

# World Journal of *Cardiology*

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2014-2017

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## Left atrial physiology and pathophysiology: Role of deformation imaging

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### Abstract

The left atrium (LA) acts as a modulator of left ventricular (LV) filling. Although there is considerable evidence to support the use of LA maximum and minimum volumes for disease prediction, theoretical considerations and a growing body of literature suggest to focus on the quantification of the three basic LA functions: (1) Reservoir function: collection of pulmonary venous return during LV systole; (2) Conduit function: passage of blood to the left ventricle during early LV diastole; and (3) Contractile booster pump function (augmentation of ventricular filling during late LV diastole). Tremendous advances in our ability to non-invasively characterize all three elements of atrial function include speckle tracking echocardiography (STE), and more recently cardiovascular magnetic resonance myocardial feature tracking (CMR-FT). Corresponding imaging biomarkers are increasingly recognized to have incremental roles in determining prognosis and risk stratification in cardiac dysfunction of different origins. The current editorial introduces the role of STE and CMR-FT for the functional assessment of LA deformation as determined by strain and strain rate imaging and provides an outlook of how this exciting field may develop in the future.

**Key words:** Left atrium; Strain; Strain rate; Physiology; Pathophysiology; Cardiovascular magnetic resonance; Echocardiography; Feature tracking; Speckle tracking; Diastolic dysfunction

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**Core tip:** Recent advances in speckle tracking echocardiography (STE) and cardiovascular magnetic resonance myocardial feature tracking (CMR-FT) allow a detailed quantification of left atrium (LA) dynamics in terms of strain and strain rate imaging. Corresponding imaging biomarkers are progressively found to have the potential to predict the outcome in a variety of cardiovascular disease states. The current editorial introduces the role of STE and CMR-FT for the functional assessment of LA deformation and provides an outlook of how this exciting field may evolve in the future.

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## INTRODUCTION

Heart failure of different origins including ischemic aetiology remains a major determinant of mortality<sup>[1]</sup>. Left atrial (LA) enlargement has been shown to be a sensitive parameter for the prediction of adverse cardiac events<sup>[2,3]</sup>. The interplay between LA enlargement and atrial remodelling in the development of atrial fibrillation (AF) has been demonstrated<sup>[4,5]</sup>. However, the pure relation of LA pathology to its enlargement within different diseases may oversimplify cardiovascular physiology. It is important to note that the LA does not merely represent a stiff chamber, which passively transports blood from the pulmonary veins to the left ventricle (LV), but a more complex and active chamber. Its role should rather be described as a dynamic modulation of LV filling by functioning as a reservoir, conduit and contractile booster pump<sup>[6,7]</sup>. There have been tremendous advances in terms of our ability to characterize all three elements of atrial function using non-invasive imaging techniques<sup>[8]</sup>. Recent advances include LA deformation analysis using speckle tracking echocardiography (STE)<sup>[9,10]</sup> as well as cardiovascular magnetic resonance myocardial feature tracking (CMR-FT)<sup>[7,11]</sup>. Corresponding imaging biomarkers are progressively found to have the potential to predict the outcome in a variety of cardiovascular disease states<sup>[6]</sup>. The current editorial introduces the role of STE and CMR-FT for the quantification of LA dynamics as expressed by strain and strain rate (SR) imaging and provides an outlook of how this exciting field may evolve in the future.

## LA DEFORMATION ANALYSIS

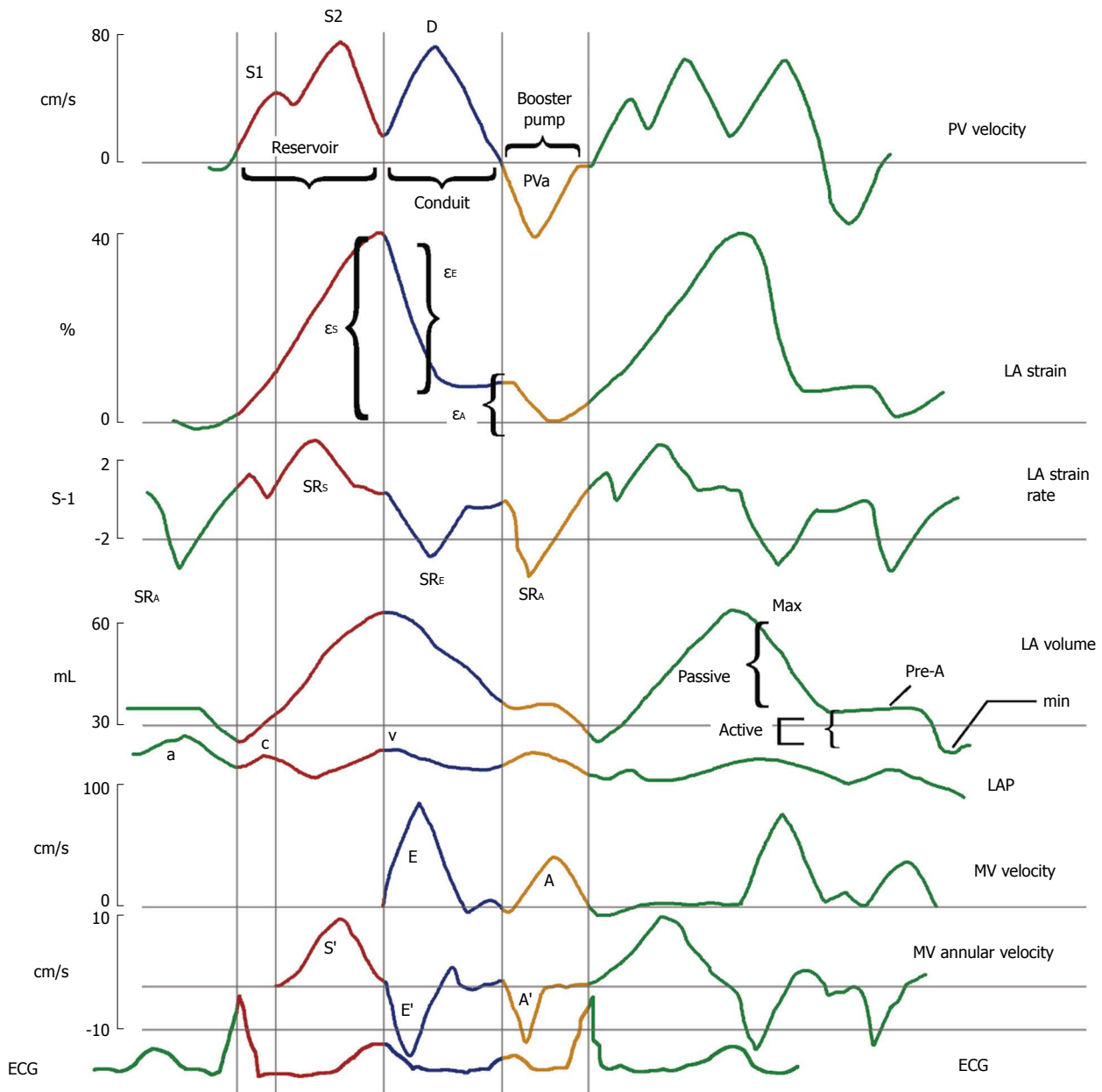
Besides conventional techniques to analyse LA func-

tional parameters (e.g., pulmonary venous velocity, LA phasic volumes, mitral valve inflow velocity or mitral annular velocity; recent advances in deformation analysis allow to quantify LA longitudinal strain and SR using STE or - more recently - CMR-FT<sup>[7,11]</sup> (Figure 1). Strain and SR represent the magnitude and rate of myocardial deformation (please see the review by Gorcsan and Tanaka for in depth explanation<sup>[12]</sup>). LA strain profiles result in three aspects of LA physiology: passive strain ( $\epsilon_E$ , representing LA conduit function), active strain ( $\epsilon_A$ , representing LA contractile booster pump function) and total strain ( $\epsilon_S$ , representing atrial reservoir function)<sup>[7]</sup> (Figure 1 and Table 1). Correspondingly, three SR parameters can be quantified: peak positive strain rate (SR<sub>S</sub>, representing LA reservoir function), peak early negative strain rate (SR<sub>E</sub>, representing LA conduit function) and peak late negative strain rate (SR<sub>A</sub>, representing LA contractile booster pump function)<sup>[7]</sup> (Figure 1 and Table 1). It is interesting to speculate on the physiological relevance of the three LA functional elements: LA reservoir function as a measure of LA compliance and LA active relaxation may represent a compensatory mechanism at early stages of congestive LV failure. Conversely, LA conduit function as a measure of LA compliance is already affected by early diastolic LV relaxation abnormalities with changes in LV stiffness and compliance. Lastly LA booster pump function representing LA contractility has impact on ventricular filling and cardiac output<sup>[13]</sup>.

LA deformation quantification comprises challenges that are not present when dealing with ventricular strain and SR imaging. These include the insertion of pulmonary veins and the presence of the LA appendage, the thin LA wall and the variable LA geometry<sup>[7]</sup>. Notwithstanding these facts, 2D STE and CMR-FT have both shown good performance and reproducibility of LA deformation analysis<sup>[7,14]</sup>. However, using two-dimensional representations of 3D structures may oversimplify the complex LA anatomy. Through-plane motion or reduced STE imaging quality with poor imaging windows can affect LA deformation analysis and may be difficult to correct. Recent advances in STE provide three-dimensional imaging that eliminates the effects of through-plane motion in patients with sufficient imaging windows and may allow the comprehensive analysis of global and regional LA strain<sup>[15,16]</sup>. At the present time, similar developments for CMR-FT based on three-dimensional imaging have not yet been introduced.

## STE

Two-dimensional STE makes use of offline software analysis using conventional gray scale B-mode images, which are typically acquired during a breath-hold. The frame rate is set between 50 and 70 frames/sec. Speckles can be described as acoustic markers distributed within the myocardium, which can be



**Figure 1 Left atrial physiology imaging using different methods.** The figure displays pulmonary venous (PV) velocity, left atrial (LA) strain ( $\epsilon$ ), LA strain rate (SR), LA volume, left atrial pressure (LAP), and mitral spectral and tissue Doppler. Displayed are two cardiac cycles and the color-coded imaging of reservoir, conduit, and booster pump functions in red, blue, and yellow lines are shown within the first cardiac cycle, respectively. Reprinted from Journal of the American College of Cardiology, Vol 63, Brian D. Hoit, Left atrial size and function: role in prognosis, 493-505, 2014 with permission from Elsevier<sup>[6]</sup>.

tracked from frame to frame<sup>[17]</sup>. This provides local myocardial displacement information, which can be utilized for the calculation of velocity, strain or SR. It is important to note that there is currently a lack of standardization for LA STE resulting in different approaches to calculate LA deformation indexes: LA strain and SR have been calculated by averaging values from a 15-segment model<sup>[18]</sup> (six equidistant segments in the apical 4-chamber view, six in the 2-chamber view and three in the 3-chamber view) or from a 12-segment model<sup>[14]</sup> (six equidistant segments in the 4-chamber view and six segments in the 2-chamber view). Usually, strain and SR indexes

are averaged from a total of three consecutive cardiac cycles that provide stable electrocardiographic recording. Furthermore, it is important to understand that there are two different approaches to quantify LA strain with STE. Based on the reference point set at the onset of the P wave (corresponding to the beginning of the atrial cycle)<sup>[10,19]</sup> or set at the QRS-complex (corresponding to the beginning of the ventricular cycle)<sup>[14,20]</sup>, different LA strain profiles are generated. The description above and the explanation in Figure 1 represent strain profiles acquired with the reference point set at the onset of the QRS-complex resulting in the acquisition of reservoir, conduit and booster pump

**Table 1 Left atrial strain and strain rate indexes as determined by speckle tracking echocardiography and cardiovascular magnetic resonance myocardial feature tracking**

LA function	Strain	Strain rate
Reservoir	$\epsilon_S$	$SR_S$
Conduit	$\epsilon_E$	$SR_E$
Booster pump	$\epsilon_A$	$SR_A$

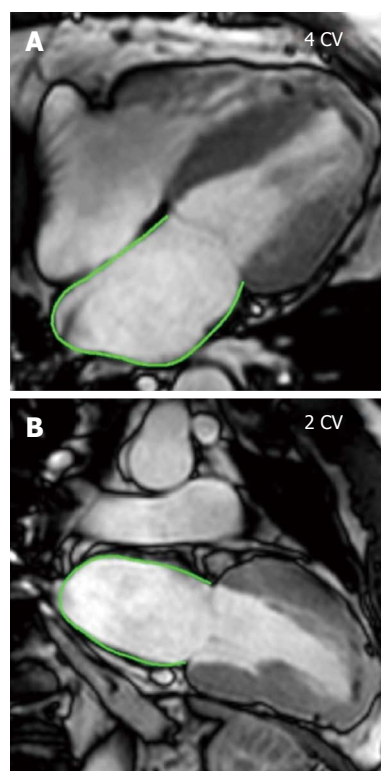
Nomenclature refers to the QRS complex set as the reference point and is therefore applicable to both speckle tracking echocardiography and cardiovascular magnetic resonance myocardial feature tracking. LA: Left atrial;  $\epsilon$ : Strain; SR: Strain rate.

function<sup>[6]</sup>. In contrast, if the reference point is set at the onset of the P wave, LA strain profiles display early negative strain (representing LA booster pump function) followed by peak positive strain (representing LA conduit function) while their sum corresponds to LA reservoir function<sup>[6]</sup>.

The wide availability and high temporal resolution of echocardiographic real time images are advantages of STE. However, due to the far-field location of the LA, the main drawback of STE is its dependency on high quality images that frequently cannot be guaranteed in patients with limited acoustic windows<sup>[14]</sup>.

### CMR-FT

CMR-FT allows tracking of tissue voxel motion directly from standard steady-state free precession (SSFP) cine CMR images and derivation of myocardial deformation (Figure 2) without the need for additional sequence acquisition as compared to myocardial MR Tagging<sup>[7]</sup>. Therefore, this technique appears particularly applicable from a clinical perspective and can be easily implemented into a running CMR laboratory. Although CMR-FT was initially validated for ventricular function analysis<sup>[21-27]</sup>, its applicability has recently been extended to quantitative longitudinal LA strain and SR analysis<sup>[7]</sup>. Typically, LA endocardial borders are initially traced in the 2- and 4-chamber views at the minimum atrial volume after atrial contraction<sup>[7]</sup>. Subsequently, an automatic tracking algorithm is applied. According to STE, LA contours are divided into six segments<sup>[20]</sup> and subsequently averaged to global strain and SR indexes using a 12-segment model (six equidistant segments in the 4 and 2-chamber views). CMR-FT benefits from high quality CMR images allowing robust contouring of the thin LA myocardium. Furthermore, CMR includes the acquisition of standardised and highly reproducible imaging planes, which is particularly important in longitudinal studies with repeated measurements<sup>[28]</sup>. Future studies will need to address whether or not CMR-FT has better inter-study reproducibility than STE. On the other hand, low temporal resolution of CMR images might affect deformation analysis, *e.g.*, the ability to accurately quantify peak strain rates<sup>[7]</sup>. Future evaluations will have to compare STE and CMR-



**Figure 2 Cardiovascular magnetic resonance myocardial feature tracking of the left atrium in a patient with hypertrophic cardiomyopathy.** Cardiovascular magnetic resonance myocardial feature tracking is performed in 4-chamber (A) and 2-chamber (B) views. Contours are based on 48 features, which are tracked throughout the cardiac cycle to generate longitudinal strain and strain rate profiles as displayed in Figure 1.

FT regarding the analysis of LA dynamics to determine whether or not results are interchangeable between modalities or one approach should be preferred over the other.

## FUTURE POTENTIAL OF LA DEFORMATION QUANTIFICATION

A growing body of literature suggests to focus on the quantification of the three basic LA functions rather than on the LA volumes only: LA reservoir function has shown to closely correlate with LV filling pressures<sup>[29]</sup> and has demonstrated to be a sensitive biomarker for the prediction of adverse cardiac events independently of other measures of cardiac dysfunction in patients with heart failure<sup>[30]</sup>. Strong association between LA conduit function and recurrent atrial fibrillation after pulmonary vein isolation has been described<sup>[31]</sup>. Accordingly, there has been tremendous effort to study LA dynamics with STE. Mounting evidence suggests that impaired LA strain and SR dynamics have the potential to serve as imaging biomarkers for the prognosis and risk stratification or the decision to intervene in heart failure<sup>[32,33]</sup>, hypertension<sup>[34]</sup>, coronary artery disease<sup>[35]</sup>, atrial fibrillation<sup>[36]</sup>, valvular heart disease<sup>[20]</sup> and cardiomyopathies<sup>[37,38]</sup> (please see reviews by Hoit<sup>[6]</sup> and



Viera *et al.*<sup>[17]</sup> for in depth information).

CMR-FT has been introduced more recently<sup>[7]</sup>. However, recent studies were able to demonstrate an association of impaired LA reservoir function and the development of heart failure in the general population<sup>[39]</sup>. Impaired reservoir function as determined by volumetric indexes, strain and SR measurements is also closely related to LV fibrosis<sup>[40]</sup>. With respect to previous reports on the relevance of LV fibrosis<sup>[41]</sup>, LA reservoir function may also represent a promising target for risk stratification. Furthermore, initial experiences on patients with hypertrophic cardiomyopathy (HCM) and heart failure with preserved ejection fraction (HFpEF) demonstrate impaired LA reservoir and conduit function in HCM and HFpEF<sup>[7]</sup>, when compared to healthy controls. In contrast, patients with HCM exhibit increased LA booster pump function while this is decreased in HFpEF<sup>[7]</sup>. Future studies will need to investigate whether or not this might refer to a potential compensatory mechanism in HCM, as opposed to a complete impairment of LA dynamics in HFpEF<sup>[7]</sup>. LA CMR-FT has not been applied to patients with atrial fibrillation yet. Deteriorated image quality, which is frequently present in patients with atrial fibrillation, might negatively impact on CMR-FT quality. It remains to be investigated whether or not CMR-FT is feasible in patients with atrial fibrillation using both, conventional ECG-gated SSFP sequences or real-time CMR techniques<sup>[42,43]</sup>, which have demonstrated improved image quality in arrhythmic patients as compared to conventional ECG-gated techniques<sup>[44]</sup>.

## CONCLUSION

LA physiology and pathophysiology as quantified by STE and CMR-FT carry promising clinical and prognostic implications. Future studies will need to apply LA deformation imaging to support our understanding of heart failure development and risk stratification in valvular heart disease, atrial fibrillation, hypertension, coronary artery disease and different types of cardiomyopathy.

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## Perspective of future drugs targeting sterile 20/SPS1-related proline/alanine-rich kinase for blood pressure control

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### Abstract

According to a genome-wide association study, intronic SNPs within the human sterile 20/SPS1-related proline/alanine-rich kinase (SPAK) gene was linked to 20% of the general population and may be associated with elevated blood pressure. As cell volume changes, mammalian SPAK kinases respond to phosphorylate and regulate cation-coupled chloride co-transporter activity. To our knowledge, phosphorylation of upstream with-no-lysine (K) (WNK) kinases would activate SPAK kinases. The activation of WNK-OSR1/SPAK cascade on the kidneys and aortic tissue is related to the development of hypertension. Several regulators of the WNK pathway such as the Kelch kinase protein 3 - Cullin 3 E3 ligase, hyperinsulinemia, and low potassium intake to mediate hypertension have been identified. In addition, the SPAK kinases may affect the action of renin-angiotensin-aldosterone system on blood pressure as well. In 2010, two SPAK knock-in and knock-out mouse models have clarified the pathogenesis of lowering blood pressure by influencing the receptors on the kidneys and aortic smooth muscle. More recently, two novel SPAK inhibitors for mice, Stock 1S-14279 and Closantel were discovered in 2014. Targeting of SPAK seems to be promising for future antihypertensive therapy. Therefore we raised some viewpoints for the issue for the antihypertensive therapy on the SPAK (gene or kinase).

**Key words:** With-no-lysine (K) kinase; Oxidative stress-responsive kinase 1/SPS1-related proline/alanine-rich kinase kinase; Na-Cl co-transporter; Na<sup>+</sup>-K<sup>+</sup>-2Cl<sup>-</sup> cotransporter; Hypertension

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**Core tip:** According to a genome-wide association study, intronic SNPs within the human sterile 20/SPS1-related proline/alanine-rich kinase (*SPAK*) gene was linked to 20% of the general population and may be associated with elevated blood pressure. Based on current studies, targeting of SPAK seems to be promising for future antihypertensive therapy. Therefore, we raised some viewpoints regarding the issue for antihypertensive therapy on the SPAK (gene or kinase).

Lin GM, Liu PY, Wu CF, Wang WB, Han CL. Perspective of future drugs targeting sterile 20/SPS1-related proline/alanine-rich kinase for blood pressure control. *World J Cardiol* 2015; 7(6): 306-310 Available from: URL: <http://www.wjgnet.com/1949-8462/full/v7/i6/306.htm> DOI: <http://dx.doi.org/10.4330/wjc.v7.i6.306>

## THE WITH-NO-LYSINE (K) KINASES AND HYPERTENSION AND HYPERKALEMIA

Pseudohypoaldosteronism type II, a disease characterizing hypertension with hyperkalemia has been caused by mutations in WNK [with-no-lysine (K)] 1 and WNK4<sup>[1]</sup>. WNK4 is predominantly produced in the kidneys and epithelial tissues and hence the expression of WNK4 is more restricted than that of WNK1. WNK4 has been shown as a potent inhibitor of diverse epithelial transporters including the renal outer medullary potassium ion channel and the thiazide-sensitive sodium chloride co-transporter (NCC)<sup>[2]</sup>. In addition, paracellular chloride ion flux is enhanced by WNK4 activity<sup>[2]</sup>. Importantly, mutations in WNK4 have divergent effects on these transport pathways. WNK4 mutations could increase the inhibition of the renal outer medullary potassium ion channel, relieve the inhibition of NCC, and further promote paracellular chloride ion flux<sup>[2,3]</sup>. These findings can support a model in which WNK4, as a molecular switch, can alter the balance between potassium ion secretion and chloride ion reabsorption and explain the physiological abnormalities in patients with pseudohypoaldosteronism type II. Other WNK kinases also distribute in diverse epithelia throughout the body and are involved in chloride ion flux, suggesting that these kinases may generally participate in the regulation of chloride ion flux.

## MOLECULAR PATHWAYS FOR WNK-SPAK/OSR1-NCC/NKCC TO CONTROL BLOOD PRESSURE

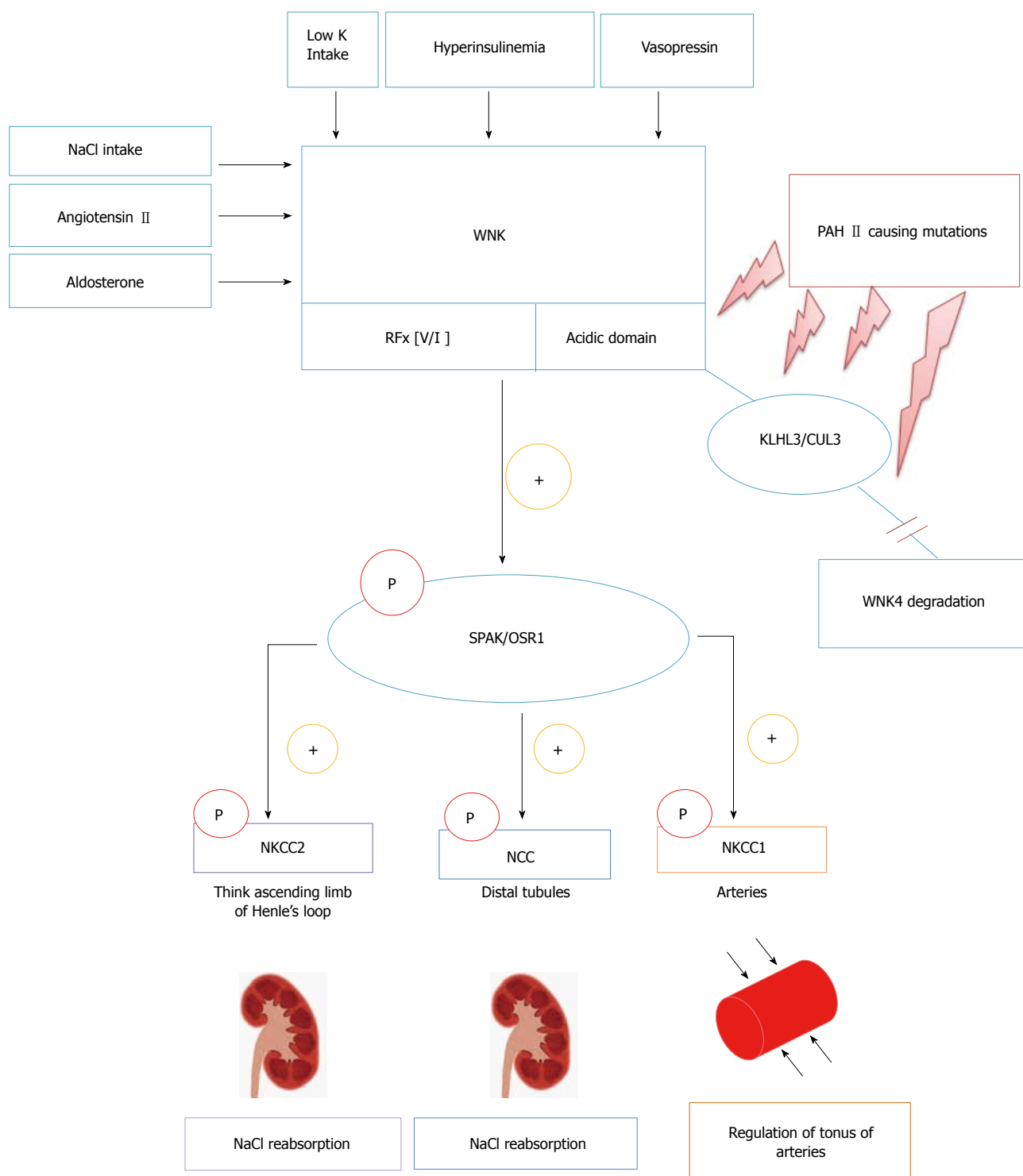
As cell volume changes, mammalian SPAK (SPS1-

related proline/alanine-rich kinase) and OSR1 (oxidative stress-responsive kinase 1) kinases respond to phosphorylate and regulate cation-coupled chloride cotransporter activity<sup>[4]</sup>. Phosphorylation of upstream WNK kinases would activate SPAK and OSR1. There are four mammalian WNK kinases: WNK1-WNK4. In humans, WNK1 and WNK4 mutations result in hyperkalemia and hypertension partly by altering renal sodium and potassium transport. WNK1 and WNK4 recruit an endocytic scaffold protein, intersectin, and thereby stimulate endocytosis of ROMK1. This recruitment occurs between the PXXP motif of the WNKs and the SH3 domain of intersectin which is independent of WNK kinase activity. WNKs regulate cation-chloride-coupled cotransporters, Na<sup>+</sup>-K<sup>+</sup>-2Cl<sup>-</sup> cotransporter (NKCC) 1 and NKCC2 (and NCC, under some conditions) dependent on kinase activity<sup>[5]</sup>. OSR1 and SPAK, two Ste20-related protein kinases, which are bound with and phosphorylated by WNK1 and WNK4, in turn bind with and phosphorylate cation-chloride-coupled cotransporters to increase their activity. Binding of OSR1/SPAK to upstream WNKs and downstream cation-chloride-coupled cotransporters are both mediated by a docking site in the C-terminus of OSR1/SPAK and RFX[V/I] motifs present in WNKs or in NKCCs and NCC<sup>[5]</sup>.

Several regulators of the activation of WNK kinase have been identified in recent animal studies as the Kelch kinase protein 3-Cullin 3 E3 ligase, low potassium intake, hyperinsulinemia, and some hormones (angiotensin II, aldosterone and vasopressin), which may act on the kidneys or aortic tissues to affect blood pressure<sup>[6-10]</sup>. Chávez-Canales *et al.*<sup>[11]</sup> showed that WNK4 could decrease the WNK1 and WNK3-mediated activation of NCC in the kidneys. This finding suggests that WNK kinases form a network in which WNK4 associates with WNK1 and WNK3 to regulate NCC. In addition, the activity of OSR1/SPAK in the kidneys could be enhanced by AMP-activated protein kinase resulting in sodium retention *via* phosphorylation of NKCC2 in obesity<sup>[12]</sup>. The effect of vasopressin on sodium reabsorption is mediated by SPAK along the distal nephron to control blood pressure as well<sup>[13]</sup>. Figure 1 shows the potential mechanisms of hypertension related to the WNK-SPAK/OSR1-NCC/NKCC cascade.

## SPAK KNOCK-IN AND KNOCK-OUT MOUSE MODELS AND THE EXPRESSION AND FUNCTION OF NCC/NKCC IN THE KIDNEY AND AORTIC TISSUE

Since intronic SNPs within the human *SPAK* gene (also known as *Stk39*) was linked to 20% of the general population and may be associated with hypertension in a genome-wide association study, targeting of SPAK seems to be promising for future



**Figure 1** Potential mechanisms of With-no-lysine (K) - SPS1-related proline/alanine-rich kinase/oxidative stress-responsive kinase 1 - Na-Cl co-transporter/Na<sup>+</sup>-K<sup>+</sup>-2Cl<sup>-</sup> cotransporter to contribute to hypertension. Several regulators of the activation of WNK cascade, such as KLHL3/CUL3, low potassium intake, hyperinsulinemia and some hormones (angiotensin II, aldosterone and vasopressin) may act on the kidneys or aortic tissues. SPAK and OSR1 are activated via phosphorylation by upstream WNK kinases using docking site in the RFX (V/I). As a result, SPAK/OSR1 may regulate cation-chloride-coupled cotransporters in kidneys, tonus of aortic tissues, and blood pressure. PAH II causing mutations in acidic domain of WNK4, KLHL3 and Cullin 3 activate SPAK/OSR1-NCC signaling by decreasing WNK4 degradation and accumulation of WNK4. KLHL3: Kelch kinase protein-3; CUL3: Cullin3; PAH II: Pseudohypoaldosteronism type II; WNK: With-no-lysine (K); SPAK: SPS1-related proline/alanine-rich kinase; NCC: Na-Cl co-transporter; NKCC: Na<sup>+</sup>-K<sup>+</sup>-2Cl<sup>-</sup> cotransporter; OSR1: Oxidative stress-responsive kinase 1.

antihypertensive therapy<sup>[14]</sup>. In 2010, Yang *et al.*<sup>[15]</sup> generated SPAK null mice in which exons 9 and 10 of the *Stk39* gene were deleted to investigate its role

in the kidneys and aortic blood vessels<sup>[15]</sup>. Earlier, Rafiqi *et al.*<sup>[16]</sup> had generated knock-in mice in which SPAK could not respond to the WNK kinases. Both

the homozygous SPAK knock-in (SPAK<sup>243A/243A</sup>) and knock-out mice (SPAK<sup>-/-</sup>) demonstrated the same phenotype of hypotension. Rafiqi *et al.*<sup>[16]</sup> accounted for the mechanisms of hypotension in knock-out mice as possibly by lowering expression and phosphorylation of NKCC2 and NCC in the kidneys. Yang *et al.*<sup>[15]</sup> further pointed out that the impaired vasoconstriction may be caused by both reduced function in aortic tissues and NKCC1 phosphorylation in addition to defects of NCC in the kidneys leading to hypotension in their SPAK null mice. However, some different characteristics are present between the SPAK knock-in and knock-out mice that need to be explained. For example, Yang *et al.*<sup>[15]</sup> reasoned the increased NKCC2 phosphorylation in the SPAK null mice due to compensatory up-regulation of OSR1 in the kidneys, which is contrary to the decreased NKCC2 phosphorylation and normal activity of OSR1 in the SPAK inactivated mice.

## A PERSPECTIVE FOR DRUG DEVELOPMENT TARGETING OF SPAK TO LOWER BLOOD PRESSURE

To our best knowledge, the SPAK knock-in mice (SPAK<sup>+/243A</sup>/SPAK<sup>243A/243A</sup>) have partial or complete inactivated SPAK function together with WNK1/4 when binding to a cluster of conserved Thr residues which are located at the N-terminal cytosolic domain of the electroneutral cation-coupled chloride cotransporters (SCL2). Because OSR1 binds to a similar cytosolic site on SCL2 with SPAK, to design a drug blocking the binding site between SPAK/OSR1 and SCL2 may affect OSR1 function and result in a hazardous effect. Therefore, the SPAK knock-in mice are more like a model for developing a new drug to target the SPAK protein instead of the binding site of SCL2. As drugs within the cells would inactivate SPAK, they would be competitive antagonist for the site of the N-terminal cytosolic domain of SCL2 with OSR1. As a result, the activity of OSR1 would not be enhanced in SPAK knock-in mice, would subsequently lead to reduced activation of NKCC2 in the kidneys when all the SPAK is inactivated. From this point of view, could we be convinced whether targeting the protein component of SPAK is a promising route? The answer may be derived partly from the blood pressure of SPAK<sup>+/243A</sup> knock-in mice, which was not reported by Rafiqi *et al.*<sup>[16]</sup>. Although SPAK<sup>+/-</sup> knock-out mice were observed to have the phenotype of hypotension, this result could not be translated to the knock-in mice directly. Since the SPAK knock-out mice had secondary hyperaldosteronism implying an aldosterone-resistant status which the SPAK knock-in mice did not have, hypotension in SPAK null mice may be associated with this condition rather than the reduction of NKCC1 activity that Yang *et al.*<sup>[15]</sup> proposed. A more definite proof of this would require tissue-specific SPAK knock-

out in the vasculature<sup>[17]</sup>, the distribution of SPAK in reference to OSR1 in the arterial vessels in mice should also be estimated. Given that the SPAK<sup>+/243A</sup> knock-in mice had either a normal range or only a little lower than normal blood pressure, drugs targeting SPAK would work ineffectively. Apparently, the importance of SPAK for the activation of different SCL2 is variable according to their affinity (K<sub>d</sub>, dissociation constant) and distributions in tissues. Pharmacokinetically, a drug should be bound to at least half of the SPAK contents to achieve 20% reduction of the epithelial functional NCC and 20% up-regulation of the functional NKCC2 in the kidneys and 40% down regulation of functional NKCC1 in the kidneys and vasculature similar to SPAK<sup>+/243A</sup> knock-in model<sup>[16]</sup>. How to determine the optimal drug concentration to obtain the goal of lowering blood pressure would also be a challenge due to different SPAK contents in the tissues and the competition from OSR1.

Alternatively, targeting the gene of SPAK in the kidneys and vasculature to produce the heterogeneous knock-out genotype of SPAK<sup>+/-</sup> with the phenotype of hypotension is a more difficult task. Secondary hyperreninemia and hyperaldosteronism standing for an aldosterone-resistant status should be highlighted in which they may be harmful to the heart with predominant OSR1 and less SPAK<sup>[16,18]</sup>. In addition, whether it is useful in people with primary or secondary hyperaldosteronism should be tested by a hypertensive mouse model with hyperaldosteronism.

Finally, there are some uncertainties regarding the inhibition of SPAK to control blood pressure including the adverse effects of infertility and reduced gastrointestinal glands secretion ability and the protective benefits from sepsis associated with the reduction of NKCC1<sup>[19-21]</sup>. Recently, Kikuchi *et al.*<sup>[22]</sup> have discovered one small-molecule compound (Stock 1S-14279) and an antiparasitic agent (Closantel) that could inhibit SPAK-regulated phosphorylation and activation of NCC and NKCC1 *in vitro* and in mice<sup>[22]</sup>.

The safety and efficacy of these novel SPAK inhibitors for mice and SPAK knock-in or knock-out mice could provide future models for the control of blood pressure and drug design for human beings. In summary, targeting of the gene or protein of SPAK should be evaluated systematically and the interactions among WNT, OSR1, SCL2 and Renin-Angiotensin-Aldosterone system would need further investigations.

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## Preliminary experience with drug-coated balloon angioplasty in primary percutaneous coronary intervention

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### Abstract

We evaluated the clinical feasibility of using drug-coated balloon (DCB) angioplasty in patients undergoing

primary percutaneous coronary intervention (PPCI). Between January 2010 to September 2014, 89 ST-elevation myocardial infarction patients (83% male, mean age  $59 \pm 14$  years) with a total of 89 coronary lesions were treated with DCB during PPCI. Clinical outcomes are reported at 30 d follow-up. Left anterior descending artery was the most common target vessel for PCI (37%). Twenty-eight percent of the patients had underlying diabetes mellitus. Mean left ventricular ejection fraction was  $44\% \pm 11\%$ . DCB-only PCI was the predominant approach (96%) with the remaining 4% of patients receiving bail-out stenting. Thrombolysis in Myocardial Infarction (TIMI) 3 flow was successfully restored in 98% of patients. An average of  $1.2 \pm 0.5$  DCB were used per patient, with mean DCB diameter of  $2.6 \pm 0.5$  mm and average length of  $23.2 \pm 10.2$  mm. At 30-d follow-up, there were 4 deaths (4.5%). No patients experienced abrupt closure of the infarct-related artery and there was no reported target-lesion failure. Our preliminary experience showed that DCB angioplasty in PPCI was feasible and associated with a high rate of TIMI 3 flow and low 30-d ischaemic event.

**Key words:** Acute myocardial infarction; Drug coated balloon; Efficacy; Primary angioplasty; Safety

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**Core tip:** Primary percutaneous coronary intervention (PPCI) is the preferred reperfusion therapy for ST-elevation myocardial infarction (STEMI). Stent implantation is considered as a routine during PPCI as it is associated with reduction of ischaemic end-points. Drug-coated balloon (DCB) has emerged as a new therapeutic option to treat coronary artery disease as stent technology has certain limitations. There is however limited data on the feasibility of using DCB as primary therapy in PPCI. We evaluated the clinical safety and efficacy of using paclitaxel-coated balloon in patients undergoing PPCI

for STEMI and report on our 30 d clinical outcomes.

Ho HH, Tan J, Ooi YW, Loh KK, Aung TH, Yin NT, Sinaga DA, Jafary FH, Ong PJL. Preliminary experience with drug-coated balloon angioplasty in primary percutaneous coronary intervention. *World J Cardiol* 2015; 7(6): 311-314 Available from: URL: <http://www.wjgnet.com/1949-8462/full/v7/i6/311.htm> DOI: <http://dx.doi.org/10.4330/wjc.v7.i6.311>

## INTRODUCTION

Primary percutaneous coronary intervention (PPCI) is the preferred reperfusion therapy for ST-elevation myocardial infarction (STEMI) if performed in a timely fashion<sup>[1]</sup>. Stent implantation<sup>[2-5]</sup> whether with bare metal stent (BMS) or drug-eluting stent (DES) is considered as a routine during PPCI as it is associated with reduction of early ischaemia, restenosis and re-occlusion of culprit artery in comparison with pure old balloon angioplasty (POBA).

Drug-coated balloon (DCB)<sup>[6-8]</sup> has emerged as a new therapeutic option to treat coronary artery disease (CAD) as stent technology has certain limitations. There is however limited data on the feasibility of using DCB as primary therapy in PPCI. Previous clinical studies<sup>[2-3]</sup> had shown no difference in the mortality rates between those who received stents or POBA during PPCI with the main difference driven largely by lower rate of target vessel revascularization (TVR) in the stenting group.

It is possible that DCB could close this gap for the POBA group and we therefore evaluated the clinical feasibility (*i.e.*, safety and efficacy) of using paclitaxel-coated balloon in our cohort of South-East Asian patients undergoing PPCI for STEMI.

## RESEARCH

Between January 2010 to September 2014, 89 STEMI patients with a total of 89 coronary lesions were treated with SeQuent Please DCB (B.Braun, Melsungen, Germany) as primary therapy during PPCI. The PPCI strategy was to perform thrombus aspiration followed by predilatation of the lesion site before treatment with DCB. Bail-out stenting was performed only when there was significant vessel recoil/coronary dissection. Clinical outcomes are reported at 30 d follow-up.

## RESULTS

Table 1 shows the baseline clinical characteristics, angiographic features, procedural data and clinical outcomes of the study patients. The mean age of the patients at presentation was  $59 \pm 14$  years with male preponderance (83%). Twenty-eight percent of the

**Table 1** Baseline clinical characteristics, angiographic features, procedural data and clinical outcomes of patients *n* (%)

	<i>n</i> = 89
Mean age (yr)	$59 \pm 14$
Male: female	74:15 (83:17)
Ever smokers	50 (56)
Diabetes	25 (28)
Hyperlipidemia	41 (46)
Hypertension	49 (55)
Previous myocardial infarction	9 (10)
LVEF	$44\% \pm 11\%$
Presentation	
Anterior MI	40 (45)
Inferior MI	49 (55)
Target vessel	
LAD	33 (37)
CIRC	12 (13)
RCA	29 (33)
Others	15 (17)
Reference diameter, mm	$2.4 \pm 0.4$
Thrombus aspiration	50 (56)
Predilatation with non-coated balloon	89 (100)
Glycoprotein 2b/3a inhibitors	71 (80)
TIMI flow	
Post-procedural TIMI 2 flow	2 (2)
Post-procedural TIMI 3 flow	87 (98)
30-d clinical outcomes	
Mortality	4 (4.5)
Target vessel revascularisation	0 (0)
Target vessel MI	0 (0)
Target lesion thrombosis	0 (0)

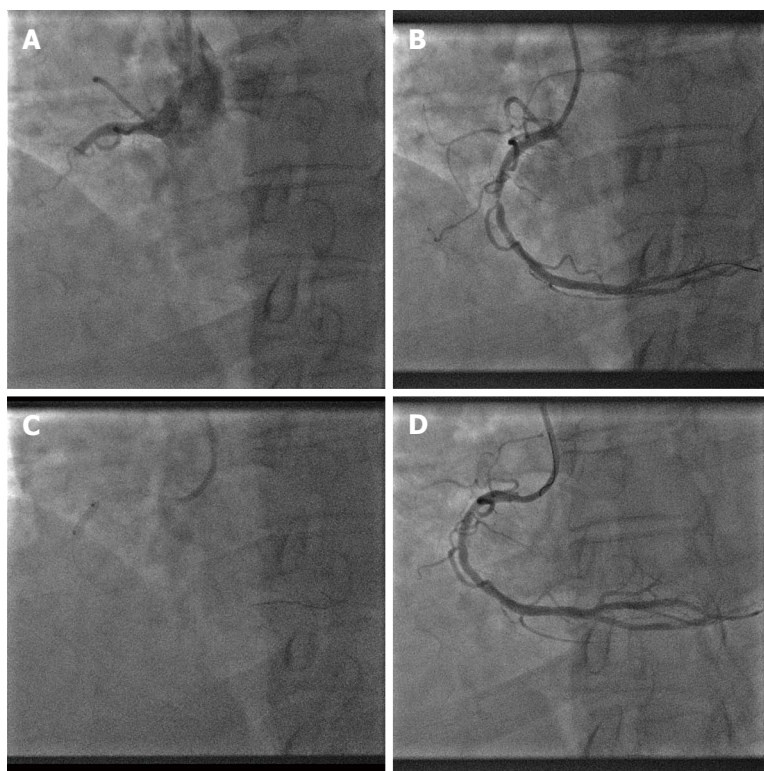
LVEF: Left ventricular ejection fraction; MI: Myocardial infarction; LAD: Left anterior descending artery; CIRC: Left circumflex artery; RCA: Right coronary artery; TIMI: Thrombolysis in myocardial infarction.

patients had underlying diabetes mellitus. Mean left ventricular ejection fraction was  $44\% \pm 11\%$ . The majority of patients presented with inferior STEMI (55%) with the left anterior descending artery (LAD) being the most common target vessel for PCI (37%) followed by right coronary artery (33%), left circumflex (13%) and others (17%).

Thrombus aspiration was performed in 50 patients (56%) with glycoprotein 2b/3a inhibitors administered in 71 patients (80%). Pre-procedural Thrombolysis in Myocardial Infarction (TIMI) flow was 0 in 70% of patients. At the end of PPCI, TIMI 3 flow was successfully restored in 98% of patients with residual stenosis of 29%.

DCB-only PCI was the predominant approach (96% of patients) with the remaining 4% of patients receiving bail-out stenting for significant recoil/dissection after treatment with DCB. An average of  $1.2 \pm 0.5$  DCB were used per patient, with mean DCB diameter of  $2.6 \pm 0.5$  mm and average length of  $23.2 \pm 10.2$  mm. The mean inflation pressure for DCB was  $10 \pm 3$  atm and mean inflation time was  $54 \pm 22$  s.

At 30-d follow-up, there were 4 deaths (4.5%). Three patients succumbed due to cardiogenic shock and 1 died of sepsis. No patient experienced abrupt closure of the infarct-related artery (IRA) and there



**Figure 1** Thrombus aspiration (for visible thrombus) and predilatation with a non-coated balloon prior to drug-coated balloon angioplasty as the final step. A: Baseline coronary angiography showing acute thrombotic occlusion of mid right coronary artery (RCA); B: Mid RCA after thrombus aspiration; C: Predilatation of mid RCA with non-coated balloon; D: Final angiography of mid RCA (after DCB angioplasty).

was no reported TVR, target-vessel-MI or target lesion thrombosis.

## DISCUSSION

When compared with fibrinolytic therapy, PPCI in STEMI<sup>1</sup> reduced the rates of death, reinfarction, and stroke. The use of POBA in PPCI has been superseded by routine stenting<sup>[2-3]</sup> in the contemporary era as the former approach was associated with recurrent ischemia, restenosis, and reocclusion of the IRA. However, prior studies so far had not shown any difference in the mortality rates between those who received stents or POBA during PPCI. The main difference is consistently a lower rate of TVR in the stenting group and it is possible that DCB could close this gap for selected group of patients in the POBA arm. From our preliminary experiences, we demonstrated that the use of DCB as primary therapy for STEMI patients in PPCI was feasible and associated with a high rate of final TIMI 3 flow and low 30-d major adverse cardiac event (MACE).

In recent years, DCB<sup>[6-8]</sup> has emerged as a viable therapeutic option for treating CAD as the current DES technology has limitations like late stent thrombosis and prolonged dual anti-platelet therapy. Paclitaxel is the drug of choice for all the commercially available DCBs because of its highly lipophilic properties which allows rapid diffusion into the vessel wall and sustained

anti-proliferative effect despite its short contact with the vessel wall. The best long term results with DCB is achieved with a DCB-only approach when compared to DCB plus BMS as the former approach is associated with a lower late lumen loss and lower target vessel revascularization.

To gain the utmost benefit from DCB<sup>[9]</sup>, adequate lesion preparation is necessary so that we can maximize balloon contact area to vessel wall for a minimum of 30 s. Similarly in PPCI, we advocate 2 key steps, *i.e.*, thrombus aspiration (for visible thrombus) and predilatation with a non-coated balloon prior to DCB angioplasty as the final step (Figure 1). Removal of thrombus will enable DCB to have better contact with the vessel wall and initial predilatation of the lesion will also allow us to evaluate whether the patient can tolerate prolonged balloon inflation with DCB.

Coronary dissection (iatrogenic) occurs inevitably as result of POBA and abrupt closure of vessel remains one of the most fearful complications. Having good knowledge on the different grades of coronary dissection according to the National Heart, Lung, and Blood Institute (NHLBI) classification<sup>[10]</sup>, one can carefully select patients for DCB angioplasty during PPCI and in our study, no patients experienced abrupt closure of IRA. Only 4% of our patients required bailout stenting for significant recoil/dissection (> Type B dissection). The incidence of abrupt closure of IRA is also significantly reduced in the current era of more

potent anti-platelet agents.

There were several limitations to our study. The number of patients is relatively small and our study was a single-center registry, subject to selection and operator bias. All patients in our study received treatment with SeQuent Please DCB and our results could only be extrapolated to those who had received similar therapy. Whether similar results would be seen with patients receiving other types of DCB is unknown as not all DCBs are equal in terms of clinical efficacy.

In conclusion, the use of DCB as primary therapy in PPCI represents a novel approach in treating STEMI patients. Our preliminary experiences were favourable ie a high rate of final TIMI 3 flow and low 30-d MACE. This approach is possible with appropriate patient selection and by performing 2 key preconditioning steps. Further studies with longer follow-up are necessary to confirm our preliminary findings.

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## Nomenclature, categorization and usage of formulae to adjust QT interval for heart rate

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### Abstract

Assessment of the QT interval on a standard 12 lead electrocardiogram is of value in the recognition of a number of conditions. A critical part of its use is the adjustment for the effect of heart rate on QT interval. A systematic search was conducted to identify studies

that proposed formulae to standardize the QT interval by heart rate. A nomenclature was developed for current and subsequent equations based on whether they are corrective (QTc) or predictive (QTp). QTc formulae attempt to separate the dependence of the length of the QT interval from the length of the RR interval. QTp formulae utilize heart rate and the output QTp is compared to the uncorrected QT interval. The nomenclature consists of the first letter of the first author's name followed by the next two consonance (whenever possible) in capital letters; with subscripts in lower case alphabetical letter if the first author develops more than one equation. The single exception was the Framingham equation, because this cohort has developed its own "name" amongst cardiovascular studies. Equations were further categorized according to whether they were linear, rational, exponential, logarithmic, or power based. Data show that a person's QT interval adjusted for heart rate can vary dramatically with the different QTc and QTp formulae depending on the person's heart rate and QT interval. The differences in the QT interval adjustment equations encompasses values that are considered normal or significant prolonged. To further compare the equations, we considered that the slope of QTc versus heart rate should be zero if there was no correlation between QT and heart rate. Reviewing a sample of 107 patient ECGs from a hospital setting, the rank order of the slope - from best (closest to zero) to worst was QTcDMT, QTcRTHa, QTcHDG, QTcGOT, QTcFRM, QTcFRD, QTcBZT and QTcMYD. For two recent formulae based on large data sets specifically QTcDMT and QTcRTHa, there was no significant deviation of the slope from zero. In summary a nomenclature permits easy reference to QT formulae that adjust for heart rate. Twenty different formulae can produce discordant calculations of an adjusted QT interval. While the formulae developed by Bazett and Fridericia (QTcBZT and QTcFRD respectively) may continue to be used clinically, recent formulae from large population studies specifically QTcDMT and QTcRTHa appear to be better

to adjust QT for heart rate in clinical practice.

**Key words:** QT interval; Heart rate adjustment

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**Core tip:** We propose a nomenclature for QT-heart rate adjustment formulae consisting of the first letter of the first author's name followed by the next two consonance with subscripts if the author develops more than one equation. Twenty different QT-heart rate formulae produced discordant calculations of adjusted QT interval. Formulae were categorized into predictive or corrective (QTc) and into linear, rational, exponential, logarithmic, or power based. QTc equations are the most suitable for clinical application. Based on the ability to minimize the slope of a best fit linear relationship between QTc and heart rate, the new formulae QTcDMT and QTcRTHa warrant introduction into clinical practice.

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## INTRODUCTION

Assessment of the QT interval on a standard 12 lead electrocardiogram is of value in the recognition of conditions such as electrolyte disturbances, drug-induced cardiac toxicity, genetic abnormalities of cardiac channels (channelopathies) and autonomic nervous system dysregulation<sup>[1-6]</sup>. Prolonged QT interval has been considered a useful biomarker for electrolyte abnormalities such as hypokalemia or hypomagnesemia<sup>[2]</sup>. In addition, the duration of the QT interval has been found in epidemiologic studies to identify individuals at high risk of subsequent sudden death<sup>[7]</sup>.

QT interval is highly dependent on heart rate, so that utilization of the QT interval, requires adjustment for the impact of heart rate on the QT interval. Formulae for the adjustment of the QT interval, for heart rate, have been used clinically for almost one hundred years<sup>[8,9]</sup>. While the original proposals of Bazett<sup>[8]</sup> and Fridericia<sup>[9]</sup> remain the most popular methods, there were many other possible choices for heart rate correction proposed in the early years of electrocardiography, as reviewed by Simonson *et al.*<sup>[10]</sup>. There have been considerable concerns about the precision and the validity of the standard QT interval-heart rate adjustments approaches<sup>[11-15]</sup> that have led to the recent development of QT adjustment formulae from larger numbers of persons<sup>[16,17]</sup>. Pharmacovigilance

data that identified the association of drug-induced sudden cardiac death with prolonged QT interval, generated recommendations by drug approval and monitoring agencies and has led to recommendations to evaluate the effect of drugs on the QT interval - the "Thorough QT Study" (TQT)<sup>[18]</sup>. Such studies require the careful assessment of the QT interval. The need for evaluation of the QT interval has generated research into how best to isolate the effect of a drug on the QT interval and minimize other factors such as heart rate which changes over time and might influence the QT interval. That research categorized QT-heart rate correction equations and expanded the development of more rate correction approaches that were based on large population studies<sup>[16,17,19-21]</sup>. This literature has often not been translated to the clinic. The objective of this study is several fold. The first objective was to assemble and review the different QT-heart rate adjustment formulae so as to construct a reference nomenclature which reflects their nature and aids future discussion. The next objective was to compare the QT-heart rate adjustment formulae. The third objective was to assess how well the clinical impact of current widely used methods, which were based on small samples of apparently healthy individuals, compare with the recently proposed formulae that have been based on large sample sizes, often population based.

Our review began with a specific and comprehensive literature search so that all relevant QT interval formulae would be included for our analysis. Second, we applied eligibility criteria to all formulae to limit formulae to those with broad clinical application. Third, we obtained ECGs from a hospital setting to apply the selected formulae to QT and heart rate values. Finally, we compared the most preferred formulae.

## LITERATURE SEARCH

A systematic search was conducted to identify studies that proposed equations to standardize the QT interval by heart rate. We searched the Medline and EMBASE databases using the PubMed and OvidSP platforms. The full electronic search strategy used was "QT interval" and "heart rate" and reference value. The reference list of publications was searched for other publications so that additional papers from these reference lists were also used for our review.

## ELIGIBILITY CRITERIA

Studies that met the following criteria were included: (1) an original study (2) development of the equation in an apparently normal population (3) an adult population (4) clear presentation of the equation, its parameters and conditions (5) equations should be based on ECG measured QT interval. Papers that dealt with cardiac systole rather than QT interval



**Table 1** QT correction equations

Ref.	Sample size	Population characteristics	Nomenclature
Linear function Sagie <i>et al</i> (1992) (Framingham) <sup>[26]</sup>	5018	Men (2239) and women (2779), aged 28 to 62 yr	QTcFRM
Rational functions Hodges <i>et al</i> (1983) <sup>[31]</sup>	607	Men (303) and women (304), aged 20 to 89 yr	QTcHDG
Rautaharju <i>et al</i> (2014) <sup>[17]</sup>	57595	Men and women, aged 5 to 90 yr	QTcRTHa
Power functions Bazett (1920) <sup>[8]</sup>	39	Men (20) and women (19), aged 14 to 53 yr	QTcBTZ
Fridericia (1920) <sup>[9]</sup>	50	Men and women, aged 30 to 81 yr	QTcFRD
Mayeda (1934) <sup>[24]</sup>	200	Men (135) and women (65), aged 18 to 64 yr	QTcMYD
Kawataki <i>et al</i> (1984) <sup>[32]</sup>	9	9 male subjects aged 18 to 71 yr, taken at rest, during exercise, and after drug administration	QTcKWT
Dmitrienko <i>et al</i> (2005) <sup>[16]</sup>	13039	Men (6351) and women (6688), aged 4 to 99 yr	QTcDMT
Goto <i>et al</i> (2008) <sup>[25]</sup>	1276	Men aged 20 to 35 yr	QTcGOT
Rautaharju <i>et al</i> (2014) <sup>[17]</sup>	57595	Men and women, aged 5 to 90 yr	QTcRTHb

measurements were excluded except for the early clinical papers. Papers were also excluded if the QT interval was measured mainly in cases with electrolyte abnormalities, only children or in persons with electronic pacemakers.

## ECG QT MEASUREMENT

Resting ECGs from a hospital ECG service were evaluated. Only ECGs with sinus rhythm and without bundle branch block, ST elevation myocardial infarction or significant ST-T wave changes were considered. There were 107 ECGs that were anonymously obtained from an acute care hospital. No clinical information is available similar to the usual clinical ECG interpretation setting. ECGs were acquired and digitally analyzed. ECG waveform were sampled at least at 500 samples per second using the Marquette 12SL analysis program (GE Healthcare, Milwaukee, WI, United States). The QT interval is measured "from the earliest detection of depolarization in any lead (QRS onset) to the latest detection of repolarization in any lead (T offset) (The Marquette 12SL analysis program was Marquette™ 12SL™ ECG Analysis Program, GE Healthcare Milwaukee, WI, United States). The QT interval and heart rate measured by the analysis program was used in the heart rate adjustment formulae.

## VALIDATION OF EXISTING QT CORRECTION FORMULAE

Recognizing that the goal of the of each formula is to produce QTc values that do not correlated with heart rate or RR interval so that the slope of QTc/RR regression should zero, we calculated the linear slope of eight corrective formulae for the 107 persons with various heart rates. The eight corrective formulae were selected based on clinical usage and relevance.

### Statistical analysis

A linear regression model was used to calculate the

slope of QTc vs heart rate relationship. The goodness of fit of the data to the linear regression (line) is indicated by the standard deviation of residuals.

## CATEGORIZATION OF QT FORMULAE

Over 25 different equations were identified. After examination of the formulae, a nomenclature was developed. Formulae were categorized into QT correction or prediction formulae. A correction formula is defined as a formula which attempts to separate the dependence of the length of the QT interval from the length of the RR interval (Table 1). The correction formulae are identified by the subscript with a lower case c. The other category includes predictive formulae, which are defined as formulae that predict an "optimal" QT interval length given the heart rate. The prediction equations are identified by the subscript with a lower case p or QTp (Table 2). Our rationale for this division is based on how each type of formulae is used. For a QTc equation, the patient's heart rate and QT interval are used to calculate a QTc value, which is compared to a standard value. For a QTp equation only the person's heart rate is required, then, the output QTp will be compared to the patient's uncorrected QT interval. QTc limits would be anticipated to be different for each equation, and the same applies to the difference between uncorrected QT and QTp.

Formulae were then divided according to the nature of correction - classified as linear, rational, power, logarithmic, or exponential<sup>[20,22]</sup> (Table 1). For our naming convention, we identify formulae by the first letter of the first author's name followed by the next two consonants (whenever possible) in capital letters. If the first author develops more than one equation, the equations are labelled by the lower case alphabetical letter as subscript. The only exception to this rule was the Framingham study which has had many authors over the years and is a population based study that has developed its own name and reputation amongst cardiovascular studies.

**Table 2** QT prediction equations

Ref.	Sample size	Population characteristics	Equation
Linear functions			
Adams (1936) <sup>[33]</sup>	104	Men (50) and women (54), mean age 28 yr	QTpADM
Schlamowitz (1946) <sup>[34]</sup>	650	Men (650) aged 18 to 44 yr	QTpSCH
Karjalainen <i>et al</i> (1981) <sup>[27]</sup>	324 ECGs	Men (military personnel) aged 18 to 28 yr	QTpKRJ
Simonson <i>et al</i> (1962) <sup>[10]</sup>	960	Men (649) and women (311), aged 20 to 59 yr	QTpSMN
Rational functions			
Boudoulas <i>et al</i> (1981) <sup>[35]</sup>	200	Men (100) and women (100), aged 18 to 79 yr	QTpBRL
Hodges <i>et al</i> (1983) <sup>[31]</sup>	607	Men (303) and women (304), aged 20 to 89 yr	QTpHDG
Wohlfart and Pahlm (1994) <sup>[36]</sup>	37	Men (16) and women (21), aged 38 to 68 yr, taken at rest and during exercise	QTpWHL
Klingfield <i>et al</i> (1995) <sup>[37]</sup>	94	Men, mean age 48 yr, taken at rest and during exercise	QTpKLN
Power functions			
Bazett (1920) <sup>[8]</sup>	39	Men (20) and women (19), aged 14 to 53 yr	QTpBZT
Fridericia (1920) <sup>[9]</sup>	50	Men and women, aged 30 to 81 yr	QTpFRD
Mayeda (1934) <sup>[24]</sup>	200	Men (135) and women (65), aged 18 to 64 yrs	QTpMYD
Schlomka and Raab (1936) <sup>[30]</sup>	336	Men and women	QTpSCH
Shipley and Hallaran (1936) <sup>[23]</sup>	200	Men and women, aged 22 to 35 yr	QTpSHP
Hegglin and Holzmänn (1937) <sup>[38]</sup>	700	Men and women	QTpHGG
Kawataki <i>et al</i> (1984) <sup>[32]</sup>	9	Men aged 18 to 71 yr	QTpKWT
Goto <i>et al</i> (2008) <sup>[25]</sup>	1276	Men aged 20 to 35 yr	QTpGOT
Logarithmic functions			
Ashman (1942) <sup>[39]</sup>	1083	Men (432), women (425), and children (226)	QTpASH
Merri <i>et al</i> (1989) <sup>[40]</sup>	364	Men (191) and women (173) aged 10 to 81 yr	QTpMRR
Exponential functions			
Sarma <i>et al</i> (1984) <sup>[28]</sup>	16	Men (10) aged 18 to 30 yr, taken at rest and during exercise	QTpSRM
Lecocq <i>et al</i> (1989) <sup>[41]</sup>	11	Men (5) and women (6), aged 22 to 26 yr, taken at rest, during exercise, and after drug administration	QTpLCC
Arrowood <i>et al</i> (1993) <sup>[42]</sup>	16	16 subjects, aged 21 to 62 yr	QTpARR

The proportion of men and women is provided when available.

### Correction formulae

The majority of corrective formulae utilize a power function to adjust the heart rate (Table 1). The first and still widely used correction equations were: Bazett's proposal, based on a very small sample of normal subjects, that the QT interval varied according to the square root of the heart rate or cycle length (RR interval)<sup>[8]</sup> and Fridericia's proposal<sup>[9]</sup> that the cube root of the RR interval was the best adjustment formula. The original Bazett formula which included constants was examined and had the constants eliminated producing the widely used Bazett formula<sup>[23]</sup>. Dmitrienko *et al*<sup>[16]</sup> reported on the ECGs from 13039 individuals (men and women) who had ECGs as part of their baseline assessment in clinical drug trials, conducted in 2000 and 2001, sponsored by Eli Lilly and Company. This correction formula was obtained by fitting a linear model to log-transformed QT and RR data. Mayeda<sup>[24]</sup> examined the ECGs of 200 apparently healthy Japanese individuals. Goto *et al*<sup>[25]</sup> studied the relationship between RR and QT, using the bootstrap method, in resting ECGs of 1276 healthy young Japanese men. The major linear equation was developed by Sagie *et al*<sup>[26]</sup> from the Framingham population in the United States. The sample size used to develop or test the equations varied dramatically between studies. The most recent equation, developed by Rautaharju *et al*<sup>[17]</sup>, was based on pooled data from

three different sources—two population studies and one large study of baseline ECGs prior to drug testing for a potential effect on QT, and consisted of 57595 individuals. These authors suggested two equations a rational and a power function formula.

### Predictive equations

The largest number of predictive equations also utilizes a power function to adjust for heart rate. The next most frequent adjustment formulae are linear or rational equations (Table 2). Some of the authors have both corrective and predictive equations which differ by the presence of relevant constants in the predictive equation. Simonson *et al*<sup>[10]</sup> proposed a logarithmic and a linear equation to predict QT interval based on the RR interval. They concluded that "because the logarithmic ...and linear ....regression equations gave identical results within the error of measurement, the simpler linear equation ... was used for further analysis."<sup>[10]</sup> Some of the predictive equations tried to adjust for the nonlinearity of the QT-RR interval relationship by considering different heart rate ranges. Karjalainen *et al*<sup>[27]</sup> measured the QT intervals in 324 electrocardiograms of healthy young men and weighted the sample for low and high heart rates equally. They concluded that the QT-RR relation does not permit the use of one simple adjustment equation and proposed formulae that provided different

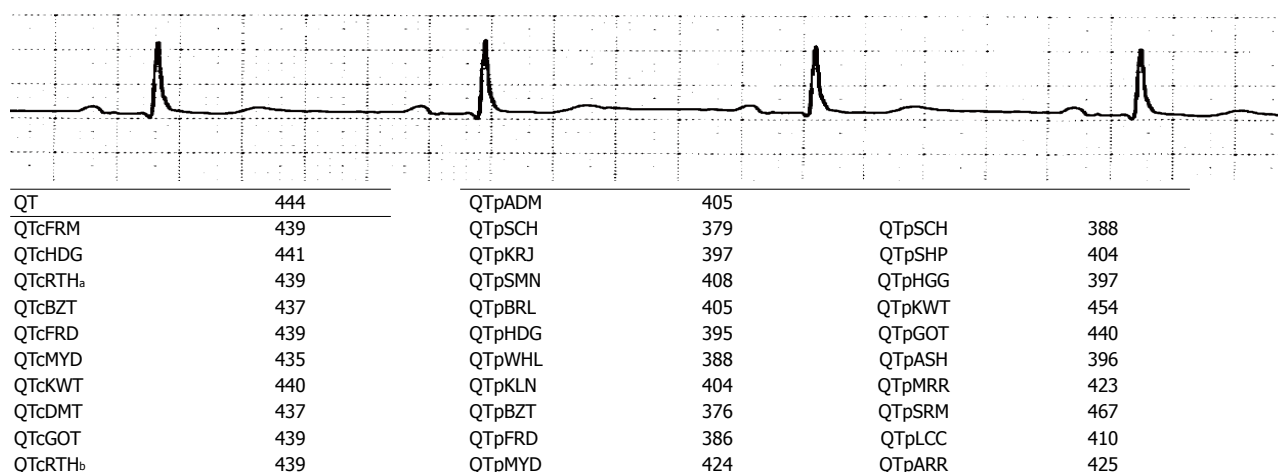


Figure 1 The QTc and QTp heart rate corrections for the uncorrected QT interval measured by computerized assessment of a digitized ECG.

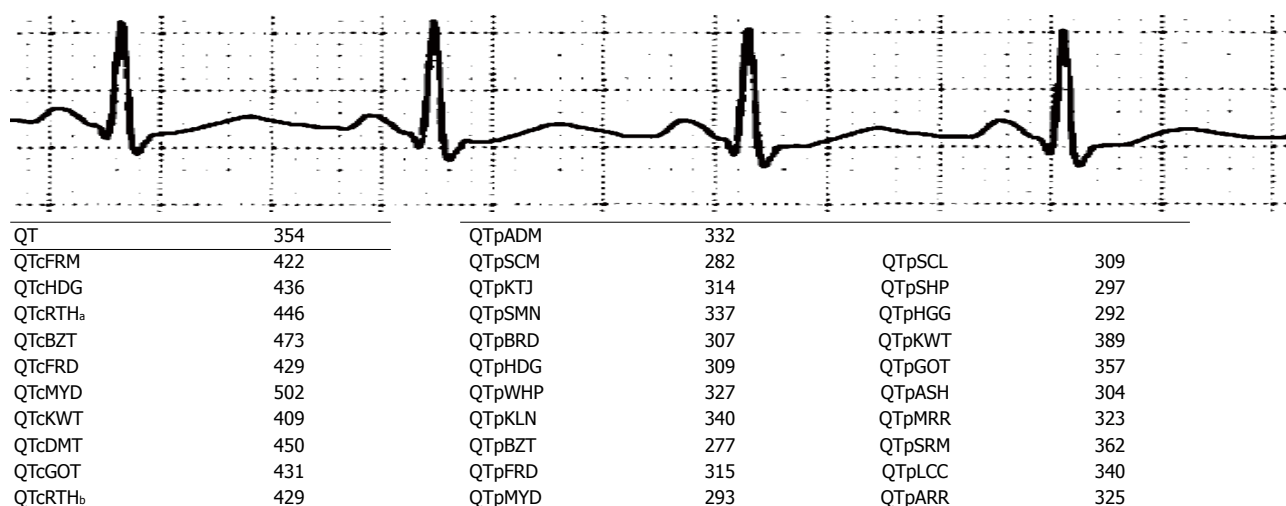


Figure 2 The QTc and QTp heart rate corrections for the uncorrected QT interval measured by computerized assessment of a digitized ECG.

parameters according to the heart rate<sup>[27]</sup>. Some predictive equations attempted to evaluate the QT-RR interval relationship using interventions to vary heart rate. Sarma *et al.*<sup>[28]</sup> studied 10 healthy, normal men who exercised on a stationary bicycle, and 6 patients with rate-programmable VVI pacemakers whose rates were changed by an external programme, and developed an equation with an exponential function.

The sample size used to develop QTp equations varied between studies but overall the sample sizes were smaller than those used to develop the QTc equations. A number of equations were derived as QTp equations and were subsequently modified to QTc equations with Bazett and Fridericia being the most well-known<sup>[8,9]</sup>.

### Application of formulae

To illustrate the application of the various QT adjustment approaches, each of them was applied to three different ECGs (Figures 1-3). The closest correlation between the equations occurred, as expected, in a 71 years old man

with a heart rate of 58 bpm where the difference in QTc was 6 milliseconds (ms) (435 to 441 ms) and for QTp the difference was 91 ms with a range from 376 to 467 ms (Figure 1). This is because QTc formulae are largely based on the assumption that the QT interval is accurate at the heart rate of 60 bpm. However, not all QTp equations are based on "normal heart rate" being at 60 bpm. In contrast, a man aged 53 years with a heart rate of 107 bpm, had a QTc ranging from 409 to 502 ms and QTp from 277 to 389 ms (Figure 2). The discrepancy between QTcBZT and QTcFRD was 44 ms. A 53 years old woman had QTc ranging from 424 to 487 ms and QTp from 305 to 408 ms (Figure 3). The discrepancy between QTcBZT and QTcFRD was 30 ms. The differences in the QT interval adjustment between formulae is readily apparent. Importantly the range encompasses values that are considered significant QT prolongation which raise the possibility of the presence of one of the causes for prolonged QT using one equation but a normal QT when considering another equation. The difference between QTcBZT and QTcFRD

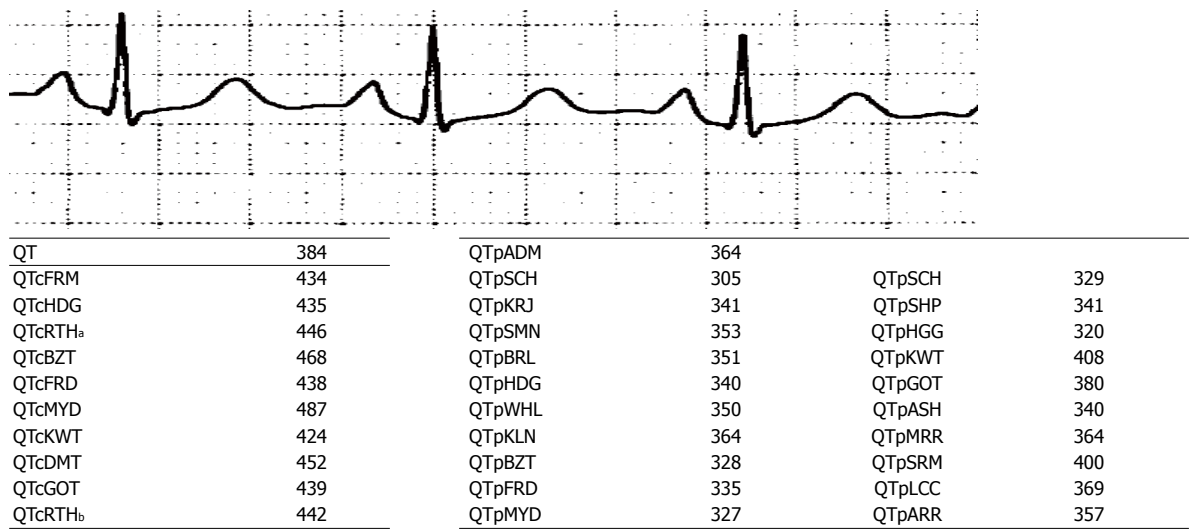


Figure 3 The QTc and QTp heart rate corrections for the uncorrected QT interval measured by computerized assessment of a digitized ECG.

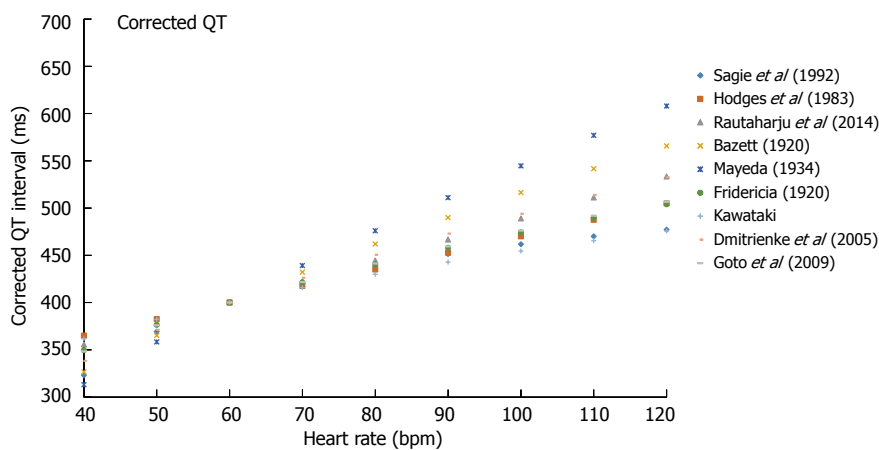


Figure 4 The corrected QT interval for the different correction formulae for a 50 years old man with a QT of 400 ms.

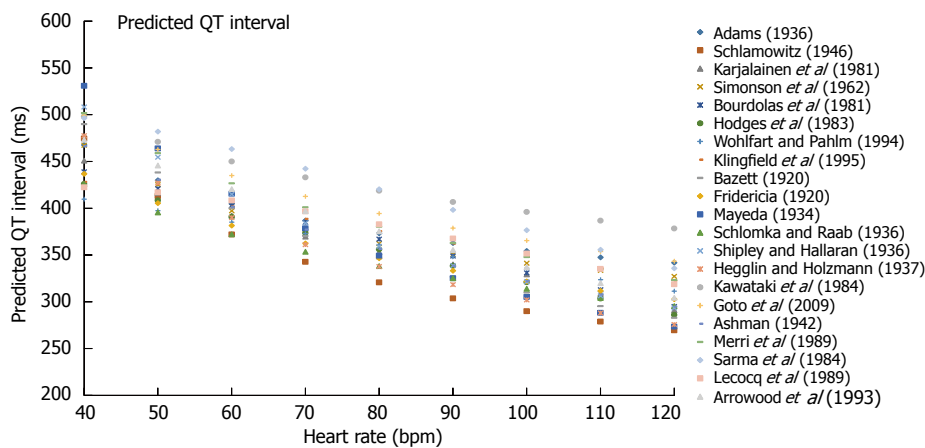
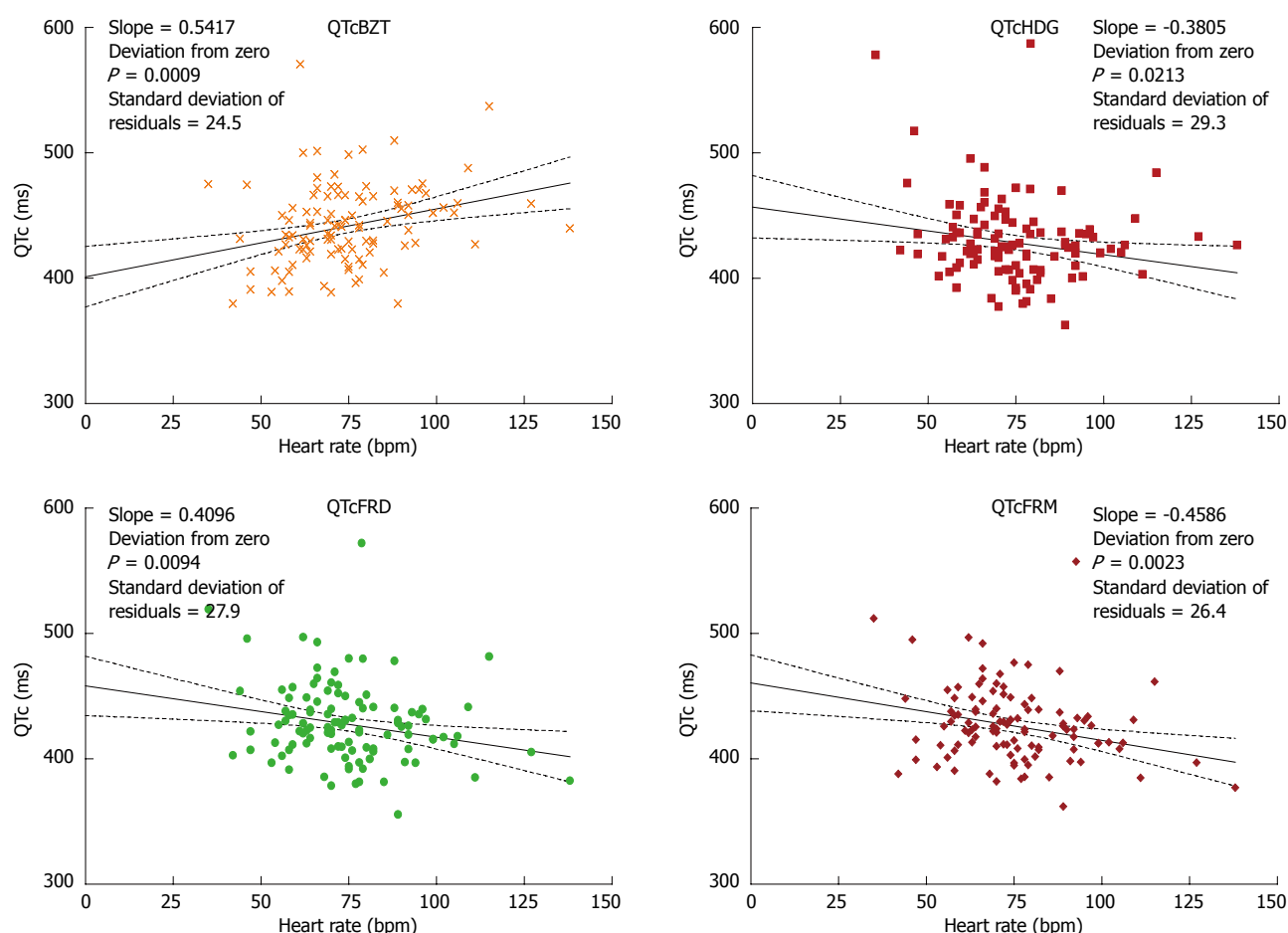


Figure 5 The predicted QT interval for the different correction formulae for a 50 years old man with a QT of 400 ms.

is apparent yet the value used to diagnose prolonged QT syndrome maybe considered to be the same by some clinicians.

To further illustrate the effect of using each of

the correction equations an example is used of of an uncorrected QT interval 400 ms in a 50 years old man (Figure 4). By definition, all QTc equations show equipoise at a heart rate of 60 bpm. The discrepancy



**Figure 6** The relationship between QTc and heart rate for QTcBZT, QTcFRD, QTcHDG, and QTcFRM. The slope of the line and how significantly it deviates from zero is shown in the insert. The goodness of fit of the data to the linear regression (line) is shown by the standard deviation of residuals.

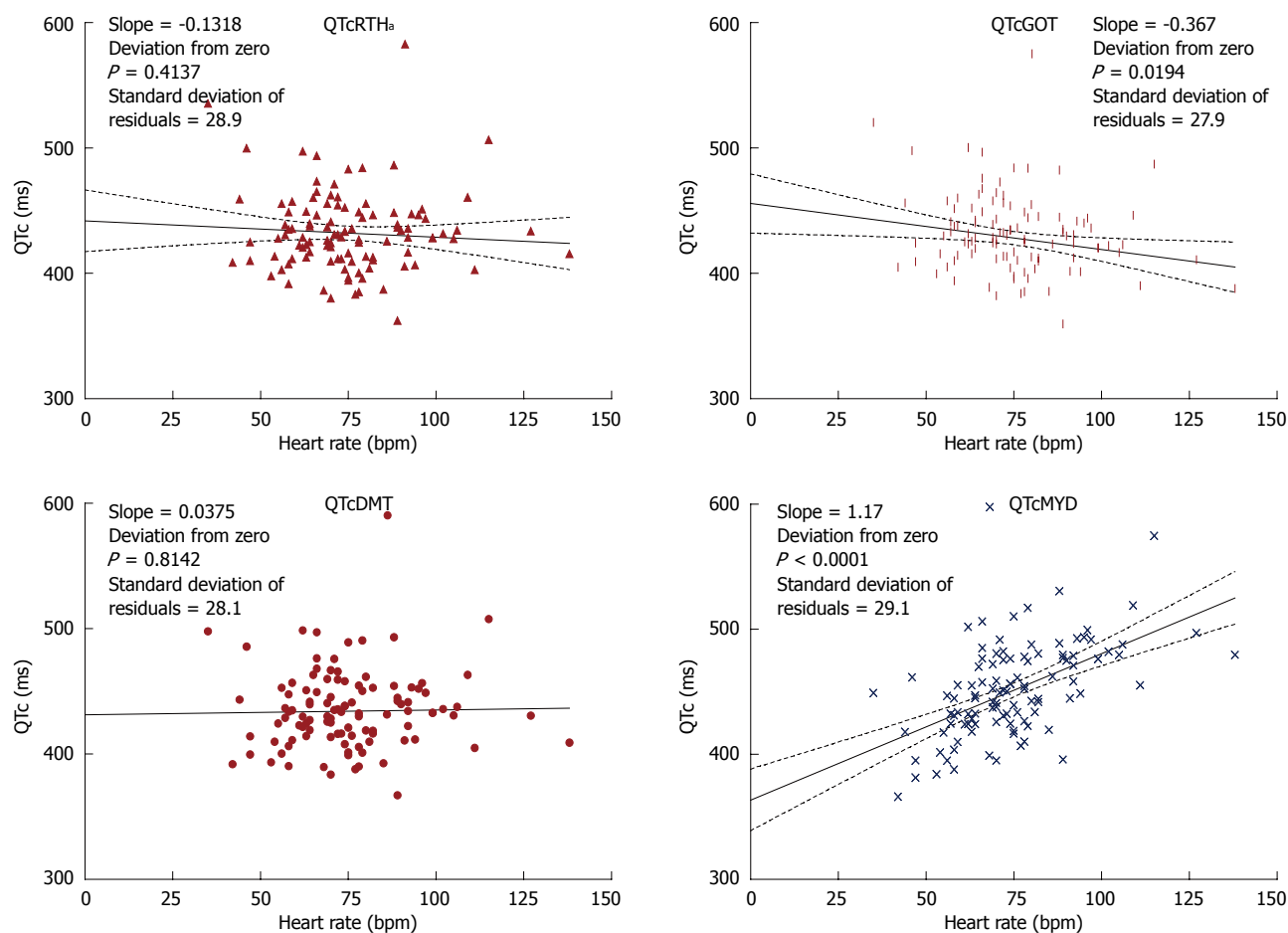
in QTc between the different formulae is apparent at slower and faster heart rates with the magnitude of the dispersion increasing at slower and faster heart rates. At a heart rate of 100 bpm, QTc ranges from 462 ms (QTcFRM) to 546 ms (QTcMYD) with QTcBZT at 516 ms and QTcFRD at 474 ms. At a heart rate of 40 bpm, QTc ranges from 313 ms (QTcMYD) to 400 ms (QTcRTHb) with QTcBZT at 327 ms and QTcFRD at 349 ms. The variation among formulae are non-linear, which is again as a result of QTc values being equipoise at 60 bpm.

Prediction equations also show a considerable range of reported QTP values. Considering the same 50 years old man with a QT of 400 ms (Figure 5), at a heart rate of 40 bpm, QTP ranges from 313 (QTPWHL) to 530 ms (QTPMYD) with QTPBZT at 453 and QTPFRD at 436 ms. At a heart rate of 100 bpm, QTP ranges from 290 (QTPSCH) to 396 ms (QTPKWT) with QTPBZT at 287 and QTPFRD at 322 ms. A hypothesis worth considering is that if we combine all QTP equations, which are based on different populations, we may construct an interval where QTP is considered to be normal.

## HEART RATE INDEPENDENCE OF QT-HEART RATE FORMULAE

Recognizing that the goal of each formula is to produce QTc values that do not correlated with heart rate, we calculated the linear slope of eight corrective formulae for the 107 persons with various heart rates. The formulae varied in their slope (Figures 6 and 7). Two equations had a slope that was not significantly different from zero namely QTc DMT and QTc RTHa with the former being closest to zero. The other 6 equations had slopes that were significantly different from zero with the largest slope for QTcMYD. Of the equations that showed slopes that deviated from zero QTcBZT was the next largest slope or highest relationship to heart rate. The goodness of fit of the data to the linear regression (line) is shown by the standard deviation of residuals.

QT-heart rate adjustment formulae can generate a range of QT-adjusted values depending on the heart rate. Furthermore a wide range of QT-adjusted values is possible for individuals at any given heart rate. The clinician is confronted with the problem of the correct



**Figure 7** The relationship between QTc and heart rate for QTcRTHa, QTcDMT, QTcGOT, and QTcMYD. The slope of the line and how significantly it deviates from zero is shown in the insert. The goodness of fit of the data to the linear regression (line) is shown by the standard deviation of residuals.

choice for adjusting the QT interval and assessing the implications of the choice.

## ABSENCE OF A “GOLD” STANDARD

The central issue is the absence of a true “gold standard” to identify the duration of cardiac repolarization and then to evaluate all the equations against this standard in order to determine the “best” one. The Bazett correction approach (QTcBZT) is a frequently used formula. It has long been known and criticized because it is purportedly “overcorrects” the measured QT interval at fast heart rates and under corrects it at low heart rates<sup>[26]</sup>. The absence of a gold standard for heart rate correction makes it difficult to know what the true correction is and what is “over” and “under”-correction. The absence of a “gold” standard has likely played a role in maintaining the use of QTcBZT despite its critics<sup>[13,26,29]</sup>. While the Fridericia formula (QTcFRD) is believed to be more accurate than QTcBZT, it has already been criticized because it retains the potential for bias at either extreme of heart rate(s)<sup>[16]</sup> but other formulae also share this feature at clinically relevant faster heart rates.

## QTp vs QTc

There are more QTp than QTc equations perhaps because of the manner in which QT adjustment equations are derived. Most QTp equations utilize regressions of population data to a pre-determined form. The procedure is briefly as follows. First, the uncorrected QT interval raw data are presented in a scatter plot. Then, a pre-determined form of equation is selected. The pre-determined form may be linear, rational, exponential, logarithmic, or power based. Next a statistical procedure to minimize the “error” generates parameters for the model. The regressed equation becomes the QTp equation. The error is usually quantified in the form of square of the residuals, but the method to quantify error is ultimately up to the discretion of each author. Predicted QT equations are dependent on the population from which they are derived. Several equations share the same raw form, but only differ in constants. For example, Fridericia<sup>[9]</sup> and Schlomka and Raab<sup>[30]</sup> both contain the RR interval raised to the power of one third and Goto *et al.*<sup>[25]</sup> raises RR to the power of 0.3409, which approximates the power of one third. The



reason behind differing constants for the same power may have several explanations. First, there may be variations between studies in selection criteria, genetic factors of the subjects, or environmental factors. Second, there may be systematic differences in data collection such as defining the end of the T wave which is essential for QT measurement. Third, the sample sizes may not be large enough to ensure accuracy for statistical modeling.

The large number of different QTp equations and the multiple different parameters across the different equations is perhaps the reason that clinicians often opt to use QTc formulae rather than QTp formulae. Generally, QTc formulae are stripped of constants and coefficients contained in the initial formula. A presumed advantage of this approach is that some sources of variation due to subject selection, systematic errors, and sample sizes are minimized or eliminated while the important coefficients are determined from the trends of data sets.

A disadvantage of QTc formulae is that while some constants are removed to be less reflective of the sample size, the same constants played a role in the value of regressed parameters. For example, the power parameters without the accompanying constants in QTcBZT and QTcFRD will not minimize the error in the initial sample. This transformation is essentially changing the form of the initial pre-determined equation, without regressing to minimize the error.

A better approach might be fitting the initial data sets without a multiplicative coefficient.

Another problem with QTc formulae is the lack of specific limits for the definition of "prolonged QT" for each QT correction equation. Assuming that each equation is derived from a sample of normal healthy subjects, it is possible to calculate a confidence interval for the predicted duration of the QT interval. There has not, however, been a standard way to determine the confidence interval of a transformed QTc equation from the original data for each formula.

QTc and QTp equations have been categorized according to whether the equations are linear, hyperbolic, parabolic, logarithmic, shifted logarithmic, exponential or general additive models<sup>[20,22]</sup>. Our classification and nomenclature simplifies the categorization. From usual clinical data, it appears that most recent power correction equations agree with each other, and all equations may use the same limit for prolonged QT. The agreement among power-based QT correction equations is generally good because most resting heart rates are sufficiently close to 60, and that the RR interval is close to 1. For example, at a heart rate of 70 beats per minute, the RR is 1.17 s. The square root of 1.17 is 1.08 and the cube root of 1.17 is 1.05, where the difference is less than 3%. Hence, it is not a coincidence that most power correction equations agree among commonly encountered heart rates. The nature of the equation demands it near the "normal

heart rates". The reported phenomenon that some equations fail at higher or lower heart rates is intrinsic to the choice of a power-based model in the regression process. Rautaharju and Zhang<sup>[15]</sup> concluded that pure power functions generate a rate-dependent bias in the upper and lower ranges of the adjusted QT distribution that can be reduced by incorporating an intercept. We found, however, that approach still led to a rate dependency but agree that the approach minimizes such rate dependency.

From our discussion, it is clear that neither corrective nor predictive formulae have an absolute theoretical benefit over the other. In fact, corrective formulae are often incorrectly derived from predictive equations. However, we advocate for the use of corrective formulae on the basis that they are already readily adopted clinically, and upper limits are already determined by clinicians through decades of experience. Clinically, it is more logical and customary to see if a given measured value (QTc in this case) is within a pre-determined range via a QTc formula rather than a QTp formula. With a QTp formula, an absolute value must be calculated, and such operations can lead to errors in certain instances. To use corrective formulae, more work needs to be done to systemically determine the appropriate upper and lower limits for the duration of QTc for each formula.

## QTc HEART RATE INDEPENDENCE

We constructed scatter plots from ECG data obtained from the patient group (Figures 6 and 7). Each QTc formula was applied according to their stated form. This includes any available considerations given to age and gender. Our evaluation begins with Bazett (QTcBZT) and Fridericia (QTcFRD), both commonly used equations in clinical practice. We observe that QTcFRD is associated with a smaller slope with a linear regression line, and this translates into QTcFRD being superior to QTcBZT in attempting to separate the dependence of QT duration on heart rate. However, it is also clear that newer equations with larger sample sizes can achieve much higher accuracy than either QTcFRD or QTcBZT. The rank order of the slope was from best (closest to zero) was QTcDMT, QTcRTHa, QTcHDG, QTcGOT, QTcFRM, QTcFRD, QTcBZT and QTcMYD. As an example, QTcDMT has a slope of 0.04, which is more accurate than other equations studied. Hence, we conclude that QTcDMT should be used in future practice as it best separates the dependence of QTc from heart rate. QTcRTHa was the next best and warrants similar consideration.

There are many steps to take before QTcDMT or QTcRTHa replaces QTcBZT or QTcFRD. First, our results should be corroborated with a larger sized clinical study, with more subjects with well-defined clinical or physiological states. Second, it is essential to determine the upper and lower limits for a normal "QTcDMT" value. We recommend that the upper

and lower bound be set at 95% inclusion of all test subjects, which can be achieved by ranking the results obtained or *via* resampling methods, such as bootstrap or jackknife methods. Lastly, it is important to validate the upper and lower limits in a clinical setting in comparison to a standard by defining the correlation - sensitivity and specificity of newer QTc formulae - QTcDMT or QTcRTH in the detection of electrolyte disturbances, drug-induced cardiac toxicity, genetic abnormalities of cardiac channels (channelopathies) and autonomic nervous system dysregulation.

## CONCLUSION

In summary, the clinician has a choice of over 20 different equations to adjust the QT interval to minimize the effect of heart rate on the QT interval. These equations should be referred to by a standard nomenclature such as the one proposed here in. The clinician should recognize that at some heart rates, there will be marked discordances between formulae both for QTc and QTp. We believe that QTc equations are preferred over QTp equations because there are more easily adopted in the clinical setting. Some equations have a slope of their QTc to heart rate close to zero but the fit of the equations may not be ideal. While none of the formulae may completely eliminate the effect of heart rate on the QT interval, some of the recent formulae based on large population samples appear to be better than the older heart rate adjustment formulae. In particular, we have found that QTcDMT and to some extent QTcRTH<sub>a</sub> are significantly more accurate than other formulae studied. Larger clinical studies are required to validate their precision. In addition, the lower and upper limits of the newer equations specifically QTcDMT and QTcRTH<sub>a</sub> should be tested under a clinical setting to compare them to the current commonly used equations such as QTcBZT and QTcFRD. With these caveats, QTcDMT and QTcRTH<sub>a</sub> warrant consideration for implementation in clinical practice.

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## Closing patent foramen ovale in cryptogenic stroke: The underscored importance of other interatrial shunt variants

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**Author contributions:** Rigatelli G designed research; Rigatelli G and Rigatelli A performed research; Rigatelli A contributed new reagents or analytic tools; Rigatelli G wrote the paper.

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### Abstract

Recent trials and metanalysis even not fully conclusive and still debated, at least suggested that mechanical device-based closure of patent foramen ovale (PFO)

is more effective than medical therapy in prevent recurrence of stroke. In a proportion ranging from 20% to nearly 40% of patients in literature, PFO is associated to atrial septal aneurysm (ASA): ASA is a well-known entity often associated with additional fenestration. Additionally small atrial septal defects ("Flat ASD") can present with signs of paradoxical embolism and cannot be easily detected by transthoracic echocardiography or even by transesophageal echocardiography and are usually discovered by intracardiac echocardiography at the moment of transcatheter closure. This evidence might change potentially the anatomical diagnosis from PFO to fenestrated ASA or as we called it to "hybrid defect", being a bidirectional flow through a small ASD or/and an additional fenestration, often present. Despite the differences in anatomy, pathophysiology and haemodynamic paradoxical embolism may occur in both entities and also may be the first appearance of fenestrated ASA. Because some overlapping do really exist between PFO and hybrid defects, which are often not clearly differentiable by standard diagnostic tools, it is likely that a proportion of patients evaluated for potential transcatheter closure of PFO had actually a different anatomical substrate. These different anatomical and pathophysiologic entities have not been address in any of the previous trials, potentially having an impact on overall results despite the similar mechanical treatment. Neurologists and general cardiologists in charge of clinical management of PFO-related cryptogenic stroke should be aware of the role of hybrid defects in the pathophysiology of paradoxical embolism - mediated cerebral ischemic events in order to apply the correct decision - making process and avoid downgrading of patients with paradoxical embolism-related interatrial shunt variants different from PFO.

**Key words:** Atrial septal defect; Patent foramen ovale; Echocardiography; Anatomy

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**Core tip:** Recent trials and met analysis suggested that mechanical device-based closure of patent foramen ovale (PFO) is more effective than medical therapy in prevent recurrence of stroke. Fenestrated atrial septal aneurysms and small atrial septal defects (hybrid defects) can present with signs of paradoxical embolism and because they are often not clearly differentiable by standard diagnostic tools, it is likely that a proportion of patients evaluated for transcatheter closure of PFO, had actually a different anatomical substrate. These different anatomical entities have not been address in any of the previous trials, potentially having an impact on overall results.

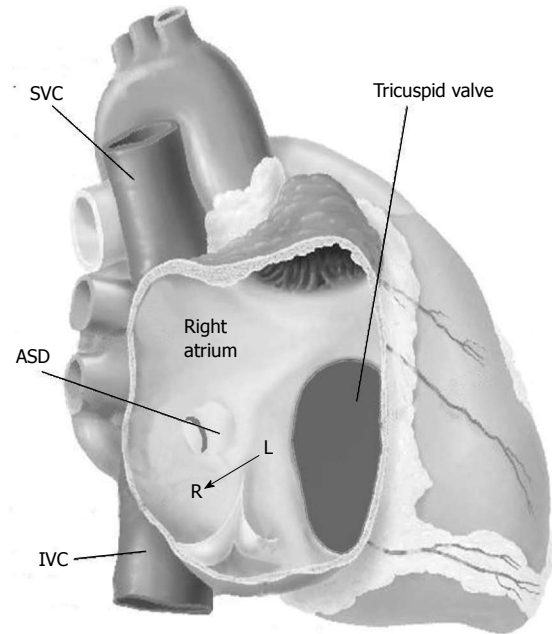
Rigatelli G, Rigatelli A. Closing patent foramen ovale in cryptogenic stroke: The underscored importance of other interatrial shunt variants. *World J Cardiol* 2015; 7(6): 326-330 Available from: URL: <http://www.wjgnet.com/1949-8462/full/v7/i6/326.htm> DOI: <http://dx.doi.org/10.4330/wjc.v7.i6.326>

## INTRODUCTION

Recent trials and metanalysis and in particular, the RESPECT trial<sup>[1]</sup>, even not fully conclusive and still debated, at least suggested that mechanical device-based closure of patent foramen ovale (PFO) is more effective in prevent recurrence of stroke by near 67%. When looking deeply into the number of different metanalysis of PFO closure for cryptogenic (or better paradoxical embolism mediated) stroke<sup>[2-7]</sup>, it appears clear that in a proportion ranging from 20% to nearly 40% of patients PFO is associated to atrial septal aneurysm (ASA): ASA is a well-known entity often associated with additional fenestration<sup>[8]</sup>. Additionally small atrial septal defects can present with signs of paradoxical embolism and cannot be easily detected by transthoracic echocardiography or even by transesophageal echocardiography and are usually discovered by intracardiac echocardiography at the moment of transcatheter closure<sup>[9]</sup>, confusing even more the diagnosis of PFO which is at the basis of all the studies about effectiveness of transcatheter closure in cryptogenic stroke. This evidence might change potentially the anatomical diagnosis from PFO to fenestrated ASA (or fenestrated secundum atrial septal defect) or to a so called "hybrid defect", [a small single atrial septal defects (ASD) associated with paradoxical embolism], being a bidirectional flow through a small ASD or and additional fenestration often present. The aim of this review is to analyse conjunction points between PFOs and hybrid defects and outlined the role of these type of interatrial shunt in the pathophysiology of paradoxical embolism.

## PRACTICAL EPIDEMIOLOGY

Isolated ASD represent 7% of all cardiac anomalies and



**Figure 1** Secundum atrial septal defect is a defect located into the limit of the fossa ovalis. The shunt usually is left-to-right because of the pressure gradient between the left (high pressure) and right (low pressure) atrium. ASD: Atrial septal defect; IVC: Inferior vena cava; L: Left; R: Right; SVC: Superior vena cava.

can present at any age<sup>[10]</sup>. Adolescents and adults with isolated atrial septal defects are more likely to reach adult age without being diagnosed. Secundum ASD is by far the most common type, occurring in 1/1500 live births, with 65% to 75% involving females<sup>[10]</sup>. On the other hand, PFO represents an endemic variant in the normal population with a prevalence of 25%-27%<sup>[11]</sup>. These two entities appear so different that is difficult to find a conjunction ring: nevertheless we use the same philosophy for the treatment. Indeed, device - based closure has been proved to be effective<sup>[12,13]</sup> in both settings.

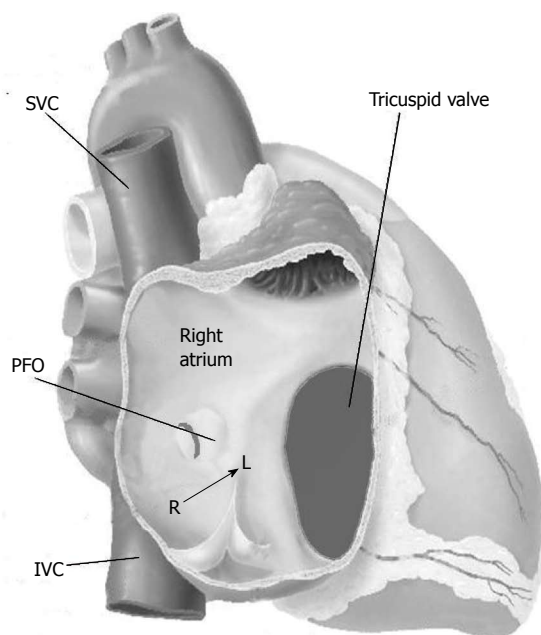
### Anatomy, pathophysiology, and haemodynamic

From an anatomic and pathophysiologic point of view these two entities are absolutely different.

The ostium secundum ASD is a defect of the atrial septum (Figure 1) within the limit of the fossa ovalis and causes usually a left-to-right shunt, being the left atrial pressure higher than the right atrial one. The volume of and direction of flow through an ASD depend on the size of the hole and the relative diastolic filling properties of the left and right chambers. Reduced left ventricle compliance and mitral stenosis increase the left-to-right shunt, whereas reduced right ventricle compliance may decrease the left-to-right shunt or may cause a right-to-left shunt. A Qp/Qs ratio > 1.5:1 or dilation of the right chambers defined a left-to-right shunt as significant<sup>[14]</sup>.

The PFO is defined as the incompetence of the fossa ovalis valve determining a right-to-left shunt (Figure 2). The reason because a right-to-left atrial





**Figure 2** Patent foramen ovale is a communication between the right and left atrium caused by the incompetence of the fossa ovalis valve. The shunt is usually right-to-left despite the gradient pressure between the atria. IVC: Inferior vena cava; L: Left; PFO: Patent foramen ovale; R: Right; SVC: Superior vena cava.

shunting occurs with normal intracardiac pressures and normal or near-normal pulmonary function through a PFO has still not been completely clarified. An explanation may arise from some few considerations. Firstly, a physiologic transient spontaneous reversal of difference between the left and the right pressure is physiologically present during early diastole and during isovolumetric contraction of the right ventricle of each cardiac cycle; this right-to-left gradient may be sustained by physiologic manoeuvres that increase the right atrial pressure such as posture, inspiration, cough or Valsalva manoeuvre, or by situation in which pulmonary vascular resistances results increased, such as acute pulmonary embolism, hypoxemia due to obstructive sleep apnoea, severe chronic obstructive pulmonary disease, right ventricular infarction and positive end-expiratory pressure during neurosurgical procedures in the sitting position. Secondly, another theory explaining the right-to-left shunting through a PFO, is represented by the "so-called" "flow phenomenon". It describes a preferential blood flow from the inferior vena cava towards the atrial septum as a part of the ancient foetal circulation pathway<sup>[15]</sup>.

Thirdly, the increasing stiffness of the right chambers compared to the left chambers caused by aging has been postulated. Finally, conditions such due to mediastinal shift or heart counter-clockwise rotation and/or distortion, following an ascending aorta enlargement, right pneumectomy or pericardial effusion may cause an anatomic disarray of the inferior vena cava relationship with the interatrial septum favouring part of the blood flow to enter the left atrium

throughout a PFO<sup>[16]</sup>.

Even from a haemodynamic point of view, ASD obviously differs from PFO. ASD are usually associated with pulmonary hypertension of different degree, an increased Qp/Qs ratio and enlarged right chambers, whereas the usual findings in PFO patients is a normal or slightly elevated pulmonary pressure, normal Qp/Qs ratio, and normal right chambers. Sometimes in presence of a PFO associated with large ASA, a mild impairment of the left atrial function can be observed<sup>[17]</sup>.

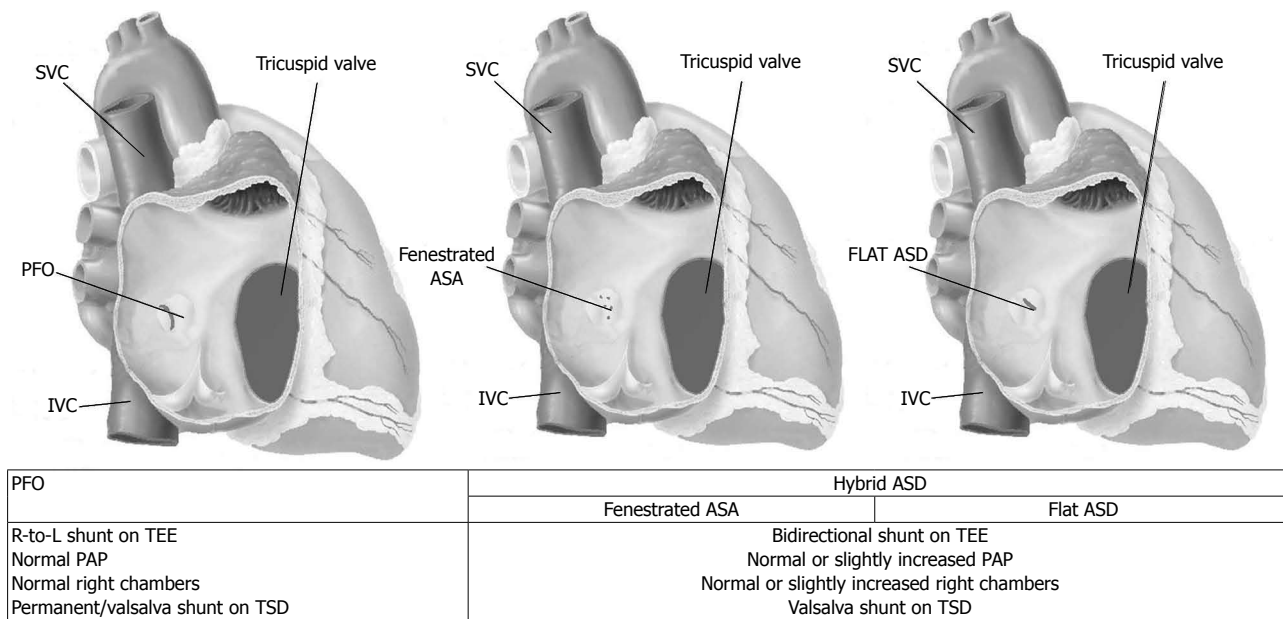
Usually also fenestrated secundum ASD with or without ASA tends to present less right chambers enlargement and only slightly increase in mean pulmonary pressure compared to secundum ASD.

## CONJUNCTION POINTS

Despite the gross differences in anatomy and haemodynamic, when we look to the clinical presentation and patho-physiology, we can find some contact points. Excepted for supraventricular arrhythmias and dyspnoea, usually present only in secundum single and fenestrated ASD, paradoxical embolism may occur in both entities and also may be the first appearance of fenestrated ASD with or without ASA.

Usually paradoxical embolism is associated with PFO but occasionally secundum ASD, pulmonary arterio-venous fistula, and other intracardiac septal defects may act as alternative pathophysiological mechanism. Microemboli from a vein thrombotic location, or as recently postulated<sup>[17]</sup> microthrombotic stratification on the surface of a huge ASA or in the left atrium itself as a result of a left atrial dysfunction induced by the PFO and ASA itself, may navigate to the left side of the circulation through the PFO causing different ischemic syndromes. Differently, the pathophysiology of paradoxical embolism through a secundum ASD is usually caused by a temporary right heart pressure increasing which induce a right-to-left shunting which allows a venous thromboembolus to enter the arterial circulation. As an alternative mechanism, Valsalva manoeuvre, coughing, or straining might increase right-to-left component of a bidirectional shunt inducing a paradoxical embolism in ASD patients, in particular in elderly patients, more prone to rapid change of right chambers pressure because of the increasing stiffness of the chambers.

Recently in an analysis of our institutional database we found 24 (6.2%) with a secundum ASD out of 386 patients evaluated for paradoxical embolism. Defects were multifenestrated in 41.6% (10/24). Single ASD (58.3%) had a "flat" elliptical shape with a major axis of  $7.6 \pm 2.4$  and minimal axis of  $2.5 \pm 1.6$  mm when assessed with intracardiac echocardiography. Patients with ASD-related paradoxical embolism had more frequently a deep venous thrombosis, bigger stroke areas compared to PFO patients, and massive curtain shunt on Valsalva maneuver on transcranial



**Figure 3 Spectrum of interatrial shunt associated with possible paradoxical embolism and potential related haemodynamic and functional characteristics.** ASA: Atrial septal aneurysm; ASD: Atrial septal defect; FO: Fossa ovalis; IVC: Inferior vena cava; PAP: Pulmonary artery pressure; PFO: Patent foramen ovale; R-to-L: Right to left shunt; SVC: Superior vena cava; TCD: Transcranial doppler; TEE: Transesophageal echocardiography.

Doppler. When compared to non-emboligenous ASD, they had lower mean pulmonary pressure, lower mean Qp/Qs, and had bidirectional shunt at rest<sup>[18]</sup>. As matter of fact, flat elliptical shape ASD and fenestrated ASD with or without ASA appear to represent the conjunction ring between ASD and PFO, being a hybrid hemodynamic and clinical profile compared to each of the others (Figure 3).

## FINAL CONSIDERATIONS: ARE THE PAST TRIALS REALLY FOCUSED ON THE PROPER ANATOMICAL ENTITY?

Because some overlapping do really exist between PFO, fenestrated ASD and hybrid defects (Figure 1) which are not always clearly differentiable by standard diagnostic tools, it is likely that a proportion of patients evaluated for potential transcatheter closure of PFO had actually a different anatomical substrate. Past trials and case series used Transeophageal guidance in the majority of patients and the severity of the shunt and presence of permanent shunt has not been evaluated systematically by Transcranial Doppler or transesophageal echocardiography in the enrolment process.

Current modern judgement about medical or mechanical closure is suggested to be based, following the only published multidisciplinary consensus<sup>[19]</sup>, on recurrent stroke or ischemic event with positive neuroimaging studies, severe shunt graded by transcranial Doppler and transesophageal echocardiography, presence of permanent shunt, and of additional anatomical features, such as ASA, tunnel-like opening, and Eustachian valve. The large and permanent shunt in particular, as

previously suggested<sup>[18,20]</sup> is one of the most influent parameters, and it appears clear that in presence of an hybrid defect, it doesn't play the same role as in true PFO, while ASA and Eustachian valve may be more influent facilitating paradoxical shunt through an hybrid defect or a fenestrated ASD when a Valsalva manoeuvre is provoked. These different anatomical and pathophysiologic pictures have not been address in any of the previous trials, potentially having an impact on overall results despite the similar mechanical treatment.

From a practical point of view, patients with deep vein thrombosis and more clinically relevant ischemic syndrome are more likely to have a hybrid defect, whereas patients with no deep vein thrombosis and mild symptomatology are more likely to have a PFO. An ideal screening of a patient with suspected paradoxical embolism should include not only the transthoracic echo, but also the transesophageal echo in order to differentiate between PFO and hybrid defects.

At the light of what we discussed above, neurologists and general cardiologists in charge of clinical management of PFO-related cryptogenic stroke should be aware of the role of hybrid defects and multi-fenestrated ASA in the pathophysiology of paradoxical embolism - mediated cerebral ischemic events in order to apply the correct decision -making process and avoid downgrading of patients with paradoxical embolism-related interatrial shunt variants different from PFO.

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## Basic Study

# Bone morphogenetic protein-4 and transforming growth factor-beta1 mechanisms in acute valvular response to supra-physiologic hemodynamic stresses

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**Data sharing:** Complete dataset and statistical analyses available from the corresponding author at [philippe.sucosky@nd.edu](mailto:philippe.sucosky@nd.edu).

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## Abstract

**AIM:** To explore *ex vivo* the role of bone morphogenetic protein-4 (BMP-4) and transforming growth factor-beta1 (TGF-β1) in acute valvular response to fluid shear stress (FSS) abnormalities.

**METHODS:** Porcine valve leaflets were subjected *ex vivo* to physiologic FSS, supra-physiologic FSS magnitude at normal frequency and supra-physiologic FSS frequency at normal magnitude for 48 h in a double-sided cone-and-plate bioreactor filled with standard culture medium. The role of BMP-4 and TGF-β1 in the valvular response was investigated by promoting or inhibiting the downstream action of those cytokines *via* culture medium supplementation with BMP-4 or the BMP antagonist noggin, and TGF-β1 or the TGF-β1 inhibitor SB-431542, respectively. Fresh porcine leaflets were used as controls. Each experimental group consisted of six leaflet samples. Immunostaining and immunoblotting were performed to assess endothelial activation in terms of intercellular adhesion molecule-1 and vascular cell adhesion molecule-1 expressions, paracrine signaling in terms of BMP-4 and TGF-β1 expressions and extracellular matrix (ECM) remodeling in terms of cathepsin L, cathepsin S, metalloproteinases (MMP)-2 and MMP-9 expressions. Immunostained images were quantified by normalizing the intensities of positively stained regions by the number of cells in each image while immunoblots were quantified by densitometry.

**RESULTS:** Regardless of the culture medium, physiologic FSS maintained valvular homeostasis. Tissue exposure to supra-physiologic FSS magnitude in standard medium stimulated paracrine signaling (TGF-β1: 467% ± 22% *vs* 100% ± 6% in fresh



controls, BMP-4:  $258\% \pm 22\%$  vs  $100\% \pm 4\%$  in fresh controls;  $P < 0.05$ ) and ECM degradation (MMP-2:  $941\% \pm 90\%$  vs  $100\% \pm 19\%$  in fresh controls, MMP-9:  $1219\% \pm 190\%$  vs  $100\% \pm 16\%$  in fresh controls, cathepsin L:  $1187\% \pm 175\%$  vs  $100\% \pm 12\%$  in fresh controls, cathepsin S:  $603\% \pm 88\%$  vs  $100\% \pm 13\%$  in fresh controls;  $P < 0.05$ ), while BMP-4 supplementation also promoted fibrosa activation and TGF- $\beta$ 1 inhibition reduced MMP-9 expression to the native tissue level (MMP-9:  $308\% \pm 153\%$  with TGF- $\beta$ 1 inhibition vs  $100\% \pm 16\%$  in fresh control;  $P > 0.05$ ). Supra-physiologic FSS frequency had no effect on endothelial activation and paracrine signaling regardless of the culture medium but TGF- $\beta$ 1 silencing attenuated FSS-induced ECM degradation *via* MMP-9 downregulation (MMP-9:  $302\% \pm 182\%$  vs  $100\% \pm 42\%$  in fresh controls;  $P > 0.05$ ).

**CONCLUSION:** Valvular tissue is sensitive to FSS abnormalities. The TGF- $\beta$ 1 inhibitor SB-431542 is a potential candidate molecule for attenuating the effects of FSS abnormalities on valvular remodeling.

**Key words:** Aortic valve; Fluid shear stress; Calcification; Bone morphogenetic protein; Transforming growth factor beta

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**Core tip:** Although flow abnormalities have been shown to promote valvular pathogenesis in a bone morphogenetic protein-4 (BMP-4)- and transforming growth factor-beta1 (TGF- $\beta$ 1)-dependent manner, the mode of action of those molecules in response to fluid shear stress (FSS) abnormalities remains unknown. This *ex vivo* study aimed at isolating the role played by those cytokines in the acute response of porcine leaflets to supra-physiologic FSS magnitude/frequency. The study reveals that: (1) valvular endothelial activation is weakly regulated by BMP-4 in response to FSS abnormalities; (2) TGF- $\beta$ 1 silencing attenuates FSS-induced extracellular matrix degradation *via* MMP-9 downregulation; and (3) BMP-4 and TGF- $\beta$ 1 do not synergistically interact in response to FSS abnormalities.

Sun L, Sucusky P. Bone morphogenetic protein-4 and transforming growth factor-beta1 mechanisms in acute valvular response to supra-physiologic hemodynamic stresses. *World J Cardiol* 2015; 7(6): 331-343 Available from: URL: <http://www.wjgnet.com/1949-8462/full/v7/i6/331.htm> DOI: <http://dx.doi.org/10.4330/wjc.v7.i6.331>

## INTRODUCTION

Calcific aortic valve disease (CAVD) affects 3% of the general population above 75 years of age and is the first indication for valvular replacement worldwide<sup>[1,2]</sup>. The

formation of calcific lesions on the valve leaflets involves active processes including inflammation<sup>[3,4]</sup>, extracellular matrix (ECM) remodeling<sup>[5-7]</sup> and osteogenesis<sup>[8-10]</sup>. Calcified valves typically exhibit increased expression of cytokines such as transforming growth factor-beta1 (TGF- $\beta$ 1)<sup>[11]</sup> and bone morphogenetic protein-4 (BMP-4)<sup>[12]</sup>. While genetic defects<sup>[13]</sup> and conventional cardiovascular risk factors<sup>[2]</sup> have been identified as potential triggers of CAVD, blood flow abnormalities have emerged as a potential concomitant contributor<sup>[14-16]</sup>. Aging, hypertension and anatomical valve defects such as the bicuspid aortic valve, which are risk factors for CAVD<sup>[17-21]</sup>, generate hemodynamic alterations that result in an abnormal friction force or "fluid shear stress" (FSS) on both sides of the leaflets<sup>[22-24]</sup>.

To date, the evidence of causality between hemodynamic abnormalities and valvular pathogenesis has been provided *ex vivo*, using sophisticated bioreactors aimed at replicating the characteristics of the leaflet FSS environment<sup>[25,26]</sup>. Due to the challenge to replicate the native side-specific leaflet FSS (*i.e.*, unidirectional on the ventricularis, oscillatory on the fibrosa), early studies investigated the role played by FSS abnormalities in valvular pathogenesis by subjecting only one leaflet surface at a time to flow. Studies conducted using this simplified model demonstrated the capability of combined alterations in FSS magnitude and pulsatility to stimulate inflammation on the leaflet fibrosa in a TGF- $\beta$ 1- and BMP-4-dependent manner<sup>[27]</sup>, and the capability of elevated FSS to activate the fibrosa endothelium *via* synergies between BMP-4 and TGF- $\beta$ 1 pathways<sup>[28]</sup>. Recent advances in bioreactor design have enabled the replication of the native side-specific leaflet FSS in the laboratory setting. Simultaneous exposure of both leaflet surfaces to abnormalities in FSS magnitude and/or frequency has revealed the high sensitivity of the leaflet tissue to elevated FSS magnitude or frequency, and the ability of FSS abnormalities to promote paracrine signaling and ECM degradation<sup>[29]</sup>.

The clear involvement of BMP-4 and TGF- $\beta$ 1 in hemodynamically induced CAVD provides a rationale for considering those molecules for targeted cell-based therapies aimed at attenuating or blocking the downstream pathological cascade. However, the upstream role of and potential synergies between TGF- $\beta$ 1 and BMP-4 in the transduction of FSS abnormalities have not been evidenced in the native (*i.e.*, side-specific) leaflet FSS environment. Supported by our previous results, the present study addresses the hypothesis that TGF- $\beta$ 1 and BMP-4 synergistically interact to regulate valvular pathogenesis in response to side-specific alterations in FSS magnitude or frequency. This hypothesis was tested *ex vivo* by exploring the effects of each cytokine on the downstream FSS-induced pathological response. This dependence was characterized by measuring endothelial activation, paracrine signaling and ECM



remodeling events secondary to FSS alterations after silencing or promoting pharmacologically the expression of each molecule.

## MATERIALS AND METHODS

### Experimental conditions

Porcine aortic valve leaflets were subjected to physiologic and supra-physiologic FSS environments *ex vivo* using our double-sided cone-and-plate bioreactor (Figure 1A)<sup>[26]</sup>. This device has been previously validated mechanically and biologically and implemented in different *ex vivo* studies to subject simultaneously but independently both leaflet surfaces to desired side-specific and time-varying FSS<sup>[29,30]</sup>. Fresh porcine valves (6–12 mo) were obtained from a local abattoir (Martin's Custom Butchering, Wakarusa, IN), immediately transported to the laboratory in ice-cold phosphate buffered saline. A circular section of 7 mm in diameter was excised from the base of each leaflet. Two samples from each valve were used as experimental samples while the third sample served as fresh control. Six experimental samples were mounted in the bioreactor, exposing both their aortic and ventricular sides to FSS. All experiments were conducted for 48 h, a duration sufficient for valve leaflets to transduce FSS abnormalities into a pathological response<sup>[29]</sup>.

Consistent with our previous studies<sup>[27–29]</sup>, the physiologic FSS environment consisted of a unidirectional FSS varying between 0 and 80 dyn/cm<sup>2</sup> on the ventricularis (leaflet surface facing the ventricle) and a reciprocal FSS varying between -8 and +10 dyn/cm<sup>2</sup> on the fibrosa (leaflet surface facing the aorta; Figure 1B). The two supra-physiologic FSS environments consisted of supra-physiologic FSS magnitude (*i.e.*, twice the physiologic level) at physiologic frequency (Figure 1C) and supra-physiologic FSS frequency (*i.e.*, twice the physiologic frequency) at physiologic magnitude (Figure 1D). Those abnormal FSS environments were selected based on their demonstrated ability to stimulate acute CAVD mechanisms<sup>[29]</sup>.

In order to isolate the possible synergies between BMP-4 and TGF- $\beta$ 1, the experiments were conducted using standard culture medium (Dulbecco's Modified Eagle Medium, Sigma) as well as four additional culture medium variations. The downstream action of BMP-4 was blocked by supplementing the standard culture medium with noggin, a well-known BMP antagonist<sup>[31–33]</sup>, while TGF- $\beta$ 1 signaling was blocked by supplementing the medium with SB-431542, a small molecule inhibitor specifically targeting the TGF- $\beta$  type-I receptor<sup>[34,35]</sup>. The inhibitor concentrations used in this study (noggin: 100 ng/mL; SB-431542: 1  $\mu$ mol/L) have been shown to effectively inhibit BMP- and TGF- $\beta$ 1 signaling in response to stretch and FSS abnormalities *ex vivo*<sup>[27,28,36]</sup>. Conversely, BMP-4 and TGF- $\beta$ 1 signaling were promoted by supplementing the standard culture medium with recombinant BMP-4 and

TGF- $\beta$ 1, respectively, using concentrations (BMP-4: 10 ng/mL; TGF- $\beta$ 1: 10 ng/mL) previously established to effectively enhance paracrine signaling processes in valvular tissue<sup>[27,28]</sup>. Fresh porcine leaflets were used as controls.

### Biological characterization

Endothelial activation was assessed in terms of inter-cellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1). Paracrine signaling events were characterized in terms of the cytokines BMP-4 and TGF- $\beta$ 1. ECM remodeling and degradation were quantified in terms of matrix metalloproteinases (MMP-2 and -9) and cathepsins (cathepsin L and S). Detailed immunostaining and immunoblotting protocols are described in Supplementary Material.

### Statistical analysis

Each experimental group consisted of six leaflet samples. Data from each group were quantified as mean  $\pm$  SD error and then normalized to the values measured in the fresh control. Following this procedure, all biomarker expressions were expressed in terms of a normalized mean value  $\pm$  normalized standard error. Data from all experiments were tested for normality by the Anderson-Darling method, then analyzed using ANOVA followed by the Bonferroni post-hoc test. A *P*-value of less than 0.05 was used as a measure of statistical significance. The statistical review of the study was performed by a biomedical statistician (Dr. Jun Li, Department of Applied and Computational Mathematics and Statistics, University of Notre Dame, Notre Dame, IN, United States).

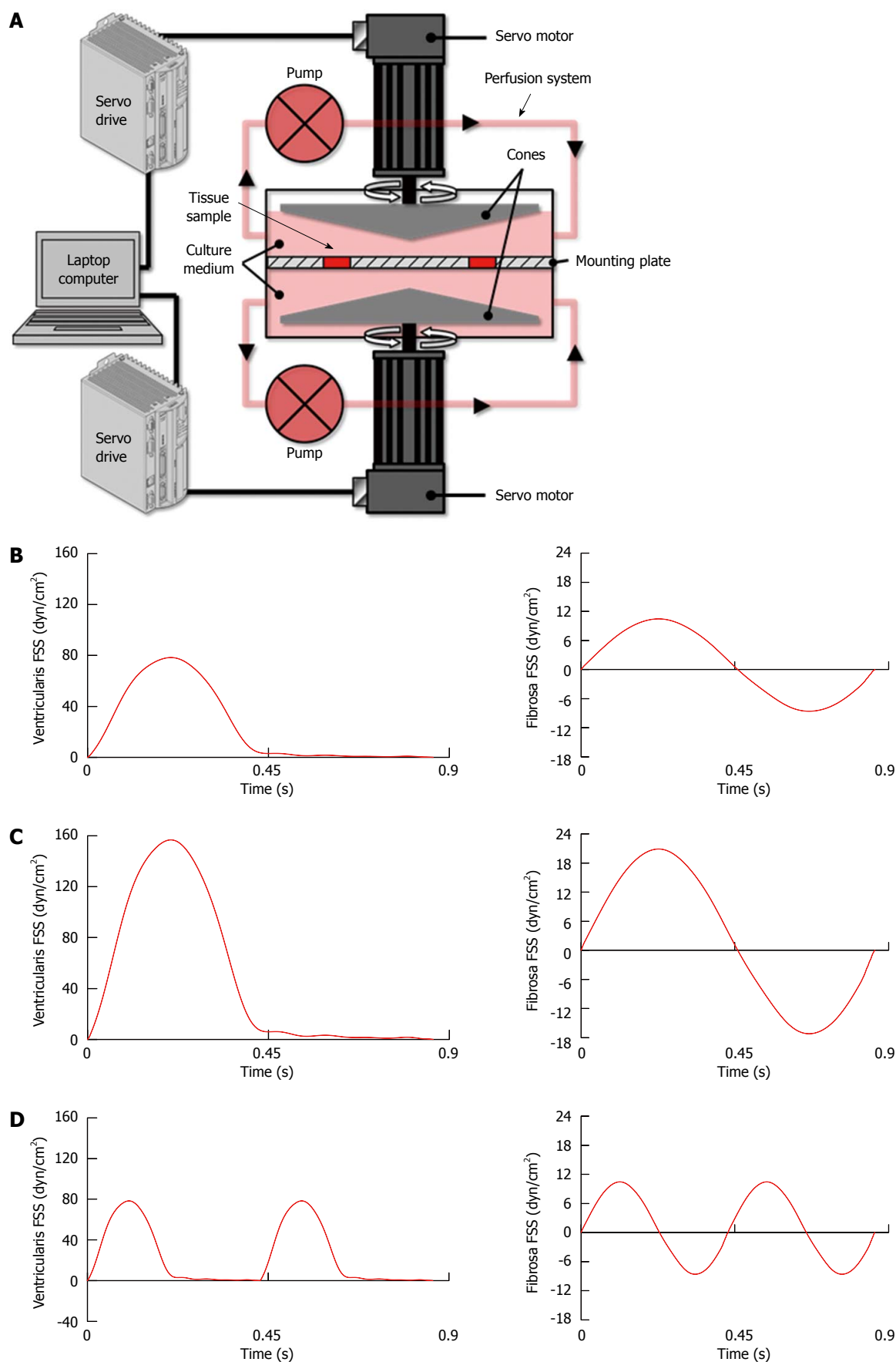
## RESULTS

### BMP-4 supplementation promotes endothelial activation in response to supra-physiologic FSS magnitude

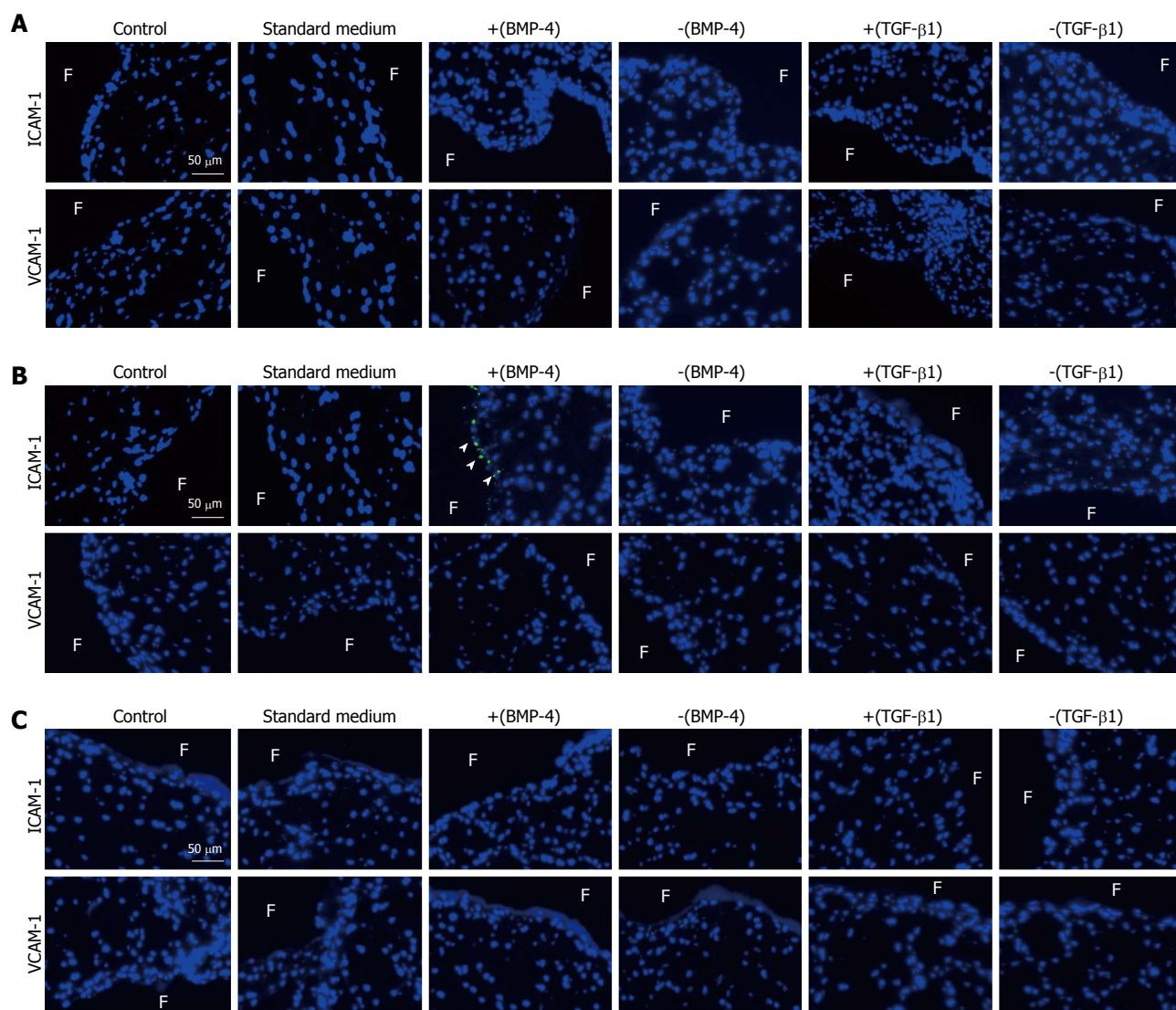
Immunostaining was performed to examine endothelial activation in response to all three FSS environments using standard, pro- and anti-osteogenic culture media. Tissue conditioned under physiologic FSS did not exhibit any positive staining for ICAM-1 or VCAM-1, regardless of the culture medium (Figure 2A). Exposure of leaflet tissue to supra-physiologic FSS magnitude exhibited a similar trend except when BMP-4 was added to the culture medium, which resulted in ICAM-1 expression on the endothelial lining of the fibrosa (Figure 2B). Similarly to the results obtained under physiologic FSS, supra-physiologic FSS frequency did not promote cell adhesion molecule expression with any culture medium (Figure 2C).

### Synergistic effects of BMP-4 and TGF- $\beta$ 1

Potential synergies between BMP-4 and TGF- $\beta$ 1 signaling in response to FSS abnormalities were investigated by quantifying the expression of one cytokine following the pharmacological inhibition or supplementation



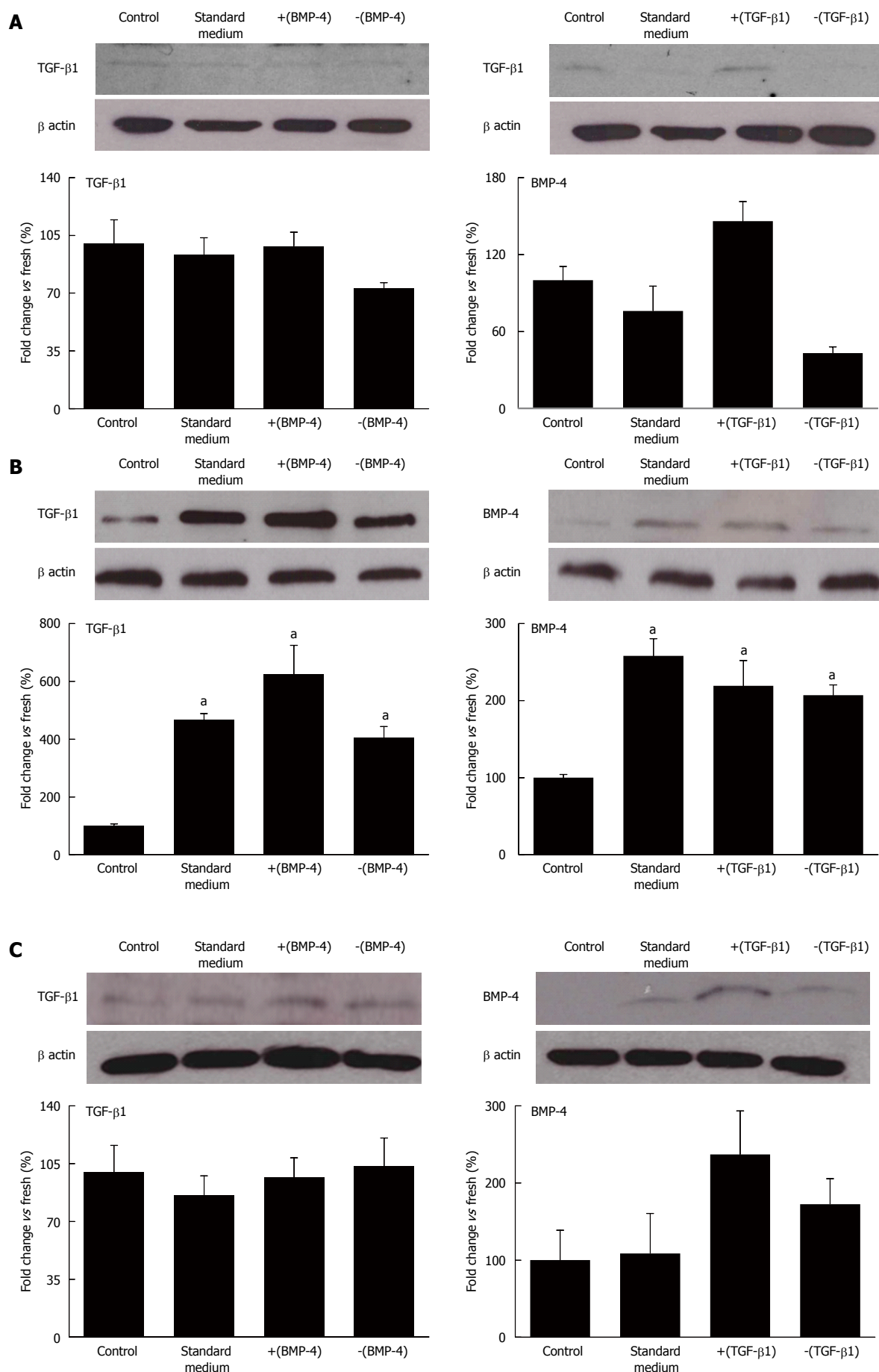
**Figure 1** Tissue conditioning methodology and fluid shear stress environments. A: Schematic of the double-sided cone-and-plate bioreactor; B: Physiologic fluid shear stress (FSS); C: Supra-physiologic FSS magnitude at physiologic frequency; D: Supra-physiologic FSS frequency at physiologic magnitude.



**Figure 2** Intercellular adhesion molecule-1 and vascular cell adhesion molecule-1 immunostaining. Tissue exposed for 48 h to: (A) physiologic fluid shear stress (FSS), (B) supra-physiologic FSS magnitude, and (C) supra-physiologic FSS frequency in standard medium and medium supplemented with BMP-4 [+(BMP-4)], noggin [-(BMP-4)], TGF-β1 [+(TGF-β1)] or SB-431542 [-(TGF-β1)] (F: Fibrosa; green: Positively stained cells; blue: Cell nucleus). ICAM-1: Intercellular adhesion molecule-1; VCAM-1: Vascular cell adhesion molecule-1; TGF-β1: Transforming growth factor-beta1; BMP-4: Bone morphogenic protein-4.

of the other. Western blot results indicate that under physiologic FSS, medium supplementation with BMP-4 or noggin had no significant effect on TGF-β1 expression, which remained statistically similar to the levels measured in fresh controls and in tissue conditioned using the standard medium (Figure 3A). Similarly, no significant difference in BMP-4 expression was detected between any culture medium treatment groups. In contrast, analysis of tissue conditioned to supra-physiologic FSS magnitude (Figure 3B) revealed a significant 4.7-fold, 6.2-fold and 4.1-fold increase in TGF-β1 expression using standard medium, medium supplemented with BMP-4 and medium supplemented with noggin, respectively, relative to the fresh controls ( $467\% \pm 22\%$ ,  $624\% \pm 100\%$ ,  $405\% \pm 38\%$ , respectively, vs  $100\% \pm 6\%$ ;  $P < 0.05$ ). However, no statistical difference in TGF-β1 expression was detected between the standard medium, BMP-4 treatment and

noggin treatment groups. While supra-physiologic FSS also resulted in a significant 2.6-fold, 2.2-fold and 2.1-fold increase in BMP-4 expression using standard medium, medium supplemented with TGF-β1 and medium supplemented with SB-431542, respectively, relative to the fresh controls ( $258\% \pm 22\%$ ,  $219\% \pm 33\%$ ,  $207\% \pm 13\%$ , respectively, vs  $100\% \pm 4\%$ ;  $P < 0.05$ ), no statistical difference in BMP-4 expression was detected between those three culture medium groups. Lastly, exposure of leaflet tissue to supra-physiologic FSS frequency using the five culture media (Figure 3C) produced results similar to those obtained under physiologic FSS, in which no significant difference in TGF-β1 or BMP-4 expression was detected between the fresh controls, the standard medium group, the pro-osteogenic medium groups (BMP-4 or TGF-β1 treatment) and the anti-osteogenic medium groups (noggin or SB-431542 treatment).



**Figure 3** Transforming growth factor-beta1 and bone morphogenic protein-4 immunoblotting. Tissue exposed for 48 h to: (A) physiologic fluid shear stress (FSS), (B) supra-physiologic FSS magnitude, and (C) supra-physiologic FSS frequency standard medium and medium supplemented with BMP-4 [+(BMP-4)], noggin [-(BMP-4)], TGF- $\beta$ 1 [+(TGF- $\beta$ 1)] or SB-431542 [-(TGF- $\beta$ 1)] (<sup>a</sup> $P$  < 0.05 vs fresh control). TGF- $\beta$ 1: Transforming growth factor-beta1; BMP-4: Bone morphogenic protein-4.



### ***TGF- $\beta$ 1 silencing reduces MMP-9 expression in response to FSS abnormalities***

MMP-2 and MMP-9 immunostaining was performed in leaflet tissue exposed to physiologic and supra-physiologic FSS using the five culture media to characterize the downstream action of BMP-4 and TGF- $\beta$ 1 on ECM degradation. No significant difference in MMP-2 and MMP-9 expression was detected between any culture medium treatment group and the fresh controls in leaflets subjected to physiologic FSS (Figure 4A). Leaflet exposure to supra-physiologic FSS magnitude resulted in a significant 9.4-fold, 8.4-fold and 11.1-fold increase in MMP-2 expression using standard medium, medium supplemented with BMP-4 and medium supplemented with TGF- $\beta$ 1, respectively, relative to the fresh controls ( $941\% \pm 90\%$ ,  $842\% \pm 126\%$ ,  $1108\% \pm 170\%$ , respectively, vs  $100\% \pm 19\%$ ;  $P < 0.05$ ; Figure 4B) but no difference in expression was detected between the five culture media. A significant 12.2-fold, 9.3-fold and 16.2-fold increase in MMP-9 expression was also observed with the standard medium, noggin and TGF- $\beta$ 1 treatment groups, respectively, relative to the fresh controls ( $1219\% \pm 190\%$ ,  $931\% \pm 104\%$ ,  $1621\% \pm 261\%$ , respectively, vs  $100\% \pm 16\%$ ;  $P < 0.05$ ), with no significant difference in MMP-9 expression between the five culture media. In contrast, TGF- $\beta$ 1 silencing resulted in a significant 75% and 81% reduction in MMP-9 expression relative to the standard culture medium and TGF- $\beta$ 1 treatment group, respectively, and resulted in a MMP-9 expression level statistically similar to that measured in fresh controls. Lastly, supra-physiologic FSS frequency resulted in a significant 12.6-fold, 13.2-fold, 14.5-fold and 13.4-fold increase in MMP-2 expression using standard medium, medium supplemented with BMP-4, medium supplemented with TGF- $\beta$ 1 and medium supplemented with SB-431542, respectively, relative to the fresh controls ( $1264\% \pm 145\%$ ,  $1318\% \pm 239\%$ ,  $1447\% \pm 278\%$ ,  $1339\% \pm 314\%$ , respectively, vs  $100\% \pm 21\%$ ;  $P < 0.05$ ) without any significant difference between any culture medium groups (Figure 4C). This FSS environment also resulted in a significant 15.7-fold, 14.9-fold and 17.3-fold increase in MMP-9 expression in the standard culture medium, noggin and TGF- $\beta$ 1 treatment groups, respectively, relative to the fresh controls ( $1571\% \pm 191\%$ ,  $1488\% \pm 316\%$ ,  $1728\% \pm 268\%$ , respectively, vs  $100\% \pm 42\%$ ;  $P < 0.05$ ). TGF- $\beta$ 1 silencing resulted in a significant 81% and 83% reduction in MMP-9 expression relative to the standard culture medium and TGF- $\beta$ 1 treatment group, respectively ( $302\% \pm 182\%$  vs  $1571\% \pm 191\%$  and  $1728\% \pm 268\%$ , respectively;  $P < 0.05$ ), and resulted in a MMP-9 expression level statistically similar to that measured in fresh controls.

### ***BMP-4 and TGF- $\beta$ 1 do not synergistically regulate cathepsin expression in response to FSS***

The synergistic effects of BMP-4 and TGF- $\beta$ 1 on FSS-mediated protease expression were characterized *via*

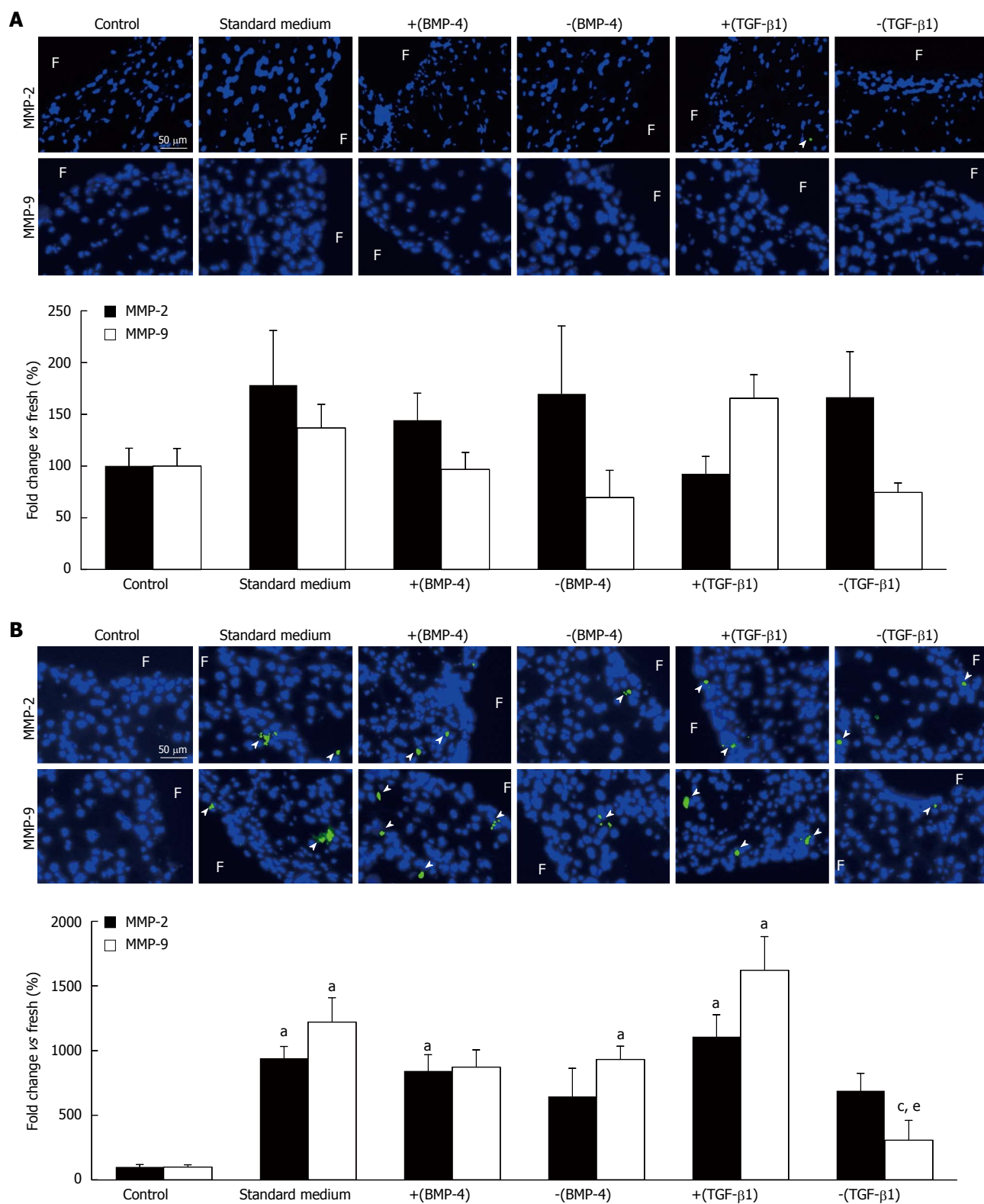
cathepsin L and cathepsin S immunostaining. Under physiologic FSS, no significant difference in cathepsin L and cathepsin S expression was detected between any culture medium treatment group and the fresh controls (Figure 5A). Tissue exposure to supra-physiologic FSS magnitude resulted in a significant 11.9-fold and 15.5-fold increase in cathepsin L expression using the standard medium and medium supplemented with TGF- $\beta$ 1, respectively, relative to the fresh controls ( $1187\% \pm 175\%$ ,  $1546\% \pm 171\%$ , respectively, vs  $100\% \pm 12\%$ ;  $P < 0.05$ ; Figure 5B). The same FSS environment resulted in a significant 6.0-fold, 6.0-fold, 5.5-fold, 5.4-fold and 3.3-fold increase in cathepsin S expression using the standard medium, BMP-4, noggin, TGF- $\beta$ 1 and SB-431542 treatment groups, respectively, relative to the fresh controls ( $603\% \pm 88\%$ ,  $598\% \pm 96\%$ ,  $554\% \pm 94\%$ ,  $541\% \pm 92\%$ ,  $325\% \pm 57\%$ , respectively, vs  $100\% \pm 13\%$ ;  $P < 0.05$ ). However, the effects of BMP-4 and TGF- $\beta$ 1 on protease expression remained limited as indicated by the absence of significant difference in cathepsin L and S expression between the different medium treatment groups. Lastly, supra-physiologic FSS frequency did not promote cathepsin L expression, regardless of the culture medium treatment group (Figure 5C). In contrast, the same mechanical treatment resulted in a significant 7.4-fold, 6.4-fold and 7.4-fold increase in cathepsin S expression in the BMP-4, noggin and TGF- $\beta$ 1 treatment groups, respectively, relative to the fresh controls ( $744\% \pm 129\%$ ,  $635\% \pm 76\%$ ,  $744\% \pm 144\%$ , respectively, vs  $100\% \pm 7\%$ ;  $P < 0.05$ ).

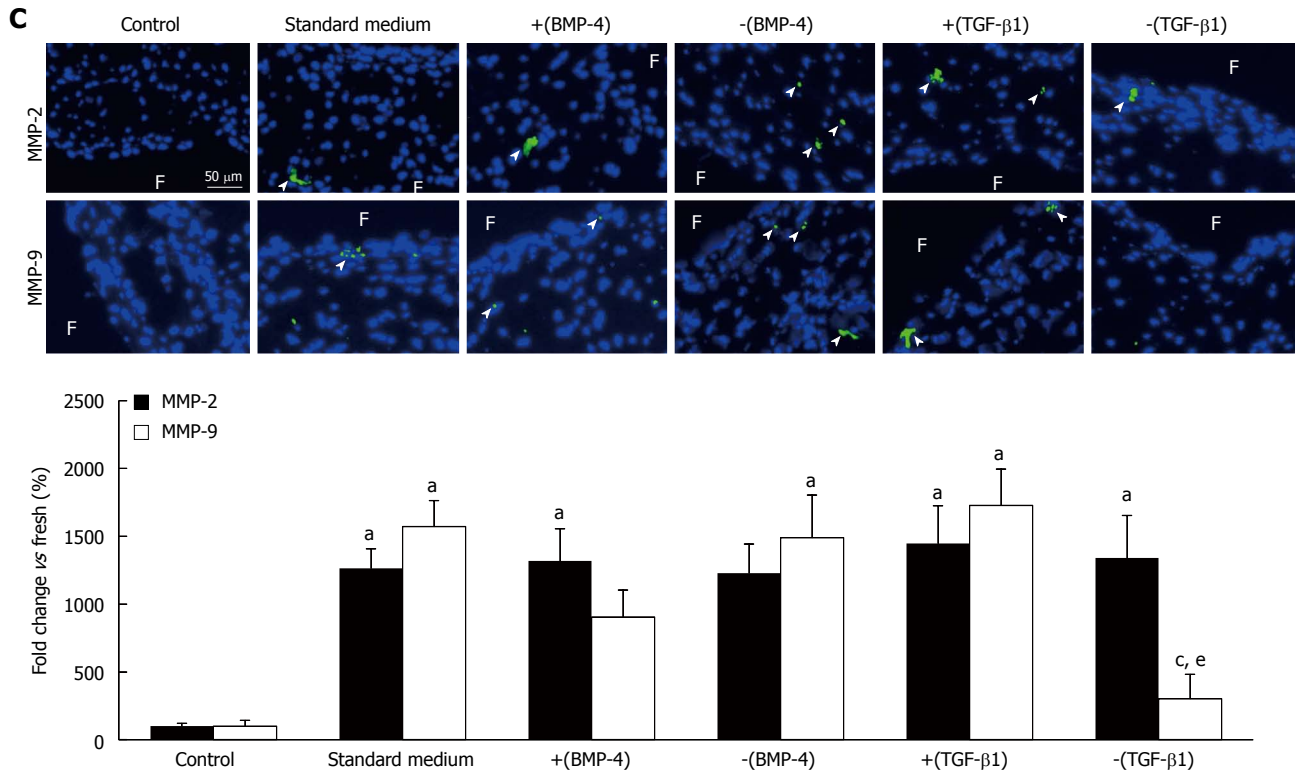
## **DISCUSSION**

In this *ex vivo* study, we investigated the role of the cytokines BMP-4 and TGF- $\beta$ 1 in the acute pathological response of porcine valve leaflets exposed to FSS abnormalities. We demonstrated that: (1) valvular endothelial activation is weakly regulated by BMP-4 in response to FSS abnormalities; (2) TGF- $\beta$ 1 silencing attenuates FSS-induced ECM degradation *via* MMP-9 downregulation; and (3) BMP-4 and TGF- $\beta$ 1 do not synergistically interact in response to FSS abnormalities.

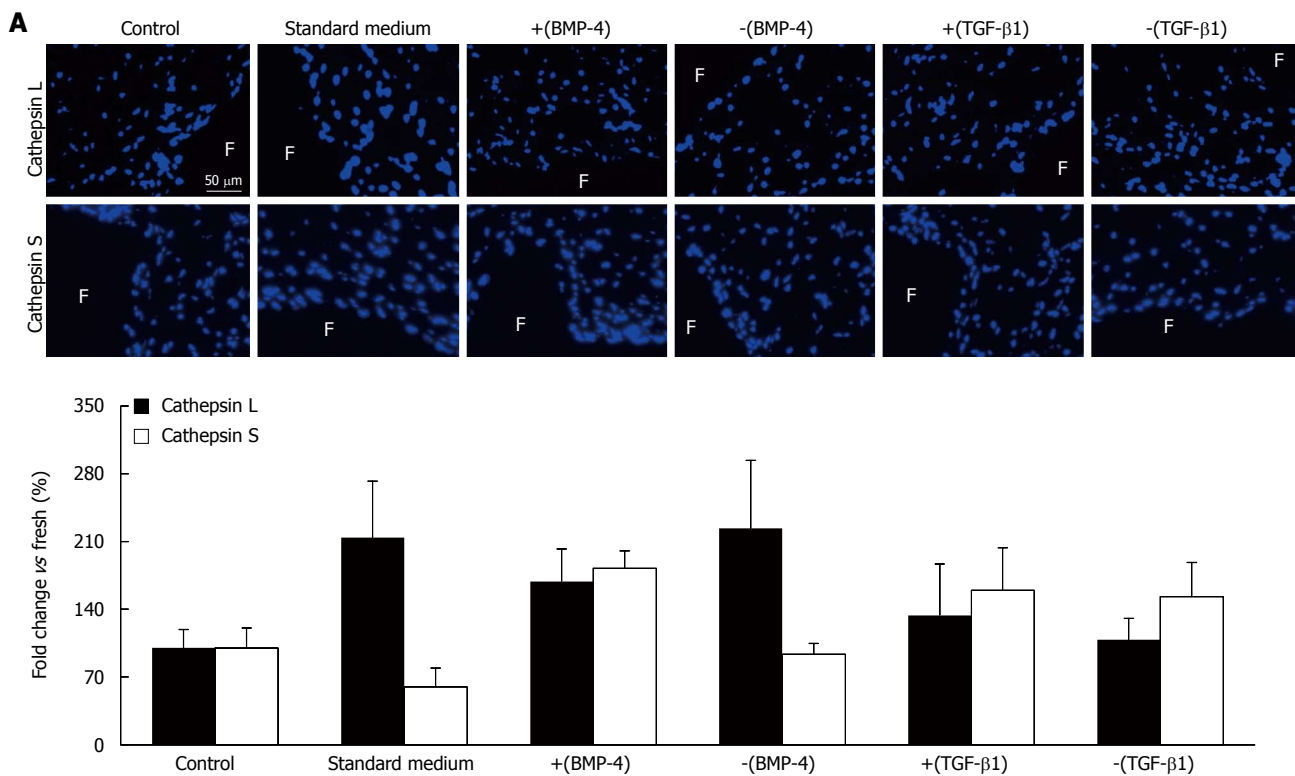
This study first confirms the key role played by FSS in the maintenance of valvular homeostasis. In fact, exposure of leaflet tissue to its native FSS environment did not stimulate any pathological event and resulted in biomarker expressions similar to those measured in fresh tissue, regardless of the culture medium. Valvular tissue has been shown to be sensitive to the forces present in its hemodynamic environment<sup>[37,38]</sup>. As compared to stretch and pressure which propagate throughout the leaflet and stimulate both valvular endothelial cells (VECs) and interstitial cells (VICs), FSS is an interfacial stress sensed primarily by VECs. Therefore, the ability of FSS alone to maintain leaflet homeostasis in the absence of any other mechanical signal demonstrates the key role played by the

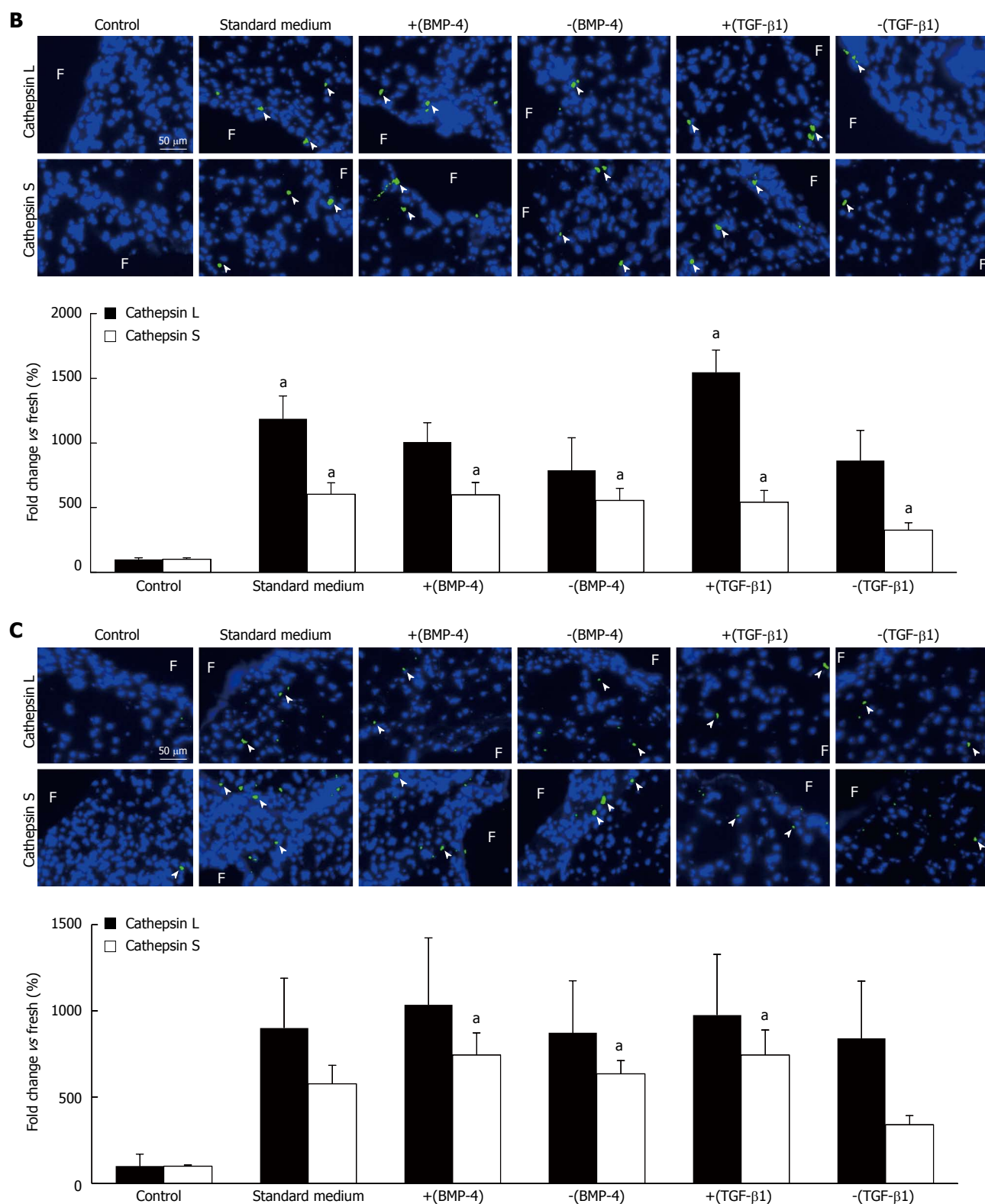






**Figure 4 Metalloproteinases-2 and metalloproteinases-9 immunostaining.** Tissue exposed for 48 h to: (A) physiologic fluid shear stress (FSS), (B) supra-physiologic FSS magnitude, and (C) supra-physiologic FSS frequency standard medium and medium supplemented with BMP-4 [(BMP-4)], noggin [-(BMP-4)], TGF-β1 [(TGF-β1)] or SB-431542 [-(TGF-β1)] (F: Fibrosa; green: Positively stained cells; blue: Cell nucleus; <sup>a</sup>*P* < 0.05 vs fresh control; <sup>c</sup>*P* < 0.05 vs standard culture medium; <sup>e</sup>*P* < 0.05 vs standard medium supplemented with TGF-β1). MMP: Metalloproteinases; TGF-β1: Transforming growth factor-beta1; BMP-4: Bone morphogenic protein-4.





**Figure 5 Cathepsin L and cathepsin S immunostaining.** Tissue exposed for 48 h to: (A) physiologic fluid shear stress (FSS), (B) supra-physiologic FSS magnitude, and (C) supra-physiologic FSS frequency standard medium and medium supplemented with BMP-4 [(BMP-4)], noggin [-(BMP-4)], TGF-β1 [(TGF-β1)] or SB-431542 [-(TGF-β1)] (F: Fibrosa; green: Positively stained cells; blue: Cell nucleus; <sup>a</sup>*P* < 0.05 vs fresh control). TGF-β1: Transforming growth factor-beta1; BMP-4: Bone morphogenic protein-4.



leaflet endothelium in valvular function. In contrast, leaflet exposure to supra-physiologic FSS resulted in increased paracrine signaling and ECM degradation. Those results confirm those of previous *ex vivo* studies on the effects of normal and abnormal FSS on valvular biology<sup>[27-29]</sup> and on the role played by FSS in bicuspid aortic valve calcification<sup>[30]</sup>.

This study is the first to report the dependence of FSS-mediated valvular ECM degradation on TGF- $\beta$ 1 signaling, as suggested by the dramatic decrease in MMP-9 expression in response to FSS abnormalities following TGF- $\beta$ 1 inhibition. The potential involvement of TGF- $\beta$ 1 in valvular ECM degradation is consistent with previous reports suggesting the modulation of MMP-9 expression by several growth factors and inflammatory cytokines in sheep VICs<sup>[39,40]</sup>. The ability of the small molecule inhibitor SB-431542 to reduce MMP-9 expression to the level measured in fresh leaflets also suggests the possible use of this molecule in drug-based therapies aimed at attenuating ECM degradation.

Interestingly, this study did not reveal the existence of clear synergies between BMP-4 and TGF- $\beta$ 1 signaling in response to FSS abnormalities, as shown by the inability of the pro- and anti-osteogenic media to alter the expression of those cytokines. This result differs from our previous *ex vivo* results on the effects of single-sided FSS magnitude and/or pulsatility abnormalities on the leaflet fibrosa<sup>[27,28]</sup>, which suggested a downregulation of FSS-induced BMP-4 expression following TGF- $\beta$ 1 inhibition. One possible explanation for this discrepancy is the difference in mechanical environment considered in those studies. While those earlier *ex vivo* studies subjected only one leaflet surface to FSS abnormalities, the present experiments were performed using a more realistic side-specific FSS environment, which potentially attenuated the severity of the pathological response.

Lastly, the interpretation of the results should be put in the perspective of two important considerations. First, noggin is a BMP antagonist that not only binds BMP-4 but also BMP-2, -5, -6 and -7<sup>[31,32]</sup>. Therefore, the observed biological response following noggin supplementation may be the result of the inhibition of other BMP members. Second, while the study only focuses on the acute biological response, the results may still be relevant to the long-term processes leading to CAVD as valve leaflets respond to FSS alterations in periods as short as 48 h and continued mechanical conditioning for up to 72 h has been shown not to alter that initial response<sup>[29]</sup>.

In summary, this study provides further evidence of the key role played by BMP-4 and TGF- $\beta$ 1 in valvular FSS mechanotransduction and the specific involvement of TGF- $\beta$ 1 in FSS-induced ECM degradation. While inhibition of those cytokines is not sufficient to completely block the FSS-induced pathological response, the TGF- $\beta$ 1 inhibitor SB-431542 emerges as a potential candidate molecule for attenuating

the adverse effects of FSS abnormalities on ECM degradation.

## COMMENTS

### Background

Calcific aortic valve disease (CAVD) is driven by inflammatory, remodeling and osteogenic processes triggered by cardiovascular risk factors and hemodynamic cues. In particular, supra-physiologic fluid shear stress (FSS) environments, which may result from hypertension, aging and valvular defects, have been shown to stimulate early CAVD signaling in a bone morphogenetic protein-4 (BMP-4) and transforming growth factor-beta1 (TGF- $\beta$ 1)-dependent manner. While the demonstrated involvement of BMP-4 and TGF- $\beta$ 1 in early CAVD provides a rationale for considering those molecules in targeted cell-based therapies aimed at attenuating or blocking the downstream pathological cascade, the synergies and modes of action of those molecules in response to FSS abnormalities have not been defined yet.

### Research frontiers

The current modality to treat CAVD consists of the complete replacement of the valve by an artificial implant, which only partially restores valvular function and does not address the root cause of the disease. The development of non-invasive pharmacological approaches requires more insights into the basic biology of CAVD. Therefore, the characterization of the signaling pathways involved in the disease and the interacting mechanisms of cardiovascular calcification, micro-scale mechano-transduction and macro-scale hemodynamics are current hotspots in valvular research.

### Innovations and breakthroughs

Their previous characterization of the contribution of side-specific FSS magnitude and/or frequency abnormalities to early valvular pathogenesis revealed the sensitivity of the leaflet tissue to elevated FSS magnitude or frequency and the ability of FSS abnormalities to promote paracrine signaling via BMP-4- and TGF- $\beta$ 1-dependent pathways. The present study is a logical extension of our previous work as it investigates the upstream roles of BMP-4 and TGF- $\beta$ 1 in the FSS-mediated valvular response. Here, the authors programmed their FSS bioreactor to generate the most unfavorable FSS environment for valvular tissue (*i.e.*, side-specific supra-physiologic FSS magnitude or side-specific supra-physiologic FSS frequency) and the authors aimed at isolating the mechanistic role played by BMP-4 and TGF- $\beta$ 1 in the FSS-mediated pathological response by either promoting or inhibiting pharmacologically the downstream action of those molecules. The results demonstrate for the first time the mechano-sensitivity of BMP-4 and TGF- $\beta$ 1 to alterations in the native valvular FSS environment and their respective role in FSS-mediated pathogenesis. While BMP-4 promotes valvular endothelial activation in response to supra-physiologic FSS, TGF- $\beta$ 1 mediates extracellular matrix (ECM) degradation.

### Applications

The ability of the TGF- $\beta$ 1 inhibitor SB-431542 to reduce flow-mediated ECM degradation suggests the possible use of this molecule in non-invasive drug-based therapies aimed at attenuating flow-induced aortic valve pathogenesis.

### Terminology

CAVD is the most common valvular disease and is characterized by the formation of calcific lesions on the valve leaflets. FSS is the frictional fluid force resulting from the relative motion between the valve leaflets and the surrounding blood flow.

### Peer-review

This is a very well conducted study.

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Prospective Study

# Utility of electrophysiological studies to predict arrhythmic events

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## Abstract

**AIM:** To evaluate the prognostic value of electrophysiological stimulation (EPS) in the risk stratification for tachyarrhythmic events and sudden cardiac death (SCD).

**METHODS:** We conducted a prospective cohort study and analyzed the long-term follow-up of 265 consecutive patients who underwent programmed ventricular stimulation at the Luzerner Kantonsspital (Lucerne, Switzerland) between October 2003 and April 2012. Patients underwent EPS for SCD risk evaluation because of structural or functional heart disease and/or electrical conduction abnormality and/or after syncope/cardiac arrest. EPS was considered abnormal, if a sustained ventricular tachycardia (VT) was inducible. The primary endpoint of the study was SCD or, in implanted patients, adequate ICD-activation.

**RESULTS:** During EPS, sustained VT was induced in 125 patients (47.2%) and non-sustained VT in 60 patients (22.6%); in 80 patients (30.2%) no arrhythmia could be induced. In our cohort, 153 patients (57.7%) underwent ICD implantation after the EPS. During follow-up (mean duration  $4.8 \pm 2.3$  years), a primary endpoint event occurred in 49 patients (18.5%). The area under the receiver operating characteristic curve (AUROC) was 0.593 (95%CI: 0.515-0.670) for a left ventricular ejection fraction (LVEF)  $< 35\%$  and 0.636 (95%CI: 0.563-0.709) for inducible sustained VT during EPS. The AUROC of EPS was higher in the subgroup of patients with LVEF  $\geq 35\%$  (0.681, 95%CI: 0.578-0.785). Cox regression analysis showed that both, sustained VT during EPS (HR: 2.26, 95%CI: 1.22-4.19,  $P = 0.009$ ) and LVEF  $< 35\%$  (HR: 2.00, 95%CI: 1.13-3.54,  $P = 0.018$ ) were independent predictors of primary endpoint events.

**CONCLUSION:** EPS provides a benefit in risk stratification

for future tachyarrhythmic events and SCD and should especially be considered in patients with LVEF  $\geq$  35%.

**Key words:** Electrophysiologic techniques; Cardiac; Arrhythmia; Cardiac; Sudden cardiac death

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**Core tip:** In our long-term prospective cohort study we could reveal several important findings about the prognostic value of programmed ventricular stimulation for risk stratification of sudden cardiac death (SCD). First, in a mixed population with different cardiac pathologies inducible sustained ventricular tachyarrhythmia during electrophysiological stimulation (EPS) identified those at higher risk for SCD or appropriate implantable cardioverter defibrillators (ICD) activation. Second, left ventricular ejection fraction (LVEF)  $<$  35% was another independent predictor of SCD surrogate. Third, in patients with LVEF  $>$  35% negative EPS had a high negative predictive value for SCD and ICD activation.

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## INTRODUCTION

Implantable cardioverter defibrillators (ICD) are an established therapy for primary and secondary sudden cardiac death (SCD) prevention. Randomized trials have shown a significant mortality reduction in implanted patients at high risk for SCD<sup>[1-4]</sup>. For ICD therapy guidance, evaluation of SCD risk is crucial. Guidelines recommend various non-invasive techniques to recognize patients at higher risk for life-threatening arrhythmias<sup>[5]</sup>. Factors associated with a significantly increased risk of ventricular tachyarrhythmia include increased resting heart rate, wide QRS, presence of late potentials, presence of heart failure, or lower left ventricular ejection fraction<sup>[6-10]</sup>. However, currently available methods for SCD risk estimation are still imprecise. Therefore, many patients, who received an ICD, are not going to suffer from a future arrhythmic event and do not benefit from ICD. On the other hand, many patients, who are not recognized at high risk, die from SCD and numbers of SCD victims are still highest in these patients with normal left ventricular ejection fraction (LVEF)<sup>[11,12]</sup>. It remains an ongoing challenge to predict an individual patient's risk.

Currently, the electrophysiological study (EPS) is widely used for risk stratification and several randomized trials suggest a significant predictive value

of this examination. However, many previous studies focused on the predictive value in one subgroup of patients with a specific cardiac pathology. Most data are available from post myocardial infarction patients in whom inducible ventricular tachycardias (VT) or ventricular fibrillation (VF) during EPS indicate higher risk for future arrhythmic events<sup>[13]</sup>. An improved risk stratification with EPS has especially been shown in patients who were preselected as a high risk population based on previous non-invasive tests<sup>[14,15]</sup>. Other studies provided a prognostic value of EPS in patients with Brugada syndrome, hypertrophic or dilated cardiomyopathy<sup>[16-18]</sup>. The discussion about the general prognostic value of electrophysiological testing is ongoing. We therefore performed an induction study of VT or VF by programmed electrical stimulation either for primary prevention of SCD, after documented VT or in SCD survivors. The usefulness of EPS for the prediction of future arrhythmic events was evaluated in a prospective long-term follow-up in patients with different cardiac pathologies.

## MATERIALS AND METHODS

### Study population

This prospective cohort study evaluated all patients who were examined by EPS at the Luzerner Kantonsspital (Lucerne, Switzerland) between October 2003 and April 2012. Patients underwent EPS for SCD risk evaluation because of structural or functional heart disease and/or electrical conduction abnormality and/or after syncope/cardiac arrest. The study population therefore embraced patients with coronary artery disease (CAD), dilated cardiomyopathy (DCM), hypertrophic cardiomyopathy, impaired LVEF, Brugada or Long QT syndrome, and other rare cardiac diseases (e.g., valvular heart disease, tetralogy of Fallot, variant angina). Some patients who underwent EPS did not have cardiac disease but were assessed because of unclear syncope or family history of cardiomyopathy. Patients who did not provide written informed consent were excluded. The study complies with the Declaration of Helsinki and was approved by the local ethics committee.

### Baseline evaluation

All participating patients were evaluated at baseline. Patient history was recorded including cardiovascular risk factors, underlying heart disease, and medication. Electrocardiogram (ECG) was recorded in all patients. LVEF was measured with transthoracic echocardiography in all patients and was determined on two- and four-chamber views using the modified biplane Simpson method.

EPS was part of the baseline evaluation and was performed according to the ACC/AHA/ESC guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death<sup>[19]</sup>. The

ventricular arrhythmia induction protocol during EPS included programmed stimulation at three basic cycle lengths (600, 450, and 350 ms) and up to three extrastimuli with a minimum coupling interval of 180 ms. A third extrastimulus was introduced during a basic drive cycle length of minimal 500 ms after completion of programmed ventricular stimulation with 1 and 2 extrastimuli during paced cycle lengths of 600, 450, and 350 ms<sup>[20]</sup>. EPS was considered abnormal, if a sustained VT was inducible.

### Follow-up

Patients with ICD were regularly followed-up at Luzerner Kantonsspital in six-month or yearly intervals. In addition, they were followed-up immediately, if shocks occurred. The clinical course and the numbers of appropriate and inappropriate ICD therapies were protocolled at each follow-up visit. In patients who had no ICD, follow-up was obtained from several sources: first, medical records at Luzerner Kantonsspital were studied, if available (*i.e.*, in patients who were re-admitted after the EPS); second, the patients and/or their general practitioner were contacted by phone and interviewed using a structured protocol. In all patients who died, additional information on the circumstances of death was collected. Death was classified as non-cardiac or cardiac. Among cardiac deaths, SCD was defined according to the Hinkle-Thaler method<sup>[21]</sup>.

### Endpoints

The primary endpoint of this study was SCD or, in implanted patients, adequate ICD activation [shock or antitachycardia pacing (ATP)]. The secondary endpoint was SCD or adequate ICD shock. For the secondary endpoint, events with ATP were not counted. If a patient experienced more than one endpoint event (*e.g.*, ICD shock in a patient who later died from SCD), only the first endpoint event was counted.

### Statistical analysis

We descriptively analyzed baseline characteristics. We then calculated sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and the area under the receiver operating characteristic curve (AUROC) with its 95%CI of the EPS for the prediction of both endpoints<sup>[22]</sup>. The diagnostic accuracy of the EPS was compared to that of the LVEF. For this purpose, LVEF was dichotomized at 35% (< 35% indicating higher risk vs  $\geq$  35% indicating lower risk). We also performed a Cox regression analysis with age, sex, EPS and LVEF as independent variables. Kaplan-Meier survivor functions were generated to illustrate the ability to stratify the risk of both dichotomized predictors separately<sup>[23]</sup>. Calculations were done for all study participants together and, in a sensitivity analysis, repeated separate for participants with CAD and DCM. Data were analyzed using Stata 11.2 (StataCorp LP, College Station, TX, United States).

## RESULTS

### Study population

Overall, 289 patients underwent EPS during the study period. Twenty-four patients (8.3%) were lost to follow-up, resulting in 265 patients who were analyzed. Table 1 shows the baseline characteristics of study participants. Mean age was  $57.4 \pm 10.7$  years with a maximum range from 21.8 to 76.7 years. Most participants were male. CAD was present in a majority of patients.

### EPS and therapeutic consequences

The EPS was performed for primary prevention in 209 patients (78.9%). In 56 patients (21.1%) the indication was secondary prevention: twenty-nine cardiac arrest survivors (10.9%), and 27 patients (10.2%) who had documented VT/VF on previous ECGs. During EPS, sustained VT was induced in 125 patients (47.2%) and non-sustained VT in 60 patients (22.6%). In 80 patients (30.2%) no arrhythmia could be induced.

In our cohort, 153 patients (57.7%) underwent ICD implantation after the EPS, and 112 patients (42.3%) received no ICD. Patients were selected for device implantation according to the specific ACC/AHA/ESC guidelines for the underlying heart disease. The decision to implant an ICD was influenced by the result of the EPS if recommended in the guidelines. Antiarrhythmic medication consisted of beta blockers in 214 patients (80.8%), amiodarone in 38 patients (14.3%), and digoxin in 37 patients (14.0%).

### Follow-up and endpoint events

The mean duration of the follow-up was  $4.8 \pm 2.3$  years (interquartile range 3.1-6.2 years, maximum range 0.2-9.2 years). During follow-up, 28 patients (10.6%) died, 12 of them due to non-cardiac causes. Among the 16 patients with a cardiac cause of death, SCD occurred in 8 patients. A primary endpoint event occurred in 49 patients (18.5%) with a mean time interval since the EPS of  $947 \pm 778$  d (maximum range 16-3050 d). Table 1 shows baseline characteristics separate for patients with and without primary endpoint event. There were no significant differences between the two groups, except for LVEF which was lower in patients with primary endpoint event, and the findings during EPS that found more sustained VTs in patients with primary endpoint event. A secondary endpoint event occurred in 33 patients (12.5%) with a mean time interval since the EPS of  $997 \pm 761$  d (maximum range 63-2709 d).

### Diagnostic accuracy

Table 2 shows the diagnostic accuracy of the EPS and the LVEF for primary and secondary endpoint. The AUROCs of EPS and of LVEF did not significantly differ ( $P = 0.427$  for primary endpoint, and  $P = 0.676$  for

**Table 1** Baseline characteristics

Characteristic	All study participants <i>n</i> = 265	Participants without primary endpoint event <sup>1</sup> <i>n</i> = 216	Participants with primary endpoint event <sup>1</sup> <i>n</i> = 49	<i>P</i> value <sup>2</sup>
Age, mean ± SD, yr	57.4 ± 10.7	57.5 ± 10.6	57.2 ± 11.3	0.848
Male sex	230 (86.8%)	185 (85.6%)	45 (91.8%)	0.350
Cardiovascular risk factors				
Hypertension	152 (57.4%)	124 (57.4%)	28 (57.1%)	0.973
Dyslipidemia	161 (60.8%)	131 (60.6%)	30 (61.2%)	0.941
Diabetes mellitus	60 (22.6%)	49 (22.7%)	11 (22.4%)	0.972
Smoking <sup>3</sup>	154 (58.1%)	121 (56.0%)	33 (67.3%)	0.147
Family history of CAD	81 (30.6%)	65 (30.1%)	16 (32.7%)	0.725
Cardiac disease				
CAD	152 (57.4%)	120 (55.6%)	32 (65.3%)	0.213
DCM	58 (21.9%)	45 (20.8%)	13 (26.5%)	0.384
HCM				
Obstructive	1 (0.4%)	1 (0.5%)	0 (0.0%)	1.000
Non-obstructive	3 (1.1%)	2 (0.9%)	1 (2.0%)	0.460
Brugada syndrome	2 (0.8%)	2 (0.9%)	0 (0.0%)	1.000
Long QT	3 (1.1%)	3 (1.4%)	0 (0.0%)	1.000
Other cardiac disease	30 (11.3%)	26 (12.0%)	4 (8.2%)	0.618
Echocardiography				
LVEF, mean ± SD	41.1% ± 15.9%	42.8% ± 16.2%	33.6% ± 11.7%	< 0.001
LVEF < 35%	106 (40.0%)	79 (36.6%)	27 (55.1%)	0.017
EPS				
Induction of sustained VT	125 (47.2%)	91 (42.1%)	34 (69.4%)	0.001
Induction of non-sustained VT	60 (22.6%)	53 (24.5%)	7 (14.3%)	0.122
No VT induction	80 (30.2%)	72 (33.3%)	8 (16.3%)	0.019

<sup>1</sup>Event of primary endpoint (sudden cardiac death, ICD shock or ATP); <sup>2</sup>*P* value for the comparison of participants without *vs* with endpoint event; <sup>3</sup>Current or former smoker. CAD: Coronary artery disease; DCM: Dilated cardiomyopathy; EPS: Electrophysiological study; HCM: Hypertrophic cardiomyopathy; LVEF: Left ventricular ejection fraction; SD: Standard deviation; VT: Ventricular tachycardia.

**Table 2** Diagnostic accuracy of the electrophysiological study and the left ventricular ejection fraction for the primary and secondary endpoint

Predictor variable	Sensitivity	Specificity	PPV	NPV	AUROC (95%CI)
Primary endpoint					
Sustained VT during EPS					
All study participants ( <i>n</i> = 265)	69.4%	57.9%	27.2%	89.3%	0.636 (0.563-0.709)
Subgroup of study participants with LVEF < 35% ( <i>n</i> = 106)	66.7%	48.1%	30.5%	80.9%	0.574 (0.468-0.680)
Subgroup of study participants with LVEF ≥ 35% ( <i>n</i> = 159)	72.7%	63.5%	24.2%	93.5%	0.681 (0.578-0.785)
LVEF < 35%	55.1%	63.4%	25.5%	86.1%	0.593 (0.515-0.670)
Secondary endpoint					
Sustained VT during EPS					
All study participants ( <i>n</i> = 265)	66.7%	55.6%	17.6%	92.1%	0.611 (0.524-0.699)
Subgroup of study participants with LVEF < 35% ( <i>n</i> = 106)	61.1%	45.5%	18.6%	85.1%	0.533 (0.406-0.660)
Subgroup of study participants with LVEF ≥ 35% ( <i>n</i> = 159)	73.3%	61.8%	16.7%	95.7%	0.676 (0.553-0.798)
LVEF < 35%	54.5%	62.1%	17.0%	90.6%	0.583 (0.491-0.675)

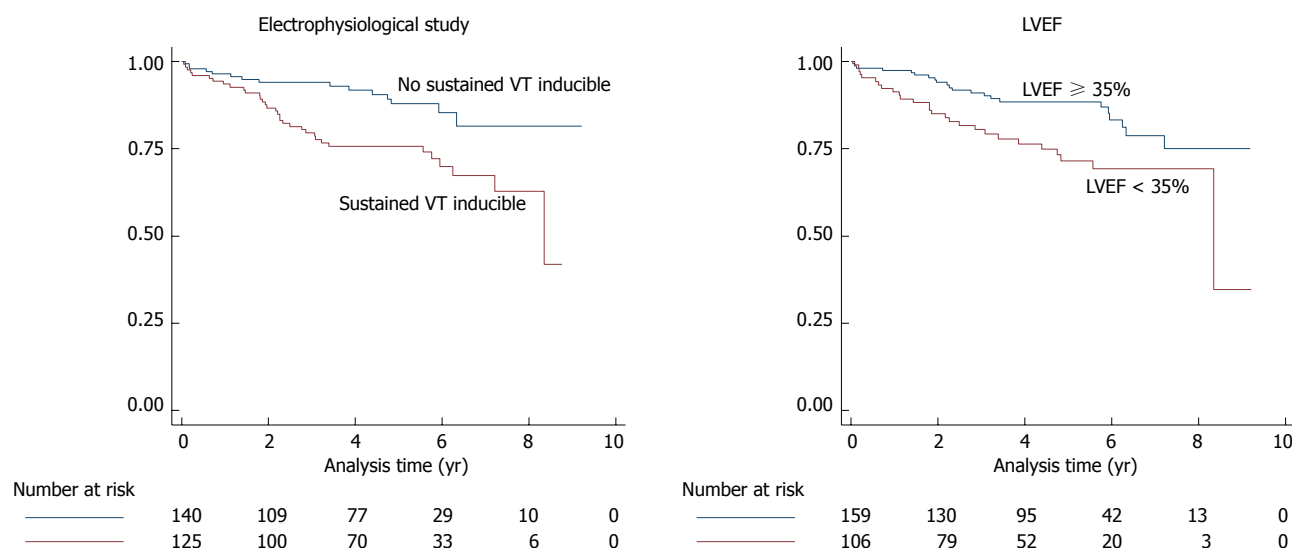
AUROC: Area under the receiver operating characteristic curve; EPS: Electrophysiological study; NPV: Negative predictive value; PPV: Positive predictive value; VT: Ventricular tachycardia; LVEF: Left ventricular ejection fraction.

secondary endpoint). There was a non-significant trend for a higher AUROC of the EPS in the subgroup of patients with an LVEF ≥ 35% as compared to the subgroup of patients with LVEF < 35% (*P* = 0.156 for primary endpoint, and *P* = 0.113 for secondary endpoint). Cox regression analysis showed that both, sustained VT during EPS (HR: 2.26, 95%CI: 1.22-4.19, *P* = 0.009) and LVEF < 35% (HR: 2.00, 95%CI: 1.13-3.54, *P* = 0.018) were independent predictors of primary endpoint events. Kaplan-Meier survivor functions of EPS and LVEF for the primary endpoint are shown in Figure 1.

### Sensitivity analysis

Main analysis were repeated separate for participants with CAD and DCM. Among the 152 CAD patients, a primary endpoint event occurred in 32 patients (21.1%). The AUROCs of the EPS (0.604, 95%CI: 0.516-0.693) and of LVEF (0.606, 95%CI: 0.509-0.704) were similar to the overall study population and did not significantly differ (*P* = 0.975). Among the 58 patients with DCM, a primary endpoint event occurred in 13 patients (22.4%). Due to the low numbers of patients, the AUROC of the EPS (0.625, 95%CI: 0.469-0.781) had a broad 95%CI. The AUROC of LVEF (0.425, 95%CI:





**Figure 1** Kaplan-Meier function of primary endpoint event-free survival for patients with or without sustained ventricular tachycardia during the electrophysiological study and for patients with left ventricular ejection fraction < 35% vs ≥ 35%. VT: Ventricular tachycardia; LVEF: Left ventricular ejection fraction.

0.268-0.582) was low ( $P = 0.105$  as compared to the AUROC of the EPS).

## DISCUSSION

This long-term prospective cohort study revealed several important findings. First, in a mixed population with different cardiac pathologies inducible sustained ventricular tachyarrhythmia during EPS identified those at higher risk for a SCD surrogate, defined either as appropriate ICD activations and/or as documented SCD. Second, LVEF < 35% was another independent predictor of primary endpoint events. Third, in patients with LVEF > 35% negative EPS had a high negative predictive value for the primary and for the secondary endpoint.

Electrophysiologic testing of ventricular tachycardia was introduced 1972<sup>[24]</sup>. Amongst others, programmed ventricular stimulation was used to assess the efficacy of antiarrhythmic drugs for suppression of inducible ventricular arrhythmias or the efficacy of antitachycardia surgery<sup>[25]</sup>. With the availability of ICDs EPS has become an important test for risk stratification to predict SCD<sup>[19]</sup>. The prognostic value of EPS is based on the assumption that patients with inducible ventricular tachyarrhythmias should have a high likelihood of spontaneous arrhythmic events and that non-inducible patients should be at low risk<sup>[26]</sup>. In the current guidelines electrophysiologic testing has a class I recommendation for diagnostic evaluation of patient with remote myocardial infarction with symptoms suggestive of ventricular arrhythmias, including palpitations, presyncope and syncope. Another class I indication is syncope of unknown cause with impaired LV function or structural heart disease<sup>[19]</sup>. In nonischemic DCM electrophysiologic testing is not recommended for risk stratification. However, in a

recent study of Gatzoulis *et al.*<sup>[18]</sup> inducibility of VT/VF in patients with idiopathic dilated cardiomyopathy was associated with an increased likelihood of subsequent ICD activation and SCD surrogate. In the present study we have shown, that EPS is useful for the prediction of future arrhythmic events in a collective of patients with different cardiac pathologies. It is well established that the predictive accuracy of LVEF for lifethreatening arrhythmic events is limited<sup>[26]</sup>. However ICD-Implantation guided by LVEF alone lacks of specificity because in progressive heart failure unexpected SCD accounted for only 30% of deaths while many were due to progressive pump failure not preventable by an ICD.

According to our findings, the additional use of electrophysiologic testing in patients with LVEF < 35% is disputable as the PPV is only improved from 25.5% to 30.5% in cases with a positive EPS. This might not influence the further clinical management of the patient because a 25.5% risk of a future tachyarrhythmic event or SCD already seems to justify ICD implantation. However in patients with LVEF > 35% and a negative EPS the NPV was improved from 86.1% to 93.5%. This means that the risk estimation for future arrhythmic events during the follow-up period of  $4.8 \pm 2.3$  years is reduced from 13.9% to 6.5%. In addition a positive EPS still exhibits a PPV of 24.2% in patients with LVEF > 35%.

Similar results were found in the MUSTT trial<sup>[27]</sup>. Both, low ejection fraction and inducible sustained ventricular tachycardia during EPS, identified patients at increased mortality risk. Inducible tachyarrhythmias identified patients for whom death was significantly more likely to be arrhythmic and this was observed especially if ejection fraction was higher than or equal to 30%. Due to our findings, invasive testing should especially be considered in this group of higher to

normal LVEF, as it might prevent implantation of ICD in patient who won't benefit.

This study has some limitations. First, the findings of this study are from a single center. Therefore, generalizability is limited and confirmation in an independent sample is of importance. Second, we included patients who underwent EPS for primary prevention as well as for secondary prevention. NPV and PPV of sustained ventricular tachycardia during EPS might differ in these subgroups, however the study population is too small to perform an independent statistical analysis.

EPS provides a benefit in risk stratification for future tachyarrhythmic events and SCD and should especially be considered in patients with LVEF > 35%.

## COMMENTS

### Background

Patients with preexisting cardiac disease are at higher risk for future cardiac arrhythmias, potentially leading to sudden cardiac death (SCD). In the study the authors evaluated the prognostic value of electrophysiological stimulation (EPS) in the risk stratification for future cardiac arrhythmias.

### Research frontiers

Guidelines recommend various non-invasive techniques to recognize patients at higher risk for life-threatening arrhythmias. Currently, the electrophysiological study (EPS) is widely used for risk stratification and several randomized trials suggest a significant predictive value of this examination.

### Innovations and breakthroughs

The authors found that in a mixed population with different cardiac pathologies inducible sustained ventricular tachyarrhythmia during EPS identified those at higher risk for SCD or appropriate activation of implantable cardioverter defibrillator (ICD). Furthermore left ventricular ejection fraction (LVEF) < 35% was another independent predictor of SCD surrogate. In patients with LVEF > 35% negative EPS had a high negative predictive value for SCD and ICD activation.

### Applications

EPS provides a benefit in risk stratification for future tachyarrhythmic events and SCD and should especially be considered in patients with LVEF > 35%.

### Peer-review

The authors have prospectively evaluated the role of programmed ventricular stimulation in the risk stratification of tachyarrhythmic events and sudden cardiac death in a large patient population; the possibility to optimize selection of patients undergoing ICD implantation is very relevant and evidence-based conclusions would be of great clinical importance.

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## Giant saphenous vein graft pseudoaneurysm to right posterior descending artery presenting with superior vena cava syndrome

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**Ethics approval:** This is a clinical case report. All patients related identification information has been avoided according to the policy of University of Iowa Hospitals and Clinics and the Health Insurance Portability and Accountability Act (HIPPA) by the United States.

**Informed consent:** All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

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### Abstract

Saphenous vein grafts (SVG) pseudoaneurysms, especially giant ones, are rare and occur as a late complication of coronary artery bypass grafting. This condition affects both genders and typically occurs within the sixth decade of life. The clinical presentation ranges from an asymptomatic incidental finding on imaging studies to new onset angina, dyspnea, myocardial infarction or symptoms related to compression of neighboring structures. An 82-year-old woman presented with acute onset back pain, dyspnea and was noted to have significantly engorged neck veins. In the emergency department, a chest computed tomographic angiogram with intravenous contrast revealed a ruptured giant bilobed SVG pseudoaneurysm to the right posterior descending artery (RPDA). This imaging modality also demonstrated compression of the superior vena cava (SVC) by the SVG pseudoaneurysm. Coronary angiogram with bypass study was performed to establish the patency of this graft. Endovascular coiling and embolization of the SVG to RPDA was initially considered but disfavored after the coronary angiogram revealed preserved flow from the graft to this arterial branch. After reviewing the angiogram films, a surgical strategy was favored over a percutaneous intervention with a Nitinol self-expanding stent since the latter would have not addressed the superior vena cava compression caused by the giant pseudoaneurysm. Intraoperative transesophageal echocardiogram demonstrated SVC



compression by the giant pseudoaneurysm cranial lobe. Our patient underwent surgical ligation and excision of the giant pseudoaneurysm and the RPDA was regrafted successfully. In summary, saphenous vein grafts pseudoaneurysms can be life-threatening and its therapy should be guided based on the presence of mechanical complications, the patency of the affected vein graft and the involved myocardial territory viability.

**Key words:** Giant saphenous graft pseudoaneurysm; Late complication of coronary artery bypass grafting; Superior vena cava syndrome; Endovascular coiling and embolization; Nitinol self-expanding stent

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**Core tip:** Saphenous vein grafts (SVG) pseudoaneurysms, especially giant ones, are rare and occur as a late complication of coronary artery bypass grafting. Although unusual, superior vena cava (SVC) syndrome has been reported as a complication of saphenous vein graft pseudoaneurysms causing compression of the SVC. Here we report a case of such condition illustrated with state-of-the-art multi-modality images which were critical for the planning of the most appropriate treatment strategy. SVG pseudoaneurysms can be life-threatening and their therapy should be guided based on the presence of mechanical complications, the patency of the affected vein graft and the involved myocardial territory viability.

Vargas-Estrada A, Edwards D, Bashir M, Rossen J, Zahr F. Giant saphenous vein graft pseudoaneurysm to right posterior descending artery presenting with superior vena cava syndrome. *World J Cardiol* 2015; 7(6): 351-356 Available from: URL: <http://www.wjgnet.com/1949-8462/full/v7/i6/351.htm> DOI: <http://dx.doi.org/10.4330/wjc.v7.i6.351>

## INTRODUCTION

Coronary saphenous vein graft pseudoaneurysms are rare complications of coronary artery bypass grafting, occurring several years after the initial procedure. Although very unusual, superior vena cava obstruction has been reported as a complication of a rupture of a coronary artery bypass vein graft<sup>[1]</sup>. It is uncommon to encounter such patients and the optimal treatment remains uncertain. The improvement of percutaneous interventions and the development of covered and Nitinol self-expanding stents have become an attractive option to spare these subjects from a repeat thoracotomy, however this is not always feasible. To our knowledge, there have been very few similar cases reported, we believe this to be the first reported case of such condition illustrated with state-of-the-art multi-modality imaging.

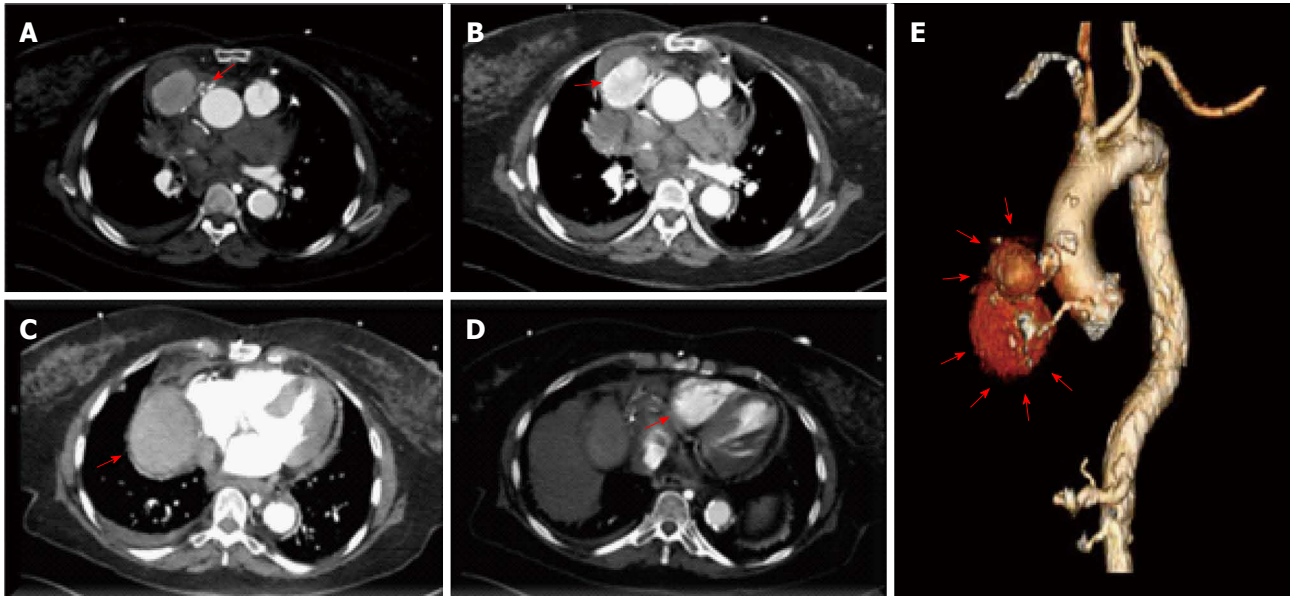
## CASE REPORT

An 82-year-old woman presented to the hospital with complaints of acute onset back pain, dyspnea for twelve hours and significantly engorged neck veins. She had undergone 3-vessel coronary artery bypass graft surgery in 1993. At the time of her coronary artery bypass operation, the left internal mammary artery (LIMA) was used to graft the first diagonal branch. Separate saphenous vein grafts were placed to the left anterior descending artery (LAD) and right posterior descending artery (RPDA). It is unknown to us the reasons for LIMA to diagonal branch anastomosis instead of arterial bypass to LAD which in turn received a venous graft. On her arrival to the emergency department, an electrocardiogram showed sinus rhythm and no ischemic changes. Her cardiac enzymes were negative. Computed tomography with IV contrast of the patient's chest ruled out pulmonary embolism and aortic dissection. Tomographic and 3D reconstruction views identified a ruptured giant bilobed SVG pseudoaneurysm to RPDA causing mass effect on the superior vena cava and right-sided cardiac chambers (Figures 1 and 2). The cranial lobe of the pseudoaneurysm measured 4.7 cm × 5.4 cm and the caudal lobe measured 8.0 cm × 7.0 cm in its larger diameter and demonstrated mural thrombosis. Coronary angiography demonstrated a giant pseudoaneurysm of the SVG with patent flow to the right posterior descending artery (Figure 3). Coiling and embolization of the SVG to RPDA was initially considered but disfavored since the coronary angiogram revealed preserved flow from the graft to RPDA branch. Also a percutaneous intervention with a covered vs a Nitinol self-expanding stent to the ruptured SVG was contemplated but ultimately surgical intervention was decided since the former strategy would have not addressed the superior vena cava compression caused by the giant pseudoaneurysm. Intraoperative echocardiography (Figure 4) showed SVC compression by the giant pseudoaneurysm cranial lobe. At surgery, the giant SVG pseudoaneurysm was ligated, excised and the RPDA was regrafted. The patient recovered uneventfully and was discharged on postoperative day 20. After completing her post-surgical rehabilitation, she returned to our clinic six weeks later, asymptomatic and in stable condition.

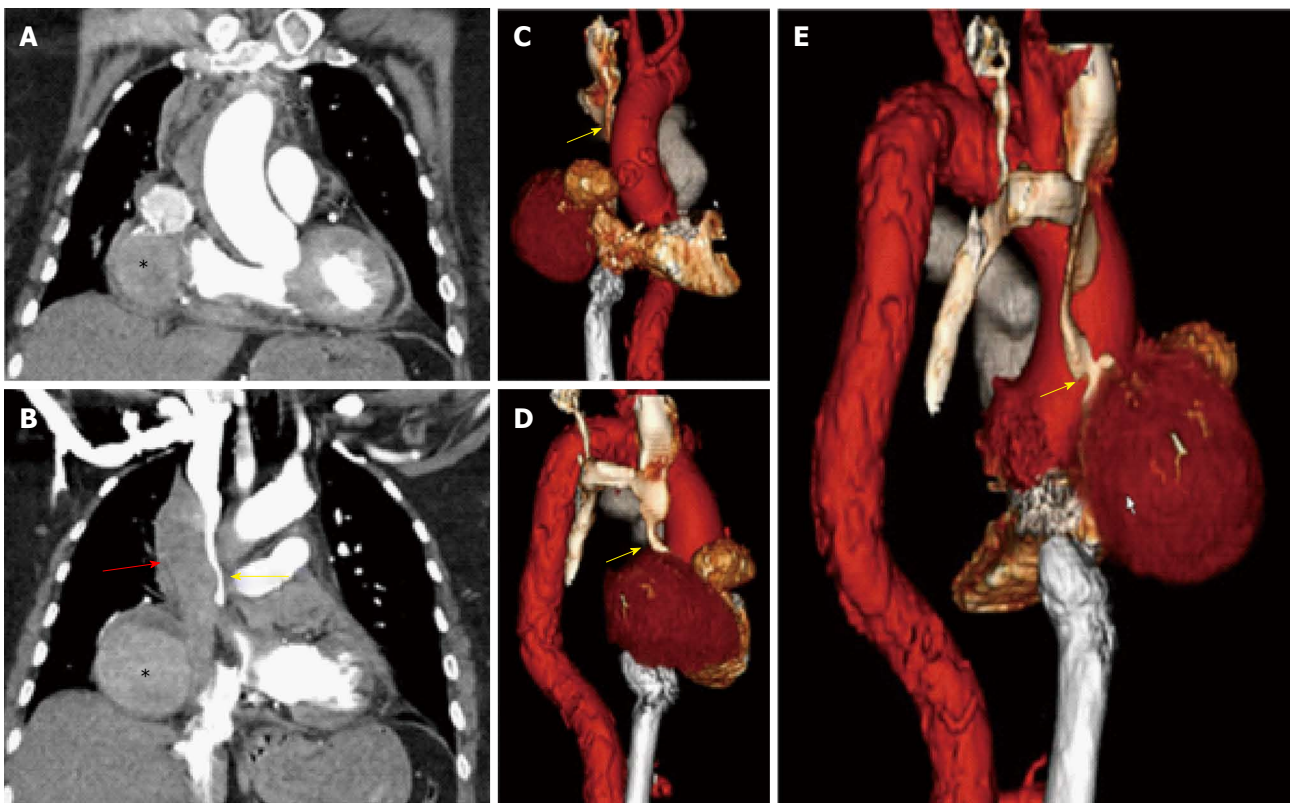
## DISCUSSION

Aneurysmal dilatation of aortocoronary saphenous vein grafts (SVG), first described by Riahi *et al*<sup>[2]</sup> in 1975 remains a rare yet widely reported phenomenon. This condition is secondary to true aneurysm or pseudoaneurysm, with the former being more common. SVC syndrome is caused by obstruction of blood flow through the superior vena cava due to thrombosis or extrinsic compression. It is a medical emergency





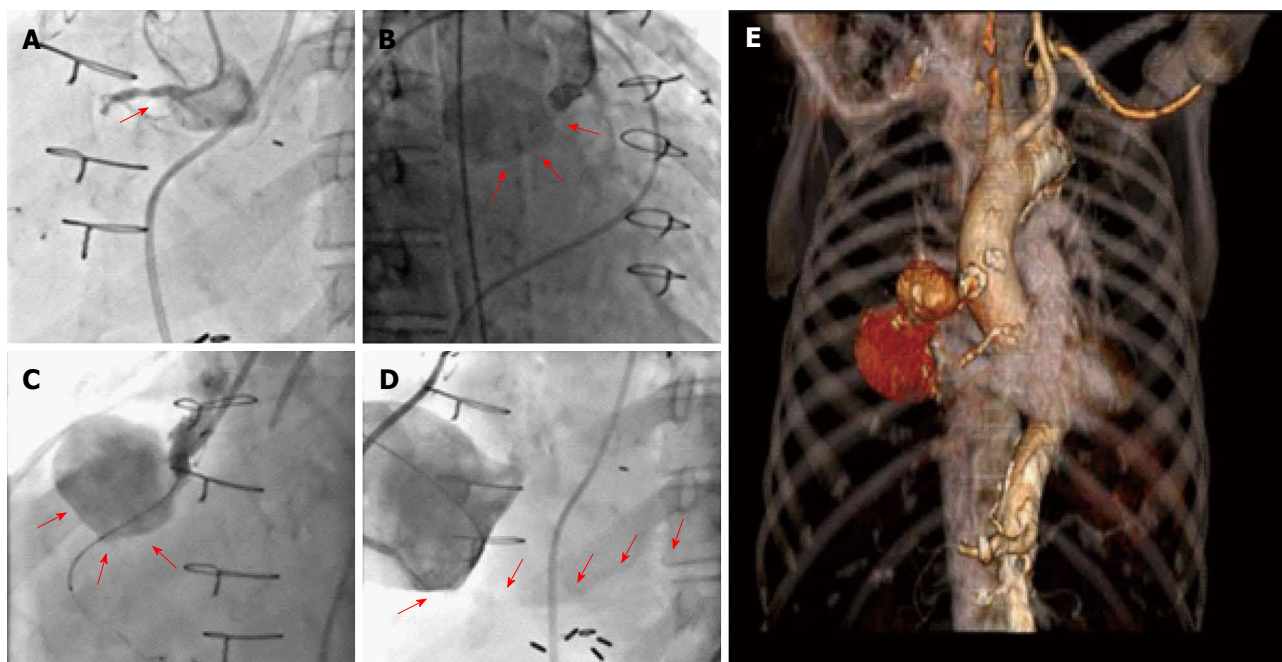
**Figure 1** Transaxial tomographic views showing the right coronary artery origin and the saphenous vein grafts pseudoaneurysm lobes. A: The more cranial lobe of the pseudoaneurysm measured 4.7 cm × 5.4 cm in diameter and demonstrated mural thrombosis; B: The caudal lobe of the pseudoaneurysm also demonstrated mural thrombosis and measured 8 cm × 7 cm in its larger diameter; C, D: The caudal lobe of the giant pseudoaneurysm was patent and demonstrated flow into the distal right coronary and right posterior descending artery; E: Computed tomographic 3-D reconstruction of the saphenous vein grafts giant bilobed pseudoaneurysm to the right posterior descending artery.



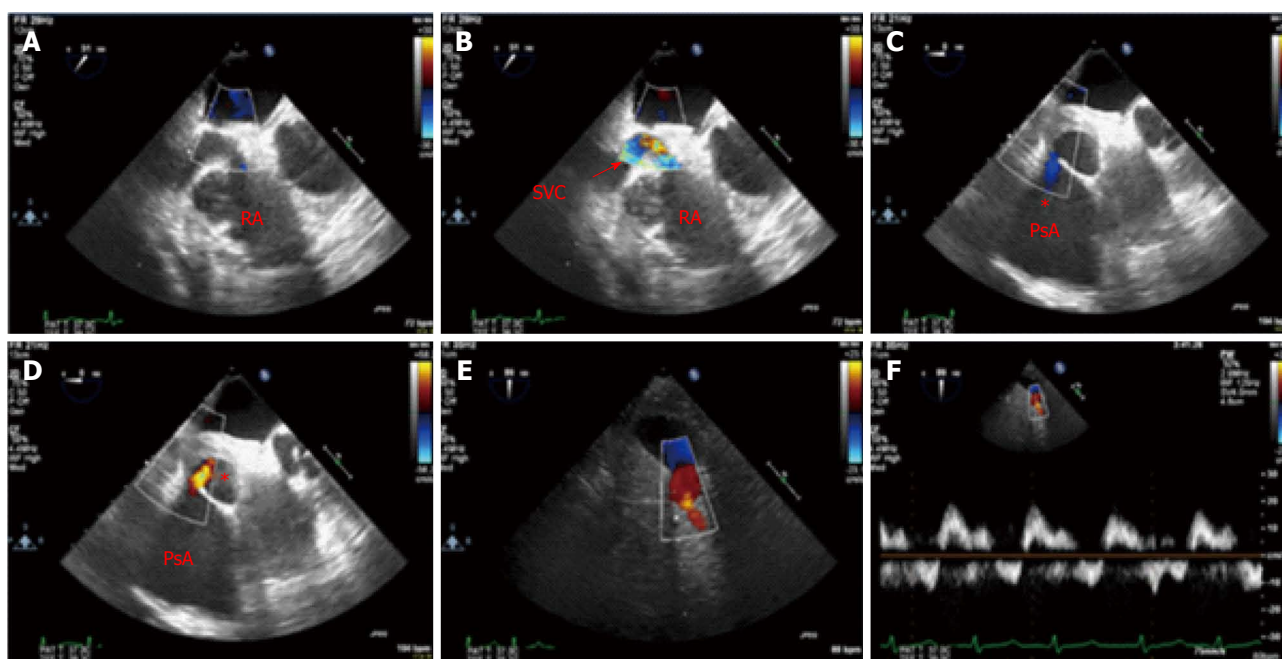
**Figure 2** Significantly distended neck veins secondary to compression of the superior vena cava by the giant saphenous vein grafts pseudoaneurysm to right posterior descending artery. A: Coronal tomographic views showing upper and lower lobes of the SVG pseudoaneurysm (asterisks); B: Large hematoma (red arrow) is shown compressing the SVC (yellow arrow); C, D, E: Computed tomographic 3-D reconstruction of the SVG giant bilobed pseudoaneurysm and SVC compression (yellow arrow) in anterior, lateral and posterior views. SVG: Saphenous vein grafts; SVC: Superior vena cava.

and most often manifests in patients with a malignant process within the thorax (particularly lung adeno-

carcinoma), however as many as 40% of cases are attributable to nonmalignant causes. The first case of



**Figure 3** Coronary angiography demonstrated a giant pseudoaneurysm of the saphenous vein grafts with patent flow to the right posterior descending art. A: Coronary angiography showing the ostial and proximal right coronary artery (RCA) occlusion; B: Angiographic image depicting the upper lobe of the SVG to RPDA giant pseudoaneurysm; C: Giant pseudoaneurysm of vein graft with wide neck beginning about 2 cm from the graft origin; D: Injection within the aneurysm sac revealing a patent bypass graft that continues into the distal right coronary artery with a sequential connection to the posterior descending artery; E: Computed tomographic 3-D reconstruction of the SVG giant bilobed pseudoaneurysm to the distal right coronary artery seen in relation to the thoracic structures. SVG: Saphenous vein grafts; RPDA: Right posterior descending artery.



**Figure 4** Intraoperative echocardiography showed superior vena cava compression by the giant pseudoaneurysm cranial lobe. A: Intraoperative transthoracic echocardiogram demonstrated normal left ventricular systolic function with left ventricular ejection fraction 60% and the giant pseudoaneurysm of SVG to RPDA in relation to the cardiac structures; B: Echocardiographic view of the pseudoaneurysm upper lobe compressing the superior vena cava (SVC); C, D: Blood flow by color Doppler of the SVC into the right atrium; E, F: Bidirectional flow is seen between the upper and lower pseudoaneurysm (PsA) lobes during diastole and systole respectively. Color Doppler and flow velocities of the giant pseudoaneurysm caudal lobe. RPDA: Right posterior descending artery.

ruptured SVG pseudoaneurysm presenting with SVC syndrome was reported by Rosin and colleagues<sup>[3]</sup> in 1989. Kavanagh *et al*<sup>[4]</sup> in 2004 reported the first case in which CT findings of this condition were described.

We presented a case of a giant saphenous vein graft pseudoaneurysm to right posterior descending artery in a patient presenting with superior vena cava (SVC) syndrome. The precise incidence of SVG aneurysms



remains difficult to ascertain and more so for SVG pseudoaneurysms. In one case series, an incidence of 0.07% was estimated from a review of 5500 grafts at a single institution<sup>[5]</sup>. This condition occurs in both genders but predominates in men (87% of reported cases on average within the sixth decade of life). Postulated mechanisms for SVGs aneurysmal dilatation include atherosclerotic degeneration of the graft, vessel wall ischemia secondary to disruption of the vasa vasorum during the harvesting and grafting process, graft endothelial dysfunction and changes in medial smooth muscle cell orientation in the vicinity of valve sites<sup>[6]</sup>. The clinical presentation is somewhat variable and ranges from an asymptomatic incidental finding on chest X-ray (12%-47%) to new onset angina (46.4%), shortness of breath (12.9%), myocardial infarction (7.7%), hemoptysis (4.8%), hemothorax, or symptoms related to compression of neighboring structures, as well as shock (3.8%) or death<sup>[7]</sup>. SVGs aneurysms predominate in the right coronary distribution thus compression of right-sided cardiac structures is more common. Our patient presented with significantly distended neck veins secondary to compression of the superior vena cava by the giant SVG pseudoaneurysm to RPDA (Figure 2). The mechanical complications include right atrial compression (11.5% of cases), right ventricular compression (7.2%) and fistula formation (7.7%)<sup>[8]</sup>. The most feared complication is aneurysm rupture which has been reported as a presenting feature in only a minority of cases. Although frequently identifiable on chest X-ray or echocardiography, coronary angiography is required to evaluate the patency of the coronary arteries and bypass grafts. Confirmation of the size of the aneurysm or pseudoaneurysm and the relationship to the surrounding structures is best achieved with CT angiography or MRA. Different treatments options exist and are applied according to the anatomy of the pseudoaneurysm, mechanical complication and the patency of the affected vein graft. Repeat coronary artery bypass grafting with aneurysmal ligation or excision is the classic approach<sup>[9]</sup>. In cases in which the affected graft remains patent despite the aneurysmal dilation and in non-surgical candidates for repeat sternotomy, percutaneous management with a covered stent should be considered. In patients in whom preservation of myocardial blood supply is not a concern or non-viable myocardium has been demonstrated, the aneurysmal neck can be occluded by Amplatzer vascular plugs<sup>[9]</sup> or the aneurysm can be thrombosed by endovascular coiling<sup>[10]</sup>. Although large-bore Nitinol stents are highly effective for superior vena cava syndrome, in our case it was decided to proceed with re-thoracotomy and excision of the graft pseudoaneurysm after rupture was demonstrated by CT imaging and coronary angiography. The SVC syndrome resolved with the surgical excision of the ruptured SVG pseudoaneurysm. The optimal treatment for this condition remains an area of uncertainty with

available data based on case reports and small case series and certainly depends upon the clinical scenario and should be made by a multidisciplinary cardiac team.

## COMMENTS

### Case characteristics

An 82-year-old woman presented with acute onset back pain, dyspnea and engorged neck veins.

### Clinical diagnosis

Dyspnea of twelve hours duration and engorged neck veins, later were found to be caused by superior vena cava syndrome from superior vena cava (SVC) compression by a giant saphenous vein grafts (SVG) pseudoaneurysm.

### Differential diagnosis

Any cause for acute onset back pain and dyspnea such as acute coronary syndrome, pulmonary embolism, aortic dissection, etc.

### Laboratory diagnosis

Lab tests result including cardiac enzymes were unremarkable.

### Imaging diagnosis

Multi-imaging modalities including computed tomography chest angiogram, coronary angiogram and TEE revealed a giant bilobed SVG pseudoaneurysm to the right posterior descending artery causing compression of the superior vena cava leading to SVC syndrome.

### Treatment

Surgical ligation and excision of the SVG pseudoaneurysm with re-grafting of right posterior descending artery.

### Experiences and lessons

Saphenous vein graft pseudoaneurysms can present as a late complication following coronary artery bypass grafting. Although most frequently asymptomatic and found incidentally by imaging modalities, the authors should consider this condition in the differential diagnoses for acute coronary syndrome and as a possible explanation of SVC syndrome in patients with prior coronary artery grafting. Different treatments options exist and are applied according to the anatomy of the pseudoaneurysm, mechanical complication and the patency of the affected vein graft.

### Peer-review

This is an interesting report for clinical practice.

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## Long term evolution of magnetic resonance imaging characteristics in a case of atypical left lateral wall hypertrophic cardiomyopathy

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### Abstract

We are reporting a long-time magnetic resonance imaging (MRI) follow-up in a rare case of cardiac left lateral wall hypertrophy. Hypertrophic cardiomyopathy (HCM) is the most common genetic cardiovascular disorder and a significant cause of sudden cardiac death. Cardiac magnetic resonance (CMR) imaging can be a valuable tool for assessment of detailed information on size, localization, and tissue characteristics of hypertrophied myocardium. However, there is still little knowledge of long-term evolution of HCM as visualized by magnetic resonance imaging. Recently, our group reported a case of left lateral wall HCM as a rare variant of the more common forms, such as septal HCM, or apical HCM. As we now retrieved an old cardiac MRI acquired in this patient more than 20 years ago, we are able to provide the thrilling experience of an ultra-long MRI follow-up presentation in this rare case of left lateral wall hypertrophy. Furthermore, this case outlines the tremendous improvements in imaging quality within the last two decades of CMR imaging.

**Key words:** Hypertrophic cardiomyopathy; Atypical; Follow-up; Cardiac magnetic resonance imaging; Left lateral wall



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**Core tip:** Cardiac magnetic resonance imaging (MRI) can be a valuable tool for assessment of detailed information on size, localization, and tissue characteristics in cases of hypertrophic cardiomyopathy. We report the thrilling experience of an ultra-long magnetic resonance imaging follow-up presentation in a rare case of left lateral wall hypertrophy with an initial cardiac MRI of patient acquired more than 20 years ago. This case outlines the tremendous improvements in imaging quality within the last two decades of cardiac MR imaging.

Gassenmaier T, Petritsch B, Kunz AS, Gkaniatsas S, Gaudron PD, Weidemann F, Nordbeck P, Beer M. Long term evolution of magnetic resonance imaging characteristics in a case of atypical left lateral wall hypertrophic cardiomyopathy. *World J Cardiol* 2015; 7(6): 357-360 Available from: URL: <http://www.wjgnet.com/1949-8462/full/v7/i6/357.htm> DOI: <http://dx.doi.org/10.4330/wjc.v7.i6.357>

## INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is the most common genetic cardiovascular disorder and a significant cause of sudden cardiac death. Cardiac magnetic resonance (CMR) imaging can be a valuable tool for assessment of detailed information on size, localization, and tissue characteristics of hypertrophied myocardium. However, there is still little knowledge of long-term evolution of HCM as visualized by magnetic resonance imaging (MRI). Recently, our group reported a case of left lateral wall HCM<sup>[1]</sup> as a rare variant of the more common forms, such as septal HCM, or apical HCM<sup>[2]</sup>. As this patient underwent initial cardiac MRI more than 20 years ago, we are able to provide the thrilling experience of an ultra-long MRI follow-up presentation in this rare case of left lateral wall hypertrophy, including the tremendous improvements in imaging quality within the last two decades of CMR imaging.

## CASE REPORT

A 52-year-old male presented himself to the emergency department of our institution suffering an episode of nocturnal chest pain. As the electrocardiogram showed ventricular tachycardia, synchronized electrical cardioversion was performed, successfully terminating the arrhythmia. Afterwards, the patient was subjected to sequential clinical investigations, excluding ischemia as cause for the serious symptoms, and CMR imaging, revealing an atypical form of HCM.

CMR was performed five days after the initial arrhythmic event on a MAGNETOM® Trio 3.0 Tesla scanner (Siemens AG Sector Healthcare, Erlangen,

Germany). In addition to these current investigations, we were now able to retrieve MR images from the year 1989 (1.5 Tesla Philips Gyroscan, Philips Medical System, Best, the Netherlands) which had been acquired in the pre-PACS era more than 23 years in advance of the current event. This enabled us to present a long term MRI follow-up of this rare manifestation of HCM and to point out the massive improvements in imaging quality of cardiac MRI, due to enormous technical development within the last two decades.

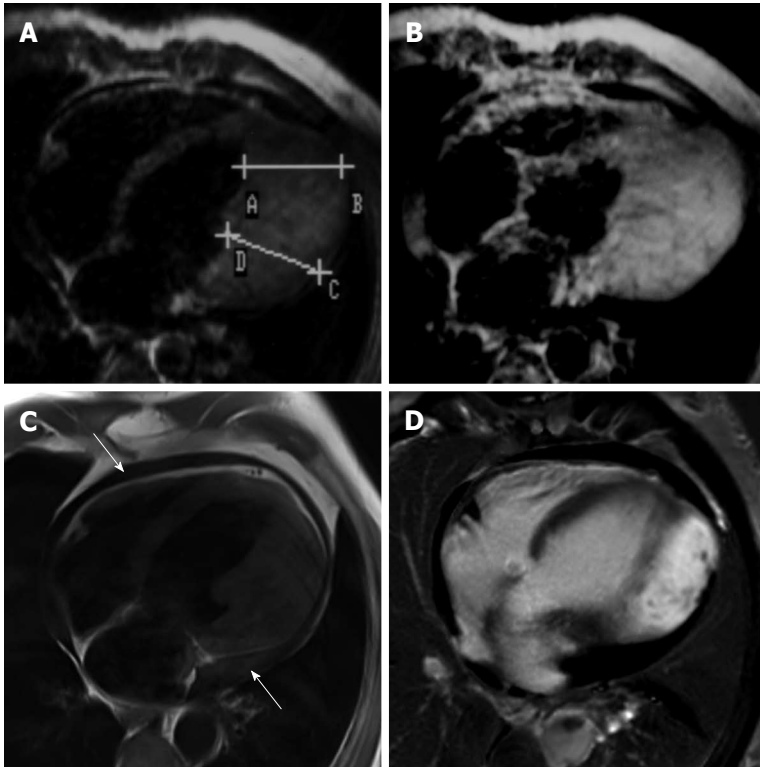
Past images from the year 1989 deliver some limited diagnostic information. Nevertheless, left ventricular wall thickening up to 45 mm was clearly seen in this patient even 23-years ago (Figure 1A). In addition, Gadolinium enhancement (GE) of the noticeable area of interest was depicted after *iv* contrast application (Figure 1B). In the late 1980s, late Gadolinium enhancement (LGE) had not yet been described as a non-invasive method for myocardial tissue characterization, including analysis for myocardial fibrosis.

Current high-quality T1 weighted turbo-spin-echo images with dark blood technique confirmed an extensive, confined thickening of the left ventricular lateral wall up to 45 mm in the 4-chamber view (Figure 1C). Cine-SSFP sequences demonstrated a prolonged longitudinal relaxation of the lateral wall (not shown). After injection of 0.2 mmol/kg intravenous contrast agent (Gadovist®, Bayer HealthCare, Leverkusen, Germany) the myocardial mass showed homogenous contrast enhancement. LGE imaging was acquired 12 min after *iv* contrast administration. PSIR-SSFP images in the 4-chamber (Figure 1D) and short axis views (Figure 2A-C) revealed a homogenous enhancement, corresponding to the left ventricular lateral wall thickening, as it can be typically observed in other, more common forms of HCM.

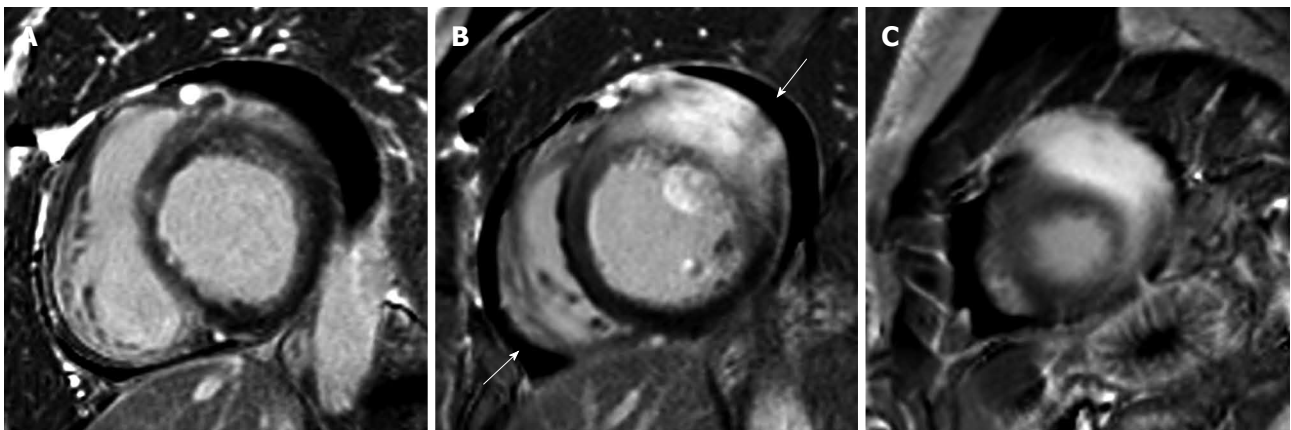
In addition, a small accompanying circular pericardial effusion (indicated with arrows) was depicted in the present CMR images (Figure 1C and 2B).

Comparison of the studies revealed no significant change over time regarding the extent of wall thickening. It is difficult to judge whether significant change in myocardial fibrosis can be detected by CMR, as LGE techniques had not been described prior to 2001 and the baseline CMR was performed prior to that in 1989<sup>[3]</sup> (Figure 1, A/B vs C/D). In 1989, the contrast enhanced images were acquired about 3 min after Gd administration, a "late-enhancement stop" and the so-called "nulling" technique were not available/invented. However, as far as one can compare the images from 1989 to 2012, no significant change in fibrotic myocardium occurred during this time span. The diagnosis of myocardial fibrosis was already proven in 1989 by myocardial biopsy, showing massive hypertrophy but no signs of malignancy.

Therefore, this intensive myocardial thickening described above has to be considered a highly



**Figure 1** Hypertrophic cardiomyopathy of the left lateral wall in 1989 (A, B) and 2012 (C, D). Note the difference of image quality especially within the GE series from 1989 (B) and the PSIR-SSFP late Gadolinium enhancement (LGE) images in 2012 (D). Within the last 23 years, there was no significant change in respect to morphology (A, C) and LGE (B, D) in this patient. Arrows indicate accompanying circumferential, increasing pericardial effusion.



**Figure 2** Late Gadolinium enhancement images in basal (A), midventricular (B) and apical (C) slices in the short axis view show significant late Gadolinium enhancement in the area of hypertrophic cardiomyopathy of the left lateral wall. Arrows indicate accompanying pericardial effusion.

uncommon manifestation of HCM limited solely to the left ventricular lateral wall.

Finally, the patient could be discharged in good general condition after the implantation of an ICD for prevention of further episodes of ventricular tachycardia.

## DISCUSSION

In a patient with atypical left wall cardiac hypertrophy, CMR was able to provide detailed information on size, localization, and tissue characteristics of the myocardial mass and allowed non-invasive long time assessment

of these parameters. Even though limited to the left ventricular lateral wall, our variant of HCM showed some typical characteristics. For instance, LGE is frequently observed in HCM patients and reflects the presence of fibrosis within the myocardium<sup>[4,5]</sup>. However, the clinical significance of change of LGE over time in HCM is still under debate<sup>[6]</sup>. Nonetheless, the presence of LGE is an independent risk factor for adverse outcome in HCM and associated with an increased frequency of ventricular tachyarrhythmia, as was the case in our patient<sup>[7,8]</sup>.

However, initial inspection of the LGE images with

the atypical site of LGE and the considerable degree of myocardial hypertrophy raised concerns whether the patient might suffer from a malignant tumor of the myocardium. Pericardial effusion fortified this impression. However, only a short period after the current CMR, reports from the old, previous CMR from 1989 were retrieved. Finally, comparison of the images from 1989 to those of 2012 confirmed that the patient suffered from HCM and excluded a malignant tumor as a potential differential diagnosis.

For future studies, T1 maps might be helpful to differentiate between a cardiac entity (HCM) and non-cardiac entity (tumor). However, this was not performed in the current case, as the utilized MR scanner was not equipped with software applicable for T1 mapping.

## COMMENTS

### Case characteristics

A 52-year-old male with an episode of nightly chest pain.

### Clinical diagnosis

Electrocardiogram showed ventricular tachycardia.

### Differential diagnosis

Ischemia, cardiac tumor, atypical hypertrophic cardiomyopathy (HCM).

### Laboratory diagnosis

Tests for exclusion of cardiac ischemia were within normal limits.

### Imaging diagnosis

Cardiac magnetic resonance imaging showed an extensive, confined thickening of the left ventricular lateral wall up to 45 mm. Comparison with a previous study from 1989 revealed that this left ventricular wall thickening was clearly seen in this patient already 23-years ago.

### Pathological diagnosis

Myocardial biopsy had shown massive hypertrophy but no signs of malignancy in 1989.

### Treatment

The patient underwent implantation of an ICD for prevention of further episodes of ventricular tachycardia.

### Related reports

Isolated left lateral wall hypertrophic cardiomyopathy is a rare variant of the more common forms, such as septal HCM, or apical HCM.

### Term explanation

Late gadolinium enhancement is frequently observed in HCM patients and reflects the presence of fibrosis within the myocardium.

### Experiences and lessons

This case report outlines the tremendous improvements in imaging quality

within the last two decades of cardiac MR imaging.

## Peer-review

This article reported a long-time MRI follow-up in a rare case of cardiac left lateral wall hypertrophy. Cardiac magnetic resonance imaging is a valuable tool for assessment characteristics of hypertrophic cardiomyopathy. And this report provided detailed information on location, size and imaging characteristics of hypertrophic cardiomyopathy.

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**E- Editor:** Zhang DN



## Reverse or inverted apical ballooning in a case of refeeding syndrome

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**Author contributions:** Robles P and Monedero I reviewed the literature and wrote the manuscript; Rubio A made the electrophysiologic analysis and contributed to the writing of the manuscript; Botas J was involved in revising the manuscript critically for important intellectual content.

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### Abstract

Takotsubo cardiomyopathy is characterized by the development of transient left ventricular regional wall motion abnormalities, in the absence of significant coronary artery obstruction. This syndrome usually occurs in women and is frequently associated with an intense emotional or physical stress. It usually involves apical segments, but in the recent years atypical forms have been described. Inverted or reverse Takotsubo is a variant in which the basal and midventricular segments are hypokinetic, sparing contractile function of the apex. In this report we describe the case of a 54-year-old woman, with chronic malnutrition, initially admitted because of hypoglycemia and severe electrolyte disturbance due to a refeeding syndrome. Within the next hours she experienced acute cardiac symptoms and developed heart failure with low cardiac output. Electrocardiogram (ECG), elevation of troponin and echocardiographic findings were consistent with inverted Takotsubo cardiomyopathy. To the best of our knowledge, this is the first incidence reported of inverted Takotsubo triggered by refeeding syndrome.

**Key words:** Apical ballooning; Refeeding syndrome; Anorexia; Atrial tachycardia; Inverted takotsubo

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**Core tip:** Inverted Takotsubo is a stress-induced cardiomyopathy type that could be encountered in patients suffering from varied physical or emotional triggers. In this report we describe the first case following a refeeding syndrome. There are reported cases of classical apical Takotsubo associated with nutrition disorders, but none of them presenting with the inverted variant.

Robles P, Monedero I, Rubio A, Botas J. Reverse or inverted apical ballooning in a case of refeeding syndrome. *World J*



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## INTRODUCTION

Takotsubo cardiomyopathy (also called apical ballooning syndrome or stress-induced cardiomyopathy) is an acute cardiac syndrome characterized by transient and reversible wall-motion abnormalities of the left ventricle.

The clinical features include an onset of acute chest symptoms, electrocardiographic changes, and elevated cardiac enzymes, mimicking myocardial infarction, but in the absence of significant obstructive coronary disease.

It is estimated that this condition probably accounts for 1% to 2% of all cases of suspected acute myocardial infarction. Approximately 90% of all reported cases have been in women and the average age of onset range between 58 and 75 years, with < 3% of the patients being < 50 years<sup>[1]</sup>.

In the most commonly described type of stress cardiomyopathy, the contractile function of the mid and apical segments of the left ventricular is depressed and there is hyperkinesis of the basal walls. Less common (atypical) variants include ventricular hypokinesis restricted to the mid-ventricle (mid-ventricular Takotsubo), hypokinesis of the base and mid-ventricle segments with sparing of the apex (reverse or inverted Takotsubo), and localized hypokinesis<sup>[2]</sup>.

The pathophysiology remains unknown, but this syndrome is frequently triggered by intense emotional or physical stress or by an acute medical illness, so catecholamine mediated myocardial stunning is the most accepted explanation<sup>[3]</sup>. We present a case of inverted Takotsubo in a woman with chronic malnutrition who experienced a rapid oral nutrition repletion. After that she developed refeeding syndrome, a potentially lethal clinical condition characterized by severe metabolic disturbances in undernourished or starved patients undergoing refeeding. Medical complications of this syndrome include cardiovascular system, but it has not usually been described to trigger Takotsubo's cardiomyopathy. The fact that the patient developed an atypical variant (inverted) instead of the classical type of apical stress cardiomyopathy, also makes this case remarkable.

## CASE REPORT

A 54-year-old woman was admitted to our hospital on Christmas day with impaired consciousness and severe hypoglycemia (19 mg/dL). She had a past medical history significant for persistent malnutrition, although main organic causes of weight loss had been excluded. The day before admission the relatives of the patient

had urged her to ingest a copious dinner on Christmas Eve.

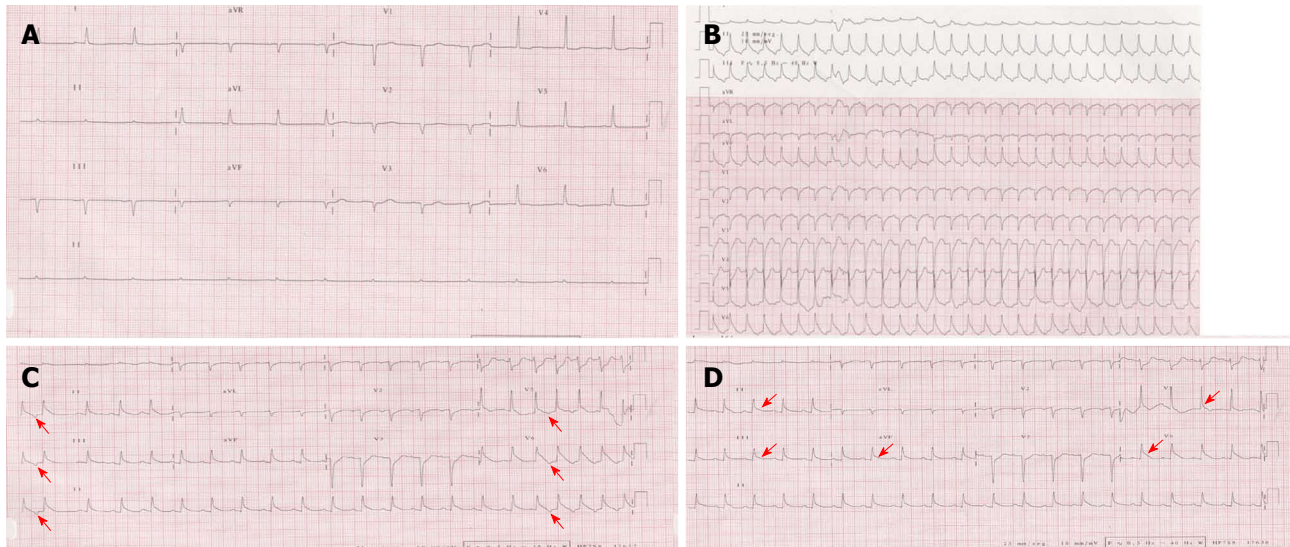
Physical examination on admission revealed marked emaciation with a body weight of 28 kg. She was 162 cm in height and her body mass index (BMI) was 10.66 kg/m<sup>2</sup> (-45% of her ideal BMI). Her body temperature was normal, but she had bradycardia (55 beats/min) and edema in her lower limbs. Her albumin (1.5 g/dL), phosphate (2.2 mg/dL), magnesium (1.6 mg/dL) and potassium (2.7 mmol/L) levels were low. Liver dysfunctions (AST: 122 IU/L, ALT: 72 IU/L) also were noted, as well as coagulation disorders (PT: 55.9%, APTT: 43 s).

First of all, she was treated with 25 g of 50% glucose administrated intravenously, with recovery of consciousness within a few minutes. Then she started receiving specific treatment for electrolyte replacement. The initial ECG showed sinus bradycardia (Figure 1A). Some hours later, the patient referred heart palpitations and a new ECG (Figure 1B and C) was obtained, showing a supraventricular tachycardia. It was remarkable the ST segment elevation in leads II, III, aVF, V5-V6. The tachycardia was terminated by the administration of adenosine (Figure 1D). Revising the whole electrocardiographic registry the episode was consistent with paroxysmal atrial tachycardia. In the next hours the clinical state of the patient progressively impaired, with development of acute dyspnea, hypotension and obtundation, suggesting heart failure and low cardiac output. Chest X-ray also demonstrated an impairment respect to the previous one on admission (Figure 2). Echocardiography showed dyskinesia of basal and mid-ventricular segments, with hyperkinesis of left ventricular apex (Figure 3). The ejection fraction was estimated at 25%. Serum troponins were mildly elevated with a peak of 4.2 ng/mL, with non-elevated creatine phosphokinase (CPK) levels (80 UI/L). The patient was treated with noninvasive positive pressure ventilation and inotropic drugs at the Intensive Care Unit. Along the next days her clinical situation progressively improved, and a echocardiogram performed one week later showed recovery of the wall motion abnormalities of the left ventricle, with hyperdynamic ejection fraction (Figure 4). Finally, as a complication she developed respiratory distress due to a *Serratia marcescens*-induced acute pneumonia, and she died. Subsequent necropsy revealed coronary arteries with non obstructive lesions.

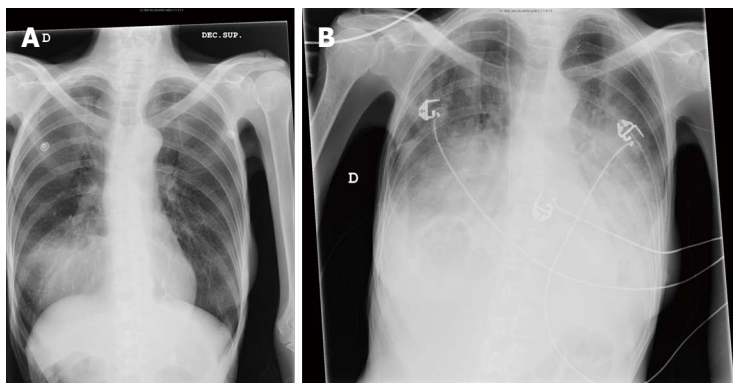
## DISCUSSION

Once other causes of weight loss had been excluded, all the evidence (clinical signs and findings, along with information provided by the family) pointed towards our patient in the present case suffered from anorexia nervosa (AN).

In patients with AN, cardiac complications can be present in up to 80% of cases and have been reported as cause of at least one-third of all deaths<sup>[4]</sup>.



**Figure 1 Change process of electrocardiogram.** Baseline electrocardiogram (ECG) showed sinus bradycardia and nonspecific repolarization abnormalities (A). Surface ECG of repetitive nonsustained atrial tachycardia (AT). Note that the first P wave of the tachycardia is similar in morphology to the subsequent P waves, consistent with abnormal automaticity as the mechanism of the AT (red arrow). In the setting of posteroseptal AT (originating below and around the coronary sinus ostium), the P wave is positive in lead V1, negative in the inferior leads, and positive in leads aVL and aVR (B and C). ECG after the completion of the tachycardia showed persistent ST elevation in leads II, III, AVF, V5 and V6 (D) (red arrows).



**Figure 2 Chest X-ray on admission (A) and after the episode of atrial tachycardia (B) showing signs of severe heart failure.**

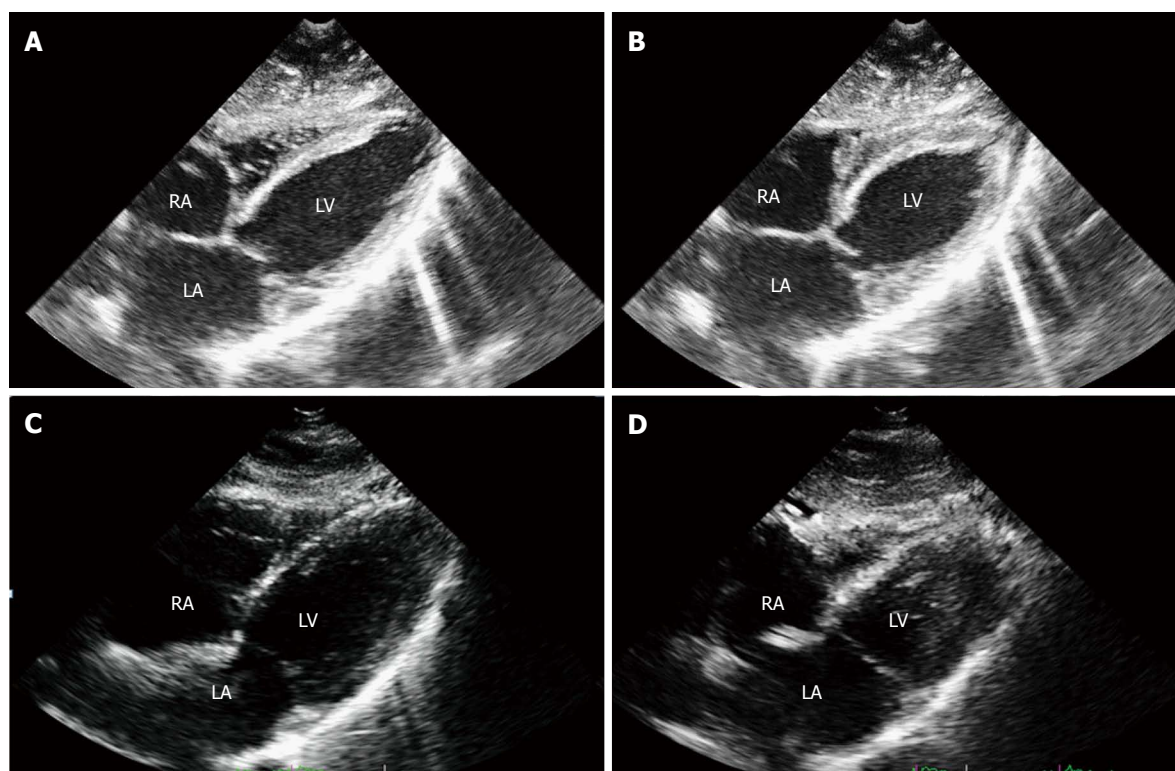
Main cardiovascular disorders include alterations in hemodynamics (mainly hypotension), in structure (radiographic evidence of decreased cardiac size associated with lower left ventricular mass) and in electrical activity, including sinus bradycardia (present in this patient), reduction in QRS voltage, alterations in ST segment, U waves and prolonged QT interval. QT prolongation may be influenced both by electrolyte abnormalities and psychotropic drugs, with subsequent higher risk of ventricular arrhythmias or torsades de pointes<sup>[5,6]</sup>. However, left ventricle function generally remains normal, and Takotsubo's cardiomyopathy has only been reported in AN in isolated cases, some of them with hypoglycaemic coma as the precipitating event<sup>[7]</sup>.

Over a chronic severe malnutrition state, the patient had been urged to ingest a copious dinner just before admission. Clinical impairment that she developed within the next hours can be attributed to

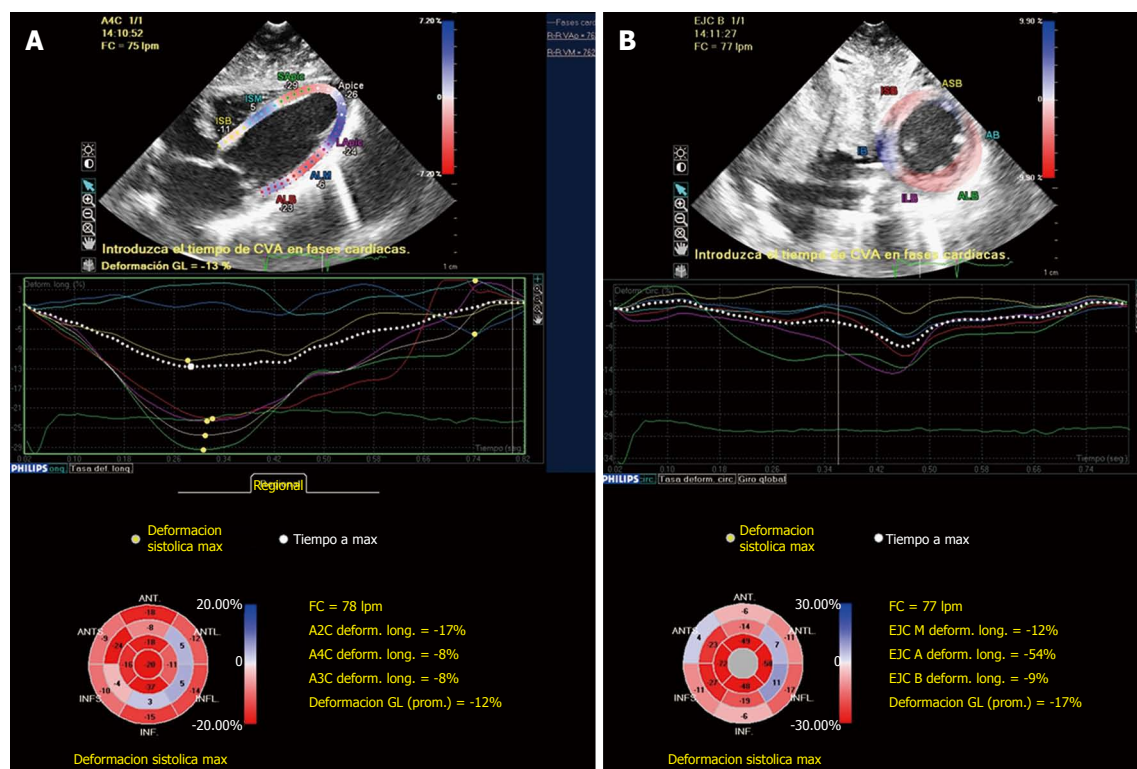
the appearance of a refeeding syndrome (RF).

RF describes a series of metabolic and biochemical changes that occur as consequence of reintroduction of feeding after a period of starvation or fasting. First reports of the syndrome appeared in the 1950s after observations of malnourished prisoners of war who developed cardiac and neurological symptoms soon after the recommencement of feeding. In 2001 Crook *et al.*<sup>[8,9]</sup> referred to a syndrome of important electrolyte and fluid shifts associated with metabolic abnormalities in malnourished patients undergoing oral, enteral or parenteral refeeding.

This potentially lethal condition encompasses a severe electrolyte disturbance, mainly low serum concentrations of intracellular ions such as phosphate, magnesium, and potassium. Hypophosphataemia is the adopted surrogate marker for diagnosing RF, though low serum phosphate is not pathognomonic. It may produce clinical complications affecting



**Figure 3** Two-dimensional echocardiogram, subcostal four chambers view, showing the anteroseptal and posterolateral walls of the left ventricle. End-diastolic (A) and mid-systolic (B) frames at the time of acute cardiac symptoms presentation showed dyskinesia of basal and medium segments, with hyperkinesia of the left ventricular apex. One week later, recovery of the wall motion abnormalities was demonstrated, with hyperdynamic ejection fraction (C and D). A previous echocardiogram performed two years before in this patient was similar to this last one. RA: Right atrium; LA: Left atrium; LV: Left ventricle.



**Figure 4** Bull's eye mapping of two-dimensional speckle tracking strain imaging longitudinal (A) and circumferential (B) showed decreased strain values of the basal and mid-ventricular segments, with normal or increased strain values of the apical segments.



the cardiac, respiratory, haematological, hepatic and neuromuscular systems and leading even to death<sup>[10,11]</sup>.

Atrophy of the heart during starvation renders the patient more vulnerable to fluid overload and heart failure, and electrolyte abnormalities may contribute to ventricular arrhythmias<sup>[12]</sup>. Nevertheless, our patient developed unusual cardiovascular complications associated with RF, as atrial tachycardia and stress-induced cardiomyopathy.

Automatic atrial tachycardias (caused by abnormal automaticity in cardiac cells) are catecholamine sensitive and the discharge of the abnormal pacemaker involved can be triggered by drugs, various forms of cardiac disease, reduction in extracellular potassium or alterations of autonomic nervous system tone. One or more of them could have influenced in the episode suffered by this patient in the context of RF<sup>[13]</sup>.

Stress-induced (Takotsubo) cardiomyopathy is characterized by the development of transient wall-motion abnormalities in the absence of obstructive coronary artery disease. It was initially described in the Japanese population in 1991 as a syndrome of reversible left ventricular dysfunction with wall-motion abnormalities that involved the apical segments<sup>[14]</sup>. This condition is typically triggered by severe emotional or physical stress, and it is thought to be caused by a catecholamine-mediated injury. Subarachnoid hemorrhage and pheochromocytoma have been described as common triggers of Takotsubo's cardiomyopathy, which supports this hypothesis, with the exact mechanism of damage caused by catecholamines being less well understood<sup>[15]</sup>.

Various patterns of stress-induced cardiomyopathy have been recently recognized and classified into 4 types based on the involvement of the left ventricle: (1) classic or apical type; (2) reverse or inverted type; (3) mid-ventricular type; and (4) and localized type<sup>[16]</sup>. We report a case consistent with the inverted type, with dyskinesia of basal and mid-ventricular segments and hyperdynamic contractility of the apex.

Clinical differences affecting inverted type in comparison to common apical and mid-ventricular type have been evaluated by several studies. They conclude that patients with reverse Takotsubo are significantly younger compared with those with other types. It might be due to an asymmetric distribution of adrenergic receptors, which seem to play an important role to determine the area of hypokinesia<sup>[17]</sup>. The hypothesis is that adrenoceptor density is highest in the apex compared with the base in postmenopausal women, explaining the occurrence of apical variant in older women. The presentation of the inverted type at an early age could be explained by the abundance of adrenoceptors at the base of the heart, compared with the apex, in younger patients<sup>[18]</sup>.

Release of troponin is higher in inverted Takotsubo compared to other patterns, which might be the

consequence of the larger muscle region involved compared to apical type. Nevertheless, in apical and midventricular patterns natriuretic peptides are more elevated and a higher prevalence of significant reversible mitral regurgitation is present, which is clinically translated by more severe heart failure symptoms and higher NYHA functional class<sup>[19]</sup>.

Inverted Takotsubo also seems to be more often associated with either mental or physical stress than other types. Different authors have described cases of inverted type associated with varied physical triggers (pheochromocytoma, pulmonary embolism, cerebellar hemorrhage, pneumomediastinum, etc.)<sup>[20-22]</sup>. Nevertheless to our best knowledge, this is the first report of a case of stress cardiomyopathy presenting with an inverted pattern following a refeeding syndrome.

Regarding to malnourished patients, there are reported cases of classical Takotsubo associated with starvation states of different etiologies, but usually with refractory hypoglycemia as characteristic feature, and none of them presenting with the inverted variant<sup>[23]</sup>. A particular group would be patients with anorexia nervosa, with some reported cases of development of stress cardiomyopathy maintaining euglycemia; in these cases the syndrome might be triggered by emotional stress or electrolyte disturbances, and neither any of them presenting with the inverted Takotsubo type in the published cases.

In our case, we hypothesize that this particularly unique cardiac manifestations of refeeding syndrome (atrial tachycardia and inverted Takotsubo) might be influenced by hypoglycemia, electrolyte abnormalities, metabolic disturbances, emotional stress....as isolated factors or by a contribution of all of them<sup>[24]</sup>.

## COMMENTS

### Case characteristics

A 54-year-old woman with chronic malnutrition who experienced a rapid oral nutrition repletion.

### Clinical diagnosis

Impaired consciousness, emaciation with a body mass index of 10.66 kg/m<sup>2</sup>, bradycardia and edema in her lower limbs.

### Differential diagnosis

Hypoglycemia, electrolyte abnormalities, heart failure, renal failure.

### Laboratory diagnosis

Severe hypoglycemia (19 mg/dL), low levels of albumin (1.5 g/dL), phosphate (2.2 mg/dL), magnesium (1.6 mg/dL) and potassium (2.7 mmol/L), liver dysfunctions (AST: 122 IU/L, ALT: 72 IU/L) and coagulation disorders (PT: 55.9%; APTT: 43 s).

### Imaging diagnosis

Chest X-ray demonstrated marked heart failure signs and echocardiography showed dyskinesia of basal and mid-ventricular segments with hyperkinesia of left ventricular apex, consistent with inverted Takotsubo, with decreased ejection fraction (estimated at 25%).

### Pathological diagnosis

Necropsy revealed coronary arteries with non obstructive lesions.

### Treatment

The patient was treated with noninvasive positive pressure ventilation and inotropic drugs, but she finally died due to a *Serratia marcescens*-induced acute pneumonia.



### Related reports

Takotsubo cardiomyopathy is a syndrome frequently triggered by intense emotional or physical stress, and although it is thought to be catecholamine mediated, the pathophysiology remains unknown.

### Term explanation

Refeeding syndrome describes a series of metabolic and biochemical changes that occur as consequence of reintroduction of feeding after a period of starvation or fasting.

### Experiences and lessons

In this report the authors describe the first case of inverted Takotsubo following a refeeding syndrome.

### Peer-review

There are reported cases of classical apical Takotsubo associated with nutrition disorders, but none of them presenting with the inverted variant.

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## Case of angina pectoris at rest and during effort due to coronary spasm and myocardial bridging

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**Author contributions:** Teragawa H wrote the manuscript; Fujii Y, Ueda T, Murata D and Nomura S collected data and evaluated the study.

**Ethics approval:** The study was reviewed and approved by the Hiroshima General Hospital of West Japan Railway Company Institutional Review Board.

**Informed consent:** Informed consent was obtained from the present patient.

**Conflict-of-interest:** All the authors have no conflict-of interest.

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### Abstract

We present a case of a 71-year-old male who had

chest symptoms at rest and during effort. He had felt chest oppression during effort for 1 year, and his chest symptoms had recently worsened. One month before admission he felt chest squeezing at rest in the early morning. He presented at our institution to evaluate his chest symptoms. Electrocardiography and echocardiography failed to show any specific changes. Because of the possibility that his chest symptoms were due to myocardial ischemia, he was admitted to our institution for coronary angiography (CAG). An initial CAG showed mild atherosclerotic changes in the proximal segment of the left anterior descending coronary artery (LAD) and mid-segment of the left circumflex coronary artery. Subsequent spasm provocation testing using acetylcholine revealed a bilateral coronary vasospasm, which was relieved after the intracoronary infusion of nitroglycerin. Finally, a CAG showed myocardial bridging (MB) of the mid-distal segments of the LAD. Fractional flow reserve using the intravenous administration of adenosine triphosphate was positive at 0.77, which jumped up to 0.90 through the myocardial bridging segments when the pressure wire was pulled back. Thus, coronary vasospasm and MB might have contributed to his chest symptoms at rest and during effort. Interventional cardiologists should consider the presence of MB as a potential cause of myocardial ischemia.

**Key words:** Coronary spasm; Myocardial bridging; Myocardial squeezing; Fractional flow reserve

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**Core tip:** Myocardial bridging (MB), an anomaly in which the myocardium overlies the intramural course of segments of the epicardial coronary arteries, is associated with cardiac events. This may be explained by myocardial ischemia, coronary spasms, and/or mechanical compression of the coronary artery by the MB itself. We encountered a patient with angina pectoris both at rest and during exercise, which was

caused by both coronary spasm and MB-induced direct myocardial ischemia. The latter finding was revealed using a pressure wire. MB sometimes causes two vascular characteristics, coronary spasms and direct myocardial ischemia, whose management is quite different.

Teragawa H, Fujii Y, Ueda T, Murata D, Nomura S. Case of angina pectoris at rest and during effort due to coronary spasm and myocardial bridging. *World J Cardiol* 2015; 7(6): 367-372 Available from: URL: <http://www.wjgnet.com/1949-8462/full/v7/i6/367.htm> DOI: <http://dx.doi.org/10.4330/wjc.v7.i6.367>

## INTRODUCTION

Myocardial bridging (MB) is an anomaly in which the myocardium overlies the intramural course of segments of the epicardial coronary arteries<sup>[1]</sup>. The frequency of MB ranges from 5.4% to 85% in autopsy series<sup>[2-4]</sup> and from 0.5% to 29.4% on coronary angiography<sup>[4-10]</sup>. It has been accepted that MB might affect the cardiovascular system<sup>[1,8,11-13]</sup>. In addition, the presence of MB is associated with myocardial infarction<sup>[14-17]</sup> and sudden cardiac death<sup>[18-20]</sup>. Myocardial ischemia due to compression of the coronary artery by MB<sup>[21,22]</sup> and/or coronary spasm at the MB segments<sup>[12,23-25]</sup> has been considered a major factor responsible for MB-related cardiac events. In this study, we report a case of angina pectoris at both rest and during exercise due to both coronary spasm and MB-related myocardial ischemia, which was documented using a pressure wire.

## CASE REPORT

A 71-year-old male had felt chest oppression on effort, such as when carrying heavy baggage, for 1 year. Recently, his chest symptoms had occurred more frequently. One month before admission he felt chest squeezing at rest in the early morning. He presented at our institution for an evaluation of his chest symptoms in May 2014. Coronary risk factors such as smoking, hypertension, and diabetes mellitus were all absent, although he had a low level of high-density lipoprotein (HDL) cholesterol. His mother had angina pectoris. He had undergone operations for appendicitis and prostate cancer at the ages of 25 and 69 years, respectively. On medical examination, his height was 1.63 m, his weight was 73 kg, and his body mass index was 27.5. His vital signs were stable with a blood pressure of 110/80 mmHg and a pulse of 59 beats/min. No cardiac murmur or abnormal respiratory sounds in the lungs were detected. Blood examinations revealed elevated levels of creatinine (1.06 mg/dL), uric acid (9.4 mg/dL), and triglycerides (227 mg/dL), and a low level of HDL cholesterol (35 mg/dL). Neither a chest X-P, electrocardiogram, nor echocardiography

showed any specific changes. He was admitted to our institution for coronary angiography (CAG) because of the possibility that his chest symptoms were due to myocardial ischemia.

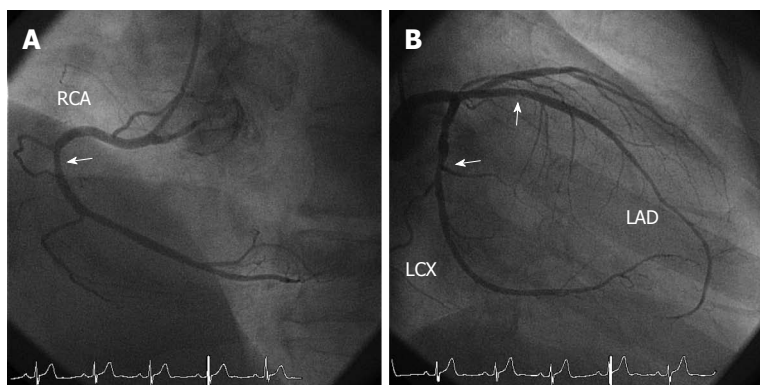
An initial CAG showed mild atherosclerotic changes at the proximal segments of the right coronary artery (RCA), the left anterior descending coronary artery (LAD) and the mid-segment of the left circumflex coronary artery (Figure 1). To clarify the cause of his chest symptoms, we performed spasm provocation testing using acetylcholine (ACh). During the spasm provocation test, a pressure wire (PrimeWire Prestige PLUS, Volcano Therapeutics Inc., Rancho Cordova, CA, USA) was inserted into the distal portion of the RCA and distal portion of the LAD. The ratio of the distal pressure, derived from the pressure wire, to the proximal one, derived from the tip of catheter (Pd/Pa), was continuously monitored.

Intracoronary infusion of 50 µg ACh caused a diffuse coronary spasm at the mid-distal portion of the RCA (Figure 2A), which was accompanied by the usual chest symptoms and a reduction in the Pd/Pa from 1.0 to 0.69 at baseline. Because of the prolonged coronary spasm, 600 µg nitroglycerin (NTG) was intracoronarily administered, which relieved the coronary spasm in the RCA (Figure 3A). The subsequent intracoronary infusion of 100 µg ACh in the LCA resulted in no chest symptoms but a diffuse spasm in the mid-distal portion of the LAD (Figure 2B), which was accompanied by a reduction in the Pd/Pa from 0.94 to 0.60 at baseline. The intracoronary infusion of 300 µg NTG relieved the coronary spasm and returned the Pd/Pa to the baseline value of 0.94. A final CAG revealed an MB of the mid-distal segments of the LAD (Figures 3B and C). The length and percent systolic narrowing of the MB segment was 38 mm and 78%, respectively. The fractional flow reserve (FFR) of the LAD, which was assessed using a pressure wire and the intravenous administration of 160 µg/min per kilogram adenosine triphosphate (ATP), was positive at 0.77 from 0.94 at baseline (Figure 4A). It then jumped to 0.90 through the MB segments when the pressure wire was pulled back (Figure 4B). Therefore, multi-vessel coronary spasms and a myocardial bridge may contribute to his chest symptoms at rest and during effort. The following day he was discharged and prescribed diltiazem (300 mg/d). Since then, he has been taking 300 mg/d diltiazem and 15 mg/d nicorandil and his symptoms have been controlled in the outpatient clinic.

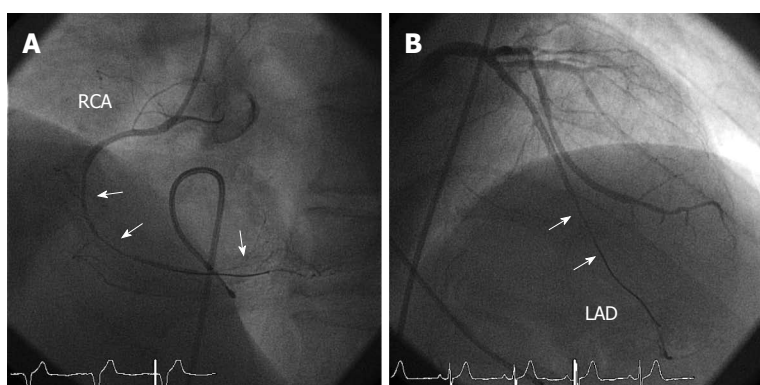
## DISCUSSION

In this study, we present a case of angina pectoris both during exercise and at rest. These symptoms were due to bilateral coronary spasms and MB-related myocardial ischemia, which was identified using a pressure wire.

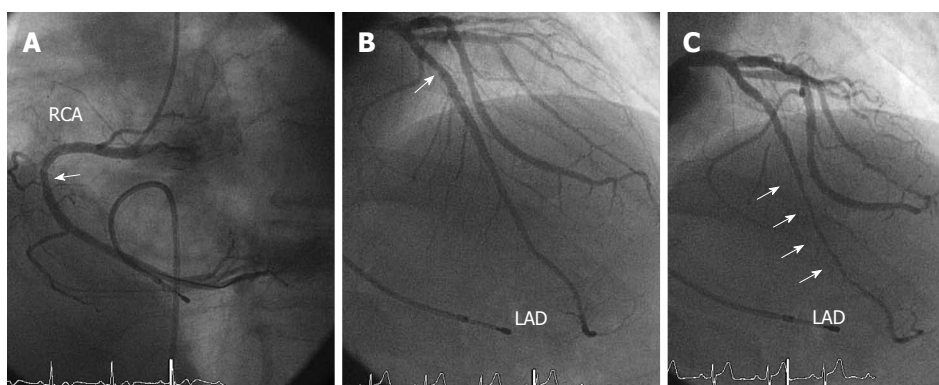
Several reports have described MB-related myo-



**Figure 1 Coronary angiography before spasm provocation tests.** A: There were mild atherosclerotic changes at the proximal segment of the right coronary artery (RCA); B: There were mild atherosclerotic changes at the proximal segment of the left anterior descending coronary artery (LAD) and at the mid-segment of the left circumflex coronary artery (LCX). The mild atherosclerotic changes are indicated using arrows.



**Figure 2 Coronary angiography during the spasm provocation tests.** A: In the right coronary artery (RCA), a diffuse coronary spasm occurred at the mid-distal segments after the intracoronary infusion of 50  $\mu$ g acetylcholine (ACh); B: In the left coronary artery, a diffuse coronary spasm occurred at the mid-distal segments of the left anterior descending coronary artery (LAD) after the intracoronary infusion of 100  $\mu$ g ACh. The coronary spasm segments are indicated using arrows.



**Figure 3 Coronary angiography after the intracoronary infusion of nitroglycerin.** A: There was a mild atherosclerotic change at the proximal segment of the right coronary artery (RCA); B: There was a mild atherosclerotic change (indicated with arrows) in the proximal segment of the left anterior descending coronary artery (LAD) at the end-diastolic phase; C: There was myocardial bridging (indicated with arrows) at the mid-distal segments of the LAD at the end-systolic phase.

cardial infarction<sup>[14-17]</sup> and sudden cardiac death<sup>[18-20]</sup>. Myocardial ischemia has been suggested to be the main cause of MB-related cardiac events due to mechanical compression of the coronary artery by the MB<sup>[21,22]</sup> and/or coronary spasm at the MB segments<sup>[12,23-25]</sup>. It is possible that coronary spasms frequently occur at MB segments because of endothelial dysfunction and/or vascular dysfunction of the coronary artery at MB segments<sup>[11,12]</sup>. Although the current case had multivessel coronary spasms, the segment of the LAD that underwent coronary spasm was the same as the MB segment, which is consistent with an MB-related coronary spasm. This suggests that cardiologists should consider the possibility of coronary spasm in patients with chest pain and MB on coronary angio-

grams. Several methods have been used to assess MB-related myocardial ischemia due to mechanical compression of the coronary artery by MB, such as pharmacological stress echocardiography<sup>[26]</sup>, stress myocardial perfusion imaging<sup>[27]</sup>, intracoronary blood flow velocity measurements<sup>[21,26]</sup>, and intracoronary pressure measurements<sup>[1,21,26,28]</sup>. In the current case, we assessed intracoronary pressure using a pressure wire because this technique has a reliable cutoff value<sup>[29]</sup> and can be used conveniently in the clinical setting.

Regarding the relationship between intracoronary pressure and MB, reports describing the pressure gradient within the MB segment vary. For example, it has been reported that a pressure gradient within



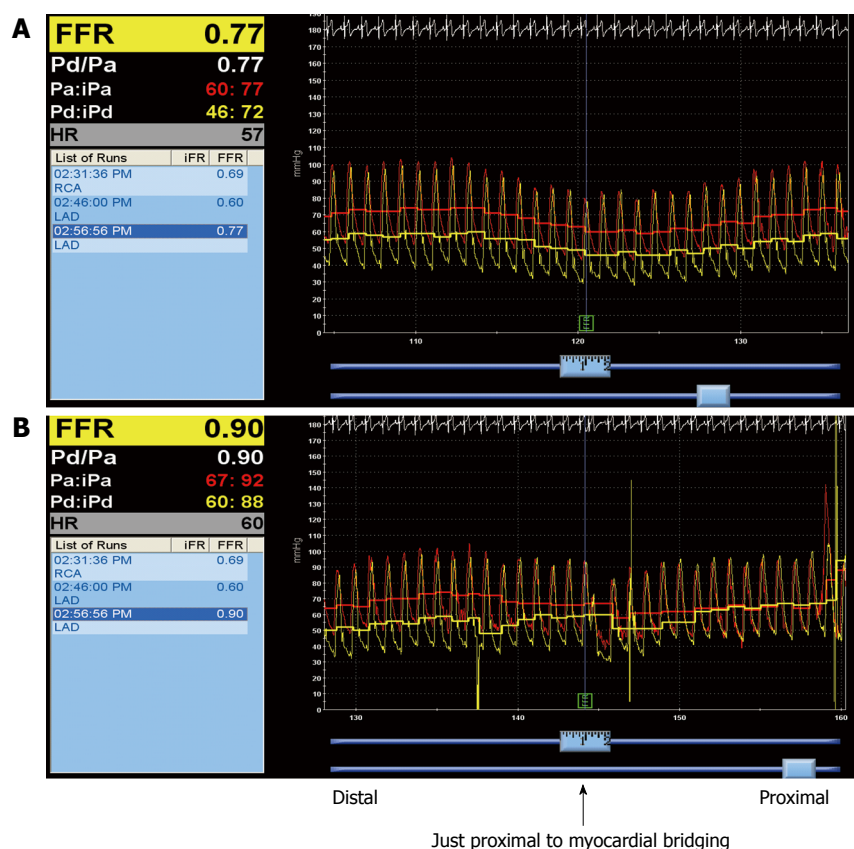


Figure 4 The fractional flow reserve using the intravenous infusion of adenosine triphosphate was 0.77 (A), which jumped up to 0.90 through the myocardial bridging during pullback (B).

the MB segment is present even at baseline<sup>[21]</sup>, only during pharmacological stress<sup>[1,26,28]</sup>, only within the MB segment<sup>[26]</sup>, or both within and beneath MB<sup>[1,21,28]</sup>. These different results may have been due to differences in the severity and degree of the MB itself as well as differences in the methods used to measure intracoronary pressure. According to the current results, where Pd/Pa was 0.94 and FFR was 0.77 at baseline and the Pd/Pa increased to 0.90 through the MB segments, a pressure gradient was present only during pharmacological stress and within and beneath the MB.

ATP is used frequently to measure FFR in the clinical setting during the assessment of MB. However, it has been reported that dobutamine is more useful as the stress agent during the assessment of MB<sup>[1,26,28]</sup> because it causes a more severe and longer compression within the MB<sup>[28]</sup>. Assessing the FFR of the vessel containing the MB can be challenging<sup>[30]</sup> because atherosclerotic changes often occur proximal to the MB<sup>[1]</sup>, which may reduce FFR. The present case had a minor atherosclerotic lesion proximal to the MB; however, the FFR increased to 0.90 just proximal to the MB when the pressure wire was pulled back. Therefore, in cases with MB and proximal atherosclerotic lesions, assessing FFR using the combination of the pullback method may be more useful.

β-blockers are the mainstay of treatment for

symptomatic patients with MB<sup>[1]</sup>. However, as shown in the present case, coronary spasms sometimes occur in patients with MB, particularly in the MB segments<sup>[12]</sup>. In general, monotherapy using β-blockers is prohibited in patients with coronary spasms<sup>[31]</sup>. Furthermore, the use of NTG, which is very effective for relieving coronary spasms, may exacerbate the systolic narrowing of the MB segments<sup>[32]</sup>. Therefore, it is important to ascertain the presence of coronary spasms in patients with MB. Furthermore, in cases with both MB and coronary spasms, calcium-channel blockers (CCB) or CCB plus β-blockers may be useful. Patients with coronary spasms and MB should be monitored carefully when these drugs are administered. In the present case, CCB with diltiazem plus nicorandil was used to treat the coronary spasm, which was the main pathology in the present case. When chest symptoms are present during exercise the use of β-blockers should be considered. It was reported that percutaneous coronary intervention is useful to relieve chest symptoms in patients with MB<sup>[1,22,30,33]</sup>; however, it was also reported that the incidence restenosis is relatively high<sup>[1,30]</sup>. Therefore, pharmacological treatment should be used even in patients with MB and a significantly reduced FFR.

In conclusion, coronary spasms sometimes consolidate in patients with MB, and the presence of coronary spasms should be assessed in such patients.

In addition, intracoronary pressure measurements using a pressure wire may be useful to assess the severity of MB. Interventional cardiologists should keep these concepts in mind.

## COMMENTS

### Case characteristics

A 71-year-old male presented chest oppression during effort and chest squeezing at rest.

### Clinical diagnosis

Angina pectoris due to coronary spasm and myocardial bridging.

### Differential diagnosis

Angina pectoris due to significant coronary stenosis, pulmonary thromboembolism.

### Laboratory diagnosis

Elevated levels of creatinine (1.06 mg/dL), uric acid (9.4 mg/dL), and triglycerides (227 mg/dL), and a low level of HDL cholesterol (35 mg/dL).

### Imaging diagnosis

Coronary angiography showed mild atherosclerotic changes. Spasm provocation testing using acetylcholine showed multi-vessel coronary spasms. Coronary angiography after an intracoronary infusion of nitroglycerin showed myocardial bridging of the left anterior descending coronary artery. The fractional flow reserve using adenosine triphosphate was positive at 0.77.

### Treatment

The patient was treated with 300 mg/d diltiazem and 15 mg/d nicorandil.

### Related reports

Angina pectoris due to coronary spasms or myocardial bridging is well-known, however, little has been reported regarding angina pectoris at rest and during effort due to both coronary spasms and myocardial bridging.

### Term explanation

Myocardial bridging is an anomaly in which the myocardium overlies the intramural course of segments of the epicardial coronary arteries and is associated with cardiac events.

### Experiences and lessons

This report presents a case of angina pectoris due to coronary spasm and myocardial bridging. Coronary spasms sometimes consolidate in patients with myocardial bridging, and the presence of coronary spasms should be assessed in such patients. In addition, intracoronary pressure measurements using a pressure wire may be useful to assess the severity of myocardial bridging.

### Peer-review

This is an interesting case. The case is well presented and the text well written.

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