez M, Martínez A, Martínez G. Takotsubo syndrome - different presentations for a single disease: A case report and review of literature. *World J Cardiol* 2018; 10(10): 187-190 Available from: URL: http://www.wjgnet.com/1949-8462/full/v10/i10/187.htm DOI: http://dx.doi.org/10.4330/wjc.v10.i10.187

INTRODUCTION

Takotsubo syndrome (TS) was described almost 3 decades ago as an entity mainly affecting older women (post menopause), triggered by emotional stress, with ST-segment elevation on the electrocardiogram and with a characteristic pattern of apical ballooning of the left ventricle[1-3]. However, it is currently recognized that TS may have a more heterogeneous presentation, affecting also men, with different electrocardiographic alterations and diverse patterns of myocardial compromise[4,5]. These atypical TS cases may comprise up to 18% of cases[4,5].

We now describe three cases of atypical TS that presented at our institution and were managed by the authors between May 2014 and September 2016.

CASE REPORTS

Case 1

A 57-year-old man presented with irregular wide-complex tachyarrhythmia at 180 beats *per* minute during anaesthetic induction for elective pituitary macroadenoma surgery. He received intravenous (IV) propranolol and adenosine, after which he reverted to sinus rhythm. However, severe hemodynamic compromise ensued, requiring support with IV norepinephrine and pseudoephedrine. The electrocardiogram showed ST-segment depression from leads V1 to V5 and a transesophageal echocardiogram demonstrated diffuse left ventricular (LV) hypokinesis, with a left ventricular ejection fraction (LVEF) of 35%. Urgent coronary angiography showed absence of obstructive coronary artery disease in the epicardial arteries, whereas a LV angiogram confirmed an extensive area of akinesis involving the basal and middle segments of the anterior and inferior walls, with concomitant hyperkinesis of the apical segments (Figure 1A and 1B). An LVEF of 20% was estimated. Initial management included hemodynamic support with IV noradrenaline and dobutamine along with mechanical ventilation. Very rapid clinical improvement was evident and the patient was extubated 24 h after the event. High-sensitivity troponin peaked at 950 pg/mL. An echocardiogram performed 48 h later showed improvement in LVEF to 60%. Two months later, on beta-blockers, the macroadenoma was resected with no adverse events.

Case 2

A 53-year-old woman with Parkinson's disease arrived to the emergency department complaining of rest angina after suffering severe emotional stress while she was attending a trial in a police court, 4 h earlier. Electrocardiography showed sinus rhythm with antero-lateral ST-segment depression. Coronary angiography showed no obstructive disease in the epicardial coronary arteries and LV angiography revealed akinesis in the midventricular segments, with LVEF 60% (Figure 1C and D). High-sensitivity troponin peaked at 108 pg/mL. Trans-thoracic echocardiography at 24 h showed a normal size left ventricle with minimal infero-lateral hypokinesis and preserve global function. Three months later, echocardiography showed complete recovery of the infero-lateral defect.

Case 3

A 70-year old female, with a prior history of hypertension and type-2 diabetes, presented to the emergency room with a 3-d history of intermittent oppressive chest pain, associated with dyspnoea and cough. On admission, she was tachycardic and hypotensive. The electrocardiogram showed sinus rhythm with ST-segment elevation in leads V1 to V4. Urgent coronary angiography revealed absence of obstructive coronary epicardial lesions and the left ventriculogram showed akinesis of the apex and anterior and inferior apical segments, associated with basal segment hypercontractility and severe mitral regurgitation (Figure 1D and F). The intraventricular pressure pullback showed a gradient at the level of the left ventricle outflow tract of 47 mmHg. She was urgently managed with intensive volume replacement with IV saline, resulting in a prompt recovery. Echocardiogram showed akinesis of the anterior and apical walls, with a LVEF of 45%. Peak high-sensitivity troponin was 240 pg/mL. Due to intense back pain and the presence of meningeal signs on physical examination, a magnetic resonance imaging of the spine was performed revealing spinal subarachnoid haemorrhage with a thrombosed aneurysm of the right posterior spinal artery at the T1-T2 level. She had uneventful neurological and cardiological recovery, and was discharged on beta-blockers, statins and acetylsalicylic acid. Follow-up echocardiogram at 1 mo showed complete recovery of the ventricular motion defect and a LVEF of 65%.

DISCUSSION

This case series highlights the heterogeneous clinical presentation of TS (Table 1). The affected myocardial segments were different in each case: (1) basal (or so called inverse TS); (2) midventricular and (3) apical with LV outflow tract obstruction and mitral regurgitation due to systolic anterior motion, secondary to hypercontractility of the basal segments. However, all three have in common the presence of a trigger factor (physical or emotional stress), dissociation between the magnitude of the myocardial damage extension and biomarker elevation, the absence of epicardial coronary disease on angiography and the complete or almost

Table 1 Overview of clinical presentation of the 3 cases

	Sex	Age	Trigger	Clinical presentation	ECG abnormalities	Type of motility defect	LVEF	Peak hsTroponin	Follow- up	Recurrence
Case 1	Male	57	Surgery / Anesthetic induction	Ventricular arrhythmia and cardiogenic shock	ST depression leads V1 to V5 QTc: 500 mseg	Basal	35%	950 pg/mL	15 mo	No
Case 2	Female	53	Emotional stress	Acute myocardial infarction without ST elevation	ST depression leads V4 to V6, DI and aVL QTc: 490 mseg	Midventricular	60%	108 pg/mL	38 mo	No
Case 3	Female	70	Spinal aneurysm rupture	Acute myocardial infarction with ST elevation and shock	2 mm ST elevation leads V1 to V4 QTc: 510 mseg	Apical ballooning, LV outflow tract obstruction	45%	240 pg/mL	16 mo	No

ECG: Electrocardiography; hsTroponin: high-sensitivity troponin; LVEF: Left ventricular ejection fraction.

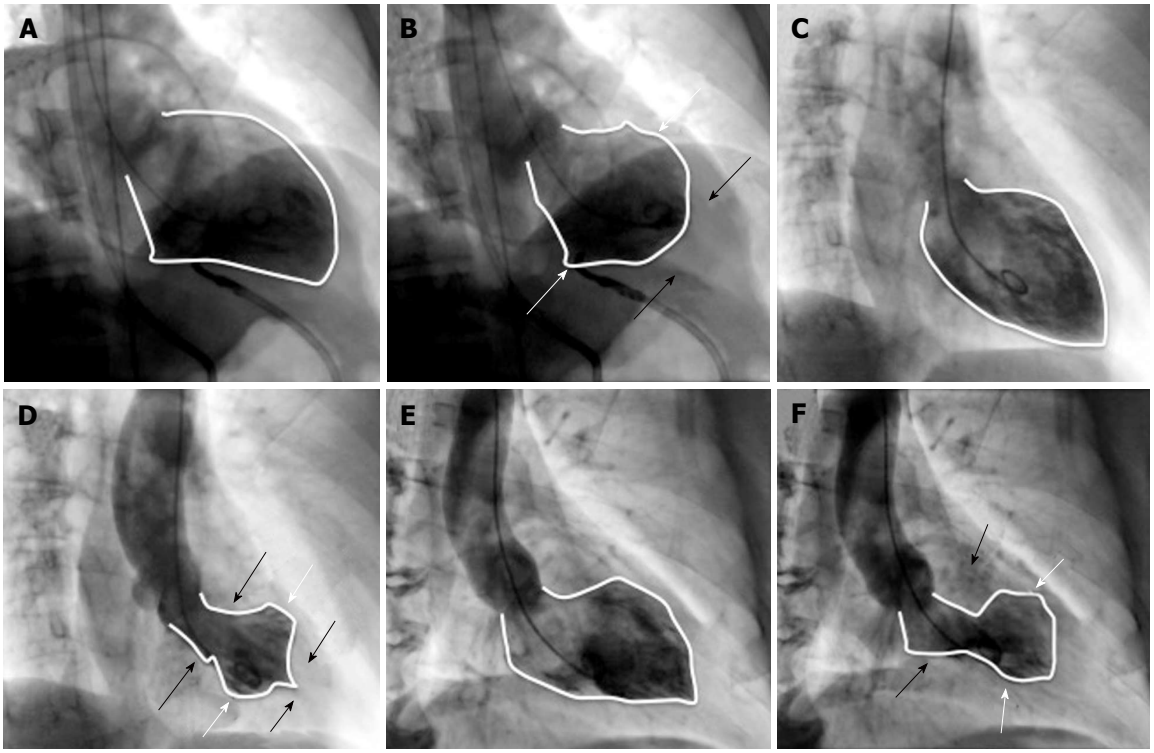

Figure 1 Ventriculography of the 3 cases. A and B are the ventriculography of case 1. A: LV at end diastole; B: LV at end systole with motion defect (white arrows show inferior and anterior basal hypokinesis; black arrows show hypercontractility of apical segments); LVEF: 20%. C and D are the ventriculography of case 2. C: LV at end diastole; D: LV at end systole with motion defect (white arrows show inferior and anterior midventricular hypokinesis; black arrows show hypercontractility of inferior and anterior basal and apical segments); LVEF: 60%. E and F are the ventriculography of case 3; E: LV at end diastole; F: LV at end systole with apical ballooning (white arrows show apical inferior and anterior hypokinesis; black arrows show inferior and anterior basal segments hypercontractility); LVEF: 45%, with severe mitral regurgitation. LV: Left ventricle; LVEF: Left ventricular ejection fraction.

complete recovery of the defect during follow-up.

The mechanisms resulting in TS are not yet fully understood, but the currently most accepted theories are transient myocardial dysfunction secondary to an exaggerated release of catecholamines, coronary vasospasm and transient microvascular dysfunction[3,6].

The management of acute heart failure is the mainstay of treatment, and in some patients it is necessary to provide support with vasoactive drugs and/or ventricular assistance to achieve hemodynamic stability[6,7]. Once the acute episode has been resolved, a favourable long-term prognosis is generally expected[3], although recent reports have challenged this notion[8]. Some series suggest that this entity can have an estimated annual rate of 9.9% major events and 5.6% mortality[5], in association with a recurrence risk of 5%-10%[6]. The magnitude of ventricular dysfunction is the main prognostic marker[4], although factors influencing late prognosis have not yet been clearly defined.

It has been reported that atypical TS has a better prognosis than the common form, which theoretically

could be explained by the lesser amount of affected myocardium and better ventricular function[4], although information regarding such cases is scarce. Finally, we believe that clinicians caring for patients with myocardial infarction should be familiar with these less common presentations of TS, which should be considered in patients with acute coronary syndromes without obstructive coronary disease and with cardiac enzyme elevations lower than expected in relation to the degree of apparent myocardial damage, particularly when triggered by obvious emotional or physical stress.

ARTICLE HIGHLIGHTS

Case characteristics

Patients presenting as acute coronary syndrome with left ventricular (LV) dysfunction, shock or LV outflow tract obstruction, and in whom no stenosis were found in angiography and full recovery of LV abnormality was achieved.

Clinical diagnosis

Acute Coronary Syndrome, cardiogenic shock.

Differential diagnosis

Acute coronary syndrome due to plaque rupture, spontaneous coronary artery dissection.

Laboratory diagnosis

Eleveted highsensitive troponin, electrocardiogram with different abnormalities such as ST depression and elevation, as well as ventricular arrhythmias.

Imaging diagnosis

Coronary angiography with no coronary arteries stenosis. LV dysfunction with distinctive wall motion abnormalities not correlated to specific arterial segments. LV function recovery in follow-up echocardiogram.

Treatment

Beta blockers, volume replacement.

Related reports

Several reports of atypical cases with wall motion abnormalities different from apical ballooning. Retrospective study, InterTAK Registry, shows incidence about 10% to 18% of atypical cases.

Term explanation

Takotsubo syndrome (TS) is a cardiomyopathy that simulate acute coronary syndrome, but no coronary abnormalities are present in angiography. Wall motion abnormality typically presents as apical ballooning, however, in some cases (as presented in this report) different LV segments might be affected.

Experiences and lessons

Myocardial compromise in TS is not limited to the classical apical involvement and clinical presentations can range from life-threatening hemodynamic compromise to low-risk chest pain. A normal coronary angiogram and discordant LV involvement are key diagnostic features. Prompt recognition of complications and subsequent treatment allow for a favourable prognosis.

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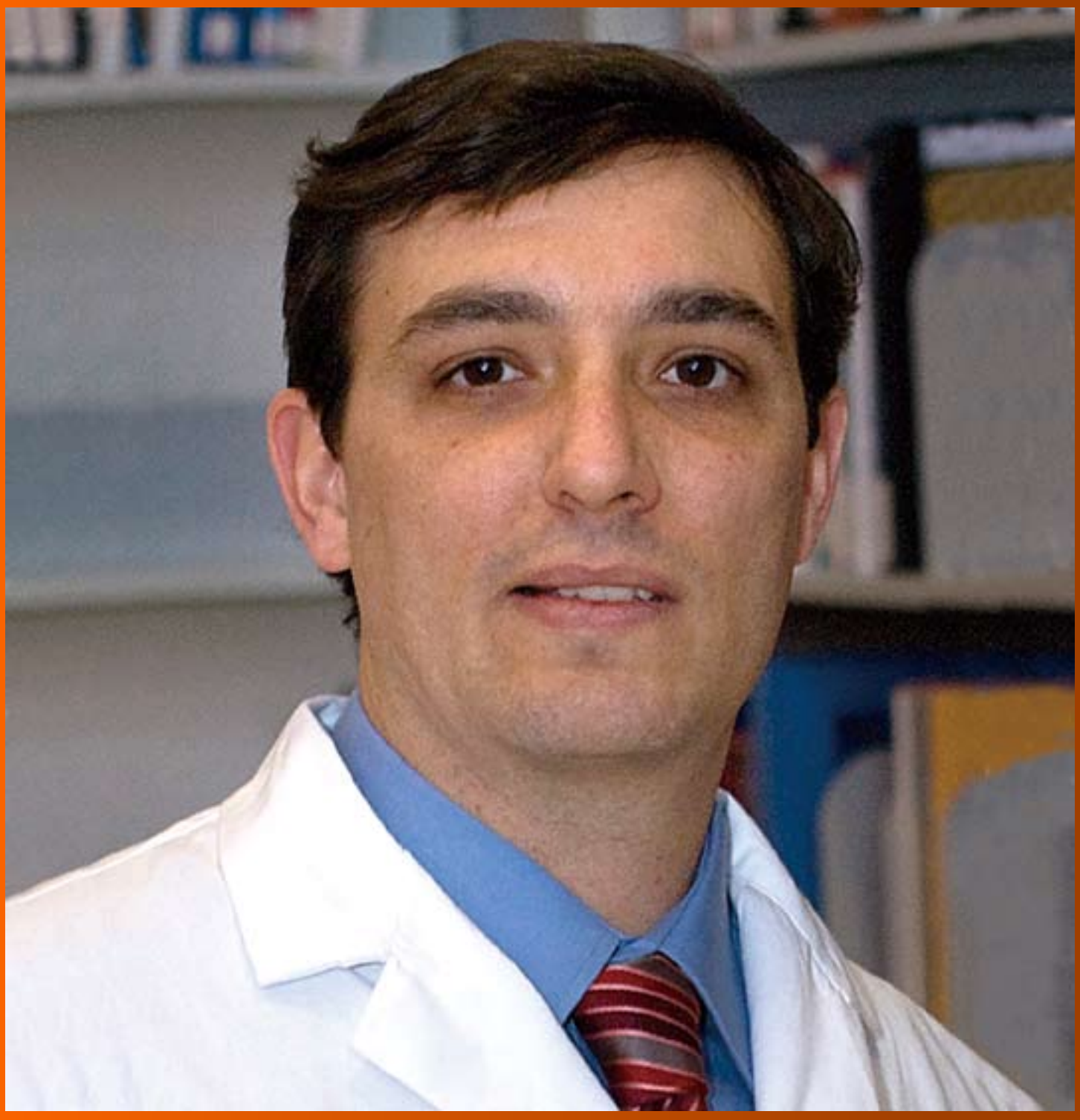

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EDITORIAL

Thin and crush: The new mantra in left main stenting?

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Abstract

Complex bifurcations have been suggested to be better approached by a planned double stent technique; however, recent randomized trials have shown better outcomes of provisional compared to planned two-stent strategy, in terms of both short-term efficacy and safety. In left main (LM) bifurcations, double kissing (DK)-Crush has demonstrated its superiority over Culotte and provisional-T in terms of restenosis and stent thrombosis, gaining respect as one of the most performant techniques for bifurcations stenting. On the other hand, the Nano-Crush technique has recently become part of the repertoire of double stenting techniques, providing evidence that the use of ultrathin strut stents and very minimal crush would be beneficial for both the physiological and rheological properties of the complex bifurcations, even in LM scenario, leading to a lower rate of thrombosis and restenosis at both side branch and true carina. Finally, the newest generation of ultrathin strut stents are gaining a re-putation for its safe and effective use in LM treatment thanks to improved design with increased expansion rate capable of LM treatment up to 5-6 mm diameter. The modern crush techniques, such as DK-Crush and Nano-Crush, are providing excellent results on mid and long-term follow up, suggesting that minimal crushing obtained using ultra-thin stents is a good way to obtain surgical-like outcomes in the treatment of complex LM bifurcation disease.

Key words: Stent; Crush; Interventional cardiology; Percutaneous coronary intervention; Percutaneous coronary intervention; Coronary bifurcation

Core tip: Modern crush techniques such as DK-Crush and Nano-Crush are providing excellent results on mid and

long-term follow-up, suggesting that minimal crushing obtained using ultra-thin stents is a good way to obtain surgical-like outcomes in the treatment of complex left main bifurcation disease.

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INTRODUCTION

Complex bifurcations have been suggested to be better approached by a planned double stent technique[1-2], although recent randomized trials have shown better outcomes of provisional compared to planned two-stent strategy in terms of both short-term efficacy and safety[3-4].The total amount of metal layers at both the carina and bifurcation angle after double stenting techniques[5-6] appeared to be important issues to achieve favorable short- and long-term outcomes.

Left main (LM) bifurcation disease is probably the only real important bifurcation in the human vascular tree. The DEFINITION trial[7] has given a practical definition of what is complex and what it is not in the treatment of coronary artery bifurcation disease. Indeed, a length of the left circumflex coronary artery (LCx) > 10 mm has already been identified as a predictor of complex LM bifurcation probably requiring a double stenting strategy.

To achieve similar or better post-procedural results guaranteed by surgical treatment from a rheolytic point of view, the use of intravenous ultrasound is mandatory[8] to properly assess the size and length of the disease in both branches and in the LM body, allowing an accurate selection of the most appropriate stenting technique and stents.

Culotte, mini-Culotte, DK-Crush, T-stent and Protrusion (TAP) are currently the most used double stenting techniques (Table 1)[9]. Recently, DK-Crush has demonstrated its superiority over Culotte[10] and provisional-T[11] techniques in terms of restenosis and stent thrombosis, gaining respect as one of the most performant techniques for bifurcation stenting.

Even more recently, the Nano-Crush technique[12-13] has become part of the repertoire of double stenting techniques, providing evidence that the use of ultrathin strut stents and very minimal crush is beneficial for both the physiological and rheological properties of the complex bifurcations, leading to a lower rate of thrombosis and restenosis at both side branch (SB) and true carina[14].

TECHNICAL COMPARISON AMONG NANO-CRUSH, DK-CRUSH AND OTHERS

Compared to the classical Crush technique introduced by Colombo *et al*[15], both the Nano- and DK–Crush

Table 1 Available techniques for left main interventions

Single stent	Double stent
Cross over-provisional	T-stenting
	T and protrusion
	Mini-Crush
	Culotte and Mini-culotte
	DK crush
	Nano-Crush

represent a further modern development of the former. Both these latter techniques require wiring and pre-dilation of both branches and in both SB stenting before main branch (MB) stenting. A different strand is represented by the entity of the SB stent protrusion, which is minimal, with only one ring if possible, in the Nano-Crush, while it appears greater, with at least 3-4 mm of protrusion, in the DK-Crush technique.

Protrusion length of the SB stent explains why kissing is required when DK-Crush is adopted. In the classical DK-Crush, rewiring of the SB generally represented the next step after MB stenting. However, more recently, the use of proximal optimization technique (POT) has been recommended, as in Nano-Crush, where POT facilitates LCx rewiring. Subsequently, both techniques included a type of kissing balloon: Classical for the DK and with snuggle configuration in Nano-Crush. Moreover, the classical DK-Crush technique has been modified introducing a POT as the final step, as in Nano-Crush (Figure 1).

Different from DK-Crush, in which the ostium circumference is completely covered by the SB stent, in the Nano-Crush, the ostium is covered at the carina by the SB stent strut and at the opposite site of the carina by the MB struts opened by the POT into the SB ostium, providing complete circumferential coverage, especially in the case of tight angles, in which the ostium coverage might be incomplete at the carina.

Among these two stenting techniques, one significant difference is represented by the most appropriate stent to implant. In DK-Crush, virtually every kind of stent can be used, while the Nano-Crush has been created to fit with the concept of less metal in the carina, so the ideal stent should have the thinnest struts possible, at least 60 to 80 microns.

TAP or standard T usually leave the SB stent strut floating into the MB; this causes a non-physiologic flow, which may induce lower wall shear stress and turbulent flow, leading to thrombosis and in-stent restenosis[16]. On the other hand, the Culotte usually leaves two or three metal layers into the carina for a length ranging from 5 to 15 mm, even in the "Mini" version.

AMOUNT OF METAL INTO THE CARINA: DOES IT REALLY MATTER?

The lack or excess amount of metal layers at the carina has been suggested to be a potential cause of

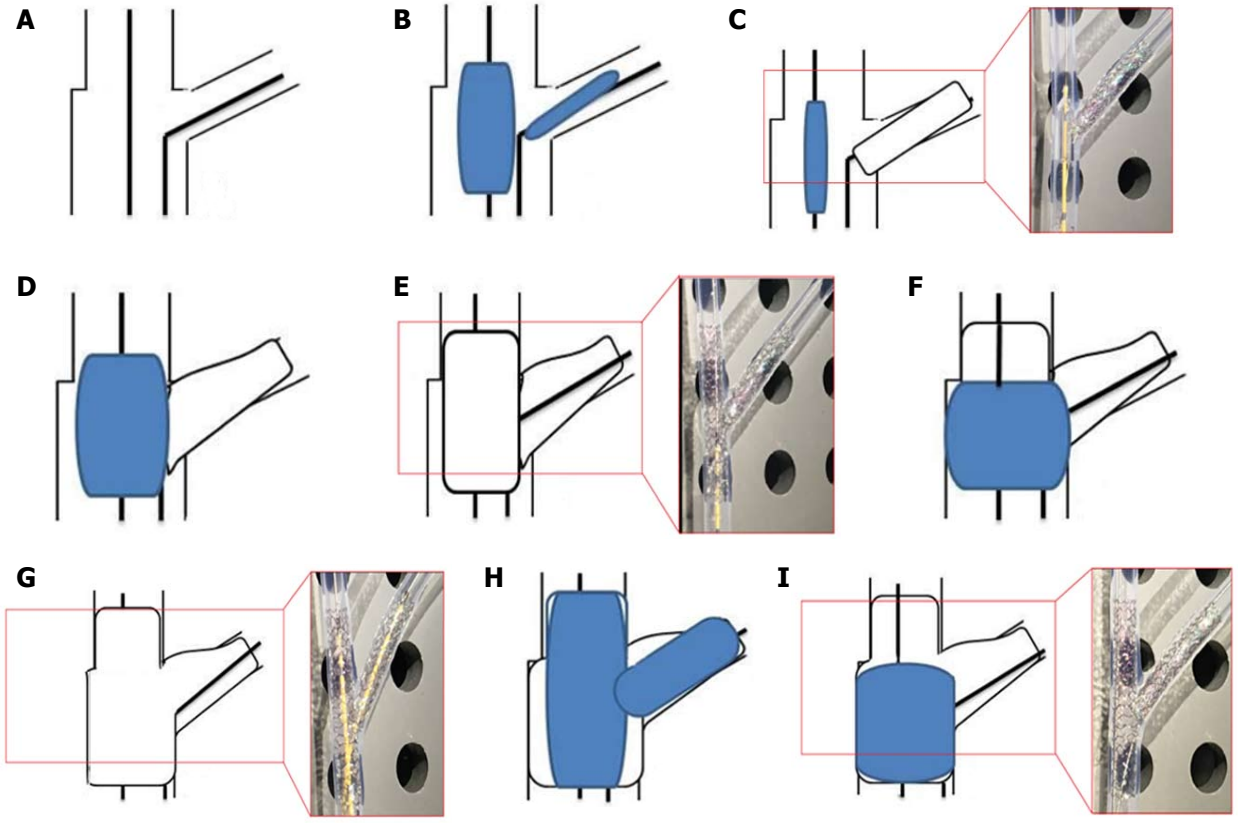

Figure 1 Key steps in the Nano-Crush stenting technique. As both branches are wired (A), both branches are predicated with non-compliant balloons (B) and the stent is deployed at the side branch (C: bench test correlate image). The balloon of the deployed stent is withdrawn and the main branch balloon is inflated in the main branch (MB) at high atmosphere (D); The MB stent of the diameter of the distal reference diameter (3.0 mm) is placed in position and deployed (E: bench test correlate image); Proximal optimization technique (POT) with non-compliant balloon of the same diameter of the MB is performed at high atmosphere (F) and after rewiring of the side branch (G: bench test correlate image), a snuggle kiss is performed with non-compliant balloons (H); Finally, a re-POT is performed with a non-compliant balloon at high atmosphere atm (I: bench test correlate image).

stent restenosis and thrombosis, respectively[17]. As recently suggested by our group, using computed fluid dynamics, the Culotte and other techniques that leave large amounts of metal at the carina unfavorably impacted the bifurcation rheology, causing an increase in lower wall shear stress (WSS) and in the SB. Indeed, low WSS is a potential substrate for restenosis and thrombosis (Figure 2).

To achieve a more physiological flow profile, there should ideally be less metal coverage in the carina side and full metal coverage in the area opposite of the carina and the ostium of the SB. DK-Crush and Nano-Crush are likely to work differently in terms of lowering WSS areas depending on the LM bifurcation. The distribution of metal and the coverage of the carina by the struts strictly depends on the angles: Sharp angles tend to increase the amount of metal at the carina, especially when a generous portion of the SB stent is protruding and should be crushed, whereas if the portion of the stent to be crushed is shorter and the angle is wider, the amount of the metal would be less and coverage might be even incomplete. Obviously, the use of ultra-thin stent struts in DK-Crush or other techniques would potentially improve both safety and long-term outcomes.

STENT ENGINEERING CONSIDERATIONS

The Orsiro (Biotronic AG, BÜlach, Switzerland) stent is considered to have the thinnest struts commercially available. In the most recent European randomized trials, this stent demonstrated a very good safety and efficacy profile. Indeed, its low rate of stent thrombosis reached the non-inferiority statistical significance compared to Xience Prime stent (Abbott Inc., United States)[18-19] with a faster strut endothelium coverage evaluated by optical coherence tomography in respect to the competitors[20]. These results could be achieved even after overcoming the major intrinsic structural limitation to the stent's design, such as longitudinal shortening[21]. Nowadays, other stents have been designed with similar ultra-thin struts, such as the Resolute Onyx stent by Medtronic Inc. or the Ultimaster by Terumo Inc., which are currently being evaluated in real-world scenarios but promise to maintain the line of their predecessor or do even better in terms of strut neointima coverage.

Nowadays, stent working size in most LMs should not be less than 4.5 mm, and all modern techniques imply the use of POT at high pressure. All of these issues

Table 2 Thinnest struts stents and their maximum expansion for left main interventions

Stent type	Strut thickness (μ)	Max size achievable (mm)
Orsiro Biotronik, Sui	60-80	5.3 (3.5 stent)
Onyx Medtronic, United States	70	6 (4.0 stent)
Ultimaster Terumo, Japan	80	5.8 (3.5 stent)
Biomime Meril	65	5.3 (4.5 stent)[1]
Synergy Boston Scientific, United States	74	5.7 (4.0 stent)

Data of maximum expansion retrieved from Sawaya FJ *et al*[24]. [1]Not verified in bench test.

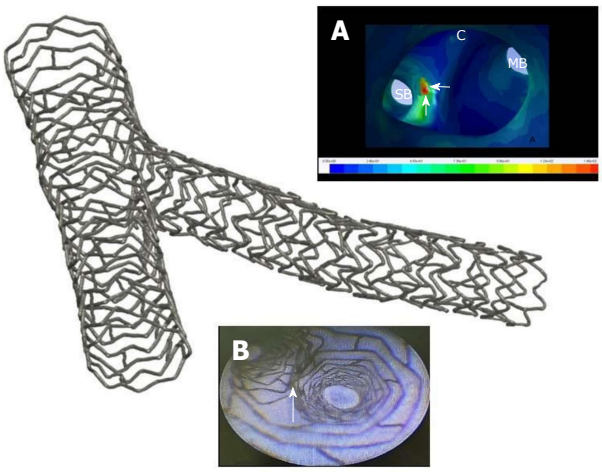

Figure 2 Microcomputed tomography picture of a bifurcation treated by the Nano-Crush technique. A: Region of the carina investigated by computed fluid dynamic showing from the inside of a vessel with high wall shear stress (red zone, white arrows) located at the side branch portion of the carina, which should potentially be in favor of less restenosis and thrombosis at that site; B: Angioscopic image of the same region showing a very smooth transition of the wall at the bifurcation with a very minimal (Nano) apposition of two stent layers. SB: Side branch; MB: Main branch.

could contribute to stent deformation and polymer rupture, both of which can influence thrombosis and restenosis rates. The availability of thin struts and different sized stents useful to treat LM bifurcation, maintaining a good radial force and minimal shortening will represent a mandatory goal to be accomplished by companies in the market in the near future (Table 2).

THE NEW MANTRA OF LM STENTING

Nowadays, LM stenting has gaining respect as an alternative to surgical treatment[22-24], but the treatment of complex LM disease distal/bifurcation disease remains a significant obstacle to overcome to achieve satisfactory results. In such disease, the double stenting technique would provide a more reliable strategy as supported by the evidence coming from both clinical and virtual studies about the benefits provided by thin strut stent technology.

The modern crush techniques such as DK-Crush and Nano-Crush are providing excellent results on mid and long-term follow up, suggesting that minimal crushing obtained using ultra-thin stents is a good way to obtain surgical-like outcomes in the treatment of complex LM bifurcation disease.

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EDITORIAL

Revisiting endovascular treatment in below-the-knee disease. Are drug-eluting stents the best option?

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Abstract

Patients with below-the-knee arterial disease are primarily individuals suffering from critical limb ischemia (CLI), while a large percentage of these patients are also suffering from diabetes or chronic renal failure or both. Available data from randomized controlled trials and their meta-analysis demonstrated that the use of infrapopliteal drug-eluting stents (DES), in short- to medium- length lesions, obtains significantly better results compared to plain balloon angioplasty and bare metal stenting with regards to vascular restenosis, target lesion revascularization, wound healing and amputations. Nonetheless, the use of this technology in every-day clinical practice remains limited mainly due to concerns regarding the deployment of a permanent metallic scaffold and the possibility of valid future therapeutic perspectives. However, in the majority of the cases, these concerns are not scientifically justified. Large-scale, multicenter randomized controlled trials, investigating a significantly larger number of patients than those already published, would provide more solid evidence and consolidate the use of infrapopliteal DES in CLI patients. Moreover, there is still little evidence on whether this technology can be as effective for longer below-the-knee lesions, where a considerable number of DES is required. The development and investigation of new, longer balloon-expanding or perhaps self-expanding DES could be the answer to this problem.

Key words: Critical limb ischemia; Infrapopliteal arterial disease; Drug-eluting stents; Peripheral arterial disease; Balloon angioplasty

Core tip: The use of infrapopliteal drug-eluting stents

(DES) remains limited in clinical practice mainly due to concerns regarding the deployment of a permanent metallic scaffold and the possibility of valid future therapeutic perspectives. However, these concerns are not scientifically justified. Large-scale, multicenter randomized controlled trials investigating a significantly larger number of patients would consolidate the use of infrapopliteal DES in critical limb ischemia patients. Moreover, there is still little evidence on whether this technology can be as effective for longer lesions, where a considerable number of DES is required. The development and investigation of longer balloon-expanding or self-expanding DES could solve this problem.

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INTRODUCTION

Patients with below-the-knee (BTK) arterial disease are mainly suffering from critical limb ischemia (CLI), the malignant expression of peripheral arterial disease[1]. Additionally, a large percentage of CLI patients with BTK disease are suffering from diabetes or chronic renal failure or both[2]. Specifically, patients with diabetes and CLI should undergo prompt revascularization, as the 5-year survival rate in such patients has been reported to be as low as 25%, while diabetes has been correlated with increased risk of limb amputation and repeat revascularization procedures[2]. These fundamental characteristics of BTK disease demarcate the therapeutic approach. More specifically, CLI sets the goal of treatment, which is limb salvage, rather than increasing walking distance, as in cases of intermittent claudication. Limb salvage is strongly related to direct, immediate and acute flow restoration to the foot, also described as immediate lumen gain.

The traditional endovascular treatment algorithm suggests the use of balloon angioplasty or bare metal stenting (BMS) as a bail-out option in cases of residual stenosis or flow-limiting dissection. However, diabetes and chronic renal failure contribute to the formation of an aggressive, hard, atherosclerotic plaque with marked calcifications that are resistant to balloon dilation, reducing the possibility of achieving an adequate acute luminal gain with the use of plain balloon angioplasty[2]. Therefore, in this specific population, the use of stents is, in many occasions, mandatory to obtain an acceptable immediate outcome. As outcomes of BMS in infrapopliteal arteries have been similar to those attained by balloon angioplasty and because short-term patency was not warranted, several studies, including multicenter randomized controlled trials (RCTs), investigated the use of infrapopliteal drug-eluting stents (DES) and the evidence in favor of this technology, which is widely used in coronary disease, began to accumulate[3,4].

Table 1 Endovascular devices for infrapopliteal arterial disease

Balloon angioplasty
Bare metal stents (balloon- or self-expandable)
Drug-eluting stents
Bioabsorbable stents
Bioabsorbable drug-eluting stents
Drug-coated balloons
Drug-infusion devices
Atherectomy devices
Lithotripsy

As a result, a significant volume of high-level evidence supporting the safety and effectiveness of infrapopliteal DES has emerged in the literature, motivating the Trans-Atlantic Society Consensus Ⅱ update to endorse the use of DES in the treatment algorithm of CLI and establish endovascular treatment as a valid and successful alternative to surgery. Notably, the specific consensus document supports the use of DES in short-length infrapopliteal lesions[1]. The endovascular devices currently available for the treatment of infrapopliteal arterial disease are summarized in Table 1.

In a 2013 meta-analysis of five RCTs (611 patients), Fusaro *et al*[5] found that infrapopliteal DES use significantly decreased major amputations and reinterventions compared to plain balloon angioplasty or BMS.

In a recent network meta-analysis of 16 RCTs (1805 patients), Katsanos *et al*[6] demonstrated that both DES and drug-coated balloons (DCBs) had significantly better results compared to plain balloon angioplasty and BMS with regards to vascular restenosis, target lesion revascularization and wound healing. Moreover, DES had also significantly better results when compared with DCB for the most important, strong clinical endpoint of amputations. The Infrapopliteal Drug-Eluting Angioplasty Versus Stenting (commonly known as IDEAS) trial by Siablis *et al*[7] is the only study so far that directly compares these state-of-the-art technologies in BTK disease. Despite the fact that DES demonstrated significantly less binary restenosis at six months follow-up, late lumen loss was similar between the two technologies. An in-depth analysis revealed that this was attributed to the superior acute luminal gain obtained by DES compared to balloon dilation. In the case of small-caliber BTK arteries, even a few millimeters of initial gain are significant, as a larger initial vessel diameter requires superior volume of hyperplasia to reach the critical point of clinically significant restenosis. Therefore, the current data demonstrate the superiority of DES technology for the management of BTK disease (Table 2). Nonetheless, the penetration of this technology in everyday clinical practice has been poorer than expected, due to several issues that remain to be addressed.

First of all, the implementation of a permanent metallic scaffold in such small-caliber vessels as the

Table 2 Randomized controlled trials for infrapopliteal drug-eluting technologies

Study	Yr of publication
Falkowski *et al*[22]	2009
BELOW. Tepe *et al*[23]	2010
ACHILLES. Scheinert *et al*[24]	2012
YUKON-BTX Rastan *et al*[25]	2012
DESTINY Bosiers *et al*[26]	2012
DEBATE-BTK. Liistro *et al*[27]	2013
IN.PACT DEEP. Zeller *et al*[28]	2014
IDEAS. Siablis *et al*[7]	2014
BIOLUX P-II. Zeller *et al*[29]	2015
PADI. Spreen *et al*[30]	2017

tibial arteries raises the issue of whether an occlusion would be re-accessible. Spiliopoulos *et al*[8] performed a retrospective analysis on the recanalization of occluded DES in BTK vessels. Within a period of seven years, a total 367 patients were treated with infrapopliteal DES and the re-occlusion rate was 11.4%. Notably, the success rate of endovascular recanalization of DES occlusions was 90.7% (49/54 cases), while endovascular recanalization was rarely technically demanding. Failure to recanalize the occluded stent(s) was associated with tandem popliteal stent occlusion and stent fractures. This concern of fracture or deformation that compromises patency and re-intervention options has been addressed in another retrospective analysis by Karnabatidis *et al*[9] in which the incidence and clinical implications of DES fracture was evaluated. In 63 CLI patients and 191 lesions, 369 stents were deployed. The follow-up period was 15 ± 11 mo. Only one (0.3%) severe stent fracture and eleven (3.0%) stent compressions were noted. The authors concluded that stent fracture or severe compression is rare and occurs in specific anatomical locations, mainly the distal anterior tibial artery. The authors recommended avoiding stenting in the specific anatomical location, as fractures lead to patency loss and inability to recanalize the occlusion[9]. The cost-effectiveness of DES was also a concern considering their higher price compared to plain balloon angioplasty and their short length, which leads to the deployment of a significant number of stents for the treatment of the characteristically long BTK lesions. This was also addressed in a cost-effectiveness study by Katsanos *et al*[10], where they concluded that the higher DES direct cost is counter-balanced by the smaller number of re-interventions required for limb salvage. Considering that the price of DES has decreased, longer stents could further diminish the direct cost and optimize the cost-effectiveness of infrapopliteal DES use. Finally, some physicians advocate that the deployment of infrapopliteal DES could compromise future surgical options. According to the authors' opinion, stenosed or occluded BTK arterial segments are not a suitable target for surgical reconstruction. Nevertheless, stent placement should always be performed with a view to future treatment options and should certainly respect non-diseased arterial segments that could be used for bypass surgery.

DCBs have been successfully used for the treatment of superficial femoral artery lesions and granted themselves an established role in the treatment algorithm, while there is already increasing evidence for their role in the treatment of dysfunctional dialysis access[11-16]. The use of this technology transformed treatment into a two-step procedure, with an initial step of mechanical treatment required to treat the immediate problem of vascular stenosis, while DCBs are implemented to slow down the process of restenosis using the cytotoxic drug paclitaxel. Several up-to-date tools are available in both the superficial femoral artery and dialysis access to perform vessel preparation[17,18]. However, in BTK vascular disease, the evidence supporting the use of DCB is rather controversial, as two large multicenter RCTs studies have failed to demonstrate the superiority of these devices over standard percutaneous transluminal angioplasty[19]. It is the authors' opinion that this disadvantage in BTK vessels is due to the deficient initial treatment vessel preparation step, which is not required when using balloon-expandable DES. Hence, it remains to be tested whether new technologies dedicated to vessel preparation and minimization of dissection will improve outcomes of infrapopliteal DCB angioplasty.

To conclude, although available data support the use of infrapopliteal DES for short- to medium-length lesions, the use of this technology in everyday clinical practice remains limited, mainly due to concerns regarding the deployment of a permanent metallic scaffold and the possibility of valid future therapeutic perspectives. However, in the majority of the cases, these concerns are not scientifically justified. Large-scale, multicenter RCTs investigating a significantly larger number of patients than those already published would provide solid evidence and would strengthen the use of infrapopliteal DES in CLI patients. Moreover, there is still little evidence on whether this technology can be as effective for longer BTK lesions, where a considerable number of DES is required[20,21]. The development and investigation of new, longer balloon-expanding or perhaps self-expanding DES could be the answer to this problem.

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EDITORIAL

Coronary spasm: It's common, but it's still unsolved

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Abstract

Coronary spasm is caused by a transient coronary narrowing due to the constriction of epicardial coronary artery, which leads to myocardial ischemia. More than 50 years have passed since the first recognition of coronary spasm, and many findings on coronary spasm have been reported. Coronary spasm has been considered as having pivotal roles in the cause of not only rest angina but also exertional angina, acute coronary syndrome, and heart failure. In addition, several new findings of the mechanism of coronary spasm have emerged recently. The diagnosis based mainly on coronary angiography and spasm provocation test and the mainstream treatment with a focus on a calcium-channel blocker have been established. At a glance, coronary spasm or vasospastic angina (VSA) has become a common disease. On the contrary, there are several uncertain or unsolved problems regarding coronary spasm, including the presence of medically refractory coronary spasm (intractable VSA), or an appropriate use of implantable cardioverter defibrillator in patients with cardiac arrest who have been confirmed as having coronary spasm. This editorial focused on coronary spasm, including recent topics and unsolved problems.

Key words: Vasospastic angina; Medically refractory coronary spasm; Variant angina; Coronary vasospasm

Core tip: Coronary spasm is the transient vasoconstriction of epicardial coronary artery, leading to myocardial ischemia. Recently, coronary spasm has become widely accepted as one of the important pathophysiologies of coronary artery disease. However, even at present, there are several unsolved problems regarding coronary spasm.

Teragawa H, Oshita C, Ueda T. Coronary spasm: It's common, but it's still unsolved. *World J Cardiol* 2018; 10(11): 201-209 Available from: URL: http://www.wjgnet.com/1949-8462/full/v10/i11/201.htm DOI: http://dx.doi.org/10.4330/wjc.v10.i11.201

INTRODUCTION

More than several decades have passed since the first recognition of coronary spasm[1-3]. Since then, numerous studies have been conducted, and many findings regarding coronary spasm have been clarified. Coronary spasm is caused by transient narrowing due to the vasoconstriction of the epicardial coronary arteries, leading to myocardial ischemia, and it plays pivotal roles in the cause of not only rest angina but also exertional angina, acute coronary syndrome, including unstable angina, acute myocardial infarction, and ischemic sudden death[4-9]. Recently, coronary spasm has been considered one of the causes of heart failure with reduced ejection fraction[10-12]. Mechanisms responsible for coronary spasm were reported to be the abnormal response of the autonomic nervous system[13], endothelial dysfunction[14-17], abnormal or hyper-reaction of vascular smooth muscles[18-20], and other factors, such as magnesium deficiency[21,22], inheritance[23], or specific anatomy of the coronary artery[24-27]. In addition, the diagnosis and treatment of coronary spasm were based on the guidelines of coronary spasm[28,29]. Its diagnosis has been based on several examinations on the presence of coronary spasm; however, coronary angiography and spasm provocation test (SPT) have been recognized as the standard and final tests[28,30]. It is mainly treated with coronary vasodilators particularly with calcium-channel blocker (CCB)[28,31]. According to the accumulations of experiences, numerous studies, and recent guidelines[6,7,28,29], recently, many physicians roughly know "coronary spasm" or "vasospastic angina" (VSA). However, even at present, there have been undoubtedly several uncertain or unsolved problems on coronary spasm, such as management of medically refractory coronary spasm (intractable VSA) and coronary microvascular angina or appropriate use of implantable cardioverter defibrillator (ICD) for patients with cardiac arrest, who were confirmed as having coronary spasm[28,32,33]. Therefore, this paper focuses on the mechanisms, diagnosis, and treatment of coronary spasm, including recent topics and uncertain or unsolved problems.

MECHANISM OF CORONARY SPASM

Several mechanisms have reported the causes of coronary spasm, such as the abnormal response of the autonomic nervous system[13], endothelial dysfunction of the coronary artery or systemic peripheral vasculature[14-17], abnormal or hyper-reaction of vascular smooth muscles[18-20], and other factors such as a magnesium deficiency[21,22], inheritance[23], or specific anatomy of the coronary artery[24-27]. Naturally, the mechanism of coronary spasm may not be always simple, but may be also multi-factorial. We have come to strongly recognize the multi-factorial mechanisms responsible for coronary spasm when we consider sex differences in the clinical characteristics of VSA patients. Smoking, presence of atherosclerosis of the coronary artery, and morphology of coronary spasm during the SPT differ in male and female VSA patients[8,34,35], indicating the presence of multi-factorial mechanisms of coronary spasm. Findings that the presence of family history of coronary artery disease is higher in women than in men or that younger female VSA patients had higher incidence of smoking than older female VSA patients did, despite the lower incidence of smoking among the whole of female VSA patients[8], are of great interest, taking into consideration the mechanisms of coronary spasm in female patients (Table 1).

Among the mechanisms of coronary spasm shown above, Ohyama *et al*[20,36] have recently reported the relationship between coronary spasm and perivascular components, such as perivascular adipose tissue and adventitial vasa vasorum (Table 1). They showed that such perivascular components play an important role as a source of various inflammatory mediators and showed that inflammatory changes of such perivascular components caused increased the formation of adventitial vasa vasorum and increased the activity of Rho-kinase, leading to the occurrence of coronary spasm[20,36]. These findings appeared to be novel and noteworthy. These findings may account for the presence of focal spasm, because it appears quite difficult to consider the presence of focal spasm based solely on endothelial dysfunction of the coronary artery. On the contrary, the studied VSA patients had coronary spasm of the left anterior descending coronary artery (LAD)[20,36]. Moreover, coronary spasm occurs more frequently in the LAD and right coronary artery (RCA) than in the left circumflex coronary artery (LCX)[37], and it remains unclear whether the findings reported by Ohyama *et al*[20,36] may also account for coronary spasm in the RCA or differences in the frequency of coronary spasm according to the territory of coronary arteries.

Recently, some interest has also focused on the specific coronary anatomy in VSA patients (Table 1): The presence of myocardial bridge (MB), which is characterized by the systolic narrowing of the epicardial coronary artery because of myocardial compression during systole[24-27]. Furthermore, coronary spasm occurs more frequently at the MB, which is in part mediated by coronary vascular dysfunction, including endothelium-dependent and endothelium-independent dysfunctions, at the MB segments. Further observation regarding the occurrence of coronary spasm at MB segments is needed in the international registry of VSA.

Previously, the prevalence of coronary spasm had been considered higher in Asians than in Caucasians[38,39], showing the presence of racial difference in the occurrence of VSA. However, recently, the presence of VSA is more frequent in Caucasians when SPT is aggressively performed[40,41]. In addition, coronary spasm is considered as playing some roles in the cause of acute coronary syndrome with plaque rupture[42] or myocardial infarction with non-obstructive coronary artery[43]. The aggressive effort of making a diagnosis of VSA may clarify the real presence of VSA worldwide (Table 1).

Table 1 Recent topics and unsolved problems regarding coronary spasm

	Previously reported or established	Recent topics	Unsolved problems
Mechanism	Abnormal autonomic nervous system		
	Endothelial dysfunction		
	Hyperreactivity of the coronary smooth muscle	Inflammation of perivascular components	
	Others	Specific anatomy of the coronary artery (myocardial bridge)	Different mechanisms in men and women
	Inheritance		Is there a racial difference in coronary spasm?
	Magnesium deficiency		
Diagnosis	Non-invasive:	Malondialdehyde-modified low-density lipoprotein	Is a biochemical marker for coronary spasm present?
	Holter ECG	Exercise ECG	
	Invasive:	Higher doses of ACh infusions	Detailed SPT protocol using EM
	SPT	Sequential SPT	Are higher doses of ACh for SPT being used?
		SPT using a pressure wire	
		Second SPT despite of negative results of first SPT	Does SPT positivity continue for decades?
Treatment	Life style		
	Stop smoking		
	Pharmacological		
	Calcium-channel blockers	Cilostazol	Treatment of intractable VSA
	Sublingual nitroglycerin during attacks	Statin	Which combinations of coronary vasodilator are the most effective?
	Combination of coronary vasodilators	Aspirin	
	Non-pharmacological	Use of ICD in VSA patients with cardiac arrest	Which is effective in preventing adverse events in VSA patients with cardiac arrest: use of ICD or aggressive medical therapy?
		Cardiac rehabilitation	Treatment of accompanying microvascular angina

ACh: Acetylcholine; ECG: Electrocardiogram; EM: Ergonovine maleate; ICD: Implantable cardioverter defibrillator; SPT: Spasm provocation test; VSA: Vasospastic angina; SPT: Spasm provocation test.

DIAGNOSIS OF CORONARY SPASM

According to the guideline on coronary spasm[28,29], the recognition of transient changes in ST-T segments on electrocardiogram (ECG) during chest symptoms, as well as the presence of chest symptoms derived from coronary spasm, including the good responses to sublingual nitroglycerin and timing of occurrence of coronary spasm at rest, during sleep, or early in the morning, is very important in the diagnosis of VSA. Thus, needless to say, Holter ECG monitoring is important in the diagnosis of VSA[28]; however, Sueda *et al*[44] reported that approximately half of VSA patients had pathologic exercise tests, showing the importance of exercise ECG testing in the clinical setting. Exercise ECG testing may be also useful in patients suspected of coronary spasm (Table 1). As a biochemical index, which has been eagerly longed for but has not been detected until now (Table 1), the level of malondialdehyde-modified low-density lipoprotein (MDA-LDL) was increased in VSA patients[45]. However, this biochemical marker is reported elevated in patients with other unstable coronary diseases[46,47]. An elevated MDA-LDL level may be carefully interpreted in the diagnosis of VSA. In general, using coronary computed tomography (CT) angiography alone, the diagnosis of VSA itself cannot be obtained, and we doubt the presence of VSA when no significant coronary stenosis is detected on coronary CT angiography. We have sometimes experienced patients with coexistence of coronary spasm and organic coronary stenosis (Figure 1), and the assessment of or exclusion for organic coronary stenosis using a coronary CT angiography may be also needed even in patients, whose diagnosis of VSA was made based on the typical chest symptoms and transient ST-T changes in ECG. Furthermore, as shown above, coronary spasm sometimes occurs at the MB segments[24-27], and the presence of MB on a coronary CT angiography[48] may be a useful clue of the possibility of VSA in patients with chest pain when atherosclerosis was absent on a coronary CT angiography. According to Ohyama *et al*[20], positron-emission tomography, which has been adopted in the assessment of inflammatory perivascular components, cannot be performed widely in the clinical setting.

Thus, SPT is considered the gold standard examination and actually has been performed frequently because transient ST-T changes on ECG during chest symptoms cannot always be obtained in the clinical setting. Furthermore, SPT may be useful not only in the diagnosis of VSA but also in providing some information in the activity of coronary spasm and prognosis; presence of organic stenosis, multi-vessel spasm, focal spasm, coronary spasm induced by a low dose of acetylcholine (ACh), and total occlusion due to coronary spasm[49-51]. The provocative drugs in SPT are ACh and ergonovine maleate (EM). The methodology of SPT using ACh infusions has been almost established[28-30,52,53], except for the use of transient pacing catheter or the maximal doses of ACh. In general, during SPT using ACh infusions, an insertion of transient pacing catheter *via* an internal

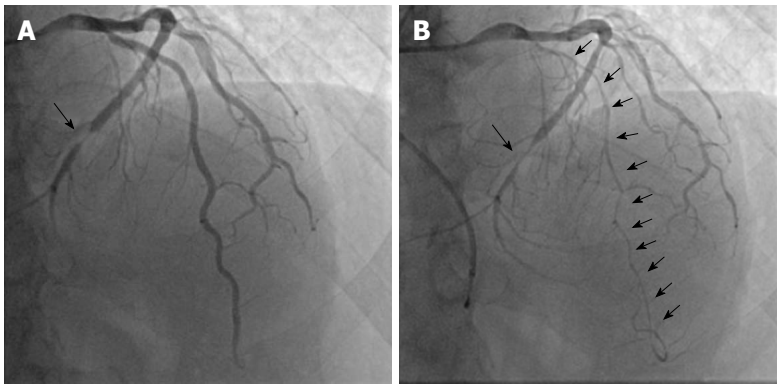

Figure 1 A representative case with coronary spasm and coronary stenosis. The patient, who had chest symptoms for 20 min at rest, accompanied with cold sweating, was admitted to our institution for the evaluation of his chest symptoms. A: Coronary angiography showed coronary stenosis at the distal segment of the left circumflex coronary artery, which cannot be considered as the cause of his chest symptoms; B: The spasm provocation test using 100 μg of acetylcholine showed diffuse coronary spasm throughout the left anterior descending coronary artery, accompanied with usual chest pain, which had been restored after nitroglycerin injection. Coronary stenosis and spastic segments were indicated by bold arrow and plain arrows, respectively.

jugular vein or a medial cubital vein may be safer to avoid ACh-induced bradycardia despite the duration of ACh infusion into the coronary artery[54]. The recommended maximal doses of ACh is 100 μg for the left coronary artery (LCA) and 50 μg for the RCA[28]; however, such maximal doses of ACh were determined based on the doses of ACh adopted for the provocation of coronary spasm in patients with variant angina[55], which involved increased coronary spasm activity[49,56]. Thus, the higher maximal doses of ACh in patients with stable VSA are reasonable. Recently, some adopt the maximal doses of ACh as 200 μg for the LCA and 80 μg for the RCA, showing the higher induction of coronary spasm without a significant increase in complications[40,57]. However, it remains unclear whether the higher doses of ACh than the above-mentioned doses are useful or harmful in the SPT (Table 1). On the contrary, the methodology of SPT using EM infusion has not been established sufficiently, compared with that of using ACh (Table 1). The total doses of EM, which are described as the doses of EM with 20-60 μg for 2-5 min for each coronary artery in the guideline[28], vary. In addition, the method of EM infusion, which was infused continuously or with a stepwise incremental dose, has still not been determined. In general, the insertion of transient pacing catheter is unnecessary, and this appears to be advantageous.

Moreover, the experienced method of SPT using ACh or EM at each institution may be performed safely; however, several tips regarding SPT using these provocative drugs have been known. Female VSA patients have more sensitivity to ACh provocation[8,34,35], and the SPT using ACh infusion may be recommended in female patients who undergo SPT. In addition, some patients have positive SPT using EM infusions despite the negative results in SPT using ACh infusions[30]. Furthermore, Sueda *et al*[58] have reported the sequential SPT, which was induced by infusions of first ACh, then EM, and finally ACh, showing the high provocative rate without a significant increase in complications[53]. Naturally, the ACh or EM working receptors are different[59], and the use of different provocative drugs for a short duration is reasonable. The sequential SPT may stimulate both receptors simultaneously, leading to a higher provocation of coronary spasm. To our knowledge, the sequential SPT may be the strongest until now. Sueda *et al*[53,58] showed no difference in complications including major ones or atrial fibrillation between the sequential and standard SPTs. On the contrary, further verification on the presence of false-positive cases will be needed using the sequential SPT. Furthermore, younger patients have a tendency of negative induction of coronary spasm in response to standard provocation[60] due to the not-severe coronary vascular dysfunction, and the sequential SPT may be useful in such patients. In addition, we have experienced some patients who showed no significant coronary stenosis on coronary angiography despite the fact that significant coronary stenosis was suspicious based on the results of examinations and patients' symptoms. In such cases, the diagnosis of VSA was possible; however, performing an SPT was difficult because an intracoronary nitroglycerin infusion had been administered or taking vasodilators before coronary angiography were continued. Under such circumstances, the sequential SPT may also be useful (Figure 2).

According to the length of coronary spasm induced by the SPT, there have been a subclassification with "focal spasm", which is defined as vasoconstriction within the confines of one isolated coronary segment, and "diffuse spasm", which is defined as the vasoconstriction of $\geqslant$ 2 adjacent coronary segments[29,50]. Sato *et al*[50] have shown poorer prognosis in focal spasm than in diffuse spasm. On the contrary, Sueda *et al*[61] have shown the importance of diffuse spasm as one of causes of medically refractory VSA. Thus, it may be an unsolved problem which "focal spasm" or "diffuse spasm" is worse in the clinical setting[50,61] (Table 1).

The positive criteria of SPT is defined as "transient, total, or sub-total occlusion (> 90% stenosis) of a coronary artery with signs/symptoms of myocardial

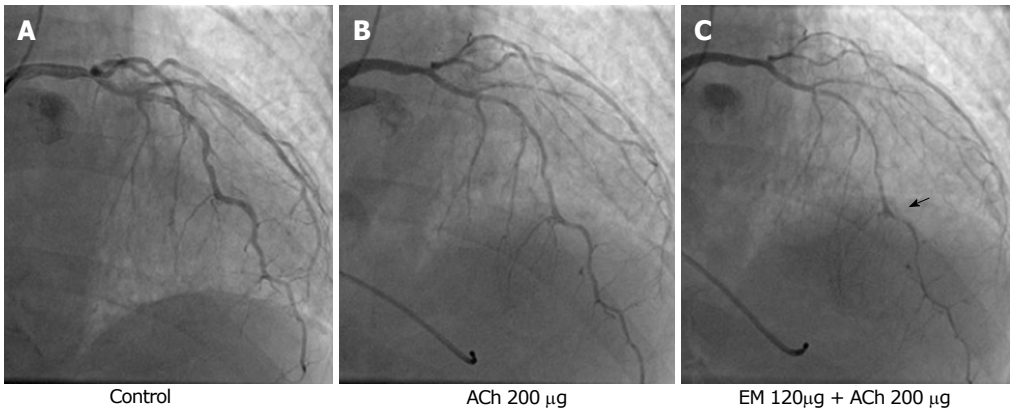

Figure 2 A case of coronary spasm, which was documented by sequential spasm provocation test, which was performed after the routine coronary angiography, vasodilator administration, and preprocedural infusion of nitroglycerin. A: The patient had chest symptoms at exercise early in the morning. Coronary computed tomography angiography showed stenosis of the left anterior descending coronary artery. However, the coronary angiography showed no significant coronary stenosis; B: Because the presence of vasospastic angina was suspicious, the spasm provocation test was performed despite the intracoronary infusion of nitroglycerin and calcium channel blocker intake. The standard doses of acetylcholine (ACh, up to maximal 200 μg) did not cause coronary spasm; C: Consequently, we performed the sequential spasm provocation test: 120 μg of ergonovine maleate was infused first followed by 200 μg of ACh, showing the presence of coronary spasm (right panel) and obtained the diagnosis of vasospastic angina. The spastic site was indicated by an arrow. Ach: Acetylcholine; EM: Ergonovine maleate.

ischemia (anginal pain and ischemic ST changes)"[28]. However, some patients have significant narrowing induced by provocative drugs despite the chest symptoms and ST-T changes on ECG. Sueda *et al*[37] showed that such patients were detected in 6.8% of studied patients who underwent an SPT. In addition, we have also experienced some patients with moderate vasoconstriction diffused with chest symptoms and/or ECG changes. Under such circumstances, the diagnosis of VSA may be difficult. At that time, other supportive index for the diagnosis of VSA may be needed. We have shown that the use of pressure wire may help in the diagnosis of VSA[62-64], showing the sudden drop of intracoronary pressure in response to ACh infusions in SPT-positive vessels and less frequency of major complications related to SPT. The validity of SPT using a pressure wire should be verified (Table 1); however, this method may be useful in the following situations: (1) when hemodynamic instability may be precipitated by coronary spasm, such as when patients have hypertrophic cardiomyopathy or left ventricular dysfunction; (2) when patients have chronic kidney disease; and (3) when cardiologists seek to clarify the disease status through a second SPT. SPT has been considered the final examination; however, the results of SPT is not absolute, and we have to make a diagnosis of VSA comprehensively, taking other conditions as well as the results of SPT into consideration. The second session of SPT may be needed in patients who had repeated chest symptoms despite the negative results of the first SPT[64].

TREATMENT OF CORONAY SPASM

Needless to say, smoking cessation is an important treatment of VSA[28]. As a pharmacological treatment for VSA, CCB as prevention and sublingual nitroglycerin during anginal attacks are the first-line therapies for VSA[28,29,31,65]. The monotherapy of β-blockers is class Ⅲ in VSA patients with organic stenosis[28]. However, VSA is accompanied with many cardiovascular diseases, in which β blockers are effective, such as left ventricular dysfunction[10-12], hypertrophic cardiomyopathy[66], and myocardial bridging[24,26,27,62,67]. Under such conditions, coronary vasodilators should be administered first, and then β blockers should be administered from small doses, observing carefully for the worsening of chest symptoms and hemodynamics.

In addition, the sudden cessation of coronary vasodilators while chest symptoms disappeared under long-term intake of coronary vasodilators may cause severe conditions due to coronary spasm[68]. Avoidance of sudden cessation of coronary vasodilators should be repeated to VSA patients, although the duration of continued coronary spasm activity has not been clarified (Table 1).

Some patients have angina attacks even while under CCB medications. In such conditions, several countermeasures should be followed. First, we must consider the type of CCB, because CCBs may differ in their ability to prevent angina attacks[31,65]. Second, the dosing regimen should be considered, such as whether a submaximal or maximal dose or medication once or twice a day would be appropriate. There are patients on a once-a-day CCB regimen who have had angina attacks just before the dosage time. Third, dosage-timing should be considered. In general, angina attacks often occur between midnight and early morning[5-7,28]. Thus, taking CCB at bedtime is usually recommended. However, for some VSA patients, taking CCB at the time of rising may be effective. Fourth, we must check whether the vasodilators prescribed are branded vasodilators. In VSA patients with high coronary spasm activities, switching from branded vasodilators to generic ones may worsen their chest symptoms[69]. Finally, another vasodilator must be added such as long-acting nitrates, nicorandil, and other type of CCBs (dihydropyridine CCB *vs* non-dihydropyridine CCB).

The combination of more than one and two kinds of coronary vasodilators varies and dependent mainly on each primary doctors' experience. However, which combination of coronary vasodilators was more useful in preventing coronary spasm is still unclear[70] (Table 1).

Recently, in a randomized, multicenter, double-blind, placebo-controlled study, Shin *et al*[71] have shown that an addition of cilostazol, which was a selective inhibitor of phosphodiesterase 3, to a CCB decreased the frequency and severity of chest symptoms in VSA patients. Moreover, they showed that an additional of cilostazol may be promising, although the finding that the CCB adopted in the present study was amlodipine, which was not the standard CCB for the prevention of coronary spasm in VSA patients, was a slightly controversial. The usefulness of other drugs such as statins[72,73] and a low-dose aspirin[74,75] on clinical outcomes has been accumulated, and these drugs may be considered to improve the clinical outcomes in VSA patients (Table 1).

UNCERTAIN OR UNSOLVED PROBLEMS REGARDING CORONARY SPASM

First, one of the unsolved problems related to coronary spasm is the presence of intractable VSA, which was defined as angina that cannot be controlled even with the administration of two types of coronary vasodilators. A study revealed that 13.7% of VSA patients had intractable VSA with a younger age at the time of onset and included higher proportions of tobacco smokers and normotensive patients[28]. Our previous report has shown that the presence of SPT-related angiographic findings, such as provocation induced by a low-dose ACh, total occlusion due to coronary spasm, and multivessel coronary spasm, were predictors for the presence of intractable VSA[51], showing the importance of performing SPT. When we have controlled the condition of taking several kinds of coronary vasodilators, as shown above, there have been many patients who were refractory to the administrations of several kinds of coronary vasodilators. Among the VSA patients, there have been some VSA patients with microvascular dysfunction[76,77]. Standard coronary vasodilators are less effective in patients with microvascular dysfunction or microvascular angina[33]. Therefore, the comorbid of VSA and microvascular dysfunction may contribute to the presence of intractable VSA. Thus, additional novel drugs may be anticipated. Cardiac rehabilitation has been reportedly effective in preventing coronary spasm in VSA patients[78], and non-pharmacological treatment may be also anticipated.

Second, the need for ICD in VSA patients with cardiac arrest has been one of the unsolved problems of coronary spasm[28,32,56,79,80]. Recently, Sueda *et al*[32] have summarized the results that appropriate ICD shocks were observed in 24.1% of VSA patients with aborted ICD. Rodríguez-Mañero *et al*[80] have shown that ICD was effective when insufficient medications were administered in VSA patients. In the clinical setting, whether sufficient medications without ICD can prevent such malignant arrhythmia due to coronary spasm is still undetermined. The physicians-in-chief of the heart team should carefully determine the ICD by taking patient background such as taking coronary vasodilators sufficiently and the results of SPT under sufficient medications[81] into consideration (Table 1).

CONCLUSION

Given the accumulation of studies on coronary spasm for more than half a century, coronary spasm is the key player and main cause in the pathophysiology of heart diseases. At present, its mechanisms, diagnosis, and treatments have been understood. Nonetheless, some unsolved problems on coronary spasm are still present, and we have to make efforts in obtaining clues to these unsolved problems.

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REVIEW

Clinical applications of feature-tracking cardiac magnetic resonance imaging

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Abstract

Cardiovascular diseases represent the leading cause of mortality and morbidity in the western world. Assessment of cardiac function is pivotal for early diagnosis of primitive myocardial disorders, identification of cardiac involvement in systemic diseases, detection of drug-related cardiac toxicity as well as risk stratification and monitor of treatment effects in patients with heart failure of various etiology. Determination of ejection fraction with different imaging modalities currently represents the gold standard for evaluation of cardiac function. However, in the last few years, cardiovascular magnetic resonance feature tracking techniques has emerged as a more accurate tool for quantitative evaluation of cardiovascular function with several parameters including strain, strain-rate, torsion and mechanical dispersion. This imaging modality allows precise quantification of ventricular and atrial mechanics by directly evaluating myocardial fiber deformation. The purpose of this article is to review the basic principles, current clinical applications and future perspectives of cardiovascular magnetic resonance myocardial feature tracking, highlighting its prognostic implications.

Key words: Left ventricular ejection fraction; Cardiac magnetic resonance; Cardiovascular disease; Strain; Feature-tracking

Core tip: Cardiac magnetic resonance feature tracking analysis is progressively establishing its role as an

accurate tool to for quantitative evaluation of cardiovascular function by directly evaluating myocardial fiber deformation. Feature-tracking derived strain parameters are able to identify subtle myocardial abnormalities before overt clinical manifestation thus allowing early diagnosis of primitive cardiomyopathies, identification of cardiac involvement in systemic diseases, detection of drug-related cardiac toxicity as well as risk stratification and monitor of treatment effects in patients with heart failure of various etiology. The present article summarizes the basic principles, current applications and future perspectives of cardiovascular magnetic resonance myocardial feature tracking.

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INTRODUCTION

The evaluation of cardiac function has a pivotal role in diagnosis, risk stratification and assessment of treatment response in several cardiac disorders. Traditionally, left ventricular ejection fraction (LVEF) defined as the ratio between systolic output and end diastolic volume, assessed by various techniques including ventricular angiography, 2D- and 3D- echocardiography, cardiac single proton emission tomography, computed tomography and cardiac magnetic resonance (CMR), has represented the gold standard for evaluating cardiac function. Current international guidelines recommend the use of LVEF to assess the risk of sudden cardiac death (SCD) in patients with ischemic and non-ischemic cardiomyopathies, being patients with LVEF $\leqslant$ 35% at particular high risk and therefore referred for primary prevention implantable cardioverter defibrillator (ICD)[1]. Assessment of LVEF is also routinely recommended for familiar screening in patients affected by cardiomyopathies as well as to early detect cardiac involvement in systemic immune-mediated diseases or cardiac toxicity in patients undergoing cancer treatments[2-4]. However, in the last decade, new imaging modalities such as echo and CMR myocardial strain have progressively emerged as superior tools to evaluate global and regional myocardial mechanics, pointing out the limitations of LVEF especially in evaluating regional myocardial function and detecting early stage subclinical cardiac disorders[5]. In the present review we will focus on CMR feature tracking (CMR-FT) imaging of myocardial strain summarizing its basic principles, current clinical applications and future perspectives.

GENERAL PRINCIPLES

Myocardial strain is a deformation index defined as the percentage change in dimension from a resting state (end-diastole) to the one achieved after contraction (end-systole)[6]. Considering a myocardial fiber, and being L0 its initial length in end-diastole and L1 its final length in end-systole, myocardial strain (S) can be defined as follow:

S = (L1 - L0)/L0 (Figure 1)

Due to the complex 3D architecture of the left ventricular (LV) musculature, systolic deformation takes place along several different directions. The evaluation of strain along each of these axes leads to the definition of different types of strain: (1) longitudinal strain (LS) represents the longitudinal shortening of the cardiac muscle, from the base to the apex, it is mostly determined by the longitudinally oriented muscle fibers in the subendocardial layer and is conventionally represented by a negative value due to systolic shortening; (2) circumferential strain (CS) is an expression of cardiomyocytes shortening along the LV circular perimeter, it is calculated in a short-axis view, it is mostly influenced by circumferentially oriented muscle fibers in the mid-wall and as well as LS it has a negative value due to systolic shortening; and (3) radial strain (RS) represents myocardial deformation toward the center of the ventricular cavity, and it is a measure of the LV thickening during systole and therefore is conventionally represented by a positive value.

Several other mechanical deformation parameters can be derived from strain analysis, of note: (1) Strain rate representing the "velocity" or rate at which the deformation occurs; and (2) LV torsion defined by the angle generated by the clockwise rotation of the basal segments and the counterclockwise rotation of the apex relatively to a stationary reference point conventionally located at a mid-ventricular level.

Myocardial CMR strain was initially investigated using tagging techniques in which magnetic labels (tags) are superimposed to the LV during cine imaging acquisition by radiofrequency spatial modulation of magnetization able to saturate parallel planes throughout the image, allowing the analysis of deformation of those lines throughout the cardiac cycle by post-processing semi-automated methods[7,8]. Soon after those initial experiences, new methods to evaluate myocardial strain based upon post-processing tracking of myocardial "features" overcame the need for prospective time-consuming image acquisition protocols. Cardiac CMR-FT is able to detect and follow over time myocardial boundaries leading to a more automatized quantification of strain parameters[9]. From a technical point of view, the features tracked by CMR-FT are anatomic elements typically identified along the cavity-myocardial interface due to the high contrast resolution between blood pool and myocardium. Every feature is tracked across the cardiac cycle by specific algorithms searching the most similar image pattern on the following frame within a small window centered around the feature[10]. The endocardial and epicardial borders are usually manually traced in the end-diastolic phase, then the CMR-FT software automatically tracks the border across the

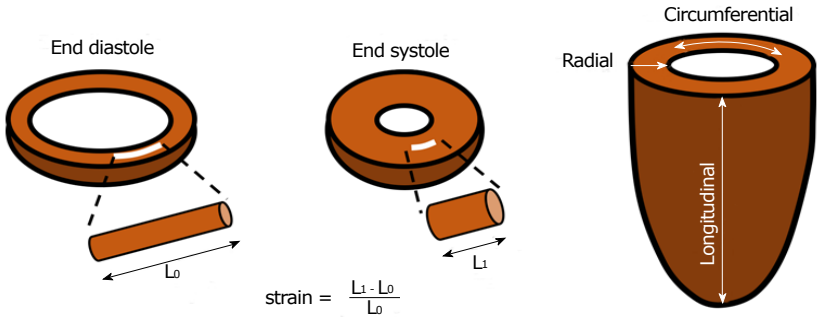


Figure 1 Schematic representation illustrating the physics principle beyond strain as well as the 3 main axes along which myocardial strain is calculated.

whole cardiac cycle. Global longitudinal strain (GLS) is derived by 2 or 3 long-axis steady state free precession (SSFP) cine images while global circumferential strain (GCS) and global radial strain (GRS) are derived from the short axis cine image stack. Several CMR-FT softwares are commercially available and can be directly applied to all CMR routine scans, as they work on standard SSFP cine images[11].

FEATURE TRACKING NORMAL VALUES

Studies investigating CMR-FT strain values in healthy subjects have repeatedly demonstrated that global measurements are more reproducible compared to regional ones that are limited by partial volume effect with features fading/leaving the image plane between end diastole and end systole[12]. In particular, GCS seems to be less affected by inter-observer and inter-vendor variability compared to GRS and GLS in which the complex anatomy of the atrio-ventricular annular region may lead to poor tracking[11]. Strain values are affected by both gender and age but in general terms, values of circumferential and LS < -17% to -20% as well as values of RS > 25%-30% are considered within normal range[12-15].

CLINICAL APPLICATIONS

Ischemic heart disease

Both global and regional strain parameters as well as dyssynchrony indices have been widely investigated in patients with ischemic heart disease. The main areas of interest include the correlation between regional strain parameters and infarct characteristics, the impact of strain parameters on long-term LV remodeling and the ability of strain to predict long-term clinical outcomes and to identify inducible ischemia[16].

All strain parameters are impaired in infarcted territories with strain values inversely related to the infarct size and infarct transmurality[17,18]. Compared to wall motion abnormalities, segmental strain values allows a more accurate discrimination between areas of subendocardial from transmural infarction and non-infarcted remote zones with only certain limitations in the early post-infarct phase due to the coexistence of edema, inflammatory cells, hemorrhage and viable and necrotic myocardial fibers[17,19-21]. Among all strain parameters, CS has shown to be the more accurate in assessing infarct extension and has also demonstrated its superiority to conventional LVEF determination in identifying subtle impairments of LV contractile function[19,22,23].

Data concerning the capability of strain analysis to predict adverse LV remodeling after acute myocardial infarction are debating[24-26]. In a study including 74 patients who underwent CMR within 4 d after successfully reperfused ST-elevation myocardial infarction (STEMI), a cut-off value of -19.3% for GCS appeared as accurate as late gadolinium enhancement (LGE) extension to identify patients with recovered LVEF ($\geqslant$ 50%) at 6-mo follow-up while no significant correlation was determined using GLS[24]. In another study including 164 STEMI who underwent CMR a median of 3 d after the acute event, CS was not inferior to the area of LGE in predicting segmental functional improvement/normalization after a median of 9-mo[25]. Conversely, Shetye *et al*[26] have recently failed to demonstrate a correlation between baseline strain parameters and the development of adverse LV remodeling after 4-mo follow-up among 65 patients with STEMI who underwent CMR within 3 d post-reperfusion, even though a good correlation was found between strain parameters, baseline LVEF and infarct size.

The correlation between scar extent determined by LGE imaging and long-term risk of major adverse cardiac events (MACE) after myocardial infarction is well known[27]. However, it has been recently pointed out how various CMR-FT derived parameters maybe able to accurately predict long-term clinical outcomes (Table 1). In a large study by Gavara *et al*[28], the prognostic value of CMR-FT was investigated among 323 patients who underwent CMR one week after a STEMI. During a median follow-up of 36-mo, all strain parameters were correlated to the incidence of a composite endpoint including cardiac death, readmission for heart failure and reinfarction. However, after adjustment for baseline and CMR variables, GLS (HR 1.21; 95%CI: 1.11-1.32; P < 0.001) was the only independent predictor of MACE. In

Table 1 Principal studies analyzing the prognostic role of cardiac magnetic resonance-feature tracking in patients with ischemic and non-ischemic cardiomyopathy

Reference	No. of patients	Herat disease	Parameters analyzed	Outcome	Occurrence of outcome, %	Independent predictors of the outcome event (HR)	Follow-up duration
Gavara *et al*[28], 2017	323	IHD (recent STEMI)	GLS GCS GRS n. segments with altered LS n. segments with altered CS n. segments with altered RS LVEF LGE MVO	Cardiac death, readmission for heart failure and reinfarction	17	GLS (1.21)	36 mo (median)
Nucifora *et al*[29], 2018	180	IHD (recent STEMI)	GCS LVEF LGE MVO	Cardiovascular death, aborted SCD and hospitalization for heart failure	22	GCS (1.16)	95 mo (median)
Muser *et al*[30], 2017	130	IHD (recent STEMI)	Mechanical dispersion LVEF LGE MVO	Cardiovascular death, aborted SCD and hospitalization for heart failure	20	Mechanical dispersion (1.39)	95 mo (median)
Buss *et al*[35], 2015	210	IDCM	GLS GCS GRS Mean LS Mean CS Mean RS LVEF LGE	Composite of cardiac death, heart transplant and aborted SCD	12	GLS (1.27) Mean LS (5.44)	5.3 yr (median)
Riffel *et al*[36], 2016	146	IDCM	Long axis strain LVEF LVEDV LGE	Composite of cardiac death, heart transplant and aborted SCD	16	Long axis strain (1.28) LVEDV/BSA (1.01) LGE (2.51)	4.3 ± 2.0 yr
Romano *et al*[37], 2017	470	IHD + IDCM	GLS LVEF LGE	All-cause death	20	GLS (2.35) LVEF (0.95)	4 yr (median)
Romano *et al*[38], 2018	1012	IHD + NICM	GLS LVEF LGE	All-cause death	13	GLS (1.89)	4.4 yr (median)
Pi *et al*[39], 2018	172	IDCM	GLS GCS GRS LVEF LGE	Composite of cardiac death and heart transplant	25	LGE (4.73)	47 mo (median)

IHD: Ischemic heart disease; STEMI: ST-elevation myocardial infarction; GLS: Global longitudinal strain; GCS: Global circumferential strain; GRS: Global radial strain; LVEF: Left ventricular ejection fraction; LGE: Late gadolinium enhancement; MVO: Microvascular obstruction; SCD: Sudden cardiac death; IDCM: Idiopathic dilated cardiomyopathy; LVEDV: Left ventricular end diastolic volume; BSA: Body surface area.

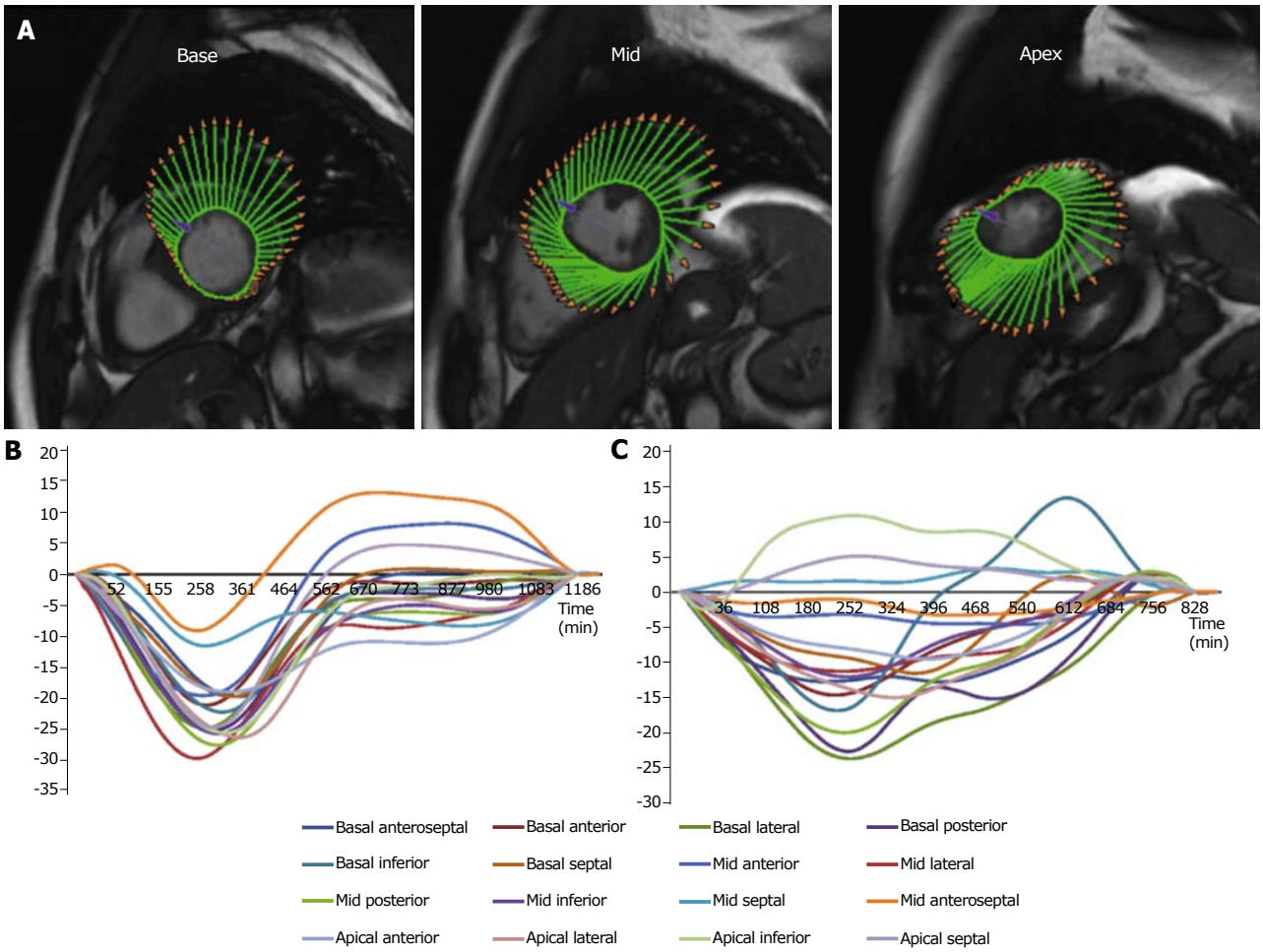


Figure 2 Example of left ventricular endocardial feature tracking. A: Example of tracking of the endocardial border of the left ventricle (LV) on basal, mid, and apical short-axis, steady-state free-precession images using an dedicated feature-tracking software. The software automatically calculates the circumferential strain of each myocardial segment; B: Example of a patient with homogenous LV contraction; C: Example of a patient with extreme regional heterogeneity of myocardial contraction. Reprinted with permission from Muser *et al*[30].

particular, MACE rate was higher in patients with a GLS $\geqslant$ -11% (22% *vs* 9%; P = 0.001). In the same study, those results were also validated in an external cohort of 190 STEMI patients confirming both the higher incidence of MACE in patients with a GLS $\geqslant$ -11% (34% *vs* 9%; $P < 0.001$) and the independent predictive value of GLS (HR 1.18; 95%CI: 1.04-1.33; P = 0.008)[28]. These findings were subsequently confirmed and extended by our group. We have reported GCS to be significantly and independently associated to the occurrence of a composite endpoint including cardiovascular death, aborted SCD and hospitalization for heart failure (HR 1.16; 95%CI: 1.07-1.25; $P < 0.001$) during a median follow-up of 95 mo in a population of 180 patients admitted for a first STEMI and who underwent CMR imaging a median of 8 d following the index event[29]. We have also reported how early assessment (median of 7 d after STEMI) of LV mechanical dispersion defined as the standard deviation of the time-to-peak CS of the LV segments, is significantly and independently related to the occurrence of MACE (HR 1.39, 95%CI: 1.20-1.62, $P < 0.001$) (Figure 2)[30].

Due to its high sensitivity in identifying contractile function compared to visual assessment of wall motion abnormalities or determination of changes in LVEF, CMR-FT has recently been proposed to evaluate inducible ischemia and establishing contractile reserve in patients with chronic ischemic heart disease[31,32]. Schneeweis *et al*[33] have demonstrated how in 25 patients with suspected or known coronary artery disease, undergoing dobutamine stress CMR, CS during high doses of dobutamine, was able to identify segments supplied by a vessel of > 70% narrowing with a sensitivity of 75% and specificity of 67% using a strain threshold of -33.2%[33]. In the same study, the authors also showed how impairment of CS already occurred at intermediate-doses of dobutamine allowing an earlier detection of inducible ischemia compared to visual assessment[33]. In another study including 15 patients undergoing viability assessment by low-dose dobutamine stress, there was no response to dobutamine in dysfunctional segments with scar transmurality > 75% while dysfunctional segments without scar showed improvement either in subendocardial and subepicardial GCS as well as in GRS. In particular, GCS improved in all segments up to a transmurality of 75% while GRS improved in

segments with < 50% transmurality and remained unchanged above 50% transmurality[32].

Idiopathic dilated cardiomyopathy

The presence and extension of scar represents a negative prognostic factor in patients with idiopathic dilated cardiomyopathy (IDCM), as well[27]. Unfortunately, no clear evidence of LGE can be found in up to 60% of these patients making extremely important to identify new potential predictors to further stratify individual risk beyond simple LVEF[34]. A study including 210 patients with IDCM found GLS to be an independent predictor of MACE including cardiac death, heart transplantation and aborted SCD (HR 1.27, 95%CI: 1.06-1.52, $P < 0.02$) during a median follow-up of 5.3-years regardless to the baseline LVEF and the presence of LGE, while no significant association was found with GCS and GRS[35]. Another study including 146 patients affected by IDCM, investigated the value of "long axis strain" defined as the distance between the epicardial border of the LV apex and the midpoint of a line connecting the origins of the mitral valve leaflets in end-systole and end-diastole in predicting a combination of cardiac death, heart transplantation and aborted SCD and found that the ratio between LV end-diastolic volume/body surface area (HR 1.01, 95%CI: 1.00-1.02, $P = 0.04$), the presence of LGE (HR 2.51, 95%CI: 1.02–6.19, $P = 0.04$) as well as long axis strain (HR 1.28, 95%CI: 1.07-1.52, $P < 0.01$) were all independent predictors of MACE[36]. The incremental value of CMR-FT strain was subsequently confirmed in a series of 470 patients of whom 140 with IDCM, in which was described an independent correlation of GLS (HR 2.35, 95%CI: 1.81-3.06, $P < 0.001$) and LVEF (HR 0.95, 95%CI: 0.91-0.99, $P = 0.038$) with the risk of death during a median follow-up of 4-years regardless to the presence and extension of LGE[37]. In a large multicenter study including 1012 patients with both ischemic heart disease and non-ischemic cardiomyopathy, GLS was an independent predictor of all-cause mortality over LVEF and presence of LGE in the all cohort (HR 1.89, 95%CI: 1.55-2.07, $P < 0.001$) as well as in the ischemic (HR 1.95, 95%CI: 1.48-2.58, $P < 0.001$) and non-ischemic (HR 2.14, 95%CI: 1.56-2.91, $P < 0.001$) subgroups[38]. The above results have not been confirmed by a recent study including 172 patients with IDCM and moderately to severely reduced LVEF (<40%). In this study, neither GLS, GCS or GRS were correlated with the risk of death or heart transplant during a median follow-up of 47-mo, while presence of LGE and serum sodium were the only independent predictors of the outcome event (Table 1)[39].

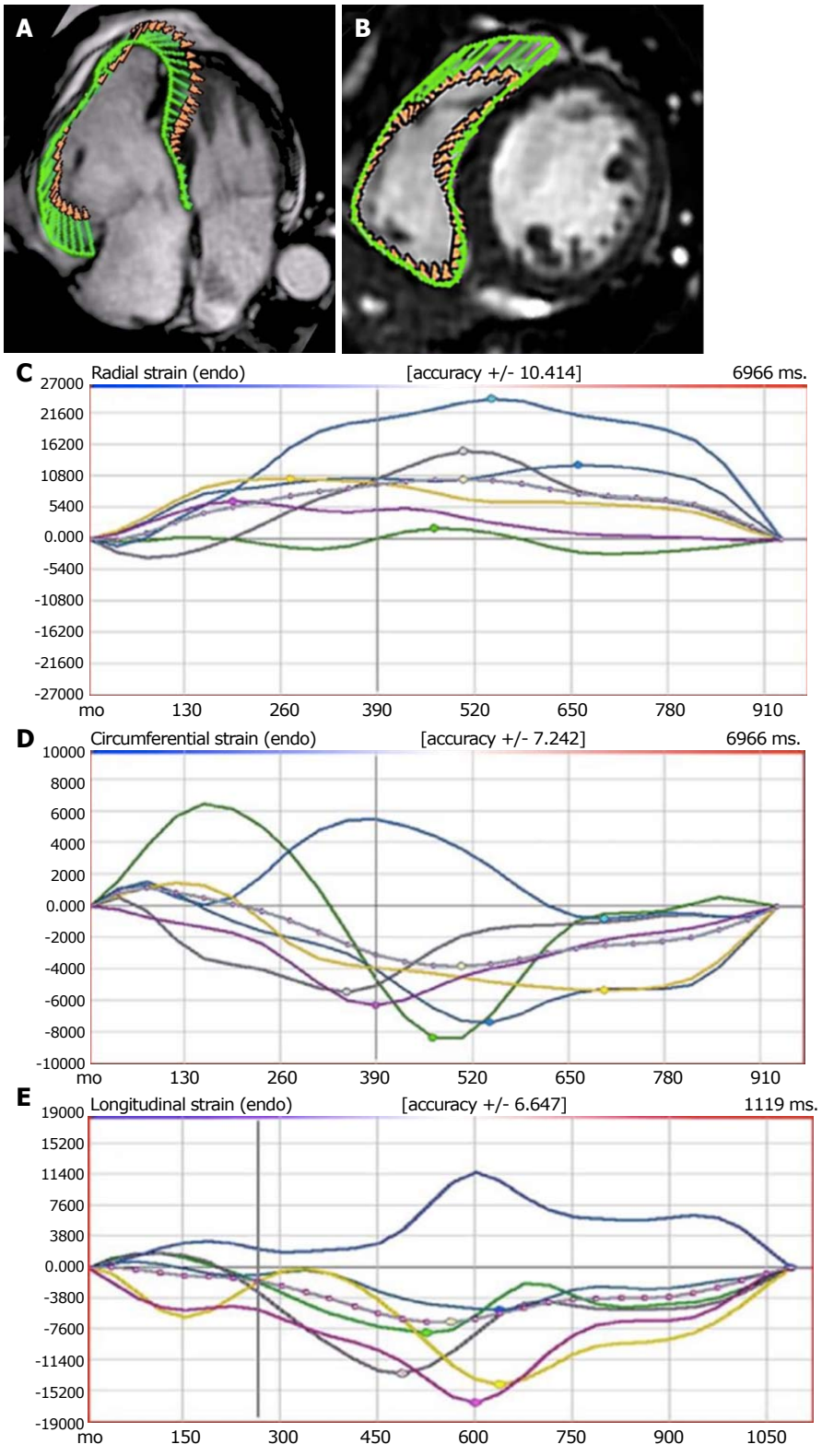
Other forms of non-ischemic cardiomyopathy

Myocardial strain has proven to be a valuable tool in early identification, staging and risk stratification of several forms of non-ischemic cardiomyopathy. In patients with hypertrophic cardiomyopathy (HCM), a direct correlation between strain parameters and the presence of LGE has been repeatedly proven, being the presence of replacement fibrosis associated to a reduction in CS[40,41]. However, intramural strain has demonstrated to be reduced in more hypertrophied segments compared to the non-hypertrophied ones regardless to the presence of LGE, proving myocardial scarring not to be the only determinant of regional contractile dysfunction[42].

Global and regional right ventricular (RV) strain parameters have shown to be impaired in patients with overt arrhythmogenic right ventricular cardiomyopathy (ARVC) regardless to RV dimensions and function[43,44]. In a study comparing RV strain parameters in 32 patients matching the task force criteria for ARVC but with no or only minor CMR criteria, to 32 patients with idiopathic RV outflow tract premature ventricular contractions and 32 healthy volunteers, we found that RV GLS, GCS and GRS were all significantly reduced in the ARVC group. In particular, a RV GLS > -23.2% was able to identify 88% of ARVC patients without definite CMR criteria showing the incremental value of CMR-FT over conventional CMR imaging in early detection of the disease (Figure 3)[45].

In the same direction, strain parameters have shown to be impaired in patients with acute or previous myocarditis and preserved LVEF regardless to the presence of LGE confirming the higher sensitivity of CMR-FT in identifying contractile impairment at a subclinical stage[46,47]. In patients affected by LV non-compaction, we have found that subclinical impairment of myocardial deformation, occurs early in the natural history of the disease, being noticeable since the pediatric age with e reduction in all global strain parameters while overt LVEF reduction tends to manifest only later in adulthood[48]. In this regard, CMR-FT may be used to early detect cardiac involvement in systemic diseases or during administration of drugs with potential cardiotoxic effects. Monitoring of cardiotoxicity during cancer therapies is currently recommended by echocardiographic evaluation of LVEF and a decline in the LVEF is needed in order to decide to suspend/modify therapy[3]. Nakano *et al*[49] have demonstrated how both GLS and GCS were significantly reduced after 6 mo of therapy with trastuzumab in 9 women treated for breast cancer. Changes in global strain parameters were correlated with changes in LVEF, however their predictive value on the development of heart failure needs to be proven[49].

Some preliminary data have shown that parameters derived from CMR-FT such as LV rotational indices are disease specific and therefore maybe be used to differentiate between cardiomyopathies. We compared LV twist and untwist rates between 20 patients with cardiac amyloidosis (CA) to 20 patients with HCM and 20 healthy controls showing how both peak LV twist and peak LV untwist rates were significantly impaired in patients with CA while peak LV twist rate was significantly increased in patients with HCM compared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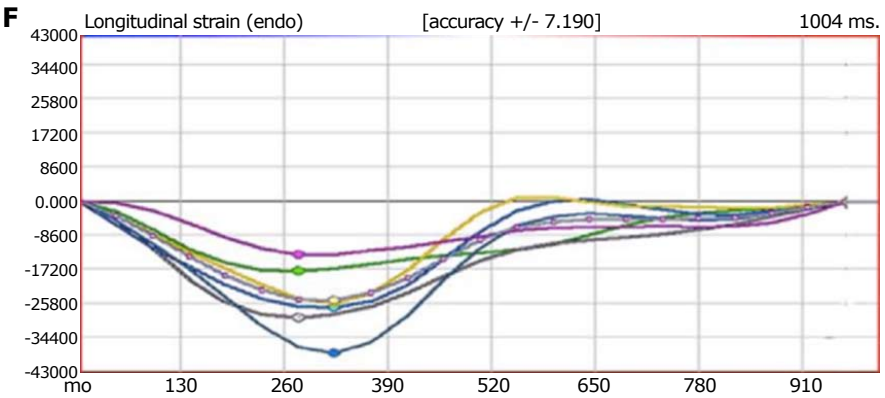

Figure 3 Example of endocardial feature tracking of the right ventricle. A: Tracking of the endocardial border of the right ventricle (RV) on a 4-chamber steady-state free precession image using a dedicated feature-tracking software; B: Example of tracking on the mid-section of a short-axis view; C: Radial; D: Circumferential; E: Longitudinal strain patterns of a patient with arrhythmogenic RV cardiomyopathy; F: Example of the RV longitudinal strain pattern of a healthy subject. Reprinted with permission from Prati *et al*[45].

to controls. Patients with HCM also presented a preserved peak LV untwist rate. The time to peak LV untwist rate was significantly prolonged both in CA and HCM compared to healthy subjects[50].

Congenital heart diseases

The follow-up of grown-up patients with congenital heart diseases (CHD) is usually based upon echocardiography, however, the poor acoustic window due to previous multiple surgical procedures or coexistence of other anatomical deformities as well the complex anatomy of repaired congenital defects represents some major limitations. For this reason, CMR imaging is increasingly becoming the imaging modality of choice for evaluation of CHD. In these terms CMR-FT derived parameters may have important clinical implications in evaluating surgical results and in early detection of complications. In patients with repaired tetralogy of Fallot (TOF), for example, a significant impairment of all global strain parameters has been described in those patients who experienced death or sustained ventricular tachycardia compared to those of similar age who did not experienced outcome events[51]. An improvement in LV GCS and GLS within 6 mo after transcatheter implantation of a pulmonic valve has also been documented in patients with repaired TOF and clinically relevant residual pulmonary regurgitation/stenosis after initial corrective surgery[52]. Moreover, RV GLS has been related to clinically relevant variables such as exercise capacity and oxygen consumption in 28 patients with repaired TOF[53]. Those findings have been further confirmed in a recent large prospective series of 372 repaired TOF patients, in which LV GCS and RV GLS independently predicted death, aborted SCD or documented ventricular tachycardia during a median follow-up of 7.4 years[54]. Similar findings have been found in 15 patients who underwent Fontan palliative intervention; GCS and GLS of the single ventricle both correlated with New York Heart Association class and peak oxygen uptake on cardiopulmonary exercise test[55]. Among patients with successful repaired coarctation of the aorta and preserved LVEF, impairment of GLS but not GCS or GRS has been associate to coexistence of LV hypertrophy[56].

Cardiac resynchronization therapy

A significant proportion of cardiac resynchronization therapy (CRT) patients may fail to reach an adequate response in terms of LVEF and HF status improvement and those patients are commonly addressed as "non-responders". Increasing efforts have been made in the last years to better select optimal candidates to CRT but also to identify the best site for LV lead implantation in order to maximize the chances of response[57,58]. For this reason, CMR has emerged as a valuable technique been able to noninvasively evaluate LV activation patterns and dyssynchrony[30,45,59]. Taylor *et al*[60] have demonstrated that CRT implantation guided by determination of segments with latest mechanical activation (defined by time to peak systolic CS) and absence of LGE is able to improve LV reverse remodeling as well as long term survival and reduce the risk of hospitalizations for heart failure. From a practical point of view, CMR derived information on scar, dyssynchrony and coronary venous anatomy maybe integrated with fluoroscopy or 3D-electroanatomical mapping systems to real-time guide LV lead placement during interventional procedures[61,62].

Atrial physiology

The application of CMR-FT techniques to the left atrium (LA) have shown to accurately characterize LA physiology compared to simple global measures such as atrial volume, area and atrial ejection fraction[63]. It has been advocated that changes in LA function precede the development of heart failure in several cardiac disorders. The development of LA dysfunction due to increased LV stiffness associated to the presence of replacement or diffuse ventricular fibrosis has been described as a potential marker of early diastolic disfunction[64].

Recent findings highlighted how there may be disease specific patterns of LA dysfunction. Patients with HCM, for example, present an increased contractile function compared with healthy controls. On the other side, patients with diastolic dysfunction and preserved LVEF have reduced atrial contractility[65]. There is some evidence that quantitative measurement of LA function may also have prognostic implications as impairment in LA strain has shown to precede development of heart failure in the general population and to improve risk stratification for cerebrovascular events in patients with atrial fibrillation[66,67].

Special populations

Analysis of CMR-FT strain parameters has been applied to patients with isolated bicuspid aortic valve (BAV) (*i.e.*, without aortic stenosis, aortic regurgitation or aortic dilatation)[68]. Interestingly, patients with "clinically normal" BAV have significant impairment of LV systolic and diastolic myocardial mechanics; furthermore, the impairment of LV systolic mechanics observed in BAV patients is independently related to the congenital abnormality of aortic valve itself. The authors postulated that the observed intrinsic impairment of LV contractility may accelerate the ominous LV remodeling pathways occurring after the development of significant aortic valve dysfunction, possibly explaining the described premature occurrence of congestive heart failure in BAV patients compared with the general population[69].

CMR-FT strain analysis has been also applied to study the adult consequences of pre-term birth. Pre-term birth interferes with the normal in-utero development of the heart, potentially leading to abnormally remodeled left ventricles. In a large study, 102 subjects have been prospectively followed since pre-term birth (gestational age = 30.3 ± 2.5 wk) to the age of 20-39 years when they underwent a CMR study. Compared to 132 subjects born at term of similar age, preterm individuals had increased LV mass proportional to the degree of prematurity and short LVs with small internal diameters and a displaced apex. Interestingly, even if LVEF was similar to subjects born at term, both longitudinal systolic (peak strain, strain rate, and velocity) and diastolic (peak strain rate and velocity) function as well as rotational (apical and basal peak systolic rotation rate, net twist angle) parameters were significantly lower[70]. Similar findings have been described by the same group affecting the RV. Pre-term subjects had smaller RV with bigger RV mass with the severity of differences proportional to gestational age. Moreover, differences in RV function were greater than those reported for the LV as subjects born pre-term had significantly lower RV ejection fraction (RVEF) with 6% of them having clear RV systolic dysfunction. In agreement with the lower RVEF, RV GLS and peak systolic strain rate were also significantly lower compared to subjects born at term[71]. The clinical implications of these findings on the potential development of overt cardiomyopathies need further prospective evaluation.

CONCLUSION

In the last years a growing amount of evidence suggests that study of cardiac function by strain analysis can accurately detect cardiac disorders at a subclinical level, improve risk stratification of patients with various cardiac conditions and potentially monitor treatment effect. In this setting, the use of CMR-FT may represent an easy and fast tool due to its applicability to routinely acquired SSFP cine images by dedicated software without need for upfront use of specific protocols. Further technical improvements able to achieve a higher level of accuracy and reproducibility in the assessment of measures and more standardization between different vendors are still required to make CMR-FT ready to use in routine clinical practice.

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ORIGINAL ARTICLE

Clinical Trials Study

Safety and efficacy of frequency-domain optical coherence tomography in evaluating and treating intermediate coronary lesions

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Abstract

AIM

To establish whether frequency-domain optical coherence tomography (FD-OCT) is safe and effective in the evaluation and treatment of angiographically-intermediate coronary lesions (ICL)

METHODS

Sixty-four patients with 2-dimensional quantitative

coronary angiography (2D-QCA) demonstrating ICL were included. OCT imaging was performed. According to predetermined OCT criteria, patients were assigned to either of 2 groups: OCT-guided percutaneous coronary intervention (PCI) or OCT-guided optimal medical therapy (OMT). The primary efficacy endpoint was to demonstrate the superiority and higher accuracy of FD-OCT compared to 2D-QCA in evaluating stenosis severity in patients with ICL. The primary safety endpoint was the incidence of 30-d major adverse cardiac events (MACE). Secondary endpoints included MACE at 12 mo and other clinical events.

RESULTS

Analysis of the primary efficacy endpoint demonstrates that 2D-QCA overestimates the stenosis severity of ICL in both the OCT-guided PCI and OMT groups, proving FD-OCT to be superior to and more precise than 2D-QCA in treating this subset of lesions. The primary safety endpoint was fully met with the incidence of 30-d MACE being nil in both the OCT-guided PCI and OCT-guided OMT groups. Incidences of secondary endpoints were found to be low in both arms, the only exception being the relatively high incidence of recurrent episodes of angina which was, however, very similar in the 2 groups.

CONCLUSION

FD-OCT is safe and effective in the evaluation and treatment of ICL. Larger studies are needed to firmly establish the efficacy and safety of FD-OCT in treating ICL across all coronary artery disease population subgroups.

Key words: Percutaneous coronary intervention; 2-dimensional quantitative coronary angiography; Frequency-domain optical coherence tomography; Intermediate coronary lesions; Optical coherence tomography

Core tip: The management of intermediate coronary lesions (ICL), defined as a diameter stenosis of 40% to 70%, remains a therapeutic dilemma. The 2-dimensional representation of the arterial lesion by angiography is limited in guiding therapy. Frequency-domain optical coherence tomography (FD-OCT) is an ultra-high resolution imaging technique that enables a detailed evaluation of the coronary lumen. Despite its undebatable superiority over angiography and other intravascular imaging techniques, the benefit of FD-OCT over its procedural risks in clinical practice is uncertain. The current study is the first to date to investigate whether FD-OCT is safe and effective in the evaluation of ICL, in guiding treatment, and optimizing procedural outcomes.

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INTRODUCTION

An intermediate coronary lesion (ICL) on angiography is defined as a luminal narrowing with a diameter stenosis ⩾ 40% but ⩽ 70%. Cardiac catheterisation laboratory assessment of a coronary lesion with intermediate severity continues to be a challenge for cardiologists both from a diagnostic and therapeutic perspective. Selective coronary angiography (CAG) is accepted as the standard for determining the presence and extent of epicardial coronary artery disease (CAD), but has obvious limitations given that it provides only a two-dimensional projection of the three-dimensional geometry of the coronary artery lumen[1,2]. Although there is little controversy regarding the usefulness of CAG in separating patients with entirely normal coronary arteries from those with severe high-grade stenotic lesions, the potential of the coronary arteriogram in predicting the hemodynamic significance of lesions that appear angiographically moderate remains controversial[3]. For this subset of obstructions, a number of adjunctive, invasive techniques have been proposed to improve the diagnostic accuracy of the coronary angiogram. Fractional-flow-reserve (FFR) represents the gold standard to evaluate ICL. Three randomized trials (DEFER, FAME-Ⅰ and FAME-Ⅱ) established FFR as the gold standard for assessing the significance of non-left main coronary artery intermediate lesions[4]. Intracoronary FD-OCT, on the other hand, is a novel, advanced imaging technique that allows ultra-high resolution evaluation of the coronary artery lumen, 10-20 times higher than the resolution obtained by intravascular ultrasound (IVUS)[5]. The superior spatial resolution of OCT could thus very well translate into meaningful clinical benefits in patients with ICL. However, while the superiority of OCT in comparison to any other available intravascular imaging modality in terms of spatial resolution is unchallenged, there is uncertainty in its risk-benefit role in routine extensive clinical practice compared to IVUS or angiography alone[6,7]. In the setting of ICL, no interventional study has to date investigated whether FD-OCT, as an invasive intracoronary imaging technique, is safe and effective in the evaluation of ICL, in guiding their treatment, and in optimizing procedural outcomes. Furthermore, the efficacy and safety of OCT in evaluating and treating ICL in patients presenting with acute coronary syndromes (ACS) as opposed to stable angina (SA) alone is unknown. We therefore designed this study aiming to explore the safety and efficacy of FD-OCT in dealing with angiographically-borderline coronary artery lesions in the

cardiac catheterisation laboratory.

MATERIALS AND METHODS

Ethics and organization

This was a single center, prospective, interventional study to investigate the safety and efficacy of FD-OCT in the evaluation and treatment of patients with ICL. The study protocol was approved by the ethics committee of the First Affiliated Hospital of Nanjing Medical University (Ethics Approval ID: 2017-SR-328). The study conforms to the Declaration of Helsinki. Each patient gave written informed consent prior to the procedure.

Study population

From August 2016 to August 2017, diagnostic CAG was performed at the interventional cardiology center of the First Affiliated Hospital of Nanjing Medical University, Nanjing, China, on patients presenting with one of the following: SA, defined as chest discomfort and associated symptoms precipitated by some form of physical activity, with minimal or non-existent symptoms at rest or after administration of sublingual nitroglycerin, unstable angina (UA, defined as chest pain occurring at rest or minimal exertion and generally lasting more than 20 min, or severe and new-onset chest pain, or chest pain manifesting in a crescendo pattern, with no biochemical evidence of myocardial damage), non ST-elevation myocardial infarction [NSTEMI, biochemical evidence of myocardial damage with no ST-elevation on electrocardiography (ECG)], or ST-elevation myocardial infarction (STEMI, biochemical evidence of myocardial damage with ST-elevation on ECG). Most of these patients had initial non-invasive testing for CAD with either Exercise Stress Test or Coronary Computed Tomography Angiography. Patients of all ages in whom assessment by 2D-QCA demonstrated ICL (considered as lesions with an angiographic stenosis severity of $\geqslant$ 45% but < 75%), and who consented to undergo further assessment with OCT, were enrolled in the study to determine whether they would benefit from PCI or OMT. Sixty-four patients with angiographically-demonstrated ICL consented to proceed with imaging. Based on the OCT findings, the patients were assigned to one of 2 arms: OCT-Guided PCI or OCT-Guided OMT. Predetermined OCT criteria used to decide which patient to assign to which arm were as follows: patients with an ICL atherosclerotic plaque burden > 76%, or a minimum luminal area (MLA) < 2.6 mm^2, or in whom unstable plaque factors existed (endocardial discontinuity, or a fibrous cap thickness < 65 μm, or a large lipid core > 180 degrees, or evidence of macrophage aggregation) were assigned to the PCI arm. On the other hand, patients with a plaque burden $\leqslant$ 76%, and with a MLA $\geqslant$ 2.6 mm^2, and in whom OCT showed no features of plaque instability were assigned to the OMT group. The inclusion criteria for this study were only those participants in whom diagnostic CAG and 2D-QCA demonstrated ICL and who consented to undergo further evaluation with OCT imaging. Exclusion criteria were subjects presenting with cardiogenic shock, acute stroke, renal dysfunction, left main stem ICL, and acute or chronic total occlusion coronary lesions.

Study endpoints

The primary efficacy endpoint of the study was to demonstrate that FD-OCT is superior to and more accurate than 2D-QCA alone in evaluating the degree of stenosis in patients with ICL. The primary safety endpoint was defined as the incidence of 30-d MACE composed of cardiac death, peri-procedural myocardial infarction (MI), acute stent thrombosis, emergency coronary artery bypass graft, significant vessel dissection or perforation, cerebrovascular accident and major vascular complications in both the OCT-guided PCI and OCT-guided OMT groups. Secondary end points were the incidence of MACE at 12 mo, plus recurrent episodes of angina, repeat hospitalisation, major bleeding events, minor bleeding episodes (defined as minimal amount of bleeding, for example bruising, bleeding gums and oozing from injection sites, not requiring intervention or treatment), stroke and heart failure. All outcomes were defined in keeping with the Academic Research Consortium recommendations[8].

Quantitative coronary angiography imaging

2D-QCA measurements of the ICL were performed offline using an automated software. These were done on image sequences adequately filled with contrast and when the vessel was not foreshortened. Calibration was performed on the contrast filled segment of the guiding catheter.

OCT image acquisition and analysis

OCT imaging was performed using a FD-OCT system (C7-XR OCT Intravascular Imaging System, St. Jude Medical, St. Paul, MN, United States). The radial approach was used in most patients (87%) for CAG and OCT imaging. Weight-adjusted, unfractionated heparin or bivalirudin was administered for anticoagulation. After placement of the guiding catheter (6 Fr) into the coronary ostium, a standard percutaneous transluminal coronary angioplasty guide wire was advanced into the coronary artery and the lesion was crossed. The C7 Dragonfly™ OCT catheter was then advanced over the wire. Once the catheter was positioned distal to the lesion, it was pulled backed manually at a speed of 15 mm/s. All images were acquired using a non-occlusive technique with manual injection of iso-osmolar iodixanol (Visipaque™ by GE Healthcare) contrast to clear the vessel of blood. OCT image analysis scrutinized serial cross-sectional images of the vessel at 1 mm intervals using the Light Lab Imaging offline software.

Measurements

Coronary artery parameters measured by 2D-QCA

Table 1 Baseline characteristics of the optical coherence tomography study population

Variable	Overall (n = 64)	OCT-guided PCI (n = 38)	OCT-guided OMT (n = 26)	P-value
Age (yr)	63.17 ± 9.68	63.42 ± 9.88	62.81 ± 9.56	0.806
Male (%)	43 (67.2)	25 (65.8)	18 (69.2)	0.773
Diabetes mellitus (%)	10 (15.6)	7 (18.4)	3 (11.5)	0.693
Hypertension (%)	39 (60.9)	22 (57.9)	17 (65.4)	0.546
Discharge treatment				
Aspirin (%)	64 (100)	38 (100)	26 (100)	1
P2Y12 inhibitor (%)	59 (92.2)	38 (100)	25 (96.1)	0.406
Statin (%)	64 (100)	38 (100)	26 (100)	1
Beta-blocker (%)	29 (45.3)	19 (50)	10 (38.5)	0.362
ACE- I /ARB (%)	33 (51.6)	23 (60.5)	10 (38.5)	0.083
CCB (%)	24 (37.5)	13 (34.2)	11 (42.3)	0.511
Nitrates (%)	36 (56.2)	21 (55.3)	15 (57.7)	0.847
Admission diagnosis				0.068
Stable angina (%)	7 (10.9)	4 (10.5)	3 (11.5)	
Unstable angina (%)	53 (82.8)	34 (89.5)	19 (73.1)	
NSTEMI (%)	2 (3.1)	0 (0)	2 (7.7)	
STEMI (%)	2 (3.1)	0 (0)	2 (7.7)	
ICL vessel				0.671
LAD (%)	37 (57.8)	21 (55.3)	16 (61.5)	
LCX (%)	12 (18.8)	6 (15.8)	6 (23.1)	
RCA (%)	15 (23.4)	10 (26.3)	5 (19.2)	

Data are expressed as mean ± SD and n (%), or median and 25th and 75th percentiles, for non-normal distribution. OCT: Optical coherence tomography; PCI: Percutaneous coronary intervention; OMT: Optimal medical therapy; ACE: Adverse cardiac events; ARB: Angiotensin receptor blockers; NSTEMI: Non ST-segment elevation myocardial infarction; STEMI: ST-segment elevation myocardial infarction; ICL: Intermediate coronary lesions; LAD: Left anterior descending; LCX: Left circumflex; RCA: Right coronary artery.

and FD-OCT in the OCT-guided PCI and OCT-guided OMT groups were the following: Reference area (RA), Minimum Luminal Area (MLA) and % Area Stenosis (AS), from which appropriate statistical analysis was performed.

Statistical analysis

No statistical sample-size calculation was undertaken in this study as this was a pioneering experience of our center in terms of use of intracoronary OCT imaging to assess ICL leading to several patients not consenting to the OCT procedure, hence automatically reducing our sample size, and given the time restriction of the current study to 1 year duration which further limits the number of subjects that could be included in the study, statistical calculation of sample size to achieve a reasonable statistical power would have been futile. Furthermore, no recently published findings from studies with a similar clinical design could be found to enable statistical determination of what sample size of subjects per group is needed to answer the research question. An independent statistician performed the statistical analysis. Continuous variables were expressed as mean ± SD and categorical variables as percentage and counts. Calculations and statistical analyses were performed by using the SPSS 19.0 software (SPSS, Statistics, IBM, United States). The Chi-square or Fisher exact test or χ^2 correction test for continuity performed on categorical variables. Continuous variables were tested using the Mann-Whitney U test, student's t test and Wilcoxon rank-sum test. A P-value of < 0.05 was considered as statistically significant.

12-mo follow-up

All patients were individually followed up for a total period of 12 mo to record the incidence of MACE, defined as the occurrence of any one or more of the following: death, recurrent MI, stent thrombosis or repeat revascularization of the target lesion. Other clinical events recorded during this 12-mo period were the incidences of recurrent episodes of angina, repeat hospitalisation, stroke, heart failure and bleeding events if any. All clinical events were recorded using a clinical report form and evaluated independently by a blinded clinical events committee.

RESULTS

Baseline characteristics

A total of 64 patients were included in the study to proceed with OCT after diagnostic angiography and 2D-QCA demonstrated an angiographically-intermediate coronary lesion. Following OCT imaging and in accordance with the predetermined OCT criteria mentioned above, 38 patients (59.4%) were assigned to the PCI arm, and the other 26 patients (40.6%) to the OMT arm (Table 1). Our study population comprised 43 males (67.2%) and 21 females (32.8%), with an overall mean age of 63.17 ± 9.68 years. 39 patients (60.9%) suffered from hypertension, 10 patients (15.6%) from diabetes, and none reported any bleeding disorder. 53 patients (82.8%) presented with UA, 7 (10.9%) with stable angina (SA), while the NSTEMI and STEMI presentations comprised only 2 patients each (3.1%). The left anterior descending artery comprised

Table 2 Two-dimensional quantitative coronary angiography findings pre-optical coherence tomography in the percutaneous coronary intervention and optimal medical therapy groups

Variable	OCT-guided PCI (n = 38)	OCT-guided OMT (n = 26)	P-value
Reference area, mm^2	7.91 (5.61-10.45)	7.97 (6.01-11.16)	0.538
Minimum luminal area, mm^2	1.97 (1.37-2.80)	2.40 (1.73-3.82)	0.029
Area stenosis %	74.02 ± 6.43	67.77 ± 6.44	0.001

Data are expressed as mean ± SD and n (%), or median and 25th and 75th. Percentiles for non-normal distribution. OCT: Optical coherence tomography; PCI: Percutaneous coronary intervention; OMT: Optimal medical therapy.

Table 3 Frequency-domain optical coherence tomography findings in the percutaneous coronary intervention and optimal medical therapy groups

Variable	OCT-guided PCI (n = 38)	OCT-guided OMT (n = 26)	P-value
Reference area mm^2	9.00 (7.56-11.21)	9.32 (7.73-12.14)	0.507
Minimum luminal area mm^2	2.44 (1.93-3.15)	3.43 (2.61-4.72)	0.001
Area stenosis %	72.22 ± 7.39	61.87 ± 7.51	< 0.001

Data are expressed as mean ± SD and n (%), or median and 25th and 75th. Percentiles for non-normal distribution. OCT: Optical coherence tomography; PCI: Percutaneous coronary intervention; OMT: Optimal medical therapy.

most of the ICL (57.8%), followed by the right coronary artery (23.4%) and circumflex artery (18.8%). The mean post-procedural in-hospital stay was 3.0 ± 0.7 d. Discharge treatment was similar in both arms with 100% prescription of aspirin, and 100% and 96.1% prescription of P2Y12 inhibitors in the PCI and OMT groups respectively.

Correlation of admission diagnosis with OCT findings and treatment modality

Of the 38 patients in the PCI group, the vast majority of them (34, 89.5%) presented with UA, only 4 (10.5%) with SA, and none with NSTEMI or STEMI (Table 1). On the other hand, out of the 26 patients treated with OMT, most of them (19, 73.1%) were also admitted with UA, while the rest were divided between SA (3, 11.5%), NSTEMI (2, 7.7%) and STEMI (2, 7.7%). UA was therefore, by far the most common admission diagnosis in both the PCI and OMT groups. Furthermore, from the UA admission subgroup of 53 patients, 34 (64.1%) were treated with PCI while the rest (19, 35.9%) were treated with OMT, while in the SA subgroup of 7 patients, 4 (57.1%) were managed interventionally, and the rest (3, 42.9%) medically. On the other hand, the 4 (6.2%) patients presenting with NSTEMI and STEMI combined were all treated with OMT after OCT imaging was performed.

2D-QCA findings

Pre-OCT 2D-QCA findings are summarized in Table 2. Retrospective analysis of parameters measured by 2D-QCA showed the following: The median RA as obtained from 2D-QCA was 7.97 (6.01-11.16) mm^2 in the OMT arm compared to 7.91 (5.6-10.45) mm^2 in the PCI arm (P = 0.538). Similarly, the median MLA measured by 2D-QCA was also comparatively larger in the OMT [2.40 (1.73-3.82) mm^2] *vs* the PCI group [1.97 (1.37-2.80) mm^2] (P = 0.029). The mean % AS was less severe (67.77% ± 6.44%) in the OMT as opposed to 74.02% ± 6.43% in the PCI arm (P = 0.001).

FD-OCT findings

These findings are summarized in Table 3. All lesions were suitable for OCT imaging analysis, which revealed a higher mean stenosis severity (mean % AS) of the ICL in the PCI group (72.22% ± 7.39%) compared to the OMT group (61.87% ± 7.51%) (P < 0.001). The median MLA measured by OCT was also smaller in the PCI [2.44 (1.93-3.15) mm^2] compared to the OMT arm [3.43 (2.61-4.72) mm^2] (P = 0.001), while there was no significant difference between the median RA obtained in the PCI *vs* the OMT arm (P = 0.507). Furthermore, the ICL in all the patients comprising the PCI group demonstrated either features of plaque instability, or a plaque burden exceeding 76%.

Efficacy assessment

OCT was successfully performed and well-tolerated in all of the intervened patients. The primary efficacy endpoint was met by comparing the mean RA, MLA and AS values obtained by 2D-QCA analysis with similar parameter values from OCT imaging (Table 4). Our results clearly demonstrate that 2D-QCA overestimates the stenosis severity of the ICL both in the OCT-guided PCI and OMT groups. In the PCI group, the mean AS was 72.22% ± 7.39% as assessed by OCT, compared to 74.02% ± 6.44% by 2D-QCA (P = 0.027). In the same group, the mean MLA was found to be 2.58 ± 1.04 mm^2 by OCT as opposed to 2.14 ± 1.00 mm^2 by 2D-QCA analysis (P < 0.001). Similarly, the mean RA was 9.39 ± 3.28 mm^2 by OCT compared to 8.16 ± 3.24 mm^2 by 2D-QCA evaluation (P < 0.001). In the OMT group, similar results were obtained in that 2D-QCA assessment demonstrated a comparatively smaller

Table 4 Two-dimensional quantitative coronary angiography vs frequency-domain optical coherence tomography findings

Group	2D-QCA	FD-OCT	*P*-value
Reference area, mm^2			
OCT-guided PCI	8.16 ± 3.24	9.39 ± 3.28	< 0.001
OCT-guided OMT	7.97 (6.01-11.16)	9.32 (7.73-12.14)	0.005
Minimum luminal area mm^2			
OCT-guided PCI	2.14 ± 1.00	2.58 ± 1.04	< 0.001
OCT-guided OMT	2.40 (1.73-3.82)	3.43 (2.61- 4.72)	< 0.001
Area stenosis %			
OCT-guided PCI	74.02 ± 6.44	72.22 ± 7.39	0.027
OCT-guided OMT	67.77 ± 7.31	61.87 ± 7.51	< 0.001

Data are expressed as mean ± SD and *n* (%), or median and 25th and 75th. Percentiles for non-normal distribution. 2D-QCA: Two-dimensional quantitative coronary angiography; FD-OCT: Frequency-domain optical coherence tomography; PCI: Percutaneous coronary intervention; OMT: Optimal medical therapy.

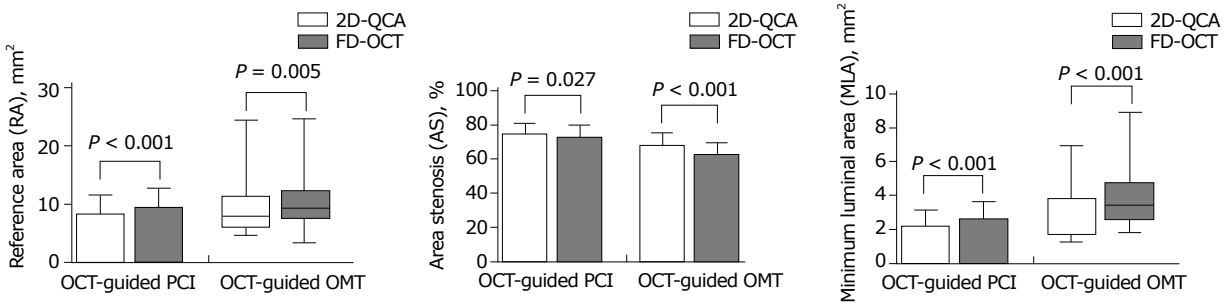

Figure 1 Box plot diagrams comparing reference area, minimum luminal area and % area stenosis parameters obtained from two-dimensional quantitative coronary angiography and frequency-domain optical coherence tomography imaging in the optical coherence tomography-guided percutaneous coronary intervention and optical coherence tomography-guided optimal medical therapy groups. 2D-QCA: Two-dimensional quantitative coronary angiography; FD-OCT: Frequency-domain optical coherence tomography; PCI: Percutaneous coronary intervention; OMT: Optimal medical therapy.

mean RA (P = 0.005) and mean MLA (P < 0.001), thereby leading to an overestimation of the mean % AS by 2D-QCA in comparison with FD-OCT (67.77% ± 7.31% *vs* 61.87% ± 7.51%), (P < 0.001). The results of the efficacy assessment of OCT compared to 2D-QCA in evaluating the stenosis severity of ICL were therefore statistically significant as illustrated by the box plot diagrams in Figure 1.

Safety assessment

No procedural complications were observed, including the no-reflow phenomenon, acute vessel occlusions, coronary vasospasm, angiographically-detectable dissections, thrombi formation or embolic phenomena. Transient chest discomfort during the procedure was rare, with no significant ECG changes. Furthermore, none of the patients in the 2 groups developed acute kidney injury following the procedure. There were also no serious in-hospital post-procedural adverse events noted. The primary safety end-point (incidence of MACE at 30 d post-procedure) was fully met in both groups, with none of the 64 patients experiencing any of the following: Cardiac death, post-procedure MI, acute stent thrombosis, significant vessel perforation or dissection, emergent revascularization, major vascular complications or cerebrovascular accidents. However, given the relatively small sample size of this study, the above results pertaining to the 30-d MACE primary safety end-point should be interpreted with caution in the current context of this study.

Clinical outcomes at 12-mo follow-up

Follow-up was undertaken in person so as to achieve optimal subjective evaluation, after each of the 64 patients was telephonically informed of his/her follow-up date. None of the patients were lost to follow up. At 12 mo, no death, thrombosis, heart failure, cerebrovascular accidents and major bleeding events was observed in either group. Only 1 recurrent MI (2.6%) was noted in the OCT-guided PCI group that had no relation with the target vessel (Table 5), while none was recorded in the OCT-guided OMT group. With regards to the rates of target lesion revascularization, no significant difference (2.6% *vs* 0%) was noted between the 2 groups. Repeat episodes of angina was the only most frequent event observed, with 13 (34.2%) patients in the PCI arm reporting recurrent chest pain, compared to 8 (30.1%) patients in the OMT arm. The incidences of the remaining 2 secondary endpoints (repeat hospitalization and minor bleeding events) were also low and similar in both groups, making the overall comparison of safety clinical outcomes between the OCT-Guided PCI and OCT-Guided OMT groups not statistically significant (P = 0.634) (Figure 2).

Table 5 Clinical outcomes at 12 mo follow-up *n* (%)

Variable	OCT-guided PCI (*n* = 38)	OCT-guided OMT (*n* = 26)	*P*-value, overall = 0.634
Myocardial infarction	1 (2.6)	0	1
Target lesion revascularisation	1 (2.6)	0	1
Re-angina	13 (34.2)	8 (30.8)	0.603
Re-hospitalisation	3 (7.9)	2 (7.7)	0.920
Minor bleeding events	5 (13.2)	1 (3.8)	0.427

Data are expressed as mean ± SD and *n* (%), or median and 25th and 75th. Percentiles for non-normal distribution. OCT: Optical coherence tomography; PCI: Percutaneous coronary intervention; OMT: Optimal medical therapy.

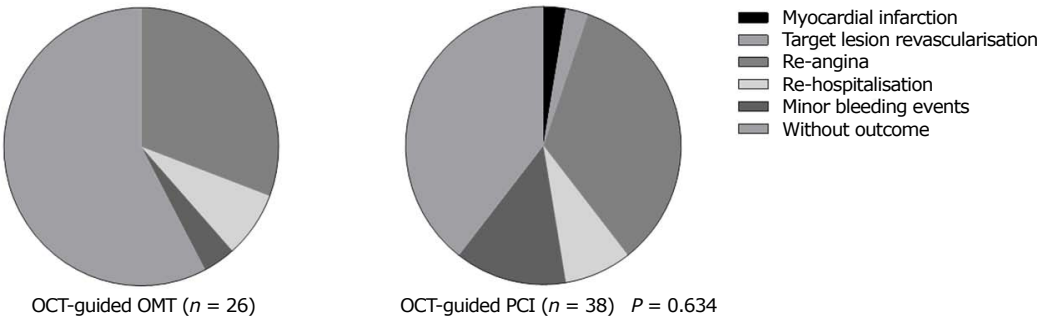

Figure 2 Pie charts comparing outcome at 12 mo between the optical coherence tomography-guided percutaneous coronary intervention and optical coherence tomography-guided optimal medical therapy groups. OCT: Optical coherence tomography; PCI: Percutaneous coronary intervention; OMT: Optimal medical therapy.

DISCUSSION

The present study is the first to date to explore the safety and efficacy of FD-OCT in evaluating and guiding the treatment of patients with ICL. Several studies have analyzed the role of OCT in guiding PCI and evaluating post-PCI results. However, none has thus far investigated the efficacy and safety of OCT in the evaluation and optimal treatment of angiographically-borderline coronary artery lesions.

The statistically significant results demonstrated by our study as reported in Table 4 and Figure 1 prove that FD-OCT is superior to and more accurate than 2D-QCA in evaluating stenosis severity in ICL owing to its superior spatial resolution, thus meeting our primary efficacy end-point. FD-OCT provides a more accurate evaluation of stenosis severity in ICL, and hence positively influences physician decision-making regarding whether to proceed with PCI or to treat the lesion medically. In addition, other parameters such as % plaque burden and unstable plaque morphology can be clearly delineated and measured by FD-OCT, crucial in influencing physician decision-making in the setting of ICL. From our results of % mean AS by OCT in Table 3 (72.22% ± 7.39% in the PCI and 61.87 ± 7.51 in the OMT group), we may conclude that it is beneficial to proceed with OMT as opposed to PCI in any ICL with an average % AS of less than 62% on FD-OCT imaging, provided that plaque stability is not compromised and the plaque burden is ⩽ 76%. These results also lead us to conclude that lesions with an average % AS greater than 72%, or demonstrating unstable plaque morphology features, or a plaque burden exceeding 76% are likely to benefit more from PCI than OMT. For ICL with a % AS between 62% and 72%, the decision whether to proceed with OMT or PCI should be taken on an individual basis, taking into account whether unstable plaque factors exist and the % of atherosclerotic plaque burden. To the best of our knowledge, the only study that compared 2D-QCA directly with OCT in the assessment of coronary artery lesion dimensions was conducted by Mazhar *et al*[9]. It showed there is a good correlation between QCA and OCT for measurement of proximal and distal reference diameters of a lesion, but the MLD was underestimated by QCA. The latter findings are in keeping with the results of our study. However, the aim of this study did not set its focus on the ICL subset of narrowings, but instead considered a whole range of coronary stenoses from moderate to severe.

The results of our study also demonstrate that the primary safety end-point (incidence of 30-d MACE) was fully met, with none of the 64 subjects experiencing any serious post-procedural adverse events such as cardiac death, post-procedure MI, acute stent thrombosis, significant vessel perforation or dissection, emergent revascularization, major vascular complications or cerebrovascular accidents. Therefore, major complications following intracoronary OCT study of ICL are highly unlikely, which can be minimized using a careful procedural scheme. Furthermore, no patients developed acute kidney injury during their in-hospital stay despite the additional amount of contrast media used during the FD-OCT procedure. However, these

results evaluating safety end-points of the current study should be interpreted with appropriate caution, given the relatively small sample size. In addition, other safety end-points such as duration of the procedure, fluoroscopy time, amount of contrast media used, and radiation dose delivered were not formally evaluated by our study.

Evaluation of the secondary end-points showed that at 12 mo, up to one-third of patients in each group experienced recurrent episodes of chest pain, the most frequent event of the secondary end-points (Table 5). Whether repeat episodes of angina has any relation to the intervened or non-intervened ICL is a difficult question to answer, and therefore cannot be used on its own as a measure to evaluate success or failure of the FD-OCT procedure. Factors such as the patient' s subjective interpretation of angina, progression of disease, de novo coronary lesions, poor compliance to anti-platelet therapy are factors that could account for recurrence of angina episodes in these patients. However, with the exception of the relatively high incidence of repeat episodes of angina in both the OCT-guided PCI and OCT-guided OMT groups, incidence of the other secondary end-points such as MACE at 12 mo and other adverse clinical events during that time period were nil or similarly very low (Figure 2), leading to the comparison of safety clinical outcomes between the 2 groups being statistically not significant. This proves that FD-OCT is a safe technique as it did not itself contribute to a worse clinical outcome whether the patient was treated with PCI or OMT following intracoronary OCT imaging.

Further deductions can be made from the results of our study. 53 of the 64 patients (82.8%) presented with UA, only 7 (10.9%) patients presented with SA, while NSTEMI and STEMI presentations accounted for 2 patients each (6.2% combined) (Table 1). From these findings, it can be inferred that patients with ICL have a high likelihood of presenting with symptoms of UA and are at increased risk of acute coronary events. OCT thus presents as a crucial investigative tool to decide whether to treat the ICL in these patients interventionally or conservatively, depending on the OCT findings of % AS, plaque instability and % plaque burden. Out of the 53 patients who presented with UA, there was a significant difference between the percentage of subjects treated with PCI (64.1%) compared to OMT (35.9%), showing that OCT is determinant in guiding optimal therapy of the ICL found in this subset of ACS patients. With regards to the SA subgroup of 7 patients, 4 (57.1%) were treated with PCI, while the remaining 3 (42.9%) were managed medically; however, the number of patients comprising this subgroup was too small to draw any definitive conclusions.

On the other hand, only 4 (6.2%) patients in our study presented with either a STEMI or NSTEMI, all of whom were treated with OMT post-OCT. In this minority of patients, no indications were found to proceed with PCI based on the predetermined OCT criteria or, the pathological hallmark in these patients comprised the entity of myocardial infarction with non-obstructive coronary arteries (MINOCA)[10]. The small number of patients comprising this subgroup limits our ability to conclude whether OCT is safe and effective in the setting of an acute myocardial infarction (AMI). However, it does importantly demonstrate that patients with AMI not always require PCI, but can be managed conservatively should OCT demonstrate no features of plaque instability or no significant stenosis. These deductions can potentially be linked to the findings of the recently published landmark ORBITA trial[11]. The latter indicated that among SA patients with anatomically and functionally significant coronary stenoses ($\geqslant$ 70% severity), PCI did not result in greater improvements in exercise times or anginal frequency compared with a placebo procedure, though it did resolve ischemia more effectively as ascertained by follow-up stress echocardiography, these findings requiring however to be validated in a larger randomized controlled trial. Even though the ORBITA trial did not involve the use of OCT as an imaging tool to evaluate the degree of stenosis on the coronary lesions and its aim was, in fact, to evaluate the efficacy of PCI compared with a placebo procedure for angina relief among patients with SA, it did however show that SA patients with severe coronary stenoses are not automatically candidates for PCI, as many of them can have an equally good outcome with OMT. In this setting, OCT can be of utmost value in guiding the interventionist to decide as to which of these patients will benefit more from PCI than OMT and vice-versa, based on accurate OCT assessment of stenosis severity, and other crucial parameters such as plaque instability and % of atherosclerotic plaque burden obtained from the OCT study.

Whether OCT is effective and safe in evaluating and treating ICL in patients presenting with an AMI, in whom emergency CAG shows no obstructive lesions, but instead borderline or even minimal coronary stenosis in accordance with the MINOCA entity, is an important issue. In the setting of an unstable patient with an AMI undergoing emergency CAG, the efficacy and safety of FD-OCT with regards to the optimal outcome for the patient is debatable. FD-OCT can be time-consuming in less experienced hands, requires additional instrumentation and increased doses of contrast agent and anticoagulants. On the other hand, it does provide vital information on plaque stability or instability of the ICL suspected to be the infarct-related lesion, crucial in aiding decision whether to proceed with PCI or OMT in the AMI setting. In their study on the OCT evaluation of intermediate coronary lesions in patients with NSTEMI, Bogale *et al*[12] showed that OCT imaging confirmed the lack of severe anatomical stenosis in most patients but also identified coronary lesions with unstable features. On the other hand, Takahashi *et al*[13] showed in their case report on an OCT-based diagnosis

in a patient with STEMI and non-obstructive coronary arteries that OCT may provide a clue to identifying the underlying pathophysiological process especially in patients with MINOCA caused by coronary disorders. Another case report by Shah and Ing on the role of OCT in managing patients with STEMI demonstrated that OCT offers significantly improved resolution over IVUS, and hence should be used for assessment of the infarct-related lesion, especially in cases where the underlying pathophysiology is not clearly evident. The authors however pointed out that performing such an investigation requires additional vessel instrumentation and increased contrast use[14]. Both of these case reports and the clinical study by Bogale *et al*[12] did not shed any light though on how safe and effective OCT is in dealing with the ICL subset of lesions in a patient presenting with an AMI.

The only 3 efficacy clinical studies conducted so far on the OCT evaluation and treatment of patients with angiographically-borderline coronary lesions mostly focused on comparing OCT with FFR, but none investigated how effective OCT is as a stand-alone technique in dealing with ICL in the cardiac catheterization laboratory[15-17]. Furthermore, the OPUS-CLASS, CLI-OPCI and ILUMIEN Ⅰ studies clearly show the advantages conferred by OCT in providing reliable quantitative measurements of coronary artery dimensions, improving clinical outcomes of patients undergoing PCI, and positively influencing both physician decision-making and procedural strategy pre and post-PCI respectively[18-20], while the ILUMIEN Ⅱ, OPINION and CLI-OPCI Ⅱ studies all investigated the efficacy of OCT in assessing stent deployment and expansion[21-23]. Despite highlighting the clinical and interventional benefits of OCT, none of these trials however explored the efficacy of this ultra-high resolution intracoronary imaging procedure in the ICL subset of stenosis alone.

On the other hand, whether the theoretical advantages of OCT also translate into safety benefits has been evaluated by only a limited number of clinical trials to date. A pioneering experience by Imola *et al*[24] on the safety of FD-OCT to guide decision making in PCI, showed OCT guidance to be safe. Furthermore, a multicenter study by Yoon *et al*[25] demonstrated that FD-OCT provides fast and reliable resolution images of the coronary artery, and the pullback can be safely performed over long segments of the artery without serious adverse events. The only 2 published randomised trials to have compared OCT-guided PCI with angiography-guided PCI (ILUMIEN Ⅲ and DOCTORS) both showed that OCT-guided PCI was safe and did not increase peri-procedural complications[26,27]. Three other studies successfully demonstrated the safety and also the efficacy of intravascular OCT for coronary artery evaluation in the clinical setting, none of which however focused on the ICL subset of coronary narrowings[28-30]. So despite demonstrating intracoronary OCT to be a safe procedure, the question as to whether the above studies would have reached similar conclusions in dealing with ICL alone cannot be answered. Therefore, in our opinion, the present study is of significant value as it is the first one ever to investigate both the efficacy and safety of FD-OCT in evaluating and guiding the optimal treatment of patients with angiographically-borderline coronary artery lesions.

Study limitations

The present study has certain noteworthy limitations. First, it was a single-center study conducted over a 1 year period with a relatively sample size which was nevertheless reasonable considering the time duration of the study and the selection criteria of the patient population being studied. Because of the small sample size, the study lacked statistical power to determine whether the more accurate mean % AS measurement obtained by FD-OCT contrasted significantly with that obtained by 2D-QCA, even though a statistically significant difference was actually observed. In addition, as explained in the methodology section, no statistical sample-size calculation was undertaken in this study. Second, this was a non-randomized study as the subjects were assigned to either arm based on specific predetermined OCT criteria. Confounding and bias resulting from non-randomization could potentially affect the results of the study. In view of the favorable experience of this study, we intend to conduct a multicenter clinical trial which is registered in ClinicalTrials.gov (NCT03229993), with a larger sample size and a longer clinical study and follow-up time duration.

CONCLUSION

Our study clearly demonstrates that in evaluating and treating patients with angiographically-intermediate coronary lesions, OCT is a safe and effective ultra-high resolution imaging technique. It is superior to and more accurate than visual diagnostic CAG and 2D-QCA, hence allowing better evaluation and treatment of the ICL subset of coronary narrowings. In experienced hands, major procedural complications are rare, as are short to medium-term MACE. The data from our study warrant a large-scale randomized controlled trial to establish if OCT is equally safe and effective in the evaluation and treatment of ICL in patients presenting with the whole spectrum of ACS and SA, and whether proceeding with OCT imaging in these subjects does actually improve clinical outcomes in comparison with decisions based on angiographic guidance alone.

ARTICLE HIGHLIGHTS

Research background

Conventional angiography and other adjunct coronary imaging techniques such as fractional flow reserve and intravascular ultrasound have in the past been used to evaluate the anatomical and physiological significance of coronary lesions considered to fall in the intermediate category (40%-70%). However, to this date, no study has been conducted to assess the safety and efficacy of

frequency-domain optical coherence tomography (FD-OCT) in the evaluation and treatment of angiographically-intermediate coronary lesions (ICL). Our interventional team wanted to explore if FD-OCT could assist us in our daily practice to better evaluate and treat this subset of coronary lesions, compared to when angiographic-guidance alone is used to guide decision making in this clinical setting.

Research motivation

The current study addresses a very important topic in interventional cardiology, as it focuses specifically on the management of ICL. Cases of coronary lesions considered to be borderline are frequently under- or over-treated, hence providing a reliable tool for the accurate assessment of these lesions is of great importance to their appropriate management. Coronary angiography has several known limitations, including a lack of correlation between the percentage of stenosis and the lesion's physiologic importance, and considerable inter-observer variability in classifying the lesion's severity. On the other hand, percutaneous coronary intervention (PCI) has inherent risks even in the most experienced hands. The possibility of procedural complications with PCI such as coronary dissection, no reflow phenomenon, in-stent restenosis, and stent thrombosis requires accurate stratification of patients with intermediate coronary lesions to appropriate therapy. The present study explores the use of FD-OCT as an ultra-high resolution intracoronary imaging tool with regards to its safety and efficacy to accurately assess and manage intermediate coronary lesions interventionally or medically, and will spark interest for further research in this specific setting to reinforce the concept being explores.

Research objectives

Our aim in designing this study was to demonstrate that FD-OCT is a safe and effective procedure to be performed when faced with intermediate coronary artery lesions during coronary angiography in the cardiac catheterization laboratory. As this is the first study to investigate the safety and efficacy of OCT in the setting of ICL, it will pave the way for further studies (multi-center, larger sample size, longer follow-up times) to be conducted to confirm our findings, and reinforce our conclusions and recommendations. In particular, these studies are expected to have higher statistical power, with a larger sample size and a more equal representation of patients from the different coronary artery disease (CAD) population subgroups. This paper will provide investigators from across the world a platform to improve on the study design, methodology in conducting studies with similar objectives, taking into account the difficulties we encountered in this study, and the related limitations that ensued.

Research methods

With the aim in mind of elucidating whether FD-OCT was safe and effective in treating ICL, we decided to conduct the study by including patients found to have borderline lesions on angiography in our cardiac catheterization laboratory, and who consented to the OCT procedure. Patients who presented with cardiogenic shock, acute stroke, renal dysfunction, left main stem ICL, and acute or chronic total occlusion coronary lesions were excluded from the study. Patients were assigned to either of the 2 arms of the study based on specific predetermined OCT criteria. Focusing importantly on the specific aim of our study, we clearly defined our primary efficacy endpoint (demonstration of the superiority and higher accuracy of FD-OCT compared to 2D-QCA in evaluating stenosis severity in patients with ICL), primary safety endpoint [incidence of 30-d major adverse cardiac events (MACE)] and secondary endpoints (MACE at 12 mo and other clinical events), and obtained the necessary 2D-QCA and FD-OCT measurements, as well as the follow-up statistical results on MACE and other clinical outcomes. These results generated enabled an in-depth discussion and appropriate conclusions to be made. We hope that the methodology and study design used in our study will be useful in assisting investigators to design further studies with similar objectives.

Research results

The primary efficacy endpoint of our study was fully met, with statistically significant results clearly demonstrating that 2D-QCA overestimates the stenosis severity of the ICL in both the OCT-guided PCI and OMT groups. Our primary safety endpoint was also fully met, with none of the patients in the study experiencing any MACE at 30 d post-procedure. Incidences of secondary endpoints were also found to be low in both arms, the only exception being the relatively high incidence of recurrent episodes of angina which was, however, very similar in the 2 groups. Analysis of the above results gives a clear insight into the superiority of FD-OCT compared to 2D-QCA in evaluating stenosis severity of ICL, and lays a foundation on which further studies to further reinforce this finding and implement its application in clinical practice in managing patients with angiographically-borderline lesions, owing to the efficacy of the FD-OCT in this setting. The findings of the present study also highlighted the safety of this intracoronary-imaging technique in the same setting. However, these results should be interpreted with appropriate caution, given the relatively small sample size of the study, which resulted in the study lacking statistical power. In addition, patients across the different CAD population subgroups are not equally represented in this study, especially patients presenting with an AMI. Further studies are required to address these limitations from our present study, so that the safety and efficacy of FD-OCT can be extrapolated to the management of ICL in patients presenting with different categories of CAD.

Research conclusions

To this date, the efficacy and safety of FD-OCT when specifically faced with an ICL in the cardiac catheterization laboratory irrespective of the clinical presentation of the patient, was unknown. The present study provides significant insight into the topic and successfully meets the objectives laid out by its investigators. It shows that in evaluating and treating an ICL, performing FD-OCT following coronary angiography adds significant value to the assessment and management of that lesion, and is found to be a safe and effective procedure in this setting. However, further studies are required with larger sample size and higher statistical power to determine whether this statement can be applicable to patients with ICL across the different CAD population subgroups, and if OCT is equally safe and effective in treating ICL in patients presenting with an AMI, compared to those presenting with UA or SA. It is expected that this pioneering study sparks further interest amongst researchers in the field of CAD and amongst interventional cardiologists in practice to design and conduct large, multicenter clinical trials in order to obtain more reliable data that can be used to implement guidelines and positively change clinical practice, as well as provide direction for future research in this field and in the clinical setting of ICL.

Research perspectives

This study shows that 2D-QCA leads to an overestimation of lesion severity in comparison to FD-OCT, which is a prerequisite for overtreatment. On the other hand, the results show that OCT-guided decision making seems to be safe. The population with intermediate coronary lesions is largely underrepresented across different randomized trials. Therefore, despite its relatively small sample size, this prospective single center interventional study adds a lot of important data to the topic and provides a good platform for future larger multicenter clinical trials to be conducted to further reinforce the utility of FD-OCT in evaluating and treating ICL with regards to its safety and efficacy in this specific clinical setting.

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ORIGINAL ARTICLE

Observational Study

Incidence and risk factors for potentially suboptimal serum concentrations of vancomycin during cardiac surgery

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Author contributions: Cotogni P designed the study and drafted the manuscript; Barbero C participated in the study design, carried out the study and helped to draft the manuscript; Rinaldi M participated in the study design and coordination and revised it critically for important intellectual content; all authors read and approved the final manuscript.

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Abstract

AIM

To investigate the incidence and risk factors for vancomycin concentrations less than 10 mg/L during cardiac surgery.

METHODS

In this prospective study, patients undergoing cardiac surgery received a single dose of 1000 mg of vancomycin. Multiple arterial samples were drawn during surgery. Exclusion criteria were hepatic dysfunction; renal dysfunction; ongoing infectious diseases; solid or hematologic tumors; severe insulin-dependent diabetes; body mass index of < 17 or > 40 kg/m^2; pregnancy or lactation; antibiotic, corticosteroid, or other immunosuppressive therapy; vancomycin or non-steroidal anti-inflammatory drug therapy in the previous

2 wk; chemotherapy or radiation therapy in the previous 6 mo; allergy to vancomycin or cefazolin; drug abuse; cardiac surgery in the previous 6 mo; previous or scheduled organ transplantation; preoperative stay in the intensive care unit for more than 24 h; emergency procedure or lack of adequate preparation for surgery; and participation in another trial.

RESULTS

Over a 1-year period, 236 patients were enrolled, and a total of 1682 serum vancomycin concentrations (median 7/patient) were measured. No vancomycin levels under 10 mg/L were recorded in 122 out of 236 patients (52%), and 114 out of 236 patients (48%) were found to have at least 1 serum sample with a vancomycin level < 10 mg/L; 54 out of 236 patients (22.9%) had at least 5 serum samples with a vancomycin level lower than 10 mg/L. Vancomycin infusion was administered for 60 min in 97 out of 236 patients (41%). In 47 patients (20%), the duration of infusion was longer than 60 min, and in 92 patients (39%) the duration of infusion was shorter than 60 min. The maximum concentration and area under the concentration-time curve were significantly higher in patients with no vancomycin levels less than 10 mg/L ($P < 0.001$). The multivariate analysis identified female gender, body mass index (BMI) > 25 kg/m^2, and creatinine clearance above 70 mL/min as risk factors for vancomycin levels less than 10 mg/L.

CONCLUSION

Results of this study identified female gender, BMI > 25 kg/m^2, and creatinine clearance above 70 mL/min as risk factors for suboptimal vancomycin serum concentration during cardiac surgery; no relationship was found between infusion duration and vancomycin levels less than 10 mg/L. These findings call attention to the risk of facilitating the emergence of vancomycin-resistant methicillin-resistant Staphylococcus aureus strains.

Key words: Cardiopulmonary; Bypass; Surgical site infections; Vancomycin pharmacokinetics; Antibiotic therapy; Methicillin-resistant *Staphylococcus aureus*

Core tip: The aim of this study was to investigate the incidence and risk factors for vancomycin concentrations less than 10 mg/L during cardiac surgery. Over a 1-year period, 236 patients were enrolled, and a total of 1682 serum vancomycin concentrations were measured. A total of 48% of patients were found to have ⩾ 1 sample with a vancomycin level < 10 mg/L. The maximum concentration and area under the concentration-time curve were significantly higher in patients with no vancomycin levels less than 10 mg/L ($P < 0.001$). The multivariate analysis identified female gender, body mass index > 25 kg/m^2, and creatinine clearance above 70 mL/min as risk factors for vancomycin levels less than 10 mg/L.

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INTRODUCTION

Surgical site infections (SSIs) related to methicillin-resistant Staphylococcus aureus (MRSA) after cardiac surgery continue to cause substantial morbidity and mortality[1-3]. Therefore, the prevention of this feared complication, particularly in terms of antimicrobial prophylaxis, is a matter of discussion in the literature. The practice guidelines from the Society of Thoracic Surgeons on antibiotic prophylaxis in patients undergoing cardiac surgery suggests combining a β-lactam (cefazolin) with a glycopeptide (vancomycin) for antimicrobial prophylaxis in the scenario of an established "high incidence" of MRSA; a dose of 1 to 1.5 g or a weight-adjusted dose of 15 mg/kg of vancomycin administered intravenously over 1 h, with the infusion ending within 1 h from the incision of the skin, is recommended[4,5]. Likewise, the 2011 guidelines of the American College of Cardiology and the American Heart Association recommend that vancomycin should be initiated 2 h before cardiac surgery and administered by a slow infusion[6]. However, a detailed protocol of administration with dose and levels of vancomycin to reach and maintain during the surgical procedure is still not reported.

In addition, evidence highlights that in the current practice there is often a gap between the duration of administration or timing of antimicrobial prophylaxis recommended in the guidelines and what is practiced[7,8]; this may increase the risk of potentially suboptimal serum vancomycin levels during surgery, jeopardizing the efficacy of antimicrobial prophylaxis. Indeed, low serum vancomycin concentrations-lower than 10 mg/L - seem to be related with the emergence of vancomycin-resistant MRSA strains: vancomycin-resistant Staphylococcus aureus (VRSA), vancomycin-intermediate Staphylococcus aureus (VISA), and heteroresistant VISA (hVISA)[9-11]. To date, strains of VRSA, VISA, and hVISA have been reported from many countries, including the United States, Japan, Australia, France, Scotland, Brazil, Korea, Hong Kong, and others[10-12].

Our group has already analyzed intraoperative vancomycin pharmacokinetics (PK) in 236 patients undergoing cardiac surgery over a 1-year period[13]. In this study, and in the same study population, the incidence of potentially suboptimal vancomycin levels during cardiac surgery was investigated.

The primary objective of the present study was to investigate the incidence of vancomycin levels less than 10 mg/L during cardiac surgery. The secondary objective was to identify risk factors for intraoperative vancomycin levels less than 10 mg/L.

MATERIALS AND METHODS

Study design

Over a 1-year period, a prospective study was carried out in the Department of Cardiovascular Surgery of a 1200-bed tertiary care university hospital, where approximately 850 cardiac operations are performed every year. The study design has been described previously[13]. The inclusion criteria included adult patients undergoing cardiac surgery, who were receiving a single 1000 mg vancomycin dose as prophylaxis, diluted in 100 mL 0.9% NaCl solution and administered by intravenous infusion over 60 min, with a skin incision made between 16 and 120 min after the end of the vancomycin infusion, as recommended by Garey *et al*[14]. The exclusion criteria included hepatic dysfunction (bilirubin $\geqslant$ 2 mg/dL); renal dysfunction [creatinine > 1.5 mg/dL or creatinine clearance (CrCl) $\leqslant$ 30 mL/min, estimated by the Cockcroft-Gault formula]; infectious diseases that required antibiotic therapy 2 wk prior to the procedure; solid or hematologic tumors; severe insulin-dependent diabetes; a body mass index (BMI) < 17 or > 40 kg/m^2; pregnancy or lactation; antibiotic, corticosteroid, or other immunosuppressive therapy; vancomycin or non-steroidal anti-inflammatory drug therapy 2 wk prior to the procedure; chemotherapy or radiation therapy in the previous 6 mo; allergy to vancomycin or cefazolin; drug abuse; cardiac surgery in the previous 6 mo; previous or scheduled organ transplantation; a preoperative stay in the intensive care unit for more than 24 h; an emergency procedure or lack of adequate preparation for surgery; and participation in another trial.

Our protocol of antimicrobial prophylaxis is also designed for a single 1000 mg cefazolin dose, diluted in a 20 mL 0.9% NaCl solution, initiated 30 to 60 min before surgery and administered as a slow intravenous bolus. Three further doses of 1000 mg of cefazolin at 8-h intervals were given postoperatively, while no further doses of vancomycin were administered postoperatively. Since 2005, our protocol has allowed the choice to combine cefazolin with vancomycin for antimicrobial prophylaxis in patients undergoing cardiac surgery[13,15]. The rationale for using vancomycin was due to an increased prevalence of MRSA infections, which exceeded 60% hospital-wide, and to the identification of isolates in cardiac surgery patients with SSIs. The vancomycin protocol and timing of administration were chosen based upon recommendations of our Hospital Infection Control Committee and guidelines from the Society of Thoracic Surgeons[5,13,15].

A healthcare provider (*i.e.,* physician, nurse or cardiovascular technician) was required to document the exact time the antibiotic infusion was initiated, as well as anesthesiologists or cardiac surgeons who recorded the exact time of the first skin incision and skin closure.

The study protocol was reviewed and approved by our Institutional Ethics Committee (approval No. 0078553), and patients provided written informed consent before their enrollment. The work was conducted in compliance with the Institutional Review Board/Human Subjects Research Committee requirements.

Vancomycin assay and pharmacokinetic analysis

The vancomycin assay and PK analysis have been reported previously[13].Briefly, for the on-pump group, arterial samples were drawn from the arterial catheter before cardiopulmonary bypass (CPB) [end of infusion maximum concentration (C_{max}) and skin incision ($C_{incision}$)], during CPB (5, 30, 60 min after the CPB start, and subsequently every 60 min to the CPB end: C_5, C_{30}, C_{60}, C_{120}, C_{180}, and C_{240}), and after CPB [wound closure ($C_{closure}$)]. For the off-pump group, some arterial samples (*i.e.,* C_5, C_{30}, C_{60}, C_{120}, C_{180}, and C_{240}) were drawn and time-matched to the CPB period of the on-pump group.

According to the Centers for Disease Control and Prevention guidelines, the definition of SSI requires positive culture results of surgical sites or drainage from the mediastinal area or evidence of infection during surgical re-exploration or fever, sternal instability, and positive blood culture results[16]. SSIs were classified as (1) superficial (infection above the sternum with no bone involvement); (2) deep (infection involving the sternum and organ/space such as mediastinitis); and (3) leg donor site infections[16].

Statistical analysis

The receiver operator characteristic (ROC) curve analysis was used to investigate the relationship between the duration of drug infusion and the occurrence of vancomycin concentrations under 10 mg/L. PK characteristics were compared between patients with vancomycin levels constantly above 10 mg/L and patients with at least 1 vancomycin level lower than 10 mg/L using the Fisher's exact test for categorical variables and the Mann-Whitney test for continuous ones. All reported *P*-values were obtained by the 2-sided exact method, at the conventional 5% significance level. A multivariate binary logistic model was used to predict risk factors for vancomycin levels less than 10 mg/L. Data were analyzed using R 3.4.0 (The R Foundation for Statistical Computing, Vienna, Austria http://www.R-project.org). The statistical methods of this study were reviewed by R Passera, a biomedical statistician.

RESULTS

Two hundred thirty-six cardiac surgery patients were enrolled in this study. The patients' characteristics are shown in Table 1. During the study, 1682 serum vancomycin concentrations were measured, and 7 (median; range 6-9) blood samples per patient were collected. Vancomycin PK during cardiac surgery has been reported previously[13]. Out of the 1682 serum samples, vancomycin levels were lower than 10 mg/L in 443 cases, between 10 and 20 mg/L in 821 cases, between 20 and 30 mg/L in 192 cases, between 30 and

Table 1 Patients' characteristics *n* (%)

Characteristics	
Patients	236
Age, median (range)	70 (25-86)
Male gender	149 (63)
BMI, kg/m^2, median (range)	26 (18-40)
Diabetes	46 (19)
COPD	0
Hypertension	151 (64)
Smoke	28 (12)
Surgical time, min, median (range)	249 (119-593)
Surgical procedure	
CABG	72 (30.5)
Valve	113 (47.9)
CABG+Valve	34 (14.4)
Other[1]	17 (7.2)
Off-pump CABG	21 (8.9)
Left IMA	53 (22.4)
Both IMA	17 (7.2)
EUROscore add, median (range)	5 (1-6)
EUROscore log, median (range)	4.8 (1-7.74)
Mechanical ventilation, d, median (range)	7 (2-912)
ICU stay, d, median (range)	1 (1-24)
RBC transfusions, *n*, median (range)	2 (0-9)

[1]Aortic, atrial or ventricular septal defect repair, and congenital surgery. BMI: Body mass index; CABG: Coronary artery bypass grafting; COPD: Chronic obstructive pulmonary disease; EUROscore: European System for Cardiac Operative Risk Evaluation; add: Additive; log: Logistic; ICU: Intensive care unit; IMA: Internal mammary artery; RBC: Red blood cell.

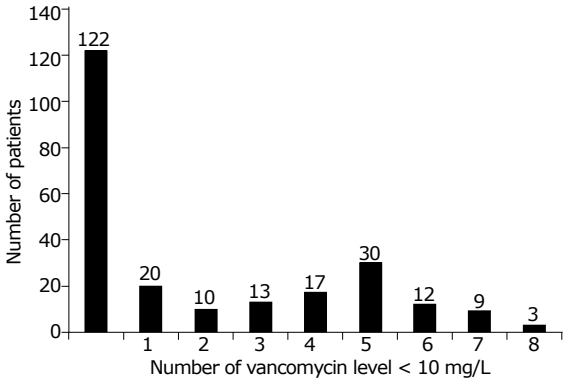

Figure 1 Distribution of patients without serum samples with a vancomycin level < 10 mg/L and of those with 1 or more serum samples with a vancomycin level < 10 mg/L during cardiac surgery.

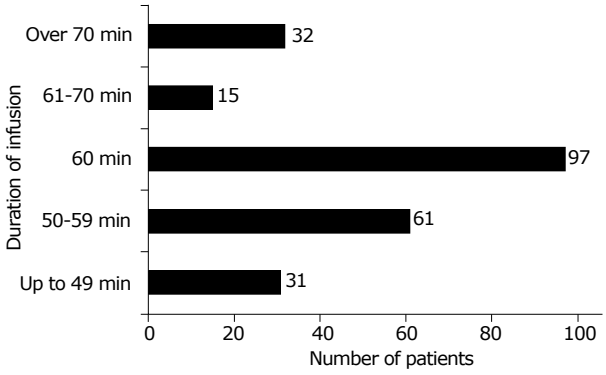

Figure 2 Distribution of patients according to the duration of vancomycin infusion. The target time for the duration of vancomycin infusion is 60 min.

40 mg/L in 73 cases, between 40 and 50 mg/L in 50 cases, and higher than 50 mg/L in 103 cases.

Three SSIs were recorded (1.3%): one was a superficial wound infection, and 2 were deep wound infections; no SSIs were detected at the donor site. Pathogens isolated in SSIs included two gram-negative bacteria or fungi and one methicillin-sensitive Staphylococcus aureus.

Figure 1 shows that, between the C_{max} time and C_{close} time, no vancomycin levels less than 10 mg/L were recorded in 122 out of 236 patients (52%) and that 114 out of 236 patients (48%) were found to have at least 1 sample with a vancomycin level < 10 mg/L. Fifty-four out of 236 patients (22.9%) had at least 5 serum samples with vancomycin levels lower than 10 mg/L.

Vancomycin infusion was administered for 60 min in 97 out of 236 patients (41%). In 47 patients (20%), the duration of infusion was longer than 60 min, and in 92 patients (39%) the duration of infusion was shorter than 60 min (Figure 2).

The ROC curve analysis showed no influences of duration of drug infusion on the occurrence of vancomycin concentrations less than 10 mg/L. No significant relationships were found between the number of episodes of vancomycin levels less than 10 mg/L and the clusters of duration of infusion ($P = 0.089$).

No significant differences were observed in terms of the SSI rate between patients with vancomycin levels constantly above 10 mg/L (2 out of 3 cases) and patients with at least 1 level less than 10 mg/L (1 out of 3 cases).

Vancomycin PK parameters were estimated and compared between above versus under 10 mg/L patient groups (Table 2): C_{max} and the area under the concentration-time (AUC) curve were significantly higher in patients with no vancomycin level under 10 mg/L, while the apparent total body clearance (Cl) and the apparent volume of distribution during the terminal phase (V_d) were significantly higher in patients with at least 1 episode of vancomycin concentration under 10 mg/L.

The multivariate binary logistic model identified female gender, BMI higher than 25, and creatinine clearance above 70 mL/min as risk factors for vancomycin levels less than 10 mg/L (Tables 3 and 4).

DISCUSSION

SSI is still one of the most serious complications after cardiac surgery, and one of the main strategies for prevention is the use of an appropriate antibiotic prophylaxis[17]. The spectrum of microorganisms related to SSIs varies among institutions; however, in the literature, MRSA and methicillin-resistant *S. Epidermidis* are the leading pathogens, and this brings attention to vancomycin as the prophylactic drug of choice[1-3].

Vancomycin has been one of the most investigated antimicrobial drugs as well as one of the most used antibiotics for the prevention and treatment of infections

Table 2 Pharmacokinetic comparison between patients with at least 1 serum sample with a vancomycin concentration < 10 mg/L (in the left column) and patients without serum samples with a vancomycin concentration < 10 mg/L (in the right column)

	Vancomycin levels < 10 mg/L (*n* = 114)	Vancomycin levels ⩾ 10 mg/L (*n* = 122)	*P*-value
C_{max} (mg/L)	33.2 (6.2-122.0)	57.9 (14.6-210.0)	<0.001
AUC (mg*h/L)	119.2 (28.3-247.7)	191.7 (95.8-467.8)	<0.001
$t_{1/2}$ (h)	3.9 (1.6-9.2)	4.0 (1.3-9.8)	0.437
CL (L/h)	8.4 (4.0-35.3)	5.2 (2.1-10.4)	<0.001
V_d (L)	47.2 (16.5-195.2)	29.8 (12.4-63.3)	<0.001

AUC: Area under the curve; CL: Total body clearance; C_{max}: Maximum concentration; $t_{½}$: Elimination half-life; V_d: Volume of distribution.

Table 3 Risk factors for vancomycin levels under 10 mg/L - univariate binary logistic model

	OR	95%CI	*P*-value
CPB (off-pump *vs* on-pump)	0.51	0.20-1.30	0.156
Vancomycin infusion (stopped *vs* non-stopped)	0.6	0.17-2.10	0.421
Age at surgery (> 70 yr *vs* ⩽ 70 yr)	0.54	0.32-0.92	0.021
Gender (Female *vs* male)	0.44	0.26-0.76	0.003
BMI (> 25 *vs* ⩽ 25)	2.3	1.36-3.88	0.002
Fluid balance (> 2000 mL *vs* ⩽ 2000 mL)	1.44	0.86-2.41	0.163
CrCl (> 70 mL/min *vs* ⩽ 70 mL/min)	2.56	1.51-4.34	<0.001
Vancomycin dosage (> 15 mg/kg *vs* ⩽ 15 mg/kg)	0.38	0.21-0.66	0.001
Vancomycin infusion duration			0.237
50-59 min *vs* < 50 min	0.5	0.21-1.21	0.123
60 min *vs* < 50 min	0.63	0.28-1.42	0.26
61-70 min *vs* < 50 min	0.48	0.14-1.69	0.254
> 70 min *vs* < 50 min	1.2	0.44-3.31	0.719

BMI: Body mass index; CPB: Cardiopulmonary bypass; CrCl: Creatinine clearance.

Table 4 Risk factors for vancomycin levels under 10 mg/L - multivariate binary logistic model

	OR	95%CI	*P*-value
Age at surgery (>70 yr *vs* ⩽ 70 yr)	0.69	0.36-1.28	0.245
Gender (Female *vs* male)	0.54	0.30-0.97	0.039
BMI (> 25 *vs* ⩽ 25)	1.99	1.15-3.45	0.015
CrCl (> 70 mL/min *vs* ⩽ 70 mL/min)	1.92	1.09-3.40	0.024
Vancomycin dosage (>15 mg/kg *vs* ⩽ 15 mg/kg)	0.75	0.36-1.57	0.451

BMI: Body mass index; CrCl: Creatinine clearance.

in cardiac surgery[10]. Several studies have investigated the association between vancomycin use as an antimicrobial prophylactic drug and the rate of SSIs in this surgical population. Different studies have analyzed vancomycin PK during cardiac surgery and the effects of CPB on serum vancomycin concentrations[13,18-20]. Other studies were carried out examining the timing of antibiotic prophylaxis, and in particular, the relationship between the end of vancomycin infusion and the first skin incision[14,15].

However, to date, no general agreement exists regarding guidelines for the dose and duration of antimicrobial prophylaxis administration, and, particularly, the level of vancomycin to reach and maintain during the surgical procedure for effective antimicrobial prophylaxis. Moreover, whether or not suboptimal intraoperative vancomycin levels are a cause of postoperative SSIs is still controversial. Studies have suggested that vancomycin operates in a concentration-independent fashion in which AUC is more effective than the drug level[10]. PK results of our study are in line with reports in the literature, even when administering vancomycin in the case of treating infections rather than antibiotic prophylaxis[10,21]; in particular, in our study, AUC was wider in the group of patients with no vancomycin levels less than 10 mg/L.

Larsson *et al*[22] simulated an *in vitro* model in which free vancomycin peak concentrations of 40, 20, 10, and 5 mg/L reported no significant difference in the corresponding bacterial kill curves for Staphylococcus aureus. On the other hand, to date, increasing evidence supports that Staphylococcus aureus exposure to trough serum concentrations of vancomycin lower than 10 mg/L can generate MRSA strains with vancomycin-resistant characteristics[5,10,11,23]. Sakoulas *et al*[24] have determined that the emergence of hVISA or VISA occurred when MRSA was exposed to suboptimal vancomycin concentrations (<10 mg/L); in this *in*

vitro study the minimal inhibitory concentration (MIC) increased from 1 to 8 mg/L. Tsuji *et al*[25] evaluated Staphylococcus aureus accessory gene regulator groups Ⅰ - Ⅳ exposed both to suboptimal and optimal vancomycin doses (1.5-10 mg/L) and reported that exposure to low vancomycin doses produced increases in the MIC to that of the VISA range.

In the present study, 114 out of 236 patients were found to have at least 1 value of vancomycin level lower than 10 mg/L between the C_{max} time and C_{close} time. The relatively small sample size and the low incidence of SSIs in this surgical population (1.3%, 3 out of 236 cases) make it difficult to obtain a significant relationship between vancomycin concentrations during surgery and the incidence of SSIs. However, this finding may be considered an indicator of the risk of selection of MRSA strains with vancomycin-resistant characteristics.

The multivariate analysis showed that female gender, BMI higher than 25, and creatinine clearance above 70 mL/min were risk factors for potentially suboptimal vancomycin concentrations. Regarding the BMI as a risk factor, our results are in line with other reports that highlight the efficacy of weight-based vancomycin dosing[26,27]. Recently, the European Medicines Agency claimed that the starting dose of vancomycin by infusion should be calculated according to the age and weight of the patient[28].

Strengths and limitations of the study

The study has many important characteristics. First of all, the results were obtained through a clinical trial and not from an analysis of a registry or database. Second, it was a prospective study. Third, only patients undergoing cardiac surgery were included. Fourth, information regarding antibiotic timing was gathered in "real-time" in the operating theater and not from the patient chart. Finally, the same protocol of antimicrobial prophylaxis was administered to all patients. Moreover, to the best of our knowledge, this is the first study investigating the incidence and risk factors for potentially suboptimal serum concentrations of vancomycin during cardiac surgery with such a large number of measured serum vancomycin concentrations (*i.e.,* 1682).

This study has some limitations. First, no statistical analysis was performed on the number of patients enrolled since the study was planned by our statistician to be continuous over 12 mo. Second, it was a single-center trial. Third, we considered vancomycin levels of 10 mg/L as an arbitrary cut-off for potentially suboptimal serum concentrations when an antimicrobial prophylaxis has been administered, referring to the level reported in the literature in the case of antimicrobial therapy. Finally, a larger study should be carried out to investigate clinical variables; indeed, the number of subjects was appropriate for a pharmacokinetic study but insufficient to find statistically significant differences in the SSI rate between patient groups with vancomycin levels above or under 10 mg/L.

In conclusion, evidence in the literature suggests that the exposure to low vancomycin levels should be considered a risk factor in the selection of MRSA strains with vancomycin-resistant characteristics. The present study on vancomycin PK in cardiac surgery patients has reported an incidence of intraoperative potentially suboptimal concentrations of vancomycin in almost 50% of patients. Our data analysis shows that female gender, BMI higher than 25, and creatinine clearance above 70 mL/min were risk factors for potentially suboptimal concentrations of vancomycin. Overall, these findings call attention to the risk of potentially suboptimal serum concentrations of vancomycin during cardiac surgery. However, further studies are needed to better define the threshold level of serum intraoperative vancomycin concentration associated with the risk for the emergence of vancomycin resistance.

ARTICLE HIGHLIGHTS

Research background

Based on evidence suggesting that Staphylococcus aureus exposure to low vancomycin concentrations can produce vancomycin-resistant strains, it is recommended that trough therapeutic serum concentrations of vancomycin are maintained above 10 mg/L.

Research motivation

There are no recommendations in the literature indicating target vancomycin concentrations to maintain intraoperatively for effective antimicrobial prophylaxis.

Research objectives

The aim of this prospective study was to evaluate the incidence and risk factors for vancomycin concentrations under 10 mg/L in adult patients undergoing cardiac surgery.

Research methods

In this study, the frequency of suboptimal vancomycin levels intraoperatively was investigated in samples collected from cardiac surgery patients receiving a single 1000 mg vancomycin dose.

Research results

We found an incidence of intraoperative potentially suboptimal concentrations of vancomycin in almost 50% of these patients. The multivariate analysis identified female gender, body mass index > 25, and creatinine clearance above 70 mL/min as risk factors for vancomycin levels less than 10 mg/L.

Research conclusions

Although we arbitrarily considered vancomycin levels of 10 mg/L as a cut-off, the findings of our study are interesting because they suggest a high incidence of potentially suboptimal serum concentrations in the case of antimicrobial prophylaxis.

Research perspectives

Further studies will be necessary to define the cut-off of intraoperative vancomycin levels representing the optimal concentration of vancomycin for appropriate antimicrobial prophylaxis in patients undergoing cardiac surgery.

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META-ANALYSIS

Surgical left atrial appendage occlusion during cardiac surgery: A systematic review and meta-analysis

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Abstract

AIM

To evaluate the safety and efficacy of surgical left atrial appendage occlusion (s-LAAO) during concomitant cardiac surgery.

METHODS
We performed a comprehensive literature search through May 31st 2018 for all eligible studies comparing s-LAAO *vs* no occlusion in patients undergoing cardiac surgery. Clinical outcomes during follow-up included: embolic events, stroke, all-cause mortality, atrial fibrillation (AF), reoperation for bleeding and postoperative complications. We further stratified the analysis based on propensity matched studies and AF predominance.

RESULTS
Twelve studies (n = 40107) met the inclusion criteria. s-LAAO was associated with lower risk of embolic events (OR: 0.63, 95%CI: 0.53-0.76; P < 0.001) and stroke (OR: 0.68, 95%CI: 0.57-0.82; P < 0.0001). Stratified analysis demonstrated this association was more prominent in the AF predominant strata. There was no significant difference in the incidence risk of all-cause mortality, AF, and reoperation for bleeding and postoperative complications.

CONCLUSION
Concomitant s-LAAO during cardiac surgery was associated with lower risk of follow-up thromboembolic events and stroke, especially in those with AF without significant increase in adverse events. Further randomized trials to evaluate long-term benefits of s-LAAO are warranted.

Key words: Left atrial appendage; Left atrial appendage occlusion; Embolic events; Stroke; Adverse events

Core tip: Surgical left atrial appendage occlusion (s-LAAO) is performed during cardiac surgeries in patients with atrial fibrillation. However, evidence to perform routinely during cardiac surgeries is conflicting and contrasting. It is currently given a class Ⅱb recommendation in the professional medical society guidelines. We sought to perform a meta-analysis of all the studies published to date to evaluate the safety and efficacy of s-LAAO.

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INTRODUCTION

The left atrial appendage (LAA) is considered to be the dominant source of embolism (> 90%) in patients with non-valvular atrial fibrillation (AF)[1]. Occlusion or resection of the left atrial appendage occlusion (LAAO) remains an important intervention for prevention of recurrent emboli in patients who are at risk of stroke. LAAO provides an opportunity to avoid systemic anti-coagulation, thereby minimizing the risk of bleeding.

Surgical LAAO (s-LAAO) usually involves LAA closure while performing other cardiac surgeries. With the increasing prevalence of AF[2], there is a growing interest in the surgical community for s-LAAO. Prior studies assessing the clinical impact of surgical occlusion of the LAA during cardiac surgery have shown contradictory results[3-14]. Furthermore, there are no large scale randomized controlled trials evaluating routine s-LAAO during cardiac surgery. Therefore s-LAAO remains a class IIb recommendation in professional medical society guidelines[15,16]. Despite this recommendation, s-LAAO is routinely performed in patients with AF undergoing cardiac surgery. Therefore, we sought to perform a meta-analysis of the available studies published to date to evaluate the safety and efficacy of concomitant s-LAAO *vs* no occlusion during cardiac surgery[3,4,6-14].

MATERIALS AND METHODS

Search strategy

The systematic review and meta-analysis was done in compliance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) guidelines[17]. The PRISMA checklist is presented in Supplementary Table 1. The initial search strategy was developed by two authors (V.A and M.A.N). We performed a systematic search, without language restriction, using PubMed, EMBASE, SCOPUS, Google Scholar, and ClinicalTrials.gov from inception to May 31st, 2018 for studies comparing s-LAAO *vs* no occlusion- only in patients undergoing concomitant cardiac surgery. We used the following keywords and medical subject heading: "Cardiac surgeries" OR "Heart surgeries" OR "Cardiac surgical procedures" AND "Left atrial appendage" OR "occlusion" OR "ligation" OR "resection" OR "excision" OR "amputation".

Study selection and data extraction

Only studies comparing s-LAAO *vs* no occlusion during any cardiac surgery were included in our analysis. The reference lists of original studies, conference abstracts and relevant review articles were further reviewed. Two investigators (V.A and M.A.N) independently performed the literature search, reviewed the originally identified titles and abstracts and selected studies for pooled analysis based on the inclusion criteria. Any divergence was resolved through discussion with a third independent reviewer (M.K.T). The quality of observational studies was assessed using the Newcastle Ottawa scale, Supplementary Table 2.

Clinical outcomes

We evaluated the following clinical outcomes during follow-up in each report: (1) embolic events; (2) stroke; (3) all-cause mortality; (4) AF; (5) postoperative

complications; and (6) reoperation for bleeding. We further performed stratified meta-analysis to evaluate the potential source of heterogeneity across the included studies. Stratification factors are inclusion of only propensity matched studies and studies with AF predominant cohort (> 50% of study population having AF). The ischemic events attributed to embolic causes in the included studies were included in the embolic events. Complications included in the analysis are appendage tears, myocardial infarction, major bleeding, septicemia, pacemaker implants, renal failure, pericardial effusion, cardiac tamponade, and stroke.

Statistical analysis

The meta-analysis was done using Review Manager (RevMan), Version 5.3. Copenhagen: The Nordic Cochrane Centre, the Cochrane Collaboration, 2014. Due to methodological and clinical heterogeneity between the included studies, a random-effects model estimating the odds ratio (OR) and the estimated 95% confidence interval (CI) of the above-mentioned outcomes were used. The OR estimate of each study was calculated by the random-effects model obtained by the DerSimonian-Lariad method[18].

Heterogeneity was assessed using Higgins' and Thompson's I2 statistic, with I2 values of > 50% was considered significant. Publication bias was visually estimated by funnel plots. A 2-tailed $P < 0.05$ was considered statistically significant for all analyses.

RESULTS

Search results

A total of 1328 reports were retrieved during the initial search (Supplementary figure 1). 1049 reports were selected after removing 279 duplicates. 387 reports were screened and 354 were excluded. 33 reports were assessed for eligibility. Finally, after excluding 21 reports (no comparison groups-14, others-7) 12 studies were included. Among these 12 studies, three were randomized controlled trials (RCTs) and nine were observational studies. Among these nine observational studies, four were propensity matching studies[5,6,10,13]. one was case matching study[12]. The inter-reviewer agreement on study eligibility was 100%.

Study characteristics

The characteristics of the included studies are presented in Table 1 and Table 2. Out of 40107 patients included, 13535 patients received s-LAAO during cardiac surgery while the remaining 26572 patients did not receive s-LAAO. The mean (SD) age of the study population ranged from 50.7 (12.4) years to 77.4 (6.8) years. The primary cardiac operation varied widely. The surgical procedures were primarily valve surgery in the studies by Garcia-Fernandez, Nagpal, Lee and Elbadawi[3,5,8,12], while they were primarily coronary artery bypass grafting (CABG) in the studies by Healey, and Elbadawi[7,11]. Remaining studies included a combination of valve surgery and CABG. Lee *et al*[5] also performed ablation of AF together with mitral valve surgery. The prevalence of AF varied in the study cohorts. The s-LAAO techniques varied; the methods variously included double suturing, exclusion, amputation, resection and stapling (Table 2). The follow-up period ranged from in-hospital only to 109.2 mo.

Clinical outcomes

s-LAAO was associated with lower risk of embolic events (OR: 0.63, 95%CI: 0.53-0.76; $P < 0.001$) and a lower risk of stroke (OR: 0.68, 95%CI: 0.57-0.82; $P < 0.0001$) (Figure 1A and 1B). There was no significant difference in all-cause mortality between the two groups (OR: 0.83, 95%CI: 0.51-1.36; $P = 0.46$) (Figure 1C). There was no significant difference in the incidence of follow-up AF between the two groups (OR: 1.41, 95%CI: 0.79-2.52, $P = 0.24$) (Figure 1D).

With regard to postoperative complications, there was no significant difference between the groups (OR: 1.44, 95%CI: 0.91-2.25; $P = 0.12$) (Figure 1F). Similarly, there was no significant difference in the incidence of reoperation for bleeding between the two groups (OR: 0.98, 95%CI: 0.57-1.69; $P = 0.94$) (Figure 1G).

Test of heterogeneity and publication bias

Test of heterogeneity was not significant for follow-up embolic events (P heterogeneity = 0.60, I2 = 0%) and stroke ($P = 0.84$, I2 = 0%), while it was significant for all-cause mortality ($P < 0.001$, I2 = 92%), AF ($P < 0.001$, I2 = 95%), postoperative complications ($P = 0.004$, I2 = 66%) and reoperation for bleeding ($P = 0.20$, I2 = 36%).

Subgroup analysis

In subgroup analysis including only propensity matched studies, s-LAAO group had a trend towards lower risk of stroke (OR: 0.78, 95%CI: 0.60-1.00; $P = 0.05$), Supplementary Figure 2A. Test of heterogeneity was not significant ($P = 0.63$, I2 = 0%). There was no significant difference in the incidence of all-cause mortality (OR: 1.10, 95%CI: 0.34-3.60; $P = 0.87$), Supplementary Figure 2B**.** In subgroup analysis including only AF predominant studies (> 50%), s-LAAO was associated with lower risk of stroke (OR: 0.60, 95%CI: 0.46-0.78; $P = 0.0002$) (Supplementary Figure 3A). There was no significant difference in all-cause mortality (OR: 0.87, 95%CI: 0.11-7.12; $P = 0.89$) (Supplementary Figure 3B). Test of heterogeneity was not significant for stroke ($P = 0.86$, I2 = 0%) while it was significant for all-cause mortality ($P < 0.001$, I2 = 94%).

Funnel plot for visual inspection of publication bias is shown in Supplementary Figure 4.

DISCUSSION

The main findings of our meta-analysis of patients un-

Table 1 Characteristics of the included studies

Study, yr	Country	Study period	Study design	Sample size		Cardiac surgery type	Follow up period (mo)
				s-LAAO	No occlusion		
García-Fernández *et al*, 2003[3]	Spain	2003	retrospective	58	147	MVS	69.4 ± 67
Healey *et al*, 2005[7]	Germany	2001-2002	RCT	52	25	CABG	13 ± 7
Nagpal *et al*, 2009[8]	Canada	2007-2007	RCT	22	21	MVS	<1
Whitlock *et al*, 2013[9]	Canada	2009-2010	RCT	26	25	CABG and VS	1
Zapolanski *et al*, 2013[4]	United States	2005-2012	retrospective	808	969	CABG and VS	NR
Kim *et al*, 2013[6]	United States	2001-2010	retrospective	631	631	CABG and MVS	1
Lee *et al*, 2014[1][5]	Korea	1999-2011	retrospective	119	119	MVS with AF ablation	63 ± 44
Melduni *et al*, 2017[1][10]	United States	2000-2005	prospective	461	461	CABG and VS	109.2
Elbadawi *et al*, 2017[2][11]	United States	1998-2013	retrospective	652	652	VS	In-hospital
Elbadawi *et al*, 2017[12]	United States	2004-2013	retrospective	2519	12595	CABG	In-hospital
Friedman *et al*, 2018[14]	United States	2011-2012	retrospective	3892	6632	CABG, MVS, AVS	31.2
Yao *et al*, 2018[1][13]	United States	2009-2017	retrospective	4295	4295	CABG, VS	25.2 ± 22.8

RCT: Randomized controlled trial; CABG: Coronary artery bypass grafting; VS: Valvular surgery; MVS: Mitral valve surgery; AVS: Aortic valve surgery; AF: Atrial fibrillation. [1]Propensity match studies. [2]Case matching study.

Table 2 Baseline and procedural characteristics of included studies

Study	Age (mean ± SD)		Hypertension		AF (%)		Technique of s-LAAO
	s-LAAO	No occlusion	s-LAAO	No occlusion	s-LAAO	No occlusion	
García-Fernández *et al*, 2003[3]	63 ± 12	62 ± 10	NR	NR	NR		Double suturing
Healey *et al*, 2005[7]	72 ± 6	71 ± 5	75	92	17	8	Suture or stapler
Nagpal *et al*, 2009[8]	57.8 ± 13.3	59.2 ± 11.9	NR	NR	18	29	Resection
Whitlock *et al*, 2013[9]	77.4 ± 6.8	74.6 ± 7.6	92.3	92	100	100	Amputation and closure or stapler
Zapolanski *et al*, 2013[4]	70.52 ± 11.83		83.9	80.6	19.9	10.7	Double ligation
Kim *et al*, 2013[6]	66.6 ± 11.4	65.8 ± 11.6	80.9	73.1	NR	NR	Ligation and excision
Lee *et al*, 2014[5]	55.9 ± 12.2	50.7 ± 12.4	19.8	14.5	100	100	Amputation
Melduni *et al*, 2017[10]	67.4 ± 12.7	67.6 ± 13.5	59	61	47	45	Amputation, suturing or stapler
Elbadawi *et al*, 2017[11]	70.8 ± 10.2	71.2 ± 11.1	70.6	52.8	100	100	NR
Elbadawi *et al*, 2017[12]	71.3 ± 9	70.6 ± 8.7	78.5	76.1	100	100	NR
Friedman *et al*, 2018[14]	75 ± 5.9	76.4 ± 6.4	14.5	12.7	50.5	43.4	Any technique
Yao *et al*, 2018[13]	68.2 ± 10.6	65.8 ± 11.3	88.6	90.4	75.4	31.4	

dergoing s-LAAO during concomitant cardiac surgery are the following: (1) s-LAAO was associated with lower rates of embolic events and stroke; and (2) there was no significant difference in the incidence of all-cause mortality, postoperative complications or reoperations for bleeding between the two groups. The reduced risk of embolic events and stroke with s-LAAO was retained in the subgroup analysis including only studies with AF predominant population (Table 3).

The estimated global prevalence of AF is on the rise due to a demographic shift with more prevalent ageing population carrying a higher burden of comorbidities[19]. About 25% of the strokes in the United States are related to AF and about 90% of the strokes in non-valvular AF are caused by thrombi originating in LAA[20]. Anticoagulants, both warfarin and direct acting oral anticoagulants (DOACs) reduce the incidence of stroke by more than 60%[21,22] but they are associated with increasing risk of bleeding, and significant drug-drug interactions[16]. The benefits of anticoagulants are also limited by other issues including underutilization, poor compliance and cost[16].

The higher risk of stroke in the ageing population with AF has led to the increased adoption of LAA occlusion in clinical practice[23]. The two largest RCTs - PROTECT-AF (WATCHMAN Left Atrial Appendage System for Embolic Protection in Patients with Atrial Fibrillation) and PREVAIL (Watchman LAA Closure Device in Patients With Atrial Fibrillation Versus Long Term Warfarin Therapy) showed percutaneous LAAO being non-inferior to warfarin with respect to stroke rates and embolic events[24,25]. Following the success with percutaneous LAAO, there has been a resurgence of interest in s-LAAO within the surgical community, especially with increase in the aging population and rising prevalence of AF[6,10,14].

Our findings show that s-LAAO was associated with lower risk of follow-up embolic events and stroke. The association of lower risk of stroke was more prominent in subgroup with AF predominant population. S-LAAO theoretically prevents formation of thrombus in LAA. However, successful s-LAAO is largely influenced by LAA morphology, occlusion technique and also operator

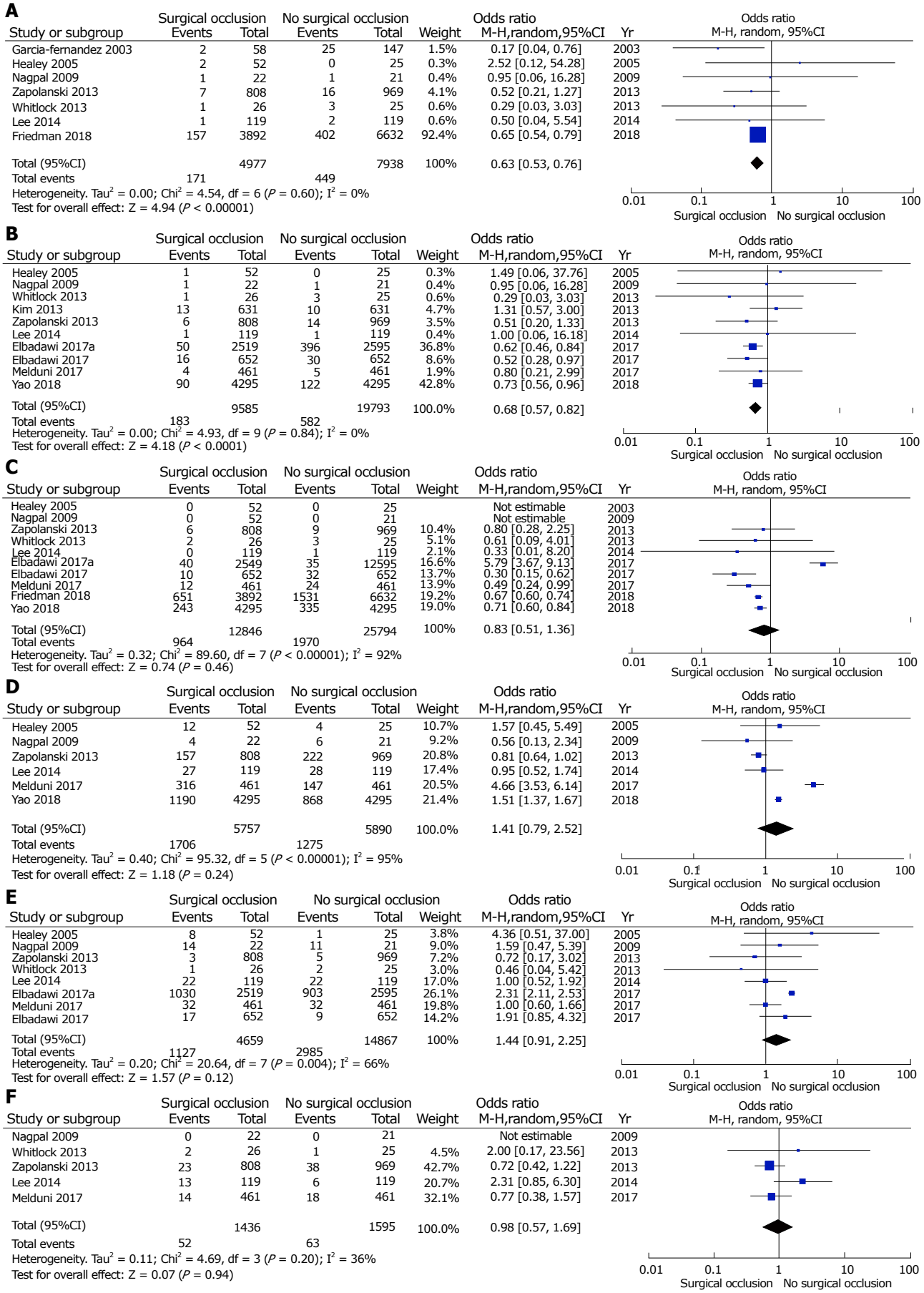

Figure 1 Forest plots for study outcomes. A: Embolic events; B: Stroke; C: All-cause mortality; D: Atrial fibrillation; E: Postoperative complications; F: Reoperation for bleeding.

Table 3 Complications reported in the individual studies

Study	Total complications	Type of complications	
	s-LAAO (%) *vs* No occlusion (%)	s-LAAO	No occlusion
Healey *et al*, 2005[7]	8 (52) *vs* 1 (4)	8- intraoperative LAA tears	1- LAA tear
Nagpal *et al*, 2009[8]	14 (63.6) *vs* 11 (52.3)	1- septicemia	1- RBC transfusion
		1- myocardial infarction	7- temporary pacemaker
		2- RBC transfusion	3- permanent pacemaker
		8- temporary pacemaker	
		2- permanent pacemaker	
Whitlock *et al*, 2013[9]	1 (3.8) *vs* 2 (25)	1- major bleeding	2- major bleeding
Zapolonski *et al*, 2013[4]	3 (0.3) *vs* 5 (0.6)	3- myocardial infarction	5- myocardial infarction
Lee *et al*, 2014[5]	22 (18.4) *vs* 22 (18.4)	9- requirement of dialysis	1- low cardiac output syndrome
		4- permanent pacemaker insertion	10- dialysis
		1- wound revision	2- permanent pacemaker insertion
		8- pericardial effusion	1- mediastinitis
			2- wound revision
			6- pericardial effusion
Melduni *et al*, 2017[10]	32 (6.9) *vs* 32 (6.9)	14- pneumonia	14- pneumonia
		18- acute renal failure	18- acute renal failure
Elbadawi *et al*, 2017[11]	17 (3.1) *vs* 9 (1.6)	17- pericardial effusion	7- pericardial effusion
			2- hemorrhage
Elbadawi *et al*, 2017[12]	1030 (40.8) *vs* 2903 (23)	16- cardiac tamponade	19- cardiac tamponade
		68- pericardial effusion	151- pericardial effusion
		917- hemorrhage	2687- hemorrhage
		29- postoperative shock	46- postoperative shock

RBC: Red blood cell; LAA: Left atrial appendage.

skill. A previous study showed that a complete LAA occlusion was achieved in only 40%-50% of the patient population[10,26]. The techniques of s-LAAO varied widely amongst the included studies as summarized in Table 2. The excision technique to exclude LAA has been shown to have a higher success rate than the other modalities of s-LAAO[24]. Currently, concomitant LAA closure is given a Class Ⅱb (level of evidence B) by the European Society of Cardiology (ESC)/European Society for Cardio-Thoracic Surgery (EACTS) guidelines and a Class IIb (level of evidence C) by the 2017 Society of Thoracic Surgeons guidelines (STS)[16]. Therefore, there is a wide practice level variation in the utilization of s-LAAO during cardiac surgery. The number of studies with a particular technique is inadequate to perform individual technique based meta-analysis so we combined all different techniques of s-LAAO in our meta-analysis. It should be noted that none of the other studies except the study from Friedman *et al*[14] reported long-term benefits. However, Friedman *et al*[14] showed a remarkable reduction in postoperative embolism at follow up. Further studies with long-term follow up of embolic events are essential. Our results are similar to a previous meta-analysis comparing s-LAAO vs no occlusion[27,28]. However, we included additional studies by Friedman *et al*[14], Elbadawi *et al*[11] and Yao *et al*[13] yielding a larger sample size. In addition, we performed a subgroup analysis of the included studies to identify the patient population that is most likely to benefit from this procedure.

In the current study, we found no significant difference in the risk of postoperative complications and reoperation for bleeding. s-LAAO is associated with inherent risk of procedural complications including LAA tears as observed in the study by Healey *et al*[7] and so learning curve plays an essential role in success of the procedure. Hypothetically, avoidance of aggressive anticoagulation after s-LAAO might have contributed to some of the benefits observed with s-LAAO. However, only few studies reported the long-term details of anticoagulation. Lee *et al*[5] reported no difference in the utilization of anticoagulation between the two groups (62.2% *vs* 55.4%). In the study by Friedman *et al*[14], anticoagulation was prescribed to 68.9% of the patients in the s-LAAO group compared to only 60.3% in the group without s-LAAO. In contrast to percutaneous LAAO, evidence regarding the utilization of anticoagulation after s-LAAO is not clear. The 2016 ESC/EACTS guidelines still recommend therapeutic anti-coagulation in all patients despite s-LAAO (Class Ⅰ, level of evidence B)[15]. With lack of long term data, there is need for prospective trials to address this issue. The ongoing LAAOS-Ⅲ (left atrial appendage occlusion study Ⅲ) and the ATLAS (AtriClip® Left Atrial Appendage Exclusion Concomitant to Structural Heart Procedures) trials should be able to provide further insights into the benefits of s-LAAO.

LIMITATIONS

Our study should be viewed in the context of following limitations. First, due to the small number of studies with small sample sizes, except the study by Friedman *et al*[14], the results might be underpowered to detect the true clinical benefits of certain clinical outcomes. Second, there was a wide variation of surgical techniques of LAAO, so we were not able to address the effect of individual techniques. Third, only Friedman *et*

al[14] reported long-term embolic events, whereas the other studies did not report long term outcomes. The study by Friedman *et al*[14] reported readmissions for embolic events, so some of the events which did not require hospitalization were not included. The effect of anticoagulation on postoperative outcomes remains unclear due to inadequate reporting in the included studies. Fourth, it is unclear if s-LAAO increases the duration of the surgical procedure as it was only reported in two studies. Fifth, the burden of AF varied among the included studies, thus carrying risk of a selection bias. Finally, publication bias is an inherent limitation of any meta-analysis.

CONCLUSION

In conclusion, our results support the safety of s-LAAO and favor its continued use in conjunction with concomitant cardiac surgery, especially in patients with AF. Randomized controlled trials are essential to evaluate the long-term benefits of s-LAAO.

ARTICLE HIGHLIGHTS

Research background

The left atrial appendage (LAA) is a common site for intracardiac thrombus formation in patients with atrial fibrillation (AF). Surgical left atrial appendage occlusion (s-LAAO) during concomitant cardiac surgery has been evaluated as an effective treatment approach to reduce the risk of stroke and embolic events.

Research motivation

Percutaneous LAAO has been shown to be non-inferior compared with warfarin in reducing the risk of stroke and embolic events in two large randomized controlled trials, PROTECT-AF and PREVAIL. However, data regarding s-LAAO is conflicting and contrasting. So, we performed a systematic review and meta-analysis of all the studies published to date to evaluate if concomitant s-LAAO during cardiac surgery is safe and effective.

Research objectives

The purpose of this study is to evaluate the safety and efficacy of concomitant s-LAAO during cardiac surgery.

Research methods

We searched five databases for studies comparing concomitant s-LAAO with no occlusion during cardiac surgery. We obtained a total of 12 studies for inclusion and performed a meta-analysis. The outcomes of interest were embolic events, stroke, all-cause mortality, AF, postoperative complications and reoperation for bleeding.

Research results

Concomitant s-LAAO during cardiac surgery was associated with lower risk of embolic events and stroke. This was evident in the AF predominant strata as well. There was no significant difference in the risk of all-cause mortality, AF, postoperative complications and reoperation for bleeding.

Research conclusions

Our meta-analysis including all the studies published to date comparing concomitant s-LAAO against no occlusion during cardiac surgery supports the use of concomitant s-LAAO during cardiac surgeries. It was associated with lower risk of stroke and embolic events.

Research perspectives

From this meta-analysis, it could be seen that concomitant s-LAAO during cardiac surgeries was associated with lower risk of stroke and embolic events compared with no occlusion. This association was prominent amongst the AF predominant strata as well. These beneficial effects could be seen due to the occlusion of LAA which is the source of 90% thrombi in non-valvular AF. Future randomized trials are needed to evaluate the long term benefits of s-LAAO.

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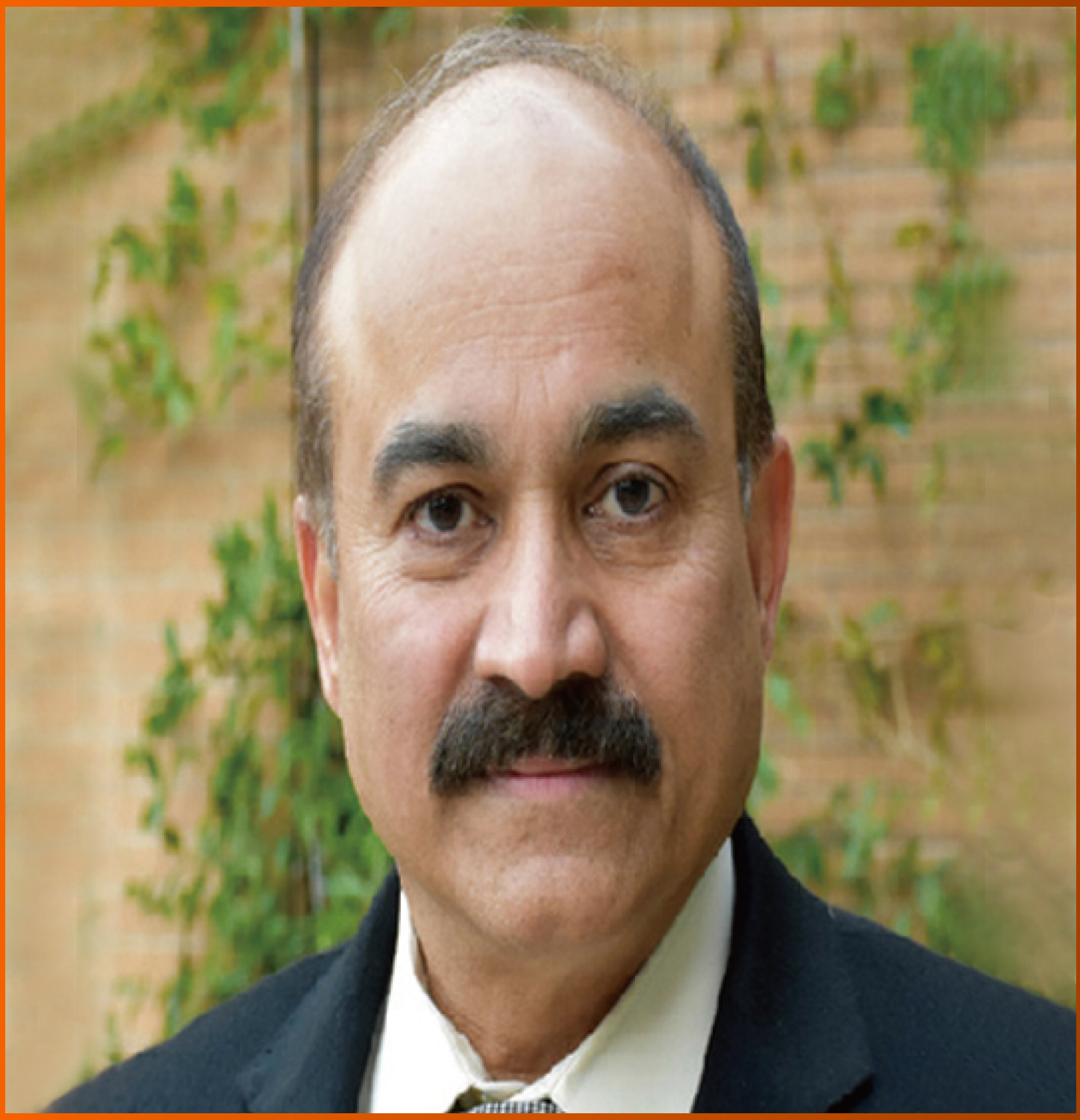

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EDITORIAL

Risk of sudden cardiac death: Are coronary chronic total occlusions an additional risk factor?

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Abstract

Sudden arrhythmic cardiac death remains a significant, potentially reversible, cardiological challenge in terms of creating accurate risk prediction models. The current guidelines for implantable cardioverter defibrillator (ICD) therapy are mainly based on left ventricular ejection fraction despite its low sensitivity and specificity in predicting sudden cardiac death (SCD). Chronic total occlusions have been associated with increased mortality but further research is required to clarify if they should be incorporated in a risk model predicting SCD aiming to identify patients that would benefit from ICD therapy even with preserved ejection fraction.

Key words: Sudden cardiac death; Chronic total occlusion; Left ventricular ejection fraction; Implantable cardioverter defibrillator

Core tip: Further research is necessary in order to clarify if chronic total occlusion can be incorporated in a risk prediction model of sudden cardiac death aiming to identify patients that would benefit from implantable cardioverter defibrillator.

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INTRODUCTION

Even though death from cardiac causes has been decreasing over the last two decades in the western world, approximately 20% of all deaths and 50% of cardiovascular deaths are due to sudden cardiac death (SCD)[1,2]. Coronary chronic total occlusions (CTO) occur in about 16% of patients with significant ischaemic heart disease and they have been associated with increased mortality in a large prospective observational study[3]. However, currently it is not well known to what extent CTO increase SCD and if these patients would benefit from implantable cardioverter defibrillator (ICD) therapy.

In this Editorial, we focus on a recent article by Chi *et al*[4] published in JACC Clinical Electrophysiology as we feel it provides a new insight into the role of CTO in relation to prognosis and identifies gaps in knowledge that warrant further research. In this study the authors aimed to understand the relationship between CTO and the occurrence of ventricular tachycardia/fibrillation (VT/VF) or appropriate ICD therapy. They performed a meta-analysis including a total of 17 studies involving almost 55 thousand patients. They found that the presence of CTO was associated with higher risk of VT/VF or appropriate ICD therapy; however it was not associated with a difference in cardiac mortality or in all-cause mortality. The higher risk of VT/VF or appropriate ICD therapy was confirmed on both univariate and multivariate analysis (in only two studies), while the risk of cardiac mortality was significantly higher on univariate but not on multivariate analysis and the risk of all-cause mortality was not significantly higher in either univariate or multivariate analysis[4].

Comparing patients with infarct-related and non-infarct related CTOs, they concluded that the former had a higher risk of VT/VF or appropriate ICD therapy, cardiac mortality and higher all-cause mortality. The higher risk of VT/VF or appropriate ICD therapy of patients with infarct-related CTOs was confirmed on univariate but not multivariate analysis while the higher risk of cardiac mortality was only significant on multivariate analysis and the higher risk of all-cause mortality was significant on both univariate and multivariate analysis. Finally, non-revascularization of CTO was associated with higher risk of all-cause mortality but this did not reach statistical significance. The authors reached the conclusion that ICD implantation for primary or secondary prevention should be considered in patients who have infarct-related CTOs[4].

According to American Heart Association/American College of Cardiology/ Heart Rhythm Society (AHA/ACC/HRS) 2017, European Society of Cardiology (ESC) 2015 and United Kingdom National Institute for Health and Clinical Excellence (NICE) 2014 guidelines, an ICD is indicated for secondary prevention in survivors of cardiac arrest provided there is no reversible cause[5-7]. The decision for primary prevention ICD therapy varies slightly according to the various guidelines however, in general it depends on the left ventricular ejection fraction (LVEF), QRS duration and New York Heart Association (NYHA) class. The AHA/ACC/HRS 2017 guidelines recommend ICD if LVEF < 35% and NYHA II-III or LVEF < 30% and NYHA I. The ESC 2015 guidelines recommend ICD if LVEF < 35% and NYHA II-III[5]. According to NICE 2014 guidelines, primary prevention ICD therapy is indicated if LVEF < 35%, NYHA I-III and QRS duration > 120 ms. For patients who fulfil the first two criteria but QRS is < 120 ms, ICD is recommended if there is a high risk of SCD[7] and in this situation the current research[4] would perhaps suggest that presence of CTO can be a qualifying criterion for "high risk"[7].

Even though LVEF has a central role in the algorithm for recommending primary prevention ICD therapy, it has both low specificity and sensitivity for predicting SCD. It is established that low LVEF predicts not only SCD but also other modes of cardiovascular death as well[8]. In addition, only a minority of patients who suffer cardiac arrest will have LVEF < 35%. It is estimated that 40% of patients who suffer SCD have known heart disease with LVEF > 40%, while only 13% of patients who suffer SCD have known heart disease and LVEF < 40%[2]. It has also been shown that myocardial scar > 5% is an independent risk factor for all-cause mortality and appropriate ICD therapy, irrespective of LVEF[9]. In addition, looking at other pathologies for example dilated cardiomyopathy[10] and aortic stenosis[11], other

parameters such as presence of myocardial fibrosis have been shown to have additional prognostic impact over and above LVEF.

CONCLUSION

Chi *et al*[4] have analysed 17 studies that had included patients with severely reduced LVEF but also patients with only mildly reduced or even normal LVEF. It remains to be seen whether CTO can be regarded as an independent factor for malignant arrhythmias over and above the information we get from LVEF, but this study certainly suggests that this should be investigated. In addition, further research can identify whether patients who have viable myocardium with evidence of reversible ischaemia in the presence of some myocardial scar in the CTO territory should also be considered for an ICD even after successful revascularisation. Even though we do not feel that definitive conclusions can be drawn from this analysis, it is an important study as it indicates that further research is needed in order to clarify the relationship of infarct-related CTO and non-infarct related CTO with SCD both in patients with reduced and preserved LVEF. It is well appreciated that the risk of SCD is continuous rather than dichotomous and no single parameter can adequately discriminate to dichotomise the risk[12]. Therefore, clarification if CTO is a high risk variable for SCD in patients with preserved LVEF (introducing a new term for such patients, the CTOpEF patients) or mid-range EF (CTOmrEF patients) or in patients with LVEF < 35% and narrow QRS would be very clinically relevant.

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REVIEW

Cardiac implications of thrombotic thrombocytopenic purpura

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Abstract

Thrombotic thrombocytopenic purpura (TTP) is a multisystem disorder that essentially can affect any organ in the human body. The hallmark of the pathogenesis in TTP is the large von Willebrand factor multimers on platelet-mediated micro-thrombi formation, leading to microvascular thrombosis. Autopsy studies showed that cardiac arrest and myocardial infarction are the most common immediate causes of death in these patients. Clinical manifestations of cardiac involvement in TTP vary dramatically, from asymptomatic elevation of cardiac biomarkers, to heart failure, MI and sudden cardiac death. There is limited knowledge about optimal cardiac evaluation and management in patients with TTP. The absence of typical cardiac symptoms, combined with complicated multi-organ involvement in TTP, may contribute to the under-utilization of cardiac evaluation and treatment. Prompt diagnosis and timely initiation of effective therapy could be critically important in selected cases. Based on our experience and this review of the literature, we developed several recommendations for focused cardiac evaluation for patients with acute TTP: (1) patients with suspected or confirmed TTP should be screened for the potential presence of cardiac involvement with detailed history and physical, electrocardiogram and cardiac enzymes; (2) clinical deterioration of TTP patients warrants immediate cardiac reevaluation; (3) TTP patients with clinical evidence of cardiac involvement should be monitored for telemetry, cardiac biomarkers and evaluated with transthoracic echocardiography. These patients require urgent targeted TTP treatment as well as cardiac-specific treatment. Aspirin therapy is indicated for all TTP patients. Since epicardial coronary artery involvement is rare, cardiac catheterization is usually not required, given the high risk for hemorrhage and kidney injury; (4) we recommend evidence-based medical therapy for ischemic symptoms and heart failure. TTP patients with evidence of cardiac involvement would also benefit from routine cardiology follow up during remission.

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Core tip: Thrombotic thrombocytopenic purpura (TTP) is a grave medical condition caused by the formation of von Willebrand factor multimers that cause large platelet plugs and diffuse microemboli, leading to life-threatening, multi-organ ischemic injuries. Although cardiac involvement commonly occurs related to TTP, these cardiac manifestations have not been well studied and may thus be overlooked in clinical practice. Management of cardiac ischemia or myocardial infarction in TTP is also challenging due to increased hemorrhagic risk in the setting of thrombocytopenia. In this report, we systematically review available clinical data in the literature and summarize clinical manifestation, diagnostic workup strategies, prognosis, and the outcomes of cardiac involvement of TTP. We provide recommendations on the strategies for clinical assessment and management of TTP patients with cardiac involvement.

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INTRODUCTION

Thrombotic thrombocytopenic purpura (TTP) is characterized by the concomitant occurrence of severe thrombocytopenia, microangiopathic hemolytic anemia (MAHA), and a variable degree of ischemic end organ damage. The pathophysiology is elicited by microthrombi forming in the arterioles and capillaries of multiple organs throughout the body. These thrombi are caused by systemic platelet activation and aggregation due to a failure of degradation of unfolded high molecular weight large von Willebrand factor (vWF). These microthrombi deposit systemically and cause widespread organ dysfunction, including pancreas, adrenals, heart, brain, and kidneys. As a result, the patient may present with acute kidney injury, stroke, seizure, or myocardial infarction (MI)[1,2]. The cardiac manifestations of TTP can be variable, ranging from silent arterial thrombosis and accelerated hypertension, to acute MI (AMI), atrial fibrillation, and congestive heart failure (CHF). In addition, these platelet and coagulation abnormalities can also be seen in cyanotic congenital heart disease.

PATHOPHYSIOLOGY AND CLINICAL MANIFESTATIONS OF TTP

The center of TTP pathophysiology is a defect of a disintegrin and metalloproteinase with a thrombospondin type 1 motif member 13 (ADAMTS13), either genetically or by the development of an autoantibody. ADAMTS13, also known as vWF-cleaving protease, is a zinc-containing metalloprotease enzyme that cleaves vWF. ADAMTS13 is a 1,427 amino acid protein that is expressed predominately in hepatic stellate cells, podocytes, renal tubular epithelial cells, platelets, and endothelial cells[1]. vWF is synthesized by megakaryocytes and endothelial cells, and is stored in the form of ultra-large multimers in granules of platelets, Weibel-Palade bodies of endothelial cells, and subendothelial connective tissue. ADAMTS13 cleaves a single peptide bond (Tyr1605-Met1606) located within the central vWF A2 domain. The proteolysis process reduces vWF multimer size and, consequently, its hemostatic function[3,4]. Lack or loss of ADAMTS13 function results in increased circulating vWF multimers, which leads to platelet adhesion to the endothelium, platelet activation, and ultimately the formation of a platelet plug.

Depending on the mechanisms of ADAMTS13 inhibition, TTP is divided into 1) an acquired form, which arises from autoantibody-mediated ADAMTS13 inhibition, and 2) a relatively rare inherited form, which results from an autosomal recessive gene mutation causing innate ADAMTS13 dysfunction. As microthrombi form, especially where arterioles and capillaries meet, end organ ischemia and injury occur due to

vascular obstructions caused by the microthrombi. In addition, the circulating red blood cells are subjected to increased shear stress, which damages their membranes, leading to schistocyte formation and anemia.

Clinically, TTP can be manifested systemically due to the involvement of multiple organs[5]. The classic presentation of TTP includes the following pentad: fever, changes in mental status, thrombocytopenia, reduced kidney function, and MAHA. MAHA and thrombocytopenia are hallmarks of TTP, and the possibility of TTP should be evaluated in any patients who present with these findings and who do not have an apparent alternative explanation.

CLINICAL CARDIAC INVOLVEMENT OF TTP

Extensive cardiac involvement was reported in the first TTP patient in 1925. This patient showed T wave inversions on the electrocardiogram (ECG) and extensive thrombi in the terminal arterioles and capillaries of the heart, as confirmed by autopsy examination[6]. Subsequently, the heart was found to be the most commonly affected organ in TTP. Additional autopsy studies of deceased patients with TTP showed that cardiac arrest and AMI are the most common immediate causes of death[7].

Clinical manifestations of cardiac involvement in TTP can vary dramatically, from an asymptomatic elevation of cardiac biomarkers, to chest pain or heart failure symptoms associated with ECG changes, elevation of cardiac enzymes, imaging evidence of massive MI, cardiomyopathy, arrhythmia, or even sudden cardiac death (SCD)[8-11].

Elevated cardiac troponin (cTn) was reported in 59% of patients with TTP upon admission. However, the majority of this group was clinically silent from a cardiac standpoint. ECG changes are common in TTP patients with elevated cardiac enzymes[12]. Hawkins *et al*[9] performed extensive analysis of 111 patients with TTP and reported the most common cardiac symptoms to be chest pain (11.7%), CHF (9.0%), and syncope (0.9%). The most frequent cardiac events in those patients included MI (23.4%), CHF (15.3%), arrhythmias (9.0%), cardiogenic shock (5.4%) and SCD (7.2%). AMI in TTP can present as ST segment elevation MI (STEMI) or non-STEMI with or without echocardiographic evidence of segmental wall motion abnormalities[11]. Patients with AMI in the setting of TTP often developed arrhythmias such as atrial fibrillation (25%), atrial flutter (13%), supraventricular tachycardia (13%) and CHF (25%)[8].

PATHOGENESIS AND AUTOPSY EVIDENCE OF CARDIAC COMPLICATIONS IN TTP

In TTP, the large vWF multimers mediate platelet plugs and microthrombi formation. Hyalinized arteriolar and microvascular microthrombosis in the coronary artery circulation has been shown in most autopsy reports. Microthrombosis is the most common finding of cardiac pathology in autopsies of deceased patients who suffered from TTP (Table 1). Epicardial coronary arterial thrombosis is rare. Large epicardial coronary arteries are commonly spared from thrombosis in TTP. However, recurrent epicardial arterial thrombosis has been reported in one TTP patient who was treated with thrombectomy, stent placement and dual antiplatelet therapy[13]. The interaction between vWF multimer-mediated thrombosis with existing vulnerable plaques in concomitant atherosclerotic coronary artery disease (CAD) was postulated to induce the arterial thrombosis[14]. Thus, arterial/arteriolar thrombosis leads to myocardial ischemia, infarction and necrosis. Thrombocytopenia and ischemia-induced damage of vascular integrity subsequently leads to myocardial hemorrhage. These processes not only lead to myocardial damage, but often cause dysfunction of the cardiac conduction system. In addition, marantic endocarditis has been reported[7,10,12]. Also, James *et al*[15] reported myocardial degeneration in atrial and ventricular myocardium in TTP patients as a result of apoptosis.

PROGNOSTIC VALUE OF CARDIAC INVOLVEMENT IN TTP

Post-mortem studies clearly demonstrated a high incidence of cardiac involvement in deceased TTP patients. Autopsy reports revealed almost all patients with TTP have cardiac involvement, and the disease process mostly affects the microvasculature of the heart. Cardiac complications directly cause death in TTP, particularly in acute

Table 1 Cardiac involvement and pathology in autopsy studies of deceased patients with thrombotic thrombocytopenia purpura

Authors	Year	Total No.	Descriptive comments of cardiac involvement and pathology			
			Microthrombi in small vessel (arteriole/capillaries)	Epicardial coronary thrombus	Hemorrhage petechiae	Other pathology
Moschcowitz[6]	1925	1	1/1	0/1	n/r	
Amorosi *et al*[45]	1966	3	3/3	1/3	3/3	AV node involvement 1/3
James *et al*[46]	1966	3	3/3	0/3	3/3	
Geisinger[47]	1979	1	1/1	0/1	1/1	
Ridolfi *et al*[48]	1979	17	17/17	0/17	13/17	AV node and his bundle involvement 7/17
Ross *et al*[49]	1987	1	1/1	0/1	1/1	
Bowdler *et al*[50]	1987	1	1/1	0/1	1/1	
Siersema *et al*[51]	1989	3	3/3	0/3	3/3	SA, AV node, His bundle involvement 3/3
Bell *et al*[52]	1990	8	8/8	0/8	8/8	SA and AV node involvement 2/3
Webb *et al*[53]	1990	1	1/1	0/1	1/1	
Eagle *et al*[54]	1994	1	1/1	0/1	1/1	
James *et al*[15]	1997	6	6/6	0/6	6/6	SA, AV nodes and His bundle involvement 6/6
Podolsky *et al*[55]	1999	1	1/1	0/1	1/1	AV node involvement 1/1
Wajima *et al*[56]	2000	1	1/1	0/1	1/1	
Hosler *et al*[57]	2003	25	25/25	n/r	n/r	
Lapp *et al*[23]	2004	1	1/1	0/1	1/1	
Brandenburg *et al*[58]	2004	1	1/1	0/1	1/1	
Gami *et al*[59]	2005	3	3/3	n/r	n/r	
Ibernon *et al*[60]	2005	1	0/1	1/1	1/1	
Arnold *et al*[61]	2006	1	1/1	0/1	1/1	
Patschan *et al*[10]	2006	4	4/4	0/4	2/4	
Sarode *et al*[62]	2009	1	1/1	n/r	n/r	
George *et al*[63]	2012	1	1/1	n/r	n/r	
Nichols *et al*[7]	2015	18	9/18	0/18	7/18	
Summary		104	94/104 (90.4%)	2/74 (2.7%)	56/73 (76.7%)	

AV: Atrioventricular; SA: Sinoatrial.

myocardial necrosis as a result of extensive circulatory microthrombosis. AMI and CHF are known independent risk factors for in-hospital mortality in patients with TTP[16,17]. Elevated LDH and troponin at presentation were found to be independent risk factors for MI[10]. cTn I above 2.5 ng/mL was found to independently predict mortality and refractory TTP. Therefore, evidence of cardiac involvement in TTP provides important prognostic value. A systematically structured approach to monitor signs and evidence of cardiac involvement may be cost-effective.

CARDIAC EVALUATION OF TTP

There is limited knowledge about optimal cardiac evaluation for patients with TTP. There are also large variations in clinical practice. Clinically, the majority of patients with TTP present without any clinical symptoms of myocardial ischemia. The traditional clinical pentad (fever, thrombocytopenia, microangiopathic anemia, neurological symptoms and acute kidney injury) of TTP does not include cardiac

symptoms. In current practice, cardiac evaluation is not part of routine initial evaluation for patients with suspected or confirmed TTP. The lack of or atypical cardiac symptoms in TTP may have contributed to the under-utilization of cardiac evaluation and delay in diagnosis. However, increasing data suggest that the presence of cardiac involvement in TTP strongly associates with an adverse outcome. Therefore, timely recognition and appropriate monitoring of cardiac status in TTP could be critically important in many cases. In recent decades, there have been dramatic advancements in laboratory, telemetric, non-invasive and invasive approaches of cardiac evaluation and therapeutics. The cost effectiveness and clinical significance of cardiac evaluation and therapeutics in TTP are thus important topics of discussion.

Cardiac biomarkers in TTP

Serial troponin-I or -T measurements are sensitive and specific biomarkers of myocardial injury. The overall incidence of troponin positivity in the TTP population has not been defined. However, multiple studies have shown that elevated troponin is a reliable biomarker for cardiac involvement in TTP. Elevated level of cTn upon admission is a risk factor for death and TTP refraction[17]. It seems reasonable to recommend a routine troponin measurement when a diagnosis of TTP is suspected or clinical deterioration is observed.

Telemetry monitoring in TTP

Considering the fact that there are consistent correlations between poor clinical outcome and evidence of cardiac involvement in TTP, it would be reasonable to monitor the patient on telemetry if cardiac involvement is suspected, *i.e*. positive troponin, abnormal admission ECG, or echocardiographic evidence of cardiomyopathy[18]. The evidence of cardiac conduction system involvement in TTP mandates telemetry monitoring. However, the cost-effectiveness of telemetry monitoring of all troponin-positive TTP patients has not been determined.

Cardiac imaging assessment of cardiac structure and function in TTP

Transthoracic echocardiography (TTE) is the most commonly used imaging modality to evaluate cardiac structure and function. In TTP patients with clinical symptoms, such as shortness of breath, palpitations, chest pain *etc*, that suggest ischemia, heart failure, arrhythmia or hemodynamic/electrical instability, a TTE should be performed[19]. TTE is also appropriate as an initial evaluation of cardiac structure and function in TTP patients with clinical data suggesting cardiac involvement, such as positive biomarkers (troponin, BNP *etc*), abnormal ECG and telemetry monitoring. Currently, there is no data available documenting the utilization and outcomes of TTE studies for TTP patients. The cost-effectiveness has also not been determined. Transesophageal echocardiography (TEE) is often unnecessary and rarely recommended for TTP patients, as thrombocytopenia is known to elevate the bleeding risk. The benefit of imaging modalities, such as cardiac magnetic resonance imaging (MRI), for assessing the impact of TTP on cardiac structure and function has not been studied.

Ischemic workup in TTP

The hallmark of TTP pathogenesis is thrombus formation in the micro-circulation. Occlusion of this micro-circulation, or less commonly of the epicardial coronary circulation, directly causes myocardial ischemia. Clinical evidence of ischemic symptoms, elevated troponin, or decreased myocardial contraction are all suggestive of myocardial ischemia in TTP. However, methods that will reliably evaluate the etiology of ischemia in these patients have not been adequately investigated. Non-invasive imaging modalities, such as Doppler coronary artery blood flow velocity and myocardial contrast echocardiography, are considered cost effective methods that correspond well with invasive techniques, but they are used less frequently in routine cardiology practice. Their role in patients with TTP has not been studied. Positron emission tomography (PET) and cardiac MRI myocardial perfusion imaging studies both measure rest and stress myocardial blood flow and enable coronary flow reserve (CFR) quantification. Both modalities are well established for the detection of CAD-related ischemia, and for the evaluation of microvascular disease. Both are sensitive in detecting the heterogeneous distribution of microvascular defects, which may indicate microvascular disease[20,21]. High resolution, ECG-gated cardiac computed tomography (CT) angiography (CTA) enables non-invasive imaging of the epicardial coronary arteries. Theoretically, CTA provides a reasonable approach to evaluate myocardial ischemia and the involvement of epicardial coronary arteries in TTP without the concern of bleeding risk associated with an invasive approach. However, its clinical significance has not been studied in this patient group.

In TTP, the high incidences of elevated cardiac enzymes and myocardial injury are mostly driven by ischemia at the level of the microvasculature. There are a few reports in the literature that describe using invasive coronary angiography to evaluate coronary artery patency in TTP patients[10]. While the majority of TTP patients had no obstructive disease in their epicardial arteries, there is a report of a patient with angiographic documentation of epicardial artery occlusion in TTP[22]. However, other TTP patients that presented with STEMI and cardiogenic shock were found to have clean coronary arteries on angiograms, with the visible "slow flow" phenomenon[23]. Therefore, diagnostic testing in this population should focus more on microvasculature of the heart rather than the epicardial arteries, especially in patients who recover from an acute episode and remain symptomatic from a cardiac standpoint. ECG evidence of acute STEMI probably deserves evaluation of the large epicardial arteries either by CTA or, more accurately, by invasive coronary angiography with the associated increased risk of hemorrhage, renal insufficiency and/or exacerbation of pre-existing anemia.

For the purpose of risk stratification and planning of both clinical treatment and monitoring when TTP is diagnosed, cardiac involvement should be systematically evaluated by ECG, cTn, and echocardiography. Patients with positive initial cardiac workup should have an Echocardiogram done during initial hospitalization, as left ventricular (LV) dysfunction has been reported in several publications[9]. A coronary angiogram may be indicated if concomitant atherosclerotic CAD is suspected based on risk profile and clinical features, but should be postponed if possible until the patient recovers from the TTP episode[14].

TREATMENT FOR CARDIAC COMPLICATIONS IN TTP

Therapeutic plasma exchange (TPE) - removing circulating anti-ADAMTS13 antibodies - is the cornerstone of TTP treatment, which resulted in reduced mortality from approximately 90% to 10%-20%. Immunosuppression with steroids or rituximab appears to be efficacious for acquired TTP, resulting in autoantibody formation against ADAMTS13. Experimental agents, such as recombinant ADAMTS13[24] as a specific protease supplement, and novel small molecules targeted on the vWF GpIbα-binding site on platelets are also promising therapies to further improve TTP treatment. In refractory TTP, other therapeutic approaches are also common, such as splenectomy, vincristine, cyclophosphamide, intravenous immunoglobulins, cyclosporine A, azathioprine, and mycophenolate mofetil, although there is not enough evidence yet to prove the efficacy of these treatment strategies. Platelet transfusion is generally not indicated; however, some authors recommend transfusing platelets in acute TTP episodes to decrease the risk of hemorrhage. As cardiac involvement is an integrated pathological process in TTP, general therapeutic strategies should also benefit the cardiac system.

Despite the recognition of the significant association between cardiac involvement and adverse clinical outcome in TTP, targeted management approaches for cardiac complications in TTP have not been well investigated. On the other hand, recent decades have seen significant advancements in evidenced-based medical and procedural treatments for acute coronary syndrome (ACS) and cardiomyopathy. Anecdotal case reports have successfully applied all the available therapeutic tools that have saved the lives of TTP patients with life-threatening cardiopulmonary complications. These reports have documented successful primary percutaneous coronary intervention (PCI) in the setting of ongoing STEMI with angiographic evidence of epicardial coronary artery occlusions[22], thrombolytic therapy for massive pulmonary embolism or STEMI in the setting of TTP[25,26], extracorporeal membrane oxygenation (ECMO) support for cardiogenic shock due to acute global ischemia resulted from diffuse microthrombi, to subsequent heart transplantation after the resolution of TTP[27]. Hemodynamic support and targeted treatment for cardiac complications of TTP may provide the opportunity for TTP-targeted therapy to take effect and eventually improve mortality, particularly in cases of severe TTP with hemodynamically-compromising cardiac complications.

Treatment for ischemic injury

In general, the most common cause of acute ischemia injury to the myocardium is ACS, as a result of an acute atherothrombotic event in the coronary arteries. Antiplatelet and anticoagulation therapies aiming to terminate or reverse the thrombotic process are the main strategy to ameliorate ongoing ischemia. In TTP, thrombocytopenia with various degrees of microthrombosis is universal, and is directly responsible for most of the cardiac complications, especially myocardial

ischemia. Existing evidence suggests that the majority of these injuries are caused by microthrombosis in the microvascular beds and rarely involve large epicardial arteries. The safety and efficacy of antiplatelet and anticoagulation therapy in the setting of TTP and ongoing myocardial ischemia is still a topic of debate.

In current practice, antiplatelet therapy is always considered in patients with TTP to prevent microthrombi formation. Aspirin is generally recommended for TTP patients as an antiplatelet agent. The effectiveness and safety of other antiplatelet agents remains less certain. In a landmark study published by Rock *et al*[28] comparing plasma exchange with plasma effusion, all patients received dipyridamole (400 mg daily) and aspirin (325 mg daily) for a period of at least 2 wk as a standard therapy. Treatment and maintenance with both aspirin and dipyridamole is suggested by some studies to prevent TTP relapse[29]. Patients receiving aspirin and dipyridamole during the acute phase were noted to have lower mortality. In addition, ticlopidine maintenance was shown to prevent relapses after 1 year[30]. Some authors even suggest intravenous infusion of dipyridamole as an adjunctive therapy[31]. However, the mechanisms of thrombi formation in TTP may differ from atherothrombotic ACS. Thus, aspirin with dipyridamole may not have the same beneficial effects in TTP as it does for ACS[32,33] . Other P2Y12 receptor inhibitors, such as clopidogrel, prasugrel and ticagrerol, have not been tested for treating acute cardiac involvement in TTP. Furthermore, these thienopyridine derivatives (ticlopidine, clopidogrel, and prasugrel) are known to possess the potential of inducing acquired TTP[34].

Unfractionated heparin (UFH) or low molecular weight heparin (LMWH) products have not been well studied in microvascular thrombi-induced myocardial injury in TTP, nor have GPIIb/IIIa inhibitors and direct thrombin inhibitors. Anticoagulation remains the treatment of choice for other thromboembolic disorders like antiphospholipid syndrome, cancer-associated thrombosis, and heparin-induced thrombocytopenia. The risk of hemorrhage in the setting of thrombocytopenia in TTP with its pathological microthrombi formation leads to the dilemma for anticoagulation therapy.

In the setting of STEMI with potentially large epicardial artery occlusion, which carries the highest risk of cardiac death, the decision of whether or not to use aggressive antiplatelet and anticoagulation (with or without pursuing invasive coronary angiography and intervention) must be decided on a case by case basis. The clinical decision is made by weighing clinical risk and benefit in adjunction with TTP therapy. There are reports of successful PCI for STEMI in TTP patients, as well as successful use of thrombolysis therapy[13,25]. Should a TTP patient undergo a primary PCI for epicardial coronary artery occlusion, the patient is probably a better candidate for bare metal stents than for drug eluting stents, so as to reduce the required dual antiplatelet therapy duration. Due to thrombocytopenia in TTP and platelet dysfunction, the risk of bleeding during procedural treatments (diagnostic cardiac catheterization and PCI, pacemaker placement *etc*) for TTP patients is high. However, the threshold of platelet counts for these procedures is not defined. Physicians will need to assess on a case-by-case basis.

Treatment of microvascular disease remains a challenge, and not much data is available on this topic. Potentially beneficial treatments of microvascular disease in patients without TTP are beta blockers, non-dihydropyridine calcium channel blockers, nitrates, angiotensin converting enzyme inhibitors, and statins. But clinical evidence is lacking in TTP patients.

Statins have an established role in lowering cholesterol and reducing cardiovascular mortality in the general population. Statins help with the remodeling of coronary vessels, plaque stabilization, and the improvement of the perfusion of myocardial muscle. There are also other benefits observed with statins, including anti-inflammatory function and improvement in endothelial function. Statins could be beneficial in the TTP cohort of patients, as they have been shown to be an inhibitor of regulated vWF secretion in human umbilical vein endothelial cells[35]. These pleiotropic effects of statins have been shown to be beneficial in patients with coronary microvascular dysfunction, and have a potential role in the treatment of microvascular disease related to TTP. A recent study showed that Simvastatin can increase the expression of ADAMTS13 in podocytes[36]. Statins are safe in the majority of cases, but statin-induced TTP has also been reported[37,38]. There is a paucity of data on the use of statins in TTP patients.

Treatment for heart failure and cardiomyopathy

Heart failure symptoms are relatively common in TTP presentation during the hospital course. With the common involvement of kidney injury, potentially significant volume changes during TPE, and ischemic injury of myocardium with potential decrease of contractile function, volume overload and pulmonary congestion may occur. Therefore, it is critical to have close clinical monitoring and to treat

decompensated heart failure with both intravenous diuretics and vasodilatory agents for afterload reduction with or without inotropic support. Hemodynamic support may also be indicated in critically ill TTP patients with cardiac complications.

β-adrenergic receptor blockers: β-blockers are proven beneficial for cardiomyopathy and ischemic heart disease at the epicardial and the microcirculation level[39]. β-blockers are indicated for patients with myocardial injury and decreased LV ejection fraction (LVEF). Although there are no direct large-scale clinical studies on the use of β-blockers in TTP patients, they intuitively should be used for TTP patients with evidence of cardiac involvement. Published reports show complete recovery of TTP-related ischemic cardiomyopathy with regimens that include β-blockers[40]. β-blockers and calcium channel blockers are commonly used to treat angina symptoms in patients with coronary microvascular dysfunction. Additionally, β-blockers like Nebivolol have been shown to improve endothelial function, which may help patients with TTP[41].

Calcium channel blockers: Calcium channel blockers are commonly used in the treatment of microvascular dysfunction. Reported anti-atherogenic and antithrombotic properties of calcium channel blockers might have significant benefits in TTP treatment[42], however their efficacy in these patients has not been established.

Angiotensin-converting enzyme inhibitor/angiotensin receptor blockers: Inhibitors of the renin-angiotensin system have a well-documented role in patients post-MI with decreased LVEF. Angiotensin-converting enzyme inhibitor (ACEi) and angiotensin receptor blockers (ARB) have been shown to be effective in the treatment of endothelial dysfunction and in the improvement of CFR. ARB is usually the choice when patients are unable to tolerate ACEi. Patients who are not candidates for either could benefit from a nitrate-hydralazine combination or Spironolactone. The addition of spironolactone was found particularly beneficial in patients with microvascular disease and diabetes. While these agents have been confirmed by large clinical trials to be beneficial in treating heart failure, cardiomyopathy, endothelial dysfunction and microcirculation dysfunction, which are all common in TTP patients, there is no data on the use or efficacy of ACEi/ARB in TTP patients.

Treatment of cardiac conduction system complication

For cardiac conduction system complications, *i.e.*, heart block, or arrhythmia, dedicated therapy will be indicated. Temporary transvenous pacemakers may be necessary for a hemodynamically significant heart block. Anti-arrhythmic agents may also be indicated for tachyarrhythmias with or without cardioversion, depending on clinical status. There are no long-term follow up data on cardiac conduction complications in TTP patients.

FOLLOW UP CARDIAC CARE OF TTP

With the advancement in understanding of the pathophysiology of TTP, as well as effective therapeutic strategies, the lethality of TTP has decreased. Its overall mortality has been reduced from 90% to 10%-20%. However, long-term follow up of TTP survivors showed their increased mortality over time when compared to the general population. Speculated causes include ADAMTS13 deficiency as a risk factor for cardiovascular disease, as well as ischemia from microvascular thrombosis, causing end organ damage over time. There are cases suggesting cardiac and renal complications to be responsible for suboptimal long-term outcomes in these patients. Therefore, routine cardiology follow up after recovery from acute TTP seems reasonable, especially for the patients with cardiac involvement during the acute phase. However, data are not available at this time to show the long-term cardiac implications of TTP and the significance of follow up cardiology care of TTP.

Ischemic workup and treatment

Considering the common occurrence of renal insufficiency and increased hemorrhagic risk during acute TTP, CAD status in the setting of ischemic injury during TTP is not often investigated. After recovery of acute TTP, ischemic workup should be performed with either a non-invasive stress test with myocardial perfusion imaging, or cardiac catheterization for patients with high pre-test probability of severe CAD.. Coronary CT angiography is also an option for defining the coronary anatomy. Exclusion of epicardial CAD and confirmation of microvascular disease may be helpful in the management of patients with chronic ischemic symptoms. Indeed, multiple reports showed adverse outcomes related to coronary microvascular

dysfunction[43]. A recent report showed that microvascular disease is directly related to increased mortality when compared to the general population[44]. However, despite the evidence of cardiac microvascular involvement in TTP, the long-term CAD risk for TTP survivors in comparison to the general population is unknown.

Other medications like ranolazine, ivabradine, amitriptyline, imipramine, or nortriptyline were found to be beneficial in the treatment of angina in coronary microvascular dysfunction, but their role in the TTP cohort is unknown. They could be considered for treatment of TTP patients who remain symptomatic with angina after recovery from an acute episode.

Cardiomyopathy follow up

TTP patients with evidence of ischemic injury and decreased LV function during the acute phase should be followed by cardiology as outpatients. It is reasonable to recommend evidence-based, guideline-directed medical therapy for cardiomyopathy with β-blockers, ACEi/ARB and other indicated agents. It is also reasonable to follow up on the recovery of EF. The long-term follow up on the trajectory of LV contractile function in TTP patients has not been established, although existing reports seem to suggest a favorable outcome commonly with full LVEF recovery. The risk of sudden cardiac death in TTP patients with severely reduced EF is unknown. The potential need for a permanent pacemaker for conduction system complications and an implantable cardioverter-defibrillator (ICD) for primary prevention of sudden cardiac death of patients with TTP is unclear.

CONCLUSION

Cardiac involvement in TTP is common. The presence of cardiac involvement is associated with adverse clinical outcomes in TTP patients. Contemporary diagnostic and therapeutic approaches provide the opportunity to improve clinical management of the cardiac complications related to TTP. Based on the above review of the literature and our own experience, we propose the following recommendations to clinicians managing TTP patients (Figure 1), in addition to the TTP routine workup and treatment. (1) All patients with suspected or confirmed TTP diagnosis should be screened for the potential presence of cardiac involvement by clinical symptoms/signs, ECG and cTn. (2) Any clinical deterioration of TTP patients with initial negative cardiac involvement warrants reassessment for the potential development of cardiac complications. (3) TTP patients with a positive screen or subsequent assessment of cardiac involvement should be monitored on telemetry, have cardiac biomarkers monitored as an indicator of disease progression, have TTE performed to assess cardiac structure and function, and have enhanced TTP-targeted treatment for disease control. (4) Aspirin therapy is indicated for all TTP patients. (5) Consider other targeted therapies (UFH, LMWH, low dose thrombolytics *etc*) for obstructive microthrombosis-related ischemia, with a balanced consideration of risk for hemorrhagic complications. (6) Apply evidence-based medical therapy for ischemia and cardiomyopathy, including diuretics, β-blockers, ACEi/ARB, statins, *etc*. (7) Treatment of arrhythmias and conduction abnormalities according to current guidelines. And (8) cardiology follow up and further evaluation as indicated after the acute phase of TTP.

Due to the lack of evidence from large clinical studies, the management of cardiac complications in TTP is largely based on the cohort data, experience and expert opinions. Future clinical studies on these topics are urgently needed. A multiple center prospective registry of TTP with a focus on cardiac implications and management is necessary to gather the evidence to better assess the clinical cost-effectiveness of these approaches.

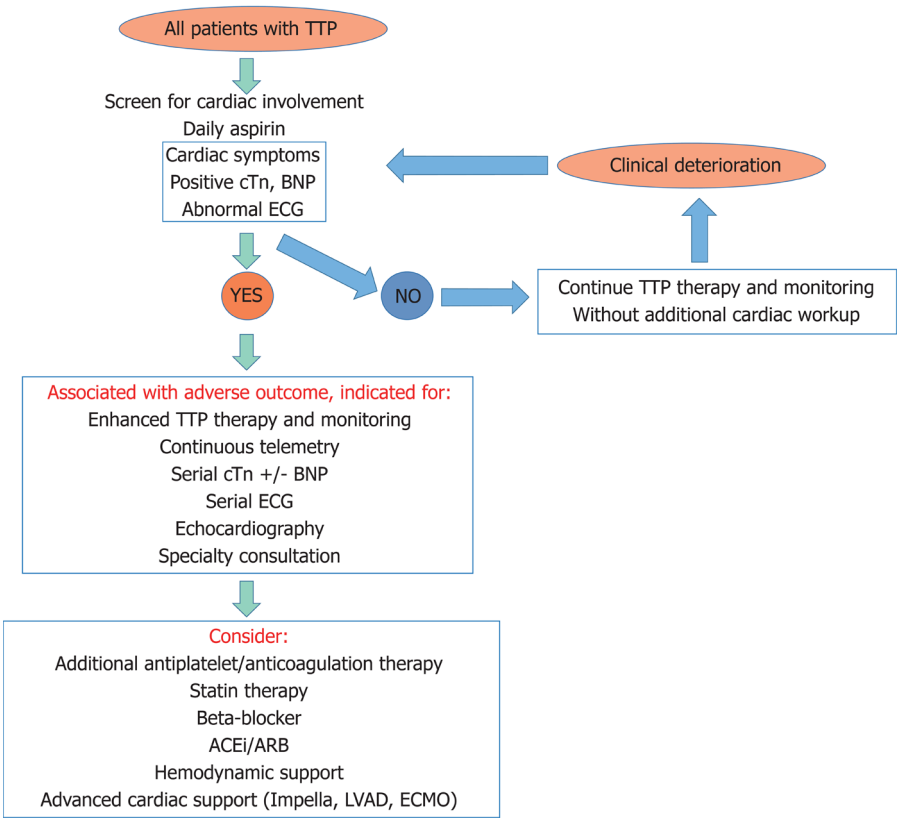

Figure 1 Recommendations on clinical assessment and management of cardiac involvement of thrombotic thrombocytopenia purpura. All patients with a diagnosis of thrombotic thrombocytopenia purpura (TTP) should be given low dose aspirin daily and screened for cardiac involvement by clinical cardiac symptoms, cardiac biomarkers (cardiac troponin, B-type natriuretic peptide *etc*) and electrocardiogram. Positive screen of cardiac involvement of TTP predicts adverse outcome, requiring further evaluation and treatment as recommended above. TTP: Thrombotic thrombocytopenia purpura; cTn, Cardiac troponin; BNP: B-type natriuretic peptide; ECG: Electrocardiogram; ACEi: Angiotensin converting enzyme inhibitors; ARB: Angiotensin receptor blockers; LVAD: Left ventricular assist device; ECMO: Extracorporeal membrane oxygenation.

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MINIREVIEWS

Instantaneous wave-free ratio (iFR®) to determine hemodynamically significant coronary stenosis: A comprehensive review

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Abstract

Coronary angiography is considered to be the gold standard in the morphological evaluation of coronary artery stenosis. The morphological assessment of the severity of a coronary lesion is very subjective. Thus, the invasive fractional flow reserve (FFR) measurement represents the current standard for estimation of the hemodynamic significance of coronary artery stenosis. The FFR-guided revascularization strategy was initially classified as a Class-IA-recommendation in the 2014 European Society of Cardiology/European Association for Cardio-Thoracic Surgery guidelines on myocardial revascularization. Both the Deferral *vs* Performance of Percutaneous Coronary Intervention of Functionally Non-Significant Coronary Stenosis and Flow Reserve *vs* Angiography for Multivessel Evaluation studies showed no treatment advantage for hemodynamically insignificant stenoses. With the help of FFR (and targeted interventions), clinical results could be improved; however, the use in clinical practice is still limited due to the need of adenosine administration and a significant prolongation of the length of the procedure. Instantaneous wave-free ratio (iFR®) is a new innovative approach for the determination of the hemodynamic significance of coronary stenosis, which can be obtained at rest without the use of vasodilators. Regarding the periprocedural complications as well as prognosis, iFR® showed non-inferiority to FFR in the SWEDEHEART and DEFINE-FLAIR trials. Furthermore, iFR®, enhanced by iFR®-pullback, provides the possibility to display the iFR®-change over the course of the vessel to create a hemodynamic map.

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Key words: Coronary stenosis; Coronary angiography; Fractional flow reserve; Instantaneous wave-free ratio; Myocardial ischemia; Coronary revascularization

Core tip: Invasive fractional flow reserve measurement represents the current standard for estimation of the hemodynamic significance of coronary artery stenosis and was initially classified as a Class-IA-recommendation in the 2014 European Society of Cardiology/European Association for Cardio-Thoracic Surgery guidelines on myocardial revascularization. Instantaneous wave-free ratio (iFR®) is a new innovative approach for the functional evaluation of a coronary stenosis, which can be obtained at rest without the use of vasodilators. The diagnostic value of iFR® showed non-inferiority compared to fractional flow reserve. It can be enhanced by iFR®-pullback, which provides the possibility to display the iFR®-change over the course of the vessel to create a hemodynamic map.

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INTRODUCTION

The optimal strategy for revascularization of hemodynamically significant coronary stenosis is an important therapeutic option in patients with coronary heart disease (CHD)[1]. Despite being the gold standard in the diagnosis of coronary stenosis, coronary angiography has a few limitations. Sometimes, the angiographic demonstration of the correct anatomy is limited due to morphologic deviations; additionally, visual evaluation of the coronary lesion is subjective and is associated with large inter-observer variability[2,3].

The current standard for invasive assessment of a coronary lesion with hemodynamic significance is the fractional flow reserve-(FFR)-measurement[4]. This was initially adopted as a Class-IA-recommendation in the European Society of Cardiology/European Association for Cardio-Thoracic Surgery (ECS/EACTS) guidelines of 2014 on myocardial revascularization[5]. Especially with intermediate coronary stenoses and in patients with a multivessel disease, FFR can help the clinician to assess the severity of the lesion and to formulate the required treatment[5]. Other than the angiographic imaging, FFR provides a direct functional assessment of coronary stenoses.

Both the Deferral *vs* Performance of Percutaneous Coronary Intervention of Functionally Non-Significant Coronary Stenosis and the FAME (Flow Reserve *vs* Angiography for multivessel Evaluation) studies could not prove a prognostic benefit of treating hemodynamically insignificant coronary stenosis through percutaneous coronary intervention (PCI)[6-8]. Furthermore, long-term analysis of the Deferral *vs* Performance of Percutaneous Coronary Intervention of Functionally Non-Significant Coronary Stenosis study showed that the use of FFR improved the clinical outcome and lowered the procedural costs[9].

Patients with stable CHD who received FFR-guided PCI along with an adequate medication appeared to be more convalescent compared to patients on the medication-only therapy and were subjected to an emergency revascularization less frequently (FAME-II-study[8]). Additionally, patients with hemodynamically insignificant coronary stenoses (FFR > 0.80) who received optimal medical treatment alone showed a very good long-term outcome.

The FFR utilizes the linear relationship between pressure and flow at a point of an increased intracoronary resistance[10]. Assuming intracoronary pressure is proportional to the flow, a pressure gradient could indicate a lowered blood flow caused by a coronary stenosis. However, the intracoronary resistance changes periodically during a cardiac cycle. The periodic variations in resistance emerge from the interaction between the myocardium and the microvasculature during systole (high intracoronary resistance, compression of the microvasculature) and diastole

(low intracoronary resistance, decompression of the microvasculature[11]). To perform the FFR-measurement, adenosine is administered to the patient to induce a hyperemic condition in order to achieve a constant blood flow, and FFR can be calculated and averaged over several cardiac cycles.

Although the clinical and economical benefits of FFR have been proven[7,9], it is only used in about 6% of patients undergoing PCI for intermediate coronary stenoses (40%-70% diameter stenosis)[12]. This is due to the high price for a single FFR-wire (600-800€[13]) as well as the use of adenosine, which is an additional expense. Furthermore, with each coronary assessment there exists a certain risk of a perforation or dissection[14] whilst applying the wire. In addition, the assessment time is longer, and adenosine administration could lead to adverse effects like dyspnea, chest pressure and discomfort, hypotension, and even atrioventricular blocks. However, vasodilators offer a pragmatic solution to achieve a constant blood flow and stable perfusion. Although FFR delivers accurate results and provides valuable information for the clinician assessing a single stenosis, the process of estimating the severity of each single stenosis in vessels with multiple lesions is difficult and time consuming[15]. The hemodynamic effect of removing a single stenosis in complex CHD is not easily predictable. The reason for this is an interdependence between multiple lesions in continuous coronary arteries under hyperemia, leading the examiner to overestimate a distal lesion and underestimate a proximal lesion. Inconveniently, after the treatment of each stenosis, the segment has to be reassessed by the clinician[16,17]. Therefore, new methods like iFR® ("instantaneous wave-free ratio", Volcano Corporation, Koninklijke Philips N.V., Amsterdam, The Netherlands) offer a different approach. iFR® is based on the hypothesis that a specific time interval during the cardiac cycle, the diastolic "wave-free" period, can be identified when microvascular resistance is naturally minimized without the need of hyperemia induced by the administration of a vasodilator[18]. Next to the two large multicenter studies Functional Lesion Assessment of Intermediate Stenosis to Guide Revascularization (DEFINE-FLAIR)[19] and Swedish Web-Based System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies (SWEDEHEART)[20], which proved the non-inferiority of iFR® towards FFR, the first meta-analysis with 23 studies including 6300 coronary lesions was just recently published. This study verified a significant correlation between iFR® and the gold standard FFR and a good performance of iFR® identifying FFR-positive stenoses[21]. Besides FFR, iFR® was just recently adopted as a Class-IA-recommendation in the ECS/EACTS guidelines of 2018 on myocardial revascularization[22].

PHYSIOLOGICAL PRINCIPLES OF iFR®-ASSESSMENT

iFR®-measurement is based on the physical law outlined by the Hagen-Poiseuille equation, which describes a laminar flow of an incompressible viscous fluid flowing through a cylindrical pipe of a constant cross section, which depends on the type of fluid and the consistency of the pipe[23]. This law is a deviation of Ohm's Law (U = RxI).

$P = Q \times R$

Pressure = Flow × Resistance

$\Delta P \approx \Delta Q \times R$

Pressure change ≈ Flow change × Constant resistance

At a constant resistance, pressure changes are proportional to change of flow. When administering a vasodilator, the FFR-measurement utilizes this constant resistance proportionality, and the iFR®-index is obtained during a period of the cardiac cycle (diastole) when the resistance is minimal and naturally stable. The unique qualities of coronary blood flow result from the proximal pressure changes through pulsatile blood ejection as well as peripheral variations in coronary microcirculation[11]. It is not adequate to assess a stenosis severity by simply measuring the drop in maximum or intermediate pressure of the vessel, since the distal predominant pressure is affected by several components and does not necessarily reflect the proximal aortic pressure. The distal predominant pressure is primarily influenced by the pressure changes in the coronary microcirculation but can significantly affect the (instantaneous) proportion of pressure and blood flow as an index of intracoronary resistance. Wave intensity analysis helps to differentiate between distal and proximal variations[11].

In early systole, pressure rises rapidly without an increase in flow velocity (Figure 1). Accordingly, the index of intracoronary resistance rises as well. The rapid increase in pressure (without the flow acceleration) develops from adaption of the ejection

wave within the aorta and the compression wave from the coronary microcirculation.

Quite the opposite happens in early diastole: Pressure decreases while flow accelerates, which leads to a rapidly decreasing intracoronary resistance and absorption of blood into the coronary microcirculation. After this short period of pressure decrease, the index of coronary resistance is almost minimal and stable, since neither from the proximal nor from the distal coronary end wave activity is emitted. This wave-free period prevails over most of the diastole and is the basis for iFR®-measurement.

FURTHER IMPROVEMENTS

Pressure-derived flow indices like FFR refer to a proportional correlation between pressure and flow when resistance is constant[24], which only applies to a specific period of the cardiac cycle. Manipulations with vasodilators primarily reduce the systolic component of the resistance and can thus be used to achieve a minimal and stable value.

Among the advantages of iFR® are a drug-free approach, as well as the ability to reach a higher flow velocity during the measurement, which allows a better discrimination of hemodynamically significant stenoses. A series of measured and reproducible data are generated during a period of five consecutive heartbeats. Indices of 0.89 or less generated by iFR® are equivalent to the common limit of 0.80 or less in FFR[4] and serve as an indicator for ischemia (Figure 2). A clinical example is presented in Figure 3.

To detect the specific time during diastole for the calculation of iFR®, it is necessary to acquire electrocardiographic signals of the patient. To simplify the assessment process it has recently become possible to calculate the index by only using the pressure signals, thus allowing the process to be run independent of electrocardiography (ECG). Specific end-systolic and end-diastolic waveform characteristics are identified to receive the accurate proximal (Pa) and distal (Pd) coronary pressure[25].

Regarding the assessment of vessels with multiple lesions, iFR®-pullback offers a technique to create a hemodynamic map of a coronary artery, which allows an individual estimation of each stenosis. The pullback itself is conducted manually and detects continuously pressure changes per millimeter for a given length[16,17]. Since the iFR® is obtained under resting conditions, whereby the autoregulatory mechanisms in the vessel ensure a stable and constant baseline-flow, serial lesions are not affected by each other[26].

Baseline physiology offers the opportunity to quantify the impact of each single stenosis and can, therefore, predict the effect of a treatment of an individual stenosis within a vessel with multiple lesions. A hemodynamic map via pullback can simultaneously display iFR®-changes over the whole vessel and track down the lesion with the predominant pressure-loss[16]. Additionally, it can be overlaid with angiographic imaging in order to locate the exact physiologically significant anatomical site of the narrowings (co-registration)[17].

Other diastolic resting indices, such as the diastolic pressure ratio (dPR) obtained in different phases of the diastole like dPR*25–75* (25% to 75% of diastole) or dPR*mid* (midpoint of diastole) along with Matlab calculated iFR® (iFR*matlab*) and iFR®-like indices shortening the length of the wave-free period by 50 and 100 ms (iFR-$_{50\ ms}$ and iFR-$_{100\ ms}$), were compared to the iFR® and found to be numerically identical. Therefore, all guidelines and cut-off values as well as clinical recommendation can be applied to these indices[27].

CLINICAL STUDIES ABOUT THE - iFR®-MEASUREMENT

During the course of the initial pilot study Adenosine Vasodilator Independent Stenosis Evaluation (ADVISE), a wave-free period during the cardiac cycle was identified for the first time, enabling to determine stenosis severity without the administration of vasodilators. It was an international, multicenter, non-randomized study (Table 1), in which the flow and pressure data from 157 stenoses were collected. The study revealed a good correlation between the FFR- and iFR®-measurements. However, with only 131 patients, the population was relatively small. In this population, the iFR®-index 0.83 showed the best correlation with the FFR-index of 0.80. A subgroup analysis in patients with multivessel disease, similar to the FAME-study collective, confirmed an excellent diagnostic correlation of 93% between iFR® and FFR.

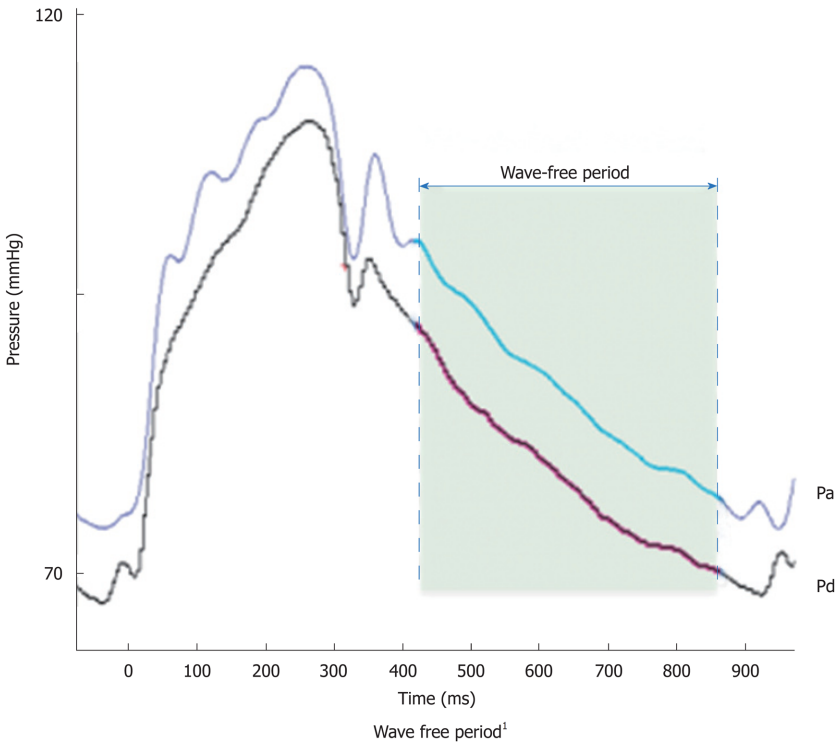

Figure 1 Proximal pressure and distal pressure during a wave-free period (grey shaded). Courtesy of Volcano Corporation, Koninklijke Philips N.V. Amsterdam, The Netherlands. Pa: Proximal pressure; Pd: Distal pressure.

The Multicenter Core Laboratory Comparison if Instantaneous Wave-Free Ratio and Resting Pd/Pa with Fractional Flow Reserve (RESOLVE)-study tried to examine the diagnostic accuracy of iFR®*vs* FFR. In the course of this retrospective, multicenter, non-randomized study, 1593 (81%) out of 1974 lesions were analyzed, as 381 lesions had to be excluded due to the inadequate image quality. Despite this, the result showed a moderate correlation between iFR® and FFR, with a diagnostic precision of 80.4%.

DEFINE-FLAIR, a leading multicenter, international, randomized, blinded study designed to prove the non-inferiority of iFR®, reiterated the findings of the previously mentioned studies. As of now, the available data are based on a 1-year-analysis. The ongoing study is conducted in 49 places in over 19 countries. Patients were included if they had at least one angiographically confirmed coronary disease, in which there was at least one stenosis of a questionable hemodynamic severity. Suitable patients were randomly assigned to a particular arm at a ratio of 1:1 FFR towards iFR®. The primary endpoint was the 1-year risk for major adverse cardiac events like cardiovascular death, nonfatal myocardial infarction, or unplanned revascularization. From January 2014 to December 2015, 2492 patients were included, 1242 in the iFR®- and 1250 in the FFR-group. The 1-year analysis showed comparable results regarding the endpoints, confirming the non-inferiority of iFR® towards FFR. The length of the procedure time was significantly shorter in the iFR®-group (iFR® 40.5 min, FFR: 45.0 min; $P < 0.001$), and less patients suffered from adverse effects like angina pectoris and dyspnea (3.1% *vs* 30.8%, $P < 0.001$), mainly because adenosine was not administered. In addition, when compared to FFR, this method was identified as more economically advantageous.

Published at about the same time, Instantaneous Wave-Free Ratio versus Fractional Flow Reserve to Guide PCI (iFR®-SWEDEHEART) also examined the non-inferiority of iFR® in the course of a multicenter, randomized, clinical study. The inclusion of eligible patients was based on the Swedish Coronary Angiography and Angioplasty Registry. Two thousand thirty-seven patients with a stable angina pectoris or an acute coronary syndrome were included and randomly allocated in a particular arm (iFR®*vs* FFR). Primary endpoint was the 1-year risk for major adverse cardiac effects like cardiovascular death, nonfatal myocardial infarction, or unplanned revascularization. Information about myocardial infarction or unplanned revascularization was gathered from the web-based register SWEDEHEART. The study was conducted in 15 places (13 in Sweden, one in Denmark, one in Iceland). The patients were recruited from May 2014 to October 2015. Of these 2037 patients, 1019 received iFR® and 1018 received FFR. Final analysis included 2019 patients, as 18 participants had to be

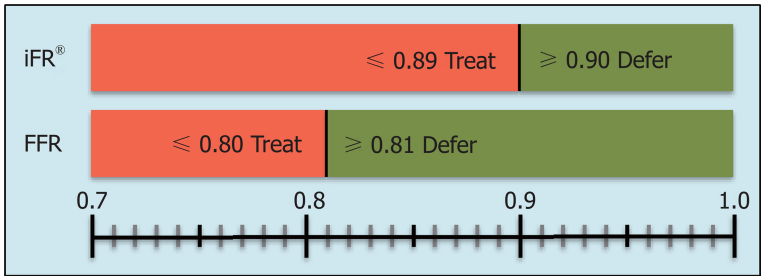

Figure 2 iFR® cut-off value and fractional flow reserve-measurement: An iFR®-value of ≤ 0. 89 indicates a hemodynamically significant stenosis (above, red bars), whereas an iFR®-value of ≥ 0.90 indicates no need for an intervention (green bar). Accordingly, FFR-indices of ≤ 0.80 lead to a revascularization, whereas FFR-indices of > 0.80 indicate a non-significant coronary stenosis. iFR®: Instantaneous wave-free ratio; FFR: Fractional flow reserve.

excluded because of the adverse effects under adenosine or technical problems.

The 1-year analysis of endpoints confirmed the non-inferiority of the iFR®-method. Especially in uncertain cases, where iFR® and FFR results differ, the data indicate that iFR® provides more accurate results. FFR-measurement tends to overrate the severity, since the vasodilator dependent hyperemia leads to a pressure decrease. The number of hemodynamically significant stenoses in this trial was much lower than in the FAME-study population, which only included patients with multivessel diseases. The iFR®-SWEDEHEART population is a better representation of the reality in clinical practice, since every patient with the indication for invasive coronary assessment could be included, independent of coronary status. Additionally, as described by Tonino and de Bruyne[7], an improvement in the clinical outcome of FFR-guided PCI was shown.

To compare ECG-independent iFR® calculation and the current method using ECG and pressure signals, Petraco *et al*[25] tested the only pressure-dependent iFR® algorithm in 320 coronary hemodynamically significant stenoses that were already included in multicenter studies (ADVISE[18], ADVISE Registry study[28], and a study by Nijjer *et al*[17]). The iFR®-indices of both methods correlated highly (r = 0.9997), which makes the ECG-independent iFR® applicable to the recent results of DEFINE-FLAIR and SWEDEHEART[25].

Based on the RESOLVE and ADVISE studies, Nijjer *et al*[17] have conducted a study (Pre-Angioplasty Instantaneous Wave-Free Ratio Pullback Provides Virtual Intervention and Predicts Hemodynamic Outcome for Serial Lesions and Diffuse Coronary Artery Disease) to create a hemodynamic map using the motorized pullback with iFR®, questioning if it helps to predict the stent impact in tandem and diffusely diseased vessels[17]. Thirty-two coronary arteries with two or more stenoses in 29 patients were assessed and underwent PCI. After physiological mapping, a computer-aided simulation calculated the best-case PCI effect. First, the virtual and real-world stents were compared to examine the predictive capability of iFR®-pullback. Second, the length of virtual stents, only positioned in areas with a high iFR®-intensity loss, was compared to the length of real world stents. **Δ**iFR®(exp) and **Δ**iFR®(obs) showed a strong relationship (r = 0.97, $P < 0.001$), and post-PCI iFR® was predicted with a 2% ± 1% error. Furthermore, the hereby examined physiological lesion length was significantly shorter than the anatomical length obtained by QCA (12.6 ± 1.5 mm *vs* 23.3 ± 1.3 mm, $P < 0.001$) and the length of the stent that was implanted in reality (27.5 ± 2.3 mm, $P < 0.001$).

Another study, published in 2017 by Kawase *et al*[29] (Residual pressure gradient across the implanted stent: An important factor of post-PCI physiological results) evaluated the accuracy of the predicted iFR®-value compared to the iFR® result, which was observed in reality after PCI. Additionally, they tried to discover potential factors for a failed prediction. iFR® ratios of 73 lesions in 71 patients were compared retrospectively before and after the coronary intervention. Pullback was conducted manually, anatomic lesion length was obtained by QCA, and the cut-off value of a difference between iFR®(pre) and iFR®(obs) was set at 0.036. The cut-off point was slightly missed, with a calculated mean difference of 0.036 ± 0.037, although the values correlated adequately (r = 0.756). In the course of a multivariate regression analysis, only a residual pressure gradient remained as an independent risk factor, leading to a failed prediction. After subtraction of the residual pressure gradient, the correlation between iFR®(pre) and iFR®(obs) improved. The only risk factors for a residual pressure gradient appeared to be a small diameter of the implanted stent and a high Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease-score[30], a score that calculates the amount of blood supplied to the myocardium by

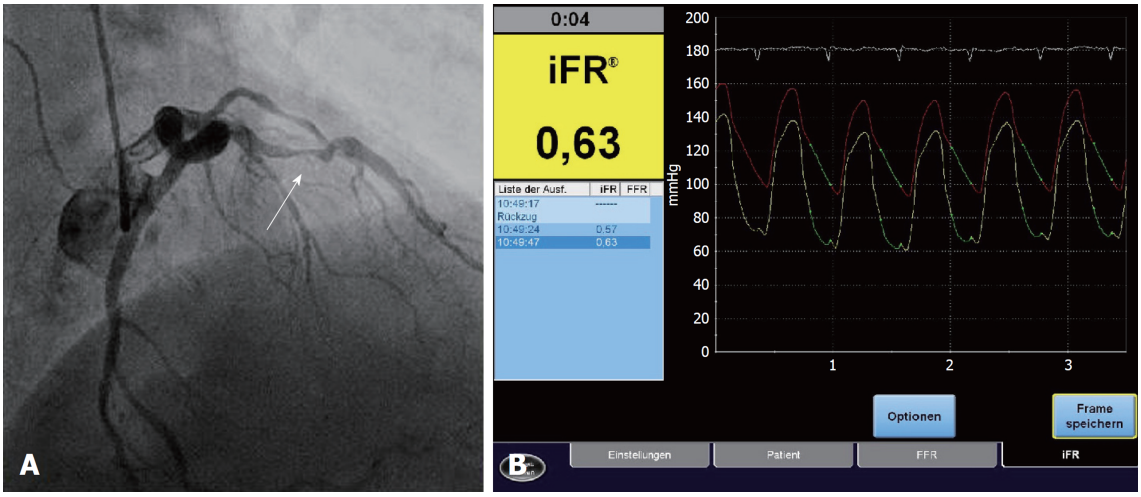

Figure 3 Case of a 69-year-old patient with symptoms of angina pectoris and a history of smoking (30 pack-years). A: Coronary angiography shows an initial two-vessel disease with a significant stenosis of the proximal LAD before percutaneous coronary intervention; B: iFR®-measurement was performed in the proximal LAD (iFR® = 0.63; bolt). FFR: Fractional flow reserve; LAD: Left anterior descending artery; iFR®: Instantaneous wave-free ratio.

the targeted vessel. Kawase *et al*[29] noted that a larger cohort study could identify additional factors that have caused a failed prediction. An overview about the most important current publications is composed in Table 1. Our manuscript is based on the review of previous published articles and did not involve animal or human subjects. Therefore, neither an ethical approval nor a patient consent was necessary.

LIMITATIONS

The process of advancing the coronary-pressure guide wire in FFR-measurement is still occasionally criticized and potentially accompanied by complications, which similarly constitutes a limitation of iFR®-measurement. This could hinder the regular clinical use of FFR- or iFR®-measurement.

It is not completely clarified how to proceed in uncertain cases and whether a stress test with adenosine is indicated. If hyperemia cannot be achieved through adequate doses, it is possible that the calculated value does not reflect the real FFR[31]. First, adenosine leads to peripheral vasoconstriction transmitted by pulmonary receptors, followed by its immediate effect on larger arteries that leads to a drop in blood pressure. This circumstance makes the ratio dependent on the time of measurement[32]. There is a small number of cases where not truly flow-limiting stenoses have led to acceptable iFR®-gradients but at the same time false positive hyperemic pressure gradients (FFR)[31]. High incidents of patient related discomfort, like dyspnea, chest pain, hypotension, and AV-blocks, or in one recorded case even ventricular fibrillation[33], still remain a limitation of the application of adenosine[34]. This limitation can be overcome by an adenosine free assessment like the iFR®.

In the analysis about the accuracy of the prediction of post-PCI iFR®, Kawase identified the residual pressure gradient as a risk factor for a the failed prediction and mentioned that its consideration might help the examining clinician[29].

Regarding microvascular diseases, studies could not prove a correlation between FFR and the index of microvasculatory resistance, an index for the microvascular status measured by the thermodilution technique[35]. This must not be seen as a shortcoming of the FFR method since it might rather show that micro- and macrovascular diseases are caused by different disease processes[36]. These findings can be employed on iFR®, since its non-inferiority towards FFR was proven.

Finally, there are currently new studies expected in which the iFR®-technique is to be subjected to the specific questioning, *i.e.*, the sequential assessment of stenosis. A reduction in costs is to be expected due to no administration of adenosine and shortened procedural time.

CONCLUSION

The current standard of cardiac invasive ischemic diagnostic is invasive FFR-measurement, which was initially adopted as a Class-IA-recommendation to the

Table 1 Significant instantaneous wave-free ratio-(iFR®)-studies

	Advise	Verify	Clarify	Park *et al*[39]	Resolve	Advise in practice	Indolfi *et al*[42]	ADVISE II	Harle *et al*[44]	Van de Hoef *et al*[45]	DEFINE-FLAIR	iFR®-SWEDEHEART
First author journal and year of Publication	Sen *et al*[18]. *J Am Coll Cardiol* 2012	Berry *et al*[37]. *J Am Coll Cardiol* 2013	Sen *et al*[38]. *J Am Coll Cardiol* 2013	Park *et al*[39]. *Int J Cardiol* 2013	Jeremias *et al*[40]. *J Am Coll Cardiol* 2014	Petraco *et al*[41]. *Am Heart J* 2014	Indolfi *et al*[42]. *Int J Cardiol* 2015	Escaned *et al*[43]. *J Am Coll Cardiol-Intv* 2015	Harle *et al*[44]. *Int J Cardiol* 2015	Van de Hoef *et al*[45]. *Euro-Interventio n* 2015	Davies *et al*[19]. *N Engl J Med* 2017	Götberg *et al*[20]. *N Engl J Med* 2017
Study design	PC, multicenter, non-randomized	PC, multicenter, non-randomized	PC, multicenter	PC, multicenter, non-randomized	RS, multicenter, non-randomized	PC, multicenter, non-randomized	PC, monocenter, non-randomized	PC, multicenter, non-randomized	PC, monocenter, non-randomized	PC, multicenter, non-randomized	PC, multicenter, randomized	PC, multicenter, randomized
Countries (centers)	2 (3)	6 (6)	2 (3)	1 (2)	7 (15)	101 (16)	1 (1)	8 (45)	1 (1)	3 (7)	19 (49)	3 (14)
Included patients	131	206	51	238	1768	313	82	598	109	228 (iFR® = 66)	2492 (iFR® = 1242)	2037 (iFR® = 1019
Stenoses	157	206	51	238	1974	392	123	690	151	299 (iFR® = 85)	3183 (iFR® = 1575)	3004 (iFR® = 1568)
Hemodynamic relevant stenoses (%)	N/A	134 (65)	N/A	103 (43.3)	N/A	153 (39)	37 (30.1)	248 (35.9)	N/A	N/A	451 (28.6)	457 (29.1)
Age in years ± SD	62.6 ± 10.2	65.2 ± 10.2	66.2 ± 9.2	62.8 ± 0.6	63.4 ± 10.3	67 ± 11	64 ± 9	63.6 ± 10.8	67 ± 11	58 ± 11	65.5 ± 10.8	67.6 ± 9.6
Men (%)	83.5	71	82.4	68	74.9	79	81.7	68.9	63.9	68	77.5	74.2
Diabetes mellitus (%)	54 (34.4)	50 (24)	14 (27.4)	66 (28)	497 (28.1)	94 (30)	14 (17.1)	209 (35)	N/A	10 (15)	382 (30.8)	232 (22.8)
Hypertonia (%)	88 (56.1)	137 (67)	18 (35.2)	133 (56)	N/A	232 (74)	61 (74.4)	471 (78.8)	N/A	25 (38)	873 (70.3)	730 (71.6)
Smoking (%)	34 (21.7)	64 (31)	15 (29.4)	64 (27)	520 (29.4)	160 (51)	49 (59.8)	135 (22.6)	N/A	21 (32)	243 (19.6)	159 (15.6)
One-vessel CAD (%)	108 (68.8)	85 (41)	N/A	N/A	N/A	113 (36)	50 (61)	N/A	75 (69.4)	N/A	N/A	452 (44.3)
Multi-vessel CAD (%)	49 (31.2)	105 (51)	N/A	N/A	951 (53.8)	197 (63)	32 (39)	N/A	33 (30.6)	N/A	505 (40.7)	364 (35.7)
Stable angina (%)	151 (96.2)	140 (68)	N/A	151 (63)	1216 (68.6)	228 (73)	29 (35)	320 (53.5)	N/A	N/A	986 (79.4)	632 (62.0)
Unstable angina (%)	6 (3.8)	46 (22)	N/A	84 (36)	255 (14.4)	85 (27)	53 (65)	151 (25.3)	N/A	N/A	186 (15.0)	211 (20.7)
iFR® cut-off	0.83	≤ 0.83	0.86	0.9	0.9	0.9	0.92	0.89	0.896	0.9	0.89	0.89
MACE-rate after 1 yr (iFR® *vs* FFR, *P*-value)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	6.8 *vs* 7.0 (*P* = 0.003)	6.7 *vs* 6.1 (*P* = 0.007)
Adverse events (iFR® *vs* FFR, *P*-value)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	3.1 *vs* 30.8 (*P* < 0.001)	3.0 *vs* 68.3 (*P* < 0.0001)

Diagnostic accuracy in % (iFR®*vs* FFR)	93	68	92.3	82	80.4	80	81.3	82.5	83.4	N/A	N/A	N/A

PC: Prospective cohort study; RS: Retrospective study; FFR: Fractional flow reserve; N/A: Not available; MACE: Major adverse cardiac events.

ECS/EACTS guidelines of 2014 on myocardial revascularization. Despite good existing evidence, the performance of pressure-derived functional assessment in daily routine is still limited. Here, iFR® provides a new innovative approach to assess coronary stenosis severity without administering vasodilators. Besides FFR, iFR® was just recently adopted as a Class-IA-recommendation in the ECS/EACTS guidelines of 2018 on myocardial revascularization[22]. Additionally, the eliminated necessity to record the electrocardiographic signals simplifies the procedure of the invasive functional assessment.

iFR®, extended by iFR®-pullback, can help achieve a better physiological result in treating vessels with multiple lesions by creating a hemodynamic map. Since implanting potentially larger stents to prevent a geographical miss is currently the standard in treating multivessel disease, a physiologically justified stent length might therefore be more hemodynamically beneficial for the vessel[16]. Therefore, factors like a residual pressure gradient and other potential not yet discovered influences that have led to an inaccurate prediction of post-PCI iFR® ratio have to be considered. Large-scale multicenter, randomized studies demonstrated the non-inferiority of iFR® to FFR, whilst requiring less procedural time, having lower costs, and having a lower number of patients who suffer from adverse effects due to a spared use of adenosine.

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