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World Journal of
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World Journal of

Cardiology

World Journal of Cardiology

Contents

ABOUT COVER

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INDEXING/ ABSTRACTING

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BRIEF ARTICLE

Evaluation of coronary microvascular function in patients with vasospastic angina

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Abstract

AIM: To investigate endothelium-dependent and -independent coronary microvascular functions in patients with vasospastic angina (VSA).

METHODS: Thirty-six patients with VSA (30 men and 6 women; mean age, 58 years) were enrolled in this study. VSA was defined as $\geqslant$ 90% narrowing of the epicardial coronary arteries on angiography performed during a spasm provocation test, presence of chest pain, and/or ST-segment deviation on an electrocardiogram (ECG). Patients (n = 36) with negative spasm provocation test results and those matched for age and sex were enrolled as a control group (nonVSA group). Low-dose acetylcholine (ACh; 3 μg/min) was infused into the left coronary ostium for 2 min during the spasm provocation test. Following the spasm provocation test, nitroglycerin (0.2 mg) was administered intracoronally. Coronary blood flow (was calculated from quantitative angiography and Doppler flow velocity measurements, and the coronary flow reserve was calculated as the ratio of coronary flow velocity after injection of adenosine triphosphate (20 μg) to the baseline value. Changes in the coronary artery diameter in response to ACh and nitroglycerin infusion were expressed as percentage changes from baseline measurements.

RESULTS: Body mass index was significantly lower in the VSA group than in the nonVSA group. The frequency of conventional coronary risk factors and the rate of statin use were similar between the 2 groups. The left ventricular ejection fraction as evaluated by echocardiography was similar between the 2 groups. The duration of angina was 9 ± 2 mo. The results of blood chemistry analysis were similar between the 2 groups. Low-dose ACh did not cause coronary spasms. The change in coronary artery diameter in response to ACh was lower in the VSA group (-1.4% ± 9.3%) than in the nonVSA group (3.1% ± 6.5%, *P* < 0.05), whereas nitroglycerin-induced coronary artery dilatation and coronary blood flow increase in response to ACh or coronary flow reserve did not differ significantly between the 2 groups.

CONCLUSION: These findings suggest that microvascular coronary function may be preserved despite endothelial dysfunction of the epicardial coronary arteries in patients with VSA.

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INTRODUCTION

Vasospastic angina (VSA) is characterized by coronary spasms, which occur because of a dynamic, transient decrease in the luminal diameter of epicardial coronary arteries due to increased vasomotor tone, ultimately leading to myocardial ischemia[1,2]. Abnormal vascular functions of the epicardial coronary arteries, including endothelial dysfunction[3,4] and vascular smooth muscle dysfunction[5-7], play pivotal roles in VSA pathogenesis. However, there are few studies that have investigated coronary microvascular function in patients with VSA[8-12] Therefore, to confirm the presence of coronary microvascular dysfunction in patients with VSA, we investigated their endothelium-dependent and -independent coronary microvascular functions and compared the results with those of patients without VSA.

MATERIALS AND METHODS

Study population

Thirty-six patients with VSA (VSA group; 30 males and 6 females; mean age, 58 years) diagnosed by a positive spasm provocation test and another 36 patients with negative results of the spasm provocation test performed for the evaluation of chest symptoms (nonVSA group) were enrolled in this study. The 2 groups were well matched with respect to age and sex. Patients with organic coronary stenosis (> 50%), history of myocardial infarction, cardiomyopathy, heart failure, or any other serious medical condition were excluded from the study. Written informed consent was obtained from all patients prior to the study. The protocol was approved by the Ethics Committee of our institution.

Study protocol

All antianginal agents were discontinued at least 48 h prior to catheterization with the exception of sublingual nitroglycerin (NTG), which was withheld for 1 h prior to catheterization. Diagnostic left heart catheterization and coronary angiography were performed using a standard percutaneous brachial approach. A 6F guide catheter was introduced into the left main coronary artery. A 0.0014 Doppler flow guidewire (Volcano FloWire; Volcano Therapeutics Inc., Rancho Cordova, CA, United States) was advanced through the guide catheter into the proximal segment of the left anterior descending coronary artery (LAD). The wire tip was positioned in a straight segment of the vessel to obtain a reliable flow velocity signal.

After baseline control conditions were established, incremental doses (3 and 30 μg/min) of acetylcholine (ACh) were infused into the left coronary artery for 2 min, with 5-min intervals between consecutive doses. If a coronary spasm was not induced by ACh, incremental doses of methylergometrine maleate (EM) were infused into the left coronary artery (10, 20, and 30 μg/min) for 1 min, with 1-min intervals between consecutive doses. If coronary spasms were not induced by this infusion

also, incremental doses (15 and 25 μg/min) of EM were infused into the right coronary artery following the same protocol as that followed for the left coronary artery. When coronary spasms were induced or EM infusion was discontinued, because coronary spasms were not provoked, NTG (200 μg) was administered by intracoronary injection. Intracoronary ACh and EM were administered using an infusion pump (TE-311; Terumo, Tokyo, Japan) at a rate of 1 mL/min. Coronary angiography was performed immediately after the appearance of chest symptoms and/or ST segment changes after each dose of ACh administration, after the last dose of EM when neither chest symptoms nor ST segment changes were induced, or 2 min after NTG injection. Finally, adenosine triphosphate (20 μg) was infused into the left coronary artery. Coronary blood flow (CBF) velocity was monitored continuously using a 12-MHz pulsed Doppler velocimeter (FloMap; Volcano Therapeutics Inc.). Arterial pressure, heart rate, and electrocardiography (ECG) readings were monitored continuously and recorded using a multichannel recorder (Polygraph 1600; Nihon Electric Corporation, Tokyo, Japan).

Quantitative coronary angiography

A method for measuring the coronary artery diameter has been described previously[13-16]. The coronary segment 2 mm distal to the Doppler wire tip, which was not the spastic segment was selected for quantitative analysis. For each patient, luminal diameters of the selected LAD segments were measured by a single investigator blinded to the clinical data, using an end-diastolic frame by a computer-assisted coronary angiographic analysis system (CAAS II/QUANTCOR; Siemens, Berlin, Germany). Measurements were performed 3 times, and the average value was used for analysis. Changes in coronary artery diameter in response to ACh and NTG infusion were expressed as percentage changes from baseline angiographic measurements obtained before infusion. Intraobserver and interobserver variability of this method were previously shown to be excellent[17].

Estimation of CBF and coronary flow reserve

Coronary flow reserve (CFR) was calculated as the product of CBF velocity and vessel diameter using the following formula: $\pi \times$ average peak velocity $\times$ 0.125 $\times$ diameter^2. For CBF calculations, the internal diameter of the vessel at the location of the flow measurements (2 mm distal to the wire tip) was measured using the method described above. CFR was calculated as the ratio of CBF velocity after adenosine triphosphate infusion to the baseline velocity.

Definitions

VSA was defined as $\geqslant$ 90% narrowing of the epicardial coronary arteries on angiography performed during the spasm provocation test, presence of characteristic chest pain, and/or ST-segment deviation on ECG[18]. The LAD trunk was divided into proximal, middle, and distal segments of equal lengths. The location of the spastic

Table 1 Patients' characteristics (mean ± SD) *n* (%)	NonVSA group (*n* = 36)	VSA group (*n* = 36)	*P* value
Age (yr)	60 ± 9	59 ± 9	NS
Male/female	31/5	30/6	NS
Body mass index (kg/m^2)	25.2 ± 3.2	23.2 ± 2.6	0.0045
Coronary risk facto			
Smoking	25 (69)	24 (67)	NS
Current/passt smoker	11/13	12/13	NS
Hypertension	21 (58)	19 (53)	NS
Dyslipidemia	11 (31)	11 (31)	NS
Diabetes mellitus	9 (25)	4 (11)	NS
Taking statins (%)	4 (11)	3 (9)	NS
LVEF on echocardiography (%)	71 ± 8	68 ± 7	NS

VSA: Vasospastic angina; NS: Not significant; LVEF: Left ventricular ejection fraction.

Table 2 Blood chemical parameters (mean ± SD)	NonVSA Group	VSA Group	*P* value
Total cholesterol (mg/dL)	196 ± 38	205 ± 27	NS
Triglyceride (mg/dL)	158 ± 63	142 ± 57	NS
HDL-cholesterol (mg/dL)	52 ± 15	55 ± 13	NS
LDL-cholesterol (mg/dL)	113 ± 30	123 ± 24	NS
Fasting blood sugar (mg/dL)	103 ± 24	97 ± 13	NS
Hemoglobin A1C (%)	5.6 ± 0.8	5.4 ± 0.6	NS
C-reactive protein (mg/L)	1.8 ± 2.9	1.6 ± 3.6	NS

VSA: Vasospastic angina; NS: Not significant; HDL: High-density lipoprotein; LDL: Low-density lipoprotein.

segment is expressed with reference to these 3 segments. When coronary spasms occurred diffusely from the proximal to the distal segment, the location was defined as proximal, middle, and distal. A diffuse spasm was defined as that when the length of the spastic segment was ≥ 20 mm, and a focal spasm was defined as that when the length of the spastic segment was < 20 mm. A totally occluded spastic segment was also considered to represent a diffuse spasm. In the present study, coronary spasms occurred in all LADs and also in the left circumflex coronary artery in some VSA patients (multivessel spasm). The duration of angina was obtained from the patients' medical examinations performed *via* interviews.

As described previously[14,17,19-21], in the present study, we adopted the percent changes in epicardial coronary diameter in response to ACh and NTG infusions as the endothelium-dependent and -independent functions of the coronary artery at the level of conduit vessels, and adopted the percent change in CBF in response to ACh infusion and CFR as the endothelium-dependent and -independent functions of the coronary artery at the level of resistance vessels.

Biochemical markers and assessment of coronary risk factors

Fasting blood samples were obtained on the same day of coronary angiography. The patients were questioned about their smoking status and classified as a current smoker, past smoker (who had stopped smoking for at least 1 mo), or nonsmoker. Blood pressure was measured, and hypertension was defined as present if systolic blood pressure was ≥ 140 mmHg, diastolic blood pressure was ≥ 90 mmHg, and/or the patient was on antihypertensive drugs. Blood chemistry parameters, including levels of total cholesterol, triglycerides, high-density lipoprotein cholesterol, fasting blood sugar, insulin, hemoglobin A1C, and creatinine were also measured. Low-density lipoprotein cholesterol was calculated using the Friedewald equation[22]. Hyperlipidemia was defined as present if low-density lipoprotein cholesterol was ≥ 120 mg/dL and/or on the patient was on medication for the same. Diabetes mellitus was defined as present if fasting blood

sugar was ≥ 126 mg/dL, hemoglobin A1C was ≥ 6.5%, and/or the patient was on medication for the same.

Statistical analysis

All data are expressed as mean ± SD. Baseline characteristics of the 2 groups were compared using the Student's unpaired *t*-test or χ^2 analysis as appropriate. The Pearson's correlation coefficient was used to investigate the relationship between coronary microvascular parameters and clinical parameters. A *P* value of < 0.05 was considered statistically significant.

RESULTS

Patient characteristics and blood chemistry parameters

Patient characteristics are presented in Table 1. Body mass index (BMI) was significantly lower in the VSA group than in the nonVSA group. The frequency of conventional coronary risk factors and the rate of statin use were similar between the 2 groups. The left ventricular ejection fraction as evaluated by echocardiography was similar between the 2 groups. The duration of angina was 9 ± 2 mo. The results of blood chemistry analysis were similar between the 2 groups (Table 2).

Angiographic characteristics of coronary spasms in the VSA group

Although coronary spasm was not induced by ACh infusion at 3 μg/min, it was induced by ACh infusion at 30 μg/min in 14 patients, EM infusion at 20 μg/min in 1 patient, and EM infusion at 30 μg/min in 21 patients. Coronary spasm occurred in the proximal segment in 1 patient; proximal and middle segments in 1 patient; middle segment in 14 patients; middle and distal segments in 8 patients; distal segment in 6 patients; and proximal, middle, and distal segments in 6 patients. Therefore, coronary spasm occurred in the distal segments in 20 patients (56%). A focal spasm was identified in 13 patients (36%), while a diffuse spasm was identified in 23 patients (64%). Multivessel coronary spasm occurred in 6 patients (17%).

Coronary vasomotion in response to drugs

Low-dose ACh infusion (3 μg/min) did not cause coronary spasms; therefore, we adopted the coronary artery response to low-dose ACh as the endothelial-dependent

Table 3 Quantitative coronary angiography and Doppler flow velocity (mean ± SD)

	NonVSA Group	VSA Group	*P* value
Heart rate at baseline (/min)	67 ± 13	67 ± 9	NS
Mean arterial pressure (mmHg)	107 ± 11	103 ± 16	NS
Coronary artery diameter (mm)			
Baseline	3.14 ± 0.48	2.95 ± 0.55	NS
Acetylcholine 3 μg/min	3.24 ± 0.55	2.90 ± 0.59	0.013
Nitroglycerin infusion	3.57 ± 0.65	3.43 ± 0.55	NS
Coronary blood flow (mL/min)			
Baseline	94 ± 48	84 ± 69	NS
Acetylcholine 3 μg/min	153 ± 15	130 ± 15	NS
Average peak velocity (cm/s)			
Baseline	21 ± 8	21 ± 12	NS
After ATP infusion	63 ± 25	64 ± 24	NS

VSA: Vasospastic angina; NS: Not significant; ATP: Adenosine triphosphate.

Table 4 Relationship between clinical parameters and coronary microvascular function (mean ± SD)

Parameters	ACh-induced increase in CBF	*P* value	CFR	*P* value
Age (yr)	*r* = 0.188	NS	*r* = 0.204	NS
Disease period (mo)	*r* = -0.016	NS	*r* = -0.260	NS
Current smoking				
(+, *n* = 12)	54.5 ± 14.0	NS	3.1 ± 0.6	NS
(-, *n* = 24)	54.4 ± 9.9		3.3 ± 0.8	
Diffuse spasm				
(+, *n* = 23)	60.8 ± 49.9	NS	3.2 ± 0.6	NS
(-, *n* = 13)	43.2 ± 43.3		3.3 ± 0.9	
Distal spasm				
(+, *n* = 20)	57.0 ± 49.3	NS	3.2 ± 0.7	NS
(-, *n* = 16)	51.3 ± 47.2		3.3 ± 0.8	
Multi-vessel spasm				
(+, *n* = 7)	41.8 ± 26.4	NS	3.1 ± 0.7	NS
(-, *n* = 29)	57.5 ± 51.5		3.3 ± 0.7	

ACh: Acetylcholine; CFR: Coronary flow reserve; NS: Not significant; CBF: Coronary blood flow.

Figure 1 Percentage changes in epicardial coronary artery diameter in response to acetylcholine and nitroglycerin infusion. A: Percentage changes in coronary artery diameter in response to low-dose acetylcholine infusion was significantly lower in the vasospastic angina (VSA) group than in the nonVSA group; B: Percentage changes in coronary artery diameter in response to nitroglycerin infusion were similar between groups. NS: Not significant.

coronary artery parameter. The results of coronary vasomotion in response to each drug are shown in Table 3 and Figures 1 and 2. Heart rate, mean blood pressure, coronary artery diameter, and CBF at baseline did not differ between groups. The change in coronary artery diameter in response to ACh infusion at 3 μg/min was lesser in the VSA group than in the nonVSA group, although NTG-induced coronary artery dilatation was similar between the 2 groups (Table 3 and Figure 1). CFR and CBF increase in response to low-dose ACh infusion did not differ between groups (Table 3 and Figure 2). Neither CFR nor the increase in CBF induced by low-dose ACh was correlated with several clinical factors, including age, duration of angina, smoking status, and presence of diffuse and distal spasms (Table 4).

DISCUSSION

In the present study, we compared endothelium-independent and -dependent coronary microvascular functions between patients with VSA characterized by coronary spasms in LAD and age-matched and sex-matched patients who tested negative in the coronary spasm provocation test. ACh-induced changes in the epicardial coronary arteries were impaired in the VSA group; however, other vascular functions, such as NTG-induced epicardial coronary artery dilatation, CFR, and ACh-induced increase in CBF, were similar between the 2 groups. Coronary endothelial dysfunction at the level of conduit vessels, but not at the level of resistance vessels, may contribute to VSA pathogenesis.

The vascular endothelium is not only a simple passive barrier between the circulating blood and surrounding tissues but also a multifunctional organ, the integrity of which is essential to normal vascular physiology[23]. It releases various vasodilators, including nitric oxide (NO), prostacyclin, and endothelium-derived hyperpolarizing factor, as well as vasoconstrictors. NO plays an important role in the regulation of vascular tone, inhibition of platelet aggregation, and suppression of vascular smooth muscle cell proliferation[24,25]. ACh causes vasodilation by releasing NO from the endothelium in healthy humans, whereas it causes vasoconstriction in patients with coronary atherosclerosis[23,26]. The coronary arteries in patients

A

B
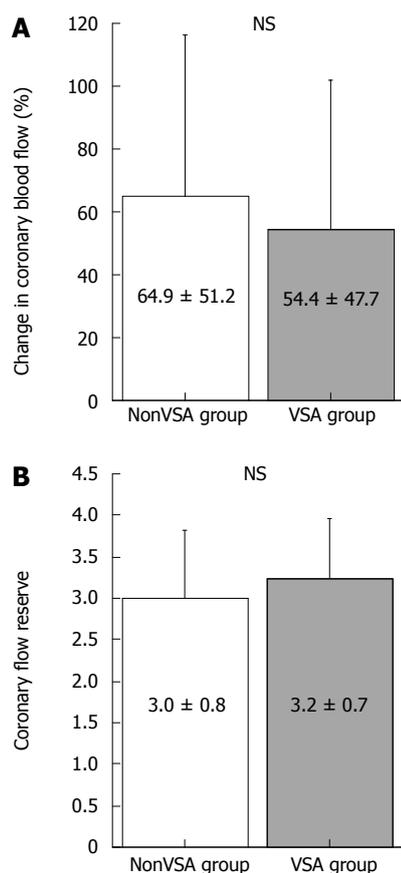
Figure 2 Percentage changes in coronary blood flow in response to acetylcholine infusion and coronary flow reserve. A: Percentage changes in coronary blood flow in response to low-dose acetylcholine infusion; B: Coronary flow reserve did not differ between the 2 groups. NS: Not significant.

with VSA are highly sensitive to the vasoconstrictive effect of intracoronary ACh infusion, thereby resulting in spasms[27-29]. Thus, intracoronary ACh injection is used as a provocative test for coronary spasm[27-29]. Therefore, in the present study, we assessed coronary endothelial function using low-dose ACh infusion (3 μg/min), which did not cause significant coronary spasms.

Regarding coronary vascular function at the level of conduit vessels, it is accepted that abnormal vascular function of the epicardial coronary arteries is present in VSA patients[3-7], although it has not been clarified whether coronary endothelial dysfunction only, coronary smooth muscle dysfunction only, or both contribute to VSA pathogenesis[3,5]. In the present study, low-dose ACh infusion caused significant vasoconstriction in patients with VSA compared with those without, whereas NTG administration did not cause significant differences between groups, suggesting that endothelial dysfunction of the epicardial coronary artery was present in patients with VSA.

Regarding coronary microvascular function in patients with VSA, several studies have investigated the coronary microvascular endothelium-independent function using CFR measurements[9-12]. According to these reports[9-12], several clinical factors, including patient age, disease

period, smoking status, and presence of diffuse and distal spasms were associated with decreased CFR. In the present study, CFR in the VSA group was not decreased compared with that in the nonVSA group. In addition, CFR in the VSA group was not associated with any clinical parameter suggested by previous studies[9-12]. Our subjects were patients with VSA characterized by coronary spasms in LADs. However, coronary spasms occur in other coronary vessels as well[30,31], and it sometimes occurs prominently in the right coronary artery. Therefore, the assessment of coronary microvascular function only in LADs may be insufficient to determine coronary microvascular function in patients with VSA. Furthermore, the nonVSA group in which patients underwent coronary angiography and spasm provocation tests for the evaluation of chest symptom s may have included patients with microvascular angina. It is well known that coronary microvascular function is impaired in such patients[32]. However, if such patients were included in the nonVSA group, CFR in this group would have already been low. Differences in these patient characteristics as well as differences in methodologies and materials, such as the stress agents, their doses, the administration sites (intravenous or intracoronary), and segments in which Doppler flow guidewires are placed, may have led to the differing results.

On the other hand, only few studies have investigated the coronary microvascular endothelium-dependent function. Okumura *et al*[8] showed that CBF significantly increased during coronary spasms in LAD, indicating that the microvascular endothelium-dependent function was preserved. Our results, assessed under the nonspastic status, showed that microvascular endothelial function was not impaired in the VSA group compared with that in the nonVSA group. As mentioned above, it was possible that the microvascular endothelial function was already impaired in the nonVSA group if patients with microvascular angina were included. However, our results showed that coronary microvascular endothelial dysfunction was not involved in the pathogenesis of VSA.

Our results suggest two clinical implications. First, endothelial dysfunction of the epicardial coronary artery, even at the nonspastic segment, was present in patients with VSA. Although endothelial dysfunction may occur throughout the vasculature, the degree of endothelial dysfunction may not always be consistent. Regarding the relationship between the presence of a myocardial bridge and VSA[53], it is possible that local external force may cause the difference in the development of endothelial dysfunction even in the same coronary artery. Therefore, the differences in the degree or development of endothelial dysfunction of the epicardial coronary artery may cause the heterogeneity of occurrence of a coronary spasm. Second, coronary microvascular function may be preserved in patients with VSA to countermeasure myocardial ischemia due to vasospasm of the epicardial coronary artery.

There were several limitations to the present study.

First, as mentioned above, coronary spasms do not always occur in LAD; therefore, our results may not have accounted for all VSA patients. Second, patients in the nonVSA group with chest symptoms, angiographically normal coronary arteries, and a negative spasm provocation test may be heterogenous; in addition, patients with microvascular angina may have been included in this group. Therefore, it was possible that the nonVSA group was not a pure control. Finally, BMI was not similar between the 2 groups. ACh doses, which were not adjusted according to BMI in the present study, may have contributed to ACh-induced coronary vascular responses. However, coronary artery diameter and CBF at baseline was similar between groups, and we believe that differences in BMI did not affect the coronary vascular responses.

In conclusion, the present study showed that coronary microvascular function, including endothelium-dependent and -independent functions, may be preserved despite coronary endothelial dysfunction at the level of conduit vessels. The latter may contribute to VSA pathogenesis.

ACKNOWLEDGMENTS

COMMENTS

Background
Vasospastic angina (VSA) is characterized by coronary spasms, which occur because of a dynamic, transient reduction in the luminal diameter of epicardial coronary arteries, leading to myocardial ischemia. It has been reported that abnormal vascular functions of the epicardial coronary arteries were involved in the pathogenesis of VSA. However, coronary microvascular function in patients with VSA remains to be elucidated.

Research frontiers
The pathogenesis of VSA remains to be unclear. Therefore, to assess coronary vascular response, especially at the level of resistance vessels, may, in part, contribute to the pathogenesis of VSA.

Innovations and breakthroughs
Several studies investigating coronary vascular function in patients with VSA have been reported and their results have identified coronary vascular dysfunction at the level of the conduit vessels. However, it has not been clarified whether coronary endothelial dysfunction only, coronary smooth muscle dysfunction only, both contribute to VSA pathogenesis. Furthermore, only a few studies have investigated coronary microvascular functions in patients with VSA. In the present study, the authors assessed coronary vascular functions using quantitative coronary angiography and Doppler velocity measurements in VSA patients whose coronary spasm occurred in the left anterior descending coronary artery, and compared them with those in nonVSA patients with negative spasm prevocational test. The results showed that the change in coronary artery diameter in response to a low dose of acetylcholine (ACh) was lower in the VSA group, whereas nitroglycerin-induced coronary artery dilatation and coronary blood flow increase in response to ACh or coronary flow reserve did not differ significantly between the 2 groups. These findings suggest that microvascular coronary function may be preserved despite endothelial dysfunction of the epicardial coronary arteries in patients with VSA.

Applications
The results suggest two clinical implications. First, endothelial dysfunction of the epicardial coronary artery was present in patients with VSA. Second, coronary microvascular functions including endothelium-dependent and may be preserved in patients with VSA. Such coronary vascular response may highlight the pathogenesis of VSA. In addition, the latter finding may countermeasure myocardial ischemia due to vasospasm of the epicardial coronary artery.

Terminology
Regarding coronary vascular functions, there are two components: at the level of conduit vessels (epicardial coronary artery) and at the level of resistance vessels (microvascular coronary artery). In addition, regarding the factors of coronary artery vasodilation, there are two factors: endothelium-dependent and -independent ones. In the present study, using quantitative coronary angiography and Doppler velocity measurements, the authors defined the percent changes in epicardial coronary diameter in response to ACh and NTG infusions as the endothelium-dependent and -independent functions of the coronary artery at the level of conduit vessels, and defined the percent change in coronary blood flow in response to ACh infusion and coronary flow reserve as the endothelium-dependent and -independent functions of the coronary artery at the level of resistance vessels.

Peer review
The results presented in this paper are good, with the references are properly Quoted and work is new. The paper is very well organized and the results presented in this paper are justified, and the paper may be accepted in the format in which it is submitted, with the references listed.

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Statistical data

Write as mean ± SD or mean ± SE.

Statistical expression

Express t test as t (in italics), F test as F (in italics), chi square test as χ^2 (in Greek), related coefficient as r (in italics), degree of freedom as υ (in Greek), sample number as n (in italics), and probability as P (in italics).

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Use SI units. For example: body mass, m (B) = 78 kg; blood pressure, p (B) = 16.2/12.3 kPa; incubation time, t (incubation) = 96 h, blood glucose concentration, c (glucose) 6.4 ± 2.1 mmol/L; blood CEA mass concentration, p (CEA) = 8.6 24.5 μg/L; CO_2 volume fraction, 50 mL/L CO_2, not 5% CO_2; likewise for 40 g/L formaldehyde, not 10% formalin; and mass fraction, 8 ng/g, *etc*. Arabic numerals such as 23, 243, 641 should be read 23 243 641.

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Italics

Quantities: t time or temperature, c concentration, A area, l length, m mass, V volume.
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Contents

Contents

ABOUT COVER

Casella M, Dello Russo A, Fassini G, Andreini D, De Iuliis P, Mushtaq S, Bartoletti S, Riva S, Tondo C. Manifold benefits of choosing a minimally fluoroscopic catheter ablation approach.

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Manifold benefits of choosing a minimally fluoroscopic catheter ablation approach

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Abstract

We report the case of a 14-year-old boy with ventricular preexcitation. A standard, fluoroscopy guided, ablation procedure was successfully performed in a posteromidseptal region with a total fluoroscopy time of about 45 min (2430 cGy.cm^2). A few hours after the procedure, preexcitation reappeared. A second ablation procedure was scheduled using the EnSite NavX™ mapping system. During mapping along the tricuspid groove, preexcitation suddenly disappeared due to mechanical "bumping" of the accessory pathway and it did not recover over the next 30 min. As per our routine practice, the phase of geometry reconstruction has been continuously recorded by the system; thus, an off-line analysis allowed to pinpoint the site of earliest activation and the site of mechanical bumping, where radiofrequency obtained the accessory pathway ablation. The second procedure was performed without using fluoroscopy at all. Thanks to the geometry reconstruction, the procedure was completely successful thus avoiding a further rehospitalization.

Casella M, Dello Russo A, Fassini G, Andreini D, De Iuliis P, Mushtaq S, Bartoletti S, Riva S, Tondo C. Manifold benefits of choosing a minimally fluoroscopic catheter ablation approach. *World J Cardiol* 2013; 5(2): 8-11 Available from: URL: http://www.wjgnet.com/1949-8462/full/v5/i2/8.htm DOI: http://dx.doi.org/10.4330/wjc.v5.i2.8

INTRODUCTION

In the last few years a growing number of papers and case-reports have been published showing the feasibility and safety of a minimally fluoroscopic approach in supraventricular tachycardias ablation[1].

CASE REPORT

We report the case of a 14-year-old boy with asymptomatic ventricular preexcitation noticed during a standard visit for competitive sports qualification (soccer). The patient underwent a transesophageal electrophysiological study, which revealed that the accessory pathway had a short refractory period (220 ms) and that preexcited atrial fibrillation could be easily induced by atrial stimulation.
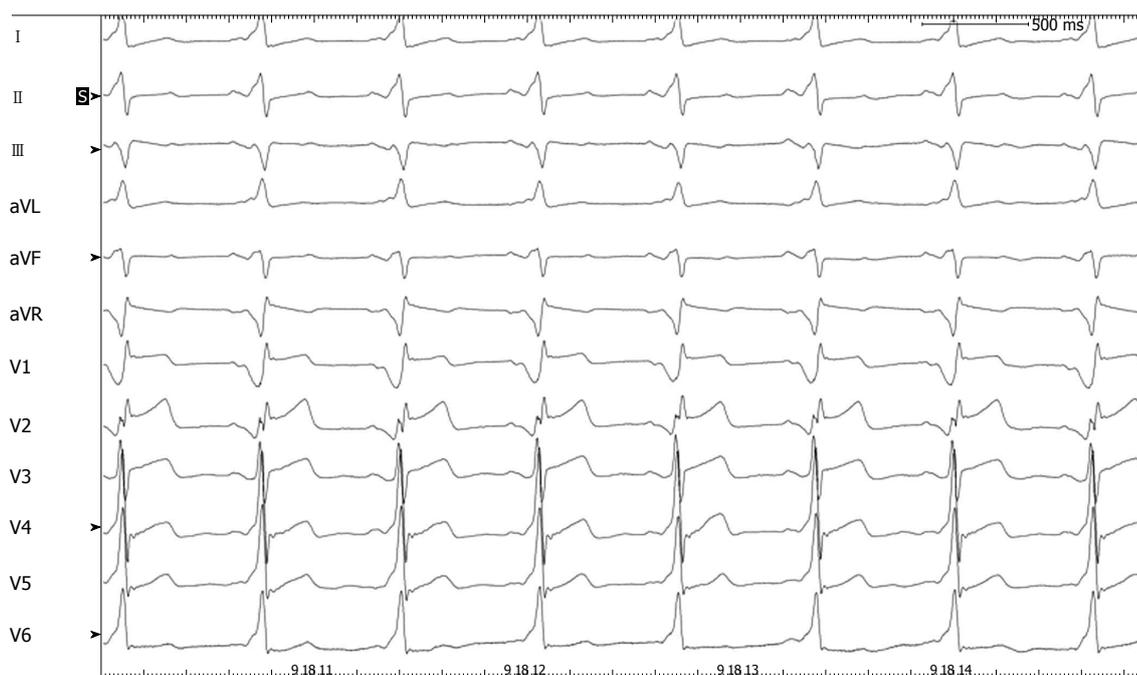
Figure 1 Basal 12-lead electrocardiograms showing constant ventricular preexcitation.

The patient was denied eligibility for competitive sports and was then referred to our institution to perform catheter ablation of the accessory pathway. With the parents' consent, the procedure was performed under general anesthesia with endotracheal intubation. Mapping along the tricuspid groove was performed with an irrigated-tip ablation catheter (Thermocool Biosense) showing fused atrioventricular potential near the roof of the coronary sinus ostium. Radiofrequency (RF) pulses delivered at that site were ineffective. Access to the left atrium was then obtained through both retrograde aortic and transseptal approach in order to map the mitral groove and three further RF pulses were delivered in the left postero-septal region, again without suppressing the preexcitation. Mapping along the tricuspid groove was performed again and a fused atrioventricular potential was observed preceding the surface delta wave by 30 ms in a location slightly higher than before, in a postero-midseptal region. A single RF pulse at this site obtained immediate disappearance of the preexcitation and elicited a junctional rhythm with 1:1 retrograde conduction; three consolidation pulses (15 W) were delivered at the same site (Figures 1 and 2). The procedure was concluded after a 30-min monitoring period followed by ventricular stimulation (which documented retrograde conduction only through the atrioventricular node) and adenosine injection (which documented transient complete atrioventricular block). The total fluoroscopy time amounted to 44 min and 53 s (2430, 41 cGy.cm^2), corresponding to 4 mSV, the same radiation dose of 40-50 chest X-rays[2]. Thus, this procedure carried, to our patient, a lifetime attributable risk of malignancy of about 5/10 000, as calculated using Table 12D-1 of the BEIR VII report[3].

A few hours after the procedure, preexcitation reappeared on electrocardiograms (ECG) with the same morphology. In view of the patient's strong motivation and after discussing the case with his parents, a second ablation procedure was scheduled for the next day, but in view of the large radiation exposure from the previous procedure, it was decided to use the EnSite NavX™ electroanatomical mapping system as a navigation tool[1]. Ablation was again performed under general anesthesia. The phase of geometry reconstruction was continuously recorded by the system, as per our routine practice. During mapping along the tricuspid groove, preexcitation suddenly disappeared due to mechanical "bumping" of the accessory pathway and it did not recover over the next 30 min. Thus, an off-line analysis of the electroanatomical mapping phase[4] was performed and the activation map obtained allowed to pinpoint the site of earliest activation and the site of mechanical bumping, where seven RF pulses (up to 30 W) were delivered (Figures 3 and 4). The procedure was concluded after a 40-min monitoring period followed by atrial and ventricular stimulation, isoprenaline infusion and adenosine injection, with no evidence of either preexcitation or atrioventricular reentrant tachycardia. The second procedure was performed without using fluoroscopy at all. The patient was discharged after 2 d, with a normal ECG. On a follow-up visit 3 mo later, he remained free of preexcitation.

DISCUSSION

This issue is of particular interest in pediatric and young patients, as in our case, because they are more vulnerable to the effects of radiation and have a longer life
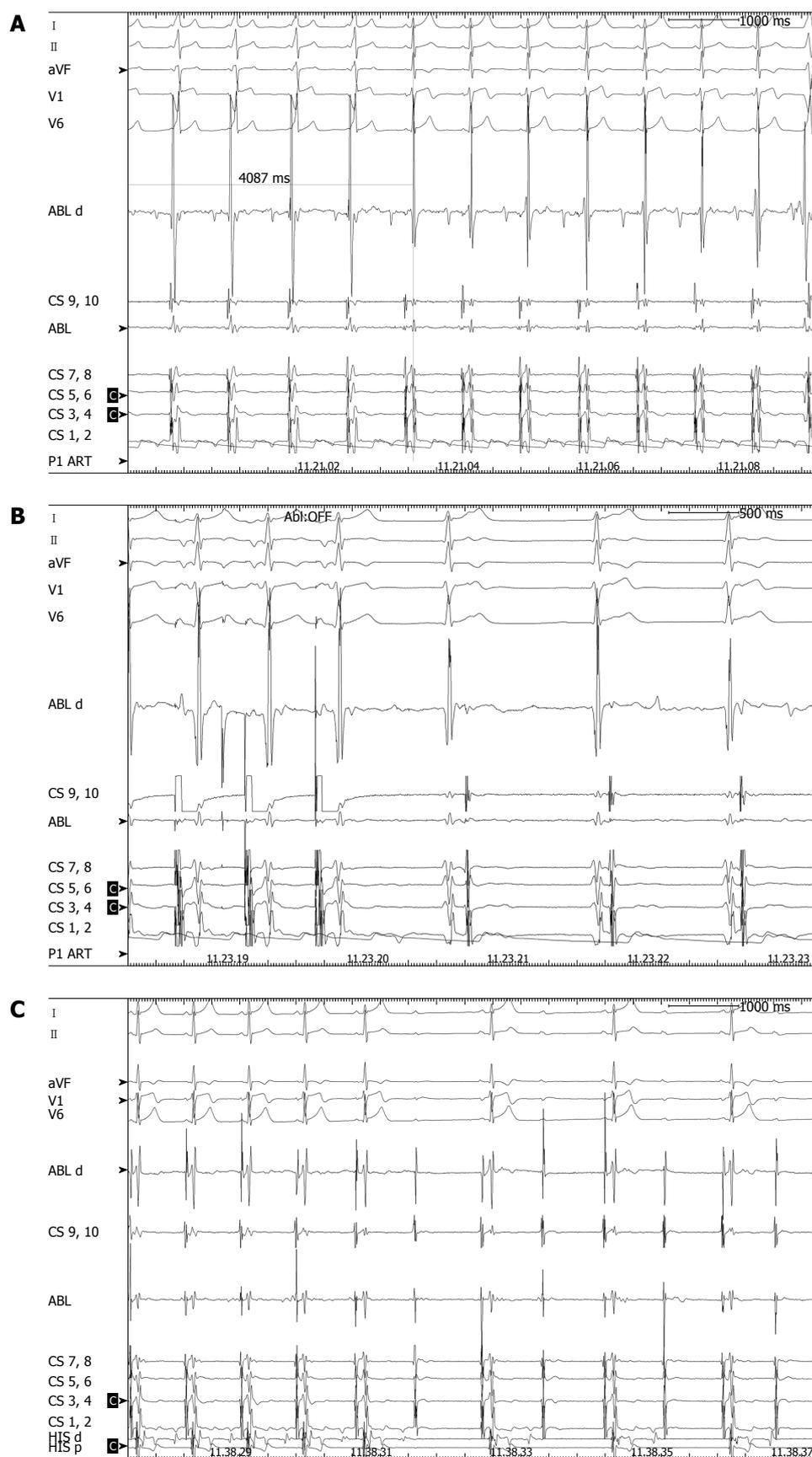
Figure 2 Three consolidation pulses were delivered at the same site. A: The effective radiofrequency (RF) pulse. Ventricular preexcitation disappeared 4 s after the pulse was started and, few beats later, a junctional rhythm with 1:1 retrograde conduction overtook sinus rhythm. Thus the RF pulse was prematurely stopped. As the phenomenon could be reliably reproduced, subsequent consolidation pulses were delivered during atrial pacing with the irrigated-tip ablation catheter up to a maximum of 15 W; B: A RF pulse delivered during atrial pacing with emergence of junctional rhythm as pacing was stopped; C: Transient complete atrioventricular block during adenosine injection at the end of the first ablation procedure.

Figure 3 Two different frames obtained from the off-line analysis of geometry reconstruction recording. A: The ablation catheter (visualized in green) is at the site of earliest ventricular activation; B: The ablation catheter is in a site slightly superior to that where mechanical "bumping" occurred.

Figure 4 Site of effective ablation. Ablation pulses (white circles) were delivered in the posterior and postero-midseptal region covering all the area where the earliest activation had been recorded and the mechanical bumping occurred. The yellow circle points out the area where the mapping catheter produced mechanical junctional beats; this area is marked as the likely site of compact atrioventricular node. Thus ablation was safely delivered up to 30 W with an irrigated tip catheter. SVC: Superior vena cava; CS: Coronary sinus.

effective during the subsequent follow-up. Thus the mapping system allowed successful ablation, despite the absence of any preexcitation to be mapped, and ensured safety from procedural complications (*i.e.*, atrioventricular node lesion) with no increase in life-term radiological risk.

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expectancy than adults. In our case, the first procedure was performed with conventional fluoroscopic guidance, according to the operator's discretion, as to date no guidelines or recommendations are available on this specific regard. The fluoroscopic procedure provided our patient with a non-negligible lifetime attributable risk of malignancy[3], while the second procedure was associated to no ionizing radiation exposure and, as a consequence, it carried no radiological risk.

As an additional peculiarity, in our case the mapping system was useful not only for non-fluoroscopic navigation but also for arrhythmia mapping. As usual in accessory pathway or complex arrhythmia ablations, we record on the system the complete phase of geometry reconstruction, a routine habit that has proved to be particularly helpful. After a lasting mechanical "bumping", in a conventional fluoroscopy-guided procedure, the study should be stopped without ablation. In our case instead, an off-line analysis of the geometry reconstruction phase allowed to obtain an activation map where the sites of bumping, earliest activation and atrioventricular node were pinpointed. The ablation guided by the off-line activation map proved

CASE REPORT

Congenital partial absence of the pericardium in a young man with atypical chest pain

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INTRODUCTION

We herein present the case of a young male with atypical chest pain and congenital partial absence of the pericardium. A brief discussion on this rare congenital defect with its clinical presentation, diagnostic workup and management is provided at the end of the case report.

CASE REPORT

A 22-year-old male with no medical background presented to the emergency department with sudden onset of sharp chest pain and dyspnea. There were no other associated symptoms and the physical examination and vital signs were all normal. Blood analysis, including hematology, biochemistry and viral serology, were unremarkable. The chest radiograph showed an apparent horizontalization of the left bronchus and images, suggestive of hilar adenopathies (Figure 1). The electrocardiogram (ECG) demonstrated sinus rhythm at 66 beats per minute with right bundle branch block. The patient was prescribed regular analgesics, with the chest pain subsiding shortly after, and was discharged and referred to the internal medicine outpatient clinic for a diagnosis work-up. In order to further evaluate the findings observed on the chest radiograph and to establish a define diagnosis and the correspondent therapeutic management, a computed tomography (CT) scan was carried out which revealed a

Abstract

Pericardial defects are infrequent congenital anomalies due to agenesis caused by premature atrophy of the common cardinal vein or Cuvier duct during the 5th or 6th week of embryonic life. These congenital defects are rare, typically observed as an incidental finding and usually remain asymptomatic. Nevertheless, the more widespread use of modern imaging techniques has contributed to an increase of its incidence in recent years. There is currently no consensus regarding therapeutic options, all of which are based on small retrospective studies that evaluate the risk of developing a life-threatening complication such as herniation and incarceration of the myocardium. We report on a 22-year-old male who presented with sudden onset of sharp chest pain and dyspnea. Computed tomography and cardiac magnetic resonance scan revealed a pericardial defect adjacent to the lateral free wall of the left atrium with associated herniation of the left atrial appendage. The patient was managed conservatively and had an uneventful clinical progress.

Figure 1 Chest radiograph. Chest radiograph showing horizontalization of the left bronchus (asterisk) initially interpreted as hilar adenopathies and later found to be secondary to herniation of the left atrial appendage through the pericardial defect.
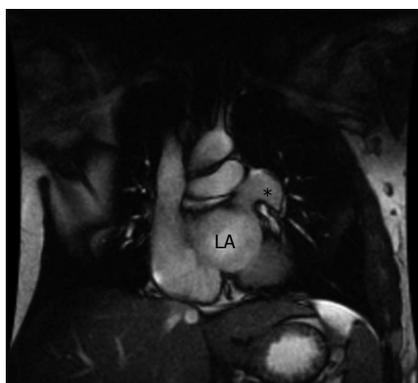
Figure 2 Cardiac magnetic resonance imaging. Cardiac magnetic resonance imaging (coronal view) displaying the partial pericardial defect (20 mm × 30 mm) localized to the left atrial (LA) wall. Herniation of the left atrial appendage can been seen (asterisk).

pericardial defect adjacent to the lateral free wall of the left atrium (20 mm × 30 mm) with associated herniation of the left atrial appendage. The same findings were confirmed by a cardiac magnetic resonance (CMR) scan (Figure 2). A transthoracic echocardiogram was also performed, with non-specific findings: mild dilatation of right atrium and ventricle, and mild tricuspid regurgitation, with the rest of the examination being normal. Given the uneventful clinical progress, a conservative approach was adopted and the patient was subsequently discharged. To date, 5 years later, he is in good health and remains asymptomatic.

DISCUSSION

The described pericardial defect is due to agenesis caused by premature atrophy of the common cardinal vein or Cuvier duct during the 5th and 6th week of embryonic life. This leads to reduced blood supply to the pericardial and pleural membranes, preventing their closure. When this defect is small, the result is usually a pleuropericardiac fistula. However, in the case of a larger defect the left lung

and the heart may coexist within the same pleural cavity. In most cases, the abnormality has been reported to involve the left lung. Congenital pericardial defects are rare: there are 400 cases reported in the literature so far. It is three times more common in males and, in 30% to 50% of the cases, associated congenital abnormalities (heart, lung, diaphragm and chest wall) have been reported[1,2].

In most instances, the pericardial defect is usually identified incidentally in an asymptomatic patient. Nevertheless, reported symptoms include stabbing chest pain and dyspnea, as in our patient. Complications depend on the extent of the pericardial defect. In general, complete absence of the entire pericardium or of the whole of the left or right side carries an excellent prognosis. A partial pericardial absence, on the other hand, has been reported to carry a higher risk due to potential herniation and strangulation of the atria, appendages or of parts of the ventricles. Furthermore, the herniating structures may compress the great vessels and coronary arteries, which may affect ventricular systolic function and lead to myocardial ischemia, respectively. The physical examination is usually non-specific but may reveal a significantly displaced apical impulse, basal ejection murmurs, apical midsystolic clicks and increased splitting of the second heart sound due to right bundle branch block[1-4].

The ECG in patients with pericardial defects may show typical findings, such as right axis deviation, incomplete or complete RBBB and poor R wave progression due to clockwise rotation in the horizontal plane. The chest X-ray may show characteristic features such as levoposition of the heart, resulting in the absence of the right heart border projecting on the right side of the vertebral column, flattening and elongation of the left ventricular contour (Snoopy sign)[1-4]. The echocardiography exam may be helpful for the initial evaluation of complete absence of the pericardium with features related to the abnormal cardiac position and movement: unusual echocardiography windows, cardiac hypermobility, "teardrop" appearance, paradoxical or flat systolic motion of the interventricular septum, severe tricuspid regurgitation and right ventricle dilatation. However, and as in our patient, the echocardiography exam of partial absence of the pericardium usually provides limited information[5].

Even although the previously discussed diagnostic tools are important in the diagnostic workup, the definite diagnosis of a pericardial defect is made by CMR and CT. Both techniques confirm the diagnosis, visualize the extent of the defect and assess associated complications that are essential for the management of the defect. The CMR is considered the gold standard since it better visualizes the pericardium compared to CT and is also capable of detecting focal myocardial infarctions[5].

There is currently no unanimity with regards to the therapeutic options, all being based on small retrospective series aimed at the evaluation of the risk of suffering life-threatening complications (herniation). A total pericardial left defect carries a small risk and in these patients no surgical treatment is usually necessary. The controversy

is related to small and moderate sized left pericardial defects where some advocate prophylactic surgery and others only treating symptomatic patients. The surgical techniques include left atrial appendectomy, division of adhesions, pericardiotomy, enlarging the defect to reduce the risk of incarceration and pericardioplasty which aims to restore the defect either by primary closure or complete reconstruction with synthetic materials. Some reports argue that diagnosis of moderate-sized pericardial defects in symptomatic or nonsymptomatic patients should be followed by prophylactic operation to reduce the risk of death from cardiac structure herniation and incarceration. Postpericardiotomy syndrome is a common reported complication following these surgical procedures[1-4].

In summary, we report a case of a left side partial pericardial defect, a rare cardiac anomaly. Given the uneventful clinical progress that our patient presented with, he was subsequently treated conservatively.

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Contents

Contents

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the current literature.

Abstract

With the publication of the Placement of Aortic Transcatheter Valves (PARTNER) trial, transcatheter aortic valve replacement (TAVR) has undoubtedly become the gold standard for severe aortic stenosis in patients that are not suitable candidate for surgical aortic valve replacement (AVR). The PARTNER trial also showed that TAVR is non-inferior to AVR in high-risk patients. A recent publication by Ben-Dor *et al* evaluated the outcome of high-risk patients with severe aortic stenosis who were referred to their institution for participation to the PARTNER trial. Only a minority of patients made it in the trial and the majority of patient ended being treated medically. Some patients were also treated with AVR outside the trial. The outcomes of all these patients were stratified by the treatment they received (AVR, TAVR or medical therapy with or without balloon aortic valvuloplasty). The 3 groups were different in their baseline characteristics. Ben-Dor *et al* found that patients treated medically had greater mortality than patients treated with TAVR or AVR. The survival of patients treated with TAVR was similar to those treated with AVR. Independent predictors of mortality were also found from their analysis. In this commentary, we discuss the finding of this study and compare it with

COMMENTARY ON HOT TOPICS

We have read with great interest the recent manuscript by Ben-Dor *et al*[1] evaluating the outcome of high-risk patients with severe aortic stenosis (AS) referred to their institution for a trial of transcatheter aortic valve replacement (TAVR) stratified by the treatment they received, and believe it is worth discussion. Symptomatic severe AS is a deadly and incapacitating disease when left untreated. For many decades, surgical aortic valve replacement (AVR) has been considered the treatment of choice because of its ability to improve survival and symptoms. It was however shown that approximately one third of patients with severe symptomatic AS do not beneficiate from AVR because of multiple of reasons[2]. Balloon aortic valvuloplasty (BAV), although less invasive than AVR is only palliative. More recently, TAVR has been shown to be superior to medical therapy (including BAV) in patients that are not candidate for AVR[3] and to be non-inferior to AVR in high-risk patients[4].

Ben-Dor *et al*[1] reviewed 900 patients who were referred for TAVR evaluation (PARTNER trial) between April 2007 and May 2011. These patients had severe AS defined by a mean gradient $\geq$ 40 mmHg or valvular area < 1 cm[2]. Only 13% (*n* = 19) of AVR and 4.9% (*n* = 29)

of medially treated patients were enrolled in the PART-NER trial. The PARTNER trial as been described in details[3,4] but in summary consisted of two parallel studies. The cohort A consisted of patients at high-risk for AVR (risk of 30-d mortality ≥ 15%) that were randomized to TAVR (from a trans-femoral or trans-apical approach) *vs* AVR. The cohort B included patients that were deemed non-operative based on an estimated risk of morality or major irreversible morbidity of ≥ 50%; which were randomized to TAVR *vs* medical therapy (including possible BAV). Ben-Dor *et al*[1] evaluated the outcomes of patients treated in their institution stratified by the treatment they received. Medical treatment was adopted in 66.1% of patients (*n* = 595), among whom 345 patients also had BAV, 17.6% (*n* = 159) had TAVR and 16.3% (*n* = 146) had AVR. Groups were significantly different in their baseline characteristics with younger and healthier patients undergoing AVR and sicker patients with lower ejection fraction and higher BNP value in the medical treatment group. The STS score was significantly different across groups with values of 8.5%, 11.8% and 12.1% for AVR, TAVR and medical treatment respectively (*P* < 0.001). The transcatheter heart valve (THV) used for TAVR was the Edwards SAPIEN THV (Edwards Life Sciences, Irvine, CA, United States). A trans-femoral (TF) approach was used in 69.1% (*n* = 110) of cases and a trans-apical (TA) approach in 30.9% (*n* = 49).

In their study, Ben-Dor *et al* found a 1-year mortality of 21.2%, 21.3% and 36.4% for patients treated with TAVR, AVR and medical therapy respectively (*P* < 0.001). In the medical therapy group, patient who had a BAV performed had higher mortality (55% *vs* 34%, *P* < 0.01). Thirty-day mortality was 11.7%, 12.8% and 10.1% for TAVR, AVR and medical therapy respectively. The STS score predicted 30-d mortality was 11.8%, 8.4% and 12.3% while the logistic Euroscore predicted 41.2%, 25.6% and 43.1% for TAVR, AVR and medical therapy respectively. Patients with STS score ≥ 15 had a significantly greater mortality (59.2%) compared with those with STS score < 15 (35.2%). In the entire cohort, atrial fibrillation and renal failure were found to be independent predictor of mortality. When stratified by the treatment received, independent predictor of mortality were STS score and renal failure for patients undergoing TAVR, renal failure and NYHA class IV for patients undergoing AVR and renal failure, pulmonary artery pressure and aortic systolic pressure for patient treated medically.

This is a retrospective, non-randomized single center study evaluating outcomes of patients referred for TAVR, stratified by the treatment received. Multiple limitations from the trial should be discussed. Because of the absence of randomization, the 3 groups compared in this study represent very different populations. The medical therapy group consisted mainly of patients that were not randomized in the PARTNER trial, most likely representing patients that are just too sick to beneficiate from TAVR (often referred has the cohort C patients). In fact, 30-d mortality was higher (10.1%) in these pa-

tients compared to the medically treated patients from the PARTNER trial (2.8%). What is surprising is that the 1-year mortality of medically treated patients in this study is lower (36.4%) then the 49.7% observed in PARTNER. These findings are hard to explain and should raise questions about the clinical follow-up of this study, which is not detailed in the manuscript. An alternative is that some patients received medical therapy because they had asymptomatic aortic stenosis, hence no indication for valve replacement. TAVR and AVR patients were also different. Non-operable patients received TAVR and lower risk patients that would not qualify for the PARTNER trial based on their risk were included in the AVR group. Despite these differences, the 1-year mortality was similar between both groups. Interestingly, the STS predicted 30-d mortality for AVR was lower than what was observed, a finding that is in contradiction with the observations from the PARTNER trial. TAVR patients, despite all being part of the PARTNER trial had a 30-d mortality (11.7%) that was worse than in the trial (5.0% for non operative and 3.4% for high-risk patients). Given the absence of randomization between the AVR and TAVR groups in this study, it would be unadvisable to conclude to the equivalence of these two approach solely based on this study. In a recent meta-analysis of 16 TAVR studies using VARC criteria and regrouping 3519 patients[5], the 1-year mortality was 22.1%, similar to what observed by Ben-Dor *et al*[1]. Significant outcomes such as vascular complications, stroke, acute kidney injury are absent from this present trial and could put some light on the early mortality.

Medically treated patients are driving the results of their multivariable analysis. Also, their multivariable analysis for TAVR and AVR patients are over fitted in relation to the number of events. Renal failure was found to be a predictor of mortality for all patients and is consistent with the current literature[6,7]. They however did not define was they considered as renal failure and did not report on acute kidney injury which has been described as an independent predictor of mortality after TAVR and AVR[8]. The proportion of patient on dialysis was also not reported in this study. The PARTNER trial excluded patients on chronic dialysis and patients with a serum creatinine ≥ 3 mg/dL. It would have been interesting to know the proportion of these patients represented in the AVR and in the medically treated groups. No data on frailty was presented in this study. Frailty is known to be an independent predictor of mortality after open-heart surgeries[9], is often a cause of non-operability and has now been characterize in the VARC-2 consensus document[10]. Frailty could be an unmeasured confounder that could alter the results of this multivariable analysis.

In conclusion, this single center, non-randomized study is globally consistent with the PARTNER trial[3,4] and larger multicenter registries[11-13]. TAVR is already recognized as the gold standard therapy for non-operative patients that cannot beneficiate from aortic valve replacement. The biggest challenge remaining will be to identify

patients that are dying with severe AS and not from AS and that would not improve after TAVR. New trials (PARTNER 2, SURTAVI)[14] are already randomizing moderate-risk patients to AVR *vs* TAVR, searching for potential benefits of TAVR in these patients.

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FIELD OF VISION

Pulmonary endarterectomy in chronic thromboembolic pulmonary hypertension: How can patients be better selected?

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Abstract

Chronic thromboembolic pulmonary hypertension (CTEPH) comprises organizing thrombotic obstructions in the pulmonary arteries by nonresolving thromboemboli, formation of fibrosis and remodeling of pulmonary blood vessels. Surgical pulmonary endarterectomy (PEA) is the therapy of choice for patients with surgically accessible CTEPH, which leads to a profound improvement in hemodynamics, functional class and survival. Selecting the candidates that will benefit from surgery is still a challenging task. Criteria for surgical suitability have been described but the decision-making for or against surgical intervention remains still subjective. The optimal characterization of the reciprocal contribution of large vessel and small vessel disease in the elevation of pulmonary vascular resistance is crucial for the indication and outcome of PEA. Recently, Toshner *et al* intended to validate the partition resistance into small and large vessels compartments (upstream resistance: Rup) by the occlusion technique in the preoperative assessment of PEA. We discuss the advantages and disadvantages of Rup and compare it with other hemodynamic predictor to evaluate operative risk in CTEPH patients.

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COMMENTARY ON HOT ARTICLES

We read with great interest the recent article by Toshner *et al*[1] describing the analysis of pressure decay curve after pulmonary arterial occlusion (between the moment of occlusion and the pulmonary artery occluded pressure, PAOP) to test if the occlusion technique distinguished small from large vessel disease in chronic thromboembolic pulmonary hypertension (CTEPH).

Pulmonary endarterectomy (PEA) of major, lobar, and segmental pulmonary arteries branches is the mainstay of therapy for patients with CTEPH. The best surgical results are achieved with complete endarterectomy and early postoperative reduction of pulmonary vascular resistance (PVR) to < 500 dyn.s.cm^{-5}[2,3]. The cause of residual pulmonary hypertension in most cases is from concomitant small vessel disease, with three possible scenarios: (1) predominant obstructions of small subsegmental elastic pulmonary arteries; (2) classic pulmonary

arteriopathy of small muscular arteries and arterioles distal to non-obstructed elastic pulmonary artery; and (3) pulmonary arteriopathy of small muscular arteries and arterioles distal to partially or totally obstructed elastic pulmonary artery[4,5].

The optimal characterization of the contribution of large vessel and small vessel disease to the elevation of afterload and its influence on the hemodynamic severity is crucial for the preoperative assessment and outcome of PEA[6-8].

An approach for the identification of distal vasculopathy in CTEPH is the analysis of pressure decay curve after pulmonary arterial occlusion (between the moment of occlusion and the pulmonary artery occluded pressure, PAOP)[9]. Such curves are made of a first fast component, which corresponds to the reduction of flow through arterial resistance, and a slower component, which corresponds to the emptying of compliant capillaries through a venous resistance. This biexponential fitting of the pressure decay curve allows identification of an inflection point (Poccl), from which one calculates an upstream resistance (Rup), essentially determined by the resistive properties of the large pulmonary arteries, and a downstream resistance determined by the cumulated resistance of small arterioles, capillaries and veinules. Rup is calculated as follows: Rup (%) = 100 × (mPAP-Poccl)/(mPAP-PAOP). In patients with small-vessel arteriopathy the Poccl pressure was higher (a longer time was required for the pressure to reach PAOP), and therefore the Rup was lower. Patients with CTEPH and Rup value < 60% appear to be at highest risk[9].

To test the hypothesis that the occlusion technique is able to discriminate large vessel organized thrombus from distal vasculopathy. Toshner *et al*[1] performed occlusion pressures on patients with operable CTEPH, distal inoperable CTEPH and post-PEA residual CTEPH. They also undertook measurements in patients with idiopathic or connective tissue associated pulmonary arterial hypertension (PAH), as additional controls, where more diffuse vasculopathy is traditionally accepted. They employed both, the standard flow-directed measurement and the wire-directed approach. The latter involved a wire being passed into an alternative segmental artery and subsequently being floated into a distal artery. The authors found that Rup as measured by the occlusion technique is increased in operable predominantly proximal CTEPH when compared with inoperable CTEPH and idiopathic PAH. However, they obtained a higher Rup cutoff value compared to Kim *et al*[9]: 79% (sensitivity 100%, specificity 57%) *vs* 60% (sensitivity and specificity 100%) and they did not explain the differences of the Rups values, including the values of the two operate patients who died (68% and 73%). They recognized that the occlusion technique would not interrogate the correct range of vessel caliber and would mislabel a significant portion of resistance in these small vessels as upstream. This can be supported by the fact that the idiopathic PAH and inoperable CTEPH cohorts had a much higher Rup than would be expected

if resistance had been accurately partitioned into clinically relevant small and large vessels[1]. Finally, they proposed the multiple wire-directed measurements in conjunction with the flow-directed one, in order to provide additional information on disease heterogeneity in CTEPH, although they recognize their data does not support the clinical use of this technique in routine assessment.

Beyond the embolic or thrombotic hypothesis of pathogenesis of CTEPH, once vessel obliteration is sufficient to cause increase of pulmonary arterial pressure, a process of pulmonary vascular remodeling like idiopathic PAH lesions is started which self-perpetuates the progression of pulmonary hypertension[10,11]. The presence of large-vessel remodeling process of thrombus organization and small vessel disease might create a wide spectrum of dynamic (steady and pulsatile) afterload in CTEPH patients[12,13]. We proposed the study of Zup, a novel hemodynamic index. Zup is calculated by (mPAP-dPAP) × 100/(mPAP-PAOP), where mPAP and dPAP are mean and diastolic pulmonary arterial pressure, respectively[14]. mPAP is the time-averaged PAP throughout cardiac cycle length and it is accurately described by cardiac output, total PVR and right atrial pressure. Previous studies have established a link between the steady and pulsatile component of PA pressure by estimating mPAP from systolic PAP (sPAP) and dPAP ('two-pressure model')[15-17]. The geometric mean of sPAP and dPAP was the most precise estimate of mPAP (mPAP2 = sPAP × dPAP). sPAP and dPAP mainly depend on total PVR and pulmonary artery stiffness and wave reflection. Increasing total PVR results in both sPAP and dPAP increase while increasing pulmonary artery stiffness and wave reflection generate a wider pPAP without significant mPAP change[14,18,19]. A more proximal occlusive site by the fibrotic organized thromboembolic material incorporated into the native vascular intima causes a higher pulmonary artery stiffness. Stiffening of proximal pulmonary arteries could increase characteristic impedance and wave reflection (higher upstream afterload), increasing total PVR but with a lower dPAP, a faster pressure decay profile and Zup increase. Therefore, the balance between mPAP and dPAP provides a rapid tool to describe the functional afterload status of a CTEPH patient, since their absolute contributions on Zup value are higher than PAOP[14].

Unlike the partition method described by Kim *et al*[9] and used by Toshner *et al*[1], Zup index can be obtained directly from hemodynamic data without assumptions or fitting, and is affected by the extent and localization of anatomic obstruction, vascular remodeling and microvascular disease, setting a wide spectrum of dynamic afterload (steady and pulsatile components)[14]. According to the univariate analysis, we showed that low Zup value (cut-off point < 47%) predicted mortality after PEA with a sensitivity of 100% and a specificity of 78%. The latter increased to 86% when we analyzed the subgroup of 23 patients with higher preoperative PVR (> 9 wood units, median of the cohort), by contrast PVR lost its capacity to predict mortality in this group[14]. In contrast
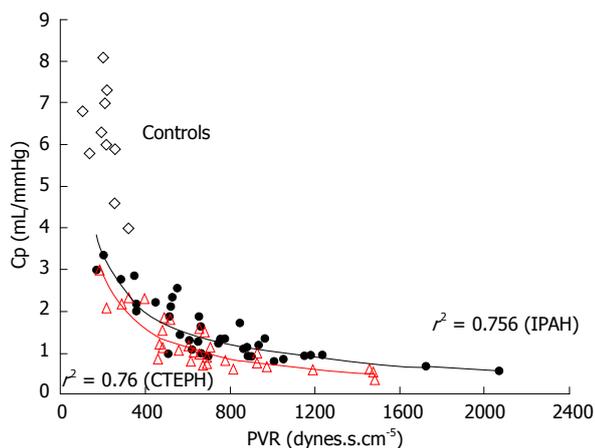
Figure 1 Inverse proportional relation between pulmonary vascular resistance and arterial compliance for operable chronic thromboembolic pulmonary hypertension and Idiopathic pulmonary arterial hypertension patients (Hollow diamonds represent ten normal subjects without pulmonary hypertension). CTEPH: Chronic thromboembolic pulmonary hypertension; IPAH: Idiopathic pulmonary arterial hypertension; PVR: Pulmonary vascular resistance.
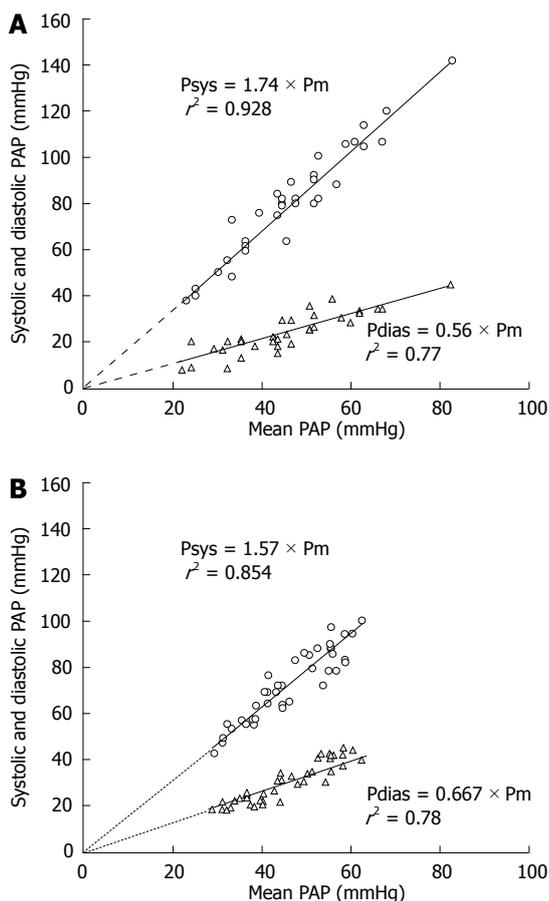
Figure 2 Interrelationship of pulmonary arterial pressures for operable chronic thromboembolic pulmonary hypertension and idiopathic pulmonary arterial hypertension patients with similar pulmonary vascular resistance. A: Chronic thromboembolic pulmonary hypertension; B: Idiopathic pulmonary arterial hypertension.

with Toshner *et al*[1], the Zup value in idiopathic PAH patients was significantly lower than in operable CTEPH

patients (43% ± 15% *vs* 57% ± 15%)[20]. Preoperative operable CTEPH is characterized by a more predominant wave reflection, explaining the lower pulmonary vascular capacitance with a downward and leftward displacement of the PVR-Capacitance curve of the CTEPH patients and a disproportionate increase in sPAP and decrease of dPAP with respect to idiopathic PAH cohort (Figures 1 and 2)[20-22].

CTEPH has been recognized as a "dual" pulmonary vascular disorder consisting in a major vessel vascular remodeling process of thrombus organization combined with a small vessel vascular disease[23,24]. PEA is the therapy of choice for patients with surgically accessible CTEPH[25]. The optimal characterization of the reciprocal contribution of large vessel and small vessel disease in the elevation of PVR is crucial for the indication and outcome of PEA[26]. This determination requires the development of diagnostic techniques capable of more objectively partitioning the central surgically correctable component of the PVR from the peripheral component[26]. Although pulmonary arterial occlusion waveform analysis has emerged as a possible way of quantifying the degree of small-vessel disease, it only evaluates the steady component of the afterload and it is possible that this technique inaccurately partitioned resistance into clinically relevant small and large vessels. We proposed a novel hemodynamic index that considers both steady (PVR) and pulsatile (Capacitance) components of the right ventricular afterload simultaneously and could therefore be a complementary tool to improve the risk assessment for PEA in patients with CTEPH.

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Treating blood pressure to prevent strokes: The age factor

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Abstract

The importance of systolic blood pressure (SBP), diastolic blood pressure (DBP), and pulse pressure (PP), on the incidence of coronary heart disease (CHD) and stroke are known. However, the importance of blood pressure (BP)-age shifts regarding the stroke incidence is not clearly known. The BP changes with the advancement of age from the predominance of DBP in the young to the predominance of SBP in the old. This change is due to the stiffening of the large arteries as a result of the aging process and the replacement of the elastic fibers with collagen fibers. This change results in the loss of compliance and the elastic recoil of these vessels leading to increase in pulse wave velocity, central SBP and widening of pulse pressure leading to an increased incidence of CHD and strokes. It has been demonstrated epidemiologically that the SBP rises linearly with age, whereas the DBP rises up to the age of 45-50 years, and then begins to decline after the age of 60 years leading to a progressive widening of PP. Several studies have shown an inverse relationship between DBP and CHD, whereas no such relationship has been demonstrated for stroke. However, a recent study showed an inverse relationship with DBP and stroke when it dropped below 71 mmHg in subjects 50 years of age or older. In contrast, there was a positive association between BP and stroke when both SBP and DBP were ≥ 71 mmHg. These findings suggest that in treating systolic hypertension in the elderly to reduce stroke risk, attention should be paid on the potential harm of low DBP and the widening of PP regarding CHD and stroke. The implications of BP shifts with age and the potential risks of low DBP regarding the risk of stroke will be discussed in this concise review.

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INTRODUCTION

The treatment of hypertension has become quite complicated lately. In the old days the physician had to measure the blood pressure (BP) in the office using a mercury sphygmomanometer, and if the BP was ≥ 140/90 mmHg, he initiated treatment. Today, the office BP is disputed as being representative of the person's actual BP, since new BP entities have been discovered, such as white coat hypertension (WCH), and masked hypertension (MH) by using ambulatory BP monitors (ABPM). These two entities have opposite meanings where WCH is the condition with elevated BP in the doctor's office or clinic and normal BP outside the doctor's office measured with either ABPM or a home BP monitor[1]. In contrast, MH is the condition with normal BP at the doctor's office and elevated BP outside the doctor's office measured by the same means[2]. Also, the use of the mercury sphygmomanometer, a gold standard for the diagnosis and treatment of hypertension has been deemphasized lately and soon will be extinct due to environmental reasons and the development of new instruments such as ABPMs and semi-automatic aneroid sphygmomanometers for home BP
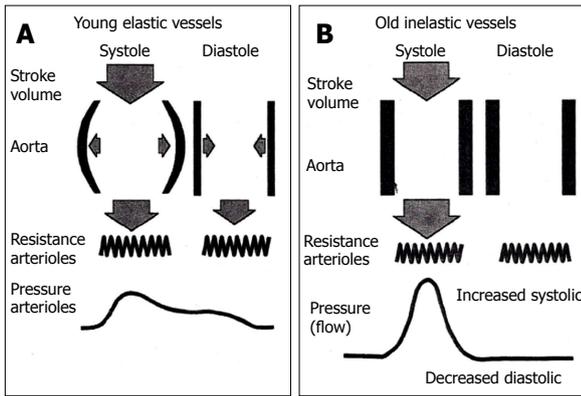
Figure 1 In a young person the elastic aorta expands during systole and absorbs part of the stroke volume. A: This figure depicts the function of the central aorta of a younger person during systole and diastole. During systole, the elastic aorta with each cardiac stroke volume (top filled arrow) is dilated and functions as a reservoir. As a result, not all stroke volume (SV) is transmitted distally. During diastole the elastic recoil of the aorta expels the remnant original SV to distal arteries and arterioles. This function results in a smooth contour of the arterial pulse wave and a narrow pulse pressure (PP) (bottom); B: In an older person, the aorta has lost most of its elasticity resulting in a reduction of its reservoir or capacitance function, resulting in the expulsion of almost the entire SV to the distal arteries with practically no diastolic blood flow (top filled arrow. This results in a distortion of the arterial pulse wave (bottom), an increase in systolic blood pressure, a decrease in diastolic blood pressure, and a widening of PP. Adapted with permission from Franklin et al[12].

monitoring. In addition, the emphasis on treating hypertension has now been shifted to systolic BP (SBP), since SBP is the most prevalent BP in older age[3], and some authors have gone into the extreme, stating that "systolic blood pressure is all that matters"[4]. This is a significant change from the early years where the focus was on treating the diastolic BP (DBP), because SBP was considered a normal development of the aging process. Even the reports of the Joint National Committees on the detection, evaluation, and treatment of high blood pressure did not emphasize the treatment of SBP till their 5th report in 1993[5]. Recently it has been suggested that in treating hypertension, the age of the subject should be considered since DBP is the predominant BP of the young and SBP is the predominant BP of the older person. The DBP rises from childhood till the age of 50 years and then begins to decline after the age of 60 years, whereas SBP rises continuously from adulthood to the old age. The significance of BP change with age was first pointed out by the Framingham Heart Study[6]. Previous studies used the BP in correlation with various age subgroups to determine its association with the risk of cardiovascular disease[7-9]. It has been suggested, that if age was used as a continuous variable, this could have offered a clearer picture at which age the relative importance of SBP begins to exceed DBP with respect to stroke incidence. This concept was tested in a recent study[10].

PATHOPHYSIOLOGY OF ARTERIOSCLEROSIS AND SYSTOLIC HYPERTENSION

The large arteries in young persons possess two func-

tions, one to act as conduits transferring the blood to vital organs and tissues, and the other to act as cushions to smooth out the pulsatile blood flow produced by the intermittent contractions of the heart into a continuous and steady blood flow[11]. However, as the person ages these functions of the large arteries are modified by arteriosclerosis, which is a consequence of the aging of blood vessels. The primary cause of arteriosclerosis is the fragmentations of the elastic lamellae which become thinned, frayed, and are replaced with collagen tissue. The fracturing of the elastic fibers is the result of the fatiguing effect produced by the cycling stress of the pulsatile blood flow. In a young person the elastic aorta expands during systole and absorbs part of the stroke volume[12]. During diastole it recoils back and sends the retained blood volume distally, thus converting the intermittent blood flow into a continuous steady flow (Figure 1A). In an elderly person, the elasticity and compliance of the aorta is lost[12] and most of the stroke volume is transmitted distally during systole with practically no blood flow during diastole (Figure 1B). The direct result of this function is an increase in SBP, a decrease in DBP, and a widening of pulse pressure (PP). This process is accelerated in the presence of hypertension. These latter changes in the older person lead to acceleration of the pulse wave velocity, which is the main diagnostic characteristic of arteriosclerosis. In addition, the morphology of the pulse wave changes (Figure 2). The pressure wave is a composite of the incident (forward) wave generated by the contraction of the heart and the reflected (backward) wave generated by the small muscular arteries and arterioles. In young persons the reflected wave travels slower and reaches the central aorta in early diastole leading to augmentation of the DBP, which is useful for the perfusion of coronary arteries. In older persons the reflected wave travels a lot faster and reaches the central aorta at the end of systole thus augmenting the central aortic SBP, which increases the pressure load on the left ventricle and leads to the development of left ventricular hypertrophy. In addition, the increased central SBP is associated with a higher incidence of cardiovascular disease (CVD) and stroke complications[13].

TREATMENT OF SBP: THE AGE FACTOR

The brain is protected against stroke through wide fluctuations of BP by the autoregulation of cerebral circulation. Cerebral autoregulation (CA) is the intrinsic capacity of the cerebral vessels to maintain constant cerebral blood flow (CBF) for the metabolic needs of the brain[14]. The CBF is also regulated, besides BP, by the arterial CO_2 level of the brain as well. The CA consists of two components, the static and the dynamic component. The static CA regulates CBF during gradual and progressive increases in BP[15], whereas the dynamic CA regulates the CBF during rapid changes in BP[16]. It has been demonstrated that the CBF remains constant through wide changes in mean arterial pressure (MAP) ranging from 60 to 150 mmHg (Figure 3) or from 40 to 125 mmHg from
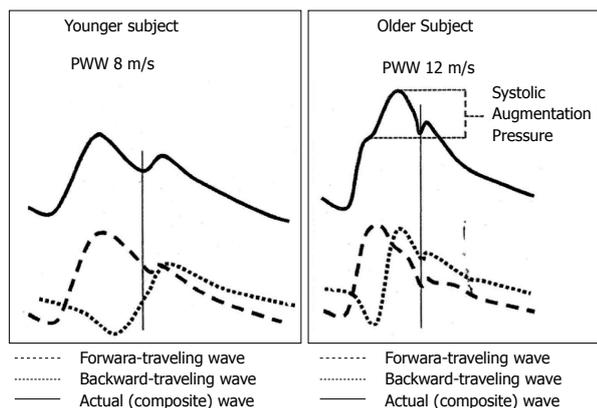
Figure 2 This figure depicts the configuration of the arterial waveforms in the younger person (left) and the older person (right). The arterial waveforms are composite waves (top heavy line), composed of a forward traveling wave (dashed line) and a backward traveling reflective wave (dotted line). The vertical line represents the closure of the aortic valve. The top solid line indicates the peak systolic blood pressure (SBP) in the younger person (left) and the older person (right) together with the augmentation pressure. The reflected wave in the younger person (left), returns to the aortic root early in diastole augmenting the diastolic blood pressure and improving the coronary circulation. In the older person (right), the reflected wave returns to the aortic root late in systole, thus augmenting the SBP and increasing the left ventricular outflow pressure leading to left ventricular hypertrophy. Due to the arterial stiffness in the older person, the pulse wave velocity is increased (12 m/s) compared to the younger person (8 m/s). Adapted with permission from Franklin et al[12].
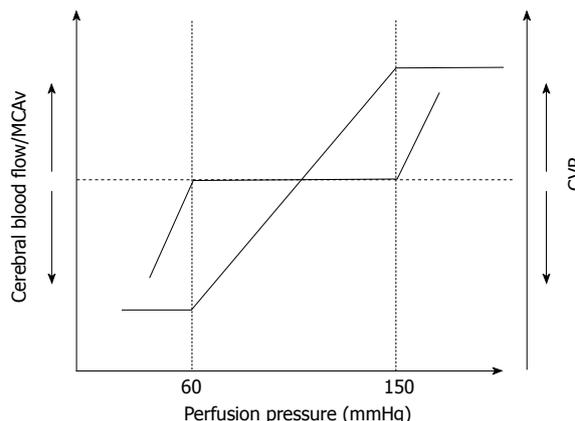
Figure 3 This figure depicts the cerebral blood flow autoregulation and the range of perfusion pressure. An autoregulatory plateau is seen between 60 to 150 mmHg of mean arterial pressure (MAP). This autoregulatory plateau is maintained through changes in cerebral vascular resistance (CVR). Once the limits of autoregulation are reached, CVR cannot correct for further changes in pressure as demonstrated by the MAP limits of < 60 mmHg (lower limit) and > 150 mmHg (upper limit). Adapted with permission from Lucas et al[14].

a recent study using transcranial Doppler[14]. These studies show that the CBF is not seriously affected even with very low DBP, and this could, perhaps, explain the lack of a J curve effect for stroke incidence with low DBP in contrast to the heart which is susceptible to a J curve effect with low DBP[17]. However, a recent study showed that there might be a J curve effect with DBP < 71 mmHg in older persons[10]. This study demonstrated the impact of age on the importance of SBP and DBP for stroke risk. In this study, 68 551 subjects 19 years to 78 years old from several European countries free of CVD and not taking antihypertensive drugs at entry of study, were followed for 13.2 years. The subjects were divided in 4 age groups, 19-39 years, 40-49 years, 50-59 years, and 60-78 years. When the SBP and DBP were considered separately, both pressures ≥ 71 mmHg were significantly associated with a higher stroke risk across the 4 age groups ($P < 0.0001$). In contrast, when the SBP and DBP were considered together, the SBP became no significant in the 19-39 year olds, and the DBP became no significant for stroke risk in the 50-59 and 60-78 year olds. However, for DBP < 71 mmHg there was an inverse relationship between DBP and stroke incidence, which became significant in the 60-78 year olds. Regarding the association of MAP and stroke risk, this was strongest in the younger ages, since MAP represents mostly the DBP, and it declined with advancing age, becoming no significant after the age of 69 years for men and the age of 73 years for women. In addition, there was a significant association between PP and stroke risk, which was independent of age and remained significant after mul-

tivariate adjustments. In this study the BP was measured at the doctor's office and might have missed subjects with WCH, or MH. However, the significance of WCH as a cardiovascular risk is debatable, because the pressure load on the heart is minimal, since WCH is elevated only during the visit at the doctor's office, and medical treatment is not associated with further lowering BP and may lead to hypotension[1]. On the contrary, MH is associated with increased cardiovascular complications, since the pressure load on the heart is prolonged. Its discovery is difficult, since the hypertension is diagnosed by office BP measurement and the BP in MH is normal at the doctor's office. Therefore, its discovery is difficult and is, usually, identified by home BP measurements or by ABPM. Treatment of MH is absolutely necessary[2].

DISCUSSION

New evidence suggests that there is an age factor on the importance of SBP and DBP regarding the incidence of fatal and nonfatal strokes[10]. In this study, participants with SBP and DBP ≥ 71 mmHg, had a higher risk for stroke until the age of 62 years, after which, only the SBP remained significant. In addition to age, there was also a sex effect between the MAP and stroke risk up to the age of 69 years for men and 73 years for women. Similar findings in shifts of BP with age have been reported from the Framingham study for coronary heart disease (CHD), but not stroke[18]. In the study by Vishram et al[10], in persons < 50 years of age, the DBP was the strongest predictor for stroke risk, whereas in persons ≥ 60 years of age the SBP was the strongest predictor. In persons 50-59 years of age, both pressures were equally important. Another significant finding of this study was the J curve effect of DBP with stroke risk for participants with a DBP < 71 mmHg. In this group there was an increase in stroke risk and this became significant after the age

of 60 years. Such an association is not commonly seen with strokes in contrast to CHD[17,19-23], although it has been reported by some investigators[24]. This is important when treating elevated SBP in the elderly. Kannel et al[25] showed that the incidence of cardiovascular events increased with a decrease in DBP < 80 mmHg, when the SBP remained ≥ 140 mmHg. Similarly Fagard et al[24] suggest that the antihypertensive treatment in subjects with systolic hypertension should be stopped when the DBP reaches the level of 55 mmHg to prevent further widening of PP and the higher risk for cardiovascular complications. In the study by Kannel et al[25], the 10-year risk ratio of cardiovascular events for men and women was 1.22 (95%CI: 0.97-1.50) with PP 46-55 mmHg, and 1.66 (95%CI: 1.32-2.07) with PP 55.5-136 mmHg. The significance of PP as a stroke risk in elderly subjects has been demonstrated besides Vishram et al[10], by other investigators as well[7,18,26-28]. The higher cardiovascular risk with wide PP has been attributed to the increased pulsatile burden on the heart and blood vessels produced by the wide PP[27]. In this report from the Framingham study, the age and sex of 4993 participants were tracked for 28 years and demonstrated that the SBP and PP became higher with older age, and were higher in older women compared to men of similar age[27]. In a large meta-analysis of older subjects with systolic hypertension it was shown that the PP was more important in inducing cardiovascular complications than the MAP[28]. Given that both PP and chronological age are positively associated with cardiovascular risk and strokes, PP may be regarded as an index of arterial aging. This could suggest that the biology of aging differs between men and women, and has been suggested that the chronological age as determined by calendar time, is distinct from the biologic age, which is a progressive and irreversible process of deterioration of the vitality of organ systems[26]. In addition, an inverse association was found between PP and telomere length suggesting that the biologic age of persons with wide PP is more advanced than their chronological age would indicate[26]. With respect to age-BP interrelationship regarding the risk of stroke, it appears that both SBP and DBP are important up to the age of 50 years after which, the significance of SBP supersedes that of DBP. In addition, in treating the SBP in older persons attention should be paid to the level of DBP not to be lower than 71 mmHg, although this finding was observed in a small number of subjects. Based on other studies, the risk of cardiovascular events increased when the DBP dropped to 55 mmHg[24], or to 80 mmHg, if the SBP was ≥ 140 mmHg[25]. The current National and International guidelines recommend reducing BP to < 130/80 mmHg in high risk subjects regardless of age[29,30]. However, some investigators suggest that the SBP and DBP not to be lower than 130-139 mmHg and 80-90 mmHg, respectively[31], whereas others propose to test the safety of SBP in the range of 130-150 mmHg[21]. Regarding drug selection for the treatment of hypertension in the elderly, drugs that block the rennin-angiotensin-aldosterone sys-

tem (RAAS) and calcium channel blockers (CCB) either alone or in combination are preferable as first line treatment, since these drugs have been shown to be more effective in lowering the central SBP and PP than b-blockers (atenolol) and thiazide diuretics[32]. Also, a recent Japanese study showed that the combination of RAAS blockers with CCBs was more effective in reducing the BP and cardiovascular complications than high dose RAAS blockers in high risk elderly hypertensive patients with or without renal disease[33]. Older b-blockers like atenolol are not as effective in lowering central aortic SBP and preventing strokes[34]. However, it would be useful, if the BP besides the doctor's office, is also measured by ABPM to diagnose the presence of WCH, where antihypertensive treatment is, usually, not necessary[1], and especially to diagnose MH, where treatment is necessary, since MH is associated with increased cardiovascular complications and death[2].

In summary, this concise review has demonstrated that the SBP increases linearly with the advancement of age and becomes the dominant factor for stoke risk after the age of 60 years. In contrast, the DBP is more dominant in younger persons and its rise with age levels off at the age of 50 years and begins to decline after the age of 60 years. In addition, new evidence suggests a J-curve effect for stroke risk with DBP < 71 mmHg or lower and the importance of wide PP as a risk factor for cardiovascular events. Finally, in treating the SBP in the elderly, drugs that block the RAAS in combination with CCBs is the best regimen in lowering the SBP. Hwever, care should be taken not to lower the DBP below 55 mmHg, because the risk for stroke and cardiovascular complications increases significantly.

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ORIGINAL ARTICLE

Cardiogenic differentiation of mesenchymal stem cells on elastomeric poly (glycerol sebacate)/collagen core/shell fibers

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Abstract

AIM: To facilitate engineering of suitable biomaterials to meet the challenges associated with myocardial infarction.

METHODS: Poly (glycerol sebacate)/collagen (PGS/collagen) core/shell fibers were fabricated by core/shell electrospinning technique, with core as PGS and shell as collagen polymer; and the scaffolds were characterized by scanning electron microscope (SEM), fourier transform infrared spectroscopy (FTIR), contact angle and tensile testing for cardiac tissue engineering. Collagen nanofibers were also fabricated by electrospinning for comparison with core/shell fibers. Studies on cell-scaffold interaction were carried out using cardiac cells and mesenchymal stem cells (MSCs) co-culture system with cardiac cells and MSCs separately serving as positive and negative controls respectively. The co-culture system was characterized for cell proliferation and differentiation of MSCs into cardiomyogenic lineage in the co-culture environment using dual immunocytochemistry. The co-culture cells were stained with cardiac specific marker proteins like actinin and troponin and MSC specific marker protein CD 105 for proving the cardiogenic differentiation of MSCs. Further the morphology of cells was analyzed using SEM.

RESULTS: PGS/collagen core/shell fibers, core is PGS polymer having an elastic modulus related to that of cardiac fibers and shell as collagen, providing natural environment for cellular activities like cell adhesion, proliferation and differentiation. SEM micrographs of electrospun fibrous scaffolds revealed porous, beadless, uniform fibers with a fiber diameter in the range of 380 ± 77 nm and 1192 ± 277 nm for collagen fibers and PGS/collagen core/shell fibers respectively. The obtained PGS/collagen core/shell fibrous scaffolds were hydrophilic having a water contact angle of 17.9 ± 4.6° compared to collagen nanofibers which had a contact angle value of 30 ± 3.2°. The PGS/collagen core/shell fibers had mechanical properties comparable to that of native heart muscle with a young's modulus of 4.24 ± 0.7 MPa, while that of collagen nanofibers was comparatively higher around 30.11 ± 1.68 MPa. FTIR spectrum was performed to confirm the functional groups present in the electrospun scaffolds. Amide Ⅰ and amide Ⅱ of collagen were detected at 1638.95 cm^{-1} and 1551.64 cm^{-1} in the electrospun collagen fibers and at 1646.22 cm^{-1} and 1540.73 cm^{-1} for PGS/collagen core/shell fibers respectively. Cell culture studies performed using MSCs and cardiac cells co-culture environment, indicated that the cell

proliferation significantly increased on PGS/collagen core/shell scaffolds compared to collagen fibers and the cardiac marker proteins actinin and troponin were expressed more on PGS/collagen core/shell scaffolds compared to collagen fibers alone. Dual immunofluorescent staining was performed to further confirm the cardiogenic differentiation of MSCs by employing MSC specific marker protein, CD 105 and cardiac specific marker protein, actinin. SEM observations of cardiac cells showed normal morphology on PGS/collagen fibers and providing adequate tensile strength for the regeneration of myocardial infarction.

CONCLUSION: Combination of PGS/collagen fibers and cardiac cells/MSCs co-culture system providing natural microenvironments to improve cell survival and differentiation, could bring cardiac tissue engineering to clinical application.

INTRODUCTION

Myocardial infarction (MI), known as "heart attack" leads to loss of cardiomyocytes and the injured heart tissue is replaced by scar tissue[1]. When the scar is large enough to interfere with the hearts normal rhythm, heart failure occurs. Nearly 8 million Americans each year experience myocardial infarction[2] and must cope with the consequences of compromised heart muscle function. The myocardial tissue lacks significant intrinsic regenerative capacity to replace the lost cells[3]. Moreover, the relative shortage of organ donors to recipients, and the ineligibility of many heart patients for transplantation revamp the search for new strategies to repair the injured myocardium. The current methods employed include cardiac restraint devices like acorn corcap heart mesh (knitted polyester)[4], marlex mesh (polypropylene)[5], and Merselene mesh (knitted polyester)[6]. Cell transplantation therapies have shown promise for improving heart function after myocardial infarction[7]. However, the cell engraftment efficiency is low due to significant loss of cells from the site of injury following transplantation.

One promising approach is to prevent the increase of heart failure after myocardial infarction is the implantation of engineered cardiac patch at the site of infarction.

In addition of having enough elasticity for mechanical support, an ideal cardiac patch material must provide an excellent milieu for cell survival. Furthermore, the ideal biomaterial should be capable of being safely replaced by newly formed tissue and also degrade appropriate time period without producing any toxic products[8]. Naturally derived materials used in experimental or clinical treatment of infarcts include tumor-derived basement membrane matrix gel (matrigel)[9], alginate[10], collagen[11], laminin[12], fibrin[13] and decellularized extracellular matrix (ECM)[14], all of which can enhance cell and tissue function in the myocardial region. They provide a natural substrate for cellular attachment, proliferation, and differentiation in its native state. For the above-mentioned reasons, natural polymers like collagen could be a favourable substrate for tissue engineering applications[15,16]. Furthermore, collagen is the most abundant protein in the human body, and imparts structural integrity and tensile strength to tissues.

Tissue disruption following injury requires collagen for the repair and restoration of structure and function. In addition, collagens have a low antigenicity, being only weakly immunogenic largely due to their homology across species and are biodegradable due to their proteinaceous nature[17]. Using matrigel, a collagen-based multicomponent mixture of ECM proteins and growth factors, Zimmermann *et al*[18] have established one of the most convincing models of three-dimensional cardiac cell cultures, where differentiation status and functional parameters are similar to that of native myocardium. However, there are concerns about Matrigel's safety because matrigel and basement membrane matrix are known to enhance tumorigenesis and tumor growth *in vivo*[19-22]. In 1997, Eschenhagen *et al*[23] reported for the first time, an artificial heart tissue, which was termed engineered heart tissue (EHT). The embryonic chick cardiomyocytes were mixed with collagen solution and allowed to form gel for EHT. By culturing the cardiomyocytes in the collagen matrix, they produced a spontaneously and coherently contracting 3D heart tissue construct *in vitro*. However, poor mechanical supportive ability of collagen gels was a major drawback associated with this approach. Hence a combination of poly (glycerol sebacate) (PGS) with collagen was suggested with an objective to overcome this drawback for cardiac tissue engineering (CTE). The elastomer PGS, recently developed for soft tissue engineering[24,25], represents a feasible substrate from the mechanical perspective; Collagen favours enhanced cell adhesion and prevents cells loss at the site of implantation. The conventional electrospinning technique is to dissolve the polymer in a solvent, which evaporates during the spinning process. However, this approach is not pragmatic with PGS. Although, there are solvents available for dissolving PGS[26], its low molecular weight results in such a low solution viscosity that even with a high concentration solution, the electrospinning of PGS fibers cannot occur. Hence, it was necessary to develop a core/shell electrospinning pro-

cess[27] to produce PGS fibers with a protective shell polymer. The combination of PGS/collagen core/shell fibers with a unique ECM like topography has been suggested to be a potential cardiac patch material for MI. Fabricated core/shell material; the core material is solely responsible for mechanical properties, whereas the shell material is responsible for extrinsic factors like cell adhesion and proliferation. The optimal cell source to create an engineered myocardial patch should be easy to harvest, proliferative, non-immunogenic and has the ability to differentiate into mature, functional cardiomyocytes. Studies have shown that after expansion, stem cells can be directed to differentiate into cardiomyogenic lineages[28,29]. Cardiomyocytes have natural contractile and electrophysiological properties, are difficult to obtain, to expand, and are allogenic. In contrast, bone marrow derived stem cells have the ability to differentiate into any desired cell type in the presence of cues and are non-immunogenic, making them an ideal cell source.

In this study, we hypothesize that a combinatorial approach of PGS/collagen core/shell fibrous patch material and stem cell therapy is of potential interest for the treatment of heart failure rather than either strategy alone. Our approach takes advantage of the ability of an elastomeric biomaterial sheet comprising of PGS/collagen fibers to act as a flexible patch; with this approach: (1) Cells would remain adhered to the nanofibrous patch preventing cell loss and providing a more site-directed repair mechanism. It is increasingly accepted that physical cues play a key role in cell growth and tissue assembly[30,31]. These signals are important in stem cells during self-renewal, proliferation, and differentiation; (2) A softer substrate and the ability to tune the mechanical properties within a given range could be advantageous as cell differentiation was shown to be affected by substrate stiffness[32]; (3) Additionally, it has been estimated that a cell number on the order of one billion would need to be replaced in patients with heart failure[33]. The present study proposed PGS/collagen core/shell fibrous scaffold similar to cardiac ECM like topography, which promotes in situ regeneration and homing of cells; thereby reducing the number of requisite cells, is desirable for cardiac tissue engineering.

MATERIALS AND METHODS

Fabrication of core/shell fibers

PGS was synthesized by the procedure described by Wang *et al*[34] a mixture of glycerol and sebacic acid in the ratio of 1:1 was reacted at 120 ℃ under nitrogen for 24 h. The pressure was then reduced to 40 m Torr and the reaction held at 120 ℃ for 48 h to synthesise PGS. Collagen type I (8%) was dissolved in 1, 1, 1, 3, 3, 3-hexafluoro-2-propanol (HFP) (Aldrich Chemical Company, Inc., St. Louis, United States) to form shell solution and PGS (15%) was dissolved in same solvent to form the core solution. The coaxial spinneret had an inner diameter of 1 mm and an outer diameter of 2.0 mm

was designed such that the fluids were immiscible before exiting the nozzle. Fluid was loaded to the nozzle by two syringe pumps (KD Scientific Inc., MA, United States) that provide a constant-volume flow rate of 0.3 mL/h for core solution and 1.2 mL/h for shell solution. A high voltage electric field (DC high voltage power supply from Gamma High Voltage Research, FL, United States) of 15 kV was applied at the tip of the spinneret. A collector plate was placed at a distance of 15 cm from the tip of the spinneret to collect core/shell fibers. Collagen nanofibers were also fabricated using 8% w/v solution in HFP separately. The electrospinning conditions used were 1.2 mL/h flow rate, 12 cm distance between the needle tip and collector plate and 12 kV voltage supply. The fibers produced were subsequently vacuum dried to remove the residual solvents. The fibers were then cross-linked using 50% glutaraldehyde (Sigma) vapour for 24 h in order to improve its mechanical stability.

Material characterization

The surface morphology of electrospun nanofibrous scaffolds was studied under scanning electron microscope (JEOL JSM-5600LV) at an accelerating voltage of 10 kV, after gold coating (JEOL JFC-1200 fine coater, Japan). For calculating the fiber diameter of the nanofibers from the SEM images, $n = 10$ fibers were chosen randomly on each of the scaffolds. For each scaffold material $n = 5$ samples were chosen for measuring the fiber diameter. The average fiber diameter along with SD was then analyzed from the SEM images using image analysis software (Image J, National Institutes of Health, United States). Functional groups present in the scaffolds were analyzed using Fourier Transform Infrared (FTIR) spectroscopic analysis on avatar 380, (Thermo Nicolet Waltham, MA, United States) over a range of 400-4000 cm^{-1} at a resolution of 4 cm^{-1}. The hydrophobic or hydrophilic nature of electrospun fibers was measured by sessile drop water contact angle measurement using VCA optima surface analysis system (AST products, Billerica, MA, United States). Tensile properties of electrospun fibrous scaffolds were determined using a tabletop tensile tester (Instron 3345, United States) at 10 mol/L load capacity under dry testing conditions. Rectangular specimens of dimensions 10 mm × 20 mm were used for testing at a rate of 10 mm/min. The data's were recorded at room conditions 25 ℃ and 34% humidity. In order to avoid uncertainty of data, only the results of those samples which have failed in the centre; giving a dog bone like appearance have been used for the stress-strain curves calibration. The data's of those samples which have failed at the grips, where the load was being applied, were not employed for the calculation. The tensile stress-strain curve was drawn using excel sheet.

Cell culture

The electrospun fibers collected on round glass cover slips of 15 mm in diameter, were placed in a 24-well plate with stainless steel rings to prevent lifting on the cover slips.

The fibers were sterilized under ultraviolet (UV) light for 2 h, washed thrice with phosphate buffered saline (PBS) for 15 min each, in order to remove any residual solvent and prevent cytotoxicity from glutaraldehyde. The fibers were subsequently immersed in Dulbecco's modified Eagle's medium (DMEM) overnight before cell seeding. The rabbit cardiac cells were isolated using collagenase treatment. The rabbit heart was fragmented into tiny pieces and washed thoroughly with 2× and 3× antibiotic solutions made in PBS, thrice for 30 min. Subsequently, it was followed by treatment with 1% collagenase in PBS at 37 ℃ for 30 min. The fragmented tissues were cultured in DMEM media supplemented with 10% FBS (GIBCO Invitrogen, United States) and 1% antibiotic and anti-mycotic solutions (Invitrogen Corp, United States) in a 75 cm^2 cell culture flask to isolate cardiomyocytes. The culture medium was changed once in every 2 d. MSCs (PT-2501, Lonza, United States) were cultured in low glucose DMEM media supplemented with 10% FBS (GIBCO Invitrogen, United States) and 1% antibiotic and antimycotic solutions (Invitrogen Corp, United States) in a 75 cm^2 cell culture flask. Cells were incubated in CO_2 incubator at 37 ℃ at 5% CO_2. Before seeding the cells were detached by adding 1 mL of 0.25% trypsin containing 0.1% EDTA. Detached cells were centrifuged, counted by trypan blue assay using a hemocytometer and seeded on the scaffolds. The scaffolds were separated into three groups-the control tissue culture plate (TCP), collagen nanofibrous scaffolds and the PGS/collagen core/shell fibers. These were further segregated into (1) co-culture scaffolds, onto which both MSCs and cardiac cells were seeded in the ratio of 1:1 at a seeding density of 10 000 cells per well (5000 MSCs:5000 cardiac cells); (2) positive control scaffolds, onto which cardiac cells were seeded at the same seeding density of 10 000 cells per well and (3) The final batch comprised of the negative control scaffolds, onto which MSCs were seeded at the same seeding density of 10 000 cells per well.

Cell proliferation

The cell proliferation on different scaffolds was analyzed using MTS assay (CellTiter 96 Aqueous One solution reagent, purchased from Promega, Madison, WI, United States). The rationale behind the MTS assay involves the reduction of yellow tetrazolium salt [3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2(4-sulfophenyl)-2H-tetrazolium] in MTS to form purple formazan crystals by the dehydrogenase enzymes secreted by mitochondria of metabolically active cells. The formazan dye shows absorbance at 490 nm and the amount of formazan crystals formed is directly proportional to the number of cells. After 5 d of cell seeding, the media was removed from the well plates and the scaffolds were washed in PBS. The scaffolds were then incubated in a 1:5 ratio mixture of MTS assay and serum free DMEM medium for 3 h at 37 ℃ in a 5% CO_2 incubator. After the incubation period, the samples were pipette out into 96 well plates. The absorbance reading was then taken at 490

nm using a microplate reader (Fluostar Optima, BMG Lab Technologies, Germany). The same procedure was repeated for day 10 and day 15 samples.

Cell morphology

The cell morphology was analyzed using SEM. After 15 d of seeding cells on the scaffolds, the media was removed from the wells and the samples were fixed with 3% glutaraldehyde in PBS for 3 h. The scaffolds were then rinsed with distilled water for 15 min and then dehydrated with a series of ethanol gradients starting from 30% to 50%, 75%, 90% and 100% (v/v). Subsequently the samples were treated with Hexamethyldisilazane (HMDS) solution (Sigma) and allowed to air-dry at room temperature in the fume hood. The samples were then gold coated and the cells morphology was analyzed using SEM.

Expression of cardiac marker protein

To observe whether the MSCs co-cultured with cardiac cells have undergone cardiogenic differentiation, immunofluorescent staining of the selected proteins of cardiomyocytes was performed. For confocal analysis, the cells were fixed with 100% ice cold methanol for 15 min. The samples were then washed with PBS once for 15 min and incubated in 0.5% Triton-X solution for 5 min to permeabilize the cell membrane. Non-specific sites were blocked by incubating the cells in 3% BSA (Sigma) for 1 h. Following which primary antibodies α-actinin and troponin-T (Sigma) were added into separate wells, at the dilution of 1:100 and incubated for 90 min at room temperature. This was followed by washing the samples thrice with PBS for 15 min, to remove the excess unbound primary antibodies; followed by incubation for 60 min with Alexa Fluor 488 secondary antibodies (Invitrogen) in the dilution of 1:250 at room temperature. The samples were again washed thrice with PBS for 15 min. Negative controls were also employed in each analysis to delete the disturbance of the primary or secondary antibody. The cell nuclei were stained using 1:5000 dilution of 4,6-diamidino-2-phenylindole hydrochloride (DAPI; Sigma) for 30 min at room temperature. The cells were again washed with PBS thrice to remove any excess staining. The samples were then removed and mounted over glass slides using H-1000 vectashield mounting medium (Vector Laboratories, United States). The edges of the coverslips were sealed using fluoromount. The samples were then viewed using fluorescence microscopy for the cardiac marker protein expression (Olympus FV 1000).

Double immunofluorescent staining was further performed on the co-culture scaffolds to confirm the differentiation of MSCs into cardiomyocytes. The MSC-cardiac cells co-culture cells cultured on TCP, collagen nanofibers and PGS/collagen core/shell fibers were stained with MSC specific marker CD 105 (abcam, United States) in the dilution 1:100 for 90 min. at room temperature; prior to which the non-specific sites were blocked with 3% BSA. This was followed by the addi-
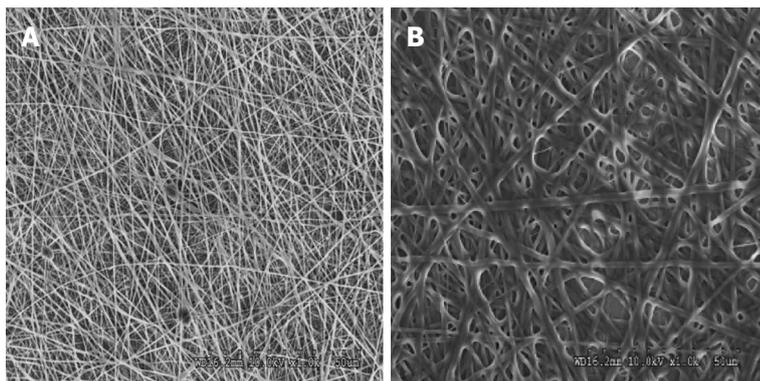
Figure 1 Scanning electron microscope image showing the fiber morphology of (A) collagen fibers with a fiber diameter of 380 ± 77 nm (B) poly (glycerol sebacate)/collagen core/shell fibers with a fiber diameter of 1192 ± 277 nm at 1000 × magnification.

Table 1 Tensile properties of collagen and poly (glycerol sebacate)/collagen fibrous membranes

Membrane	Tensile stress (MPa)	Tensile strain at maximum load	Tensile strain at break	Young's modulus (MPa)	Water contact angle mean ± SD
Collagen	2.79	13.59%	47.92%	30.11	30 ± 3.2
PGS/collagen	2.06	57.87%	83.65%	4.24	17.9 ± 4.6

PGS: Poly (glycerol sebacate).

tion of secondary antibody Alexa Fluor 488 (green) in the dilution 1:250 for 60 min. at room temperature. The samples were washed with PBS thrice to remove the excess staining. The samples were then treated with cardiac specific marker protein actinin in the dilution 1:100 for 90 min at room temperature. This was followed by the addition of the secondary antibody Alexa Fluor 594 (red) (Invitrogen) in the dilution 1:250 for 60 min. at room temperature. The samples were washed with PBS thrice to remove the excess staining. The samples were then incubated with DAPI in the dilution 1:5000 for 30 min at room temperature. The samples were then removed and mounted over a glass slide using vectashield mounting agent and examined under the fluorescent microscope (Olympus FV 1000).

Statistical analysis

For each experiment $n = 5$ samples were tested and all the data presented are expressed as mean ± SD and were analyzed using Student's *t*-test for the calculation of statistical significance. Differences were considered statistically significant at $P \leqslant 0.05$ and $P \leqslant 0.01$.

RESULTS

Material characterization

Electrospinning is a versatile technique for bio-mimicking the natural environment similar to that of ECM for better cell adhesion and tissue growth[35]. It has been estimated that a cell number on the order of one billion would need to be replaced in patients with heart failure[33]. The proposed scaffold with ECM like topography is desirable as it has been suggested that the ECM scaffold itself contains components that are chemo-attractants to endogeneous stem cells[36]. Collagen lacks mechanical integrity upon hydration in an electrospun form for tissue engineering. Without cross-linking electrospun structure it

does not have sufficient mechanical strength. Previously established methods of cross-linking with glutaraldehyde, was successful in increasing the strength of electrospun structures[37]. Moreover, the existence of collagen on the surface provides uninterrupted cell recognition signals with polymer degradation, which is essential for cell function and development[38]. SEM micrographs (Figure 1) of electrospun fibrous scaffolds revealed porous, beadless, uniform fibers with a diameter in the range of 380 ± 77 nm and 1192 ± 277 nm for collagen fibers and PGS/collagen core/shell fibers respectively. The PGS/collagen core/shell fibers have a contact angle of 17.9 ± 4.6° compared to collagen 30 ± 3.2°. FTIR spectrum was carried out to confirm the functional groups present in electrospun scaffolds. Amide I and amide II of collagen were detected at 1638.95 cm^{-1} and 1551.64 cm^{-1} in the electrospun collagen fibers and at 1646.22 cm^{-1} and 1540.73 cm^{-1} for PGS/collagen core/shell fibers respectively as shown in Figure 2. The characteristic peak of PGS at 1740 cm^{-1} is absent in the PGS/collagen core/shell FTIR spectrum because PGS has been incorporated as the core material in the core/shell system.

For any tissue-engineered construct to be functional, it is imperative to determine its material properties and compare against the native heart muscle. A comparison of tensile properties of nanofibers with respect to tensile stress and strain is illustrated in Table 1. We found that the Young's modulus of collagen decreases further in the presence of PGS from 30.11 ± 1.68 MPa to 4.24 ± 0.7 MPa. The principal structural protein of adult myocardium is collagen and of the total collagen in the myocardium 85% is type I and 11% is type III[39]. The roles of collagens I and III are different: collagen I is thicker and provides stiffness and structural support while collagen III is thinner and provides flexibility and elastic recovery[40]. The two types of collagens jointly support and maintain the myocyte alignment, whereas their
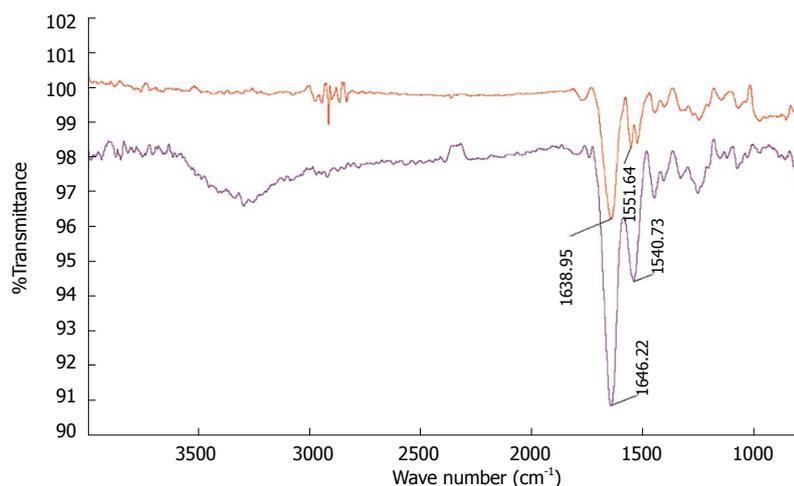
Figure 2 Fourier transform infrared spectroscopy images of red curve-collagen fibers showing characteristic amide peaks at 1638.95 cm^{-1} and 1551.64 cm^{-1} blue curve-poly (glycerol sebacate)/collagen core/shell fibers showing characteristic amide peaks at 1646.22 cm^{-1} and 1540.73 cm^{-1}.
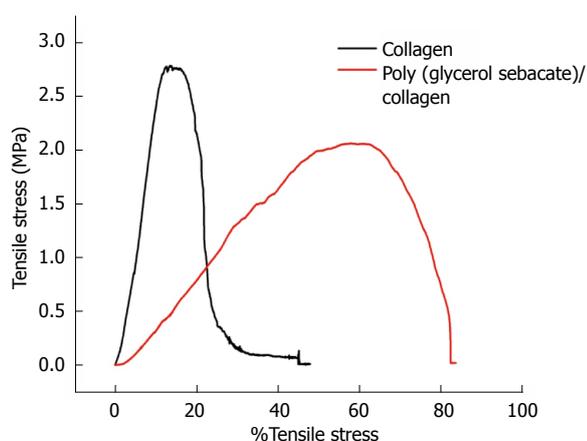
Figure 3 Tensile stress-strain curves of collagen fibers and poly (glycerol sebacate)/collagen core/shell fibers.

tensile strength and resilience resist the deformation, thereby contributing to the passive and active stiffness of the myocardium[41]. Radisic *et al*[42] applied electrical signals onto ultrafoam collagen sponges using matrigel seeded with rat cardiomyocytes to mimic the native heart for cardiac tissue engineering. However, poor mechanical properties, the lack of stability and large degree of swelling (approximately 30%) immediately following hydration in culture medium[43], hampered its clinical applications. Figure 3, we observed that the elastic modulus of PGS/collagen core/shell fibers is 4.24 ± 0.7 MPa, which is nearing to native myocardium, while that of collagen nanofibers was comparatively higher around 30.11 ± 1.68 MPa. Hence, PGS/collagen core/shell fibers are a novel concept for improving the mechanical stability as well as not compromising on the biocompatibility of the patch material. Additionally, PGS has other desirable properties including control of its mechanical properties, which can match those of native myocardium[44], and support of adhesion and phenotypic protein expression for a variety of primary cell types *in vitro*[45].

DISCUSSION

The scaffold properties play an important role in influ-

encing the cell responses for cardiac tissue engineering. Cell behaviour such as adhesion and proliferation represent the initial phase of cell-scaffold communication that subsequently influences the cell differentiation[46]. The cell proliferation results as shown in Figure 4, we observed that the MSC and co-culture cells adhesion and proliferation were significantly ($P \leqslant 0.05$) higher on day 10 and day 15 on PGS/collagen scaffold compared to the TCP. This was because of the nanofibrous scaffold which resembles the ECM and thereby provides necessary cues, promoting cell proliferation and differentiation as discussed in our previous studies[46-49]. Moreover, studies have reported that cardiomyocyte adhesion and organization into a contractile tissue have been far superior on natural scaffolds compared to synthetic scaffolds[50]. The results observed that the proliferation of co-culture cells was significantly ($P \leqslant 0.01$) higher on PGS/collagen core/shell fibers compared to collagen nanofibers on day 10 and day 15 (Figure 4). Additionally, the MSCs proliferation was also significantly higher on day 10 and day 15 on PGS/collagen scaffolds compared to collagen fibers. The percentage increase in the rate of proliferation of co-culture cells from day 5 to day 15 has been calculated to be 87.45% and 118.91% on collagen nanofibers and PGS/collagen core/shell fibers respectively. Enhanced cell population on the co-culture group maybe due to the synergistic effect of cardiac cells and MSCs. The MSCs provide the necessary paracrine signals to prevent apoptosis of the cardiac cells. Recent studies suggest that the transplanted MSCs interact with local tissues in the heart, releasing paracrine factors that support the regenerative process. Thus the beneficial effects of MSCs transplantation are probably mediated primarily through the preservation of cardiac myocytes within the infarction[51]. Additionally, large amount of protective cytokines secreted by MSCs, functioned as the limitation of inflammation, inhibition of apoptosis, and stimulating myoangiogenic differentiation[52]. Stem cell/cardiomyocyte interactions regulate not only cardiac development[53] but also cardiomyocyte function in the adult heart[54]. In MSC-cardiomyocyte co-culture environment, stem cells may promote cardiomyocyte survival[55]. Given the rapid loss
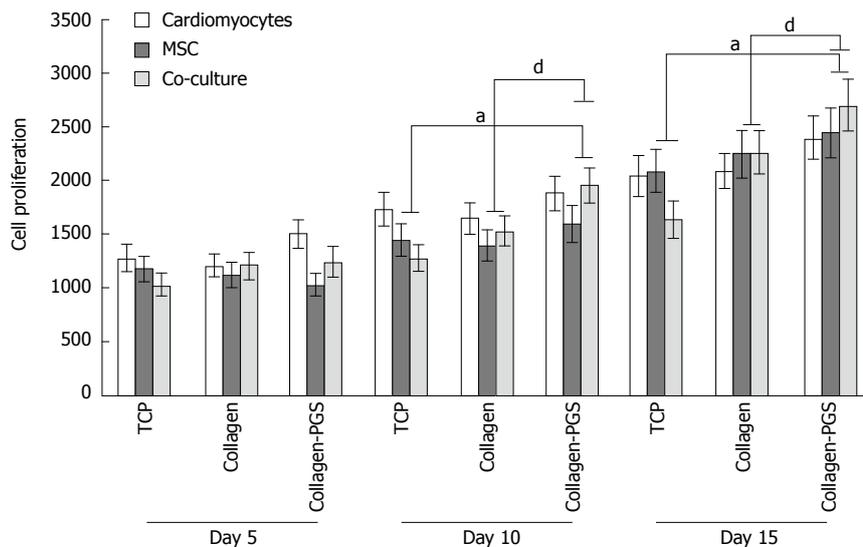
Figure 4 Cell proliferation study for days 5, 10 and 15 on tissue culture plate, poly (glycerol sebacate)/collagen core/shell fibers and collagen nanofibers using cardiomyocytes, mesenchymal stem cells and cardiomyocytes-mesenchymal stem cells co-culture. Denotes statistical significant difference MSC [a]$P \leqslant$ 0.05 *vs* co-culture cells cultured on TCP and PGS/collagen core/shell fibers; Denotes statistical significant difference MSC [d]$P \leqslant$ 0.01 *vs* co-culture cells cultured on collagen and PGS/collagen core/shell fibers. TCP: Tissue culture plate; PGS: Poly (glycerol sebacate); MSCs: Mesenchymal stem cells.

of cardiomyocytes after ischemic injury, promoting cardiomyocyte survival is an efficient strategy for preserving viable myocardium[56].

To observe the cellular responses of the patches to the myocardiogenic differentiations of MSCs, the immunofluorescence stains of specific proteins of cardiomyocytes like troponin T and α-actinin were selected[57-59]. Troponin-T is important for effective cardiomyocytes which contain contractile proteins, as it regulates the force and velocity of myocardial contraction[57], and actinin is an important constituent of the contractile apparatus. Many investigators agree that hMSCs also exhibit some cardiogenic potential but the frequency at which cardiac differentiation occurs without any added induction factors is small[60]. Figure 5D-F and Figure 6D-F, demonstrated that the cardiogenic choice can be enhanced *in vitro* by co-culturing MSCs with cardiac cells. The biological cues secreted by cardiac cells would drive the differentiation of MSCs into cardiac lineage. It has been reported that, in the presence of certain physical and chemical cues, MSCs differentiate into cells that resemble cardiac myocytes and may be applicable for cardiac regeneration[46]. Figure 5 observed that the expression of cardiac proteins actinin (Figure 5D-F) and troponin (Figure 6D-F) are higher in co-culture environment compared to individual cell culture systems of MSCs (Figure 5G-I and Figure 6G-I and cardiac cells (Figure 5A-C and Figure 6A-C). As shown in Figure 5G-I and Figure 6G-I, the MSCs did not express the marker proteins actinin and troponin-T in their undifferentiated state. Hence they express DAPI alone which stains the nucleus of MSCs. It is increasingly accepted that physical cues play a role in cell growth and tissue assembly[30,31]. These signals are important in stem cells (SCs) during self-renewal, proliferation and differentiation. Hence the presence of cardiac cells in the stem cell-cardiac cells co-culture provides the nec-

essary cues to trigger the cardiogenic differentiation of MSCs, in the absence of any other soluble differentiating factors. Furthermore, the cardiac marker expression was higher on the PGS/collagen scaffold compared to the collagen nanofibers. This increase in protein expression is because of the difference in the mechanical property between PGS/collagen and collagen substrates. It has been shown that a softer substrate and the ability to tune the mechanical properties within a given range could be advantageous as cell differentiation was shown to be affected by substrate stiffness[32]. Owing to the favourable mechanical properties of PGS, the cell differentiation was more on PGS/collagen scaffolds compared to collagen scaffolds. There was no protein expression in MSC culture group (Figure 5G-I and Figure 6G-I) proving that in the absence of cues, the cardiogenic differentiation of MSCs may not occur. However in the co-culture environment we found that more cells express the cardiac specific marker proteins, indicating that the MSCs have differentiated into cardiac cells and therefore express troponin T and actinin markers. This cardiogenic differentiation of MSCs was further confirmed by dual immunostaining. Figure 7A, D, G shows the expression of MSC specific marker protein CD 105 by the MSCs cultured in the co-culture environment on TCP, collagen and PGS/collagen core/shell fibers. Figure 7B, E, H shows the expression of cardiac marker protein actinin. The MSCs which have undergone cardiogenic differentiation, express both CD 105 and the cardiac specific marker protein actinin. This result in dual expression of both CD 105 and actinin by the MSCs which have undergone cardiogenic differentiation, as shown in Figure 7C, F, I. We observed that PGS/collagen core/shell fibers (Figure 7I) express higher level of actinin expression in differentiated MSCs compared to collagen scaffolds (Figure 7F). However, the differentiated MSCs did not exhibit any contraction. A similar
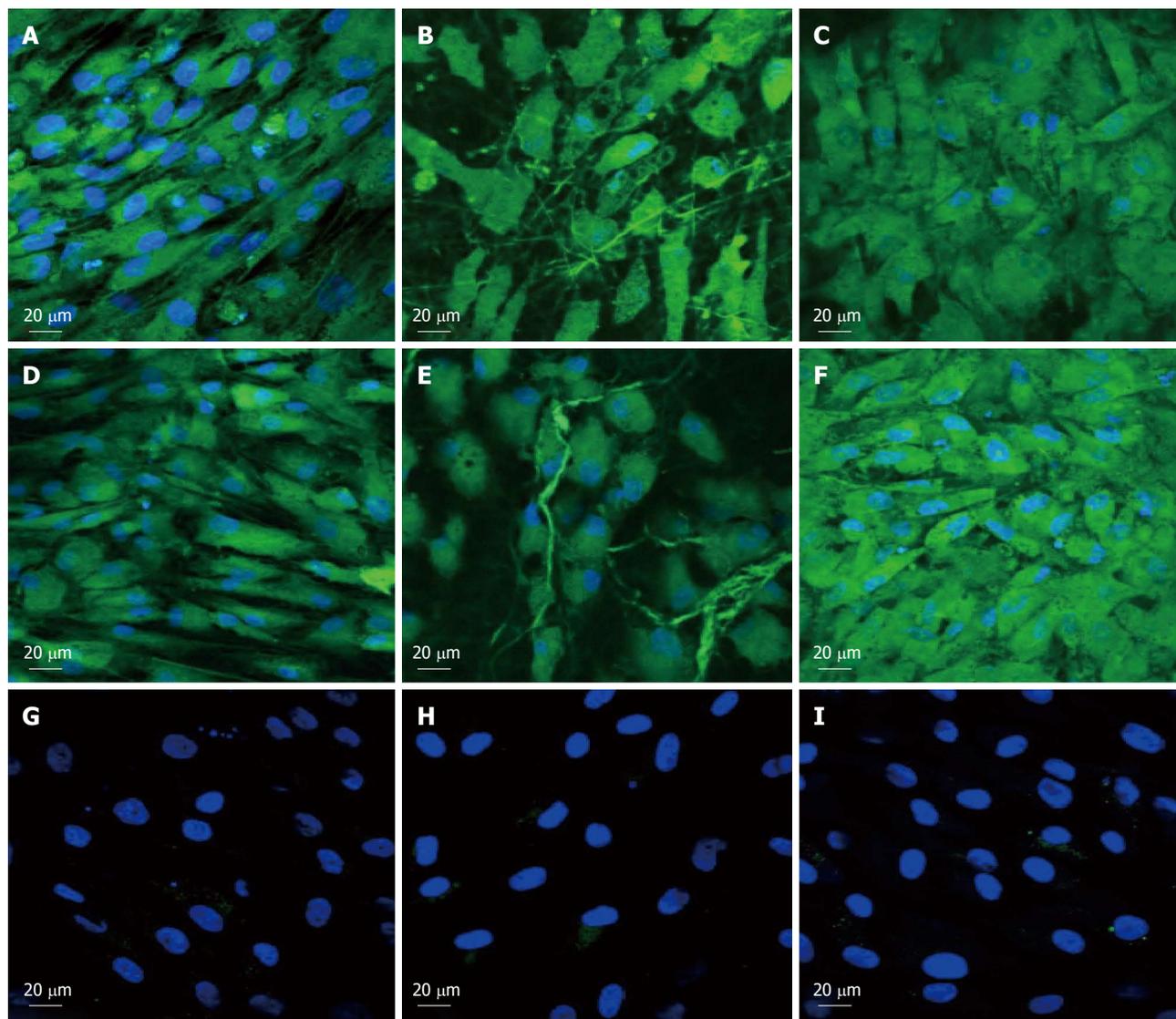
Figure 5 Immunocytochemical analysis for the expression of cardiac marker protein actinin at 60 × magnification on the tissue culture plate (A, D, G), collagen nanofibers (B, E, H) and poly (glycerol sebacate)/collagen core/shell fibers (C, F, I) comprising of cardiomyocytes (A-C), mesenchymal stem cells-cardiomyocytes co-culture group (D-F) and mesenchymal stem cells (G-I). Nucleus stained with 4,6-diamidino-2-phenylindole hydrochloride.

study was reported[61], where stem cells were delivered to the canine RV on an ECM patch, and tracked with quantum dots, some of these cells were demonstrated to differentiate to mature myocytes. Similar to our study, these cells were considered "cardiogenic", since they express cardiac markers like troponin T, but do not contract *in vitro* and have not fully differentiated into functional cardiac myocytes. Moreover, the study also suggested that since the cardiogenic cells did not exhibit the complete cardiac phenotype *in vitro*, it remained possible that the 'committed' cells retained the capacity to proliferate *in vitro*. Ideally, it has been reported that a full cardiogenic differentiation of stem cells should not occur until the cells are transplanted into the heart, since different regions of the heart have unique ion currents and the expression of these currents may be affected by the local environment[62].

The ability of seeded cells to adhere, survive and

migrate within a scaffold is crucial when trying to regenerate a tissue *in vivo*. Previous reports of cardiac tissue engineering noted that even if the surface layers of the construct were filled with cells, its interior was frequently devoid of tissue regeneration[63]. Since the fibrous scaffolds are highly porous, it favours the cells to penetrate deep within the scaffold. This was further confirmed by 3D confocal images, as shown in Figure 8, processed using Imaris software. It was observed that the cells penetrated more profoundly within the PGS/collagen fibers (542 nm) when compared to the collagen scaffolds (475 nm). This is because of the favourable mechanical property and flexibility of PGS, which favours easier cell migration, causing the cells to crawl inside, towards the interior of the scaffold.

Quantification of the number of cells present on nanofibrous scaffolds and cellular behaviour is also another pivotal indicator to determine the potential appli-
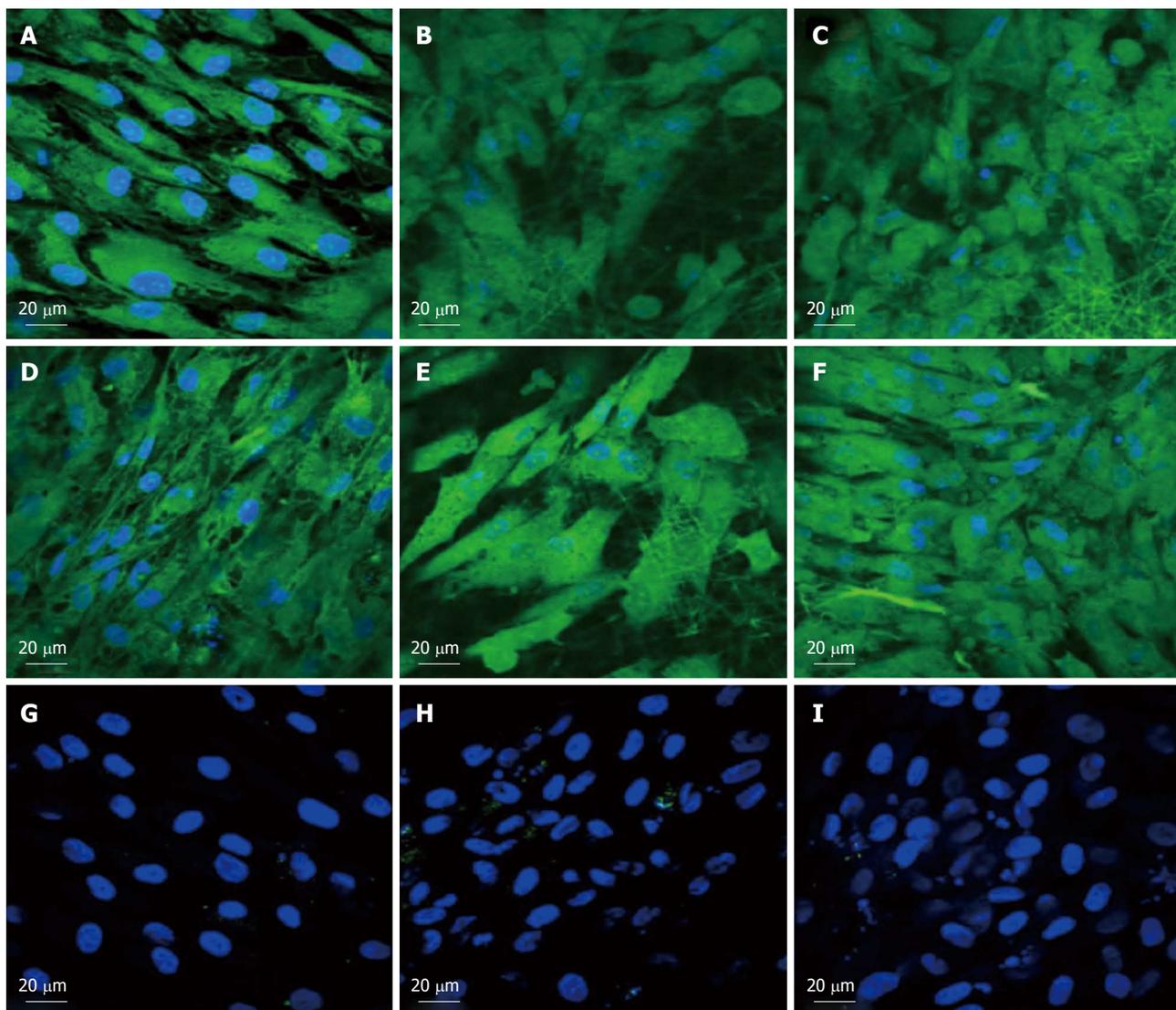
Figure 6 Immunocytochemical analysis for the expression of the cardiac marker protein Troponin at 60 × magnification on the tissue culture plate (A, D, G), collagen nanofibers (B, E, H) and poly (glycerol sebacate)/collagen core/shell fibers (C, F, I) comprising of cardiomyocytes (A-C), mesenchymal stem cells-cardiomyocytes co-culture group (D-F) and mesenchymal stem cells (G-I). Nucleus stained with 4,6-diamidino-2-phenylindole hydrochloride.

cation of a material construct for any tissue engineering application. The cell morphology was studied using SEM images as shown in Figure 9. It showed that the nanofiber contour allowed the cardiac cells to make extensive use of available cues for isotropic or anisotropic growth, and to some degree even to crawl inside and pull the fibers, as evidenced in Figure 9A-C. The results showed that the cell-to-cell interaction between the MSC and cardiac cells group, leading to cell fusion, was observed in co-culture group (Figure 9D-F). This cell-to-cell interaction favoured the MSCs to undergo cardiogenic differentiation. The differentiated MSCs in the co-culture system acquired the cardiomyocyte phenotype as revealed in Figure 9D-F. MSCs also showed favourable growth on the nanofibers with the greater cell-to-cell contact and extension of filopodia as evidenced in Figure 9G-I.

We have employed the use of co-culture system of stem cells with scaffold microenvironments engineered to improve tissue survival and enhance differentiation.

Transplanted MSCs may differentiate *in situ* into cells of cardiomyogenic lineage, promoted by the local microenvironment. These in turn could integrate into the myocardium and help to regenerate damaged tissue. We have reported that direct cell-to-cell contact between MSC and adult cardiac cells is necessary for the differentiation of MSC into cardiac cells. This integrative approach of PGS/collagen core/shell nanofibrous cardiac patch material, to prevent cell loss, and stem cell therapy, would maximize the capacity of myocardial tissue regeneration.

In conclusion, even though the implanted stem cells survived and regenerated the infarcted myocardium, the site of MI is a poor environment for cell growth. To increase cell viability, some factors to improve such an infertile environment are desirable. We aimed at improving the quality of the local microenvironment by trapping the cells within the nanofiber mesh and then transplanting to the infarcted site, which may in turn improve survival of the cells and facilitate the biological behaviour
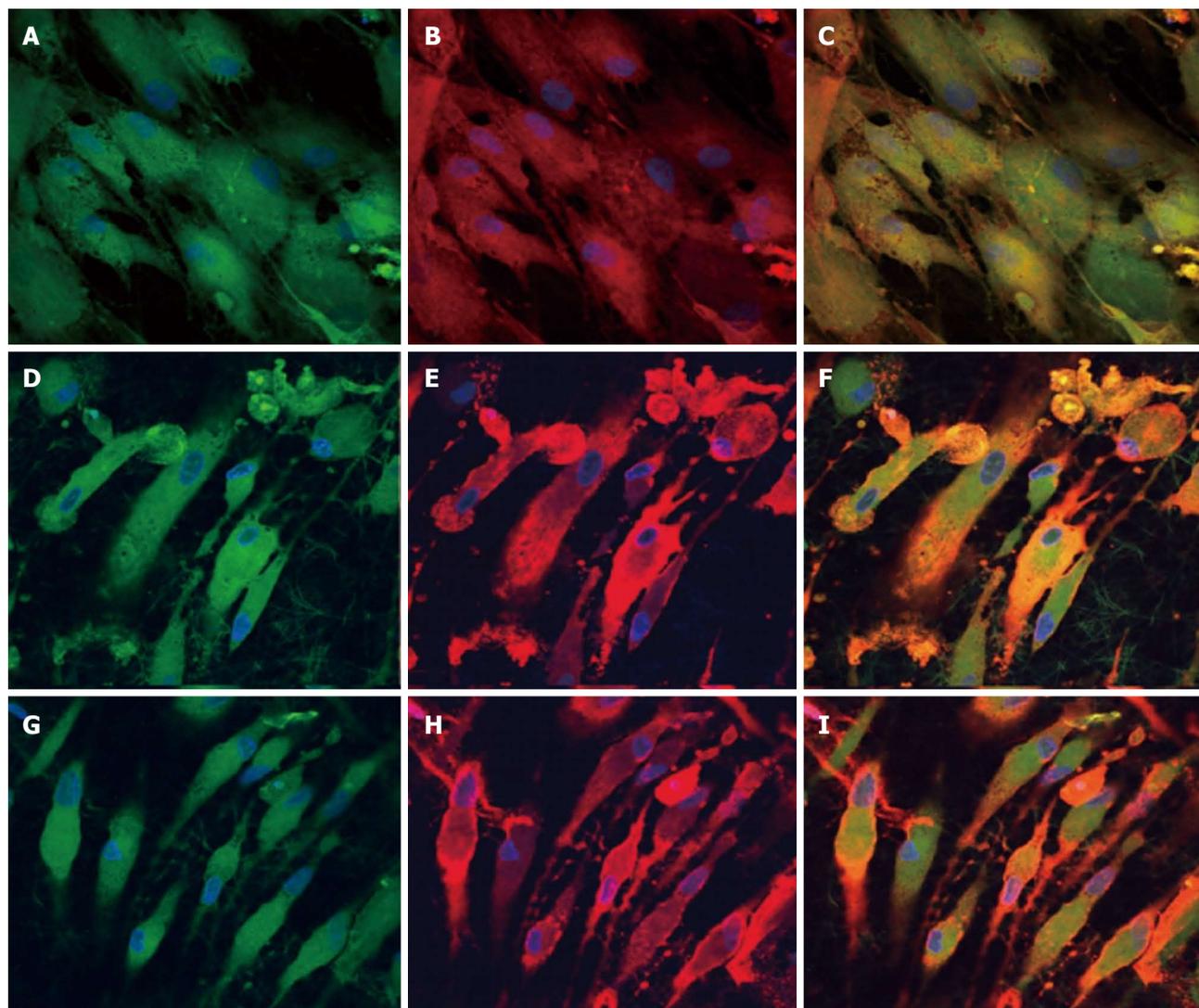
Figure 7 Dual immunocytochemical analysis for the expression of mesenchymal stem cells marker protein CD 105 (A, D, G) and cardiac marker protein Actinin (B, E, H) in the co-culture samples and the merged image showing the dual expression of both CD 105 and Actinin (C, F, I); on the tissue culture plate (A, B, C), collagen nanofibers (D, E, F) and poly (glycerol sebacate)/collagen core/shell fibers (G, H, I) at 60 × magnification. Nucleus stained with 4,6-diamidino-2-phenylindole hydrochloride.
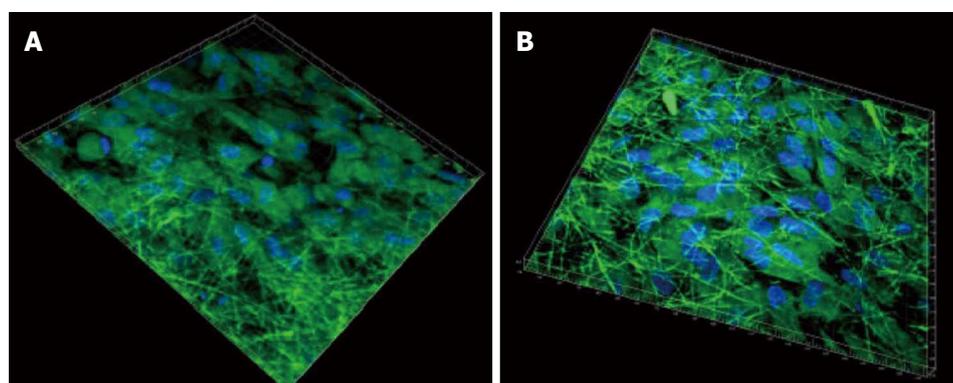
Figure 8 3D image using Imaris software of cardiomyocytes-mesenchymal stem cells co-culture group stained with cardiac specific marker protein troponin at 60 × magnification on (A) collagen fibers (B) poly (glycerol sebacate)/collagen core/shell fibers. Nucleus stained with 4,6-diamidino-2-phenylindole hydrochloride.
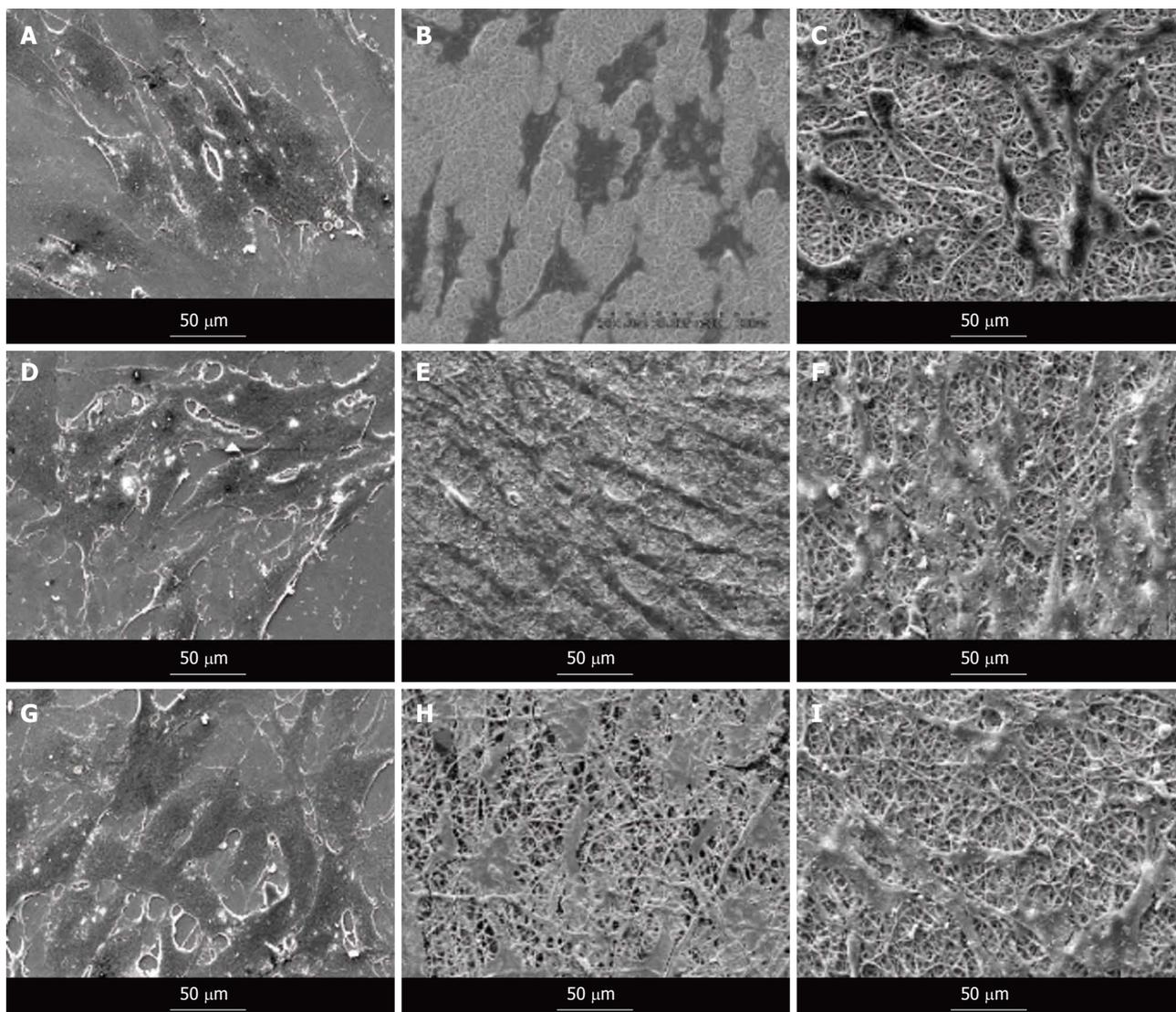
Figure 9 Scanning electron microscope images showing the cell morphology of cardiomyocytes (A-C), cardiomyocytes-mesenchymal stem cells co-culture cells (D-F) and mesenchymal stem cells (G-I) grown on tissue culture plate (A, D, G), collagen nanofibers (B, E, H) and poly (glycerol sebacate)/collagen core/shell fibers (C, F, I) on day 15 at 500 × magnification.

of implanted cells. Electrospun fibrous scaffolds provide both flexibility and guidance for cardiac cells growth and MSC differentiation into cardiac lineage and thus can be successfully applied to obtain structurally and functionally competent cardiac tissue constructs. There have been several studies of different scaffolds for cardiac tissue engineering, but there has been few research focused on elastomeric scaffolds like PGS for CTE. In fact, no research has been done so far on the PGS/collagen scaffold material for MI. New solutions including the recruitment, *in vitro* proliferation and homing of the patients own stem cells, combined with biocompatible and biomimicking materials will open new doors in the field of cardiac tissue engineering for MI. The biomaterial employed should be able to interact on the molecular level, with the cells in a precise and controlled manner, similar to the natural interactions existing between cells and the native ECM. We have shown that the direct cell-to-cell contact between MSCs and adult cardiac cells, governed the differentiation of MSCs into cardiac cells. This novel combinatorial paradigm of a PGS/collagen mechanical construct with MSC-cardiac cells co-culture environment might ultimately bring cardiac tissue engineering into clinical application.

COMMENTS

Background

Myocardial infarction leads to weakening of collagen extracellular matrix leading to loss of ventricular function and the injured heart tissue ultimately becomes scar tissue. When the scar is large enough to interfere with the hearts normal rhythm, heart failure occurs. One promising approach is to prevent the increase of heart failure after myocardial infarction is the implantation of engineered cardiac patch at the site of infarction.

Research frontiers

Poly (glycerol sebacate) (PGS) is an elastomeric material recently applied in the area of soft tissue engineering. In the area of cardiac tissue engineering, the research hotspot is how to fabricate PGS nanofibers by electrospinning technique to engineer a cardiac patch with mechanical properties similar to that of the heart tissue.

Innovations and breakthroughs

The conventional electrospinning technique is to dissolve the polymer in a solvent, which evaporates during the spinning process. However, this approach is not pragmatic with PGS, due to its low molecular weight which results in such a low solution viscosity that even with a high concentration solution, the electrospinning of PGS fibers cannot occur. Hence, the authors developed a core/shell electrospinning process to produce PGS fibers with a protective shell polymer.

Applications

The combination of PGS/collagen core/shell fibers with a unique extracellular matrix like topography has been suggested to be a potential cardiac patch material for myocardial infarction.

Terminology

Myocardial Infarction, known as "heart attack" leads to weakening of collagen extracellular matrix leading to the loss of left ventricular function and the injured heart tissue ultimately becomes scar tissue. When the scar is large enough to interfere with the hearts normal rhythm, heart failure occurs.

Peer review

The article by Ravichandran *et al* is an interesting article that addresses the important issue of optimizing biomaterials as scaffolding for stem cells. The methodology and data is well presented.

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BRIEF ARTICLE

Ultrasound-assessed non-culprit and culprit coronary vessels differ by age and gender

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Abstract

AIM: To investigate age- and gender-related differences in non-culprit versus culprit coronary vessels assessed with virtual histology intravascular ultrasound (VH-IVUS).

METHODS: In 390 patients referred for coronary angiography to a single center (Luzerner Kantonsspital, Switzerland) between May 2007 and January 2011, 691 proximal vessel segments in left anterior descending, circumflex and/or right coronary arteries were imaged by VH-IVUS. Plaque burden and plaque composition (fibrous, fibro-fatty, necrotic core and dense calcium volumes) were analyzed in 3 age tertiles, according to gender and separated for vessels containing non-culprit or culprit lesions. To classify as vessel containing a culprit lesion, the patient had to present with an acute coronary syndrome, and the VH-IVUS had to be performed in a vessel segment containing the culprit lesion according to conventional coronary angiography.

RESULTS: In non-culprit vessels the plaque burden increased significantly with aging (in men from 37% ± 12% in the lowest to 46% ± 10% in the highest age tertile, $P < 0.001$; in women from 30% ± 9% to 40% ± 11%, $P < 0.001$); men had higher plaque burden than women at any age ($P < 0.001$ for each of the 3 age tertiles). In culprit vessels of the lowest age tertile, plaque burden was significantly higher than that in non-culprit vessels (in men 48% ± 6%, $P < 0.001$ as compared to non-culprit vessels; in women 44% ± 18%, $P = 0.004$ as compared to non-culprit vessels). Plaque burden of culprit vessels did not significantly change during aging (plaque burden in men of the highest age tertile 51% ± 9%, $P = 0.523$ as compared to lowest age tertile; in women of the highest age tertile 49% ± 8%, $P = 0.449$ as compared to lowest age tertile). In men, plaque morphology of culprit vessels became increasingly rupture-prone during aging (increasing percentages of necrotic core and dense calcium), whereas plaque morphology in non-culprit vessels was less rupture-prone and remained constant during aging. In women, necrotic core in non-culprit vessels was very low at young age, but increased during aging resulting in a plaque morphology that was very similar to men. Plaque morphology in culprit vessels of young women and men was similar.

CONCLUSION: This study provides evidence that age- and gender-related differences in plaque burden and plaque composition significantly depend on whether the vessel contained a non-culprit or culprit lesion.

INTRODUCTION

Age and gender have well-established relations to the prevalence of coronary artery disease (CAD) and the incidence of coronary events[1-5]. A few pathologic studies evaluated age- and gender-related differences in coronary plaques and found significant differences[6-9]. However, these studies were restricted to patients who died from a coronary event. Only two studies so far characterized age- and gender-related differences in coronary plaques *in vivo* with the use of virtual histology (VH) intravascular ultrasound (IVUS)[10,11]. Both studies reported that plaque burden as well as necrotic core and dense calcium increased with increasing patient age, that at any age men had a more rupture-prone plaque morphology than women and that gender differences diminished with increasing age. However, in these studies the compositional characteristics of non-culprit and culprit lesions were not distinguished. The present study therefore examines age- and gender-related differences in non-culprit versus culprit coronary vessels assessed with VH-IVUS.

MATERIALS AND METHODS

Study population

Consecutive patients referred for coronary angiography during daytime to a single center (Luzerner Kantonsspital, Switzerland) between May 2007 and January 2011 were evaluated for this study. Patients presented with stable angina or acute coronary syndromes (ACS) (*i.e.*, unstable angina, non-ST-elevation myocardial infarction or ST-elevation myocardial infarction). The decision to perform coronary angiography was taken according to the local guidelines. Patients in cardiogenic shock and hemodynamically unstable patients depending on inotropes were excluded. Patients with total or subtotal stenosis of the proximal left anterior descending (LAD) or circumflex (CX) artery as well as high-grade left main coronary artery stenosis with potential for hemodynamic instability during the IVUS procedure were also excluded. Finally, 390 patients qualified for inclusion in the study and were willing to participate. All patients provided written informed consent. The institutional ethical committee approved the study, which was conducted in accordance with the declaration of Helsinki.

Measurements

In all 390 patients, clinical characteristics (age, sex, cardio-vascular risk factors, clinical presentation) were assessed at baseline. Hypertension was defined as a repeatedly elevated blood pressure > 140/90 mmHg according to current guidelines[12-14]. Dyslipidemia was defined as total cholesterol > 234 mg/dL (6.0 mmol/L) or low-density lipoprotein cholesterol > 117 mg/dL (3.0 mmol/L)[15]. Diagnosis of diabetes mellitus was made if fasting plasma glucose was ≥ 7 mmol/L on at least two different days or if postprandial plasma glucose was ≥ 11.1 mmol/L[16]. Patients were considered as smokers, if they currently smoked ≥ 1 cigarette per week. Patients who previously stopped smoking were considered non-smokers[17]. A positive family history of CAD was defined as evidence of CAD in a parent or sibling before 60 years of age[18]. ACS was defined according to guidelines of the European Society of Cardiology and the American College of Cardiology/American Heart Association[19,20].

IVUS procedure and outcome

In all 390 participating patients, IVUS was performed in the proximal 4 cm of LAD, CX and right coronary artery (RCA). If the coronary anatomy was unsuitable for the IVUS procedure (*e.g.*, small or tortuous vessels), the IVUS procedure was not performed in the corresponding vessel. IVUS was acquired using an Eagle Eye® Gold Catheter (20 MHz) and an automatic continuous pullback device (Volcano Corp., Rancho Cordova, CA, United States)[21-24]. Pullback velocity was 1 mm/s. Frames were acquired ECG-gated/R-wave triggered. The vessels in which the IVUS was performed were classified into either vessels containing a culprit lesion or vessels containing non-culprit lesions. To classify a vessel as vessel containing the culprit lesion, the following criteria had to be fulfilled: (1) the patient had an ACS; and (2) the IVUS was performed in the vessel segment containing the culprit lesion according to conventional coronary angiography. All other vessels were classified as vessels containing non-culprit lesions.

Analysis of the IVUS procedure was performed offline by a specially trained single investigator who was blinded to the clinical and angiographic data. The analysis embraced the whole vessel segment in which the IVUS was performed. Contours of lumen and media-adventitia interface were detected semi-automatically. For every cross-sectional area, vessel and lumen diameters as well as the area for the different plaque components were calculated using a special software package (pcVH2.2, Volcano Corp., Rancho Cordova, CA, United States). Spectral analysis of IVUS radiofrequency signals provided a histology of the plaque identifying 4 major plaque components, namely fibrous, fibro-fatty, necrotic core and dense calcium[25]. After manual detection, the software calculated the absolute volumes of each of the 4 plaque components as well as their relative amounts expressed as percentages of the total volume of the 4 components within the 4 cm segment. Total plaque volume was calculated as the sum of the volumes of all 4 plaque components and of the media-adventitia. Plaque burden was defined as the ratio between plaque volume and the sum

Table 1 Baseline characteristics (*n* = 130) *n* (%)

Characteristic	Patients in the lowest age tertile	Patients in the middle age tertile	Patients in the highest age tertile	*P* value[1]
Age, mean ± SD (range), yr	47.6 ± 6.8 (20.5-55.5)	59.6 ± 2.4 (55.5-64.2)	70.9 ± 4.8 (64.3-83.7)	< 0.001
Female sex	29 (22.3)	36 (27.7)	43 (33.1)	0.053
Body mass index, mean ± SD, kg/m^{2}	26.9 ± 5.1	28.0 ± 4.9	27.4 ± 3.6	0.408
Obesity[2]	25 (19.2)	37 (28.5)	30 (23.1)	0.466
Systolic BP, mean ± SD, mmHg	128 ± 19	134 ± 19	133 ± 20	0.017
Diastolic BP, mean ± SD, mmHg	77 ± 12	77 ± 11	73 ± 11	0.007
Cardiovascular risk factors				
Hypertension	58 (44.6)	85 (65.4)	95 (73.1)	< 0.001
Dyslipidemia	77 (59.2)	101 (77.7)	90 (69.2)	0.082
Current smoker	47 (36.2)	30 (23.1)	16 (12.3)	< 0.001
Diabetes	11 (8.5)	23 (17.7)	30 (23.1)	0.001
Positive family history	47 (36.2)	48 (36.9)	51 (39.2)	0.609
Manifest atherosclerosis				
CAD	78 (60.0)	101 (77.7)	112 (86.2)	< 0.001
ACS	35 (26.9)	32 (24.6)	33 (25.4)	0.777
Previous stroke	1 (0.8)	5 (3.9)	7 (5.4)	0.038
Peripheral artery disease	2 (1.5)	11 (8.5)	6 (4.6)	0.250
Medication[3]				
ACE inhibitor	29 (22.3)	46 (35.4)	52 (40.0)	0.002
Betablocker	47 (36.2)	60 (46.2)	67 (51.5)	0.013
Statin	36 (27.7)	57 (43.9)	62 (47.7)	0.001
Other measurements				
LDL, mean ± SD, mmol/L	2.8 ± 1.0	2.7 ± 1.2	2.6 ± 1.0	0.263
LVEF, mean ± SD, %	70 ± 11	68 ± 13	70 ± 12	0.875

[1]*P* value for trend across age groups was calculated using linear regression; [2]Defined as body mass index ≥ 30 kg/m^{2}; [3]Long-term medication in the two weeks before intravascular ultrasound. ACE: Angiotensin converting enzyme; ACS: Acute coronary syndrome; BP: Blood pressure; CAD: Coronary artery disease; LDL: Low-density lipoprotein cholesterol.

of plaque and lumen volumes.

Statistical analysis

Data were analyzed using Stata software (Stata 11.2, Stata-Corp LP, College Station, TX, United States). For two-group comparisons, Student's *t* test was used after checking for normal distribution; Mann-Whitney rank-sum test was used for non-normally distributed continuous variables. Distributional differences between categorical variables were assessed by a χ^2 test and Fisher's exact test. The *P* value for a trend across age groups was calculated using linear regression. In the regression model, age was analyzed as tertile. For all statistical comparisons, a *P* value < 0.05 was considered significant.

RESULTS

Baseline characteristic are shown in Table 1. Mean age was 59.4 ± 10.7 years with a range from 20.5 to 83.7 years. Hypertension, dyslipidemia and diabetes were increasingly prevalent with increasing patient age. Fewer patients in the highest age tertile were current smokers as compared to younger patients. Prevalence of CAD increased with increasing patient age, whereas patients with ACS were similarly prevalent in all age tertiles (Table 1).

Overall, 691 vessel segments in LAD, CX and/or RCA were imaged by IVUS in the 390 participating patients. The LAD was imaged in 319 patients, the CX in 214 patients, and the RCA in 158 patients. All three vessels were depicted in 84 patients (21.5%), two vessels in 133 patients (34.1%), and only one vessel in 173 patients (44.4%).

618 vessels (89.4%) contained non-culprit lesions and 73 vessels (10.6%) contained culprit lesions of patients with ACS. Age- and gender-related differences of plaque components in vessels containing non-culprit or culprit lesions are summarized in Table 2 and in Figure 1.

Age- and gender-related differences in non-culprit vessels

In non-culprit vessels plaque burden as well as fibrous and necrotic core volumes were higher in young men than in young women (Table 2). The plaque burden in men increased significantly with age; however, the plaque component characteristics of young age were preserved until old age. Women also had a significant increase in plaque burden during aging, but plaque burden remained generally lower than in men. In contrast to men, plaque composition of non-culprit vessels in women altered during aging with increasing volumes of fibrous and necrotic tissue, so that differences in plaque composition between women and men disappeared in the elderly. Old women had a plaque composition that was similar to men, even compared to young men. Interestingly, the most important change of plaque composition in women occurred between the lowest and middle age tertile (*i.e.*, after menopause).

Age- and gender-related differences in culprit vessels

Table 2 summarizes plaque burden and composition of culprit vessels. The plaque composition of culprit vessels in young men and women presenting with ACS was very similar. In contrast to women, plaque composition

Table 2 Age- and gender-related differences of plaque burden and plaque components in vessels containing non-culprit or culprit lesions (mean ± SD)

Plaque component	Patients in the lowest age tertile			Patients in the middle age tertile			Patients in the highest age tertile			P value[1]	P value[2]
	Male	Female	P value	Male	Female	P value	Male	Female	P value		
Non-culprit vessels											
Segments available for analysis	n = 154	n = 44		n = 159	n = 54		n = 140	n = 67			
Plaque burden, %	37 ± 12	30 ± 9	< 0.001	42 ± 11	35 ± 12	< 0.001	46 ± 10	40 ± 11	< 0.001	< 0.001	< 0.001
Fibrous volume, %	53 ± 12	44 ± 20	< 0.001	51 ± 12	54 ± 13	0.161	52 ± 11	53 ± 12	0.947	0.949	0.005
Fibro-fatty volume, %	13 ± 11	17 ± 19	0.966	11 ± 9	17 ± 15	0.053	13 ± 9	12 ± 10	0.365	0.992	0.060
NC volume, %	18 ± 8	15 ± 10	0.033	21 ± 9	16 ± 10	< 0.001	20 ± 8	19 ± 9	0.646	0.13	0.017
DC volume, %	17 ± 14	24 ± 22	0.324	17 ± 12	13 ± 14	0.003	15 ± 10	16 ± 12	0.814	0.323	0.028
Lumen volume, mm^3	398 ± 182	342 ± 115	0.053	348 ± 133	308 ± 130	0.057	310 ± 133	332 ± 127	0.267	< 0.001	0.815
Culprit vessels											
Segments available for analysis	n = 22	n = 5		n = 19	n = 3		n = 16	n = 8			
Plaque burden, %	48 ± 6	44 ± 18	0.376	43 ± 11	47 ± 14	0.578	51 ± 9	49 ± 8	0.724	0.523	0.449
Fibrous volume, %	57 ± 9	58 ± 8	0.795	51 ± 10	67 ± 12	0.026	44 ± 12	57 ± 11	0.024	< 0.001	0.727
Fibro-fatty volume, %	13 ± 9	13 ± 6	0.683	9 ± 5	8 ± 2	0.562	7 ± 5	11 ± 7	0.069	0.006	0.561
NC volume, %	19 ± 8	19 ± 7	0.930	23 ± 9	17 ± 8	0.285	28 ± 7	20 ± 7	0.018	0.003	0.697
DC volume, %	11 ± 8	10 ± 8	0.851	17 ± 8	8 ± 7	0.113	22 ± 12	13 ± 12	0.040	0.001	0.655
Lumen volume, mm^3	340 ± 144	398 ± 340	0.541	385 ± 171	236 ± 133	0.168	271 ± 82	307 ± 116	0.394	0.201	0.505

[1]*P* value for trend across age groups in men. [1]*P* value was calculated using linear regression; [2]*P* value for trend across age groups in women. *P* value was calculated using linear regression. DC: Dense calcium; NC: Necrotic core.

in culprit vessels of men changed significantly during aging with increasing volumes of necrotic core and dense calcium (*i.e.*, old men need a rupture-prone plaque morphology to present as ACS). Plaque composition in old women was similar to that in young women, therefore leading to significant differences in plaque composition between men and women in the highest age tertile. Old women also presented as ACS with less necrotic core and dense calcium than men. Plaque burden remained similar between men and women and also between the three age groups.

Differences between non-culprit and culprit vessels
In the lowest and middle age tertiles, differences between non-culprit and culprit vessels were similar for men and women. In the lowest age tertile, plaque burden in culprit vessels was significantly higher than that in non-culprit vessels (*P* < 0.001 for men and *P* = 0.004 for women), but no significant differences in plaque composition were found between non-culprit and culprit vessels. In the middle age tertile of men and women, there were no significant differences of plaque burden and composition between non-culprit and culprit vessels. In men of the highest age tertile, plaque composition in non-culprit and culprit vessels differed significantly with more necrotic core (*P* < 0.001), more dense calcium (*P* = 0.012), less fibrous (*P* = 0.003) and less fibro-fatty (*P* = 0.004) volume in the culprit vessel, whereas plaque burden was not significantly (*P* = 0.110) different. In women in the highest age tertile, plaque burden in culprit vessels was significantly higher than in non-culprit vessels (*P* = 0.017), whereas no significant differences in plaque composition were found.

Analysis of combined non-culprit and culprit vessels
If non-culprit and culprit vessels are combined for analysis, plaque burden increased significantly in men (*P* <

0.001) and women (*P* < 0.001). Men had more plaque burden than women in every age tertile (*P* < 0.001 for lowest, middle or highest age tertile). Percentages of necrotic core increased with increasing patient age in both men (*P* = 0.019) and women (*P* = 0.016). Plaque composition significantly differed between men and women in the lowest and middle age tertile, whereas in the highest age tertile no significant differences were found.

DISCUSSION
This study provides evidence that age- and gender-related differences in plaque burden and plaque composition significantly depend upon whether the vessel contained a non-culprit or culprit lesion. Effects of pathophysiologic processes during aging are presumably better observable in non-culprit lesions where acute processes play a minor role. In non-culprit vessels of men, plaque burden increases with increasing age, but plaque composition remains constant during aging. Compared with men, young women have a significantly lower plaque burden and lower amount of necrotic core which may reflect protective effects of female hormones. After menopause the plaque composition in non-culprit vessels of women approximates that of men. The plaque burden of women increases during aging like men, but it remains lower than in men until old age. In culprit vessels the situation is different. Culprit lesions reflect an acute stage of disease and influencing factors other than the long-term pathophysiologic processes which occur during aging presumably come to the fore. Thus, culprit vessels of young women and men exhibit similar rupture-prone plaque morphology with a high percentage of necrotic core and a relatively high plaque burden. In men, a significant increase of necrotic core and dense calcium is required to result in a rupture-prone morphology at old age. In old women, morphology similar to young women and men is
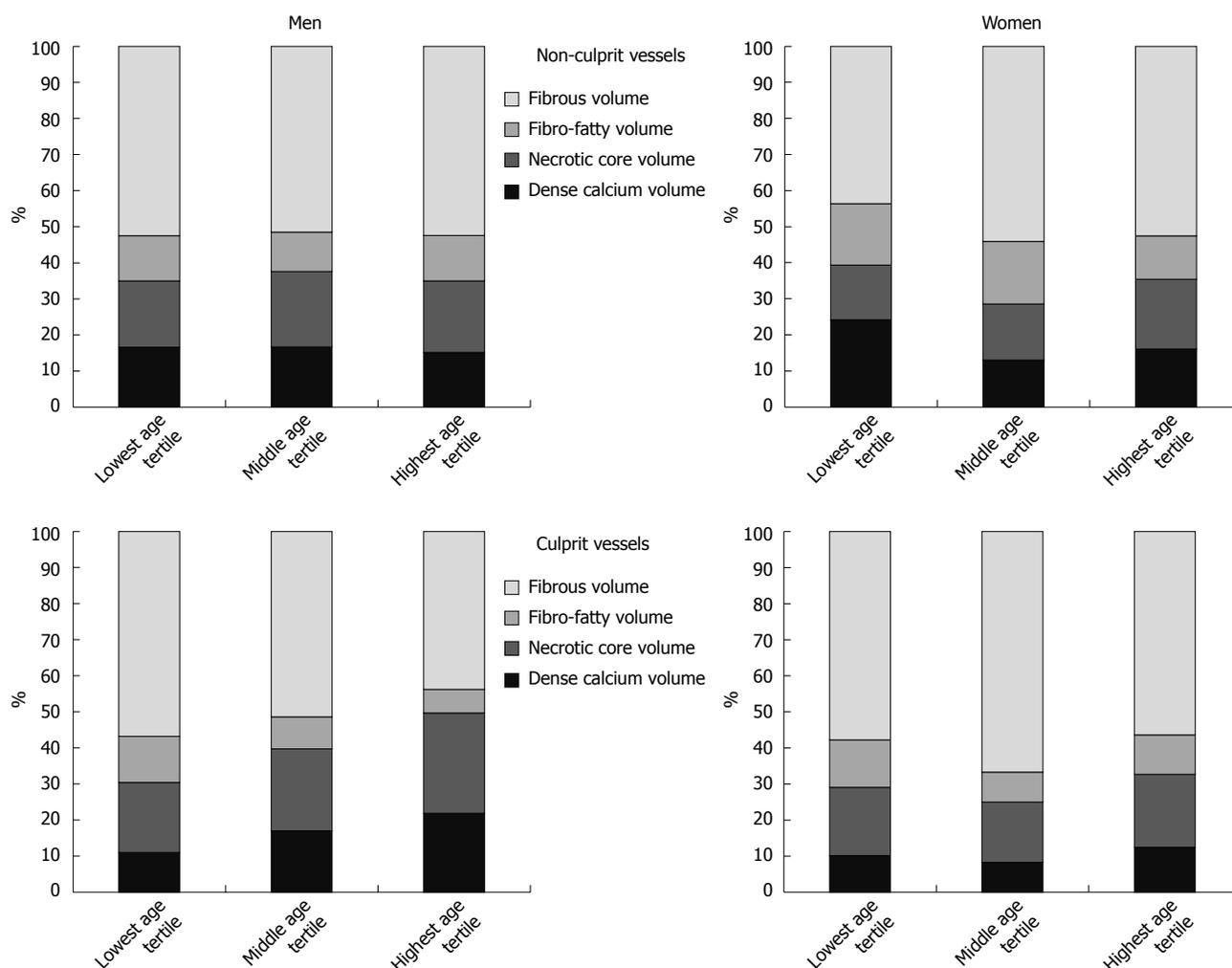
Figure 1 Plaque composition in men and women during aging in non-culprit and culprit vessels.

sufficient to result in a rupture-prone culprit lesion.

Qian *et al*[10] reported that both women and men had an increase in plaque with increasing age, that at any age, men had more plaque than women, that percentages of dense calcium and necrotic core increased with age in both men and women, and that gender differences were lowest in the oldest tertile. Our study confirms these findings, if non-culprit and culprit lesions are analyzed together. However, if non-culprit and culprit lesions are analyzed separately, then age- and gender-related differences are more complex.

Our study is in accordance with previous pathologic studies although comparability of IVUS and pathologic studies is limited due to several reasons[6-9]. Dollar *et al*[6] reported that young women had more fibrous and fibro-fatty tissue and less necrotic core than old men. Our study confirms this finding. Burke *et al*[8] reported that plaque erosion, the major substrate for thrombosis in premenopausal women, does not appear to be inhibited by estrogen. Presumably this could explain why we did not find any differences in the plaque composition of culprit vessels between young men and women.

The present study has limitations. First, study participants underwent coronary angiography for stable angina or ACS. This might restrict extrapolation of our findings to a more healthy general population. Second, this was not a lesion-specific analysis; rather, LAD, CX and/or RCA were imaged in a proximal 4 cm segment. However, it has been shown that vessel-based measurements correlate well with lesion-specific analysis[26]. Third, the number of culprit vessels available for analysis in women was too low to exclude type II error. Fourth, in culprit vessels it may be difficult to differentiate plaque from thrombi by 20 MHz IVUS. Therefore, plaque composition in culprit vessels may be affected by thrombi. Fifth, hormone replacement therapy was not assessed in women.

In conclusion, the present study has revealed that age- and gender-related differences in plaque burden and plaque composition significantly depend upon whether the vessel contained a non-culprit or culprit lesion. More research is needed to understand the pathophysiology of plaque morphology changes during aging in women and men.

COMMENTS

Background

Only few studies so far characterized age- and gender-related differences in coronary plaques *in vivo* with the use of virtual histology (VH) intravascular

ultrasound (IVUS). In these studies the compositional differences of non-culprit and culprit vessels were not distinguished. The present study therefore examines age- and gender-related differences in non-culprit versus culprit coronary artery vessels assessed with VH-IVUS.

Research frontiers
Differences in the plaque composition of non-culprit and culprit vessels according to age and gender have not been described so far.

Innovations and breakthroughs
The present study shows that age- and gender-related differences in plaque burden and plaque composition significantly depend on whether the vessel contained a non-culprit or culprit lesion. More research is needed to understand the pathophysiology of plaque morphology changes during aging in women and men.

Applications
The present study has research implications. More research is needed to understand the pathophysiology of plaque morphology changes during aging in women and men.

Terminology
Vessel containing a culprit lesion: To classify as vessel containing a culprit lesion, the patient had to present with an acute coronary syndrome, and the VH-IVUS had to be performed in a vessel segment containing the culprit lesion according to conventional coronary angiography.

Peer review
The authors showed the characteristics of coronary disease according to gender and age and different patterns of plaque composition between culprit and non-culprit vessels. However, several issues should be considered and clarified more (*e.g.*, lesion inclusion criteria and the definition of culprit/non-culprit vessels should be clarified).

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BRIEF ARTICLE

Air pollution and heart failure: Relationship with the ejection fraction

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Abstract

AIM: To study whether the concentrations of particulate matter in ambient air are associated with hospital admission due to heart failure in patients with heart failure with preserved ejection fraction and reduced ejection fraction.

METHODS: We studied 353 consecutive patients admitted into a tertiary care hospital with a diagnosis of heart failure. Patients with ejection fraction of $\geq 45\%$ were classified as having heart failure with preserved ejection fraction and those with an ejection fraction of $< 45\%$ were classified as having heart failure with reduced ejection fraction. We determined the average concentrations of different sizes of particulate matter (< 10, < 2.5, and < 1 μm) and the concentrations of gaseous pollutants (carbon monoxide, sulphur dioxide, nitrogen dioxide and ozone) from 1 d up to 7 d prior to admission.

RESULTS: The heart failure with preserved ejection fraction population was exposed to higher nitrogen dioxide concentrations compared to the heart failure with reduced ejection fraction population (12.95 ± 8.22 μg/m^3 *vs* 4.50 ± 2.34 μg/m^3, $P < 0.0001$). Multivariate analysis showed that nitrogen dioxide was a significant predictor of heart failure with preserved ejection fraction (odds ratio ranging from (1.403, 95%CI: 1.003-2.007, $P = 0.04$) to (1.669, 95%CI: 1.043-2.671, $P = 0.03$).

CONCLUSION: This study demonstrates that short-term nitrogen dioxide exposure is independently associated with admission in the heart failure with preserved ejection fraction population.

Key words: Air pollution; Heart failure; Preserved ejection fraction; Reduced ejection fraction; Nitrogen dioxide

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INTRODUCTION

Ambient air pollution is a recognized risk factor for cardiovascular morbidity and mortality[1-3]. Nitrogen dioxide (NO_2) is a strong respiratory irritant gas originating from high-temperature combustion. Main outdoor sources of NO_2 include vehicle exhausts (particularly those equipped with diesel engines) and fossil-fuel power plants, whereas the most important indoor sources are gas heaters, stoves, and environmental tobacco smoke[4].

Large meta-analyses of studies on the short-term health effects of NO_2 have been carried out in Europe[5,6], the United States[7,8], and Canada[9]. The results indicate a positive association between daily increases of NO_2, cardiovascular and respiratory mortality. Several studies using administrative databases have shown a positive association between short-term increases in respirable or fine particles and the risk of hospitalization for congestive heart failure (HF)[10-12].

The aim of this investigation was to study whether the concentrations of particulate matter in ambient air are associated with hospital admission due to HF in patients with HF with preserved ejection fraction (HF-PEF) and reduced ejection fraction (HF-REF).

MATERIALS AND METHODS

Study population

We prospectively enrolled 458 consecutive patients admitted into a tertiary care hospital with a diagnosis of HF. The diagnosis of HF had to be established according to the clinical Framingham criteria[13]. We did not include patients with severe primary valve heart disease ($n = 13$), chronic obstructive pulmonary disease ($n = 30$), airway hyperresponsiveness ($n = 25$), asthma ($n = 16$) and presence of respiratory infection 15 d before admission ($n = 21$). Hence, 353 patients were included in the study. Patients with ejection fraction of $\geq$ 45% were classified as having HF-PEF and those with an ejection fraction of < 45% were classified as having HF-REF[14].

The study was planned according to the Declaration of Helsinki and approved by the local ethics committee, and all patients provided signed informed consent. Clinical data, including age, sex, arterial hypertension (> 140/90 mmHg), hypercholesterolemia (> 5.17 mmol/L), smokers, diabetes and left ventricular ejection fraction, were analyzed as baseline variables on admission. The left ventricular ejection fraction was measured using the modified Simpson's rule[15].

Air pollution measurements

The atmospheric pollutants were measured in an urban background monitoring station using reference methods (Directive 2008/50/EC). Concentrations of particulate matter (PM) smaller than 10, 2.5 and 1 μm (PM10, PM2.5 and PM1 respectively) were measured with automatic analyzer and the gravimetric method[16].

The concentrations of gaseous pollutants were measured using different methods: (1) sulphur dioxide was measured using ultraviolet fluorescence (Thermo Electron Corporation™, model 43C); (2) NO_2 was measured using chemiluminescence (Thermo Electron Corporation™, model 42C); (3) ozone was measured using ultraviolet absorption (Thermo Electron Corporation™, model 49C); and (4) carbon monoxide was measured using the technique NDIR-Gas Correlation Filter Analyser (Thermo Electron Corporation™, model 48C). The analyzers were calibrated every 3 mo and they always had a high linearity ($r^2 = 0.99$)[17]. Meteorological variables (temperature, relative humidity and wind speed) were measured using standard techniques. These variables were measured with 1 min resolution. Then, 24 h averages from the previous day up to 7 d prior to admission were calculated.

Statistical analysis

Results for normally distributed continuous variables are expressed as mean ± SD. Continuous variables with non-normal distribution are presented as median values and interquartile intervals; categorical data are expressed as percentages. Analysis of normality of the continuous variables was performed with the Kolmogorov-Smirnov test. Differences between groups were assessed by unpaired 2-tailed t test and the Mann-Whitney U test for continuous variables, as appropriate. Categorical data and proportions were analyzed by use of χ^2 or Fisher's exact test when required. In our study, all of the pollutants were expressed as the 24 h average concentrations from the previous day up to 7 d prior to admission.

A multivariate analysis was carried out using a binary logistic regression model to estimate the risk of admission for HF-PEF compared to admission for HF-REF, according to sizes of particulate matter and concentrations of gaseous pollutants during 7 d prior to admission. All of the variables with a value of $P < 0.05$ in the univariate analysis were included in the model. Differences were considered statistically significant if the null hypothesis could be rejected with > 95% confidence. All probability values are 2 tailed. The SPSS 15 statistical software package (SPSS Inc, Chicago, IL, United States) was used for all calculations.

RESULTS

According to the pre-established criteria, 124 patients were classified as HF-PEF. The baseline characteristics of the patients with HF-PEF and HF-REF are listed in Table 1. The HF-PEF population was significantly older and included a larger proportion of women. There were no significant differences between groups regarding presence of conventional coronary risk factors for coronary

Table 1 Clinical variables of 353 consecutive patients with heart failure: Comparison between patients with heart failure and preserved ejection fraction and patients with heart failure and reduced ejection fraction *n* (%)

Variables	HF-PEF (*n* = 124)	HF-REF (*n* = 229)	*P* value
Age (yr)	69 ± 8	66 ± 12	0.01
Male gender	56 (45.2)	154 (67.2)	< 0.001
Hypertension	75 (60.5)	84 (36.7)	< 0.001
Hypercholesterolemia	35 (28.2)	52 (22.7)	0.25
Smokers	14 (11.3)	40 (17.5)	0.12
Diabetes	45 (36.3)	104 (45.4)	0.09
LVEF (%)	55 ± 9	33 ± 6	< 0.001

Data are expressed as mean ± SD, and *n* (%) for categorical variables. HF-PEF: Heart failure with preserved ejection fraction; HF-REF: Heart failure with reduced ejection fraction; LVEF: Left ventricular ejection fraction.

Table 2 Data on atmospheric pollution in ambient air and meteorological variables between the previous day and the 7 d prior to admission for both of the study group

	HF-PEF (*n* = 124)	HF-REF (*n* = 229)	*P* value
Meteorological variables			
Wind speedy (m/s)	2.72 ± 0.68	2.62 ± 0.78	0.21
Temperature (℃)	19.76 ± 2.52	20.08 ± 2.82	0.32
Relative humidity (%)	67.68 ± 6.10	66.85 ± 7.02	0.29
Gaseous pollutants (mg/m^3)			
CO	172.44 ± 23.89	177 ± 27.10	0.11
SO$_2$	8.1 ± 4.40	7.33 ± 3.46	0.06
NO$_2$	12.95 ± 8.22	4.50 ± 2.34	< 0.0001
O$_3$	59.80 ± 12.52	61.25 ± 11	0.26
Atmospheric particles (mg/m^3)			
PM10	21 (13-30)	25 (17.5-32)	0.02
PM2.5	13.5 (9-21)	16.5 (11-21)	0.12
PM1	8 (6-16)	9.5 (7-13)	0.42

All of the pollutants are expressed as the average concentration of the pollutant. Data are expressed as mean ± SD, and median values (interquartile intervals). HF-PEF: Heart failure with preserved ejection fraction; PM: Particulare material with an aerodynamic diameter; PM10: PM < 10 μm; PM2.5: PM < 2.5 μm; PM1: PM < 1 μm.

Table 3 Multivariate binary logistic regression analysis including nitrogen dioxide as the main independent variable

	OR	95%CI	*P* value
Model 1 (unadjusted)			
NO$_2$	1.428	1.001-2.055	0.04
Model 2			
NO$_2$	1.669	1.043-2.671	0.03
Age	1.278	0.912-1.618	0.33
Model 3			
NO$_2$	1.429	0.992-2.058	0.05
Gender	0.948	0.111-8.067	0.96
Model 4			
NO$_2$	1.403	1.003-2.007	0.04
Hypertension	0.36	0.037-3.482	0.37
Model 5			
NO$_2$	1.516	1.005-2.397	0.01
LVEF	1.024	0.791-1.324	0.85
Model 6			
NO$_2$	1.489	1.009-2.453	0.01
PM10	1.124	0.997-1.974	0.94

LVEF: Left ventricular ejection fraction; NO$_2$: Nitrogen dioxide; PM: Particulare material with an aerodynamic diameter; PM10: PM < 10 μm.

DISCUSSION

Short-term exposure to air pollution is associated with acute cardiovascular events[18-20]. Our results show that HF-PEF is common and accounts for a significant proportion of admissions in patients with HF, 35% of our patients. This rate of patients is similar to that reported in previous studies[14,21]. This group of patients had different characteristics from those of patients with HF-REF, including older population, higher proportion of women, and more frequent history of hypertension. In the present study, we demonstrated that short-term exposure to raised NO$_2$ levels are an independent risk factor for admission to hospital for HF-PEF population, even superior to classical described predictors, such as age, sex, hypertension and left ventricular ejection fraction[21,22].

Despite the large body of evidence linking NO$_2$ with daily mortality, few studies have addressed the issue of susceptibility to NO$_2$ by performing analyses by age, sex, and chronic morbidity[6]. Recents epidemiology studies have focused on cardiopulmonary dysregulation, including the role of air pollutant exposure in provoking decompensated congestive HF[3,10,23]. A number of mechanisms have been proposed to explain the cardiovascular effects of air pollutant. At the cellular level, these various mechanisms involve free radical production, oxidative stress, cytokine release, inflammation, endotoxin-mediated damage, stimulation of capsaicin receptors, autonomic nervous system activity and covalent modification of key cellular molecules[24-27].

Ongoing investigation suggests that, although diastolic abnormalities may be present in many patients with HF-PEF, other aspects of pathophysiology likely also contribute to symptoms. Previous studies have concluded that inflammation contributes to diastolic abnormalities in HF-PEF[28]. In our study, we discovered that NO$_2$ may

artery disease, with the exception of hypertension, which were higher in the patients with HF-PEF. Left ventricular ejection fraction was significantly reduced in the patients with HF-REF.

No statistically significant differences were found in the meteorological variables between both groups. Regarding gaseous pollutants, we found no statistically significant differences, except that there were higher concentrations of NO$_2$ exposure in patients with HF-PEF. When comparing, exposure to concentrations of sizes of particulate matter, between patients with HF-PEF and HF-REF, the first group tended to have lower values of PM10 (Table 2). We carried out partial multivariable binary logistic regression analyses, using a stepwise selection model. This analysis showed that exposure to NO$_2$ was a significant predictor of HF-PEF [odds ratio ranging from (1.403, 95%CI: 1.003-2.007, *P* = 0.04) to (1.669, 95%CI: 1.043-2.671, *P* =0.03); Table 3].

be a precipitating factor for admission for HF-PEF rather than the cause of this condition. The short-term elevations of NO_2 could play an important pathophysiologic role in HF-PEF population, perhaps through of the activation of molecular inflammatory pathways that could be transduced systemically even in the absence of obvious alveolitis or interstitial pneumonitis[29]. In this way, Briet et al demonstrated that exposure to urban gaseous pollutant (including NO_2) affect artery endothelial function in patients as well as healthy control subjects[30].

Our study has some limitations. We did not use time series analysis in our study to examine the short-term relationship between the variations in atmospheric pollution and HF. This was because daily variations in the pollutants during the 7 d prior to admission were small enough to allow us to exclude the time series analysis[29]. Moreover, the sample size could be small, but the association between NO_2 and HF-PEF was highly significant.

This is the first study that demonstrates that short-term exposure to NO_2 is independently associated with the HF-PEF population, when compared to the HF-REF population.

COMMENTS

Background
Several studies using administrative databases have shown a positive association between short-term increases in respirable or fine particles and the risk of hospitalization for congestive heart failure.

Research frontiers
Heart failure is of growing incidence and prevalence and is now the main cause for hospital admission among the elderly and increasing expenditure in medicine. Ambient air pollution is a recognized risk factor for cardiovascular morbidity and mortality. Despite the large body of evidence linking nitrogen dioxide with daily mortality, few studies have addressed the issue of susceptibility to nitrogen dioxide by performing analyses by age, sex, and risk of admission for heart failure with preserved ejection fraction and reduced ejection fraction.

Innovations and breakthroughs
Nitrogen dioxide is a strong respiratory irritant gas originating from high-temperature combustion. Main outdoor sources of nitrogen dioxide include motor vehicles (particularly those equipped with diesel engines) and fossil-fuel power plants, whereas the most important indoor sources are gas heaters, stoves, and environmental tobacco smoke. In this study, authors found statistically significant association between nitrogen dioxide and admission in the heart failure with preserved ejection fraction population.

Applications
Several precautionary recommendations can be made for healthcare providers who interact with individuals who are at risk for cardiovascular diseases. Although they have not been clinically tested or proven to reduce mortality, they are practical and feasible measures that may help to reduce exposures to air pollution and therefore potentially lower the associated cardiovascular risk. These recommendations can be: (1) all patients with cardiovascular disease should be educated about the cardiovascular risks posed by air pollution; (2) part of patient education should include the provision of information regarding the available sources (local and national newspapers) that provide a daily air quality index; and (3) on the basis of the forecast air quality index, prudent recommendations for reducing exposure and limiting activity should be provided based on the patient's level of risk.

Terminology
Heart failure is a condition that is usually caused by a reduction of the contractile function of the ventricular chambers or an impairment of the relaxation properties of the cardiac chambers. Air pollution is the introduction into the atmosphere of chemicals, particulate matter, or biological materials that cause discomfort, disease, or death to humans.

Peer review
This is a good descriptive study in which the authors analyze effect of short-term exposure of nitrogen dioxide in patients with the clinical syndrome of heart failure with preserved and depressed left ventricular ejection fraction. The results are interesting and suggest that other aspects, as the exposure of nitrogen dioxide can contribute to pathophysiology of the heart failure with preserved ejection fraction. These data are of public health importance.

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BRIEF ARTICLE

Myocardial perfusion imaging in patients with a recent, normal exercise test

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Abstract

AIM: To investigate the added value of myocardial perfusion scintigraphy imaging (MPI) in consecutive patients with suspected coronary artery disease (CAD) and a recent, normal exercise electrocardiography (ECG).

METHODS: This study was a retrospective analysis of consecutive patients referred for MPI during a 2-year period from 2006-2007 at one clinic. All eligible patients were suspected of suffering from CAD, and had performed a satisfactory bicycle exercise test (*i.e.*, peak heart rate > 85% of the expected, age-predicted maximum) within 6 mo of referral, their exercise ECG was had no signs of ischemia, there was no exercise-limiting angina, and no cardiac events occurred between the exercise test and referral. The patients subsequently underwent a standard 2-d, stress-rest exercise MPI. Ischemia was defined based on visual scoring supported by quantitative segmental analysis (*i.e.*, sum of stress score > 3). The results of cardiac catheterization were analyzed, and clinical follow up was performed by review of electronic medical files.

RESULTS: A total of 56 patients fulfilled the eligibility criteria. Most patients had a low or intermediate ATPⅢ pre-test risk of CAD (6 patients had a high pre-test risk). The referral exercise test showed a mean Duke score of 5 (range: 2 to 11), which translated to a low post-exercise risk in 66% and intermediate risk in 34%. A total of seven patients were reported with ischemia by MPI. Three of these patients had high ATPⅢ pre-test risk scores. Six of these seven patients underwent cardiac catheterization, which showed significant stenosis in one patient with a high pre-test risk of CAD, and indeterminate lesions in three patients (two of whom had high pre-test risk scores). With MPI as a gate keeper for catheterization, no significant, epicardial stenosis was observed in any of the 50 patients (0%, 95% confidence interval 0.0 to 7.1) with low to intermediate pre-test risk of CAD and a negative exercise test. No cardiac events occurred in any patients within a median follow up period of > 1200 d.

CONCLUSION: The added diagnostic value of MPI in patients with low or intermediate risk of CAD and a recent, normal exercise test is marginal.

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INTRODUCTION

Treadmill or bicycle exercise electrocardiography (ECG) has been the test of choice for many years for the diagnosis of coronary artery disease (CAD) for reasons of diagnostic performance, cost, and availability. According to the American guidelines, exercise testing remains the test of choice among symptomatic patients with low or intermediate pre-test risk of CAD, provided the patient is able to exercise and the ECG is analyzable for ischemia[1]. A normal exercise test is consistent with a good prognosis with regard to cardiac events and cardiovascular and overall mortality[2].

In patients with intermediate or high pre-test risk of CAD, non-invasive imaging methods and invasive coronary catheterization are preferred[3-6]. Myocardial perfusion scintigraphy imaging (MPI) is one of the most frequently used non-invasive methods for the assessment of the extent and severity of ischemia in patients with intermediate risk of CAD[6]. Several studies have shown that exercise or pharmacological MPI is superior to exercise ECG for the identification of ischemic heart disease in these patients[7-9]. Still, the use of MPI is considered inappropriate in patients with a low risk of CAD and the ability to exercise with an analyzable ECG[1]. Thus, the diagnostic performance of MPI in low-risk patients and its added value to a normal exercise ECG remain unclear. There are contradictory recommendations in the international guidelines on the management of patients with a normal exercise test but continued suspicion of CAD[1,10]. Apparently, no trials have directly addressed this issue. The purpose of this study was to evaluate the diagnostic outcome of MPI in patients with a recent history of a normal bicycle exercise ECG.

MATERIALS AND METHODS

Patients

Retrospective data were extracted from consecutive patients who performed a bicycle exercise MPI from January 1, 2006 through December 31, 2007 in a single nuclear medicine center at a regional hospital. The inclusion criteria included the following: (1) the patient was referred for MPI due to suspicion of CAD; (2) the patient had performed a bicycle exercise ECG within six months of referral; (3) the symptoms were unchanged from the time of the exercise ECG to MPI, and no cardiovascular events had occurred; (4) the maximum heart rate obtained at the referral exercise ECG test was at least 85% of the expected age-related maximum; (5) the exercise test was not terminated due to exercise-limiting angina; (6) the baseline ECG was suitable for the assessment of exercise-induced ischemia; and (7) the exercise ECG was classified as negative for ischemia according to the European guidelines for exercise ECG[10]. Patients with known CAD were excluded. Pre-test risk of CAD was calculated per the ATP Ⅲ classification.

Referral exercise ECG

All original exercise ECGs were evaluated and reported by a trained cardiologist at the time of testing. Additionally, all exercise tests were retrospectively reviewed by another board-certified cardiologist. In the case of discrepancy between the initial reading and the second opinion, a third cardiologist read the test, and a decision was made based on majority voting. The post-test risk of cardiovascular events was calculated with DanStress® software (Svendborg, Denmark) using the algorithm provided by Mark *et al*[2].

Myocardial perfusion scintigraphy

All MPIs were performed as a two-day, stress-rest standard protocol with two days between the stress and the rest tests, as previously described[11]. No attenuation correction was used. Patients with a normal stress MPI did not have a rest MPI. All MPIs were initially reported as positive or negative for ischemia by subjective analysis only. Therefore, all MPIs were retrospectively reviewed in a blinded fashion by a board-certified nuclear medicine physician without any clinical information. Manual segmental scoring was performed using a 17-segment model with a score from 0 to 4 for each segment, from which the sum of stress score (SSS), the sum of rest score (SRS), and the sum of difference score between stress and rest images (SDS) were calculated[12]. In addition, SSS, SRS and SDS were automatically calculated with dedicated software. A SSS score of 0 to 3 was considered to be normal, and SSS > 3 to be abnormal[13]. In the case of discrepancy in disease classification (*i.e.*, normal or abnormal) between the automatic and manual score, a second nuclear medicine physician performed an additional manual segmental score, and the decision was determined by majority voting. Further in this manuscript, ischemia was present only if confirmed by subjective visual interpretation as well a SSS > 3.

Coronary catheterization

Cardiac catheterization was performed in accordance with the standard institutional practice and current guidelines[10]. A significant stenosis required any luminal narrowing of 70% or more of the diameter of a major epicardial vessel or 50% or more of the diameter of the left main coronary artery. Any investigation with no more than 20% luminal narrowing of any vessels was classified as normal. Results other than stenosis or normal were reported as indeterminate. All findings by angiography were assessed by a board of cardiologists, and the report represented their consensus.

Clinical follow up

Clinical follow up was performed to assess the cardiovascular event rates in the study population. The institutional electronic patient file system was reviewed for hospital admissions and outpatient contacts for the study population, and any cardiovascular events (cardiac and non-

Table 1 Patient demographics and clinical variables *n* (%)	
Men/women (*n*)	**32/24**
ATPⅢ 10-year CAD risk	
Low (< 10%)	33 (59)
Intermediate (10% to 20%)	17 (30)
High (20% and above)	6 (11)
Individual CAD risk factors	
Hypertension	22 (39)
Diabetes	1 (2)
Hypercholesterolemia	21 (38)
Body mass index > 30 kg/m²	8 (14)
Family history of CAD	25 (47)
Smoking (current or former)	31 (55)
Current medication	
Beta blockers	3 (5)
ACE inhibitor or Angiotensin Ⅱ receptor antagonists	4 (7)
Diuretics	4 (7)
Calcium channel blockers	5 (9)
Aspirin	33 (59)
Clodipogrel	1 (2)
Statins	10 (18)
Slow release nitrates	1 (2)
Prior non cardiac vascular conditions	
Stroke or TIA	2 (4)
PAD	0 (0)

CAD: Coronary artery disease; PAD: Peripheral arterial occlusive disease; TIA: Transient ischemic attack.

cardiac) were recorded.

Ethical approval
The study was approved by the Danish Data Protection Agency. Retrospective informed consent to obtain data from patient files was obtained through an approval by the Danish Board of Health. Due to the retrospective design, no approval by an Ethical Committee was required.

Statistical analysis
Descriptive statics comprised means and standard deviations of the mean (SD) and proportions (%). Exact confidence limits of proportions were read from Geigy Scientific Tables (volume 2, 1998; CIBA-GEIGY Ltd, Basel, Switzerland). No analytical statistics were used.

RESULTS

Patient population
Of 179 patients who underwent exercise MPI during the observation period, 56 patients fulfilled the eligibility criteria. The main reasons for exclusion were no prior exercise test (*n* = 97), known CAD (*n* = 5), and criteria related to the referral exercise test such as ECG compatible with ischemia (*n* = 15), insufficient heart rate response (*n* = 4), and lack of access to the original exercise test data (*n* = 2). The mean time from exercise ECG to MPI was 82 d (range: 8-179 d). Patient demographics and clinical variables are shown in Table 1. A large proportion of patients had hypertention and hypercholesterolemia so mild that is it was not considered therapy-requiring by the referring physicians. A total of 35 patients were asymptomatic at baseline. Functional grading of angina showed Canadian Cardiovascular Society (CCS) grades 1-2 in 11 patients and grades CCS 3-4 in 8 patients; data was missing in two patients. No patients had known heart failure.

Referral exercise ECG
All patients terminated the exercise test because of exhaustion or muscle fatigue. No patients had exercise-limiting angina. The mean peak heart rate was 164 beats per minute, which corresponded to 102% (range 87% to 128%) of the predicted, age-adjusted peak heart rate. The mean workload was 155 W (96%, range 60% to 160%). Twelve patients (21%) reported non-specific chest pain, and the remainder of the patients (79%) were asymptomatic during the exercise test. The mean post-test Duke score was 5 (range -2 to 11), which translated into a low post-test risk in 37 patients (66%) and a moderate risk in 19 patients (34%).

MPI
A total of 53 of 56 patients completed the exercise MPI with a heart rate of least 85% of the age-predicted peak heart rate (mean 99.4%). The mean workload was 166 W. One patient was stopped at 84% of the peak heart rate due to exercise-limiting angina (see later). Two patients failed to reach their target heart rate, and they underwent an adenosine stress test with 25 W of bicycle exercise[11]. Stress-only MPI was performed in 14 (25%) of the patients. The criteria for accepting a stress-only test were as previously described[14].

A total of 7 patients were reported as suffering from ischemia and presented also with quantitative, documented ischemia (SSS > 3) with reversible defects in most patients (Table 2).

Three patients were reported as normal in the original MPI report (two patients with low risk and one patient with intermediate risk) but showed SSS > 3 by segmental score as performed as part of this retrospective analysis. None of these patients had reversible defects. MPI was performed without attenuation correction, and segmentation may be falsely high. Based on minor fixed perfusion defects, and normal wall motion pattern in the affected regions, such patients are mostly reported as normal. None of these patients underwent catheterization or experienced cardiac events during the follow up period.

Coronary catheterization
All patients but one in Table 2 with reported ischemia as well as SSS > 3 underwent cardiac catheterization. MPI served as a gatekeeper for catheterization. Thus, the remainder 49 patients with a visual normal MPI (as well as a normal exercise test) were not routinely referred for cardiac catheterization. However, 3 of these 49 patients underwent catheterization during the follow up and none showed significant stenosis.

One patient with a positive MPI and SSS > 3 was diagnosed with significant CAD (patient 4, Table 2). This

Table 2 Clinical and imaging data for patients classified with coronary artery disease by myocardial perfusion imaging

Patient No	Gender	Age (yr)	ATPⅢ pre test risk	Duke post test risk	SSS > 3	SDS > 3	Cardiac catheterization
1	Male	79	High	Intermediate	+	+	Indeterminate
2	Male	52	Intermediate	Intermediate	+	+	Normal
3	Male	71	Intermediate	Low	+		Normal
4	Male	43	High	Intermediate	+	+	Significant stenosis
5	Female	65	Low	Low	+	+	Not done
6	Male	63	Intermediate	Low	+		Indeterminate
7	Male	48	High	Low	+	+	Indeterminate

SSS: Sum of stress score; SDS: Sum of difference score.

patient with significant two-vessel stenosis had a high pre-test risk of CAD, completed the referral exercise test with non-specific chest pain, reached 104% of peak heart rate, presented an exercise capacity of 200 W, showed no ECG changes, and had an intermediate Duke post-test risk score. He experienced no cardiac events or aggravation of symptoms from referral exercise test to MPI. During MPI exercise testing 4.5 mo later, he experienced exercise-limiting angina and received the radiotracer at 84% of his predicted peak heart rate. There were no ECG changes; however, the MPI showed significant ischemia.

Among the 50 patients with a low or intermediate pre-test risk of CAD, the final diagnostic work up, with the clinical MPI report as a gatekeeper for cardiac catheterization, showed no significant anatomical stenosis in any of these patients (0/50; 0%, 95%CI: 0.0-7.1). One of these patients had an indeterminate lesion (patient 6 in Table 2).

Clinical follow-up

The median follow up time was 1277 d (range 917-1566 d). No patients had any documented cardiac events, such as non-fatal myocardial infarction, cardiac interventions (percutaneous coronary interventions or bypass surgery), or sudden cardiac death (0/56; 0% 95%CI: 0.00-6.38). All patients were alive at follow up. One patient experienced a non-fatal stroke (patient 7 in Table 2).

DISCUSSION

In this study, we investigated the diagnostic value of MPI in patients with a recent, normal exercise ECG. To the best of our knowledge, this study is the first of its kind. Among 56 patients one patient had a significant stenosis as shown by cardiac catheterization. This patient had a high pre-test risk of CAD and should, according to current guideline recommendations, be referred directly for coronary catheterization. By contrast, an exercise MPI did not reveal any significant anatomical stenosis in any of 50 patients with low to intermediate pre-test risk of CAD and a recent, normal exercise ECG test. The majority of these patients had a negative MPI (and thus no subsequent catheterization) or a positive MPI with either normal vessels or insignificant anatomical stenosis).

MPI has solid documentation for the diagnosis and risk stratification of patients with CAD[6]. Several groups have documented that the imaging results from MPI have higher sensitivity and specificity compared to exercise data obtained from the same exercise MPI[7-9]. However, results from a recent, large study showed that the perfusion imaging component of an exercise MPI did not add diagnostic value in patients who were able to perform an adequate workload[15]. Most studies with exercise MPI include patients with intermediate risk of CAD, *i.e.*, the target population for MPI. The difference in diagnostic performance between exercise ECG and MPI in low-risk patients with a low prevalence of CAD remains unknown. Despite guideline recommendations against the use of MPI in low-risk patients, MPI is used widely for such patients[1,16]. The European Society of Cardiology (ESC) gives a class I recommendation for MPI in patients with an inconclusive exercise ECG but reasonable exercise tolerance and a low to intermediate risk of CAD in whom the diagnosis is still in doubt[10]. The clinical documentation for this recommendation is mainly based on patients with established CAD, including patients with prior coronary artery bypass grafting[17]. The ESC guidelines also give a class I recommendation for exercise ECG in patients with intermediate risk of CAD and a class Ⅱb recommendation for low-risk patients[10], which is in direct contrast to US guidelines, which recommend exercise ECG for low-risk patients and MPI for intermediate risk patients[1]. The discrepancy in recommendations across guidelines has been the subject of several recent systematic reviews[18,19]. There is a need for evidence-based guidelines for cardiovascular imaging[20].

In patients with low or intermediate risk of CAD and the ability to exercise, exercise ECG may still provide a sufficient diagnostic test and be a valid gate-keeper modality for additional anatomical and/or functional investigations. This is in accordance with US guidelines[1]. Our findings are also consistent with a recent, large study showing that the perfusion imaging component of an exercise MPI did not add diagnostic value in patients who were able to perform an adequate workload[15].

There are several limitations to this study. First, we recognize that the size of this study population is limited. However, we included well-characterized patients with a technically successful but negative exercise ECG referred for MPI for further diagnostic work up. To the best of our knowledge, no prior studies have described such pa-

tients. Second, cardiac catheterization was not performed in all of the patients, and this may influence the diagnostic accuracy. However, it would not be appropriate to do cardiac catheterization in low-risk patients with a normal exercise and MPI. Even with a positive MPI, catheterization should be optional, depending on the symptoms and extent of functional ischemia. This situation reflects the emerging scenario where only patients with notable ischemia are candidates for revascularization. Recent studies have confirmed clinical benefit to intervention beyond optimal medical therapy in cases of severe ischemia only[21,22]. The extent of symptoms and co-morbidities may have influenced the decision among cardiologists not to perform coronary catheterization. Nevertheless, our study has sufficient power with regards to the negative predictive value of a normal exercise test in patients with low or intermediate risk. None of 50 patients with low or intermediate risk by exercise test were found to have significant stenosis with MPI as the gatekeeper for catheterization (one patient had a non-significant stenosis).

In recent years, a number of new non-invasive tests have been introduced for the diagnosis of CAD, with computerized tomography angiography as one of the most promising techniques[3]. In centers where non-invasive imaging methods are available, such methods will eventually be used as a first-line option for the non-invasive diagnosis of CAD. In other situations, exercise ECG may persist as a gatekeeper modality for further diagnostic work up. Recent studies have shown that coronary computerized tomography angiography surpasses exercise-ECG in cost only, but not in diagnostic performance[23]. Further information is expected from large, ongoing trials comparing different types of anatomical and functional testing methods in patients with low to intermediate risk of CAD.

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COMMENTS

Background

Diagnosis of coronary artery disease (CAD) is important to initiate appropriate interventions and to prevent future major cardiovascular events. Depending of the risk of disease, different diagnostic tests are recommended. The choice of test reflects the diagnostic characteristics of the test (*e.g.*, positive and negative predictive diagnostic values and prognostic value), availability, cost, and risk of procedure. Generally, tests at each level serve as a gate keeper for next-level tests.

Research frontiers

Myocardial perfusion scintigraphy imaging (MPI) is generally indicated for patient with intermediate risk of CAD. International guidelines display diverging recommendations for additional imaging in low risk patients with normal exercise tests.

Innovations and breakthroughs

Prior studies have examined the importance of exercise data with imaging

results in exercise MPI. The independent values of these data are relevant for intermediate risk patients referred directly for MPI. This is the first study examining directly the added value of MPI in low to intermediate risk patients who recently performed a normal exercise test.

Applications

By studying the diagnostic value MPI, used as a gate keeper for subsequent cardiac catheterization, for identification of significant stenosis, it was revealed that the diagnostic value of additional imaging was marginal in patients with low and intermediate risk of CAD. The data on high risk patients are not powered to provide firm conclusions.

Terminology

MPI is a functional test for myocardial ischemia. The relation of functional assessment of ischemia and anatomical stenosis is much debated.

Peer review

The authors demonstrated that myocardial perfusion imaging following normal exercise electrocardiography (ECG) did not add diagnostic value in patients with a low or intermediate risk of coronary artery disease, if they could be able to perform an adequate work. No significant conclusions could be made in the subgroup of patients with high-risk. These results support the current and logical clinical management in CAD-suspected patients with normal maximal ECG-stress tests. The study results are in line with previous studies.

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BRIEF ARTICLE

Electrocardiographic features of patients with earthquake related posttraumatic stress disorder

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Abstract

AIM: To analyze electrocardiographic features of patients diagnosed with posttraumatic stress disorder (PTSD) after the Van-Erciş earthquake, with a shock measuring 7.2 on the Richter scale that took place in Turkey in October 2011.

METHODS: Surface electrocardiograms of 12 patients with PTSD admitted to Van Erciş State Hospital (Van, Turkey) from February 2012 to May 2012 were examined. Psychiatric interviews of the sex and age matched control subjects, who had experienced the earthquake, confirmed the absence of any known diagnosable psychiatric conditions in the control group.

RESULTS: A wide range of electrocardiogram (ECG) parameters, such as P-wave dispersion, QT dispersion, QT interval, Tpeak to Tend interval, intrinsicoid deflection durations and other traditional parameters were similar in both groups. There was no one with an abnormal P wave axis, short or long PR interval, long or short QT interval, negative T wave in lateral leads, abnormal T wave axis, abnormal left or right intrinsicoid deflection duration, low voltage, left bundle branch block, right bundle branch block, left posterior hemiblock, left or right axis deviation, left ventricular hypertrophy, right or left atrial enlargement and pathological q(Q) wave in either group.

CONCLUSION: The study showed no direct effect of earthquake related PTSD on surface ECG in young patients. So, we propose that PTSD has no direct effect on surface ECG but may cause electrocardiographic changes indirectly by triggering atherosclerosis and/or contributing to the ongoing atherosclerotic process.

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Key words: Earthquake; Posttraumatic stress disorder; Cardiovascular disease; Electrocardiogram

INTRODUCTION

Posttraumatic stress disorder (PTSD) is a psychiatric disease that is characterized by recurrent symptoms of stress and anxiety that develop after exposure to an extreme psychological trauma, such as earthquake, war or accidents[1]. Although acute cardiovascular events, such as sudden death, myocardial infarction and Takotsubo cardiomyopathy, are frequently reported, especially during the early phases of these mental stressors[2-5], cardiovascular effects of PTSD are not well known. While there are a few studies examining electrocardiographic features of veterans with PTSD[6,7], we did not encounter any study examining electrocardiographic features of patients with PTSD re-

lated to an earthquake. In this study, we aimed to analyze electrocardiographic features of patients diagnosed with PTSD after the Van-Erciş earthquake, with a shock measuring 7.2 on the Richter scale that took place in Turkey in October 2011.

MATERIALS AND METHODS

Patients

Twelve patients with PTSD admitted to Van Erciş State Hospital (Van, Turkey) from February 2012 to May 2012 were included in the study. Anyone in the study population with a rhythm other than sinus rhythm, a history of cardiovascular or other chronic medical disorders, or using beta-blockers, tricyclic antidepressants or other medications that affect autonomic function and electrocardiogram (ECG) patterns was excluded from the study. Transthoracic echocardiography was performed in all subjects of the study and subjects with any chamber enlargement, systolic or diastolic dysfunction, valvular heart disease, pulmonary hypertension or any other detectable heart disease were excluded from the study. Psychiatric interviews of the sex and age matched control subjects who had experienced the earthquake confirmed the absence of any known diagnosable psychiatric conditions.

Analysis of electrocardiograms and definitions

Recording of a 12-lead ECG was performed after 10 min of supine rest at standard sensitivity (10 mm = 1 mV) and a paper speed of 50 mm/s. ECG was obtained at the same time of the day (between 09:00 AM and 11:00 AM) for all participants and in a quiet room to minimize external noise. ECGs were scanned to digital media in 300 dpi. Then they were transferred to high-resolution computer screens and evaluated by two of the investigators who were blind to clinical and patient information. Three consecutive beats were used for analysis.

PR interval, R wave amplitude and QRS duration were calculated in lead V5. A PR interval longer than 200 ms was defined as long PR and shorter than 120 ms was defined as short PR. A QRS duration longer than 120 ms was defined as long QRS. The presence and site of pathological Q waves were recorded. A Q wave in any leads longer than 40 ms was defined as pathological q(Q) wave. Abnormal P wave axis was defined as P axis < 0 degrees or > 75 degrees[8]. Intrinsicoid deflection is the duration of the earliest appearing Q or R wave to the peak of the R wave. It was calculated in V2 for the right ventricle and V5 for the left ventricle. Abnormal intrinsicoid deflection was defined > 35 ms and > 45 ms for right and left ventricle respectively.

P wave duration was defined as the time measured from the onset to the end of the P wave deflection. The onset of the P wave was considered as the junction between the isoelectric line and first visible upward or downward slope of the trace. The return of the trace to the isoelectric line was considered to be the end of the P wave. P wave dispersion (Pd) was defined as the difference between maximum and minimum P wave durations

(Pmax and Pmin, respectively) occurring in any of the 12 leads[9]. QT interval was defined as the interval from the beginning of the QRS complex to the end of the T wave. The end of the T wave was defined as intersection of the terminal limb of the T wave with the isoelectric baseline[10]. The longest and shortest QT intervals across 12 leads were defined as the maximum QT (QTmax) and the minimum QT (QTmin) intervals, respectively. They were corrected according to heart rate by using the Bazett formula and were defined as corrected QTmax (cQTmax) and corrected QTmin (cQTmin), respectively. cQT dispersion (cQTd) was defined as the difference between cQTmax and cQTmin. For the Tpeak to Tend interval (TpTe) measurement, time interval between the peak of T wave, *i.e.*, the time point in which T wave had highest amplitude and end of the T wave which also was defined as the crossing point of the T wave and isoelectric line, was noted as a function of time. TpTe was also corrected according to heart rate and referred to as cTpTe. Abnormal ECG recordings with ambiguous T-waves, distorted, flat or with high noise levels by any means were excluded.

Left atrial enlargement was defined as a P wave with a broad and negative (> 1 mm) terminal part in lead V1 and/or P wave duration ≥ 120 ms in leads I or II. Right atrial enlargement was defined as P wave amplitude > 0.2 mV in leads II and aVF and/or > 0.1 mV in lead V1 and V2. Supraventricular or ventricular ectopic beats were defined as one or more supraventricular or ventricular extrasystoles in 10 s. A QRS duration ≥ 120 ms was defined as prolonged QRS. Ventricular conduction abnormalities were classified as right bundle branch block (RBBB), left bundle branch block (LBBB), left anterior hemiblock (LAH) or left posterior hemiblock (LPHB). Deviation of the QRS or T wave axis to the left (-30 <) or to the right (> 90) was defined as an abnormal QRS axis. The QT interval was corrected using the Bazett formula (QTc = QT/√RR). Left ventricular hypertrophy was defined by the Sokolow-Lyon criterion (S in V1 + R in V5 or V6 ≥ 3.5 mV). Low voltage was diagnosed when the amplitude of the QRS complex in each of the three limb leads (I, II, III) was < 5 mm. Repolarization abnormalities included ST segment elevation, ST segment depression and T-wave inversion.

Statistical analysis

Statistical analysis was performed with SPSS 16.0 (IBM Inc., New Orchard Road, Armonk, NY, United States). Continuous variables were given as mean ± SD and categorical variables were given as percentages. Due to small sample size, comparisons between groups were performed with nonparametric tests. For continuous parameters, Mann-Whitney U test was used, while χ^2 or Fisher's exact test was used as appropriate for categorical variables. All statistical comparisons were made within 95%CI. A P value of less than 0.05 was accepted as statistically significant.

RESULTS

Except for diastolic blood pressure, demographic fea-

Table 1 Demographic and clinical features of the groups (mean ± SD)

	PTSD (*n* = 12)	Controls (*n* = 12)	*P* value
Age (yr)	28.4 ± 7.5	28.5 ± 7.2	NS
Gender (%female)	91.6	83.30	NS
Body mass index (kg/m^2)	23.8 ± 4.3	24.3 ± 3.1	NS
Creatinine Clearance (mL/min)	99.4 ± 26	99.8 ± 16	NS
Current smoker (%)	16.6	16.6	NS
Family history of coronary artery disease (%)	0	8.3	NS
Systolic blood pressure (mmHg)	103.5 ± 8.8	110.4 ± 11.4	NS
Diastolic blood pressure (mmHg)	64.5 ± 6	71.9 ± 7	0.03
Heart rate (beat/min)	78.7 ± 18.6	78.8 ± 13.5	NS

PTSD: Posttraumatic stress disorder; NS: Not significant.

Table 2 Transthoracic echocardiographic features of the groups (mean ± SD)

	PTSD (*n* = 12)	Controls (*n* = 12)	*P* value
Left ventricular end diastolic diameter (mm)	42.8 ± 2.6	43.1 ± 3.4	NS
Left ventricular end systolic diameter (mm)	23.3 ± 1.7	24.9 ± 3.8	NS
Left ventricular ejection fraction (%)	63.3 ± 2.3	63.7 ± 1.8	NS
Interventricular septum thickness (mm)	8 ± 0.6	8.3 ± 0.7	NS
Left ventricular posterior wall thickness (mm)	7.8 ± 0.4	8.2 ± 0.6	NS
Left atrial anteroposterior diameter (mm)	31.5 ± 4.8	29.2 ± 4.1	NS

PTSD: Posttraumatic stress disorder; NS: Not significant.

tures of the groups were comparable (Table 1). There was no one with a history of hypertension, hyperlipidemia or diabetes mellitus in either group. Transthoracic echocardiography was available in all patients and control subjects. Basic echocardiographic measurements of the groups were also similar (Table 2).

Electrocardiographic features of the groups are presented in Table 3. There was no difference between ECG parameters of the groups. There was no one with abnormal P wave axis, short or long PR interval, long or short QT interval, negative T wave in lateral leads, abnormal T wave axis, abnormal left or right intrinsicoid deflection duration, low voltage, left bundle branch block, right bundle branch block, left posterior hemiblock, left or right axis deviation, left ventricular hypertrophy, right or left atrial enlargement and pathological q(Q) wave in either group.

DISCUSSION

Unanticipated catastrophic events resulting in acute psychological stress have been extensively reported as a cause of cardiovascular events and mortality[1]. Kim *et al*[4] reported the relationship between severe emotional stress and vasospastic angina in patients without organic coronary heart disease. Meisel *et al*[11] documented an increase in the incidence of acute MI and sudden death in the Tel Aviv area during the initial phases of the Gulf War in 1991. An increase in hospital admissions for acute MI in England on the day of the 1998 World Cup match against Argentina has also been reported[12]. There is also extensive literature demonstrating increased cardiovascular events and mortality after earthquakes which are good examples of unique unpredictable disasters resulting in severe mental stress. Tsuchida *et al*[13] demonstrated that severe earthquakes result in an increased incidence of acute coronary syndromes and cerebral hemorrhage. Increased cerebrovascular events were also reported after the Hanshin-Awaji earthquake[14,15]. Although the precise pathophysiological mechanism of the cardiovascular consequences of acute mental stressors are not well known, some physiological responses have been proposed to be

Table 3 Electrocardiographic features of the groups (mean ± SD)

	PTSD (*n* = 12)	Control (*n* = 12)	*P* value
P wave parameters			
Pmax (ms)	96 ± 15	96.6 ± 11.5	NS
Pmin (ms)	67.7 ± 14.4	72.5 ± 8.6	NS
Pd (ms)	27.7 ± 11.3	24.2 ± 11.6	NS
QT parameters			
QT V5 (ms)	361 ± 41.3	350 ± 37.7	NS
cQT V5 (ms)	403.4 ± 35.1	401.2 ± 20.2	NS
Qtmax (ms)	373.3 ± 44.6	358.3 ± 32.4	NS
Qtmin (ms)	340 ± 36.2	325.8 ± 36.3	NS
QTd (ms)	33.3 ± 26.1	32.5 ± 17.6	NS
cQTmax (ms)	415.5 ± 27.5	411.5 ± 23.2	NS
cQTmin (ms)	380 ± 37.5	373.8 ± 30.3	NS
cQTd (ms)	35.5 ± 26.8	37.7 ± 19.5	NS
T wave parameters			
TpTe V5 (ms)	80.4 ± 17.4	83.3 ± 12.3	NS
cTpTe V5 (ms)	89.3 ± 15.2	95.4 ± 10.9	NS
Presence of negative T wave (anterior leads) (%)	66.6	58.3	NS
Presence of negative T wave (inferior leads) (%)	16.6	0	NS
Presence of U wave (%)	8.3	8.3	NS
PR interval (ms)	145.83 ± 23.53	143.33 ± 16.70	NS
QRS duration (ms)	73.3 ± 9.6	82.5 ± 11.4	NS
Right ventricle intrinsicoid deflection (ms)	26.6 ± 6.8	28.9 ± 4.9	NS
Left ventricle intrinsicoid deflection (ms)	34.5 ± 4	34.4 ± 5.1	NS
R wave amplitude	0.9 ± 0.3	1.2 ± 0.5	NS
Infra HIS conduction abnormalities			
Left anterior hemiblock (%)	0	8.3	NS
Left axis deviation (%)	0	8.3	NS
ST segment elevation (%)	0	16.6	NS

PTSD: Posttraumatic stress disorder; NS: Not significant; Pmax: Maximum P wave duration; Pmin: Minimum P wave duration; Pd: P wave dispersion; cQT: Corrected QT interval; QTd: QT dispersion; cQTd: Corrected QT dispersion; QTmax: Maximum QT interval; cQTmax: Corrected maximum QT interval; QTmin: Minimum QT interval; cQTmin: Corrected minimum QT interval; TpTe: Tpeak to Tend interval; cTpTe: Corrected Tpeak to Tend interval.

potential triggers of myocardial supply-demand and by atherosclerotic plaque disruption, thrombus formation and eventually ischemia-arrhythmia[16,17]. Increase in heart

rate and blood pressure[18], rising sympathetic activation, decreased parasympathetic tone[1] and sudden catecholamine discharge[19] are some of the blamed psychobiological triggers of cardiovascular events during these catastrophes. All these factors along with vasoconstriction may result in increased shear stress on the vasculature, causing endothelial damage with the potential to disrupt vulnerable plaque[16]. On the other hand, activation of the inflammatory process seems to be most important contributor. Steptoe *et al*[17] showed increased interleukin-6 and tumor necrosis factor alpha following emotional stress, which are stimulators of macrophages/T-lymphocytes, leading to matrix metalloproteinases secretion and atherosclerotic fibrous cap degradation[1,20]. Diminished fibrinolytic activity and increased fibrinogen, von Willebrand factor, Factors VII and VIII could lead to a prothrombotic imbalance during acute mental stress[21,22]. Platelet activation was also shown to be increased during emotional stress secondary to sympathetic activity in plasma, caused by platelet-derived growth factors[23,24]. In addition, in some animal models, phenylephrine or electric shock and noise induced stress gave rise to increased blood pressure, heart rate, ejection fraction, maximal systolic flow velocity, norepinephrine and fibrinogen levels and eventually plaque rupture[25,26].

However, short or long term impact of repetitive mental stress on cardiovascular system in patients with PTSD is much less known. Weiss *et al*[27] found an association between increased rates of metabolic syndrome and PTSD. In another study, PTSD patients were found to have diminished levels of high-density lipoprotein cholesterol and elevated levels of serum cholesterol, triglycerides and low-density lipoprotein cholesterol[28]. One of the few studies examining the long-term mortality risk of patients with PTSD has been published recently[29]. In that study, PTSD was found to be an independent predictor of mortality in multivariate analysis for their study population, 891 military veterans (HR: 1.79, 95%CI: 1.15-2.79, $P = 0.001$). In addition, patients with PTSD ($n = 91$, 98% male) had a trend toward worse survival on Kaplan-Meier analysis ($P = 0.057$). Heart failure, increased end-systolic left ventricular diameter, left ventricular systolic dysfunction and arrhythmia were more frequent in patients with PTSD. In another study, PTSD was prospectively associated with heart disease mortality among veterans free of cardiac disease at baseline[30].

There are few studies comparing ECGs of patients with PTSD and healthy controls[6,7]. Boscarino *et al*[6] showed increased signs of atrioventricular conduction abnormalities and myocardial infarction in male veterans with PTSD. In the other study, Kazaie *et al*[7] examined ECGs of patients with post-war PTSD and detected more ECG abnormalities (abnormal QT interval, inverted T waves, ST segment depression, low voltage QRS complex, sinus tachycardia) in PTSD patients than in controls. However, the patients were older, mostly male and had the disease much longer in those studies than in ours. Therefore, ECG abnormalities found in those stud-

ies seem to be a consequence of ischemic heart disease caused by traditional risk factors with a probable contribution of PTSD. On the contrary, in our study, which is the first one comparing the ECGs of patients with earthquake related PTSD and healthy subjects, we could not find any electrocardiographic difference between groups.

In conclusion, our study showed no direct effect of earthquake related PTSD on surface ECG, at least not in short term follow up. Although long term follow up may disclose some ECG changes, most probably these changes will be due to atherosclerotic coronary artery disease. Therefore, we propose that PTSD has no direct effect on surface ECG but may cause electrocardiographic changes indirectly by triggering and/or contributing to the ongoing atherosclerotic process.

COMMENTS

Background
Acute mental stress is a well known trigger of myocardial infarction and anxiety has been recently found to be an independent risk factor for incident coronary heart disease. However, the effects of repetitive anxiety on electrocardiography are not well known.

Research frontiers
This study aimed to analyze electrocardiographic features of patients diagnosed with posttraumatic stress disorder, a psychiatric disease that is characterized by recurrent symptoms of stress and anxiety.

Innovations and breakthroughs
That study is the first one comparing the electrocardiograms (ECGs) of patients with earthquake related posttraumatic stress disorder (PTSD) and healthy subjects in an early period after the disaster.

Applications
The study's results showed no direct effect of earthquake related PTSD on surface ECG in young patients.

Peer review
The article is short, concise and the authors found no ECG abnormalities (such as P-wave dispersion, QT dispersion, QT interval, Tpeak to Tend interval, intrinsicoid deflection durations and other traditional parameters) in victims of an earthquake who developed PTSD compared to control subjects exposed to the same trauma (earthquake) but who did not develop PTSD.

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CASE REPORT

Pacemaker implantation in a patient with brugada and sick sinus syndrome

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Abstract

Brugada syndrome (BrS) is a rare and inherited primary arrhythmic syndrome characterized by ST-segment elevations in the right precordial leads (V_1-V_3) with an increased risk of sudden cardiac death (SCD). Arrhythmias in BrS are often nocturne, and brady-arrhythmias are often seen in patients with loss-of-function mutations in *SCN5A*. In this case-report we present a 75-year old woman referred to our outpatient clinic for inherited cardiac diseases for a familial clinical work-up. Since childhood she had suffered from dizziness, absence seizures, and countless Syncope's. In 2004 sick sinus syndrome was suspected and she was treated with implantation of a pacemaker (PM) at another institution. An inherited cardiac disease was one day suddenly suspected, as the patient had a 61-year old brother who was diagnosed with symptomatic BrS, and treated with an implantable cardioverter defibrillator (ICD) after aborted SCD. A mutation screening revealed a *SCN5A* [*S231CfsX251 (c.692-693delCA)*] loss-of-function mutation not previously reported, and as a part of the cascade screening in relatives she was therefore referred to our clinic. In the 7 year period after PM implantation she had experienced no cardiac symptoms, although her electrocardiogram changes now were consistent with a BrS type 1 pattern. A genetic test confirmed that she had the same mutation in *SCN5A* as her brother. In this case-report we present a loss-of function mutation in *SCN5A* not previously associated with BrS nor presented in healthy controls. Sinus node dysfunction has previously been documented in patients with symptomatic BrS, which suggests it is not a rare concomitant. The only accepted treatment of BrS is today implantation of an ICD. In the future studies should evaluate if PM in some cases of symptomatic BrS can be used instead of ICDs in patients with a loss-of-function *SCN5A* mutations

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INTRODUCTION

Brugada syndrome (BrS) is a rare and inherited primary
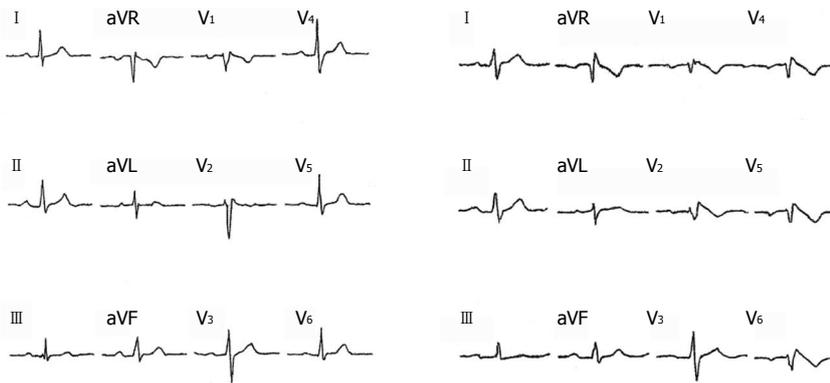
Figure 1 Baseline and Brugada type 1 electrocardiogram. A: Baseline electrocardiogram (ECG) recording; B: Brugada type 1 ECG under 150 mg Flecanide over 10 min intravenously. In V$_{4-6}$ in the recording were placed as elevated electrode position in IC2 at V$_1$ at sternum and V$_2$, respectively.

arrhythmic syndrome characterized by ST-segment elevations in the right precordial leads (V$_1$-V$_3$) with an increased risk of sudden cardiac death (SCD) due to malignant ventricular arrhythmias in the absence of a structural heart disease[1]. Arrhythmias in BrS are often nocturne, and brady-arrhythmias are often seen in patients with loss-of-function mutations in the *Sodium channel gene* (*SCN5A*)[2]. *SCN5A* encodes the alpha subunit (Na$_v$1.5) of the cardiac sodium channel complex and it is the only recommended gene for targeted screening in BrS[3]. Mutations in *SCN5A* have been reported to be associated with several other types of disease entities such as lone atrial fibrillation and the Long QT Syndrome[4]. It is suggested that the loss-of-function mutations in *SCN5A* create the substrate for a re-entry circuit in the ventricular myocardium, but may also increase vagal activity, thus facilitating development of arrhythmias[1].

CASE REPORT

A 75-year old woman was in 2011 referred to our outpatient clinic for inherited cardiac diseases for a familial clinical work-up. Since childhood she had suffered from dizziness, absence seizures, and countless syncope's. In 2004 sick sinus syndrome was suspected as a 24 h Holter monitoring revealed 67 sinus arrests [electrocardiogram (ECG) not available] of more than 2.5 s with the longest being 6.85 s. The asystole were followed by dizziness but no syncope's appeared under surveillance. The SSS diagnosis seemed obvious, and she was treated with implantation of a pacemaker (PM) at another institution.

An inherited cardiac disease was one day suddenly suspected, as the patient had a 61-year old brother who was diagnosed with symptomatic BrS, and treated with an implantable cardioverter defibrillator (ICD) after aborted SCD. A mutation screening revealed a *SCN5A* [*S231CfsX251* (*c.692-693delCA*)] loss-of-function mutation not previously reported, and as a part of the cascade screening in relatives she was therefore referred to our clinic.

In the 7 year period after PM implantation she had experienced no cardiac symptoms. An ECG and elevated electrode placement ECG (EEP-ECG) showed no BrS

pattern. However, BrS was suspected due to the family history and a Flecanide test (150 mg intravenously) was performed. After infusion, 1 and 2 mm ST elevations appeared in V$_1$ and V$_2$, respectively (Figure 1). Changes were consistent with a BrS type 1 ECG pattern and a genetic test confirmed that she had the same mutation in *SCN5A* as her brother. As the patient had been free of symptoms after PM implantation, it was decided not to upgrade to an ICD unless syncope would re-appear.

DISCUSSION

In this case-report we present a loss-of function mutation in *SCN5A* not previously associated with BrS nor presented in healthy controls[5]. It has been suggested that the loss-of-function mutations in *SCN5A* create the substrate for a re-entry circuit in the ventricular myocardium, but may also increase vagal activity, thus facilitating development of arrhythmias in BrS[1]. The mutation, that we report, was initially found in a brother diagnosed with BrS after aborted SCD and hereafter in our patient, initially diagnosed with SSS. Sinus node dysfunction has previously been documented in patients with symptomatic BrS, which suggests it is not a rare concomitant[6,7]. However, PM implant in this case kept the patient free of symptoms for several years, and this support the theory that increased vagal tonus may cause bradycardia-related arrhythmias which in other isolated cases have been treated successfully with rapid pacing as well[1]. The only accepted treatment of BrS is today implantation of an ICD. In the future studies should evaluate if PM in some cases of symptomatic BrS can be used instead of ICDs in patients with ICDs in patients with *SCN5A* loss-of-function mutations.

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World Journal of *Cardiology*

Contents

Contents

ABOUT COVER

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FRONTIER

From the epicardial adipose tissue to vulnerable coronary plaques

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most common underlying substrate in patients suffering acute coronary thrombotic events. Recently, an interesting association between TCFAs and a particular depot of visceral fat called epicardial adipose tissue has been suggested. In this study, we review some basic and clinical aspects of behind this interesting association as well as the value of optical coherence tomography in the diagnosis of TCFAs.

Abstract

Thin cap fibroatheromas (TCFAs) are thought to be the most common underlying substrate in patients suffering acute coronary thrombotic events. Recently, an interesting association between TCFAs and a particular depot of visceral fat called epicardial adipose tissue (EAT) has been suggested. In this article, we discuss some basic and clinical aspects of this association and then briefly review some of the pathophysiological characteristics attributed to EAT that explain why this particular depot of fat has been attracting the attention of the cardiological scientific community in recent years. Finally we discuss the value of optical coherence tomography in the diagnosis of TCFAs and the role of multislice computed tomography to assess EAT.

Core tip: Thin cap fibroatheromas (TCFAs) are the

SEARCH FOR THE "GUILTY" SUBSTRATE BEHIND CORONARY THROMBOTIC EVENTS

Despite widespread adoption of preventive measures and remarkable improvements in medical treatment and revascularization strategies for patients with coronary artery disease (CAD), atherosclerosis and its thrombotic complications continue to be the most deadly and disabling disease in industrialized countries[1]. As cardiologists, we have struggled for decades in accurately, identifying individuals that despite being asymptomatic have a high individual risk of developing thrombotic coronary events. Accordingly, the identification of the so-called "vulnerable" or "high risk plaque" in the coronary tree has been one of the main challenges and pivotal areas of research in modern cardiovascular medicine.

Combined evidence provided by autopsy as well as from invasive studies has shown that rupture-prone plaques have certain characteristics: a thin fibrous cap, a large lipid-rich pool and increased macrophage activity (Figure 1)[2-5]. Currently, there is sound evidence suggest-

ing that these plaques, namely "thin cap fibroatheromas" (TCFAs), are the most common underlying "guilty" substrate in patients suffering acute coronary thrombotic events[3,6]. Moreover, an in-depth analysis of the PROS-PECT trial demonstrated that, in spite of significant efforts in secondary prevention, TCFAs remain powerful independent predictors of recurrent adverse cardiovascular events[7].

Considering this pathological and clinical background, great efforts have been made in order to identify TCFAs with the ultimate goal of preventing plaque rupture and thereby averting acute coronary syndromes and sudden cardiac death. However, the correct diagnosis of these vulnerable plaques by non-invasive imaging techniques (potentially available and suitable in large patient populations) remains a challenge[8]. Therefore, new diagnostic clues aiming to the identification of these vulnerable plaques, are always received with major enthusiasm by the scientific community. On these grounds, the recently reported association between coronary TCFAs and a specific, readily-accessible, depot of visceral fat called "epicardial adipose tissue" (EAT) (Figure 2) reported by Ito *et al*[9] deserves to be highlighted as a valuable step-forward in the right direction.

EPICARDIAL ADIPOSE TISSUE AND THIN CAP FIBROATHEROMAS: A RECENTLY SUGGESTED ASSOCIATION

Very recently, Ito *et al*[9] reported for the first time the relationship between EAT, as quantified with multislice computed tomography (MSCT), and plaque vulnerability, as assessed with intracoronary optical coherence tomography (OCT). This is of remarkable importance because at this moment and notwithstanding well-recognized limitations, MSCT and OCT are the "gold standards" for assessing EAT and plaque vulnerability *in vivo*, respectively (Figure 3). In their study, Ito *et al* made a profound examination of a total of 180 vessels form 117 patients with stable angina or acute coronary syndromes that underwent OCT during cardiac catheterization and also a MSCT study within an interval of 9.8 ± 8.8 d. TCFAs were assessed with OCT and defined as plaques with necrotic lipid pools ≥ 2 quadrants and minimum fibrous cap thickness measuring < 65 μm. EAT, coronary plaques, coronary plaques attenuation and the remodeling index which are MSCT findings associated with plaque vulnerability[10,11] were evaluated from MSCT images. Notably, both of these techniques were performed following a rigorous methodology, as demonstrated by their very low inter and intraobserver variability. After categorizing the patients according to EAT tertiles, they found that all of the aforementioned indexes of plaque vulnerability provided by OCT and MSCT, were higher in those within the highest tertile of EAT (high-EAT). Moreover, EAT was significantly correlated with the extension of the necrotic lipid pool and inversely correlated with the

thickness of the fibrous cap by OCT (r = -0.400, P < 0.01). Finally, high-EAT was an independent predictor of TCFAs [RR, 2.92 (1.13-7.55)] and of acute coronary syndromes as a clinical presentation [RR, 2.89 (1.14-7.29)].

Therefore, the authors have provided for the first time strong evidence *in vivo* linking EAT with the vulnerable or high-risk plaques behind coronary thrombotic events and unstable clinical presentations. The authors are to be congratulated on executing this cleverly designed study although a few minor limitations and future challenges are nonetheless worth noting. First, as in all cross sectional studies, causality cannot be assumed and, therefore, these findings should be taken as hypothesis generating and confirmed by prospective studies. Second, the relatively small sample size could be a limitation when drawing conclusions. Third, all of the patients included in the study had already symptoms of CAD so the translation of these findings to an asymptomatic population in terms of primary prevention is unclear. Finally, OCT and MSCT have well-acknowledged limitations in identifying plaque vulnerability and TCFAs but by far, are the best available tools for this purpose *in vivo*[3,6,10,11]. This study is also an excellent opportunity to briefly review some basic and clinical characteristics attributed to EAT that explains why this particular adipose tissue has been attracting the physician's attention in the recent years.

ANATOMY AND PHYSIOLOGY OF EPICARDIAL ADIPOSE TISSUE

EAT is an intrathoracic depot of visceral fat that lays over the myocardium and coronary arteries that has received increased attention in the literature in recent years, due to some unique and very interesting characteristics. Embryologically, EAT originates from the splachnopleuric mesoderm and evolves from brown adipose tissue[12]. In the normal human heart, EAT follows the adventitia of coronary arteries, is concentrated in the atrioventricular and interventricular grooves and represents approximately 20% of the heart mass[13]. Remarkably, no structures resembling a fascia (as found on skeletal muscle) separates EAT from the myocardium and coronary vessels and therefore these three tissues share the same circulation and innervation[14]. Because of this anatomical contiguity, it was proposed that EAT could interact locally with the myocardium and coronary arteries through paracrine or vasocaine pathways and a growing amount of evidence is currently supporting this assumption[15].

Besides its embryology and anatomy, the physiology of EAT is also quite special and important differences have been shown in its metabolism when compared with other depots of corporal fat. For example, a higher rate of lipolysis and insulin-induced lipogenesis has been observed in EAT from animal models[12]. Human EAT appears to be richer in saturated fatty acids than subcutaneous fat and, interestingly, the rates of free fatty acids synthesis, incorporation and breakdown are significantly
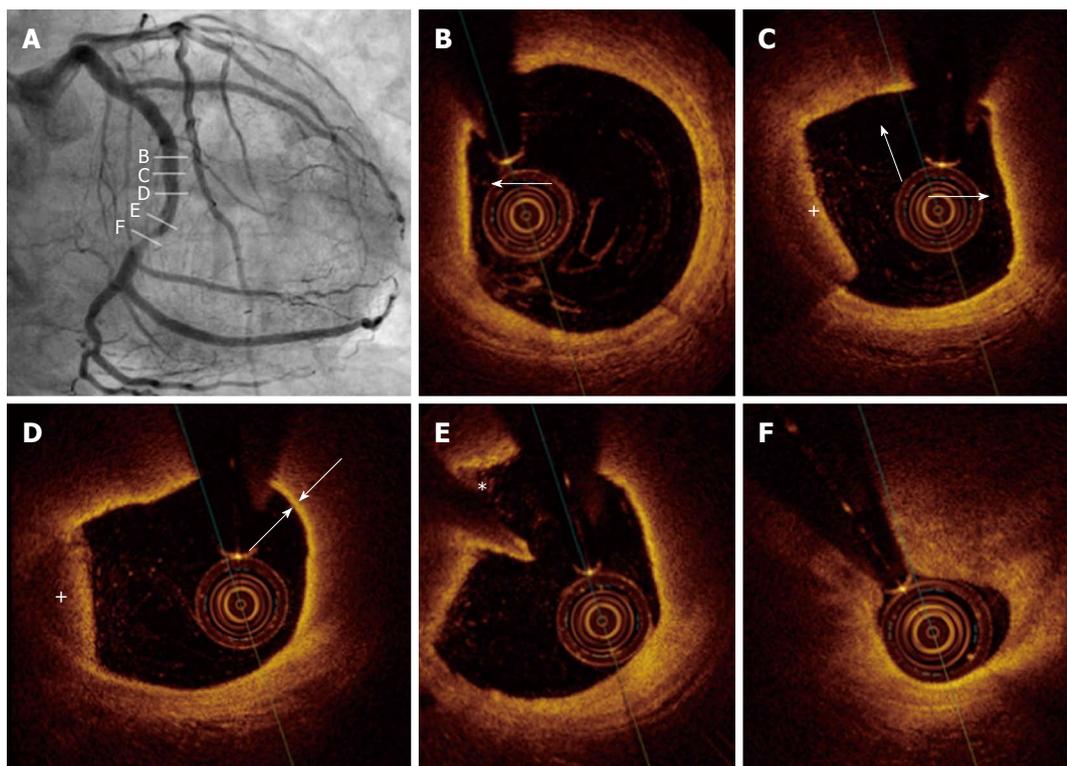
Figure 1 A 64-year-old male was admitted at our hospital because of progressive angina. A: Coronary angiogram demonstrated a complex stenosis in the mid segment of the circumflex coronary artery; B-F: Optical coherence tomography revealed a large complex thin-cap fibroatheroma (arrows) proximal and at the site of the stenosis. The fibrous cap covering the lipid rich plaque had a variable thickness and in its thinnest part measured 55 μm (arrows in D). Distally, the same plaque had large lipidic core and an image compatible with a rupture site (*) (E). Please note that residual lining red thrombus with a clear dorsal shadowing was also detected at some sites (+). Finally, at the most severe site (F), a fibrous plaque was noted.
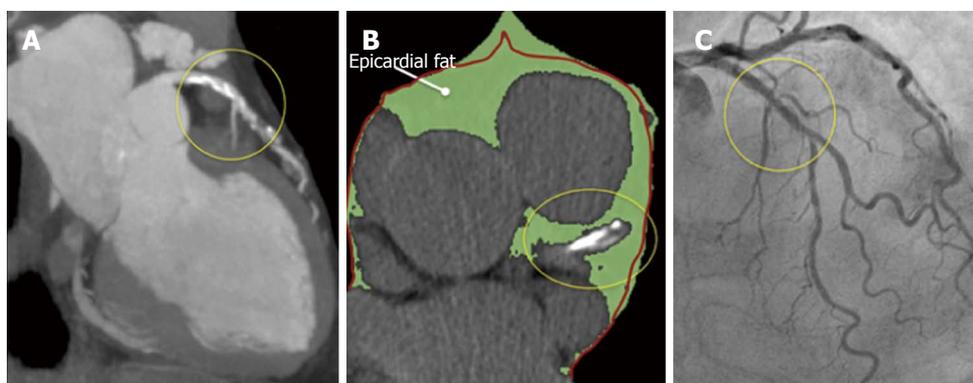
Figure 2 A multislice computed tomography was performed in a 68-year old male because of atypical chest pain. A: This study revealed a long mixed, calcific and non-calcific plaque in the proximal and mid segments of the left anterior descending artery; B: A large amount of epicardial adipose tissue (EAT) [(159.2 cm³ (green) (figure 3)] was also calculated. Please note that the left anterior descending artery is embedded in EAT (yellow circles). The red line represents the pericardium; C: A coronary angiogram was scheduled and revealed intermediate stenoses in the same arterial segment that was subsequently studied with optical coherence tomography.

higher in EAT[12,16]. Since 50%-70% of the energy requirements of the heart are supplied by free fatty acids oxidation, it has been proposed that EAT might provide large amounts of energy to the myocardium under non ischemic conditions[15]. Besides its role in the energetic metabolism, other physiological functions of EAT have been proposed. Indeed, EAT may be a source of anti-atherogenic and anti-inflammatory adipokines, such as adiponectin and adrenomedullin, may influence vasomo-tion of coronary arteries and may also provide mechanical and thermogenic cardioprotection to the myocardium and coronary arteries by attenuation of vascular tension and torsion[15,17,18].

Altogether, current evidence supports the hypothesis that under physiological conditions, EAT supplies energy and heat to the coronary arteries and myocardium and may also exert a protective modulation on the coronary vessels[15,17,19]. However, as will be discussed in the next
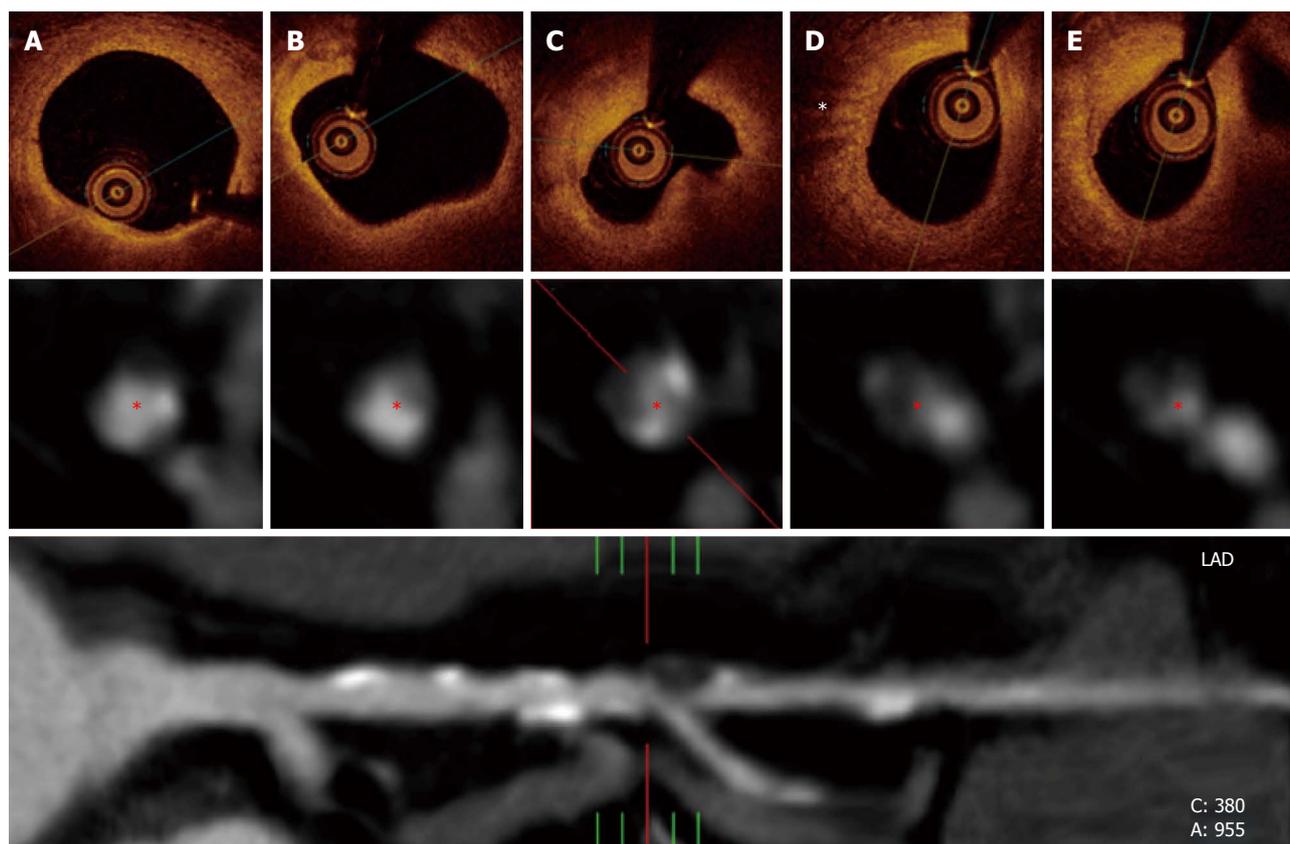
Figure 3 Optical coherence tomography and multislice computed tomography findings of the same patient in figure 2. A and B: In the upper panel, optical coherence tomography revealed a complex plaque affecting a long portion of the vessel with calcified and lipidic regions; C: Also, a complex fibroatheroma that included a lipidic core was observed at the site of the most severe stenosis; D: A high light attenuation band with distal shadowing can be attributed to macrophage infiltration (*). The middle panel represents cross-sectional views of the vessel at the same stenosis as visualized by multislice computed tomography (MSCT). Calcified and non-calcified regions including eccentric plaques were found within the diseased segment. The inferior panel shows a MSCT multiplanar reconstruction of the vessel and its anatomical bookmarks.

paragraph, a growing body of evidence is associating EAT with pathological states from which atherosclerotic plaque development and instability are of substantial importance.

EPICARDIAL ADIPOSE TISSUE AND ITS IMPACT ON THE DEVELOPMENT OF ATHEROSCLEROTIC PLAQUES

From a clinical perspective, several clinical and epidemiological studies have associated EAT with different cardiometabolic risk factors and with early stages of atherosclerosis and plaque formation[20-24]. Moreover, the presence and severity of CAD and coronary calcification, indicating more advanced states of atherosclerosis, have been also associated with EAT[25-28]. This association has been reinforced by a recent meta-analysis (*n* = 2872 patients) that found that when compared with patients without CAD, EAT thickness and volume were significantly higher in those with documented CAD[29]. These epidemiological findings have been supported by a large amount of basic evidence pointing at the same

direction. Indeed, when compared to subcutaneous fat, EAT shows a more dense inflammatory cell infiltrate, predominantly represented by macrophages[30]. The secretion of some highly atherogenic and inflammatory adipokines such as tumor necrosis factor alpha (TNF-α), monocyte chemoattractant protein-1 (MCP-1), interleukin-6 (IL-6), IL-1b, plasminogen activator inhibitor-1 (PAI-1) and resistin are significantly higher in EAT from patients with CAD[18,31-35]. Interestingly, another supporting evidence comes from a "natural experiment", since as shown by animal and human studies, increased atherosclerosis is observed in the segments of the coronary arteries proximal to myocardial bridges, where EAT is present, whereas intramyocardial segments of the vessels are free of atherosclerosis[36-38]. Altogether, current evidence supports the hypothesis that under pathological conditions, EAT may become an adverse lipotoxic and proinflammatory organ that could play a significant role in the development of coronary atherosclerosis. Notably, however, it was not until very recently that EAT was linked with different characteristics of coronary atherosclerotic plaques and more importantly, plaque vulnerability.
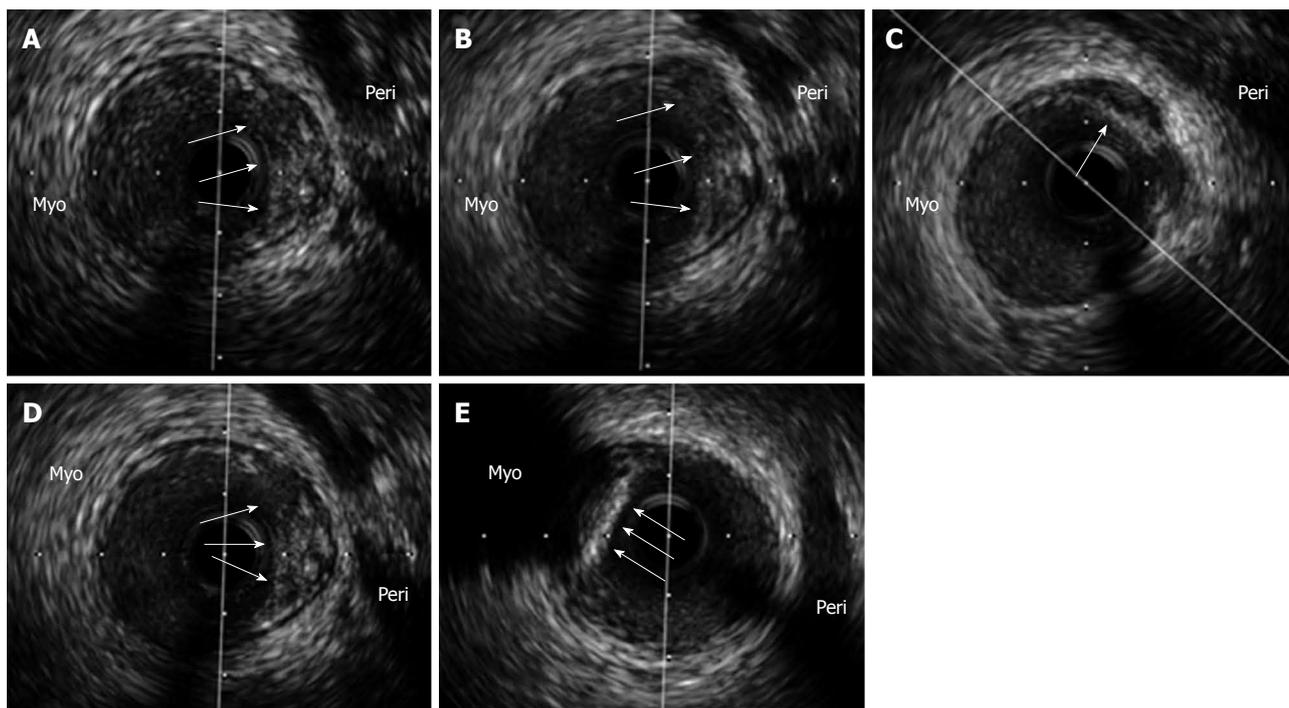
Figure 4 An intravascular ultrasound analysis of the left anterior descending coronary artery in an asymptomatic patient with a previously deployed stent (not shown) that underwent this study as part of an institutional protocol. A-D: In the pericardial side (Peri) of the vessel, an eccentric and positively remodeled plaque with heterogenic echo-reflection that included a hypoechogenic area, suggestive of a potentially "high risk" plaque, was found (arrows); E: Interestingly, just adjacently and in the opposite vessel side [myocardial side (Myo)], a calcified plaque with intense posterior shadowing, highly suggestive of a stable fibro-calcific plaque (arrows), was also observed. The patient has been asymptomatic during a 3-year clinical follow-up.

EPICARDIAL ADIPOSE TISSUE AND PLAQUE VULNERABILITY

Although the precise mechanisms of plaque rupture are poorly understood, it is widely accepted that the disruption occurs at the site of the fibrous cap, which is usually thin, heavily infiltrated by macrophages and T-lymphocytes and where the underlying necrotic core is also typically large[2]. Various factors and hypothesis have been implicated and proposed in order to explain these phenomena. These include arterial remodeling[39,40], inflammation and apoptosis within the plaque[41,42], impaired collagen synthesis and breakdown in the fibrous cap[43] and local mechanical stress[44]. EAT, interestingly, appears to be related to some of these. For example, some adipokines highly expressed by EAT, such as TNF-α, IL-1 and MCP-1, have been associated with macrophage and smooth muscle cell apoptosis within the plaque, which may contribute to both, the formation of the necrotic core and thinning of the fibrous cap[45]. Moreover, the uptake of fluorodeoxyglucose in the left anterior descending artery (LAD), which is a potential marker of inflammatory activity of the vessel wall, has been significantly correlated with EAT volume in one study[46]. Also, in an intravascular ultrasound analysis of LADs performed by Prati *et al*[47], most of the plaques with positive remodeling were located towards the epicardial side of the vessel rather than at the myocardial one (Figure 4). Finally, a recent study performed by Alexopoulos *et al*[48]

linked non-invasive characteristics of plaque vulnerability by MSCT with EAT, since it was observed that EAT was an independent predictor of coronary artery calcium [exp(B) = 3.916, $P < 0.05$], atherosclerotic plaques of any type [exp(B) = 4.532, $P < 0.01$], non-calcified plaques [exp(B) = 3.849, $P < 0.01$], and obstructive CAD [exp(B) = 3.824, $P < 0.05$]. Therefore, the possible mechanisms and pathways through which EAT could be related to plaque vulnerability are many, of significant importance, and a growing body of evidence supporting this association is currently being acquired.

Finally and although at this stage, many basic and cross-sectional studies have shown positive associations between increased EAT and the development and (now) the instability of the atherosclerotic process, these findings should be still interpreted as hypothesis generating and EAT measurement cannot be recommended for clinical practice. However, the scientific basis of the relationship between EAT and the aforementioned phenomena seem to be solid and warrants further studies. Since EAT can be measured by non invasive methods such as transthoracic 2D echocardiography (Figure 5), MSCT and magnetic resonance imaging[49-51], its clinical use for primary prevention purposes could be readily available. A critical aspect in the near future will be the assessment of the incremental predictive value of EAT over established cardiovascular risk factors, if are proved or, more convincingly a cause-effect interaction is established, the introduction of EAT measurement into clinical practice
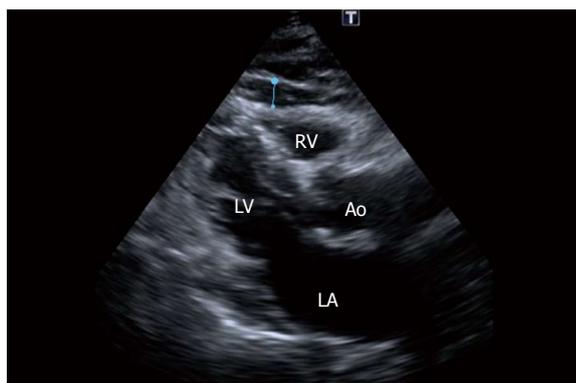
Figure 5 Echocardiogram in the parasternal long-axis view revealing a large amount of epicardial fat (thickness of 6 mm) over the free wall of the right ventricle (blue line) of the patient in figure 1. RV: Right ventricle, LV: Left ventricle, LA: Left atrium; Ao: Aortic root.

could be taken as one step forward to the "holy grail" for the effective risk stratification[52] and prevention of coronary thrombotic events.

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REVIEW

Sphingolipids in cardiovascular and cerebrovascular systems: Pathological implications and potential therapeutic targets

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Abstract

The sphingolipid metabolites ceramide, sphingosine, and sphingosine-1-phosphate (S1P) and its enzyme sphingosine kinase (SphK) play an important role in the regulation of cell proliferation, survival, inflammation, and cell death. Ceramide and sphingosine usually inhibit proliferation and promote apoptosis, while its metabolite S1P phosphorylated by SphK stimulates growth and suppresses apoptosis. Because these metabolites are interconvertible, it has been proposed that it is not the absolute amounts of these metabolites but rather their relative levels that determine cell fate. The relevance of this "sphingolipid rheostat" and its role in regulating cell fate has been borne out by work in many labs using many different cell types and experimental manipulations. A central finding of these studies is that SphK is a critical regulator of the sphingolipid rheostat, as it not only produces the pro-growth, anti-apoptotic messenger S1P, but also decreases levels of pro-apoptotic ceramide and sphingosine. Activation of bioactive sphingolipid S1P signaling has emerged as a critical protective pathway in response to acute ischemic injury in both cardiac and cerebrovascular disease, and these observations have considerable relevance for future potential therapeutic targets.

Core tip: The sphingolipid pathway has received considerable attention recently, because its active metabolites appear to have salutary effects on cytoprotection in experimental cardiac and cerebral ischemia. Both inhibitors and antagonists of the sphingolipid sphingosine-1-phosphate (S1P) pathway appear to limit ischemic injury through a variety of mechanisms. Because of the clinical availability of Fingolimod (FTY720), a S1P analog, for use in multiple sclerosis, preclinical and clinical studies should focus on the development of this and similar pharmaceuticals for a new indication.

INTRODUCTION

Sphingolipids were first described in late 19th century and have long been viewed as merely ubiquitous components of the cell membrane. Recently, sphingolipids have been increasingly revaluated because they are now recognized to not only regulate vital cell functions, but also form cell membrane microdomain "lipid rafts" for integrating cell signaling[1,2]. Sphingolipids are formed *via* the metabolism of sphingomyelin, a ubiquitous constituent of the plasma membrane, or by *de novo* synthesis. Enzymatic pathways result in the formation of several different lipid mediators such as ceramide, sphingosine, and sphingosine-1-phosphate (S1P). Several studies now showed that these sphingolipid mediators and their enzymes, especially sphingosine kinase (SphK), are likely to have an integral role in different cell processes including proliferation, inflammation, apoptosis and migration. The mode of action of each sphingolipid is different. A significant body of research now indicates that sphingolipids are intimately involved in disease progression and that these lipids, together with associated enzymes and receptors, can provide effective drug targets for the treatment of pathological states. This review will highlight the current knowledge of research where sphingolipids are involved with focus on cardiovascular and cerebrovascular disease, and the mechanisms of action of each sphingolipid mediator. In addition, the therapeutic potential of drugs that alter sphingolipid actions with focus on SphK/S1P signaling pathway that appears to be a target of interest for therapeutic manipulation.

METABOLISM AND SIGNALING PATHWAYS OF SPHINGOLIPIDS

Sphingolipids are complex lipids comprised of a sphingoid base, and are one of the major lipid components of cell membrane as well as glycerophospholipid and cholesterol. A schematic diagram of sphingolipid metabolism is depicted in Figure 1. *De novo* biosynthesis of sphingolipids begins with the conversion of serine and palmitoyl-CoA into 3-ketosphinganine. 3-ketosphinganine is then converted to dihydrosphingosine. Dihydroceramide synthase acrylates dihydrosphingosine to form dihydroceramide, which is then reduced to ceramide by dihydroceramide desaturase. Sphingomyelin can also be converted to ceramide by sphingomyelin synthase, and a reverse reaction is catalyzed by sphingomyelinase. Ceramide can also be degraded by ceramidase to form sphingosine, which can, in turn, be phosphorylated to S1P by two enzymes SphK1 or 2. The bioactive lipid ceramide-1-phosphate (C1P) is formed by phosphorylation of ceramide by ceramide kinase; it can also be reverted to ceramide by ceramide phosphatase. The reverse reaction from S1P is catalyzed by sphingosine-1-phophate phosphatases and ceramide synthase that yield sphingosine and ceramide respectively[3]. S1P can be further metabolized by S1P lyase, yielding hexadecenal and ethanolamine phosphate[4].

Ceramide

Ceramides are a family of lipids that consist of sphingosine covalently linked to a fatty acid and are densely located at the cell membrane. Ceramides are the key component lipids that constitute sphingomyelin, the major source of the human sphingolipids, and one of the major components which form the phospholipid bilayer[5]. Discovery over the last few decades reveal that all stress stimuli, such as inflammatory mediators, heat, ultraviolet radiation, hypoxia, chemotherapeutics, and oxidative stress increase ceramide production as part of an evolutionarily conserved cellular response[6-13] and toll like receptor 4 seems to be involved in ceramide synthesis[14]. Consecutively ceramides not only promote cell cycle arrest and promote apoptosis, a form of programmed cell death, but also play an important role in the regulation of autophagy, cell differentiation, and inflammatory responses[9,15-18]. Ceramide is also involved in dephosphorylation and inactivation of one major mediator of cell survival; protein kinase Akt, (Akt/PKB)[19-21]. On the other hand, recent data shows that phosphorylated ceramide, C1P seems to have the opposite effects from ceramide; by inducing prosurvival functions, such as cell growth and survival, control of inflammation and mediation of macrophage migration[22-24].

Sphingosine

Sphingosine is also a bioactive sphingolipid formed from ceramide as a result of ceramidase activity. It was first described as the physiological inhibitor of the survival signal protein kinase C (PKC), and was also found to upregulate caspase 3 in the cascade of apoptosis[25-28]. There are many reports showing that PKC is inhibited by exogenous sphingosine, and it has been demonstrated that endogenously generated sphingosine is a potent PKC inhibitor[29]. In turn, sphingosine can control the activity of other key enzymes involved in the regulation of metabolic or cell signaling pathways such as the Mg^{2+} dependent form of phosphatidate phosphohydrolase[30,31], phospholipase D (PLD)[32], or diacylglycerol kinase[33,34]. Although there is abundant evidence that sphingosine is toxic to cells[25,28], diverse function by concentration dependence of sphingosine has been reported. Vessey *et al*[35] recently reported that at lower dose (submicromolar), a more physiologic concentrations, sphingosine has been shown to be cardioprotective in isolated Langendorff-perfused rat hearts subjected to ischemia/reperfusion injury. Unlike S1P, sphingosine-induced cardioprotection seems to be mediated by cyclic nucleotide-dependent protein kinase A and G (PKA and PKG) pathways[35]. While, at the higher concentrations usually employed, sphingosine is toxic to cells[27].

S1P

S1P is a bioactive lipid signaling molecule formed when either one of two isoforms of the enzyme SphK1 or 2 catalyzes the addition of a phosphate group to sphingosine. S1P exerts a wide variety of biological activities in
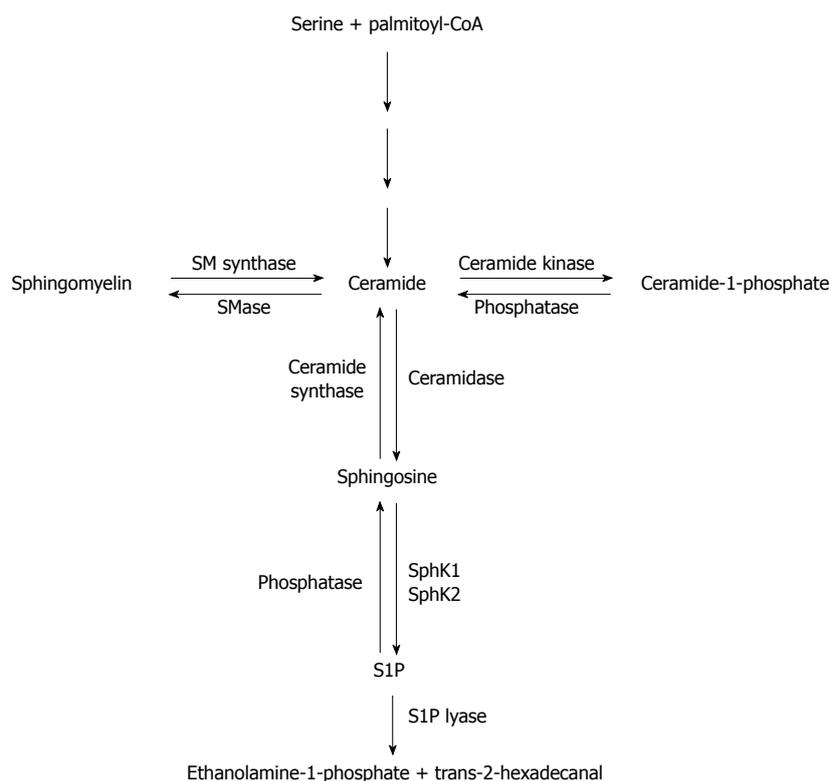
Figure 1 Schematic outline of sphingolipid metabolism. Names of the major intermediates and abbreviations of the enzymes involved are included. SM: Sphingomyelin; SphK: Sphingosine kinase; S1P: Sphingosine-1-phosphate.

many eukaryotic cell types[36-38]. It was initially proposed to act as an intracellular second messenger, based on the ability of extracellular growth factors to activate SphK and increase intracellular S1P levels. The discovery and cloning of five G protein-coupled receptors (S1P₁, S1P₂, S1P₃, S1P₄, S1P₅) expressed on the cell membrane has stimulated the notion that S1P is an extracellular signaling ligand, regulating a host of cellular functions such as proliferation, survival, immunomodulation, apoptosis, migration, cytoskeletal organization, and differentiation/morphogenesis[39]. Basal plasma and serum concentration levels of S1P are generally low ranging within 200-900 nmol/L, but can increase rapidly and transiently when cells are exposed to various agonists[40,41]. The concentration of S1P is controlled by two enzyme, SphK and S1P lyase. While SphK activity can be upregulated by a variety of growth factors, S1P lyase activity in other hand is constantly at the high level, and this makes the intracellular S1P level very low in most tissues. However, erythrocytes and platelets have low S1P lyase activity resulting in high S1P concentration in blood plasma[38,42]. This concentration gradient is presumed to provide the basis for the integral role for the bioactivity of S1P involved in lymphocyte trafficking[43].

After the discovery of S1P receptors, there has been extensive work aimed at understanding the role of S1P as extracellular ligands. A schematic of the S1P receptors are shown in Figure 2. S1P mediates its effects through binding to G protein-coupled receptors (S1P₁₋₅) which

activates a variety of signaling *via* transduction of G proteins isoforms (Gₛ, Gᵢ, Gq, and G₁₂/₁₃). The prosurvival phosphatidylinositol-3-kinase (PI3K)/Akt have been shown to be downstream molecules regulated by the S1P₁ receptor signaling, Akt activation is a principal factor in the prevention of apoptosis[44,45]. S1P also stimulates cell growth and proliferation *via* activation of mitogen-activated protein kinase extracellular signal-regulated kinases (ERK)[46]. It is believed that elevated ERK phosphorylation plays a role in cell survival and proliferation in the penumbra, and ERK activity may block apoptosis by enhancing the level of the antiapoptotic protein Bcl-2 through cAMP responsive element binding protein activation[44]. S1P is also assumed to prevent necrosis mediated by the PKCε pathway[47].

Sphingosine kinase

The synthesis of S1P is catalyzed by SphK which is responsible for linking a phosphate group to sphingosine. There are two isozymes of SphK designated as SphK1 and SphK2. SphK1 and SphK2 show different subcellular localizations and enzymatic properties as well as different expression in various tissues. Mouse and human SphK1 exhibit substantial homology and SphK2 is highly homologous to SphK1 except for 240 additional amino acids located at the N terminus and in the center of the enzyme. The genes encoding these isozymes are localized on different chromosomes[48]. Genetic deletion of both isozymes results in fetal death from severe bleeding,
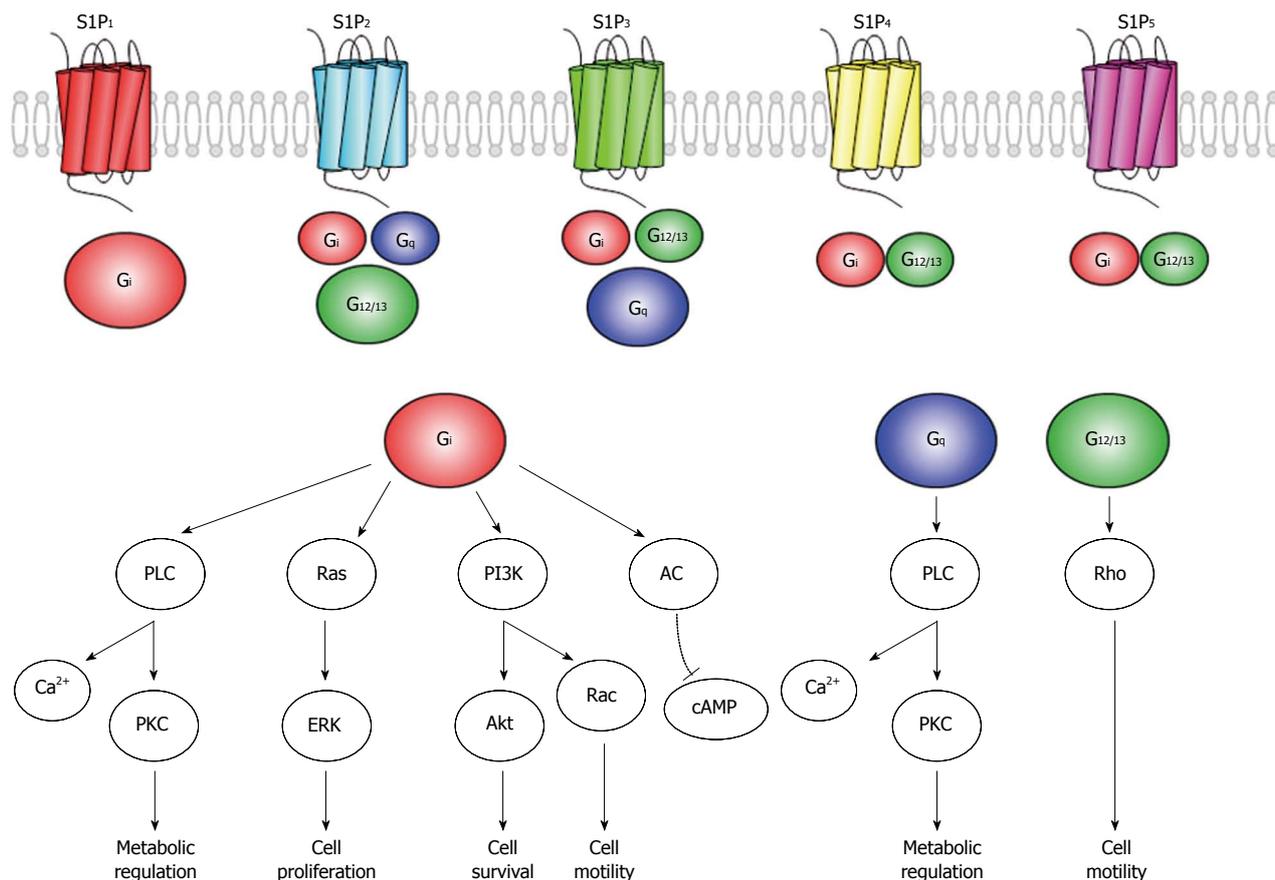
Figure 2 Schematic outline of sphingosine-1-phosphate signaling through receptors. S1P: Sphingosine-1-phosphate; ERK: Extracellular signal-regulated kinases; PKC: Protein kinase C; PLC: Phospholipase C.

inadequate vasculogenesis, and incomplete neural tube closure[48,49]. In contrast, mice null for either the SphK1 or the SphK2 isozyme exhibit normal development and are otherwise unremarkable in the basal state[49]. It is presumed that these isozymes have the complementary functions. The regulation of SphK activity is complex. It is stimulated by G-protein coupled receptor agonists (muscarinic receptor agonists[50], formyl peptide[51], nucleotides, bradykinin[52], lysophosphatidic acid[53], and S1P[54]), agonists at receptor tyrosine kinases (platelet-derived growth factor[55], endothelial growth factor[56], nerve growth factor[57], fibroblast growth factor[57], vascular endothelial growth factor[58]), immunoglobulin receptor crosslinking[59], monoganglioside (GM1)[60], estrogen[61] and activators of PKCε[62]. Both TNF-α and phorbol ester, which stimulates PKC, phosphorylate and thus activate SphK1 at serine225 mediated by ERK1/2[63,64]. The tumor necrosis factor (TNF) α response requires binding by TNF receptor-associated factor-2 (TRAF2). Other interacting proteins that stimulate SphK include delta-catenin/NPRAP (neural plakophilin-related armadillo repeat protein), aminoacylase 1, and eukaryotic elongation factor 1A (EEFA1)[65]. Reported inhibitory interacting proteins are SKIP (SK1-interacting protein), PECAM-1 (platelet endothelial adhesion molecule-1), and FHL-2 suppressed VEGF-induced PI-3 kinase/Akt activation *via*

interactions with SphK1[66-69].

Despite the structural similarities and even though it catalyses the production of S1P, SphK2 has shown to have opposing actions to SphK1[70]. Thus, SphK2 inhibits cell growth and enhances apoptosis, in part by regulating ceramide levels[70]. Downregulation of SphK2 reduced conversion of sphingosine to ceramide, while downregulation of SphK1 increased it. The pathway of sphingosine into pro-apoptotic ceramide is dependent on SphK2, but not SphK1, acting in concert with S1P phosphohydrolase 1[71]. And also interestingly, there are organ specific deviations of SphK. While SphK1 is the more abundant isozyme in lung, spleen, kidney, heart, renal proximal tubules and cardiomyocytes, SphK2 isozyme predominates in the brain[72-74]. The intracellular locations of two enzymes are also different. SphK1 is localized predominantly in the cytoplasm while, SphK2 is mainly localized in the nucleus[75]. The reason of this deviation difference is that SphK1 has two functional nuclear export signal (NES) sequences which positively direct SphK1 to an extranuclear location. On the other hand, a nuclear localization signal (NLS) sequence has been found in SphK2 which keeps SphK2 in the nucleus and NES shuttles SphK2 between the cytoplasm and the nucleus according to demand[75]. The underlying reasons for this and its functions have yet to be elucidated.

ROLE OF SPHINGOLIPIDS IN CARDIOVASCULAR DISEASE

S1P in cardioprotection

The cardioprotective effect of S1P was first reported in 2001[76]. In neonatal rat cardiac myocytes, exogenously applied S1P enhanced cardiac myocyte survival during hypoxia[76]. Subsequent studies were undertaken using cultured adult mouse cardiac myocytes subjected to hypoxia *in vitro* that mimics ischemia *in vivo* during coronary artery occlusion. This system permitted measurements of S1P effects on myocyte viability during stress and activation of cell signaling from plasma membrane to mitochondria. There were three major findings that advanced understanding of S1P prosurvival effects during hypoxia[77]. First, it was found that $S1P_1$ receptors are abundantly expressed by adult mouse cardiac myocytes[78]. Second, exogenously applied S1P enhanced survival during prolonged *in vitro* hypoxia through mechanisms that required $S1P_1$ receptor function and G protein G_i-independent activation of the prosurvival kinase Akt/PKB. Finally, Akt-mediated phosphorylation of myocyte substrates that interact with mitochondria, such as GSK-3 and BAD, contributed to cardioprotection. In these studies the selective $S1P_1$ receptor agonist SEW2871 and the S1P analog FTY720 were as effective as S1P in preserving myocytes viability during hypoxia[77]. In contrast, Means *et al*[79] were unable to demonstrate prosurvival signaling mediated by the $S1P_1$ receptor. The divergent observations surrounding the cardioprotective effects of $S1P_1$ agonism may result from methodologic differences. Even though, these data strongly suggest that the $S1P_1$ receptor, which is the most abundant S1P receptor subtype in cardiac myocytes, is at least partially responsible for S1P-mediated prosurvival signaling and for maintaining myocytes viability during hypoxia[77], and during hypoxia/reoxygenation[37]. In a study of the other receptors, it was shown that combined deletion of $S1P_2$ and $S1P_3$ receptors augmented infarct size in mice subjected to ischemia/reperfusion injury[80]. In these hearts, activation of Akt was markedly attenuated compared to wildtype mice, but the absence of either receptor subtype alone affected neither infarct size nor Akt activation after ischemia/reperfusion injury. S1P augmented Akt activity in control murine myocytes, but was not effective in the double knockout cells[80]. Thus, these observations suggest that the less abundant cardiac myocyte S1P receptors ($S1P_2$ and $S1P_3$) may also be necessary for cell survival during ischemia/reperfusion injury.

In SphK1 null ventricular myocytes subjected to *in vitro* hypoxia, cell death and cytochrome c release were greater than in wild-type controls[36]. Exogenous S1P enhanced survival of both wild-type and SphK1 null cells. GM-1 treatment, which activates PKC domain and subsequently upregulates SphK to produce S1P, induced cytoprotection in wild-type cardiac myocytes but not in SphK1 null cells. These observations indicate that GM-1 activates SphK1, presumably *via* PKCε-mediated phos-

phorylation. Interestingly, the beneficial effects of GM-1 on wild-type cardiac myocytes were abolished by pretreatment with either an $S1P_1$ receptor antagonist or pertussis toxin, which ADP-ribosylates and thereby inactivates G_i, suggesting that endogenous S1P was transported to the extracellular space for activation of its cognate G-protein coupled receptors[36]. A potential mechanism for extrusion of S1P is *via* ABC transporters, which have been demonstrated in a variety of cell types[81,82], as well as in murine and human hearts[83,84]. Recently, a specific S1P transporter, SPN2, which also transports the phophorylated form of FTY720, has also been described[85]. Knapp *et al*[86] also mentioned the importance of the S1P/ceramide levels ratio which could be responsible for increased apoptosis in the myocardial infarction in the rat.

Sphingosine kinase in cardioprotection

As noted above, GM-1 enhanced the survival of cardiac fibroblasts subjected either to PKC inhibition or to C2-ceramide (N-acetyl-sphingoid bases) treatment[62]. GM-1 also increased S1P levels, an effect abrogated by the SphK inhibitor, DMS[62]. Using isolated adult mouse hearts, exogenous S1P and GM-1 separately induced substantial resistance to ischemia-reperfusion injury in wild-type mice[87]. Similar experiments were reported by Lecour *et al*[88] in isolated rat heart. The importance of the prosurvival kinase, PKCε, was emphasized by experiments in which GM-1 proved to be ineffective in PKCε-null hearts. In addition, GM-1, but not exogenous S1P, stimulated translocation of activated PKCε to myocyte particulate fractions[87]. Nevertheless, exogenously administered S1P was effective both in isolated PKCε-null hearts subjected to ischemia/reperfusion injury[87] and in isolated cardiac myocytes from these hearts subjected to hypoxia[36]. Thus, S1P acting at cell surface receptors or activation of intracellular SphK confers cardioprotection during acute ischemia/reperfusion injury. Consistent with this hypothesis, it was shown that PKCε activation is essential for cardioprotection induced by ischemic preconditioning (IPC)[89]. PKCε peptide agonists mimicked preconditioning effects on contractile recovery and tissue viability in wild-type hearts after prolonged ischemia-reperfusion injury[90]. In contrast, inducible cardioprotection was blocked by PKC peptide antagonists and targeted deletion of the *PKCε* gene[91]. A subsequent series of experiments directly tested the hypothesis that SphK activation mediates IPC in isolated mouse hearts[90]. It was determined that IPC sufficient to reduce infarction size in wild-type hearts increased SphK localization and activity in tissue membrane fractions. Interestingly, IPC triggered SphK translocation to tissue membrane fractions in PKCε-null hearts but did not enhance enzymatic activity or decrease infarction size after ischemia-reperfusion injury[90]. As noted above, DMS, the endogenous sphingolipid generated by *N*-methylation of sphingosine, inhibited tissue SphK activity, while 10 μmol/L of DMS pretreatment abolished IPC-induced cardioprotection in wild-type hearts[90]. Sub-

sequent experiments elucidated unpredicted effects of low DMS concentrations on SphK[92]. In contrast to moderate dose DMS (10 μmol/L), low-dose DMS stimulated translocation of activated PKCε to tissue particulate fractions and reduced cardiac ischemia-reperfusion injury. Importantly, low-dose DMS effects were abolished in PKCε-null hearts, and SphK1 was found to co-immunoprecipitate with activated PKC phosphorylated at serine729. Low-dose DMS induced translocation of total Akt from Triton-insoluble fractions to cytosol and increased activated Akt phosphorylated at serine473[92].

When tested with the classic SphK inhibitor, DMS, the activity of SphK2 was unaffected by concentrations as high as 20 μmol/L. Consistent with this observation, DMS was only a partial inhibitor of total cytosolic SphK activity[93]. Also SphK2 was not inhibited by the sphingosine analogue, FTY720. As noted earlier, SphK1 was efficiently inhibited by both DMS and FTY720. Furthermore, when the cytosolic fraction from SphK1 knockout mouse hearts was tested, residual activity due to SphK2 was not inhibited by DMS or FTY720[93]. These observations confirmed the specificity of SphK1 inhibition and indicated the lack of inhibition of SphK2 was not an artifact of purification. SphK2 from rat liver and spleen was also not inhibited by DMS. In contrast, l-sphingosine was an effective inhibitor of both forms[93]. Taken together, along with data obtained in SphK1-null hearts, these observations indicated that DMS inhibits only the SK1 form in the heart. Thus, prior experiments in other cells and tissues in which DMS was used as inhibitor of SphK may require reinterpretation.

The time course of SphK activity in adult rat hearts subjected to ischemia/reperfusion injury and preconditioning has been reported[94]. Cytosolic SphK activity declined by 61% during ischemia and did not recover upon reperfusion, paralleling the effects on left ventricular developed pressure (LVDP). IPC reduced the decrease in enzyme activity during ischemia by half and, upon reperfusion activity, returned to normal. LVDP recovered to 79% of control values, and infarct size was reduced. The low baseline-specific activity of SphK declined by 67% after 45 min of ischemia and remained at that level during reperfusion. IPC restored SphK activity almost to normal during reperfusion. Parallel effects were observed in mitochondria from the same hearts[94]. In these experiments[94], total S1P in cardiac tissue was quantified by liquid chromatography followed by tandem mass spectrometry[38]. In non-preconditioned hearts, S1P content declined from base line after both ischemia and reperfusion. Preconditioned hearts had higher S1P levels after ischemia/reperfusion relative to control hearts. Treatment of non-preconditioned hearts at reperfusion (pharmacologic postconditioning) with 100 nmol/L of S1P improved recovery of LVDP. Thus, maintenance of SphK activity resulting from higher S1P levels is critical for recovery from ischemia/reperfusion injury. In this connection, the activity of S1P phosphatases and lyase has not been reported during experiments involving isch-

emia/reperfusion injury in the heart.

Despite compelling evidence that DMS modulates resistance to injury by inhibiting SphK1, however, this drug also has been shown to alters other kinases such as PKC activity[92]. Accordingly, SphK1 knockout mice have been employed in a series of subsequent studies[95,96]. SphK2 expression increased in hearts after *SphK1* gene disruption, resulting in total SphK activity half that of wild type. Although SphK1-null hearts exhibited normal hemodynamic performance under baseline conditions, contractile abnormalities and infarction were more severe after ischemia/reperfusion than in wild-type hearts[95]. As predicted, targeted disruption of the *SphK1* gene abolished IPC-induced cardioprotection[95]. Importantly, when the index ischemia time was reduced from 50 to 40 min, infarct size in the *SK1* knockout hearts declined to the level seen in the wild type hearts subjected to ischemia/reperfusion injury. At this reduced level of injury, IPC was still ineffective in producing cardioprotection in the knockout hearts. However, exogenous S1P retained the ability to induce cardioprotection in these *SphK1*-null hearts. Despite an increase in SphK2 expression in the *SphK1*-null hearts, infusion of DMS did not affect infarct size, confirming prior *in vitro* experiments and suggesting that the absence of SphK1 rather than the increased presence of SphK2 was critical to the loss of cardioprotection in myocardium null for SphK1[95]. However, Vessey *et al*[97] recently demonstrated that myocardial damage is enhanced after ischemia/reperfusion in mice null for SphK2 and that the cardioprotective intervention of preconditioning is abolished by deletion in the *SphK2* gene. These observations are contrary to prior suggestions derived from *in vitro* models that SphK1 and SphK2 drive opposing functions that regulate cell fate[97].

In another recent study, it was reported that previous adenoviral gene transfer of *SphK1* protected against hemodynamic deterioration and reduced creatine kinase release and arrhythmias during acute ischemia/reperfusion injury in isolated rat hearts[96]. When gene transfer was performed at the time of acute left anterior descending coronary artery ligation, studies 2 wk later revealed improved left ventricular function in the treated mice, reduced infarct size, more neovascularization, and reduced collagen content[96].

Like IPC, ischemic postconditioning is cardioprotective[98], and this observation has recently been extended to patients undergoing percutaneous coronary interventions[99]. To ascertain whether the SphK/S1P pathway is a determinant of successful postconditioning, isolated wild type and *SphK1*-null mouse hearts were subjected to ischemia/reperfusion injury[100]. At the onset of reperfusion, hearts selected for treatment underwent 3 brief cycles of postconditioning (5 s of ischemia followed by 5 s of reperfusion). Results were similar to the preconditioning studies cited above: hemodynamics were improved and infarction size reduced compared with untreated hearts[100]. Phospho-Akt and phospho-ERK were enhanced. None of these findings were present in *SphK1*-

null hearts. Thus, SphK1 is also critical for successful ischemic postconditioning. In this connection, it has recently been found that a ramped ischemic postconditioning protocol combined with low-dose sphingosine + S1P given at the time of reperfusion can rescue isolated hearts from as much as 90 min of ischemia[101].

ROLE OF SPHINGOLIPIDS IN CEREBROVASCULAR DISEASE

Distribution and function of S1P and SphK in the brain

While S1P signaling has long been known to mediate protection in peripheral and cardiac ischemia, only recently has this bioactive lipid pathway drawn attention in cerebral ischemia.

S1P has shown many neuroprotective mechanisms in both *in vitro* and *in vivo*. S1P is presumed to protect central nervous system through many different ways[102,103]. In addition to the above mentioned prosurvival effect of S1P, S1P may also protect the brain vasculature by reducing leukocyte adhesion secondary to altering endothelial adhesion molecule expression and preventing endothelial apoptosis through Bcl-2 activation. There is also evidence that S1P may act as a proximal trigger of cerebroprotection (both neuronal and vascular) through activation of signaling molecules such as endothelial nitric oxide synthase[102].

In models of stroke, Kimura *et al*[104] found that S1P concentrations in the brain were significantly decreased 3 d after ischemia. However, S1P in the brain was increased thereafter and reached a maximum 14 d after the insult. Upregulation of S1P was observed at the infarct border zone and at the infarct core, and mostly colocalized to microglia and some astrocytes, indicating that microglia may be the main source of S1P production in ischemic brain[104].

Moreover, the S1P regulating enzymes SphKs show differential tissue expression patterns and different subcellular localization[72]. Although SphK1 has greater expression and activity than SphK2 in many organs such as lung and spleen, SphK2 expression levels are greater than SphK1 in the brain, suggesting a more prominent physiological role for SphK2 in the brain and brain vasculature[73,74]. Among brain resident cells, primary glial cells express more SphK2 mRNA than primary neurons, and the highest mRNA concentrations were found in cortex, while mRNA was least abundant in striatum[74]. Increased SphK2 was observed in response to cerebral ischemia both *in vitro* and *in vivo*[74]. As mentioned earlier, SphK2 could promote apoptosis, instead of cell survival as SphK1 shows at the non-central nervous system[70], there is also accumulated evidence that SphK2 could play an important role as a prosurvival factor in the central nervous system[73,105,106].

A widely used anesthetic agent isoflurane is now considered to be one of the promising therapeutic strategies for many neurological diseases including ischemic stroke[107]. Zhou *et al*[107] reported that isoflurane given post injury attenuated brain damage after subarachnoid hemorrhage, and that the neuroprotective effect was associated with decreased neuronal apoptosis partly through the antiapoptotic effect of sphingosine-related pathway activation including SphK1 and S1P$_{1,3}$ receptors. Isoflurane-mediated neuroprotection has also been examined during neonatal hypoxia ischemia through the S1P/PI3K/Akt signaling. The PI3K/Akt signaling cascade has been shown to play a key role in preventing apoptosis under hypoxic or ischemic conditions. Hypoxic preconditioning (HPC) has also been investigated in the contest of cerebral ischemia[105,108]. With respect to elucidating the molecular basis of preconditioning-induced tolerance, Yung *et al*[106] showed that hypoxic preconditioning significantly reduced infarct volume and improved neurological outcome in wild-type and SphK1-/-, but not in SphK2-/- mice. Wacker *et al*[105,108] also documented HPC-induced ischemic tolerance and the concomitant protection of the blood-brain-barrier depended on SphK2 signaling. SphK2-generated S1P participates in both the normal maintenance of occlusion at cytoskeletally linked cell junctions, as well as the mediation of HPC-induced increases in the expression of claudin-5 and VE-cadherin at these junctions, which may be compulsory for induction of the vasculoprotective phenotype by HPC. The present data demonstrates that SK2 is a universal mediator of isoflurane- and hypoxia-induced preconditioning.

Role of FTY720 in cerebrovascular disease

FTY720 (Fingolimod) is a novel immunomodulatory agent, which in its phosphorylated form acts as a high affinity agonist of S1P receptors[109,110]. It became the first oral drug to be FDA-approved for clinical use in the treatment of multiple sclerosis. FTY720 readily crosses the blood-brain barrier and exerts a number of direct effects in the central nervous system. FTY720 is phosphorylated by SphK, mainly by SphK2[73,111], into the active compound phospho-FTY720, which then acts on 4 of the 5 known S1P receptor subtypes (S1P$_1$, S1P$_3$, S1P$_4$, S1P$_5$), and shows neuroprotective effect against many central nervous system disease including cerebral ischemia[73,112-115]. Mechanisms include regulation of myelination and microglial activation following injury, proliferation and migration of neural precursor cells toward injury sites, and potentiation of growth-factor regulated neuronal differentiation, survival, and process extension, and also antiapoptotic and anti-inflammatory pathways[104,113,115-119]. FTY720 also exerts immunomodulatory actions by affecting lymphocyte production, trafficking, and apoptosis through S1P receptors which induces a depletion of circulating lymphocytes by preventing the egress of lymphocytes from the lymph nodes. Mechanistically, this is due to a downregulation of the S1P type 1 receptor (S1P1). Expression levels of endothelial adhesion molecules such as E-selectin, P-selectin, intracellular adhesion molecule-1 or vascular cell adhesion molecule-1 were shown to be induced by FTY720 treatment, and therefore might contribute to the prevention of early infiltration of neurotrophils and activation of microglia/macrophages. These findings suggest that anti-inflamma-

tory mechanisms, and possibly vasculoprotection, rather than direct effects on neurons, underlie the beneficial effects of fingolimod after stroke. Most of the past reports have shown beneficial effect of S1P in the field of ischemia, but by contrast, Liesz *et al*[120] showed opposite results. These authors found that S1P treatment did show a reduction of lymphocyte brain invasion but could not achieve a significant reduction of infarct volumes and behavior dysfunction[120]. Liu *et al*[121] recently published a systematic meta-analysis of the efficacy of FTY720 in animal model of stroke. In this study, they concluded that FTY720 reduced infarct volume and improve functional outcome. However, the authors also indicated that more experimental studies should be performed to evaluate the safety of FTY720 in the future. Thus, taken this recent scientific highlights together, it is obvious that S1P receptor pathways and sphingolipids regulating enzymes are a highly promising target in stroke treatment.

CONCLUSION

During the past few years, a plethora of new information identifying the importance of sphingolipid signaling pathways in the cardiovascular and cerebrovascular diseases has accumulated. The potential for the development of new therapeutic agents based on this understanding is high, but this is clearly a new area of investigation that is still in its infancy.

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REVIEW

Drugs to be avoided in patients with long QT syndrome: Focus on the anaesthesiological management

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Abstract

Long QT syndrome incidence is increasing in general population. A careful pre-, peri- and post-operative management is needed for patients with this syndrome because of the risk of Torsades de Pointes and malignant arrhythmias. The available data regarding prevention of lethal Torsades de Pointes during anesthesia in patients with long QT syndrome is scant and conflicting: only case reports and small case series with different outcomes have been published. Actually, there are no definitive guidelines on pre-, peri- and post-operative anesthetic management of congenital long QT syndrome. Our review focuses on anesthetic recommendations for patients diagnosed with congenital long QT syndrome furnishing some key points for preoperative optimization, intraoperative anesthetic agents and post-operative care plan, which could be the best for patients with c-long QT syndrome who undergo surgery.

Core tip: Long QT syndrome is a cardiac conduction disorder characterized by prolongation and increased dispersion of ventricular repolarization, manifested by lengthening of the QT interval on the surface electrocardiography. This review furnishes important key points for preoperative optimization, intraoperative anesthetic agents and postoperative care in order to fill the lack of definitive guidelines on anesthetic management of c-long QT syndrome.

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INTRODUCTION

Long QT syndrome (LQTS) is a cardiac conduction disorder characterized by prolongation and increased dispersion of ventricular repolarization, manifested by lengthening of the QT interval on the surface electrocardiography (ECG). This abnormal repolarization, when amplified by sympathetic activity, can lead to the formation of reentry circuits and may present with syncope, seizures, or torsades de pointes (TdP), ventricular fibrillation and, therefore sudden cardiac death[1]. Moreover, there are other signs of the torsadogenic property of a drug: QT dispersion (difference between the longest and the shortest QT interval) and the transmural dispersion of repolarization (TDR) (time between the peak and the end of the T wave in a precordial lead)[2]. Traditionally, LQTS is divided into congenital (c-LQTS) and acquired

(a-LQTS) forms. Drug-induced LQTS is the most common cause of a-LQTS; as a matter of fact, a survey by Schwartz *et al*[3] of 670 patients in the International LQTS Registry revealed that anesthesia can trigger LQTS.

Ninety-five percent of drug-induced LQTS is due to the obstruction of the rapid component of the late correcting potassium current (I_k-r), which physiologically allows the rapid potassium outflow[4]. I_{kr} and the slow component of the same channel (I_k-s) are responsible for the repolarization of cardiomyocytes. Some anesthetics and some drugs used in premedication may lead to QT-prolongation. The available data on the prevention of lethal TdP during anesthesia in patients with c-LQTS is scant and conflicting: only case reports and small case series with different outcomes, even when using the same anesthetic agent, have been published[2,5-19]. Although a-LQTS is of significant interest, this review focuses on the anesthetic recommendations for patients diagnosed with c-LQTS. Our aim is to provide some key points which could help both the cardiologists and the anesthetists when approaching a patient with LQTS candidate for anaesthesiological procedures. Firstly, we describe which drugs should be avoided in LQTS and then we move on the specific topic of the review describing the anaesthesiological management of patients with LQTS.

DRUGS TO BE AVOIDED IN LQTS

Certain drugs, including some anesthetics, are known to contribute to QT prolongation. Considering that not all agents that prolong the QT interval increase TDR, drugs can be distinguished into the following groups depending on their simultaneous effects on the QT corrected using the Bazzet's formula (QTc) interval and on TDR[20]: (1) drugs inducing both QTc prolongation and increased TDR, characterized by a high torsadogenic potential; (2) drugs causing QTc prolongation but with a slight effect on TDR and little, if any, ability to induce TdP; and (3) drugs causing both QTc prolongation and increased TDR below a certain concentration, but inducing TdP once a critical value of TDR is exceeded.

Drugs that prolong the QT interval and/or induce Torsades de Pointes in patients with diagnosed or suspected c-LQTS are shown on Table 1[21] and can be found on the web pages www.torsades.org. Some of these drugs are not available in every country (many of them have been withdrawn from the market in several countries). However, this list doesn't include some anesthetic agents which have an influence on cardiac conduction and can lead to intraoperative TdP; hence, they are discussed throughout the text.

ANAESTHETICS IN LQTS

Despite an adequate β-blocking, patients with LQTS candidate to surgical or anesthetic procedure have an increased risk of developing perioperative ventricular arrhythmias. The probability of developing these arrhythmias significantly decreases with a careful pre-, intra- and post-operative management.

Preoperative management
A good anaesthesiological preoperative physical examination should be the cornerstone, mostly in childhood and adolescence. Moreover, an ECG at rest is always needed in order to reveal a QT prolongation. Patients treated with beta-blockers should continue their medication throughout the perioperative period until the operating day. Electrolytes should be normalized. Drugs known to induce TdP (Table 1) should be discontinued or the dose should be decreased if it cannot be discontinued. The presence of a pacemaker or implantable cardioverter defibrillator should be checked.

Perioperative management
Some anesthetics and some drugs used for premedication may lead to QT-prolongation. The torsadogenic effect is related both to the drug and to the anaesthesiological and surgical manoeuvres.

Drugs used for premedication and sedation
Since anxiety and pain can trigger arrhythmias in patients with LQTS, pre-anesthetic medication is recommended. Anesthetic premedication is usually performed using vagolytic and sedative/analgesic drugs. Among these drugs, atropine causes a lengthening of the QT interval and should not be used[22]. On the other hand many studies demonstrated that midazolam does not modify either QT$_c$ or TDR[23,24]; hence, it should be used for premedication in patients with c-LQTS. Midazolam reduces sympathetic activity in unstimulated patients but it does not blunt the hemodynamic response to oral or nasal intubation[23]. Few authors verified the utility of different drugs to prevent lengthening of QTc interval associated to intubation: Owczuk *et al*[25] demonstrated that the use of intravenous lidocaine (1.5 mg/kg) before laryngoscopy and intubation prevented prolongation of the QTc interval induced by the maneuver. Therefore, it seems useful the association of midazolam in premedication and lidocaine before intubation.

Droperidol, used for neuroleptanalgesia in intensive-care treatment since 1970, extends the QTc interval by the IKr current blockade through the HERG channel; because of this effect on QTc this drug was withdrawn from the market in 2001[26,27]. This decision was focus of debate;hence, the drug was licensed again in 2008 and it is used in premedication both for sedation and antiemetic treatment[28-31]. However, Staikou *et al*[32] advise against the use of droperidol in patients with LQTS in a recent review.

Lastly, an adequate sedoanalgesia reduces catecholamine release; the most used drugs are morphine, meperidin and fentanyl. Though the effects of fentanyl on QTc interval are conflicting, fentanyl and morphine have been used in patients with c-LQTS without any adverse effect[17,33-36]. On the other hand, Song *et al*[37] recently re-

Table 1 Drugs that prolong the QT interval and/or induce torsades de pointes

Drugs to be avoided in patients with c-long QT syndrome	
Class	Generic name
Anesthetic	Sevoflurane
Anti-anginal	Ranolazine, Bepridil
Anti-arrhythmic	Sotalol, Quinidine, Amiodarone, Ibutilide, Disopyramide, Procainamide, Flecainide, Dofetilide, Dronedarone
Antibiotic	Moxifloxacin, Clarithromycin, Ciprofloxacin, Gemifloxacin, Ofloxacin Telithromycin, Levofloxacin, Roxithromycin, Trimethoprim-Sulfa, Gatifloxacin, Sparfloxacin, Azithromycin Erythromycin
Anti-cancer	Tamoxifen, Lapatinib, Nilotinib, Arsenic trioxide, Eribulin, Sunitinib Vandetanib
Anti-convulsivant	Fosphenytoin, Felbamate
Anti-depressant	Mirtazapine, Citalopram, Venlafaxine, Paroxetine, Fluoxetine, Sertraline, Trazodone, Escitalopram, Clomipramine, Amitriptyline, Imipramine, Nortriptyline, Desipramine, Doxepin, Trimipramine, Protriptyline
Anti-fungal	Voriconazole, Fluconazole, Ketoconazole, Itraconazole
Antihistamine	Astemizole, Terfenadine, Diphenhydramine, Diphenhydramine
Anti-hypertensive	Nicardipine, Isradipine, Moexipril/HCTZ
Anti-infective	Pentamidine
Antilipemic	Probucol
Anti-malarial	Artenimol + piperaquine, Chloroquine, Halofantrine
Anti-mania	Lithium
Anti-nausea/antiemetic	Granisetron, Dolasetron, Ondansetron
Anti-psychotic	Clozapine, Ziprasidone, Thioridazine, Risperidone, Mesoridazine, Quetiapine, Haloperidol, Pimozide, Amisulpride, Sertindole, Sertindole, Iloperidone, Paliperidone, Chlorpromazine
Anti-viral	Foscarnet, Ritonavir, Atazanavir
Appetite suppressant	Phentermine, Fenfluramine, Sibutramine
Bladder Antispasmodic	Tolterodine
α1-blocker	Alfuzosin
Bronchodilator/decongestant	Albuterol, Salmeterol, Metaproterenol, Terbutaline, Metaproterenol, Levalbuterol, Ephedrine, Phenylpropanolamine, Pseudoephedrine
Cholinesterase inhibitor	Galantamine
CNS stimulant	Amphetamine
	Methylphenidate
	Amphetamine
	Dexmethylphenidate
	Methylphenidate
	Lisdexamfetamine
Diuretic	Indapamide
Dopaminergic/anti-viral/anti-infective/	Amantadine
Endocrine	Ocreotide
GI stimulant	Cisapride
H2-receptor antagonist	Famotidine
Imaging contrast agent	Perflutren lipid microspheres
Immunosuppressant	Tacrolimus, Fingolimod
Inotropic agent/vasconstrictor	Dopamine, Isoproterenol, Dobutamine, Epinephrine, Norepinephrine, Phenylephrine
Local anesthetic	Cocaine
Muscarinic receptor anatagonist	Solifenacin
Muscle relaxant	Tizanidine
norepinephrine reuptake inhibitor	Atomoxetine
Opiate agonist	Methadone, Levomethadyl
Oxytocic	Oxytocin
phosphodiesterase inhibitor/vasodilator	Vardenafil
Sedative	Chloral hydrate
Sedative; Anti-nausea/anesthesia adjunct	Droperidol
Uterine relaxant	Ritodrine
Vasconstrictor	Midodrine

A continuously updated list of these drugs is available at www.torsades.org (accessed December 16, 2012). CNS: Central Nervous System.

ported that the intravenous injection of meperidine led to QTc prolongation, polymorphic ventricular tachycardia and ventricular fibrillation, in a 16-year-old boy without neither underlying cardiac disease nor mutation in *LQTS* genes, but with a single nucleotide polymorphism, including H558R in *SCNA5A* and K897T in *KCNH2*. Alfentanil does not extend repolarization time[2]. On the contrary, sufentanil prolongs QTc interval[38].

General anesthesia

Induction and maintenance: Induction of anesthesia can be done using halogenated volatile anesthetics or using intravenous agents, which are distinguished in barbiturates (sodium thiopental) and non barbiturates

Table 2 Normal QT corrected using the Bazzet's formula duration by age and gender

QT corrected using the Bazzet's formula			
QTc value (s)	Children (1-15 yr)	Male (> 15 yr)	Female (> 15 yr)
Normal	< 0.44	< 0.43	< 0.45
Borderline	0.44-0.46	0.43-0.45	0.45-0.46
Prolonged	> 0.46	> 0.45	> 0.46

QTc: QT corrected using the Bazzet's formula.

(Propofol or Ketamine). Maintenance of anesthesia is usually achieved by allowing the patient to breath a carefully controlled mixture of oxygen, nitrous oxide, and a volatile anaesthetic agent or by having a total intravenous anesthesia (TIVA) using intravenous agents in infusion together with analgesia.

Halogenated volatile anesthetics (Halothane, Enfluorane, Isoflurane, Desflurane and Sevoflurane) prolong the QTc interval, even if data is controversial for some of them[39-43]. Isoflurane has been used safely in patients with LQTS[13,44]. Sevoflurane produced significant arrhythmias in a pediatric patient with c-LQTS[10]; moreover, it causes lengthening of QTc interval both in young and adults[5,45-49]. The clinical significance of these findings in patients with LQTS is unclear[50], but it is recommended to avoid these agents.

Thiopental (sodium thiopental) has been used safely in patients with c-LQTS even if it causes QTc prolongation in humans[13,51-53]. Thiopental may reduce TDR through a longer prolongation of the action potential duration in endocardial and epicardial cells compared to M-cell and theoretically it could prevent the spontaneous onset of TdP[51,54].

Data about the effect of Propofol on QTc is conflicting, while we certainly know that this drug does not modify TDR[55-58]. Moreover, Propofol rapidly reverses Sevoflurane-induced QTc prolongation in healthy patients and therefore may be beneficial[59]. Although Ketamine was used in premedication in children with undiagnosed c-LQTS, it is not recommended in patients with LQTS because its sympathomimetic properties can favor incidents of TdP[51]. Etomidate does not affect the duration of ventricular repolarization[25,60]. However, Erdil *et al*[61] compared the effect of Propofol and Etomidate during electroconvulsive therapy, which may cause an acute rise in QT dispersion, and they found out that Etomidate increased QT more than Propofol.

Anesthesiologic maneuvers

Intubation and extubation: Usually the prophylactic administration of muscle relaxants eases intubation. Succinylcholine has been used in some patients with c-LQTS but it may either prolongs the QT interval in patients with c-LQTS, especially during tracheal intubation, or determine a vagal stimulation or result in asystole after pacemaker inhibition by fasciculations; for these reasons it should be avoided[19,22,62-64]. The effects of succinylcho-

line on QTc can be reversed by alfentanil; the same is not possible with fentanyl[65]. Moreover, alfentanil was better than esmolol in preventing the increase in QTi induced by succinylcholine during tracheal intubation[66]. Rocuronium, vecuronium, atracurium, and cisatracurium do not extend the QTc interval and can be used in c-LQTS, while pancuronium should be avoided because of its vagolytic properties and because it caused ventricular fibrillation in a case report[14,23,35,51,52].

Both intubation and extubation may trigger a TdP in patients with c-LQTS: hence, additional care should be taken during these maneuvers and analgesic or beta-blockers should be administered before them. As aforementioned, the use of lidocaine before intubation proved to be safe to prevent arrhythmias[25]. Finally, during ventilation with positive pressure, anesthesiologists should avoid high inspiratory pressure peaks and wide inspiratory/expiratory ratios, since the Valsalva maneuver also prolongs the QTc interval[65].

Postoperative management

Postoperative management of patients with c-LQTS should include the permanence in a postsurgical intensive care unit for at least 24 h, avoiding stimuli that could trigger TdP. An adequate postoperative analgesia and beta-blocking must be guaranteed. Postoperative nausea and vomiting (PONV) prevention can not be performed with setrones (ondansetron, granisetron and dolasetron) in patients with c-LQTS because these drugs block not only the 5HT₃ receptors but also the HERG channel, determining a prolongation of repolarization. A study by Charbit *et al*[67] demonstrated that 4 mg of ondansetron induced prolongation of the QTc, similar to the effect of 0.75 mg of droperidol, therefore questioning the greater safety of ondansetron when compared to droperidol in the treatment of PONV; Accordingly Staikou *et al*[32] advise against its use in patients with c-LQTS.

CONCLUSION

The prevalence of Long QT syndrome is close to 1/3000-1/5000[68,69]. The QT interval duration is physiologically variable : the QTc is calculated using the Bazett's formula [(QTc = QT/√RR), Table 2][70,71]. Genetic testing can help to recognize specific subtypes of c-LQTS. The most common phenotypes are LQT1, LQT2 and LQT3. People with LQT1, the most common variant of LQTS, are more likely to have a cardiac event during exercise than patients with LQT2 or LQT3. LQT1 is associated with a mutation in the *KvLQT1* gene (also known as KCNQ1), which codes for a protein that co-assembles with another protein (minK) to form the I$_k$-s[72]. In patients with LQT2 arrhythmic events are usually triggered by auditory stimuli or sudden startle[73]. LQT2 is caused by the loss of Ikr[72]. Patients with LQT3 are prone to syncope or cardiac arrest at rest or during sleep; as a matter of fact, their electrocardiographic abnormalities become less marked at increased heart rate[72,74]. Table

Table 3 Electrocardiograph pattern in long QT syndrome

ECG in LQTS	
LQT1	Prolonged QT, T wave normal or with increased amplitude with a wide base
LQT2	Prolonged QT, T wave with low amplitude and often bifid
LQT3	Late onset of the T wave, prolonged isoelectric segment

ECG: Electrocardiography; LQTS : Long QT syndrome.

3 shows the electrocardiographic patterns of the most common phenotypes of LQTS. Both in the a-LQTS and in the c-LQTS, the blockade of ionic channels, the lengthening of the QT interval and the intensification of QTD can provoke the induction of TdP[75]. A careful pre-, peri- and post-operative management is needed for patients with this syndrome because of the risk of TdP and malignant arrhythmias. We speculate that genetic subtyping of patients with LQTS could help tailor anesthetic therapy for these high-risk patients.

Actually, there are no definitive guidelines for pre-, peri- and post-operative anesthetic management of c-LQTS. After reviewing the literature, we furnish some key points for preoperative optimization, intraoperative anesthetic agents and postoperative care plan that may be the best for patients with c-LQTS who undergo surgery. In the preoperative period it is necessary to calculate QTc, perform a 12-lead ECG at rest, discontinue or decrease the dose of drugs which could increase QTc interval and trigger a TdP in these patients (Table 1), continue beta-blocking therapy until the operating day and maintain calm and quiet environment. Defibrillator must be available for immediate use during the perioperative period.

In the perioperative period, it would be better to do premedication with midazolam, sedoanalgesia with morphine or fentanyl, induction and maintenance of anesthesia with thiopental or propofol TIVA avoiding halogenated volatile anesthetics and ketamine. Before intubation and extubation, the use of a topic anesthetic, an analgesic or a beta-blocker could be recommended. Among muscle relaxant drugs, we should prefer vecuronium and atracurium. It is important to monitor not only heart rate, blood pressure, oximetry, capnometry but also ECG in at least two leads, as short episodes of TdP are hardly distinguished from monomorphic VT, when traced in one lead. In the postoperative the patient must be monitored and ECG should last until patient emerges from anesthesia and QTc turns into preoperative values. Any kind of stimulus should be avoided since they could trigger TdP and pain must be adequately controlled.

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Renal sympathetic denervation in resistant hypertension

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Abstract

Resistant hypertension remains a major clinical problem despite the available multidrug therapy. Over the next decades, its incidence will likely increase given that it is strongly associated with older age and obesity. Resistant hypertension patients have an increased cardiovascular risk, thus effective antihypertensive treatment will provide substantial health benefits. The crosstalk between sympathetic nervous system and kidneys plays a crucial role in hypertension. It influences several pathophysiological mechanisms such as the central sympathetic tone, the sodium balance and the systemic neurohumoral activation. In fact, studies using several animal models demonstrated that the renal denervation prevented and attenuated hypertension in multiple species. Large reductions in blood pressure were also observed in malignant hypertension patients submitted to sympathectomy surgeries. However, these approaches had an unacceptably high rates of periprocedural complications and disabling adverse events. Recently, an innovative non-pharmacological therapy that modulates sympathetic activation has been successfully developed. Renal sympathetic percutaneous denervation is an endovascular procedure that uses radiofrequency energy to destroy the autonomic renal nerves running inside the adventitia of renal arteries. This method represents a promising new approach to the strategy of inhibiting the sympathetic nervous system. The aim of this review is to examine the background knowledge that resulted in the development of this hypertension treatment and to critically appraise the available clinical evidence.

Core tip: Renal percutaneous denervation allows modulating the central sympathetic tone and is a promising new approach to our old strategy of inhibiting sympathetic system. In this review we describe the pathophysiological knowledge that encouraged the development of this procedure. We critically examine the available clinical evidence of the impact of renal denervation on resistant hypertension. After describing the procedure and how to select the adequate patients, we discuss the future potential therapeutic roles in other disease conditions beyond resistant hypertension.

INTRODUCTION

Essential hypertension remains an important clinical challenge for both the individual as well as the public perspective[1]. Despite the several available antihypertensive drugs and their unquestionable beneficial effects, hypertension control is still unsatisfactory[2,3]. This problem can be explained by several factors, such as inappropriate blood pressure measurement, physician inertia, poor ad-

herence to therapy, excessive salt intake or the existence of secondary causes of hypertension[4]. Nevertheless, even after addressing these factors, uncontrolled hypertension persists in a significant proportion of patients. Resistant hypertension is defined as blood pressure that remains above the goal pressure despite the use of at least 3 antihypertensive drugs of different classes (one being a diuretic)[5]. The prevalence of resistant hypertension varies between 8.9% in the National Health and Nutritional Examination Survey and 50% in the ALLHAT Study[6]. Recently, in a large Spanish cohort of treated hypertensive patients, 12.2% exhibited resistant hypertension[7]. Over the next few decades, this incidence will likely increase given that it is strongly associated with older age and obesity[8]. The treatment of resistant hypertensive patients has not been directly studied[9]. However, their increased cardiovascular risk suggests that effective antihypertensive treatment will provide substantial health benefits.

Accumulated evidence indicates that human sympathetic nervous system deregulation contributes to the development of arterial hypertension[10]. Sympathetic overactivity has been demonstrated in both essential and secondary forms of hypertension patients, such as obstructive sleep apnea and obesity-related hypertension[11]. Over the last few decades, the focus of hypertension research has been the renin-angiotensin system[12]. Despite the indisputable efficacy and safety of drugs that inhibit the renin-angiotensin axis, reducing sympathetic chronic activation could be important in a significant proportion of uncontrolled hypertensive patients[13]. The aim of this review is to critically examine the relevance of renal sympathetic denervation in hypertension treatment.

RENAL SYMPATHETIC DENERVATION: FROM THE BENCH TO THE BEDSIDE

Rationale for renal sympathetic denervation

On the one hand, renal sympathetic nerve fibers critically influence renal function[14]. Adrenergic fibers innervate the most relevant renal structures such as the renal vasculature, the tubular epithelial cells throughout the nephron and the juxtaglomerular apparatus[15]. Increased renal sympathetic nerve activity results in a decrease in renal blood flow mediated by vasoconstriction (α1a adrenoceptors)[16], increased renal tubular sodium and water reabsorption (α1b adrenoceptors)[17,18], and an increased renin secretion rate (β1 adrenoceptors)[19,20]. These effects are dependent on the degree of sympathetic activation and are considered to play an important role in the development and maintenance of hypertension[21].

On the other hand, the kidneys can also influence the sympathetic system activity. Renal structures are richly innervated with baroreceptors and chemoreceptors[22]. These afferent nerves respond to various stimuli such as renal ischemia, hypoxia and oxidative stress[23,24]. The afferent signaling from the kidneys is transmitted to the central nervous system and enhances sympathetic outflow[25], not only to the kidneys but also to other structures such as the heart and peripheral arterioles[26].

It has been feasible to study the sympathetic activation in hypertensive patients by using different methods that measure sympathetic activity, such as microneurography[27,28], noradrenaline spillover[29,30] and heart rate variability[31]. A higher sympathetic nervous activation was documented in essential hypertension, obesity-related hypertension, end-stage renal disease hypertension and in obstructive sleep apnea[29,32-34]. Interestingly, multiple studies have shown that 50% of hypertensive patients had an increased sympathetic activity in the kidneys and skeletal muscle vessels[11,28].

In conclusion, this crosstalk between the kidneys and sympathetic nerves, and its role in hypertension pathophysiology disclosed renal nerves as an interesting potential therapeutic target.

RENAL SYMPATHETIC DENERVATION

Preclinical studies

The importance of renal sympathetic nerves in hypertension was suggested when its increased activity was described in genetically spontaneously hypertensive rats compared with normotensive controls[35]. Several animal models had been used to study the influence of renal sympathetic fibers on hypertension[36]. In an experimental model of hypertension associated with obesity, high-fat diet-fed dogs that underwent renal denervation did not exhibited a significant increase in blood pressure compared with the sham group and had a 50% reduction of sodium retention[37]. Additionally, in a chronic renal failure rat model, where the animals underwent a 5/6 nephrectomy, bilateral dorsal rhizotomy prevented blood pressure increases. The procedure also resulted in lower neuroadrenergic activity in integrative central nervous structures[38]. It was also effective in a salt-sensitive hypertension model, where renal denervation prevented blood pressure increase and normalized the sodium balance[39]. Ye *et al*[40] elegantly demonstrated the importance of the renal sympathetic nervous system in hypertension. In this study, kidney damage was induced by intrarenal injection of phenol in rats, which caused a persistent elevation of the blood pressure and an increase in norepinephrine secretion in the hypothalamus, even in the absence of renal failure. In this model, performing renal denervation prevented the blood pressure increase.

The efficacy of renal denervation in several models and in multiple species established the key role of renal nerves in hypertension pathophysiology.

Clinical studies

Surgical sympathectomy: Before antihypertensive drugs became available, the therapeutic option for severe or malignant hypertension was almost limited to surgical sympathectomy. Several surgical approaches with different degrees of aggressiveness were undertaken, which determined the therapeutically effectiveness and the extent of the side effects[41]. Total sympathectomy (or splanchnicectomy) surgeries were very aggressive and

were later replaced by a more conservative approaches consisting of the removal of the sympathetic ganglia from the 8th to the 12th vertebra[42]. Several studies in patients with malignant hypertension documented that sympathectomy surgeries were associated with substantial reductions in blood pressure and an increased survival rate[43]. Favorable changes in target organ damage were also confirmed[44]. However, these approaches were associated with high periprocedural complication rates and common adverse events such as orthostatic hypotension and tachycardia, intestinal disturbances, anhidrosis, and sexual dysfunction[45]. After the development of pharmacological treatment options, these surgeries were reserved only for severe hypertension patients refractory to pharmacological treatment. Surgical and renal percutaneous sympathectomies are quite different procedures concerning the extent of denervation in particular. Nevertheless, the surgical sympathectomy studies were important because they first demonstrated that the disruption of human splanchnic autonomic fibers was associated with significant reductions in blood pressure.

Percutaneous sympathectomy: The first clinical study that assessed the effect of percutaneous sympathetic renal denervation in hypertension patients was published in 2009. Simplicity HTN-1[46] was a safety and proof-of-principle cohort study that enrolled 45 patients (mean age 58 ± 9 years) with resistant hypertension (defined as systolic blood pressure > 160 mmHg despite the use of at least 3 antihypertensive drugs, including a diuretic). These patients underwent a bilateral application of radiofrequency to the renal arteries. The office blood pressures after the procedure were reduced by 14/10 mmHg at 1 mo and 27/17 mmHg at 12 mo. No favorable change in blood pressure occurred in 13% of patients. This antihypertensive effect is sustained at least up to 24 mo after the procedure[47]. Additionally, a significant reduction (42%) in renal and total body norepinephrine spillover was observed in a small subgroup of the patients who underwent sympathetic activity measurements[46].

This cohort study was followed by a multicentre, prospective, randomized trial named Simplicity HTN-2 trial[48] published in 2010. One hundred and six patients with resistant hypertension were randomly allocated to renal denervation plus conventional antihypertensive drugs versus antihypertensive drugs only. The primary end-point was an office systolic blood pressure at the 6-mo follow-up visit. The office blood pressure in the catheter-based sympathectomy group indicated a reduction of 32/12 mmHg at the end of this period. The home and ambulatory blood pressure confirmed the observed office blood pressure changes falling by 20/12 and 11/7 mmHg, respectively, at 6 mo. No blood pressure changes occurred in the control group. At 12-mo follow-up, the magnitude of clinical response was sustained[49]. Although these trials have shown a significant blood pressure overall reduction, 13% (*n* = 6) and 10% (*n* = 5) of patients that underwent renal denervation had no decrease in systolic blood pressure in Simplicty HTN-1 and Simplicity

HTN-2, respectively. No predictor of nonresponse was found in univariate analysis of these patients' clinical and procedural characteristics. We can speculate that the procedure might have failed to obtain an adequate renal denervation. Another hypothetical explanation is the heterogeneous contribution of sympathetic activity to hypertension pathophysiology. The identification of the appropriate candidates to renal denervation is a challenge that should be answered by forthcoming studies. Recently, the published interventional and observational studies on renal denervation have been systematically reviewed[50]. All studies reported significant reductions in blood pressure of resistant hypertension patients.

Brandt *et al*[51] demonstrated that renal denervation in resistant hypertension patients was associated with a regression of left ventricle hypertrophy and an improvement of the diastolic function at 6-mo follow-up visit, compared with the control group. Interestingly, a significant decrease in the left ventricular mass was also observed in patients who did not have a significant decrease in blood pressure.

CRITICAL APPRAISAL OF TREATMENT STUDIES RESULTS

The results of the Simplicity trials are promising. Nevertheless, several limitations must be considered. Simplicity HTN-2 was an open-label trial, which means that the physician who performed the blood pressure measurement was not blinded to the type of treatment. Therefore, we cannot rule-out an ascertainment bias. In addition, there was no sham procedure in the control group, thus we cannot measure the extent of the placebo effect. The effect of treatment in the office blood pressure was concordant but more pronounced than the ambulatory blood pressure. Although this observation could represent a higher sympathetic activation with the office blood pressure measurement than during ambulatory monitoring, this discrepancy needs further elucidation. The small number of patients, the short period of follow-up and the absence of studies with hard clinical end-points precludes the establishment of the true antihypertensive effect and its prognostic importance. Some of these limitations will be addressed by the Simplicity HTN-3 trial[52]. This prospective, masked procedure, single-blind trial will randomize 530 patients and will include as a major secondary end-point, the change in the average 24-h systolic blood pressure by ambulatory blood pressure monitoring.

SAFETY DATA

In the larger cohort of patients that underwent percutaneous renal denervation (*n* = 153)[47], 97% experienced no complications. The four procedural complications included three pseudoaneurysm-hematomas in the arterial access site and one renal artery dissection that occurred before radiofrequency energy delivery in that artery. They were all managed without any long-term sequelae. The
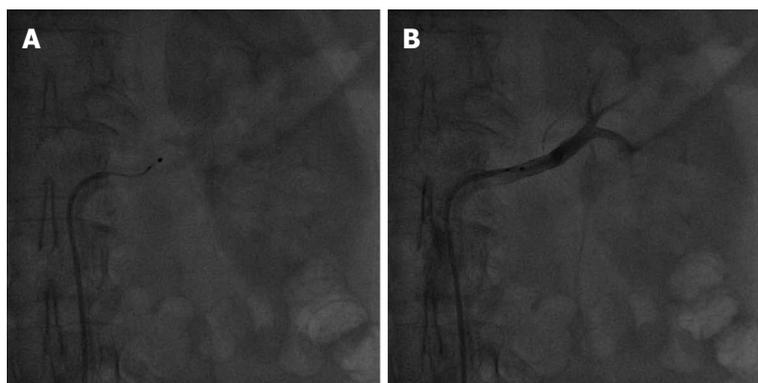
Figure 1 Left renal artery angiogram showing the catheter inside the artery.
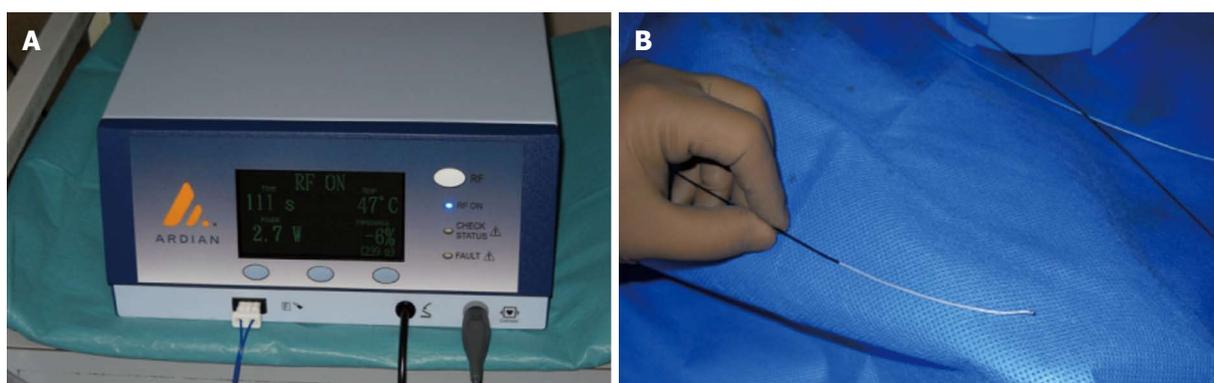
Figure 2 The Symplicity catheter and the radiofrequency console.

small number of procedures does not allow a strong conclusion to be made about the periprocedural safety of renal percutaneous denervation. Nevertheless, considering that the technique and the diameter of catheters are the same of coronary angiography, local femoral artery complications will likely have an incidence similar to coronary interventional procedures. In Symplicty HTN-2[48], there was one pseudoaneurysm-hematoma and no other major complication. Although the intensity of the radiofrequency energy is lower than the one used for pulmonary vein isolation in atrial fibrillation ablation, renal artery stenosis is a concern. In Symplicity HTN-2, 43 of 49 patients in the intervention group underwent renal artery imaging at the 6-mo follow-up, and no significant stenosis was diagnosed. Regarding renal function, the estimated glomerular filtration rate was stable up to 24 mo of follow-up[47,53].

The available evidence from clinical studies reveals that catheter-based renal denervation has an excellent short-term safety profile. Although unlikely, a risk of renal artery stenosis during long-term follow-up cannot be excluded.

RENAL SYMPATHETIC DENERVATION: FROM TRIALS TO REAL LIFE

Description of the procedure

The purpose of catheter-based renal sympathetic nerve ablation is to destroy the renal nerves that form a mesh-like organization inside the adventitia. This destruction is accomplished by inserting a catheter capable of delivering radiofrequency energy into the renal artery lumen. First, a guide catheter is engaged in the renal artery osteum by femoral percutaneous access. Then, a catheter specifically designed for renal denervation[54] (Symplicity, Ardian, Palo Alto, CA, United States) is introduced into the renal artery. The tip of the catheter has an electrode that is positioned, under fluoroscopic guidance (Figure 1), in contact with the artery wall to deliver low-power (less than 8 watts) radiofrequency energy for short time intervals (up to 2 min). During ablation, the catheter system continually monitors the temperature and impedance to adjust the energy that is being delivered (Figure 2). The procedure elicits abdominal visceral pain that can be managed with analgesic and sedative drugs. The denervation requires up to six separate ablations, longitudinally and circumferentially in each renal artery. The duration of this minimally invasive procedure is approximately 45 min.

Starting a program of percutaneous renal denervation: our experience

We deal with an increasing number of resistant hypertension patients during our daily clinical activity. When general measures and drug therapy optimization fail to control hypertension, we then consider another treatment option for our patients. The implementation of our percutaneous renal denervation program was governed by two main concerns: minimizing the risk of the procedure
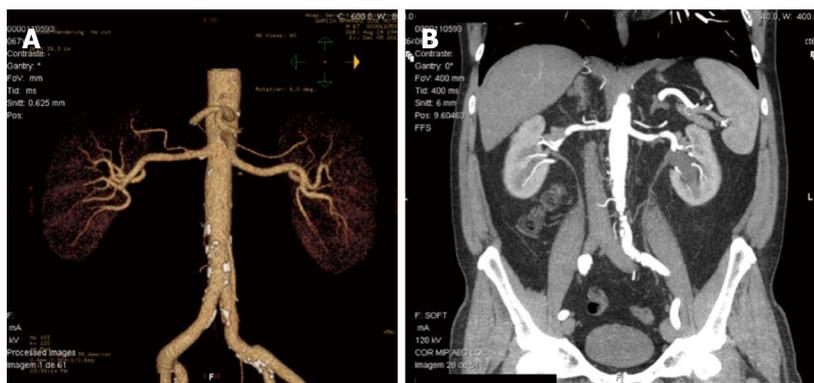
and selecting the adequate patients.

How to minimize the risk of the procedure?

Despite the simplicity of this minimally invasive technique, an experienced interventional cardiologist performs the procedure. In addition to the skills needed to deal with arterial access, the certified training in this specific technique is important to assure a safe and efficient procedure. We also collaborate with an anesthesiologist, which is extremely helpful in managing the visceral pain commonly induced during the radiofrequency ablation. Our patients remain in the hospital for 24 h after the procedure for clinical monitoring. After discharge, we schedule clinical appointments at one, three, six and twelve months after the intervention.

How to select the patients?

Based on the available clinical studies, adult hypertensive patients are eligible for renal denervation if they have a systolic blood pressure of 160 mmHg or more (> 150 mmHg in patients with type 2 diabetes) despite treatment with three or more antihypertensive drugs, including one diuretic. Patients are not candidates for renal denervation if they have a renal artery anatomy that precludes treatment such as a diameter less than 4 mm, length less than 20 mm or the presence of more than one main renal arteries (Figure 3). Another exclusion criterion is an estimated glomerular filtration rate of less than 45 mL/min per 1.73 m^2.

Before assessing whether patients meet the inclusion or exclusion criteria for the clinical studies, we evaluate the patients according to a clinical protocol[9,55]. First, we exclude those with pseudoresistance hypertension by repeating office blood pressure measurements, and we rule-out the common white-coat effect with an ambulatory blood pressure monitoring. Then, we screen for secondary causes of hypertension and, subsequently, confirm an adequate treatment regimen (up titrate to maximum tolerated doses) and patient adherence. If the blood pressure is still not controlled, we prescribe other agents as needed and tolerated such as beta-blockers, chlorthalidone or furosemide, spironolactone, and/or centrally acting sympathetic suppressants. At the end of this work-up, if the blood pressure is higher than the target goals, we assess the patient eligibility criteria for renal denervation.

FUTURE PERSPECTIVES

This new treatment explores a revolutionary principle that allows the modulation of the sympathetic central tone and can have a beneficial role in cardiovascular diseases beyond resistant hypertension[56,57]. Renal denervation has the potential of being beneficial in milder forms of hypertension[58] or secondary forms such as end-stage renal disease-related hypertension[59,60] where sympathetic overactivity has been demonstrated. Insulin sensitivity was improved in essential hypertensive[61] and obstructive sleep apnea-related hypertension patients[62], revealing a potential role in metabolic syndrome management[63]. The maladaptive role of the chronic activation of the sympathetic nervous system is a well-known hallmark of heart failure pathophysiology[64]. Clinical studies with renal sympathetic denervation in heart failure patients are currently being performed[65,66]. We are tempted to speculate on the potential therapeutic role of renal denervation in other diseases such as hepatorenal syndrome and polycystic ovary syndrome[67]. Selective renal sympathetic denervation is a novel and promising technique that opened a new window of opportunities that deserve to be explored.

CONCLUSION

Over the last few decades, growing knowledge about the role of the sympathetic chronic activation in the pathophysiology of hypertension has resulted in the development of the catheter-based renal sympathetic nerve ablation. This minimally invasive procedure pursues the efficacy of surgical sympathectomy and the safety of drug therapy. So far, clinical studies have demonstrated impressive and consistent blood-pressure reductions in resistant hypertensive patients. We acknowledge that there is still a lack of evidence from large placebo-controlled randomized clinical trials that are currently being conducted. Nevertheless, considering the available efficacy and safety data, renal percutaneous denervation should be considered for carefully selected patients with resistant hypertension.

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CASE REPORT

Papillary fibroelastoma of the aortic valve: An unusual cause of angina

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Abstract

Papillary fibroelastoma of the aortic valve is an uncommon benign tumor of the heart that can present with embolic events. We report a case of 54-year-old lady with exertional chest pain and prior history of ST segment elevation myocardial infarction who was subsequently found to have a fibroelastoma of the aortic valve. The absence of angiographically significant coronary artery disease and resolution of anginal symptoms post-surgery in our patient points to the possibility of fibroelastoma causing these anginal symptoms. Although uncommon, fibroelastoma are being recognized more frequently with the help of transesophageal echocardiography. Hence, in the absence of significant coronary artery disease, we emphasize the importance of consideration of papillary fibroelastoma of the aortic valve as a cause of angina. We also discuss the key aspects of the fibroelastoma including presentation, diagnostic modalities and treatment options.

INTRODUCTION

Papillary fibroelastoma (PFE) is the third most common benign primary tumor of the heart that usually involves the cardiac valves. Clinical presentation of PFE varies widely, ranging from asymptomatic to severe ischemic or embolic events. PFE are being recognized more frequently with the help of transesophageal echocardiography (TEE) and should be differentiated from thrombus, vegetation, myxoma and Lambl's excrescence. Symptomatic cardiac PFE should be surgically removed whereas asymptomatic lesions that are left-sided, mobile or larger than 1 cm should be considered for surgical excision. Recurrence after surgery has not been reported, and the long-term postoperative prognosis is excellent.

Here in this report, we present a case of 54-year-old female patient with prior history of ST segment elevation myocardial infarction (STEMI) who presented with exertional chest pain. She was subsequently found to have a PFE of the aortic valve.

CASE REPORT

A 54-year-old female with history of obesity, hyperlipidemia and hypertension and prior STEMI presented with exertional chest tightness of 3 mo duration. Two years prior to this presentation, she had suffered an anterior STEMI. Emergent cardiac catheterization at that time had revealed a total occlusion of distal left anterior descending (LAD) artery with no angiographic evidence of coronary atherosclerosis elsewhere. She was treated with primary balloon angioplasty and stenting was not done secondary to a small vessel caliber. She had a TTE done afterwards, which showed apical akinesis and an ejection fraction of 45%. Rest of the TTE was within normal limits including valvular anatomy and function. She was discharged on aspirin, simvastatin and metoprolol. She remained symptom free till 3 mo before presentation. She had started noticing chest tightness after joining exercise classes to lose weight. The tightness was similar in quality to her STEMI pain but much less intense in severity and resolved in 5 min after rest. Rest of her review of systems was negative.

Physical examination was unremarkable, except for obesity. Electrocardiogram did not reveal any pathological Q waves or evidence of ischemia or infarction. A treadmill stress test with myocardial perfusion imaging revealed a predominantly fixed defect at the lateral cardiac apex suggestive of the prior infarct; no ischemia was noted. A TTE done to assess left ventricular function revealed normal left ventricular function with mild hypokinesis in the prior infarct territory. However, TTE incidentally revealed a well-circumscribed 1 cm mass on the aortic side of the right coronary cusp of the aortic valve, concerning for a PFE. She had no risk factors, symptoms or signs suggestive of infective endocarditis or valvular thrombus. Further review of systems at this point failed to reveal any systemic embolic phenomenon. TEE was done to further characterize the mass. TEE revealed a well-circumscribed echo dense mass adherent to the edge of the right coronary cusp with a thin stalk and with minimal independent motion (Figure 1). The mass measured 0.9 cm in diameter. The aortic leaflets appeared normal in thickness and flexibility.

With her history of prior STEMI in the LAD territory without coronary atherosclerosis elsewhere, a concern was raised for a possible "embolic MI" in the past. As PFEs are known to cause embolic complications, especially when they are large, stalked and mobile, a recommendation was made for surgical resection of the mass. She underwent cardiac computed tomography (CT) angiography in preparation for the valve surgery to rule out obstructive coronary artery disease (instead of cardiac catheterization to prevent mass embolization with catheter manipulation). CT angiography failed to reveal any coronary atherosclerosis and reconfirmed the presence of PFE (Figure 2). Surgical removal of the mass without valve replacement was performed without complications.

The mass measured 1.0 cm × 0.8 cm × 0.5 cm and
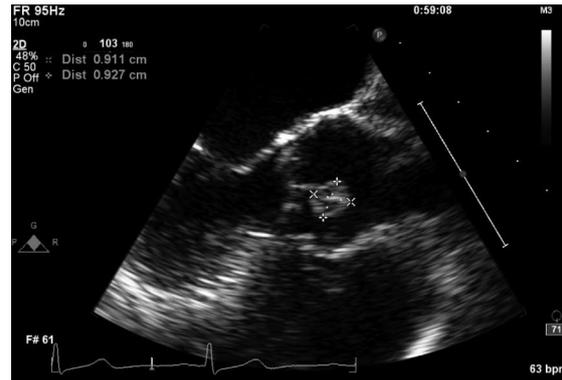
Figure 1 Mid esophageal aortic valve long axis view showing the papillary fibroelastoma attached to the aortic side of the right coronary cusp.

Figure 2 Cardiac computed tomography five chamber view showing the papillary fibroelastoma attached to the right coronary cusp.
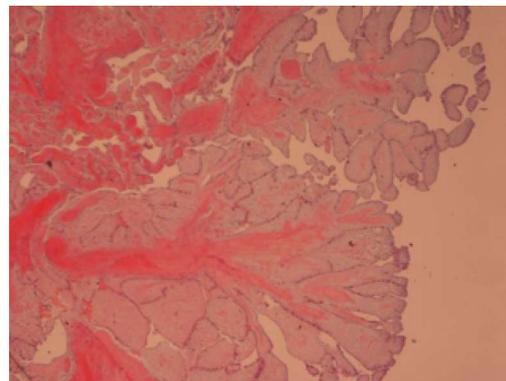
Figure 3 Histopathology. Hematoxylin and eosin stain showing papillary fibroelastoma with narrow, elongated and branching papillary fronds with central avascular collagen and elastic tissue (Low power view, 40 × magnification).

histopathological examination was consistent with benign papillary fibroelastoma (Figure 3). Patient remained free of symptoms after surgery.

DISCUSSION

The prevalence of primary cardiac tumor ranges from 0.002%-0.28%[1]. Papillary fibroelastoma originates most commonly from the valvular endocardium (85%). Aortic

valve is most often involved (29%), followed by mitral valve (25%), tricuspid valve (17%) and pulmonary valves (13%)[2]. Although highest prevalence is seen in the eighth decade of life, it has been described in patients aged 6 d to 92 years[2]. Embolization is the most common clinical presentation, which may include but are not limited to stroke, myocardial infarction, mesenteric ischemia, renal infarction, limb ischemia, pulmonary embolism, and pulmonary hypertension. Patients can also present with heart failure, ventricular fibrillation and sudden death. Fibroelastoma arising from the aortic valve have been implicated in occurrence of sudden death by causing transient or complete obstruction of the ostium of coronary arteries[1,2]. Atrioventricular valve fibroelastoma can obstruct ventricular filling resulting in recurrent pulmonary edema and right-heart failure, mimicking a clinical picture of mitral or tricuspid valve stenosis. Conduction system disturbances and complete atrioventricular block have also been reported[3]. Rarely, aortic valve PFE is also noted to cause angina secondary to transient obstruction of the coronary ostium[2].

The common differential diagnosis of PFE includes other cardiac tumors (myxoma), vegetation, thrombus and Lambl's excrescence. These can be differentiated by clinical presentation, location and character of the mass on TTE, TEE, cardiac CT or magnetic resonance imaging (MRI). The diagnosis is usually made by TTE or TEE, although, TEE is more sensitive. Echocardiography shows a small, pedunculated or sessile valvular or endocardial mobile mass, with a pedicle attached to the valve or endocardial surface and a frond-like appearance with or without multifocal involvement into the cardiac chambers. Echocardiographically, papillary fibroelastomas appear speckled with echolucencies near the edges. They have stippled edges. Mobility of the tumor is an independent predictor of nonfatal embolization and death. Computed tomography is inferior to transesophageal echocardiography in demonstrating the small moving structures. However, MRI is more valuable than computed tomography by imaging in multiple planes and better soft-tissue characterization of tumor. Gadolinium may enhance the differences between tumor and surrounding normal cardiac structures. 3-D echocardiography has also been used for better delineation of cardiac tumors[4]. Cardiac catheterization prior to resection of a PFE is subject to debate because of the friable nature of the lesion and because of the potential risk of embolization. On coronary angiography, the total occlusions or narrowing of distal coronary branches due to tumor emboli can be seen[5].

Grossly, PFE looks like a sea anemone because of its multiple papillary fronds. Papillary fibroelastoma are small avascular tumors with a single layer of endocardial cells covering the papillary surface[5]. Matrix consists of elastic fibers, proteoglycans, and spindle cells that resemble smooth muscle cells or fibroblasts. The layer of elastic fibers is a hallmark of this tumor. The connective tissue of fibroelastoma contains longitudinally oriented collagen with irregular elastic fibers[6].

Asymptomatic patients can be treated surgically if the tumor is mobile. Patients with asymptomatic non-mobile papillary fibroelastoma can be followed-up closely with periodic clinical evaluation and echocardiography, and they receive surgical intervention when the tumor becomes mobile or symptomatic[7]. Shave excision is successful in 83% of patients without the need for valvular repair or replacement[8]. TEE can also guide the surgical resection and assess the adequacy of valve repair both perioperatively and postoperatively. The surgical resection is curative, safe and well tolerated. Mechanical damage to the heart valve or adhesion of tumor to valve may necessitate valve repair or replacement[9]. Sastre-Garriga *et al*[10] recommend long-term anticoagulation for symptomatic patients who are not surgical candidates.

In our case, occurrence of STEMI in distal LAD with normal coronary artery elsewhere does raise a question of possible embolic myocardial infarction. The mass could have been small, or partially embolized and hence missed by the TTE at that time. PFE grows at a rate of 2-70 mm over a 1-year period[7]. The absence of angiographically significant coronary artery disease and resolution of anginal symptoms post-surgery in our patient points to the possibility of PFE causing these anginal symptoms. It is possible that the proximity of the stalked PFE on the right coronary cusp to the ostium of the right coronary artery (RCA) caused dynamic obstruction to the flow in the RCA, especially during exercise (demand ischemia); although, we could not explain the lack of ischemic findings during exercise myocardial perfusion imaging. Also, coronary vasospasm and multiple embolic events seem to be unlikely in our case as the symptoms occurred only during exertion, there was lack of electrocardiographic abnormalities and new perfusion defects during the exercise myocardial perfusion imaging. In summary, we presented a case of papillary fibroelastoma of the aortic valve causing anginal symptoms and possibly a myocardial infarction in the past.

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CASE REPORT

Concept of defibrillation vector in the management of high defibrillation threshold

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Abstract

We present a case where defibrillation threshold was dangerously elevated to the point that the patient had no safety margin, and his implantable cardioverter-defibrillator generator was discovered to have migrated. Generator migration reduces the distance between the can and the coil, effectively creating a smaller bipolar current and sparing the left ventricle from the current needed for defibrillation. This case underscores the importance of securing the generator in place, as this patient would have been spared multiple shocks and an invasive medical procedure had his generator been better secured.

Key words: Ventricular tachycardia; Defibrillation threshold; Implantable cardioverter-defibrillator; Pacemaker

Core tip: Defibrillation threshold can be altered by a myriad of factors including generator migration. We report a case to illustrate the concept of implantable cardioverter-defibrillator defibrillation vectors and its effect on defibrillation threshold.

INTRODUCTION

Defibrillation threshold (DFT) is routinely performed at the time of implantable cardioverter-defibrillator (ICD) implantation, but can be altered by a myriad of factors: lead placement, medications, sympathetic tone, electrolyte alterations, and shock vectors[1,2]. "High DFT" is defined as an absolute shock value of > 25 J or a safety margin of < 10 J below the maximum device output. Elevated DFTs put the patient at heightened risk for sudden cardiac death due to inadequate defibrillation. Reports from the literature demonstrate the incidence of high DFTs between 2% and 24%[3]; however, two large studies agree on a rate of 6.2%[4,5]. Recommended approaches to the patient with high DFTs vary in the medical literature. Following options are recommended: reverse the shock polarity, change the shock configuration (*e.g.*, tip-to-generator, ring-to-generator, tip-to-coil), modify the waveform, exchange the generator to a high-output device, discontinue medications that increase DFT if possible, add a superior vena cava coil, add a subcutaneous array, or move the generator to the left pectoral region if it is located on the right[6]. Some ICD brands allow

reprogramming of the shock configuration even within a single treatment window, which theoretically increases the chance of successful defibrillation. Data suggests that a configuration where the right ventricular (RV) lead is the anode results in the highest success of defibrillation, but a small population of patients benefits from the reverse configuration[3].

CASE REPORT

Eighty years old Caucasian male presented to device clinic for management of sustained monomorphic ventricular tachycardia (VT) leading to multiple ICD shocks. Medical history included coronary artery disease status post 3 vessel coronary artery bypass grafting in the remote past and severe ischemic cardiomyopathy with ejection fraction of 10%. Attempts were made to ablate his VT, but he continued to have episodes of appropriate ICD therapies. He had a bi-ventricular ICD (Bi-V ICD) with a lower rate of 80 beats per minute. Patient has had multiple hospitalizations in the past for appropriate ICD therapies.

Medical management of VT of the patient was complicated. He was previously managed on amiodarone, but this was stopped when his DFT became prohibitively high and obliterated the 10-joule safety margin. He was then managed with maximum dose of long acting metoprolol and did well until he started having appropriate shocks for recurrent VT. He was finally started on mexiletine, which he tolerated. One week after initiation of mexiletine he underwent repeat DFT testing. Multiple configurations and device outputs were tried unsuccessfully: 25 and 35 J from can and coil to tip; 25 and 35 J from tip to can and coil; 25 J from can to tip and tip to can. The patient was finally successfully defibrillated with 35 J from can to tip, again demonstrating a loss of safety margin.

His most recent cardiovascular work-up, including left heart catheterization, echocardiogram, and electrocardiogram showed stable, severe coronary artery disease and systolic dysfunction. A recent chest X-ray (Figure 1) shows his device in the left chest with a right atrial lead, a RV ICD lead, and a left ventricular pacing lead in the coronary sinus. He reported New York Heart Association class Ⅱ symptoms, but was in good spirits. After careful review of the case, decision was made to place a right sided endocardial lead to the RV true apex which would then be tunneled to the left side. Attempts to place a pace-sensing lead from the left side at the time of ICD generator change had failed due to too many leads on the left side. If repositioning of the RV lead fails, placement of a subcutaneous array was planned. In the operating room, the device pocket was opened and it was noted that the generator had migrated substantially inferiorly across the chest wall. At this time, the generator was moved up to the subclavicular position and DFTs were retested. He was successfully defibrillated with 25 J, twice. A post-operative chest X-ray shows higher positioning of
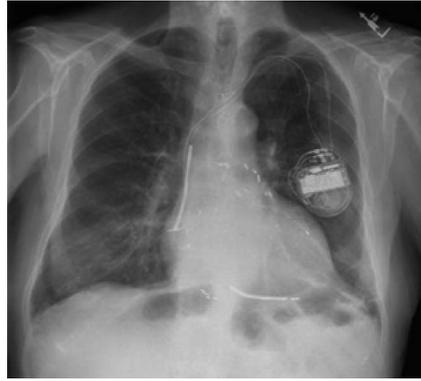
Figure 1 Chest X-ray demonstrating bi-ventricular implantable cardioverter defibrillator.
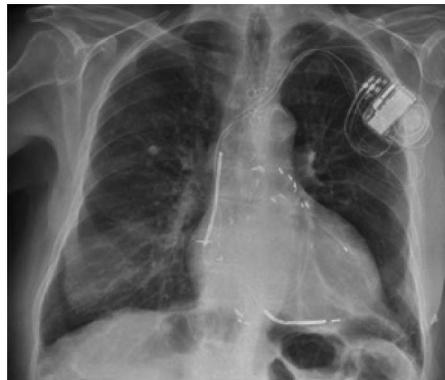
Figure 2 Note the changed position of the implantable cardioverter defibrillator Generator.

the ICD can in the subclavian position (Figure 2). He was discharged home the next day safely.

DISCUSSION

This case elegantly illustrates the concept of ICD defibrillation vectors. When the patient arrived, his DFTs were dangerously elevated to the point that he had no safety margin, and his ICD generator was discovered to have migrated. At the time of his procedure, the generator was nearly lateral to the left heart border. This malpositioning altered the electric field in that it allowed current to move anteriorly from the coil to the can, reducing the involvement of the posteriorly positioned left ventricle. Additionally, it reduced the distance between the can and the coil, effectively creating a smaller bipolar current and sparing the left ventricle from the current needed for defibrillation. This case underscores the importance of securing the generator in place, as this patient would have been spared multiple shocks and an invasive medical procedure had his generator been better secured. Even the newer, entirely subcutaneous ICD systems are reliant on proper positioning. In a recent article describing the initial Dutch experience with the device, three patients received inappropriate shocks due to lead migration. This complication was solved by adding an additional suture

sleeve[7].

It is suggested that the RV lead be positioned to the true ventricular apex[1]. More proximal positioning of the lead results in higher DFTs, but if the RV lead is positioned closer to the interventricular septum or RV outflow tract, DFTs are improved[3]. A recent study reported similar rates of high DFTs in patients with RV apical leads (3/108) *vs* RV septal leads (3/107)[8]. The Septal Positioning of Ventricular ICD electrodes trial is currently underway and should help to answer the question of optimal RV lead position. It is important to consider that as ICD systems adopt the dual coil single lead configuration it will become more difficult to manipulate positioning to optimize DFTs.

With repositioning of his ICD generator, we were able to restore his DFTs to a safe level by correcting the malpositioning and optimizing the shock vector. To our knowledge, this is the only such case reported in the medical literature.

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CASE REPORT

Transvenous defibrillator implantation in a patient with persistent left superior vena cava

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Abstract

Persistent left superior vena cava (LSVC) can be incidentally detected during pacemaker implantation through left pectoral side. There is technical difficulty of optimal site pacing and lead stability for right ventricle lead in such situation. We hereby report a case of successful single-chamber implantable cardioverter defibrillator (ICD) implantation in a 50 years-old male with LSVC. The practical issues related with right ventricle lead implantation and pacing/defibrillation parameters for ICD device are discussed.

Key words: Cardioverter defibrillator; Left superior vena cava; Myocardial infarction; Ventricular tachycardia

Core tip: Persistent left superior vena cava (LSVC) can be incidentally detected during pacemaker implantation through left pectoral side. we hereby report a case of persistent LSVC, who had successful single chamber implantable cardioverter defibrillator (ICD) implantation with dual coil active fixation lead. We achieved good functional parameters of the ICD and had uneventful 6 mo of follow-up.

INTRODUCTION

The presence of persistent left superior vena cava (LSVC) can be incidentally detected during pacemaker implantation from left pectoral side. There is technical difficulty for optimal site pacing and lead stability of right ventricle (RV) lead in such a situation. There is also a concern about optimal vector for defibrillation potential following implantable cardioverter defibrillator (ICD) implantation. We hereby report a case of single chamber ICD implantation in a 50 years-old male, who had persistent LSVC. The issues related to RV lead implantation and defibrillation threshold is discussed.

CASE REPORT

A 50-years-old hypertensive, chronic smoker male had anterior wall myocardial infarction in November 2007, for which he underwent coronary stenting of proximal left anterior descending and proximal left circumflex arteries. Later in January 2012, he had inferior wall myocardial infarction, for which he underwent coronary stenting of mid right coronary artery. One month later, he presented with hemodynamically unstable monomorphic ventricular tachycardia of rate 200 beats/min, which was reverted by electrical cardioversion. His left ventricle (LV) ejection fraction was 0.30. A repeat coronary angiography revealed patent stents in all three coronary arteries. He was taken up for ICD implantation for secondary prevention of
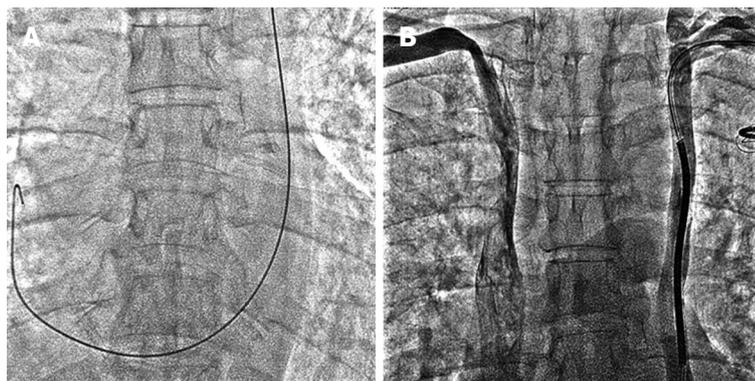
Figure 1 X-ray in Antero-posterior view shows. A: Guide wire course from left subclavian vein to right atrium across the left heart border, suggesting left superior vena cava draining into right atrium; B: Simultaneous venogram shows individual drainage of both right and left superior vena cava (SVC) to right atrium, without any bridging communicating vein between the two. Left SVC shows lead *in-situ*.
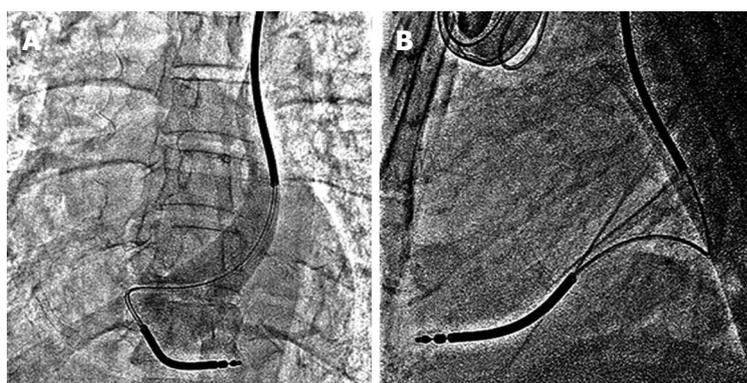
Figure 2 X-ray in Antero-posterior (A) and lateral (B) view shows dual coil right ventricle lead implanted at right ventricle apex. Venogram in figure (A) confirms persistence of left superior vena cava.

sudden cardiac death. After conventional left subclavian vein puncture, the guide wire took the unusual course by descending across the left heart border to reach the right atrium, suggesting a persistent LSVC (Figure 1A). A contrast injection from left ante-cubital vein confirmed the presence of LSVC. There was no communicating vein between left and right superior vena cava (Figure 1B). An active fixation, dual coil RV lead (Medtronic Sprint Quattro Secure, Model No.6947, length 65 cm, 8.2 F) was passed through the LSVC-coronary sinus for implantation. A U shaped stylet was used to direct the lead from right atrium to RV. A wide loop of the lead was made in right atrium and the tip of the lead was directed towards tricuspid valve with the help of curved stylet. After few manipulations, the lead could be positioned at RV apex (Figure 2). The lead parameters were satisfactory-pacing threshold was 1.2 V at 0.5 milli-seconds pulse width, with a pacing impedance of 1098 Ω, R wave amplitude was 7.8 milli-Volts with slew rate of > 2.0 Volts/s. The RV and SVC defibrillation impedance was 41 and 46 ohms, respectively. The device (Medtronic Maximo II VR, Model D284VRC) was connected with the lead and implanted in left pectoral region. The total fluoroscopy time for the procedure was 12 min. An initial 15 J shock could revert the ventricular fibrillation to normal sinus rhythm during defibrillation testing (DFT), with SVC coil in on-mode. During 6 mo of follow-up, he did not have any shock or anti-tachycardia pacing for ventricular tachycardia.

DISCUSSION

The persistent LSVC is a remnant of embryologic venous system[1]. Its prevalence is 0.3%-0.5% in normal population[2,3]. There is considerable anatomic variation in venous drainage with persistent LSVC. A right side superior vena cava (SVC) may be absent, or both right and left SVC if present may or may not be connected with a bridging innominate vein[3-5]. It is technically challenging to direct the pacing lead at appropriate RV site in the presence of LSVC[3,6], as forward movement of the lead in right atrium is commonly towards SVC or IVC side and remain away from the tricuspid valve. As reported by others, we also made a manual U turn in the stylet to direct the active fixation lead from right atrium to right ventricle. After few manipulations, we could successfully screw the active fixation lead at RV apex and achieved satisfactory pacing parameters. The fluoroscopy time of 12 min was also comparable with others[4]. We have used active fixation RV lead to have adequate lead stability, as being used by other operators[3-6]. There is also a concern about optimum vector for defibrillation potential in these patients, as SVC coil is in coronary sinus and on the left side, instead of its usual right SVC position[4,7]. Few operators have used additional subcutaneous patch[8,9] or defibrillation coil[10] for the optimal defibrillation potential. Even, Tauras *et al*[11] had performed innominate vein angioplasty to put defibrillation lead via right SVC in a patient with LSVC. As there was absent bridging innominate vein in the index case (Figure 1B), we could not approach to right SVC from left side. Various authors have used a single coil lead in such a situation to avoid high defibrillation threshold[4,7], however we achieved effective 15 J defibrillation threshold (DFT) even with dual coil lead. A newer generation device like the one we implanted (Medtronic Maximo II,

Model No. D284VRC), have an option to turn-off the SVC coil, thus make it functional as a single coil lead. This option can be tried in the index case, if tachycardia therapy is not effective at follow-up.

In conclusion, we hereby report a case of persistent LSVC, who had successful single chamber ICD implantation with dual coil active fixation lead. We achieved good functional parameters of the ICD and had uneventful 6 mo of follow-up.

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CASE REPORT

A case of type I variant Kounis syndrome with Samter-Beer triad

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Core tip: When there is a young individual with no predisposing factors of atherosclerosis and apparent coronary lesion, with or without electrocardiography and biochemical markers of infarction, the possibility of Kounis syndrome should be kept in mind. In such a situation, intracoronary vasodilators, nitrates, nicorandil or diltiazem should be used before proceeding with a coronary intervention. An urgent eosinophil count should be done before proceeding with a coronary intervention to rule out coronary spasm.

Abstract

Kounis syndrome is defined as the coexistence of acute coronary syndromes with situations associated with allergy or hypersensitivity, as well as anaphylactic or anaphylactoid reactions, to a variety of medical conditions, environmental and medication exposures. We report a case of Kounis-Zavras syndrome type I variant in the setting of aspirin-induced asthma, or the Samter-Beer triad of asthma, nasal polyps and aspirin allergy. When there is a young individual with no predisposing factors of atherosclerosis and apparent coronary lesion, with or without electrocardiography and biochemical markers of infarction, the possibility of Kounis syndrome should be kept in mind.

Key words: Kounis syndrome; Samter-Beer triad; Nasal polyps; Coronary spasm; Aspirin allergy

INTRODUCTION

Kounis syndrome is defined as the coexistence of acute coronary syndromes with situations associated with allergy or hypersensitivity, as well as anaphylactic or anaphylactoid reactions, to a variety of medical conditions, environmental and medication exposures. Patients undergoing stent implantation receive several substances which have antigenic properties. Many etiologies have been reported[1,2], including drugs (antibiotics, analgesics, antineoplastics, contrast media, corticosteroids, intravenous anesthetics, non-steroidal anti-inflammatory drugs, skin disinfectants, thrombolytics, anticoagulants), various conditions (angioedema, bronchial asthma, rhinitis, nasal polyp, urticaria, food allergy, exercise-induced allergy, mastocytosis, serum sickness), environmental exposure (stings of ants, bees, wasps and jellyfish, grass cuttings, millet allergy, poisoning, latex contact, eating shellfish, viper venom poisoning) and stent implantation (nickel, chromium, manganese, titanium, molybdenum, polymers), which can induce allergy,

either separately or synergistically[3].

CASE REPORT

A 19 year old male presented with history of dyspnoea. Over the past 2 d, he had chest pain and the first episode of syncope and was admitted to hospital. On physical examination, he was sweaty but hemodynamically stable. He had no family history of coronary artery disease. Electrocardiography (ECG) showed ventricular tachycardia (VT). On arrival, his Troponin-T was elevated (0.26 ng/mL, reference range: 0-0.03 ng/mL). A diagnosis of non-ST segment myocardial infarction with complete heart block was made. Cardiac catheterization demonstrated 99% lesion in mid right coronary artery (RCA). The ejection fraction was 60%. The percutaneous coronary intervention was performed *via* the right femoral artery access route. A sirolimus-eluting stent (3.5 mm × 23 mm) was deployed with an excellent angiographic result. The patient was discharged on the fifth day.

Two months later, the patient was again hospitalized with a second episode of syncope arrest and chest pain. In the brain magnetic resonance image, no significant focal intracranial abnormality was detected. An absolute eosinophil count was 645 cumm/μL (reference range: 40-440 cumm/μL). Check angiogram revealed a well flowing RCA stent with 40% *de novo* lesion. The remaining coronary arteries were normal. The patient was recommended for medical management and was discharged on the seventh day.

Five months later, the patient had a 3rd episode of syncope, and hence was rehospitalized for clinical evaluation with twenty-four hour electrocardiographic (Holter) monitoring, which was normal. At this time, ECG and echocardiography were normal. Patient developed VT during hospitalization which was reverted with direct current shock and beta blockers were started. During the hospital stay, on the 3rd day, the patient had chest pain again. Troponin-I was positive. A 12-lead electrocardiogram showed ST elevation in anterior leads, suggestive of hyper acute stage of anterior wall myocardial infarction. The patient was transferred to the intensive cardiac care unit and there the ST elevation disappeared. Echocardiography showed mid apical septum and apex hypokinesia. Glycoprotein IIb/IIIa inhibitors were given.

DISCUSSION

When the fourth check angiography was done, it revealed a mid to distal left anterior descending (LAD) 90% discrete lesion with sluggish flow and a well flowing RCA stent. The patient was taken for percutaneous transluminal coronary angioplasty (PTCA) to LAD after 3 d. During coronary angiography, prior to PTCA, another 80% lesion proximal to previous 90% lesion was revealed where previously no plaque was present. After repeated administered nicorandil and nitrates, both lesions became insignificant. Hence, we suspect it might due to coronary
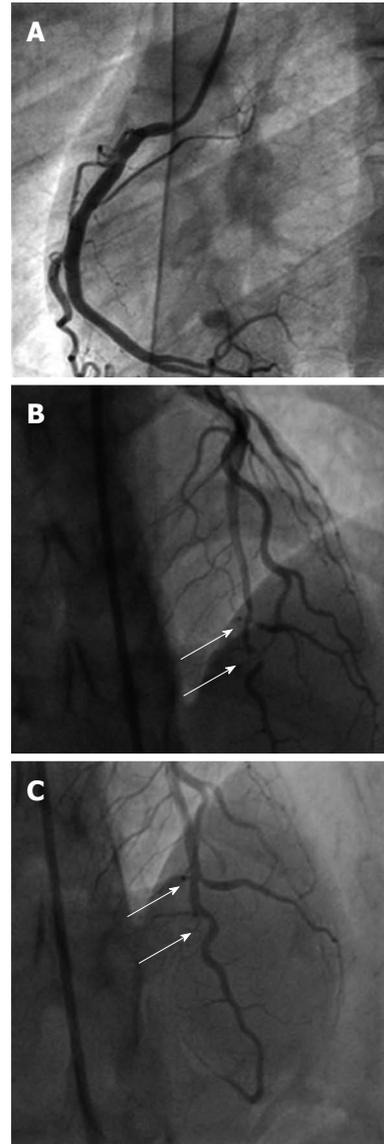
Figure 1 Angiographic images. A: Well flowing patent right coronary artery; B: Angiography revealed mid left anterior descending (LAD) two consecutive lesions (arrows) at D2 bifurcation; C: After *iv* nicorandil and nitroglycerin, mid LAD lesions (arrows) at D2 bifurcation.

spasm. The patient was discharged under treatment with oral nicorandil, nitrates, diltiazem and antiplatelets. Beta blockers were omitted (Figure 1).

After discharge, patient had difficulty in breathing due to some nasal obstruction, so an Ear Nose and Throat (ENT) surgeon consultation was done. Subsequently, a nasal ethmoidal polyp was detected by the ENT surgeon on the basis of a computed tomography scan. The chest physician's opinion was taken and pulmonary function tests were done, which were suggestive of mild obstructive lung disease. Bilateral functional endoscopic sinus surgery was also done (3.5 cm × 2.5 cm, reference range: 0.2 cm × 0.2 cm up to 1.4 cm × 0.8 cm). The histopathological examination of polyps was suggestive of inflammatory nasal polyps. An immunoglobulin E level was 396 kU/L (reference range: 20-100 kU/L). Normal range for

all allergens is less than 0.35 U/L. Within food, cucumber 1.70 U/L, wheat 2.00 U/L, groundnut 1.80 U/L and yeast 1.60 U/L induce mid high allergy. Within inhalants, house dust 1.90 U/L, dog dander 1.10 U/L and paper dust 1.10 U/L induce mid high allergy, while house dust mite 3.50 U/L induces high allergy. Within contact, perfume 1.40 U/L induces mid high allergy. Within drugs, ciprofloxacin 1.70 U/L, cloxacillin 1.30 U/L and diclofenac 1.10 U/L induce mid high allergy, while oxacillin 0.90 U/L, tetracycline 0.60 U/L and norfloxacin 0.80 U/L induce mild allergy. During allergic screening tests (by immune-enzyme immune assay), it was found that the patient was allergic to contact, drugs, food and inhalants. The patient was advised to avoid these allergens and put on topical steroids, cetrizine and montelukast. Aspirin was omitted. To date, the patient has been doing well for the last 9 mo.

Today, allergic angina and allergic myocardial infarction are referred as "Kounis syndrome". Aspirin-induced asthma was first described by Widal *et al* in 1922 and later by Samter *et al*[4] in 1967. The term Samter's triad (asthma, aspirin sensitivity and nasal polyps) became popular. The Samter-Beer triad generally starts as chronic rhinitis with development of nasal polyposis. Salicylate intolerance and asthma develop over 1 to 5 years[5].

When there is a young individual with no predisposing factors of atherosclerosis and apparent coronary lesion, with or without ECG and biochemical markers of infarction, the possibility of Kounis syndrome should be kept in mind. In such situations, intracoronary vasodilators, nitrates, nicorandil or diltiazem should be used before proceeding with a coronary intervention. An urgent eosinophil count should be done before proceeding with coronary interventions to rule out coronary spasm.

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LETTERS TO THE EDITOR

Evaluation of myocardial infarction patients after coronary revasculation by dual-phase multi-detector computed tomography: Now and in future

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Abstract

Multidetector-row computed tomography (MDCT) has become one of the major tools in diagnosing and evaluating patients with coronary artery disease in recent years. In selected patients, MDCT has been shown to provide more reliable accuracy in detection of stent patency than invasive coronary angiography. Chiou *et al* reported a delicate infarcted myocardium at-risk score. According to their results, the MDCT-based myocardium at-risk score had a good correlation with the thallium 201 ST-segment elevation myocardial infarction-based summed difference score ($r = 0.841$, $P < 0.001$). They claimed that dual-phase MDCT is useful in detecting different patterns of obstructive lesions and the extent of myocardium at risk. In this commentary, we discuss the current status of the clinical application of MDCT in patients with myocardial infarction in relation to evaluating the myocardial perfusion defect, detecting reversible myocardial ischemia, assessing myocardial viability, estimating target lesion restenosis, and calculating of fractional flow reserve from MDCT.

Core tip: Chiou *et al* reported that dual-phase multidetector-row computed tomography (MDCT) is useful in detecting different patterns of obstructive lesions and the extent of myocardium at risk. In this commentary, we discuss the current status of the clinical application of MDCT in patients with myocardial infarction in relation to evaluating the myocardial perfusion defect, detecting reversible myocardial ischemia, assessing myocardial viability, estimating target lesion restenosis, and calculating of fractional flow reserve from MDCT.

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TO THE EDITOR

We have read the recent published article by Chiou *et al*[1] which reported that the dual-phase multidetector-row computed tomography (MDCT) is useful in detecting dif-

ferent patterns of obstructive lesions and the extent of myocardium at risk in patients with ST-segment elevation myocardial infarction (STEMI). We think that this article is interesting and would strongly recommend it to readers.

With its rapid advancement in recent years, MDCT has become one of the major tools in diagnosing and evaluating patients with coronary artery disease. The high negative predictive rate has made MDCT a powerful tool in excluding occlusive coronary lesions in symptomatic patients with low probability of disease[2,3]. In selected patients, MDCT has also been shown to provide more reliable accuracy in detection of stent patency than invasive coronary angiography[4]. Chiou *et al*[1] reported a delicate infarcted myocardium at-risk score. According to their results from 135 ST-segment elevation myocardial infarction (STEMI) patients with recurrent symptoms 9 mo after revascularization and analysis of 1966 segments, the myocardium at-risk score has higher sensitivity, specificity, and positive- and negative-predictive values (98.7%, 76.1%, 87.5%, and 97.2% respectively) than analysis from stress-redistribution thallium-201 SPECT plus invasive coronary angiography. In 124 (91.9%) patients in whom all segments were assessable, the MDCT-based myocardium at-risk score had a good correlation with the SPECT-based summed difference score (SDS) ($r = 0.841$, $P < 0.001$). With a cutoff value of 2.68, the area under the receiver operating characteristic curve was 0.874 (95%CI: 0.805-0.942) for the MDCT-based infarcted myocardium at-risk score[1]. Although additional studies with a larger population are required, MDCT-based risk stratification has been shown to be a promising noninvasive tool with good correlation to the current standard for evaluating obstructive lesions and the severity of the myocardium at risk in patients with STEMI who develop recurrent symptoms.

Correct identification of flow-limiting coronary artery stenosis is the cornerstone of interventional treatment in patients with ischemic angina[5]. However, the correlation of morphological severity with myocardial blood flow reduction is low[6].

Functional studies with nuclear myocardial imaging, including SPECT and positron emission tomography, are the current major modalities[7], but attenuation artifacts, high radiation dose and prolonged examination time limit the clinical benefits. Several computed tomography (CT) techniques have been developed to evaluate the myocardial blood supply[5]. During the early phase of contrast medium passage through the myocardium, perfusion defects can be delineated by analysis of reconstruction images based on systolic and diastolic cycles[8,9] and optimal timing of first-pass scans[10]. Dual source CT reduces beam-hardening artifacts significantly by use of monochromatic image handling technology, and further improves the accuracy of myocardial perfusion quantification[11]. Dynamic time phases may be useful in prediction of myocardial perfusion defects[12], which may be related to left ventricular functional recovery in patients with

acute myocardial infarction[13]. Injection of adenosine before scanning has also been an well-accepted pharmacological stress method for detecting reversible myocardial ischemia[14].

The other important action during the planning of coronary revascularization is to estimate myocardial viability and predict the possible recovery of ventricular function[15]. Differential contrast enhancement of infarcted myocardial tissue was initially recognized on CT images and was also reported for gadolinium-enhanced cardiac magnetic resonance imaging (MRI). In the normal condition, the iodinated and gadolinium contrast medium distribute through the cardiac extracellular space but are excluded from healthy myocardial cells. After ischemic injury, differences in distribution volume occurring after loss of myocardial membrane integrity enable delayed gadolinium-enhanced MRI to define the periinfarction area of edema and the central core of necrosis[16,17]. In a study of preoperative evaluation before coronary artery bypass surgery, the extent of delayed transmural hyperenhancement in MRI images has been shown to have strong correlation with the recovery of regional ventricular function after 6 mo[18]. In the acute myocardial infarction, delayed-enhancement MRI also provides prediction of recovery of function after successful primary angioplasty by analysis of microvascular obstruction[19]. Assessment of myocardial viability using MDCT has been validated by a number of studies. The detection of periinfarction edema[20] and nonreperfused area[21] in the setting of acute myocardial infarction was shown to have good correlation with MRI imaging and myocardial histological staining. In a recent study, myocardial contrast delayed enhancement of MDCT was shown to be well correlated with nonviable myocardium and a significant independent predictor of clinical outcome[22]. The viability evaluation of myocardium by CT is still under verification. However, CT warrants a future role in this area as it is less time-consuming and patient-limiting than MRI[5].

Recently, a novel method of calculation of fractional flow reserve (FFR) from MDCT has been reported[23]. FFR is the ratio of the mean coronary pressure distal to a stenotic coronary lesion to the mean aortic pressure, as measured during invasive coronary angiography[24]. FFR has been shown to have greater accuracy than exercise electrocardiography, myocardial perfusion scintigraphy, and stress echocardiography in determination of hemodynamically significant stenoses[25]. Advancement of technology has enables calculation of FFR from MDCT without additional imaging, change of MDCT protocols, or pharmacological administration[23,26]. In other words, FFR derived from coronary computed tomography is a noninvasive method for diagnosis of lesion-specific ischemia. From the initial data published to date[19,27], use of noninvasive FFR from MDCT for patients with suspected coronary artery disease improves diagnostic accuracy in comparison with MDCT alone. In a recently published multicenter international study, FFR from MDCT showed a diagnostic accuracy, sensitivity, specificity value

of 73%, 90%, and 54%, respectively, on a per-patient basis compared to traditionally invasive FFR[23]. In another study, a good correlation was shown between per-vessel FFR from MDCT and invasive FFR values (Spearman's rank correlation = 0.717, $P < 0.0001$; Pearson's correlation coefficient = 0.678, $P < 0.0001$)[28]. Calculations of FFRs from MDCT were performed by computational fluid dynamic modeling after semiautomated segmentation of coronary arteries and left ventricular mass. This process currently requires approximately 6 h per case[23]. With further improvement of the computation technology, we believe that the processing time will be much shorter, making it feasible for clinical use in the near future.

Noninvasive identification of the patency of culprit vessels remains a challenging issue in patients of STEMI. We and others have reported that MDCT could accurately and safely identify occluded culprit lesions in patients early after acute myocardial infarction (AMI), which may provide important information to aid in risk stratification[29,30]. In patients with acute coronary syndrome sowing ambiguous ST segment changes on electrocardiogram, MDCT adds diagnostic accuracy and helps to exclude pulmonary embolism, aortic dissection, and other thoracic disease[31]. For patients with complex coronary artery disease who require bypass surgery, the 3D-image reconstruction from MDCT also provides additional details to operators[32]. Furthermore, it has been reported that the myocardial viability assessment derived from MDCT after primary revascularization may help to predict the clinical outcome in patients with AMI[22].

In summary, the evaluation of STEMI patients with recurrence of chest symptoms remains a challenge. Utilization of state-of-the-art MDCT for delayed myocardial enhancement and calculation of infarcted myocardium at-risk score helps therapeutic planning and risk stratification. In the near future, we believe that the FFR obtained from MDCT may also contribute to coronary ischemia assessment.

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Contents

Contents

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Editorial on hemoglobin A1c, blood pressure, and low-density lipoprotein cholesterol goals in diabetics

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Abstract

The American Diabetes Association (ADA) 2013 guidelines state that a reasonable hemoglobin A1c goal for many nonpregnant adults with diabetes is less than 7.0% a hemoglobin A1c level of less than 6.5% may be considered in adults with short duration of diabetes, long life expectancy, and no significant cardiovascular disease if this can be achieved without significant hypoglycemia or other adverse effects of treatment. A hemoglobin A1c level less than 8.0% may be appropriate for patients with a history of severe hypoglycemia, limited life expectancy, advanced macrovascular and microvascular complications, extensive comorbidities, and long-standing diabetes in whom the hemoglobin A1c goal is difficult to attain despite multiple glucose-lowering drugs including insulin. The ADA 2013 guidelines recommend that the systolic blood pressure in most diabetics with hypertension should be reduced to less than 140 mmHg. These guidelines also recommend use of an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker in the treatment of hypertension in diabetics unless they are pregnant. Diabetics at high risk for cardiovascular events should have their serum low-density lipoprotein (LDL) cholesterol lowered to less than 70 mg/dL with statins. Lower-risk diabetics should have their serum LDL cholesterol reduced to less than 100 mg/dL. Combination therapy of a statin with either a fibrate or niacin has not been shown to provide additional cardiovascular benefit above statin therapy alone and is not recommended. Hypertriglyceridemia should be treated with dietary and lifestyle changes. Severe hypertriglyceridemia should be treated with drug therapy to reduce the risk of acute pancreatitis.

Core tip: 2013 guidelines state that a reasonable hemoglobin A1c goal for diabetics is less than 7.0% a hemoglobin A1c level less than 8.0% may be appropriate for patients with a history of severe hypoglycemia, limited life expectancy, advanced macrovascular and microvascular complications, and extensive comorbidities. The systolic blood pressure in most diabetics with hypertension should be reduced to less than 140 mmHg. Diabetics at high risk for cardiovascular events should have their serum low-density lipoprotein (LDL) cholesterol lowered to less than 70 mg/dL with statins. Lower-risk diabetics should have their serum LDL cholesterol reduced to less than 100 mg/dL. Combination therapy of a statin with either a fibrate or niacin is not recommended.

INTRODUCTION

The American Diabetes Association (ADA)/American Heart Association (AHA) 2007 scientific statement recommended that diabetics should have a hemoglobin A1c level less than 7.0% and as close to normal (less than 6.0%) without causing significant hypoglycemia[1]. This scientific statement also recommended that diabetics with hypertension should have their blood pressure lowered to less than 130/80 mmHg[1]. In addition, this scientific statement recommended that combination therapy of statins with fibrates or niacin may be necessary to achieve lipid targets. This editorial will discuss clinical trial data showing why these recommendations needed to be changed.

HEMOGLOBIN A1C GOALS

The action in diabetes and vascular disease: preterax and diamicron modified release controlled evaluation trial randomized 11140 type 2 diabetics, mean age 66 years, to intensive glucose control with a hemoglobin A1c of 6.5% reached or to standard glucose control with a hemoglobin A1c of 7.3% reached[2]. At 5-year median follow-up, death from cardiovascular causes, nonfatal myocardial infarction (MI), or nonfatal stroke and all-cause mortality were similar in both treatment groups. Severe hypoglycemia occurred in 2.7% of the intensive glucose control group vs 1.5% in the standard glucose control group (hazard ratio = 1.86; 95%CI: 1.42-2.40; P < 0.001)[2]. However, major microvascular events (new or worsening nephropathy or retinopathy) were reduced from 10.9%-9.4% by intensive glucose control (hazard ratio = 0.86; 95%CI: 0.77-0.97; P = 0.01), primarily because of a reduction in nephropathy[2].

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) Study Group randomized 10251 type 2 diabetics, mean age 62.2 years, to intensive glucose control with a hemoglobin A1c of 6.4% reached or to standard glucose control with a hemoglobin A1c of 7.5% reached[3]. At 3.5-year mean follow-up, the incidence of cardiovascular death, nonfatal MI, or nonfatal stroke was not significantly different between both treatment groups. However, all-cause mortality was 5.0% in the intensive glucose control group vs 4.0% in the standard glucose control group (hazard ratio = 1.22; 95%CI: 1.01-1.46; P = 0.04). Hypoglycemia requiring medical assistance occurred in 10.5% of the intensive glucose control group vs 3.5% in the standard glucose control group (P < 0.001)[3].

The Veterans Affairs Diabetes Trial randomized 1791 type 2 diabetics, mean age 60.4 years, to intensive glucose control with a hemoglobin A1c of 6.9% reached or to standard glucose control with a hemoglobin A1c of 8.4% reached[4]. At 5.6-year median follow-up, cardiovascular death, nonfatal MI, nonfatal stroke, congestive heart failure, surgery for vascular disease, inoperable coronary artery disease, or amputation for ischemic gangrene and all-cause mortality were not significantly different between both treatment groups. Microvascular complications were not significantly different between both treatment groups. Adverse events, predominantly hypoglycemic episodes were more frequent in the intensive glucose treatment group (24.1% vs 17.6%, P < 0.001)[4].

The ADA 2013 guidelines state that a reasonable hemoglobin A1c goal for many nonpregnant adults with diabetes is less than 7.0%[5]. A hemoglobin A1c level of less than 6.5% may be considered in adults with short duration of diabetes, long life expectancy, and no significant cardiovascular disease if this can be achieved without significant hypoglycemia or other adverse effects of treatment. A hemoglobin A1c level less than 8.0% may be appropriate for patients with a history of severe hypoglycemia, limited life expectancy, advanced macrovascular and microvascular complications, extensive comorbidities, and long-standing diabetes in whom the hemoglobin A1c goal is difficult to attain despite multiple glucose-lowering drugs including insulin[5].

The American Geriatrics Society website on February 21, 2013 stated that reasonable glycemic targets would be hemoglobin A1c levels of 7.0%-7.5% in older adults with long life expectancy, 7.5%-8.0% in older adults with moderate comorbidities and a life expectancy of less than 10 years, and 8.0%-9.0% in older adults with multiple comorbidities and shorter life expectancy. Tight control of blood sugar causes higher rates of hypoglycemia in older adults.

BLOOD PRESSURE GOALS

The 2009 European Society of Hypertension guidelines recommended that lowering the blood pressure to less than 130/80 mmHg in patients at high risk for cardiovascular events was unsupported by prospective trial data, and that the systolic blood pressure should be lowered to less than 140 mmHg in these patients[6]. The American College of Cardiology Foundation/AHA 2011 expert consensus document on hypertension in the elderly recommended that the blood pressure should be reduced to less than 140/90 mmHg in adults younger than 80 years at high risk for cardiovascular events[7]. On the basis of data from the Hypertension in the Very Elderly trial[8], these guidelines recommended that the systolic blood pressure should be reduced to 140-145 mmHg if tolerated in adults aged 80 years and older[7].

In the International Verapamil SR-Trandolapril Study, 6400 patients had diabetes mellitus and coronary artery disease[9]. These patients were categorized as having tight control of their blood pressure if they could maintain their systolic blood pressure below 130 mmHg and their diastolic blood pressure below 85 mmHg, usual control if they could maintain their systolic blood pressure between 130-139 mmHg, and uncontrolled if their systolic blood pressure was 140 mmHg or higher. During 16893

patient-years of follow-up, a cardiovascular event rate (all-cause mortality, nonfatal MI, or nonfatal stroke) of 12.6% occurred in patients with usual control of blood pressure *vs* 19.8% in patients with uncontrolled hypertension (adjusted hazard ratio = 1.46; 95%CI: 1.25-1.71; $P < 0.001$) [9]. The incidence of cardiovascular events was 12.6% in patients with usual control of blood pressure *vs* 12.7% in patients with tight control of blood pressure (*P* not significant). The all-cause mortality rate was 11.0% with tight control of blood pressure *vs* 10.2% with usual control of blood pressure ($P = 0.06$). When extended follow-up to 5 years following the close of INVEST was included, the all-cause mortality rate was 22.8% with tight control of blood pressure *vs* 21.8% with usual control of blood pressure (adjusted hazard ratio = 1.15; 95%CI: 1.01-1.32; $P = 0.04$) [9].

The ACCORD blood pressure trial randomized 4733 patients with type 2 diabetes mellitus to intensive blood pressure control with a target systolic blood pressure of less than 120 mmHg or to standard blood pressure control with a target systolic blood pressure less than 140 mmHg [10]. After 1 year, the mean systolic blood pressure was 119.3 mmHg in the intensive blood pressure control group *vs* 133.5 mmHg in the standard blood pressure control group. Mean follow-up was 4.7 years. The primary composite outcome of nonfatal MI or nonfatal stroke or cardiovascular death and the annual rate of death from any cause were not significantly different between both treatment groups. The annual stroke rate was 0.32% in the intensive blood pressure control group *vs* 0.53% in the standard blood pressure control group (hazard ratio = 0.59; 95%CI: 0.39-0.89; $P = 0.01$) (number needed to treat to reduce 1 stroke = 476 patients). Serious adverse events attributed to antihypertensive treatment occurred in 3.3% of the intensive blood pressure control group *vs* 1.27% of the standard blood pressure control group, $P < 0.001$ (number needed to treat to increase 1 serious adverse event = 49 patients) [10].

The Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint trial included 9603 diabetics, mean age 66.1 years, and 15981 nondiabetics, mean age 66.6 years, with hypertension at high risk for cardiovascular events [11]. Mean follow-up was 4.6 years. The primary endpoint was cardiovascular death, nonfatal MI, nonfatal stroke, or hospitalization for heart failure. Compared to nondiabetics, diabetics had a 48% significant increase in the primary endpoint (hazard ratio = 1.48; 95%CI: 1.38-1.57). In patients with and without diabetes, antihypertensive drug treatment reduced the primary outcome if the baseline systolic blood pressure was 143 to 155 mmHg. The lowest incidence of death from cardiovascular causes in diabetics occurred with a systolic blood pressure of 135.6 mmHg (range 130.6 to 140.5 mmHg). The lowest incidence of death from cardiovascular causes in nondiabetics occurred with a systolic blood pressure of 133.1 mmHg (range 128.8 to 137.4 mmHg). For the primary outcome, the highest risk in those with and without diabetes occurred in patients

with the lowest or highest in-trial diastolic blood pressures (67.2 and 86.7 mmHg, respectively) [11].

The ADA 2013 guidelines recommend that the systolic blood pressure in most diabetics with hypertension should be reduced to less than 140 mmHg [5]. These guidelines also recommend use of an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker in the treatment of hypertension in diabetics unless they are pregnant [5].

DYSLIPIDEMIA

Numerous studies have demonstrated that statins reduce cardiovascular events including stroke and mortality in diabetics [12-15]. A meta-analysis was performed of 14 randomized trials of statins used to treat 18686 diabetics (1466 with type 1 diabetes and 17220 with type 2 diabetes) [14]. Mean follow-up was 4.3 years. All-cause mortality was reduced 9% per mmol/L reduction in serum low-density lipoprotein (LDL) cholesterol, $P = 0.02$. Major cardiovascular events were reduced 21% per mmol/L reduction in serum LDL cholesterol, $P < 0.0001$. Statins caused in diabetics a 22% reduction in MI or coronary death ($P < 0.0001$), a 25% reduction in coronary revascularization ($P < 0.0001$), and a 21% reduction in stroke ($P = 0.0002$). After 5 years, 42 fewer diabetics per 1000 diabetics treated with statins had major cardiovascular events [15].

In the Fenofibrate Intervention and Event Lowering in Diabetes study, 9795 type 2 diabetics (2131 with cardiovascular disease) were randomized to fenofibrate or placebo [16]. Mean follow-up was 5.0 years. The primary outcome of coronary events was not significantly reduced by fenofibrate. Fenofibrate insignificantly increased CAD mortality 19% [16].

In the ACCORD trial, 5518 type 2 diabetics at high risk for cardiovascular disease were randomized to simvastatin plus fenofibrate or to simvastatin plus placebo [17]. Mean follow-up was 4.7 years. Compared with simvastatin plus placebo, simvastatin plus fenofibrate did not reduce the rate of fatal cardiovascular events, nonfatal MI, or nonfatal stroke. Among 3414 patients with atherosclerotic cardiovascular disease and low serum high-density lipoprotein (HDL) cholesterol levels treated with simvastatin plus ezetimibe if needed to maintain the serum LDL cholesterol less than 70 mg/dL, at 36-mo follow-up, patients randomized to niacin had improvements in serum HDL cholesterol and triglyceride levels but no clinical improvement compared to patients randomized to placebo [18].

Professor Jane Armitage presented on March 9, 2013 at the Annual Scientific Meeting of the American College of Cardiology in San Francisco, California the results of HPS₂-THRIVE (Heart Protection Study 2-Treatment of HDL to Reduce the Incidence of Vascular Events). In this study of 25673 patients at high risk of cardiovascular events, adding extended-release niacin plus the anti-flushing agent laropriprant to treatment

with simvastatin or simvastatin/ezetimibe did not reduce at 3.9-year follow-up cardiovascular events. However, there were 31 serious adverse events among every 1000 niacin-treated patients including 3.7% excess diabetic complications ($P < 0.0001$) and 1.8% excess new onset diabetes ($P < 0.0001$).

Diabetics at high risk for cardiovascular events should have their serum LDL cholesterol lowered to less than 70 mg/dL with statins[5]. Lower-risk diabetics should have their serum LDL cholesterol reduced to less than 100 mg/dL[5]. Combination therapy of a statin with either a fibrate or niacin has not been shown to provide additional cardiovascular benefit above statin therapy alone and is not recommended[5]. Hypertriglyceridemia should be treated with dietary and lifestyle changes[5]. Severe hypertriglyceridemia should be treated with drug therapy to reduce the risk of acute pancreatitis[5].

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Gender differences related to the presence of atrial fibrillation in older hypertensive patients

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Abstract

AIM: To determine whether there are gender differences in the epidemiological profile of atrial fibrillation (AF) and to characterise the clinical, biochemical, and therapeutic factors associated with AF.

METHODS: Each investigator (primary care physicians or physicians based in hospital units for hypertension treatment) recruited the first 3 patients with an age of ≥ 65 years and a clinical diagnosis of hypertension (ambulatory blood pressure monitoring and an electrocardiogram, were performed) on the first working day of the week for 5 wk and identified those individuals with atrial fibrillation. A binary logistic regression was performed, including all of the variables that were significant in the univariate analysis, to establish the variables that were associated with the presence of arrhythmia.

RESULTS: A total of 1028 patients were included in the study, with a mean age of 72.8 ± 5.8 years. Of these patients, 47.3% were male, 9% were smokers, 27.6% were diabetics, 48.3% had dyslipidaemia, 10.9% had angina, and 6.5% had experienced a myocardial infarction. Regarding gender differences, the men exhibited a larger waist circumference, a lower body mass index, less obesity, and a more extensive history of diabetes, smoking, ischaemic heart disease, kidney failure, peripheral arterial disease and carotid disease than the women. There were no differences, however, in the prevalence of AF between the men and the women (11.5% *vs* 9.2%, respectively; *P* = no significant). Regarding treatment, the women received antiplatelet agents and diuretics less frequently, but there were no other differences in the use of antihypertensive and antithrombotic therapies. In the multivariate analysis, AF in the total study population was associated with age, alcohol consumption, the presence of heart disease, and decreased glomerular filtration. In the women, AF was associated with all of the factors included in the overall analysis, as well as the presence of left ventricle hypertrophy. In contrast, in the men, the only risk factors associated with AF were age, the presence of heart disease and alcohol consumption.

CONCLUSION: In patients with hypertension over 65 years of age, there are relevant gender differences in the factors associated with AF.

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Key words: Atrial fibrillation; Hypertension; Gender differences

Core tip: The presence of atrial fibrillation (AF) in hypertensive patients with an age of $\geq$ 65 years was associated with age, alcohol consumption, the presence of heart disease, and decreased glomerular filtration. In women, AF was associated with all of the factors included in the overall analysis, as well as the presence of left ventricle hypertrophy, whereas in men, the only risk factors associated with AF were age, the presence of heart disease and alcohol consumption. Thus, in patients with hypertension who are over 65 years of age, there are relevant gender differences in the factors associated with AF.

INTRODUCTION

Although cardiovascular disease (CVD) has historically been considered to affect mainly men, we now know that CVD is the main cause of death in both men and women worldwide[1]. However, a number of occasionally significant gender differences can be observed in the morbidity, mortality, risk-factor profiles, and clinical presentation of CVD. These differences are consistent between all of the populations and regions analysed and are thus relevant to the development of programmes for the prevention and treatment of CVD.

The INTERHEART study found that, on average, women experience their first myocardial infarction 9 years later than men[2]. Similarly, a recent review reported that men experience their first stroke 4.3 years before women, on average[3]. However, as the prevalence of atrial fibrillation (AF) has increased in recent years due to the ageing of the population, the longer survival of patients with heart disease and, of course, more frequent diagnosis, among other factors, AF has become a major public health problem, particularly due to the associated risk of stroke and mortality[4]. Women are not exempt from this disease, as in addition to presenting several cardiovascular risk factors, their life expectancy is longer. The incidence in women is thus not negligible, and the probability of complications, and particularly cerebrovascular problems, is relatively high. This phenomenon is likely due to the prevalence of hypertension in women, which is the most important risk factor for both AF and stroke.

The purpose of this sub-study is to establish whether there are any gender-related epidemiological, clinical, biochemical, or therapeutic differences or differences in the factors associated with AF in hypertensive patients over 65 years of age.

MATERIALS AND METHODS

The FAPRES registry is a healthcare, teaching and research project sponsored by the Valencian Society of Hypertension and Vascular Risk and supported by the Spanish Society of Hypertension-Spanish League for the Fight Against Hypertension (SEH-LELHA). The current study was designed to establish the prevalence of AF in patients of $\geq$ 65 years of age with a clinical diagnosis of hypertension (HT) in the region of Valencia, Spain. This study involved the participation of 69 primary care physicians and physicians based in HT hospital units, a proportion similar to the population census of each of the three provinces. Written informed consent was obtained from all of the patients, and the study was performed following the principles of the Declaration of Helsinki (Edinburgh Amendment, 2000) and after approval by a hospital ethics committee (Clinical Research Ethics Committee of the Hospital General Universitario of Castellon). The general study methods and the determination of the sample size were described in previous publications[5,6]. This study is a subanalysis of these data, focusing on differential issues based on gender.

Patients

Each investigator recruited the first three patients who attended the outpatient clinic on the first working day of the week for 5 wk during the recruitment period and who met all of the inclusion criteria and none of the exclusion criteria. The inclusion criteria were as follows: (1) over 65 years of age; (2) a previous diagnosis of HT, at least 3 mo before the start of the study, according to the Good Clinical Practice (GCP) guidelines[7]; and (3) consent to participate in the study. The exclusion criteria were an arm circumference greater than 42 cm, the presence of conditions ineligible for the study or for performing ambulatory blood pressure monitoring (ABPM), and the inability to understand and sign the consent form.

Clinical blood pressure (BP) measurement was performed following the GCP recommendations[8,9], using a validated automatic electronic device. The patient was considered to have good HT control when the mean systolic BP (SBP) and diastolic BP (DBP), based on the two measurements obtained at the visit, were below 140 and 90 mmHg, respectively.

The 24-h ABPM was performed using SpaceLabs 90207 devices (SpaceLabs, Inc. Richmond, WA, United States) specifically supplied for the project. The monitors were scheduled to perform a BP measurement every 20 min during the activity period and every 30 min during the night rest period. Each period was defined individually in each registry according to the bedtime and wake-up time reported by the patient. Registries not meeting the pre-established quality standards were excluded[10]. According to the guidelines of the European Societies of Cardiology and Hypertension (ESH/ESC)[8], a good ambulatory control was defined as having BP values of <

130/80 mmHg (SBP/DBP) in a 24-h period.

Variables

The variables collected *via* clinical interview were age; gender; weight; height; body mass index (BMI) (obesity was defined when this parameter was $\geq$ 30 kg/m^2); waist circumference (abdominal obesity was defined when this parameter was $\geq$ 102 cm in men or $\geq$ 88 cm in women)[11]; time from the onset of HT; excessive alcohol intake (over 30 g/d)[12]; and known cardiovascular risk factors (CVRFs), such as smoking, diabetes, dyslipidaemia (total cholesterol > 250 mg/dL, low-density lipoprotein (LDL)-cholesterol > 155 mg/dL, high-density lipoprotein (HDL)-cholesterol < 40 mg/dL in men or < 48 mg/dL in women, or receiving lipid-lowering treatment), and a family history of early cardiovascular disease (< 55 years of age in men or < 65 years of age in women).

All of the patients underwent an electrocardiogram that was sent by regular mail to a reference centre, where two expert cardiologists who were not familiar with the patients' clinical data analysed the heart rhythm independently. In the case of a disagreement between the experts, another specialist was asked to participate. Data on lesions in the target organs and associated clinical conditions were also collected, as follows: the presence or absence of left ventricular hypertrophy (Sokolow or Cornell electrocardiographic criteria), renal damage (increased serum creatinine from 1.3-1.5 mg/dL in men or 1.2-1.4 mg/dL in women), microalbuminuria, an albumin/creatinine ratio of 22-300 mg/g in men or 31-300 mg/g in women or albuminuria of 30-300 mg/24 h, and a glomerular filtration rate (GFR) estimated from the serum creatinine values according to the abbreviated formula from the Modification of Diet in Renal Disease study[13] (renal disease was defined for a GFR of < 60 mL/h peer m^2). Further data were collected on carotid disease (when the patient was diagnosed with an intima-media thickness > 0.9 mm or plaque) and previous heart disease (defined as the presence of ischaemic heart disease, heart failure or both). Additionally, we recorded the presence of previous cerebrovascular disease and peripheral arterial disease. The class and number of therapeutic subgroups of antihypertensives used for the treatment of HT were also recorded. AF was defined as having a history of arrhythmia beginning at least 3 mo before the study, as determined by medical records), even if the patients were now experiencing sinus rhythm or were diagnosed by the ECG performed on all of the patients.

An external audit of 10% of the questionnaires was performed randomly to verify the reliability of the data included in the study.

Statistical analysis

The results were expressed as frequencies and percentages for the qualitative variables and as averages with standard deviations for the quantitative variables. The 95%CI was calculated for the variables of interest assuming normality using a Kolmogorov-Smirnov test. For the comparison of means, a Student's t test for independent data was used; when comparing quantitative data not following a normal distribution, the nonparametric Mann-Whitney test was used; and for the possible association between qualitative variables, the χ^2 test was implemented, establishing statistical significance at $P < 0.05$. Finally, to establish the variables that were associated with the presence of AF, a binary logistic regression was performed that included all of the variables that were significant in the univariate analysis. The presence of confounding factors was evaluated by the analysis of interactions. The calibration of the multivariate model was tested using the Hosmer-Lemeshow statistic and the discriminative power using the area under the receiver operating characteristic (ROC) curve obtained by analysing the probability of the prognosticated value of the multivariate model. A general analysis and an analysis for each gender were conducted. All of the analyses were performed using the SPSS statistical package, version 15.0 (SPSS Inc., Chicago, Illinois, United States).

RESULTS

During the period from June to December 2008, 1028 patient records were included in this study, 954 of which (92.8%) met the pre-established quality standards for evaluation (lacking incomplete data and protocol deviations, for example)[10]. The mean age of the patients was 72.8 ± 5.8 years, and 486 (47.3%) were men, 48.3% had dyslipidaemia, 27.6% were diagnosed with diabetes mellitus, 36.2% performed physical exercise at least twice a week, 3.7% reported regular alcohol intake, 10.9% had a history of angina, 6.5% presented with myocardial infarction, and 5% experienced coronary revascularisation. Other associated diseases were heart failure in 7.3% of patients, stroke in 7.5%, and renal failure in 6.1%. Of the patients included in the study, 37.4% were obese based on BMI, and 75.8% were obese based on waist circumference. The prevalence of AF was 10.3% (9.2% in women and 11.5% in men), with 6.7% evidencing AF when an electrocardiogram (ECG), was performed and the other 3.6% having a history of AF, but at the time of analysis, experiencing sinus rhythm. Additionally, 1.7% of patients had no history of AF but were currently experiencing this arrhythmia. The laboratory, electrocardiographic and treatment data are included in Table 1.

BP control and treatment in the study population

The mean duration of HT in the overall sample was 10.9 ± 8.2 years, and 35.3% of the patients were treated according to the BP measured at the clinic, whereas 50.9% were treated according to the BP determined by ABPM. The mean BP measured at the clinic was 146.7/81.1 mmHg and determined by ABPM was 128.5/70.8 mmHg. Only 6% of the patients were not being treated with antihypertensive drugs, 35.6% were taking a single drug, 35.6% were taking two, and 22.7% were taking three or more.

Table 1 Baseline characteristics of the study population, including biochemical, electrocardiogram and treatment data (mean ± SD) *n* (%)

Characteristics	Data
WBC, mm^3	6727 ± 1774
Haemoglobin, g/dL	13.6 ± 1.8
Glucose, mg/dL	108 ± 31
LDL-cholesterol, mg/dL	118 ± 34
Triglycerides, mg/dL	129 ± 73
Uric acid, mg/dL	5.2 ± 1.1
Creatinine, mg/dL	0.97 ± 0.28
Glomerular filtration rate, mL/min	75 ± 22.5
Albumin/creatinine ratio	39.4 ± 109.8
Heart rate, bpm	71.7 ± 14
Normal QRS	794 (77.2)
Q waves	25 (2.4)
Sokolow LVH	15 (1.5)
Cornell LVH	103 (10)
Strain	84 (8.2)
Global LVH	177 (17.2)
Measurement of anti-HT	1.7 ± 0.87
Diuretics	535 (52.1)
Beta-blockers	240 (23.4)
Calcium antagonists	199 (19.4)
ACEI	265 (25.8)
ARB	611 (59.5)
Antiplatelet agents	196 (19.1)
VKA	72 (7.0)
No anti-HT drugs	62 (6)
Monotherapy	366 (35.6)
2 drugs	366 (35.6)
3 or more anti-HT drugs	234 (22.7)

WBC: White blood cell; LVH: Left ventricle hypertrophy; HT: Hypertension; ACEI: Angiotensin-converting enzyme inhibitors; ARB: Angiotensin receptor blocker; VKA: Vitamin K antagonist; LDL: Low-density lipoprotein.

Table 2 Epidemiological, clinical and therapeutic differences between genders (mean ± SD) *n* (%)

	Females (*n* = 542)	Males (*n* = 486)	*P* value
Mean age, yr	72.7 ± 5.8	72.8 ± 5.8	NS
Abdominal circumference, cm	96.6 ± 11.8	100.4 ± 11.0	< 0.001
Weight, kg	71.4 ± 11.5	79.5 ± 11.5	< 0.001
Mean height, cm	155.2 ± 6.7	166.7 ± 6.7	< 0.001
BMI	29.6 ± 4.5	28.6 ± 3.6	< 0.001
Obesity	224 (41.4)	160 (32.9)	0.005
Years from the onset of HT	11.0 ± 8.2	10.8 ± 8.1	NS
Diabetes mellitus	134 (24.7)	150 (30.9)	0.03
Dyslipidaemia	267 (49.3)	230 (47.3)	NS
Smokers	17 (3.1)	76 (15.6)	< 0.001
Sedentariness	352 (70.5)	274 (56.4)	< 0.001
Regular alcohol intake	5 (0.9)	33 (6.8)	< 0.001
History of stroke	32 (6.0)	32 (6.7)	NS
History of IHD	55 (10.1)	124 (25.5)	< 0.001
History of HF	35 (6.5)	39 (8.1)	NS
History of renal insufficiency	24 (4.5)	38 (7.9)	0.025
Peripheral arterial disease	15 (2.7)	37 (7.7)	0.001
Carotid disease	2 (0.4)	13 (2.8)	0.003
Atrial fibrillation	50 (9.2)	56 (11.5)	NS
CHADS ⩾ 2	275 (50.7)	272 (56.0)	NS
LVH by ECG	111 (20.5)	66 (13.6)	0.004
LVH_Sokolow	6 (1.1)	9 (1.9)	NS
LVH_Cornell	91 (16.8)	12 (2.5)	< 0.001
Mean HR, bpm	75.4 (10.7)	72.1(10.7)	< 0.001
Mean number of anti-HT	1.7 ± 0.87	1.8 ± 1.0	NS
Diuretics	304 (56.1)	226 (46.5)	0.002
Beta-blockers	105 (19.4)	98 (20.2)	NS
Calcium antagonists	93 (17.2)	80 (16.5)	NS
ACEI	118 (21.8)	128 (26.3)	NS
ARB	318 (58.7)	294 (60.5)	NS
Antiplatelet agents	90 (16.6)	112 (23.0)	0.012
VKA	33 (6.1)	32 (6.6)	NS

BMI: Body mass index; IHD: Ischaemic heart disease; HF: Heart failure; LVH: Left ventricle hypertrophy; HR: Heart rate; HT: Hypertension; ACEI: Angiotensin-converting enzyme inhibitors; ARB: Angiotensin receptor blocker; VKA: Vitamin K antagonist. NS: No significant.

Gender differences

Table 2 shows the differences between the men and the women in epidemiological, biochemical, BP and therapeutic characteristics. The women exhibited more obesity, greater sedentariness, a higher systolic and diastolic BP in the first clinic measurement, a higher heart rate, a higher percentage of BP control during ABPM (55.7% in women *vs* 45.7% in men, *P* < 0.001), and higher HDL-cholesterol values (56.1 ± 13.5 in women *vs* 49.4 ± 15.1 in men, *P* < 0.001). In addition, the women had a higher percentage of LVH, as determined by ECG (Cornell voltage criterion), and more frequently used diuretics than the men. In contrast, the men exhibited a greater abdominal circumference and a higher prevalence of a history of diabetes, active smoking, alcohol consumption, ischaemic heart disease, peripheral arterial disease, renal disease, and carotid disease. Regarding the control of BP at the clinic, this parameter was higher in the men (39.9% in men *vs* 31.2% in women, *P* = 0.004), who also had higher uric acid values and more frequently used anti-aggregation drugs. There were no differences in the presence of AF; the use of other antihypertensive treatments, such as beta-blockers, ARA-2, and ACEIs; or other biochemical data, including blood sugar, total cholesterol, LDL-cholesterol, triglycerides and creatinine levels and

GFR.

AF-related risk factors

No significant interactions were determined between gender and other clinical features in AF patients (Table 3). However, the presence of AF in the total study population was associated with age, with a 10% increase in AF prevalence per year; alcohol intake; previous heart disease; and GFR reduction.

In the gender-specific multivariate analysis, the presence of AF in the women was related to all of the overall analysis factors, in addition to the presence of strain in the ECGs (associated with LVH). In contrast, there was no association between AF and regular alcohol intake. In the men, unlike in the women, AF was only associated with age, the presence of heart disease (ischaemic or heart failure or both), and regular alcohol intake. The multivariate analysis was accurately calibrated [*P* = no significant (NS) and χ^2 = 16.5] and had discriminative power (for the total study population, an area under the curve of 0.78, 95%CI: 0.74-0.83, and *P* < 0.01; for the analysis of the men only, an area of under the curve of 0.75,

Table 3 Independent predictors of global atrial fibrillation in the total study population and in subgroups according to gender

Variable	Total OR (95%CI)	Females OR (95%CI)	Males OR (95%CI)
Age, yr	1.1 (1.1-1.1)	1.1 (1.1-1.1)	1.1 (1.03-1.13)
	P < 0.001	*P* = 0.010	*P* = 0.003
Alcohol abuse	5.2 (2.1-12.2)	7.0 (0.6-82.9)	4.2 (1.5-11.4)
	P = 0.001	NS	*P* = 0.005
Heart disease	4.7 (3.0-7.5)	6.1 (3.1-12.4),	3.4 (1.9-6.2)
	P < 0.001	*P* < 0.001	*P* < 0.01
GFR, mL/min per m^2	0.98 (0.97-0.99)	0.98 (0.96-0.99)	0.99 (0.9-1.0)
	P = 0.027	*P* = 0.039	NS
Strain on ECG	1.8 (0.9-3.4)	2.97 (1.1-8.1)	1.2 (0.53-2.81)
	P = NS	*P* = 0.032	NS

Multivariate analysis: Age, gender, body mass index, physical exercise, alcohol use, time from the onset of hypertension, clinical blood pressure, 24-h ambulatory blood pressure monitoring result, family history of early cardiovascular disease, diabetes, smoking, obesity, dyslipidaemia, abdominal obesity, left ventricular hypertrophy, atherosclerotic plaque, renal damage, coronary disease, heart failure, renal disease, and treatment type. GFR: Glomerular filtration rate; ECG: Electrocardiogram; NS: No significant.

95%CI: 0.68-0.81, and *P* < 0.01; and for the analysis of the women only, an area under the curve of 0.82, 95%CI: 0.76-0.88, and *P* < 0.01).

Treatment differences in patients with AF

Regarding the treatment of patients diagnosed with AF (Table 4), statistically significant differences were observed between the men and the women in their use of calcium antagonists (8.9% *vs* 30%, respectively; *P* = 0.007) and antiplatelet agents (26.8% *vs* 8%, respectively; *P* = 0.01). The rates of use of antiplatelet agents and anticoagulants was higher in the men than in the women, although this disparity was also not significant (71.4% *vs* 66%, respectively; *P* = NS).

After stratification according to the CHADS$_2$ calculated score in patients with AF, we observed that the women and men had a similar rate of using oral anticoagulation therapy in all degrees of CHADS$_2$, except in CHADS$_2$ = 2, in which the use of anticoagulation therapy in the women was nearly double the use in the men (Figure 1).

DISCUSSION

This study is one of the few in our country that analysed the prevalence of AF[5] and epidemiological differences by gender in a hypertensive population of over 65 years of age visiting outpatient clinics. The AF prevalence determined here (10.3%) is the same as the prevalence in another national registry, the CARDIOTENS 2009, which reported AF in 10.22% of patients with cardiovascular disease or other risk factors and in 6.22% of patients in the overall sample of the registry[14]. These data are equal to twofold the prevalence reported in 1999[15], which did not include patients diagnosed "*de novo*" by ECG, and are

Table 4 Treatment differences between genders in patients with atrial fibrillation (*n* = 106) *n* (%)

	Females (*n* = 50)	Males (*n* = 56)	*P* value
Diuretics	34 (68.0)	30 (53.6)	NS
Beta-blockers	16 (32)	17 (30.4)	NS
Calcium antagonists	15 (30)	5 (8.9)	0.007
ACEI	12 (24)	14 (25)	NS
ARB	32 (64)	31 (55.4)	NS
Antiplatelet agents	4 (8)	16 (26.8)	0.010
VKA	29 (58)	25 (44.6)	NS
ATG or VKA	33 (66)	41 (71.4)	NS

ACEI: Angiotensin-converting enzyme inhibitors; ARB: Angiotensin receptor blocker; VKA: Vitamin K antagonist; ATG: Anti-aggregants. NS: No significant.
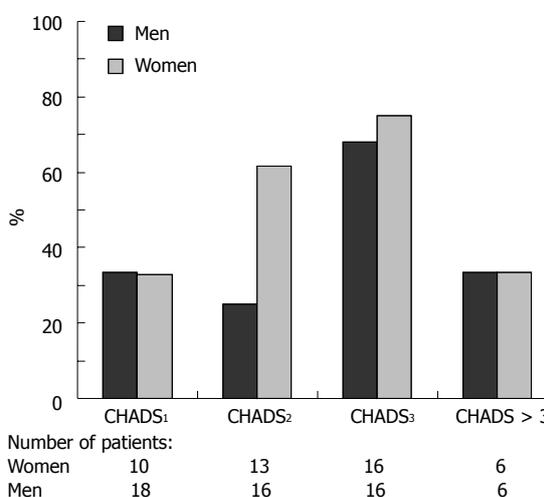
Figure 1 Gender differences in the use of anticoagulation therapy between groups according to CHADS$_2$ score.

slightly higher than the AF prevalence of 8.5% reported for the PREV-ICTUS registry, which analysed 7108 subjects of over 60 years of age[16]. The higher AF prevalence reported in the current study is likely due to the different mean age of the two study populations (72.8 years in the current study *vs* 71.9 years in the PREV-ICTUS study), the origin of the recruited patients (here, primary care and hypertension units), and the method of AF detection (here, presence in ECGs and history of AF).

Furthermore, in our study, we noted gender differences between the classic epidemiological factors. Women exhibited a higher prevalence of non-abdominal obesity, whereas men more frequently presented a history of diabetes; smoking; alcohol use; target-organ lesions; and established cardiovascular disease, such as ischaemic heart disease, peripheral arterial disease, and stroke. However, unlike in other studies[16], no significant differences were detected in the presence of AF between men and women, although a slight disparity was noted (11.5% in men *vs* 9.2% in women).

Regarding the risk factors related to the presence of AF in women, the involvement of the target organ, as in

the cases of LVH and renal dysfunction, and heart disease are significant conditions associated with this arrhythmia. In contrast, in men, excessive alcohol intake has a strong association with this condition, possibly due to the toxic effect of alcohol on the myocardium[17]. This knowledge can help clinicians to develop strategies to prevent AF in the hypertensive population. In women, our effort should be aimed at a greater control of BP to prevent the occurrence of lesions in target organs and of cardiovascular disease, whereas in men, the reduction of alcohol intake should be an additional objective, as described in other recent studies[18,19].

Moreover, an important finding of our study is the treatment differences between genders in patients with AF, and particularly differences in the use of antiplatelet agents and anticoagulants. Although the data were is not significant, we observed greater use in men, in contrast to the results obtained by Riesgo *et al*[20], who reported more frequent use in women. However, the patient profile of this prior study was different, as the subjects were recruited only from primary care, and the results were also not significant. Our results are similar to the findings of another recent report indicating higher rates of anticoagulation therapy use in men but no significant gender-related differences for other treatments[21]. Yet, when the population was stratified into groups based on CHADS2 score, women with a score of 2 had a nearly twofold higher rate of using oral anticoagulants than men. One potential reason for this discrepancy is the perception that women have a higher incidence of stroke as a complication of the evolution of AF[22,23]. This perception could lead to the expectation that women receive anti-aggregation and anticoagulation more frequently than men, as recommended in the most recent practice guidelines published[24], in which the female gender is assigned one point on the new CHADS2-VAS2C scale. Thus, hypothetically, if the practice guidelines were applied to this study, the rate of anticoagulant use in women should approach 100% if there is no contraindication (the CHADS2-VAS2C score in the women included in this study was 3). One of the main limitations of this sub-study is that it was not specifically designed to analyse differences between genders. Additionally, the sub-study did not analyse the initial reason for a consultation to diagnose arrhythmia, which would have contributed to a better interpretation of the results. There also may be other unknown confounding factors related to practitioner preferences and guideline adherence, which could explain the presence or absence of gender-related differences. Finally, the nonrandomised selection of physicians and patients may reduce the external validity of the study.

ACKNOWLEDGMENTS

COMMENTS

Background
The incidence of atrial fibrillation (AF) is important in the general population but is even more so in hypertensive patients. As atrial fibrillation increases cardiovascular risk, knowledge of the factors that are associated with this condition is highly clinically relevant. Furthermore, the incidence of atrial fibrillation in women is different than in men, and therefore, the factors associated with atrial fibrillation in women may also be different.

Research frontiers
Risk factors related to the presence of atrial fibrillation are under investigation, as knowledge of these factors can aid the development of preventive strategies. The difference in risk between men and women is also being studied in the field of cardiovascular medicine.

Innovations and breakthroughs
It is possible that the more aggressive treatment of these patients, particularly by administering cardiovascular drugs, could improve the patients' prognosis.

Applications
The main application of this registry is to determine the risk factors associated with atrial fibrillation. By targeting these factors, we can avoid the development of this disease in both men and women, which has been little studied in large clinical trials.

Terminology
AF is the most common cardiac arrhythmia (irregular heart beat). It may cause no symptoms, but it is often associated with palpitations, fainting, chest pain, or

congestive heart failure. However, in some people atrial fibrillation is caused by otherwise idiopathic or benign conditions. Hypertension or high blood pressure, arterial hypertension, is a chronic medical condition in which the blood pressure in the arteries is elevated. ROC curve, is a graphical plot which illustrates the performance of a binary classifier system as its discrimination threshold is varied. It is created by plotting the fraction of true positives out of the positives true positive rate (TPR) *vs* the fraction of false positives out of the negatives false positive rate (FPR), at various threshold settings. TPR is also known as sensitivity (also called recall in some fields), and FPR is one minus the specificity or true negative rate. Univariate analysis is the simplest form of quantitative (statistical) analysis. The analysis is carried out with the description of a single variable and its attributes of the applicable unit of analysis. For example, if the variable age was the subject of the analysis, the researcher would look at how many subjects fall into a given age attribute categories.

Peer review

This study is one of the few in our country that analyses the prevalence of AF and the epidemiological differences by gender in a hypertensive population of over 65 years of age attended in outpatient clinics.

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BRIEF ARTICLE

Association of the level of heteroplasmy of the 15059G>A mutation in the MT-CYB mitochondrial gene with essential hypertension

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Abstract

AIM: To examine whether the heteroplasmy level for 15059G>A mutation in the mitochondrial genome might be associated with essential hypertension.

METHODS: This cross-sectional study involved 196 unrelated participants randomly selected from general population (90 males and 106 females) who underwent a regular medical check-up at the Institute for Atherosclerosis Research (Moscow, Russia). One hundred and twenty of them (61%) had essential hypertension, and 76 (39%) were apparently healthy normotensive persons. The level of heteroplasmy for 15059G>A mutation occurring in the coding region of cytochrome b gene (*MT-CYB*) of mtDNA isolated from the blood leukocytes, was quantified using DNA pyrosequencing method.

RESULTS: The 15059G>A heteroplasmy level ranged between 4% and 83%, with a median level of 31%. Between the upper and lower quartiles of 15059G>A heteroplasmy distribution, significant differences were observed for patients' age, systolic blood pressure, and triglyceride levels. 15059G>A heteroplasmy correlated both with age ($r = 0.331$, $P < 0.001$) and the presence of hypertension ($r = 0.228$, $P = 0.002$). Regression analysis revealed that the age explains 12% variability of 15059G>A heteroplasmy, and hypertension independently explains more 5% variability. The 15059G>A heteroplasmy exceeding 31% was found to be significantly associated with a higher risk of essential hypertension (odds ratio 2.76; P (Fisher) 0.019]. The study participants with high 15059G>A heteroplasmy level were found to have significantly higher age ($P < 0.001$) and the prevalence of essential hypertension ($P = 0.033$), as compared to those with low 15059G>A heteroplasmy level. These observations suggested a positive correlation between the level of 15059G>A heteroplasmy and essential hypertension.

CONCLUSION: This study provides the evidence of association of mtDNA 15059G>A mutation heteroplasmy with essential hypertension.

Key words: Essential hypertension; Heteroplasmy; Mi-

tochondrial DNA; 15059G>A mutation

Core tip: The pathophysiology of essential hypertension (EH) is insufficiently understood; in particular, the impact of mitochondrial DNA mutations on the development of EH is poorly investigated. We undertook this study in order to see whether the level of heteroplasmy for the 15059G>A mutation in the mitochondrial cytochrome b gene might be associated with EH. The 15059G>A heteroplasmy level in mtDNA in blood leukocytes obtained from 196 study participants, randomly selected from general population (120 of whom had EH), exceeding 31%, was found to be significantly associated with a higher risk of EH.

INTRODUCTION

It is known that mutations in mitochondrial DNA (mtDNA) cause a variety of hereditary disorders with complex phenotypes including those that have hypertension as one of their clinical outcomes (such as the HUPRA syndrome comprising hyperuricemia, metabolic alkalosis, pulmonary hypertension, and progressive renal failure in infancy)[1].

Essential hypertension (EH), that represents a common form of hypertension, is a highly polygenic pathological condition which is caused by a combination of small-scale changes in the expression of many genes, in conjunction with a variable collection of environmental factors[2-4]. To the date, in total, 14 independent chromosome loci have been recognized for blood pressure traits that reached genome-wide significance including replication in independent cohorts[2]. Nevertheless, these variants explain just a very small fraction of the heritability of blood pressure traits[2]. Because chromosomal DNA variants exhibit only a modest effect in EH[2], it is impossible to exclude that, in contrast, somatic mtDNA mutations might importantly contribute to the development of hypertension and that a genetic predisposition to EH may be influenced by a ratio between mutated and wild-type mtDNA, *e.g.*, by heteroplasmy level. In support of this possibility, a non-redundant role of mtDNA heteroplasmy has been reported in human aging[5] and several age-related pathologic conditions including atherosclerosis[6,7], Alzheimer's disease[8], and diabetes[9]. It has been also reported that the entire mtDNA sequencing in United States pedigrees of African and European descent allowed to identify significant changes in the mtDNA sequence of hypertensive probands, which implies a potential role

of mtDNA mutations in EH[10]. To the date, the role of somatic mtDNA mutations in EH is poorly studied and poorly understood. Therefore, it is obvious that any report dealing with the consideration of the involvement of mtDNA sequence alterations in hypertension may represent interest for further understanding of "genetic roots" and the mechanisms of the development of EH.

Initially, a G-to-A mutation at nucleotide 15059 of the mtDNA sequence was described in a patient with mitochondrial myopathy[11]. It has been established that G-to-A mutation occurs as a result of replacement of glycine at amino acid position 190 of mitochondrial cytochrome b with a stop codon leading to a truncated protein that misses 244 amino acids at the C-terminus of cytochrome b[12]. Earlier it was shown that 15059G>A heteroplasmy is associated with fibro-fatty atherosclerotic plaques which suggests a potential involvement of 15059G>A heteroplasmy in atherosclerosis[6,7]. In the present report, we proved the results of a study that involved an analysis of 196 randomly selected individuals which indicate an association of this mtDNA mutation with EH.

MATERIALS AND METHODS

Patients

This study was conducted in accordance with the Helsinki Declaration of 1975 as revised in 1983. All participants gave their written informed consent prior to their inclusion in the study, and the protocol was approved by the ethics committee of the Institute for Atherosclerosis Research, Moscow, Russia.

The study involved 196 unrelated patients (90 males and 106 females) who underwent a regular medical check-up at the Institute for Atherosclerosis Research, Moscow. On admission, a careful analysis of history was taken with special attention to cardiovascular risk factors, including a family history of cardiovascular diseases.

EH was diagnosed according to the European Society of Hypertension and the European Society of Cardiology classifications[13]. The presence of concomitant coronary heart disease (CHD) was evaluated according to American College of Physicians/American College of Cardiology Foundation/American Heart Association guidelines[14]. Standard 12-lead echocardiography was used for the diagnosis of left ventricular hypertrophy (LVH)[13]. Myocardial infarction (MI) was diagnosed according to the joint criteria of the Expert Consensus Document[15].

Biochemical measurements

The venous blood for lipid analysis was taken after overnight fasting. To obtain serum, the blood was incubated for 1 h at 37 ℃ and centrifuged for 15 min at 1500 *g*, and serum was stored at -70 ℃. Serum concentrations of cholesterol and triglycerides were measured by enzymatic method using commercially available kits (Analyticon Biotechnologies AG, Germany)[16]. High density lipoprotein (HDL) cholesterol was measured enzymatically in
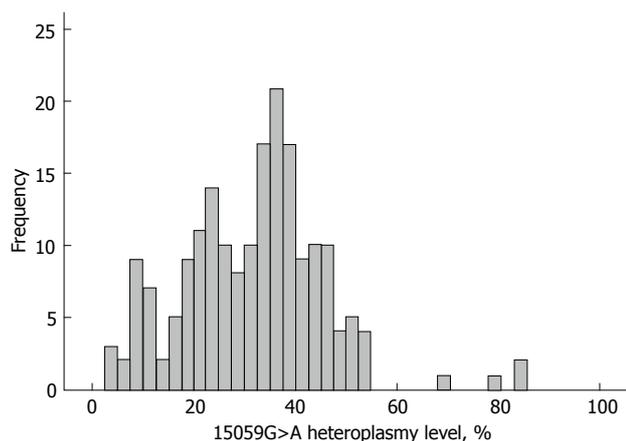
Figure 1 A frequency distribution histogram of the mtDNA 15059 G>A mutation heteroplasmy level in 191 studied individuals. The bell-shaped curve represents the expected normal frequency distribution of the mutated allele.

Table 1 Antropometric, clinical and biochemical characteristics of study participants (mean ± SD) *n* (%)	
Characteristics	
Age, yr	65.1 ± 9.8
BMI, kg/m^2	26.2 ± 4.7
SBP, mm/Hg	138 ± 19
DBP, mm/Hg	83 ± 9
Cholesterol, mg/dL	234 ± 49
TG, mg/dL	125 ± 70
HDL cholesterol, mg/dL	66 ± 11
LDL cholesterol, mg/dL	143 ± 47
EH	120 (61)
LVH	53 (27)
CHD	45 (23)
Type 2 diabetes	23 (12)
Myocardial infarction	8 (4)
Family history of EH	75 (38)
Family history of myocardial infarction	51 (26)

BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; EH: Essential hypertension; LVH: Left ventricular hypertrophy; CHD: Coronary heart disease; TG: Triglycerides; HDL: High density lipoproteins; LDL: Low density lipoproteins.

the supernatant after the precipitation of apolipoprotein B-containing lipoproteins[17], and low density lipoprotein (LDL) cholesterol were calculated using the Friedewald formula[18].

DNA analysis

Mitochondrial DNA was isolated with the Aquapure Genomic Tissue Kit (Bio-Rad Laboratories, Hercules, CA, United States) according to the manufacturer's protocols. The heteroplasmy level of the mtDNA mutation 15059G>A was quantified by the pyrosequencing method using the automated pyrosequencing machine PSQ HS96MA (Pyrosequencing AB, Uppsala, Sweden). Briefly, a 450-bp polymerase chain reaction (PCR) fragment of mtDNA was amplified using forward primer 5'-Bio-CAT-TATTCTCGCACGGACT-3' and reverse primer 5'-GC-TATAGTTGCAAGCAGGAG-3' and then sequenced using the primer 5'-TTTCTGAGTAGAGAAATGAT-3'. The quantitative assay of the mutant allele 15059A was performed by peak height analysis of the pyrogram in the studied domain of a single strand PCR fragment of the mitochondrial genome as previously described[6]. Primers were synthesized by Syntol (Moscow, Russia).

Statistical analysis

Data were analyzed using a software package SPSS 14.0 (SPSS Inc., Chicago, IL, United States). The comparisons of mean values were performed by the Mann-Whitney *U*-test for continuous variables, and by chi-square Pearson's test for categorical variables. The data are presented in terms of mean and SD. The normality of the 15059G>A heteroplasmy distribution was estimated from normal probability plots and by the Shapiro–Wilk *W*-test[19]. Quartiles with their confidence intervals (CI) were computed according to Aczel[20] and Conover[21] and analyzed by *t*-test. Odds ratios (OR) and their 95%CI were calculated using the Calculator for Confidence Intervals of OR[22]. Two-tailed Fisher's exact test was used to examine whether the 15059G>A heteroplasmy level is associated with EH. The significance of differences was defined at the 0.05 level of confidence.

RESULTS

The characteristics of study participants are presented in Table 1. Of 196 participants, 120 (61%) and 45 (23%) had clinically manifested EH and CHD, respectively. Compared to 76 normotensive subjects, hypertensive patients were significantly older [66.3 (SD 8.7) *vs* 62.1 (SD 9.0) years, *P* < 0.001], had higher systolic blood pressure [systolic blood pressure (SBP) 147 (SD 16) *vs* 127 (SD 13) mmHg, *P* < 0.001], elevated plasma triglycerides [127 (SD 55) *vs* 112 (SD 47) mg/dL, *P* < 0 .001], and had a more frequent family history of EH (45% *vs* 28%, *P* = 0.034). Compared to 151 CHD-free study participants, CHD patients exhibited no significant differences in clinical characteristics, except for age [69.9 (SD 8.6) *vs* 63.4 (SD 9.1) years, respectively, *P* < 0.001].

The distribution histogram of the 15059G>A heteroplasmy level in 196 study participants is presented in Figure 1. The heteroplasmy percentage ranged between 4% and 83%, with a median level of 31%. Except for three samples, the 15059G>A heteroplasmy level fitted the normal distribution (Shapiro-Wilk *W*-test; *P* = 0.18), with a mean level of 30.4% (SD 17.9%).

Clinical characteristics of patients were compared using a quartile scale of the 15059G>A heteroplasmy level distribution, with the first quartile being the lowest, and the fourth quartile being the highest. Between the upper and lower quartiles, significant differences were observed for patients' age, SBP, and triglycerides (TG) levels (Table 2). However, there was no significant correlation between age and the level of SBP in the given sample (*r* = 0.108, *P* = 0.2). On the other side, 15059G>A heteroplasmy level correlated both with age (*r* = 0.331, *P* < 0.001) and the presence of hypertension (*r* = 0.228, *P* = 0.002). Regression analysis revealed that the age explains 12% variability of 15059G>A heteroplasmy level, and hypertension independently explains more 5% variability.

Table 2 Antropometric, clinical and biochemical characteristics of study participants from the 1st and 2nd quartiles of distribution of 15059G>A heteroplasmy level *n* (%)

Characteristics	15059G>A heteroplasmy level[1]		*P* value
	Quartile 1 (*n* = 49)	Quartile 4 (*n* = 48)	
Age, yr	60.1 ± 7.1	66.2 ± 9.9	0.001
BMI, kg/m^2	26.4 ± 4.5	27.1 ± 5.1	0.41
SBP, mm/Hg	132 ± 18	143 ± 22	0.022
DBP, mm/Hg	83 ± 12	84 ± 12	0.50
Cholesterol, mg/dL	228 ± 42	243 ± 43	0.10
TG, mg/dL	112 ± 57	141 ± 61	0.021
HDL cholesterol, mg/dL	66 ± 14	68 ± 19	0.69
LDL cholesterol, mg/dL	140 ± 40	147 ± 44	0.44
EH	22 (45)	30 (63)	0.17
LVH	13 (27)	13 (27)	0.97

[1]Data are mean ± SD. BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; EH: Essential hypertension; LVH: Left ventricular hypertrophy; TG: Triglycerides; HDL: High density lipoproteins; LDL: Low density lipoproteins.

Table 3 Antropometric, clinical and biochemical characteristics of coronary heart disease patients from the 1st and 2nd quartiles of distribution of 15059G>A heteroplasmy level *n* (%)

Characteristics	15059G>A heteroplasmy level[1]		*P* value
	Quartile 1 (*n* = 11)	Quartile 4 (*n* = 10)	
Age, yr	63.2 ± 7.0	72.9 ± 8.7	0.011
BMI, kg/m^2	27.2 ± 6.2	26.1 ± 5.9	0.69
SBP, mmHg	129 ± 22	153 ± 22	0.03
DBP, mmHg	80 ± 12	85 ± 13	0.32
Cholesterol, mg/dL	224 ± 54	236 ± 49	0.59
TG, mg/dL	130 ± 77	121 ± 56	0.78
HDL cholesterol, mg/dL	62 ± 15	69 ± 15	0.39
LDL cholesterol, mg/dL	136 ± 47	143 ± 42	0.69
EH	7 (64)	7 (70)	0.86
LVH	4 (36)	4 (40)	0.68

[1]Data are mean ± SD. BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; EH: Essential hypertension; LVH: Left ventricular hypertrophy; TG: Triglycerides; HDL: High density lipoproteins; LDL: Low density lipoproteins.

In the subgroup of CHD patients, significant differences between the upper and lower quartiles of 15059G>A heteroplasmy level were found for patients' age and SBP (Table 3). In CHD-free patients, significant differences between the upper and lower quartiles of 15059G>A heteroplasmy level remained for patients' age and TG levels (Table 4). Thus, in comparison with study participants who had a lower level of the 15059G>A heteroplasmy, the presence of CHD in those with higher heteroplasmy positively correlated with increased SBP but not with elevated serum TG.

Using a two-step cluster analysis, the 15059G>A heteroplasmy level was classified as "low heteroplasmy" and "high heteroplasmy". In the "high heteroplasmy" group, study participants were found to have significantly higher age (*P* < 0.001) and EH prevalence then those from "low heteroplasmy" group (Table 5). These observations suggest an association between the level of 15059G>A heteroplasmy and EH. The 15059G>A heteroplasmy level exceeding 31% was associated with increased risk of EH [OR =2.76, *P* (Fisher) = 0.019] (Table 6). The relative risk accounted for 1.47 (95%CI: 1.15-1.84; *P* = 0.002).

The presence of CHD in study participants with high 15059G>A heteroplasmy seemed to further increase the risk for EH by -1.2-fold but this association did not reach statistical significance [OR = 3.31, *P* (Fisher) = 0.18], obviously due to insufficient sample size.

DISCUSSION

The pathophysiology of essential hypertension (EH) is insufficiently understood; in particular, the impact of mitochondrial DNA mutations on the development of EH is poorly investigated. We undertook this study in order to see whether the level of heteroplasmy for the 15059G>A mutation in the mitochondrial cytochrome *b* gene might be associated with EH. The 15059G>A heteroplasmy level in mtDNA in blood leukocytes obtained from 196 study participants, randomly selected from general population (120 of whom had EH), exceeding 31%, was found to be significantly associated with a higher risk of EH.

Compared to the nuclear DNA, mitochondria are known to lack the efficient DNA repair and protection

Table 4 Antropometric, clinical and biochemical characteristics of CHD-free study participants from the 1st and 2nd quartiles of distribution of 15059G>A heteroplasmy level *n* (%)

Characteristics	15059G>A heteroplasmy level[1]		*P* value
	Quartile 1 (*n* = 38)	Quartile 4 (*n* = 37)	
Age, yr	59.4 ± 7.2	64.7 ± 8.8	0.005
BMI, kg/m^2	26.0 ± 4.0	27.4 ± 5.3	0.2
SBP, mmHg	132 ± 14	141 ± 21	0.17
DBP, mmHg	84 ± 11	84 ± 10	0.99
Cholesterol, mg/dL	231 ± 41	246 ± 47	0.14
TG, mg/dL	106 ± 46	147 ± 61	0.003
HDL cholesterol, mg/dL	67 ± 14	67 ± 18	0.99
LDL cholesterol, mg/dL	143 ± 37	150 ± 42	0.44
EH	15 (39)	23 (62)	0.19
LVH	10 (26)	10 (27)	0.98

[1]Data are mean ± SD. BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; EH: Essential hypertension; LVH: Left ventricular hypertrophy; TG: Triglycerides; HDL: High density lipoproteins; LDL: Low density lipoproteins.

Table 5 Comparison of antropometric, clinical and biochemical characteristics of study participants from "low heteroplasmy" and "high heteroplasmy" groups *n* (%)

Characteristics	15059G>A heteroplasmy level[1]		*P* value
	Low (*n* = 99)	High (*n* = 97)	
Age, yr	60.2 ± 8.4	68.6 ± 8.4	< 0.001
BMI, kg/m^2	26.3 ± 4.1	27.0 ± 5.0	0.52
SBP, mmHg	133 ± 16	142 ± 18	0.024
DBP, mmHg	82 ± 11	84 ± 11	0.39
Cholesterol, mg/dL	232 ± 48	241 ± 48	0.27
TG, mg/dL	118 ± 56	135 ± 62	0.065
HDL cholesterol, mg/dL	67 ± 14	66 ± 15	0.92
LDL cholesterol, mg/dL	141 ± 42	148 ± 44	0.49
EH	51 (52)	69 (71)	0.033
LVH	20 (20)	33 (34)	0.1

[1]Data are mean ± SD. BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; EH: Essential hypertension; LVH: Left ventricular hypertrophy; TG: Triglycerides; HDL: High density lipoproteins; LDL: Low density lipoproteins.

Table 6 Association between the 15059G>A heteroplasmy level and essential hypertension prevalence

15059G>A heteroplasmy level	No hypertension, *n*	Hypertension, *n*	Odds ratio (95%CI)	*P* value
Low (< 31%)	51	51		
High (> 31%)	25	69	2.76 (1.45-5.27)	0.019
Total	76	120		

systems[23]. Because of the large number of mitochondrial genome copies exist within each cell, a ratio of mutated to wild-type mtDNA that represents significant determinant of phenotype[24]. In a number of studies, including the analysis of a large Han Chinese pedigree with suggestively maternally transmitted hypertension, the role of homoplasmic, inherited mtDNA mutations in etiology of familial, maternally inherited forms of hypertension (MIH) has been acknowledged[3,25-29]. It is known that all homoplasmic mtDNA mutations which are associated with MIH cause functional defects[3,25-29]. The 4435A>G mutation which is located at 3' end to the anticodon (cor-

responding to the conventional position 37 of tRNA^{Met}) affects the fidelity of codon recognition, structural formation, and stabilization of functional tRNAs[27]. The 4263A>G mutation resided at the processing site for the tRNA^{Ile} 5'-end precursor results in reduced efficiency of the tRNA^{Ile} precursor 5'-end cleavage catalyzed by RNase P[28]. The 4401A>G mutation that is situated at the spacer immediately to the 5' end of *tRNA^{Met}* and *tRNA^{Gln}* genes causes a reduction in the steady-state levels of both mitochondrial tRNAs[25]. The 4295 A>G mutation, which is located at immediately 3' end to the anticodon, corresponding to conventional position 37 of tRNA^{Ile}, has a

functional effect similar to that of the 4435A>G mutation[3]. The mitochondrial hypertension-associated ND1 T3308C mutation that locates in two nucleotides which are located to be adjacent to the 3' end of mitochondrial tRNA[Leu] UUR has been shown to result in a change of the H-strand polycistronic RNA precursor processing as well as in the destabilization of ND1 mRNA[26]. Despite a high penetrance, these mutations are thought to be infrequent as such mutations were identified in just a few families. In relation to the 4263A>G mutation. This mutation was identified only in one family and was not detected in 49 other families with matrilineal hypertension[28].

The fact that we observed higher levels of the 15059G>A mutation heteroplasmy in the elderly is not unexpected and is formally consistent with a theory of aging purports[30]. According to this theory, reactive oxygen species (ROS), normally produced by mitochondrial respiration, affect mitochondria by causing oxidative damage to the mitochondrion membrane components and cytosolic elements[30-34]. This eventually leads to dysfunction and further production of ROS and an increase in mtDNA mutation[30-34]. An increase in the ratio of mutated to wild-type mtDNA in mitochondrial genes encoding the respiratory chain subunits might thus lead to reduced steady-state levels of respiratory chain proteins and respiratory chain deficiency.

It has been reported that the nonsense 15059G>A mutation affecting the mitochondrial cytochrome b results in the formation of an inactive truncated product lacking a pair of ubiquinol/ubiquinone-binding sites that is likely to uncouple the mitochondrial respiratory chain[11]. Practically all homoplastic mutations found in the *MT-CYB* gene have been found to lead to deleterious effects associated with the respiratory chain complex III deficiency in muscles and clinical presentation involving exercise intolerance[31]. For example, truncating mutations 15242G>A and 15761G>A in MT-CYB, which, similar to 15059G>A, result in loss of the last N-terminal amino acids of cytochrome b, were heteroplasmic and abundant (87% and 73% respectively) in affected tissue (skeletal muscle) but were rare (0.7%) or absent in unaffected tissue (blood) of patients with symptoms of mitochondrial myopathy[32,33]. The 15059G>A homoplasmy might lead to pathological consequences, and the severity of clinical outcomes caused by this mutation should correlate with the percentage of the mutated mtDNA[30-34]. However, compared to blood cells, effects of truncating heteroplasmic mutations in *MT-CYB* are likely to be more harmful in tissues involved in active mitochondrial glucose oxidation and high energy consumption such as skeletal muscle[30-34]. The information about the dynamic nature of mitochondria has been outlined in large number original studies and reviews[35-43]. The dynamic nature of mitochondria is a concept that includes the movement of mitochondria along the cytoskeleton, the regulation of mitochondrial architecture (morphology and distribution), and connectivity mediated by tethering and fusion/

fission events[35]. This dynamic networks are essential in order to maintain normal mitochondrial functions and participate in key functional processes including development, metabolic efficiency, apoptosis, and aging[36].

One cannot exclude that a positive correlation between the high 15059G>A heteroplasmy and increased plasma TG levels in non-CHD patients, found in our study, may reflect an insufficient lipid intake in individuals with increased levels of the mutant allele 15059A. This may result from the reduced capacity of mutant mitochondria to metabolize fatty acids. Elevated plasma TG itself and a high TG/HDL-cholesterol ratio indicate an atherogenic lipid profile that predisposes to atherosclerosis and CHD[42,43]. Increased plasma TG were shown to predispose to CHD more strongly in the subsets of hypertensive patients[44,45]. This is in accordance with our observations that showed a high frequency of EH subjects in CHD-free patients who had the highest 15059G>A heteroplasmy levels.

There are no doubts that the present study has limitations. First of all, the sample size was rather small in order to detect significant differences in the level of 15059G>A heteroplasmy between EH-free individuals and EH patients. Secondly, the study participants with known EH were on treatment; and thirdly, although not all of them reached treatment goals, blood pressure levels were affected anyway. We have found an association of heteroplasmy both with the prevalence of EH and SBP, but not DBP. This difference was observed for the whole group of study participants; on the subdivision into CHD patients and CHD-free subjects, the difference in EH prevalence was not significant. The observed findings are not extremely big, and reliable statistical hints were applied: two-step cluster analysis was able to demonstrate an association of EH and G15059A heteroplasmy. It should also be noted that the sample was taken from ethnically heterogeneous population of Moscow inhabitants of senior and elderly ages. Therefore, at present there is insufficient evidence to interpolate the results of this study to other populations and age groups. Finally, the given study was cross-sectional, and the assessment of actual risk of EH due to the presence of a high level of 15059G>A heteroplasmy requires further prospective studies.

The precise mechanism by which 15059G>A mutation might affect in the development of EH is currently unknown. Earlier, Wang *et al*[28] showed that the homoplasmic 4263 A>G mutation in the *MT-T1* gene associated with familial MIH also involved in changes of codon AGA to AGG in *MT-ND1* gene coding for NADH dehydrogenase subunit 1 of the respiratory chain complex I. Functional assays have revealed that this mutation results in a marked reduction in substrate-dependent oxygen consumption reflective of complexes I, III, and IV by 70%-80% and increased ROS levels in the lymphoblastoid cell lines derived from mutation carriers[28]. The 15059G>A mutation associated with a deficiency in the production and activity of mitochondrial cytochrome

b may contribute to EH involving a similar mechanism associated with defects in oxidative phosphorylation, reduced mitochondrial-dependent oxygen consumption, and increased ROS generation[28]. Elevated ROS levels may induce oxidative stress, which represents a ubiquitous risk factor for a variety of vascular diseases including EH[46]. There is a strong possibility that ROS may directly alter vascular function as well as may be responsible for changes in vascular tone by several actions, for example, altering nitric oxide (NO) bioavailability or signaling[46]. It is well known that a reduced bioavailability of NO represents one of the key processes by which endothelial dysfunction is manifested in hypertension[46]. As a result, an imbalance of counteracting mechanisms, designed to maintain vascular homeostasis, occurs and this leads to vasoconstriction, impaired vascular function, and chronic hypertension[47].

It is well known that a variety of cell types, including endothelial cells, smooth muscle cells, pericytes and dendritic cells reside in the intact vascular wall[48,49]. However, it is currently unknown in which cell type(s) of the vessel wall the mitochondrial 15059G>A mutation may exert its effects associated with EH. A quantification of the 15059G>A heteroplasmy in different vascular cells in autopsy samples derived from patients with chronically manifested EH should help with unraveling this puzzle. It is worth to noting here that an ultrastructural examination of arterial cells in a variety of vascular pathologies allowed to reveal that marked alterations in the structural appearance of mitochondria occur[50-52]. These alterations include a reduction in number of mitochondrial cristae and changes in electron density of mitochondrial matrix[50-52]. However, the question whether the structural alterations of mitochondria might reflect the presence of mitochondrial mutation(s) in these organelles requires further investigation.

In conclusion, the present study provides the evidence of mtDNA 15059G>A mutation heteroplasmy association with EH.

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BRIEF ARTICLE

Mechanical breakdown and thrombolysis in subacute massive pulmonary embolism: A prospective trial

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Abstract

AIM: To assess role of combined modality of mechanical fragmentation and intralesional thrombolysis in patients with massive pulmonary embolism presenting subacutely.

METHODS: Eight of 70 patients presenting in tertiary care centre of North India with massive pulmonary embolism within 4 years had subacute presentation (symptom onset more than 2 wk). These patients were subjected to pulmonary angiography with intention to treat basis *via* mechanical breakdown and intra lesional thrombolysis. Mechanical breakdown of embolus was accomplished with 5-F multipurpose catheter to re-establish flow, followed by intralesional infusion of urokinase (4400 IU/kg over 10 min followed by 4400 IU/kg per hour over 24 h).

RESULTS: Eight patients, mean age 47.77 ± 12.20 years presented with subacute pulmonary embolism (mean duration of symptoms 2.4 wk). At presentation, mean heart rate, shock index, miller score and mean pulmonary pressures were 101.5 ± 15.2/min, 0.995 ± 0.156, 23.87 ± 3.76 and 37.62 ± 6.67 mmHg which reduced to 91.5 ± 12.2/min (P = 0.0325), 0.789 ± 0.139 (P = 0.0019), 5.87 ± 1.73 (P = 0.0000004) and 27.75 ± 8.66 mmHg (P = 0.0003) post procedurally. Mean BP improved from 80.00 ± 3.09 mmHg to 90.58 ± 9.13 mmHg (P = 0.0100) post procedurally. Minor complications in the form of local hematoma-minor hematoma in 1 (12.5%), and pseudoaneurysm (due to femoral artery puncture) in 1 (12.5 %) patient were seen. At 30 d and 6 mo follow up survival rate was 100% and all the patients were asymptomatic and in New York Heart Association class 1.

CONCLUSION: Combined modality of mechanical fragmentation and intralesional thrombolysis appears to be a promising alternative to high risk surgical procedures in patients with subacute massive pulmonary embolism.

Key words: Mechanical breakdown; Subacute; Thrombolysis; Thromboembolic; Intra pulmonary; Catheter directed

Core tip: Patients with massive pulmonary embolism presenting subacutely (> 2 wk) have high mortality and older clots in these patients may be less amenable to thrombolysis with increased likelihood of recurrence and thromboembolic pulmonary hypertension. Eight of 70 patients with massive pulmonary embolism presenting subacutely were subjected to mechanical breakdown and intra lesional thrombolysis with urokinase (4400 IU/kg over 10 min followed by 4400 IU/kg per hour over 24 h). Post procedurally, patients documented significant improvement in hemodynamic parameters with 100% survival at 30 d and 6 mo followup. This modality appears to be a promising alternative to high risk surgical procedures in such patients.

INTRODUCTION

Massive pulmonary embolism (PE) is a life-threatening condition with a high early mortality rate due to acute right ventricular failure and cardiogenic shock[1-3]. In addition to the rapid initiation of anticoagulation therapy with intravenous (IV) unfractionated heparin, potentially life-saving therapy includes thrombolysis, surgical embolectomy, or catheter thrombectomy. The traditional window period for thrombolysis in patients presenting with acute massive pulmonary embolism is two weeks[4]. In the present review we propose another subset of patients with massive pulmonary embolism presenting subacutely (> 2 wk) who appear to benefit maximally with mechanical breakdown and thrombolysis. These patients presenting subacutely have high mortality and may not respond to standard anticoagulant or thrombolytic therapy with high likelihood of recurrence and development of thromboembolic pulmonary hypertension[5].

MATERIALS AND METHODS

The present study has been conducted as an open non comparative prospective trial in the department of cardiology of our institution, a tertiary care centre in North India over a time span of four years (2007-2011). Approval for the same was obtained from ethical committee of the institute.

Eight of the 70 patients presenting with massive pulmonary embolism had subacute presentation with presenting symptoms of two to four weeks duration. Massive pulmonary embolism was defined as pulmonary arterial occlusion of more than 50% as confirmed by pulmonary angiographic score (Miller Index) and/or presence of hemodynamic impairment *i.e.*, mean pulmo-

nary artery pressure > 25 mmHg and/or shock index > 1. Shock index equals heart rate divided by systolic systemic blood pressure.

After obtaining bed side transthoracic echocardiography to confirm the suspicion of pulmonary embolism, to estimate pulmonary arterial pressure and to exclude right atrial or ventricular thrombi, patients underwent emergent right heart catheterization and pulmonary angiography. Patients who showed a rapid deterioration of their cardiopulmonary condition were put on oxygen supplementation with noninvasive pressure support or intubation. Positive inotropic and vasoactive support with catecholamines was supplemented according to the patient's hemodynamic condition prior to right heart catheterization and pulmonary angiography.

The criteria for inclusion were patients who received emergency catheter directed intervention due to angiographically confirmed subacute massive PE (miller index > 0.6) with involvement of central pulmonary artery and hemodynamic shock defined as shock index (*i.e.*, heart rate/systolic blood pressure) score of > 0.8. Patients with acute presentation (< 2 wk) and those who were hemodynamically stable (shock index < 0.8) and sub massive PE (Miller index of < 0.6 and central pulmonary artery not involved) were excluded. Echocardiographic criteria for diagnosis of subacute PE were right ventricular (RV) wall thickness > 5 mm; tricuspid regurgitant jet velocity > 3.7 m/s; the occurrence of both a dilated RV cavity with normal interventricular septal motion; an inspiratory collapse of the inferior vena cava[6].

Informed, written consent was obtained. Under local anaesthesia, 5F femoral sheath was introduced in femoral vein for procedure. Initially with 5F multipurpose catheter, right heart study was performed and pulmonary artery pressure recorded. Subsequently, 5F multipurpose (cordis) catheter was used to obtain pulmonary angiogram after injecting 10-15 mL non ionic contrast dye with hand injection (Figure 1A). After confirming the diagnostic criteria, mechanical fragmentation was initiated; 0.35" guide wire was passed; multiple rotatory movements were given in embolus. Further mechanical breakdown was done with 5F multipurpose catheter and pig tail catheter (Figure 1B). The pig tail was kept inside the large significant embolus for urokinase therapy.

After ensuring flow across pulmonary artery; urokinase in dosage of 4400 IU/Kg body weight was given intralesional over 10 min and 4400 IU/kg per hour for 24 h through pig tail catheter kept in pulmonary artery. Follow up angiogram was done 24 h post procedure (Figure 1C). Patient's blood pressure and heart rate were monitored every hour. Clinical follow up and simultaneous hemodynamic data was obtained. Shock index was calculated on hourly basis. Technical success was defined as reduction in baseline miller index following treatment. Clinical success was defined as stabilization of hemodynamic parameters, resolution of shock, complete weaning off of inotropic support and survival until discharge from the hospital.
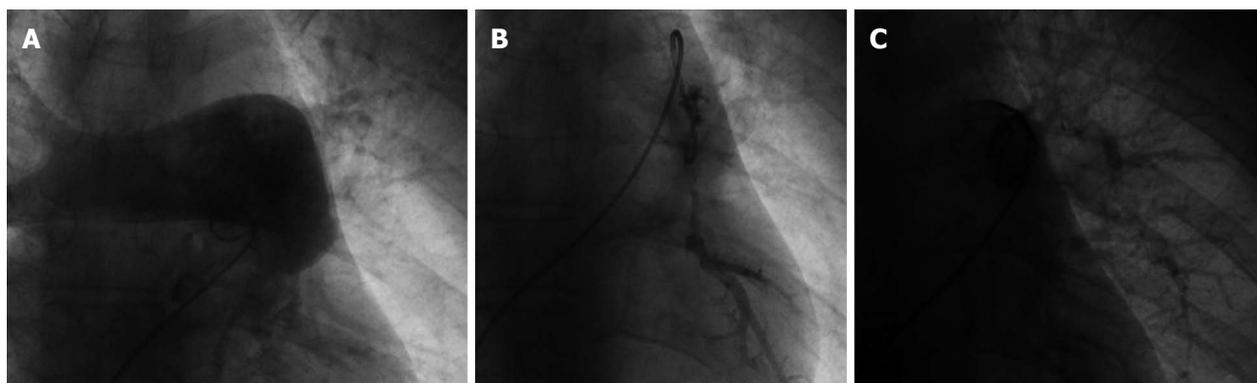
Figure 1 Pulmonary angiography. A: Total cut off of right pulmonary artery; B: Mechanical breakdown and intra pulmonary urokinase administration; C: Post procedural pulmonary angiography revealing restoration of pulmonary flow in right pulmonary artery and its branches.

Table 1 Clinical profile and hemodynamic data of patients with subacute pulmonary embolism at presentation

No.	Duration	PA involved	PAP		Mean PAP		Heart rate		BP		Mean BP		SI		Miller score	
			Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After
1	2 wk	RPA	88/26/48	58/18	46	30.66	84	72	100/70	130/70	80	90	0.84	0.55	22	3
2	15 d	Both PA	46/24/34	28/12	31.33	17.33	102	90	106/72	110/80	83.33	90	0.96	0.81	26	8
3	15 d	RPA occlusion	70/30	60/30	43.33	40	102	110	110/70	120/80	83.33	93.33	0.92	0.91	22	5
4	15 d	B/L PE (TB)	50/24	40/14	32.66	22.66	98	94	100/70	130/90	80	103.33	0.98	0.72	25	5
5	4 wk	B/L PTE	89/20	68/20	43	36	122	96	100/70	100/70	80	80	1.22	0.96	26	8
6	3 wk	Clot at MPA	50/70	28/10	30	16	102	90	100/70	130/90	80	103.33	1.02	0.69	25	7
7	2 wk	B/L main segment	78/25	50/24	42.66	32.66	122	102	100/70	110/70	80	83.33	1.22	0.92	28	6
8	2 wk	B/L	56/20	50/15	32	26.66	80	78	100/60	104/70	73.33	81.33	0.8	0.75	25	5

PA: Pulmonary artery; MPA: Main pulmonary artery; RPA: Right pulmonary artery; PAP: Pulmonary arterial pressure; Mean PAP: Mean pulmonary arterial pressure; BP: Blood pressure; Mean BP: Mean blood pressure; SI: Shock index; PE: Pulmonary embolism; B/L: Bilateral; PTE: Pulmonary thromboembolism; TB: Tuberculosis.

Miller index was used to calculate the angiographic scores for the degree of pulmonary embolism[7]. The Miller score is composed of an objective score for arterial obstruction and a subjectively determined score for reduction of peripheral perfusion. The right pulmonary artery is assigned 9 and the left is assigned 7 segmental arteries. Partial or complete occlusion of a segmental artery receives a point score of 1. Proximal pulmonary embolism is scored equal to the number of segmental arteries arising distally according to the anatomic subdivisions. The maximal score for obstruction is 16. Reduction of peripheral perfusion is scored by dividing each lung into upper, middle and lower zones and using a four point scale. Maximal score of reduced perfusion in both lungs is 18. The maximal Miller score for both lungs is 34. A Miller score of 17 or more indicates a greater than 50% obstruction of pulmonary vascular bed and forms an angiographic definition of a massive PE. The Miller index is Miller score divided by 34 (range 0.0 to 1.0)[8].

The Miller index was recorded in our study at the time of initial pulmonary angiogram and after 24 h of urokinase infusion. Major procedural complications were defined as: hemorrhage requiring transfusion, perforation of cardiopulmonary structures, anaphylaxis from contrast injection, arrhythmias with hemodynamic decompensation (blocks), worsening pulmonary artery hypertension,

hypoxia or shock and/or death during the procedure.

Minor complications were defined as transient catheter-induced arrhythmia, mild contrast reactions, catheter-related infection and small hematomas not requiring transfusion. Major hematoma was defined as hematoma requiring one or more blood transfusion. Minor hematoma was defined as spontaneously resolving hematoma not requiring blood transfusion. The data was analyzed using students t test for comparison of paired samples. A *P* value of < 0.05 was considered to be statistically significant.

RESULTS

Over the span of four years, 70 patients presented with massive pulmonary embolism of whom 8 (11.43%) presented subacutely (2-4 wk). There were 6 males and 2 females and the average age of patients was 47.77 ± 12.20 years. The average duration of symptoms prior to presentation in emergency was 2.4 wk (range: 2-4 wk). All the patients had tachycardia (heart rate > 100/min) and tachypnoea at the time of presentation (Table 1).

Catheter directed mechanical breakdown combined with intraembolus thrombolysis with urokinase was performed in all cases with subacute massive PE. There was a statistically highly significant fall in mean pulmonary

Table 2 Statistical analysis of hemodynamic parameters of patients

	PAP		HR		BP		SI		Miller score	
	Before	After	Before	After	Before	After	Before	After	Before	After
mean ± SD	37.62 ± 6.67	27.75 ± 8.66	101.5 ± 15.2	91.5 ± 12.2	80.00 ± 3.09	90.58 ± 9.13	0.995 ± 0.156	0.789 ± 0.139	23.87 ± 3.76	5.87 ± 10.73
mean ± SE	37.62 ± 2.4	27.75 ± 3.1	101.5 ± 5.4	91.5 ± 4.3	80.00 ± 1.1	90.58 ± 3.2	0.995 ± 0.055	0.789 ± 0.049	23.87 ± 1.3	5.87 ± 0.61
t	6.346		2.659		3.499		4.809		17.686	
P	0.0003		0.0325		0.0100		0.0019		0.000000	
d*f*	7 (highly significant)		7 (significant)		7 (significant)		7 (highly significant)		7 (highly significant)	

PAP: Pulmonary arterial pressure; BP: Blood pressure; SI: Shock index; HR: Heart ratio.
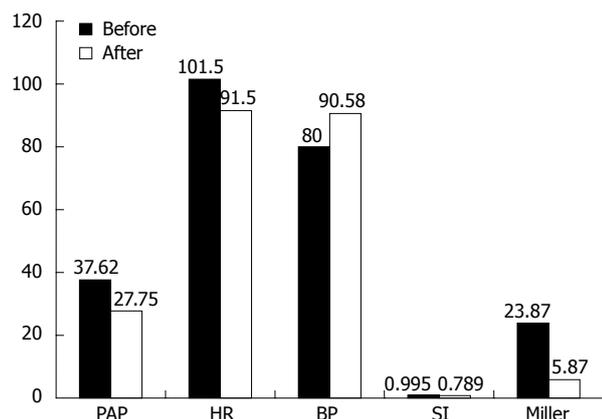
Figure 2 Hemodyamic parameters of 8 patients with subacute pulmonary embolism at presentation and 24 h post procedure. Highly significant improvement in mean pulmonary artery pressure (PAP), stroke index (SI) and millers index and significant improvement in heart rate (HR) and blood pressure (BP) post procedure.

artery pressure from 37.62 ± 6.67 to 27.75 ± 8.66 mmHg (*P* = 0.0003) 24 h post procedure, Mean systemic blood pressure rose significantly from 80.00 ± 3.09 mmHg to 90.58 ± 9.13 mmHg post procedure (*P* = 0.0100), The arterial oxygen saturation showed significant rise from base line levels 88.5% ± 2.8% to 98.6% ± 2.07% (*P* < 0.001). The mean heart rate prior to procedure was 101.5 ± 15.2 beats per minute. Twenty-four hours post procedure it showed a significant decrease to 91.5 ± 12.2 bpm (*P* = 0.0325). There was a highly significant fall in mean shock index from 0.995 ± 0.156 prior to procedure to 0.789 ± 0.139 (*P* = 0.0019) post procedurally. The 2 hourly change in shock index was also recorded. It was found that shock index continued to decrease up to 24 h with significant abrupt fall within first 8 h. The decrease in Miller score was highly significant when check pulmonary angiography was performed after 24 h [23.87 ± 3.76 to 5.87 ± 1.73 pre procedure (*P* = 0.0000004)] after 24 h (Table 2 and Figure 2).

Minor complications in the form of local hematomaminor hematoma in 1 (12.5%), and pseudoaneurysm (due to femoral artery puncture) in 1 (12.5%) patient were seen.

All the patients were discharged on oral anticoagulants. At 30 d and 6 mo of follow up survival rate was 100% and all the patients were asymptomatic and in New York Heart Association class 1.

DISCUSSION

Pulmonary embolic disease can present in many ways ranging from mild pleuritic pain to sudden fatal collapse. Since the presentation is so varied, classification of these patients into different clinical subgroups using the history, echocardiography and pulmonary angiographic findings is needed before possible differences in clinical course, response to treatment, and late prognosis can be considered[9].

Major pulmonary embolism occurring insidiously over several weeks (subacute massive pulmonary embolism) has a high mortality and may not respond well to standard anticoagulant or thrombolytic treatment[5]. Treated acute massive pulmonary embolism has a good long-term prognosis[3,10-12], and recurrent pulmonary embolism, poor resolution of pulmonary artery obstruction, and the development of pulmonary hypertension are extremely rare[13,14]. This is not surprising since most of these patients have welldefined and often temporary factors predisposing to embolism, the embolus is of recent formation, and it is susceptible to both therapeutic and natural lysis. In contrast, in subacute massive pulmonary embolism the predisposing factor is often unknown and potentially might continue to operate after initial treatment, causing recurrence of emboli. Furthermore, older clot, accumulated in the pulmonary circulation over a period of weeks, might be expected to lyse less easily. If so, thromboembolic pulmonary hypertension ought to be more likely to develop in subacute rather than in acute massive pulmonary embolism. Henceforth in this subset of patients presenting subacutely, mechanical breakdown and intrapulmonary thrombolysis might be more effective than usual intravenous thrombolysis or anticoagulation. In patients with subacute PE, with hypotension and borderline hemodynamics, systemic thrombolysis might not be possible making local thrombolysis with mechanical breakdown an attractive possibility. Moreover, mechanical breakdown might be less invasive and score over the traditional surgical approach (thromboendarterectomy) for these patients.

The thrombolytic employed in our study, urokinase (UK), specifically catalyzes the cleavage of the Arg-Val bond in plasminogen to form plasmin which breaks down the fibrin polymers of blood clots. Among the plasminogen activators, UK provides a superior alternative for the simple reasons of it being more potent

as compared to tissue-plasminogen activator and non-antigenic by virtue of its human origin unlike streptokinase[15]. Weitz *et al*[16] in a study found that UK has direct catalytic activity against fibrinogen and renders it less clottable by thrombin by releasing fibrinopeptide B, a potent chemoattractant. Henceforth they concluded that urokinase may participate in processes extending beyond fibrinolysis, a property which might especially be relevant in our patients with subacute PE and relatively older thrombus in process of organization. Moreover in a randomized controlled multicenter trial of recombinant tissue plasminogen activator[17] (rt-PA) versus urokinase in the treatment of acute pulmonary embolism, Goldhaber *et al*[3] found that despite rapid clot lysis at 2 h by rt-PA; at 24 h both drug regimens had produced equally good reperfusion. Also, in terms of cost and availability in developing nations UK might be a preferred option.

In our study significant reduction in shock index, Miller index and mean pulmonary artery pressure was recorded in 8 patients 24 h post procedure. The hemodynamic improvement recorded was maximum in first 8 h after procedure, though the improvement continued to occur over period of 24 h. At 6 mo of follow up survival rate was 100% and all the 8 patients were asymptomatic. The proposed mechanisms of early rapid hemodynamic improvements in our patients could be increased exposure of fibrin on clot surfaces caused by fragmentation accelerating the thrombolytic action. Also when there is total occlusion of pulmonary artery occlusion by an embolus, any fluid infused will theoretically make only evanescent contact with thrombus and be washed into the non occluded ipsilateral and contralateral pulmonary artery. After fragmentation, infused thrombolytics will have greater contact with the distal thrombus throughout the pulmonary arterial tree. This especially could be helpful in patients with subacute PE in whom older clot, accumulated in the pulmonary circulation over a period of weeks, might be expected to lyse less easily. Moreover 5F multipurpose and then pigtail catheter was employed in our study for mechanical fragmentation of this organizing old clot, which could be an added advantage[18-21].

The consensus statement recommends IV fibrinolytic therapy for patients with massive PE with low risk of bleeding complications (class IIa; level of evidence B) and for patients with submassive PE judged to have clinical evidence of adverse prognosis (new hemodynamic instability, worsening respiratory insufficiency, severe RV dysfunction, or major myocardial necrosis) and low risk of bleeding complications (class IIb; level of evidence C). Fragmentation of clot in the main or lobar pulmonary arteries to restore pulmonary perfusion alone or followed by local thrombolysis is an alternative for patients with massive PE and contraindications to fibrinolysis or who remain unstable after receiving fibrinolysis (class IIa; level of evidence C) and emergency surgical thrombectomy is unavailable or not preferred[22].

Patients presenting with systolic pulmonary artery pressures $\geq$ 50 mmHg at the time of acute pulmonary embolism are very likely to suffer from chronic thromboembolic pulmonary hypertension (CTEPH) even if the diagnosis has not been established earlier. Beyond 2 wk, patients with subacute massive pulmonary embolism are no longer candidates for traditional thrombolytic therapy and in presence of massive PE the modality of treatment for is pulmonary endarterectomy (PEA). When performed in experienced centers and in carefully selected patients, PEA in patients with CTEPH provides remarkable results with a periprocedural mortality rate of < 5% to 11%, nearly normalized hemodynamics, and substantial improvement in clinical symptoms[23-25]. In a comprehensive review of 1500 PEA procedures performed at a center in California, there was an almost linear relationship between preoperative pulmonary vascular resistance and perioperative mortality. In a series from France[25], the mortality rate was 4% when the preoperative pulmonary vascular resistance was < 900 dyne.s/cm^5 but increased to 10% in patients with resistances between 900 and 1200 dyne.s/cm^5 and to 20% for higher resistances[25]. Postoperative residual pulmonary hypertension has been identified as the most important predictor of death. In the largest series published thus far, patients with a postoperative pulmonary vascular resistance > 500 dyne.s/cm^5 had a mortality rate of 30.6% (15 of 49 patients), whereas those with a postoperative resistance < 500 dyne.s/cm^5 had a mortality rate of 0.9% (4 of 434 patients)[24]. Taken together, these data suggest that technical operability must not necessarily confer a benefit to every patient with CTEPH. Dartevelle *et al*[25] have suggested that patients should be selected for PEA only if a reduction in pulmonary vascular resistance by > 50% can be predicted.

The 8 patients with massive PE presenting sub acutely who underwent mechanical breakdown and thrombolysis had significant immediate, 30 d and 6 mo improvement in hemodynamics and clinical profile. This technique is less invasive, inexpensive with probably similar if not more mortality benefits than surgical procedure (100% survival at 6 mo in this study). Moreover, it may prevent development of CTEPH in patients presenting with subacute massive pulmonary embolism in whom window period for traditional systemic thrombolysis is over and thrombus is in process of organizing. Larger, multicenter and randomised trials should be performed to further study the role of mechanical breakdown and intrapulmonary thrombolysis in this subset of patients[26,27].

In conclusion, subacute massive pulmonary embolism has a high mortality and may not respond well to standard anticoagulant or thrombolytic treatment, as older clot accumulated in the pulmonary circulation over a period of weeks might be expected to lyse less easily. With survival rate of 100%, improved hemodynamics and clinical profile at 6 mo, in this subset of patients, mechanical breakdown followed by intrapulmonary thrombolysis appears to be an attractive option. Larger, multicenter and randomised trials with longer follow up are required to study the role of this less invasive and inexpensive

technique in terms of immediate mortality benefits and prevention of recurrent PE/progression to CTEPH.

COMMENTS

Background

In subacute massive pulmonary embolism older clots accumulated over period of weeks may be less amenable to thrombolysis with increased likelihood of recurrence and development of thromboembolic pulmonary hypertension. In these patients mechanical breakdown of thrombus followed by urokinase infusion may be cost-effective, minimally invasive, and potentially life-saving procedure by accelerating velocity of thrombolysis and increasing surface area of clot being lysed. Moreover, combined modality of mechanical fragmentation and intralesional thrombolysis appears to be a promising alternative to high risk surgical procedures in patients with subacute massive pulmonary embolism.

Research frontiers

Though not many areas are involved in studying the combined modality of mechanical breakdown and intralesional thrombolysis in patients with subacute massive pulmonary embolism; Kuo *et al*, based on a recent meta-analysis of 594 patients from 35 nonrandomized studies (six prospective with 94 patients, 29 retrospective with 500 patients) reported pooled clinical success rate from catheter based therapy to be 86.5% (95%CI: 82.2-90.2) in patients with massive pulmonary embolism. Moreover, pulmonary endarteractomy is being performed in patients with chronic thromboembolic pulmonary hypertension at specialized centers in California and France and have reported an almost linear relationship between preoperative pulmonary vascular resistance and perioperative mortality.

Innovations and breakthroughs

This is the first study conducted in the patients of subacute massive pulmonary embolism with mechanical breakdown and thrombolysis as a method of treatment. Prior studies on combined modality of mechanical breakdown and intralesional thrombolysis have involved patients with acute massive pulmonary embolism. Moreover at our tertiary care centre in North India, authors have reported excellent outcomes when this modality was employed in patients with failed thrombolysis as published in *JOIC*.

Applications

The study highlights the role of combined modality of mechanical breakdown and intralesional thrombolysis in patients with subacute massive pulmonary embolism. This modality is an attractive, less invasive alternative and might help to avoid surgical management (pulmonary endarterectomy) with excellent long term results in these patients. Moreover, in developing nations where cost is an important issue, this technique appears to be cost effective.

Terminology

Subacute pulmonary embolism: Patients with massive pulmonary embolism presenting subacutely *i.e.*, more than 2 wk from symptom onset. Massive pulmonary embolism: Defined as pulmonary arterial occlusion of more than 50% as confirmed by pulmonary angiographic score (miller index) and/or presence of hemodynamic impairment *i.e.*, mean pulmonary artery pressure > 25 mmHg and/or shock index > 1. Shock index equals heart rate divided by systolic systemic blood pressure.

Peer review

The paper is interesting and well written, my major comment refers to overall presentation of data: this paper is a report of 8 cases and should be presented as is.

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Heart stopping tick

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Abstract

Although Lyme carditis is relatively rare within 4-6 wk of exposure, it can uncommonly present as the first sign of disseminated Lyme disease. Here we present 17 year old boy who presented to the emergency department with chest discomfort and was later found to have complete atrioventricular block due to lyme carditis. He had uneventful recovery after empiric treatment with ceftriaxone. Our case highlights the importance of considering reversible causes of complete AV block since appropriate therapy can avoid the need for permanent pacemaker insertion.

Core tip: Seventeen-year man presented with acute chest discomfort following a tick bite 5 wk back. His hospital course was complicated with the development of first degree AV block which rapidly deteriorated to total AV block. Due to high grade of suspicion of lyme disease and positive lyme enzyme-linked immunosorbent assay and Lyme IgM (Western blotting), treatment with Ceftriaxone and doxycycline was started with complete remission. It is important to consider the reversible causes of complete AV block since appropriate therapy can avoid the need for permanent pacemaker insertion.

INTRODUCTION

The incidence of cardiac involvement in Lyme disease has been estimated to be 4%-10% in the adult population in the United States[1,2]. Lyme disease should be suspected as a cause of AV block in a patient living in an endemic area or a recent trip to an endemic area. Our case depicts the importance of starting treatment early awaiting serology in order to prevent serious morbidity and mortality. We also discuss the clinical presentation, diagnosis and treatment.

CASE REPORT

A 17-year-old man presented to the Emergency Department with acute chest discomfort for 1 d. Two weeks ago, he had developed a febrile illness with headache. At that time he was seen in outpatient clinic and was diagnosed with a viral illness and sent home with supportive care. Over the course of the week his fever resolved, however, he reported some nonspecific chest discomfort which became progressively worse. His social history was significant for living in woody area and being bitten by a tick 5 wk back. However, he denied being tested or treated for lyme disease, history of rash and joint pain. His family history was not significant for any heart disease or sudden cardiac death.

His physical examination was unremarkable with normal vital signs. Electrocardiography (ECG) revealed

Figure 1 Electrocardiography. A: AV-dissociation (Ⅲ degree heart block) in lead Ⅱ; B: first degree AV block in lead Ⅱ following regression of complete heart block 2 d after treatment.

sinus arrhythmia and first degree AV block with a ventricular rate of 97 beats/min. Echocardiogram showed no evidence of structural heart disease. His complete blood count, basic metabolic panel and urine analysis were all within normal limits. Streptococcal throat swab done 2 wk ago was normal. He was placed in observation unit and monitored on telemetry. In the subsequent 24 h he had first degree heart block initially followed by intermittent episodes of complete heart block with AV dissociation (Figure 1A). However he was hemodynamically stable during the whole time. ECG showed sinus tachycardia with an atrial rate in the range of 100 beats/min with complete heart block with narrow escape beat. Empirical treatment with Ⅳ Ceftriaxone 2 g once a day was started and patient was monitored on telemetry. Further tests done including peripheral smear, serological titers for ehrilichiosis, Rocky Mountain spotted fever, streptococcal throat culture blood and urine culture were all negative. Lyme enzyme-linked immunosorbent assay (ELISA) was positive. Lyme IgM through Western blotting was consistent with early infection. After 2 d he had regression of his complete heart block to first degree heart block (Figure 1B). He was discharged on doxycycline to be taken for total of 3 wk. He remains asymptomatic with normal ECG after 3 wk.

DISCUSSION

Lyme disease, caused by spirochaete Borrelia burgdorferi is transmitted by the bite of Ixodes tick. It constitutes one of the most common tickborne infections in the Northern hemisphere[3] and can involve multiple organs. The clinical manifestations of Lyme disease can be divided into 3 stages. Stage 1 is the acute illness, usually presenting 2 wk after the initial infection with erythema migrans with or without constitutional symptoms. Approximately two thirds of patients progress to stage 2 or dissemination phase, which can involve cardiac or neurologic abnormalities, weeks to months later[4]. Stage 3 or late chronic phase presents months to years later and classically involves the musculoskeletal system with destructive chronic arthritis, with the potential for late neurologic abnormalities[5].

Lyme carditis is defined as myocarditis, pancarditis or acute AV conduction disturbance, usually above the bundle of His[1,2]. It is usually clinically apparent 3 wk after

the onset of erythema migrans. Generally, cardiac complications occur in the early disseminated phase. Disturbance of AV nodal conduction is the most common cardiac manifestation of Lyme disease. This is usually self-limited and does not require permanent cardiac pacing[6]. Patients usually complain of dizziness, shortness of breath, substernal chest pain, and palpitations. ECG findings include T-wave flattening or inversions in the lateral and inferior leads[1]. Other conduction disturbances in Lyme disease with unfavourable prognosis are low escape rhythms with severe AV block, which are slow and of wide QRS pattern; transient lack of any escape rhythm, with brief asystoles; and fluctuating bundle branch block depicting either transient His-Purkinje involvement or intranodal AV block[7]. In addition, pericarditis. endocarditis, myocarditis, pericardial effusion, myocardial infarction, coronary artery aneurysm, QT interval prolongation, tachyarrhythmias and congestive heart failure have been reported[8]. Myopericarditis is rare but may lead to transient cardiomegaly or pericardial effusion with non-specific ST and T wave changes on the electrocardiogram[9].

Although the cause of the AV nodal dysfunction in Lyme carditis is unknown, autopsy findings of transmural lymphoplasmacytic infiltrate, necrosis of myocardial fibers, and spirochetes in the endomysial space of myocardial cells[4] have been reported. Direct dissemination of spirochetes into cardiac tissues, the inflammatory response associated with the infection, or both have also been implicated as the cause of AV nodal dysfunction[10].

The diagnosis of Lyme carditis can be challenging if it is the initial presentation of the disease process and patient does not remember having a tick bite. AV block may be the first and only sign of Lyme disease. ELISA testing is preferred for early diagnosis, but most patients are seropositive for IgG antibody only after several weeks. Immunofluorescence assays and Western blotting can also be used[11]. A two-step protocol for the evaluation of *Borrelia burgdorferi* antibodies in sera has been recommended in the United States[12]. The history of tick bite, positive lyme serology, negative serology for babesiosis, ehrlichiosis, in our case helped us to establish the cause of complete heart block.

More than 90% of the patients with Lyme carditis have complete recovery with only up to a third of the patients requiring temporary cardiac pacing[13]. Although

recovery may be delayed and late complications such as dilated cardiomyopathy may occur, the overall prognosis of Lyme carditis is very good. It has recently been demonstrated that, unless meningitis is present, oral doxycycline is as effective as parenterally administered ceftriaxone in preventing the late manifestations of Lyme disease[6]. Patients with minor cardiac involvement (first-degree AV block with PR interval < 0.3 s) could be treated orally with doxycycline, tetracycline, or amoxicillin. Doxycycline is the drug of choice as it is also effective for other tick borne diseases (babesiosis, ehrlichiosis, anaplasmosis) that could be co-transmitted and lead to a more serious outcome[14-16]. Patients with more severe conduction system disturbances (first-degree AV block with a PR interval > 0.3 s, second or third-degree AV block) should be hospitalised in a coronary care unit and treated with either intravenous antibiotics like ceftriaxone or high-dose penicillin G. Insertion of a temporary transvenous pacemaker may be required[5]. As in our case the degree of heart block can fluctuate rapidly from first degree to second degree to complete AV block very quickly in minutes to hours so careful observation is prudent. Treatment with an antibiotic can revert the AV block within 48 h of therapy[1].

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CASE REPORT

Impact of cardiac magnet resonance imaging on management of ventricular septal rupture after acute myocardial infarction

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Abstract

A 74-year-old man was admitted to the cardiac catheterization laboratory with acute myocardial infarction. After successful angioplasty and stent implantation into the right coronary artery, he developed cardiogenic shock the following day. Echocardiography showed ventricular septal rupture. Cardiac magnet resonance imaging (MRI) was performed on the critically ill patient and provided detailed information on size and localization of the ruptured septum by the use of fast MRI sequences. Moreover, the MRI revealed that the ventricular septal rupture was within the myocardial infarction area, which was substantially larger than the rupture. As the patient's condition worsened, he was intubated and

had intra-aortic balloon pump implanted, and extracorporeal membrane oxygenation was initiated. During the following days, the patient's situation improved, and surgical correction of the ventricular septal defect could successfully be performed. To the best of our knowledge, this case report is the first description of postinfarction ventricular septal rupture by the use of cardiac MRI in an intensive care patient with cardiogenic shock and subsequent successful surgical repair.

Core tip: We report on the case of a 74-year-old man who developed cardiogenic shock and ventricular septal rupture following an episode of acute myocardial infarction. Cardiac magnet resonance imaging (MRI) provided detailed information on size, localization and tissue integrity of the ruptured septum with respect to the myocardial infarction zone, followed by successful surgical repair of the defect. To the best of our knowledge, this case report is the first description of post-infarction ventricular septal rupture by the use of cardiac MRI in an intensive care patient with cardiogenic shock and subsequent successful surgical repair.

Gassenmaier T, Gorski A, Aleksic I, Deubner N, Weidemann F, Beer M. Impact of cardiac magnet resonance imaging on management of ventricular septal rupture after acute myocardial infarction. *World J Cardiol* 2013; 5(5): 151-153 Available from: URL: http://www.wjgnet.com/1949-8462/full/v5/i5/151.htm DOI: http://dx.doi.org/10.4330/wjc.v5.i5.151

INTRODUCTION

Ventricular septal rupture after myocardial infarction is

a rare complication but associated with a high mortality rate[1,2]. Cardiac magnetic resonance imaging (MRI) can provide detailed information on size and localization of the ruptured myocardium with respect to the myocardial infarction zone. We present a case of postinfarction ventricular septal rupture that was examined via cardiac MRI prior to surgical repair.

CASE REPORT

A 74-year-old man presented with a new episode of chest pain to his local general practitioner. Because the on-site electrocardiogram (ECG) showed ST-segment elevations, the patient was referred directly to our cardiac catheterization laboratory.

Physical examination showed hypotension but no dyspnea and no peripheral edema. The 12-lead ECG demonstrated sinus rhythm with a heart rate of 80/min, ST-segment elevation in the inferior leads (Ⅱ, Ⅲ, and aVF), and ST-segment depression in leads V3 to V5. Cardiac catheterization showed an occlusion of the right coronary artery, which was successfully recanalized by angioplasty and implantation of a bare metal stent. It was decided to postpone additional stenosis of the left main artery and the left circumflex artery for intervention in a later session. Afterwards, the patient was initially symptom-free with persistent hypotonic blood pressure. Echocardiography showed inferior wall akinesis with preserved left ventricular function and no aneurysm or ventricular septal defect.

The following day, the patient developed cardiogenic shock with supraventricular tachycardia. Echocardiography showed septal dyskinesia, a ventricular septal rupture basal inferoseptal of about 8 mm, and a left-to-right shunt of about 30%. Medical therapy included a daily dose of 100 mg aspirin, 75 mg clopidogrel, 40 mg simvastatin, and 2.5 mg fondaparinux. Norepinephrine was applied, adapted to the mean arterial blood pressure at a target pressure of 60-70 mmHg. Because the patient was stable at this mean arterial pressure of only 70 mmHg despite administration of norepinephrine and considering the high operative mortality, it was decided to first adopt a conservative approach and gain additional information in order to plan surgical repair.

Therefore, the next day, a cardiac MRI in short axis and four-chamber view was performed on a MAGNETOM® Avanto 1.5 Tesla (Siemens AG Sector Healthcare, Erlangen, Germany). The main questions were size and localization of MI, and whether the rupture was located inside nonviable tissue or surrounded by viable tissue for surgical closure of the myocardial defect. The MRI was performed under emergency conditions and administration of analgesics and sedatives. Heart rate during MRI was 105 beats/min. The ventricular septal rupture first diagnosed by echocardiography was confirmed by cardiac MRI. Although the patient was under mild sedation, there was severe movement of the patient, making fast MRI sequences necessary. Therefore, a fast HASTE 2D for morphologic analysis, a fast SSFP LGE (7 heart beats), and a SSFP cine (not shown) were performed and allowed sufficient discrimination between scar, edema, and movement artifacts. Using these sequences, the rupture previously described by echocardiography was detected in the posterior septum with a defect size of about 2 cm and a surrounding wall edema with a diameter of about 4 cm. Late Gadolinium enhancement (LGE) imaging with PSIR-SSFP revealed an infarction area reaching from basal septal inferior to apical inferolateral, which, with a size of 3-4 cm, was substantially larger than the ventricular septal defect. Furthermore, it showed that the defect was within the infarction area (Figure 1).

As the patient's condition worsened, he was intubated and had an intra-aortic balloon pump (IABP) implanted. Extracorporeal membrane oxygenation (ECMO) was initiated three days after the initial event, bridging the time until surgical repair in order to relieve secondary end organ failure, namely acute renal and liver failure.

During the following days, the patient's situation improved, and surgery could be performed on day six after the onset of the myocardial infarction based on the results of cardiac MRI, knowing the extent of the septal defect, and the fact that viable tissue existed, making surgical repair of the defect possible.

Three target vessels were revascularized utilizing the left internal thoracic artery and saphenous vein grafts. The left ventricle was longitudinally opened posteriorly and parallel to the septum. The excision of the fragile infarction zone resulted in a large septum defect. The myocardial edges were stabilized with Teflon felts in sandwich technique, and the defect was covered with a Dacron patch reaching from the posterior mitral annulus to the left ventricular apex. The anterolateral papillary muscle had to be refixed. The intraoperative echo showed a competent mitral valve and no residual shunt.

The ECMO-support was continued until the first and the IABP-support until the fourth postoperative day. After prolonged weaning, the patient was eventually discharged to rehabilitation in subjective well-being almost two months after the initial event. He is alive and in NYHA class Ⅱ six months after the operation.

DISCUSSION

In a patient with acute myocardial infarction, cardiac MRI was able to provide detailed information on size, localization, and tissue integrity of the ruptured septum with respect to the myocardial infarction zone.

Cardiac MRI has previously been utilized for characterization of ventricular septal defects, *e.g.*, following chest trauma[3,4]. Nonetheless, none of these patients had been in a critical condition when cardiac MRI was performed. To the best of our knowledge, this case report is the first description of post-infarction ventricular septal rupture by the use of cardiac MRI in an intensive care patient with cardiogenic shock and subsequent successful surgical repair.

Interestingly, previous implantation of coronary bare-metal or drug-eluting stents is not a contraindication for cardiac MRI since various studies have confirmed the safety of both in MRI at 3 Tesla or less[5,6]. Operative

Figure 1 Cardiac magnet resonance imaging revealed size and localization of the ruptured septum with respect to the myocardial infarction zone. Ventricular septal rupture in the infarction zone. A: Late Gadolinium enhancement in short axis view; B: On TRUFI localizer; C: On HASTE in short axis view; D: Long axis view. Solid arrows indicate ventricular septal rupture, dashed arrows indicate myocardial infarction zone.

mortality is about 54% if the surgical repair is performed within seven days from acute myocardial infarction[1]. Both timing and method of choice for correction of ventricular septal defect are still being debated[2], and percutaneous closure of ventricular septal defects is a new alternative to surgical repair[7]. However, to date, no studies have compared this new approach to surgical correction.

As postmyocardial infarction ventricular septal rupture is a severe and life-threatening complication, several limitations such as heart rate or circulatory stability exist for performing cardiac MRI in critically ill patients. Therefore, cardiac MRI may not be applicable in all patients, and its overall role in acute postinfarction ventricular septal defect can be considered marginal. However, when being performed, it can provide precise information on localization and size of the defect with respect to the myocardial infarction zone, which is of particular interest before surgical correction.

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Echocardiographic features of an atypical presentation of rapidly progressive cardiac amyloidosis

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INTRODUCTION

Amyloidosis is a disease that is characterised by the extracellular deposition of proteinaceous material (amyloid). A distinction has to be made between the (rare) AM-amyloidosis and the more common AL-amyloidosis on which this report will focus.

CASE REPORT

A 66-year old man was referred to our outpatient clinic for a second opinion because of slowly increasing shortness of breath on exertion, fatigue and reduced exercise tolerance over the previous year. His medical history included a non-ST segment elevation myocardial infarction with preserved left ventricular (LV) function and mild chronic obstructive pulmonary disease. Family history did not reveal any cardiovascular diseases or sudden cardiac death. On physical examination, blood pressure was 130/80 mmHg, a third heart sound was detected but there were no signs of heart failure. Electrocardiography showed microvoltages in the limb leads, a first degree atrio-ventricular block and Q-waves in the anterior and inferior wall leads. Laboratory tests revealed a ferriprive anaemia Hb 6.6; normal (N) = 8.5-11.0 mmol/L), elevated creatinine (150 μmol/L, N < 100 μmol/L), γ-glutamyltransferase (292 U/L, N < 35 E/L) and alkaline phosphatase (200 U/L, N < 120 E/L). Previous echocardiography 8 years before presentation demonstrated preserved LV function with ejection fraction (EF) of 64%, concentric LV hypertrophy with a width of the interventricular septum (IVS) and LV poste-

Abstract

We present the case of a 66 year old male who presented with dyspnea and reduced exercise tolerance. Echocardiography demonstrated impaired left ventricular (LV) function and restrictive diastolic function with pronounced concentric left ventricular hypertrophy (LVH) without a history of hypertension and no aortic valve stenosis. Differential diagnostics of concentric LVH are discussed in detail. In the current case, cardiac amyloidosis (AL) amyloidosis was diagnosed and confirmed by serum amyloid P (SAP) scintigraphy and abdominal fat aspiration biopsy. This case shows the rapid decline in clinical condition with progression of cardiac involvement of AL. As discussed in detail, cardiac involvement in AL-amyloidosis generally denotes a poor prognosis, regardless of the method of treatment.

Key words: Amyloidosis; Cardiac involvement; Echocardiography; Treatment; Prognosis
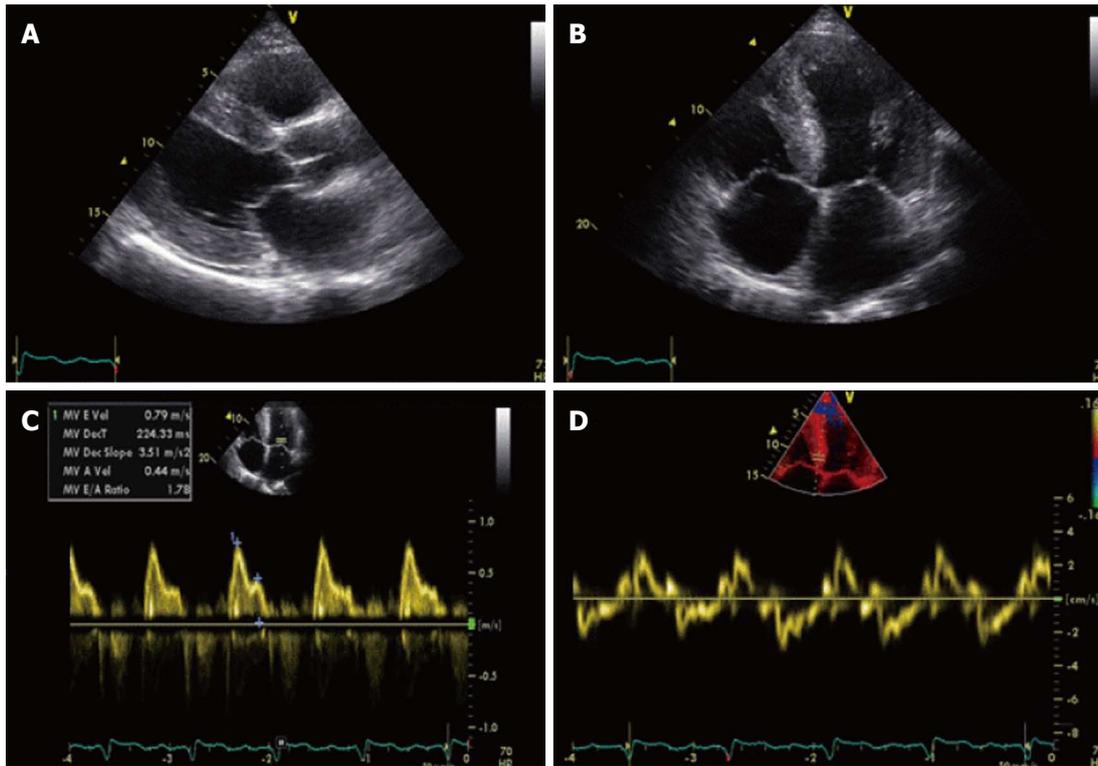
Figure 1 Transthoracic echocardiography images. A: Parasternal long axis view diastolic still frame demonstrating thickened myocardium with sparkling of the septum. IVSd 19 mm, LPWd 19 mm; B: Apical four chamber view end diastolic still frame demonstrating thickened myocardium and normal appearance of heart valves; C: PW Doppler measurement of MV inflow. MV E/A ratio 1.8; E-vel 0.80; A-vel 0.57; IVRT 77 ms; dt 224 ms; D: Tissue Doppler Imaging with PW Doppler measurement on medial annulus of MV with E' 3 cm/s E/E' ratio 26.2 confirming the diastolic dysfunction. S' 3.5 cm/s associated with impaired left ventricular function.
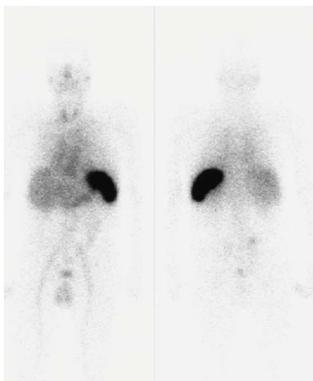
Figure 2 Serum amyloid P scintigraphy 24 h after intravenous injection of ^{123}I-serum amyloid P. Serum amyloid P (SAP) scintigraphy 24 h after intravenous injection of ^{123}I-SAP. Total body uptake from the side (left image) and back (right image). Normal blood pool activity is present in organs such as liver, heart, and kidneys. Intense uptake is present in the spleen.

rior wall of 18 and 12 mm, respectively. Diastolic function was normal (E/A ratio 0.80; Evel 0.49 m/s; Avel 0.61 m/s) with a normal right ventricular systolic pressure (RVSP). Subsequent echocardiograms demonstrated a progressive decline in EF, progressive diastolic dysfunction to grade Ⅱ and pronounced concentric LV hypertrophy (LVH) without sparkling. During follow-up the patient remained asymptomatic until the year before his appearance at our centre. At presentation, echocardiography showed a moderately impaired LV function (EF 34%) with a sparkling IVS of 19 mm diameter. Diastolic dysfunction had worsened to grade Ⅲ with E/A ratio of 1.8 [E-vel 0.80 A-vel 0.57; S' 3.5 cm/s (N > 5 cm/s); E/E' ratio 26.2 (N < 15)] with an increased RVSP of 41 mmHg with moderate tricuspid insufficiency (Figure 1). Values of S' and E/E' reflected the poor systolic function and raised filling pressures in our patient. The decline in ejection fraction and pronounced concentric LVH without a history of hypertension or aortic valve stenosis on echocardiography with new complaints of exertional dyspnea were reasons for further investigation to rule out or demonstrate other causes of concentric LVH such as amyloidosis, Fabry's disease *etc*.[1,2]. Blood tests showed no para-proteinemia, but free light chains were found in urine (0.06 g/L) and serum samples. Based on the latter finding AL-amyloidosis was suspected[1,2]. This diagnosis was confirmed by serum amyloid P (SAP) scintigraphy (Figure 2) and abdominal fat aspiration biopsy (Figure 3). Bone biopsy revealed mild clonal plasma cell dyscrasia with excess of light chains and total plasma cells of 5%. Cardiac magnetic resonance imaging (CMR) confirmed cardiac involvement with areas of fibrosis in the inferolateral wall[1,2]. Upon diagnosis, chemotherapy with Melfalan, Thalidomide and prednisolone was initiated according to the Palumbo-schedule[3,4]. Chemotherapy did not have any effect on the clinical condition and nine months after the diagnosis of cardiac amyloidosis, the patient died of heart failure.
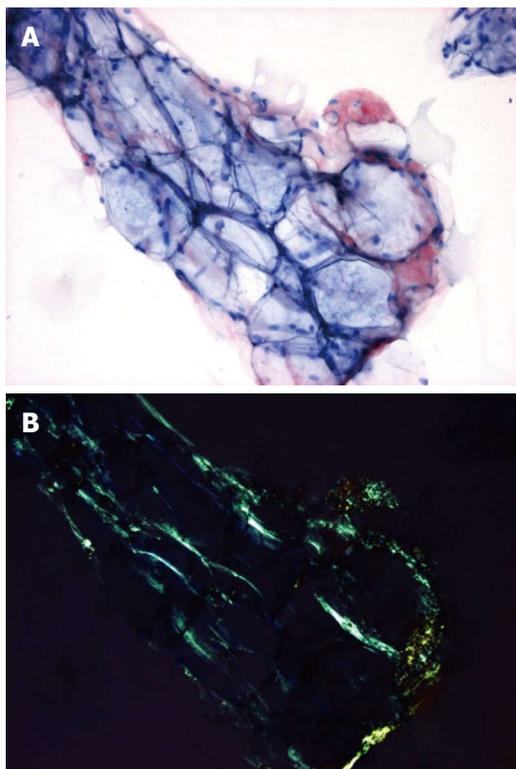
Figure 3 Abdominal subcutaneous fat aspirate of the patient stained with Congo red, magnification x 30. Amyloid score 3+ (10%-60% of the surface is occupied by amyloid). A: When viewed in normal light, amyloid is stained red; B:The same specimen viewed in polarised light: amyloid shows apple-green birefringence.

DISCUSSION

In AL-amyloidosis the amyloid is produced by clonal light chains made by disrupted plasma cells (plasma cell dyscrasia). The extracellular deposition of AL-amyloid can occur in all tissues and organs, but predominates in heart, liver and kidney[3-5]. Cardiac involvement can vary from being absent to severe and is present in approximately 50% of cases. In half of these cases congestive heart failure (CHF) is the presenting symptom and when CHF is present, median survival is less than six months in untreated patients[3-5]. When the heart is involved, amyloid infiltration is generalised: ventricular and atrial myocardium, vasculature, conduction system and valves are equally affected. In 95% of patients with cardiac amyloidosis other organs or tissues are also affected, so signs or symptoms of extra-cardiac manifestations should not be ignored[3-5].

Electrocardiography usually shows low voltages in the limb leads and poor R wave progression in the precordial leads. Due to amyloid infiltration in the conduction system, several conduction disorders and arrhythmias can occur. Reduced myocardial relaxation is an early echocardiographic finding that usually progresses into restrictive patterns. There may also be left ventricular hypertrophy, granular sparkling, atrial dilation, valvular thickening and pericardial effusion[3-5].

The diagnosis of systemic amyloidosis can be confirmed by SAP scintigraphy and Congo red staining of abdominal fat aspiration biopsy[3-5]. Immunohistochemical staining determines the kind of protein from which the amyloid originates. When abdominal fat aspiration biopsy does not result in diagnosis, endomyocardial biopsy should be considered. The latter has a sensitivity of near 100%. Plasma cell dyscrasia in a bone marrow biopsy and free lambda or kappa (less common) light chains in serum and/or urine samples then confirm the diagnosis AL-amyloidosis[3-5].

This case shows the rapid decline in clinical condition with the progression of cardiac involvement in AL-amyloidosis[5]. Regardless of the method of treatment, cardiac involvement in AL-amyloidosis generally denotes a poor prognosis,. As in our patient, the median survival rate from the onset of symptoms of congestive heart failure is only 6 mo [6].

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Atrial fibrillation in obstructive sleep apnea

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Abstract

Atrial fibrillation (AF) is a common arrhythmia with rising incidence. Obstructive sleep apnea (OSA) is prevalent among patients with AF. This observation has prompted significant research in understanding the relationship between OSA and AF. Multiple studies support a role of OSA in the initiation and progression of AF. This association has been independent of obesity, body mass index and hypertension. Instability of autonomic tone and wide swings in intrathoracic pressure are seen in OSA. These have been mechanistically linked to initiation of AF in OSA patients by lowering atrial effective refractory period, promoting pulmonary vein discharges and atrial dilation. OSA not only promotes initiation of AF but also makes management of AF difficult. Drug therapy and electrical cardioversion for AF are less successful in presence of OSA. There has been higher rate of early and overall recurrence after catheter ablation of AF in patients with OSA. Treatment of OSA with continuous positive airway pressure has been shown to improve control of AF. However, additional studies are needed to establish a stronger relationship between OSA treatment and success of AF therapies. There should be heightened suspicion of OSA in patients with AF. There is a need for guidelines to screen for OSA as a part of AF management.

Core tip: Obstructive sleep apnea (OSA) has been linked with the initiation and progression of atrial fibrillation (AF). Patients with OSA have lower success with therapies for AF. Continuous positive airway pressure has been shown to be effective in treatment of OSA and there is some evidence suggesting its role in improving AF control in patients with OSA. In this article, we review and discuss the available data explaining the potential pathophysiological mechanisms linking OSA and AF as well as the therapeutic and prognostic implications of the presence of OSA in AF patients.

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INTRODUCTION

Atrial fibrillation (AF) is the most common cardiac arrhythmia and its prevalence has increased significantly in past three decades[1-3]. Hypertension, thyroid disease, coronary artery disease, cardiomyopathy and structural heart diseases are conventionally associated with high risk of AF[2,3]. Recently, a high prevalence of obstructive sleep apnea (OSA) has been noted among patients with AF indicating that OSA might be contributing to initiation and progression of AF[4,5].

OSA is a relatively common disorder and the prevalence of sleep apnea has been noted to be as high as 16% among men and 5% among women between 30 and 65

years of age[6]. Five percent of adults have undiagnosed sleep apnea[7]. OSA is even more common among patients with cardiovascular disorders and is associated with multiple autonomic and metabolic derangements. Sleep apnea has been implicated in pathogenesis of multiple cardiovascular disorders including arrhythmias, hypertension, heart failure and stroke[4-9]. Its modifiable nature and high prevalence makes it a potential therapeutic target. In this article, we review and discuss the available data explaining the potential pathophysiological mechanisms linking OSA and AF, as well as the therapeutic and prognostic implications of the presence of OSA in AF patients.

OSA is characterized by episodes of nocturnal hypoxemia secondary to diminished and/or interrupted airflow during sleep. Apneic episodes are defined by complete cessation of airflow for $\geq$ 10 s, while hypopnea episodes are characterized by either $\geq$ 30% reduction in airflow and $\geq$ 4% reduction in blood oxygen saturation from baseline for at least 10 s or 50% reduction in air flow and $\geq$ 3% reduction in oxygen saturation from baseline for at least 10 s or arousal from sleep. It can be categorized as central (absence of inspiratory effort), obstructive (intermittent airway obstruction with preserved/increased respiratory efforts) or mixed sleep apnea (combination of central and OSA). Several easy to use questionnaires have been developed to screen patients for sleep apnea including the Epworth Sleepiness scale[10], the Berlin Questionnaire[11], the STOP and STOP-BANG Questionnaires[12]. Overnight polysomnography is the gold standard test to diagnose and stratify sleep apnea based on the apnea/hypopnea index (AHI)[13,14]. OSA is defined as five or more episodes of apnea and hypopnea per hour of sleep (AHI $\geq$ 5) and can be classified as mild (AHI 5-15), moderate (AHI 16-30), or severe (AHI > 30)[13,15].

EPIDEMIOLOGY

Obesity, OSA and AF have a multifaceted relationship. Obesity increases risk of OSA and is also an independent risk factor for development of AF. The risk of AF increases by 4% for every one-unit increase in body mass index (BMI)[16-18]. This association is stronger for patients aged < 65 years[19]. Sleep apnea (both central and OSA) is more common in patients with congestive heart failure (CHF), and CHF itself is associated with high risk of AF[20-23]. Hence, several confounders must be taken into consideration while analyzing the multidimensional relationship between AF and OSA.

AF IN SLEEP APNEA PATIENTS

The first insight into a potential link between OSA and AF came from an observational study which reported episodes of AF seen on ambulatory electrocardiographic monitoring among 3% of subjects with OSA[24]. This association was supported by the complete resolution of paroxysmal AF episodes among those who were successfully treated for OSA[24]. Higher prevalence of cardiac arrhythmias among patients with OSA has been confirmed in subsequent studies[25]. The Sleep Heart Health Study

reported four times higher prevalence of AF in patients with sleep apnea *vs* those without sleep apnea (4.8% *vs* 0.9%)[26]. High frequency paroxysmal AF and persistent AF are both associated with presence of OSA[27]. The episodes of AF and nonsustained ventricular tachycardia have been noted to be significantly higher during the night after apneic episodes, an observation that further supports the temporal association between AF and sleep apnea[28]. Sleep apnea is also an independent predictor for occurrence of postoperative AF among coronary artery bypass surgery patients. In a study by Mooe *et al*[29], the rate of postoperative AF was significantly higher (32% *vs* 18%) among patients with OSA (AHI $\geq$ 5) compared to those without OSA.

SLEEP APNEA IN AF PATIENTS

Obstructive sleep apnea is more prevalent among patients with AF than the general population. Gami *et al*[4] reported significantly higher prevalence (49% *vs* 32%) and a strong association (adjusted odds ratio of 2.19) between sleep apnea and AF in patients undergoing electrical cardioversion as compared patients without AF. This association was independent of age, sex, body mass index, hypertension and heart failure. High rates of sleep apnea are seen among patients with chronic persistent and permanent AF even after matching for age, sex and other relevant co morbid conditions[5]. The association between AF and sleep apnea may be underestimated, as most studies have reported a strong association between AF and sleep apnea despite using higher (AHI > 15) than standard (AHI > 5) threshold to diagnose OSA.

The association between AF and sleep apnea could be attributed to a higher prevalence of traditional risk factors for AF (especially obesity and hypertension) among OSA patients[30,31]. However, the association between AF and sleep apnea is found to be stronger than that of sleep apnea and traditional risk factors for AF[4]. OSA is more prevalent even among younger AF patients with normal left ventricular function[27]. This association remains statistically significant even after adjustment for covariates including hypertension, body mass index, and neck circumference. These findings highlight OSA as an independent risk factor for AF.

PATHOPHYSIOLOGY

The suspected role of OSA in the pathogenesis of AF is based on sound physiological observations (Figure 1). OSA is characterized by repeated episodes of nocturnal hypoxemia. Intermittent hypoxemia causes mitochondrial dysfunction by altering redox state of cytochrome oxidase and results in repetitive oxidative stress[32,33]. Hypoxemic episodes induce transcription factors like nuclear factor kappa-B leading to increased production of inflammatory cytokines such as tumor necrosis factor α and interleukin 6. These cytokines, in concert with increased oxidative stress, lead to endothelial dysfunction, insulin resistance, hypercoagulability, and adverse myocar-
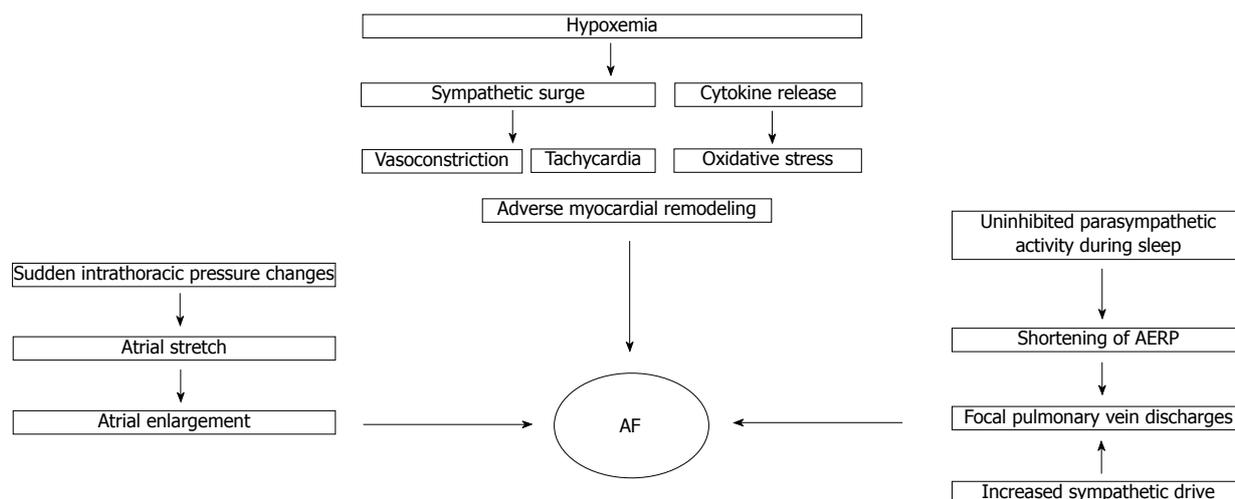
Figure 1 Schematic illustration of multiple pathophysiological mechanisms contributing to atrial fibrillation in obstructive sleep apnea. AERP: Atrial effective refractory period; AF: Atrial fibrillation.

dial remodeling[34-37].

Hypoxemic episodes induce sympathetic surges leading to vasoconstriction, hypertension and tachycardia[38,39], and ultimately increased myocardial oxygen demand. This increased stress on myocardium results in adverse myocardial remodeling, which is a substrate for cardiac arrhythmias[40,41].

Autonomic tone instability seen in OSA also contributes to pathogenesis of AF. Increases in parasympathetic and sympathetic tone are known to trigger AF[42]. During normal sleep afferent inputs from stretch receptors in lung tissue inhibit the paroxysmal parasympathetic discharges that occur during rapid eye movement sleep[43,44]. These receptors are activated due to lung expansion during normal ventilation. However, in apneic patients this response is attenuated due to pauses in breathing. Uninhibited paroxysmal parasympathetic discharges lead to marked paroxysmal bradycardia. Bradycardia is associated with decrease in atrial effective refractory period (AERP). The reduction in AERP promotes rapid electrical firing from atrial tissue in pulmonary vein ostia, thereby leading to AF[42,45,46]. Hypoxemia and hypercapnea associated with apneic episodes promote chronically heightened sympathetic activity[38,47,48]. Heightened sympathetic tone induces focal discharges from pulmonary veins, which have high concentration of adrenergic and vagal nerve endings[49-51]. Hypoxemia may exert an effect on cardiac arrhythmias that is independent and additive of sleep apnea. This hypothesis is supported by increased rates of ventricular ectopy among chronic obstructive pulmonary disease patients who have nocturnal hypoxemia without sleep apnea[52-54].

OSA is also associated with sudden and frequent changes in intrathoracic pressures, which are transmitted to thin walled atria and cause atrial stretch. Repetitive stretch may result in atrial enlargement and structural changes in pulmonary vein ostia, predisposing to development of AF[42,45].

EFFECT OF OSA ON TREATMENT OF AF

AF patients with OSA respond poorly to both pharmacological and non-pharmacological therapy (cardioversion or ablation) with high rate of recurrence[55-58].

Pharmacotherapy

The rate of non-response to pharmacologic treatment increases with the increase in OSA severity[56]. Apneic patients have higher awake and nocturnal sympathetic tone, which may explain the suboptimal response to rate control strategy in AF patients with OSA[38]. Autonomic tone instability contributes to the genesis and propagation of AF in OSA. Acetylcholine-dependent potassium channels (I_{KACh}) are thought to be one of the most relevant components by which vagal tone induces AERP shortening in the atrium[59]. Antiarrhythmic drugs such as amiodarone, which block acetylcholine-dependent activation of I_{KACh}, along with beta-receptors and other potassium channels, could be superior in maintaining sinus rhythm over those antiarrhythmic drugs that do not block I_{KACh}. However, studies showing superiority of amiodarone did not specifically address AF patients with sleep apnea. The clinical efficacy of such pharmacotherapy in patients with OSA needs to be investigated in future clinical trials[60].

Direct current cardioversion

Kanagala *et al*[58] followed 118 patients after direct current cardioversion (for AF/atrial flutter) and found that the presence of polysomnography-established OSA was associated with significantly higher rates of recurrent AF. Increased risk among patients with OSA was independent of age, sex, body mass index, hypertension, diabetes, echocardiographic parameters or antiarrhythmic therapy. Patients with OSA who were treated appropriately with continuous positive airway pressure (CPAP) had 82% lower rate of recurrence than patients who did not received treatment[58].

AF ablation

The presence of OSA is associated with a high rate of recurrent AF after ablation[61]. In a retrospective study, Jongnarangsin *et al*[62] reported presence of OSA as a strong predictor of AF recurrence after radiofrequency catheter ablation. This risk was independent of atrial size and body mass index. Chilukuri *et al*[63] reported high rates of recurrence after catheter ablation among patients who were classified as high risk for OSA on Berlin questionnaire. Tang *et al*[64] classified 178 patients into high risk and low risk for OSA depending on Berlin questionnaire and prospectively followed them for 11 mo after pulmonary vein isolation. They reported no statistically significant difference in the rate of AF recurrence among patients with different risk profiles for OSA at the end of the follow up period. These patients were classified in different risk categories for OSA based on Berlin questionnaire, but no confirmatory test was performed to establish diagnosis of OSA. Thus, misclassification bias cannot be excluded. Matiello *et al*[65] overcame this limitation; They prospectively followed 174 patients after circumferential pulmonary vein isolation and classified them as low or high risk for OSA on Berlin questionnaire. High-risk patients underwent a sleep study to diagnose OSA and classify its severity. OSA was an independent predictor for AF recurrence after ablation, and risk of recurrence increased with increasing severity of OSA. Naruse *et al*[66] prospectively studied 153 patients who underwent pulmonary vein isolation for drug refractory AF. The standard overnight polysomnographic evaluation was performed one week after ablation, and the total duration and the number of central or OSA or hypopnea episodes were examined. Of 153 patients, 116 patients were identified as having OSA. Eighty-two patients with OSA underwent CPAP therapy as 34 patients with OSA refused CPAP therapy. Data regarding the use of CPAP and recurrences of AF were obtained in all patients. During a mean follow-up period of 18.8 ± 10.3 mo, 51 (33%) patients experienced AF recurrences after ablation. A Cox regression analysis revealed that the left atrial volume (HR = 1.11; 95%CI: 1.01-1.23; $P < 0.05$), concomitant OSA (HR = 2.61; 95%CI: 1.12-6.09; $P < 0.05$), and usage of CPAP therapy (HR = 0.41; 95%CI: 0.22-0.76; $P < 0.01$) were associated with AF recurrences during the follow-up period.

Available evidence supports the role of effective OSA therapy in reducing the risk of AF recurrence[24,58]. The exact mechanism by which CPAP use improves success of AF therapies in OSA is not clear. The use of the CPAP may reduce the structural and electrical remodeling of the atria due to OSA, resulting in a lower AF recurrence rate. Serum markers of oxidative stress and free radical production predict AF recurrences after AF ablation[67]. CPAP therapy has been known to decrease oxidative stress in OSA[68,69]. An improvement in the oxidative stress by using CPAP could help attenuate the risk of recurrent AF.

However, currently available data is not robust, and supporting studies have small sample size and several limitations[24,58,62,66]. CPAP therapy is known to be associated with a reduction in preload. Its use in patients with systolic heart failure and AF may compromise diastolic ventricle filling, which is already compromised due to loss of organized atrial contraction[70]. Hence careful patient selection is warranted. Further data from prospective randomized control trials is needed before advocating widespread use of CPAP in patients with systolic heart failure and AF.

CONCLUSION

Several observational studies have indicated a high prevalence of OSA among patients with AF. Concomitant OSA is associated with poor response to treatment for AF. Limited data indicate that treatment of OSA results in a lower rate of AF recurrence. Patients with AF may be screened for OSA with a simple tool such as Berlin questionnaire, and high-risk patients should be considered for formal sleep study. The educational, behavioral and therapeutic interventions for sleep apnea should be offered to AF patients with OSA.

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REVIEW

Peroxisome-proliferator-activated receptors regulate redox signaling in the cardiovascular system

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Abstract

Peroxisome-proliferator-activated receptors (PPARs) comprise three subtypes (PPARα, δ and γ) to form a nuclear receptor superfamily. PPARs act as key transcriptional regulators of lipid metabolism, mitochondrial biogenesis, and anti-oxidant defense. While their roles in regulating lipid metabolism have been well established, the role of PPARs in regulating redox activity remains incompletely understood. Since redox activity is an integral part of oxidative metabolism, it is not surprising that changes in PPAR signaling in a specific cell or tissue will lead to alteration of redox state. The effects of PPAR signaling are directly related to PPAR expression, protein activities and PPAR interactions with their coregulators. The three subtypes of PPARs regulate cellular lipid and energy metabolism in most tissues in the body with overlapping and preferential effects on different metabolic steps depending on a specific tissue. Adding to the complexity, specific ligands of each PPAR subtype may also display different potencies and specificities of their role on regulating the redox pathways. Moreover, the intensity and extension of redox regulation by each PPAR subtype are varied depending on different tissues and cell types. Both beneficial and adverse effects of PPAR ligands against cardiovascular disorders have been extensively studied by many groups. The purpose of the review is to summarize the effects of each PPAR on regulating redox and the underlying mechanisms, as well as to discuss the implications in the cardiovascular system.

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Core tip: Numerous studies have shown that peroxisome-proliferator-activated receptors (PPARs) ligands can modulate antioxidants *via* various mechanisms. Importantly, direct transcriptional regulation of antioxidant genes, such as *vthioredoxin-1*, *glutathione peroxidase 3*, *sestrin-1*, *catalase*, *superoxide dismutase* (*SOD*)*1*, *SOD2*, and *heme oxygenase*, is established by identifying functional PPAR responsive element in promoter regions of the above genes. This review summarizes how these important antioxidant genes are regulated by each subtype of PPARs in response to oxidative stress in the cardiovascular system and how oxidative stress affects PPAR function, as well as the biological implications in the cardiovascular system.

INTRODUCTION

Mitochondria are the powerhouse for cells and are vulner-

able targets of oxidative damage. The maintenance of redox homeostasis is critical for normal cellular function. The utilization of oxygen for ATP generation in the mitochondria accompanies the production of reactive oxygen species (ROS) and reactive nitrogen species (RNS) from electron transport chain complex Ⅰ, Ⅱ and Ⅲ[1]. Mitochondrial ROS further triggers ROS production from other sources, such as Ang Ⅱ, hyperglycemia, hypoxia, oxidized low-density lipoprotein, and nicotinamide adenine dinucleotide phosphate (NADPH) oxidases (NOXs)[2,3]. NOXs are membrane-bound enzyme complexes that generate superoxide by transferring electrons from intracellular NADPH across the membrane and coupling these to molecular oxygen[4]. In general, the balance between ROS formation and endogenous antioxidant defenses enable redox homeostasis in cells. Under normal conditions, ROS and RNS also serve as signaling molecules[5]. Oxidative stress occurs when the balance between ROS/RNS production and the endogenous antioxidant defense. Oxidative stress is associated with major pathological development of cardiovascular disease[5]. Macrophage-derived ROS contribute to the initiation and development of atherosclerosis. Vascular dysfunction in response to reactive ROS plays an important role in the pathological development and progression of atherosclerotic lesions and heart failure. Oxidative damages are also the main features during the pathological development of cardiac hypertrophy, ischemia/reperfusion and heart failure[6,7].

Several key endogenous antioxidants play crucial roles in maintaining cellular homeostasis, especially in those cells with actively oxidative metabolism. Superoxide dismutase (SOD) is a major superoxide-scavenging enzyme converting superoxide (O_2^-) to O_2 and hydrogen peroxide (H_2O_2), which is further converted into H_2O by catalase[8], thioredoxin (Trx)[9], or glutathione peroxidases[10-12]. In mammals, three isoforms of SOD have been reported: the cytosolic Cu/Zn SOD (SOD1)[13], the mitochondrial manganese SOD (SOD2 or MnSOD)[8,12,14], and the extracellular form of Cu/Zn-SOD (SOD3 or ecSOD)[15]. Trx reduces the oxidized form of Trx peroxidase, and this reduced form of Trx peroxidase scavenges ROS in both cytosol and nucleus, where it modifies the activity of transcription factors[9]. In addition, heme oxygenase (HO) is an antioxidant enzyme family, consisting three isoforms: the oxidative stress-inducible HO-1 (HSP32), constitutive HO-2, and less active HO-3. HO protects cells against oxidative stress by degrading the prooxidant heme to carbon monoxide (CO), biliverdin, and ferrous iron[16]. These multiple endogenous antioxidants are crucial in maintaining cellular redox balance. If this balance is interrupted, oxidative stress increases, resulting in damage of essential cellular components.

Peroxisome-proliferator-activated receptors (PPARs) including, α, δ and γ, comprise a subfamily of the nuclear receptor superfamily. Similar to other nuclear receptor superfamilies, PPARs share the typical domain structure, including a central DNA-binding domain, an N-terminal ligand-independent activation domain and a C-terminal ligand binding domain[17]. Each PPAR subtype mostly forms heterodimer with the retinoid X receptor (RXR) before binding to PPAR responsive element (PPRE) of their target genes and the subsequent synergistic activation of these genes[18]. Fatty acids and lipid metabolites serve as endogenous PPAR ligands, which exert adaptive metabolic responses to changes in metabolic status in various tissues[18]. In addition to those identified synthetic compounds *via* high throughput screening, many compounds of natural products and modern medicine have been identified as exogenous PPAR ligands with a wide range of specificities and potencies. Despite the past success of a few of those PPAR subtype specific ligands in the clinical treatment of type Ⅱ diabetes and dyslipidemia in patients, the potential side effects of these compounds have become a major concern. In-depth understanding of the molecular mechanisms underlying PPAR's action has become even more important in our effort to rescue and improve this class of drugs with clinically proven effectiveness.

In the past decades, numerous studies elucidated the main functional role of PPAR as key transcriptional regulators of lipid metabolism, mitochondrial biogenesis, and anti-oxidant defense. While PPAR's role in regulating lipid metabolism is well-established, their role in regulating redox activity remains incompletely understood. Since redox activity is an integral part of oxidative metabolism, changes in PPAR signaling in a specific cell or tissue will lead to alterations of redox state. PPAR's regulation of cellular redox states appears to be a highly diversified function that is mostly dependent on the specific subtype at a particular tissue under different metabolic and stress conditions. The molecular mechanisms underlying PPAR's role in redox regulation are not fully understood. While numerous studies demonstrate the indirect influence of PPAR activation on the redox state, the role of PPAR in direct transcriptional regulation of redox has emerged. Given the importance of redox regulation in the pathophysiology of the cardiovascular system, this review will give an overview of PPAR's function in regulating redox activity, particularly in the cardiovascular system.

EFFECTS OF OXIDATIVE STRESS ON PPAR SIGNALING

PPAR expression, PPAR activities and PPAR interactions with their coregulators are the factors that directly determine the effects of PPAR signaling. Oxidative stress is a common cellular stress condition that can trigger a series of responses leading to altered PPAR expression and activity by different mechanisms. Increased oxidative stress regulates a variety of signaling pathways that subsequently affect gene expression by modulating a large number of transcription factors, including PPARs. Additionally, redox states may also regulate PPAR signaling *via* transcriptional regulation and post-translational modification. PPAR expression and functional activity have recently been observed in the vasculature such as endothelial cells[19] and vascular smooth muscle cells (VSMCs)[20], sug-
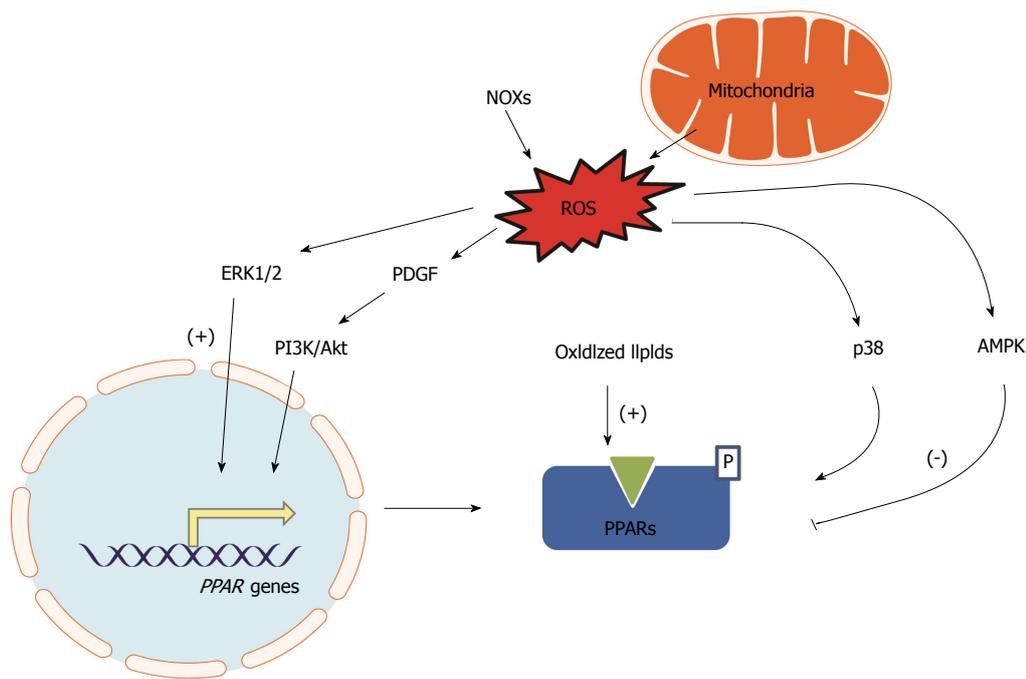
Figure 1 Oxidative stress-induced signaling pathways affecting peroxisome-proliferator-activated receptor transcript and protein activity. Oxidative stress triggers activation of ERK1/2, platelet-derived growth factor (PDGF), and phosphatidylinositol 3-kinase (PI3K)/Akt resulting in increased transcription of peroxisome-proliferator-activated receptors (PPARs) as a defense mechanism. Oxidized lipids activate transcription and activation of PPARs. Oxidative stress increases p38 mitogen-activated protein kinase and 5'AMP-activated protein kinase (AMPK) resulting in the phosphorylation of PPAR proteins resulting in suppressed transcription of PPARs. NOX: Nicotinamide adenine dinucleotide phosphate oxidase; ROS: Reactive oxygen species.

gesting that PPARs could be redox sensitive transcription factors in the vasculature and could be selectively activated by oxidized-fatty acids. PPARγ is abundantly expressed in macrophage/foam cells of atherosclerotic lesions[21,22]. *In vitro* experiments confirmed that ROS-related increase of oxidized low-density lipoprotein in macrophage up-regulates PPARγ expression[21]. In contrast, H_2O_2 induced oxidative stress in vascular endothelial cells attenuates PPARγ expression and activity through suppression of PPARγ transcription, potentially *via* activating inhibitory redox-regulated transcription factors[19]. Similar ROS-related alteration of PPARγ expression may occur in other tissues too. Increased lipid oxidation not only causes oxidative stress, but also increases PPARγ expression in the skeleton (osteoblasts)[23]. Moreover, peroxidized polyunsaturated fatty acids promote PPARγ-mediated transcription and binding of PPARγ to specific target genes, including PPARγ itself[23]. PPARγ is inhibited by histone deacetylase 4 in cortical neurons under oxidative stress in neurons[24]. Treating the cultured cells with a glutathione-depleting agent diethylmaleate reduces DNA-binding activity of PPARα[25]. Supplement of an antioxidant, vitamin E, can effectively restore PPARα expression in aged mice to levels seen in younger mice[26]. This may also occur in cells of the cardiovascular system. This observation implicates that balancing the cellular redox state may serve as an essential transcriptional regulation for PPARα. ERK1/2 activation is one of the common consequences of oxidative stress[27]. Activation of ERK1/2 signaling can induce the expression of PPARγ during the differentiation of 3T3-L1 preadipocytes[28]. Another oxi-

dative stress induced factor, Platelet-derived growth factor (PDGF), has been shown to upregulate *PPARδ* gene expression in VSMCs by the phosphatidylinositol 3-kinase (PI3K)/Akt signaling pathway[29]. Therefore, it appears that oxidative stress may influence individual PPAR activity in a tissue specific manner.

The transcriptional activity of PPARs can be regulated by post-translational modifications such as phosphorylation, SUMOylation, and ubiquitination[30,31]. Increase in ROS levels is accompanied by p38 mitogen-activated protein kinase and 5'AMP-activated protein kinase (AMPK) activation in the heart[32-34]. The PPARα phosphorylation by the p38 MAPK decreases the transcriptional activity of PPARα[35].

As summarized in Figure 1, PPAR expression and activity may be altered by the status of cellular energy metabolism (redox), and oxidative stress is attributed to altered PPAR expression and activity as an adaptive feedback or a maladaptive feedback that leads to a vicious cycle.

SUBTYPE SPECIFIC ROLE OF PPARS ON THE REGULATION OF REDOX PATHWAY

The three subtypes of PPARs regulate cellular lipid and energy metabolism in most tissues in the body with overlapping and preferential effects on different metabolic steps depending on a specific tissue. Adding to the complexity, specific ligands of each PPAR subtype may also display different potencies and specificities of their role on regulating the redox pathways. Each PPAR

subtype regulates redox status with various intensity and extension in a tissue and cell type specific manner. Many studies revealed the beneficial effects of PPAR ligands against cardiovascular disorders, although recent studies demonstrate potential adverse effects of synthetic PPAR ligands on cardiovascular disease models. This section summarizes how each PPAR regulates redox mainly in the cardiovascular system.

PPARα and oxidative stress

PPARα is expressed in various cell types related to the cardiovascular system, including cardiomyocytes[36], endothelial[37,38], smooth muscle cells[20] and monocytes/macrophages[39]. The role of PPARα in lipid and lipoprotein metabolism is well established[36,40]. Fibrates are drugs that selectively target PPARα and have been clinically used to lower hypertriglyceridemia, a risk factor of cardiovascular disease. Moreover, PPARα is a critical regulator of intra- and extracellular lipid metabolism. In addition, the therapeutic efficacy of fibrates in inhibiting atherogenesis may also in part attribute to its capacity to regulate cholesterol efflux[41] and redox signaling. Activation of PPARα protects the heart from ischemia/reperfusion injury[40,42,43].

Evidence supporting the role of PPARα in regulating redox pathways remains relatively superficial and paradoxical. Most of the early studies are based on *in vitro* and *in vivo* experiments using PPARα-selective ligands, such as clofibrate, fenofibrate and Wy14643. It has been shown that clofibrate protects rat hearts from coronary artery occlusion-induced myocardial ischemia by reducing ROS production and lipid peroxidation. These protective effects are mainly attributed to significantly increased expression and activity of SOD1, SOD2, and catalase in the heart tissue[43]. Furthermore, clofibrate is able to suppress the upregulation of Ang Ⅱ, Ang Ⅱ AT1-receptor and subsequently the related oxidative stress in the heart, at least partially contributing to the improved cardiac function[43]. Another synthetic ligand of PPARα, Wy14643, also protects rabbit hearts from ischemia/reperfusion injury by increasing HO-1 expression and decreasing caspase-3 activation[44]. In human macrophage, PPARα activation by another subtype selective ligand, GW647, can upregulate the transcript and protein expression of Trx-1[45]. Moreover, PPARα activation could also enhance the Trx-1 activity by indirect down-regulation of the natural Trx-1 inhibitor, vitamin D3 up-regulated protein 1[45]. Therefore, stimulation of PPARα could exert a beneficial effect against the development of atherosclerosis. The remaining questions are whether PPARα ligand treatments could alleviate specifically oxidative stress and contribute to their beneficial effects *via* a PPARα dependent or independent mechanism. Studies on mouse models of transgenic overexpression and/or knockout of PPARα specifically in the cardiovascular system solved some of the puzzles. However, discrepancies among different studies exist. PPARα knockout mice showing minimal phenotypic changes in the heart are probably in different genetic backgrounds from those showing major pheno-

typic changes. In a study reporting cardiac contractile dysfunction in PPARα null mice, a mechanism of oxidative damage in sarcomere proteins and lipid peroxidation was proposed based on the observation that a significant decrease of SOD2 protein and the corresponding activity with no change of other antioxidant enzymes such as Cu/ZnSOD (SOD1), catalase, and glutathione peroxidase (GPx) was reported[46]. It is not clear if the repression of SOD2 protein level and activity also occurred at the transcript level. Moreover, another study could not confirm the downregulation of SOD2 transcript and protein in the PPARα null heart[47]. Therefore, strong evidence of a direct interplay between cardiac SOD2 and PPARα is still lacking and whether the observation recorded is due to a lack of genuine regulation by PPARα or a long-term developmental adaptation to the absence of PPARα remains yet to be established.

It is well established that PPARα specific ligands activate fatty acid oxidation. However, it remains unclear, at least in cardiovascular tissues, whether this increased lipid oxidation would subsequently lead to oxidative stress due to the augmented respiration. There is evidence that activation of PPARα in the heart either by transgenic overexpression or PPARα selective ligand treatment causes increased fatty acid oxidation[48,49]. Activation of PPARα may be associated with the repression of estrogen related receptors (ERRs). ERRs are members of another nuclear receptor subfamily that governs mitochondrial biogenesis[50], thus exacerbating pressure overload-induced cardiac hypertrophy and heart failure due to mitochondrial dysfunction[51]. However, the subsequent changes of ROS in the heart have not been well characterized. In human and murine macrophages, different PPARα, but not PPARγ, agonists increase the production of ROS (H_2O_2 and superoxide)[52]. Most importantly, this study excluded the potential off-target effects of the tested PPARα ligands by showing the mediating role of PPARα agonists. PPARα agonists induce ROS production by increasing NOXs expression and stimulating its activity, which will generate more endogenous PPARα ligands. This vicious cycle will lead to augmented oxidative stress in macrophages. It has become obvious that the activation of PPARα in macrophage could have opposite effects on regulating redox state in other tissues showing increase in the expression and activity of either Trx-1 or NOXs. The consequences of PPARα activation on ROS production in macrophage are not clear. Overwhelming evidence supports the fact that PPARα activation suppresses atherogenic inflammation in macrophage[39,53]. It is likely that ROS will be reduced in PPARα ligand treated macrophages.

Overall, it is likely that PPARα plays certain roles in regulating redox state in the cardiovascular system. However, supporting evidence will be needed to further address the mechanistic aspects of PPARα related redox changes.

PPARγ and oxidative stress

PPARγ is a primary regulator of lipid storage and adipogenesis mainly in adipose tissue. However, it also

plays an important role in other tissues and cells of the cardiovascular system, since PPARγ is expressed in the heart and vasculature[42,54]. Activation of PPARγ may exert anti-atherogenic[41,55] and anti-hypertrophic effects[56]. Despite the relatively low expression in the myocardium, cardiomyocyte-restricted PPARγ knockout in mice leads to cardiac hypertrophy and even heart failure[57,58]. On the other hand, PPARγ activation substantially reduces myocardial infarct size, significantly improve aortic flow during reperfusion in both normal and diabetic hearts and substantially ameliorate post-ischemic functional recovery in rats[42,59,60]. These observations suggest an important role of PPARγ in the heart.

While the transcriptional transrepression of nuclear factor kappa-B (NF-κB) signaling by PPARγ has been suggested as a mechanism in most of above studies, the role of PPARγ as a transcriptional regulator of endogenous antioxidants is another mechanism. Our previous study on the cardiomyocyte-restricted PPARγ knockout mice unveiled that oxidative stress plays an essential role in the development of progressive cardiac hypertrophy and dilated cardiomyopathy in these mice[58]. However, further study from our group on adult mice with short term cardiac-specific PPARγ knockout showed only modest cardiac hypertrophy without oxidative stress, though fatty acid utilization was impaired and cardiac performance was compromised. Neither the mitochondrial ultrastructure nor mitochondrial copy number was altered compared with control mice[61]. These two contrast outcomes of PPARγ knockout suggest that cardiac oxidative stress may cause chronic damage instead of acute lethality. The deteriorating phenotype of PPARγ knockout was prevented by administration of MnTBAP, which mimics SOD by scavenging superoxide. Therefore, both PPARα and PPARγ are involved in the regulation of mitochondrial SOD2 under specific conditions, playing a crucial role in cardiac redox balance.

Treatment of PPARγ-specific ligands, rosiglitazone and pioglitazone, can ameliorate H_2O_2-induced oxidative damages in the newborn rabbit heart. These oxidative damages feature repressed left ventricular developed pressure, sarcomere shortening, decreased catalase expression level, and increases lactate dehydrogenase. The protective effect of PPARγ ligands against oxidative damage seems to be mediated by catalase, since the effect is abolished by PPARγ blocker or catalase inhibitor, indicating that the PPARγ-regulated catalase is crucial for cardioprotective effect of PPARγ ligands[62]. Studies also have shown that PPARγ ligands have protective effects against hypertrophy, induced by ischemia/reperfusion or angiotensin Ⅱ, in rodents *via* various mechanisms[63]. Ang Ⅱ inhibits PPARγ transcriptional activity, which in turn suppresses expression of antioxidant enzymes. PPARγ agonists, pioglitazone and 15d-PGJ2, reverse the Ang Ⅱ-induced suppression of catalase in adventitial fibroblasts of rat aorta[64]. Pioglitazone also attenuates atrial fibrillation, in which oxidative stress plays an important role in the pathophysiology and often complicated by ischemic heart

disease, valvular disease, and left ventricular hypertrophy[65]. PPARγ plays an important role in macrophage inflammatory homeostasis, partly by regulating cholesterol efflux[41]. On the other hand, lipopolysaccharide and IFN-γ in macrophages upregulates PPARγ activity and attenuates the oxidative burst[66]. PPAR-γ ligands can directly alter vascular endothelial function by enhancing endothelial NO bioavailability, in part by altering endothelial superoxide metabolism through suppression of NOXs and induction of SOD1[67]. This effect is also found in the vasculature of diabetic mice independent of correction of diabetic metabolic derangements[68]. Moreover, another PPARγ ligand rosiglitazone can attenuate high glucose induced oxidative stress and subsequent monocyte-endothelial interactions by attenuating NF-κB/p65 activation and NOX4 expression, thus favorably modulating endothelial responses in the diabetic vasculature[69]. Therefore, it is clear that PPARγ is an essential regulator of redox signaling in the cardiovascular system and can protect against many cardiovascular disorders *via* transcriptional activation of antioxidant genes.

PPARδ *and oxidative stress*

PPARδ is ubiquitously expressed with differential expression abundances in various tissues depending on pathophysiological condition. PPARδ is abundantly expressed in the heart and plays an essential role in regulating fatty acid oxidation in cardiomyocytes[70]. The essential role of PPARδ in the heart is further demonstrated by the striking cardiac pathological development in mice with cardiomyocyte-restricted knockout of PPARδ[71]. Several other studies confirmed the myocardial protective effects either with the treatment of PPARδ ligands in rats[72,73] or cardiomyocyte-restricted overexpression in transgenic mice[74,75]. PPARδ is also expressed in VSMCs and upregulated after vascular injury[76]. PPARδ activation facilitates VSMC proliferation causing matrix modulation and vascular remodeling. This is an opposite outcome to the activation of PPARα and PPARγ by which inflammation is decreased[76,77]. A PPARδ-specific ligand compound promotes lipid accumulation in human macrophages by increasing the expression of genes involved in lipid uptake and storage, whereas this treatment represses lipid metabolism and efflux[78]. However, another PPARδ-specific ligand GW501516 increases expression of the reverse cholesterol transporter, ATP-binding cassette A1, and induced apolipoprotein A1-specific cholesterol efflux in macrophages[79]. This observation of PPARδ activation is similar to the effects of PPARα and PPARγ activation in macrophages by which cholesterol is removed from foam cells[41]. In addition, it has been reported that PPARδ ligand L-165041 inhibits VCAM-1 expression and cytokine-induced MCP-1 secretion in endothelial cells and increases high-density lipoprotein (HDL) levels in *db/db* mice[80]. Since the increased HDL levels are well associated with decreased risk of atherosclerosis, it appears PPARδ activation may inhibit atherogenesis.

While the role of PPARδ activation in protecting

against pathogenesis in the cardiovascular system is established, how much of the protective mechanisms are involved in the anti-oxidation effects remains obscure. However, the role of PPARδ activation in anti-oxidant defense of the cardiovascular system is unraveling. A recent study demonstrated that the PPARδ counteracts Ang Ⅱ-induced ROS production in VSMCs. A PPARδ-specific ligand GW501516 significantly reduced Ang Ⅱ-induced ROS generation in VSMCs via inhibiting PTEN-mediated modulation of PI3K/Akt/Rac1 signaling[81,82]. Activation of PPARδ suppresses the translocation of Rac1 to the plasma membrane, a key step in NOXs-induced ROS production, in VSMCs[82]. Another recent study focusing on human endothelial cells demonstrates similar findings. PPARδ activation by GW501516 inhibits angiotensin Ⅱ-induced premature senescence featured with elevated ROS production in human coronary artery endothelial cells[83]. These results illustrate that ligand-activated PPARδ plays an important role in the cellular response to oxidative stress by decreasing Ang Ⅱ-induced ROS in vascular cells. In addition, we have recently demonstrated that PPARδ is essential for not only the constitutive function of fatty acid metabolism and mitochondrial biogenesis, but also in maintaining antioxidant defense of the heart[84]. Cardiomyocytes-restricted PPARδ knockout from adult heart leads to oxidative damages with repressed expression of SOD1 and SOD2[84]. Interestingly, the PPARα null mice with additional PPARδ knockout from the heart showed similar results. Both the transcript and protein expression of SOD1 and SOD2 was repressed in PPARδ, but not PPARα deficient hearts[47]. In this study, none of the endogenous antioxidants appears to be affected at basal condition in the *PPARα* null heart. Therefore, it appears repressed antioxidant expression is the main reason for the major oxidative damages in the hearts of *PPARδ* knockout and *PPARδ/PPARα* double knockout mice. The effects of PPARδ activation in regulating cardiac antioxidant defense have also been proven in mouse models with cardiomyocyte-restricted overexpression of a constitutively active PPARδ. The enhanced antioxidant defense in these mice enables them to have improved cardiac performance under left ventricular pressure overload condition[75]. However, the transcriptional regulation of antioxidants by PPARδ in the heart may depend on various metabolic conditions with different pathological development. The myocardial protective effects of PPARδ ligand treatment and transgenic PPARδ overexpression have been attributed to their roles in ameliorating lipid profile by increasing fatty acid β-oxidation[72] and in enhancing myocardial glucose utilization[74]. Nevertheless, it is likely that the PPARδ mediated upregulation of the antioxidants defense may also contribute to the beneficial effects.

The effects of each of the three PPARs on redox signaling in the cardiovascular system are generally beneficial in the cardiovascular system. However, contradicting results from various studies exist. It is far from clear as how each of the three PPARs differentially regulates redox signaling in various tissues and cells of the cardiovascular system.

MECHANISMS OF ACTION OF PPARS IN REGULATING REDOX

The molecular mechanisms underlying the PPAR-mediated regulation of redox signaling have been extensively studied. There is emerging evidence supporting that PPAR activation exerts direct transcriptional regulation on the expression of several key endogenous antioxidants, including SOD1[13], SOD2[14], catalase[58,85,86], GPx, OH-1 and Trx-1[45].

Rat SOD1, which is analogous to human SOD1, has PPRE consensus sequence in its promoter region[87]. SOD1 is induced in HepG2 human hepatoma cells by arachidonic acid (polyunsaturated fatty acid), one of the peroxisome proliferators, as a defense system. A promoter analysis of *SOD1* gene revealed a conserved PPRE sequence located in -797 and -792 nt, which is able to induce CAT reporter gene activity. The HepG2 nuclear extract showed PPRE-binding in gel mobility shift assay and nuclear extract from retinoic acid-treated HepG2 cells increased the intensity of the DNA-protein complex indicating *SOD1* gene is induced by arachidonic acid through the binding of PPAR to the PPRE of the *SOD1* gene[85]. PPARγ ligands have been shown to reduce superoxide by stimulating both activity and expression of SOD1 in human umbilical vein endothelial cell and suppressing NOXs[67].

Our previous study showed that PPARγ is essential for the full expression of SOD2 transcript in the heart[58]. SOD2 expression level in cardiac-specific *PPARγ* knockout mice heart is significantly decreased, and mitochondrial superoxide production was significantly increased compared to that in control mice. We have further confirmed that the *PPRE* sequence found between -985 and -935 nt in the *SOD2* promoter region is functioning. The truncated promoter fragments did not transactivate luciferase reporter gene by rosiglitazone[58]. Therefore, both SOD1 and SOD2 are regulated by direct interaction of PPARs on the PPRE of their promoters under specific conditions.

Cat (catalase; EC 1.11.1.6) plays an important role in cellular protection against oxidative stress by scavenging H_2O_2 generated from peroxisomal fatty acid β-oxidation. Numerous studies have shown that ligands of PPARα, PPARδ, and PPARγ increase catalase expression level and activity. Catalase has been characterized as PPARγ target gene with a PPRE consensus sequence on its promoter region. One study reported that *in vitro* translated protein PPARγ/RXRα heterodimer binds 5'-proximal promoter region (5 kb) of catalase. The putative PPRE fragment increased reporter gene activity in the presence of PPARγ ligands and deletion of the region containing PPRE abolished the response to the ligand. Further promoter deletion assay revealed that the PPRE was located between -1027 and -1015 nt. Tandem repeated 3 × PPRE significantly increased PPARγ-stimulated promoter
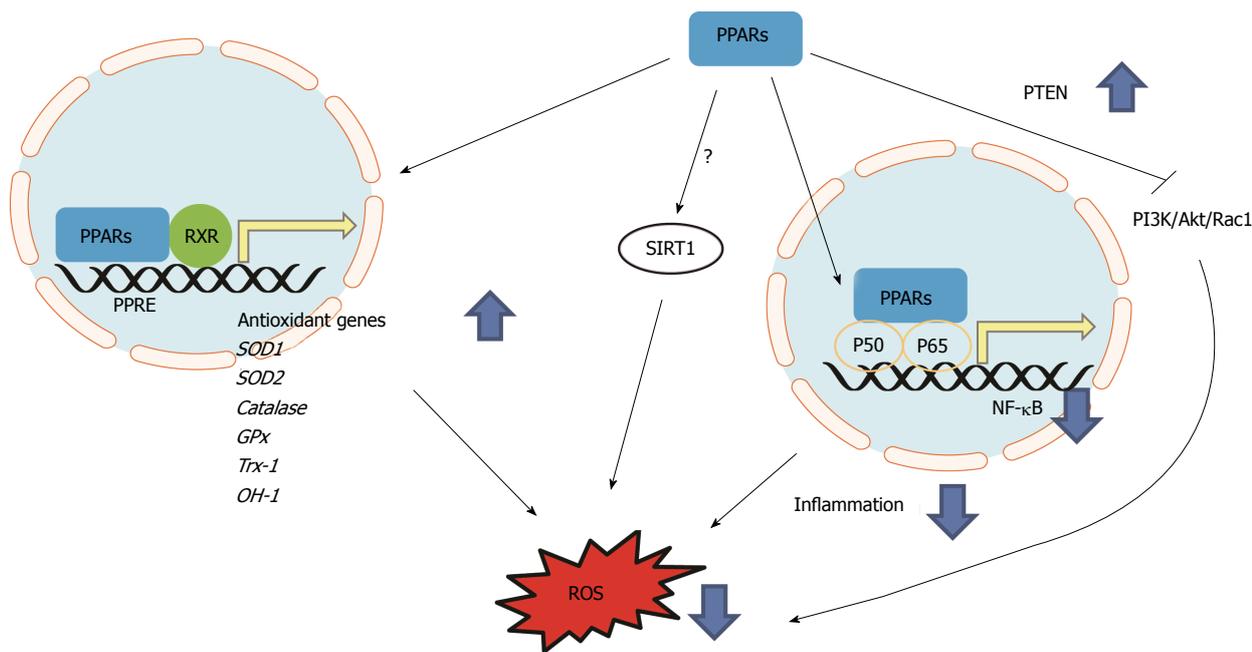
Figure 2 Antioxidant mechanisms of peroxisome-proliferator-activated receptors. Peroxisome-proliferator-activated receptors (PPARs) activate antioxidant genes *via* transcriptional regulation by binding on PPAR response element (PPRE) of promoter region of target genes. PPARs suppress nuclear factor kappa-B (NF-κB)-light-chain-enhancer of activated B cells *via* interaction with p50 and p65 resulting in decreased inflammatory response and oxidative stress. PPARs suppress phosphatidylinositol 3-kinase (PI3K)/Akt/Rac1 signaling axis *via* activation of PTEN resulting in decreased reactive oxygen species (ROS). RXR: Retinoid X receptor; *sod*: Superoxide dismutase; *trx*: Thioredoxin; *gpx*: Glutathione peroxidase; *ho*: Heme oxygenase.

activity, suggesting that PPRE alone is enough to induce transactivation of target gene[86].

The selective PPARα ligand GW647 significantly increases Trx-1 expression and activity in human macrophage. A luciferase reporter assay on human macrophage and detailed computer analysis revealed that PPRE is located between -2185 and -2198 nt of Trx-1 promoter. Mutated PPRE abolished transactivation activity on luciferase reporter assay. In an electrophoretic mobility shift assay, *in vitro* translated RXRα and PPARα proteins bind this PPRE by heterodimerization.

The GPx3 expression level in the skeletal muscles is significantly decreased in *db/db* relative to control mice[88]. Additionally, the plasma GPx3 levels are significantly decreased in type 2 diabetic patients compared to normal subjects. PPARγ ligands troglitazone, rosiglitazone, and pioglitazone decrease extracellular H_2O_2 levels and prevent H_2O_2-induced insulin resistance by increasing the expression of GPx3 in human skeletal muscle cells[88]. This increase of GPx3 is PPARγ-specific and exclusive to GPx3, but not other GPx family. Whereas the PPARγ siRNA represses TZD-induced GPx3 expression, GPx3 siRNA inhibits the H_2O_2 scavenging antioxidant effect of TZD. These data indicate that GPx3 is regulated by PPARγ playing cellular protective role against oxidative stress. In the luciferase reporter assay GPx3 promoter -2294 nt region shows strong trans-activation of reporter gene and PPRE is found between -2186 and -2174 nt[88].

In addition to the direct transcriptional effects of PPARs, the interaction of PPAR signaling with many other cell signals can also mediate PPAR's effects on regulating redox state in cells of the cardiovascular system.

PPARδ can act through inhibiting the PI3K/Akt signaling pathway to suppress the marked increase in ROS levels induced by Ang Ⅱ. Ligand-activated PPARδ also blocked Ang Ⅱ-induced translocation of Rac1 to the cell membrane, inhibiting the activation of NOXs and consequently ROS generation[82]. The activation of NF-κB is the main signaling event that triggering the inflammatory responses and the subsequent oxidative stress. It has been well recognized that PPAR can exert transrepression effects on the NF-κB signaling and suppress inflammatory responses; hence oxidative stress is ameliorated[89-92]. Therefore, it appears that PPARs may exert their antioxidant effects by direct transcriptional regulation of endogenous antioxidants and by directly or indirectly interfering/coordinating the related signaling transduction pathways to reduced ROS production (Figure 2). However, the mechanisms of how PPARs as a transcription factor would perturb these signaling pathways remain incompletely understood. This is especially the case in understanding how each of the three PPARs exerts antioxidant effects. While PPARδ activation appears to exert most of the direct and indirect inhibitory effects on ROS production in the cardiovascular system, the effects of PPARα and PPARγ appear to be more complicated depending on cell types and specific conditions. Investigations on the potential beneficial effects of duel or triple PPAR ligands are emerging. This novel class of PPAR ligands may be able to avoid potential side effects of each single ligand[93]. Phase Ⅱ clinical trials for a dual PPARα/γ agonist, aleglitazar, validate their hypoglycemic and hypolipidemic effects[94]. An ongoing phase Ⅲ clinical trial[95] will reveal the efficacy against cardiovascular event. However, a few dual agonists, such

as ragaglitazar, MK-0767, and naveglitazar, cause bladder cancer in rodents suggesting tissue-specific response should be meticulously tested. However, whether these upcoming new agonists modulate oxidative stress in cardiovascular system remains unclear. Further studies should be conducted.

Another difficulty involved in dissecting the antioxidant role of PPARs is the potent effects of PPAR activation in many other metabolic pathways, which all pose major influences on the redox balance. Therefore, we will have to interpret many of the current findings in contexts of specific cell types, specific animal strain/species and specific disease states.

FUTURE PERSPECTIVES AND CONCLUSIONS

The PPARs are one of the most extensively studied members among the nuclear hormone receptor family. Compounds (fibrate and TZD drugs) targeting PPARα and PPARγ have been used broadly in treating diabetes and dyslipidemia. While the effects of PPAR signaling on redox regulation in the cardiovascular system are major indications of the therapeutic potential, use of clinically available PPAR agonists for heart failure and atherosclerosis remains controversial for major safety concerns[96,97]. The main issues concern whether the risk outweighs the benefit. Current literatures strongly support a key role of PPARs as regulators of redox signaling in response to oxidative stress in the cardiovascular system by exerting antioxidative effects through transcriptional or post-translational regulations. It remains crucial to confirm many of the *in vitro* findings on the role of PPARs as redox regulators in intact animals under normal physiological and pathological conditions. Preclinical studies on animal models with temporal and spatial genetic manipulations have emerged as powerful tools for preclinical understanding of PPAR's roles in regulating redox signaling in the cardiovascular system. Most importantly, these studies will provide insights into the potential development of partial PPAR modulators that regulate specific cellular redox state without major unwanted effects.

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REVIEW

Mechanisms of drug-induced proarrhythmia in clinical practice

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Abstract

Drug-induced proarrhythmia represents a great challenge for those involved in the development of novel pharmaceuticals and in the regulatory bodies for drug approval as well as for the prescribing clinicians. Our understanding of the mechanisms that underlie drug-induced proarrhythmia has grown dramatically over the last two decades. A growing number of cardiac and non-cardiac agents have been shown to alter cardiac repolarization predisposing to fatal cardiac arrhythmias such as ventricular tachycardia or ventricular fibrillation and sudden cardiac death. These agents may induce the phenotype of long QT syndrome and less commonly of short QT syndrome and Brugada syndrome (BS). Although, genetic susceptibility underlie drug-induced proarrhythmia in certain cases, current data are limited regarding this topic. The present review surveys the current published literature on the mechanisms and the offending medical agents that predispose to drug-induced long QT syndrome, short QT syndrome and BS. Drug-induced proarrhythmia should be considered as a predictor of sudden cardiac death and should prompt critical re-evaluation of the risks and benefits of the suspicious medication. Survivors of drug-induced proarrhythmia and family members require careful examination and possibly genetic testing for the presence of a channelopathy. Treating physicians are advised to follow the lists of agents implicated in drug-induced proarrhythmia in order to minimize the risk of arrhythmia and sudden cardiac death.

Core tip: A growing number of cardiac and non-cardiac agents have been shown to alter cardiac repolarization predisposing to the most dangerous cardiac arrhythmias such as ventricular tachycardia or ventricular fibrillation and sudden cardiac death. These agents may induce the phenotype of long QT syndrome and less commonly of short QT syndrome and Brugada syndrome. Treating physicians are advised to follow the lists of agents implicated in drug-induced proarrhythmia in order to minimize the risk of arrhythmia and sudden cardiac death.

INTRODUCTION

A growing number of cardiac and non-cardiac agents

have been shown to alter cardiac repolarization predisposing to fatal cardiac arrhythmias such as ventricular tachycardia or ventricular fibrillation and sudden cardiac death (SCD). SCD accounts for approximately 50% of all deaths from cardiovascular diseases, and this proportion remains the same despite the overall decrease in cardiovascular mortality the last decades. In the past 30 years ventricular tachycardia or fibrillation was thought to be the most common cause of out-of hospital cardiac arrest, accounting for approximately three-quarters of cases, the rest 25% caused by bradyarrhytmias or asystole[1-9]. More recent studies suggest that the incidence of ventricular fibrillation or ventricular tachycardia as the first recorded rhythm in out-of-hospital cardiac arrest has declined to less than 30%, presumably due to the decline of coronary artery disease mortality[10,11]. An exception may exist in the setting of drug-induced proarrhythmias where the most common rhythm is polymorphic ventricular tachycardia termed torsades de pointes (TdP) or ventricular fibrillation. A national survey in England about sudden unexpected cardiac deaths have demonstrated that postmortem examination fails to identify a cause in 4% of sudden deaths in the 16-64 age group, yielding a default diagnosis of sudden arrhythmic death syndrome[6]. Recent data have shown that SCD occurs in the absence of coronary heart disease or other cardiomyopathy in about 5%-10% of cases. Certain primary electrical diseases such as the long QT syndrome, the short QT syndrome, the Brugada syndrome (BS), and the catecholaminergic polymorphic ventricular tachycardia may be underling cause of SCD in this group of subjects without overt structural heart disease[6,8,9,12]. Apart from the congenital form of these syndromes, accumulating data have shown that an increasing number of drugs commonly prescribed in routine clinical practice are implicated in acquired forms of long QT, short QT, and BS predisposing to SCD in the absence of structural heart disease. Drug-induced proarrhythmia is a growing challenge for the clinicians and for those involved in the development of novel pharmaceuticals and in the regulatory bodies charged with evaluating and monitoring drug safety. The present review describes the underlying mechanisms of drug-induced proarrhythmia and presents the drugs that predispose to this potentially life-threatening condition.

DRUG-INDUCED LONG QT SYNDROME

Several cardiac and non-cardiac agents have been shown to prolong cardiac repolarization (QT interval) predisposing to TdP and SCD[13-19]. Drug-induced QT interval prolongation is considered the most frequent cause of withdrawal or relabeling of marketed drugs in the last decade[15,16]. In a survey in United Kingdom and Italy, noncardiac agents that have pro-arrhythmic potential (defined as QT interval prolongation or TdP) represented 3% and 2% of total prescriptions in both countries, respectively[19]. Antimicrobials and psychotropic drugs are the most common non-cardiac drugs involved in drug-induced QT interval prolongation, which in the vast majority of cases are prescribed by non-cardiologists. The prescription of

Category	Drugs
Table 1 Drugs implicated in acquired long QT syndrome	
Antianginal	Bepridil
Antiarrhythmic	Disopyramide, procainamide, quinidine, mexiletine, propafenone, flecainide, d,l-sotalol, amiodarone, dronedarone, bretylium, dofetilide, ibutilide, azimilide, ajmaline
Anticancer	Tamoxifen, lapatinib, vandetanib, nilotinib, arsenic trioxide
Antifungal	Itraconazole, ketoconazole, fluconazole, voriconazole
Antimicrobial	Erythromycin, clarithromycin, azithromycin, spiramycin, telithromycin, levofloxacin, moxifloxacin, sparfloxacin, gatifloxacin, grepafloxacin, gemifloxacin, ofloxacin, trimethoprim-sulfamethoxazole, pentamidine, quinine, chloroquine, mefloquine, halofantrine
Antiviral	Foscarnet
Antihistamine	Astemizole, diphenhydramine, ebastine, terfenadine, hydroxyzine
Antidepressant	Doxepin, venlafaxine, fluoxetine, desipramine, imipramine, clomipramine, paroxetine, sertraline, citalopram, escitalopram
Antipsychotic	Chlorpromazine, prochlorperazine, trifluoperazine, fluphenazine, felbamate, haloperidol, thioridazine, droperidol, mesoridazine, pimozide, risperidone, quetiapine, ziprasidone, lithium, chloral hydrate, pericycline, sertindole, sultopride, zimeldine, maprotiline, tiapride
Antimigraine	Naratriptan, sumatriptan, zolmitriptan
Bronchodilators	Albuterol, salmeterol
Diuretics	Indapamide, thiazide, furosemide
Gastrointestinal stimulants	Cisapride, metoclopramide, domperidone
Hormones	Octreotide, vasopressin
Immunosuppressives	Tacrolimus
Others	Probucol, methadone, cocaine, amantadine, aconitine, veratridine, vincamine, terodiline, budipine, tizanidine, organophosphorus compounds

The full list can be accessed *via* the internet (www.torsades.org, www.qtdrugs.org, www.longqt.org, www.sads.org).

non-cardiac QT-prolonging agents has been associated with a significantly increased risk of SCD in the general population. The risk of death has been reported to be higher in women and in recent starters[20]. Drugs implicated in QT interval prolongation and TdP are listed in Table 1. This list can be accessed *via* the internet (www. torsades.org, www.qtdrugs.org, www.longqt.org, www. sads.org). The incidence of drug-induced TdP in the general population is unknown[15,16]. In addition, the likelihood of drug-induced TdP is difficult to be predicted in routine clinical practice. Most of our understandings are derived from epidemiological studies, case reports, clinical studies during drug development, and post-marketing surveillance. Nevertheless, the absolute total number remains very low (less than one in 100000)[15].

ECG MARKERS OF VENTRICULAR REPOLARIZATION IN LONG QT SYNDROME

The QT interval is considered as the electrocardiographic

(ECG) index of ventricular repolarization. Correct measurement of the QT interval is of paramount importance for the diagnosis of drug-induced QT interval prolongation. Most physicians, including many cardiologists, cannot recognize a long QT interval. Viskin *et al*[21] have shown that correct classification of the QT interval as either "long" or "normal" was achieved by 96% of QT experts and 62% of arrhythmia experts, but by less than 25% of cardiologists and non-cardiologists. The QT interval is measured from the beginning of the QRS complex to the end of the T-wave on the surface ECG. Despite the fact that there are no sufficient data regarding which lead or leads to use for QT interval measurement, lead II is considered the most appropriate because the vectors of repolarization result in a long single wave rather than discrete T- and U waves[22]. U waves should be ignored in QT measurements. However, whether total repolarization time should include the entire QU complex still remains a subject of controversy. The QT interval is influenced by the heart rate. Rate acceleration normally leads to QT shortening, whereas bradycardia leads to QT lengthening. The RR interval preceding the QT interval should be measured for rate correction. Several formulas may be used to correct the QT interval (QTc). The most commonly used formulas are Fridericia's cube root formula (QTc = QT/RR1/3) and Bazett's square root formula (QTc = QT/RR1/2). Although the Bazett's formula is widely accepted, it overestimates the QT interval during tachycardia and underestimates it during bradycardia. Fridericia's equation is preferred at extremes of physiological heart rate[23-25]. Individualised regression formulae are often preferred. Apart from heart rate, the duration of the QT interval is also influenced by the gender (females display longer QT intervals), autonomic tone, drugs, genetic abnormalities, electrolyte disorders (hypokalemia, hypomagnesemia, hypocalcemia), cardiac (congestive heart failure, cardiac hypertrophy) or metabolic diseases (starvation, anorexia nervosa, drug-interactions) and changes of cardiac afterload[24]. These intra-patient variations in the QT interval cannot be captured on a single twelve-lead ECG, which may be taken to evaluate the effect of a drug on the QT interval. Isolated measurements of the QT interval without reference to these QT dynamics can lead to inaccurate estimations of the risk of TdP. For these reasons, the intra-patient variability in the QT interval can be appreciated by examining ambulatory Holter recordings. QTc values greater than 450 ms in men and 470 ms in women are considered abnormal. Values ranging between 430-450 ms in men and 450-470 ms in women are considered borderline[24]. A recent scientific statement from the American Heart Association and the American College of Cardiology Foundation recommends that a QTc over the 99th percentile should be considered abnormally prolonged. Estimated 99th percentile QTc values for otherwise healthy postpubertal individuals are 470 ms for men and 480 ms for women. A QTc > 500 ms is considered abnormal and dangerous for both males and females[26].

In the setting of prolonged QRS duration (bundle branch block, pre-excitation, paced rhythm) the total QT interval will be increased. One method to adjust the QT measurement after the development of bundle brunch block is to subtract the difference of the QRS duration before and after the block. Another method is to measure the JT interval from the J point, which is the end of QRS complex to the end of T-wave. The most important issue is to apply the same adjustment method consistently when a patient is being monitored over time[26]. The current standard practice of periodic manual measurement of the QT interval and even the use of electronic callipers has drawbacks. Errors can occur in determining the beginning or end of QT interval, in the application of a heart rate formula, and from inconsistency in the choice of lead for QT measurement. Automated measurement by electrocardiographs is preferred over manual measurement[26].

The QTc interval is the best available predictor of TdP episodes[25]. The majority of drug-induced TdP occur with QTc values of more than 500 ms[27]. Data from patients with congenital long QT syndrome (LQTS) have shown that a QTc interval greater than 500 ms is related to an increased risk for arrhythmic events[28]. However, there is not a clear, linear incremental relationship between QTc prolongation and the risk of TdP, and therefore, there is no established threshold below which prolongation of the QTc interval is considered free of proarrhythmic events[29-32]. Notably, some agents that substantially prolong the QTc interval produce very low rates of clinical TdP, while other agents with much smaller QTc effects are considerably more proarrhythmic. A typical example is amiodarone[14]. In terms of QTc change from baseline on treatment, it has been recommended that an increase of 30 ms is a potential cause for concern and that a 60 ms increase is a definite cause for concern[27]. Additionally, QT dispersion (defined as the difference between the maximum and minimum QT interval of the twelve-leads) greater than 100 ms is considered abnormal[32].

An increased transmural dispersion of repolarization (TDR) is probably the best predictor of TdP, but this is measurable only in preclinical studies of limited availability[29-32]. Increased TDR by reflecting the intrinsic heterogeneities within the myocardium is postulated to contribute to the development of TdP by increasing the vulnerable window during repolarization, facilitating propagation of early afterdepolarizations (EADs). The TDR can be measured indirectly using novel ECG markers, such as the Tpeak-end interval and the Tpeak-Tend/QT ratio. In isolated ventricular wedge preparations, the peak of the T-wave was shown to coincide with epicardial repolarization and the end of the T-wave with repolarization of the M-cells, so that the Tpeak-Tend the interval as well as the Tpeak-Tend dispersion of the precordial leads provides a measure of TDR[33-36].

The Tpeak-Tend interval has been reported to be prolonged in congenital LQTS and to predict TdP in acquired LQTS[37]. Yamaguchi *et al*[38] have demonstrated
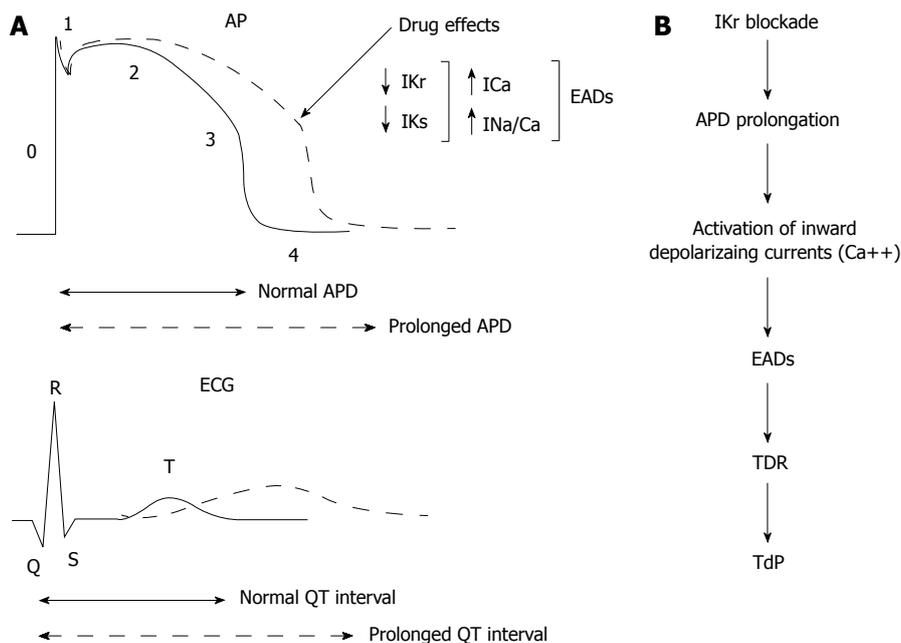
Figure 1 Relationship between the phases of ventricular transmembrane action potential and the surface electrocardiogram. A: A reduction of outward currents (IKr, IKs) during phase 2 and 3 leads to action potential duration (APD) prolongation and QT interval prolongation. Activation of inward depolarizing currents (ICa, INa/Ca) may then give rise to early afterdepolarizations (EADs) and torsades de pointes (TdP). B: This scheme is showing that APD prolongation caused by IKr blockade is not the sole determinant for TdP. Transmural dispersion of repolarization (TDR) is required in order to form a zone of functional refractoriness in the mid myocardial layer, which is probably the basis of the re-entry that is sustaining TdP. ECG: Electrocardiographic.

that the Tpeak-Tend/QT ratio is a better predictor of TdP as compared to QTc interval and QT dispersion in patients with acquired LQTS. In their study, a Tpeak-Tend/QT ratio greater than 0.28 was strongly associated with risk of developing TdP. T-wave alternans, defined as a change in amplitude or polarity of the T-wave on alternating beats, have been also considered as a precursor of TdP in LQTS[39]. T-wave alternans is thought to result from alternation of the M-cell action potential duration (APD), leading to exaggeration of TDR during alternate beats[33,40-42].

MECHANISMS OF DRUG-INDUCED QT INTERVAL PROLONGATION AND TDP: THE COMBINED ROLE OF LONG QT INTERVAL AND TDR

The knowledge of the different phases of the cardiac action potential is important for understanding the pathogenesis of drug-induced LQTS[18]. Figure 1 illustrates the normal cardiac action potential in ventricular myocytes. Phase 4 represents the resting membrane potential (-85 to -95 mV) as determined by the inward rectifier IK1 potassium current. Phase 0 of the cardiac action potential is the rapid depolarization phase. Depolarization of a sufficient area of a given cell membrane allows the rapid influx of sodium ions into the cell. The fast influx of sodium demonstrates a positive feedback, allowing even more INa channels to open and more sodium to enter the cell more rapidly, thereby depolarizing the cell to a

point at which it overshoots the membrane potential to +20 to +30 mV. Phase 1 is the early rapid repolarization phase that results from potassium ions being driven out of the cell and the membrane potential returning to near 0 mV. Ito is a potassium current (transient outward current) that is rapidly activated at this phase. Phase 2 is the plateau period. Net potential derives from competition between outward currents of potassium efflux and chloride influx and inward currents from the L-type calcium channels (ICa-L). At the end of the phase 2, calcium entry slows and calcium is removed from the cell by the Na/Ca exchanger pump. Two important potassium currents participating in ventricular repolarisation are the components of the delayed rectifier current, IKr (rapid) and IKs (slow). Phase 3 is the rapid phase of final repolarization and is determined by competition between time-dependent deactivation of the ICa-L channels versus the IKr and IKs channels.

The majority of non-cardiac QT-prolonging agents exhibit direct electrophysiological effects on the rapidly activating delayed rectifier IKr current encoded by the human ether-a-go-go related gene (HERG, now termed KCNH2)[13-19]. An increase in ICa or late INa current may also prolong the APD. Many drugs act on multiple cardiac ion channels (IKr, IKs, INa, ICa) leading to a more complex shift of action potential morphology. As shown in Figure 1, IKr and/or IKs blockade leads to a delay in phase 3 of repolarization of the action potential (reflected as QT interval prolongation on surface ECG). These phenomena are more readily induced in M-cells from the mid ventricular myocardium. Compared to subendocardial or subepicardial cells, the M-cells show much more pro-

nounced action potential[29-31,43-46]. This feature of M-cell is due to weaker repolarizing current during phases 2 and 3 secondary to smaller IKs and a larger late INa and INa/Ca compared to epicardial and endocardial cells. These ionic distinctions sensitize M-cells to a variety of pharmacological agents and pathophysiological states. Agents that block IKr, IKs or increase ICa-L or late INa generally produce a much greater prolongation of the APD of M-cells than of epicardial or endocardial cells. Activation of inward depolarizing currents (most likely L-type ICa or INa/Ca exchange current) may then give rise to EADs that appear as depolarizing oscillations in membrane voltage during phases 2 and 3 of the action potential. Phase 2 may be interrupted due to augmented opening of the L-type ICa channels, while phase 3 interruptions are facilitated by the INa/Ca exchanger pump which exchanges 3 Na ions for 1 Ca ion, producing an inward current when extruding Ca from the cytoplasm. EADs that reach the threshold voltage cause ventricular extrasystoles.

As previously mentioned, there are agents that significantly prolong the QTc along with very low rates of clinical TdP[29-31]. This indicates that the QTc interval is not the sole or optimal determinant for arrhythmogenesis. TDR has been proposed to play a key-role in both acquired and congenital LQTS[29,44]. Amiodarone is a well-known class Ⅲ antiarrhythmic agent. Despite QTc interval prolongation, the drug exhibits a very low torsadogenic activity (< 1%)[47]. Chronic administration of amiodarone produces a greater prolongation of APD in epicardium and endocardium compared to M-cells, thereby reducing TDR[48]. Sodium pentobarbital is another agent that blocks multiple currents and prolongs the QT interval but reduces TDR[41]. Both amiodarone and pentobarbital produce a homogeneous APD lengthening and the EADs does not occur. On the contrary, d-sotalol causes a significant increase in M-cell APD in relation to the epicardial cell layer. This amplified TDR explains the high incidence of TdP observed with d-sotalol[40]. Bepridil and ranolazine are anti-anginal agents that both prolong the QT interval by blocking multiple ion channels but have very different torsadogenic properties. Bepridil amplifies TDR creating the substrate for a sustained TdP[49]. In contrast to bepridil, TDR was decreased with ranolazine and EADs could not initiate TdP, despite the dose-dependent increase in QT interval[50]. Cisapride, another agent that blocks both inward and outward currents, produces a biphasic concentration-dependent prolongation of the QT interval. A parallel biphasic dose-response relationship is seen for TDR, peaking at 0.2 μmol/L, and it is only at this concentration that TdP is observed. Higher concentrations of cisapride further prolong the QT interval and reduce TDR thereby preventing TdP induction[51]. These data suggest that the propensity of a drug to increase TDR across the ventricular wall is more important than the prolongation of the QTc interval in determining the substrate for TdP. The resultant heterogeneity in ventricular repolarization creates a zone of functional refractoriness in the mid myocardial layer, which is probably

the basis of the re-entry by sustaining the TdP[29,44]. A "short-long-short" sequence (an extrasystole, followed by a post-extrasystolic pause) precedes the onset of TdP in most cases[52]. The "short-long-short" sequence provides a repolarization delay which in animal models is necessary to allow the late-plateau depolarizing currents (*e.g.*, ICa-L channel and INa/Ca exchanger current) to initiate EADs[53]. Compounds that block the late INa suppress the EADs and prevent TdP[50,54]. The anatomic origin of these extrasystoles can also be traced to late-repolarizing Purkinje fibers or M-cells[29].

Pharmacokinetic interactions with drugs known to inhibit cytochrome P450 isoenzymes (CYP3A4 or CYP2D6) may enhance the torsadogenic potential of certain agents by decreasing their clearance[15,16,18]. CYP3A4 activity can be inhibited by a wide variety of drugs including some macrolide antibiotics, antifungals, cimetidine, fluoxetine, protease inhibitors, and amiodarone. In addition, many non-drug factors including age, smoking, hepatic disease, genetic polymorphisms and grapefruit juice may lead to CYP3A4 inhibition[14]. Finally, cytochrome P450 CYP2D6 is functionally absent in approximately 7% of white and black individuals (poor metabolizer group) because of loss of function gene variants[55,56].

DRUG-INDUCED SHORT QT SYNDROME

The short QT syndrome (SQTS), a new highly arrhythmogenic syndrome affecting young and healthy individuals without structural heart disease, is associated with a predisposition to atrial fibrillation and SCD[57,58]. The definition of the short QT interval varies significantly in the literature. In a recent review of 61 cases with SQTS, the mean and median QTc values of the overall cohort were 306.7 ± 26.5 ms and 310 ms (IQR: 293-320 ms), respectively[59]. Other ECG findings include the absence of the ST-segment and the presence of tall, narrow, and symmetrical T-waves[57,58]. The diagnosis of SQTS is usually made in patients with a short QTc interval who present with additional clinical findings, such as syncope, episodes of atrial fibrillation, polymorphic ventricular tachycardia or ventricular fibrillation, or a family history of unexplained SCD[57,58]. In particular, in the cohort described by Gollob *et al*[59], the presence of symptoms associated with SQTS, including SCD, aborted cardiac arrest, syncope, and atrial fibrillation, occurred in 35 of the 61 (57.4%) subjects. There were 5 cases of SCD and 15 of aborted cardiac arrest, whereas an isolated, unexplained syncope occurred in an additional 9 subjects. Atrial fibrillation was experienced in 18% (11 of 61) of cases within the cohort.

Although the true prevalence is unknown, the congenital SQTS appears to be relatively rare[57,58]. Gain-of-function mutations in potassium channel genes (*KCNH2*, *KCNQ1* and *KCNJ2*) and loss-of-function mutations in CACNA1C, CACNB2, and CACNA2D1 have been reported as the genetic basis of this syndrome[60-66].

Limited data exist regarding the incidence and the

underlying mechanisms of drug-induced QT/QTc shortening. This is due to the fact that there has been relatively little research in this area compared to drug-induced QT/QTc prolongation. Although more work is required to elucidate the mechanism(s) of action of compounds which shorten QT/QTc, there are at least two mechanisms that have been demonstrated; activation of the IK_r current and of the ATP-sensitive potassium current (IK_{ATP})[67]. In both cases, there is an increase in the repolarizing currents leading to a shortening of the APD and resulting in reduction of ventricular refractory periods and shortening of QT interval. Although inherited SQTS is a recent acquisition, the existence of an acquired short QT interval has been known for a long time. Acquired short QT intervals can be secondary to hypercalcemia, hyperkalemia and other situations such as increased acetylcholine and catecholamine plasma levels, hyperthermia, alterations of the autonomic tone, acidosis and increased heart rate. The industry-wide survey (53 total responses representing 45 different companies) indicates that the number of compounds that induce QT/QTc shortening has increased over the last 5 years with 51% of responses reporting QT/QTc shortening in pre-clinical studies and 22% a corresponding clinical experience. The reason for the increase is not clear but there is a clear business impact with 13% (7/56) of these compounds being discontinued in the pre-clinical phase due to QT/QTc shortening[68].

Rufinamide, a recently approved anticonvulsant indicated for Lennox-Gastaut syndrome which has a prevalence of 1 per 10000 of population, had a QT shortening effect > 20 ms at peak concentrations when compared with placebo rates of 5%-10%. The FDA, in contrast to the European labeling which advices use of judgment, contraindicates its use in patients with familiar SQTS and recommends caution when administering with other drugs that shorten the QT interval[69]. In a recent observational study, QTc interval shortening following oral rufinamide administration was not associated with significant clinical adverse effects. However, the ability of rufinamide to significantly shorten the QT interval portends a potential arrhythmogenic risk that may best be guarded against by periodic ECG recordings[70].

DRUG-INDUCED BS

The BS is a primary electrical disease characterized by coved type ST-segment configuration in right precordial leads, the absence of structural heart disease, and a high risk of ventricular tachycardia/ventricular fibrillation and SCD[71-73]. The clinical phenotype is 8 to 10 times more prevalent in males than in females[72,73]. BS typically manifests with syncope or SCD, occurring in the third and fourth decade of life, and usually at rest or during sleep[71-73]. The diagnosis of Brugada sign is strictly based on the recommendations of the Second Expert Consensus Conference on BS[73]. According to this report, three types of ECG repolarisation patterns in right precordial leads (V_1-V_3) have been recognized. Type 1 is considered

diagnostic and is characterized by a coved ST-segment elevation ⩾ 2 mm followed by a negative T-wave in more than one right precordial leads (Figure 2). Type 2 ST-segment elevation displays a saddleback configuration with a high take-off ST-segment elevation of ⩾ 2 mm, a trough displaying ⩾ 1 mm ST-segment elevation, and either a positive or biphasic T-wave. Type 3 has either a saddleback or coved appearance with an ST-segment elevation of ⩽ 1 mm. The diagnosis of BS requires the presence of type 1 ECG pattern with at least one of the recognized diagnostic criteria: syncope, prior cardiac arrest, documented or inducible polymorphic ventricular tachycardia or ventricular fibrillation, a family history of sudden death, 45 years old, or type 1 Brugada pattern and/or nocturnal agonal respiration[73]. The ECG features of BS are often concealed requiring a pharmacological challenge (sodium channel blocking test) with a Class I antiarrhythmic agent (ajmaline, flecainide, procainamide) to unmask the characteristic ST-segment elevation in the right precordial leads. The diagnosis of BS is afterwards considered positive when the baseline type 2 or type 3 ST-segment elevations converted to the diagnostic type 1 pattern (ST-segment elevation ⩾ 2 mm). In a Consensus report published this year, only 2 ECG types are considered: type 1 which is identical to the classic type 1 ECG pattern of the other Consensus (coved pattern) and type 2 that joins ECG patterns 2 and 3 of previous Consensus (saddleback pattern)[74]. In this new type 2 ECG, the high take-off is ⩾ 2 mm with respect to the isoelectric line and is followed by ST-segment elevation ⩾ 0.05 mV with positive or flat T-wave in V2 and T-wave variable in V1[74].

Mutations of the *SCN5A* gene leading to loss of function of the INa by different mechanisms is the most common genotype found among these patients (20% of BS cases; range 11%-28%)[75]. To date, almost 300 mutations in *SCN5A* gene have been described in association with BS[75]. Putative mutations were also found in calcium channel genes (*CACNA1C*, *CACNB2b* and *CACNA2D1*)[60]; sodium channel β-subunit genes (*SCN1B*, *SCN3B*)[76]; glycerol-3 phosphate dehydrogenase 1-like enzyme (GPD1L) and MOG1, which affects trafficking of sodium channels[77,78]; and in genes that affect transient outward current (Ito) (KCNE3, KCND3 and KCNE5) in single cases and families with BS[79,80].

MECHANISMS OF DRUG-INDUCED BS

The pathophysiology of the BS is only partially resolved. There are 2 principal hypotheses on the pathophysiologic basis of BS: the "depolarization hypothesis", namely right ventricular conduction delay, and the "repolarization hypothesis", namely transmural dispersion of right ventricular action potential morphology, driven by the loss of the spike and dome action potential morphology at right ventricular epicardium[81,82]. So far, both repolarization and depolarization abnormalities are thought to be related to the development of ventricular fibrillation in
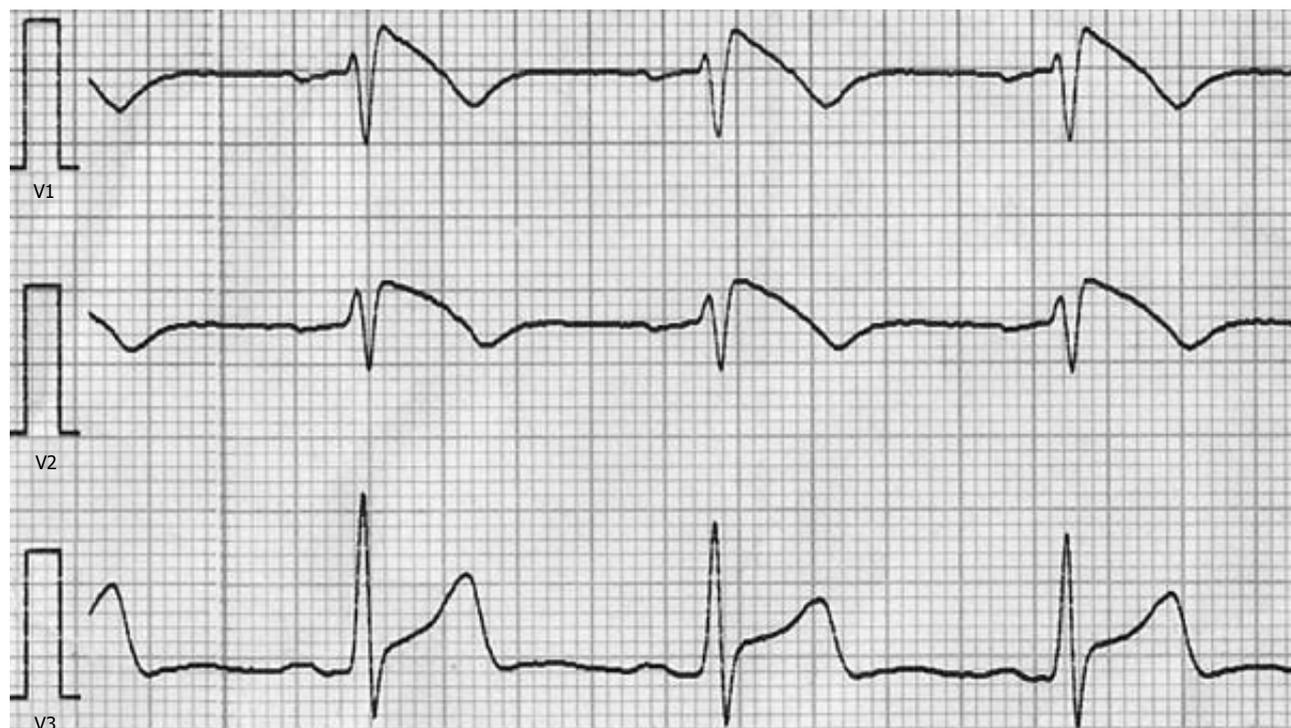
Figure 2 Diagnostic type 1 electrocardiographic pattern of Brugada syndrome.

BS patients[83].

The seminal work by Yan and Antzelevitch[84] had clearly demonstrated regional heterogeneities in action potential characteristics between the right and left ventricles, as well among epicardium, mid-myocardium and endocardium. A loss of the action potential dome at the epicardium but not at the endocardium creates a transmural voltage gradient that may be responsible for the ST-segment elevation. The Ito current seems to have an important role in the Brugada ECG pattern, evidenced by the fact that the right ventricle has a higher density of this channel compared with the left ventricle and it is suggested that the thinner endocardium of the right ventricle relative to its epicardium results in a more marked spike and dome pattern in this region[73,75,84]. This mechanism properly accounts for not only the ST-segment elevation but also for the premature ventricular contraction ("phase 2 re-entry") and re-entrant substrate for ventricular fibrillation in BS. Recent studies strongly support the depolarization hypothesis[85-88]. Postema *et al*[86] have shown conduction slowing and abnormal conduction velocity restitution in the right ventricle (with no significant regional differences) of patients with BS. Using a non-contact endocardial mapping technique, Lambiase *et al*[87] have demonstrated significant regional conduction delay, reduction in activation gradient and formation of lines of functional conduction block in the anterolateral free wall of the right ventricular outflow tract compared with the right ventricular body and apex of BS patients. Fractionated electrograms in the right ventricle, possibly due to subtle structural abnormalities, have been also reported in patients with BS[88]. In both mechanisms, a reduction in

INa or other depolarizing and repolarizing ion currents have a central role. The cells with impaired sodium channel function may fail to propagate the action potential, resulting in localized conduction block. These cells have also a shorter refractory period and recover excitability from the surrounding cells. The combination of localized conduction block and a shortened refractory period provide the substrate for localized "phase 2 re-entry".

An increasing number of drugs have been reported to induce type 1 ECG pattern of BS and/or (fatal) arrhythmias in BS patients (Table 2). Postema *et al*[89] have initiated a website (www.brugadadrugs.org) to ensure worldwide availability on safe drug use in BS patients. As previously mentioned, Class I antiarrhythmic agents (ajmaline, flecainide, procainamide, pilsicainide, propafenone) unmask the diagnostic type 1 ECG pattern of BS. Calcium channel blockers and β-blockers have also been implicated in the acquired form of BS. Psychotropic agents are commonly implicated in drug-induced BS. Tricyclic antidepressants (TCA) have a quinidine-like antiarrhythmic action which effects repolarization. The most common adverse cardiovascular effects of 4s are slowing of intraventricular conduction, manifested by prolongation of PR and QRS intervals, QT prolongation, TdP and postural hypotension[90]. The primary mechanism of these ECG changes is likely to be sodium channel antagonism. TCAs cause a decrease in the maximum rate of rise (Vmax) of phase 0 of the action potential in canine Purkinje fibres. The shortened APD may therefore induce an intramyocardial electrical gradient, the Brugada ECG pattern and possibly the substrate for re-entry. Lithium is a commonly used drug in the treatment

Category	Drugs
Table 2 Agents implicated in drug-induced Brugada electro-cardiographic pattern	
Antiarrhythmic	Ajmaline, flecainide, pilsicainide, procainamide, propafenone
Antidepressant	Amitriptyline, nortriptyline, clomipramine, desipramine, imipramine, doxepin, dosulepine, maprotiline, lithium, fluoxetine, paroxetine, fluvoxamine,
Antipsychotic	Loxapine, trifluoperazine, cyamemazine, perphenazine, thioridazine
Anti-epileptic	Oxcarbazepine
Anesthetics/analgesics	Bupivacaine, propofol
Antihistamines	Diphenhydramine, dimenhydrinate
Other substances	Cocaine, alcohol, metoclopramide, acetylcholine, ergonovine maleate, edrophonium

The full list can be accessed *via* the internet (www.brugadadrugs.org).

of depressive and bipolar affective disorders. Cardiac side effects have been described at both therapeutic and toxic serum levels in adult patients. Lithium has been associated with non-specific T-wave abnormalities (inverted, flattened, or bifid T-waves), conduction defects and rhythm disturbances. The possible mechanism of action in unmasking patients with underlying BS is that lithium chloride causes a potent INa blockade in a concentration-dependent manner[91]. Selective serotonin-reuptake inhibitors have also been implicated in drug-induced BS[92,93].

The type 1 ECG pattern of BS has been also elicited in patients treated with first-generation antihistamines, anaesthetics, and cocaine[94]. Exposure to long-acting local anaesthetic, bupivacaine, has been reported to induce ECG manifestations of BS and ventricular tachycardia in an otherwise silent carrier of an *SCN5A* mutation[95]. Propofol is the commonest anaesthetic used in modern medicine and few significant side effects. However, there have described cases of SCD in patients with high doses of propofol infusion have been described when given for several days a condition termed "propofol infusion syndrome". Vernooy *et al*[96] described six patients with "propofol infusion syndrome" who developed a Brugada-like ECG pattern and died within hours of irrecoverable electrical storm. Some cases of unexpected SCD due to cocaine in young otherwise healthy individuals have occurred. Cocaine-induced BS has been reported in previous case reports[97-99]. In addition to indirect sympathomimetic actions, cocaine has a potent INa blocking effect resembling that of flecainide[100].

CONCLUSION

A continuously rising number of cardiac and non-cardiac agents have been implicated in proarrhythmia and SCD. Abnormalities in repolarization and/or depolarization of cardiac cells through changes in ion channels and myocardial zones are the main pathophysiological mechanisms manifested as long QT, short QT and BS in routine clinical practice. Drug-induced proarrhythmia should always

be considered as a predictor of SCD and should prompt critical reevaluation of risks and benefits of the suspicious medication. In clinical practice, adverse effects of QT-prolonging drugs can be prevented by not exceeding the recommended dose, by restricting the dose in patients with pre-existing risk factors and avoiding concomitant administration of agents that inhibit the metabolism of known drugs that prolong the QT interval. Survivors of drug-induced TdP and family members of drug-induced TdP fatalities require careful examination and possibly genetic testing for the presence of congenital LQTS-associated channelopathies. Similarly, drugs that shorten the QT interval should be avoided. Sodium channel blocking test, family screening for BS, and possibly genetic analysis may be performed in a subject with an acquired form of Brugada ECG phenotype by non-cardiac agents. Although the most appropriate treatment in BS is under discussion, avoidance of potential proarrhythmic drugs is an important part of prophylactic treatment. Rigorous treatment of fever, a well known trigger of arrhythmic events in BS, is also advised in subjects with acquired BS ECG pattern by non-cardiac agents[73]. Treating physicians are advised to follow the lists of agents implicated in drug-induced proarrhythmia in order to minimize the risk of arrhythmia and SCD.

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Depression in adults with congenital heart disease-public health challenge in a rapidly expanding new patient population

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Abstract

There is a growing population of adults with congenital heart disease (CHD) due to improved survival beyond childhood. It has been suggested that adults with CHD may be at increased risk for mental health problems, particularly depression. The reported incidence of depression in CHD varies from 9% to 30%. This review examines the evidence for a higher depression rate in CHD *vs* general population. Possible explanations are offered from a variety of disease models, ranging from brain injury to the psychoanalytical approach. Risk factors for an abnormal emotional adjustment and depression include early exposure to stress from illness and medical interventions in infancy, separation from the parents during hospitalizations and brain organic syndromes. Later in life, patients often have to cope with physical limitations. Recent improvements in care may be protective. Current patients may benefit from an earlier age at first surgical intervention, fewer reoperations and inclusion to the mainstream schooling, among other factors. At this point, there is little systematic knowledge about evidence-based therapeutic interventions for depression in adults with CHD. Health care providers of patients with CHD should be aware of mental health challenges and may take a more proactive approach to identifying patients at risk for depression.

Core tip: More and more adults with congenital heart disease (CHD) survive to adulthood. Having survived grave illness in infancy, these patients appear to be at increased risk for mental health problems as adults. This review specifically examines the relationship of CHD and depression. Risk factors and protective strategies are explored. There still is little knowledge on specific treatment for depression in the growing patient population of adults with CHD. When health care providers are aware of depression in adults with CHD this may improve access to appropriate care.

INTRODUCTION

Adults with congenital heart defects are a growing population since the results of open heart surgery in children constantly improve. At the same time, this growing number may be at risk for psychiatric problems, particularly depression. An increased incidence of depression in adults with congenital heart disease (CHD) was first suggested by studies conducted in Boston[1,2]. The first study included 29 adults with CHD from a medical follow up clinic at Massachusetts General Hospital[1]. It identified major depression in 4 (14%) and dysthymic disorder in 11 more (38%) of these patients using DSM-Ⅲ-R crite-

ria[1]. Another early study used a structured interview in addition to a questionnaire in 22 different adult survivors of CHD[2]. Here, 27% of the patients fulfilled DSM-IV criteria for depression. Remarkably, neither the cardiology care providers nor the patients themselves had voiced concerns prior to the testing.

Since then a number of population-based studies from multiple cultural backgrounds have raised similar concerns. Eslami et al[3] found increased problems with anxiety but depressive symptoms were similar to matched control population in 347 Swedish adults with CHD. In another Swedish cohort of 1274 patients (with a mean age of 33 years) 29.8% of the participants self-reported symptoms of anxiety or depression[4]. In Portugal, Freitas et al[5] documented a 21.8% lifetime prevalence of psychopathology in a cohort of 110 CHD patients. A Korean study examined 210 Korean 19 years old males of military draft age to 300 controls and found an increased incidence of psychological abnormalities[6]. Among 119 Australian adolescents with CHD, 9% were positive on a screening test for depression; anxiety was even more prevalent[7].

The impact of physical symptoms on quality of life and depression is somewhat unclear: One study in 53 patients with Fontan for single ventricle hearts also found an increased incidence of depressive symptoms[8]. In a German study 8.6% of 767 patients with CHD (median age 26 years old) exhibited depressive symptoms when they presented for a formal exercise stress test[3]. The authors concluded that the effect of physical limitations on quality of life was relatively smaller than that of depression, highlighting the complex interactions between physical and psychological well being[9].

Pediatric follow up studies using parental observations also indicate an increased risk of mental health problems in CHD patients[10,11]. In a Dutch study, parents completed a child-behavior checklist for a cohort of 125 children aged 10-16 years old from a single surgical center[10]. The incidence of emotional and behavioral problems in CHD patients was increased. Behavior problems were more common in patients who had more hospital admissions and operations[10]. A follow-up study on 430 Norwegian children with CHD had the same conclusion. In this study, boys with CHD had a greater incidence of behavioral problems than girls but both groups were higher than expected[11]. Another study utilized the "Mood and Feelings Questionnaire" in 58 children awaiting heart or heart and lung transplantation including 32 children with CHD[12]. Patients and parents were interrogated. In this population, depression scores were higher than reference values before and after transplant. Pre-transplant, 21% of all children with CHD scored in the abnormal range; however, children with other diagnosis like cardiomyopathy or cystic fibrosis fared even worse. Parent and child scores on depression agreed to some degree but the correlation coefficient was relatively low at R = 0.5. These studies offer good evidence that adults with CHD are at higher risk for depression than the general population. This has now affected treatment guidelines for adults with CHD[13,14]. At this point, however, there are still more studies focusing on children with CHD than on adults[13].

In general, the co-morbidity of medical illness and depression is well described[14]. For instance, several studies in adults have focused on the relationship of depression and coronary artery heart disease[15]. Depression appears to be a risk factor for the manifestation of coronary artery disease[15]. It is also more prevalent in patients after heart attacks[15]. In a large study, 39% of all patients with acute myocardial infarction (MI) had criteria for depression (ENRICHD)[14]. Moreover, MI patients with depression have less favorable outcomes in terms of morbidity and survival. Significant differences persisted 5 years after the event when compared to controls without depressive symptoms[14].

Can treatment of depression make a difference? The ENRICHD trial randomly assigned 1238 MI patients to a 6-mo period of cognitive therapy. Both these patients and a matching control group of MI patients had access to antidepressant medication[15]. The study did not find a benefit for the psychotherapy group with regards to event-free-survival but symptoms improved. On posthoc analysis, there was a survival benefit for those MI patients on serotonin re-uptake inhibitory drugs (with or without psychotherapy).

In light of the experience in coronary artery disease, it would seem important to aggressively address and treat depression in adults with CHD. However, this area appears to be largely unexplored: There were no randomized controlled trials on psychological interventions in adolescents and adults with CHD based on a Cochrane review from 2003[16].

This problem has another important aspect. Depression is a silent epidemic[17,18]. When it comes to unrecognized mental health issues, the situation of patients with heart disease may not be so different from the general population. Disability due to depression has a similar incidence as coronary artery disease and cancer[18], yet it is more hidden from the public eye, perhaps due to the stigma still associated with mental illness. Epidemiological studies suggest a lifetime prevalence of 16.2% for major depressive disorder with a 1-year-prevalence of 6.6% in the general population in the United States[19]. The prevalence of severe mental disorders (of about 7%) appears to be stable over 2 decades[19]. Even after diagnosis, only about half of all patients receive treatment[20]. These are the findings of the National Co-morbidity Survey which included adults from 18 and 54 years of age[19].

Under-diagnosed, under-treated and still a shameful illness-depression poses a major public health challenge for the general population. Are adults with CHD at a higher risk than the general population?

ADULTS WITH CHD-A GROWING POPULATION AT RISK FOR DEPRESSION?

CHD affects about 0.8% of all live-born infants, based

Table 1 Selected quality of life indicators in adult congenital heart disease

Study	n	Exercise tolerance[1]	Health Self-assessment	Unemployed	Site
Nieminen et al[27]	2896	97% good	77% good	Not increased	Finland
Crossland et al[28]	299	N/A	N/A	33%, increased	United Kingdom
Lane et al[29]	276	Diminished	Diminished	Increased	United Kingdom
Moons et al[30]	629	95% < class 3	Good	6.7%	Belgium
Jefferies et al[31]	32	Diminished	Diminished	47%, increased	KY, United States
Kamphuis et al[32]	156	N/A	N/A	36%, increased	Holland

[1]New York Heart Association Classification. N/A: Not assessed.

on the data of the Baltimore-Washington Infant study[20]. About half of these children require a surgical or catheter intervention to survive beyond infancy. Palliative heart operations started in 1944[21]. The development of the heart-lung machine by Gibbons in the early 1950s opened the era of open-heart surgery[21]. It is estimated, that 10% of all patients with complex congenital heart defects born in the era from 1940-1959 were still alive in the year 2000 compared to 50% from the surgical era 1960-1979 and 80% of those infants with CHD born in the 1980s[22]. Children with significant CHD requiring surgery now have an estimated 85% chance to survive to age 16 years old[23]. The overall surgical mortality for CHD most recently had fallen to about 5% with further improvements expected[24].

As a result of this progress, the adult CHD population is growing rapidly. For the first time, there are more adults than children with CHD in the United States. Therefore, several working groups have tried to address the medical needs of these adult survivors of what once used to be a pediatric illness, including mental health needs[13,24-26].

Mental health is related to the economic and social circumstances of the population. How do adults with CHD fare in this regard? Several outcome studies from different countries have addressed these issues. Table 1 gives an overview. Overall, adults with CHD tend to have lower employment rates, less exercise tolerance and a lower self-assessment of good health than population average.

Nevertheless, most patients with CHD appear to enjoy a good quality of life as adults[27-32]. In a detailed quality of life study from Belgium, 514 adults with CHD were compared to a matched control group from the general population at a median age of 23 years[33]. Employment was similar in this sample but the highest educational achievement and marriage rate were slightly lower than controls. There also was a (statistically insignificant) trend to fewer children in patients. The most striking difference, however, was that patients stood out for their different values: These adults with CHD ranked "financial means and material well-being" as less important to their well-being than their healthy peers. A recent population study in Finland found similar results[27]. The investigators evaluated 2896 adults with CHD using a self-report from a standardized questionnaire[27]. The response rate was high at 76% of the national adult CHD population. The Finish patients were older than the group from Belgium with a mean age of 33 years (ranging from 15 to 59

years). Their employment and marriage (or cohabitation) rates were similar to the general population. However, both men and women with CHD were less likely to have children than controls[27].

Another study based on quality of life questionnaires conducted in the United Kingdom found significantly diminished scores compared to population normative data in adults with CHD, including "emotional role"[29]. It is unclear whether patients with palliated heart disease and cyanosis as adults fare worse. In the study by Lane et al[29] the subgroup of patients with cyanotic heart disease scored worse than those with acyanotic defects. In contrast, Moons et al[30] found similar quality of life in cyanotic and acyanotic patients. Even in this study, cyanotic patients perceived the severity of their disease as higher those with acyanotic defects but this did not seem to affect their overall quality of life[30]. The severity of disease had an influence on the perceived quality of life but there was only a weak correlation. In Moons's study, 95.8% of the 628 patients had an ability index above class 3, defined as being able to work and bear children. This is similar to the findings in the study from Munich, Germany, comparing objective exercise tolerance on formal stress test with quality of life scores in 767 patients[11]. In contrast to these favorable results, unemployment among the patients was high in Kentucky[31]. Nevertheless, even here, 66% of adults were married and social support was deemed "good" in 91% by the patients themselves.

In summary, several studies found increased unemployment and indicators of a diminished quality of life in adult survivors of CHD (Table 1). Yet other studies present evidence that the majority of patients can attain a high level of functioning under the right circumstances. There is potential for a normal or near normal quality of life. Therefore, it is an important public health goal to assist this rapidly growing population to realize their full potential and to achieve the highest possible degree of independence. Mental health issues are an important component of this process as it will empower the patients to find their own solutions in a challenging environment where they may face disadvantages at the work place.

EPIDEMIOLOGY OF DEPRESSION IN ADULTS WITH CHD

Several investigators have studied depression in adults with CHD but the design of the studies varied mak-

ing a direct comparison between studies difficult[1-9]. Some studies contract a cohort of patients operated at a single surgical center while others used a sample of convenience from an outpatient clinic. Methods applied included standardized questionnaires and interviews where the controls were taking from normative data or matched controls. Some studies indicate an increased risk for adults with CHD while others found a similar profile as in the comparison group as will be discussed in more detail below. The conflicting results of different studies may be related to the heterogeneity of the methodology used.

Studies supporting a higher risk for depression in adult CHD

As mentioned in the introduction, two small studies from Boston found diagnostic criteria for depression in about one third of adults attending a CHD outpatient clinic[1,2]. Both studies concluded that these patients may have a higher risk for depression than the general population. As an important limitation, both studies had small sample sizes with 22 and 29 participants, respectively. In addition, there may have been selection bias due to the recruitment from an outpatient clinic.

According to a recent Canadian study, patients attending specialized follow-up clinics at tertiary care centers represent only about half of all adults with complex CHD (47%)[34]. In this national survey, 27% of patients with complex heart defects simply had no further cardiologist visits after age 18 years old[52]. The others took their follow up care to a non-specialist[52]. Recruiting patients in a specialized follow-up setting could therefore lead to the wrong conclusion. It is conceivable that the more symptomatic patients prefer specialist care and would also be more likely to be referred back to a specialist if they went to see another doctor because of the obvious complexity of their medical needs. The severity of the illness appears to impact on the patient's quality of life to a degree that is somewhat disputed[8,9,30]. Patients in a tertiary care center outpatient clinic may therefore represent a group with higher risk factors than the average adult with CHD.

However, the relationship between the type of heart defect and quality of life is not straight-forward[29,30]. One would expect that patients who had successful surgery ("surgically cured") should also consider themselves as fully functional in their self-perception. Lane et al[29] assessed the quality of life of 276 patients with CHD, including 68 with "surgically cured" disease. This "surgically cured" group had diminished scores for "role-emotional" with 70 compared to the population normative value of 83, a significant difference. The 18 patients with cyanotic heart disease in this study had an even lower score than the acyantic control group of patients. All other patients including those with inoperable disease scored similar to normal population[29]. In the Korean cohort of 19 years old males there were no differences between patients with and without history of open heart surgery although both groups differed from the controls[6].

These findings illustrate the difficulty of detecting mental health issues in adults with CHD as they are not a homogeneous group. The experience appears to vary in relationship to the underlying diagnosis and severity of the illness. However, the relationship may be complicated as highlighted by the fact that in Lane et al[29] found abnormal "quality of life" scores in patients who were considered "surgically cured" with little physical impairment and low probability of further complications.

More recently, van Rijen studied a cohort of 362 adults with CHD from a single surgical center[35]. At follow-up, patients were 20-46 years old. Most patients were well adjusted or in some aspects even better adjusted than age-matched normal controls. However, the investigators identified sub-groups of patients at higher risk for depression. These risk factors included female sex, low exercise capacity, more physician-ordered restrictions, worse self-perception of scars (as opposed to physician assessment of the appearance of scars), early hospitalizations and the number of re-operations[35]. In addition, patients with 2 common diagnoses, ventricular septal defect and complete transposition of the great arteries, also had a significantly higher risk of emotional mal-adjustment.

In summary, there are several studies pointing to an increased risk of depression in adults with CHD. However, this finding may not be true across the spectrum of all congenital heart defects but only for specific sub-groups including: (1) cyanotic heart disease; (2) ventricular septal defect; and (3) complete transposition of the great arteries. However, all studies were relatively small and there are no large-scale or population-based studies addressing this issue.

Studies contradicting a higher risk for depression in adult CHD

Some studies suggest that adults with CHD are at similar risk for mental health problems as the general population or even, in some aspects, better adjusted than others[36,37]. Cox et al[37] compared 87 patients from a hospital-based adult CHD outpatient clinic to a control group of 45 patients attending the orthopedic outpatient department at the same institution using a questionnaire approach. In this study, CHD patients had similar Hospital Anxiety and Depression Scale (HADS) scores as orthopedic patients; 36% of the cardiac patients and 51% of the orthopedic patients scored higher than 11, a difference that did not reach statistical significance. On the "General Health Questionnaire 30", cardiac patients perceived themselves as healthier than their orthopedic patient control group. The investigators concluded that psychopathology was less prevalent than expected in the adult CHD group. However, this result may have been influenced by the low response rates and the unusual characteristics of the control group. In a large United States study, the National Comorbidity Survey, 29% of the general population had evidence of mental disorders of any kind[20]. While a direct comparison would not be valid, the rate of 36% abnormal results on the HADS questionnaire in adults with

CHD certainly does not seem to be particularly low.

van Rijen *et al*[36] performed a very detailed psychological follow-up evaluation of a cohort of 363 consecutive patients operated at the Throraxcenter Rotterdam in the Netherlands in the years between 1968 and 1980. After the initial study, patients were studied again following a 10 year interval using the Heart Patients Psychological Questionnaire and a number of other tools[38]. The response rate was high, 90.7% of the patient treated at that institution. The reference group was carefully chosen and consisted of 1742 Dutch citizens who completed the "Short Form-36 health survey", based on an unrelated study published in 1998. Compared to this reference population, adults with CHD generally scored lower for physical functioning; however, the difference was small with 90.3 *vs* 93.1 on a scale from 0 to 100 for patients and controls[36]. Patients reported more bodily pain. Nevertheless, the subjective perception of health was similar in the patients and in the reference population. For "social functioning", "general mental health" and "limitations of role due to emotional problems" adults with CHD rated themselves higher than the reference population[38]. The self-assessment of emotional health suggested that these patients functioned better than the population average.

However, even in this Dutch study, comparison of the earlier findings with the follow up study ten years later revealed an increase in "displeasure (negative moods and emotions)" based on the Heart Patients Psychological Questionnaire. This score for "displeasure" was reportedly at the lower limit of the scoring range. Overall, older women reported a decrease in their well-being as they grew older while men improved.

So both the study by Cox *et al*[37] and the Dutch study support that adults with CHD are emotionally well adjusted when compared to controls but on closer examination this statement only holds true when some special considerations are taken into account[38]. The Dutch investigators from Rotterdam identified certain subgroups at higher risk, including those with early hospitalizations and re-operations, as mentioned above. Moreover, they discovered that young women with CHD, particularly those between 20 and 27 years of age, were significantly more likely to express symptoms of depression than the reference population. This was the result of a related study in which the same investigators analyzed 252 patients aged 20-32 years old from the same center. Women with CHD had abnormal results on the "Young Adult Self Report", confirmed by the "Young Adult Behavior Checklist" which was completed by parents and partners[33]. The 28-32 years old counterparts did better while still at slightly higher risk for anxiety and depression than control.

Overcompensation and denial may influence patient's self-reported symptoms. In the study from Rotterdam, patient responses were compared to the assessment of parents and partners which suggested more problems than self-report[38,39]. The scores based on the responses of family members were more abnormal as those reported by the patients themselves.

It is difficult to reconcile all the findings. It is pos-sible that there truly could be regional differences or, as discussed above, selection bias due to overrepresentation of symptomatic adults with CHD in specialty outpatient clinics at tertiary care centers.

Depression in the families of patients with CHD

Closely related to the question of depression in adult with CHD is the mental health and incidence of depression in their parents[40-43]. A Swedish study found an increased incidence of depression in parents of children with CHD among 1092 members of the Swedish Heart Child Foundation[40]. They were parents to 691 children with heart defects[40]. The 2 control groups consisted of 293 parents of 162 healthy children and 112 parents of 74 children with other disease in a cross-sectional study using questionnaires. In all 3 groups, mothers had higher scores than fathers. Parents of children with CHD, older and unemployed parents were more likely to be depressed. Overall, 18% of the parents of children with congenital heart defects had abnormal scores for depression, nearly twice as many as in the control group with health children and ill children (10% in both groups)[40].

Another study assessed the parents of 75 children before and one year after open heart surgery[41]. Indicators of "psychological distress" were present in 63% of the mothers before surgery with a decrease to 25% at follow up[41]. Again fathers were less distressed than mothers with abnormal scores in 48% preoperatively and 17% at follow-up, compared to 13% fathers of healthy children. Prenatal diagnosis of CHD also impacts parental mental health[42].

When confronted with CHD, parents appear to be at high risk for depression. Yet, it is unclear how depression in the parents will affect their children, the CHD patients. One study from Leuven, Belgium, suggested that a more controlling parenting style may negatively impact the psychological well-being of children with CHD[43]. Overall, this question seems to be under-studied.

ETIOLOGICAL CONSIDERATIONS FOR DEPRESSION IN CHD PATIENTS

Are there any psychological or medical reasons why patients with CHD would be at increased risk for depression? The theoretical foundation of psychotherapy is still characterized by pluralism with a number of competing schools of thought coexisting at the same time. As a consequence, there are several disease models for depression (Table 2). Yet it appears that when it comes to risk factors for depression and CHD, the case can be made regardless of the disease model (Table 2).

Psychoanalytical model

In 1917, Freud S[44] published his basic idea of the pathogenesis of depression in a short essay entitled "Trauer und Melancholie", mourning and melancholia. According to Freud, the self-tormenting and low self-regard characteristic of depression are possible only because

Table 2 Risk factors for depression in congenital heart disease and theoretical model

Disease model	Risk factor in congenital heart disease patients
Psychoanalytical model (Freud S)	Psychological trauma in oral phase) due to illness, hospitalizations and separation from parents.
Attachment theory (Bowlby)	Separation from parents. Parent's subconscious fear of bonding with a sick child that may not live long?
Biological model: Neurotransmitter imbalance	High stress during a vulnerable phase of development permanently alters physiological stress response.
Biological model: Brain organic cause	Cerebral insults secondary to heart disease and open-heart surgery.
Learning theory	"Learned helplessness" due to chain of adverse life-events, perceived or real lack of control during illness and hospitalizations, and socio-economic disadvantages.

the patient displaced a love-object taken from him (or her) early in life into his own self in a pathological manner. During depression, patients really wish to punish the source of their earlier frustration but instead redirect the destructive impulse against their own self, as internalization. The lost object could be a nurturing parent who disappears during a hospitalization. Freud also observed that depressed patients often refuse oral gratification from food. Depression has since been linked to a trauma in the oral phase, the earliest stage of psychological development in early infancy according to the Freudian school.

Freud's observation still stands that difficult life experiences during infancy (and particularly early parental loss) are associated with depression[45]. The studies of van Rijen et al[35] have demonstrated a higher risk for depression and emotional problems in patients with ventricular septal defects and complete transposition of the great arteries, two defects that require repair in early infancy with all the necessary hospital admissions and separation from the parents. Utens et al[10] also showed a link between early hospitalizations and behavior problems in children with CHD.

Insecure attachment due to separation in infancy

According to Bowlby, difficult adult relationships and depression derive from the infant's difficulty in forming a strong bond to his or her parents, resulting in an insecure attachment. In a large survey in 879 college students, poor quality of the relationship with the parents was associated with the incidence of depression, based on self-report data[45]. Among the respondents, 26% had been verbally, physically and sexually abused as children, and this subgroup had more depression than others. Differences were primarily related to the lower quality parental relationships in the group with childhood abuse rather than to the abuse itself. A Canadian study analyzed depressive symptoms in college students with a similar approach and also confirmed the close relationship between the quality of the primary attachment to the parents and

depression[46]. It is conceivable that illness and hospital admissions and operations in early childhood with the separation of parents and children at times hinder a secure attachment.

Biological model: Altered neurotransmitter pathways, stress and cerebral insults

It is now widely accepted that depression is associated with a neuro-transmitter imbalance in the brain and that it may improves if the cerebral metabolism is normalized as a result of pharmacotherapy[18]. Animal experimental data show that stressful life events in early life (for instance repeated short separations from the mother animal) result in an activation of the hypothalamic-pituitary-cortical axis with permanent alterations of the stress response in the exposed animals[47]. Investigators also showed loss of volume of the hippocampus area of the brain, a part of the limbic system that is involved in the serotonin pathways[47]. This biological model therefore provides a potential explanation for the link between early life stress and adult depression[48].

Agid et al[49] proposed a disease model where adverse life events in infancy make the individual more vulnerable for an abnormal stress response later in life when they are again confronted with challenges; depending on the presence or absence of genetic predisposition, the mal-adaptive psychological response may then take the form of post-traumatic stress disorder, depression or schizophrenia, with female sex as a modulating factor. Applied to CHD, the infant would become more vulnerable to depression when exposed to the stress of separation from the parents during hospitalization. In addition, these infants experience physical stress from pain related to blood draws, intravenous access and from the operation itself. Their cries may go unanswered creating the experience of an unresponsive environment. According to the animal research these repetitive stress events could alter the patient's stress response permanently. These abnormal patterns can surface when the patient is again confronted with adverse life events during adult life. The fact that adults with multiple hospitalizations, hospital admissions early in life and re-operations appear to have more depression would support this model indirectly.

Another important argument for a possible anatomic basis for depression in adults with CHD derives from recent neuroimaging studies on the brains of infants before and after open-heart surgery. In the Boston Cardiac Arrest Trial, there was a 15% incidence of abnormal brain scans in a group of children operated during the newborn period for transposition of the great arteries early on with higher rates in the subgroup presenting for follow up brain magnetic resonance imaging at age 16[50-52]. Two more recent studies also obtained magnetic resonance imaging of the brain not only after but also before open heart surgery[53,54]. They found an even higher incidence of cerebral insults pre- and post-open heart surgery during infancy: In the first study, the incidence

Table 3 Improvements in the treatment of children with congenital heart disease	
Previously	**In the current era**
Difficult diagnosis-invasive testing	Noninvasive diagnosis by ultrasound
Presentation in critical condition	Earlier diagnosis, newborn intensive care
Emergency surgery or interventions	Emergency treatment rare
Long hospitalizations for weight gain	Neonatal surgery and short hospital stays
Limited visiting hours for parents	Parents involved in hospital care
Medical focus	Child life teams and psycho-social support
High surgical mortality and morbidity	Improved surgical mortality and morbidity
Admissions for infections	New immunization, improved antimicrobial treatment
Re-operation	More catheter interventions, shorter admissions
Limited rehabilitation options	Early intervention programs
Special education placement	Integration in the main-stream
Limited opportunities for peer support	Self-help groups, internet resources

of abnormal brain scans was 28% before surgery and in the second study 24% with an increase to 67% on post-operative follow up[51-53].

Children with CHD appear to have multiple organic reasons to be at risk for depression. They live through high stress situations in the context of their hospitalizations and heart operations. Some patients even experienced resuscitation events. Stressors like this in early infancy may permanently alter the physiological stress response of the individual. In addition, a significant proportion of CHD patients suffer cerebral insults secondary to their disease and also in the peri-operative period[50-53].

Yet, the exact relationship of these brain injuries for patient behavior and emotional adjustment remain murky as the presence of magnetic resonance imaging abnormalties didn't predict behavior problems in the Boston Cardiac arrest trial[51].

Learning theory and environmental risk factors

Depression can also be conceived as "learned helplessness"-in experiments, an animal looses the initiative to escape or fight and becomes passive when repeatedly exposed to an unalterable stress situation[48]. A small infant could arguable perceive medical and surgical treatment in a similar way. As an aggravating factor, patients may feel more helpless because of their physical appearance and self-image[55]. Their higher unemployment rates (Table 1) and greater physical limitations may also contribute to a sense of being helpless[38,39].

Are adults with CHD at risk for depression?

The life experience associated with open-heart surgery in early childhood entails multiple risk factors for later emotional mal-adjustment. Despite these risk factors, studies indicate that many adults with CHD are well adjusted with good problem solving skills[38]. In addition, it even appears that things get better as they age: Their "social isolation" decreased during follow up based on the Rotterdam study[38]. However, there the good outcome in the Dutch and German experience may not be representative for the universal experience as studies from other countries now indicate a significant increase in depressive symptoms in diverse populations[1-9].

PREVENTIVE STRATEGIES AND PROTECTIVE FACTORS

Preventive factors and resilience

Despite the risk for mental health problems, the real story of depression in adults with CHD may be their resilience-the ability to remain fully functional in the face of adversity[55,56]. The parents of patients with CHD may experience more psychological distress than the patients themselves although this review didn't find any study using direct comparison[40-42]. While risk factors are present overall outcomes appear to be good. The topic of specific protective factors in children with CHD appears to be largely unexplored at this time.

Finally, it is important to remember that today's adults with CHD grew up in an era where hospital visiting hours were shorter and mortality rates were higher (Table 3). Because of the harsher conditions in the past, it may well be that the current adult survivors of CHD represent a selection of only the most resilient individuals. In a study by Wray et al[57] children who perceived themselves as more "weak" or "miserable" before surgery were less likely to survive. Today's adults with CHD are these survivors. However, the same investigators did not see a difference of the psychological profile of survivors and patients with adverse outcomes in a second, smaller study on 32 children with CHD awaiting heart or heart-and-lung transplantation; the psychological profile of the 18 surviving children were similar to those who died in the context of cardiac transplantation[12].

Differences of current and previous treatment

Table 3 summarizes some important changes implemented in recent years that are likely to improve the psychological outcome of children with CHD. Many changes were introduced because of better insight into the psychological and developmental needs of sick children. It would be an important goal to build on that and improve primary prevention of mental health issues in these patients. Secondary prevention would consist of early identification and improved access to treatment for depression in adult survivors of CHD.

SUMMARY AND CONCLUSION

There is an increasing population of adults with CHD. Most of these patients could potentially be fully functional in society. CHD impacts on risk factors for depression in multiple ways. Whether depression in adults with CHD is increased or just under-diagnosed and under-treated- it is an issue for these patients. Cardiac diagnosis, medical history and patient sex appear to affect the relative risk of depression, particularly early hospitalizations and re-operations. Little is known about protective factors and the personality profiles of the higher functioning survivors and their parents. Systematic studies on treatment of depression in adult CHD are lacking.

In conclusion, it appears to be an important public health goal to increase the awareness of adults with CHD and their medical caretakers for the significant incidence of depression in this patient population. While the exact incidence of depression in the adult CHD population is unknown, it is clear that these patients potentially benefit from routine mental health screening.

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BRIEF ARTICLE

BLEED-Myocardial Infarction Score: Predicting mid-term post-discharge bleeding events

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Abstract

AIM: To derive and validate a score for the prediction of mid-term bleeding events following discharge for myocardial infarction (MI).

METHODS: One thousand and fifty patients admitted for MI and followed for 19.9 ± 6.7 mo were assigned to a derivation cohort. A new risk model, called BLEED-MI, was developed for predicting clinically significant bleeding events during follow-up (primary endpoint) and a composite endpoint of significant hemorrhage plus all-cause mortality (secondary endpoint), incorporating the following variables: age, diabetes mellitus, arterial hypertension, smoking habits, blood urea nitrogen, glomerular filtration rate and hemoglobin at admission, history of stroke, bleeding during hospitalization or previous major bleeding, heart failure during hospitalization and anti-thrombotic therapies prescribed at discharge. The BLEED-MI model was tested for calibration, accuracy and discrimination in the derivation sample and in a new, independent, validation cohort comprising 852 patients admitted at a later date.

RESULTS: The BLEED-MI score showed good calibration in both derivation and validation samples (Hosmer-Lemeshow test P value 0.371 and 0.444, respectively) and high accuracy within each individual patient (Brier score 0.061 and 0.067, respectively). Its discriminative performance in predicting the primary outcome was relatively high (c-statistic of 0.753 ± 0.032 in the derivation cohort and 0.718 ± 0.033 in the validation sample). Incidence of primary/secondary endpoints increased progressively with increasing BLEED-MI scores. In the validation sample, a BLEED-MI score below 2 had a negative predictive value of 98.7% (152/154) for the occurrence of a clinically significant hemorrhagic episode during follow-up and for the composite endpoint of post-discharge hemorrhage plus all-cause mortality. An accurate prediction of bleeding events was shown independently of mortality, as BLEED-MI predicted bleeding with similar efficacy in patients who did not die during follow-up: Area Under the Curve 0.703, Hosmer-Lemeshow test P value 0.547, Brier score 0.060; low-risk (BLEED-MI score 0-3) event rate: 1.2%; intermediate risk (score 4-6) event rate: 5.6%; high risk (score $\geq$ 7) event rate: 12.5%.

CONCLUSION: A new bedside prediction-scoring model for post-discharge mid-term bleeding has been derived and preliminarily validated. This is the first score designed to predict mid-term hemorrhagic risk in patients discharged following admission for acute MI. This model should be externally validated in larger cohorts of patients before its potential implementation.

Core tip: Prediction of mid- to long-term clinically significant bleeding following discharge for a myocardial infarction has received scarce attention from the scientific community. The BLEED-myocardial infarction (MI) prediction model is the first score designed to predict mid-term hemorrhagic risk in these patients. Easy to use and comprising clinical and analytical items that can be collected in a few minutes, BLEED-MI showed good calibration, accuracy and discriminative performance for predicting post-discharge hemorrhagic episodes and a composite endpoint of bleeding events plus all-cause mortality. Importantly, an accurate prediction of bleeding events was shown independently of mortality. Furthermore, a progressively increasing risk of the primary and secondary endpoints was seen with increasing BLEED-MI scores and our results suggested a very high capability of the BLEED-MI rule in identifying low-risk patients. Depending on its potential external validation in larger cohorts of patients, the BLEED-MI score may eventually help tailor therapeutic decisions

INTRODUCTION

Bleeding has emerged as a predictor of early and late mortality in patients with a myocardial infarction (MI)[1-5]. Extensive data indicate that bleeding complications occur with relative frequency (up to 11.4% of patients depending on the type of MI, comorbid illnesses, performance of coronary revascularization procedures or whether patient was given thrombolytic therapy[6-9]), independently affect outcomes, carry similar importance in adversely influencing mortality risk as ischemic events, can be grossly predicted by recognizing patient, presentation, treatment and procedural risk factors for hemorrhagic complications and may be prevented by pharmacologic or non-pharmacologic measures[10].

Despite the proven benefits of anti-platelet or anti-thrombotic drugs, they are mechanistically linked to an increased risk of bleeding. Newer, more potent, agents may decrease risk of further ischemic events at a cost of increased bleeding risk, which may decrease compliance[11,12].

A thorough understanding of the prediction of hemorrhagic complications following discharge for acute coronary syndromes is therefore a particularly sensitive concern, as we pursue our common goal of maximizing efficacy of antithrombotic drugs while minimizing bleeding risk. Multiple studies have addressed the prediction of bleeding events in the acute/sub-acute phases of a MI or early post-discharge period (30 d within admission) or in patients undergoing percutaneous coronary interven-

tions[7,8,10,13-15]. However, prediction of mid- and long-term hemorrhagic events following an acute coronary syndrome has received surprisingly scarce attention from the scientific community. To the best of our knowledge, to this date no risk score has been developed for predicting the mid-term risk of bleeding complications following discharge for a MI. In the context of bleeding assessment, evidence-based decision making should lead to selection of appropriate pharmacologic and nonpharmacologic treatments, invasive or conservative strategies that may offer the best balance of benefit and risk. Furthermore, identification of those patients at highest hemorrhagic risk allows application of more aggressive preventive strategies and potential optimization of outcomes.

The purpose of this investigation was to derive and preliminarily validate a new risk score for the prediction of mid-term bleeding events in patients discharged following admission for a MI.

MATERIALS AND METHODS

Study design
We included all patients admitted at our hospital's Acute Coronary Care Unit (ACCU) with a diagnosis of MI between December 1, 2006 and August 31, 2009 in a derivation cohort. Using collected baseline data at the time of MI diagnosis and outcome data from this cohort, we developed a new algorithm for the prediction of post-discharge bleeding events-BLEED-MI score. This model was evaluated for its overall predictive performance, discriminatory power and calibration in the derivation sample and in a different cohort comprising patients admitted at our institution for a MI between September 1, 2009 and September 30, 2011.

Patients and eligibility criteria
One thousand and fifty patients consecutively admitted to the ACCU of a tertiary referral hospital and university centre with a MI were included in the derivation sample, while 852 patients admitted at a later date to the ACCU with a MI were assigned to the validation cohort. Eligible patients were required to have a diagnosis of MI according to the Universal Definition of MI[16]. Patients were classified as having acute MI with ST-segment elevation (STEMI) or MI without ST-segment elevation (NSTEMI). Patients with previously known left bundle branch block or ventricular pacemaker rhythm were included in the NSTEMI group.

Data collection
The following data were collected: demographic features, cardiovascular risk factors and previous medical history, physical examination (including weight, height, body mass index, blood pressure and heart rate) and analytical study at admission (including complete blood count, glycaemia, NT-proBNP, C-reactive protein, creatinine, urea, troponin I), maximum troponin I levels, results of coronary angiography and eventual revascularization pro-

	Bleeding event	No bleeding event	*P* value
Age (yr)	74.6	67.2	< 0.001
Female gender	41.40%	34.50%	0.292
NSTEMI	67.20%	57.50%	0.095
Diabetes mellitus	50.00%	33.50%	0.011
Previous arterial hypertension	84.50%	73.80%	0.072
Smoking habits	29.30%	17.20%	0.049
History of stroke/TIA	17.50%	8.10%	0.015
Atrial fibrillation at admission	16.70%	13.50%	0.516
Bleeding during hospitalization	19.30%	7.10%	0.001
Maximum killip class	1.62	1.39	0.004
Hemoglobin at admission (g/dL)	12.0	13.5	< 0.001
GFR at admission (mL/min)	55.0	71.6	< 0.001
Blood urea nitrogen at admission (mg/dL)	13.5	8.7	< 0.001
Submitted to revascularization procedures	58.60%	63.90%	0.422

Table 1 Prediction of mid-term bleeding events in univariate analysis

NSTEMI: Non-ST elevation myocardial infarction; TIA: Transient ischaemic attack; GFR: Glomerular filtration rate.

cedures, inhospital bleeding complications, pre-discharge thoracic echocardiogram (when performed) and post-discharge antithrombotic therapies. Glomerular filtration rate (GFR by MDRD formula) and the GRACE scores for intrahospital and 6-mo post-discharge mortality were calculated for all patients.

Study end points

The primary endpoint of this study was the occurrence of clinically significant bleeding events during follow-up. In-hospital bleeding events were censored, as only post-discharge hemorrhage was considered. Clinical significance of a documented hemorrhage was analyzed according to its severity, localization and associated hemodynamic compromise. Heterogeneous definitions are frequently observed in the trials assessing the benefits of antithrombotic drugs in acute coronary syndromes (ACS), with the Thrombolysis in MI (TIMI) and GUSTO being the two bleeding definitions most commonly used in trials on ACS[17,18].

Therefore, clinically significant hemorrhage included: (1) major, severe or life-threatening bleeding events, namely those at intracerebral location, those resulting in substantial hemodynamic compromise requiring treatment or in reduction of hemoglobin of 5 g/dL or more (or > 15% in hematocrit); and (2) moderate bleeding, defined by the need for transfusion, a drop in hemoglobin of 3-5 g/dL (or in hematocrit from 10% to 15%) from previous blood tests to the time of admission, the occurrence of spontaneous gross hematuria or hematemesis even in the absence of hemoglobin drop higher than 3 g/dL, or unobserved loss of 4 g/dL or more in hemoglobin

Minor bleeding, referring to hemorrhagic events not

included in the previous categories, nor requiring transfusion or causing hemodynamic compromise or substantial fall in haemoglobin levels, was not assigned to the primary endpoint. Also, blood loss attributable to new revascularization or other surgical procedures was not included.

The secondary endpoint of this study was a composite outcome of post-discharge clinically significant bleeding event plus all-cause mortality.

Patient follow-up

Patients assigned to the derivation cohort were followed for 19.9 ± 6.7 mo following their discharge, while those in the validation sample were followed for a mean period of 13.4 ± 8.1 mo. Follow-up data was obtained from clinical records from outpatient clinic and hospital ward and emergency department admission(s), and through phone calls by the end of a 2-year period after discharge for patients not followed at our hospital.

Statistical analysis

Statistical analysis was done using SPSS, v.17.0. When needed, baseline characteristics are described with mean ± SD for continuous data and counts and proportions for categorical data. The Kolmogorov-Smirnov test was used to test the normal distribution of continuous variables. A model for the prediction of post-discharge midterm clinically significant bleeding episode was developed in the derivation cohort, comprising several parameters that have been shown before to predict bleeding events in different clinical contexts: age, hemoglobin at admission, GFR by MDRD formula at admission, blood urea nitrogen at admission, history of stroke, bleeding event during hospital stay for the index MI or history of major hemorrhage (defined as non-fatal hemorrhagic stroke or history of serious bleeding requiring transfusion), signs of heart failure before discharge, previously known hypertension, diabetes mellitus, smoking habits and post-discharge treatment with anti-platelet or anticoagulant agents. Gender was indirectly considered, as it is one of the parameters used for the GFR calculation with the MDRD formula. Type of MI, performance of revascularization procedures, implanted stent type per se and atrial fibrillation at admission have not been consistently shown before to predict mid to long-term bleeding events following a MI. Furthermore, as these parameters did not help predict the occurrence of bleeding events during follow-up in univariate analysis, they were not included in our model. Table 1 unveils predictors of clinically significant hemorrhage in univariate analysis and Table 2 illustrates BLEED-MI score calculation.

Patients were divided into three risk categories: (1) BLEED-MI score 0-3: Low risk; (2) BLEED-MI score 4-6: Intermediate risk; and (3) BLEED-MI score ≥ 7: High risk.

In both the derivation and validation cohorts, we assessed the discriminatory power of the BLEED-MI model by calculating the area under each receiver operating characteristic (ROC) curve [area under the curve

Table 2 Calculation of the BLEED-myocardial infarction score

Variable	Points assigned
Age (yr)	
< 65	0
65-74	1
≥ 75	2
GFR at admission (MDRD formula, mL/min)	
≥ 60	0
30-59.9	1
< 30	2
History of stroke or transient ischemic attack[1]	
No	0
Yes	1
Heart failure during hospitalization[2]	
No	0
Yes	1
History of hypertension	
No	0
Yes	1
Antithrombotic therapy[3]	
1 agent	1
2 agents	2
3 agents	3
Hemoglobin at admission (g/dL)	
≥ 12	0
10-11.9	1
< 10	2
Blood urea nitrogen at admission (mg/dL)	
< 10	0
10-25	1
> 25	2
History of major hemorrhage or bleeding event during hospitalization[4]	
No	0
Yes	1
Smoking habits (until hospitalization)	
No	0
Yes	1
History of diabetes mellitus	
No	0
Yes	1

The BLEED-myocardial infarction (MI) score is obtained by summing all the points assigned for each predictor. [1]Previous neurologic events were defined as history of sudden onset of a focal neurologic deficit in a location consistent with the territory of a major cerebral artery or the radiological documentation of previous cerebral infarction (irrespective of the presence/absence of symptoms); [2]Heart failure was defined as a maximum Killip Class > 1 at any time during hospitalization. Therefore, it includes both patients with previous history of heart failure and those with de novo heart failure during hospitalization; [3]Including anti-platelet agents (such as Acetylsalicylic Acid and Clopidogrel) and/or anticoagulants (such as Warfarin). At the time patients assigned to the derivation sample were admitted to our Acute Cardiac Care Unit, agents such as Prasugrel, Ticagrelor or Dabigatran were not available; [4]History of major hemorrhage defined as previous non-fatal hemorrhagic stroke or history of serious bleeding requiring transfusion. Bleeding event during hospitalization represents the occurrence of a hemorrhagic episode during hospitalization for the MI index, as described for the primary endpoint, plus any significant bleeding event attributable to revascularization procedures (again, as described for the primary endpoint). GFR: Glomerular filtration rate.

(AUC)]. Discrimination, measured in terms of the AUC, refers to BLEED-MI score's ability to assign a higher probability to patients with hemorrhagic events than to those without bleeding episodes. The same analysis was performed for the secondary endpoint, post-discharge all-cause mortality.

Binary logistic regression was performed including the BLEED-MI model exclusively to obtain estimated probabilities of significant bleeding event. Thereafter, the accuracy of the score was analyzed through the Brier score[19]. Accuracy is a measure of the average distance (residual) between the observed outcome and its predicted probability for each individual patient. A popular accuracy measure is the Brier score, which is the squared mean of the residual values. The Brier score is sensitive to both discrimination as well as calibration of the predicted probabilities and describes how well a particular model predicts the likelihood of an outcome in an individual patient (a score of 0.0 implies perfect prediction, while a Brier score of 0.25 suggests lack of utility in endpoint prediction).

The overall tendency of increasing event rates with increasing risk score was tested using chi-square for trend (gamma) and Kaplan-Meier curves were created in the validation sample to evaluate bleeding risk during follow-up and overall event-free survival in each risk category.

Finally, comparison through ROC curve analysis and the integrated discrimination improvement index (IDI) was performed between the BLEED-MI model and the CRUSADE score[20]. The IDI, which may be seen as a continuous form of the net reclassification improvement index, assesses improvement in risk discrimination by estimating the change in the difference in the mean predicted probabilities of the outcome between those with and without the outcome in question. This comparison was performed in the validation sample only.

RESULTS

Baseline characteristics

Table 3 describes both study samples. Of the 1050 patients assigned to the derivation cohort, 91 (8.6%) died during hospitalization, 62 (6.2%) and 200 (21.8%) reached the primary and secondary endpoints during the 19.9 ± 6.7 mo follow-up, respectively. Significant bleeding events occurred in 7.5% (*n* = 60) of patients included in the validation cohort, while 15.6% (*n* = 124) reached the secondary outcome during a 13.4 ± 8.1 mo follow-up.

Fifteen point seven percent of patients in the derivation sample were assigned to the low-risk category, while 49.9% and 34.4% were included in the intermediate and high risk strata, respectively. Similarly, 22.9% of patients in the validation sample were assigned to the low risk sub-group, while 39.4% and 37.7% were included in the intermediate and high risk categories, respectively.

Validation of BLEED-MI

Derivation sample: The *P* value for the Hosmer and Lemeshow goodness-of-fit test confirmed the good calibration of BLEED-MI model (*P* = 0.371), indicating that the overall model fit was good.

Incidence of the primary and secondary endpoints according to risk category is reported on Table 4.

Mean BLEED-MI score in patients reaching the pri-

Table 3 Description of derivation and validation samples		
Characteristic	Derivation sample (*n* = 1050)	Validation sample (*n* = 852)
Age (yr)	67.9 ± 13.5	67.9 ± 13.6
Male gender	686 (64.7)	578 (68.0)
Type of myocardial infarction		
STEMI	42.1%	38.8%
NSTEMI	57.9%	61.2%
Diabetes mellitus	380 (35.9)	266 (31.2)
Previous hypertension	796 (75.2)	631 (74.2)
Hyperlipidemia	59629 (56.3)	475 (59.6)
Smoking habits	287 (27.1)	281 (33.1)
Previously known coronary disease	283 (26.7)	243 (28.6)
History of stroke/TIA	94 (9.0)	77 (9.1)
Atrial fibrillation at admission	144 (13.7)	99 (12.4)
Admission killip class	1.40 ± 0.6	1.36 ± 0.7
Maximum killip class	1.56 ± 0.8	1.46 ± 0.8
Average number of vessels with significant lesions	1.60 ± 0.97	1.54 ± 0.99
GFR at admission	68.6 ± 38.4	72.6 ± 32.0
BUN at admission (mmol/L)	9.58 ± 6.81	8.85 ± 6.20
Hemoglobin at admission (mg/dL)	13.3 ± 2.1	13.8 ± 6.14
NT-proBNP at admission (ng/L)	4202 ± 13400	6393 ± 15950
Submitted to revascularization procedures	645 (61.4)	663 (77.8)
Clinically significant bleeding during hospitalization	87 (8.3)	55 (6.5)
Average GRACE score for intrahospital mortality	153.9 (P25 124; P50 151; P75 179)	145.6 (P25 114; P50 143; P75 173)
Average GRACE score for 6-mo mortality	128.0 (P25 102; P50 125; P75 149)	121.0 (P25 94; P50 118; P75 145)
Moderate-severe left ventricular systolic dysfunction	19.50%	23.00%
Discharged on dual anti-platelet therapy	818 (89.2)	723 (90.6)
Discharged on anticoagulant treatment	36 (3.9)	37 (4.6)
Intrahospital mortality	8.60%	6.10%
Post-discharge mortality (mo)	165 (16.5) (Follow-up: 19.9 ± 6.7)	88 (11.0) (Follow-up: 13.4 ± 8.1)
Bleeding events during follow-up (mo)	62 (6.8) (Follow-up: 19.9 ± 6.7)	60 (7.5) (Follow-up: 13.4 ± 8.1)

Data are expressed as absolute numbers (percentage) or mean ± SD. TIA: Transient ischaemic attack; BUN: Blood urea nitrogen; CRP: C-reactive protein; NSTEMI: Non-ST elevation myocardial infarction; STEMI: ST elevation myocardial infarction.

mary endpoint was 7.9 ± 2.4 (*vs* 5.6 ± 2.2 for those without significant hemorrhage, *P* < 0.001). Brier score analysis using this model demonstrated a mean value of 0.061, which suggests a high predictive capacity within individual patients. BLEED-MI score's discriminatory power was assessed by calculating the AUC for the occurrence of significant hemorrhagic events or the composite endpoint of post-discharge bleeding event plus all-cause mortality: (1) Bleeding event: AUC 0.753 ± 0.032, 95%CI: 0.690-0.816, *P* < 0.001; and (2) Composite endpoint: AUC 0.808 ± 0.018, 95%CI: 0.772-0.844, *P* < 0.001.

A BLEED-MI score below 4 had a negative predictive value of 99.2% for the occurrence of a clinically significant hemorrhagic episode during follow-up and for

the composite endpoint of post-discharge hemorrhage plus all-cause mortality.

Incidence of primary and secondary endpoints increased progressively with increasing BLEED-MI scores, as shown in Table 5.

The BLEED-MI score predicted ischaemic events (non-fatal reinfarction and ischaemic stroke) with reasonable, yet lower, discriminative performance (AUC 0.682 ± 0.028, 95%CI: 0.627-0.738, *P* < 0.001), suggesting a higher utility in the prediction of bleeding. In addition, it was useful in the evaluation of the net clinical risk (composite of death, non-fatal reinfarction, stroke and significant bleeding): AUC 0.760 ± 0.018, 95%CI: 0.724-0.797, *P* < 0.001.

Validation sample: The Hosmer-Lemeshow test confirmed that there were no statistically significant differences between observed and expected post-discharge hemorrhages across risk groups (*P* = 0.444).

Incidence of the primary and secondary endpoints according to risk category is reported on Table 6.

Mean BLEED-MI score in patients reaching the primary endpoint was 8.0 ± 2.7 (*vs* 5.8 ± 2.8 for those without significant hemorrhage, *P* < 0.001). Brier score analysis using this score demonstrated a mean value of 0.067, suggesting high predictive capacity within each individual patient. BLEED-MI score's discriminatory power was assessed by calculating the AUC for the occurrence of significant hemorrhagic events or the composite endpoint of post-discharge bleeding event plus all-cause mortality: (1) Bleeding event: AUC 0.718 ± 0.033, 95%CI: 0.652-0.783, *P* < 0.001; and (2) Composite endpoint: AUC 0.774 ± 0.022, 95%CI: 0.731-0.818, *P* < 0.001.

A BLEED-MI score below 4 had a negative predictive value of 98.9% for the occurrence of a clinically significant hemorrhagic episode during follow-up and for the composite endpoint of post-discharge hemorrhage plus all-cause mortality.

Incidence of primary and secondary endpoints increased progressively with increasing BLEED-MI scores, as shown in Table 5.

Kaplan-Meier curves illustrate the occurrence of the primary endpoint during follow-up and event-free survival (Figure 1) according to risk-group stratification by the BLEED-MI model. As suggested in Figure 1A and Table 6 (which reveals number of patients reaching the primary endpoint at different time points), all bleeding events in the low and intermediate risk categories occurred in the first 12 mo, while hemorrhagic events in the high risk strata were strongly concentrated in the first trimester but otherwise seen until the end of the second year of follow-up. Figure 2 shows the curvilinear change in expected risk of bleeding with increasing BLEED-MI scores (as mentioned before, Table 5 illustrates the actual risk of bleeding in the validation sample).

In patients who did not die during follow-up, the BLEED-MI predicted bleeding with similar efficacy: AUC 0.703, Hosmer-Lemeshow test *P* value 0.547, Brier

Table 4 Hemorrhagic and combined event rates according to the BLEED-myocardial infarction score risk-group stratification

	Category	Low risk	Intermediate risk	High risk	Gamma for trend	*P* value
Clinically significant bleeding events						
Derivation cohort (follow-up: 19.9 ± 6.7 mo)	Incidence	0.80%	3.40%	14.40%	0.70 ± 0.08	< 0.001
Validation cohort (follow-up: 13.4 ± 8.1 mo)	Incidence	1.30%	5.00%	14.10%	0.61 ± 0.08	< 0.001
Composite endpoint (bleeding + all-cause mortality)						
Derivation cohort (follow-up: 19.9 ± 6.7 mo)	Incidence	3.10%	11.40%	45.70%	0.76 ± 0.04	< 0.001
Validation cohort (follow-up: 13.4 ± 8.1 mo)	Incidence	1.30%	9.30%	31.30%	0.73 ± 0.05	< 0.001
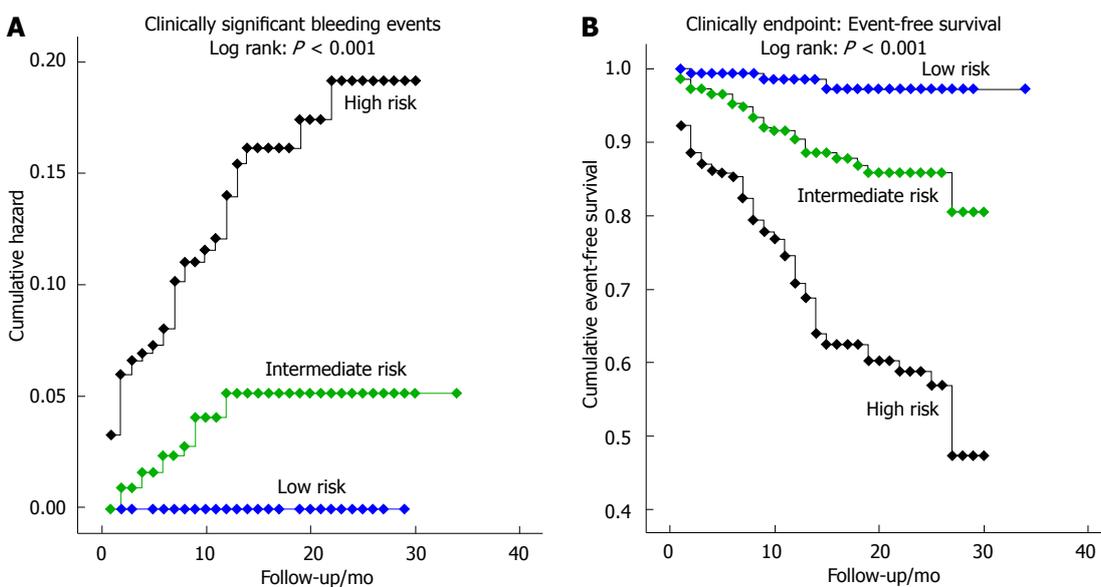
Figure 1 Kaplan-Meier curves illustrating. A: The occurrence of significant bleeding events during follow-up in the validation sample according to risk-group stratification; B: Event-free survival in the validation sample according to risk-group stratification.

Table 5 Primary and secondary endpoint event rates according to the BLEED-myocardial infarction score

Sample	BLEED-MI score	Bleeding event rate	Composite endpoint event rate
Derivation sample	0-1	0.80%	3.10%
	2-3	2.70%	10.00%
	4-5	7.90%	19.10%
	6-7	13.60%	50.40%
	8-9	20.00%	65.90%
	10-11	25.00%	71.40%
Gamma for trend		0.60 ± 0.07	0.70 ± 0.04
P value		< 0.001	< 0.001
Validation sample	0-1	0.00%	0.00%
	2-3	1.20%	1.80%
	4-5	5.40%	8.80%
	6-7	6.50%	16.10%
	8-9	13.90%	25.70%
	10-11	17.80%	39.70%
	12-13	23.10%	48.00%
	14-15	-	60.00%
Gamma for trend		0.52 ± 0.07	0.63 ± 0.05
P value		< 0.001	< 0.001

MI: Myocardial infarction.
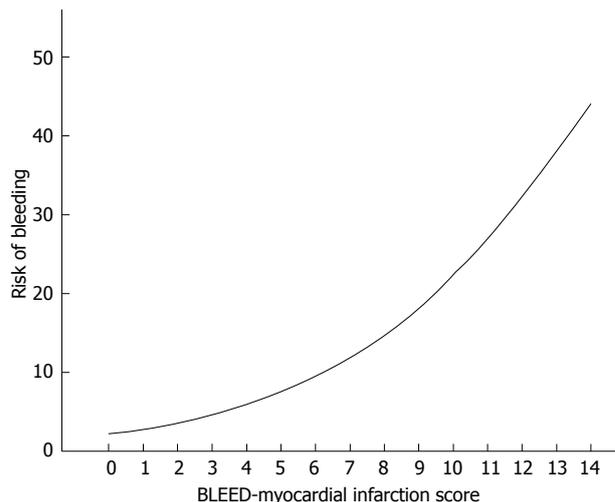
Figure 2 Curvilinear change in expected risk of bleeding with increasing BLEED-myocardial infarction scores (Table 5 illustrates the actual risk of bleeding with increasing BLEED-myocardial infarction scores).

score 0.060. Low-risk (BLEED-MI score 0-3) event rate: 1.2%; intermediate risk (score 4-6) event rate: 5.6%; high risk (score ≥ 7) event rate: 12.5%. In patients who died

during follow-up, no clinically significant non-fatal bleeding event occurred in patients assigned to BLEED-MI low and intermediate risk categories, while BLEED-MI high risk patients had a 20.7% bleeding rate.

The BLEED-MI model was superior to the CRU-

Time (mo)	Low risk	Intermediate risk	High risk
0-3	1	4	21
4-6	0	5	3
7-9	1	4	6
10-12	0	3	4
13-15	0	0	3
16-18	0	0	0
19-21	0	0	1
22-24	0	0	1

Table 6 Number of patients reaching the primary endpoint in the validation sample at different time points

SADE score in the prediction of post-discharge mid-term bleeding events (AUC 7.18 ± 0.033 *vs* AUC 0.696 ± 0.036, respectively). The IDI and relative IDI were 0.024 and 15.6%, respectively, translating significant improvement in risk classification. BLEED-MI was also more effective in predicting inhospital major hemorrhage when both scores were calculated at admission (AUC 7.19 ± 0.032 *vs* AUC 0.642 ± 0.038, respectively).

The BLEED-MI score predicted ischaemic events (non-fatal reinfarction and ischaemic stroke) with reasonable, yet lower, discriminative performance (AUC 0.670 ± 0.029, 95%CI: 0.612-0.727, *P* < 0.001), suggesting a higher utility in the prediction of bleeding, similar to what had been reported in the derivation sample. In addition, it was useful in the evaluation of the net clinical risk (composite of death, non-fatal reinfarction, stroke and significant bleeding): AUC 0.736 ± 0.020, 95%CI: 0.696-0.776, *P* < 0.001.

DISCUSSION

We have derived and preliminarily validate a new bedside prediction-scoring model for clinically significant bleeding events following discharge for acute MI. The score is easy to use and comprises clinical and analytical items that can be collected in a few minutes. The BLEED-MI rule showed good calibration, accuracy and discriminative performance for predicting post-discharge hemorrhagic episodes and a composite endpoint of bleeding events plus all-cause mortality. Importantly, an accurate prediction of bleeding events was shown independently of mortality. Furthermore, a progressively increasing risk of the primary and secondary endpoints was seen with increasing BLEED-MI scores and our results suggested a very high capability of the BLEED-MI rule in identifying low-risk patients, which may be of particular clinical utility.

To the best of our knowledge, this is the first score designed to predict mid-term hemorrhagic risk in patients discharged following admission for acute MI. Other risk scores have been developed to evaluate bleeding risk, but they were designed for patients with atrial fibrillation on oral anticoagulants[21], for the prediction of inhospital hemorrhages in individuals with ACS[20] or following percutaneous coronary interventions[15], or for stable outpatients with or at risk or atherothrombosis-the REACH score[22]. The utility and reliability of the REACH score

for the prediction of post-discharge bleeding was recently and preliminarily evaluated in a contemporary cohort of patients with acute coronary syndrome. It showed good calibration and reasonable discriminative performance (c-statistic values of 0.65 in the whole population (1548 patients), 0.63 for those without coronary revascularization and 0.67 for those treated with PCI[23].

All risk factors included in the BLEED-MI score have been demonstrated before to predict hemorrhagic risk in different or similar clinical contexts: (1) Smoking increases the risk of hemorrhagic stroke both in men[24] and women[25], with a graded increase in risk proportional to how many cigarettes are smoked, and is also considered a risk factor for bleeding and perforated peptic ulcers[26]. The REACH risk score, developed for evaluation of the risk of hemorrhagic episodes in stable outpatients with or at risk of atherothrombosis, included "smoking" as one of its variables[22]; (2) A recently published population-based cohort study demonstrated diabetes mellitus was independently associated with an increased risk of major bleeding episodes[27]. The CRUSADE Bleeding score, developed for the prediction of inhospital major bleeding, incorporates Diabetes[21]. The REACH risk score included diabetes mellitus as well[22]; (3) Age, history of stroke, bleeding history or predisposition and arterial hypertension have been included in the HAS-BLED[28] and HEMORR2HAGES risk scores[21], created for the prediction of bleeding events in patients with atrial fibrillation. Age, hypertension and history of stroke are also among the nine-item REACH risk score[22]; (4) The association between renal dysfunction and bleeding is well documented[7,21,29-31], although a complete understanding of the underlying patophysiology is still lacking. Impaired platelet function, uremic toxins and anemia are some of the determinants of uremic bleeding. Renal dysfunction is also a predictor of hemorrhagic episodes in patients with atrial fibrillation, justifying its inclusion in HAS-BLED (defined as the presence of chronic dialysis or renal transplantation or serum creatinine ≥ 200 μmol/L)[28] and HEMORR2HAGES (defined as a creatinine clearance < 30 mL/min)[21] risk scores; and (5) A low baseline haemoglobin level is an independent predictor of the risk of major bleeding in ACS as well as of the risk of death[32]. Some authors have proposed a reverse J-shaped relationship between baseline hemoglobin values and major adverse cardiovascular events[33], but whether this J-shaped relationship applies to bleeding events as well is still unknown.

Some risk factors for bleeding previously identified in studies of hospitalized patients were not included in this outpatient score. For example, type of MI (STEMI *vs* NSTEMI) and anthropometric variables such as weight and body mass index did not help predict hemorrhagic episodes in univariate analysis and were therefore excluded from the model. This decision was substantiated by the lack of studies demonstrating a potential association between the type of MI and mid to long-term hemorrhagic risk and the fact that the inclusion of anthropo-

metric variables or "type of MI" considerably lowered the c-statistic for post-discharge bleed prediction in both the derivation and validation samples.

The BLEED-MI model can accurately predict post-discharge bleeding events when it is calculated at the patient's admission, before treatment decisions that affect outcome are made. However, as the occurrence of heart failure or bleeding events during hospitalization and the type of antithrombotic therapies prescribed at discharge are also strong predictors of post-discharge bleeding events, they were incorporated in the score as well. Therefore, the BLEED-MI may be calculated any time during hospitalization, depending on the clinical progress and potential complications such as heart failure or significant bleeding.

Depending on its potential external validation in larger cohorts of patients, the BLEED-MI score may eventually help tailor therapeutic decisions, which include the choice of invasive *vs* conservative strategies, the selection of the most appropriate revascularization modality or stent, the prescription of long-term dual-antiplatelet therapy or anti-coagulation or the selection of the best candidates for gastroprotection with proton pump inhibitors. Beyond its potential value in ascertaining relative changes in the risk of bleeding depending on the choice of therapy by including anti-coagulation and anti-platelet therapy in its construction, the BLEED-MI score helps estimate the baseline risk for future treatment decisions.

The c-statistic of BLEED-MI for predicting post-discharge hemorrhage might not be considered particularly impressive. However, performance of a score is evaluated by its discrimination, accuracy and calibration, which were rather good in both the derivation and validation samples. Even so, our c-statistic (0.753 in the derivation cohort, 0.718 in the validation sample) was higher than that of the CRUSADE (0.71)[20], HEMORR2HAGES (0.67)[21], TIMI (0.65)[17] and REACH (0.68)[22] risk scores, and similar to the c-statistic of the HAS-BLED model[28].

Additional considerations concerning the secondary endpoint must be stated. Patients at risk for bleeding events are also at higher post-discharge mortality risk. Although the BLEED-MI model predicted bleeding independently of mortality, major bleeding also identifies patients with an underlying risk for mortality. The true incidence of hemorrhagic events may be underestimated, as patients at higher hemorrhagic risk may die before actually having a significant hemorrhage. Also, some deaths could have been caused by a severe bleed. However, as many patients were not autopsied, it is impossible to know whether a bleeding event was responsible for the death. Therefore, we considered important to test the BLEED-MI rule as a predictor of a composite endpoint of significant bleed plus all-cause mortality. Our model performed even better for this particular endpoint, which reinforces its clinical applicability.

Limitations of this study
The moderate size of our derivation and validation

samples should be considered the main limitation of this study. In fact, the relatively low absolute number of bleeding events during follow-up (62 in the derivation cohort, 60 in the validation sample) and the low event-per-variable ratio posing the risk of over-fitting[34] reinforces the need for external validation in larger cohorts of patients. However, as no other post-discharge mid-term hemorrhage prediction score has been developed to this date, a comparison between derivation cohorts is not possible.

Another limitation of this investigation concerns the different lengths of follow-up in the derivation (19.9 ± 6.7 mo) and validation (13.4 ± 8.1 mo) samples, which was due to the later admission to our hospital of patients assigned to the validation cohort. This explains why post-discharge mortality rate was slightly higher in the derivation sample compared to the validation cohort. However, this limitation is mitigated by the fact that the majority of hemorrhagic episodes occurred in the first year following the MI index (as expected). Also, as most patients stop dual anti-platelet therapy at the end of the 12th month, their bleeding risk is very likely to decrease. Considering the length of follow-up in the derivation sample was > 1 full year, this limitation did not significantly influence the validation of the model.

An internationally accepted, meaningful and standardized approach for reporting bleeding events is lacking. A fixed definition may not work for all disease states throughout ACS and percutaneous revascularization procedures. Definitions of bleeding overlap to a degree but still differ substantially, which may lead to markedly different conclusions regarding incidence of hemorrhagic episodes, predictors and magnitude of short- and long-term prognostic impact. The clinically important goal of identifying patients at very low or high risk of post-discharge bleeding events increases the need for standardized bleeding definitions. The definition of significant hemorrhagic events used in this study partially overlaps with those of the TIMI[17] and GUSTO[18] trials, but it is unclear whether these definitions remain clinically relevant in the era of routine PCI and aggressive antithrombotic therapy[35]. This should be considered a limitation of the present investigation. Also, our study and model is not yet powered to prediction of clinically significant hemorrhages according to severity (life-threatening *vs* moderate episodes), due to the overall low number of events in each isolated category.

Recurrent bleeds were not counted and minor bleeding during follow-up was not systematically assessed. This could be viewed as a limitation of the present study, as minor bleeding also affects quality of life and increases health care costs.

A lower rate of revascularization was reported in the derivation group (61% *vs* 78%), which adds some imbalance to our study populations and may have affected statistical analysis.

Furthermore, although we validated the BLEED-MI score in an independent patient sample and demonstrated

its overall applicability, internal validation cannot control for unrecognized biases in different institutions. This model should be externally validated in larger cohorts of patients, preferably involving multicentre and prospective registries, before its potential implementation. As external validation requires a second large population for whom all necessary data and long-term outcomes are available, we encourage other institutions to test our score in their populations.

In conclusion, a new risk score for predicting post-discharge mid-term hemorrhagic risk has been derived and preliminarily validated in an independent patient sample. The BLEED-MI model has good calibration, accuracy and discriminatory performance in the prediction of bleeding events or a composite endpoint of bleeding plus all-cause mortality. As it is both easy to use and easy to calculate from routinely available clinical data, it may eventually help clinicians take the most appropriate therapeutic decisions in patients with a MI. Nevertheless, the BLEED-MI score needs external validation in larger cohorts of patients before its potential implementation. We encourage other investigators or institutions to test our model in their patients.

COMMENTS

Background
Bleeding has emerged as a predictor of early and late mortality in patients with a myocardial infarction (MI). However, prediction of mid- to long-term haemorrhagic risk following an acute coronary syndrome has received scarce attention, as, to this date, no risk score has been developed for this purpose. In the context of bleeding assessment, evidence-based decision making should lead to selection of appropriate pharmacologic and non-pharmacologic treatments, invasive or conservative strategies that may offer the best balance of benefit and risk. The identification of those patients at highest hemorrhagic risk allows application of more aggressive preventive strategies and potential optimization of outcomes.

Research frontiers
Haemorrhagic events predict early and late mortality in most cardiovascular conditions. Several risk scores have been developed for the prediction of bleeding risk in different clinical contexts. In the area of prediction of bleeding risk in patients with a MI, the research hotspot is how to identify those patients at highest haemorrhagic risk who could eventually benefit from a more conservative strategy regarding revascularization and antithrombotic therapy, and those individuals at lower bleeding risk who may be safely submitted to more aggressive antithrombotic treatment. Optimization of outcomes through efficient thrombotic and haemorrhagic risk stratification is a major research field.

Innovations and breakthroughs
This is the first score designed to predict mid-term hemorrhagic risk in patients discharged following admission for acute MI. Their new bedside prediction-scoring model is easy to use and comprises clinical and analytical items that can be collected in a few minutes. It has shown to be reliable and accurate in the prediction of post-discharge hemorrhagic episodes and a composite endpoint of bleeding events plus all-cause mortality. Importantly, an accurate prediction of bleeding events was shown independently of mortality. Furthermore, a progressively increasing risk of the primary and secondary endpoints was seen with increasing BLEED-MI scores and our results suggested a very high capability of the BLEED-MI rule in identifying low-risk patients, which may be of particular clinical utility. The BLEED-MI model's c-statistic (0.753 in the derivation cohort, 0.718 in the validation sample) was higher than that of the CRUSADE (0.71), HEMORR2HAGES (0.67), TIMI (0.65) and REACH (0.68) risk scores in their respective clinical contexts, and similar to the c-statistic of the HAS-BLED model.

Applications
Depending on its potential external validation in larger cohorts of patients, the BLEED-MI score may eventually help tailor therapeutic decisions, which include the choice of invasive *vs* conservative strategies, the selection of the most appropriate revascularization modality or stent, the prescription of long-term dual-antiplatelet therapy or anti-coagulation or the selection of the best candidates for gastroprotection with proton pump inhibitors. Beyond its potential value in ascertaining relative changes in the risk of bleeding depending on the choice of therapy by including anti-coagulation and anti-platelet therapy in its construction, the BLEED-MI score may help estimate the baseline risk for future treatment decisions.

Terminology
The definition of significant hemorrhagic events used in this study partially overlaps with those of the TIMI and GUSTO trials. Therefore, clinically significant hemorrhage included any major, severe or life-threatening bleeding event, namely those at intracerebral location, those resulting in substantial hemodynamic compromise requiring treatment or in reduction of hemoglobin of 5 g/dL or more (or > 15% in hematocrit). They also included moderate bleeding, defined by the need for transfusion, a drop in hemoglobin of 3-5 g/dL (or in hematocrit from 10% to 15%) from previous blood tests to the time of admission, the occurrence of spontaneous gross hematuria or hematemesis even in the absence of hemoglobin drop higher than 3 g/dL, or unobserved loss of 4 g/dL or more in hemoglobin.

Peer review
This is an interesting study developing and validating a novel risk score for post-discharge bleeding in patients with acute MI.

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CASE REPORT

Unique presentation of Twiddler's syndrome

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Abstract

We present a rare case of Twiddler's syndrome diagnosed in an asymptomatic patient on a routine follow up. This case reiterates the need for frequent monitoring of the implanted device. In addition, it was detected 4 years after implantation of an automatic implantable cardioverter defibrillator. This late representation is extremely uncommon.

Key words: Twiddler's syndrome; Defibrillator; Complication; Malfunction; Lead dislodgement

Core tip: Our case points out few unique points to be remembered in regards to Twiddler's syndrome: (1) Twiddler's syndrome can present without any symptoms. Our case was diagnosed with the help of gradually increasing lead impedance. Ours is the first report-ed case of such a unique presentation; (2) Twiddler's syndrome, although more common in first few months of implantation, can present very late; and (3) frequent monitoring of permanent pacemaker/automatic implantable cardioverter defibrillator is always needed.

INTRODUCTION

Twiddler's syndrome is defined as permanent malfunction of automatic implantable cardioverter defibrillator (AICD) or permanent pacemaker due to conscious or subconscious manipulation of pulse generator within subcutaneous pocket, resulting in dislodgement and/or retraction of leads, leading to loss of device function[1]. First described in 1968, it is one of the rare complications involving a device[1]. Some of the predisposing factors such as female gender, old age, obesity, weight loss, excessive movements of the upper limbs, active manipulation of the generator and large size pockets have been identified[2-5]. However, the exact mechanism behind it remains elusive.

The benefit of the AICD has been established in the primary and secondary prevention of ventricular arrhythmias and sudden cardiac death. Regular monitoring of the AICD is required to ensure normal function. Twiddler's syndrome, in which the pacemaker is rotated manually repeatedly, has been described as a pacemaker complication by Bayliss *et al*[1]. The syndrome has been described in the AICD population as well, and has been implicated in device failure leading to various clinical manifestations including sudden cardiac death[6,7]. However, it presented in a unique manner in our case.
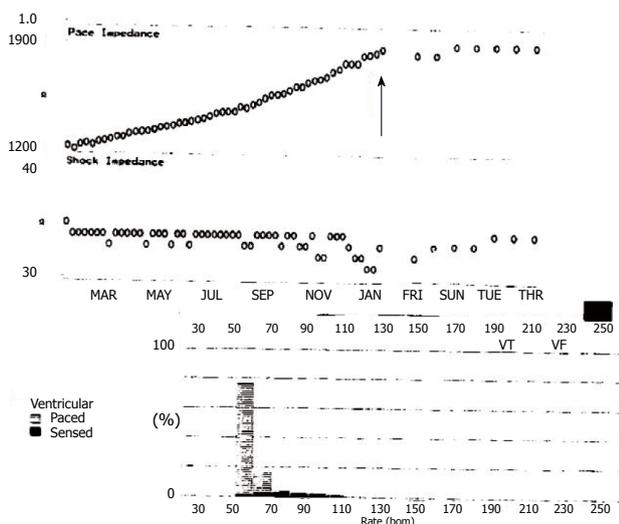
Figure 1 Automatic implantable cardioverter defibrillator interrogation showing gradually increasing pacing impedance over a period of 8 mo (arrow).
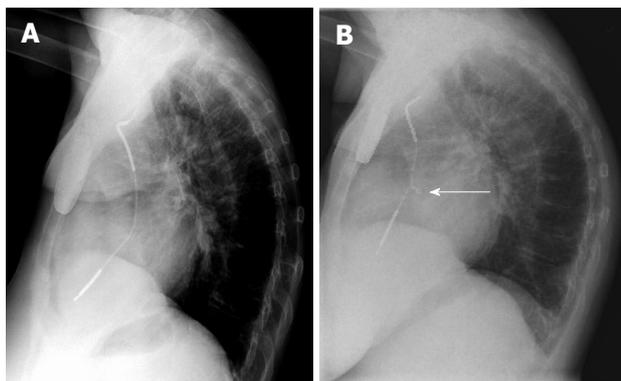
Figure 2 Chest X-ray. A: Normal appearing lead without any twirling; B: A visible twirling is seen at right atrio-ventricular junction (arrow).

Figure 3 Antero-posterior fluoroscopic images. A: Twisting of leads at right atrio-ventricular junction (arrow); B: Near generator in shoulder area (arrow).
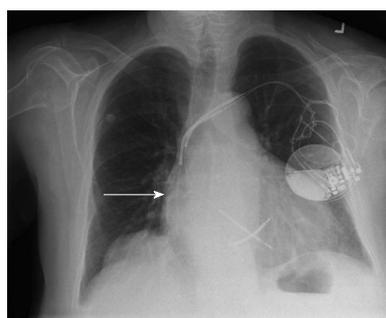
Figure 4 Antero-posterior chest X-ray after successful placement of new ventricular lead (arrow). Abandon ventricular lead can be also be seen.

CASE REPORT

A seventy-three years old woman with history of hypertension, atrial fibrillation and non ischemic cardiomyopathy status post AICD placement for primary prevention 4 years ago, presented to office for routine check-up. Patient denied any palpitation, shortness of breath, fatigue or any other complaints at presentation. Electrocardiogram showed 100% demand ventricular pacing. On routine AICD interrogation, gradually increasing pacing impedance of right ventricular (RV) pace/sense lead over 8 mo, reaching a maximum of 1862 ohms, was found (Figure 1). RV pacing and sensing threshold, and shock parameters were unchanged from last interrogation. A chest X-ray revealed twirling of the ventricular lead (Figure 2). The decision was made to perform a lead revision. During the procedure, fluoroscopy of the leads confirmed a twist in the lead in the right atrio-ventricular junction. Additionally, there was also significant twisting in the shoulder area, partly intravascular and partly in the pocket (Figure 3). The ventricular lead was tested and

showed impedance > 2000 ohms. Due to extensive fibrosis, it was impossible to extract the lead and decision was made to abandon it. A new ventricular lead was placed under fluoroscopic guidance with satisfactory parameters (Figure 4). Since then, the patient is being followed up with no recurrence of this complication or malfunction.

DISCUSSION

Usually presenting in the first year of implantation, Twiddler's syndrome causes RV lead malfunction, usually in the pace/sense lead, and more rarely in the high energy coils. As such, it can lead to under or over sensing, loss of capture, and inappropriate AICD shocks. Usually, these cause symptoms of fatigue and lightheadedness. Rarely, it can lead to heart failure, phrenic nerve stimulation and sudden cardiac death[6,7].

In conclusion, our case is a unique presentation of Twiddler's syndrome in that its initial presentation is in linearly increasing RV lead impedance, without symptoms. We believe this linear increase demonstrates a slowly progressing twist, propagating from the pocket

site down the lead to its distal tip. Moreover, our case is unique regarding the site of the twist as well, located in two different locations. With this, we confirm the importance of regular follow up for patients with AICDs.

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Contents

Contents

APPENDIX

ABOUT COVER

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AIM AND SCOPE

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

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

INDEXING/ ABSTRACTING

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FLYLEAF

EDITORS FOR THIS ISSUE

FIELD OF VISION

High density lipoprotein and cardiovascular diseases

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Core tip: Epidemiological studies have shown that low plasma levels of high density lipoprotein cholesterol (HDL-C) represent a cardiovascular disease (CVD) risk factor. However, recent studies challenge the concept that an increase of plasma HDL-C will uniformly translate into a reduction in CVD risk. Certain patients with atherosclerosis may have "dysfunctional" HDL despite normal HDL-C levels. Furthermore, HDL-C levels are influenced by dietary patterns, drugs or concomitant diseases. The association of the structure of HDL particle with its functionality and metabolism has not been fully clarified. More research is needed to assess the association of HDL functionality with CVD risk.

Abstract

Several epidemiological studies have clearly shown that low plasma levels of high density lipoprotein cholesterol (HDL-C) represent a cardiovascular disease (CVD) risk factor. However, it is unclear if there is a causal association between HDL-C concentration and CVD. A recent study published in the Lancet, which performed two Mendelian randomization analyses, showed that increased HDL-C levels were not associated with a decreased risk of myocardial infarction. These findings, together with the termination of the niacin-based AIM-HIGH trial and the discontinuation of cholesteryl ester transfer protein inhibitor dalcetrapib, challenge the concept that raising of plasma HDL-C will uniformly translate into reductions in CVD risk. HDL particles exhibit several anti-atherosclerotic properties, such as anti-inflammatory and anti-oxidative activities and cellular cholesterol efflux activity. Furthermore, HDL particles are very heterogeneous in terms of size, structure, composition and metabolism. HDL functionality may be associated more strongly with CVD risk than the traditional HDL-C levels. More research is needed to assess the association of the structure of HDL particle with its functionality and metabolism.

COMMENTARY ARTICLE

Several epidemiological studies have clearly shown that low plasma levels of high density lipoprotein cholesterol (HDL-C) represent a cardiovascular disease (CVD) risk factor[1-5]. Furthermore, some large randomized clinical trials have provided evidence of a clinical benefit of drugs increasing HDL-C, such as fibrates, in patients with combined low HDL-C and high triglyceride levels[6-12]. However, whether there is a causal association between HDL-C concentration and CVD is unclear.

A recent study published in the *Lancet* performed two mendelian randomisation analyses, testing a single nucleotide polymorphism (SNP) in the endothelial lipase gene (LIPG Asn396Ser) in 20 studies (20913 myocardial infarction cases, 95407 controls) and a genetic score con-

sisting of 14 common SNPs that exclusively associate with HDL-C (12482 cases of myocardial infarction and 41331 controls)[13]. Carriers of the LIPG 396Ser allele (2.6% frequency) had significantly higher HDL-C levels (0.14 mmol/L higher, $P < 0.001$) but similar levels of other lipid and non-lipid CVD risk factors compared with non-carriers. This difference in HDL-C is expected to decrease the risk of myocardial infarction by 13% (OR = 0.87, 95%CI: 0.84-0.91). However, the LIPG 396Ser allele was not associated with a reduced risk of myocardial infarction (OR = 0.99, 95%CI: 0.88-1.11, $P = 0.85$). Furthermore, whereas it is expected from observational epidemiology that an increase of 1 SD in HDL-C will be associated with a 38% reduced risk of myocardial infarction (OR = 0.62, 95%CI: 0.58-0.66), an 1 SD increase in HDL-C due to genetic score was not associated with a reduced risk of myocardial infarction (OR = 0.93, 95%CI: 0.68-1.26, $P = 0.63$)[13]. These results became more intriguing when a genetic score of 13 common SNPs exclusively associated with low density lipoprotein cholesterol (LDL-C), used as a positive control, was associated with myocardial infarction risk in concordance with observational epidemiology[13].

Additionally, the termination of the cholesteryl ester transfer protein (CETP) inhibitor dalcetrapib was recently announced. Dalcetrapib, in contrast with torcetrapib, was not associated with non-lipid adverse effects[14]. In the dal-VESSEL trial, dalcetrapib reduced CETP activity and increased HDL-C levels without affecting nitric oxide-dependent endothelial function, blood pressure, or markers of inflammation and oxidative stress[15]. Furthermore, co-administration of dalcetrapib with pravastatin resulted in decreased CETP activity, increased HDL-C, apolipoprotein (apo) A-Ⅰ and A-Ⅱ levels and increased CETP mass. A relative increase in large HDL and LDL subfractions, combined with adenosine triphosphate (ATP)-binding cassette A1- and scavenger receptor type BI-mediated cholesterol efflux increase were also observed[16]. These effects seemed promising, but recently Roche announced that, following the results of the second interim analysis of the dalcetrapib dal-OUTCOMES Phase Ⅲ trial (aimed to evaluate the efficacy and safety profile of dalcetrapib when added to existing standard of care in patients with stable coronary heart disease following an acute coronary syndrome), the independent Data and Safety Monitoring Board recommended stopping the trial due to a lack of clinically meaningful efficacy[17].

Furthermore, the results of two large studies of niacin were recently added to these disappointing results. In AIM-HIGH (Atherothrombosis Intervention in Metabolic Syndrome With Low HDL/High Triglycerides: Impact on Global Health Outcomes) trial there was no incremental clinical benefit from the addition of niacin to statin therapy during a 36 mo follow-up period, despite significant improvements in HDL-C and triglyceride levels[18]. More specifically, 3314 patients with atherosclerotic CVD and LDL-C levels < 70 mg/dL (1.81 mmol/L), were randomly assigned to extended-release

niacin (1500-2000 mg/d) or placebo. All patients received simvastatin (40-80 mg/d) plus ezetimibe (10 mg/d), if needed, to maintain an LDL-C level of 40-80 mg/dL (1.03-2.07 mmol/L). The trial was stopped after a mean follow-up period of 3 years owing to a lack of efficacy. At 2 years, niacin therapy had significantly increased the median HDL-C level from 35 mg/dL (0.91 mmol/L) to 42 mg/dL (1.08 mmol/L) and decreased triglyceride level from 164 mg/dL (1.85 mmol/L) to 122 mg/dL (1.38 mmol/L) and LDL-C concentration from 74 mg/dL (1.91 mmol/L) to 62 mg/dL (1.60 mmol/L). However, the primary end point did not differ significantly between niacin (282 patients, 16.4%) and placebo (274 patients, 16.2%) groups (HR = 1.02; 95%CI: 0.87-1.21; $P = 0.79$)[18]. In the HPS2-THRIVE (Heart Protection Study 2-Treatment of HDL to Reduce the Incidence of Vascular Events) study, the combination of niacin and laropiprant in addition to statin therapy did not significantly reduce the risk of major vascular events in patients with well-controlled LDL-C levels[19,20]. More specifically, the primary end point (the combination of coronary death, nonfatal myocardial infarction, stroke, or coronary revascularization) occurred in 13.7% of patients in the control arm and 13.2% of patients in the niacin/laropiprant arm (RR = 0.96, 95%CI: 0.90-1.03, $P = 0.29$)[20].

These data challenge the concept that an increase of plasma HDL-C will uniformly translate into a reduction in CVD risk. HDL-C may simply be a marker of CVD risk, or, alternatively, may represent a biomarker of adverse metabolic processes, as for example of insulin resistance and inflammation.

Some investigators proposed that the failure of dalcetrapib and niacin is related to the only moderate elevation of HDL-C and we have to wait until more potent HDL-increasing drugs to be tested. This thought is based on findings from previous trials. A meta-analysis of 23 trials showed that the sum of percent reduction in LDL-C plus the percent increase in HDL-C predicts CVD benefits much more effectively than either lipoprotein component[21]. Hence, in populations that have already low LDL-C we need potent HDL-elevating drugs to produce significant increases in HDL-C in order to show clinical benefit.

Moreover, differences between levels of LDL-C and HDL-C and their corresponding particle number measures were observed in many trials. This may be of clinical importance since recent studies have shown that CVD risk in patients with discordance between cholesterol and particle measures of LDL and HDL may be associated more with particle measures[22,23]. For example, the significant CVD event reduction in the Veterans Affairs High-Density Lipoprotein Intervention Trial (VA-HIT) could not be fully explained by the 6% increase in HDL-C with gemfibrozil[6,8]. When HDL subpopulations (characterized by 2-dimensional gel electrophoresis) were determined in subjects who were treated with gemfibrozil ($n = 754$) or placebo ($n = 741$), it was shown that gemfibrozil-mediated improvement in CVD risk might not be reflected

by changes in blood lipids and HDL subpopulations[24]. In contrast, when nuclear magnetic resonance (NMR) spectroscopy was used to quantify levels of LDL and HDL particle subclasses and mean particle sizes during treatment with gemfibrozil (364 men) or placebo (697 age-matched controls), it was shown that gemfibrozil increased LDL size and lowered numbers of LDL particles (-5%), whereas it increased the numbers of HDL particles (+10%) and small HDL subclass particles (+21%). In fact, the concentrations of these LDL and HDL particles achieved with gemfibrozil were independent predictors of new CHD events [total LDL particles: OR = 1.28 (95%CI: 1.12-1.47), total HDL particles: OR 0.71 (95%CI: 0.61-0.81)], whereas mean LDL and HDL particle sizes were not associated with CHD events[25]. Additionally, a nested case-control study within the EPIC (European Prospective Investigation into Cancer and Nutrition)-Norfolk cohort showed that both HDL size and HDL particle concentration were independently associated with coronary artery disease (CAD), but only HDL particle concentration was independently associated with CAD risk after adjustment for apoB and triglyceride levels [adjusted OR = 0.50 (95%CI: 0.37-0.66)][26]. These findings suggest that increasing HDL-C without increasing HDL particle number may influence the clinical outcome. The results of AIM-HIGH could be partly explained by these observations[27]. Niacin, similarly to CETP inhibitors, alters the composition of HDL, making the particle larger. However, whereas it significantly decreases the mean number of small HDL particles and increases the mean number of large HDL particles, niacin does not significantly alter the total number of NMR-determined HDL particles[28]. If these effects played significant role in the negative clinical outcomes of AIM-HIGH remains to be established.

HDL particles exhibit several anti-atherosclerotic properties, such as anti-inflammatory and anti-oxidative activities and cellular cholesterol efflux activity[29-32]. In this setting it is important that certain patients with atherosclerosis may have "dysfunctional" HDL despite normal HDL-C levels[33-35]. Furthermore, HDL-C levels are influenced by many factors, such as dietary patterns, drugs or concomitant diseases[36-42]. The heterogeneity in functionality should be taken into account when assessing the association of HDL with CVD risk[43]. HDL functionality may be associated more strongly with CVD risk than the traditional HDL-C levels. However, we do not know which of the HDL functions is more strongly associated with CVD in order to use it in clinical trials. Furthermore, there are several methods assessing different aspects of HDL functionality and many of them are complex and not part of routine bioassays[44]. More research is needed to assess the association of HDL functionality with CVD risk and to simplify its determination.

Additionally, HDL particles are very heterogeneous in terms of size, structure, composition and metabolism[45]. These characteristics may play divergent roles and result in different clinical outcomes[46-48]. Hence, the association of the structure of HDL particle with its functionality

and metabolism should be clarified and accordingly used in the clinical setting.

The role of HDL in CVD may be clarified by the Randomized EValuation of the Effects of Anacetrapib Through Lipid-modification (REVEAL) trial which includes 30000 patients and is currently testing whether the CETP inhibitor anacetrapib (which markedly increases HDL-C along with a lowering of LDL-C) on top of statin therapy will reduce the incidence of major coronary events (coronary mortality, myocardial infarction, and coronary revascularization) in patients with a history of CVD[49]. This phase III study is expected to be completed by 2017. It should be mentioned that niacin and other HDL-increasing drugs, such as anacetrapib, also exhibit beneficial effects on atherogenic lipoproteins, such as LDL or lipoprotein a, so the results of on-going trials will not definitely answer the HDL hypothesis. In this setting, the results of on-going trials with drugs increasing apolipoprotein A- I [50,51] may help to clarify the role of HDL in CVD.

Overall, based on the current evidence, it is unclear if there is a causal association between HDL-C concentration and CVD. HDL particles are very heterogeneous in terms of size, structure, composition and metabolism and exhibit several anti-atherosclerotic properties. The conflicting results of epidemiological and interventional studies may be attributed to the fact that HDL functionality may be associated more strongly with CVD risk than the traditional HDL-C levels. More research is needed to assess the association of CVD risk with HDL functionality and metabolism.

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Atrial fibrillation in heart failure: The sword of Damocles revisited

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Abstract

Heart failure (HF) and atrial fibrillation (AF) frequently coexist and have emerged as major cardiovascular epidemics. There is growing evidence that AF is an independent prognostic marker in HF and affects patients with both reduced as well as preserved LV systolic function. There has been a general move in clinical practice from a rhythm control to a rate control strategy in HF patients with AF, although recent data suggests that rhythm control strategies may provide better outcomes in selected subgroups of HF patients. Furthermore, various therapeutic modalities including pace and ablate strategies with cardiac resynchronisation or radiofrequency ablation have become increasingly adopted, although their role in the management of AF in patients with HF remains uncertain. This article presents an overview of the multidimensional impact of AF in patients with HF. Relevant literature is highlighted and the effect of various therapeutic modalities on prognosis is discussed. Finally, while novel anticoagulants usher in a new era in thromboprophylaxis, research continues in a variety of new pathways including selective atrial anti-arrhythmic agents and genomic polymorphisms in AF with HF.

Core tip: Atrial fibrillation commonly coexists with heart failure and there is growing evidence that it confers an adverse prognostic impact on the natural course of the disease. This review analyses the demographics and relevant literature highlighting this impact as well as the effect of various therapeutic modalities in improving outcomes. Finally some of the future trends in this exciting cardiovascular discipline are discussed.

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INTRODUCTION

Heart failure (HF) and atrial fibrillation (AF) have emerged as major global epidemics[1]. Both frequently coexist and are associated with several common predisposing risk factors such as hypertension, coronary artery disease, structural heart disease (non-ischaemic, valvular), diabetes mellitus, obesity and obstructive sleep apnoea. This co-prevalence increases with advancing age and each predicts/compounds the course of the other[2,3].

Data from Acute Decompensated Heart Failure National Registry demonstrated a 30% prevalence of AF among patients admitted with acute decompensated HF[4].

The EuroHeart survey looked at HF hospitalisation data from 24 countries over a 6-wk duration. It revealed that out of a total of 10701 patients, 34% were known to have AF previously while 9% developed new onset AF[5]. There is good data suggesting that AF is more prevalent in HF with preserved ejection fraction as compared to HF with reduced ejection fraction[6-8]. The prevalence of AF also correlates directly with the severity of HF symptoms. It can vary from under 10% in those with functional New York Heart Association (NYHA) class 1 to as high as 50% in those in NYHA class 4[9]. Similar prevalence figures have been reported from the T-wave Alternans in Patients with Heart Failure[10] as well.

PATHOPHYSIOLOGICAL INTER-RELATIONSHIP

The interplay between HF and AF is complex. HF predicts the development of AF and conversely AF predisposes to HF[2]. There are a number of mechanisms through which HF predisposes to an arrhythmogenic atrial substrate. These include elevated left sided-filling pressures, mitral regurgitation, atrial enlargement, interstitial fibrosis and electromechanical remodelling[3]. Activation of autonomic and renin-angiotensin axis contributes while changes in the intracellular calcium are thought to play a role as well[11].

Conversely, AF can lead to HF through multiple adverse effects including loss of atrial systole, functional mitral/tricuspid regurgitation, tachycardiomyopathy and reduced ventricular diastolic filling time[2]. Irregularity in the RR interval can also have a potentially deteriorating influence on cardiac output irrespective of the heart rate[12]. Moreover, deterioration of sinus rhythm into AF in patients with HF can lead to acute decompensation. A prospective study of 344 HF patients (who were in sinus rhythm at baseline) revealed significant haemodynamic deterioration with the onset of AF. Development of AF in this cohort led to reduced cardiac output, bi-atrial dilatation and functional atrioventricular valve regurgitation. This was reflected as a decline in the functional NYHA symptom class as well as peak exercise oxygen consumption[13]. Details of the pathophysiological pathways involved are beyond the remit of this review and have been reviewed well previously[14].

EPIDEMIOLOGY

According to the National Health And Nutrition Examination Survey, the prevalence of HF in Americans older than 20 years of age, is around 5.7 million (2.4%). It ranges from around 1.5% in those over 40 years to as high as 11% in the above 80 years age group. The lifetime likelihood of developing HF at the age of forty years has been estimated as 1 in 5[15]. Similarly, estimate from existing data suggests that as many as 30 million people in Europe are living with HF[16]. HF incidence also increases progressively with age ranging from a rate of 1.4 per 1000 person-years in 55-59 year-old group to 47.4 per 1000 person-years in above 90-year-old bracket[17].

AF is the commonest arrhythmia encountered in medical practice[18]. The prevalence of AF in the United States is estimated between 2.7 and 6.1 million. This is projected to increase to between 5.6 and 12.0 million[15] rising progressively to two and a half-fold by 2050[19]. According to the Rotterdam as well as the Framingham studies, the lifetime risk of developing AF has been estimated to be around 1 in 4[20,21]. Incidence of AF also increases progressively with age approaching a risk of 11%-18% by 90 years[22].

IMPACT OF AF ON HF PROGNOSIS

There has been increasing evidence regarding the adverse role of AF in patients with HF, both in terms of morbidity as well as prognosis (Table 1).

Mountantonakis *et al*[23] analysed the data from patients enrolled in the Get With The Guidelines-Heart Failure Registry between 2005 and 2010. They looked at 99810 patients hospitalised with HF across 255 United States sites. One-third of the cohort had AF and when compared to those in sinus rhythm, it was independently associated with a longer length of hospital stay (mean 5 *vs* 4 d; *P* < 0.001) as well as higher in-hospital mortality (4.0% *vs* 2.6%, *P* < 0.001). A post hoc analysis of the data from the Efficacy of Vasopressin antagonism in hEart failuRE: outcome Study with Tolvaptan looked at the clinical characteristics of 4133 patients out of which 29% had atrial fibrillation/atrial flutter at baseline. In contrast to patients in sinus rhythm, AF was found to confer an increased risk of death (HR = 1.23, 95%CI: 1.04-1.46) and cardiovascular mortality/HF admission (HR = 1.26, 95%CI: 1.07-1.47)[24]. Retrospective subset analysis of studies of left ventricular dysfunction (SOLVD) looked at 6517 patients with LVEF less than 35%[25]. It showed that patients in AF had an increased risk of all-cause mortality of 34% as compared to 23% for those in sinus rhythm. The higher mortality was largely attributable to increased risk of pump failure deaths. These findings were applicable to symptomatic as well as asymptomatic patients. Data from the Candesartan in Heart failure Assessment of Reduction in Mortality and morbidity trials demonstrated an independent detrimental effect of AF on long term cardiovascular outcomes in HF patients (either reduced or preserved LV systolic function)[26]. Similarly, an adjusted meta-analysis by Mamas *et al*[27] has demonstrated a worse prognostic impact of AF in HF. This was based on 16 studies including 7 randomised trials and 9 observational studies and included data from 53969 patients. The impact of AF on mortality was reflected by an OR of 1.40 (95%CI: 1.32-1.48, *P* < 0.0001) in randomised trials and an OR of 1.14 (95%CI: 1.03-1.26, *P* < 0.05) in observational trials. This was irrespective of the LV systolic function. Middlekauff *et al* conducted a prospective study of 390 patients with NYHA class 3-4 symptoms and a mean LV Ejection Fraction (LVEF) of

Table 1 Prognostic impact of atrial fibrillation in heart failure

Ref.	Setting	*n*	LVEF	Mean follow up (yr)	AF	Deaths *n* (%) SR	Deaths *n* (%) AF	*P*-value
Randomised trials								
Dries *et al*[25]	SOLVD	6517	< 35%	2.8	6%	1395 (23)	149 (34)	< 0.0001
Olsson *et al*[26]	CHARM	7601	All LVEF included	3.1	15%	1466 (23)	365 (32)	< 0.001
Swedberg *et al*[38]	COMET	3029	< 35%	4.8	20%	874 (36)	258 (43)	< 0.0005
Carson *et al*[109]	V-HEFT I&II	1427	< 45%	2.5	19%	480 (39)	75 (36)	NS
Mathew *et al*[110]	DIG	7788	All LVEF included	3.1	11%	2231 (32)	375 (43)	< 0.0001
Crijns *et al*[111]	PRIME II	409	< 35%	3.4	21%	153 (47)	50 (60)	< 0.05
Pederson *et al*[112]	DIAMOND	3587	< 35%	N/A	24%	1951 (73)	634 (77)	< 0.001
Observational studies								
Rivero-Ayerza *et al*[5]	EuroHeart Failure Survey	10701	All LVEF included	N/A	43%	419 (7)	372 (8)	< 0.05
Ahmed *et al*[28]	Medicare AL	944	All LVEF included	4.0 yr	27%	439 (62)	166 (71)	< 0.01
Mahoney *et al*[37]	Heart Transplantation	234	< 45%	1.1 yr	27%	26 (15)	14 (22)	NS
Middlekauff *et al*[113]	Heart Transplantation	390	< 35%	265 d	19%	123 (29)	36 (48)	< 0.005
Stevenson *et al*[114]	Heart Transplantation	750	< 40%	2.0 yr	22%	336 (45)	104 (61)	< 0.01
Wojtkowska *et al*[115]	Bilaystok, Poland	120	< 30%	3.0 yr	50%	26 (43)	33 (55)	NS
Corell *et al*[116]	Danish HF clinic Network	1019	< 45%	1.9 yr	26%	180 (24)	89 (33)	< 0.05
Pai *et al*[117]	Loma Linda VA	8931	All LVEF included	2.5 yr	18%	2164 (28)	529 (44)	< 0.0001
Rusinaru *et al*[118]	Somme, France	368	> 50%	N/A	36%	125 (53)	84 (64)	< 0.05
Hamaguchi *et al*[119]	Japanese Registry data	2659	All LVEF included	2.4 yr	35%	N/A	N/A	NS
Shotan *et al*[120]	National HF Survey, Israel	4102	All LVEF included	4	33%	1480 (54.3)	882 (64.9)	0.000

SR: Sinus rhythm; AF: Atrial fibrillation; LVEF: Left ventricular ejection fraction; NS: Not significant; N/A: Not applicable; SOLVD: Studies of left ventricular dysfunction; CHARM: Candesartan in heart failure assessment of reduction in mortality and morbidity; COMET: Carvedilol or metoprolol European trial; DIG: Digitalis investigation group; DIAMOND: Danish investigations of arrhythmia and mortality on dofetilide.

around 20%. Nineteen percent of this cohort had AF and this was shown to be an independent predictor of all-cause mortality (actuarial survival at 1 year with AF 52% *vs* 71% with sinus rhythm). A retrospective study of 944 Medicare beneficiaries looked at 30-d re-hospitalisation and 4-year mortality figures in HF patients older than 65 years (mean age of 79 years). No distinction was made between reduced and preserved LV systolic function. Risk of readmission was not significantly higher[28] but patients in AF had a 52% increased likelihood of mortality over 4 years as compared to the ones in sinus rhythm. Finally, Caldwell *et al*[29] studied a cohort of 162 patients who had received biventricular device implants for advanced HF (NYHA 3 and 4). Almost a third of the patients (who were thought to be in sinus rhythm) were found to have silent episodes of paroxysmal AF. There was a trend of increased mortality but not towards thromboembolic episodes or hospitalisation.

Studies have also focused specifically on the prognostic effect of AF in ischaemic cardiomyopathy. The VALsartan In Acute myocardial iNfarction Trial involved over 14000 patients who had suffered from acute myocardial infarction complicated with LV systolic dysfunction. Patients in AF (both chronic AF at baseline as well as new-onset) had higher mortality at 3 years follow up as compared to those in sinus rhythm (37% *vs* 20%)[30]. Analysis of the danish investigations of arrhythmia and mortality on dofetilide in congestive heart failure (DIAMOND-CHF) data compared ischaemic *vs* non ischaemic subsets[31]. Three thousand five hundred and eighty-seven HF patients were followed for up to 8 years. AF had a

significant prognostic effect in those with ischaemic heart disease (HR = 1.25, 95%CI: 1.09-1.42, $P < 0.001$] as compared to those without ischaemic heart disease (HR = 1.01, 95%CI: 0.88-1.16, $P = 0.88$]. A likely explanation may be that AF aggravates ischaemia in such cases (due to its association with increased coronary vascular resistance and reduced myocardial perfusion) thus affecting prognosis adversely[32]. Four-year follow up of 2881 participants of the EChocardiographic Heart Of England Screening study showed similar results[33].

A limited number of small studies have been conducted to evaluate the temporal significance of AF and it is not entirely clear whether AF prior to HF portends a worse prognostic influence or vice versa. The Euro-Heart Failure survey indicated that new onset acute AF is associated with increased mortality as compared to chronic AF (12% *vs* 7%). The likely explanation may be related to tachycardia-related adverse haemodynamics as well as higher utilization of anti-arrhythmic agents in the acute setting[5]. Data from the community-based study by Chamberlain *et al*[34] divided 1664 HF patients into 3 groups namely HF without AF (*n* = 727), HF with AF preceding HF (*n* = 553) and HF with onset of AF after developing HF (*n* = 384) . In comparison to the group in sinus rhythm, the prior-AF group had 29% higher all-cause mortality. This contrasted to the AF-after-HF group who had more than twice the mortality. Similarly, in the cohort assessed by Smit *et al*[35], prognosis of patients who developed AF first was comparatively better as compared to those who developed AF after HF. A hundred and eighty two consecutive AF patients admitted for HF were

followed up for 16 ± 11 mo looking at the primary composite end point of cardiovascular hospitalisation and all-cause mortality. Seventy five percent of the cohort were known to have AF prior to onset of HF while 25% developed AF proceeding HF. When compared to the HF-first group, AF-first cohort was less likely to reach the primary end-point (49.6% *vs* 77.7%, *P* = 0.001). The recently published Worcester HF Study has also demonstrated higher inpatient death rates as well as post-discharge mortality in HF patients with concurrent AF[36].

Other studies, however, have not corroborated this independent impact of AF in HF. For instance, Mahoney *et al*[37] showed that in patients referred for cardiac transplantation, AF was not associated with an increased mortality. However, given the end-stage disease (where prognosis is poor irrespective of AF) and small numbers involved (as well as the cross-sectional design of the study), it is difficult to generalize these results to a wider non-selected HF population. Similarly, an analysis of the Carvedilol Or Metoprolol European Trial data looked at the potential prognostic effect of AF in HF. When corrected for other prognostic markers, AF lost its independent effect on mortality[38]. However, the criterion for diagnosing AF was limited to a single baseline ECG. This may have failed to pick up paroxysmal AF or future AF events. Thus, the reported prevalence of 19.8% of the study cohort who had AF may represent an underestimate.

Conversely, HF also impacts prognosis in AF. This is in keeping with the bidirectional interaction between the two disorders. For instance, the Framingham studies as well as EuroHeart Survey have demonstrated the vicious effect one condition has on the prognosis of the other[39,40].

EFFECT OF AF THERAPY ON PROGNOSIS

Although several of the studies outlined above demonstrate an adverse prognostic influence of AF in HF, yet the optimal approach of managing such patients still remains unclear.

Pharmacological therapy

Rate control: Ventricular rate control remains a major therapeutic target for AF in HF patients. Beta-blockers and digoxin (as adjunctive therapy) are the main agents available for systolic HF. In addition, non-dihydropyridine calcium channel antagonists (verapamil, diltiazem) can be used instead of beta-blockers in HF with preserved EF. Finally, amiodarone can be considered for rate control if combination of beta-blocker and digoxin is inadequate[41]. A number of studies have demonstrated prognostic benefit of beta-blockers in AF with HF. A retrospective analysis of the US Carvedilol HF trial data focused categorically on patients who had AF at the time of enrolment. In comparison to the placebo arm, the beta-blocker group had improved LV ejection fractions and better physician-determined global assessment. Moreover, there was a tendency towards reduced combined cardio-

vascular mortality and hospitalisation[42]. The Digitalis Investigation Group trial showed that although digoxin did not affect mortality in HF, it reduced the number of hospital admissions. AF was among the exclusion criteria and as such these results may not be applicable to AF in HF[43]. Moreover, digoxin loses its effect during periods of catecholamine excess and is not recommended as monotherapy. Of note, a recent post-hoc analysis of the the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial has cast doubt on the safety of digoxin in HF patients[44]. It was shown that digoxin is associated with increased all-cause mortality including a 41% increased risk of death in patients with CHF or LVEF of less than 40%. This should, however, be interpreted with caution as AFFIRM was designed to compare rate and rhythm control and patients were not randomised to digoxin therapy. Moreover, only 25% of the AFFIRM cohort had HF. Moreover, a propensity matched analysis of the same cohort failed to demonstrate any increase in mortality with digoxin. It is likely that the patients on digoxin in the study had higher risk of mortality[45]. Finally, data on the use of verapamil and diltiazem in HF is limited[46]. Verapamil has been shown to be useful in HF patients with normal LV systolic function[47] and current ESC guidelines recommend their use in HF with preserved ejection fraction as an alternative to beta-blockers[41]. However, these should be avoided in HF with reduced ejection fraction due to negative inotropic effect on LV contractility[41,48].

Another point that needs further clarification relates to the optimal target ventricular rate for permanent AF patients in HF. Rate control efficacy in permanent Atrial fibrillation: a Comparison between lenient *vs* strict ratE control Ⅱ (RACE Ⅱ) trial looked at lenient (110 bpm) *vs* strict (< 80 bpm) ventricular rate control in patients with AF. The primary end-point was a composite of cardiovascular death, HF admission, bleeding and embolic events including stroke. No significant difference was observed in the two arms[49]. Again less than 35% of the cohort had HF (15% in NYHA class 4) and results may not be generalizable to the HF patients. Routine versus Aggressive upstream rhythm Control for prevention of Early atrial fibrillation in HF (RACE Ⅲ) is currently recruiting and will provide definitive answers for the HF population[50].

Rhythm control: Amiodarone and dofetilide are the main anti-arrhythmic agents assessed in HF patients with AF. Survival trial of antiarrhythmic therapy in congestive heart failure (CHF-STAT) and atrial fibrillation and congestive heart failure (AF-CHF) trials have demonstrated the efficacy of amiodarone in cardioversion and maintenance of sinus rhythm in patients with moderate to severe LV systolic dysfunction[51,52]. Its overall effect on mortality was shown to be neutral but long-term clinical use remains limited due to a risk of significant side effects. DIAMOND-CHF trial looked at the effect of dofetilide on a cohort of mainly ischaemic HF patients.

A pooled sub-study analysis incorporated 506 patients who were in AF. Dofetilide was shown to be safe with an overall neutral effect on mortality. It was superior to placebo in cardioversion and patients on the drug were more likely to be in sinus rhythm at one year as compared to placebo (79% *vs* 42%). Moreover, it was also associated with reduced HF admissions[53]. Importantly, patients who converted to sinus rhythm had lower all-cause mortality (in the dofetelide as well as placebo arms) signifying the beneficial prognostic impact of sinus rhythm. However, torsade de pointes (1.6%) remains a cause for concern with dofetilide and requires initiation in hospital under close monitoring. Furthermore, it is not available in Europe. Subsequently, dronedarone (an iodine-free amiodarone derivative) was introduced with a promising adverse effect profile. A post hoc analysis of the ATHE-NA (A Trial with dronedarone to prevent Hospitalization or death in patiENts with Atrial fibrillation) looked at stable patients with LVEF less than 40% and NYHA 2-3 symptoms. It showed a reduced risk of all-cause mortality and/or hospitalisation due to cardiovascular events[54]. However, ANtiarrhythmic trial with dronedarone in Moderate-to-severe congestive heart failure Evaluating morbidity DecreAse (ANDROMEDA) trial (which looked at patients with severe HF in sinus rhythm and not AF) had to be terminated prematurely because dronedarone increased mortality in such patients[55]. As a result, it is no longer licensed for use in patients with unstable/severe HF.

Rate *vs* rhythm control: There is no convincing scientific evidence so far to support a rhythm control strategy in preference to rate control. Given the negative impact of AF in HF, the concept of maintaining sinus rhythm appears attractive, yet a number of randomised trials have failed to demonstrate improved long-term outcomes with a rhythm control approach[56-59]. The results are, however, limited by the fact that these trials were not exclusive to HF (for instance only 25% of the AFFIRM cohort had depressed LV function) and it may be difficult to apply these findings to the HF population. On the other hand, there have been trials looking exclusively at HF patients as well. AF-CHF enrolled 1376 patients with systolic HF. They were randomized to either rhythm or rate control and followed up for 3 years looking at prospective data for mortality, HF admissions and stroke[52]. The difference in cardiovascular mortality observed in the two arms was not significant (27% in rhythm control *vs* 25% in rate control respectively). It is noteworthy, however, that only 80% of patients in the rhythm control arm remained entirely AF-free (65% when looking at overall 3 year follow up visits as well as the 21% who crossed over to rate control arm)[11]. Interestingly, a post hoc analysis of the AFFIRM trial looked at the rhythm control arm of the trial. Sinus rhythm was associated with less severe NYHA symptomatic class and better functional capacity (assessed by 6-min walk test)[60]. Similarly, in a subgroup analysis of CHF-STAT trial, Kaplan-Meier analysis of the survival

curves for those who converted to SR with amiodarone showed significantly better survival as compared to those who remained in AF[51]. Same conclusion can be derived from the DIAMOND sub-study as well[53]. However, these results are based on post-hoc subgroup analyses and should be applied with caution. A recent meta-analysis of the 4 main randomised control trials of AF rate vs. rhythm control in HF (incorporating 2486 patients) has demonstrated no significant difference in terms of mortality and thromboembolic events[61].

Thromboprophylaxis: Although beyond the scope of this review, it would be amiss not to mention the enormous clinical, social and economic impact of stroke in HF patients with AF. Due to various co-morbidities, patients with HF have a significantly higher risk of thromboembolic events particularly stroke. Hence, oral anticoagulation is imperative unless there are equally binding contraindications. ACCF/AHA/HRS guidelines have kept the option of either aspirin or anticoagulation for patients with a CHADS2 score of 1 while European Society of Cardiology (ESC) and Canadaian Cardiovascular Society (CCS) guidelines indicate anticoagulation for such patients in preference to aspirin. Nevertheless, there is unanimous agreement in recommending long-term anticoagulation for all patients with a CHADS2 score of 2 and above[62]. Warfarin is well recognized in this regard and has been the mainstay of thromboprophylaxis in AF[63] for the last 60 years. It has been shown to reduce the risk of stroke by as much as 65% and is thrice as efficacious as aspirin[64]. Its clinical utility, however, is fraught with a variety of limitations (both real and perceived, by patients and physicians alike). These include a narrow therapeutic window, need for meticulous monitoring of INR levels, unreliable blood levels due to interaction with various drugs/food and risk of bleeding in an increasingly frail/ ageing population.

The last few years have witnessed the exciting development of a novel group of oral anticoagulants (NO-ACs) with the advantage of rapid onset of action, fewer drug/food interactions and predictable blood levels thus exonerating patients from laborious INR monitoring. They have been shown to carry a lesser risk of intracranial bleeding in comparison to warfarin while maintaining the same level of protection against stroke. However, widespread use is restricted by higher costs, unavailability of a reversal agent in the event of a major bleed and no validated lab markers of anticoagulant effect[65]. The two main classes consist of direct thrombin inhibitors (dabigatran) and activated factor X inhibitors (apixaban, rivaroxaban, edoxaban) while several others are under development. Dabigatran was the first to be approved by Food and Drug Administration in 2010 for non-valvular AF following the Randomized Evaluation of Long-term anticoagulation therapY (RE-LY) trial[66] which enrolled 18113 patients with AF. One-third of the study population had symptomatic HF or LVEF < 40%. Patients were randomized to receive either 150 or 110 mg twice daily

(blinded dose groups) of dabigatran or INR-guided warfarin therapy. In comparison to warfarin, 110 mg twice daily dose was non-inferior in efficacy and superior in safety while the 150 mg twice daily dose was superior in efficacy and had similar rates of major bleeding. Consequently, dabigatran has been recommended as an alternative to warfarin in recent ESC, AHA/ACCF as well as CCS guidelines[67-69]. Similarly, Rivaroxaban was studied in the Rivaroxaban Once daily oral direct factor Xa inhibition Compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF) looking at over 14000 patients. Data demonstrate non-inferiority to warfarin in terms of efficacy. It was associated with less intracranial haemorrhage as well albeit a higher risk of gastrointestinal bleed[70]. Finally, Apixaban is the only one so far which has been shown to be superior to warfarin in reducing the primary end-point of thromboembolic events including stroke (annual event rate 1.27% *vs* 1.60%; $P < 0.001$ for noninferiority; $P = 0.01$ for superiority). This is derived from the Apixaban in Preventing Stroke and Systemic Embolism in Subjects With Nonvalvular Atrial Fibrillation trial which enrolled over 18000 patients. The 21% reduction in primary safety end-point was mainly derived from a lower likelihood of haemorrhagic strokes. There was no significant difference in the rates of ischaemic strokes between the two[71]. All three NOACs available so far have been licensed for use in non-valvular AF.

Non-pharmacological therapy

Drug therapy is the mainstay of AF management. However, many patients are unable to achieve rhythm or rate control targets due to therapeutic inefficacy or side effects respectively. Consequently, device therapy and electrophysiological catheter interventions have gained importance.

"Pace and ablate" strategy: Atrio-ventricular node (AVN) ablation accompanied by a permanent pacemaker is often used as an extreme option for definitive rate control. However, AF is not eliminated per se and rate control with a regular RR length may not suffice in compensating for the haemodynamic detriment caused by A-V dys-synchrony and loss of atrial systole. Thus, arguably, the procedure may only be of symptomatic benefit[72]. Moreover, there is a potential for progressive inter-ventricular dys-synchrony due to chronic RV pacing. Hence, cardiac resynchronisation therapy (CRT) has emerged as the pacing option of choice in all patients with systolic HF[73,74] who require pacing for AVN ablation. On the other hand, it is well recognized that clinical response to CRT is hampered if adequate AF rate control cannot be achieved. This is likely to be due to a lower percentage of biventricular pacing and here AVN ablation can be very helpful. This has been demonstrated in a recent meta-analysis of 23 observational studies involving 7495 CRT patients (25% of the total had AF). When compared to patients in sinus rhythm, presence of AF conferred a

higher likelihood of CRT non-response and increased all-cause mortality (10.8% *vs* 7.1% per year, pooled RR = 1.50, 95%CI: 1.08-2.09, $P = 0.015$). In addition, there was a lesser improvement in quality of life, exercise capacity and LV end-systolic dimensions. On the other hand, in patients with AF, AVN ablation not only improved response to CRT (RR = 0.40, 95%CI: 0.28-0.58, $P < 0.001$) but was associated with a reduced risk of mortality as well[75]. A number of other small, mostly single-centre, non-randomized studies of CRT (in HF patients with AF) have also shown improvement in soft end-points such as reduced mitral regurgitation, improved LV ejection fraction and better exercise capacity but clearly more data is required[76-78]. For instance, a registry-based analysis of patients with severe HF compared 139 patients who had AF with 445 in sinus rhythm. One year follow up revealed comparable CRT-related improvement in NYHA symptom class and LV ejection fractions in the two cohorts. Of note, mortality was higher in the AF group (12% *vs* 7%; OR = 1.80, 95%CI: 0.95-3.4)[78]. Although the results are encouraging, yet large scale placebo controlled randomised trials are still required to confirm long term prognostic benefit.

AF ablation: As noted above, "pace and ablate" strategy is effective in controlling the ventricular rate but it does not eliminate AF as such. Also, like all invasive procedures CRT is not free of potential complications. Consequently, radio-frequency catheter ablation (RFA) using pulmonary vein isolation (PVI) has gained momentum in the management of AF. A number of observational studies (albeit small) provide supportive data for such a strategy. The non-randomized observational study by Hsu *et al*[79] compared 58 patients in HF with an equivalent number of age/sex matched controls without HF. All underwent RFA for AF. At the completion of one year, 78% of the HF cohort and 84% of controls remained in sinus rhythm (although 50% had required a second procedure due to recurrence of AF). RFA led to significantly improved LV function (mean increase 21%) in the HF cohort. In addition, significant improvement was seen in NYHA symptom class, quality of life (assessed by SF-36 QoL scores) and exercise capacity (assessed by bicycle-ergometer stress test) as well. The trial was, however, not powered to look at mortality trends. Similar results have been obtained in a number of other small non-randomized studies demonstrating improvement in LVEF and patient symptoms[80-82]. Pulmonary vein Antrum isolation *vs* atrioventricular node ablation with Biventricular pacing for treatment of atrial fibrillation in patients with congestive heart failure (PABA-CHF) was a multi-centre study which prospectively randomized 81 drug-refractory AF patients (with a LVEF of 40% or less and NYHA functional class 2-3) to undergo PVI or AVN ablation with biventricular ICD implant. They were followed up at 6 mo. The composite primary end point consisted of LVEF, 6-min walk distance and Minnesota Living with Heart Failure score. PVI patients fared better in all

three components of the end point than the cohort who underwent AVN ablation and biventricular pacing[83]. Recently, MacDonald *et al*[84] conducted a randomised controlled trial in HF patients comparing rhythm control by RFA (*n* = 22) to rate control by medical therapy (*n* = 19). RFA failed to show any significant improvement in radionuclide LV ejection fractions as compared to the rate control arm. Only 50% were able to retain sinus rhythm at the end of one year and a significant (15%) complication rate was observed. A meta-analysis of AF ablation trials in patients with moderate LV systolic dysfunction looked at 9 studies involving a total of 354 patients. RFA led to an overall improvement in LV systolic function. However, the results are limited by heterogeneous study cohorts and lack of long-term outcome data[85]. Hence, large scale, multicentre, randomized controlled trials with longer follow up will be required for further definitive clarification. Finally, in patients undergoing cardiac surgery, surgical ablation techniques (variations of Cox Maze procedure) are available as a safe and effective alternative[86] including for those with depressed LV function[87].

FUTURE TRENDS

Selective AV nodal stimulation

Selective AV nodal vagal stimulation (AVN-VS) has emerged as a potentially viable therapeutic intervention for ventricular rate control in AF. Loss of vagal tone followed by sympathetic overstimulation is thought to contribute to the pathophysiology of HF. Epicardial AV nodal fat pad stimulation (using catheter electrodes) targets parasympathetic efferents in the vagal ganglia and confers negative chronotropic and dromotropic effects. This can then be potentially used to modulate AF rate control in patients with HF. Small-scale, randomised preclinical case-control studies have shown effective heart rate control along with improvement in LV function in acute[88] as well as chronic settings[89]. Investigators induced HF and AF in canine models using rapid ventricular pacing for 4 wk followed by continued rapid atrial pacing respectively. Similar reversible negative chronotropic effects have been demonstrated in a cohort of 25 patients who underwent efferent vagal nerve stimulation with a multipolar catheter in superior vena cava or coronary sinus[90]. Although it is only hypothesis generating at this stage, yet it showed consistent slowing of the heart rate and this was associated with improved LV function. Larger trials are needed to ascertain the true potential of this technique.

Atrial-specific anti-arrhythmic agents

Currently available anti-arrhythmic agents used for AF act on multiple ion-channels located in the atria as well as ventricles. Consequently, there is a risk of ventricular pro-arrhythmia and this is a particular concern in patients with structural heart disease/HF. Development of atrial specific anti-arrhythmics with a reduced risk of ventricular pro-arrhythmia is indeed an attractive strategy[91]. Vernakalant is a potassium-channel blocker which has undergone successful phase Ⅱ and Ⅲ trials. It is different to the conventional class Ⅲ agents in that it selectively delays atrial repolarization by blocking atrial specific potassium-channels. As a result it suppresses AF by prolonging the atrial refractory period and is not associated with ventricular pro-arrhythmic effects such as QT prolongation and torsades[92]. A phase Ⅲ superiority study of Vernakalant *vs* Amiodarone in Subjects With Recent Onset Atrial Fibrillation (AVRO) demonstrated superior efficacy of vernakalant as compared to amiodarone[93]. However, only 20% of the patients in the cohort had HF. Also, there is no experience yet in advanced HF as patients with unstable congestive HF, NYHA class 4 symptoms, or HF requiring inotropes were excluded from the study.

Left atrial appendage occlusion devices

A significant minority of patients in AF are unable to benefit from oral anticoagulation-either due to contraindications (bleeding, allergy) or therapeutic failure (ischaemic stroke despite effective anticoagulation). Studies have shown that in non-rheumatic AF, left atrial appendage serves as the source of thromboemboli in around 90% of cases[94]. Consequently, percutaneous devices for the occlusion/exclusion of the left atrial appendage have emerged as a potentially promising answer to this challenging conundrum[95]. Results from the recent randomised WATCHMAN left atrial appendage system for embolic PROTECTion in patients with Atrial Fibrillation (PROTECT AF) trial have established the feasibility of this technique[96] while demonstrating non-inferiority with warfarin therapy. The initially high rate of procedural complications has subsequently improved with greater operator experience[97] and combination with PVI has been successfully carried out[98] as well. Long term outcome data is not available yet. Trials are also underway assessing further devices such as the Amplatzer cardiac plug and LARIAT suture delivery system[99].

Genomics

Despite the frequent coexistence of AF and HF, it is intriguing that more than half of even severe HF patients do not develop AF. It is postulated that there may be a genetic predilection for AF in certain HF patients. If such is the case, then modulating these factors may provide a potential therapeutic target. Indeed, familial clustering of AF is well recognized. Moreover, genome wide association studies have demonstrated several common AF-related mutations and polymorphisms[100]. Recently, a large population study showed a strong genetic association between AF and a polymorphism in the *ZFHX3* gene (which encodes a cardiac transcription factor). This was associated with increased AF risk in HF patients when compared to the general population[101]. The mechanism by which this translates into pathology is not known. Polymorphisms have also been identified in the beta1-adrenergic receptor gene in patients with systolic HF and AF[102]. Again the exact significance is not clear yet but it may help risk stratify HF patients in terms of favourable response to beta blocker therapy[103].

Upstream therapy

Apart from ion-channel blockers, other pharmacologic agents have been investigated for potential anti-AF effects with the hope that modification of the arrhythmogenic atrial substrate and neuroendocrine axis may be of benefit. Limited data is available for polyunsaturated fatty acids[104], statin therapy[105] and renin-angiotensin-aldosterone system blockade[106,107]. At best, the findings have been inconclusive so far and larger randomized controlled trials are required[108].

CONCLUSION

HF and AF have emerged as global cardiovascular epidemics. They commonly coexist accounting for an enormous clinical and economic burden on healthcare. Emerging evidence suggests that AF confers an adverse prognostic impact on HF. Despite the negative impact of AF in HF, to date there is no definite evidence that rhythm control is prognostically superior to a rate control strategy. Trials of AF ablation have been encouraging yet larger studies (looking at hard end-points) are required before it can be incorporated into mainstream clinical practice. Development of novel anticoagulants constitutes an important step towards minimizing the thromboembolic toll of AF. Genomics, pharmacological "upstream" modification of the atrial substrate and development of selective atrial anti-arrhythmic agents provide further insights into this exciting field. It is not clear yet whether these will translate into clinically tangible benefits for the HF patient.

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ORIGINAL ARTICLE

Initial clinical presentation of Takotsubo cardiomyopathy with-a focus on electrocardiographic changes: A literature review of cases

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Abstract

AIM: To review the initial presentation and demonstrate the importance of Takotsubo cardiomyopathy.

METHODS: A PubMed search using the terms "Takotsubo cardiomyopathy (TC)" and "apical ballooning syndrome" yield 211 publications. Only those that were relevant were fully reviewed. The gender, age, precipitating stressor, main complaint at presentation, electrocardiogram (ECG) at admission and serum cardiac markers of patients diagnosed with TC, were extracted as available. The data were organized in tables and graphics, and the incidence of the disorder was calculated and analyzed.

RESULTS: A total of 250 clinical cases were examined. The predominant gender that was affected was female, with a prevalence of 87.5%. The mean age of presentation was 64 ± 14 years. The cases were divided by age into 10-year intervals. The age interval of 60-69 years showed the highest frequency of TC, accounting for 79 cases. The most common precipitating stressor was physical (50% of cases). Chest pain was the primary complaint at presentation (58.8% of cases) followed by dyspnea (30% of cases). The ST segment changes category was the most common (60%), followed by T wave changes (39.6%). Of the 60% of cases with ST segment changes, 12% had concomitant T wave changes. This means that for 27.6% of the cases, the primary abnormality in the ECG was T wave changes; 87.6% of cases with TC had a change in the ST segment, in the T wave or in both. The percentage of ECGs presenting with changes in the anterior wall was 54.4% (35.6% of ST segment elevation + 1.6% of ST segment depression + 17.2% of T wave inversion). The percentage of patients presenting with changes in the lateral segment of the heart was 46.8%, while the percentage of patients with changes in the inferior heart was 21.6% and the percentage of patients with changes in the apical region was only 16%. The prevalence of elevated creatinine kinase and/or troponin on initial presentation was 89.3%.

CONCLUSION: It is essential that every physician consider Takotsubo cardiomyopathy as a possible differential diagnosis when a patient is classified with acute coronary syndrome. To do so, it is necessary to know the clinical presentation of this syndrome in its early stages.

Core tip: Takotsubo cardiomyopathy is a syndrome that, while frequently not recognized, has a significant impact and represents a significant percentage of diagnosed acute coronary syndromes. The importance of its recognition by physicians should be stressed. There are no previously published articles that analyze a sig-

nificant number of reported cases of Takotsubo cardiomyopathy, nor are prior literature reviews available that examine all the points discussed by this author relative to the initial stages of the disease.

INTRODUCTION

Takotsubo cardiomyopathy (TC), apical ballooning syndrome and stress cardiomyopathy have all been used to refer to a syndrome that was described for the first time in 1991 in Japan. Five such were shown to have left ventriculograms with transient akinesis in the apical diaphragmatic and/or anterolateral wall but hyperkinesis in the basal wall of the heart[1].

Many hypotheses have been proposed to explain the pathophysiology of TC, including multivessel coronary vasospasm, abnormalities of coronary microvascular function, and catecholamine-mediated cardiotoxicity[2]. Some authors consider estrogen an important factor because it changes the $\beta1:\beta2$ adrenoreceptor (AR) ratio in favor of the $\beta2$ AR-Gi protein, which protects the myocardium from catecholamines in stressful situations[3].

The typical initial presentation pattern as chest pain and/or dyspnea, the electrocardiographic changes and elevated serum cardiac markers observed in TC patients often result in the misdiagnosis of TC as acute coronary syndrome (ACS). For the diagnosis of TC, it is necessary to perform echocardiography to observe the wall motion abnormality and coronary angiography to confirm the absence of significant stenotic lesions[2-4]. For some authors, cardiac magnetic resonance imaging (CMRI) (Figure 1) is very important due to its unique ability to assist diagnosis with noninvasive techniques; certainly, CMRI is very helpful in the differential diagnosis of TC and myocarditis, and with patient follow-up[5].

Many authors mention that the electrocardiographic changes that are seen in the presentation of TC are similar to those of ACS, particularly ST segment elevation myocardial infarction (STEMI); the similarities may include ST segment changes, T wave changes and QT interval changes[6].

This article analyzes the initial clinical presentation of a large number of cases of TC that have been describe in the literature and assesses various parameters with a focus on electrocardiographic changes.

MATERIALS AND METHODS

The reviewed articles were found on PubMed using the search terms "Takotsubo cardiomyopathy" and "api-cal ballooning syndrome". Three filters, namely "case reports", "free text available" and "humans", were used. After setting those filters, 211 articles were found. Of these, only those relevant to TC, which accounted for 197 articles, were fully reviewed. Of these, eight were eliminated because they did not include electrocardiograms or because the final diagnosis was not TC. Therefore, the study was conducted using 189 articles in total.

The criteria used to define TC, were those used by each author in each clinical case. One case of right ventricular Takotsubo[7] and several cases of reverse Takotsubo, broken-heart syndrome and stress cardiomyopathy were also included.

The following data were extracted upon availability: gender, age, precipitating stressor, main complaint at presentation, electrocardiogram (ECG) at admission and serum cardiac markers.

There was no age restriction for inclusion of cases in the study. Cases were classified by age using intervals of 10 years for better management of information. Two patients, a 16-year-old and a 90-year-old, fell outside the first interval of 20-29 years and the last interval of 80-89 years. The median and mean age of the patients and the standard deviations of these values were calculated.

The precipitating stressors were grouped into four categories: physical (physical effort, organic disease or medical condition); emotional (psychological, anxiety or family situation); undetermined (unclear whether the precipitating stressor was emotional, physical or both); no stressor (no identifiable stressor in the history); and not available (not available in the review article). The prevalence of each precipitating stressor was then calculated.

Due to the variable nomenclature assigned by the authors to the main complaint at presentation, it was decided that this nomenclature should be merged into single terms that described all patients who showed similar symptoms. The term "chest pain" was used to include chest discomfort, chest tightness and retrosternal discomfort. "Dyspnea" was used to include respiratory distress, shortness of breath, orthopnea and pulmonary congestion. "Hypotension" included hemodynamic instability, right heart failure and cardiogenic shock. "Loss of consciousness" included ventricular fibrillation and cardiopulmonary arrest, and "palpitations" included tachycardia. After all signs and symptoms were classified, they were listed and their prevalence was calculated based on the total number of cases.

The presence of a minimum of one ECG description was set when choosing the articles. The first ECG was extracted and was preferred for every case. If the time at which the test was taken was not specified, the test made available in the article was assumed to be the first and only test performed and was used in this study. If multiple tests were performed during the initial case presentation, the test that was performed first was extracted. All electrocardiographic descriptions of each case were obtained. The ECG data were grouped into the following categories: ST segment changes, T wave changes, Q wave changes, QT prolonged, normal category and others. If
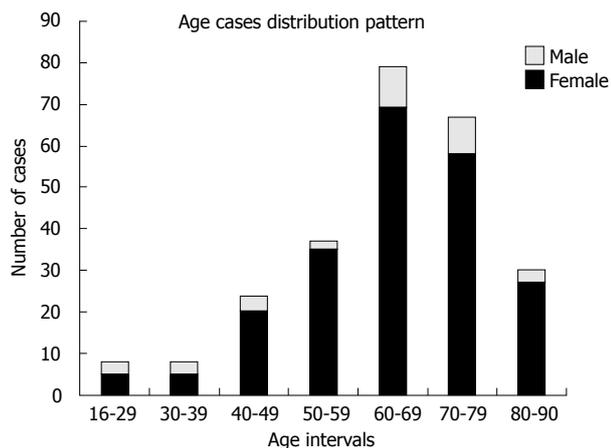
Figure 1 Graphic showing total cases grouped by age intervals.
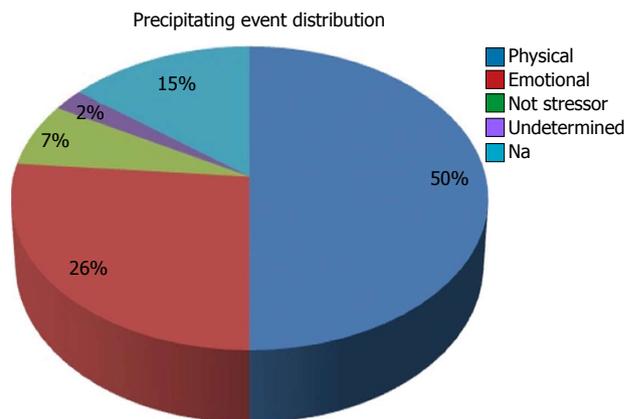
Figure 2 Graphic showing precipitating stressors grouped in categories for all cases studied.

Table 1 Electrocardiographic findings organized by frequency in presentation

Electrocardiogram description	Cases (*n*)	Incidence (%)
ST segment changes	150	60.00
T wave changes	99	39.60
Prolonged QT	26	10.40
Normal	16	6.40
Q wave	11	4.40
AV block	7	2.80
LBBB	6	2.40
RBBB	6	2.40
AF	5	2.00
VT	3	1.20
VF	3	1.20
Ventricular bigeminy	2	0.80
Other[1]	1	0.40

[1]Other: U wave, Osborn wave, Torsade de Pointes, ventricular atrial retrograde conduction, ventricular pace rhythm, premature ventricular contractions, ventricular ectopic beats, multifocal ventricular contractions, ventricular asystole and escape junctional rhythm. AV block: First, second and third degree atria-ventricular block; LBBB: Left bundle branch block; RBBB: Right bundle branch block; AF: Atrial fibrillation; VT: Ventricular tachycardia; VF: Ventricular fibrillation.

the ECG showed documented long-standing changes such as LBBB (left bundle branch block) or AV block, the cases were not considered in this study. The incidence of each of these categories in the ECG data was calculated (Table 1).

The ST segment category was also divided into four groups based on the following specific changes: ST segment elevation, ST segment depression, flattened ST segment and non-specific ST segment changes (Table 2). The incidence of each based on the ST segment changes category and on the total population was calculated.

The analysis of the T wave changes was also divided into four groups: T wave inversion, hyperacute T wave, flattened T wave and non-specific T wave changes (Table 2), and the incidence of each based on both the T wave category and the total cases was calculated.

The ECG findings were classified by anatomical re-

gion of the heart into inferior, lateral, septal, anterior and non-specific, based on the altered leads[8]. The incidence of abnormalities in each region was calculated and further analyzed (Table 3).

The serum cardiac markers creatinine kinase (CK-MB) and/or troponin were classified as normal or elevated; the latter category included mild, moderate and severe elevation. The results extracted were the first test during the admission or the first test result after suspecting a case. The prevalence of each marker elevation was calculated.

RESULTS

One hundred and eighty-nine case report articles, each of which included one or more individual clinical cases, were analyzed; in total, 250 clinical cases were examined (Table 4).

Gender
The predominant gender was female; it accounted for 219 cases with a prevalence of 87.5%.

Age
The age of the patients ranged from 16-90 years. The mean age at presentation was 64 ± 14 years, with a 95%CI of 64 ± 2 years and a median of 66 years. Figure 1 shows the number of cases grouped by 10-year intervals with respect to age. The age interval with the highest number of cases is 60-69 years; it includes 79 cases.

Precipitating stressor
Figure 2 shows the distribution of precipitating events among all cases. The 6 (2%) cases listed as "undetermined" were difficult to categorize. For example, a patient who had an operation was very stressed and anxious about the surgery results[9]. In the cases where the stressor was not available, the author did not mention whether there was a precipitating factor.

Main complaint at presentation
Table 5 shows the frequency of presentation of all cases

Table 2 ST segment, T wave change categories organized by incidence

	Cases (*n*)	Category incidence[1] (%)	Global incidence[2] (%)
ST segment changes			
ST segment elevation	135	90.00	54.00
ST segment depression	11[3] (21[4])	7.30	4.40
ST segment non-specific changes	3	2.00	1.20
ST segment flattened	1	0.70	0.40
T wave changes			
T wave inversion	91	91.90	36.40
Hyperacute T wave	4	4.00	1.60
Flattened T wave	2	2.00	0.80
Non-specific T wave changes	2	2.00	0.80

[1]Percentage calculated based on total ST segment changes cases (150); percentage calculated based on total cases with T wave changes (99); [2]Percentage calculated based on total cases in the study (250); percentage calculated based on total cases in the study (250); [3]Total number of cases presenting with ST segment depression alone (without concomitant ST segment elevation); [4]Total number of cases presenting with ST segment depression.

Table 3 Incidence of electrocardiographic change categories shown by anatomical region

Category and Localization	Cases (*n*)	Category incidence[1] (%)	Global incidence[2] (%)
ST segment elevation			
Anterior	89	65.90	35.60
Lateral	66	48.90	26.40
Inferior	26	19.30	10.40
Septal (apical)	24	17.80	9.60
Not specified	22	16.30	8.80
ST segment depression[3]			
Anterior	4	36.40	1.60
Lateral	6	54.50	2.40
Inferior	5	45.50	2.00
Septal (apical)	0	0.00	0.00
Not specified	2	18.20	0.80
T wave changes[4]			
Anterior	43 (2[5])	43.40	17.20
Lateral	45 (1[5])	45.50	18.00
Inferior	23	23.20	9.20
Septal (apical)	16	16.20	6.40
Not specified	15	15.20	6.00

[1]Percentage calculated based on the total number of cases in each category; [2]Percentage calculated based on the total number of cases in the study (250); [3]Only cases with ST segment depression as the main finding; [4]Only cases with T wave changes as the main finding, does not include T wave changes accompanying ST segment elevation or ST segment depression; [5]Only 3 cases that were not T wave inversions.

grouped with respect to symptoms and signs. Chest pain and dyspnea together were encountered in only 49 (20%) cases.

Electrocardiogram at admission

Table 1 shows the incidences of various types of electro-cardiographic abnormalities in the TC cases. Of the 60% of cases with ST segment changes, 12% had concomitant T wave changes, indicating that the main abnormality in the ECG for 27.6% of cases was T wave changes and that 87.6% of cases with TC had a change in the ST segment, in the T wave or both. Slow R progression was found in 3 cases, and tachycardia was found in 17 cases; one case of an anterior infarct of indeterminate age[10] was classified into the normal category.

Table 2 shows the incidence of specific ST segment changes. The incidence of ST segment depression in the total population (250 cases) and in the ST segment category (150 cases) was 4.4% and 7.3%, respectively. These calculations are based on 11 cases that presented with ST segment depression alone without concomitant ST segment elevation. The total number of cases regarding ST segment depression was 21; thus, 10 cases had concomitant ST segment elevation changes in the ECG. Table 2 shows the incidence of the T wave changes by group.

Table 3 shows the relative frequency at which various anatomical regions were affected in the electrocardiogram. The percentage of ECGs that showed changes in the anterior wall was 54.4% (35.6% of ST segment elevation + 1.6% of ST segment depression + 17.2% of T wave inversion), and the percentage that showed changes in the lateral segment of the heart was 46.8%. The percentage of ECGs showing changes in the inferior heart was 21.6%, while the percentage that showed changes in the apical region was only 16%.

Serum cardiac markers

The prevalence of elevated serum cardiac markers or normal cardiac markers was calculated from the extracted data. The "not available" data cases were not considered in the calculation. The prevalence of elevated CK-MB and/or troponin in patients initially presenting with TC was 89.3%, and the prevalence of negative or normal levels of these cardiac enzymes at presentation was 10.7%.

DISCUSSION

After an exhaustive search of articles describing clinical cases of TC, with emphasis on those that provided the minimum electrocardiographic data, a large number of articles and cases were found. These were analyzed to obtain the data required for this research.

The data obtain in this study indicate a pyramidal trend in age of occurrence of TC. The peak of TC incidence occurs in the 60 s; from this point, there is a gradual decrease in TC incidence as age increases or decreases, with a steeper slope in the direction of the younger population. The high female prevalence of the disease and the age distribution of its occurrence provide support for at least one hypothesis of its pathophysiology, *i.e.*, that lack of estrogen is an important causal factor of this syndrome[11].

A newly diagnosed disease, an upcoming operation, the induction of anesthesia, a new medication, a stress test or a major physical effort are only some of the physical stressors that can cause TC. This research show that

Table 4 Total number of cases analyzed tables

No.	Age (yr)	Ref.	No.	Age (yr)	Ref.	No.	Age (yr)	Ref.
1	30	Muller et al[8]	85	69	Haghi et al[70]	169	68	Lisi et al[140]
2	67	Yaoita et al[9]	86	69	Haghi et al[70]	170	71	Rotondi et al[141]
3	73	Izumi et al[10]	87	43	Haghi et al[70]	171	82	Kawano et al[142]
4	62	Kobayashi et al[11]	88	69	Haghi et al[70]	172	79	Hutchings et al[143]
5	65	Ker et al[12]	89	52	Di Valentino et al[71]	173	55	Hutchings et al[143]
6	78	Lau et al[13]	90	68	Stähli et al[72]	174	82	Zuhdi et al[144]
7	62	Hayashi et al[14]	91	65	Vivo et al[73]	175	45	Stout et al[145]
8	65	Peraira Moral et al[15]	92	81	Sacha et al[74]	176	76	Daly et al[146]
9	81	Wedekind et al[16]	93	53	Fiol et al[75]	177	78	Daly et al[146]
10	81	Davin et al[17]	94	61	Oberson et al[76]	178	65	Saito et al[147]
11	79	Teo[18]	95	29	Magno et al[77]	179	75	Silberbauer et al[148]
12	51	Arroyo et al[19]	96	82	Kim et al[78]	180	47	Biteker et al[149]
13	79	Consales et al[20]	97	71	Kume et al[79]	181	74	Merli et al[150]
14	64	Maruyama et al[21]	98	78	Kume et al[79]	182	72	Merli et al[150]
15	80	Nguyen et al[22]	99	77	Kume et al[79]	183	71	Merli et al[150]
16	84	Nishikawa et al[23]	100	74	Kume et al[79]	184	75	Merli et al[150]
17	53	Sakihara et al[24]	101	78	Kume et al[79]	185	57	Virani et al[151]
18	66	Ono et al[25]	102	78	Ahn et al[80]	186	64	Virani et al[151]
19	48	Daly et al[26]	103	55	Mahida et al[81]	187	44	Virani et al[151]
20	76	Iengo et al[27]	104	53	Bianchi et al[82]	188	64	Virani et al[151]
21	44	Pison et al[28]	105	61	Hwang et al[83]	189	69	Chia et al[152]
22	52	Pison et al[28]	106	55	Ikeda et al[84]	190	57	Yazdan-Ashoori et al[153]
23	81	Desmet et al[29]	107	75	Ikeda et al[84]	191	78	Shah et al[154]
24	78	Desmet et al[29]	108	64	Suzuki et al[85]	192	24	Volman et al[155]
25	65	Desmet et al[29]	109	88	Teraoka et al[86]	193	68	Salemi et al[156]
26	71	Desmet et al[29]	110	60	Hara et al[87]	194	50	Coutance et al[157]
27	48	Desmet et al[29]	111	89	Kurisu et al[88]	195	66	Salemi et al[158]
28	66	Desmet et al[29]	112	77	Kurisu et al[88]	196	81	Oe et al[159]
29	52	Desmet et al[29]	113	73	Verberne et al[89]	197	68	Fazal et al[160]
30	48	Desmet et al[29]	114	60	Subramanyam et al[90]	198	46	Afonso et al[161]
31	45	Desmet et al[29]	115	41	Sanchez-Recalde et al[91]	199	38	Afonso et al[161]
32	66	Desmet et al[29]	116	41	Barriales-Villa et al[92]	200	52	Afonso et al[161]
33	57	Desmet et al[29]	117	60	Fuse et al[93]	201	54	Sacco et al[162]
34	60	Desmet et al[29]	118	80	Kawano et al[94]	202	73	Daly et al[163]
35	69	Desmet et al[29]	119	63	Wong et al[95]	203	55	Jabiri et al[164]
36	41	Manivannan et al[30]	120	54	Kimura et al[96]	204	58	Madaria Marijuan et al[165]
37	60	Prasad et al[31]	121	77	Varela et al[97]	205	50	Traullé et al[166]
38	65	Chandrasegaram et al[32]	122	55	Elkhateeb et al[98]	206	32	D'Amato et al[167]
39	84	Wang et al[33]	123	59	Kaushik et al[99]	207	44	Artukoglu et al[168]
40	73	Wani et al[34]	124	53	Uechi et al[100]	208	85	Shah et al[169]
41	54	Wani et al[34]	125	67	To et al[101]	209	61	Cruvinel et al[170]
42	63	Wani et al[34]	126	72	To et al[101]	210	55	Lateef[171]
43	70	Schmidt et al[35]	127	46	Mehta et al[102]	211	70	Potter et al[172]
44	46	Zaman et al[36]	128	63	Oomura et al[103]	212	73	Agarwal et al[173]
45	73	Meimoun et al[37]	129	27	Volz et al[104]	213	72	Opolski et al[174]
46	22	Sasaki et al[38]	130	79	Miyazaki et al[105]	214	67	Y-Hassan et al[175]
47	86	Surapaneni et al[39]	131	83	Akashi et al[106]	215	87	Kurisu et al[176]
48	24	Park et al[40]	132	81	Wissner et al[107]	216	78	Kurisu et al[176]
49	85	Cherian et al[41]	133	47	Papanikolaou et al[108]	217	70	Gotyo et al[177]
50	41	Lee et al[42]	134	62	Bonnemeier et al[109]	218	79	Singh et al[178]
51	30	Lee et al[42]	135	60	Haghi et al[110]	219	44	Núñez et al[179]
52	89	Korlakunta et al[43]	136	78	Rau et al[111]	220	62	Núñez et al[179]
53	69	Magri et al[44]	137	53	Dahdouh et al[112]	221	52	Núñez et al[179]
54	65	Rahman et al[45]	138	69	Moriya et al [113]	222	69	Núñez et al[179]
55	63	Khallafi et al[46]	139	44	Hasdemir et al[114]	223	69	Núñez et al[179]
56	75	Demirelli et al[47]	140	53	Mariano et al[115]	224	29	Jayaraman et al[180]
57	75	Latib et al[48]	141	36	Sun et al[116]	225	71	Carxvalho et al[181]
58	58	Altman et al[49]	142	75	Dandel et al[117]	226	78	Guttormsen et al[182]
59	65	Bagga et al[50]	143	65	Ionescu et al[118]	227	53	Mrdovic et al[183]
60	61	Buchholz et al[51]	144	16	Maruyama et al[119]	228	84	Auer et al[184]
61	61	Zhou et al[52]	145	70	Sato et al[120]	229	64	Auer et al[184]
62	74	Mittal et al[53]	146	63	Shah et al[121]	230	64	Auer et al[184]
63	47	Kim et al[54]	147	62	Lee et al[122]	231	82	Auer et al[184]
64	60	Doesch et al[55]	148	67	Merchant et al[123]	232	63	Arslan et al[185]
65	66	Lopes et al[56]	149	86	Merchant et al[123]	233	66	Arslan et al[185]
66	64	Lopes et al[56]	150	76	Merchant et al[123]	234	70	Arslan et al[185]
67	76	Lopes et al[56]	151	42	Merchant et al[123]	235	71	Arslan et al[185]

68	58	Lopes et al[56]	152	76	Nault et al[124]	236	76	Barriales Vila et al[186]
69	51	Lopes et al[56]	153	62	Nault et al[124]	237	78	Barriales et al[186]
70	63	Sealove et al[57]	154	71	Novo et al[125]	238	70	Barriales et al[186]
71	82	Inoue et al[58]	155	68	Blázquez et al[126]	239	74	Guardado et al[187]
72	25	Maréchaux et al[59]	156	74	Ramanath et al[127]	240	45	Cho et al[188]
73	77	Arias et al[60]	157	70	Biswas et al[128]	241	68	Gallego Page et al[189]
74	76	Vasconcelos Filho et al[61]	158	61	Preti et al[129]	242	64	Sousa et al[190]
75	61	Margey et al[62]	159	59	Selke et al[130]	243	68	Jakobson et al[191]
76	67	Purvis et al[63]	160	74	Alves et al[131]	244	49	Jakobson et al[191]
77	59	Biłan et al[64]	161	83	Yeh et al[132]	245	74	Otomo et al[192]
78	53	Lentschener et al[65]	162	68	Kurisu et al[133]	246	75	Otomo et al[192]
79	61	Kyuma et al[66]	163	57	Rotondi et al[134]	247	55	Gomes et al[193]
80	76	Kyuma et al[66]	164	84	Guevara et al[135]	248	61	Furushima et al[194]
81	76	Kyuma et al[66]	165	69	Ukita et al[136]	249	84	Sakai et al[195]
82	81	Figueredo et al[67]	166	73	van de Donk et al[137]	250	64	Hakeem et al[196]
83	60	Naganuma et al[68]	167	66	Mawad et al[138]			
84	61	Laínez et al[69]	168	90	Xu et al[139]			

Table 5 Frequency of the main complaints reported in the cases studie

Main complaint	Presentation frequency (%)
Chest pain	58.80
Dyspnea	30.00
Hypotension	8.40
Nausea and/or vomiting	8.00
Syncope	6.40
Palpitations	5.20
Asymptomatic	4.80
Loss consciousness	5.20
Headache	3.60
Epigastric pain	2.00
Dizziness	2.00
Weakness	2.00
Cough	1.60
Back pain	1.60
Pedal edema	1.20
Seizure	0.80
Othersa	0.40

a physical stressor is by far the most common stressor reported in TC patients. Emotional stressors are reported in a quarter of all cases and can be as serious as the death of a relative[12]; they may also be less serious, such as watching a soccer team losing[13]. The asymptomatic presentations include patients undergoing anesthesia[14] and/or medical procedures, for example, tracheal intubations[15]. In these cases, the lack of symptoms can occur due to the sedation.

The chief complaint of the TC patients varied, depending on the causative factor, the trigger stressor and the presentation of each case. TC presents as an ACS; in the latter, the most common clinical presentation is chest pain and the second is dyspnea; this suggests that chest pain and dyspnea will be the most common presentation of stress cardiomyopathy[16]. In this study, chest pain was the most common initial symptom of the cases presented, and dyspnea was the second most common symptom. Hypotension and cardiopulmonary arrest were relatively common findings, most likely because of the severity of presentation in those patients. Furthermore, the initial symptoms of TC are often related to the factors causing stress cardiomyopathy. For example, a patient with a seizure[17,18] or a stroke[19] can only present neurological signs and symptoms.

A very important tool used by physicians in emergency departments and hospital settings to evaluate chest pain, ACS and preoperative patients is the electrocardiogram, which is very easy to perform and is associated with very low cost. Although percutaneous coronary intervention and CMRI are also sometimes useful tools, and the initial suspicion of the TC is usually confirm by echocardiography; it is very important for physicians to know how the TC present in terms of electrocardiography because these findings, together with the patient's clinical characteristics, should orient the physician to consider this syndrome as a differential diagnosis.

Notably, the definitive diagnosis of TC is confirmed by echocardiographic follow-up performed days or weeks after the initial presentation and showing normalization of the wall motion and left ventricular abnormalities. The CMRI has demonstrated value in the evaluation and follow-up of patients with TC; however, the test of choice is the echocardiography due to its low cost and accessibility[20,21](Figure 3).

Changes in the ST segment of the ECG were the most common finding in all cases; these changes are typical of the presentation of ACS and are most likely the reason for the initial management of most TC cases as ACS[22,23]. Changes in the T wave are the second most common finding in the study population. Again, changes in the T wave are very common in acute myocardial ischemia and infarction[23], explaining the frequent initial diagnosis of ACS in patients with TC. Notably, for some authors, T wave changes are the most common findings among TC patients[24]. The QT interval is prolonged in approximately 10% of patients, a substantially high incidence. There is perhaps a relationship between the QT interval measurement and TC; there is a need for more research into this possibility. The ischemic heart can present with increased QT dispersion, but this observation has not yet been proven to have any practical useful-
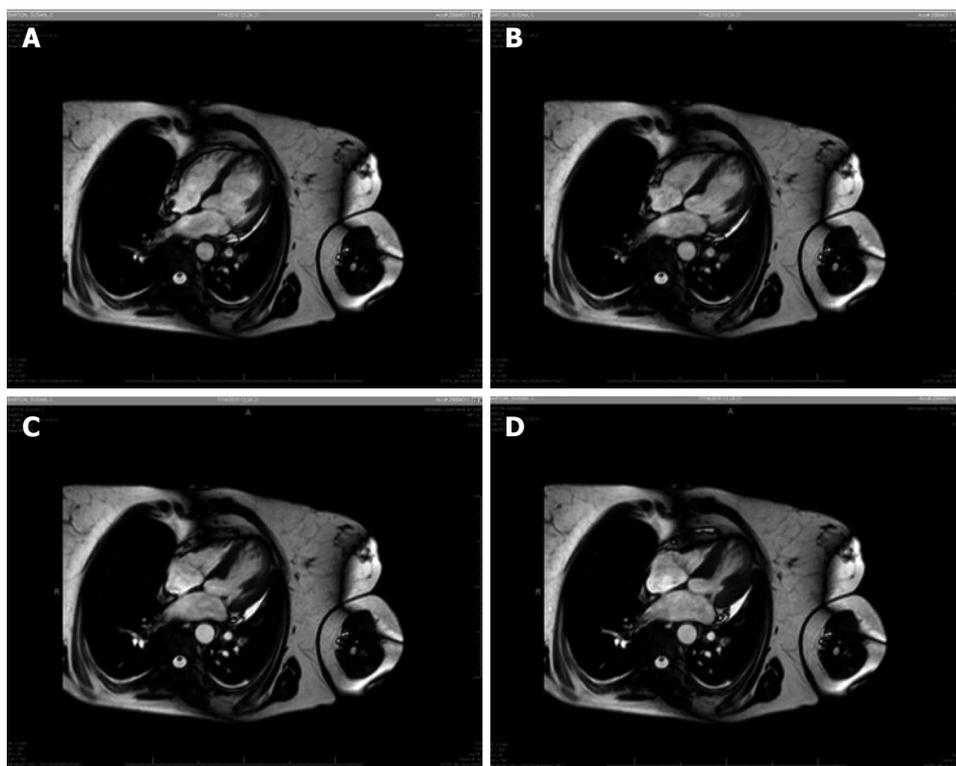
Figure 3 Cardiac magnetic resonance imaging for Takotsubo cardiomyopathy. A: Diastole: both ventricles are distended and full of blood; B and C: Systole: both ventricles contracting; D: End of systole: the right ventricle shows a normal pattern, while the left ventricle has a ballooning shape.

ness[25]. For the physician, it is important to know that a small percentage (approximately 6%) of TC cases present with a normal ECG during admission. There were also a few cases of multiple presentations in the study; ventricular tachycardia or ventricular fibrillation, for example, can hide the expected electrocardiographic changes.

Among the ST segment changes, ST segment elevation was the most common finding, accounting for 90% of the ST changes. It is the most common presentation of a STEMI, and in this study it occurred in more than half of all cases. Although it was present in almost 10% of incidences, ST depression was not very prominent finding; in half of the cases in which it occurred, it was accompanied by other major findings such as ST segment elevation. Other ST segment presentations, such as flattened ST segments, were not commonly found in the initial ECG at admission.

T wave changes showed a distribution similar to that of ST segment changes. The incidence of the T wave inversion was very high, approximately 92% of all T wave changes. This pattern is very common in the ischemic heart. In fact, in this study, overall T wave presentation occurred in almost one third of the patients, a very significant number. When this type of electrocardiographic change is present, TC should be considered a probable diagnosis. Other T wave presentations, such as hyperacute T wave, flattened T wave and nonspecific changes, very uncommonly presented as the only finding in the ECG.

The anatomical site most commonly affected by stress cardiomyopathy is the left ventricle, but there have been cases with right ventricular akinesis[7] and even cases in which both ventricles are affected[10]. Electrocardiographic presentations of this syndrome are highly variable. In this study, it was documented that in TC the ECG changes in frequency starting from the anterior region as the most commonly affected, followed by the lateral, the inferior and finally the septal region. The clinician must remember these patterns when making a differential diagnosis and never rule out the possibility of a TC based on the ECG.

During the initial presentation of TC patients, there is a very high prevalence of serum cardiac marker elevation, making this diagnosis consistent with ACS (specifically STEMI and NSTEMI). Some authors have indicated that the distinction between TC and ACS is reflected in the level of cardiac enzyme elevation[26,27]. These finding contain important information that should raise the physician's clinical suspicions regarding this syndrome.

COMMENTS

Background
Takotsubo syndrome has the same presentation as acute coronary syndrome (ACS) but is usually associated with history of a trigger stressor, which can be emotional or physical. Although a number of ideas have been proposed to explain its pathophysiology, there is evidence that catecholamines and estrogen play an important role. Many physicians do not readily think of Takotsubo cardiomyopathy (TC) when presented with a patient with cardiac chest pain or even with a ST segment elevation myocardial infarction (STEMI), and other physicians are not even aware of the existence of the syndrome. For this reason, it is likely that many patients are misdiagnosed. The presentation similarities of TC with ACS include symptoms, electrocardiogram (ECG) changes and serum cardiac marker levels.

Research frontiers
In some health facilities, the initial management of a STEMI is based on intra-

venous fibrinolysis, which is performed without confirmation of coronary artery obstruction using percutaneous coronary intervention (PCI). Takotsubo patients can have the same presentation as STEMI patients but normal or clean coronary arteries. This and other evidence makes the PCI management of choice in STEMI patients.

Innovations and breakthroughs

Although this article does not focus on patient prognosis, it is important that future research addresses the relationship between initial presentation/initial electrocardiographic changes and prognosis. Cardiac magnetic resonance imaging is a new tool that may prove useful in both initial diagnosis and noninvasive follow-up of this syndrome.

Applications

The results of the study are important in clinical practice. They can help inform physicians to include TC in the differential diagnosis of patients who present to the emergency department with cardiac chest pain.

Terminology

TC is a condition that has acquired many names over time; these include Takotsubo syndrome, stress cardiomyopathy, apical ballooning syndrome and TC. ACS is a term applied to situations in which the blood supplied to the heart muscle is suddenly blocked; it includes unstable angina, STEMI and non-ST segment elevation myocardial infarction. Troponin and creatinine kinase (CK-MB) are cardiac markers used to classify and assist with the diagnosis of myocardial infarction. CK-MB is an isoenzyme composed of a muscle portion and a brain portion; it is very specific for myocardial muscle.

Peer review

It is necessary for every physician to know the clinical presentation of TC in its early stages. As mentioned above, this entity should be included in the differential diagnosis of "ACS" patients. The present work represents an interesting examination of value for clinical practice and stresses an important issue in the field of cardiology.

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BRIEF ARTICLE

Ibutilide and novel indexes of ventricular repolarization in persistent atrial fibrillation patients

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Abstract

AIM: To examine the effect of ibutilide on novel indexes of repolarization in patients with persistent atrial fibrillation (AF).

METHODS: We studied consecutive patients scheduled for elective electrical cardioversion. Intravenous ibutilide (1 + 1 mg) was administered before the electrical cardioversion while close electrocardiographic (ECG) monitoring was performed. ECG indexes such as corrected QT interval (QTc), the interval from the peak until the end of T wave (Tpe), and the Tpe/QT ratio were measured before ibutilide infusion and 10 min after the end of infusion.

RESULTS: The final study population consisted of 20 patients (mean age: 67.1 ± 9.9 years, 10 men). Six patients were cardioverted pharmacologically and did not proceed to electrical cardioversion. Two patients developed short non-sustained episodes of torsades de pointes ventricular tachycardia. All but one of the aforementioned ECG indexes increased significantly after ibutilide administration. In specific, the QTc interval increased from 442 ± 29 to 471 ± 37 ms ($P = 0.037$), the Tpe interval in precordial leads from 96 ms (range 80-108 ms) to 101 ms (range 91-119 ms) ($P = 0.021$), the Tpe interval in lead Ⅱ from 79 ms (range 70-88 ms) to 100 ms (range 87-104 ms) ($P < 0.001$), the Tpe/QT ratio in precordial leads from 0.23 ms (range 0.18-0.26 ms) to 0.26 ms (range 0.23-0.28 ms) ($P = 0.028$), and the Tpe interval dispersion from 25 ms (range 23-30 ms) to 35 ms (range 27-39 ms) ($P = 0.012$). However, the Tpe/QT ratio in lead II did not change significantly.

CONCLUSION: Ibutilide increases the duration and dispersion of ventricular repolarization. The prognostic value of Tpe and Tpe/QT in the setting of drug-induced proarrhythmia needs further study.

Core tip: In this pilot study we examined the effect of ibutilide on novel indexes of repolarization in patients with persistent atrial fibrillation scheduled for electrical cardioversion. Electrocardiographic (ECG) indexes such as corrected QT interval, the interval from the peak until the end of T wave (Tpe), and the Tpe/QT ratio were measured. We showed that ibutilide significantly increases the dispersion of ventricular repolarization as assessed by modern ECG markers such as Tpe interval and Tpe/QT ratio. These indexes may have a prognostic value with regard to drug-induced proarrhythmia.

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INTRODUCTION

Drug-induced proarrhythmia represents a significant problem that poses special risks in the implementation of drug therapy[1]. Several antiarrhythmic drugs seem to have proarrhythmic potential[2,3]. Ibutilide is a class III antirrhythmic agent effective for pharmacological cardioversion of recent-onset atrial fibrillation (AF) or atrial flutter[4,5]. It is administered intravenously and has a rapid onset of action[5]. In addition, ibutilide pretreatment facilitates external electrical cardioversion of persistent AF[6-8]. However, its QT-prolonging properties and the increased risk for torsades de pointes (TdP) ventricular tachycardia raise safety concerns and limit its widespread use[5].

A well-known pathogenetic factor for malignant ventricular arrhythmias is the increased dispersion of repolarization which reflects the heterogeneity rather than the total duration of repolarization[9]. The T peak-to-end (Tpe) interval and the Tpe/QT ratio represent novel electrocardiographic indexes of arrhythmic risk that possibly correspond to the spatial dispersion of ventricular repolarization[9-11]. It has also been demonstrated that in the setting of acquired QT prolongation the Tpe/QT ratio is a better predictor of TdP compared to the corrected QT interval (QTc) interval and QT dispersion[12]. Thus, in this pilot observational study we sought to investigate the impact of ibutilide pretreatment on the aforementioned electrocardiographic (ECG) indexes in the setting of persistent AF before electrical cardioversion.

MATERIALS AND METHODS

We screened consecutive patients with persistent AF scheduled for elective electrical cardioversion. Patients taking drugs or having conditions that affect the QT interval were excluded. In specific, exclusion criteria were recent acute coronary syndrome within the past 6 mo, recent percutaneous coronary intervention or cardiac surgery, congestive heart failure with New York Heart Association class > Ⅱ, presence of nonsustained ventricular tachycardia on Holter monitoring, presence of bundle brunch block, QRS duration > 120 ms, previous implantation of a pacemaker or a defibrillator, administration of antiarrhythmic drugs, administration of drugs that prolong the QT interval, thyroid dysfunction, renal failure, and electrolyte disturbances. All patients were on b-blockers and/or digoxin for rate control as well as on vitamin K antagonists for anticoagulation treatment.

The patients were admitted to the coronary care unit in the morning hours. After checking the laboratory examinations, intravenous ibutilide (1 mg for 10 min +

1 mg after 20 min if the patients were still in AF) was administered at a fasting state before the electrical cardioversion while close ECG monitoring was performed. ECG indexes such as QTc, the interval from the peak until the end of T wave (Tpe) and the Tpe/QT ratio were measured before ibutilide infusion and 10 min after the end of administration.

The ECG indexes were assessed at baseline in the supine position and calculated as described in our previous reports[13-15]. Specifically, the QT and the QTpeak intervals were measured manually on ECG recordings at a paper speed of 50 mm/s. QT interval was assessed as the time between the first deflection of QRS and the point of return of the T wave to the isoelectric line. The Tpe interval was calculated as QT-QTpeak. The QT interval was measured in as many of the 12 leads as possible while Tpe interval was assessed in lead Ⅱ and in the precordial leads[10,13-15]. The Tpe interval and the Tpe/QT ratio were calculated using the corresponding values from each lead. The measurements were obtained in 5 consecutive complexes of each lead and the resulting average value was finally accepted. In order to avoid diurnal variations, all procedures were performed during the same time interval (from 9.00 am to 11.00 am). QT interval corrected for heart rate (QTc) was calculated using the Bazett's formula ($QTc = QT/RR^{-2}$)[16]. The Tpe and QTc reported values were the maximum obtained values. All measurements were performed by one experienced investigator (Korantzopoulos P) who was unaware of the clinical characteristics of the study participants. To identify intraobserver variability, the ECG tracings of 6 randomly selected patients were reexamined 10 d after the initial evaluation. Intraobserver variation was less than 5%.

Statistical analysis

Continuous variables are expressed as mean ± SD, or as median (25th-75th percentile) if their values are not normally distributed. The examination of normality was performed by the Kolmogorov-Smirnov test. Categorical variables are presented as frequencies. Comparisons of the continuous variables performed using the paired *t*-test or the non-parametric Wilcoxon signed-rank test. A two-tailed *P* value < 0.05 was considered significant. All analyses were performed using the SPSS software (version 16.0; SPSS Inc., Chicago, IL, United States).

RESULTS

The final study population consisted of 20 patients (mean age: 67.1 ± 9.9 years, 10 men). The baseline clinical and demographic characteristics of the patients are presented in Table 1. The mean duration of persistent AF before the attempted electrical cardioversion was 3 mo while the patients had preserved left ventricular ejection fraction and marginally dilated left atria (Table 1).

Six patients were cardioverted pharmacologically and did not proceed to electrical cardioversion. Two patients

Table 1 Baseline and clinical charactersistics of the study population

Patients' characteristics	Value
Age (yr)	67.1 ± 9.9
Men	50%
Duration of atrial fibrillation (d)	94 ± 51
Baseline heart rate (beats per minute)	87 ± 19
Hypertension	65%
Diabetes	30%
Coronary artery disease	25%
Left ventricular ejection fraction	58% ± 7%
Left atrial diameter (mm)	41.7 ± 4.3
Sodium (mEq/L)	139.0 ± 3.0
Potassium (mEq/L)	4.4 ± 0.4

Table 2 Electrocardiographic variables before and after ibutilide infusion

Variables	Before ibutilide	After ibutilide	*P* value
QTc (ms)	442 ± 29	471 ± 37	0.037
Tpe in lead Ⅱ (ms)	79 (70-88)	100 (87-104)	< 0.001
Tpe in precordial leads (ms)	96 (80-108)	101 (91-119)	0.021
Tpe dispersion (ms)	25 (23-30)	35 (27-39)	0.012
Tpe/QT in lead Ⅱ	0.22 (0.18-0.24)	0.24 (0.22-0.28)	0.12
Tpe/QT in precordial leads	0.23 (0.18-0.26)	0.26 (0.23-0.28)	0.028

The parameters are presented as means ± SD or as median values (25th-75th percentile). QTc: Corrected QT interval; Tpe: T peak-to-end.

developed short non-sustained episodes of TdP ventricular tachycardia a few minutes after the infusion of the second dose. All but one of the aforementioned ECG indexes increased significantly after ibutilide administration. In specific, the QTc interval, the Tpe interval in precordial leads, the Tpe interval in lead Ⅱ, the Tpe/QT ratio in precordial leads, and the Tpe interval dispersion increased (Table 2). However, the Tpe/QT ratio in lead Ⅱ did not change significantly (Table 2).

DISCUSSION

In this pilot study we demonstrated that ibutilide significantly increases the total duration of repolarization reflected by the QTc interval and more importantly the dispersion of ventricular repolarization as assessed by modern ECG markers such as Tpe interval and Tpe/QT ratio.

Ibutilide confers a high risk of TdP (up to 9% of cases), although most episodes are self-terminated and do not require electrical termination[17]. However, its proarrhythmic potential may hamper its use in several clinical settings. Besides its use for pharmaceutical cardioversion of recent-onset AF or atrial flutter, ibutilide increases the success rates of electrical cardioversion of these arrhythmias, facilitates electrical cardioversion of refractory persistent AF, and lowers energy requirements during the procedure[6-8,17,18]. Of note, ibutilide infusion must be followed by 3-4 h of ECG monitoring to exclude TdP[5-8].

Ibutilide prolongs repolarization by inhibition of the rapidly activating component of the delayed rectifier potassium currents (I$_{Kr}$) and by selective enhancement of the slow inward sodium current[19]. It should be pointed out that the heterogeneity of ventricular repolarization is a much more important parameter for proarrhythmia compared to the total duration of repolarization. For example, it is well known that amiodarone carries a very low risk for proarrhythmia despite its QT prolonging effects[20]. This apparent paradox is explained by the fact that amiodarone prolongs the ventricular repolarization homogeneously and does not increase transmural dispersion of repolarization[20].

Spatial dispersion of repolarization reflects the heterogeneity of repolarization which creates voltage gradients and thus promoting ventricular arrhythmias. Tpe interval represents a promising marker of total dispersion of ventricular repolarization (transmural, apicobasal, or global)[10]. However, the Tpe/QT ratio appears to be a more sensitive arrhythmogenic index since it remains constant despite changes in the heart rate (dynamic changes in Tpe and QT interval occur in a proportional and parallel fashion)[10,12,21]. Remarkably, an increased Tpe/QT ratio has been associated with arrhythmic events in patients with acquired long QT syndrome[12], in patients with hypertrophic cardiomyopathy[22], and in cardiac resynchronization therapy patients[23]. Also, the Tpe interval is independently associated with sudden cardiac death in the general population[24], as well as with mortality after acute myocardial infarction[25]. In the setting of stable coronary artery disease where exercise-induced arrhythmias represent a specific problem, we recently demonstrated that Tpe/QT ratio significantly increases at peak exercise[13]. Very recently we also showed that these novel indexes of dispersion of repolarization including Tpe/QT are increased in individuals with early repolarization[14] and also after hemodialysis in patients with end-stage renal disease[15].

Taking into account the aforementioned considerations we focused on the measurement of the novel indexes Tpe and Tpe/QT in order to investigate the effects of ibutilide administration on the dispersion of ventricular repolarization in patients with AF. Accumulating evidence suggests that the older index "QTc dispersion" does not actually reflect the dispersion of ventricular repolarization[26] and therefore we did not assess this parameter. In experimental models such as in the rabbit left ventricular wedge preparation the estimation of transmural dispersion of repolarization represented by Tpe interval and Tpe/QT ratio proved to be a useful tool for the prediction of drug-induced QT prolongation and proarrhythmic potential[27]. In this context, Yamaguchi *et al*[12] showed that Tpe/QT ratio is a better predictor of TdP compared to QTc interval and QT dispersion in the setting of acquired QT prolongation. With regard to ibutilide, Kannankeril *et al*[28] recently demonstrated that QT prolongation by the drug does not correlate to baseline QTc and does not differ between the 2 sexes. Given that

the QT prolongation by ibutilide is highly variable and does not accurately predict the occurrence of TdP the assessment of dispersion of ventricular repolarization may confer an advantage for this purpose.

Limitations

We feel that our study adds to the current knowledge of drug-induced proarrhythmia and its evaluation through novel ECG markers of dispersion of repolarization. However, some limitations are apparent. Firstly, the study population was small. Secondly, due to the limited number of patients it was not feasible to compare the indexes of repolarization between patients who suffered short episodes of TdP ($n = 2$) and patients who did not suffer any ventricular arrhythmia ($n = 18$). Thirdly, we have to acknowledge that our patients did not have significant comorbidities and especially they did not have significant LV dysfunction. The effect of ibutilide on ventricular repolarization may be more prominent in more advanced heart disease states. Finally, although we measurements of the ECG were obtained in 5 consecutive complexes of each lead and the resulting average value was finally accepted, we have to admit that the high variability of the RR intervals during AF poses specific problems in the accuracy of measurements.

In conclusion, ibutilide administration increases the duration and the dispersion of ventricular repolarization. Therefore, Tpe interval and Tpe/QT ratio may represent useful prognostic markers for the occurrence of TdP after ibutilide infusion. Undoubtedly, the prognostic role of these ECG indexes and their variations in the setting of drug-induced proarrhythmia needs further study.

COMMENTS

Background

Drug-induced proarrhythmia represents a significant problem that poses special risks in the implementation of drug therapy. Several antiarrhythmic drugs seem to have proarrhythmic potential. Ibutilide is a class Ⅲ antirrhythmic agent effective for pharmacological cardioversion of recent-onset atrial fibrillation (AF) or atrial flutter. It is administered intravenously and has a rapid onset of action. In addition, ibutilide pretreatment facilitates external electrical cardioversion of persistent AF.

Research frontiers

Electrocardiographic (ECG) indexes such as corrected QT interval, the interval from the peak until the end of T wave (Tpe), and the Tpe/QT ratio were measured.

Innovations and breakthroughs

In this pilot study authors examined the effect of ibutilide on novel indexes of repolarization in patients with persistent atrial fibrillation scheduled for electrical cardioversion. Authors showed that ibutilide significantly increases the dispersion of ventricular repolarization as assessed by modern ECG markers such as Tpe interval and Tpe/QT ratio. These indexes may have a prognostic value with regard to drug-induced proarrhythmia.

Peer review

According to this report 10% of the subjects developed short episodes of TdP and 30% were pharmacologically converted into sinus rhythm. It demonstrated the significant side effects and proarrhythmic profile of ibutilide. It has been nicely shown that the novel tools of Tpe interval and Tpe/QT are useful for the prediction of ibutilide-induced QT prolongation compared the classic QTc interval.

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BRIEF ARTICLE

Response of blood pressure after percutaneous transluminal renal artery angioplasty and stenting

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Abstract

AIM: To evaluate the short and intermediate term outcome of percutaneous transluminal renal artery angioplasty (PTRA) and stenting particularly on blood pressure (BP) control and renal function and to evaluate predictors of poor BP response after successful PTRA and stenting.

METHODS: We conducted a prospective analysis of all patients who underwent PTRA and stenting in our institute between August 2010 to September 2012. A total number of 86 patients were underwent PTRA and renal stenting. Selective angiography was done to confirm at least 70% angiographic stenosis. The predilation done except few cases with critical stenosis, direct stenting was done in the rest of cases. All patients received aspirin 325 mg orally, and clopidogrel 300 mg orally within 24 h before the procedure. Heparin was used as the procedural anticoagulant agent. Optimal results with TIMI-III flow obtained in all cases. Follow-

ing stent placement, aspirin 150 mg orally once daily was continued for a minimum of 12 mo and clopidogrel 75 mg orally once daily for at least 4 wk. The clinical, radiological, electrocardiography, echocardiography and treatment data of all patients were recorded. The BP measurement, serum creatinine and glomerular filtration rate (GFR) were recorded before the procedure and 1 and 6 mo after PTRA.

RESULTS: A total of 86 patients were included in the study. The mean age of study population was 55.87 ± 11.85 years old and 67 (77.9%) of patients were male. There was a significant reduction in both systolic and diastolic BP at 1 mo after the procedure: 170.15 ± 20.10 mmHg *vs* 146.60 ± 17.32 mmHg and 98.38 ± 10.55 mmHg *vs* 89.88 ± 9.22 mmHg respectively (P = 0.0000). The reduction in BP was constant throughout the follow-up period and was evident 6 mo after the procedure: 144.23 ± 18.19 and 88.26 ± 9.79 mmHg respectively (P = 0.0000). However, no improvement in renal function was observed at any time during the follow-up period. After multivariate analysis, we found male sex, low GFR (< 60 mL/min) and higher baseline mean BP as a poor predictors of successful outcome on BP response after PTRA and stenting.

CONCLUSION: The PTRA and stenting can be considered as an effective therapeutic intervention for improving BP control with minimal effect on renal function. The male sex, higher baseline BP and low GFR are associated with poor BP response after successful PTRA and stenting.

Core tip: To evaluate the short and intermediate term

outcome of percutaneous transluminal renal artery angioplasty (PTRA) and stenting particularly on blood pressure (BP) control and renal function and to evaluate predictors of poor BP response after successful PTRA and stenting. The PTRA and stenting can be considered as an effective therapeutic intervention for improving BP control with minimal effect on renal function. The male sex, higher baseline BP and low glomerular filtration rate are associated with poor BP response after successful PTRA and stenting.

INTRODUCTION

Renovascular hypertension occurs in 1% to 5% of all patients with hypertension. Renovascular hypertension is the most common form of secondary hypertension. Renal artery stenosis (RAS) is caused often by atheromatous plaques (80% of the cases over 40 years), but can also be due to fibromuscular dysplasia (10% of the cases and more often in young patients), arteritis (Takayasu's disease), neurofibromatosis and post radiation injury[1-4]. It can also occur in post renal transplant patients or after a renal bypass graft[4].

RAS is associated with increased cardiovascular events and mortality. Its prevalence varies from 7% in individuals over 65 years of age to 20%-30% in high risk group of patients. It may affect up to 30% of patients with coronary artery disease and nearly 50% of those with significant peripheral vascular disease (PVD)[5,3-7]. Atherosclerotic RAS is a progressive disease associated with loss of renal mass over time, despite control of hypertension. Progression of RAS to complete occlusion is more likely with more severe (> 60%) lesions and may occur at a rate of up to 20%/year[4,8-10].

Atherosclerotic RAS is an important cause of renal insufficiency, refractory hypertension, and cardiac destabilization syndromes (unstable angina and flash pulmonary edema)[11,12]. Unilateral RAS manifests clinically as a vasoconstrictor-mediated hypertension, whereas bilateral RAS causes hypertension caused by volume overload. Up to 20% of patients older than 50 years of age requiring renal dialysis have atherosclerotic RAS (ischemic nephropathy) as the cause of their renal failure. The treatment of RAS includes medical therapy, balloon angioplasty and surgery. Surgery has been replaced by percutaneous transluminal renal artery angioplasty (PTRA) and stenting and remains at high risk with a 2%-7% perioperative mortality rate, a 17%-31% morbidity, deterioration rate in renal function in 11%-31% of patients

and reocclusion and restenosis in 5%-18%. Indications for surgery are limited and include failed percutaneous approach, hostile aorta, infra-renal total occlusion and in association with aortic surgery[4,13-15].

The PTRA technique has become the cornerstone for treatment of RAS and is now the first line treatment to be proposed. Balloon angioplasty alone was first proposed but several series reported the successful use of endovascular stents for treating suboptimal angioplasty results and as a primary intervention for atherosclerotic lesions and particularly ostial lesions with better immediate and long-term results than with balloon angioplasty alone[16-21]. Despite many reports of clinical success in selected and carefully chosen patient groups, the enthusiasm for widespread treatment of mild or moderate renovascular disease has waned. Recent published data from the Angioplasty and Stenting for Renal Artery Lesions (ASTRAL) trial, in which patients were randomized to revascularization *vs* continued medical therapy alone, did not show a clear benefit of renal revascularization, although its design and conclusions have been criticized[22]. We designed this study to evaluate the short and intermediate term outcome of PTRA and stenting particularly on blood pressure (BP) control and renal function and to evaluate predictors of poor BP response after successful PTRA and stenting.

MATERIALS AND METHODS

Study population

This study was carried out in the Department of Cardiology, UN Mehta Institute of Cardiology and Research, from August 2010 to September 2012. This institute is tertiary care center situated in Ahmedabad, Gujarat, India. A total number of 86 patients were underwent PTRA and renal stenting with following inclusion criteria: (1) significant renal artery stenosis (70% or more stenosis); (2) onset of hypertension before 30 years and after 55 years; (3) exacerbation of previously well controlled hypertension; (4) malignant hypertension and Refractory hypertension; (5) azotemia shortly after institution of therapy with ACE inhibitors or ARB blockers; (6) hypertension and atrophic kidney or discrepancy in kidney size (> 1.5 cm); (7) hypertension and recurrent episodes of acute pulmonary edema or unexplained heart failure; (8) hypertension and systolic-diastolic abdominal bruit that laterlise to one side; and (9) hypertension and progressive unexplained azotemia. The exclusion criteria were: (1) serum creatine value > 3 mg/dL; (2) small kidney; and (3) total renal artery occlusion.

Informed written consent was obtained from all patients before treatment. This study conducted in accordance with the International Conference on Harmonization guidelines Good Clinical Practices, Declaration of Helsinki, and medical ethics committee requirements.

All patients' systolic BP, diastolic BP, serum creatinine and GFR were measured at baseline, 1 mo and 6 mo respectively. The BP was measured in supine position in

Table 1 Baseline characteristics of study population: Clinical, laboratory and imaging data *n* (%)

Variables	*n* = 86
Male gender	67 (77.9)
Age (yr)	55.87 ± 11.85
Background diseases	
Stage-1 (malignant) hypertension	14 (16.3)
Stage-2 hypertension	65 (75.6)
Diabetes mellitus	34 (39.5)
Smoking	61 (70.9)
Clinical features of left ventricular dysfunction	23 (26.7)
Left ventricular hypertrophy	29 (33.7)
Coronary artery disease	72 (83.7)
Blood pressure	
Systolic (mmHg)	170.15 ± 20.10
Diastolic (mmHg)	98.38 ± 10.55
Antihypertensive drugs (*n*)	3.07 ± 0.69
Indication criteria	
Hypertension resistant to standard medication	71 (82.6)
Renal bruit	53 (61.6)
Serum creatinine (mg/dL)	20 (23.3)
Stenosis	
Bilateral	23 (26.7)
Coronary angiography	
Single vessel disease	25 (29.1)
Double vessel disease	14 (16.3)
Triple vessel disease	28 (32.6)
Normal vessel	19 (22.1)

Values are presented as percentage (%) and mean ± SD.

Table 2 Blood pressure, antihypertensive medication, serum creatinine and glomerular filtration rate initial *vs* follow-up measurements

Time of follow-up	mean ± SD	*P* value
Systolic blood pressure (mmHg)	170.15 ± 20.10	< 0.0001
Baseline		
1 mo	146.60 ± 17.32	
6 mo	144.23 ± 18.19	
Diastolic blood pressure (mmHg)	98.38 ± 10.55	< 0.0001
Baseline		
1 mo	89.88 ± 9.22	
6 mo	88.26 ± 9.79	
Antihypertensive drugs (*n*)	3.07 ± 0.69	< 0.0001
Baseline		
1 mo	2.37 ± 0.84	
6 mo	2.25 ± 0.94	
Serum creatinine (mg/dL)	1.21 ± 0.66	0.964
Baseline		
48 h	1.29 ± 0.88	
1 mo	1.33 ± 1.27	
6 mo	1.21 ± 0.79	
GFR estimation (mL/min)	65.71 ± 25.20	0.546
Baseline		
6 mo	66.68 ± 25.03	

Values are presented as mean ± SD, *P* value compares baseline to 6 mo. GFR: Glomerular filtration rate.

both upper limbs and lower limbs with mercury manometer with standard cuff size after adequate rest. Patients were not allowed to have tea, coffee, smoking and alcohol 1 h prior to procedure. Patients were allowed to continue their antihypertensive medicines. Patients were on primarily b blocker, diuretics, ace inhibitors/ARB or calcium channel blockers.

Procedure
All patients who underwent PTRA and stenting received anticoagulation as per hospital protocol. Selective angiography was done to confirm at least 70% angiographic stenosis. PTRA was performed with either 6/7 F RDC or JR 3.5 guiding catheter and work hoarse guidewire. The predilatation done except few cases with critical stenosis, direct stenting was done in the rest of cases. Post dilation was done if required. The study included bare metal stent (BMS) of 12, 15, and 18 mm lengths with diameters ranging from 4 to 7 mm.

All patients received aspirin 325 mg orally, and clopidogrel 300 mg orally within 24 h before the procedure. Heparin was used as the procedural anticoagulant agent. Optimal results with TIMI-Ⅲ flow obtained in all cases. Following stent placement, aspirin 150 mg orally once daily was continued for a minimum of 12 mo and clopidogrel 75 mg orally once daily for at least 4 wk.

Statistical analysis
All collected data entered into the "IBM SPSS STAISTICS version 20". The quantitative data expressed as mean and standard deviation (SD) where qualitative data expressed in percentage (%). The independent and dependent student's *t*-test have been used to carry out significant changes in paired and non-paired quantitative data. Also, χ^2 and Fisher exact test have been used to carry out significant change in qualitative data. The *P* value < 0.05 consider as a statistically significant. All statistically significant variables taken for univariate binary logistic regression and for univariate significant variables entered into multiple step wise logistic regression for further analysis of the variables.

RESULTS
Out of 86 patients, 6 patients were lost follow-up and 5 patients developed non procedural related mortality in follow-up. All baseline characteristics of study population were shown in Table 1. The BP, antihypertensive medication, serum creatinine and GFR data compared at preprocedure and follow-up period in Table 2. There was no procedure related mortality. Two patients had local vascular complications which were managed conservatively. Out of 86 patients, 83 patients had atherosclerosis RAS and 3 patients takayasu arteritis.

The mean systolic BP was reduced from 170.15 ± 20.10 to 146.60 ± 17.32 mmHg and diastolic BP from 98.38 ± 10.55 to 89.88 ± 9.22 mmHg at one mo follow-up. This significant reduction in BP after PTRA was maintained at 6 mo follow up of 144.23 ± 18.19 systolic and 88.26 ± 9.79 diastolic BP respectively (Table 1). There was a statistically significant reduction in systolic BP compared to pre-intervention (paired *t* test: *P* <

Table 3 Levels of sIL-2R, alanine aminotransferase, and hepatitis B virus DNA in the sera of patients with chronic HBV infection (mean ± SD)

Group[1]	n	mean ± SD	P value
Age (yr)			0.51
A	26	56.81 ± 13.87	
B	49	54.80 ± 11.55	
Initial systolic BP (mmHg)			0.01
A	26	179.31 ± 20.32	
B	49	166.00 ± 18.76	
Initial diastolic BP (mmHg)			0.04
A	26	101.92 ± 10.90	
B	49	96.79 ± 10.14	
Initial mean BP (mmHg)			0.01
A	26	141.00 ± 17.73	
B	49	129.00 ± 16.76	
No. of medications			0.01
A	26	3.26 ± 0.77	
B	49	2.87 ± 0.57	
Creatinine (mg/dL)			0.07
A	26	1.38 ± 0.48	
B	49	1.11 ± 0.66	
Diameter of stent			0.23
A	26	5.76 ± 0.94	
B	49	6.05 ± 0.98	
Percent of renal artery stenosis (RAS)			0.05
A	26	87.65 ± 7.71	
B	49	83.79 ± 8.40	
GFR (mL/min)			0.01
A	26	54.03 ± 24.22	
B	49	72.97 ± 25.43	
Duration of HT (yr)			0.55
A	26	4.00 ± 3.96	
B	49	3.40 ± 3.32	

Values are presented as mean ± SD. [1]Group A: Patients who did not show blood pressure reduction after percutaneous transluminal renal artery (PTRA) (26 patients); group B: Patients who showed blood pressure reduction after PTRA (49 patients). HT: Hormone Therapy; BP: Blood pressure; GFR: Glomerular filtration rate.

0.0001). The 65.33% of patients showed reduction in BP. There was no difference in the magnitude of systolic BP response among patients treated for bilateral RAS compared with those treated for unilateral RAS.

Mean intake of total number of medicines at baseline was 3.07 ± 0.69. At 1 mo follow-up, number of medicines reduced to 2.37 ± 0.84 and at 6 mo to 2.25 ± 0.94. There was statistically significant reduction in mean number of medicines intake (*P* < 0.0001).

At baseline, mean serum creatinine value was 1.21 ± 0.66 mg/dL. After PTRA and stenting, at 48 h there was mild elevation in serum creatinine to 1.29 ± 0.88 mg/dL. At 1 mo of follow up, serum creatinine was 1.33 ± 1.27 mg/dL and at 6 mo was 1.21 ± 0.79 mg/dL. There was no statistically significant difference in serum creatinine value after PTRA. At baseline mean GFR was 65.71 ± 25.20 mL/min. After PTRA and stenting at 6 mo of follow up, GFR was 66.68 ± 25.03 mL/min. There was no statistically significant difference in GFR at follow up after PTRA and stenting (Table 1).

PTRA and stenting to renal artery significantly lowers BP and mean number of drug intake but not cause signif-

Table 4 Clinical features of resistant hypertensive group: Responsive *vs* unresponsive to percutaneous transluminal renal artery n (%)

		Group A	Group B	P value
		n = 26	n = 49	
	Male gender	24 (92.3)	33 (67.3)	0.016
	Smoker	22 (84.6)	33 (67.4)	0.1
	Ischemic heart disease	21 (80.8)	35 (71.4)	0.376
	Diabetes mellitus	8 (30.8)	19 (38.8)	0.49
	C/f of LVF	5 (19.2)	11 (22.4)	0.746
	Smoking	22 (84.6)	33 (67.4)	0.1
	Renal bruit	20 (76.9)	29 (59.2)	0.124
	Refractory HT	23 (88.5)	37 (75.5)	0.182
	LVH	14 (53.9)	14 (28.6)	0.031
	LAD	19 (73.1)	34 (69.4)	0.733
	TVD	12 (46.2)	13 (26.5)	0.08
Renal artery stenosis (unilat *vs* bilat)	Unilateral RAS	15 (57.7)	40 (81.6)	0.026
	Bilateral RAS	11 (42.3)	9 (18.4)	
LMCA disease	Absent	23 (88.5)	47 (95.9)	0.218
	Present	3 (11.5)	2 (4.1)	

Group A: Patients who did not show blood pressure reduction after percutaneous transluminal renal artery (PTRA) (26 patients); and group B: Patients who showed blood pressure reduction after PTRA (49 patients). HT: Hormone therapy; LVH: Left ventricular hypertrophy; TVD: Triple vessel disease; LAD: Left anterior descending; LVF: Left ventricular function; RAS: Renal artery stenosis; LMCA: Left main coronary artery.

icantly reduction in serum creatinine or change in GFR.

Prediction of BP reduction after PTRA among resistant hypertensive patients

In order to evaluate predictors of poor BP reduction after successful PTRA and stenting, we divided 75 patients into two groups: group A, the non-responsive group, which included patients without significant BP reduction after PTRA (26 patients), and group B, the responsive group, which included patients who showed significant BP reduction followed PTRA (49 patients) (BP reduction < 140/90 mmHg with or without drugs was considered significant reduction).

Higher baseline systolic and diastolic BP (number value < 0.01 and < 0.04, respectively) and higher mean intake of no. of medications (*P* value < 0.01) for control of BP was associated with poor response of BP control after successful PTRA and stenting. Non-responsive group associated with higher mean baseline serum creatinine (1.38 mg/dL *vs* 1.11 mg/dL) but not statistically significant (*P* = 0.07). But baseline low GFR < 60 mL/min was associated with poor response after PTRA and stenting (*P* < 0.01). Higher initial % of RAS was also associated with poor response (*P* = 0.05). Between these groups, neither duration of Hormone Therapy nor diameter of stent used was significantly different (Table 3).

Clinical features in the resistant hypertensive group

Comparing various characteristics between both groups reveals male sex (*P* = 0.016), left ventricular hypertrophy (*P* = 0.031), presence of triple vessel disease (*P* = 0.08)

Table 5 Multivariate analysis: The independent predictors for poor blood pressure response after percutaneous transluminal renal artery					
Variables	Univariate *P* value	Multivariate analysis			95%CI
		P value	β	Exp β	
Male sex	0.02	0.046	1.797	6.032	1.028–35.380
High mean SBP	0.01	NS			
High mean DBP	0.05	NS			
High mean BP	0.09	0.013	-0.044	0.957	0.925–0.991
Low GFR	0.01	0.015	1.377	3.965	1.308–12.020
(< 60 mL/min)					
LVH	0.03	NS			
Drugs (*n*)	0.01	NS			
Bilateral *vs*	0.02	NS			
unilateral RAS					
Percent of stenosis	0.06	NS			
Presence of TVD	0.09	NS			
Constant			2.365	10.65	

TVD: Triple vessel disease; BP: Blood pressure; RAS: Renal artery stenosis; GFR: Glomerular filtration rate; LVH: Left ventricular hypertrophy; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; NS: Not significant.

and presence of bilateral RAS ($P = 0.026$) were associated with poor outcome after PTRA and stenting (Table 4).

DISCUSSION

In the current study we demonstrated that in patients with significant RAS, PTRA improved BP control and decreased mean number of drug intake significantly and this improvement was maintained during the entire follow-up period of 6 mo. PTRA and stenting did not cause significant improvement in renal function (*P* value for both serum creatine and GFR was not significant).

In recent years, role of PTRA and stenting in management of RAS has been questioned. In the early 1980s the concept was that revascularization of the stenotic atherosclerotic renal artery will salvage the ischemic kidney and will cure hypertension[23]. Revascularization methods and medication have improved considerably over the past 20 years and the aims of managing patients with atherosclerotic renal artery stenosis (ARAS) have progressed from focusing on BP control to stabilizing renal function and finally to preventing clinical events. However, as the procedure became broadly applied during the 1990s mixed results emerged. Some patients showed major benefit after PTRA, while others experienced further deterioration of renal function and major morbidity[24]. Today it is acknowledged that ARAS is a complex clinical entity that ranges from asymptomatic disease discovered incidentally on imaging to high grade bilateral disease complicated by recurrent pulmonary edema, severe hypertension, and progressive renal failure. RAS is generally associated with high incidence of associated CAD and target organ damage. Mortality in these patients is high and mostly related to cardiovascular events regardless of whether renal revascularization was performed[25].

In recent years several controlled trials were designed

to evaluate the effectiveness of PTRA *vs* medical treatment in patients with severe ARAS. The DRASTIC study included a cohort of 106 hypertensive subjects with ARAS. The patients were randomly assigned to revascularization or medical treatment, but after 12 mo of follow-up no difference in BP control or renal function was demonstrated between the groups[26]. The STAR study, which included 140 patients with creatinine clearance < 80 mL/min per 1.73 m^2 and ARAS $\geq$ 50%, also failed to show benefit of the invasive approach *vs* medical treatment[27].

The largest randomized trial, the ASTRAL study, comparing revascularization to medical treatment for ARAS, examined 806 subjects who were followed for 5 years. This study concluded that revascularization for ARAS has more risk than benefit[23]. But important limitation of the trial was the selected population. Patients were enrolled in the trial only if their own physician was uncertain as to whether revascularization would provide a worthwhile clinical benefit. Patients with symptomatic ARAS such as uncontrolled hypertension despite optimal medical treatment, or with recurrent episodes of flush pulmonary edema were not included in the study[23]. This study is at the top of the list with ASTRAL, raised considerable debate regarding the management of patients with ARAS[28]. The main claim of the ASTRAL critics was that the success of PTRA for ARAS is strongly dependent on the selection of the right patients for this procedure.

In our study, we found PTRA and stenting associated with significant improvement in BP control with reduced mean intake of drugs without improvement in renal function. We also sought predictors of poor BP control after successful PTRA and stenting.

The predictors of poor response to BP control after PTRA and stenting by univariate analysis were male sex, high baseline systolic, diastolic and mean BP, low GFR , presence of LVH, high baseline mean intake of number of drugs, presence of bilateral stenosis, higher angiographic % diameter of stenosis and presence of TVD. But on multivariate analysis; the independent predictors for poor BP response after PTRA were male sex ($P = 0.046$), higher baseline mean BP ($P = 0.013$) and low GFR (< 60 mL/min) ($P = 0.015$) (Table 5).

Patients with poor BP response (34.66%) may be considered for renal sympathetic denervation therapy. As early studies in animals and in humans suggested that the renal nerves play a role in BP regulation. A series of pilot studies as well as a clinical trial (symplicity HTN-2) involving patients with uncontrolled hypertension then showed that a catheter-based system can safely denervate the kidney and produce notable and sustained reductions in BP. Ongoing symplicity HTN-3: Renal Denervation in Patients With Uncontrolled Hypertension trial will help us to establish whether therapeutic renal denervation using a catheter-based approach is a safe and effective therapy for patients with uncontrolled hypertension.

Study limitations
Given that the majority of patients were Asian, the find-

ings in our trial may not be generalized among other ethnic and racial populations. Another limitation of this study is that we have not used any emboli protection device. As atheroembolism is major concern in percutaneous intervention of renal artery and associated with different degree of renal impairment. Atheroembolism may impair outcome of PTRA and stenting particularly on renal function. Use of distal embolic protection device may be associated with improved outcome. We have not used FFR to evaluate lesion severity in our study. FFR can predict individual response to renal artery stenting and improve outcome of PTRA and stenting.

In conclusion, considering the results of our study and previous works it appears that the main effect of renal artery revascularization in ARAS is on BP control in patients with resistant hypertension, with minimal influence on renal function. Male sex, higher baseline BP and low GFR (< 60 mL/min) are associated with poor BP response after successful PTRA and stenting. Further studies with emboli protection devices and FFR to assess severity of lesion may be helpful to validate this observation.

COMMENTS

Background
Percutaneous transluminal renal artery angioplasty (PTRA) and stenting is an established procedure for the treatment of renovascular hypertension caused by renal artery stenosis (RAS). Recently published trials have questioned the efficacy of PTRA and stenting of renal artery.

Research frontiers
The PTRA technique has become the cornerstone for treatment of RAS and is now the first line treatment to be proposed. Balloon angioplasty alone was first proposed but several series reported the successful use of endovascular stents for treating suboptimal angioplasty results and as a primary intervention for atherosclerotic lesions and particularly ostial lesions with better immediate and long-term results than with balloon angioplasty alone.

Innovations and breakthroughs
They found PTRA and stenting associated with significant improvement in blood pressure (BP) control with reduced mean intake of drugs without improvement in renal function. Authors also sought predictors of poor BP control after successful PTRA and stenting.

Peer review
This is a study on percutaneous transluminal renal artery dilatation and stenting in a cohort of 86 patients with significant renal artery stenosis.

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Hypoxemia without persistent right-to-left pressure gradient across a patent foramen ovale: A clinical challenge

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Abstract

Patent foramen ovale (PFO) closure for systemic hypoxemia is controversial. The first systematic, albeit retrospective, study was recently presented which showed good procedural and clinical success for PFO closure for this indication. We present a case of acute right to left intra-cardiac shunt across PFO where the shunting is not persistent. Hence making a decision on PFO closure based on the aforementioned promising trial may not have been the right decision for the patient. This case highlights that the decision on PFO closure for such indication needs to be individualized. We also review the sparse literature on PFO closure for this indication and discuss how the decision making for such indication needs to be individualized.

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Key words: Patent foramen ovale; Hypoxemia; Right-to-left shunt; Shunt closure; Pulmonary embolism; Atrial septal defect

Core tip: Patent foramen ovale (PFO) is a common, yet benign entity most of the time. Rarely, it is known to play role in causation of stroke, migraine and even rarely, profound hypoxemia. We report a rare case of severe hypoxemia due to PFO where the shunting is not persistent. We also review the sparse literature on PFO closure for this indication and discuss how the decision making for such indication needs to be individualized.

INTRODUCTION

Patent foramen ovale (PFO) closure for systemic hypoxemia is controversial. The first systematic, albeit retrospective, study was recently presented which showed good procedural and clinical success for PFO closure for this indication.

CASE REPORT

A 83-year-old female was transferred from an outside facility after an extensive evaluation for acute hypoxemia. She initially presented with worsening shortness of breath over a few days, aggravated by exertion but without any orthopnea or paroxysmal nocturnal dyspnea. She denied cough or chest pain. Her past medical history was significant for hypertension, osteoarthritis, transient ischemic attacks, gastroesophageal reflux disease, osteoporosis and coronary artery disease. During the recent admis-
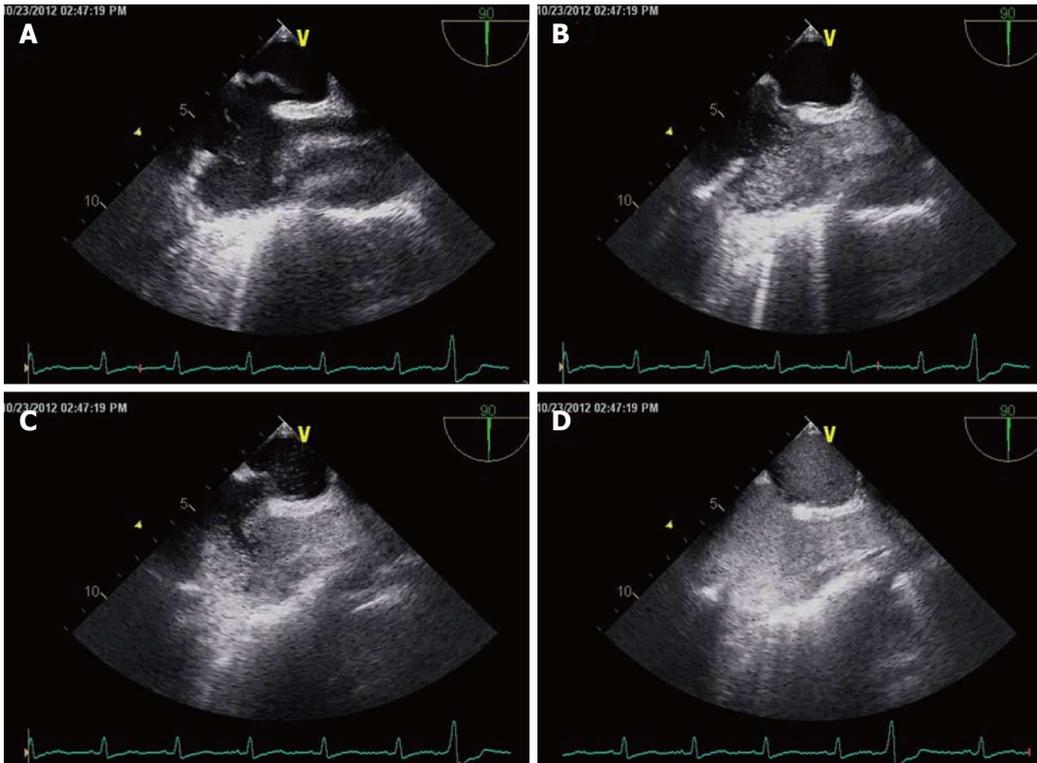
Figure 1 Transesophageal echocardiography with bubble study. A: Transesophageal echocardiography (TEE) of the patient with a patent foramen ovale (PFO) showing a wide separation in the inter-atrial septum; B: TEE with injected agitated saline showing the presence of bubbles in the right atrium; C: TEE of the patient within the same cardiac cycle showing jet of bubbles crossing the inter-atrial septum through the PFO; D: Opacification of entire left atrium as the jet of bubbles gushes through the PFO.
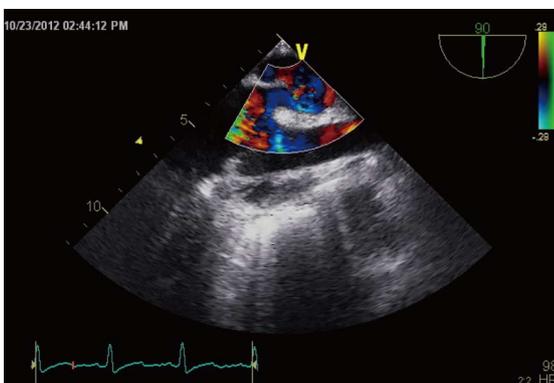
Figure 2 Transthoracic echocardiography with Doppler showing significant flow of blood across the inter-atrial septum.

sion to the outside facility, she had undergone a left heart catheterization (LHC) with stenting of the left circumflex and obtuse marginal arteries. The right coronary was chronically totally occluded and attempt to revascularize it was unsuccessful. The pressure and oxygen saturation data is presented in Table 1. Ventilation/perfusion scan showed low probability for pulmonary embolism (PE). Lung perfusion scintigraphy demonstrated increased uptake underlying the calvarium suspicious for right to left shunt.

At presentation to our facility, her blood pressure was 139/73 mmHg, heart rate 113 beats per minute, respira-

tory rate 23 and oxygen saturation was 90% on nasal canula oxygen of 15 L/min. Systemic examination was unremarkable. Arterial blood gas on admission was pH 7.5, pCO_2 25 mmHg, pO_2 54 mmHg and HCO_3^- 19.5 mEq/L. Chest roentgenogram was normal. Computed tomography angiogram chest PE protocol was negative. The possibility of intra-cardiac shunt was initially thought less likely in the absence of a right-to-left pressure gradient on recent heart catheterization. The patient continued to remain hypoxemic. Blood gas evaluation performed with and without oxygen revealed no significant improvement in PaO_2 with oxygen, suggesting right to left shunting at the intracardiac or intrapulmonary level. A transesophageal echocardiogram with bubble and doppler studies was subsequently done (Figures 1 and 2). Significant right to left shunting across a PFO was observed. The inter-atrial septum was markedly deviated to the left atrial side during systole and represented an atrial septal aneurysm. QP (pulmonary flow): QS (systemic flow) ratio could not be precisely estimated due to limited views of the right ventricular outflow tract but was approximately 0.7. This observation suggested significant right to left shunting. She was also found to have healthcare associated pneumonia during that time which was adequately treated with antibiotics. PFO closure was considered but it was thought that the large right to left shunting at the atrial level observed earlier was likely related to pulmonary vasoconstriction related to her pneumonia. After a few days, her oxygen re-

Table 1 Pressure and oxygen saturation in various chambers measure on cardiac catheterization		
Location	Pressure (mmHg)	Oxygen saturation
Right atrium	2	
High		65%
Medium		63%
Low		67%
Right ventricle	2/18	60%
Pulmonary artery	20/6	61%
Left atrium	3	95%
Aorta		95%
Inferior venacava		73%
Superior venacava		70%

quirement decreased. Blood gas evaluation was performed with (pH 7.3, pCO_2 37 mmHg, pO_2 68 mmHg and HCO_3^- 22 mEq/L) and without oxygen (pH 7.4, pCO_2 34 mmHg, pO_2 56 mmHg and HCO_3^- 21 mEq/L). Repeat echocardiogram showed persistent but decreased shunting. She was subsequently discharged to a nursing home on 2 L oxygen.

DISCUSSION

PFO occurs in nearly 30% of the adult population[1]. During the last decade, PFO and right-to-left shunting of venous blood has been linked to a number of disorders including cryptogenic headache, migraine and vascular headache, and decompression sickness with air embolism[2-4]. Recent reports have documented that acute right-to-left inter-atrial shunt (ARLIAS) across PFO may cause profound and difficult-to-treat hypoxemia[5-7]. This is often diagnosed unexpectedly during investigation for other causes of acute hypoxia. Echocardiography with bubble contrast remains the most sensitive, non-invasive and first line investigation for detection of ARLIAS[5]. The data on closure of PFO for hypoxemia derives mainly from case reports and series. Successful closure in these cases demands not only an acceptable peri-procedural and long term risk (known as "procedural success") but also a complete reversal of the shunt and resolution of hypoxemia (known as "clinical success"). A systematic review by Khairy *et al*[7] in 2003 found that the incidence of major and minor complications of PFO closure was 1.5% and 7.9% respectively. Cardiac arrhythmias, device embolization, hemopericardium, right heart failure, transient ischemic attack and residual moderate to severe shunt are the known complications of device closure[7-9]. The indication for transcatheter closure of PFO reviewed by Nguyen *et al*[10] was for presumed paradoxical emboli. Over the last decade, there has been significant progress made in PFO closure terms of device technology, as well as the technique. Recently, a single-center, retrospective study of 104 patients undergoing PFO closure for systemic hypoxemia showed a good clinical safety as well as mechanical effectiveness of PFO closure using Amplatzer Cribriform atrial septal defect Occluder or Helex

Septal Occluder.

The two prerequisite for development of ARLIAS arepresence of an interatrial shunt such as PFO or less commonly, atrial septal defect and a functional component that promotes abnormal shunting of the blood through the shunt. This includes various cardiac or pulmonary insults such as pulmonary embolus, severe asthma and right ventricular infarction or coronary artery bypass grafting that raises right atrial pressure above left atrial pressure. Treatment of such precipitating factors may cause resolution of hypoxemia as evident in our patient. Hence, the shunting process may not be persistent, as a result of which, the atrial chamber pressures could have been normal in our patient at the time of catheterization. A similar case of hypoxemia, without a persistent right-to-left pressure gradient has been reported by Marples *et al*[6]. As the underlying process progresses, a pressure gradient may develop across the PFO leading to right-to-left shunting. The process of shunting further worsens the hypoxia. This may tempt physicians to decide on PFO closure to correct the hypoxemia. However, such decision would have only invited more complications to our patient (such as right ventricular failure) and may not have been the right therapy for the patient's hypoxemia. Hence, it is necessary to carefully consider the risk-to-benefit ratio and give due importance to physiological considerations before deciding on percutaneous device closure as a treatment modality for hypoxemia. If a reversible trigger for development of acute right-to-left shunting exists, appropriate management of that process may alleviate the need for device closure and related complications as seen in our patient.

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CASE REPORT

Multi-vessel percutaneous coronary intervention in a patient with a type B aortic dissection-transradial or transfemoral?

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Abstract

Patients with chronic aortic dissections are at high risk of catheter-induced complications. We report a 41-year-old patient with a type B aortic dissection (Stanford) who underwent successful three-vessel percutaneous coronary intervention *via* the right radial artery approach following a non-ST elevation myocardial infarction. The patient remained asymptomatic at 6 mo follow-up. Trans-radial approach for coronary interventions can be used safely in patients with Stanford type B aortic dissection without increasing the risk of procedure- related complications in this high-risk group of patients.

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Key words: Aortic dissection; Type B; Percutaneous coronary intervention; Transfemoral

Core tip: The case highlights the use of a transradial approach to carry out multivessel percutaneous coronary intervention (PCI) in a patient with a chronic aortic dissection. There is a paucity of literature on this subject. This case discusses the possible mechanisms of dissection propagation with a transfemoral approach and highlights the need for training in both approaches. Decision making in choosing arterial access for PCI in patients with aortic dissection.

INTRODUCTION

A 41-year-old male patient was admitted with cardiac chest pain and elevated troponin. His 12 lead electrocardiogram showed widespread T wave inversion. A diagnosis of non-ST elevation myocardial infarction (NSTEMI) was made. He was known to have a chronic Stanford type B aortic dissection, extending in the descending aorta from beyond the left subclavian artery down to the abdominal aorta, and was under regular medical surveillance.

CASE REPORT

His cardiovascular risk factors included hypertension, hypercholesterolemia and smoking. He had been given standard NSTEMI treatment with dual antiplatelets (aspirin 300 mg and clopidogrel 300 mg) and low-molecular weight heparin (weight adjusted) at admission. While an inpatient, he had further cardiac chest pains and therefore, was transferred to the catheter-lab for cardiac catheterisation. Prior to
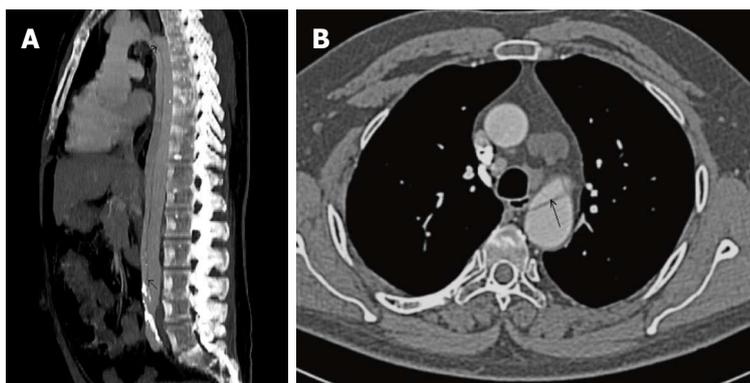
Figure 1 Computed tomography aorta. A: Sagittal view; B: Transverse view. Computed tomography aorta showing the chronic aortic dissection extending from the upper descending aorta down to the abdominal aorta. Arrows indicate dissection flap entry and exit points (A) and flap (B).
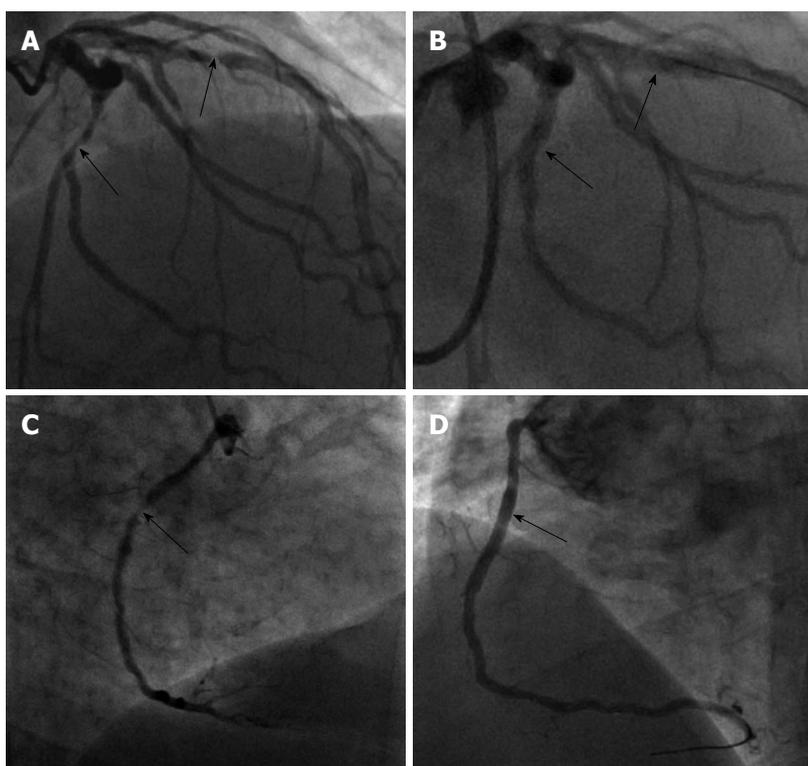
Figure 2 Coronary angiogram image. A: Lesions in left anterior descending (LAD), left circumflex (LCx). Coronary angiogram image showing severe lesions in LAD and LCx arteries (arrows); B: Percutaneous coronary intervention to LAD and LCx. Post-percutaneous coronary intervention (PCI) images showing successful PCI to lesions in LAD and LCx (arrows); C: Lesion in right coronary artery (RCA). Coronary angiogram image showing tight lesion in RCA (arrow); D: PCI to RCA. Successful PCI to RCA with a DES (arrow).

the procedure, he received further loading with clopidogrel 300 mg. During the procedure, he received weight adjusted unfractionated heparin intravenously. The decision to use standard acute coronary syndrome (ACS) peri-procedural therapy was made in view of the fact that the patient had been stable from his chronic aortic dissection and that his recent electronic computer X-ray tomography technique (CT) of the aorta showed no extension of his dissection (Figure 1). Informed consent was obtained prior to the percutaneous coronary intervention.

The coronary diagnostic procedure was performed *via* the right radial artery approach. Five French JR4® and JL 3.5® diagnostic catheters were used for the right and left coronary systems respectively. This confirmed a normal left main stem. The left anterior descending (LAD), left circumflex (LCx) and right coronary artery (RCA) had severe mid-vessel lesions (Figure 2A and C). Due to the complexity of the case, it was decided to treat all three lesions at the same procedure.

A Medtronic Launcher EBU 5.0 (6F)® (Medtronic) guide catheter was used to cannulate the left system. Two 0.014" BMW® guidewires (Abbott Vascular) were advanced to the distal LAD and LCx. The lesion in the LAD was directly stented using a 4.0 mm × 15 mm Resolute Integrity® drug eluting stent (DES) (Medtronic). The LCx lesion was pre-dilated using a 2 mm × 15 mm Maverick Balloon® (Boston Scientific), followed by a 2.75 mm × 22 mm Resolute Integrity® DES.

An Amplatz (AL2) guide catheter was used to cannulate the RCA. A 0.014" BMW® guidewire was advanced to the distal RCA. The lesion was pre-dilated with a 2.0 mm × 15 mm Maverick Balloon® followed by a 3.0 mm × 22 mm Resolute Integrity® DES. Excellent final angiographic results were obtained (Figure 2B and D) A Terumo TR band® (Terumo) was deployed to the radial access site at the end of procedure. There were no peri or post procedure complications. A total of 300 mL contrast (Visipaque®) and 7000 units heparin were given. His

repeat blood tests including haemoglobin, urea, creatinine and electrolytes were normal post-procedure. The patient made an uneventful recovery and was discharged a few days later on dual antiplatelets (aspirin 75 mg and clopidogrel 75 mg daily) and standard secondary prevention. He was instructed to continue on dual antiplatelets for 1 year and aspirin for lifelong thereafter.

DISCUSSION

Aortic dissection can be classified according to the location of the dissection and the relevance to patient management. The commonly used Stanford classification distinguishes aortic dissections by whether the ascending aorta is involved (type A) or not (type B)[1]. The incidence of aortic dissection in the general population is approximately 2.6-3.5 per 100000 person-years[2,3]. In a study by Islamoğlu *et al*[4], 11 of 76 patients with aortic dissection (acute and chronic) ie 14.5% had concomitant coronary artery disease. However, none of the chronic type B dissection patients who underwent coronary angiography had coronary artery disease. CT angiography allows the fast and reliable detection of aortic dissections and delineation of the dissection flap anatomy.

Since the introduction of trans-radial coronary angioplasty[5], procedural success rates have evolved remarkably and complex coronary artery lesions can be treated with minimal complications. Our patient had a chronic Stanford type B aortic dissection. A transfemoral approach would carry a high risk of complicating the existing dissection. Hildick-Smith *et al*[6] published a large case series looking at transradial coronary angiography in patients with contraindications to a femoral approach. Of 500 patients in that series, 10 patients had aortic dissection and had a transradial approach. However, there is no series looking solely at patients with aortic dissection and the best approach for PCI. Furthermore, there is a paucity of literature discussing the possible mechanisms of catheter-related complications in relation to aortic dissections in cases similar to ours. Mechanisms would include entry of the catheter tip into the false lumen. Using a femoral approach, this could happen at the exit site of the existing dissection. Continued advancement of the catheter would then risk propagation of the dissection into the ascending aorta as well as rupture of the vessel. Additional risks would include catheter entry into the false lumen *via* puncturing the wall between the true and false lumens. In our patient, to avoid these potential complications, we safely used the right trans-radial approach for three-vessel PCI without any procedural complications. This would appear to be the ideal approach in patients with Stanford type B aortic dissections as it avoids the descending aorta and thus, the potential to worsen an existing dissection. However, a radial approach is not without risk of aortic dissections. Indeed, there are case reports of iatrogenic aortic dissections due to aggressive catheter manipulation during PCI *via* a radial approach[7]. Furthermore, in patients with aberrant right subclavian artery (aretria lusoria), PCI *via* a right radial approach can be extremely difficult and there are reports of iatrogenic aortic dissections during such procedures[8].

This case highlights the importance of choosing the right access approach in patients with a complicated background like ours. It also highlights the importance of training interventionalists in both the transradial and tranfemoral approaches as each has its own merits and is sometimes the only feasible approach in certain patient groups.

In conclusion, trans-radial approach for coronary interventions can be used safely in patients with Stanford type B aortic dissection without increasing the risk of procedure-related complications in this high-risk group of patients.

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Berberine behind the thriller of marked symptomatic bradycardia

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Abstract

Berberine is used in traditional Chinese medicine for the treatment of congestive heart failure, hypertension, diabetes, and dyslipidaemia and has a good safety profile. We report a case of a 53-year-old sportsman referred to our hospital for the onset of fatigue and dyspnoea upon exertion after he started berberine to treat hypercholesterolaemia. An electrocardiogram showed sinus bradycardia (45 bpm), first-degree atrioventricular block, and competitive junctional rhythm. An ergometric stress test showed slightly reduced chronotropic competence and the presence of runs of competitive junctional rhythm, atrial tachycardia, and sinus pauses in the recovery. After 10 d of wash-out from berberine, the patient experienced a complete resolution of symptoms, and an ergometric stress test showed good chronotropic competence. An electrocardiogram Holter showed a latent hypervagotonic state. This is the first case report that shows that berberine could present certain side effects in hypervagotonic people, even in the absence of a situation that could cause drug accumulation. Therefore, berberine's use should be carefully weighed in hypervagotonic people due to the drug's bradycardic and antiarrhythmic properties, which could became proarrhythmic, exposing patients to potential health risks.

Core tip: Berberine is widely used in traditional Chinese medicine for the treatment of congestive heart failure, hypertension, diabetes, and dyslipidaemia. We report a case of marked symptomatic sinus bradycardia with competitive junctional rhythm caused by berberine, showing that berberine, due to its antiarrhythmic properties, can cause the onset of bradyarrhythmia. In this case report, we focus on the possible side effects of so-called natural medicine based on holistic, home, and herbal remedies, which is considered to be safe only because the treatment is natural. However, under certain conditions, natural medicine can lead to potential health risks in patients.

INTRODUCTION

Berberine is an alkaloid from *Hydrastis canadensis* L., the
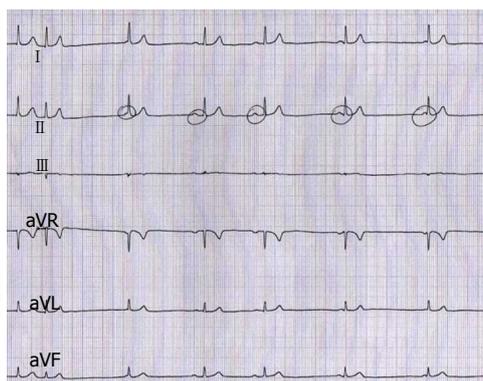
Figure 1 Competitive junctional rhythm.

Figure 2 Junctional beats, premature supraventricular beats, sometimes aberrant starting brief runs of atrial tachycardia.

Chinese herb Huang Lian, and many other plants. Berberine is widely used in traditional Chinese medicine for the treatment of congestive heart failure[1-3], hypertension[3], diabetes, and dyslipidaemia[4-5]. Berberine has multiple cardiovascular effects, including negative chronotropic, antiarrhythmic and vasodilatory properties[1,2] and an anti-inflammatory effect[6]. Several cardiovascular effects of berberine are attributed to the blockade of K^+ channels [delayed rectifier and K(ATP)], the stimulation of Na^+-$Ca(^{2+})$ exchangers[2,7], and the activation of cardiac M2 muscarinic cholinergic receptors[8].

Berberine has been tested in acute coronary syndrome patients following percutaneous coronary intervention (PCI)[6], in congestive heart failure secondary to ischemic or idiopathic dilated cardiomyopathy[3], in menopausal women[9], in elderly hypercholesterolaemic patients[10], and in patients with metabolic syndrome[11], offering various therapeutic strategies without evidence of side effects.

CASE REPORT

We report a brief case that shows that berberine could cause side effects under specific conditions.

A 53-year-old man was referred to the emergency room of our hospital after the onset of fatigue and dyspnoea upon exertion, with evidence of bradycardia. He was overweight and hyperlipidaemic and used to swim three times per week. His medical history was unremarkable, except that he had started berberine 6 d before to treat hypercholesterolaemia. Upon physical examination, the patient presented a normal blood pressure and oxygen saturation but an irregular heart rate of 50 bpm. He did not present signs of heart failure, and cardiac, pulmonary, and vascular examinations were normal. The electrocardiogram (ECG) showed sinus bradycardia with a heart rate of 45 bpm, first-degree atrioventricular block (PR interval of 280 ms), and a competitive junctional rhythm at 55 bpm (Figure 1). Both blood analysis and echocardiography did not show any justification for the marked bradycardia. An overdose of berberine was ruled out because the patient consumed the correct daily dose. Because berberine excretion is hepatobiliary[12], the presence of any predisposing factor for reduced excretion, such as hepatic or biliary disease, was examined and ruled out.
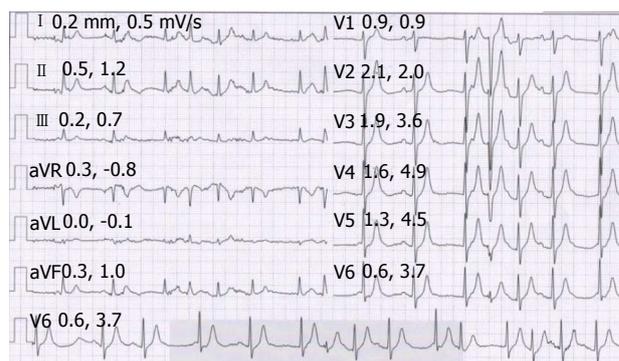
Given the bradycardic and antiarrhythmic properties of berberine, we decided to discontinue the drug, and based on the presence of dyspnoea upon exertion, an ergometric stress test was performed to evaluate chronotropic competence. A 24-h wash-out from berberine was sufficient before the test, as berberine's half-life is less than 30 min[12]. The ergometric stress test showed slightly reduced chronotropic competence, with an increase in the heart rate from 45 bpm to 127 bpm, equivalent to 76% of the maximal prediction. The test also showed a reduction in the atrioventricular conduction delay, with a PR that reached 180 ms for a heart rate of 127 bpm. The patient presented a good functional class (the test was stopped at the second minute of the step second Bruce protocol, METs 13.5). The recovery was characterised by the presence of runs of competitive junctional rhythm; premature supraventricular beats that were occasionally aberrant, sporadically starting brief runs of atrial tachycardia (Figure 2); and a sinus pause with an RR of a maximum of 1.7 s (Figure 3A). Most likely, the patient's symptoms were not closely related to bradycardia at rest but rather to the loss of AV synchronisation during the junctional rhythm and to the reduction in chronotropic competence during stress.

Over the following days, the patient experienced a complete resolution of symptoms and performed normal life activities and his usual sport activity (swimming) without experiencing dyspnoea or fatigue. After 10 d of wash-out from berberine, he underwent a new ergometric stress test and an ECG Holter. The ergometric stress test was normal. The ECG at rest was characterised by the presence of sinus bradycardia with a heart rate of 43 bpm and first-degree atrioventricular block (PR at rest of 280 ms), as presented several days before. However, the test presented better chronotropic competence. The test was maximal (86% of the predicted heart rate), despite the patient having reached the same workload as in the first test. The presence of first-degree atrioventricular block was consistent with a PR interval normalised at a high rate.

During the ECG-Holter monitoring, we observed a
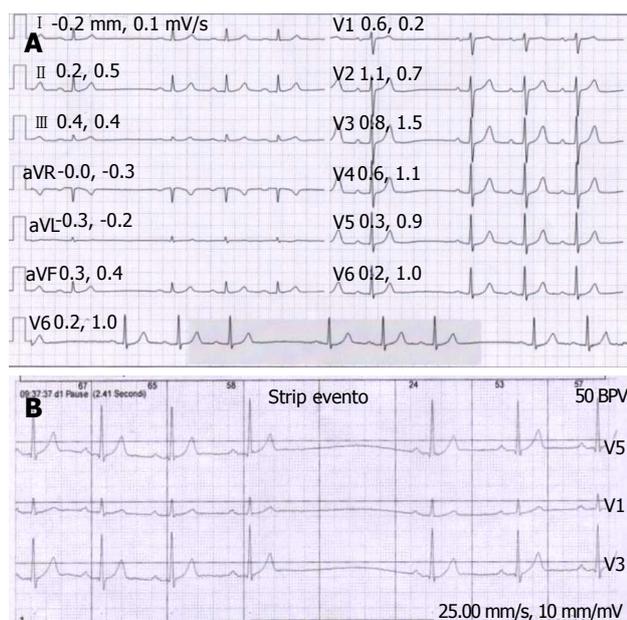
Figure 3 Sinus pause. A: With an RR of max 1.7 s; B: With an RR 2.4 s.

sight typical of a hypervagotonic state: bradycardial sinus rhythm with normal variation of the heart rate with a circadian cycle and physical activity (FC maximum 104, average 56, minimum 40 bpm); several nocturnal runs of sinus bradycardia at 30 bpm; and several, especially nocturnal sinus pauses, with an RR interval of 2.4 s (Figure 3B).

The patient continued to be asymptomatic and to practice his normal life and sport activities and treated his dyslipidaemia with diet.

DISCUSSION

This is the first case report that shows that berberine could present certain side effects in hypervagotonic people, even in the absence of a situation that could cause drug accumulation. Indeed, berberine has been found to have a good safety profile[2,3,5,6,9-11] in patients with pathological conditions characterised by a hyperadrenergic state, such as acute coronary syndrome[13], heart failure[14,15], diabetes[16], hypertension[17], and menopause[18]. In a murine model, it has been proven that berberine reduces plasma adrenaline and noradrenaline levels[19]. We do not know whether the bradycardic and antiarrhythmic properties of berberine are vagally mediated by the activation of muscarinic receptors, as shown by Salehi *et al*[8], or are not vagally mediated, as reported by Shaffer[20]. However, it is possible that in hypervagotonic people with marked sinus bradycardia, berberine's bradycardic effect can induce the onset of competitive junctional rhythm, causing a loss of atrioventricular synchronisation, and can reduce chronotropic competence with the onset of symptoms upon exertion. Therefore, berberine's use should be carefully weighed in hypervagotonic people due to the drug's bradycardic and antiarrhythmic proper-

ties, which could become proarrhythmic, exposing patients to potential health risks.

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CASE REPORT

Non-coronary myocardial infarction in myasthenia gravis: Case report and review of the literature

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Core tip: Cardiovascular adverse events in patients with myasthenia gravis (MG) are rare, but the early recognition of such events is crucial. We describe a case of a non-coronary myocardial infarction during the initial treatment period with pyridostigmine bromide in a female patient with MG. In this case report possible causes of myocardial adverse events in the context of MG, which may occur during the ongoing treatment and the clinical course of the disease, are discussed.

Abstract

Cardiovascular adverse events in patients with myasthenia gravis (MG) are rare, but the early recognition of such events is crucial. We describe a case of a non-coronary myocardial infarction (MI) during the initial treatment period with pyridostigmine bromide in a female patient with MG. Clinicians should be cautious about the appearance of potential MI in patients with MG. A baseline electrocardiogram is advocated, when the early recognition of the MI clinical signs and the laboratory findings (myocardial markers) are vital to the immediate and appropriate management of this medical emergency, as well as to prevent future cardiovascular events. In this case report possible causes of myocardial adverse events in the context of MG, which may occur during the ongoing treatment and the clinical course of the disease, are discussed.

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INTRODUCTION

Myasthenia gravis (MG) is a neuromuscular disorder characterized by weakness and fatigability of skeletal muscles. The number of available acetylcholine receptors at the neuromuscular junction is decreased because of an antibody-mediated autoimmune attack. Anticholinesterase medications are widely used to treat MG as they act by blocking hydrolysis of acetylcholine by acetylcholinesterase, consequently allowing acetylcholine to interact repeatedly with the limited number of acetylcholine receptors[1]. Apart from their muscarinic side effects, it has been shown that they can rarely cause cardiovascular side effects[2,3].

CASE REPORT

A 71-year-old female patient presented with a 4-wk his-
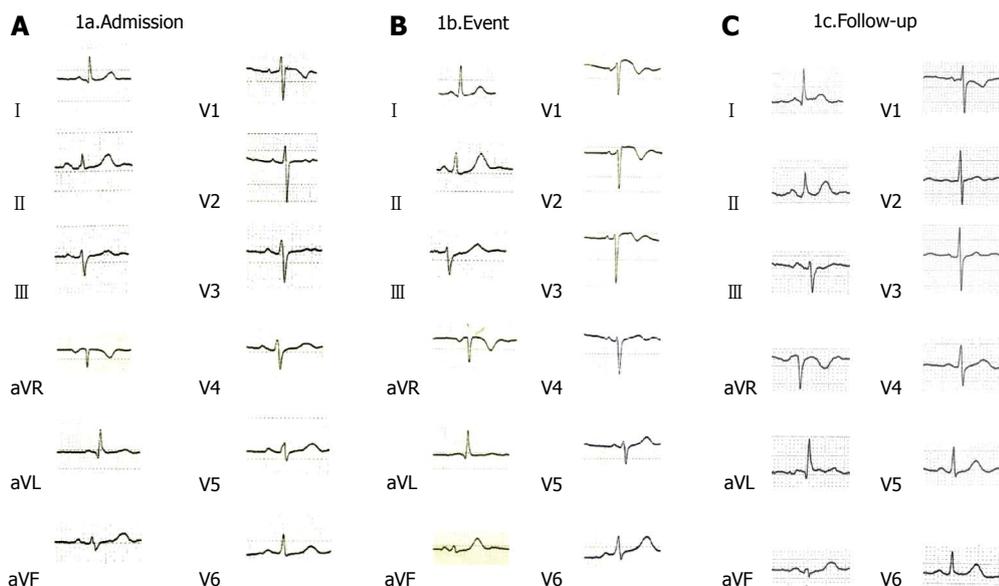
Figure 1 The electrocardiogram. A: A 12-lead standard electrocardiogram (ECG) of the patient at hospital admission; B: At 10th day after admission. An ST elevation in leads V1-V2 and T-wave abnormalities can be noted; C: In the repeat ECG, all changes noted in the abnormal ECG have resolved, as can be noted.

tory of worsening dysphagia and dysarthria. The edrophonium test that was performed in the emergency department was positive and therefore she was admitted to the Department of Neurology for further investigation and management. Past medical history included arterial hypertension well controlled on carvedilol and diet controlled dyslipidaemia. There was no history of diabetes, smoking or alcohol abuse. The rest of the medical history included a hip replacement surgery 12 mo prior to the current admission, which was complicated by deep venous thrombosis for which she received oral anticoagulant therapy for 12 mo. Finally, she was receiving a low-dose benzodiazepine on an as-required basis for anxiety disorder.

On admission the patient was alert and orientated with normal observations (blood pressure 140/74 mmHg, pulse 94/min, saturation 96% on FiO₂ 21%). The electrocardiogram (ECG) revealed no signs of ischemia (Figure 1) and routine blood and biochemical tests were within normal values [haemoglobin 15.0 g/dL, serum glucose 83 mg/dL, urea 47 mg/dL, creatinine 0.76 mg/dL, aspartate aminotransferase (AST) 32 IU/L, alanine aminotransferase 16 IU/L, potassium 5.0 mmol/L, sodium 136 mmol/L]. Thyroid hormones were within normal limits. Neurological examination revealed mild proximal weakness in all four limbs, dysphagia and nasal speech. Physical examination was otherwise unremarkable.

A diagnosis of MG was confirmed by positive rapid decremental responses of muscle action potentials to repetitive nerve stimulation and an elavated anti-acetylcholine receptor antibody count (titer 135 nmoles/L, normal values < 0.5 nmoles/L). Pyridostigmine bromide 60 mg tds and prednisolone, 10 mgs OD were commenced to treat MG.

Three days later muscarinic side effects such as diarrhea, abdominal cramps and salivation appeared while

there was a significant improvement in neurological examination with regards to dysarthria and dysphagia. On the 4th day the patient complained of chest pain (with a duration of less than 30 min) accompanied by an intense sense of discomfort (emotional stress similar to an acute panic attack). There were no changes in the ECG and serial measurements of troponin, creatine kinase (CK), CK-MB, AST, lactate dehydrogenase (LDH) and ProBNP levels were normal.

However, the frequency of such episodes of chest pain was increased from one every two days to twice a day and on day 10th the ECG revealed ST elevation in leads V1-V2 and T-wave abnormalities (Figure 1) with a subsequent significant elevation in troponin and ProBNP level (Figure 2). At that point blood pressure was 160/80 mmHg, pulse 69/min and oxygen saturation 96% (on oxygen nasal cannula, 2 L/min). Chest radiography was within normal limits, D-dimers were within normal values and the arterial blood gases did not show hypoxaemia and hypocapnia consistent with pulmonary embolism, therefore the latter was highly unlikely in our differential diagnoses. A subsequent spiral chest CT, with intravenous contrast, performed a few days later confirmed that there was no evidence of pulmonary embolism.

Based on the ECG and the increase in troponin and ProBNP levels a diagnosis of myocardial infarction (MI) was made and the patient was transferred to the intensive coronary care unit where treatment with nitrates, aspirin, clopidogrel and heparin was initiated. The cardiac ultrasound showed concentric hypertophy of the left ventricle (left ventricle ejection fraction 55%) with anteroseptal hypokinesia and type I diastolic dysfunction.

The chest pain resolved within hours. The patient underwent coronary angiography a few days later (as she did not consent to the procedure in the acute phase), which
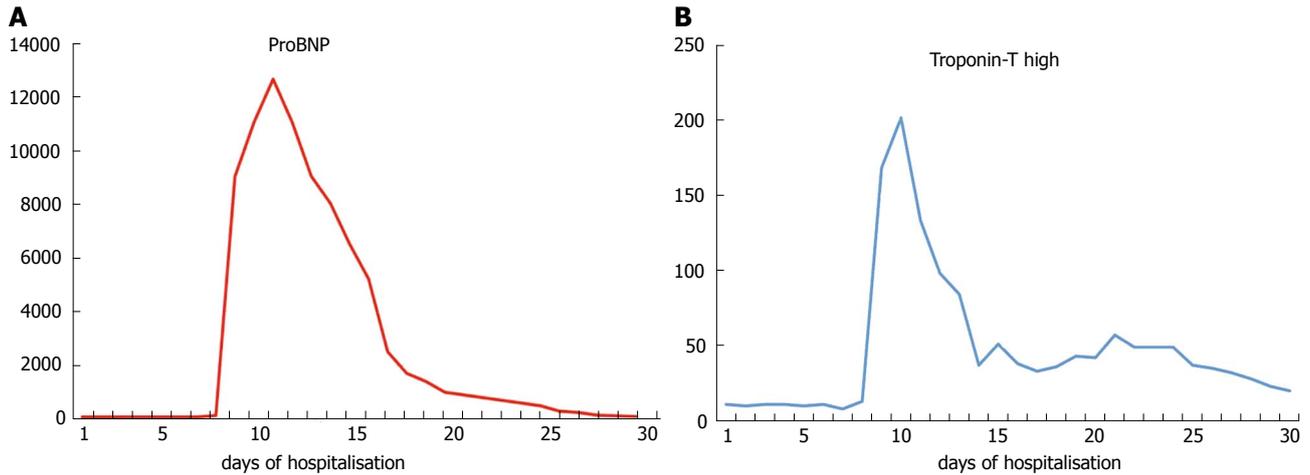
Figure 2 The frequency of such episodes of chest pain was increased. A: ProBNP; B: Troponin-T. ProBNP, troponin-T high levels during clinical presentation of patient's symptomatology. In Y axis, both ProBNP and troponin are measured in pg/mL (normal values; ProBNP < 150 pg/mL, troponine < 14 pg/mL).
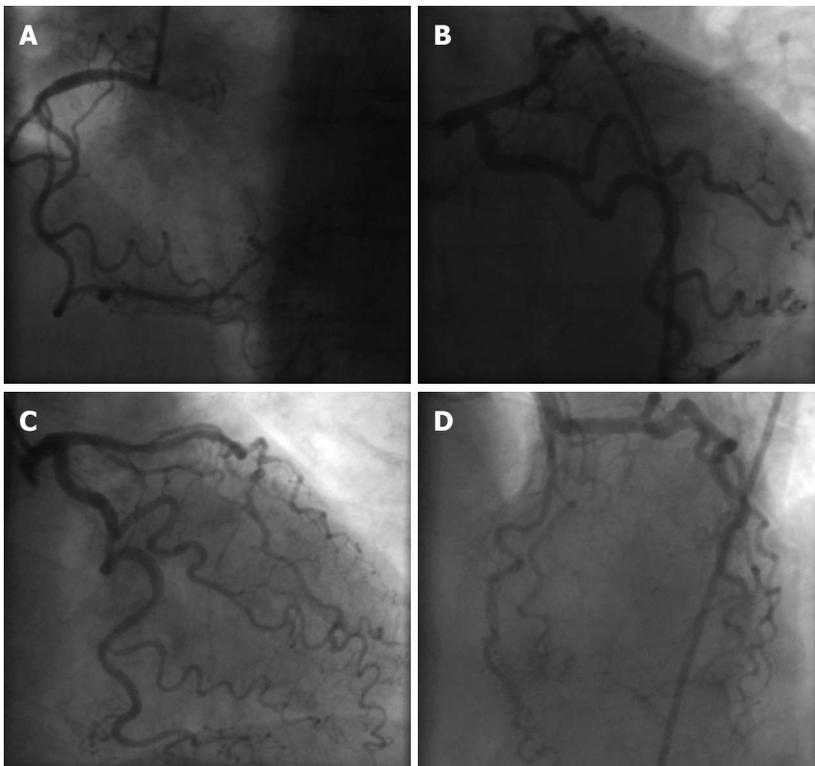
Figure 3 A normal coronary angiography performed at the patient. A: Right coronarogram; B: Left coronarogram; C: Left coronary artery-right anterior oblique; D: Left coronary artery-left anterior oblique.

revealed a normal right coronary artery and a narrowing of less than 30% in the left anterior descending (Figure 3). Moreover, serial measurements of CK, AST and LDH did not show significant variation. The patient remained afebrile and the C-reactive protein and erythrocyte sedimentation rate values were normal.

During her hospital stay the patient was further investigated with chest axial computed tomography, which revealed a type A thymoma (N1M0) that was successfully surgically removed. Because of the initial difficulty in weaning from the mechanical ventilation a tracheostomy was performed and she was transferred to the medical intensive care unit. Her pyridostigmine dose was gradually reduced and was eventually stopped. The patient continued to receive only prednisolone in a high dose (75 mg/d), which was gradually reduced to 30 mg once daily.

The patient presented with weakness acquired during the intensive care unit (ICU) stay, which was gradually improved, tracheostomy was removed and she was discharged from the hospital in a generally good clinical condition. The neurological examination for MG was unremarkable at hospital discharge.

However, one month later, while she was in a sitting position, talking with her relatives she had a sudden cardiac death as reported from the last phone follow-up communication.

DISCUSSION

We present a case of a non-coronary MI in a patient with MG. A non-coronary MI, defined alternatively as a MI with normal coronary arteries, is a medical condition, which has been described in the literature for more than 30 years[4]. Its prevalence varies between 1% and 12% depending on the definition of "normal" coronary arteries, which usually includes no luminal irregularities (strict definition) or arteries with some degree of stenosis (less than 30%)[5-7].

Patients with MG under treatment complain frequently of the anticholinesterase medications muscarinic side effects, including diarrhea, abdominal cramps, salivation and nausea. However, cardiovascular adverse events in MG are rare. They occur mainly as a consequence of the MG treatment and less frequently in the context of a MG crisis through a possible immunological mechanism.

To the best of our knowledge three cases of cardiovascular side effects in patients with myasthenia gravis induced by anticholinesterase medication have been reported so far; a case of coronary spastic angina induced by ambenonium chloride[2], a case of coronary spastic angina induced by distigmine bromide[3] and a case of coronary vasospasm secondary to hypercholinergic crisis caused by pyridostigmine[8]. Cases of coronary vasospasm have also been described in anaesthetic practice where anticholinesterases are used to reverse the action of non-depolarizing muscle relaxants[9].

The exact mechanism under which cardiovascular side effects during treatment with acethylcholinesterase inhibitors occur remains unknown. However, it is well recognized that the coronary artery response to acethylcholine is very sensitive, constricting abnormally when the endothelium is damaged, in contrast to normal coronary arteries showing coronary vasodilation by acethylcholine[2]. One possible mechanism is that since pyridostigmine inhibits acetylcholinesterase in the synaptic cleft, thus slowing down the hydrolysis of acetylcholine and increasing the attachment of acetylcholine to the limited acetylcholine receptors, the exposure of coronary artery to acetylcholine might be increased. Furthermore, the use of prednisone decreases the anti-acetylcholine receptor antibody and enhances the effect of pyridostigmine[2].

In MG cardiovascular side effects can also occur during intravenous immunoglobin infusion (IVIg). IVIg has been associated with several possible adverse reactions including induction of a hypercoagulable state. IVIg-induced hypercoagulability has been associated with both non-ST elevation myocardial infarction[10] and ST elevation myocardial infarction[11]. The risk of acute MI seems to be increased with the use of high-dose IVIg in older individuals as well, especially those with at least one cardiovascular risk factor[12,13]. Takotsubo cardiomyopathy has also been observed in a patient during plasmapheresis treatment for myasthenic crisis[14]. In our case, the cardiac ultrasound during the MI did not show any contractile dysfunction suggestive of Takotsubo cardiomyopathy.

Moreover, in our case the patient neither received IVIg nor did she undergo plasmapheresis.

Previous case studies have indicated a possible link between MG and cardiovascular disorders[15-18]. It has also been suggested that myocarditis may occur in MG through the effects of striational muscle antibodies that cross-react with both skeletal muscles and myocardial tissue[16]. However, our patient remained afebrile, C-reactive protein and CK levels were normal and ECG did not show diffuse T-wave inversion. For these reasons myocarditis was an extremely unlikely diagnosis of our case.

In a recent case report it was shown that acute emotional stress may be a triggering factor for both Takotsubo cardiomyopathy and MG crisis[19], the mechanisms, however, remain unclear. In our case report acute emotional stress was involved in myocardial infarction presentation and might also have been a triggering factor even though contrary to that case report[19]-a MG crisis was not manifested. The exact role of emotional stress is unclear in our case presentation as emotional stress can be both a precipitant and a consequence of the MI itself in a patient with a history of an anxiety disorder.

As our patient was haemodynamically stable with normal arterial blood gases, no evidence of sepsis and no anaemia, we believe that her MI did not occur because of demand ischemia but due to coronary vasospasm. The time interval between treatment initiation with pyridostigmine bromide and the myocardial infarction suggests that there may be a link between the two events. Moreover, apart from the pyridostigmine and the prednisolone there were no other changes in our patient's drug regime. The subsequent sudden death of the patient, however, occurred while she was not on pyridostigmine and is, therefore, against this hypothesis.

The coronary slow flow phenomenon is characterized by angiographically normal coronary arteries with delayed opacification of the distal vasculature[20]. Although slow coronary flow can induce abortive sudden death[21] our patient did not have risk factors such as smoking that could have caused endothelial dysfunction. Further studies are needed to explore a possible pathophysiological link between MG and non-coronary MI.

Limitations
Our patient suffered a sudden cardiac death a few months after the first MI while she was not on pyridostigmine bromide but only on prednisolone. Unfortunately, autopsy was not performed to identify the exact cause of death and to identify whether the two incidents, the MI and the cardiac death, share a common pathophysiological mechanism. However, being on prednisone, which decreases the antiacetylcholine receptor antibody levels, might have still induced an iatrogenic hypercholinergic crisis. Another possible explanation is that a sudden arrhythmic cardiac event (ventricular fibrillation/ventricular tachycardia) may be the cause of sudden death due to the recent history of MI.

We excluded Takotsubo cardiomyopathy based on the cardiac ultrasound, which did not show any relevant con-

tractile dysfunction. However, we did not perform a ventriculography to confirm this. Moreover, we have ruled out pulmonary embolism based on the normal arterial blood gases and D-dimers titer, which was normal. The spiral chest CT, with intravenous contrast, that took place few days later was normal.

Finally, we did not measure anti-striatal antibodies and we did not perform a magnetic resonance scan of the heart, so we cannot rule out the possibility that MG had an indirect autoimmune adverse effect in the myocardial tissue of our patient; however, the presence of these antibodies have not been associated with an isolated myocardial infarction so far. Despite the fact that we cannot exclude that the MG itself has been involved with the non-coronary MI, the patient, at the time of the MI, was stable with regards to the MG symptoms and as she was not in MG crisis, and therefore the link between MG and MI is less likely.

In conclusion, we describe a case of a non-coronary MI during the initial treatment period with pyridostigmine bromide in a female patient with MG. Clinicians should be cautious about the appearance of potential MI in patients with MG. A baseline ECG is advocated, when the early recognition of the MI clinical signs and the laboratory findings (myocardial markers) are vital to the immediate and appropriate management of this medical emergency, as well as to prevent future cardiovascular events.

ACKNOWLEDGEMENTS

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Contents

Contents

ABOUT COVER

Arora M, Kaul D, Sharma YP. Blood cellular mutant LXR-α protein stability governs initiation of coronary heart disease. *World J Cardiol* 2013; 5(8): 305-312

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REVIEW

Early detection of cardiac involvement in thalassemia: From bench to bedside perspective

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Abstract

Myocardial siderosis is known as the major cause of death in thalassemia major (TM) patients since it can lead to iron overload cardiomyopathy. Although this condition can be prevented if timely effective intensive chelation is given to patients, the mortality rate of iron overload cardiomyopathy still remains high due to late detection of this condition. Various direct and indirect methods of iron assessment, including serum ferritin level, echocardiogram, non-transferrin-bound iron, cardiac magnetic resonance T2*, heart rate variability, and liver biopsy and myocardial biopsy, have been pro-posed for early detection of cardiac iron overload in TM patients. However, controversial evidence and limitations of their use in clinical practice exist. In this review article, all of these iron assessment methods that have been proposed or used to directly or indirectly determine the cardiac iron status in TM reported from both basic and clinical studies are comprehensively summarized and presented. Since there has been growing evidence in the past decades that cardiac magnetic resonance imaging as well as cardiac autonomic status known as the heart rate variability can provide early detection of cardiac involvement in TM patients, these two methods are also presented and discussed. The existing controversy regarding the assessment of cardiac involvement in thalassemia is also discussed.

Core tip: The mortality of thalassemia major (TM) patients due to iron overload cardiomyopathy is still high even though it can be prevented with effective chelation. The role of reliable methods to determine cardiac iron status is very important in order to give a timely effective treatment. This review article provides a comprehensive summary and discussion of various iron assessment methods as well as their existing controversy for use from both basic and clinical reports that have been proposed or used to directly or indirectly determine the cardiac iron status in TM.

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INTRODUCTION

Thalassemia major (TM) is an inherited anemia caused by impaired synthesis of the beta goblin chain. The prevalence of thalassemia is high in the Mediterranean countries, the Middle East, Central Asia, India, Southern China and Thailand[1]. Approximately 60000 TM infants are reportedly born each year[2]. Due to severe hemolytic anemia, TM patients need to habitually receive blood transfusions beginning in infancy. Regular blood transfusions, increased intestinal iron absorption as well as the lack of active excretion of iron inevitably lead to an excess accumulation of iron in the body of TM patients including not only in the reticuloendothelial cells, but also in the parenchymal tissues as well[3]. Excess free iron participating in the Fenton-type reaction has been shown to contribute to the pathogenesis of hemochromatosis[4]. Among many complications due to iron overload, myocardial siderosis is the major cause of mortality in these TM patients[5].

At present, although bone marrow transplantation has been shown to effectively cure some selected patients, the cornerstone of treatment in TM is still with blood transfusion and iron chelation therapy. The effectiveness of iron chelation has markedly improved since the introduction of oral chelators, such as deferiprone[6] and deferasirox[7], resulting in prolonged life expectancy and increased quality of life in TM patients. Despite the effectiveness of iron chelators, iron overload cardiomyopathy can be reversible only if early intensive chelation has been initiated[8,9]. Once TM patients develop clinical symptom such as heart failure or arrhythmia, the prognosis usually becomes poor and death thereafter in spite of intensive chelation[10]. These findings indicate the importance of early detection of cardiac iron accumulation prior to the development of cardiac dysfunction, and that the intensive chelation can be given promptly to those patients who are at risk. Currently, various methods for the detection of cardiac involvement in iron overload condition have been reported both in animal models as well as in clinical studies. Nevertheless, there are still limitations of their use in TM patients due to controversial reports on their reliability or limited access to the machine used for the detection as well as their high cost. In this review article, various methods that have been proposed or used to directly or indirectly determine the cardiac iron status in TM reported from basic and clinical studies are comprehensively summarized and presented. The existing controversy regarding the assessment of cardiac involvement in thalassemia is also discussed.

ASSESSMENT OF CARDIAC INVOLVEMENT IN THALASSEMIA

Since clinical evaluation is unreliable to detect an early stage of iron overload cardiomyopathy in TM patients, several approaches have been used to determine cardiac iron status in-stead. These include the indirect cardiac iron assessment such as serum ferritin, echocardiogram, and electrocardiogram (ECG) as well as the direct but invasive assessment such as myocardial biopsy and liver biopsy. Since there has been growing evidence in the past decades that cardiac magnetic resonance imaging (MRI) as well as cardiac autonomic status known as the heart rate variability (HRV) can provide early detection of cardiac involvement in TM patients, these two methods will also be presented and discussed.

Serum ferritin
Serum ferritin has been used for decades as a predictor of iron overload status in clinical practice due to its strong correlation with hepatic iron[11], representing an indirect index for estimating the total body iron stores. It is inexpensive and accessible worldwide. Serum ferritin has been shown to have a positive relationship with the amount of blood transfusion in beta-thalassemia patients[12]. Furthermore, it has been shown that a serum ferritin level greater than 1800 μg/L was associated with the increased concentration of cardiac iron, and that serum ferritin greater than 2500 μg/L was associated with the increased prevalence of cardiac events[13].

The downturn of using serum ferritin as an assessment of iron overload is due to the fact that the increased level of serum ferritin is not specific to iron overload condition since its level can also be increased in other conditions such as inflammation, collagen diseases, hepatic diseases, and malignancy[14]. Evidence indicated that an increased serum ferritin levels might be a defense mechanism of the body against oxidative stress[15]. Moreover, a low serum ferritin level does not necessarily designate low risk of iron-induced cardiomyopathy[16]. Several studies in the last decade demonstrated that serum ferritin is not suitable for its use as a predictive indicator of myocardial iron deposition due to its lack of relationship with cardiac iron[17,18]. A recent study reported that many unexplained cardiac deaths in TM patients were found even though they had low serum ferritin levels[19], emphasizing the unreliable use of serum ferritin as a predictor for iron overload cardiomyopathy in TM patients.

Echocardiogram
Echocardiogram is a valuable tool for cardiac function monitoring in clinical practice. However, several studies demonstrated that it is not sensitive enough for early detection of the preclinical stage of cardiac involvement in TM patients due to the typical late onset of symptoms and signs[20]. Once cardiac dysfunction is detected by an echocardiogram, the survival rate of these patients is reduced[21,22], suggesting a late stage detection of the disease by this assessment. In addition, it has been shown that the absence of a reduced left ventricular ejection fraction (LVEF) does not exclude a significant risk of sudden potential cardiac decompensation from iron overload[23]. Since left ventricular function is often slightly higher than normal in thalassemia patients in the absence of

myocardial iron overload[24], the normal values of cardiac function by echocardiogram may not be able to rule out cardiac impairment by iron deposition in these patients. Therefore, routine monitoring of cardiac function by echocardiogram is not reliable in early detecting thalassemia patients with high risk of cardiac involvement in order to provide timely intensive treatment.

Electrocardiogram

Since most of TM patients with early cardiac involvement are asymptomatic, ECG has no value for screening of cardiac involvement in this group of patients[25]. Similar to echocardiogram, once the development of cardiac arrhythmias, such as premature atrial or ventricular contractions, first-degree atrioventricular block, atrial flutter, atrial fibrillation, ventricular tachycardia, and second-degree or complete heart block[26-28], is detected by ECG, it usually implies an advanced stage of disease[29,30]. Furthermore, a normal ECG does not exclude a risk of significant arrhythmia development in iron overload patients[25]. In a retrospective analysis, which included 27 transfusion-dependent thalassemia patients who underwent annual 24-h electrocardiographic monitoring, two patients developed significant clinical symptoms secondary to cardiac arrhythmias within one year of follow-up[31]. This result indicated that a 24-h electrocardiogram might be useful for arrhythmia detection, but is not totally predictive for life-threatening cardiac events. Therefore, both ECG and conventional 24-h ECG monitoring are not appropriate markers for early detection of cardiac involvement in thalassemia patients.

Liver and myocardial biopsy

Liver biopsy is a direct determination of liver iron concentration closely reflecting total body iron storage[32]. However, a previous study demonstrated that hepatic iron concentration correlates poorly with cardiac iron status and cardiac function[33]. These findings indicated that determination of iron level *via* liver biopsy does not reflect cardiac iron deposition. Moreover, this technique is an invasive procedure that is not suitable for regular monitoring of iron status in thalassemia patients.

A previous study has also shown that iron level determined by an invasive myocardial biopsy was not correlated with cardiac iron status and cardiac function[34]. This could be due to the fact that myocardial iron deposition was inhomogeneous in the heart[35]. As a result, myocardial biopsy is not recommended to be used as an indicator for cardiac iron overload assessment.

Superconducting quantum interference device

Superconducting quantum interference device (SQUID) biomagnetic liver susceptometry (BLS) has become a standard method in monitoring iron in the liver[36,37]. However, it has many limitations including its availability, cost, technical demands, and suboptimal reproducibility[38]. Together with the lack of heart data, SQUID has not been recommended for its use in the evaluation of

cardiac iron status in patients with thalassemia.

Non-transferrin-bound iron

Non-transferrin-bound iron (NTBI), a free-form iron, can be detected in plasma when the iron binding capacity of transferrin is saturated[39]. This form of iron is able to generate free radical *via* the Fenton-type reactions, leading to peroxidative damage to membrane lipid and protein[40]. The rate of NTBI uptake into cells is approximately 300-fold greater than that of transferrin-bound iron[41] due to its independence on the presence of transferrin receptor[42] and none of feedback-regulated process[43]. Moreover, there is a positive correlation between the rate of NTBI uptake and cellular iron content[44]. Furthermore, a recent study demonstrated a direct correlation between NTBI and vital organ damage in thalassemia patients[45]. In a normal individual, there is no detectable NTBI[46]; on the other hand, hemochromatosis patients exhibit higher NTBI levels than controls[47]. The growing evidence on NTBI suggests that it could be a good index of iron overload in TM patients.

Despite these facts, currently there is neither a cut-point threshold to imply cardiac iron overload status nor even a universally accepted method for NTBI measurement at the present time[48]. Importantly, a poor correlation was found between the methods in a recent inter-laboratory survey[49]. As a consequence, these limitations minimize its use in clinical practice.

Cardiac magnetic resonance T2*

Cardiac magnetic resonance T2* (CMR T2*) has become a widely used tool for its accurate and non-invasive technique to measure iron deposition in heart[50]. Currently, this technique has been proven to be the most sensitive index and reproducible to assess cardiac iron available today[50,51]. Anderson *et al*[16] first reported a significant relationship between myocardial T2* below 20 ms and cardiac function parameters, such as LVEF ($r = 0.61$, $P < 0.0001$), left ventricular (LV) end-systolic volume index ($r = 0.50$, $P < 0.0001$), and LV mass index ($r = 0.40$, $P < 0.001$). A later study confirmed the correlation of myocardial T2* with not only systolic function but also diastolic function as well[52]. Moreover, an increase of myocardial T2* was also in accordance with improved cardiac function[17]. Previous studies in a fresh postmortem iron overloaded heart[53] and a gerbil model of iron overload[54] clearly demonstrated a negative correlation between CMR T2* values and myocardial iron deposition. It also confirmed the earlier studies that iron loading was deposited mostly in the epicardium and myocardium[35,55]. Until now, no clinical scenario other than cardiac iron overload is found to cause myocardial T2* below 20 ms[50]. Thus, these data implied that CMR T2* is more specific to cardiac iron status than other previously mentioned methods.

The prospective study by Kirk *et al*[56] indicated the significant strong association between cardiac T2* values and risk of heart failure development in TM patients. It

Table 1 Summary of the controversial correlation between cardiac magnetic resonance T2* and serum ferritin in thalassemia major

Population/size	Type of study	Findings	Correlation	Ref.
TM/652 patients	Prospective	Significant correlation between cardiac T2* and ferritin (r^2 = 0.003, P = 0.04)	/	Kirk *et al*[56]
TM/776 patients	Retrospective	Significant relationship between cardiac R2* and ferritin (r = -0.359, P < 0.0001)	/	Marsella *et al*[59]
TM/167 patients	Prospective	Myocardial T2* was correlated with serum ferritin (r = -0.34, P < 0.001)	/	Tanner *et al*[60]
TM/19 patients, SCD/17 patients	Cross sectional	Cardiac 1/T2* was correlated with ferritin level (r^2 = 0.33, P = 0.01)	/	Wood *et al*[61]
TM/106 patients	Prospective	No significant correlation between heart T2* and serum ferritin	×	Anderson *et al*[16]
TM/60 patients	Prospective	Serum ferritin did not correlate with cardiac iron values	×	Merchant *et al*[57]
TM/20 patients	Prospective	No correlation between serum ferritin and cardiac T2*	×	Kolnagou *et al*[58]
TM/47 patients	Retrospective	Cardiac T2* was not associated with the serum ferritin	×	Bayraktaroğlu *et al*[22]

TM: Thalassemia major; SCD: Sickle cell disease.

Table 2 Summary of the correlation between cardiac magnetic resonance T2* and cardiac function in thalassemia major

Population/size	Type of study	Findings	Correlation	Ref.
TM/776 patients	Retrospective	Significant correlation between LVEF and cardiac R2* (r = -0.327, P < 0.0001)	/	Marsella *et al*[59]
TM/106 patients	Prospective	Significant correlation of myocardial T2* below 20 ms with LVEF (r = 0.61, P < 0.0001), LVESVi (r = 0.50, P < 0.0001), and LV mass index (r = 0.40, P < 0.001)	/	Anderson *et al*[16]
TM/167 patients	Prospective	Significant relationship between myocardial iron and LVEF (r = 0.57, P < 0.001)	/	Tanner *et al*[60]
TM/67 patients	Cross sectional	Myocardial T2* related to LV diastolic function (EPFR, r = –0.20, P = 0.19; APFR, r = 0.49, P < 0.001; EPFR/APFR ratio, r = –0.62, P < 0.001)	/	Westwood *et al*[52]
TM/33 patients	Cross sectional	Good correlation of DT, Tei index and E/Em index with cardiac T2* values (P < 0.05, r = 0.70-0.81) and weak correlation of E/A with T2* (P < 0.05, r = -0.44)	/	Barzin *et al*[84]
TM/47 patients	Retrospective	Significant correlations of the myocardial T2* with LVESVi and LVEDVi (r = -0.32, P = 0.027; r = -0.29, P = 0.046, respectively)	/	Bayraktaroğlu *et al*[22]
TM/19 patients, SCD/17 patients	Cross sectional	Significant relationship between LVEF and myocardial T2*	/	Wood *et al*[61]

TM: Thalassemia major; SCD: Sickle cell disease; LVEF: Left ventricular ejection fraction; LVESVi: Left ventricular end systolic volume index; LVEDVi: Left ventricular end diastolic volume index; EPFR: Early peak filling rate; APFR: Atrial peak filling rate; DT: Deceleration time; E/Em: Early diastolic peak inflow velocity and early diastolic myocardial velocity ratio; E/A: Early and late transmittal peak flow velocity ratio.

demonstrated that 98% of patients who developed heart failure had the cardiac T2* less than 10 ms, with a relative risk (RR) of 160 (95%CI: 39-653). In the same study, the RR for cardiac T2* less than 6 ms was 270 (95%CI: 64-1129). Moreover, T2* threshold of 10 ms for predicted heart failure had a sensitivity of 97.5% (95%CI: 91.3-99.7) and a specificity of 85.3% (95%CI: 83.3-87.2). This study also demonstrated the significant relationship between cardiac T2* values and a risk of cardiac arrhythmia development in TM patients, but weaker than a risk of heart failure. A cardiac T2* less than 20 ms was figured in 83% of patients who develop arrhythmia, with a RR of 4.60 (95%CI: 2.66-7.95). The RR for a cardiac T2* less than 6 ms was 8.79 (95%CI: 4.03-19.2). The T2* threshold of 20 ms for predicted cardiac arrhythmia had a sensitivity of 82.7% (95%CI: 73.7-89.6) and a specificity of 53.5% (95%CI: 50.8-56.2). In addition, this prospective study clearly demonstrated the link between myocardial T2* and cardiac events. The one year risk of heart failure development was shown to be 14%, 30%, and 50% for T2* between 8-10, 6-8 and less than 6 ms, respectively. Therefore, myocardial T2* less than 10 ms

strongly indicated clinically significant cardiac iron overload and an increase in risk of developing heart failure in TM patients.

When compared with conventional iron monitoring parameters, the correlation between CMR T2* and serum ferritin in TM patients has not been concluded (Table 1). Several studies indicated that serum ferritin was not correlated with cardiac T2*[16,22,57,58]. However, other studies with larger population size showed a weak relationship between serum ferritin and heart T2*[56,59-61]. Because serum ferritin is raised even in many common conditions such as inflammation or hepatic disease[14], the controversial correlation could be from subjects with a different underlying status included in each study. As a result, a guideline for intensive chelation therapy based on serum ferritin may be inappropriate for cardiological management in TM patients.

A prospective study of Tanner *et al*[62], which recruited 167 TM patients, showed the significant association between heart T2* values and LVEF. Patients with mild, moderate and severe cardiac iron overload (T2* 12-20, 8-12 and less than 8 ms, respectively) had impaired LVEF in

Table 3 Comparison of various methods to evaluate cardiac iron overload in thalassemia patients

Method	Advantages	Disadvantages
Serum ferritin	Easy and available Inexpensive	Poor predictor of iron overload[85,86] Nonspecific for cardiac iron Altered by many conditions[14]
Echocardiogram	Easy and available Inexpensive	Late indicator of cardiac involvement[21,23]
Liver biopsy	Total body iron estimation[32]	Invasive No correlation with myocardial iron deposition[33]
Myocardial biopsy		Invasive No correlation with cardiac iron status and function[34]
ECG	Easy and available Inexpensive	Ineffective screening parameter for cardiac iron overload[25,31]
SQUID	Standardized noninvasive index for liver iron[36]	Lack of availability, technical demands, and reproducibility Costly Application for the study of heart iron pending
NTBI	Direct parameter of freeform iron resulting in peroxidative damage[87]	Limited availability No generally accepted method[48], and poor correlation between methods[49]
CMR T2*	Method of choice for the assessment of tissue iron deposition in last decade[51] Noninvasive measurement of cardiac iron deposition[50] Available High sensitivity and reproducible[50] Correlation with clinical outcome[16,17,56,62,63]	Costly

ECG: Electrocardiogram; SQUID: Superconducting quantum interference device; NTBI: Non-transferrin-bound iron; CMR T2*: Cardiac magnetic resonance T2*.

5%, 20% and 62%, respectively ($P < 0.001$). Table 2 summarized studies that showed the significant correlation between CMR T2* and cardiac function in TM patients. These studies suggest that myocardial T2* could be a useful application to determine cardiac iron overload tending to deteriorate cardiac function. As a result, CMR T2* may be suitable for use as an assessment of cardiac iron deposit in thalassemia patients for early detection of the cardiac iron status before the detection of clinical signs and symptoms of iron overload cardiomyopathy.

Since several studies showed a remarkably strong correlation of heart T2* value with clinical cardiac complications, including heart failure and arrhythmia, CMR T2* had been applied to monitor cardiac iron deposition in TM patients in UK[63,64]. Interestingly, the mortality rate was significantly reduced. Nowadays, CMR T2* is recognized as the method of choice for evaluation of cardiac iron deposition in TM patients[51]. However, the limitation of this technique is its rather expensive cost and only limited medical centers around the world are equipped with this technique.

The pros and cons of different approaches that monitor cardiac iron overload condition in thalassemia patients are summarized in Table 3.

HRV IN THALASSEMIA MAJOR

HRV is used to indicate the variation over time of the period between successive heartbeats and determine cardiac autonomic function and overall cardiac health[65]. HRV analysis has been used to determine the cardiac autonomic function in patients with post-myocardial infarction[66,67]. Reduced HRV parameters were associated with a significant increased mortality in these patients[68,69]. A prospective study indicated that HRV analysis on 1-year post-myocardial infarction follow-up patients also had prognostic significance[70]. Furthermore, HRV parameters have been shown to a strong predictor of mortality in patients with heart failure[71,72], cardiac transplantation[73], and diabetic neuropathy[74].

Due to its non-invasiveness and easy derivation, HRV has been investigated as one of the promising parameters to initially detect cardiac involvement and has been widely studied in thalassemia in the last decades. A number of studies on HRV in TM patients have been reported since Franzoni *et al*[75] first proposed that HRV was depressed in TM patients. A summary of previous studies that exhibited the significantly reduced HRV parameters in TM patients and thalassemic mice is described in Table 4. All of previous studies reported that HRV parameters were reduced both in TM patients and thalassemic mice, indicating that thalassemic condition exerted some degrees of cardiac autonomic dysfunction. A recent study which investigated autonomic function by six quantitative autonomic function tests demonstrated that the prevalence of subclinical autonomic function impairment was higher in thalassemia patients compared to controls[76]. This result confirmed that thalassemia patients have autonomic dysfunction in some degree. In prospective studies by Kardelen *et al*[77] and De Chiara *et al*[78], no evidence of abnormal echocardiographic finding was shown in TM patients with reduced HRV. Therefore, a significantly reduced HRV could be an early indicator of preclinical stage of heart disease in TM group. Nevertheless, the evidence of HRV in TM patients has not been extensively

Table 4 Summary of heart rate variability findings from both clinical and basic studies in thalassemia

Population/size	Type of study	Findings	Ref.
34 TM patients and 20 healthy subjects	Prospective	Significantly depressed both time and frequency domain HRV parameters in TM patients	Rutjanaprom *et al*[20]
32 TM patients and 46 control subjects	Prospective	Significantly reduced all HRV parameters in TM patients	Kardelen *et al*[77]
19 TM patients and 19 healthy volunteers	Cross sectional	Significantly lower both time and frequency domain HRV parameters in the TM group	Franzoni *et al*[75]
100 TM patients and 60 healthy controls	Cross sectional	Lower SDNN in TM with ectopia while markedly increased LF/HF ratio in this group.	Oztarhan *et al*[88]
48 Thalassemia patients and 45 healthy subjects	Cross sectional	Significantly reduced time domain parameters in the thalssemia group	Gurses *et al*[89]
9 TM patients and 9 healthy subjects	Cross sectional	Significantly lower LF/HF ratio during tilt in TM patients than in control subjects	Veglio *et al*[90]
21 TM patients and 15 healthy subjects	Cross sectional	Significantly lower in all HRV parameters in TM group than in control group	Ma *et al*[91]
13 wildtype, 13 HbE/β thalassemia and 13 *mu*β+/− mice	Cross sectional	Depressed all HRV parameters in the heterozygous βglobin knockout mice (*mu*β+/−)	Incharoen *et al*[92]
810 wildtype and 810 heterozygous betaknockout mice	Prospective	Higher LF/HF ratio in thalassemic mice than those in the wild type	Kumfu *et al*[82]
12 wildtype and 12 heterozygous betaknockout mice	Prospective	Depressed HRV in betathalassemic mice compared to wild type	Thephinlap *et al*[93]

TM: Thalassemia major; HRV: Heart rate variability; SDNN: Standard deviation of all NN intervals; LF: Low frequency power; HF: High frequency power.

Table 5 Summary of the correlation between HRV and serum ferritin in thalassemia major

Population/size	Type of study	Findings	Correlation	Ref.
34 TM patients and 20 healthy subjects	Prospective	No correlations between HRV parameters and serum ferritin	×	Rutjanaprom *et al*[20]
19 TM patients and 19 healthy volunteers	Cross sectional	No correlation between HRV parameters and serum ferritin	×	Franzoni *et al*[75]
21 TM patients and 15 healthy subjects	Cross sectional	No relationship of HRV parameters with serum ferritin	×	Ma *et al*[91]

TM: Thalassemia major; HRV: Heart rate variability.

Table 6 Summary of the relationship between heart rate variability and cardiac function in thalassemia major

Population/size	Type of study	Findings	Correlation	Ref.
34 TM patients and 20 healthy subjects	Prospective	None of the echocardiographic parameters was correlated with HRV	×	Rutjanaprom *et al*[20]
32 TM patients and 46 control subjects	Prospective	Reduced HRV were described in TM despite no echocardiographic abnormality	×	Kardelen *et al*[77]
19 TM patients and 19 healthy volunteers	Cross sectional	No correlation between HRV parameters and echocardiographic parameters	×	Franzoni *et al*[75]
20 TM patients	Prospective	Abnormal HRV in TM with no evidence of ventricular dysfunction	×	De Chiara *et al*[78]

TM: Thalassemia major; HRV: Heart rate variability.

investigated when compared to that in post-myocardial infarction patients. Until now, none of studies has focused on the association between HRV and mortality in TM patients.

After the first report of HRV in TM patients by Franzoni *et al*[75], several studies have examined HRV in TM patients in order to seek the correlation between HRV and currently used iron overload parameters. No correlation between HRV parameters and serum ferritin in TM patients has been demonstrated (Table 5). Moreover,

no correlation between HRV parameters and cardiac function in TM patients has been shown (Table 6). It is possible that HRV is not correlated with iron overload condition because several anemic diseases other than thalassemia, including sickle cell anemia[79], iron deficiency anemia[80], vitamin B12 deficiency anemia[81], could also impair cardiac autonomic function. Nevertheless, some evidence demonstrated that autonomic status determined by HRV is correlated with iron overload condition. In a study with thalassemic mice[82], it has been shown that

those thalassemic mice had a higher Lfnu, lower Hfnu, and higher Lf/Hf ratio than those in the wild-type mice. More interestingly, iron administration in both types of mice resulted in significantly higher NTBI levels concomitant with increased Lfnu and Lf/Hf ratio and decreased Hfnu. Moreover, iron chelator significantly decreased the Lfnu, Lf/Hf ratio, and increased the Hfnu in those iron overload thalassemic mice. This prospective study suggested that iron overload condition could contribute to progressive deterioration of the impaired cardiac autonomic function.

In conclusion, although CMR T2* is now recognized as the method of choice in evaluation of iron deposition in the heart[51], evidence suggested that TM patients must be prevented rather than treated even before cardiac iron loading becomes detectable on CMR T2* because of leading causes of cardiac tissue damage by other iron mediated mechanisms, such as those induced by labile plasma iron[83]. HRV might be used as an alternative approach to assess cardiac involvement in TM patients. Due to its easy access and much lower cost compared to CMR T2*, 24-h Holter monitoring for HRV analysis can be performed in most health providing centers. However, more evidence is needed to validate its use before it can be applied in clinical practice. Further studies are also needed to demonstrate the correlation between HRV and CMR T2* as well as the clinical application of HRV as a predictive marker in TM patients.

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BRIEF ARTICLE

Catheter ablation of atrial fibrillation: Radiofrequency catheter ablation for redo procedures after cryoablation

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Abstract

AIM: To evaluate the effectiveness of two different strategies using radiofrequency catheter ablation for redo procedures after cryoablation of atrial fibrillation.

METHODS: Thirty patients (paroxysmal atrial fibrillation: 22 patients, persistent atrial fibrillation: 8 patients) had to undergo a redo procedure after initially successful circumferential pulmonary vein (PV) isolation with the cryoballoon technique (Arctic Front Balloon, CryoCath Technologies/Medtronic). The redo ablation procedures were performed using a segmental approach or a circumferential ablation strategy (CARTO; Biosense Webster) depending on the intra-procedural findings. After discharge, patients were scheduled for repeated visits at the arrhythmia clinic. A 7-day Holter monitoring was performed at 3, 12 and 24 mo after the ablation procedure.

RESULTS: During the redo procedure, a mean number of 2.9 re-conducting pulmonary veins (SD ± 1.0 PVs) were detected (using a circular mapping catheter). In 20 patients, a segmental approach was sufficient to eliminate the residual pulmonary vein conduction because there were only a few recovered pulmonary vein fibres. In the remaining 10 patients, a circumferential ablation strategy was used because of a complete recovery of the PV-LA conduction. All recovered pulmonary veins could be isolated successfully again. At 2-year follow-up, 73.3% of all patients were free from an arrhythmia recurrence (22/30). There were no major complications.

CONCLUSION: In patients with an initial circumferential pulmonary vein isolation using the cryoballoon technique, a repeat ablation procedure can be performed safely and effectively using radiofrequency catheter ablation.

Key words: Atrial fibrillation; Catheter ablation; Cryoablation; Pulmonary veins; Supraventricular arrhythmias

Core tip: Cryoablation has been shown to be a safe technique for pulmonary vein isolation. However, the arrhythmia recurrence rate is high. Therefore, we have summarized our initial experience with two different strategies for redo procedures using radiofrequency catheter ablation. Thirty patients had to undergo a redo procedure after initially successful circumferential pulmonary vein isolation with the cryoballoon technique. The redo ablation procedures were performed using a segmental approach or a circumferential ablation strategy depending on the intra-procedural findings. All recovered pulmonary veins could be isolated successfully again. At 2-year follow-up, 73.3% of all patients were free from an arrhythmia recurrence.

Kettering K, Gramley F. Catheter ablation of atrial fibrillation: Radiofrequency catheter ablation for redo procedures after cryo-

INTRODUCTION

Catheter ablation has become the first line of therapy in patients with symptomatic, recurrent, drug-refractory atrial fibrillation (AF)[1-7]. Cryoablation has been shown to be a safe and effective technique for pulmonary vein (PV) isolation[1]. Although the acute success rates are high there is a significant arrhythmia recurrence rate after cryoablation during midterm follow-up[8-14]. According to a recently published study, catheter ablation with the cryoballoon technique resulted in maintenance of sinus rhythm in 74% of patients with paroxysmal atrial fibrillation and in 42 % of patients with persistent atrial fibrillation [median follow-up: 12 (7-16) mo[15-21]. Recovery of pulmonary vein conduction is one major reason for recurrences of atrial fibrillation. This is a crucial issue for cryoablation of AF because the cryoballoon is available with a rigid uniform design only (size: 23 or 28 mm; CryoCath Technologies, Quebec, Canada/Medtronic, Minneapolis, MN, United States). Taking into account the high degree of variability of the pulmonary vein anatomy it becomes clear that the contact between the balloon catheter and the pulmonary vein ostium cannot be equally good in all parts of the PV ostium. Therefore, insufficient tissue contact of the cryoballoon seems to be a key mechanism for recovery of initially successfully isolated pulmonary veins and AF recurrences in these patients during follow-up[22-26].

There are no established strategies for redo procedures after pulmonary vein isolation with the cryoballoon technique. From a theoretical point of view it seems to be reasonable to use the cryoablation technique for the redo procedure again because of its favourable lesion characteristics[1,22]. Such procedures can be performed either by using the cryoballoon technique again or by using a standard cryoablation catheter (*e.g.,* Freezor Max; Medtronic). The major concern with the cryoballoon technique for redo procedures is that there might be insufficient tissue contact in the same areas as during the initial procedure again. This might be a risk factor for further arrhythmia recurrences. Alternatively, repeat ablations can be performed with a segmental approach and a standard cryoablation catheter (*e.g.,* Freezor Max; Medtronic), However, a segmental approach using a cryoablation catheter is limited by the long duration of the cryoapplications required for achieving permanent lesions and by the fact that the position of the cryoablation catheter cannot be optimized during energy delivery.

Because of these limitations radiofrequency catheter ablation seems to be a promising approach. Therefore, the aim of our study was to analyse the data on pulmonary vein conduction recovery after pulmonary vein isolation with the cryoballoon technique and to evaluate two different strategies for redo procedures using radiofrequency catheter ablation.

Depending on the extent of pulmonary vein conduction recovery we performed either a segmental pulmonary vein re-isolation or an anatomically-based circumferential pulmonary vein ablation in combination with a potential-guided segmental approach using radiofrequency energy application[19,20].

MATERIALS AND METHODS

Patient population

A total of 30 patients (21 men, 9 women; mean age 59.6 ± 10.0 years) with a recurrence of symptomatic atrial fibrillation after pulmonary vein isolation with the cryoballoon technique were enrolled in this study. Table 1 summarizes clinical characteristics of the patients enrolled in our study. A repeat procedure was planned because of recurrent episodes of paroxysmal atrial fibrillation in 23 patients or persistent AF in 7 patients. The redo procedures were performed at a mean interval of 12.5 ± 9.3 mo) after the initial ablation procedure. Prior to the initial ablation procedure paroxysmal AF had been present in 22 patients and persistent AF had been present in 8 patients. The initial ablation procedures had been performed at our University Hospital Center (between November 2007 and July 2009). The initial patient cohort consisted of 103 patients undergoing cryoablation as the primary procedure. Thus, the overall arrhythmia recurrence rate was 29.1% after the initial cryoablation procedure. For the initial procedure a cryoballoon device had been used in all patients who had to undergo a repeat ablation procedure (23 mm: 0 patients, 28 mm: 30 patients; CryoCath Technologies/Medtronic). In addition, a standard cryoablation catheter (Freezor Max 3; Medtronic) had been used in 4 patients. During the initial procedure a mean number of 11.6 ± 4.9 cryoapplications had been made using the cryoballoon device and a mean number of 4.0 ± 2.0 cryoapplications had been made in those patients in whom the standard cryoablation catheter (Freezor Max; Medtronic) had been used. At the end of the initial ablation procedure all pulmonary veins were isolated successfully. There were no major complications during or after the initial ablation procedure.

The repeat ablation procedures were performed at our University Hospital Center between March 2008 and November 2009. Inclusion criteria were (1) documented episodes of recurrent atrial fibrillation (≥ 30 s) after an initial ablation procedure with the cryoballoon technique (taking into account a blanking period of 3 mo after the initial ablation procedure); (2) severe symptoms despite antiarrhythmic drug therapy (including beta-blockers) or prior attemps of electrical cardioversion; (3) ability and willingness to give informed consent; and (4) age between 18 and 85 years. Patients were not accepted for catheter ablation if one of the following conditions was present: severe valvular heart disease or any other concomitant

Table 1 Clinical data

Clinical data	Group A	Group B	Total	*P* value
Patients (men/women)	20 (13/7)	10 (8/2)	30 (21/9)	0.67
Age (yr, mean ± SD)	60.0 ± 10.7	58.9 ± 9.2	59.6 ± 10.0	0.81
Cardiac disease				0.84
None	8	6	14	
CAD	3	1	4	
DCM	2	1	3	
Valvular heart disease[1]	5	1	6	
Other	2	1	3	
Left ventricular ejection fraction mean (SD)	54.7% (12.0%)	53.8% (10.3%)	54.4% (11.2%)	0.86
Previous cardiac surgery	1	1	2	1.00
Current antiarrhythmic drug therapy prior to the initial ablation procedure				0.94
Class Ⅰc (*e.g.*, Flecainide, Propafenone)	3	2	5	
Class Ⅲ (*e.g.*, Amiodarone, Sotalol)	6	1	7	
Beta-Blocker in combination with a class Ⅰc or class Ⅲ antiarrhythmic drug	4/2	3/1	7/3	
Beta-Blocker	2	1	3	
Digitalis	1	1	2	
Other	2	1	3	
Current antiarrhythmic drug therapy prior to the repeat ablation procedure				0.57
Class Ⅰc (*e.g.*, Flecainide, Propafenone)	2	1	3	
Class Ⅲ (*e.g.*, Amiodarone, Sotalol)	4	1	5	
Beta-Blocker in combination with a class Ⅰc or class Ⅲ antiarrhythmic drug	4/2	2/1	6/3	
Beta-Blocker	4	1	5	
Digitalis	2	0	2	
Other	2	4	6	

[1]Not requiring surgery. CAD: Coronary artery disease; DCM: Dilated cardiomyopathy (left ventricular ejection fraction < 40 %).

cardiac disease requiring surgery, severely impaired left ventricular function (left ventricular ejection fraction < 20%), left atrial diameter > 65 mm (parasternal long-axis view), left atrial thrombus, hyperthyroidism, severe renal insufficiency (creatinine ≥ 3 mg/dL) or another severe concomitant illness.

Cardiac imaging

A three-dimensional transesophageal echocardiography (3-D TEE) was performed in all patients prior to the ablation procedure (X7-2t, 7 MHz/IE 33; Philips Health-care). The images were available throughout the ablation procedure. The 3-D TEE reconstructions provided an excellent overview over the individual left atrial morphology thereby facilitating the ablation procedure.

Ablation procedure

AF ablation procedures were performed under conscious sedation at our institution. For the electrophysiological study, vascular access was obtained *via* both femoral veins and the left femoral artery. A 2500-U IV bolus of heparin was given shortly thereafter. First, a 6-F decapolar catheter (Bard, Electrophysiology Division, Lowell, MA, United States) was positioned within the coronary sinus (CS). Then, a single (or double) transseptal puncture was performed under fluoroscopic guidance. Immediately before the transseptal puncture, a 5-F catheter was placed in the ascending aorta to mark this area and to enhance the safety of the procedure. In some patients no transseptal puncture was necessary because of a patent foramen ovale or a residual defect of the atrial septum. Then,

a pulmonary vein angiography was performed. After that, all four pulmonary veins were reevaluated during sinus rhythm and during CS pacing using a Lasso-catheter (2515, 7F; Biosense Webster, Diamond Bar, CA, United States). If atrial fibrillation was present at the beginning of the ablation procedure an electrical cardioversion was performed. The further strategy was based on the findings documented by the circular mapping catheter: if there were 1-3 pulmonary veins with recovered PV conduction we decided to perform a re-isolation of the recovered pulmonary veins using a segmental approach (group A). If there was reconnection of all four pulmonary veins, an anatomically-based circumferential pulmonary vein ablation in combination with a potential-guided segmental approach was performed (group B)[20]. In addition, we classified the degree of PV reconnection as minor (PV spike visible on ≤ 4 bipoles of the Lasso catheter) or major (PV potential visible on ≥ 5 bipoles of the Lasso catheter).

Then, a standard irrigated-tip ablation catheter (7F; D-type, 3.5-mm-tip; Biosense Webster, Diamond Bar, CA, United States) or a CARTO-catheter (NAVI-STAR; 7F; D-type; 4-mm-tip; Biosense Webster) was positioned within the left atrium. After that, a second iv bolus of heparin was administered. During the procedure, the activated clotting time (ACT) was determined at regular intervals to ensure an adequate anticoagulation (ACT between 250 and 300 s).

Then, a segmental re-isolation of the pulmonary veins was performed in the patients assigned to group A using the above-mentioned irrigated-tip ablation catheter (43°;

25-35 W). Pulmonary vein ablation was performed during sinus rhythm and pacing from the coronary sinus. Pacing was performed from the distal CS during isolation of the left pulmonary veins and from the proximal CS during right PV ablation. If atrial fibrillation was present at the beginning of the ablation procedure or recurred during the procedure an electrical cardioversion was performed. Successful pulmonary vein isolation was assumed if one of the following criteria was met: complete disappearance of the pulmonary vein potential or appearance of a dissociated PV potential (circumferential mapping catheter).

In group B, a circumferential pulmonary vein ablation was performed in combination with a potential-guided segmental approach in order to achieve complete pulmonary vein isolation. Furthermore, a linear lesion was created at the roof of the left atrium in some patients with persistent atrial fibrillation. In addition, catheter ablation of the mitral isthmus was performed in selected cases.

First, a circumferential pulmonary vein ablation was performed targeting the both left-sided pulmonary veins [43°; 30 W (posterior wall) - 35 W (anterior wall)]. In addition, a Lasso-catheter was placed in the left superior or left inferior pulmonary vein. After completing the circumferential ablation line around the left-sided PVs, the left superior pulmonary vein and the left inferior pulmonary vein were reevaluated using the circular mapping catheter. If there was no complete PV isolation additional RF energy applications [43°; (25) -30 W] were applied using a segmental approach (during sinus rhythm/CS pacing or recurrent AF). If the isolation of the left-sided PVs was assumed to be complete the right-sided PVs were targeted in the same way. Then, a linear lesion at the LA roof was created in selected patients [43°; 30(-35) W]. In a few patients an additional mitral isthmus ablation was performed (if there was evidence for left atrial isthmus-dependent flutter [43°; 35(-40) W].

If atrial fibrillation was still present thereafter, an electrical cardioversion was performed. Then, all four pulmonary veins were reevaluated during sinus rhythm using the circumferential mapping catheter.

If necessary additional RF applications were performed using a segmental approach to achieve complete isolation of all four pulmonary veins. Then, the linear lesions at the LA roof were reevaluated during sinus rhythm. The ablation catheter was navigated back along the entire lesion to assess the presence of low-amplitude electrograms and the presence of double potentials or fractionated electrograms. If sharp high-amplitude electrograms were noted, additional RF applications were delivered at these sites in order to achieve a complete ablation line.

In addition, the linear lesions to the mitral annulus were reevaluated (anterior mitral isthmus line). The presence of bidirectional mitral isthmus conduction block was assumed if the following criteria were met: (1) presence of an unidirectional conduction block documented by activation mapping during pacing from the distal bipole of the CS catheter (placed far within the coronary sinus) or the left atrial appendage; (2) documentation of a similar conduction time during pacing from the anteroseptal mitral annulus (*via* the ablation catheter) *vs* the distal coronary sinus or the left atrial appendage; and (3) a conduction time > 150 ms in both directions.

In all patients (group A/B), a standard stomach tube (Flocare Nutrisoft M; Nurtica Healthcare, Châtel-St.Denis, Switzerland) or a special EP catheter (7 F; Osypka, Rheinfelden-Herten, Germany) had been introduced *via* a nasogastric route immediately before the ablation procedure in order to mark the esophagus. RF energy applications were avoided if there was a close anatomical relationship to the esophagus (or the power output was reduced as described previously[19]).

Finally, the completeness of the pulmonary vein isolation and of all linear lesions was reassessed after a waiting period of at least 20 min. Repeat selective pulmonary vein angiographies were performed of all targeted PVs. In addition, catheter ablation of the right atrial isthmus was performed in patients with inducible or clinically documented episodes of typical atrial flutter. The completeness of the right atrial isthmus lines was confirmed by differential pacing manoeuvres in all cases.

For the ablation procedure, a Bard EP system (Lab-System Pro, EP Recording System; Bard, Electrophysiology Division, Lowell, MA) and a Stockert RF generator (EP-shuttle; Stockert, Freiburg, Germany) were used. High-resolution x-ray imaging was provided by a Philips device (Philips Medical Systems, Best, The Netherlands).

Follow-up

After hospital discharge, patients were seen regularly on an outpatient basis. One month after the procedure, a physical examination, a resting electrocardiogram (ECG) and a transthoracic echocardiogram were performed. The patients were questioned whether there was any evidence for an arrhythmia recurrence. In addition, a long-term ECG recording (24-h) was performed.

Three months after the ablation procedure, the patients were re-examined in the same way except for the fact that a 7-d Holter monitoring was performed and that each patient underwent a repeat three-dimensional transesophageal echocardiography to rule out a pulmonary vein stenosis. Then, the patients were seen at 3-mo intervals if asymptomatic. If there was an arrhythmia recurrence or other problems occurred, the further follow-up and future strategy (*e.g.,* electrical cardioversion, repeat ablation procedure) were planned on an individual basis.

Twelve months and 24 mo after the ablation procedure another 7-d Holter monitoring was performed. A blanking period of 3 mo was employed after ablation when evaluating the follow-up results. In addition, all patients were given a questionnaire 24 mo after the ablation procedure. The aim of this questionnaire was to evaluate the clinical status of the patients and to reveal whether there was any evidence for arrhythmia recurrences not detected by the long-term ECG recordings[20].

Oral anticoagulation was continued for at least 3 mo

after the procedure in all patients. During the first three mo after catheter ablation the patients received the same antiarrhythmic medication as prior to the ablation procedure. If there was no evidence for an arrhythmia recurrence all antiarrhythmic drugs were discontinued thereafter except for beta-blockers. The beta-blocker therapy was continued thereafter in order to reduce the risk of arrhythmia recurrences during long-term follow-up and to achieve an adequate rate control if such arrhythmia recurrences occurred.

Statistical analysis

All parameters with a normal distribution are given as mean ($\pm$ 1 SD). All other parameters are presented as median and $25^{th}/75^{th}$ percentiles. χ^2 tests, t-tests, and Fischer's exact test were used to compare nominal, continuous, and dichotomous characteristics of the two study groups at baseline as well as during follow-up. Significance was accepted if the P value was < 0.05. The statistical package of JMP (Version 3.2.6, SAS Institute, Cary, NC, United States) was used for data analysis.

RESULTS

Thirty patients were enrolled in this study between March 2008 and November 2009. All of them had to undergo a repeat ablation procedure because of a recurrence of symptomatic atrial fibrillation after pulmonary vein isolation with the cryoballoon technique. Prior to the redo procedure, 23 patients suffered from recurrent episodes of paroxysmal atrial fibrillation and 7 patients suffered from persistent AF. The repeat ablation procedure could be performed as planned in all patients.

Procedural results

Evaluation of the pulmonary veins: During the repeat procedure, a mean number of 2.9 $\pm$ 1.0 PVs with recovered PV conduction were detected (using a circular mapping catheter). In all patients at least one pulmonary vein with recovered PV conduction was observed. In 4 patients, there was only one pulmonary vein with recovered PV conduction. There were 6 patients with two reconnected veins and 10 patients with three reconnected pulmonary veins. In 10 patients, all four pulmonary veins showed recovered PV conduction. Seven out of 10 patients with four reconnected pulmonary veins suffered from persistent AF.

Minor PV reconnection (PV spike visible on 4 $\leqslant$ bipoles of the Lasso catheter) was present in 77 out of 86 reconnected veins (89.5%). Major PV reconnection (PV spike visible on > 4 bipoles of the Lasso catheter) was found in 9 out of 86 reconnected PVs (10.5%).

Ablation strategy

After evaluating the pulmonary veins the further ablation strategy was planned based on the intraprocedural findings. In 20 patients (with 1-3 reconnected PVs) re-isolation of the recovered pulmonary veins was performed

using a segmental approach (group A). In 10 patients, all four pulmonary veins showed recovered PV conduction. In these patients, an anatomically-based circumferential pulmonary vein ablation in combination with a potential-guided segmental approach was performed (group B). In 3 out of 10 patients in group B, an additional linear lesion was created at the LA roof. In 2 patients in group B, catheter ablation of the mitral isthmus was performed. In addition, catheter ablation of the right atrial isthmus was performed in 5 patients in group A and in 2 patients in group B (P = 1.0).

The ablation procedure could be performed as planned in all patients. The mean procedure time was 156 $\pm$ 41 min; group A: 147 $\pm$ 32 min; group B: 175 $\pm$ 58 min; P = 0.07. This included all preparations and a waiting period (20 min) at the end of the procedure for a final reevaluation of the completeness of the pulmonary vein isolation/linear lesions. The mean fluoroscopy dosage was 2520 $\pm$ 2055 cGycm²; group A: 2556 $\pm$ 2178 cGycm²; group B: 2450 $\pm$ 1810 cGycm²; P = 0.87.

The segmental approach could be performed successfully in all patients in group A. A mean number of 2.3 $\pm$ 0.8 PVs were re-isolated per patient. At the end of the procedure the complete isolation of all four pulmonary veins could be documented in all patients using a circumferential mapping catheter.

In group B, an anatomically-based circumferential pulmonary vein ablation in combination with a potential-guided segmental approach was performed successfully in all patients. In this group, all four pulmonary veins could be re-isolated successfully in all patients (documented using a circular mapping catheter).

There were no major complications (*e.g.,* cardiac tamponade, transient ischemic attacks (TIAs) or stroke, significant pulmonary vein stenosis ($\geqslant$ 70%), periprocedural death) during the procedure in both groups. A transseptal puncture had to be performed in 17 out of 30 patients. In the other patients no transseptal puncture was necessary because of a patent foramen ovale (7 patients) or a residual defect of the atrial septum (6 patients).

Clinical outcome

The mean follow-up was 1004 $\pm$ 751 d in group A and 821 $\pm$ 435 d in group B (P = 0.53). The mean overall follow-up was 940 $\pm$ 653 d. Six months after the redo procedure, 85.0% of the patients in group A (17/20) and 80.0% of the patients in group B (8/10) were free from an arrhythmia recurrence [P = 1.0; in total: 25/30 patients (83.3%)]. Twelve month after the repeat ablation procedure, 80.0% of all patients in group A (16/20) were still free from an arrhythmia recurrence compared to 70.0% of patients in group B (7/10; P = 0.66). Thus, the overall success rate was 76.7% at 1-year follow-up (no arrhythmia recurrence in 23 out of 30 patients). Two years after the redo procedure, the overall success rate was 73.3% (no arrhythmia recurrence in 22 out of 30 patients). Fifteen out of twenty patients in group A (75.0%) and 7 out of 10 patients in group B (70.0%) were still free from an ar-

rhythmia recurrence ($P = 1.0$).

According to the analysis of the questionnaire, 24/30 patients (80.0%) were completely asymptomatic at 24-mo follow-up. There were no major complications during or after the ablation procedures (including a follow-up duration of 24 mo). Minor complications were observed in 2 patients (pulmonary vein stenosis < 70%: 2 patients).

Analysing the clinical course of the patients who experienced an arrhythmia recurrence during follow-up, 7-d Holter monitoring revealed paroxysmal atrial fibrillation in 5 patients and persistent atrial fibrillation in 3 patients. No modification of the antiarrhythmic medication and no repeat ablation procedure was required in 2 patients with an arrhythmia recurrence because they were almost asymptomatic. In 2 patients with a symptomatic arrhythmia recurrence symptoms could be controlled by modifying the antiarrhythmic drug therapy. Four patients with symptomatic arrhythmia recurrences had to undergo a third ablation procedure.

DISCUSSION

Catheter ablation has become an important therapeutic option for patients with highly symptomatic and drug-refractory atrial fibrillation. Cryoablation is a safe and effective technique for pulmonary vein isolation[1,21], which is the cornerstone of catheter ablation in patients with paroxysmal or persistent atrial fibrillation. However, there is a significant arrhythmia recurrence rate after cryoablation during midterm follow-up. Catheter ablation with the cryoballoon technique was reported to result in maintenance of sinus rhythm in 74% of patients with paroxysmal AF and in only 42% of patients with persistent AF during a median follow-up of 12 (7-16) mo[21]. Therefore, strategies for redo procedures are of major importance. However, there are no established strategies for redo procedures after PV isolation with the cryoballoon technique so far. Currently applied strategies for redo procedures are repeat ablation procedures with the cryoballoon technique and a segmental approach using a standard cryoablation catheter. Repeat ablation procedures with the cryoballoon technique are limited by the fact that the rigid design of the cryoballoon might result in insufficient tissue contact in the same areas during both procedures (thereby triggering further arrhythmia recurrences). Repeat ablation procedures with a standard cryoablation catheter and a segmental approach are mainly limited by the long duration of (repeated) cryoapplications required for creating permanent lesions.

Therefore, we have evaluated two different strategies for redo procedures using radiofrequency catheter ablation. These ablation strategies included either a mere segmental pulmonary vein re-isolation or alternatively an anatomically-based circumferential PV ablation in combination with a potential-guided segmental approach[19,20]. The decision about the ablation strategy was based on the extent of pulmonary vein conduction recovery (documented using a circular mapping catheter at the beginning of the redo procedure).

Main results

During the redo procedures, a mean number of 2.9 re-conducting PVs (SD ± 1.0 PVs) were detected. In 20 patients, 1-3 re-conducting PVs were detected. There were only 10 patients in whom all four pulmonary veins showed recovered PV conduction. Minor PV reconnection (PV spike visible on 4 ≤ bipoles of the Lasso catheter) was present in 77 out of 86 reconnected veins (89.5%). Major PV reconnection (PV spike visible on > 4 bipoles of the Lasso catheter) was found in 9 out of 86 reconnected PVs (10.5%).

In 20 patients (with 1-3 reconnected PVs) re-isolation of the recovered pulmonary veins was performed using a segmental approach (group A). An anatomically-based circumferential pulmonary vein ablation in combination with a potential-guided segmental approach was performed in 10 patients, because recovered PV conduction of all four pulmonary veins was detected in these patients (group B).

Two years after the repeat ablation procedure, 75.0% of all patients in group A (15/20) were still free from an arrhythmia recurrence compared to 70.0% of patients in group B (7/10; $P = 1.0$). The overall success rate was 73.3% at 2-year follow-up. There were no major complications during or after the ablation procedures in both groups.

The results of our study demonstrate that a repeat ablation procedure after initial PV isolation using the cryoballoon technique can be performed safely and effectively using radiofrequency catheter ablation. In most cases only a few re-conducting PV fibres were found and therefore, a segmental re-ablation approach seems to be sufficient in the majority of patients.

There are two major advantages of radiofrequency catheter ablation over cryoablation for redo procedures after pulmonary vein isolation with the cryoballoon technique. First, due to the high degree of variability of the PV anatomy the contact between the cryoballoon catheter and the pulmonary veins cannot be equally good among all parts of the PV ostium. This limitation can be overcome during the redo procedure in most cases because the majority of areas with insufficient tissue contact during the initial procedure with the cryoballon technique can be easily reached with a standard RF ablation catheter.

Second, the use of radiofrequency energy delivery after prior cryoablation might result in a very stable lesion formation. Although there are no larger studies analysing the histological characteristics in this setting this effect might have contributed to the favourable results of our study. Nevertheless, further studies are necessary to evaluate the histological changes after repeated cryoablation in comparison to lesions created using RF ablation for redo procedures after cryoablation.

Limitations

This is a single centre study and, therefore, it is of mod-

erate size. However, follow-up was meticulous including repeat three-dimensional transesophageal echocardiography 3 mo after the procedure to rule out a pulmonary vein stenosis. Furthermore, a 7-d Holter monitoring was performed twelve months and twenty-four months after the ablation procedure. The follow-up duration is longer than in many other studies and all patients underwent the final evaluation 2 years after the redo ablation procedure. Therefore, this study provides very reliable information about the long-term outcome of this patient cohort.

Obviously, the extent of pulmonary vein conduction recovery after cryoablation should be evaluated in a larger patient cohort in a future study. A large randomized study is needed to compare the effectiveness of different strategies for redo procedures after initial pulmonary vein isolation with the cryoballoon technique (*i.e.*, repeat ablation with the cryoballoon technique or a segmental approach using a standard cryoablation catheter, a segmental pulmonary vein re-isolation using a standard irrigated-tip RF ablation catheter and a circumferential ablation strategy using radiofrequency catheter ablation).

In conclusion, a repeat ablation procedure after initial pulmonary vein isolation using the cryoballoon technique can be performed safely and effectively using radiofrequency catheter ablation. In most cases only a few re-conducting PV fibres were found and therefore, a segmental re-ablation approach seems to be sufficient in the majority of patients. Alternatively, a circumferential approach can be performed using RF catheter ablation in patients with complete recovery of all four pulmonary veins. Obviously, the results of this study have to be confirmed in a larger randomized trial.

COMMENTS

Background
Catheter ablation has become the first line of therapy in patients with symptomatic, recurrent, drug-refractory atrial fibrillation. Cryoablation has been shown to be a safe and effective technique for pulmonary vein isolation.

Research frontiers
However, the arrhythmia recurrence rate is high after cryoablation procedures and there are no established strategies for redo procedures in these patients. It is a matter of discussion whether cryoablation should be used for the redo procedures in these patients again or whether radiofrequency catheter ablation might be advantageous.

Innovations and breakthroughs
We have summarized our initial experience with two different strategies for redo procedures after cryoablation of atrial fibrillation using radiofrequency catheter ablation. The redo ablation procedures were performed using a segmental approach or a circumferential ablation strategy depending on the intra-procedural findings (1-3 versus 4 reconnected pulmonary veins). In 20 patients, a segmental approach was sufficient to eliminate the residual pulmonary vein conduction because there were only a few recovered pulmonary vein fibres. In the remaining 10 patients, a circumferential ablation strategy was used because of a complete recovery of the PV-LA conduction. At 2-year follow-up, 73.3 % of all patients were free from an arrhythmia recurrence. The results demonstrate that a repeat ablation procedure after initial circumferential pulmonary vein isolation using the cryoballoon technique can be performed safely and effectively using radiofrequncy catheter ablation.

Applications
The results suggest that radiofrequency catheter ablation is a good therapeutic option for the treatment of recurrences of atrial fibrillation after circumferential pulmonary vein isolation using the cryoballoon technique.

Terminology
Catheter ablation: interventional technique for the treatment of cardiac arrhythmias. Atrial fibrillation: disorganized atrial arrhythmia which is mostly induced by ectopic beats originating from the pulmonary veins.

Peer review
Well written, interesting review experience of the authors about the challenges and difficulties of redo-atrial fibrillation ablation.

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Patients with cardiac disease: Changes observed through last decade in out-patient clinics

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Abstract

AIM: To describe current profile of patients with cardiovascular disease (CVD) and assessing changes through last decade.

METHODS: Comparison of patients with established CVD from two similar cross-sectional registries performed in 1999 ($n = 6194$) and 2009 ($n = 4639$). The types of CVD were coronary heart disease (CHD), heart failure (HF) and atrial fibrillation (AF). Patients were collected from outpatient clinics. Investigators were 80% cardiologist and 20% primary care practitioners. Clinical antecedents, major diagnosis, blood test results and medical treatments were collected from all patients.

RESULTS: An increase in all risk factors, except for smoking, was observed; a 54.4% relative increase in BP control was noted. CHD was the most prevalent CVD but HF and AF increased significantly, 41.5% and 33.7%, respectively. A significant reduction in serum lipid levels was observed. The use of statins increased by 141.1% as did all cardiovascular treatments. Moreover, the use of angiotensin-renin system inhibitors in patients with HF, beta-blockers in CHD patients or oral anticoagulants in AF patients increased by 83.0%, 80.3% and 156.0%, respectively ($P < 0.01$).

CONCLUSION: The prevalence of all cardiovascular risk factors has increased in patients with CVD through last decade. HF and AF have experienced the largest increases.

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Key words: Cardiovascular disease; Trends; Heart failure; Coronary heart disease; Atrial fibrillation

Core tip: Reduction in acute phase of cardiovascular disease (CVD) has lead to a progressive increase in patients with chronic CVD that are considered high-risk patients and mostly attended in outpatient clinics.

The prevalence of all cardiovascular risk factors has increased in patients with CVD through last decade. Heart failure and atrial fibrillation have experienced the largest increases.

INTRODUCTION

Cardiovascular disease (CVD) remains as the leading cause of mortality in the world despite the progressive decrease in last decades and this has been largely due to risk factors control and improvements of acute phases management[1-4]. This positive results has lead to a large increase in the prevalence of patients with chronic CVD in the population[5,6] that are high-risk patients and benefit from the highest risk factors control[2] as well as treatment implementation[6,7]. Moreover, the progressive ageing of the population and patients has contributed to increase the complexity of patients, with higher comorbidities and polivascular disease that have higher risk of future cardiovascular events[8,9].

Coronary heart disease (CHD) and heart failure (HF) represent more than half of the mortality attributed to CVD what highlights they relevancy in public health[1]. Several registries have depicted the changing profile of patients with CHD[4,10-12] or other types of CVD[3,8,13] but there scare evidence concerning the changing prevalence of CVD in outpatient clinics. With the objective of describing current profile of patients with CVD and assessing changes through last decade we compared two clinical registries performed in Spain in 1999 and 2009.

MATERIALS AND METHODS

Study design

The CARDIOTENS 2009 registry is a cross-sectional, multicentre and nationwide study of patients with risk factors or cardiovascular disease[14], with similar methodology of CARDIOTENS registry performed in 1999[15]; both studies were promoted the Working Group of Hypertension of the Spanish Society of Cardiology and endorsed by the Agencia de Investigación de la Sociedad Española de Cardiología (Research Agency of the Spanish Society of Cardiology). From the 32051 subjects include in the 1999 registry 6194 (19.3%) had established CVD and were compared to the 4639 (18.2% of the 25856) patients with established CVD collected in 2009.

As defined in the 1999 registry established CVD was defined as: (1) CHD if antecedents of angina, myocardial infarction, coronary revascularization or positive stress test were present; (2) HF if patients had at least one hospitalization with such as main diagnosis at discharge medical report as well as those with typical signs and symptoms of HF that had a compatible imagine diagnosis (X-ray or echocardiogram); and (3) atrial fibrillation (AF) if the diagnosis was present in a medical report or any electrocardiographic registry. A brief analysis of guideline-recommended treatments was performed based on the use of beta-blockers in patients with CHD, angiotensin converter-enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB) in patients with HF, and oral anticoagulants in AF patients.

Investigators were randomly selected from primary care (88%) and cardiology outpatient clinics (12%). During the first week of November 2009 investigators included all consecutive patients that they attended; if patients had no risk factors or cardiovascular disease, only age. In patients with any risk factor or established cardiovascular disease a more extended protocol was performed in which all risk factors, clinical antecedents, treatments, physical examination and Inclusion criteria were: age ≥ 18 years, capability to access to full medical antecedents related to cardiovascular risk factors or events and allowance to participate by singing the informed consent. Exclusion criteria were addiction or consumption of illegal substances (cocaine, cannabis or other) or denial of the informed the consent. The study protocol and informed consent was approved by the ethics committee of the Hospital Universitario de San Juan (Alicante, Spain) and the Agencia of Investigación of the Spanish Society of Cardiology.

A specific collection data report in paper was designed for the study; a modification had to be added once printed and approved by the ethic committee due to an error in the codification of diuretics treatment. Electrocardiogram and biochemical determinations had to be obtained in within the last 6 mo. Blood pressure was measured after ten minutes of resting in the inclusion visit and two determinations were collected. Heart rate had to be measured during the physical examination.

Variables definition

Hypertension was defined according to the 2007 European Society of Hypertension-European Society of Cardiology guidelines if 2 determinations of blood pressure were ≥ 140/90 mmHg or specific treatments with previous diagnosis were present[16]. Dyslipidemia was collected if any antecedent of such diagnosis or values of total cholesterol > 220 mg/dL or low-density lipoproteins > 160 mg/dL had been registered previously. The diagnosis of diabetes mellitus was accepted if it had been previously diagnosis in a medical report, specific drug-treatment or 2 consecutive glucose determinations were > 126 mg/dL. Obesity was considered for those with body mass index > 30 kg/m^2 and abdominal obesity if waist circumference was > 102 cm in men or > 88 cm in women. Chronic obstructive pulmonary disease was registered
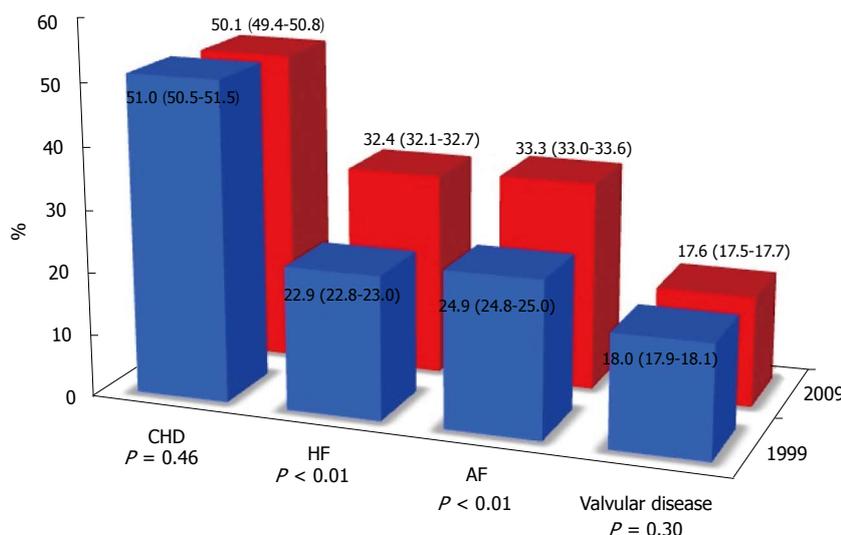
Figure 1 Trends in cardiovascular disease prevalence between 1999 and 2009 in both CARDIO-TENS registries. AF: Atrial fibrillation; CHD: Coronary heart disease; HF: Heart failure. Data presented as percentage (99%CI).

if specific treatments were present or previous diagnosis was present. Glomerular filtration rate was assessed by the Modification of Diet in Renal Disease equation: $(186 \times \text{creatinine}^{-1.154} \times \text{age}^{-0.203}) (\times 0.742$ in women).

Statistical analysis

Data management was made with statistical package SPSS 15.0 (SPSS Inc, Chicago, IL, United States) and 10.0/SE (Stata Corp, College Station, Tex). All variables had normal distribution so are presented as mean (standard deviation), except triglycerides that are presented as median (intercuartilic range); mean comparisons were made with ANOVA test and non-parametric χ^2. Percentages were compared by *t*-Student and non-parametric Kolmogorov-Smirnov test were used for comparison of means and medians respectively. Comparisons of percentages between the 2 registries were performed by *t*-Student contrast using the analysis of variance of the estimated percentages of each registry. Statistical significance was accepted for $P < 0.05$.

RESULTS

As presented in Table 1, patients of the 2009 registry had higher mean age, as well as higher prevalence of all risk factors except for current-smoking; the most significant raise was noted in patients aged > 70 or > 80 years. A significant reduction in mean systolic and diastolic BP was observed that lead to a 54.4% relative increase in blood pressure control. CHD was the most prevalent from of established CVD and its prevalence remained similar in both registries, as well as valvular heart disease that were the least prevalent CVD; a significant increase in the prevalence of HF (41.5% relative increase) and AF (33.7% relative increase) was observed (Figure 1).

We also observed a significant reduction in serum lipid levels although the prevalence of dyslipidemia increased between both registries (Table 2); in concordance,

a large relative increase in the use of statins, as well as all cardiovascular treatments was observed between both registries, except nitrates (Table 3). Moreover, the use of guideline-recommended treatments, such as ACEI or ARB in patients with HF, beta-blockers in the setting of CHD or oral anticoagulants in patients with AF, increased 83.0%, 80.3% and 156.0% (Figure 2).

DISCUSSION

The comparison of two large clinical registries performed with similar design and methodology allowed the description of risk factors and CVD prevalence evolution through last decade in Spain. Hypertension was the most prevalent risk factor in 1999 and was present in almost all patients with CVD 10 year later. Moreover, a relevant relative improvement in blood pressure control and guidelines-recommended treatments was observed, despite a slight reduction in mean systolic and diastolic blood pressure values. The prevalence of risk factors, mean age and medical treatments of patients included in 2009 was similar to contemporary registries[17-22] what reflects that this population might be representative of clinical relative.

Our results highlight that hypertension is present almost all patients with established CVD and is prevalence experienced a relative increase of 32% through last decade. This overwhelming rise can be explained by several facts; first, blood pressure is usually reported to be one the risk factors with poorest control what leads to a high prevalence of hypertension in patients with incident CVD[19,23]; second, the antecedent of hypertension does not impair the prognosis in the acute setting of CVD what leads to a increasing percentage of patients with hypertension and established CVD[24,25]; third, subjects with hypertension have benefit from a significantly higher decrease in cardiovascular mortality through last decades[21]; and fourth, population has experienced a relevant
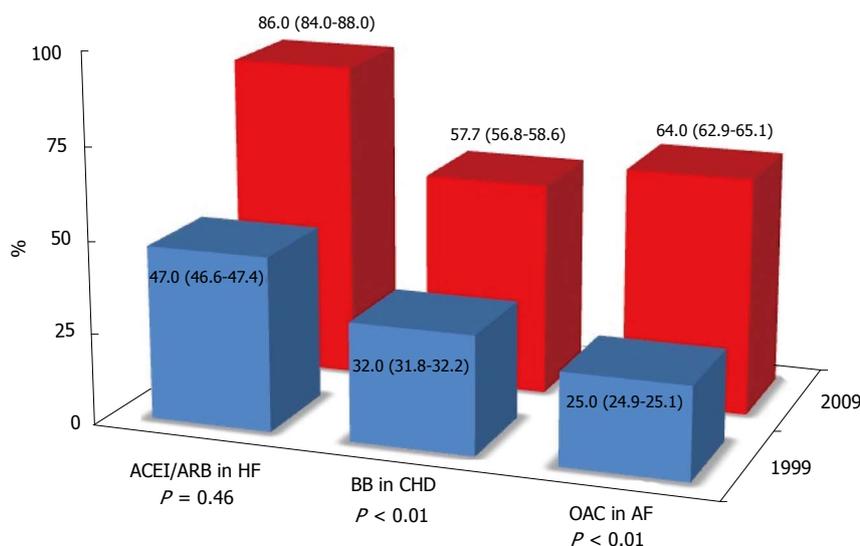
Figure 2 Changes in use of guideline-recommended treatments in each compelling indication between 1999 and 2009 in both CARDIOTENS registries. ACEI: Angiotensin-converter enzyme inhibitors; AF: Atrial fibrillation; ARB: Angiotensin-receptor blockers; CHD: Coronary heart disease; HF: Heart failure; OAC: Oral anticoagulation. Data presented as percentage (99%CI).

Table 1 Comparative characteristics of the patients included in each registry

	1999	2009	*P* vaule
Number	6194	4639	
Age (yr)	66.7 ± 10.8	70.6 ± 11.3	< 0.01
Age >70 yr	45.1% (44.7-45.5)	56.9% (56.0-57.8)	< 0.01
Age > 80 yr	13.0% (12.9-13.1)	18.6% (18.5-18.7)	< 0.01
Males	54% (53.4-54.6)	57.2% (56.3-58.1)	< 0.01
BMI > 30 mg/m^2	30% (29.8-30.2)	31.9% (31.6-32.2)	0.02
Hypertension	65% (64.1-65.9)	85.8% (83.8-87.8)	< 0.01
Diabetes	21% (20.9-21.1)	38.2% (37.8-38.6)	< 0.01
Dyslipidemia	40% (39.7-40.3)	59.2% (58.2-60.2)	< 0.01
Current smokers	20% (19.9-20.1)	12.1% (12.0-12.2)	< 0.01
Left ventricle hypertrophy	24.0% (23.9-24.1)	30.9% (30.6-31.2)	< 0.01
Systolic BP (mmHg)	138.2 ± 15.2	136.6 ± 16.0	< 0.01
Diastolic BP (mmHg)	79.1 ± 10.9	78.6 ± 11.5	< 0.01
BP < 140/90 mmHg	36.0% (35.7-36.3)	55.6% (54.8-56.4)	< 0.01

Data collected from CARDIOTENS registries, Spain. Data are presented as mean ± SD or percentage (99%CI). BMI: Body mass index; BP: Blood pressure.

Table 2 Lipid profile of patients included in each registry

	1999	2009	*P* vaule
Total cholesterol (mg/dL)	218.3	196.3 (45.8)	< 0.01
HDL (mg/dL)	49.5	50.2 (15.3)	< 0.01
LDL (mg/dL)	145.1	117.0 (37.5)	< 0.01
Triglycerides (mg/dL)	142.6	145.1 (70.5)	0.02

Data collected from CARDIOTENS registries, Spain. HDL: High-density lipoproteins; LDL: low-density lipoproteins.

Table 3 Medical treatments in each registry

	1999	2009	*P* vaule
Antiplatelets	42.0% (41.6-42.4)	76.8% (75.2-78.4)	< 0.01
Diuretics	32.0% (31.8-32.2)	4.4% (4.39-4.41)	< 0.01
ACEI	30.2% (30.0-30.4)	43.6% (43.1-44.1)	< 0.01
Statins	27.0% (26.9-27.1)	65.1% (63.9-66.3)	< 0.01
CCB	27.8% (27.6-28.0)	36.7% (36.3-37.1)	< 0.01
Nitrates	25.0% (24.9-25.1)	26.3% (26.1-26.5)	0.06
Beta-blockers	22.2% (22.1-22.3)	44.6% (44.1-45.1)	< 0.01
Oral anticoagulants	17.5% (17.4-17.6)	27.0% (26.8-27.2)	< 0.01
ARB	11.1% (11.0-11.1)	38.6% (38.2-39.0)	< 0.01
Insulin	5.1% (5.09-5.10)	13.7% (13.6-13.8)	< 0.01
Oral antidiabetics	10.0% (9.9-10.1)	43.7% (43.2-44.2)	< 0.01

Data collected from CARDIOTENS registries, Spain. Data presented as percentages (99%CI). ACEI: Angiotensin converter-enzyme inhibitors; ARB: Angiotensin receptor blockers; CCB: Calcium channel blockers.

increase in clinical features in the population that are closely related to high-blood pressure, as advanced age[16], obesity[26] or diabetes[27] predispose to a increasing pattern in hypertension prevalence. Our registry included stable patients with CVD and strongly supports these four key-points and provides not only a reasonable profile of

patients with hypertension and CVD but, also, a clinical perspective of its evolution through last decade.

CHD remained as the most prevalent forms of established CVD but experienced no relative change through last decade; nevertheless, the presence of HF and AF increased largely; the study protocol on the 1999 registry did not other forms of CVD, such as stroke or peripheral arterial disease, and we could not obtain data of these two relevant clinical entities[1]. HF and AF have been clearly related to age and hypertension and have been reported to rise in the overall population steeply through last decades[1,28]. Blood pressure control has been outlined as major target for prevention of HF[29] and AF[30] especially by the use of ACEI or ARB[31] and target organ damage prevention. In contrast, mean age increased in the comparison between both registries and the prevalence of octogenarians reached almost 20%. The evidence of BP control and the optimal objective in elderly patients has been less studied[16]; only the Hypertension in the Very Elderly Trial[32] study was specifically designed to assess the benefit of BP control and target BP was < 150/80 mmHg. The study demonstrated both

significant improvement in cardiovascular events and mortality in patients actively treated with a diuretic and an ACEI. These results added to net benefit of ACEI or ARB in patients with established CVD might explain the large increase in the use of these treatments observed in our results.

Our results show at least two positive messages: the increase in blood pressure control and the improvement in medical treatments. All guideline-recommended treatments experienced significant increases, being the use of statins, ACEI and ARB the most prominent. The use of statins has spread to majority of patients with established CVD, especially in the patients with CHD[17,18,23] and its use in patients with HF is much lower because its clinical benefit in absence of underlying CHD is not clear. Nonetheless, our results highlighted a very relevant increase in the use of ACEI or ARB in patients with HF that agrees with previous reports of other registries[22,28]. The use of beta-blockers in patients with CHD also increased but only reached 57%, a very similar percentage of registries that included chronic and stable patients[6,17,18]. The increase in the oral anticoagulants in patients with AF was remarkable and treatment rate in our registry was similar to the last report of the European Heart Survey[33].

Our study has several limitations that deserve consideration, mainly derived from its design; for being a cross-sectional study it can only describe clinical associations and causal effects. Moreover, it only included consecutive patients that were attended in outpatient clinics and, therefore, our results are not representative of overall population. The study protocol did not include stroke or peripheral disease as established CVD and, therefore, we can not provide actualized data on these two relevant diseases. Finally, there was an error in the typing of diuretics and, therefore, data collection concerning this medication was not accurate.

In conclusion, the prevalence of all cardiovascular risk factors has increased in patients with established CVD, except smoking. Hypertension is most prevalent risk factors in these patients and a significant improvement in BP control has been achieved although it is still far from optimal goals. A relevant improvement in guideline-recommended treatments could be demonstrated, as well as major cardiovascular treatments, being the use of statins the most remarkable. We describe a positive trend in blood pressure control and guidelines-recommended treatments but there are still opportunities for further improvement.

COMMENTS

Background
Reduction in acute phase of cardiovascular disease (CVD) has lead to a progressive increase in patients with chronic CVD that are considered high-risk patients and mostly attended in outpatient clinics.

Research frontiers
Risk factors control and medical treatment has been usually reported as lower in high-risk patients. Many registries have reported relevant increases in blood pressure or cholesterol control, although the changing pattern in clinical profile and risk factors control of patients with established cardiovascular disease has been far less studied.

Innovations and breakthroughs
The prevalence of heart failure and atrial fibrillation has increased significantly through the last decade, meanwhile coronary heart disease remained as the most prevalent. Similarly, authors have noted an increase in mean age, especially in the percentage of elderly patients, and all risk factors but smoking. Risk factors control has increases as well as guidelines-recommended medical treatments.

Applications
Out patients clinics should be prepared, focused and organized to attended more patients with heart failure or atrial fibrillation that have very specific considerations, such as weight-gain, symptoms control, medication use, anticoagulants complications.

Terminology
Coronary heart disease: patients with the antecedent of myocardial infarction, angina, acute coronary syndromes or any kind of coronary revascularization.

Peer review
This is a good descriptive study in which authors analyze changes in clinical profile and medical treatments of patients with cardiovascular disease. The results are interesting and highlight the increasing trend in the prevalence of heart failure and atrial fibrillation, two clinical entities that deserve very specific considerations in out-patient clinics.

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BRIEF ARTICLE

Central obesity in Yemeni children: A population based cross-sectional study

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Abstract

AIM: To establish percentile curves and to explore prevalence and correlates of central obesity among Yemeni children in a population based cross-sectional study.

METHODS: A representative sample of 3114 Yemeni children (1564 boys, 1550 girls) aged 6-19 years participating in the HYpertension and Diabetes in Yemen study was studied. Data collection was conducted at home by survey teams composed of two investigators of both genders. Study questionnaire included questions about demographics, lifestyle, and medical history. Anthropometric measurements included body weight, height, waist circumference (WC) and hip circumferences. Waist to hip ratio (WHR) and waist-to-height ratio (WHtR) were then calculated. Age and gender specific smoothed percentiles of WC, WHR, and WHtR were obtained using lambda-mu-sigma parameters (LMS method). The independent predictors of central obesity defined as (1) WC percentile $\geq$ 90th; (2) WHtR $\geq$ 0.5; or (3) WC percentile $\geq$ 90th and WHtR $\geq$ 0.5, were identified at multivariate logistic regression analysis adjusted for age, gender, urban/rural location, years of school education, sedentary/active life-style.

RESULTS: Percentile curves for WC, WHR and WHtR are presented. Average WC increased with age for both genders. Boys had a higher WC than girls until early adolescence and thereafter girls had higher values than boys. WHR decreased both in boys and girls until early adolescence. Thereafter while in boys it plateaued in girls it continued to decrease. Mean WHtR decreased until early adolescence with no gender related differences and thereafter increased more in girls than in boys towards adult age. Prevalence of central obesity largely varied according to the definition used which was 10.9% for WC $\geq$ 90th percentile, 18.3% for WHtR $\geq$ 0.5, and 8.6% when fulfilling both criteria. At adjusted logistic regression WC $\geq$ 90th percentiles and WHtR $\geq$ 0.5 were less prevalent in rural than in urban areas (OR = 0.52, 95%CI: 0.41-0.67 and 0.66, 0.54-0.79 respectively), being more prevalent in children with sedentary lifestyle rather than an active one (1.52, 95%CI: 1.17-1.98 and 1.42, 95%CI: 1.14-1.75, respectively).

CONCLUSION: Yemeni children central obesity indices

percentile curves are presented. Central obesity prevalence varied according to the definition used and was more prevalent in urban sedentary subjects.

Core tip: This study presents the first central obesity percentile curves of waist circumference (WC), waist-to-height ratio (WHtR) and waist to hip ratio (WHR) for Yemeni children aged six to nineteen years. WC, WHtR and WHR changed similarly in girls and boys until early adolescence. Thereafter, differently from what observed in Western countries, obesity increased more in girls than in boys. Prevalence of central obesity in Yemeni children is low, being associated with urbanization and sedentary lifestyle, and varied according to the definition used: (1) WC percentile $\geq$ 90th (10.9%); (2) WHtR $\geq$ 0.5 (18.3%); (3) WC percentile $\geq$ 90th and WHtR $\geq$ 0.5 (8.6%).

INTRODUCTION

Childhood obesity is a matter of growing concern not only in developed but also in developing countries[1]. In the Middle Eastern Crescent (MEC) rates of adolescent overweight and obesity, assessed by the use of body mass index (BMI), are among the highest in the world[2]. The same world area is also characterized by a high prevalence of childhood central obesity as assessed by measuring waist circumference (WC)[3,4]. WC was consistently reported as a more sensitive indicator than BMI of metabolic abnormalities[5], and insulin resistance[6], also at young ages.

Measurements of BMI or WC in children have to be expressed in relation to their sex and age peers, and age and gender specific reference values are required for the diagnosis. Differently from WC, waist to hip ratio (WHR) and BMI a recently proposed index, waist-to-height ratio (WHtR), is only weakly associated with age, and gender[7,8]. Different studies are suggesting a single cut-off value for defining central obesity (WHtR $\geq$ 0.5)[9]. However, ethnicity and environmental differences might influence body proportions, and it was suggested to use national references to control for variations between populations[10].

Considerable variation in the prevalence of risk factors was reported among different MEC countries[11]

and few information is available in the pediatric population. According to a single study performed in Lahore (Pakistan), 16% of children aged 5-12 years had WHtR above the cut off value of 0.5[12]. HYpertension and Diabetes in Yemen (HYDY) study was thus also designed to provide age- and gender-specific WC, WHR and WHtR smoothed percentiles, and to explore prevalence and correlates of central obesity, among Yemeni children and adolescents aged six to nineteen years.

MATERIALS AND METHODS

Study sites and study population
Target population of the study was the population of the country aged 6-19 years. A representative sample of 3114 Yemeni children (1564 boys, 1550 girls) aged 6 to 19 years (median age 13.5 years) participating in the HYDY survey was studied[13]. The survey used a multi-stage stratified sampling method to select households as the setting for data collection[13]. Briefly in the first stage, Yemen was stratified into three areas, the capital area, the inland, and the coastal area. The governorate of Sana'a (capital area), the governorate of Taizz (inland), and the governorates of Al Hudaydah and Hadramaut (coast) were selected to be representative of the geographic, economic, and climatic characteristics of the three areas. The number of subjects in each area was estimated using the preliminary data provided by the United Nations Population Fund that is the same source used to stratify Yemen population by age and gender[14]. In the second stage, rural and city regions were identified from each study area. In the third stage, districts were arbitrarily identified within each urban and rural region, boundaries being defined using local maps or in consultation with the local health workers. Households were selected because in developing countries not all children in the age groups of interest may have access to school. The survey was completed within 16 mo. The response rate for subjects aged 6-19 years was 96% in urban and 97% in rural locations. The study was approved by the Ethical Committee of the University of Science and Technology, Sana'a, Yemen (Ref. 1-2007). Informed consent was obtained from participants and their parents before data collection. The procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1964, as revised in 2004.

Data collection
Data collection was conducted at home by centrally trained survey teams composed of two investigators of both genders. Children were evaluated between February 2008 and May 2009. Study questionnaire included questions about demographics, lifestyle, and medical history. Anthropometric measurements were taken on standing participants wearing light clothing and without shoes using standard techniques[13]. In the HYDY survey we used a pre-calibrated digital Laica PS6010 scale with a 150 kg capacity (accuracy 100 g) which was frequently checked

Table 1 Descriptive statistics by age group of the 3114 study participants are reported

Age (yr)	*n*	Weight	Height (cm)	BMI (kg/m^2)	WC	WHtR	HC	WHR
Boys								
6	47	17.4 ± 3.5	104.7 ± 8.4	16.0 ± 3.6	48.6 ± 6.5	0.47 ± 0.06	55.3 ± 9.1	0.88 ± 0.08
7	90	18.8 ± 3.5	109.9 ± 8.8	15.7 ± 2.8	50.8 ± 5.7	0.47 ± 0.07	57.2 ± 6.6	0.89 ± 0.07
8	99	21.3 ± 4.5	114.7 ± 9.4	16.4 ± 3.8	52.2 ± 7.1	0.46 ± 0.07	59.6 ± 7.6	0.88 ± 0.08
9	101	24.3 ± 7.4	120.5 ± 10.6	16.8 ± 4.6	55.6 ± 8.5	0.46 ± 0.08	63.8 ± 8.9	0.87 ± 0.07
10	132	26.8 ± 6.6	126.9 ± 10	16.9 ± 4.1	56.3 ± 7.5	0.45 ± 0.06	64.6 ± 9.1	0.88 ± 0.09
11	102	26.7 ± 4.8	129.3 ± 7.9	16.0 ± 2.8	57.0 ± 7.0	0.44 ± 0.05	65.2 ± 7.5	0.88 ± 0.07
12	157	29.9 ± 7.1	133.6 ± 8.4	16.7 ± 3.5	57.1 ± 8.4	0.43 ± 0.06	67.3 ± 9.0	0.85 ± 0.07
13	116	34.7 ± 8.2	141.5 ± 9.9	17.2 ± 3.4	61.4 ± 8.2	0.43 ± 0.05	71.7 ± 9.1	0.86 ± 0.07
14	158	39.2 ± 8.5	148.1 ± 9.7	17.8 ± 2.9	62.6 ± 8.1	0.42 ± 0.05	73.3 ± 8.5	0.86 ± 0.07
15	112	43.2 ± 11.7	150.3 ± 12.8	18.9 ± 4.0	66.8 ± 9.5	0.45 ± 0.06	77.2 ± 10.2	0.87 ± 0.08
16	100	47.3 ± 8.9	155.2 ± 9.6	19.7 ± 3.9	67.9 ± 9.2	0.44 ± 0.06	79.9 ± 9.3	0.85 ± 0.10
17	119	50.1 ± 9.3	160.1 ± 10.6	19.7 ± 3.9	68.1 ± 9.4	0.43 ± 0.06	80.3 ± 9.7	0.85 ± 0.08
18	133	51.4 ± 9.2	160.0 ± 11.1	20.1 ± 3.2	67.9 ± 8.7	0.43 ± 0.05	80.3 ± 9.1	0.85 ± 0.10
19	98	53.8 ± 11.3	161.3 ± 11.2	20.7 ± 4.0	70.3 ± 11.9	0.44 ± 0.07	82.8 ± 12.2	0.85 ± 0.08
Girls								
6	51	17.8 ± 2.8	104.5 ± 10.5	17.0 ± 3.8	48.7 ± 7.9	0.47 ± 0.07	56.6 ± 10.7	0.87 ± 0.10
7	79	18.2 ± 4.0	109.4 ± 10.0	15.6 ± 3.9	49.8 ± 6.3	0.46 ± 0.07	57.2 ± 7.8	0.88 ± 0.09
8	86	23.2 ± 7.2	115.4 ± 11.4	17.6 ± 5.2	51.7 ± 9.7	0.45 ± 0.08	59.2 ± 9.4	0.87 ± 0.09
9	122	23.5 ± 5.3	118.6 ± 10.7	17.1 ± 4.6	52.3 ± 8.8	0.44 ± 0.09	60.6 ± 10.4	0.87 ± 0.09
10	164	25.8 ± 6.4	122.7 ± 10.3	17.1 ± 3.8	54.9 ± 8.3	0.45 ± 0.07	64.1 ± 10.1	0.86 ± 0.07
11	123	29.2 ± 7.5	130.9 ± 9.9	17.2 ± 4.5	56.6 ± 8.7	0.43 ± 0.07	66.2 ± 10.4	0.86 ± 0.10
12	124	32.5 ± 7.3	133.6 ± 10	18.2 ± 3.6	59.0 ± 9.9	0.44 ± 0.06	69.7 ± 11.4	0.85 ± 0.08
13	133	35.6 ± 6.7	138.2 ± 9.9	18.7 ± 3.6	59.3 ± 10.0	0.43 ± 0.07	70.3 ± 11.6	0.85 ± 0.07
14	130	41.1 ± 7.3	143.9 ± 8.7	19.9 ± 3.3	63.7 ± 9.3	0.44 ± 0.06	75.2 ± 11.1	0.86 ± 0.10
15	102	44.6 ± 10.3	147.9 ± 10.1	20.3 ± 3.9	67.8 ± 8.8	0.46 ± 0.05	80.8 ± 10.3	0.84 ± 0.08
16	108	47.6 ± 9.4	149.9 ± 8.1	21.1 ± 3.5	68.0 ± 9.5	0.45 ± 0.06	82.4 ± 10.2	0.83 ± 0.10
17	97	46.1 ± 8.7	151.4 ± 9.6	20.0 ± 3.1	68.1 ± 9.6	0.45 ± 0.06	82.3 ± 9.9	0.83 ± 0.08
18	128	48.9 ± 8.9	150.5 ± 8.2	21.6 ± 3.6	70.2 ± 9.2	0.47 ± 0.06	84.3 ± 9.8	0.84 ± 0.09
19	105	50.9 ± 10.3	152.2 ± 7.9	21.9 ± 4.0	70.2 ± 11.9	0.46 ± 0.07	86.1 ± 11.5	0.82 ± 0.09

Sample sizes, mean ± SD for weight, height, body mass index (BMI), waist circumference (WC), waist-to-height ratio (WHtR), hip circumference (HC), and waist to hip ratio (WHR) for Yemeni boys and girls six to nineteen years of age (*n* = 3114).

by a known-weighing object. The CV for inter- and intra-observer effects for most anthropometric measures was < 5%. Height was measured to the nearest 0.5 cm using a stadiometer. WC was measured with a non-elastic tape positioned at a point midway between the lower border of the rib cage and the top of the iliac crest, and hip circumference (HC) was measured at the widest part of the hip at the level of the greater trochanter. WC and HC were measured to the nearest 0.5 cm and WHR and WHtR were then calculated.

BMI was computed as the weight in kilograms divided by the square of the height in meters. Central obesity was evaluated by analyzing WHtR ≥ 0.5, WC ≥ 90th percentile and the combination of both WHtR ≥ 0.5 and WC ≥ 90th percentile. Overweight and obesity were also defined as having a BMI above the age and sex-specific thresholds of the international obesity task force (IOTF) respectively the equivalent of BMI > 25 kg/m^2 and the equivalent of BMI > 30 kg/m$^{2[15]}$.

Statistical analysis

Description and validation of the database can be found elsewhere[16]. Data were preliminary checked for outliers using a cut-off of ± 5 SD of the corresponding age and sex Z-scores[17]. Smoothed age (by year) and gender-spe-

cific percentiles (3rd, 5th, 10th, 25th, 50th, 75th, 90th, 95th, and 97th) for WC, WHR and WHtR were then constructed by means of a comprehensive method of smoothing for growth curves using lambda-mu-sigma parameters according to Cole (LMS method)[18,19].

The LMS method summarizes the growth reference curve with three curves representing the median (M), the coefficient of variation (S) and the power to remove skewness from the data (L) by age and was implemented in the Generalized Additive Model for Location, Scale and Shape (GAMLSS) package included in R 2.14.0 software for Windows. In LMS method, GAMLSS parameters and the parameters of Box-Cox power exponential distribution were used for model fitting to data. These reference curves were fitted on the original data and the best fit was used to construct smoothed percentile curves. After the application of the BoxCox power transformation the data at each age were normally distributed and the points on each centile curve were defined in terms of the formula: $M = (1+LSz)^{1/L}$ where L, M, and S are values of the fitted curves at each age, and z indicates the z score for the required centile.

WC, WHR, and WHtR differences between genders were tested within age groups using Mann-Whitney *U*-test. Data are expressed as crude values. Comparisons

Age (yr)	n	3rd	5th	10th	25th	50th	75th	90th	95th	97th
Boys										
6	47	36.60	38.50	41.30	45.40	48.90	52.50	57.20	60.70	63.30
7	90	37.60	39.70	42.60	46.80	50.40	54.10	58.90	62.50	65.20
8	99	38.80	40.90	43.90	48.20	52.00	55.80	60.80	64.50	67.30
9	101	40.00	42.20	45.30	49.80	53.60	57.60	62.70	66.50	69.40
10	132	41.20	43.40	46.60	51.20	55.10	59.20	64.40	68.40	71.30
11	102	42.20	44.50	47.70	52.50	56.50	60.70	66.10	70.10	73.10
12	157	43.40	45.80	49.10	54.00	58.10	62.40	68.00	72.10	75.20
13	116	44.90	47.40	50.80	55.80	60.10	64.60	70.30	74.70	77.90
14	158	46.70	49.20	52.80	58.00	62.40	67.10	73.00	77.50	80.80
15	112	48.40	51.00	54.70	60.10	64.70	69.50	75.70	80.30	83.80
16	100	49.70	52.40	56.30	61.80	66.60	71.50	77.80	82.60	86.20
17	119	50.80	53.50	57.40	63.10	67.90	73.00	79.40	84.30	87.90
18	133	51.60	54.30	58.30	64.10	69.00	74.10	80.70	85.60	89.30
19	98	52.30	55.10	59.10	65.00	70.00	75.20	81.80	86.80	90.60
Girls										
6	51	34.30	36.50	39.70	44.40	48.70	53.10	58.00	61.30	63.60
7	79	35.10	37.40	40.60	45.50	49.90	54.30	59.30	62.70	65.10
8	86	36.00	38.30	41.70	46.60	51.10	55.70	60.80	64.30	66.80
9	121	37.10	39.40	42.90	48.00	52.60	57.30	62.60	66.20	68.70
10	164	38.40	40.80	44.40	49.60	54.50	59.30	64.70	68.50	71.10
11	123	39.80	42.40	46.10	51.50	56.50	61.60	67.20	71.10	73.80
12	124	41.40	44.00	47.90	53.50	58.70	64.00	69.80	73.90	76.70
13	132	43.00	45.70	49.70	55.60	61.00	66.50	72.60	76.70	79.70
14	130	44.70	47.50	51.70	57.80	63.40	69.10	75.40	79.80	82.80
15	102	46.20	49.20	53.50	59.80	65.60	71.50	78.00	82.50	85.70
16	108	47.40	50.50	54.90	61.40	67.30	73.40	80.10	84.70	87.90
17	97	48.40	51.50	55.90	62.60	68.70	74.80	81.60	86.30	89.60
18	128	49.10	52.30	56.90	63.60	69.80	76.00	83.00	87.70	91.10
19	105	49.80	53.00	57.60	64.50	70.70	77.10	84.10	88.90	92.30

Table 2 Age, and gender specific smoothed waist circumference percentiles for Yemeni children and adolescents aged 6 to 19 years (cm)

Age, and gender specific smoothed waist circumference percentiles for Yemeni children and adolescents aged 6- 19 years (*n* = 3114).

were performed by using logistic regression with adjustment for confounding variables including age (years), gender, years of school education, urban/rural residency and sedentary/active lifestyle. Results are expressed as adjusted odd ratio (OR) with 95% confidence interval (CI). Test of hypothesis was done at significance level 0.05 two sided. SPSS software, version 19.0 (SPSS Inc., Chicago., IL, United States) was used for statistical comparisons.

RESULTS

Descriptive statistics for weight, height, BMI, WC, WHtR, HC, and WHR by age group of the 3114 study participants are reported in Table 1. Age and gender specific WC, WHR and WHtR smoothed percentiles are presented in Tables 2-4 respectively. Mean BMI increased with age in both genders. However, girls aged 11 years or more had BMI values higher than boys (19.8 kg/m^2, 95%CI: 19.6-20.0 and 18.4 kg/m^2, 95%CI: 18.2-18.7 for girls and boys respectively). Overall 13.9% of participants (females 15.8%; 95%CI: 14.0-17.6; males 12.1%; 95%CI: 10.5 to 13.7) were overweight according to the IOTF criteria, 5.0% being obese (females 5.7%; 95%CI: 4.6-6.9; males 4.2%; 95%CI: 3.2-5.2).

WC increased with age among both boys and girls (Table 1). Boys had a non-significantly higher WC than girls until early adolescence (54.1 ± 7.7 cm *vs* 53.1 ± 8.7 cm, *P* = 0.09 respectively for subjects aged ⩽ 11 years). Thereafter girls had higher WC values than boys (65.5 ± 10.7 cm *vs* 64.8 ± 10.0 cm, *P* < 0.05 respectively for subjects aged > 11 years). Girls had lower 50th and 90th WC than boys in younger ages (6-11 years), but higher in older ages (12-19 years) (Table 2) (Figure 1A and D).

Mean WHR decreased with age among both boys and girls until early adolescence. Thereafter values plateaued in boys whereas in girls it continued to decrease. Boys had a higher WHR than girls in early adolescence (0.88 ± 0.08 *vs* 0.87 ± 0.09, *P* < 0.01 respectively for subjects aged ⩽ 11 years) as well as thereafter (0.85 ± 0.08 *vs* 0.84 ± 0.09, *P* < 0.01 respectively for subjects aged > 11 years). Girls always had lower 50th and 90th WHR than boys (Table 3) (Figure 1B and E).

Mean WHtR was slightly higher among boys than girls for subjects aged ⩽ 11 years (0.455 ± 0.067 and 0.448 ± 0.075 respectively, *P* = 0.07). Thereafter WHtR values were higher in girls (0.450 ± 0.063) than in boys (0.431 ± 0.059, *P* < 0.01). WHtR 50th percentile in both sexes decreased from the age of 6 years reaching the minimum at the age of 13 years, increasing thereafter mainly in girls. Girls had higher 50th and 90th WHtR percentiles than boys between the age of 14-19 years (*P* < 0.05) (Table 4) (Figure 1C and F).

Table 3 Age, and gender specific smoothed waist hip ratio percentiles for Yemeni children and adolescents aged 6 to 19 years

Age (yr)	n	3th	5th	10th	25th	50th	75th	90th	95th	97th
Boys										
6	47	0.73	0.76	0.79	0.84	0.89	0.93	0.99	1.03	1.05
7	90	0.73	0.75	0.79	0.84	0.88	0.93	0.98	1.02	1.04
8	99	0.72	0.75	0.78	0.83	0.88	0.92	0.97	1.01	1.04
9	101	0.72	0.74	0.78	0.83	0.87	0.92	0.97	1.01	1.03
10	132	0.72	0.74	0.77	0.82	0.86	0.91	0.96	1.00	1.03
11	102	0.71	0.73	0.77	0.82	0.86	0.90	0.96	0.99	1.02
12	157	0.71	0.73	0.76	0.81	0.85	0.90	0.95	0.99	1.01
13	116	0.70	0.73	0.76	0.81	0.85	0.90	0.95	0.98	1.01
14	158	0.70	0.73	0.76	0.81	0.85	0.89	0.95	0.98	1.01
15	112	0.70	0.73	0.76	0.81	0.85	0.89	0.95	0.98	1.01
16	100	0.70	0.72	0.76	0.80	0.85	0.89	0.94	0.98	1.01
17	119	0.70	0.72	0.76	0.80	0.85	0.89	0.94	0.98	1.00
18	133	0.70	0.72	0.76	0.80	0.85	0.89	0.94	0.98	1.00
19	98	0.70	0.73	0.76	0.81	0.85	0.90	0.95	0.98	1.01
Girls										
6	51	0.70	0.73	0.77	0.82	0.87	0.93	0.98	1.01	1.04
7	79	0.70	0.73	0.76	0.82	0.87	0.92	0.98	1.01	1.03
8	86	0.70	0.72	0.76	0.81	0.87	0.92	0.97	1.00	1.03
9	121	0.69	0.72	0.75	0.81	0.86	0.91	0.96	1.00	1.02
10	164	0.69	0.71	0.75	0.80	0.86	0.91	0.96	0.99	1.02
11	123	0.68	0.71	0.75	0.80	0.85	0.90	0.95	0.99	1.01
12	124	0.68	0.71	0.74	0.80	0.85	0.90	0.95	0.98	1.01
13	132	0.68	0.70	0.74	0.79	0.84	0.90	0.95	0.98	1.00
14	130	0.68	0.70	0.74	0.79	0.84	0.89	0.94	0.98	1.00
15	102	0.67	0.70	0.73	0.79	0.84	0.89	0.94	0.97	0.99
16	108	0.67	0.69	0.73	0.78	0.83	0.88	0.93	0.97	0.99
17	97	0.67	0.69	0.73	0.78	0.83	0.88	0.93	0.96	0.98
18	128	0.66	0.69	0.72	0.78	0.83	0.88	0.93	0.96	0.98
19	105	0.66	0.68	0.72	0.77	0.82	0.87	0.92	0.95	0.97

Age, and gender specific smoothed waist hip ratio percentiles for Yemeni children and adolescents aged 6-19 years (*n* = 3114).
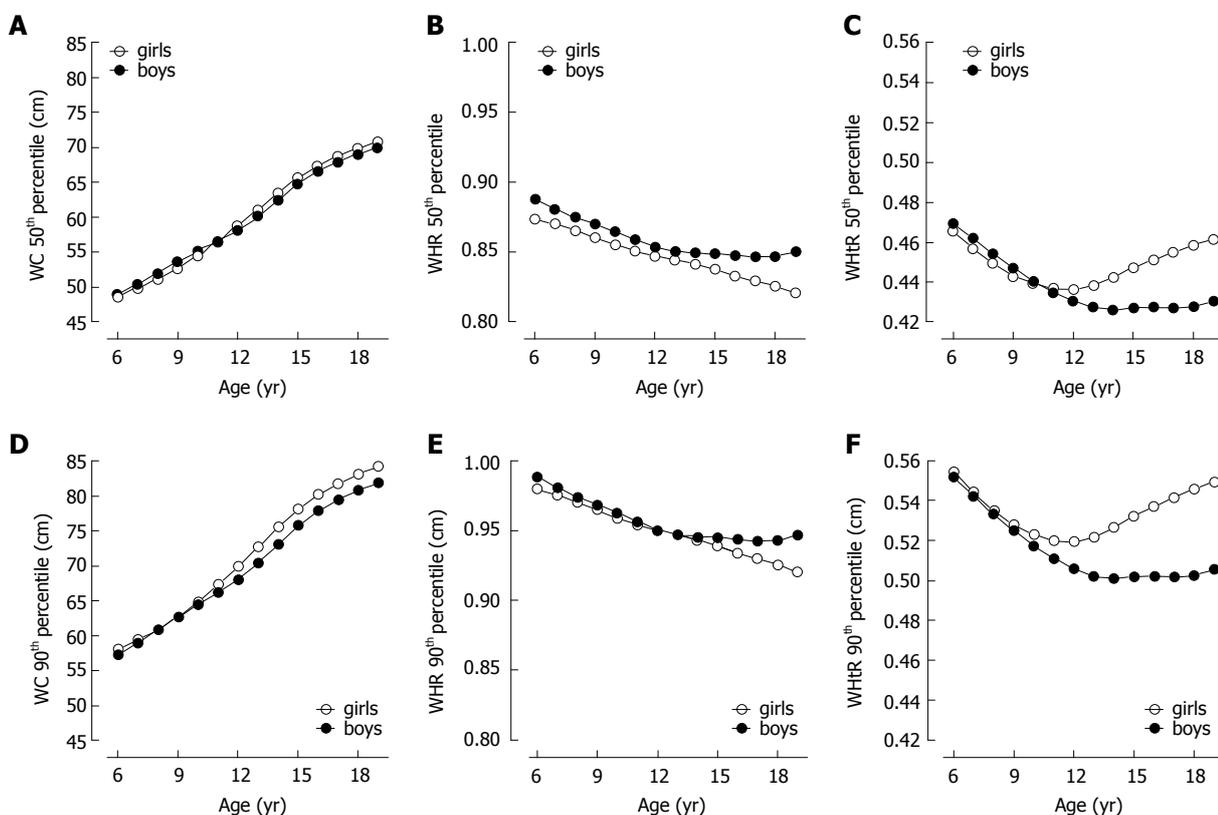
Figure 1 50th and 90th percentile curves. Waist circumference (WC, A and D), waist to hip ratio (WHR, B and E), and waist to height ratio (WHtR, C and F) for Yemeni boys (filled circles) and girls (empty circles).

Table 4 Age, and gender specific smoothed waist-to-height ratio percentiles for Yemeni children and adolescents aged 6 to 19 years

Age (yr)	n	3rd	5th	10th	25th	50th	75th	90th	95th	97th
Boys										
6	47	0.35	0.37	0.4	0.44	0.47	0.51	0.55	0.59	0.61
7	90	0.35	0.36	0.39	0.43	0.46	0.50	0.54	0.58	0.60
8	99	0.34	0.36	0.38	0.42	0.45	0.49	0.53	0.57	0.59
9	101	0.34	0.35	0.38	0.41	0.45	0.48	0.53	0.56	0.58
10	132	0.33	0.35	0.37	0.41	0.44	0.47	0.52	0.55	0.57
11	102	0.33	0.34	0.37	0.40	0.44	0.47	0.51	0.54	0.57
12	157	0.32	0.34	0.36	0.40	0.43	0.46	0.51	0.54	0.56
13	116	0.32	0.34	0.36	0.40	0.43	0.46	0.50	0.53	0.56
14	158	0.32	0.34	0.36	0.40	0.43	0.46	0.50	0.53	0.55
15	112	0.32	0.34	0.36	0.40	0.43	0.46	0.50	0.53	0.56
16	100	0.32	0.34	0.36	0.40	0.43	0.46	0.50	0.53	0.56
17	119	0.32	0.34	0.36	0.40	0.43	0.46	0.50	0.53	0.56
18	133	0.32	0.34	0.36	0.40	0.43	0.46	0.50	0.53	0.56
19	98	0.32	0.34	0.36	0.40	0.43	0.46	0.51	0.54	0.56
Girls										
6	51	0.34	0.36	0.38	0.43	0.47	0.51	0.55	0.59	0.61
7	79	0.33	0.35	0.38	0.42	0.46	0.50	0.54	0.58	0.60
8	86	0.32	0.34	0.37	0.41	0.45	0.49	0.53	0.57	0.59
9	121	0.32	0.34	0.36	0.41	0.44	0.48	0.53	0.56	0.58
10	164	0.32	0.34	0.36	0.40	0.44	0.48	0.52	0.55	0.58
11	123	0.32	0.33	0.36	0.40	0.44	0.48	0.52	0.55	0.57
12	124	0.32	0.33	0.36	0.40	0.44	0.48	0.52	0.55	0.57
13	132	0.32	0.33	0.36	0.40	0.44	0.48	0.52	0.55	0.57
14	130	0.32	0.34	0.36	0.40	0.44	0.48	0.53	0.56	0.58
15	102	0.32	0.34	0.37	0.41	0.45	0.49	0.53	0.56	0.59
16	108	0.33	0.34	0.37	0.41	0.45	0.49	0.54	0.57	0.59
17	97	0.33	0.35	0.37	0.42	0.45	0.50	0.54	0.57	0.60
18	128	0.33	0.35	0.38	0.42	0.46	0.50	0.55	0.58	0.60
19	105	0.33	0.35	0.38	0.42	0.46	0.50	0.55	0.58	0.60

Age, and gender specific smoothed waist-to-height ratio percentiles for Yemeni children and adolescents aged 6-19 years (*n* = 3114).

Table 5 Logistic regression of factors associated to different definitions of central obesity

Variables	WHtR ≥ 0.5 OR (95%CI)	WC ≥ 90th OR (95%CI)	WHtR ≥ 0.5/WC ≥ 90th OR (95%CI)
Age (yr)	0.98 (0.94-1.02)	0.95 (0.90-1.00)	0.96 (0.90-1.01)
Gender (girls *vs* boys)	1.55 (1.29-1.89)	0.97 (0.77-1.22)	1.22 (0.94-1.57)
Location (rural *vs* urban)	0.66 (0.54-0.79)	0.52 (0.41-0.66)	0.52 (0.40-0.67)
Education (yr)	0.99 (0.95-1.03)	1.08 (1.02-1.14)	1.05 (0.99-1.11)
Sedentary (*vs* active)	1.42 (1.14-1.75)	1.52 (1.17-1.98)	1.65 (1.24-2.19)

Logistic regression of factors associated to different definitions of central obesity: waist-to-height ratio (WHtR) ≥ 0.5, waist circumference (WC) ≥ 90th percentile, and the combination of WHtR ≥ 0.5, and WC ≥ 90th percentile. Data are reported as adjusted odd ratio (OR) with 95%CI.

Prevalence of subjects with WC ≥ 90th percentile, WHtR greater than 0.5, and of those fulfilling both criteria were 10.9%, 18.3%, and 8.6% in the overall population. More precisely 10.8% of girls (95%CI: 9.2-12.3), 11.0% of boys (95%CI: 9.4-12.5) had WC ≥ 90th percentile; 21.7% of girls (95%CI: 19.6-23.7), 14.9% of boys (95%CI: 13.1-16.6) had WHtR ≥ 0.5; 9.5% of girls (8.0-11.0), 7.8% of boys (95%CI: 6.4-9.1) had both WC ≥ 90th percentile and WHtR ≥ 0.5. Characteristics more frequently associated with reported criteria for central obesity were investigated at multivariate logistic regression, main results being reported in Table 5. In particular WC ≥ 90th percentiles and WHtR ≥ 0.5 were less prevalent in rural than in urban areas (OR = 0.52, 95%CI: 0.41-0.67 and 0.66, 0.54-0.79 respectively), being more prevalent in children with sedentary lifestyle (OR = 1.52, 95%CI: 1.17-1.98 and 1.42, 1.14-1.75 respectively). Differences by gender were evident only when considering a cut-off which is independent from the Yemeni population (WHtR ≥ 0.5). A minor association was observed between years of school education and WC ≥ 90th.

DISCUSSION

This study, to our knowledge provides the first gender- and age-specific WC, WHR and WHtR percentiles for Yemeni children 6 to 19 years of age. As observed in other studies WC increases with age, boys having higher WC

Table 6 Comparison between waist-to-height ratio 10th, 50th and 90th percentiles for Yemeni, Pakistani (*n* = 12), and Norwegian (*n* = 22) boys and girls

Age	10th percentiles			50th percentiles			90th percentiles		
	Y	P	N	Y	P	N	Y	P	N
Boys									
6	0.4	0.41	0.41	0.47	0.46	0.45	0.55	0.52	0.49
7	0.39	0.4	0.4	0.46	0.45	0.44	0.54	0.52	0.48
8	0.38	0.4	0.39	0.45	0.45	0.43	0.53	0.52	0.48
9	0.38	0.39	0.38	0.45	0.45	0.42	0.53	0.52	0.48
10	0.37	0.39	0.38	0.44	0.44	0.42	0.52	0.52	0.48
11	0.37	0.38	0.37	0.44	0.44	0.42	0.51	0.52	0.48
12	0.36	0.38	0.37	0.43	0.44	0.41	0.51	0.52	0.47
13	0.36	-	0.36	0.43	-	0.41	0.5	-	0.47
14	0.36	-	0.36	0.43	-	0.41	0.5	-	0.46
15	0.36	-	0.37	0.43	-	0.41	0.5	-	0.46
16	0.36	-	0.37	0.43	-	0.41	0.5	-	0.47
17	0.36	-	0.38	0.43	-	0.42	0.5	-	0.47
18	0.36	-	0.38	0.43	-	0.43	0.5	-	0.48
19	0.36	-	-	0.43	-	-	0.51	-	-
Girls									
6	0.38	0.41	0.42	0.47	0.45	0.45	0.55	0.51	0.49
7	0.38	0.4	0.4	0.46	0.45	0.43	0.54	0.52	0.49
8	0.37	0.4	0.4	0.45	0.45	0.43	0.53	0.52	0.48
9	0.36	0.4	0.39	0.44	0.45	0.42	0.53	0.53	0.48
10	0.36	0.39	0.39	0.44	0.44	0.41	0.52	0.53	0.47
11	0.36	0.38	0.38	0.44	0.44	0.41	0.52	0.53	0.46
12	0.36	0.37	0.38	0.44	0.43	0.4	0.52	0.52	0.46
13	0.36	-	0.37	0.44	-	0.4	0.52	-	0.45
14	0.36	-	0.37	0.44	-	0.4	0.53	-	0.45
15	0.37	-	0.37	0.45	-	0.4	0.53	-	0.45
16	0.37	-	0.38	0.45	-	0.4	0.54	-	0.45
17	0.37	-	0.38	0.45	-	0.41	0.54	-	0.46
18	0.38	-	0.39	0.46	-	0.42	0.55	-	0.47
19	0.38	-	-	0.46	-	-	0.55	-	-

Comparison between waist-to-height ratio 10th, 50th and 90th percentiles for Yemeni (Y), Pakistani (P), and Norwegian (N) boys and girls.

than girls at childhood[3,4,12,20-24]. In Yemen central obesity is more prevalent in adult women than in men[13] and, according to the present findings, this difference originates at early adolescence when WC starts to be higher in girls than in boys. A WC level of action of 80 cm has been proposed for adult women[25]. The 90th percentile of WC in Yemeni girls crosses this limit already at the age of 16 years. Conversely boys never reach the WC level of action of 94 cm proposed for adult men[25]. According to the present findings the prevalence of central obesity (WC ≥ 90th percentile, or WHtR ≥ 0.5, or both WHtR ≥ 0.5 and WC ≥ 90th percentile) was higher in urban than in rural settings, and in subjects with sedentary than active lifestyle. Years of school education, which can be considered an index of census, was predictor of having a WC ≥ 90th. Cut off values of WC have to be based on percentiles to compensate for variation in child development. WHtR was more recently proposed to overcome this limit and to offer the simplest cut-off value for screening central obesity in the clinical practice: "keep your WC to less than half your height"[9]. Also when considering WHtR, the prevalence of central obesity in Yemen was higher among girls than boys, differences being evident after early adolescence. Similarly after early

adolescence WHR in boys had a plateau while in girls it continued to decrease. The clear identification of a high risk subgroup is important. According to the present survey girls at early adolescence, living in urban areas, educated, with sedentary lifestyle have to be considered as a target for future educational programs aimed at limiting central obesity in Yemeni adult women. Furthermore central obesity in children was reported to be an independent predictor of insulin resistance, lipid levels, and high blood pressure[6,26]. As suggested by the international diabetes foundation[27] outcome studies investigating future metabolic syndrome, diabetes and cardiovascular disease in developing countries are required.

During the last decades, age and sex-specific WC percentiles have been obtained in different western, and MEC countries. In Yemen early adolescence is the starting point for the increase of the 90th percentile of WC in girls differently from what observed in Norway[23] where at this age the same increase was reported to occur in boys (Figure 2). A low physical activity for girls living in Yemen might be considered. This age related change was however not reported in Turkish girls[21]. The differences among females in Yemen may be related to other factors such as weather, absence of sidewalks and parks, and cul-
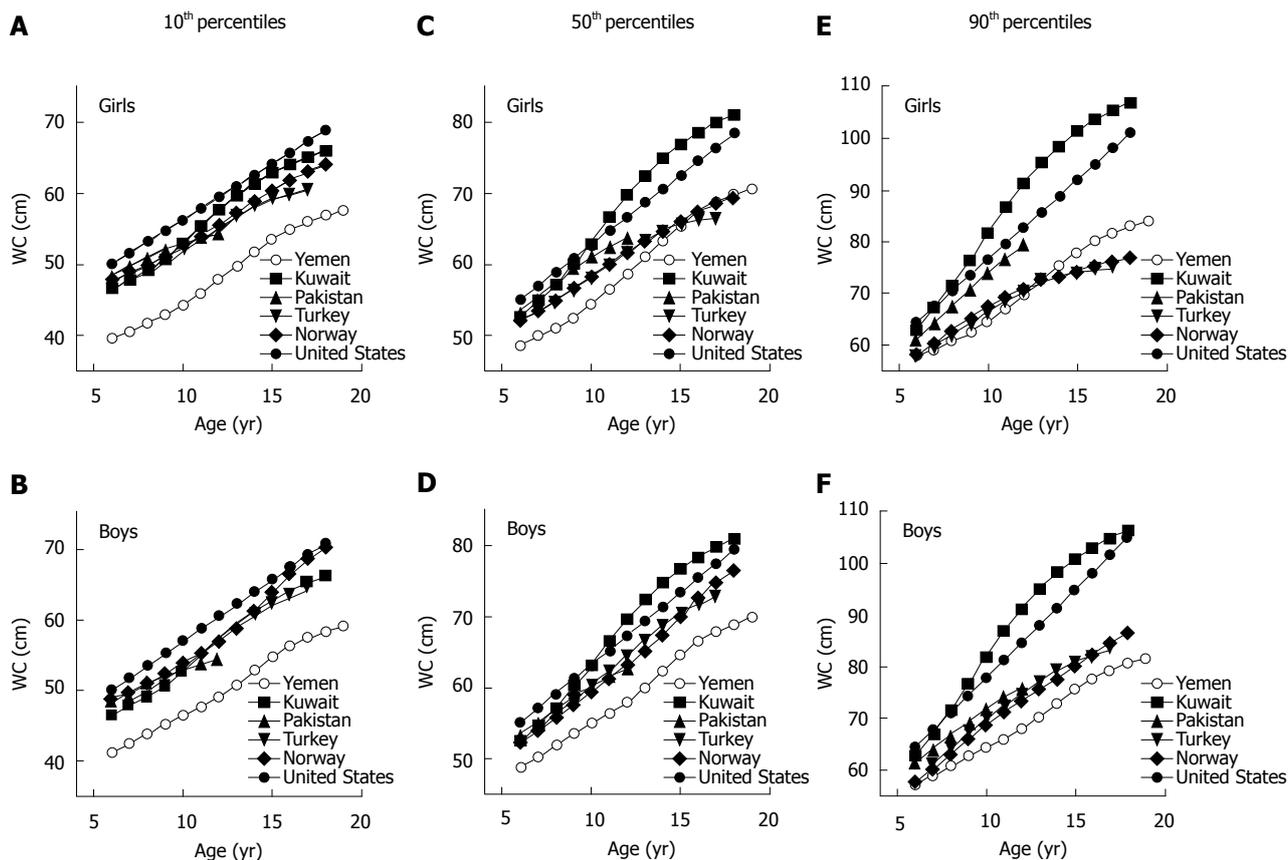
Figure 2 Comparison of waist circumference 10th, 50th, and 90th percentile curve. Waist circumference (WC) 10th, 50th, and 90th percentile curves for Yemeni, Kuwaiti[3], Pakistani[12], Turkish[20], United States[21], and Norwegian[22] girls (A, C, E) and boys (B, D, F).

ture such as attitudes of males towards women walking for leisure. Other cultural aspects, such as the adoption of western aesthetic values modifying the traditional consideration of plumpness as an index of beauty might also play a role[28]. In Kuwait[3] early adolescence is the starting point for central obesity both in girls and in boys probably because of the high income of the country (Figure 2). Comparison with data obtained in United States[22] might be more complex due to the composite ethnicity of participants.

When considering WHtR data from different countries, the average height in the country has to be considered. In Yemen the 90th percentile values were comparable to those found in Pakistan[12] although significantly higher than those found in Norway[23] (Table 6). More precisely, when considering this index in developing countries the possible contribution of malnutrition on height should be taken into account. According to the present findings more than 50% of Yemeni girls and boys aged 6 to 18 years have WC values below those of the United States 10th percentiles[22] (Figure 2). Even when considering subjects living in the MEC, more than 25% of Yemeni children have WC values below those of the 10th percentiles measured in Kuwait[3] and Pakistan[12] (Figure 2).

There are limitations and strengths in this study. A first limitation is the unequal number of subjects in the

28 age strata. The population sample in the HYDY study was stratified by decades of age rather than by years of age. However discrepancy between age groups is limited and the less numerous group included an acceptable number of subjects. Secondly, the Tanner stage was not assessed. A third limitation is that in the HYDY study biochemical investigations on blood (glucose, cholesterol, and triglycerides) were not assessed in subjects aged less than 14 years. This decision, which precluded us drawing conclusions about the associations with obesity indices, was taken considering the child's perceptions and fears of the procedure of blood collection. The strengths of our study are (1) the novelty in Yemeni children; (2) the large sample size of children studied over different areas of the country with a constantly reproducible study procedure; and finally (3) the door to door approach adopted in the sampling procedure. We decided to adopt a door-to-door procedure rather than performing a school-based study because in low income countries not all children may have access to school. Considering the very high response rate we can exclude the presence of relevant selection bias. Our data provide the first description of the percentile distribution, derived from a large nationally representative sample of 6-19 year old children, of WC, WHR and WHtR in urban and rural Yemeni population.

In conclusion, HYDY data show a large discrepancy of central obesity prevalence among Yemeni children

probably because the country is still in an early stage of the nutritional transition and there are population segments which are affected by malnutrition[29]. Prevalence of central obesity in Yemeni children is low, being associated with urbanization and sedentary lifestyle. WC, WHtR and WHR changed similarly in girls and boys until early adolescence. Thereafter, differently from what observed in Western countries, WC, WHtR and WHR changes increased more in girls than in boys. The importance of changes observed at early adolescence among girls living in urban areas, might be relevant for future National programs aimed at promoting physical activity and control of central obesity in women.

ACKNOWLEDGMENTS

COMMENTS

Background

Children obesity also in the Middle Crescent Area is a matter of growing concern. Childhood central obesity is assessed by measuring waist circumference (WC). However, ethnicity and environmental differences might influence body proportions, and the usefulness of national references to control for variations between populations was suggested.

Research frontiers

In children WC has to be expressed relatively to their sex and age peers. Differently from WC and waist to hip ratio (WHR) a recently proposed index, waist-to-height ratio (WHtR), is only weakly associated with age and gender, and different studies are suggesting a single cut-off value for defining central obesity (WHtR $\geqslant$ 0.5).

Innovations and breakthroughs

Prevalence of central obesity in Yemeni children is low, being associated with urbanization and sedentary lifestyle. WC, WHtR and WHR changed similarly in girls and boys until early adolescence. Thereafter, differently from what observed in Western countries, WC, WHtR and WHR changes increased more in girls than in boys.

Applications

The importance of the changes observed at early adolescence among sedentary girls living in urban areas, might be relevant for future National program aimed at promoting physical activity and control of central obesity in women.

Terminology

Central obesity measures the abdominal obesity using parameters such as WC, WHR and WHtR, and seems to be better correlated with cardiovascular disease and mortality than general obesity measured using the body mass index.

Peer review

The authors provided the first central obesity percentile curves of WC, WHtR and WHR for Yemeni children aged six to nineteen years. As expected the prevalence of central obesity in Yemeni children is low, being associated with urbanization and sedentary lifestyle. The study showed also that WC, WHtR and WHR values changed similarly in girls and boys until early adolescence. However, thereafter, differently from what observed in Western countries, these changes increased more in girls than in boys indicating that this is a crucial moment in the arising of adult women central obesity.

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BRIEF ARTICLE

Blood cellular mutant LXR-α protein stability governs initiation of coronary heart disease

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Abstract

AIM: To investigate the role of [breast and ovarian cancer susceptibility 1 (BRCA1)-associated RING domain 1 (BARD1)]/BRCA1 E3-ubiquitin ligase complex in governing the stability of mutant liver X receptor-α (LXR-α) protein in coronary heart disease (CHD) subjects.

METHODS: The expression analysis of various genes was carried out by quantitative real time polymerase chain reaction and western blotting within blood mononuclear cells of human CHD subjects at various stages of coronary occlusion and their corresponding normal healthy counterparts. Immunoprecipitation experiments were performed to establish protein interactions between LXR-α and BARD1. Peripheral blood mononuclear cells were cultured and exposed to Vitamin D_3 and Cisplatin to validate the degradation of mutant LXR-α protein in CHD subjects by BARD1/BRCA1 complex.

RESULTS: The expression of mutant LXR-α protein in CHD subjects was found to decrease gradually with the severity of coronary occlusion exhibiting a strong nega-tive correlation, $r = -0.975$ at $P < 0.001$. Further, the expression of BARD1 and BRCA1 also increased with the disease severity, $r = 0.895$ and 0.873 respectively ($P < 0.001$). Immunoprecipitation studies established that BARD1/BRCA1 complex degrades mutant LXR-α *via* ubiquitination. The absence of functional LXR-α protein resulted in increased expression of inflammatory cytokines such as interleukin (IL)-6, IL-8 and interferon-γ and decreased expression of ABCA1 (ATP-binding cassette A1) ($r = 0.932, 0.949, 0.918$ and -0.902 with respect to Gensini score; $P < 0.001$). Additionally, cell culture experiments proved that Vitamin D_3 could prevent the degradation of mutant LXR-α and restore its functional activity to some extent.

CONCLUSION: Mutant LXR-α protein in CHD subjects is degraded by BARD1/BRCA1 complex and Vitamin D_3 can rescue and restore its function.

Core tip: The present study proposes that the stability of mutant liver X receptor-α (LXR-α) protein in blood mononuclear cells of human coronary heart disease (CHD) subjects is governed by its ubiquitination dependent degradation by [breast and ovarian cancer susceptibility 1 (BRCA1)-associated RING domain1 (BARD1)]/BRCA1 E3 ubiquitin ligase complex. Additionally, BARD1/BRCA1 expression shows an increasing trend with respect to severity of coronary occlusion. This degradation is rescued to some extent by the ability of Vitamin D_3 to bind mutant LXR-α protein thus providing warranted evidence that dietary supplementation of Vitamin D_3 in such subjects may be exploited therapeutically.

INTRODUCTION

Liver X receptor-α (LXR-α) is a ligand activated transcription factor that plays a pivotal athero-protective role by regulating genes involved in lipid metabolism and reverse cholesterol transport [*e.g.,* ATP-binding cassette A1 (ABCA1), ABCG1, Apolipoprotein E] and by inhibiting nuclear factor kappa-B mediated inflammatory responses and proliferation of vascular smooth muscle cells[1-7]. Several *in vitro* and *in vivo* studies in animal models of atherosclerosis have shown that LXR-α agonists can attenuate lesion progression and also lead to regression of an already established plaque[8-14]. The observation that statins as well as vitamin C, both have an inherent ability to upregulate LXR-α[15] further underline its importance. Findings from our laboratory have demonstrated that both normolipidemic and hyperlipidemic human coronary heart disease (CHD) subjects have significantly higher expression of blood cellular LXR-α as compared to the corresponding controls[16]. This is in sharp contrast with the observed protective role of LXR-α. Paradoxically there is an increased expression of LXR-α with the corresponding increase in severity of coronary occlusion[17]. Further work has partly resolved this paradox by revealing three critical mutations in its ligand binding domain involving Asp324, Pro327 and Arg328 which compromises its ability to interact and get activated by its natural ligands[17]. But to fully understand this apparent paradox it is imperative to explore the stability and expression of this mutant LXR-α protein. Recently Kim *et al*[18] have shown that ligand free LXR-α interacts with an E3 ubiquitin ligase heterodimer complex of breast and ovarian cancer susceptibility 1 (BRCA1) and BRCA1-associated RING domain 1 (BARD1), and is subsequently degraded. Since mutant LXR-α in CHD patients is also unable to bind to its ligand, the present study was addressed to explore the role of BARD1/BRCA1 (breast and ovarian cancer susceptibility 1) complex in governing the stability of mutant LXR-α in these subjects.

MATERIALS AND METHODS

Subject selection

Freshly diagnosed male subjects (*n* = 40) with confirmed coronary heart disease (diagnosed for the first time upon coronary angiography) and control subjects (*n* = 10, age and gender matched with angiographically proven normal coronary arteries) were selected for the study from the outpatient clinic of Department of Cardiology, Postgraduate Institute of Medical Education and Research, Chandigarh, with their prior informed consent. Females,

diabetics, individuals suffering from cardiomyopathies, any infectious disease, systemic illness, serious organ disease, serious psychiatric illness, chronic alcohol abuse and anti-convulsant therapy were excluded from this study. Further, subjects taking any drug namely lipid lowering drugs or antihypertensive or anti-diabetic drugs (which could interfere with the study) were also excluded from the study. The study was approved by institute's ethical committee and conforms to the principles outlined in the declaration of Helsinki[19]. The laboratory variables of the patients are given in Table 1. The severity of coronary occlusion in CHD patients was measured by Gensini Score[20] and the subjects were categorized into five groups as described in Table 2.

Gene expression analysis and immunoprecipitation

Peripheral blood mononuclear cells (PBMCs) were isolated from 5 mL of heparinized blood using Ficoll-Hypaque density gradient method[21]. RNA was isolated using standard guanidinium thiocynate method[22]. The extracted RNA was reverse transcribed using Revert Aid™ first strand synthe 2.3). β-actin (Sigma Aldrich) was taken as an invariant control for both transcriptional and translational expression studies.

Immunoprecipitation and western blotting

The cells were lysed with non-denaturing lysis buffer [20 mmol/L Tris HCl (pH = 8), 137 mmol/L NaCl, 10% glycerol, 1% Triton X-100 and 2 mmol/L EDTA (Ethylene Diamine Tetraacetic Acid)] containing protease inhibitor cocktail (Sigma Aldrich). For immunoprecipitation, equal amounts of total cell extracts from CHD subjects (GS = 10-20) and healthy controls were incubated with LXR-α antibody, and the immunoprecipitated complexes were collected using protein-G sepharose beads (Sigma Aldrich). Further, pellets were washed 3 times with 1 mL non-denaturing lysis buffer, protein eluted in sample buffer (0.125 mol/L Tris, 2%SDS, 5% 2-mercaptoethanol) and subjected to western blotting. For direct western blotting, protein extracts were electrophoresed by SDS-PAGE (125 mL/L, Sodium dodecyl sulphate-poly-acrylamide gel electrophoresis), transferred to nitrocellulose membranes and probed using specific antibodies against LXR-α, BARD1, BRCA1 and β-actin. β-actin was used as an invariant control. Each band on the immunoblot was scanned densitometrically using Scion Image Analysis software. The results were expressed as intensity ratio of target protein to β-actin protein taken as arbitrary unit (AU).

Cell culture experiments

PBMCs from healthy subjects and CHD subjects were seeded in RPMI 1640 medium containing 10% FCS at 37 ℃ in 5%CO$_2$ atmosphere and exposed to Vitamin D$_3$ (1 μmol/L) or Cisplatin (30 μmol/L) for 36 h. After the incubation period, cells were harvested and processed for RNA and protein isolation by employing standard methods[22,23].

Table 1 Laboratory variables of subjects employed in the study

	Control (*n* = 10)	CHD subjects (*n* = 40)	*P* value
Age (yr)	51 ± 8	53 ± 4	NS
Sex	M	M	NA
TC (mg/dL)	179.5 ± 4.7	182.0 ± 3.6	NS
TG (mg/dL)	156.2 ± 6.3	167.1 ± 8.7	NS
HDL-C (mg/dL)	49.8 ± 1.3	42.6 ± 3.9	NS
LDL-C (mg/dL)	93.24 ± 5.67	102.0 ± 5.3	NS
Serum CRP (mg/dL)	0.63 ± 0.32	1.10 ± 0.51	NS
Serum 25 (OH) Vitamin D_3 (ng/mL)	16 ± 2.3	7.3 ± 3.2	S

CHD: Coronary heart disease; TC: Total cholesterol; TG: Triglyceride; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; M: Male; NS: Not significant; NA: Not applicable; S: Significant; CRP: C-reactive protein.

Table 2 Subject groups formed on the basis of severity of coronary occlusion as measured by gensini score

Group	Gensini score	No. of subjects
Control	0	10
Group I	1-10	10
Group II	11-20	10
Group III	21-30	10
Group IV	> 30	10

Statistical analysis

Statistical analyses were performed by SPSS Windows version 19. Correlation between severity of CHD and expression of various genes was evaluated by Spearman rank-correlation coefficient, *P* value < 0.01 taken as statistically significant. Data were presented as mean ± SD. Statistical comparisons between multiple groups were made by ANOVA (One way Analysis of Variance). *P* value < 0.05 was considered statistically significant.

RESULTS

As reported earlier[17], we observed similar pattern of 3 critical mutations in the ligand binding domain and increased transcriptional expression of LXR-α with respect to increasing coronary occlusion (data not shown) in all subjects employed in this study. In contrast, LXR-α protein expression was found to decrease with increasing severity of coronary occlusion and exhibited a strong negative correlation with gensini score (Figure 1A and B). Correspondingly, the expression of ubiquitin ligase heterodimer BARD1/BRCA1 increased with respect to increasing severity of coronary atherosclerosis (Figures 1C and 2E), showing a strong positive correlation with gensini score (Figure 3A and B). Consequently, the expression of inflammatory genes such as interleukin (IL)-6, IL-8 and interferon (IFN)-γ was found to increase and ABCA1, a direct target of LXR-α responsible for cholesterol efflux, decreased with increasing severity of disease (Figures 1D and 3C-F). Our previous studies have proved that Vitamin D_3 can bind to mutant LXR-α ligand

Table 3 Primers sequences employed for transcriptional expression analysis of various genes

No.	Gene	Primer pair
1	*ABCA1*	Forward: 5'-ACCTCGGGCACCGCCTACAT-3'
		Reverse: 5'-CGAAGGCCCGCCTGTTTCGT-3'
2	*BARD1*	Forward: 5'-GCCAAAGCTGTTTGATGGAT-3'
		Reverse: 5'-CGAACCCTCTCTGGGTGATA-3'
3	*BRCA1*	Forward: 5'-TAGGGCTGGAAGCACAGAGT-3'
		Reverse: 5'-AATTTCCTCCCCAATGTTCC-3'
4	*IFN-γ*	Forward: 5'-CGTTTTGGGTTCTCTTGGCTGTT-3'
		Reverse: 5'-CTCCTTTTTCGCTTCCCTGTTTT-3'
5	*IL-6*	Forward: 5'-TGGGCACAGAACTTATGTTG-3'
		Reverse: 5'-TTGAGGTAAGCCTACACTTTCC-3'
6	*IL-8*	Forward: 5'-ATGACTTCCAAGCTGGCCGTGGCT-3'
		Reverse: 5'-TCTCAGCCCTCTTCAAAAACTTCT-3'
7	*β-actin*	Forward: 5'-CATGTACGTTGCTATCCAGGC-3'
		Reverse: 5'-CTCCTTAATGTCACGCACGAT-3'

binding domain[23]. So, in order to confirm that inability of LXR-α protein to bind to its natural ligands is responsible for its degradation, we exposed patient cells to Vitamin D_3 (1 μmol/L). The significant increase in the expression of LXR-α protein in these patient cells unambiguously revealed that Vitamin D_3 bound LXR-α is resistant to degradation by BARD1/BRCA1 complex (Figure 2A). Further, though the expression of BARD1/BRCA1 complex in patient PBMCs decreased upon Vitamin D_3 exposure, the difference was not significant as compared to patient cells alone (Figure 2B). Also, the significantly increased expression of ABCA1 in patient cells exposed to Vitamin D_3 further validated our previous findings[23] that Vitamin D_3 is able to restore the functional activity of mutant LXR-α to some extent (Figure 2B). As expected, Vitamin D_3 treatment did not have any significant effect on LXR-α protein expression in normal cells which harbor wild type LXR-α (Figure 2A). To ascertain the role of BARD1/BRCA1 dependent ubiquitination in the degradation of mutant ligand-free LXR-α protein, we examined their interaction in patient PBMCs by co-immunoprecipitation assays. CHD subjects with GS = 10-20 were selected as per statistical analysis since such subjects have appreciable expression of both LXR-α and BARD1/BRCA1 complex. Total cell lysates from PBMCs derived from CHD subjects and normal healthy individuals were immune-precipitated with anti LXR-α antibody and immune-blotted with anti-BARD1 antibody. The results revealed that the mutant LXR-α protein strongly associated with BARD1 in CHD subjects as compared to that in healthy controls (Figure 2E). Additionally, direct western blotting also demonstrated the increased expression of BARD1 and BRCA1 protein in PBMCs of CHD subjects as compared to their healthy counterparts (Figure 2E). To further precipitate the role of BARD1/BRCA1 complex in degradation of ligand-free LXR-α in CHD subjects, patient PBMCs were exposed *in vitro* to cisplatin (30 μmol/L) which has recently been shown to inhibit the E3 ubiquitin ligase activity of BARD1/BRCA1 heterodimer[24]. The observed increase in the expression of LXR-α protein in patient cells treated with cisplatin in the absence of Vitamin D_3 undoubtedly established the role of BARD1/BRCA1
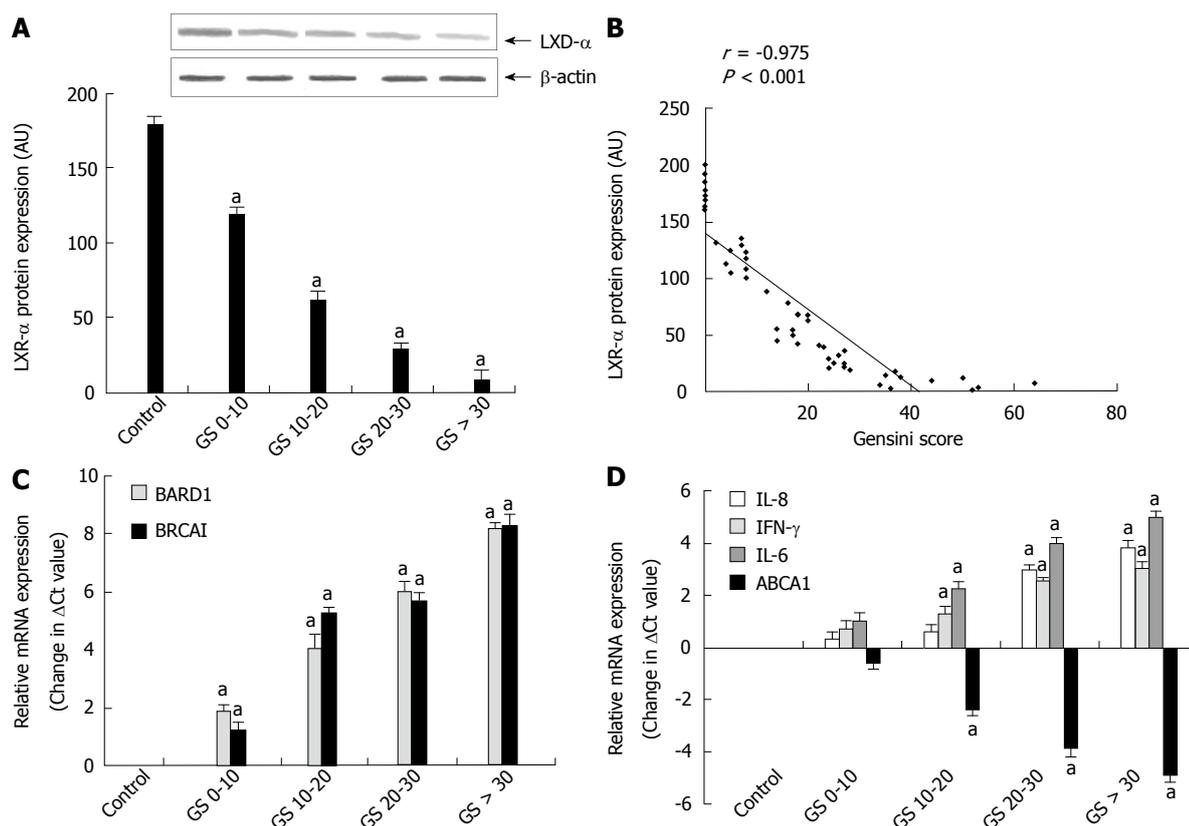
Figure 1 Gene expression analysis of various genes with respect to gensini score. A: Mean values of liver X receptor-α (LXR-α) protein levels in peripheral blood mononuclear cells (PBMCs) isolated from coronary heart disease (CHD) subjects and healthy controls with respect to increasing gensini score (reflecting the severity of coronary occlusion). Each bar represents mean ± SD for 10 different individuals in each group. The means were compared with one way ANOVA and [a]$P < 0.05$ vs control group; B: Statistical correlation between translational expression of mutant LXR-α and gensini score within PBMCs. Values of r show Spearman rank correlation coefficient and $P < 0.01$ was considered statistically significant; C, D: Mean values of [breast and ovarian cancer susceptibility1 (BRCA1)-associated RING domain 1] (BARD1) and BRCA1 (C) and interleukin (IL)-8, interferon (IFN)-γ, IL-6, and ATP-binding cassette A1 (ABCA1) (D) mRNA expression (change in ΔCt values) in PBMCs derived from CHD patients and healthy controls with respect to increasing Gensini Score. Each bar represents mean ± SD for 10 different individuals in each group. The means were compared with one way ANOVA and [a]$P < 0.05$ vs control group.

complex in the degradation of mutant LXR-α (Figure 2C). Despite the increased expression of LXR-α protein upon cisplatin exposure, due to the absence of any ligand to activate mutant LXR-α, there was no effect on the expression of ABCA1 in both normal and patient cells (Figure 2D). BARD1/BRCA1 inhibition also causes a non-significant increase in LXR-α expression in normal cells where wild type ligand free LXR-α might escape degradation (Figure 2C).

DISCUSSION

An alarming increase in CHD cases all over the world warrants molecular micro-dissection of pathways involved in the initiation and progression of CHD. LXR-α has been widely recognized as a master gene that plays a crucial role in cholesterol homeostasis, lipid peroxidation and inflammation responsible for the initiation of CHD and its clinical implications[1-7]. Apart from the observed protective effects of LXR-α agonists in the various cellular and animal model systems[8-14], the importance of LXR-α in pathogenesis of CHD is further highlighted by the studies from our laboratory which showed that both statins (drug of choice for CHD) and vitamin C have an inherent capacity to upregulate LXR-α expression[15] and

also that human CHD subjects (with or without hyperlipidemia) have conspicuously higher blood cellular LXR-α mRNA expression as compared to their normal healthy counterparts[16]. However, synthetic agonists for the LXR-α activation designed as therapeutic agents for the regression of coronary atherosclerosis did not meet the expected success. This anomaly got further compounded by the observation in CHD patients who exhibited increasing transcriptional expression of LXR-α, within their PBMCs, with corresponding increase in severity of coronary occlusion[17]. This paradox was partly resolved by our earlier studies which showed that ligand binding domain of LXR-α protein in CHD subjects harbors a unique genetic aberration (involving Asp324, Pro327 and Arg328) which prevents its physiological ligands from binding and activating the LXR-α protein, thus rendering it non-functional[17]. Further, this mutant *LXR-α* gene product was shown to acquire by default affinity for Vitamin D3 which can restore the function of mutated LXR-α protein to some extent[23].

The present study is based on the fact that ligand free LXR-α gets degraded by BARD1/BRCA1 heterodimer[18]. Since mutant LXR-α in CHD subjects is also unable to bind its natural physiological ligands, we at-
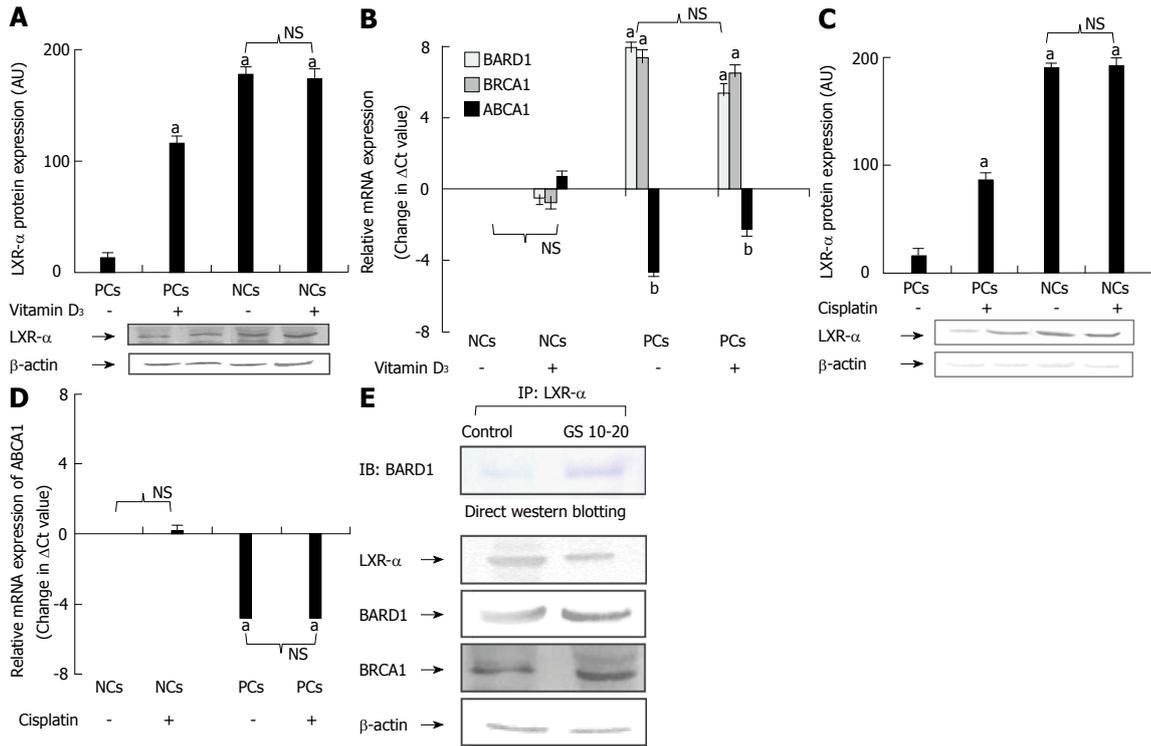
Figure 2 Expression analysis of various genes upon exposure to Vitamin D₃ and Cisplatin in peripheral blood mononuclear cells of coronary heart diseasesubjects and their healthy counterparts. A: Protein expression of liver X receptor-α (LXR-α) within peripheral blood mononuclear cells (PBMCs), isolated from coronary heart disease (CHD) subjects (GS > 30) as well as normal healthy controls, exposed to culture medium enriched with and without Vitamin D₃ (1 μmol/L); B: Relative mRNA expression (change in ΔCt values) of [breast and ovarian cancer susceptibility 1 (BRCA1)-associated RING domain 1] (BARD1), BRCA1 and ATP-binding cassette A1 (ABCA1) upon Vitamin D₃ exposure in normal and patient cells; C: Protein expression of LXR-α within PBMCs, isolated from CHD subjects (GS > 30) as well as normal healthy controls, exposed to culture medium enriched with and without Cisplatin (30 μmol/L); D: Relative mRNA expression (change in ΔCt values) of ABCA1 upon Cisplatin exposure in normal and patient cells. Each bar represents mean ± SD for the combined results of three independent experiments from different individuals in triplicate. The means were compared with one way ANOVA and [a]P < 0.05 *vs* control group (A-D); E: Total cell lysates from PBMCs derived from CHD subjects and normal healthy individuals were immunoprecipitated with anti LXR-α antibody and immunoblotted with anti-BARD1 antibody. The direct western blotting shows the expression of LXR-α, BARD1, BRCA1 and β-actin (Sigma Aldrich) in PBMCs of CHD subjects and normal healthy controls. The experiments were repeated three times from different individuals and representative results are shown. IB: Immunoblotting; IP: Immunoprecipitation; NC: Normal cells; NS: Non-significant; PC: Patient cells.
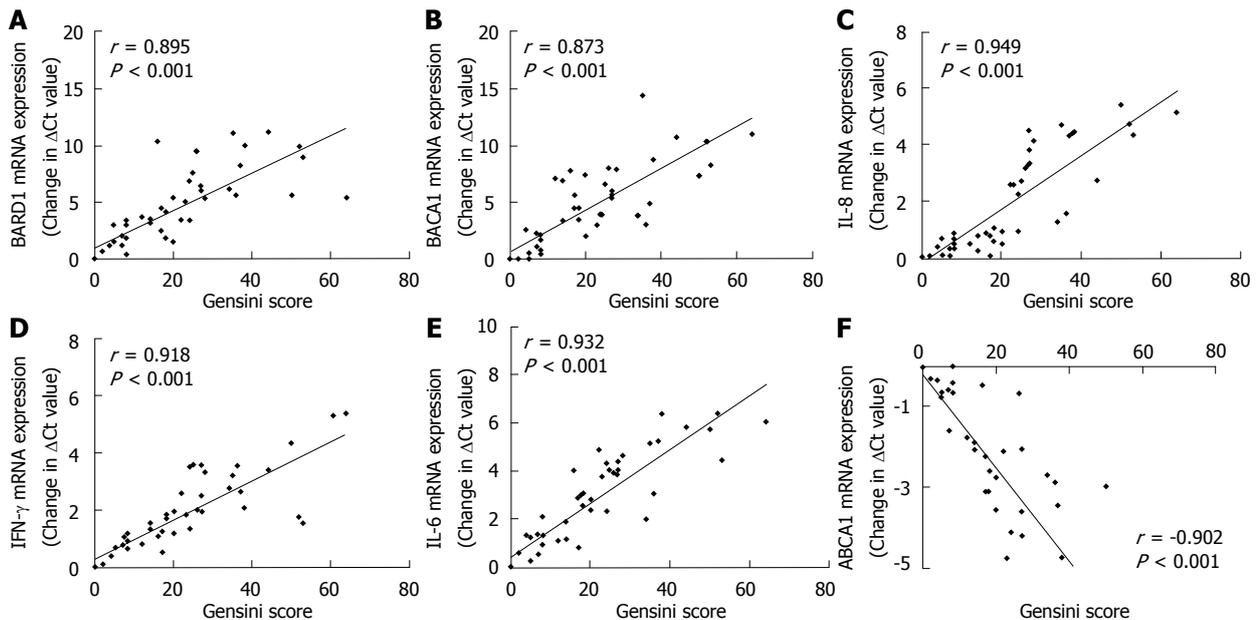
Figure 3 Correlation of mRNA expression of various genes with the gensini score. Statistical correlation between transcriptional expression of [breast and ovarian cancer susceptibility1 (BRCA1)-associated RING domain1] (BARD1) (A), BRCA1 (B), interleukin (IL)-8 (C), interferon (IFN)-γ (D), IL-6 (E) and ATP-binding cassette A1 (ABCA1) (F) and gensini score within peripheral blood mononuclear cells derived from CHD subjects and normal healthy controls. Values of r show Spearman rank correlation coefficient.
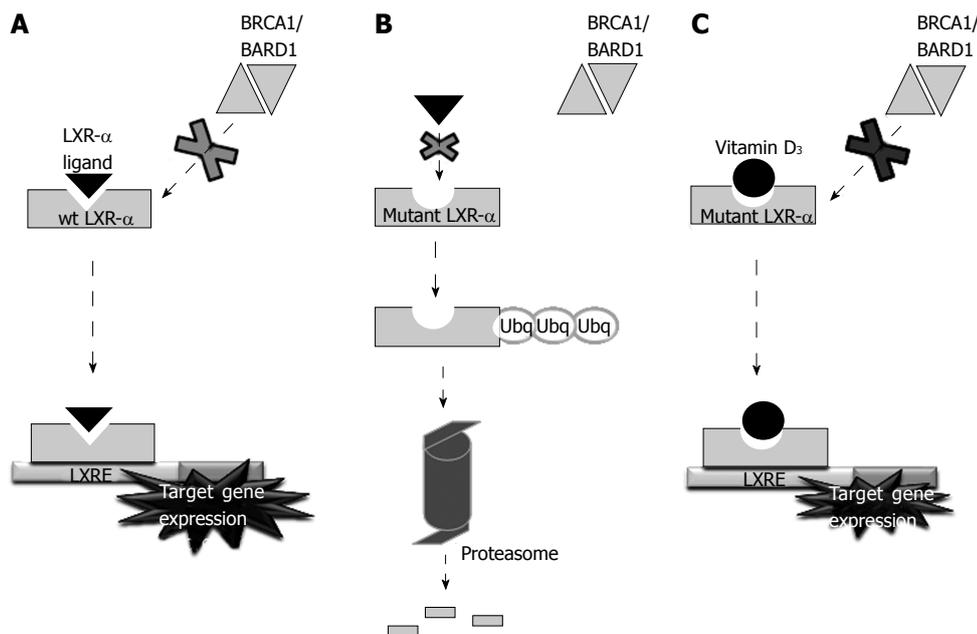
Figure 4 Schematic diagram representing the mechanism of action of liver X receptor-α. A: Wild type functional liver X receptor-α (LXR-α) in healthy controls; B: Mutant non-functional LXR-α in coronary heart disease patients; C: Mutated but functional (to some extent) LXR-α when rescued by Vitamin D₃. BRCA1: Breast and ovarian cancer susceptibility 1; BARD1: BRCA1-associated RING domain 1; LXRE: liver X receptor.

tempted to explore whether this heterodimeric complex plays any role in the decrease of LXR-α protein levels in such subjects. We performed certain preliminary experiments which showed strong correlation in the degradation of LXR-α and corresponding increase of BARD1/BRCA1 levels along with increasing disease severity (Figures 1A-C, 3A and B). This degradation of LXR-α protein also explains the increasing expression of inflammatory cytokines IFN-γ, IL-6 and IL-8 and decreasing expression of ABCA1 (responsible for cholesterol efflux particularly from macrophages) with increasing coronary occlusion (Figures 1D and 3C-F), which would ultimately result in increased vascular inflammation and foam cell formation. Thus, though the expression of LXR-α increases with the severity of the disease at the transcriptional level[17] (data not shown for subjects employed in present study), there is absence of functional LXR-α protein in CHD subjects (Figure 1A and B). To confirm the interaction between the two proteins, immunoprecipitation studies were performed which showed a strong association between mutant LXR-α and BARD1 in CHD subjects as compared to the normal healthy counterparts. A weak interaction observed between the two proteins in the healthy subjects could be explained by the presence of any ligand free wild type LXR-α which could also be bound and subsequently ubiquitinated by BARD1 (Figure 2E). To further precipitate the role of BARD1/BRCA1 in degradation of LXR-α *via* ubiquitination in CHD subjects, patient PBMCs were exposed to cisplatin (inhibitor of E3 ubiquitin ligase activity of BARD1/BRCA1[24]) *in vitro*. Though we observed an appreciable increase in LXR-α protein levels in PBMCs derived from CHD subjects upon cisplatin exposure, but it was still lower as compared to that in normal cells (Figure 2C). This may be explained by the fact that we used 30 μmol/L concentration of cisplatin as compared to 60 μmol/L used by Atipairin *et al*[25] (which reduced the E3 ubiquitin ligase activity of the BARD1/BRCA1 complex by half) which would have been toxic to the cells as in our case. Further since there is no ligand to modulate LXR-α transcriptional activity, the expression of ABCA1 is not affected upon cisplatin treatment (Figure 2D). In the previous study we have shown that Vitamin D₃ has an inherent capacity to activate mutant LXR-α in a dose dependent fashion[23]. Hence, it becomes imperative to examine whether or not the Vitamin D₃ bound to mutant LXR-α inhibits its degradation by BARD1/BRCA1. The results clearly showed that mutant LXR-α bound to Vitamin D₃ is rescued from degradation and not only brings the protein level of LXR-α close to that of normal healthy control (Figure 2A) but also activates it to some extent as can be seen by the increased expression of ABCA1 in patient cells exposed to Vitamin D₃ (Figure 2B). Further, Vitamin D₃ does not affect BARD1/BRCA1 expression (Figure 2B). But, Vitamin D₃ levels in the serum of CHD patients are significantly low[23,25-27] as can also be seen by the low serum Vitamin D₃ levels of the CHD subjects employed in the present study in comparison to their healthy counterparts (Table 1). The fact, that statins can upregulate Vitamin D₃ levels might add to their pleiotropic beneficial effects[23,28,29].

In conclusion, our findings provide evidence that mutant LXR-α in CHD patients is degraded by BARD1/BRCA1 E3 ubiquitin ligase complex and since Vitamin D₃ can rescue and simultaneously activate this mutant LXR-α (Figure 4), dietary supplementation of Vitamin

D₃ in such subjects may be exploited therapeutically. Further, *LXR-α* gene mutation and the extent of LXR-α protein degradation may be exploited as potential non-invasive markers for early diagnosis and prognosis, as well as for predicting the susceptibility of an individual to develop the disease in future. However, population studies are warranted to substantiate these propositions.

COMMENTS

Background
Atherosclerosis and its clinical manifestations, such as myocardial infarction or stroke, are the leading causes of morbidity and mortality in the modern world. Lipid peroxidation and inflammation are the two hallmarks of atherosclerotic lesion development. Though lipid-lowering agents like statins are the drug of choice, they do not provide complete protection, thus necessitating an in-depth dissection of other critical molecular pathways that could alter the disease course.

Research frontiers
Liver X receptor-α (LXR-α) is a key athero-protective molecule regulating cholesterol homeostasis as well as inflammation. Various *in vitro* and *in vivo* studies in mice models have demonstrated the protective role of LXR-α. The use of various ligands for activating LXR-α, while avoiding its side effects, is a research hotspot in this area. Also, the association of Vitamin D₃ deficiency with atherosclerosis progression and its dietary supplementation to prevent or treat atherosclerosis is another major area of research in relation to atherosclerosis.

Innovations and breakthroughs
Previous studies in the authors' laboratory have demonstrated that the ligand binding domain of LXR-α is mutated in coronary heart disease (CHD) subjects, thus rendering it incapable of binding and getting activated by its natural physiological ligands. Recent studies have established that ligand-free LXR-α gets ubiquitinated and subsequently targeted for proteasomal degradation, by [breast and ovarian cancer susceptibility1 (BRCA1)-associated RING domain1 (BARD1)]/BRCA1 E3 ubiquitin ligase complex. Accordingly, in the present study we explored the role of BARD1/BRCA1 complex in governing the stability of mutant LXR-α in these subjects. Also a specific inhibitor of BARD1/BRCA1 complex, Cisplatin, was used to warranty the claimed results. They also investigated the role of Vitamin D₃, a natural ligand of mutant LXR-α, in preventing its degradation by ubiquitination.

Applications
The authors' findings suggest that dietary supplementation of Vitamin D₃ in CHD subjects may be exploited therapeutically. Further, *LXR-α* gene mutation and the extent of LXR-α protein degradation may be exploited as potential non-invasive markers for early diagnosis and prognosis, as well as for predicting the susceptibility of an individual to develop the disease in future.

Terminology
Atherosclerosis is a chronic inflammatory response to the accumulation of macrophages and white blood cells in the walls of arteries, promoted by low-density lipoproteins without adequate removal of fats and cholesterol from the macrophages. LXR-α is a ligand dependent transcription factor belonging to nuclear receptor super-family. It forms heterodimer with the LXR and binds to the regulatory region of target genes, modulating their expression upon ligand binding. BARD1/BRAC1 forms a functional heterodimer having an ubiquitin ligase activity that targets specific proteins for proteasomal degradation.

Peer review
The authors explored the role of BARD1/BRCA1 heterodimer in governing the stability of mutant LXR-α protein in CHD subjects. It is an excellent study.

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CASE REPORT

Longitudinal stent compression of everolimus-eluting stent: A report of 2 cases

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Abstract

Second generation drug eluting stents (DES) have shown better safety and efficacy in comparison to first generation DES, because of thinner struts, nondurable polymers and coating with better anti-proliferative drugs. The newer DES with cobalt alloy base have demonstrated a greater trackability, deliverability, conformability, flexibility and radio-opacity. However, these thin strut stents have a downside of poor longitudinal axial strength, and therefore get easily deformed/compressed at their end with a slight trauma during exchange of various catheters. We hereby report two cases of "longitudinal stent compression (LSC)" of everolimus-eluting stent, which happened during percutaneous coronary intervention of right coronary artery. Both the cases were successfully managed with non-compliant balloon dilatation. Various reasons for LSC and its management are discussed in the article.

Core tip: The newer second generation drug eluting stent (DES) have shown a greater safety and efficacy compared to first generation DES, because of thinner struts, nondurable polymers and coating with better anti-proliferative drugs. Though their performance is excellent for various type of coronary lesions, one downside is that they are susceptible for compression/deformation because of poor longitudinal axial strength. We came across longitudinal stent compression (LSC) of everolimus-eluting stent in two cases, which was successfully managed by balloon dilatation. Various reasons for LSC and its management are discussed in the article.

INTRODUCTION

Second generation drug eluting stents (DES) have shown better safety and efficacy in comparison to first generation DES, because of thinner struts, nondurable polymers and coating with better anti-proliferative drugs[1,2]. A change in stent platform from stainless steel to cobalt alloy and a change in stent design have improved the performance of newer DES in terms of trackability, deliverability, conformability, flexibility and radio-opacity. However, these thin-strut stent have a downside of poor longitudinal axial strength, resulting into a newly described observation of "longitudinal stent compression (LSC)"[3]. We hereby report two cases of LSC with everolimus-eluting PROMUS Element stent.
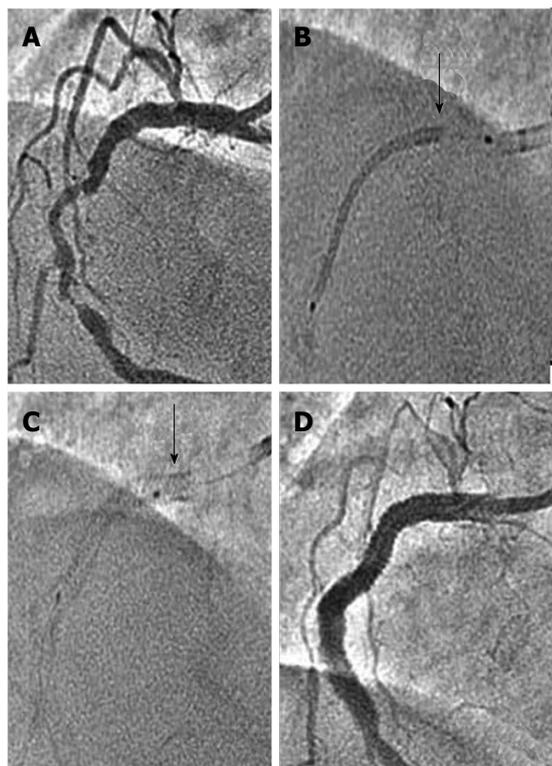
Figure 1 Percutaneous intervention of mid right coronary artery in case 1.
A: 90% eccentric, calcified, type C lesion of mid right coronary artery (RCA); B: Longitudinal compression of un-inflated stent in proximal RCA as marked by a black arrow; C: Post stent deployment, the longitudinally compressed proximal part of stent as marked by a black arrow; D: Final result showing thrombolysis in myocardial infarction-3 flow in RCA.

CASE REPORT

Case 1

A 62-year-old hypertensive male presented with acute anterior wall myocardial infarction (MI) in July 2012. He underwent primary angioplasty and stenting of mid left anterior descending (LAD) artery. Five days later, he had elective percutaneous coronary angioplasty (PCI) of right coronary artery (RCA). The dominant mid RCA showed a 90% type C, eccentric, calcified lesion (Figure 1A). The RCA was cannulated with JR 3.5, 6F guide catheter, lesion was crossed with 0.014 inch guide wire (Zinger-Support wire; Medtronic, Inc., Minneapolis, Minnesota), and dilated with 2.5 mm × 15 mm semi-compliant balloon (Sprinter balloon, Medtronic). Thereafter, a 3.5 mm × 38 mm PROMUS Element™ stent (Boston Scientific, Natick, MA, United States) was taken for deployment, but it could not be pushed across the calcified mid RCA lesion. During forceful manipulations to push it, the distal end of stent got stuck-up at mid RCA. Thereafter, an attempt to pull it back into the guide catheter resulted into longitudinal compression of proximal end of the stent (Figure 1B and C). The stent got dislodged from the stent balloon at its proximal position (Figure 1B). At this point, the stent was deployed at same position without any further manipulation. Following stent deployment, the stented segment was post-dilated with 3.5 mm × 15 mm

non-compliant (NC) balloon (Sprinter balloon, Medtronic). The residual mid RCA lesion, distal to the deployed stent was dilated with 3.0 mm × 15 mm NC balloon, and a 3.5 mm × 25 mm bare-metal stent (Skylor stent, Medtronic-Invatec, Roncadelle, Italy) was deployed, overlapping the proximal stent. The whole stented segment was post-dilated with 3.5 mm × 15 mm NC balloon at 18 atmospheres. RCA had a thrombolysis in myocardial infarction (TIMI)-3 flow at the end of procedure (Figure 1D). There was no hemodynamic instability during the intervention. He remained asymptomatic during follow-up and a check angiogram at 9-mo showed patent RCA and LAD stents.

Case 2

A 65-years-old male presented with 15-d old anterior wall MI in July 2012. He was in gross congestive heart failure, which improved with diuretic therapy. Echocardiography revealed akinetic anterior wall, no mitral regurgitation and ejection fraction of 0.30. Coronary angiogram revealed 100% occluded proximal LAD with thrombus, and a 90% eccentric, calcified, type C lesion at proximal RCA (Figure 2A). He was subjected for PCI to LAD. The left coronary artery was cannulated with JL 3.5, 6 F guide catheter and proximal LAD lesion was crossed with 0.014 inch guide wire (Zinger-Support wire, Medtronic). The lesion was dilated with 2.5 mm × 15 mm balloon and thrombus aspiration with 6F Export aspiration catheter (Medtronic) was performed. There was TIMI-0 flow despite repeated thrombus aspiration and intra-coronary bolus of abciximab. He was put on abciximab infusion and shifted back to coronary care unit. Later, a check angiogram showed occluded proximal LAD. This time no further intervention was performed to LAD considering it as a non-viable territory; and was taken up for PCI to RCA. The RCA was cannulated with JR 3.5, 6 F guide catheter and proximal RCA lesion was crossed with 0.014 inch guide wire (Zinger-Support wire, Medtronic). The lesion was dilated with 2.5 mm × 15 mm semi-compliant balloon (Sprinter, Medtronic). Thereafter, a 2.75 mm × 38 mm PROMUS Element™ stent (Boston Scientific) was taken for deployment, but it could not be pushed across calcified proximal RCA lesion. During forceful manipulations to push it, the distal end of stent got stuck-up at proximal lesion site. Thereafter, an attempt to pull it back into the guide catheter resulted into longitudinal compression of proximal end of the stent (Figure 2B and C). The stent got dislodged from the stent balloon at its proximal position (Figure 2C). The stent was deployed at same position without any further manipulation. Post stent deployment, the stented segment was post-dilated with 2.75 mm × 15 mm NC balloon (Sprinter, Medtronic). The residual RCA lesion, distal to the deployed stent was dilated with 2.75 mm × 15 mm NC balloon and a 2.75 mm × 16 mm PROMUS Element™ stent (Boston Scientific) was deployed, overlapping the proximal stent. The whole stented segment was post-dilated with 2.75 mm × 15 mm NC balloon at 18 atmospheres. He remained he-
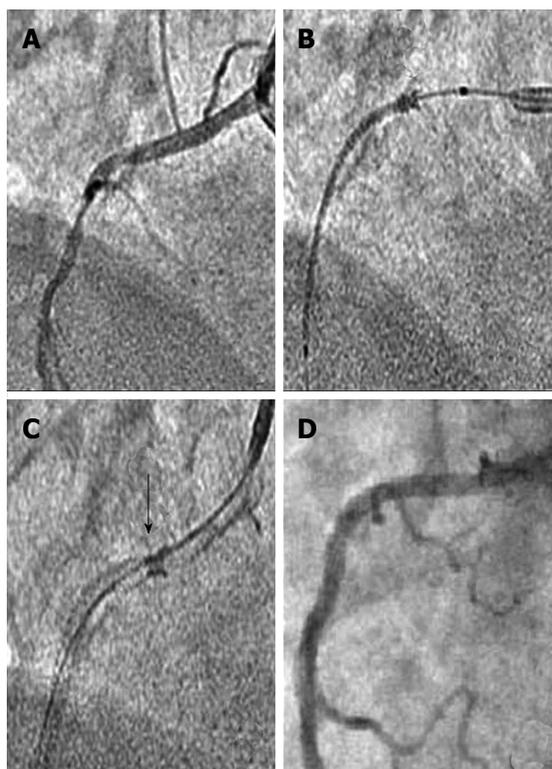
Figure 2 Percutaneous intervention of mid right coronary artery in case 2.
A: 90% eccentric, calcified, type C lesion of proximal right coronary artery (RCA); B: Longitudinal compression of un-inflated stent in proximal RCA as marked by a black arrow; C: Post stent deployment, the longitudinally compressed proximal part of stent as marked by a black arrow; D: Final result showing thrombolysis in myocardial infarction-3 flow in RCA.

modynamically stable during PCI and had a TIMI-3 flow in RCA (Figure 2D). Twenty-four hours later, he had an episode of massive hematemesis followed by hypotension, which was appropriately managed. There was no chest pain and no ST-segment elevation in inferior electrocardiogram leads, which rule out a possibility of acute stent-thrombosis. Later in the course, he had recurrent ventricular tachycardia followed by asystole, from which he could not be revived and expired.

DISCUSSION

Longitudinal stent compression has been described by various authors in newer generation cobalt alloy stents. It is commonly reported with PROMUS Element stent, though isolated report of other stents such as Taxus Liberte (Boston Scientific Co., Natick, MA, United States), Biomatrix (Biosensors Interventional Technologies, Singapore), Endeavor (Medtronic Inc., Minneapolis, Minnesota) and Xience (Abbott Vascular, Santa Clara, CA, United States) is also available[4,5]. Our incidence of 0.8% LSC (2 out of 250 deployed PROMUS Element stents in 6 mo, from July 2012-December 2012) is similar to the reported incidence of 0.6%-0.8% by other authors[4-6]. A bench testing for longitudinal strength of various DES as studied by Ormiston *et al*[7] and Prabhu *et al*[8], have demonstrated that a 2-link offset peak-to-peak stent design

of PROMUS Element has the lowest resistance for longitudinal compression. A relatively better radio-opacity of PROMUS Element is another reason for frequent recognition of LSC during fluoroscopy[9]. The incidence can be much higher with various stents, if a routine intravascular ultrasound (IVUS) or optical coherence tomography (OCT) is performed[3,10]. Various reasons for LSC can be guide catheter induced deformation of a stent at osteal or proximal lesions and a compression by un-inflated balloon or IVUS catheter[3,4]. In both of our cases, the stent got stuck up in calcified RCA lesion, and during attempted withdrawal of stent in guide catheter, it got longitudinally compressed at proximal end by catheter tip. A guide catheter induced compression was the reason for stent deformation in all the three reported cases by Hanratty *et al*[3]. We personally feel that a better plaque modification in a calcified/hard lesion is mandatory prior to stent deployment to avoid such complication. Proper handling and a resistance free passage of various catheters across the stented segment can prevent LSC. The treatment of LSC includes dilatation of deformed segment with adequate size non-compliant balloon and if required another stent for favorable end results[4]. In both the cases, we had favorable outcome after non-compliant balloon dilatation and without putting an additional stent at deformed site. Though, fluoroscopy has a limited value in comparison to IVUS or OCT for diagnosis of malapposition of deformed stent segment, we did not perform it in both the cases. Willims *et al*[4] have reported a case of stent thrombosis following LSC at mid LAD. The reasons for death of 2nd index case were multi-factorial including upper gastro-intestinal bleed, hypotension secondary to blood loss, ischemic heart failure, and recurrent ventricular tachycardia; however a possible acute stent thrombosis of RCA could not be ruled out.

In conclusion, LSC is a rare phenomenon, which is observed with most of newer thin-strut DES. PROMUS Element having a 2-link offset peak-to-peak stent design is more prone to longitudinal compression in comparison to other stents. A meticulous PCI technique with proper handling of various catheters across the ostio-proximal lesions and stented segment is important to avoid such complication. A timely recognition with available imaging modality such as fluoroscopy, IVUS or OCT and an appropriate treatment is essential to avoid unfavorable clinical outcome.

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| Contents | Monthly Volume 5 Number 9 September 26, 2013 |

Contents

ABOUT COVER

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Hyponatremia in patients with heart failure

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Abstract

The present review analyses the mechanisms relating heart failure and hyponatremia, describes the association of hyponatremia with the progress of disease and morbidity/mortality in heart failure patients and presents treatment options focusing on the role of arginine vasopressin (AVP)-receptor antagonists. Hyponatremia is the most common electrolyte disorder in the clinical setting and in hospitalized patients. Patients with hyponatremia may have neurologic symptoms since low sodium concentration produces brain edema, but the rapid correction of hyponatremia is also associated with major neurologic complications. Patients with heart failure often develop hyponatremia owing to the activation of many neurohormonal systems leading to decrease of sodium levels. A large number of clinical studies have associated hyponatremia with increased morbidity and mortality in patients hospitalized for heart failure or outpatients with chronic heart failure. Treatment options for hyponatremia in heart failure, such as water restriction or the use of hypertonic saline with loop diuretics, have limited efficacy. AVP-receptor antagonists increase sodium levels effectively and their use seems promising in patients with hyponatremia. However, the effects of AVP-receptor antagonists on hard outcomes in patients with heart failure and hyponatremia have not been thoroughly examined.

Core tip: Patients with heart failure and hyponatremia have increased morbidity and mortality compared with subjects with normal sodium levels. Established treatment options for hyponatremia in heart failure such as fluid restriction or the use of hypertonic saline with loop diuretics have limited efficacy and compliance issues. Arginine vasopressin (AVP)-receptor antagonists increase sodium levels and exhibit beneficial effects on hemodynamic variables in patients with heart failure. However, double-blind, placebo-controlled trials examining the effects of AVP-receptor antagonists on mortality, quality of life and length of hospital stay in patients with heart failure and hyponatremia are missing.

Filippatos TD, Elisaf MS. Hyponatremia in patients with heart failure. *World J Cardiol* 2013; 5(9): 317-328 Available from: URL: http://www.wjgnet.com/1949-8462/full/v5/i9/317.htm DOI: http://dx.doi.org/10.4330/wjc.v5.i9.317

INTRODUCTION

Hyponatremia is defined as a serum sodium concentration lower than 136 mmol/L[1]. It is recognized as the most common electrolyte disorder both in the clinical setting and in hospitalized patients[2,3]. The prevalence of hyponatremia in hospitalized patients varies depending on the sodium level used to define the condition and the patient population[4-13]. Patients with hyponatremia may suffer major neurologic complications since low sodium concentration produces brain edema, but the rapid correction of hyponatremia is also associated with increased morbidity and mortality[14-18]. It should be mentioned that elderly women and subjects who also have hypokalemia
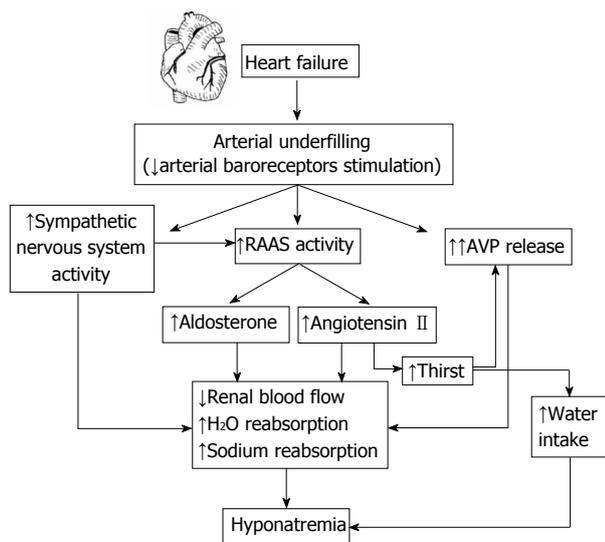
Figure 1 Mechanisms of hyponatremia in patients with heart failure. RAAS: Renin-angiotensin-aldosterone system; AVP: Arginine-vasopressin.

are characterized by an increased risk for neurologic complications following rapid correction of hyponatremia[19-24]. The mortality rates associated with hyponatremia range from 5% to 50% depending on severity and acuity of onset[25].

Heart failure is a disabling and growing disease associated with high morbidity and mortality rates and with annually increasing costs[26-29]. Hyponatremia is often encountered in patients with heart failure[30-33]. In a study of our group, 33.7% of patients with congestive heart failure had hyponatremia, which was the most common electrolyte abnormality in the study population[34]. Aim of the present review is to demonstrate the mechanisms relating heart failure and hyponatremia, to present the association of hyponatremia with the progress of disease and morbidity/mortality in heart failure patients and to describe treatment options focusing on the role of arginine-vasopressin (AVP)-receptor antagonists.

A PubMed/Scopus search was performed up to June 2013 using combinations of "heart failure" with the following keywords: sodium, hyponatremia, vasopressin, aldosterone, diuretics, morbidity, mortality, hospital stay, water restriction, vaptans, vasopressin-receptor antagonists, tolvaptan, conivaptan, lixivaptan, electrolyte. Randomised controlled trials, original papers, review articles and case reports are included in the present review. References of these articles were scrutinised for relevant articles.

MECHANISMS OF HYPONATREMIA IN PATIENTS WITH HEART FAILURE

Neurohormonal mechanisms

Many factors are implicated in the pathogenesis of hyponatremia in patients with heart failure (Figure 1)[6]. Heart failure reduces cardiac output and results in arterial underfilling, which induces the activation of the sympa-

thetic nervous system (SNS). This leads to peripheral and renal vasoconstriction and decreases glomerular filtration rate, effects that combined with arterial underfilling result in increased reabsorption of sodium and water and induce the activation of the renin-angiotensin-aldosterone system (RAAS)[31,32,35]. The subsequent increase of angiotensin II results in peripheral and renal vasoconstriction and induces aldosterone release from the adrenal gland causing further sodium retention[36-43]. Arterial underfilling and the activation of both SNS and RAAS lead to increased release of AVP. Angiotensin II also stimulates the thirst center of the brain and increases water intake and the release of AVP[44-46]. AVP binds to the vasopressin-2 (V2) receptor subtype and increases the number of aquaporin-2 water channels, leading to increased permeability of water in the collecting duct and enhanced free water retention[47-50]. Aquaporin water channels consist of six membrane-spanning domains that form water channels within collecting duct membranes[50-52].

In agreement with the above mechanisms patients with heart failure and hyponatremia have higher levels of plasma renin, angiotensin II, aldosterone, epinephrine, norepinephrine, and dopamine compared with patients with normal sodium levels[40,53,54]. It has been shown that heart failure patients exhibit increased AVP production and generally a dysregulation of AVP characterised by an elevation of its levels despite the presence of volume overload, atrial distension and low plasma osmolality[55-61]. Furthermore, the urinary excretion of aquaporin-2 is increased in heart failure patients with elevated AVP[48]. Notably, the elevated plasma AVP levels are not appropriately reduced even with acute water loading in hyponatremic patients with advanced heart failure[62]. These observations led to the hypothesis that hyponatremia may be a marker of neurohormonal activation that reflects the severity of heart failure[63].

AVP plays an important role in the development of hyponatremia in heart failure but unfortunately it cannot reliably determined by the current laboratory methods. Copeptin, the C-terminal part of the AVP precursor peptide, is secreted in an equimolar ratio to AVP and is a sensitive and stable surrogate marker for its release[64]. Copeptin levels have been used as a prognostic marker in patients with acute diseases such as lower respiratory tract infection, heart disease and stroke. Copeptin is also a promising marker in the differential diagnosis of hyponatremia[64]. In a study plasma copeptin and N-terminal pro-B-type natriuretic peptide were evaluated in 340 patients with left ventricular systolic dysfunction, who were divided into 3 groups according to copeptin tertiles and followed for 55 mo[65]. Copeptin, although it did not predict the future development of hyponatremia, was a significant predictor of hospitalization or death (HR = 1.4, 95%CI: 1.1-1.9, $P < 0.019$) even after adjustment for plasma sodium, loop diuretic dose, and N-terminal pro-B-type natriuretic peptide levels[65]. However, a secondary analysis of three prospective studies of patients with lower respiratory tract infections and acute cerebrovascu-

Table 1 Treatment options in patients with heart failure and hyponatremia

Indication	Intervention	Comments	Citations
Acute symptomatic hyponatremia with severe neurologic symptoms	Infusion of hypertonic saline to increase serum sodium by 1-2 mEq/L per hour until symptoms subside	The rate of sodium correction should not exceed the recommended limit of 8 mEq/L in any 24-h period.	Adrogué et al[1] Ghali et al[54] Fraser et al[114]
Chronic hyponatremia (the rate of correction of sodium levels should not exceed 8 mEq/L per hour the first 24 h, in order to avoid central pontine myelinolysis)	Fluid restriction (< 800-1000 mL/d)	The least expensive option. Many patients with heart failure have increased thirst, which reduces the compliance in fluid restriction.	Adrogué et al[1] Fraser et al[114] Ghali et al[54] Albert et al[123]
	Loop diuretics	The mainstay of treatment in patients with heart failure with fluid overload. The combination of angiotensin-converting enzyme inhibitors with furosemide improves sodium concentration in heart failure patients with hyponatremia.	Chow et al[71] Dzau et al[124] Elisaf et al[125]
	Infusion of hypertonic saline (*e.g.*, 150 mL 1.4%-4.6% NaCl in 30 min for 6 to 12 d) combined with high-dose diuretics (furosemide 500 to 1000 mg)	Two studies (167 patients with heart failure) showed increased serum sodium levels, improvement in symptoms, decreased length of stay and re-admissions compared with furosemide infusion alone.	Paterna et al[126] Licata et al[127]
	Tolvaptan	Oral, selective V2-receptor blocker. Many studies showed efficacy in increasing serum sodium levels and improving heart failure symptoms. The drug should be initiated in hospital for safety reasons. It should not be administrated for more than 30 d or in patients with underlying liver disease, because of the danger of significant liver injury, potentially leading to liver transplant or death.	Berl et al[140] Gheorghiade et al[145] Gheorghiade et al[146] Rossi et al[147] Udelson et al[148] Gheorghiade et al[150] Konstam et al[151] Hauptman et al[152]
	Lixivaptan	Oral, highly selective V2-receptor antagonist. Studies have shown improvement of heart failure symptoms.	Ghali et al[154] Abraham et al[155] Ghali et al[156]
	Conivaptan	Only intravenous administration. The drug is both V1A- and a V2-receptor blocker, but the aquaretic effect is due to antagonism of the V2 receptor. Studies have shown significant increase in urine volumes in the first 48 h. It is a potent inhibitor of the cytochrome P450 isoenzyme CYP3A4.	Ali et al[158] Yatsu et al[159] Verbalis et al[160] Udelson et al[166] Goldsmith et al[167] Goldsmith et al[168]

V2: Vasopressin-2; V1A: Vasopressin-1A.

lar events showed that plasma copeptin levels did not add significant information to the investigation of sodium imbalance states in hospitalized patients[66]. It should be mentioned that this analysis was based on a small sample size and did not focus on patients with heart failure[66].

Another molecule that may play role in the development of hyponatremia in patients with heart failure is apelin, which is an endogenous ligand of the orphan APJ receptor. Apelin has a wide tissue distribution and is implicated in the regulation of body fluid homeostasis, cardiovascular functions, glucose homeostasis, cell proliferation, and angiogenesis[67]. Apelin has diuretic properties and it has been shown that it is regulated in opposite directions with AVP to maintain body fluid homeostasis[67,68]. There is evidence of apelin dysregulation in patients with cardiac failure since it has been shown that the observed increase in plasma apelin cannot compensate for the higher levels of AVP and may contribute to the corresponding water metabolism defect[69].

Diuretics

Diuretics are one of the most common causes of drug-induced hyponatremia[70,71]. The great majority of cases of diuretic-induced hyponatremia are caused by thiazide diuretics, which act solely in the distal tubules and do not interfere with urinary concentration and the ability of AVP to promote water retention[24,70,72,73]. Thiazide-induced hyponatremia is usually mild, but acute severe hyponatremia is occasionally developed as an idiosyncratic reaction[70,72,74].

It should also be mentioned that the hydrochlorothiazide and amiloride combination appears to increase the risk of hyponatremia. This increment is probably because of the direct effect of amiloride on the collecting tubule increasing sodium loss[75-77]. Moreover, amiloride spares potassium and, hence, aggravates thiazide-induced hyponatremia as a consequence of potassium retainment by exchanging it for sodium in the distal tubule. Indapamide administration has also been associated with hyponatremia[78-80].

EFFECTS OF HYPONATREMIA IN THE PROGNOSIS OF PATIENTS WITH HEART FAILURE

A large number of clinical studies have confirmed the

association of hyponatremia with increased morbidity and mortality in patients hospitalized for heart failure or outpatients with chronic heart failure[10,11,42,81-94]. A recent meta-analysis that included 14766 patients from 22 studies and used as endpoint the death from any cause at 3 years showed that the risk of death is linearly increasing with serum sodium levels < 140 mmol/L[95]. Moreover, hyponatremia was predictive of death in both patients with reduced or preserved ejection fraction[95]. Another recent study, which enrolled 1000 consecutive patients with heart failure of any cause and severity for a median duration of 5.1 years, showed that hyponatremia was associated with a significantly increased mortality risk (HR = 2.10, 95%CI: 1.60-2.77)[96]. Notably, it was shown that serum sodium within the reference range has a U-shaped association with mortality risk; specifically, sodium levels of 135-139 mmol/L indicated an increased mortality risk, whereas sodium levels of 140-145 mmol/L were associated with the best prognosis[96]. Hyponatremia has also been found to be an important predictor of survival in several risk models in patients with heart failure[83,84,97-101].

Hyponatremia is associated with increased rate of re-hospitalization[102], increased length of stay[10,84,103], increased hospital resource use[104], increased complications[81,105] and increased costs[106-108]. Furthermore, the presence of hyponatremia in patients with acute ST-elevation myocardial infarction is associated with the development of acute heart failure and with in-hospital adverse outcomes[109]. Moreover, the risk of in-hospital mortality was associated with the severity of hyponatremia in patients with acute ST-elevation myocardial infarction[109,110].

Recent studies have also shown the role of copeptin in the prognosis of heart failure. In the Biomarkers in Acute Heart Failure trial, which enrolled 1641 patients with acute dyspnea, of whom 557 patients had acute heart failure, copeptin concentrations in the highest quartile were associated with increased 90-d mortality (HR = 3.85, $P < 0.001$)[111]. The combination of elevated copeptin and hyponatremia was associated with a higher risk of 90-d mortality (HR = 7.36, $P < 0.001$). Of note, no correlation was found between copeptin and sodium concentration[111]. Similarly, marked elevations of copeptin were independent predictors of poor outcomes in a cohort of 157 patients with class Ⅲ or Ⅳ heart failure prospectively evaluated for 2 years[112]. Furthermore, the combination of increased copeptin levels with hyponatremia was a stronger predictor[112].

TREATMENT OF ACUTE SYMPTOMATIC HYPONATREMIA IN PATIENTS WITH HEART FAILURE

In acute symptomatic hyponatremia serum sodium concentrations decrease rapidly resulting in the appearance of neurologic symptoms[25,113]. These neurologic symptoms are due to brain edema resulting from fluid shifts from the hypotonic extracellular fluid into the more

hypertonic brain[1]. In acute symptomatic hyponatremia with severe neurologic symptoms (for example seizures and/or obtundation) immediate treatment is required to reduce the risk of neurologic complications[1,114]. The proposed treatment for symptomatic hyponatremia is the infusion of hypertonic saline to increase serum sodium by 1-2 mEq/L per hour until symptoms subside[54]. After this emergency intervention, the treatment should continue with the measures that are analysed below for the correction of chronic hyponatremia. Notably, in any case the rate of sodium correction should not exceed the recommended limit of 8 mEq/L in any 24-h period.

TREATMENT OF CHRONIC HYPONATREMIA IN PATIENTS WITH HEART FAILURE

In patients with chronic hyponatremia the rate of correction of sodium levels should not exceed the rate of 8 mEq/L per day in any 24-h period[115,116]. A more rapid correction increases the danger of central pontine myelinolysis[1,117,118]. Central pontine myelinolysis is a neurological disease caused by the rapid rise in serum sodium levels during treatment in individuals with hyponatremia. It is characterised by severe damage of the myelin sheath of nerve cells in the pons area in the brainstem, leading to confusion, horizontal gaze paralysis, spastic quadriplegia, dysphagia, dysarthria and other neurological symptoms. The neurologic deterioration occurs 48-72 h after the rapid correction of hyponatremia. Death is common, but if the patient survives chronic neurologic deficits including locked-in syndrome and spastic quadriparesis are usually observed[117-120]. Brain magnetic resonance imaging is used to reveal the demyelination in the brainstem pons[121,122].

Fluid restriction
Fluid is restricted to amounts less than 800-1000 mL/d in order to achieve a negative water balance[54]. It is the least expensive treatment option. In a randomized study, patients with hyponatremia (serum sodium ≤ 137 mg/dL) received usual care ($n = 26$) or 1000 mL/d fluid restriction ($n = 20$) at discharge[123]. After 60 d patients in the group of fluid restriction had significantly better scores of symptom burden, total symptoms and overall quality of life. In this study there were no differences in thirst or adherence to fluid restriction between groups[123]. However, many patients with heart failure have increased thirst, which reduces the compliance in fluid restriction[54].

Diuretics
The use of diuretics is the mainstay of treatment in patients with heart failure with fluid overload. Loop diuretics are preferred because they increase electrolyte-free water clearance[71]. It has been shown that the addition of a loop diuretic to an angiotensin-converting enzyme inhibitor reversed hyponatremia in heart failure patients[124]. Furthermore, a study of our group showed that the com-

bination of angiotensin-converting enzyme inhibitors with furosemide improves sodium concentration in heart failure patients with hyponatremia[125]. Specifically, six patients with congestive heart failure and serum sodium of 125-128 mmol/L treated with furosemide received captopril in progressively increasing doses. The addition of captopril resulted in clinical improvement and induced a significant increase in serum sodium levels, which was associated with a rise in the diluting ability of the kidney[125].

It has also been shown that the infusion of hypertonic saline combined with high-dose diuretics was associated with increase in serum sodium levels and a potential improvement in outcomes in heart failure patients[126,127]. One study enrolled 60 patients with New York Heart Association Class IV heart failure, who received infusion of furosemide (500 to 1000 mg) plus hypertonic saline (150 mL 1.4%-4.6% NaCl) in 30 min for 6 to 12 d. The combination of furosemide and hypertonic saline increased serum sodium levels and decreased length of stay and readmissions compared with furosemide infusion alone[126]. In a larger study, which enrolled 107 patients with heart failure, the infusion of furosemide plus hypertonic saline was associated with improvement in symptoms and reduction of re-admissions and mortality[127].

AVP-receptor antagonists

AVP has three different receptor subtypes[128]. V1A receptors are found in vascular smooth muscle and cardiac myocytes causing vasoconstriction and hypertrophy, as well as in platelets and hepatocytes regulating platelet aggregation and glycogen metabolism[129-135]. V1B receptors are found in the anterior pituitary gland and are associated with adrenocorticotropic hormone and b-endorphin release[136]. Interestingly, these receptor subtypes have been also linked to the regulation of glucose homeostasis[137]. V2 receptors are found on the renal collecting ducts and cause free-water reabsorption leading to increased water retention[50,51,138]. V2 receptors are mainly linked to the development of hyponatremia in heart failure patients.

The central role of AVP in hyponatremia is targeted with the AVP-receptor antagonists (vaptans) conivaptan, tolvaptan and lixivaptan, which differ in their affinity for the V1A and V2 receptor[139].

Tolvaptan: Tolvaptan is an orally active, selective V2-receptor blocker. It is recommended to initiate the drug in hospital for safety reasons, although patients have been receiving tolvaptan safely as long as 3 years[140].

Tolvaptan has been extensively studied in patients with heart failure. The administration of tolvaptan at a single oral dose (15, 30 or 60 mg) in 181 patients with advanced heart failure on standard therapy resulted in favourable changes in filling pressures and a significant increase in urine output[141]. The low-dose (7.5 mg/d) tolvaptan for seven days improved hemodynamic parameters and resulted in significant fluid removal in 22 patients with chronic heart failure[142]. Tolvaptan administration for 7 consecutive days reduced body weight and improved symptoms

compared with placebo in patients with heart failure and volume overload despite the use of conventional diuretics[143,144]. Tolvaptan administration in 254 stable patients with heart failure decreased body weight and increased urine volume[145]. Similarly, in the Acute and Chronic Therapeutic Impact of a Vasopressin Antagonist in Congestive Heart Failure (ACTIV in CHF) trial tolvaptan administration in hospitalized patients with systolic heart failure (*n* = 319) resulted in a significant decrease in body weight at 24 h without any changes in heart rate or blood pressure or increase in the rates of hypokalemia or worsening renal function[146]. Of note, a lower 60-d mortality was observed in post hoc analyses in patients with renal dysfunction or severe systemic congestion[146,147]. In the Multicenter Evaluation of Tolvaptan Effect on Remodeling (METEOR) study tolvaptan for 54 wk did not show any beneficial or detrimental effects on remodeling compared with placebo in 240 patients with stable systolic heart failure[148]. Moreover, tolvaptan administration prevented the worsening of renal function compared with conventional therapy in patients with acute decompensated heart failure and high risk of renal failure[149].

The larger trial of tolvaptan is the Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan (EVEREST), which enrolled 4133 patients hospitalized with systolic heart failure. A significant reduction in body weight on day 7 after discharge was demonstrated[150]. During a median follow-up of 9.9 mo a significant increase in sodium levels was observed in patients with hyponatremia[151]. However, tolvaptan had no effect on long-term mortality or heart failure-related morbidity. Specifically, 537 patients (25.9%) in the tolvaptan group and 543 (26.3%) in the placebo group died (HR = 0.98, 95%CI: 0.87-1.11, *P* = 0.68). The composite of cardiovascular death or hospitalization for heart failure occurred in 42% of patients receiving tolvaptan and 40.2% of patients receiving placebo (HR = 1.04, 95%CI: 0.95-1.14, *P* = 0.55)[151]. It should be mentioned that EVEREST did not enrol solely patients with heart failure and hyponatremia, who in theory could benefit from the administration of tolvaptan. A recent analysis of patients with hyponatremia from the EVEREST trial (*n* = 475) showed that tolvaptan was associated with greater likelihood of normalization of serum sodium, greater weight reduction and greater relief of dyspnea at discharge than placebo (all *P* < 0.05)[152]. Tolvaptan did not reduce long-term outcomes compared with placebo among all patients with hyponatremia. However, the administration of tolvaptan in patients with pronounced hyponatremia (< 130 mEq/L; *n* = 92) resulted in a significant reduction in cardiovascular morbidity and mortality after discharge (*P* = 0.04)[152].

A recent study showed that the use of a single dose tolvaptan in pediatric patients with heart failure (*n* = 28) significantly increased serum sodium concentration (*P* < 0.001)[153]. Furthermore, urine output was significantly increased at 24 h (*P* < 0.001).

Lixivaptan: Lixivaptan is an oral, highly selective V2-

receptor antagonist[154]. The administration of lixivaptan in 42 patients with mild to moderate heart failure was associated with significant increases in urine volume and solute-free water excretion without any significant change in plasma renin, norepinephrine, aldosterone, atrial natriuretic peptide and endothelin-1 levels[155]. Treatment with lixivaptan 100 mg/d for 8 wk (in addition to standard therapy) in outpatients with heart failure and volume overload significantly reduced body weight and improved dyspnea and orthopnea[156]. Lixivaptan was generally well tolerated but thirst and polyuria occurred more frequently in the active drug group compared with the placebo group[156].

The effectiveness and safety of lixivaptan for 60 d in patients with heart failure and hyponatremia are being evaluated in a double-blind, placebo-controlled study, the Treatment of Hyponatremia Based on Lixivaptan in NYHA Class Ⅲ/Ⅳ Cardiac Patient Evaluation (BALANCE) study[157]. Primary endpoint is the effect of lixivaptan on serum sodium in patients hospitalized with worsening heart failure (target $n = 650$), signs of congestion and serum sodium concentrations < 135 mEq/L. Other endpoints include assessment of dyspnea, body weight, cognitive function and days of hospital-free survival[157].

Conivaptan: Conivaptan is both a V1A- and a V2-receptor blocker; the aquaretic effect is due to antagonism of the V2 receptor[158-161]. The drug is a substrate and potent inhibitor of the cytochrome P450 isoenzyme CYP3A4 and may result in significant drug-drug interactions[158]. The drug is given only intravenously (20 mg bolus, then continuous infusion 20-40 mg/24 h) over up to 4 d in hospital[139]. It has been shown that volume status or the presence of congestive heart failure do not alter the pharmacokinetics of conivaptan 20 or 40 mg/d[162].

The effects of conivaptan in hyponatremia of various origin were evaluated in 3 randomized double-blind, controlled studies which showed significant improvement in serum sodium levels[163-165]. The acute hemodynamic effects of conivaptan (single intravenous dose of 10, 20 or 40 mg) in heart failure were examined in 142 patients with symptomatic heart failure (New York Heart Association class Ⅲ and Ⅳ)[166]. The administration of conivaptan resulted in favourable changes in hemodynamic variables and urine output without affecting blood pressure or heart rate[166]. In a double-blind trial, which randomised 170 patients hospitalized for worsening heart failure receiving standard therapy to conivaptan (20 mg loading dose followed by 2 successive 24-h continuous infusions of 40, 80, or 120 mg/d) or placebo, conivaptan significantly increased urine output at 24 h compared with placebo (1-1.5 L difference, $P \leqslant 0.02$ for all doses)[167]. Body weight was decreased with the 40 and 80 mg/d dose in parallel with the increase in urine output but this reduction was not significant. Global and respiratory status at 48 h did not differ significantly between conivaptan and placebo groups. Conivaptan was well tolerated with the most common adverse events being infusion-site reac-

tions[167]. Another study assessed the role of conivaptan, furosemide or their combination in 8 patients with chronic stable heart failure on standard medical treatment[168]. Both conivaptan and furosemide monotherapy increased urine volume, but the combination treatment significantly augmented this effect. Although conivaptan did not increase urinary sodium excretion compared with furosemide, the combination led to a greater urinary sodium excretion compared with furosemide monotherapy. There were no significant effects of conivaptan, furosemide or their combination on heart rate, arterial pressure, systemic vascular resistance, cardiac output, glomerular filtration rate, renal blood flow, plasma catecholamines, renin activity, AVP and B-type natriuretic peptide levels[168].

Other considerations: Fluid should not be restricted in patients with hyponatremia who start AVP-receptor antagonists and serum sodium concentration should be monitored every 6-8 h in order to avoid rapid correction of sodium levels[139]. Although osmotic demyelination has not been reported with the use of AVP-receptor antagonists in studies with heart failure patients, a warning letter was recently published concerning the occurrence of neurological sequelae in some patients treated with tolvaptan in whom the correction of serum sodium exceeded the suggested rate[169].

AVP-receptor antagonists should not be used in patients with hypovolemic hyponatremia, who should instead be treated with isotonic saline. Adverse effects of AVP-receptor antagonists include dry mouth, thirst and increased urination in most patients. These agents may not be effective in patients with advanced acute or chronic renal failure[139]. Furthermore, the United States Food and Drug Administration based on a recent large clinical trial of tolvaptan in patients with autosomal dominant polycystic kidney disease[170] has recently determined that tolvaptan should not administrated for more than 30 d or in patients with underlying liver disease, because of the danger of significant liver injury, potentially leading to liver transplant or death[171].

CONCLUSION

Many patients with heart failure have decreased sodium levels due to neurohormonal mechanisms. Patients with heart failure and hyponatremia have increased morbidity and worse prognosis compared with subjects with normal sodium levels. Treatment options for hyponatremia in heart failure such as fluid restriction or the use of hypertonic saline with loop diuretics have limited efficacy and compliance issues. AVP-receptor antagonists increase effectively sodium levels and their use seems promising in patients with hyponatremia. However, it is not clear whether normalization of serum sodium also leads to an improved prognosis. Furthermore, the effects of AVP-receptor antagonists on the mortality, quality of life and length of hospital stay, as well as their cost-effectiveness, have not been thoroughly examined in double-blind,

placebo-controlled trials in patients with heart failure and hyponatremia.

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Coronary-cameral fistulas in adults (first of two parts)

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Abstract

This is a case series and review of the literature adding 11 new cases. Coronary-cameral fistulas (CCFs) are infrequent anomalies which are in general co-incidentally found during diagnostic coronary angiography (CAG). To delineate the characteristics of congenital and acquired CCFs in adults, we performed a PubMed search for papers dealing with congenital or acquired CCFs in adults. Publications on coronary-vascular fistulas or paediatric subjects were not included. From the world literature, a total of 243 adult patients were identified who had congenital (65%) or acquired (35%) CCFs. In this review, which is part one of a two-part series on CCFs, we describe and discuss the congenital fistulas, give an overview on the published literature and report details of our own series of 11 patients with MMFs and solitary macro CCFs. Of the congenital group, 85% were small or large solitary macro CCFs (cut-off 1.5 mm) and 15% were coronary artery-ventricular multiple micro-fistulas (MMFs). Apical hypertrophic cardiomyopathy was reported in some of the reviewed subjects with MMFs (3/24 = 13%) but not was seen in our own series. Conservative medical management was generally the treatment of choice in congenital MMFs; prophylactic implantable cardioverter defibrillators (ICD) were implanted in 2/24 (8%) of subjects, especially when extensive micro-fistulisations were involved. None of the patients of our own series required an ICD, as the MMFs were of limited size. Congenital or acquired CCFs in adults are infrequent anomalies having a wide spectrum of clinical presentation may varies from asymptomatic to severely devastating states requiring different treatment modalities.

Core tip: A case series and review of the literature adding 11 new cases. A total of 243 adult patients were identified who had congenital (65%) or acquired (35%) coronary-cameral fistulas. Of the congenital group, 56% were small or large solitary macro CCFs (cut-off 1.5 mm) and 9% were coronary artery-ventricular multiple micro-fistulas (MMFs). T-waves were inverted in the anterior precordial leads in 38% and apical hypertrophic cardiomyopathy was reported in 13% of the subjects. Conservative medical management was generally the treatment of choice in congenital MMFs; prophylactic implantable cardioverter defibrillators were implanted in 8% of subjects, especially when extensive micro-fistulisations were involved.

INTRODUCTION

Coronary-cameral fistulas (CCFs) are defined as single or multiple, small or large direct communications that arise from one or more coronary arteries and enter into one of the four cardiac chambers (right atrium (RA) and ventricle (RV) and left atrium (LA) and ventricle (LV))[1,2]. These arterio-venous or arterio-arterial connection, giving rise to left-right or left-left shunts, respectively. In general, CCFs are invariably congenital[3,4], but they may also have an acquired etiology[5] which will be addressed in the second part of this review. The congenital entity can be distinguished into coronary artery-ventricular multiple micro-fistulas[2,6-9] or small or large solitary macro fistulas[1], the latter making up the vast majority[10].

Eleven adult patients with congenital multiple micro-fistulas (MMFs) and solitary macro CCFs from our own patient population are presented and discussed. The present part I of the review is confined to congenital CCFs discusses development, clinical presentation, diagnosis and therapy of this infrequent entity and finally review the published literature.

LITERATURE RESEARCH

PubMed was searched for the terms "CCFs", "congenital" and "acquired" combined with "adult". English and non-English publications were screened for both types of congenital and acquired CCFs in an adult population. The definitions used for congenital and acquired traumatic accidental or iatrogenic CCFs were adopted from previous publications[1,11,12]. The following criteria were stipulated to include homogenous subsets for analysis: congenital solitary macro (small and large) coronary cameral fistulas or coronary artery-ventricular multiple micro-fistulas MMFs (first part) and acquired traumatic accidental, iatrogenic or spontaneous CCFs (second part). Manuscripts were checked for completeness and a meticulous search was performed for fistula termination into any of the cardiac chambers. Review subjects were tabulated according to the etiology, age, gender, clinical presentations, complications and management. Patients with coronary-vascular fistulas (CVFs) and publications considering a paediatric population were not included. Data of 11 adult patients with congenital MMFs and solitary macro CCFs are presented (Table 1).

Definitions

The definitions offered by Chiu *et al*[1] and Gupta-Malhotra[12] were applied.

Congenital coronary-cameral fistulas: Small or large, single or multiple fistulous connections originating from any of the coronary arteries and terminating into any of the cardiac chambers (RA, RV, LA and LV)[1,12,13].

Solitary macro-fistulas: These are single or multiple, small (< 1.5 mm) or large fistulas (> 1.5 mm), originating mainly from the proximal segment of a coronary artery

and entering into a cardiac chamber[1,10,11].

Coronary artery-left: Ventricular MMFs: These are multiple small channels originating from the mid or distal part of one or more coronary arteries fistulating more often into the left than the right ventricular cavity[2,6-9].

Statistical analysis

Continuous variables are expressed as means and ranges and categorical variables were presented as percentages.

RESULTS

From the published literature, 243 adult patients were selected with 65% congenital (159/243) and 35% acquired (84/243) CCFs. Of the congenital group, 56% (135/243) were solitary macro (large or small) coronary artery-cameral fistulas and 9% (24/243) coronary artery-ventricular multiple micro-fistulas. The congenital subgroup will be presented here (first part). This review focuses on and pertains to different aspects with regard to etiology, clinical presentation and management (Tables 2 and 3).

Literature review

Congenital coronary artery-cameral fistulas: Sixty-five percent (n = 159) of the 243 CCFs were congenital[9,13-32]. Fifteen percent (24/159) of whom, (15 females, 63%) had multiple micro-fistulas (MMFs). The mean age was 62.7 years (range 39-85); 9 patients had known hypertension and 2 diabetes mellitus. The origin of the fistulas was the left coronary artery (LCA) in 23, the right coronary artery (RCA) in 8 and from the left sinus of Valsalva in 1 of the fistulas. Unilateral fistulas were present in 15, bilateral fistulas in 8 and multilateral fistulas in 1 of the patients. Origin from the distal segment of the involved coronary artery was documented in 5 of the subjects. The fistulas terminated into the LV in 24 patients and into the RV in 1 patient.

The main clinical presentations were angina pectoris (n = 10), chest pain (n = 10), dyspnoea (n = 4), supraventricular tachycardia (n = 3), acute coronary syndrome (n = 3), ventricular fibrillation (n = 1), syncope (n = 3), fatigue (n = 1), congestive heart failure (n = 1), family history of sudden death (n = 1) and abnormal ECG (n = 1). Among the diagnostic modalities implemented were besides ECG and conventional coronary angiography, ambulatory Holter ECG monitoring (n = 4), exercise tolerance testing (n = 7) (1 was non-diagnostic and 6 were positive for ischemia), transthoracic echocardiography (n = 17), cardiovascular magnetic resonance (CMR) (n = 4), myocardial perfusion test (n = 11) (5 were negative and 6 were positive for ischemia) and multi-detector computed tomography (MDCT) (n = 1). Sinus rhythm was demonstrated in 22, atrial flutter in 1 and supraventricular tachycardia in 2 of the patients. Significant coronary artery disease was present in only 2 patients. Dilated and tortuous coronary arteries were reported in 6 (25%) subjects.

The major treatment modality was conservative medi-
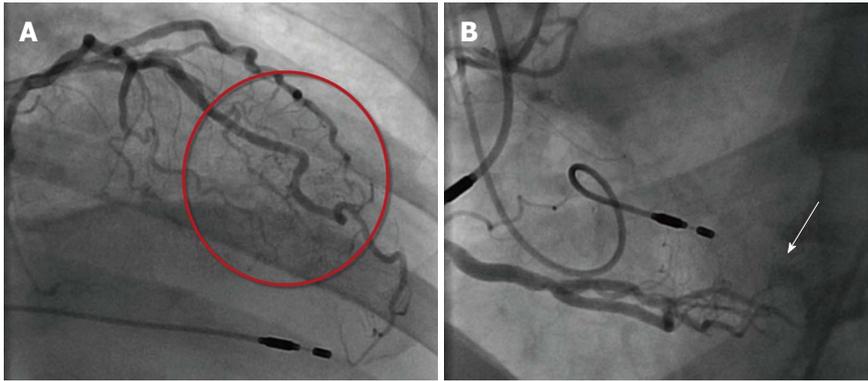
Figure 1 From the distal segment. A: The left anterior descending coronary artery/diagonal branch multiple micro-fistulas (red circle) to the left ventricle (LV) lumen are visible; B: The right coronary artery multiple fistulas (arrow) to the LV cavity. Dual endocardial pacing leads are appreciated.
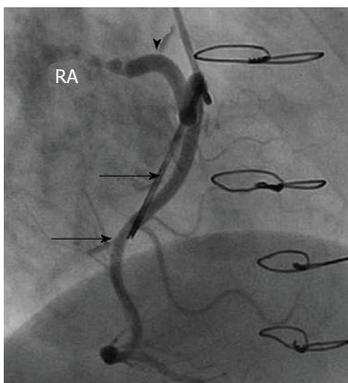
Figure 2 Dilated fistulous vessel (arrow head) originating from the proximal segment of the right coronary artery (solid arrow) and terminating into the right atrium. The mitral valve ring is visible (hollow arrow). RA : Right atrium.

cal management (CMM) with pharmacological agents including β-blockers (n = 14), angiotensin converting enzyme inhibitors (n = 6), calcium channel blockers (n = 5), aspirin (n = 4), nitrates (n = 5), oral anticoagulants (n = 2), lipid lowering agent (n = 2), angiotensin-receptor blocker (n = 1), clopidogrel (n = 1) and Ivabradine (n = 1). In two patients successful percutaneous coronary intervention (PCI) procedures for fistula-bearing and non-fistula-bearing vessels were performed for the relief of complaints. In another 2 of the 3 patients presented with syncope, with extensive MMFs, a prophylactic implantable cardioverter-defibrillator (ICD) was implanted. One patient refused further treatment. Concomitant congenital anomalies were single coronary artery (n = 1) and cor triatriatum (n = 1) as well as apical hypertrophic cardiomyopathy (n = 3).

Solitary macro-fistulas CCFs[11,33-35]: A total of 135 patients with solitary congenital small or large CCFs (135/159; 85%) were reviewed and included. They were part of a previous publication[11]. Mean age of these patients was 46.2 years (range 18-85), and 50% were females. CCFs with single (unilateral) origin were 87% and CCFs with multiple (bilateral and multilateral) in 13% of subjects. In fistulas with single or multiple origins, the share from the RCA or LCA to the fistula formation was equally distributed.

Fistula-related complications such as aneurysmal formation (18.2%), infective endocarditis (8%) and pericar-

dial effusion (2.9%) were reported. None of the patients with CCFs developed a myocardial infarction (MI). It was observed that the presence of CCFs predisposed to the development of infective endocarditis as compared to the patients with CVFs.

Current own series
There were 11 patients with congenital MMFs mean age of 61.5 years (range 44-79) (6 females) having 16 MMFs (Figure 1A and B) and 1 patient with congenital solitary *macro* CCF (Table 1) (Figure 2). The clinical presentations were chest pain (n = 4), angina pectoris (n = 4), non-ST elevation MI (n = 1) and dyspnoea on exertion (n = 2). None of the patients had an infective endocarditis. The concomitant disorders and risk factors were transient ischemic attack (n = 2), sick sinus syndrome (n = 1), aortic and mitral regurgitation (n = 2), previous MI (n = 3), diabetes mellitus (n = 1), chronic obstructive pulmonary disease (n = 2), arterial hypertension (n = 3), obstructive sleep apnoea syndrome (n = 1), glomerulonephritis (n = 1), coronary artery disease (n = 3) [coronary artery bypass grafting (n = 1), percutaneous coronary intervention (n = 1)] and aortic or mitral valve replacement (n = 2). The ECG depicted sinus rhythm in 10 and atrial fibrillation in 1 patient without T wave inversion in the anterior chest leads.

Transthoracic (n = 10) and transesophageal (n = 2) echocardiography were performed. Of these, 6 were normal, 1 showed left ventricular hypertrophy, 1 demonstrated moderate LV systolic function, 1 had severe mitral regurgitation and 1 showed hypokinesia of the inferior wall. Three patients underwent myocardial perfusion tests (1 was negative and 2 were positive for ischemic changes). MDCT was performed in 1 patient and revealed normal coronary arteries without identification of the MMFs. Bilateral fistulas were seen in 6 and unilateral fistulas in 5 patients. They originated from the RCA (n = 7) and from the left coronary artery (n = 9) and terminated into the left ventricle in 15 and the right ventricle in 1 of the fistulas. In 1 patient the CCF originated from the RCA and terminated into the right atrium. He underwent mitral valve repair and surgical ligation of the fistula. Significant coronary artery disease was found in 3 subjects, of whom 2 had one vessel disease (VD) and 1 had 3-VD, while 8 were free of atherosclerotic lesions.

Conservative medical management was applied in all

Table 1 Data of adult patients with congenital coronary artery-ventricular multiple micro-fistulas and solitary macro fistulas

Case Age/gender	Clinical presentation	Previous history	Concomitant disorders	MMFs fistula	ECG	Echocardiography	Myocardial perfusion test	Management
1, 44M	CP	TIA/Lyme disease	-	D-LV Unilateral 0-VD	SR	N	-	CMM
2, 73M	CP	SSS	COPD/RR/GN	D-LV dRCA-LV Bilateral 0-VD (Figure 1 A and B)	SR	N	Apical ischemic changes	CMM, DDDR
3, 62F	NSTEMI	-	-	D-LV dRCA-LV Bilateral 0-VD	SR	N	-	CMM
4, 45F	CP	-	RR	D-LV dRCA-LV Bilateral 0-VD	SR	N	-	CMM
5, 65F	AP	Old IMI/ breast carcinoma	COPD/RR/ hypothyroidism	Cx-LV dRCA-LV Bilateral 1-VD	SR old IMI	Hypokinesia inferior	Mid baso-inferior EF 60%	CMM, PCI RCA
6, 62M	AP	-	RR	D-LV Unilateral 3-VD	SR	Anterolateral hypokinesia and apical akinesia	-	CMM, CABG
7, 70F	CP	TIA	-	AL-LV Unilateral 0-VD	SR	N	Negative	CMM
8, 65M	AP	Old IMI	DM/OSAS	RCA-RV Unilateral 1-VD	SR icRBBB	N	-	CMM
9, 79F	AP	-	RR	LAD-LV RCA-LV Bilateral 0-VD	SR LVH	LVH	-	CMM
10, 64F	DOE	Old ILMI	AF/AR/epilepsy	Cx-LV RCA-LV Bilateral 0-VD	AF LBBB	Moderate LV systolic function	-	CMM, AVR
11, 52M	DOE	MR/MVP/PAF	RR	Solitary macro CCF RCA-RA	SR RBBB	Severe MR	-	MVR/PVI/SL

AR: Aortic regurgitation; AL: Anterolateral branch; AP: Angina pectoris; AVR: Aortic valve replacement; CABG: Coronary artery bypass grafting; CP: Chest pain; CMM: Conservative medical management; COPD: Chronic obstructive pulmonary disease; Cx: Circumflex coronary artery; d: Distal; D: Diagonal branch; DM: diabetes mellitus; DOE: Dyspnoea on exertion; EF: Ejection fraction; F: Female; GN: Glomerulonephritis; ic: Incomplete; ILMI: Inferolateral myocardial infarction; IMI: Inferior myocardial infarction; LAD: Left anterior descending coronary artery; LBBB: Left bundle branch block; LV: Left ventricle; LVH: Left ventricular hypertrophy; M: Male; MMFs: Coronary artery-ventricular multiple micro-fistulas; MR: Mitral regurgitation; MVP: Mitral valve plasty; MVR: Mitral valve replacement; N: Normal; NSTEMI: Non-ST elevation myocardial infarction; OSAS: Obstructive sleep apnoea syndrome; PCI: Percutaneous coronary intervention; PAF: Paroxysmal atrial fibrillation; PVI: Pulmonary vein isolation; RA: Right atrium; RBBB: Right bundle branch block; RCA: Right coronary artery; RR: Hypertension; SL: Surgical ligation; SR: Sinus rhythm; SSS: Sick sinus syndrome; TIA: Transient ischemic attack; VD: Vessel disease.

patients, which consisted of aspirin (*n* = 9), lipid lowering drug (*n* = 6), β-blocker (*n* = 5), angiotensin-receptor blocker (*n* = 5), calcium channel blocker (*n* = 2), angiotensin-converting enzyme inhibitor (*n* = 3) and an oral anticoagulant (*n* = 1).

COMMENTS

Congenital coronary cameral fistulas encompass a group of solitary macro (small or large) or multiple micro coronary cameral communications that are increasingly recognized due to sophistication and wide spread application of non-invasive and invasive angiographic imaging modalities[10,30,36]. Both entities, solitary macro and multiple micro coronary cameral fistulas, have rarely been reported in a single symptomatic patient[37]. Congenital CCFs may develop due to a disturbance of embryonic development with partial persistence of the embryonic intertrabecular vascular network[9,38]. Congenital MMFs terminate mainly into the LV, and in congenital solitary macro CCFs the outflow sites are the right atrium, coronary sinus, right ventricle, left atrium and left ventricle[11]. Congenital coronary cameral fistulas vary widely in their clinical presentation. While most patients are asymp-

tomatic or have non-specific complaints, bilateral MMFs draining into the LV may remain clinically silent[39] or may produce diastolic murmur[40] and diastolic volume overload, mimicking aortic valve insufficiency.

Congenital coronary artery-ventricular multiple micro-fistulas

Among the reviewed subjects, only a single asymptomatic patient with (silent MMFs) was assessed because of an abnormal ECG at rest (1/24; 4%). Moreover, the clinical diagnosis of congenital MMFs can be difficult because as laboratory tests and ECG manifestations are non-specific and the imaging modalities may sometimes be non-interpretable. Moreover, the diagnostic capabilities of CMR and MDCT have failed to demonstrate congenital MMFs[22,24]. On the contrary, MDCT is a readily valuable tool for the detection of congenital solitary macro CCFs[41].

ECG findings

Of great interest are the ECG findings in the 24 literature review subjects, of whom sinus rhythm was depicted in the majority of cases (23/24; 96%) and atrial flutter in a single patient (4%), T-waves were inverted in the anterior

Table 2 Results of literature review of 243 subjects with coronary-cameral fistulas (65% congenital and 35% acquired)

Condition	n (%) female %	Mean age /range yr	Etiology	Management
MMFs	24 (15) Female 63%	62.7 (39-85)	Congenital part I	CMM 100%
CCFs	135 (85) Female 50%	46.2 (18-85)	Congenital part I	CMM 22%, SL 56%, PTE 22%
CCFs	7 (3) Female 0%	24.1 (17-38)	Accidental part II	Emergent surgical intervention 100%
CCFs	8 (3.3) Female 38%	55.8 (46-73)	Iatrogenic (pacing) part II	CMM Spontaneous resolution
CCFs	7 (3) Female 29%	66.5 (58-75)	Iatrogenic (PCI) part II	CMM
CCFs	25 (10.3) Female 22%	50.8 (43-64)	Iatrogenic (EMB) part II	CMM Spontaneous resolution 27%
CCFs	5 (2.1) Female 20%	61 (40-78)	Iatrogenic (surgery) part II	CMM
CCFs	20 (8.2) Female unknown	45 (32-74)	Iatrogenic (SM) part II	CMM 11%, PTE 11% Spontaneous resolution 78%
CCFs	12 (5) Female 0%	61 (29-75)	Spontaneous (post-MI) part II	CMM 60%, SL 30% Spontaneous resolution 10%

CCFs: Coronary cameral fistulas; CMM: Conservative medical management; EMB: Endomyocardial biopsy; MI: Myocardial infarction; MMFs: Coronary artery-ventricular multiple micro-fistulas; PCI: Percutaneous coronary intervention; PTE: Percutaneous therapeutic embolization; SL: Surgical ligation; SM: Septal myectomy.

Table 3 Fistula characteristics in congenital and acquired coronary-cameral fistulas in adults

	Congenital CCFs (0.07%)[1]			Acquired CCFs			
				Iatrogenic CCFs			Accidental CCFs
	Solitary Macro CCFs (large ≥ 1.5 mm)	Solitary Macro CCFs (small ≤ 1.5 mm)	Multiple Micro MMFs	Post-SM	Post-EMB	Post-pacing	Blunt or sharp chest trauma
Prevalence/incidence Fistula characteristics	0.03%[1]	0.04%[1]	0.09%[1]	19%-23%[5,56]	2.8%-23.2%[57-60]	Unknown	Unknown
Origin	Proximal segment of coronary arteries		Distal segment of coronary arteries	Septal perforator	RCA>LAD> Cx	LCA	RCA or LAD
Termination	Any cardiac chamber		LV > RV	LV	RV	Any cardiac chamber	RV or LV
Management	CMM/SL/PTE		CMM (100%) Incidentally ICD	SC (78%)/ CMM 11% PTE 11%	SC (27%)	CMM/SC	Surgical repair (100%)

CMM: Conservative medical management; EMB: Endomyocardial biopsy; LA: Left atrium; LAD: Left anterior descending artery; LCA: Left coronary artery; LV: Left ventricle; PTE: Percutaneous therapeutic embolization; RA: Right atrium; RCA: Right coronary artery; RV: Right ventricle; SC: Spontaneous closure; SL: Surgical ligation; SM: Septal myectomy; CCFs: Coronary-cameral fistulas.

precordial leads in 9 (38%) subjects, and 3 of them had LVH and apical hypertrophic cardiomyopathy (AHCM). Therefore, congenital MMFs may be included in the differential diagnosis of anterior precordial T-wave inversion. Reversible[42] or permanent[43] T-wave inversions either associated with multilateral or unilateral congenital MMFs have been reported. However, in our own series, none of the patients showed T-wave inversion in the precordial leads and T-wave inversions in the anterior chest wall leads were absent in patients with solitary macro CCFs.

Shunt characteristics

The magnitude of the shunt of MMFs may be considerable. In MMFs, Cottier *et al*[44], measured a reduction of 28% of total coronary blood flow during recumbent bicycle exercise whereas greater cardiac vein flow increased by 66% in the presence of typical anginal pain and ischemic LV dysfunction. Furthermore, Meissner *et al*[45] measured coronary artery flow velocity with intravascular Doppler guide wire for hemodynamic quantification of shunt flow, which revealed a left-to-left shunt of 23% of the total LV output. Oh *et al*[43] assessed the hemodynamic significance of unilateral MMFs by fractional flow reserve (FFR) and found no evidence of hemodynamic compromise. These investigations may provide interesting data but were not performed either in the reviewed subjects (*n* = 24) or in our own current series (*n* = 11). Non-invasive, myocardial perfusion tests may, incidental-

ly, demonstrate reversible perfusion defects in congenital MMFs[46] as was depicted in 2 patients of our own series and in 6 of the reviewed subjects.

Incidence of congenital MMFs

The angiographic incidence of congenital MMFs in the Chinese adult population is estimated at 0.09% with slight female predominance (58%) as was found in the review subjects (63%) and in our own series (60%). Origin from mid or distal segment of the LAD is highly prevalent, occurring in 88% of patients. Symptoms ensued in the 6th decade of life. Our findings were similar and in accordance with the findings of others[1]. The mean age in the reviewed subjects was 62.7 years and, in our own series of 10 patients with MMFs, it was 69.1 years.

Associated disorders

Concomitant AHCM was detected in 13% of the reviewed MMFs subjects and was not observed in any of the solitary CCFs patients[23-25]. AHCM, a variant of hypertrophic cardiomyopathy, is rare among Caucasians but more common in the Asian population, especially in the Japanese[25]. This association between MMFs has recently been observed not only with AHCM[47,48] but also with non-compaction cardiomyopathy (NCCM)[49]. Alternatively, one can assume and may speculate that an early common pathway may exist, yet not detected, for their development. In addition, pre-existent congenital multilateral fistulas (from all 3 epicardial coronary arteries) have been reported in a heart transplant recipient, which were detected after transplantation during routine coronary angiography[50].

Autopsy findings

Autopsy of patients with congenital multilateral MMFs to both ventricles depicted insignificant atherosclerotic coronary artery disease, cardiac dilatation and hypertrophy, and dilated coronary arteries with histologically, numerous small vessels of various diameters across the myocardium with patchy subendocardial fibrosis[51,52]. This was in accordance with the necropsy findings of Honey and Lau in solitary *macro* congenital CCFs[53,54], the only difference being the presence of a single fistulous vessel.

Congenital solitary macro coronary-cameral fistulas

On the other hand, congenital solitary *macro* coronary-cameral fistulas (small and large)[11,33-35] showed an incidence of 0.07%. Of these, 0.03% were large and 0.04% were small CCFs[1]. CCFs with single (unilateral) origin presented 87% and CCFs with multiple (bilateral and multilateral) origin 13% of subjects. Fistula-related complications such as aneurysmal formation (18.2%), infective endocarditis (8%) and pericardial effusion (2.9%) were reported. None of the CCFs patients developed MI, however, and subjects with CCFs were susceptible for the development of infective endocarditis compared to

the group presented with coronary-vascular fistulas[11]. In bilateral CCFs, hemodynamic significance was assessed by FFR and ischemia was ruled out[43]. In our patient with congenital solitary macro fistula from RCA to RA, the fistulous vessel was surgically ligated during redo of mitral valve repair for mitral valve prolapse accompanied with symptomatic severe mitral regurgitation.

Supraventricular (SV) and ventricular arrhythmias have been associated with coronary cameral fistulas (solitary or MMFs). In our own series ($n = 11$), atrial fibrillation/flutter (AF) was present in only 1 patient (10%), and AF and supraventricular tachycardia were present in 2 of the MMFs reviewed subjects (8%). However, neither ventricular arrhythmias nor infective endocarditis were reported in the MMFs subjects.

Myocardial infarction

In the absence of atherosclerosis, MI may develop in the presence of MMFs originating from all 3 coronary arteries terminating into both ventricles[55]. One patient of our own series (1/10; 10%) sustained inferior wall MI, in which the fistula-bearing RCA was involved.

Management

In all 24 reviewed subjects, conservative medical management was conducted including β-blockers[17], calcium channel blockers[18] and ivabradine[19] as was previously reported[1]. While congenital MMFs are generally treated conservatively, congenital solitary CCFs may undergo percutaneous occlusion or surgical ligation in the presence of substantial significant shunts. Only in few of the reviewed subjects, having morphologically extensive MMFs, a prophylactic ICD was implanted (8%). None of the patients in our own series required an ICD as the MMFs were not widespread.

CONCLUSION

In almost 40% of the reviewed subjects with congenital coronary artery-ventricular multiple micro-fistulas, T-wave inversion was present in the precordial leads of the electrocardiogram in association with or without apical hypertrophic cardiomyopathy. For adult patients with congenital coronary artery-ventricular multiple micro-fistulas, conservative medical management is the treatment of choice. Due to the multiplicity of the fistulas, they are inaccessible for percutaneous or surgical intervention which may be considered in large solitary coronary-cameral macro fistulas with hemodynamically significant shunts. Limited data were reported on adult patients with solitary CCFs. Within the entity of CCFs, each subtype has its own specific characteristics such as origin, termination of fistulas and treatment options. In addition, there were few reports on the implantation of an ICD in patients with extensive congenital MMFs in association with syncope.

ACKNOWLEDGEMENTS

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Relationship between vitamin D deficiency and cardiovascular disease

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Abstract

Epidemiological studies have found that low 25-hydroxyvitamin D levels may be associated with coronary risk factors and adverse cardiovascular outcomes. Additionally, vitamin D deficiency causes an increase in parathyroid hormone, which increases insulin resistance and is associated with diabetes, hypertension, inflammation, and increased cardiovascular risk. In this review, we analyze the association between vitamin D supplementation and the reduction in cardiovascular disease. The role of vitamin D deficiency in cardiovascular morbidity and mortality is still controversial, and larger scale, randomized placebo controlled trials are needed to investigate whether oral vitamin D supplementation can reduce cardiovascular risk. Given the low cost, safety, and demonstrated benefit of higher 25-hydroxyvitamin D levels, vitamin D supplementation should become a public health priority for combating common and costly chronic cardiovascular diseases.

Core tip: We performed an extensive review to determine whether vitamin D supplementation reduces cardiovascular risk. Only double-blind, placebo- and randomized-controlled trials were included. The role of vitamin D deficiency in cardiovascular morbidity and mortality is still controversial, and larger scale, randomized placebo controlled trials are underway to address this issue. These results from these studies will likely not be available for another 3-5 years. At this stage, we propose recommendations for preventing of vitamin D deficiency and conclude that there is a benefit to vitamin D supplementation.

INTRODUCTION

Vitamin D is likely one of the oldest hormones, having existed for at least 750 million years[1]. Studies have demonstrated that low levels of vitamin D represent a problem of global dimensions[2-13]. A recent Workshop Consensus for Vitamin D Nutritional Guidelines estimated that approximately 50% and 60% of the elderly in

North America and the rest of the world, respectively, do not have satisfactory vitamin D levels[14]. The situation is similar in younger subjects. Reasons for this widespread deficiency remain unclear but are likely related to factors such as urbanization, demographic shifts, decreased outdoor activity, air pollution and global dimming, as well as decreases in the cutaneous production of vitamin D with age. Epidemiological pooled analysis of prospective observational studies of diverse populations demonstrates that hypovitaminosis D is associated with a modest risk of cardiovascular events[15-20]. The amount of vitamin D obtained from dietary sources is generally viewed as too low in many regions of the world to have an effect on the vitamin D status at the population level[14]. This review introduces the general concept of vitamin D, defines vitamin D deficiency, evaluates the relationship between vitamin D deficiency and cardiovascular disease, proposes a recommendation for preventing vitamin D deficiency and offers conclusions.

NATURE OF VITAMIN D

There are 2 major forms of vitamin D, vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol). Vitamin D2 is found in plants and can be consumed in fortified foods or as a supplement. Vitamin D3 is obtained from either dietary sources or through the conversion of 7-dehydrocholesterol in the skin upon exposure to ultraviolet B (UVB) radiation[10,21]. Vitamin D3 from the skin is bound to the vitamin D-binding protein, whereas vitamin D2 and vitamin D3 from diet are bound to vitamin D-binding protein and lipoproteins. Both forms are hydroxylated in the liver to 25-hydroxyvitamin D [25(OH)D; D represents D2 or D3]. However, 25(OH)D is inactive and requires hydroxylation in the kidney to form 1,25-dihydroxyvitamin D [1,25(OH)2D, calcitriol]. Calcitriol [1,25(OH)2D] maintains calcium in the blood and has an array of effects on the body's organs. Calcitriol acts in an endocrine manner to regulate calcium metabolism by enhancing intestinal calcium absorption and mobilizing calcium from the skeleton[10,19,22,23]. Although 1,25(OH)2D is considered to be the active form of vitamin D, its levels in the serum do not correlate with overall vitamin D status, whereas the 25(OH)D levels is a more clinically relevant marker[24]. Vitamin D activity is measured in μg of 25(OH)D (1 μg = 40 International Units, IU). The minimum desirable serum level of 25(OH)D has been suggested to be 20-30 ng/mL according to the consensus conference[14].

Dietary sources of vitamin D are limited to fatty fish (wild or farm salmon, mackerel, tuna fish, sardines, and cod liver oil) and products fortified with vitamin D, which include dairy products, cereals, margarine, flour, and orange juice[24,25].

DEFINITION OF VITAMIN D DEFICIENCY

Several measures have been used to define vitamin D deficiency, insufficiency, and adequacy. A 25(OH)D of < 20 ng/mL is associated with suppressible levels of parathyroid hormone when challenged with pharmacologic dosages of vitamin D[26]. Parathyroid hormone levels begin to reach their nadir when the 25(OH)D levels are > 30 ng/mL[27,28]. Intestinal calcium absorption in adults is maximized when 25(OH)D is > 30 ng/mL[29]. Thus, many experts define vitamin D deficiency, insufficiency, and sufficiency as levels of < 20, 21 to 29, and > 30 ng/mL, respectively. To achieve these levels, a minimum of 1000 IU of vitamin D2 or vitamin D3 is needed daily when sun exposure is either unavailable or inadequate for producing vitamin D3, such as during the winter or when a sunscreen is used[30,31].

In the United States, Europe, India, Asia, Middle East, New Zealand, and Australia, vitamin D deficiency is common in pregnant women, newborns, young and adolescent children, and the elderly[32-37]. Serum vitamin D levels are lower in European young adults than in North American young adults during winter[37]. Vitamin D deficiency is especially common in people of color or who avoid sunlight[38].

RELATIONSHIP BETWEEN VITAMIN D DEFICIENCY AND CARDIOVASCULAR DISEASE

Numerous studies have found high rates of CV diseases among patients with lower levels of vitamin D. More recently, low levels of 25(OH)D have been linked to the presence of cardiovascular disease, hypertension, and the metabolic syndrome[39-42]. It is still unclear whether supplementation with vitamin D is beneficial to cardiovascular health. To this end, we have performed an extensive survey of published studies. Only double-blinded and randomized controlled trials (RCT) were included. The databases searched include MEDLINE, EMBASE, and PUBMED from January 1966 to May 2013. We selected search terms that capture generic and specific words relevant to the exposure and outcome on the basis of Medical Subject Heading terms and text words from a priori identified key articles. The terms selected for vitamin D were the following: "vitamin D intake, vitamin D supplement, calcidiol, calcitriol, cholecalciferol, and ergocalciferol". The terms selected for cardiovascular disease (CVD) were the following: "cardiovascular disease, ischemic heart disease, coronary artery disease, cardiovascular mortality, myocardial infarction, and stroke". We restricted the search to articles published in English and studies of humans that double-blinded and RCT. We applied the same search strategy to each database. Because of the limitations in assessing cause-effect relationships, we excluded ecological, cross-sectional, and retrospective case-control studies. By screening abstracts, we also excluded case reports, studies of vitamin D combination treatment (*e.g.*, combined vitamin D + calcium supplementation), and studies that did not assess the use of
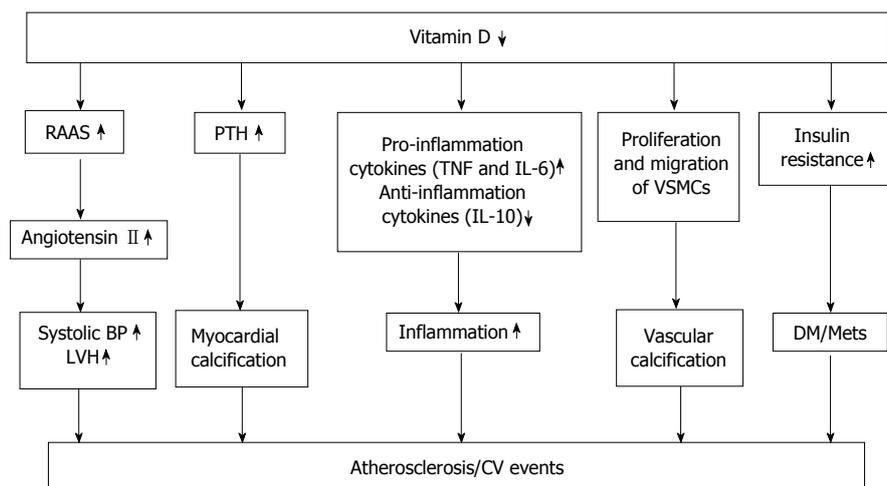
Figure 1 Potential mechanisms for cardiovascular effects of vitamin D deficiency. The data were modified from References 51, 52, and 54. RAAS: Renin-angiotensin-aldosterone system; PTH: Parathyroid hormone; BP: Blood pressure; LVH: Left ventricular hypertrophy; TNF: Tumor necrosis factor; IL-6: Interleukin-6; VSMCs: Vascular smooth muscle cells; DM: Diabetes mellitus; MetS: Metabolic syndrome; CV: Cardiovascular.

vitamin D supplementations. We retrieved articles that passed the abstract screening test for a full-text review, and we further excluded review articles, editorials, or letters to editors as well as studies lacking a comparison between participants who received vitamin D supplementation and non-recipients.

After the abstract screening and full-text review, we selected 19 eligible articles. Ten articles favored beneficial cardiovascular effects after supplementation with vitamin D (Table 1)[43-52]. A trial in the United States randomly assigned 283 African American subjects into a 4-arm, double-blind trial of placebo, 1000, 2000, or 4000 IU of oral cholecalciferol per day. At baseline and 3 mo, the systolic and diastolic pressure and 25(OH)D were measured. This study found that although cholecalciferol supplementation did not affect the diastolic pressure (P = 0.37), the difference in systolic pressure between baseline and 3 mo was +1.7 mmHg for those receiving placebo, -0.66 mmHg for 1000 U/d, -3.4 mmHg for 2000 U/d, and -4.0 mmHg for 4000 U/d of cholecalciferol (-1.4 mmHg for each additional 1000 U/d of cholecalciferol; P = 0.04). For each 1-ng/mL increase in the plasma 25(OH)D, there was a significant 0.2-mmHg reduction in the systolic pressure (P = 0.02)[43]. Larsen et al[45] investigated the effect of 3000 IU vitamin D per day for 20 wk in a randomized, placebo-controlled, double-blind study in 130 hypertensive patients residing in Denmark. Vitamin D supplementation reduced the systolic pressure significantly. In a post-hoc subgroup analysis of 92 subjects with baseline p-25(OH)D levels < 32 ng/mL, significant decreases in the 24-h systolic and diastolic BP were observed in response to cholecalciferol supplementation[45]. Similar reports[44,46-52] relevant to "vitamin D supplementation produces beneficial cardiovascular effects" are summarized in Table 1.

In contrast, the remaining nine articles did not find a cardioprotective effect of vitamin D supplementation (Table 2)[53-61]. In Ireland, 202 healthy adults (20-40 years

old) and 192 healthy elders ($\geq$ 64 years old) were recruited and received vitamin D supplementation at a dosage of 0, 200, 400, or 600 IU for 22 wk. Serum 25(OH)D, intact parathyroid hormone, systolic and diastolic blood pressure, fasting lipids, glucose and insulin, high-sensitivity CRP, matrix metalloproteinase-9, and its inhibitor (tissue inhibitor metalloproteinase-1) were measured at baseline and 22 wk later, which was the endpoint. This study revealed that there were no significant effects of supplementation on the CVD risk biomarkers in either age group[56]. Wood et al[60] conducted a parallel-group, double-blind, placebo- and randomized-controlled trial in 305 healthy postmenopausal women to test whether daily doses of vitamin D3 at 400 or 1000 IU/d for 1 year affected the conventional markers of cardiovascular disease risk. The serum lipid profile (total, high-density lipoprotein, and low-density lipoprotein cholesterol; triglycerides; and apolipoproteins A-1 and B100), insulin resistance (homeostatic model assessment), inflammatory biomarkers (high-sensitivity C-reactive protein, IL-6, and soluble intracellular adhesion molecule-1), and blood pressure were studied. They found that dietary vitamin D supplementation is unlikely to reduce CVD risk factors, such as serum lipid profile, insulin resistance, inflammatory biomarkers, and blood pressure[60]. Additional reports that did not find a cardioprotective effect of vitamin D supplementation are summarized in Table 2[53-55,57-59,61].

MECHANISMS FOR THE CARDIOVASCULAR EFFECTS OF VITAMIN D DEFICIENCY

The results of recent nationwide investigations showed an association between low 25(OH)D levels and important cardiovascular risk factors[40,62], and further supported the findings of preclinical and clinical investigations that demonstrated positive effects of vitamin D and its

Table 1 Double-blind, placebo- and randomized-controlled trials that favor supplement with vitamin D may have a beneficial cardiovascular effects

Ref.	Country	Participants	Intervention	Duration of follow-up	Results
Forman *et al*[43]	United States	283 African-American subjects	Oral vitamin D3 (cholecalciferol, 1000, 2000, or 4000 IU), or placebo per day for 3 mo	6 mo	Reduction in systolic pressure.
Harris *et al*[44]	United States	45 African-American adults	60000 IU monthly oral vitamin D(3) or placebo for 16 wk	16 wk	Effective at improving vascular endothelial function
Larsen *et al*[45]	Denmark	112 Hypertensive patients	75 µg (3000 IU) cholecalciferol per day or placebo for 20 wk	20 wk	Significant decreases in systolic blood pressure
Lind *et al*[46]	Sweden	65 subjects with impaired glucose tolerance	Alphacalcidol (0.75 microgram daily) or placebo over 12 wk	12 wk	Significant reduction of blood pressure
Lind *et al*[47]	Sweden	65 Hypertensive patients with primary hyperparathyroidism	Alphacalcidol, (1 microgram daily) or placebo over 6 mo	6 mo	Significant reduction of blood pressure
Longenecker *et al*[48]	United States	45 HIV-infected individuals with vitamin D deficiency	Vitamin D3 4000 IU daily or placebo for 12 wk	12 wk	Modestly improved cholesterol
Salehpour *et al*[49]	Iran.	77 healthy premenopausal overweight and obese women	Vitamin D (25 µg/d as cholecalciferol) or the placebo group for 12 wk	12 wk.	Significantly improvement of HDL-cholesterol, apoA-I concentrations and LDL-cholesterol: apoB-100 ratio.
Shedeed[50]	Egypt	80 infants with CHF	Vitamin D(3) oral drops or placebo oral drops for 12 wk	12 wk	Significant improvement of HF score, LV end-diastolic diameter, LV end-systolic diameter, LV ejection fraction%, and myocardial performance index.
Witham *et al*[51]	United Kingdom	58 stroke patients	100000 units of a single oral dose of vitamin D2 or placebo	16 wk	Short-term improvement in endothelial function (Flow mediated dilatation was significantly higher in the intervention group at 8 wk)
Zittermann *et al*[52]	Germany	200 healthy overweight subjects in a weight-reduction program	Vitamin D (83 microg/d) or placebo for 12 mo	12 mo	Significant improvement of cardiovascular disease risk markers

LV: Left-ventricular; CHF: Congestive heart failure; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; IU: International units.

analogues on fibrinolysis, blood lipids, thrombogenicity, endothelial regeneration, and smooth muscle cell growth[63-69]. Together, these findings strongly suggest that 25(OH)D has beneficial effects, some involving the cardiovascular system, that are independent of calcium metabolism. Several mechanisms might be responsible for the protective effect of calcitriol on atherosclerotic lesions and vascular calcification (Figure 1). First, vascular smooth cells express vitamin D receptors. Calcitriol inhibits proliferation of these cells with an acute influx of calcium into the cells[69]. Second, a lack of calcitriol results in an increase in the serum parathyroid hormone (PTH) levels. Excess PTH levels may at least in part promote cardiovascular disease by increased the cardiac contractility and myocardial calcification[70]. Third, experimental studies have shown that calcitriol suppresses the release of the inflammatory cytokines such as tissue necrosis factor-α (TNF-α), IL-6, and IL-10. There is now increasing evidence that inflammatory processes play an important role in the development of a vascular insult[71-88]. Fourth, calcitriol is a negative endocrine regulator of the rennin-angiotensin-aldosterone system (RAAS) The RAAS plays a central role in the regulation of blood pressure, electrolytes, and volume hemostasis. Calcitriol treatment reduces blood pressure, plasma rennin activity and angiotensin Ⅱ levels[89]. Fifth, vascular smooth muscle cell proliferation and migration, as well as the osteogeneic processes may contribute to the vascular calcification, which may eventually cause the thrombogenesis[90]. Sixth, vitamin D plays a role in the insulin sensitivity, which has a role in diabetes and in metabolic syndrome[78,90].

Essential hypertension is related to several disturbances in the systemic and cellular calcium metabolism. Extracellular ionized or ultrafiltrable calcium levels are decreased while intracellular cytosolic calcium concentrations are increased. Dietary calcium intake is often lower and renal calcium loss is higher in hypertensive than in normotensive subjects. Epidemiologic studies have demonstrated an inverse association between serum 25(OH)D levels and diastolic blood pressure[91]. Moreover, Afro-Americans have a significantly higher prevalence of diastolic hypertension and have lower 25(OH)D levels compared with white Americans[88,92,93]. In clinical trials, the daily administration of 5 µg of vitamin D showed no effects on blood pressure in normotensive subjects. However, some studies have demonstrated a blood pressure lowering effect with 0.75 or 1.0 µg vitamin D/d in hypertensive patients[94]. Short-term supplementation with 20 µg of vitamin D/d significantly reduced diastolic blood pressure. A reduction in the diastolic and systolic blood pressure was observed in mildly hypertensive patients after 6 wk of UV-B exposure[88,94]. A normalization

Table 2 Double-blind, placebo- and randomized-controlled trials that do not favor supplementation with vitamin D

Ref.	Country	Participants	Intervention	Duration of follow-up	Results
Gepner et al[53]	United States	114 post-menopausal women	Vitamin D3 2500 IU or placebo, daily for 4 mo	4 mo	No significant effects of vitamin D supplementation to reduce cardiovascular disease risk
Jorde et al[54]	Norway	330 overweight or obese subjects	Vitamin D [cholecalciferol, vitamin D(3)] 40000 IU, vitamin D 20000 IU, or placebo per week for 1 yr	1 yr	No significant effect of vitamin D on glucose tolerance, blood pressure or serum lipids
Marckmann et al[55]	Denmark	52 chronic kidney disease patients with vitamin D deficiency	40000 IU of cholecalciferol orally per week for 8-wk	8 wk	No significant impact on functional markers and plasma concentrations of biomarkers related to cardiovascular disease
Muldowney et al[56]	Ireland	394 healthy participants	Cholecalciferol at doses of 0, 5, 10, or 15 μg/d (0-600 IU) for 22 wk	22 wk	No significant effects of supplementation on CVD risk biomarkers
Scragg et al[57]	United Kingdom	95 elderly adults	A single oral dose of 2.5 mg cholecalciferol or placebo	5 wk	No significant effect of vitamin D supplementation to change blood pressure or serum cholesterol
Stricker et al[58]	Switzerland	62 peripheral arterial disease patients with vitamin D deficiency	A single, oral supplementation of 100000 IU vitamin D3 or placebo	1 mo	Unlikely to influence endothelial function, arterial stiffness, coagulation and inflammation
Thadhani et al[59]	United States	227 patients with chronic kidney disease	Paricalcitol or placebo over 48 wk	48 wk	Unlikely to alter left ventricular mass index or improve certain measures of diastolic dysfunction
Wood et al[60]	United Kingdom	305 healthy postmenopausal women	A daily capsule of 400 or 1000 IU vitamin D(3) or placebo for 12 mo	12 mo	Unlikely to reduce CVD risk factors
Yiu et al[61]	Hong Kong	100 patients with type 2 DM	Oral vitamin D (5000 IU/d) or placebo per day for 12 wk	12 wk	No significant effect on vascular function or serum biomarkers of inflammation and oxidative stress

CVD: Cardiovascular disease; IU: International units; DM: Diabetes mellitus.

of the enhanced intracellular calcium levels seems to be an important measure for reducing blood pressure, which can explain the therapeutic effects of calcium-channel blockers in hypertensive patients[95,96]. Low adenylate cyclase activity can result in a decreased calcium re-uptake into the sarcoplasmic reticulum and can contribute to an accumulation of intracellular free calcium and to an increase in vascular reactivity and blood pressure[97]. Activity of the intracellular adenylate cyclase is calcitriol-dependent and improvement of the activity of this enzyme may thus reduce free cellular calcium concentrations.

Hyperlipidemia, diabetic mellitus, and an increase in blood coagulation factors, blood viscosity, and leukocyte counts are important risk factors for the development of arteriosclerosis. There is now increasing evidence that arteriosclerosis is a low-grade systemic inflammatory disease. An increase in serum C-reactive protein levels is an important indicator of inflammatory reactions and also of the risk of developing arteriosclerosis[98]. The synthesis of C-reactive protein is regulated by IL-6 and IL-10 as well as TNF-α[73,99]. Animal studies have demonstrated that IL-6 and IL-10 accelerate arteriosclerosis[100]. Calcitriol can suppress the secretion of TNF-α and IL-6 in vitro in a dose-dependent manner[101]. A recent study identified an inverse association between TNF-α and 25(OH)D levels in human subjects[102].

PREVENTION OF VITAMIN D INSUFFICIENCY

Preventive measures must take into account that there is a high risk of vitamin D insufficiency in the whole population during winter and that the elderly population, especially institutionalized subjects, are at an increased risk for vitamin D insufficiency or even deficiency. There are two prevention models available: increased exposure to ultraviolet light and increased oral vitamin D intake. Sunlight provides the most potent source of vitamin D, with approximately 3000 IU vitamin D3 for 5 to 10 min of mid-day, mid-year exposure of the arms and legs for a light-skinned Caucasian[10]. Adequate daily oral vitamin D intake could be an easy and effective measure for maintaining a physiological vitamin D status. In November 2010, the Institute of Medicine of the National Academies of United States provided an update to the recommended intakes of calcium and vitamin D. For vitamin D intake, the committee assumed that North Americans need on average 400 IU of vitamin D daily; people 71 years old and older may require as much as 800 IU per day[103]. However, nutrition experts have suggested that vitamin D intake of 800 to 2000 IU daily may be needed. These doses are quite difficult to obtain without routine supplementation, particularly in areas with extreme win-

ter climates and higher latitudes[104]. The United States Food and Drug Administration reported that a dose of 2000 IU daily is safe[21]. The Institute of Medicine of the National Academies has recently suggested a new tolerable upper intake level of only 4000 IU of vitamin D per day for the general adult population[103] because of the concern about potential toxicity at higher levels of 25(OH)D[103-106]. However, currently there is no recommended daily intake dose for vitamin D. For a practical approach, maintenance therapy can be continued by routine sunlight exposure or by administering vitamin D supplements, 800 to 2000 IU vitamin D3 daily or 50000 IU of either D2 or D3 every 2 wk[10,21,107].

RECOMMENDATIONS

It is still unproven whether supplementation with vitamin D reduces the cardiovascular risks. Autier et al[108] analyzed 18 independent randomized controlled trials of more than 57000 participants with mean follow-up of 5.7 years. Although there was considerable variability in the dose of vitamin D administered (from 300 to 2000 IU daily), the summary relative risk for all-cause mortality was reduced by 7% with vitamin D therapy[109]. Wang et al[106] performed a meta-analysis of 8 randomized trials, showing a slight, but statistically nonsignificant, 10% reduction in CV disease risk with vitamin D supplementation at moderate to high doses (approximately 1000 IU daily). Another meta-analysis evaluated the relationship between vitamin D levels and cardiovascular risk and reported that vitamin D was associated with nonsignificant effects on the patients' death, myocardial infarction and stroke rates[109]. However, this study did not focus on the effect of vitamin D supplementation in the reduction of cardiovascular risks. At the present stage, we still feel confident that the benefits of vitamin D will likely outweigh the risks. A large double-blind randomized placebo-controlled trial (Vitamin D and Omega-3 Trial, VITAL) sponsored by the National Institutes of Health and run by Harvard Medical School and the Brigham and Women's Hospital is underway[110]. This study should help to determine whether increasing low vitamin D levels will reduce the risk of CV events, depression, and death. O'Keefe et al[111] have claimed that several large scale trials have just started but the results of these trials will not be available for another 3-5 years or more; in the meantime, they recommend a daily intake of 1500 to 2000 IU of vitamin D3 for most American adults.

CONCLUSION

On the basis of this review, hypovitaminosis D has been observed worldwide, and many studies have demonstrated a strong association between vitamin D status and cardiovascular disease risk factors, including hypertension, diabetes, metabolic syndrome and inflammation. In the meantime, health professionals should be aware of the potential negative implications of vitamin D insufficiency

and make recommendations for their patients to improve their vitamin D status. We suggest that to maintain health in younger and older adults and prevent hypertension, chronic heart diseases, and cardiovascular events, an increase in the current recommended intake of vitamin D is warranted. However, definitive randomized controlled trials are still needed to determine whether vitamin D therapy is beneficial to preventing cardiovascular disease. Given the low cost, safety, and demonstrated benefits of higher 25(OH)D concentration, vitamin D supplementation should become a public health priority to combat these common and costly chronic cardiovascular diseases.

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MINIREVIEWS

Subcutaneous implantable defibrillator: State-of-the art 2013

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Abstract

The subcutaneous implantable cardioverter-defibrillator (S-ICD) has recently been approved for commercial use in Europe, New Zealand and the United States. It is comprised of a pulse generator, placed subcutaneously in a left lateral position, and a parasternal subcutaneous lead-electrode with two sensing electrodes separated by a shocking coil. Being an entirely subcutaneous system it avoids important periprocedural and long-term complications associated with transvenous implantable cardioverter-defibrillator (TV-ICD) systems as well as the need for fluoroscopy during implant surgery. Suitable candidates include pediatric patients with congenital heart disease that limits intracavitary lead placements, those with obstructed venous access, chronic indwelling catheters or high infection risk, as well as young patients with electrical heart disease (*e.g.*, Brugada Syndrome, long QT syndrome, and hypertrophic cardiomyopathy). Nevertheless, given the absence of intracavitary leads, the S-ICD is unable to offer pacing (apart from short-term post-shock pacing). It is therefore not suitable in patients with an indication for antibradycardia pacing or cardiac resynchronization therapy, or with a history of repetitive monomorphic ventricular tachycardia that would benefit from antitachycardia pacing. Current data from initial clinical studies and post-commercialization "real-life" case series, including over 700 patients, have so far been promising and shown that the S-ICD successfully converts induced and spontaneous ventricular tachycardia/ventricular fibrillation episodes with associated complication and inappropriate shock rates similar to that of TV-ICDs. Furthermore, by using far-field electrograms better tachyarrhythmia discrimination when compared to TV-ICDs has been reported. Future results from ongoing clinical studies will determine the S-ICD system's long-term performance, and better define suitable patient profiles.

Core tip: The subcutaneous implantable cardioverter-defibrillator (S-ICD) has recently been commercialized in Europe, New Zealand and the United States and implanted in over 2000 patients so far worldwide. It represents an important innovation in the field of device therapy since it avoids the potential periprocedural and long-term complications associated with endovascular leads used with conventional transvenous ICDs. Future studies will better define patient target groups and thereby establish the therapeutic potential of this new device technology.

INTRODUCTION

The implantable cardioverter-defibrillator (ICD) effec-
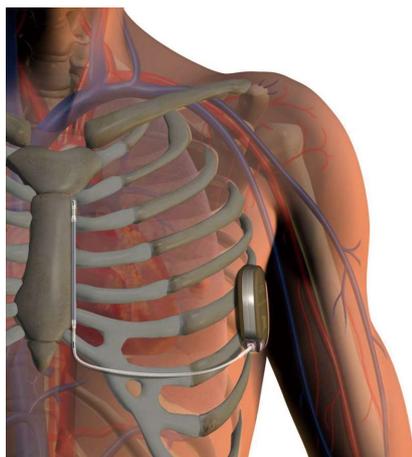
Figure 1 The subcutaneous implantable cardioverter-defibrillator system with the pulse generator implanted subcutaneously in a left lateral position, and the parasternal lead-electrode positioned parallel to and 1 to 2 cm to the left of the sternal midline. The lead-electrode contains two sensing electrodes separated by an 8 cm shocking coil.

Figure 2 Chest X-ray of a patient with a subcutaneous implantable cardioverter-defibrillator system. The cardiac rhythm is detected by 1 of the 3 available vectors, formed between the 2 sensing electrodes and the pulse generator: B-Can, A-Can, and A-B. B-Can: Proximal-to-can; A-Can: Distal-to-can; A-B: Distal to proximal.

tively prevents sudden cardiac death, when used both in primary[1,2] and secondary prevention[3]. To date the vast majority of implanted systems utilize a conventional design, consisting of a transvenous lead for arrhythmia detection and treatment (antitachycardia pacing or defibrillation) positioned in the right ventricle. Nevertheless, transvenous ICD (TV-ICD) is associated with significant periprocedrual and long-term complications. A recent observational large-scale study reported 1.5% major complications (in-hospital death, cardiac arrest, cardiac perforation, cardiac valve injury, coronary venous dissection, hemothorax, pneumothorax, deep phlebitis, transient ischemic attack, stroke, myocardial infarction, cardiac tamponade, and arterial-venous fistula)[4]. Over time, the incidence of intrinsic lead defects, mainly due to insulation defects, invariably increases with a reported annual failure rate at 10-year-old leads of up to 20%[5]. Furthermore, the problem of defibrillation lead recalls is frequent and relevant[6] and revision or extraction of a chronic indwelling lead is frequently a difficult procedure with significant associated morbidity and mortality[7]. Therefore, although the TV-ICD is highly effective in treating ventricular arrhythmias its associated adverse effects are of relevance. A non-TV-ICD system is therefore an attractive option that would overcome many of these problems. Recently, a dedicated entirely subcutaneous ICD (S-ICD, Cameron Health, Inc, San Clemente, California, United States) system has been developed and recently approved for commercial use in Europe, New Zealand, and the United States with more than 2000 successful device implants so far worldwide.

IMPLANTATION, OPERATING AND PROGRAMMING FEATURES

The S-ICD system is comprised of a pulse generator, subcutaneous electrode, electrode insertion tool, and de-

vice programmer. The pulse generator has an estimated longevity of 5 years, is slightly larger and weights approximately the double (145 g) of a modern TV-ICD generator. It provides high-energy defibrillation shocks (80 J) therapy through the use of a constant tilt biphasic waveform, and is capable of delivering post-shock bradycardia pacing at 50 impulses per minute, using a 200 mA biphasic transthoracic pulse for a period of up to 30 s if > 3.5 s of post-shock asystole is detected. Since implantation is guided by anatomic landmarks, fluoroscopy is unnecessary and the operator and patient radiation exposure is subsequently avoided. The generator is placed subcutaneously in a left lateral position over the 6th rib between the midaxillary and anterior axillary lines. *Via* two parasternal incisions, a 3 mm tripolar parasternal electrode (polycarbonate urethane) is positioned parallel to and 1 to 2 cm to the left of the sternal midline with the distal sensing electrode localized adjacent to the manubriosternal junction and the proximal sensing electrode positioned adjacent to the xiphoid process. The 8 cm shocking coil is found between the two sensing electrodes (Figure 1). The cardiac rhythm is detected by the use of 1 of the 3 vectors, which are formed between the sensing electrodes and the pulse generator (proximal-to-can, distal-to-can, and distal to proximal) (Figure 2). The S-ICD automatically selects the most suitable vector for rhythm detection with a satisfactory R-wave/T-wave ratio, in order to minimize the risk for oversensing. In addition, the manufacture recommends carrying out a screening ECG template to confirm a satisfactory R-wave/T-wave ratio in at least 1 of the 3 available sensing configurations pre-implantation. During device insertion effective conversion of induced similar to ventricular fibrillation (VF) using 65 J is tested, nevertheless once implanted, the S-ICD only delivers a non-programmable 80 J shock to ensure a 15 J safety margin[8]. Noteworthy, since the device safety and effectiveness data comes from studies that utilized defibrillation testing this constitutes an obligatory step during

TREATED EPISODE 007:03/29 12:01:52 AM 25 mm/s 2.5 mm/mV
SHOCK IMPEDANCE = 79 Ohms FINAL SHOCK POLARITY = STD

Figure 3 Subcutaneous implantable cardioverter-defibrillator electrogram showing a sustained monomorphic ventricular tachycardia that is terminated by a shock (lightning symbol). The subcutaneous implantable cardioverter-defibrillator (S-ICD) system uses an 18/24 interval criterion for tachycardia detection (T) which is reconfirmed after capacitor charging (C), but before shock delivery, to exclude the presence of non-sustained tachyarrhythmias. S: Sensed event not classified as tachycardia.

implantation of the S-ICD, as opposed to the TV-ICD system where this is no longer considered necessary[8,9].

The S-ICD system calculates the heart rate as the average of the last 4 intervals, and performs tachycardia analysis using an 18/24 duration criteria. Tachycardia is reconfirmed after capacitor charging (average time of 14 ± 2 s) but before shock delivery to exclude the presence of non-sustained tachyarrhythmias[8]. Apart from a shock zone [VF zone in TV-ICDs], the device offers an optional conditional discrimination zone that involves 3 distinct rhythm analyses to distinguish atrial from ventricular tachyarrhythmia and avoid inappropriate shocks of the former: (1) Correlation waveform analysis of up to 41 points of each ventricular complex comparing the current tachycardia beat with the stored template acquired at rest. More than 50% of correlation is considered normal activity and suggests an atrial tachyarrhythmia; (2) Beat-to-beat analysis that evaluates monomorphic or polymorphic beat relationships. In the case of a polymorphic relationship, ventricular tachyarrhythmia is suspected and in the case of monomorphic relationship the algorithm continues; (3) QRS width analysis, using the baseline template, that indicate ventricular tachycardia (VT) if the QRS complex is wide and if the beat-to-beat analysis registered a monomorphic relationship. If the QRS complex is narrow, atrial tachyarrhythmia is assumed[8]. If ventricular tachyarrhythmia is confirmed the device is able to deliver up to 5 shocks of 80 J with shock polarity reversed if the first shock is unsuccessful (Figure 3). A total of 24 episodes can be stored with a maximum of 120 s of recorded electrograms per event. A software update, aimed at reducing the incidence of inappropriate shocks due to oversensing, was introduced in October 2009[8].

The programming of the S-ICD is simple since almost all device settings are automated apart from shock

Table 1 Subcutaneous implantable cardioverter-defibrillator programming	
Device options	**Nominal settings**
Shock therapy ("ON/OFF")	ON
Post shock pacing ("ON/OFF")	ON
Conditional discrimination zone ("ON/OFF"; rate cutoff: 170 to 250 bpm)	ON (200 to 220 bpm)

therapy (on/off), pacing after shock (on/off), and conditional discrimination zone (on/off) with a programmable rate cutoff between 170 to 250 bpm[8] (Table 1). The device is not adequate for patients with symptomatic bradycardia and/or frequent ventricular tachycardia episodes likely to benefit from antitachycardia pacing (ATP), or concurrent use of unipolar pacemakers (that would interfere with the S-ICD arrhythmia detection).

EARLY CLINICAL STUDIES: VALIDATING DEVICE SAFETY AND EFFICACY

The results of 4 small non-randomized initial studies using the S-ICD system in patients with standard indication for ICD implantation were published in 2010 by Bardy *et al*[8]. The first short-term study determined the best electrode configuration in a total of 78 patients, and led to the selection of the shock configuration currently available for clinical use. Subsequently, using the best shock configuration previously determined, a second short-term study compared defibrillation thresholds between S-ICD and TV-ICD systems that were simultaneously implanted in 49 patients. The mean defibrillation threshold was 11.1 ± 8.5 J with the TV-ICD and 36.6 ± 19.8 J with the S-ICD ($P < 0.001$). In one patient the S-ICD failed to defibrillate the induced VF, however this was due to incorrect electrode positioning, approximately 6 cm to the left of the sternum. Following this, two clinical studies evaluated the performance of permanently implanted S-ICD, in 6 patients from New Zealand and 55 from Europe, respectively. Those with a history of VT < 170 bpm, and documented VT known to be reliable terminated with ATP were excluded. The primary endpoint was successful conversion of 2 subsequent episodes of induced VF at 65 J out of 4 attempts. In the pilot trial, consisting of 6 patients, all 18 episodes of induced VF were appropriately detected and defibrillated, and after 16 mo follow-up there were no occurrence of VT/VF episodes, device-related complications or inappropriate shocks. In the European cohort, there were a total of 137 induced VF episodes, all appropriately detected by the S-ICD, and in 98% of the tested patients, the 2 consecutive VF episodes were successfully converted at 65 J. Mean time to shock delivery was 14.0 ± 2.5 s. In one patient (2%) defibrillation was achieved during the first induction but not during the second induction, and received as per protocol a TV-ICD. After a 10 mo follow-up 12 episodes of spontaneous VT were detected and successfully treated

in 3 patients. Five patients presented minor complications (pocket infections, parasternal subcutaneous lead dislodgement). Oversensing occurred in 5 patients [muscle noise (*n* = 3), inadequate electrode placement (*n* = 1), and rate-dependent right bundle branch block (*n* = 1)], in all instances resolved by device reprogramming. There were no inappropriate shocks due to atrial tachyarrhythmias when such episodes occurred above > 170 bpm. Following these positive results the S-ICD was approved for commercial use in the European Union and New Zealand (June 2009).

The Subcutaneous versus Transvenous Arrhythmia Recognition Testing (START) study[10] further evaluated the accuracy of rhythm confirmation and discrimination algorithms of the S-ICD system in a prospective, multicenter, head-to-head comparison with conventional TV-ICDs from three device manufactures. Atrial and ventricular arrhythmias were induced and simultaneously recorded by transvenous and cutaneous electrodes, in 64 patients with standard indication for dual-chamber ICD or cardiac resynchronization therapy defibrillator implantation. Cutaneous electrodes were placed on the patient's skin at locations that represented the subcutaneous position of the S-ICD system's implanted electrode and hence simulated the 3 previously mentioned sensing vectors. A test library was developed based on data from induced atrial arrhythmias with duration ≥ 30 s and ventricular response > 170 bpm (*n* = 50), and ventricular arrhythmias with duration ≥ 10 s and rates > 170 bpm (*n* = 46). Sensitivity performance for appropriate detection of ventricular tachyarrhythmias was first assessed by comparing single-chamber TV-ICDs with S-ICD using a single-zone (VF ≥ 170 bpm) configuration, and subsequently repeated using a dual-zone (VF ≥ 240 bpm; VT ≥ 170 bpm) in order to test the impact of discrimination algorithms on the detection of ventricular arrhythmias. The dual-zone S-ICD was subsequently compared to dual-chamber TV-ICDs, in order to assess whether the addition of atrial lead information would impact on arrhythmia detection sensitivity. Finally, specificity performance for discrimination of supraventricular tachycardias of the S-ICD and single- and dual-chamber TV-ICDs was undertaken. All ventricular tachyarrhythmia were detected in all systems using a single-zone configuration, and with the dual zone configuration all but one episode were detected (a single-chamber TV-ICD failed to detect one of the ventricular episodes). There was no significant difference in the sensitivity performance to detect ventricular tachyarrhythmias between the S-ICD and the single- and dual-chamber TV-ICDs. However, specificity for supraventricular arrhythmias was significantly superior for the S-ICD when compared to 2 of the 3 TV-ICDs, and when compared to the composite of the 3 TV-ICDs [98.0% (S-ICD) *vs* 76.7% (single-chamber TV-ICDs) *vs* 68.0% (dual-chamber TV-ICDs); *P* < 0.001]. No clear benefit of dual-chamber over single-chamber TV-ICDs was observed. Therefore, the results of the START study not only confirm the accuracy of ventricular tachyar-

rhythmia detection but also suggest a potential reduction in inappropriate therapies when compared to TV-ICDs. It should be noted however, that the START study included a limited number of patients, only evaluated induced arrhythmias and that most of the atrial tachyarrhythmias were atrial fibrillation. Furthermore, given that 3 different TV-ICD systems were included, comparison of the composite performance of these systems *vs* S-ICD should be interpreted with caution since their arrhythmia detection algorithms are not identical.

Following the initial clinical study by Bardy *et al*[8] and the European commercialization, the prospective, multi-center, international S-ICD System Clinical Investigation study [the investigational device exemption (IDE) study][9] was commenced in order to gain approval of the Food and Drug Administration in the United States. The primary endpoints of the study were complication-free rate at 180 d post-implant of ≥ 79% and induced VF conversion rate of ≥ 88%. Chronic performance of the S-ICD was also evaluated. The (unpublished) study results were presented at the Heart Rhythm Society conference in May 2012[9]. A total of 321 patients were included in the safety cohort and of those 92% had met the procedure-related complication-free rate at 180 d. Complications included (number of patients) system infections (4), suboptimal pulse generator and and/or electrode position (4), lead dislodgement (2), oversensing (3), inappropriate shock (3) and premature battery depletion (2). In 10 patients the device was explanted due to system infection (4), oversensing (2), pre-mature battery depletion (1), CRT indication (1), need for ATP (1), and elective due to patient request (1). The device successfully converted 100% of the induced VF episodes. During the total follow-up of a mean 321 d, 16 patients presented a total of 109 spontaneous VT/VF episodes, all of which were successfully converted with 80 J or spontaneously converted. Thirty-eight patients received inappropriate shocks (15 = atrial tachyarrhytmias with rates > discrimination zone; 24 = oversensing). On the basis of the results from the IDE study the FDA subsequently approved the S-ICD for commercial use in September 2012.

POST COMMERCIALIZATION CASE SERIES: THE INITIAL EUROPEAN EXPERIENCE

Since the European approval 6 early "real-life experience" case series have been reported from Germany[11,12], the Netherlands[13,14], and the United Kingdom[15,16] (Table 2). These studies include a total of 354 patients (32 and 41 patients with appropriate and inappropriate episodes respectively), the majority diagnosed with ischemic cardiomyopathy or idiopathic dilated cardiomyopathy and a primary prevention ICD indication[17]. Overall, the results confirm that the S-ICD effectively converts both induced and spontaneous VT/VF episodes, and indicate that complication rates and inappropriate shock (mainly due to

Table 2 Clinical subcutaneous implantable cardioverter-defibrillator case series *n* (%)

	Bardy *et al*[8] (2010)	Jarman *et al*[15] (2012)	Aydin *et al*[11] (2012)	Olde Nordkamp *et al*[14] (2012)	Köbe *et al*[12] (2013)	Jarman *et al*[16] (2013)	Burke *et al*[9] (ongoing, initial results)
Number of patients	55	16	40	118	69	111	304
Male	80%	56%	70%	75%	73%	N/A	74%
Age [median (range)/ mean ± SD]	56 ± 13	23 (10-48)	42 ± 15	50 ± 15	46 ± 16	33 (10-87)	52 ± 16
Primary prevention	78%	N/A	44%	60%	59%	50%	79%
Secondary prevention	22%	N/A	56%	40%	41%	50%	21%
Underlying pathology							
Ischemic cardiomyopathy or idiopathic dilated cardiomyopathy	85%	0%	45%	57%	52%	19%	52%
Hypertrophic cardiomyopathy	N/A	0%	13%	N/A	15%	20%	9%
Congenital heart disease	4%	25%	3%	1%	4%	12%	N/A
Electrical heart disease[1]	N/A	75%	33%	26%	20%	43%	12%
Others	11%	0%	6%	16%	10%	7%	27%
Follow-up							
Mean/median follow-up (mo)	10	9	8	18	7	13	N/A
Patients with re-interventions	6 (11)	3 (19)	5 (13)	16 (14)	3 (4)	19 (17)	92% procedure-related complication-free rate at 180 d
Patients with inappropriate shocks	5 (9)	4 (25)	2 (5)	15 (13)	3 (4)	17 (15)	38 (13)
Patients with appropriate shocks	3 (5)	4 (25)	4 (10)	8 (7)	3 (4)	13 (12)	16 (5)
Spontaneous VT/VF episode successfully converted by S-ICD or spontaneously converted	100%	100% [2 VF episodes with prolonged time (24 and 27 s) to therapy]	96% (1 episode of electrical storm was terminated by external shocks)	100%	100%	96% (1 death, see text for details)	100%

[1]Brugada syndrome; long QT syndrome; catecholamine polymorphic ventricular tachycardia; idiopathic ventricular fibrillation. N/A: Data not available; S-ICD: Subcutaneous implantable cardioverter-defibrillator; VT: Ventricular tachycardia; VF: Ventricular fibrillation.

T-wave oversensing) rates are similar to that of previous TV-ICD studies[1,18]. An interesting observation in some of the studies was that more complications occurred with the first implants, suggesting a physician-related learning curve[14,16]. The 2 United Kingdom registries by Jarman *et al*[15,16] from 2012 and 2013 that included 16 and 111 patients respectively, are of particular interest since they report on a different patient profile - younger individuals (23 and 33 years) with a higher prevalence of electrical inherited heart diseases (43 and 75%) and congenital structural heart diseases (12 and 25%). Both registries informed a higher rate of re-operations (17 and 19%) and inappropriate shocks (15 and 25%) than the other 4 case series. These findings were in part related to the greater incidence of T-wave oversensing (10% and 25%), since this not only caused inappropriate shocks but also led to device-explantation (0 and 5%) when present in multiple vectors. Therefore and with the study limitations (retrospective case series) in mind, it seems like T-wave oversensing may be a greater problem in young patients. As suggested by the authors, this could be ameliorated by increasing the pre-implantation requisite of satisfactory R-wave/T-wave ratio templates to > 1 in the three available sensing configurations (the manufacture currently recommends 1 satisfactory template). Furthermore, screening during exercise may be useful to assess for R-wave/T-wave ratio template changes during exertion[15,16].

Finally, one arrhythmic death has so far been re-ported, however without evidence of device malfunction since the lowest detection rate was programmed to 180 bpm, and a monomorphic VT was appropriately detected at first but later fell below 180 bpm and therapy was subsequently aborted with the VT continued for a significant amount of time below the programmed rate limit. The VT later degenerated into VF, which was appropriately detected and shocked into a slow ventricular escape rhythm that did not respond to post-shock pacing[16].

ONGOING CLINICAL STUDIES

There are currently several ongoing clinical studies that shall help to provide more information on the safety and effectiveness of S-ICD, and importantly, compare its performance to the conventional TV-ICD system. Two important studies are the Evaluation of factors impacting clinical outcome and cost effectiveness of the S-ICD (EFFORTLESS S-ICD) Registry (NCT01085435)[19], and the Prospective randomized comparison of subcutaneous and transvenous implantable cardioverter-defibrillator therapy (PRAETORIAN) trial (NCT01296022)[20].

The EFFORTLESS S-ICD Registry[19] is an observational, nonrandomized study assessing the standard of care in approximately 50 investigational centers in Europe and New Zealand where the device had been approved for commercial use at the start of the study. The endpoints of the main registry, with an estimated target

Table 3 Subcutaneous implantable cardioverter-defibrillator patient suitability

Suitable	Unsuitable
Young and active	Present (or high risk of) AV conduction loss requiring pacing
No venous access	Recurrent monomorphic VT
Permanent indwelling catheters	CRT indication
High infection risk	
Electrical heart disease	
Congenital structural heart disease	

AV: Atrioventricular; CRT: Cardiac resynchronization therapy; VT: Ventricular tachycardia.

sample size of 1000 patients and at least 60 mo' follow-up, are perioperative (30 d post-implant) complication-free rate, 360-d complication free-rate, and proportion of inappropriate shocks for atrial tachyarrhythmias. The study will also enroll 250 patients from the main registry to the PRO substudy (12 mo follow-up) that will evaluate the patient perspective (*e.g.*, quality of life) and hospital personnel implant and follow-up experience with the S-ICD. Initial results from the EFFORTLESS S-ICD Registry were presented in June 2012 by which time 219 patients had been enrolled[21]. Fourteen patients had experienced 19 VT/VF episodes with successful conversion in all instances. In addition, the proportion of device-related complications and inappropriate shocks were lower than previously reported in the IDE trial[10].

For the first time, in the randomized prospective PRAETORIAN trial[20] which aims to recruit 700 patients from various centers from the Netherlands with class I or II a ICD indication[17] and without indication for pacing therapy, the S-ICD is being compared against conventional TV-ICD systems. The primary study objective is to demonstrate non-inferiority of the S-ICD to the TV-ICD in terms of the composite of inappropriate shocks and ICD-related complications. The follow-up is estimated to a median of 30 mo. The S-ICD will be programmed with the conditional zone activated with the discriminator rate cutoff between 180 and 250 bpm. The TV-ICDs will be programmed with a monitor zone (> 167 bpm), fast VT zone (> 182 bpm) with 1 sequence of ATP followed by shocks, and a VF zone with high-energy shocks only (> 250 bpm).

WHAT PATIENTS SHOULD RECEIVE A SUBCUTANEOUS CARDIAC DEFIBRILLATOR?

Given the lack of long-term data on the S-ICD safety and performance in comparison with the conventional TV-ICDs, one can only speculate on different patient group's suitability for the subcutaneous system (Table 3). Nevertheless, patients with pacing indication (bradycardia pacing, CRT, and ATP for recurrent monomorphic VTs) should not receive an S-ICD since this feature is not offered. Furthermore patients with documented slow VTs

(< 170 bpm) represent another patient group unsuitable for the S-ICD since the VT rate would fall below the programmable VT zone (minimum of 170 bpm) and subsequently not be treated. On the contrary, in certain patient groups (congenital heart disease, indwelling catheters, or immunocompromised), where implantation of the TV-ICD system is either technically difficult (or even impossible) and/or is associated with increased procedural risk, the S-ICD represents an attractive and suitable therapeutic option. Moreover, in young and active patients with a long life expectancy, a TV-ICD is associated with significant risk of lead failure and need for reinterventions. Thus, young patients with electrical heart diseases (*e.g.*, Brugada syndrome, long QT syndrome, and hypertrophic cardiomyopathy) with low risk of bradycardia and monormophic VT, theoretically constitute another group where the S-ICD may be the preferred device. However, caution in this patient group is at present warranted since the S-ICD system longevity (including the subcutaneous leads) is currently unknown, and initial data indicate a higher rate of inappropriate shocks due to T-wave oversensing in younger individuals[15,16].

Nonetheless, in real life clinical practice the majority of patients with ICD indication have ischemic cardiomyopathy or idiopathic dilated cardiomyopathy and they do not belong to any of the previously discussed groups. The initial clinical studies showed that the S-ICD was safe and effective in this patient profile, however long-term prospective data evaluating important aspects like the development of a pacing indication is missing. Nevertheless, this issue has been addressed by a recently published single-center retrospective analysis of 2712 patients that received an ICD during 2002 and 2011[22]. Half of the patients had a pacing indication and were excluded from the analysis, and of the remaining 1345 patients, the majority with ischemic cardiomyopathy, the combined endpoint (necessity for cardiac pacing, appropriate ATP without subsequent shock or device upgrade) was reached in 34% after a median follow-up of 3.4 years. Secondary prevention, NYHA class III/IV, QRS duration were independent determinants of future unsuitability for the S-ICD. Despite its obvious limitations, the study provides data from a real-life cohort, which shows that a large proportion of patients could represent potential suitable S-ICD candidates.

CONCLUSION

The S-ICD represents an important innovation that has recently gained approval for commercial use in Europe, New Zealand and the United States. Compared to the conventional TV-ICD it avoids the potential risks associated with the periprocedural and long-term complications associated with endovascular leads. Currently ongoing clinical studies shall help to establish the S-ICD system's long-term performance, including subcutaneous lead longevity, better define optimal patient groups that would benefit more, and offer prospective comparisons against

the conventional TV-ICD system, thereby determine the therapeutic potential of this new device technology.

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CASE REPORT

Cardiac resynchronization therapy in acute pulmonary edema: A case report

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Abstract

We are reporting a case of 71-year old lady with a dual chamber demand pacemaker, who developed acute pulmonary edema due to an acute left ventricular (LV) dysfunction and worsening in mitral valve regurgitation after atrioventricular nodal ablation for uncontrolled atrial fibrillation. This was attributed to right ventricular apical pacing leading to LV dyssynchronization. Patient dramatically improved within 12-24 h after upgrading her single chamber pacemaker to biventricular pacing. Our case demonstrates that biventricular pacing can be an effective modality of treatment of acute congestive heart failure. In particular, it can be used when it is secondary to LV dysfunction and severe mitral regurgitation attributed to significant dyssynchrony created by right ventricular pacing in patients with atrioventricular nodal ablation for chronic atrial fibrillation.

Core tip: Our case demonstrates that biventricular pacing (cardiac resynchronization therapy pacemaker, CRT-P) can be an effective modality of treatment in acute congestive heart failure. In particular, it can be used when it is secondary to left ventricular dysfunction and severe mitral regurgitation attributed to significant dyssynchrony created by right ventricular pacing in patients with atrioventricular (AV) nodal ablation for chronic atrial fibrillation. our case matches recent update to guidelines that CRT can be useful in patients with atrial fibrillation and left ventricular ejection fraction (LVEF) ≤ 35% if AV nodal ablation will allow ventricular pacing with CRT except our patient has LVEF > 35%.

Barsoum EA, Bhat T, Asti D, Kowalski M, Vazzana T. Cardiac resynchronization therapy in acute pulmonary edema: A case report. *World J Cardiol* 2013; 5(9): 355-358 Available from: URL: http://www.wjgnet.com/1949-8462/full/v5/i9/355.htm DOI: http://dx.doi.org/10.4330/wjc.v5.i9.355

INTRODUCTION

The detrimental effects of right ventricular apical (RVA) pacing on left ventricular (LV) hemodynamics have been well documented and a higher incidence of heart failure hospitalizations or death in patients with chronic RVA pacing has been attributed to the ventricular dyssynchronization[1,2]. Theoretically, acute RVA pacing could induce discrepancy between electric and mechanical ventricular synchronization resulting in asynchronous left ventricular contraction and relaxation. However, the exact mechanisms of acute LV dysfunction after RVA pacing are not fully understood.

Biventricular pacing (BVP) in chronic heart failure patients within the New York Heart Association (NYHA) functional class Ⅲ or Ⅳ with LV dysfunction and prolonged QRS duration have led to improvement in both
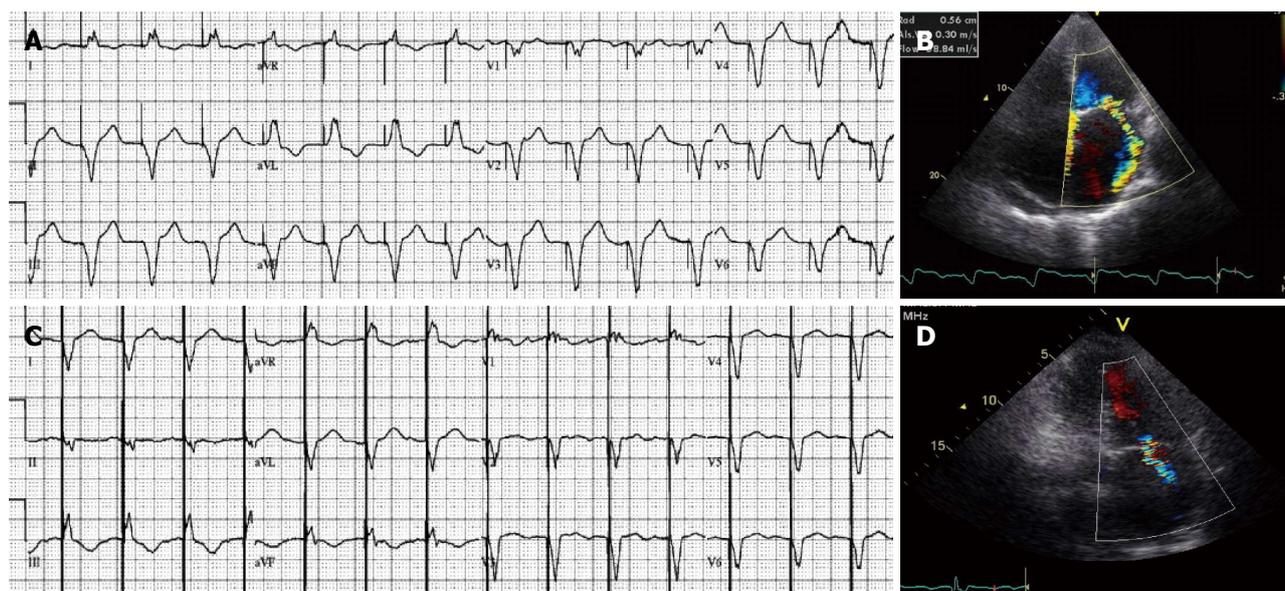
Figure 1 Electrocardiogram and echocardiographic examination. A: Twelve lead electrocardiogram after atrioventricular nodal ablation showing pacing rhythm by dual-chamber pacing pacemaker; B: Echocardiography showed moderate to severe mitral regurgitation before cardiac resynchronization therapy pacemaker (CRT-P); C: Twelve lead electrocardiogram after cardiac resynchronization therapy pacemaker; D: Echocardiography showed mild mitral regurgitation after CRT-P.

morbidity and mortality[3-8]. In addition, cardiac resynchronization therapy (CRT) became the innovative treatment of congestive heart failure, and its use has been extended to patients with NYHA functional class I or II [9-11].

In our case report, we address the benefit and therapeutic role of CRT pacing in patients who developed acute ventricular dysfunction and worsening in mitral regurgitation due to RVA pacing after atrio-ventricular node ablation for refractory atrial fibrillation.

CASE REPORT

A 71-year old woman presented to the emergency department with a chief complaint of worsening dyspnea and orthopnea for three days (NYHA class IV), she had an atrioventricular (AV) nodal ablation for refractory atrial fibrillation five days prior to presentation. Patient had a history of atrial fibrillation, mild mitral regurgitation, hypothyroidism, hypertension, hypercholesterolemia, chronic obstructive pulmonary disease, obstructive sleep apnea, chronic kidney disease, primary biliary cirrhosis. She had a history of permanent dual chamber pacemaker that was inserted two years ago for symptomatic bradycardia secondary to sick sinus syndrome after atrial fibrillation cardioversion.

On admission she was orthopneic, tachycardic and hypoxic that partially improved by using bi-level positive airway pressure. Physical exam revealed positive S1 and S2 heart sounds with a summation gallop, a grade 4/6 apical systolic murmur and a left parasternal systolic murmur that accentuates with inspiration. There was a jugular venous distention up to jaw line. On lung auscultation, there were bibasilar crackles heard. The patient also had bilateral pedal edema. An electrocardiogram (EKG) showed ventricular pacing with a rate of 90 beats per minute (bpm) and QRS duration of 200 ms with positive

R in Lead I (Figure 1A). Echocardiographic examination demonstrated decreased left ventricular function (40%), a LV end-diastolic volume (LVEDV) of 97 mL, markedly dilated left atrium (6.1 cm). There were moderate to severe mitral regurgitation (Figure 1B) and moderate to severe tricuspid regurgitation. Pacemaker interrogation showed that the pacemaker was programmed in a DDD mode with lower rate of 60 bpm and upper tracking rate of 120 bpm.

The patient was diagnosed as pulmonary edema and was admitted to the coronary care unit (CCU). She was placed on maximal medical therapy for five days without improvement. Acute ischemic event was ruled out by serial cardiac enzymes. The worsening symptoms and LV dysfunction were attributed to RVA pacing, which then was leading to dyssynchrony and worsening mitral regurgitation.

We decided to upgrade her pacemaker to biventricular (cardiac resynchronization therapy pacemaker, CRT-P), by adding new lead through the coronary sinus to accomplish left ventricular pacing. The old right atrial and right ventricular leads were connected to the CRT pacemaker. Immediately post operatively, the patient reported feeling better and her symptoms improved (NYHA class III). Follow up EKG showed ventricular pacing with a rate of 90 bpm with reduction in QRS duration to 156 ms with negative R in Lead I (Figure 1C). Forty-eight hours after surgery echocardiography demonstrated improvement in LV function (45%) with a reduction in LVEDV to 88 mL and improvement in mitral regurgitation (Figure 1D). The patient was discharged without complication from CCU.

DISCUSSION

Since the introduction of cardiac pacing five decades ago

as an effective treatment for symptomatic bradyacardia, scientists have pursued the goal of better approximating the normal cardiac physiology leading to more highly sophisticated devices[12,13]. BVP has been found to resynchronize ventricular contraction in heart failure patients with wide QRS complexes, leading not only to reversal of LV remodeling over time but also increased functional capacity with an improvement in mortality and quality of life[14,15].

The main indication for CRT is congestive heart failure patients with wide QRS and left ventricular dysfunction (ejection fraction ≤ 35%), who are symptomatic even while on maximal medical therapy. Also, CRT can be useful in patients with atrial fibrillation and left ventricular ejection fraction ≤ 35% if AV nodal ablation will allow ventricular pacing with CRT[16]. According to recent guidelines from the European Society of Cardiology, CRT can be an alternative to traditional right ventricular pacing in patients with heart failure and LV dysfunction who have a standard indication for pacing[17].

Although, biventricular pacing can reverse the dyssynchronization induced by RVA pacing and trials have shown the benefit of biventricular pacing in patients with symptomatic atrial fibrillation after AV nodal ablation[18-20]. A recent meta-analysis of four trials did not demonstrate improvement in mortality with BVP in comparison with RVA pacing[21].

Mitral regurgitation is common in patient with left ventricular dysfunction that negatively affect the survival of patients with congestive heart failure[22], but CRT has been shown to reduce functional mitral regurgitation by optimizing the force balance acting on the mitral valve[23].

Our patient developed acute pulmonary edema after two days of atrio-ventricular node ablation, mostly secondary to left ventricular dyssynchrony, which led to worsening of her mitral regurgitation. This in turn caused pulmonary edema. Despite optimization of medical treatment, her symptoms didn't improve for five days in CCU, the patient dramatically improved within hours of changing the right ventricular pacemaker to CRT-P. This improvement included a reduction in severity of the status of her mitral regurgitation as well as an alleviation of her symptoms.

Our case demonstrates that biventricular pacing (CRT-P) can be an effective modality of treatment of acute congestive heart failure. In particular, it can be used when it is secondary to LV dysfunction and severe mitral regurgitation attributed to significant dyssynchrony created by right ventricular pacing in patients with AV nodal ablation for chronic atrial fibrillation.

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CASE REPORT

Exercise-induced left bundle branch block: an infrequent phenomenon: Report of two cases

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Abstract

Exercise-induced left bundle branch block (EI-LBBB) is infrequent phenomenon. We present two patients with angina pectoris who developed EI-LBBB during exercise tolerance test. The first patient with typical angina pectoris had significant obstructive coronary artery disease (CAD) requiring percutaneous coronary intervention of multiple lesions including placement of drug eluting stents. The second patient had atypical chest pain without signs of CAD at all. EI-LBBB occurred at a heart rate of 80 bpm and 141 bpm in the first and second patient, respectively. EI-LBBB remained visible through the test till the recovery period in the first patient at a heart rate of 83 bpm and disappeared at 96 bpm in the second patient. Both patients with this infrequent phenomenon are discussed and the literature is reviewed.

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Key words: Angina pectoris; Electrocardiography; Exercise tolerance test; Left bundle branch block; Coronary artery disease.

Core tip: Two patients who presented with angina pectoris and exercise-induced left bundle branch block are described. The first patient with typical angina pectoris had significant obstructive coronary artery disease (CAD) requiring percutaneous coronary intervention of multiple lesions including placement of drug eluting stents. The second patient had atypical chest pain without signs of CAD at all. Both patients are discussed and the literature is reviewed.

INTRODUCTION

The estimated prevalence of permanent left bundle branch block (LBBB) in the general population is 1.5%[1], 0.43% for men and 0.28% for women of middle age[2]. Exercise-induced transient LBBB (EI-LBBB) is infrequent and occurs in 0.4%-0.5% of patients undergoing exercise tolerance tests (ETT)[3-5]. Grady et al[5] have shown that transient EI-LBBB is an independent predictor for major cardiovascular morbidity and mortality. A longitudinal study demonstrated that coronary artery disease and heart failure were more prevalent in patients with EI-LBBB[4]. The mechanism of transient EI-LBBB remains unclear, it may reflect concomitant valvular heart disease, cardiomyopathy, congenital heart disease, conduction abnormalities or coronary artery disease (CAD). Generally, permanent LBBB may be associated with a deterioration of left ventricular function, mechanical dyssynchrony and heart failure[6]. Furthermore, it has also been reported that transient EI-LBBB may result in reversible left ventricular dyssynchrony[7].

In some patients, EI-LBBB may be the first manifestation of diffuse heart disease and its presence is associ-
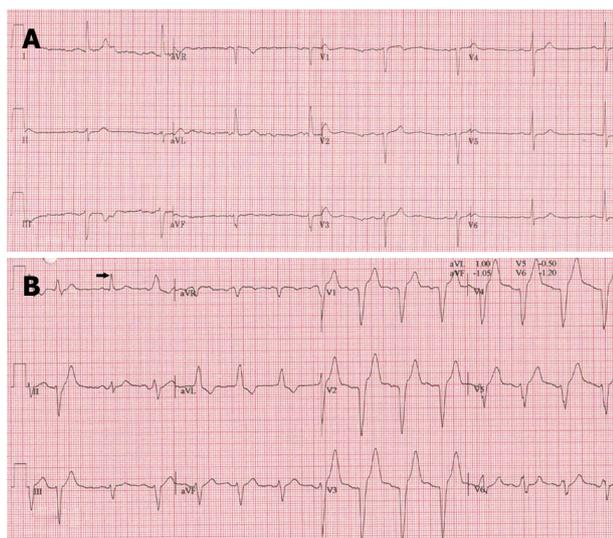
Figure 1 Resting electrocardiogram demonstrating sinus rhythm at 48 bpm with slow progression of R wave in the right precordial leads V₁-V₄ without delayed conduction (A) and during exercise tolerance testing at a heart rate of 80 bpm a left bundle branch block occurred which persisted into the recovery period (B).

ated with a poorer prognosis compared to normal intraventricular conduction and right bundle branch block (RBBB) without concomitant cardiac disorders[8]. We present two adult patients with exercise-induced LBBB in the presence or absence of CAD and an attempt is made to review the international literature.

CASE REPORT

Case 1

An 80-year-old male with well treated hypertension and paroxysmal atrial fibrillation was evaluated for chest pain exaggerated by physical stress with a good reaction to sublingual nitroglycerin. On examination his body mass index (BMI) was 29 kg/m², rest blood pressure was 129/81 mmHg and rest heart rate of 60 bpm. Neither cardiac murmur or signs of congestive heart failure were present. The rest of the examination was normal. Resting electrocardiogram (ECG) depicted sinus rhythm (SR) with left axis deviation and slow progression of R-waves in V₁-₄ (Figure 1A). Transthoracic echocardiography (TTE) revealed a normal left ventricle ejection fraction (LVEF) of 0.64, LV hypertrophy, inferior wall hypokinesia, bi-atrial dilatation, mild mitral and tricuspid regurgitation with normal estimated pulmonary artery pressure of 20 mmHg. On routine ETT 120% of target exercise tolerance was reached and 87% of the maximal heart rate. He developed EI-LBBB at frequency of 80 bpm (Figure 1B), which lasted, through the third minute of the recovery period, till the end of the test at a heart rate of 83 bpm. At coronary angiography, significant stenoses were found in the left anterior descending and circumflex coronary arteries. Percutaneous coronary intervention was performed and both lesions were dilated with placement of DES. Accordingly a drug therapy was started composed

of aspirin for 1 mo, clopidogrel for 1 year and oral anti-coagulant, lipid lowering drug, hydrochloorthiazide and irbesartan as a maintenance drug regimen.

Case 2

A 58-year-old female with known subclinical hypothyroidism without risk factors for CAD was analyzed for exercise-related oppressive chest pain. She had no previous history of cardiovascular disease. On physical examination, BMI was 21 kg/m², rest blood pressure of 117/70 mmHg and rest heart rate regular of 85 bpm, central venous pressure was not elevated and further physical examination was otherwise unremarkable. Resting ECG (Figure 2A) revealed SR with normal findings and biochemical values, all were within normal limits. Findings of TTE were all normal. On echocardiography no intraventricular dyssynchrony was observed as TTE was performed at rest during normal conduction. The LVEF was 0.65. Nuclear stress myocardial perfusion studies revealed no reversible or irreversible defects, but EI-LBBB developed during the exercise phase at a heart rate of 141 bpm (Figure 2B) and a QRS width of 138 ms which was accompanied with chest discomfort. EI-LBBB disappeared at a frequency of 96 bpm. Beta blocker was initiated and on repeated bicycle ergometer test performed one month later, EI-LBBB accompanied with chest pain occurred at a slower heart rate of 129 bpm (Figure 2C) which recovered at a rate of 100 bpm (Figure 2D). Due to persistence of the chest complaints and occurrence of EI-LBBB during myocardial perfusion test despite normal findings (resting ECG and failure to demonstrate any reversible/irreversible defects in the nuclear stress myocardial perfusion), a decision was made to perform CAG which revealed normal coronary arterial tree. The β-blocker therapy was discontinued. An explanation for the failure of beta-blocker to abolish EI-LBBB may be related to inappropriate dose of the drug used for an "unknown" substrate.

Definitions

Maximal heart rate: Was calculated as (220 - age), predicted maximal heart rate and directly measured maximal heart rate from the ECG.

Target heart rate: About 85% of the maximal heart rate, based on age, gender and length. Exercise tolerance test (ETT): were performed on a bicycle ergometer in accordance with the guidelines for exercise testing[9]. All exercise tests were assessed by a cardiologist, specialized nurse and/or a nurse practitioner. Exercise test end points were defined by the following: (1) Positive: ECG evidence of myocardial ischemia, ⩾ 1.0 mm horizontal shift of the ST segment at 80 ms after the J point in comparison with the baseline ECG and/or a 30 mmHg decrease in systolic blood pressure and/or ventricular arrhythmia and/or typical limiting anginal complaints; (2) Negative: in the absence of any of the above cited criteria; (3) Intermediate: < 1.0 mm ST segment depres-
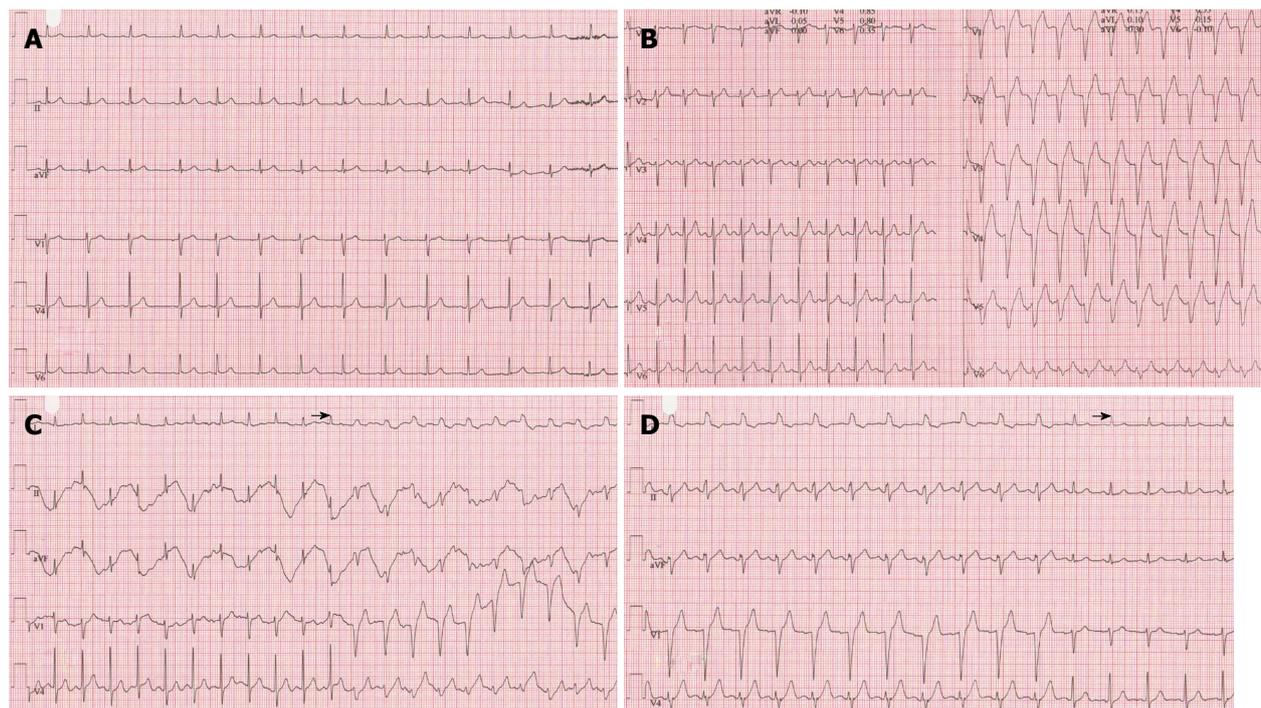
Figure 2 Resting electrocardiogram depicting normal sinus rhythm at a rate of 85 bpm with normal conduction (A), during exercise tolerance testing normal conduction till a frequency of 129 bpm (left panel) and at a heart rate of 141 bpm (right panel) a left bundle branch block occurred which recovered at a frequency of 96 bpm (not shown) (B), on repeat exercise tolerance tests, under β-blocker therapy, exercise-induced left bundle branch block occurred at a heart rate of 129 bpm (C) and disappeared at a frequency of 100 bpm (D). Black arrows indicate the transition from normal to abnormal conduction and vice versa.

sion as compared to baseline ECG and/or non-specific anignal complaints in the absence of ECG evidence of ischemia; and (4) Non-interpretable: if less than 85% of the target heart rate was reached and absence of the criteria of a positive test.

Left bundle branch block: The diagnosis of complete LBBB was made from the 12-lead ECG if all the following criteria were accordingly met: (1) a QRS duration ⩾ 120 ms, (2) predominantly upright complexes with broad-slurred R waves in leads I and V6, (3) a QS or rS pattern in V1 and (4) absence of q wave in leads I or V6.

DISCUSSION

Intermittent bundle branch block was first described by Lewis in 1913[10]. Exercise-induced LBBB associated with angina pectoris in the presence of normal coronary arteries is infrequent but a well known clinical entity and has been reported earlier by Vieweg *et al*[11] in 1976. It has been found in association with underlying structural heart disease[12], slow arterial coronary flow[13], coronary spasm[14] and also in subjects without heart disease[15]. Virtanen *et al*[16] defined the chest complaints as atypical characterized by sudden onset, starting simultaneously with the appearance of EI-LBBB, not radiating and associated with palpitation and walk through phenomenon. EI-LBBB occurs when the frequency reaches or exceeds the refractory period of one of the bundles. Both transient RBBB and LBBB may be induced during exercise

tolerance test. On follow-up, significant CAD was detected in all patients with EI-RBBB and in only 70% of patients with EI-LBBB[3]. EI-LBBB is more prevalent (74%) than RBBB (26%), with a heart rate at onset varying from 74 to 170 bpm and associated with high prevalence of significant CAD (70%)[3]. In the first patient, EI-LBBB ensued at a heart rate of 94 bpm, later coronary angiography showed multi-vessel disease requiring percutaneous intervention which was successfully performed. In our second patient, EI-LBBB accompanied with chest pain started at a frequency of 141 bpm with a QRS width of 138 ms and following treatment with B-blocker, EI-LBBB occurred at a heart rate of 129 bpm without alteration of QRS width. An explanation for the failure of beta-blocker to abolish EI-LBBB may be related to inappropriate dose of the drug used for an "unknown" substrate.

In a study by Schultz *et al*[17] in 1986, in 4 patients with EI-LBBB compared with normal controls, significant differences between the left and the right ventricle were observed in a mean phase imaging. When typical angina was present in association with EI-LBBB, abnormal myocardial perfusion scans were significantly frequent (68%) *vs* (25%) of atypical chest pain[18]. In our second case, no abnormalities were depicted on stress myocardial perfusion test. Mechanism of rate-dependent-LBBB has been delineated by Neuss *et al*[19] in 1974, they postulated that rate-dependent-LBBB during rapid atrial stimulation is due to increased recovery time of the involved bundle branch, failure of anticipated shortening of action poten-

tial with increasing heart rate and postdrive depression of conductivity. Another possible mechanism for EI-LBBB, is the presence of microcirculatory ischemia undetectable by coronary angiography as proposed by Loubeyre *et al*[20]. Furthermore, paradoxical septal motion may be responsible for the chest discomfort in EI-LBBB [16].

In 2011, Tanaka *et al*[7] demonstrated in a case report that EI-LBBB occurring at a heart rate of 100 bpm during treadmill exercise testing is associated with significant left ventricular intraventricular mechanical dyssynchrony, confirmed by speckle tracking radial time strain which has resolved after pharmacological intervention with β-blocker and angiotensin II antagonist.

On the other hand, transient LBBB at a heart frequency of 100 bpm on a "resting" ECG and echocardiographic confirmation of interventricular dyssynchrony (80 ms difference in aortic and pulmonary preejection time) have been described in a patient with flecainide self intoxication, both have resolved after discontinuation of the drug[21]. None of our patients was on flecainide therapy.

The prognostic significance of EI-LBBB has been variably reported[22]. Grady *et al*[5] have shown that EI-LBBB independently predicts a higher risk of death (29%) and major cardiac events (19%) compared with matched control group, (25%) and (10%), respectively. The total event rate was 76% for EI-LBBB (28/37) group versus 24% for the control group (9/37). In the study of Candell Riera *et al*[15], they found that the prognosis of patients with EI-LBBB associated with chest pain and normal coronary arteries is favorable but on follow-up permanent LBBB developed (5 out of 8 patients) and atrioventricular block rarely occurred requiring pacemaker implantation (1 out of 8 patients)[15]. Hertzeanu *et al*[22] suggested that heart rate at which EI-LBBB is a prognostic factor, *i.e.*, the onset of EI-LBBB at a heart rate of ≤ 120-125 bpm correlated with the occurrence of occlusive CAD, as was the case in our first patient, whereas subjects who develop EI-LBBB at a heart rate of ≥ 120-125 bpm have a normal coronary arterial tree and a better prognosis which was demonstrated in our second patient. However, when coronary artery disease is the cause of asymptomatic (silent ischemia) EI-LBBB occurring even at a heart rate of 188 bpm, the overall prognosis tends to be poor[12]. It has been suggested that the onset of EI-LBBB at a heart rate of ≥ 125 bpm is highly correlated with the presence of normal coronary arteries[23], but in some cases it has been observed to occur at a lower heart rate of 105 bpm[24]. Our second patient developed EI-LBBB at heart rate of 141 bpm without β-blocker and at 129 bpm under β-blocker therapy without evident significant CAD.

The importance of history taking regarding the nature of presenting chest pain, typical or atypical has been elaborated by Vasey *et al*[23]; CAD was present in EI-LBBB with classic angina but otherwise absent when atypical chest pain was prevalent. In the eighties, in the study of Hardarson *et al*[2], no increase in mortality rate due to CAD or hypertension was observed among subjects with permanent LBBB. Recently, it has been shown in phar-

macologically and invasively treated patients with permanent LBBB and high-risk myocardial perfusion SPECT, that cardiac deaths, mostly sudden, occurred in 18% of patients[25]. These findings renders the current treatment policy of such group of patients to be revisited.

Not only EI-LBBB may be associated with CAD in 70% of patients but also CAD had been documented in 100% of patients with EI-RBBB[3]. Recently, Bussink *et al*[26], delineated that newly acquired RBBB in adult population is associated with increased risk of myocardial infarction and pacemaker implantation but not with chronic heart failure, atrial fibrillation or chronic obstructive pulmonary disease. On the contrary to the findings of Breithardt[8], RBBB is found to be associated with increased cardiovascular risk and all-cause mortality in men and women. Thus even the development of RBBB in asymptomatic individuals should attract our attention for cardiovascular risk[26].

ACKNOWLEDGEMENTS

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CASE REPORT

Complete regression of cardiac involvement associated with lymphoma following chemotherapy

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Abstract

Cardiac involvement as an initial presentation of malignant lymphoma is a rare occurrence. We describe the case of a 26 year old man who had initially been diagnosed with myocardial infiltration on an echocardiogram, presenting with a testicular mass and unilateral peripheral facial paralysis. On admission, electrocardiograms (ECG) revealed negative T-waves in all leads and ST-segment elevation in the inferior leads. On two-dimensional echocardiography, there was infiltration of the pericardium with mild effusion, infiltrative thickening of the aortic walls, both atria and the interatrial septum and a mildly depressed systolic function of both ventricles. An axillary biopsy was performed and reported as a T-cell lymphoblastic lymphoma (T-LBL).

Following the diagnosis and staging, chemotherapy was started. Twenty-two days after finishing the first cycle of chemotherapy, the ECG showed regression of T-wave changes in all leads and normalization of the ST-segment elevation in the inferior leads. A follow-up Two-dimensional echocardiography confirmed regression of the myocardial infiltration. This case report illustrates a lymphoma presenting with testicular mass, unilateral peripheral facial paralysis and myocardial involvement, and demonstrates that regression of infiltration can be achieved by intensive chemotherapy treatment. To our knowledge, there are no reported cases of T-LBL presenting as a testicular mass and unilateral peripheral facial paralysis, with complete regression of myocardial involvement.

Core tip: In this report, we describe the case of a 26 year old man who was admitted with infiltration of the pericardium, aortic walls, both atria and the interatrial septum. An axillary biopsy was performed and reported as a T-cell lymphoblastic lymphoma (T-LBL). Following the diagnosis and staging, chemotherapy was started. Twenty-two days after finishing the first cycle of chemotherapy, a follow-up two-dimensional echo confirmed regression of the myocardial infiltration. We describe an unusual case of precursor T-LBL presenting with cardiac involvement and demonstrate that regression of myocardial infiltration can be achieved by intensive chemotherapy treatment.

Vinicki JP, Cianciulli TF, Farace GA, Saccheri MC, Lax JA, Kazelian LR, Wachs A. Complete regression of cardiac involvement associated with lymphoma following chemotherapy. *World J Cardiol*

INTRODUCTION

Gross tumor formation in any of the cardiac chambers is rare, particularly at the time of presentation and in cases of lymphoma[1-4]. Symptoms are usually very subtle and non-specific, particularly in the setting of co-existing morbidities. We report an unusual case of a 26 year old man presenting with a gross intracardiac mass, testicular mass and unilateral peripheral facial paralysis, who was ultimately diagnosed with T-cell lymphoblastic lymphoma (T-LBL).

CASE REPORT

The patient is a 26-year-old man, presenting with a testicular tumor and peripheral facial paralysis noted 21 d before admission. Physical exam revealed a left peripheral facial paralysis and ipsilateral conjunctival congestion, bilateral supraclavicular and inguinal lymph nodes, left axillary nodes and a left testicular tumor measuring 7 cm × 5 cm, as well as signs consistent with bilateral (predominantly right sided) pleural effusion. On electrocardiograms (ECG), there was sinus tachycardia, ST-segment elevation in leads Ⅱ, Ⅲ and aVF and negative T waves in all leads except aVR. Laboratory values were remarkable for anemia (hematocrit 36%), leukocytosis (13000/mL), thrombocytosis (615000/mL) and lactate dehydrogenase of 1787 UI/L.

The computed tomography (CT) showed an orbit with diffuse thickening of the inferior, medial and lateral rectus muscles, a right maxillary sinus filled with a polypoid structure and soft tissue density, a cluster of lymph nodes in the mediastinum causing a mass effect in the adjacent vessels, pericardial thickening and another lymph node cluster in the abdomen involving areas of the aorta and its branches (celiac axis, left iliac artery and left renal artery). On 2-dimensional echocardiography (2D-echo) (Figures 1A and 2A), there was pericardial infiltration with very mild effusion, infiltrative thickening of the aortic walls, left atrium, right atrium, interatrial septum and the tricuspid annulus, and mildly depressed systolic function of both ventricles. The axillary biopsy revealed findings consistent with T-LBL.

Following diagnosis and staging, chemotherapy was started, according to the HyperCVAD regimen (hyperfractionated cyclophosphamide, vincristine, adriamycin and dexamethasone). Treatment consisted of Ⅳ cyclophosphamide and mesna during the first three days, combined with high dose dexamethasone 4 times a week during the first 15 d. Additionally, methotrexate, citarabine and dexamethasone were injected into the intrathecal space once a week during the first two weeks. Doxorubicin and vincristine were administered the day after discontinuing cyclophosphamide and on day 11 a new dose of the second agent was added.
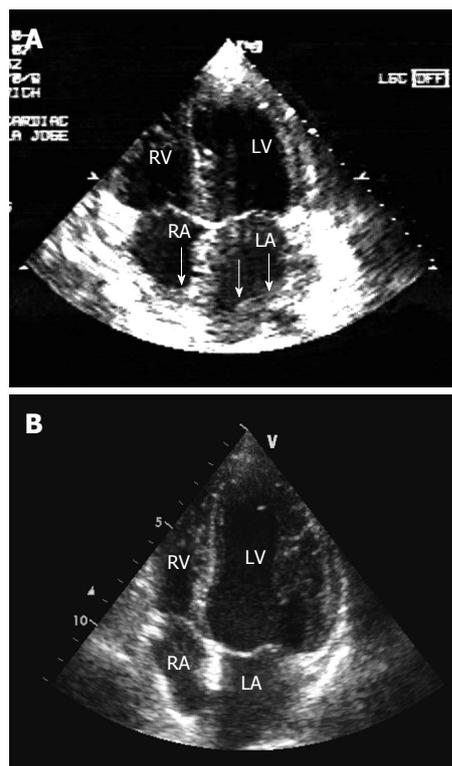
Figure 1 Two-dimensional echocardiography - 4-chamber view. A: Before chemotherapy, the echocardiogram showed tumor infiltration of the myocardium of both atria and the atrial septum (see arrow); B: After chemotherapy, the echocardiogram showed total regression of myocardial infiltration. RA: Right atrium; RV: Right ventricle; LA: Left atrium; LV: Left ventricle.

Twenty-two days after finishing the first course of chemotherapy, the ECG showed significant regression of the negative T waves in all leads and of the ST segment elevation in the inferior leads. Follow-up 2D echo confirmed total regression of the cardiac and aortic infiltrate (Figures 1B and 2B).

The patient required multiple admissions due to progression of his baseline disease; dissemination was found in the bone marrow, nerve roots, meninges, cranial nerves and bone, with partial response to chemotherapy. Other regimens were tried and despite maximum support measures the patient died after the fourth hospital admission.

DISCUSSION

In our patient, cardiac involvement was not the main pathological process and the systemic component was quite evident. Hence, the case is consistent with a diffuse cardiac infiltration by lymphoma.

In the literature, the majority of patients reported present with various and non-specific symptoms, such as dyspnea, edema, arrhythmia, cardiac tamponade (metastatic tumors of the heart have also been associated with pericardial effusion, particularly hemorrhagic effusion), palpitations and congestive heart failure, and are related to the location and volume of the tumor as well as the functional status of the heart[1,5-8]. In one large study, the incidence of signs and symptoms plus electro-
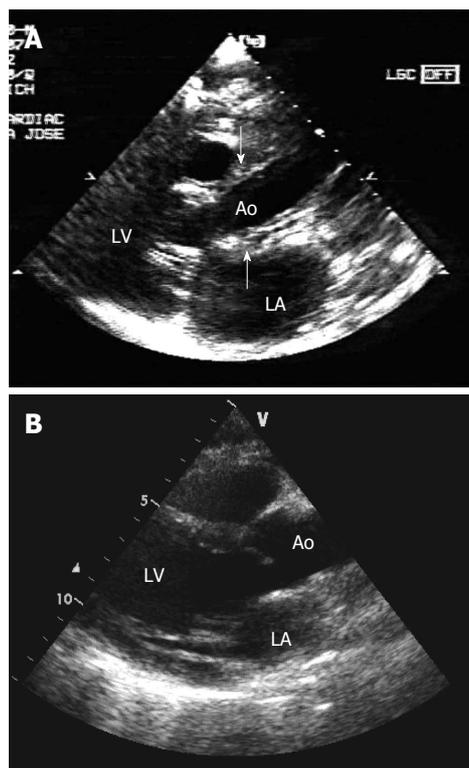
Figure 2 Two-dimensional echocardiography - parasternal long-axis view. A: Before chemotherapy, the echocardiogram showed tumor infiltration of the aorta (see arrows). B: After chemotherapy, the echocardiogram showed total regression of aortic infiltration. LA: Left atrium; LV: Left ventricle; Ao: Aorta.

cardiographic abnormalities in patients who died with malignant lymphoma was similar in those with cardiac metastases when compared to those without cardiac metastases[9]. Scott *et al*[10] stated that the most important sign of cardiac invasion in a patient with malignant disease is the onset of congestive heart failure without another apparent cause. The presence of cardiac arrhythmias under similar conditions is also suggestive.

Based upon the data of 22 large autopsy series, Reynen *et al*[11] established that the frequency of primary cardiac tumors is approximately 0.02%, corresponding to 200 tumors in 1 million autopsies[8]. Most of these primary cardiac tumors are intracavitary and preferentially develop in the left atrium, thereby leading to left ventricular inflow obstruction. Embolism is also common[8]. Primary cardiac lymphoma, defined as a lymphoma involving only the heart and pericardium, is extremely rare, with a reported incidence ranging from 0.15% to 1%[1,5]. Secondary cardiac infiltration from nodal lymphoma of the mediastinum appears to be more common with approximately 35%-40% of patients dying with malignant lymphomas reported to have myocardial involvement. The majority of reported cases were diagnosed at autopsy because of the rapid progression and non-specific clinical symptoms[1-4]. In our case, this entity was prospectively diagnosed *in vivo* by two-dimensional echocardiography. We have found only 4 reports previous to the present case (Table 1)[12-17] of metastatic cardiac lymphoma[13-16].

Roberts *et al*[9] carried out a necropsy study of 196 patients with malignant lymphoma and found cardiac disease in 48 cases. Among all lymphoma subtypes, cardiac infiltration was seen in 16% of patients with Hodgkin's lymphoma, 25% of patients with non-Hodgkin's lymphoma, and 33% of patients with mycosis fungoides. Of these 48 patients, lymphoma was identified grossly in the heart in 27 cases and found on microscopical examination alone in 21. The pericardium and epicardial fat, particularly in the atrioventricular sulci, were most commonly affected. Nodular deposits within the cardiac chambers were also found[8,18,19]. According to a study of 25 autopsy cases, T-cell lymphomas, compared with B-cell lymphomas, invade the heart more frequently and aggressively and are associated with a variety of cardiac manifestations[4].

Most cases of cardiac lymphoma are solid, infiltrative nodular tumors affecting 1 or several cardiac chambers[13-17]. The right heart is the most common site of cardiac lymphoma. Lymphomatous infiltration of the pericardium is also seen in a number of cases. In contrast, cardiac valve involvement with hematogenous malignancies is uncommon and has been rarely reported to occur as a result of the direct extension of malignant lymphoma from extravascular lesions[2]. In our patient, the initial description of the first 2D-echo in the clinical case showed severe thickening and infiltration of the myocardium and its subsequent regression after chemotherapy.

The method of choice to detect cardiac metastases and their complications is 2D-echo. It is a simple, safe and non-invasive method and can provide better anatomic details than other more invasive studies[8,11,18,20].

The infiltrating masses have a peculiar, granular echocardiographic texture which is always different to normal myocardium. The ventricular walls appear thickened and hypokinetic or even akinetic in the area of infiltration. The transmural invasion modifies the epicardial and endocardial contours. All these aspects allow the differential diagnosis with thrombi or other masses, which can be adherent to the endocardium[17].

Although cardiac metastases may rarely be the first presenting sign of an underlying malignancy, the presence of malignant disease elsewhere is an important clue to the etiology of an intracavitary infiltration[11].

In 1992, Lestuzzi *et al*[21] studied the usefulness of transesophageal echocardiography (TEE) performed on 70 patients for the evaluation of paracardiac neoplastic masses (26 patients had non-Hodgkin's lymphoma, 23 had Hodgkin's lymphoma and the rest corresponded to isolated cases of mediastinal tumors). Twenty-three patients underwent repeat TEE after medical or radiation therapy treatments: a total of 101 TEE examinations were performed. The TEE allowed better visualization of the mass, cardiac chambers and great vessels than transthoracic echocardiography in 68 of 101 examinations. Most of the patients underwent CT within 2 wk of TEE. The TEE and CT data were comparable in 58

Table 1 Characteristics of 7 reported cases of cardiac metastatic lymphoma

Ref.	Age/sex	Symptoms	Type of lymphoma	Localization in heart	Diagnostic tools	Therapy and evolution
Wiernik et al[12]	42/M	Ureteral obstruction Acute myocardial infarction Heart failure	Lymphocytic lymphoma	Gross infiltration of the lateral wall of the left ventricle	Autopsy	Chemotherapy Radiotherapy Died 9 yr later
Lestuzzi et al[13]	23/F	None	Lymphoblastic lymphoma	Cardiac apex	2D-echo	Local radiotherapy Died 12 mo later
	53/F	Dyspnea	Burkitt's lymphoma	Epicardium, posterior ventricular wall and interventricular septum	2D-echo	Local radiotherapy Died 20 d later
Lynch et al[14]	NA	NA	NA	Pericardial and myocardial	NA	Chemotherapy
Cracowski et al[15]	25/M	Dyspnea	High grade malignant lymphoma	Left ventricular hypertrophy with increased echogenicity of the myocardial walls and marked decrease in left ventricular ejection fraction	2D-echo, EMB	Chemotherapy
Cho et al[16]	39/F	Dyspnea and palpitation	Diffuse large cell type non-Hodgkin's lymphoma	Interventricular septum and left ventricular posterior wall	2D-echo	Chemotherapy
Bergler-Klein et al[17]	34/F	None	Burkitt's lymphoma	Asymmetric hypertrophy of the mid and distal septum with a speckled appearance of the myocardium and LV apical region	2D-echo MRI, PET	Chemotherapy Died 9 mo later
Vinicki et al	26/M	Testicular mass and unilateral peripheral facial paralysis	T-cell lymphoblastic lymphoma	Pericardial, aorta, both atrial and the interatrial septum	2D-echo	Chemotherapy Died 4 mo later

2D-echo: Two-dimensional echocardiography; EMB: Endomyocardial biopsy; F: Female; M:Male; MRI: Magnetic resonance imaging; NA: Not applied.

cases. In 14 of 58 cases, the anatomic data (site, size of the mass, cardiovascular infiltration) obtained by TEE fully corresponded to those obtained by CT. In 3 cases, TEE clearly demonstrated an intracardiac extension of the mass not detected by CT. In 30 cases in which CT was not diagnostic, TEE allowed diagnosis of or exclusion of the infiltration of cardiovascular structures. In 34 patients, TEE contributed additional hemodynamic data not obtained by any other imaging technique. As a conclusion, they consider that CT scan is less precise in defining highly mobile structures, does not provide real-time images, structures are shown on a smaller scale and transthoracic echocardiography is limited mostly to neoplasms of the anterior mediastinum. In contrast, TEE allows a better visualization of the mediastinum (albeit with "blind areas" due to the airway) which allows making the differential diagnosis between vascular and nonvascular lesions, assessing the superior vena cava and pulmonary vein flow, the infiltration of the descending thoracic aorta and the pulmonary artery and its branches[21].

Compared to ultrasound, computed tomography and magnetic resonance imaging (MRI) provide tissue differentiation between solid, liquid, hemorrhagic and fatty lesions and myocardial metastases can be better delineated. The most compelling indication for MRI is pre-operative assessment of patients with known cardiac masses. According to Lund et al[22], it helps to determine the need to operate and aided in surgical planning[8,22,23].

Cardiac treatment is mostly confined to palliative measures. Surgical resection is only indicated in exceptional cases of solitary intracavitary heart metastases, leading to obliteration of cardiac chambers or valve obstruction if the tumor of origin was surgically resected *in toto* and the patient appears to have a good progno-

sis[8,20,24,25]. Frequently, however, complete resection fails and postoperative mortality is high[2,8]. Usually, cardiac infiltrates in leukemia and lymphoma respond well to radio- or chemotherapy[1,7,8].

Here, we describe an unusual case of precursor T-LBL presenting with a testicular mass, unilateral peripheral facial paralysis and cardiac involvement, and demonstrate that regression of myocardial infiltration can be achieved by intensive chemotherapy treatment. The definitive diagnosis should have been made by myocardial biopsy, which was certainly not indicated in our patient given his severe systemic involvement.

Although the progression of the disease could be suppressed during chemotherapy, it relapsed early after completing the treatment cycles. Interestingly, although the relapse occurred at several sites different from the initial site of presentation, it did not involve the myocardium.

Secondary neoplastic myocardial infiltration, although frequent at autopsy, is rarely recognized *in vivo*. In our case, this entity was prospectively diagnosed *in vivo* by 2D-echo echocardiography. In addition, it allowed recognition of myocardial infiltration and definition of the location and size of metastases and it helped to decide the most appropriate therapy and to assess the results. Identification and treatment of all secondary neoplastic localizations, however, is important and of clinical relevance, mainly for tumors entailing a less guarded prognosis.

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CASE REPORT

Endovascular technique using a snare and suture for retrieving a migrated peripherally inserted central catheter in the left pulmonary artery

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Abstract

We report a successful endovascular technique using a snare with a suture for retrieving a migrated broken peripherally inserted central catheter (PICC) in a chemotherapy patient. A 62-year-old male received monthly chemotherapy through a central venous port implanted into his right subclavian area. The patient completed chemotherapy without complications 1 mo ago; however, he experienced pain in the right subclavian area during his last chemotherapy session. Computed tomography on that day showed migration of a broken PICC in his left pulmonary artery, for which the patient was admitted to our hospital. We attempted to retrieve the ectopic PICC through the right jugular vein using a gooseneck snare, but were unsuccessful because the catheter was lodged in the pulmonary artery wall. Therefore, a second attempt was made through the right femoral vein using a snare with triple loops, but we could not grasp the migrated PICC. Finally, a string was tied to the

top of the snare, allowing us to curve the snare toward the pulmonary artery by pulling the string. Finally, the catheter body was grasped and retrieved. The endovascular suture technique is occasionally extremely useful and should be considered by interventional cardiologists for retrieving migrated catheters.

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Key words: Port catheter; Catheter migration; Endovascular suture technique

Core tip: Catheter migration has been reported as a delayed complication of peripherally inserted central catheter (PICC). Retrieval by the endovascular technique using a snare is usually attempted in cases of PICC migration, but there have been some difficulties in retrieving the broken catheter. We encountered a patient with an ectopic PICC in the left pulmonary artery; the ectopic PICC could not be retrieved by the usual method using a snare, but was successful retrieved using a snare and suture technique. The endovascular suture technique is a useful method to retrieve a dislocated or broken catheter and should be considered by interventional cardiologists.

INTRODUCTION

Chemotherapy drug administration through a peripher-

ally inserted central catheter (PICC) has been widely used because of several advantages such as easier PICC insertion and improved patient satisfaction[1]. The main complications of PICC are bloodstream infection and venous thrombosis[1,2], although catheter migration has been reported as a delayed complication[1,3,4]. In cases of PICC migration to the heart or pulmonary artery, retrieval by the endovascular technique using a snare is usually attempted[4,5], but some difficulties have been reported and the procedure requires several devices and advanced techniques[4-7]. We describe a patient with an ectopic PICC in the left pulmonary artery, which was successfully retrieved using a snare with a suture technique on the second attempt.

CASE REPORT

A 62-year-old male, who underwent surgeries for advanced colon cancer in November 2008 and for lung metastasis in February 2010, was receiving monthly chemotherapy through a central venous port to his right subclavian vein since March 2010. The last chemotherapy session was performed on November 22, 2010 and no problems occurred during this time. On December 20, 2010, he experienced pain in the right subclavian area during chemotherapy. Subsequent contrast-enhanced computed tomography (CT) showed an ectopic PICC in his left pulmonary artery (Figure 1); therefore, the patient was presented and admitted to our hospital for retrieval of the ectopic PICC on the same day. On admission, his vital signs were stable. Blood examination showed increase in D-dimer (3.6 mg/dL) and C-reactive protein (0.96 mg/dL) levels. In addition, he had poorly controlled diabetes mellitus, with hemoglobin A_1C level of 8.4%.

After informed consent was obtained, we attempted retrieval of the ectopic PICC through the right internal jugular vein using a 12-Fr sheath and 8-Fr guiding catheter. CT and pulmonary arteriography revealed that the distal end of the broken catheter was present in the left branch of the pulmonary artery and the proximal end was present in the left pulmonary artery trunk. Therefore, we decided to grasp the ectopic PICC from the proximal end of the catheter. Two goose neck snares (Amplatz GooseNeck, COVIDIEN) measuring 15 and 25 mm were used in our first attempt, but the PICC body could not be grasped because it was lodged in the pulmonary artery wall; we therefore discontinued the attempt because of the extended procedure time. The patient and his family were explained about the possible consequences of the presence of an ectopic PICC in the left pulmonary artery and they requested a second attempt at retrieval.

Three days later, the second retrieval attempt was made through the right femoral vein using 12 and 6-Fr long sheaths (Parent Plus, Medikit). At first, a balloon-occluded pulmonary arteriography (BOPA) was performed using a wedge balloon catheter (Selecon MP Catheter II, Terumo Clinical Supply), which showed

thrombosis of the arterial branch housing the distal end of the ectopic PICC. The proximal end of the ectopic PICC could not be grasped using a snare equipped with triple loops (En Snare, SHEEN MAN). Other catheters such as a 4-Fr Judkins right catheter and pig-tail catheter were inserted through the left femoral vein to lift the proximal end of PICC lodged in the pulmonary artery wall. However, these attempts failed to grasp the ectopic PICC. Finally, an endovascular suture technique was attempted. Several 2.0 sutures were tightly combined and tied to the bottom of the snare loops (Figure 2A) to guide the snare downward. The 6-Fr guiding catheter was switched for an 8-Fr guiding catheter because the 2.0 sutures could not be inserted into a 6-Fr sheath. After the snare was inserted into the left pulmonary artery, it was curved downward toward the pulmonary artery by pulling the string, thus allowing us to grasp the proximal end of the ectopic PICC (Figure 3) and retrieve it (Figure 2B). Two days later, the patient was discharged without any complications.

DISCUSSION

We encountered a patient with an ectopic PICC in the left pulmonary artery; the ectopic PICC could not be retrieved by the usual method using a snare, but was successfully retrieved using a snare/suture technique.

Although the main complications of PICC are bloodstream infection and venous thrombosis[1,2,8], migration of a broken catheter has been reported as a delayed complication[1,3]. Catheters can migrate at an estimated rate of 0%-3.1%[9,10] within 1.5 years[4]. The most common sign of catheter migration is irrigation resistance to infusion[4], which indicates that a few weeks have elapsed since the onset of an ectopic PICC. Even in the present case, the exact time of the ectopic PICC migration was unknown, and a few weeks may have elapsed before it was detected. The delayed discovery of the ectopic PICC in our case and the use of a thicker catheter, may have caused the catheter to lodge in the pulmonary artery wall, thereby complicating the retrieval procedure.

In general, ectopic PICC management includes percutaneous transcatheter retrieval, open thoracotomy, and long-term anticoagulation therapy[6]. However, cases of fatal cardiac tamponade following migration of a broken catheter have been reported[2]; therefore, percutaneous transcatheter retrieval is usually performed as the first treatment. In the present case, an ectopic PICC extended from the left pulmonary artery trunk to the branch of the left pulmonary artery, in which a thrombosis occurred. Although, cardiac tamponade and pulmonary artery perforation seldom occur, an ectopic PICC may cause an increased incidence of thrombosis in the left pulmonary artery, which may cause clinical symptoms or may act as a source of potential infection. Therefore, after we considered the patient's requests and the possibility of complications, we attempted percutaneous transcatheter retrieval twice.
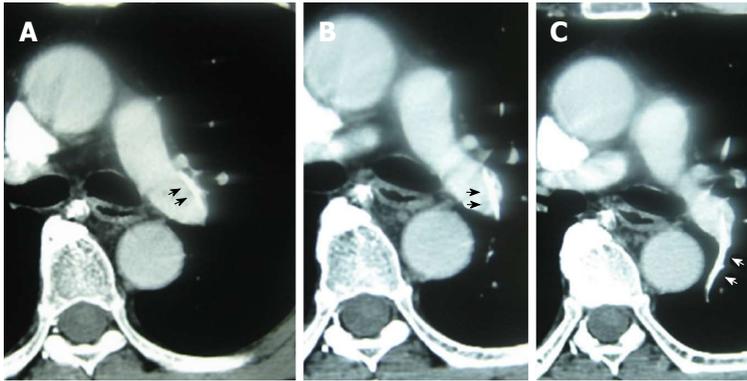
Figure 1 Contrast-enhanced computed tomography showing the proximal end of the catheter lodged in the wall of the left pulmonary artery trunk (A and B); the distal catheter end was in the small branch of left pulmonary artery (C). The broken catheter is indicated by arrows.
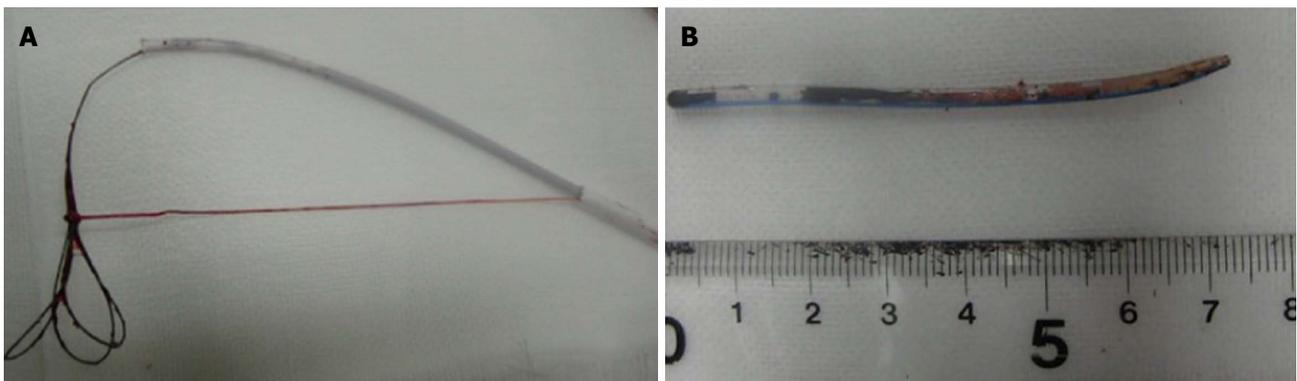

Figure 2 Snare with a suture technique and the retrieved catheter. A: A snare with a suture was curved downward by pulling the string; B: The retrieved catheter.
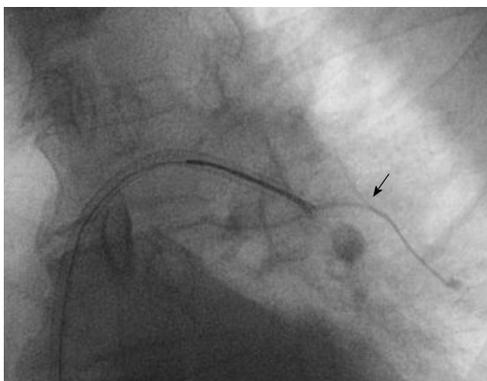
Figure 3 Image of the procedure. The second attempt using the snare with a suture technique was successful to grasp of the body of broken catheter. The broken catheter is indicated by an arrow.

There have been several reported percutaneous transcatheter retrieval techniques using a snare, basket catheter, pigtail catheter, or ablation catheter[4-7]. However, it may be important to grasp the center of the catheter body to contain it within a guiding catheter or a long sheath. Contrast-enhanced CT and/or pulmonary arteriography, including BOPA, are useful to assist the surgeon in deciding the catheter end to be grasped. Furthermore, it may be more important to remove the end of catheter from the vessel wall or myocardium to enable the surgeon to grasp the catheter body using a snare. However, in the present case, other devices such as a pigtail catheter did not help to retrieve the broken catheter end

because it was lodged in the vessel wall. Therefore, we had to guide the snare downward toward the vessel wall and subsequently use the snare with an endovascular suture technique[7]. The guidewire or catheter can be easily controlled by pulling the attached string. Although this technique is interesting and a useful method to control catheter movement, it may be associated with the risk of vascular injury and other unresolved problems such as the thickness and type of suture used.

In conclusion, the endovascular suture technique is occasionally an extremely useful method to retrieve a dislocated or broken catheter and should be considered by interventional cardiologists.

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LETTERS TO THE EDITOR

Persistent left superior vena cava and pacemaker implantation

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Core tip: The letter focuses in detail on the noninvasive diagnosis of persistent superior left vena cava, which is mandatory before pacemaker implantation.

Abstract

Our study group read with interest the paper from Vijayvergiya *et al* describing the implantation of an implantable cardioverter-defibrillator lead in the presence of the persistence of the left superior vena cava. The issue of the identification a persistent left superior vena cava is of paramount importance in interventional cardiology, being the most common venous anomaly of the thoracic distribution, and because it may create some problem to any physician while performing a pacemaker lead implantation. In our letter we underscore the specific issues related to pacemaker implantation while encountering a persistent left superior vena cava (and maybe the absence of the right vena cava) and the workup that should be performed to obtain the preoperative diagnosis of the venous anomaly. More specifically, we consider avoiding any kind of defibrillator lead implantation through the coronary sinus for safety issues, and underscore the straightforward transthoracic ultrasound approach to identify the left superior vena cava.

TO THE EDITOR

We have read with interest the contribution from Vijayvergiya *et al*[1], who describe a tricky case of implantable cardioverter-defibrillator (ICD) implantation facing the persistence of the left superior vena cava (PLSVC).

A few years ago we experienced a similar situation with a VVI pacemaker implantation[2]: nonetheless, we would like to underscore some peculiar and personal features we think should always be born in mind before a pacemaker is implanted. Firstly, a complete ultrasound examination should be obtained before implantation in order to rule out anatomical difficulties, *e.g.*, PLSVC. In our case we did not perform an echocardiogram because of the precipitating clinical situation, but in routine settings the EP physician should always be aware of detailed cardiac anatomy. Secondly, we discourage lead implantation-especially of an ICD lead, when the existence of a right vena cava has been proven even though the procedure has started with a left-side approach. Caution is needed when trying to place any kind of lead through the coronary sinus in order to avoid ominous tears or dissections[3].

Moreover, as we describe in a previous paper regarding the diagnostic features of this venous anomaly, the evaluation of venae cavae anatomy with transthoracic echocardiography is not difficult[4], and in the presence of a poor acoustic window a transesophageal approach may be helpful. The pre-operative diagnosis of PLSVC may be suspected whenever a dilated coronary sinus is identified at transthoracic echocardiography and it can be confirmed by sequential injection of agitated saline in both left and right arm veins, avoiding further invasive examinations and favoring a correct planning of the implantation technique.

PLSVC still remains a ghost-like entity, usually passing unobserved or diagnosed by chance. On the contrary, its recognition before invasive procedures is paramount to avoid medical errors, loss of time and suboptimal results.

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Contents

Contents

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AIM AND SCOPE

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BRIEF ARTICLE

Migraine attack restores the response of vascular smooth muscle cells to nitric oxide but not to norepinephrine

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Abstract

AIM: To clarify whether the vasoconstrictory response is impaired and to study vascular function in patients with migraine during the headache attack.

METHODS: We studied vascular reactivity in the resistance arteries by using the forearm perfusion technique associated with plethysmography. We measured forearm blood flow by strain-gauge plethysmography during intra-brachial infusion of acetylcholine, sodium nitroprusside or norepinephrine in 11 controls and 13 patients with migraine, 11 of them (M) in the interval between the migraine attacks and 4 during a headache attack (MH). Written informed consent was obtained from patients and healthy controls, and the study was approved by the Ethics Committee of the University Federico II.

RESULTS: Compared to healthy control subjects, in patients with migraine studied during the interictal period, the vasodilating effect of acetylcholine, that acts through the stimulation of endothelial cells and the release of nitric oxide, was markedly reduced, but became normal during the headache attack ($P < 0.05$ by analysis of variance). The response to nitroprusside, which directly relaxes vascular smooth muscle cells (VSMCs), was depressed in patients with migraine studied during the interictal period, but normal during the headache attack ($P < 0.005$). During norepinephrine infusion, forearm blood flow decreased in control subjects (-40% ± 5%, $P < 0.001$). In contrast, in patients with migraine, either when studied during or free of the headache attack forearm blood flow did not change compared to the baseline value (-3% ± 13% and -10.4% ± 15%, $P > 0.05$).

CONCLUSION: In migrainers, the impaired relaxation of VSMCs is restored during the headache attack. The vasoconstrictory response is impaired and remains unchanged during the migraine attack.

Key words: Migraine; Nitric oxide; Endothelium; Vascular smooth muscle cells

Core tip: Patients with migraine without aura studied in the interictal period are characterized by impaired abil-

ity of vascular smooth muscle cells (VSMCs) to relax in response to nitric oxide and to contract in response to norepinephrine. We hypothesize that the two defects compensate for each other and this provides for the maintenance of normal vascular resistance and blood pressure homeostasis. In contrast, during the headache attack, the VSMCs regain their ability to respond to nitric oxide, but remain unresponsive to norepinephrine. Such differential effect of the migraine attack is not surprising, given that nitric oxide and norepinephrine activate different intracellular signaling pathways in VSMCs.

INTRODUCTION

Migraine is a widely common disease. Two thirds of migraineurs suffer from migraine without aura, whereas a third of patients present with migraine preceded by aura. Migraine has been associated with an increased risk of cardiovascular events, including myocardial infarction and ischemic stroke[1-3]. However, we have recently demonstrated that patients with migraine without aura, studied during the interictal period, do not present peripheral endothelial dysfunction, which is classically associated with a worse cardiovascular risk profile, but rather an abnormal relaxation of the vascular smooth muscle cells (VSMCs), that results in impaired vasodilation[4,5]. However, it is unclear whether the inability of VSMCs to respond to vasodilators is an isolated abnormality or, rather, reflects a more complex hemodynamic alteration, also involving the vasoconstrictory component. Furthermore, the peripheral vascular function in patients with migraine has been studied mainly during the interictal period. Therefore, whether the abnormalities in vascular function observed in patients with migraine are also present during the headache attack is unknown. Elucidation of the vascular response in patients with migraine both free of and during the headache episode would be of great importance to our understanding of the mechanisms involved in the pathogenesis of the disease and to better design appropriate therapeutic approaches.

MATERIALS AND METHODS

Patients

We studied 13 patients affected by migraine without aura and eleven healthy subjects in whom migraine was excluded, who served as controls (Table 1). The control subjects (C group) were recruited from hospital and laboratory personnel and were matched to the patients with

Table 1 Baseline clinical characteristics of the subjects studied (mean ± SE)

	Sex (male/female)	Age (yr)	BMI (kg/m²)	SBP (mmHg)	DBP (mmHg)	HR (beats/min)
Controls (n = 11)	5/6	33 ± 3.4	24 ± 0.8	127 ± 2.1	60 ± 1.8	65 ± 2
M (n = 11)	4/7	34 ± 1.9	24 ± 1.1	125 ± 3.3	65 ± 2.6	68 ± 3
MH (n = 4)	0/4	28 ± 3.9	24 ± 0.9	115 ± 4.2	60 ± 1.8	68 ± 2

The patients with migraine were studied during the interictal period (group M) or the headache attack (group MH). BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; HR: Heart rate.

regard to age, body mass index and sex. The diagnosis of migraine was made according to the criteria of the International Headache Society[6,7]. Subjects with hypertension, diabetes, high cholesterol, history of cardiovascular events and cigarette smoking were excluded from the study. None of the patients was taking any medication except those to treat the migraine attack. On the day of study, patients were either headache free for at least five days (11 subjects, M group) or were experiencing a headache attack that had started a few hours earlier (4 patients, MH group). These patients abstained from taking any medication until the end of the study period. Two patients underwent both studies (free of or during the headache attack). Written informed consent was obtained from patients and healthy controls, and the study was approved by the Ethics Committee of the University Federico Ⅱ. This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Vascular reactivity

We studied vascular reactivity in the resistance arteries by using the forearm perfusion technique associated with plethysmography, as previously described[4,8-11]. Briefly, a plastic cannula (20 G) was inserted into the brachial artery of the nondominant arm under local anesthesia and used for the infusion of the test substances and the monitoring of arterial blood pressure and heart rate. Forearm blood flow (FBF) was measured in both forearms by strain gauge plethysmography, with a calibrated mercury-in-silastic strain gauge applied around the forearm and connected to a plethysmography (Hokanson 045 EC4, PMS. Instruments, Berks, United kingdom) associated with a McLab computer. Each subject underwent the following step-wise infusions into the brachial artery: (1) acetylcholine (Ach) to assess endothelial-mediated vasodilation; and (2) sodium nitroprusside (NP), a nitric oxide (NO) donor that directly stimulates VSMCs, to assess non-endothelial-mediated vasodilation. At least half an hour after the NP infusion and when baseline FBF was restored, each subject received the infusion into the brachial artery of norepinephrine (NE) at the rate of 280 μg/L per minute for 5.5 min to assess the vascular response to sympathetic stimulation. This dose of NE was chosen on the basis of our previous experiments that
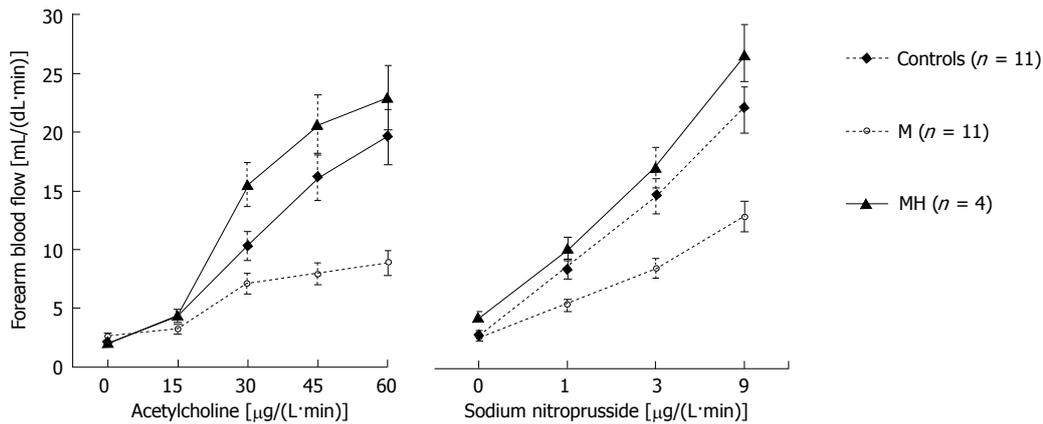
Figure 1 Forearm blood flow response to infusion of acetylcholine or sodium nitroprusside into the brachial artery in patients with migraine during or free from headache, and control subjects. The patients with migraine were studied during the interictal period (group M) or the headache attack (group MH). Data (mean ± SE) were analyzed by analysis of variance for repeated measures. *P* < 0.05 for the effect of migraine in the acetylcholine (Ach) test and *P* < 0.05 for the interaction between migraine and Ach. *P* < 0.005 for the effect of migraine in the nitroprusside test and *P* < 0.05 for the interaction between migraine and nitroprusside.

showed a near half-maximal fall in FBF. The investigators making the measurements of vascular reactivity were blind to the clinical status of the subjects undergoing the experiments.

Calculations

Based on previously published data[4], we computed the minimum sample size with respect to a two-tailed Student *t* test, considering: (1) a difference for the slope of the dose response curve to Ach to be detected between controls and migrainers as δ ≥ 0.25 mL/(dL·min·μg); (2) a value of SD = 0.156 mL/(dL·min·μg); and (3) a type I error probability = 0.05 and a power = 0.90. This results in a minimum sample size of *n* = 9 subjects for group. Since no data are available in the literature regarding the response to norepinephrine of FBF in migrainers, we decided to increase the number of subjects to be recruited to 11 per group.

Statistical analysis

The differences in clinical and metabolic parameters between the three study groups were analyzed by the unpaired Student's *t* test with Bonferroni correction for multiple comparisons. Vascular reactivity data are expressed as absolute values of FBF. Comparison between migraine and control subjects was performed by a two-way analysis of variance for repeated measures (General Linear Model, version 13.0, SPSS Inc., Chicago, IL, United States) and Least Significant Difference test was used for post hoc analysis. Comparison between baseline and NE infusion data was performed by the paired Student's *t* test. Results are expressed as mean ± SE.

RESULTS

The baseline values of FBF were similar in the three groups (Figure 1). Infusion of ACh, an endothelium-dependent vasodilator, elicited a progressive vasodilatory response in all groups (*P* < 0.001). However, in patients

with migraine studied during the interictal period, FBF response was lower than that of control subjects (*P* < 0.05). In contrast, patients studied during the headache attack showed a more intense response to Ach infusion (*P* < 0.02 *vs* M; Figure 1). In response to the highest dose of Ach, FBF rose to 19.6 ± 3.1, 8.8 ± 2.4, and 22.9 ± 2.2 mL/dL per minute in controls and migraine patients without or with headache attack, respectively (*P* = 0.036 for M group *vs* C and *P* < 0.02 *vs* MH). The response to ACh was also analyzed using the slope of the dose-response curves. In the patients with migraine without headache the average slope was markedly less steep than in controls (0.11 ± 0.05 and 0.31 ± 0.05 mL/(dL·min·μg), respectively; *P* = 0.03). In contrast, the slope of the dose response curve to Ach in migraine patients during the headache attack was similar to controls (0.39 ± 0.04 mL/(dL·min·μg), *P* < 0.02 *vs* M, *P* = NS *vs* C).

The dose-response curve to NP, an NO donor directly acting on VSMCs, is shown in Figure 1. As compared with controls, patients with migraine without headache showed a significantly lower response at all infusion rates (*P* = 0.004 *vs* C). In contrast, patients with migraine during the headache attack showed a response to NP similar to controls and markedly increased when compared to migrainers studied during the interictal period (*P* = NS *vs* C and *P* = 0.002 *vs* M). The maximal response of FBF to NP was 22.2 ± 1.9, 12.8 ± 1.9 and 26.6 ± 3.8 mL/dL per minute in controls and migraine patients without or with headache attack, respectively (*P* < 0.02 for M group *vs* C and MH). The response to NP was also analyzed using the slope of the dose-response curves. In the patients with migraine without headache the average slope was markedly less steep than in controls [1.05 ± 0.19 and 1.96 ± 0.20 mL/(dL·min·μg), respectively; *P* < 0.01]. In contrast, the slope of the dose response curve to NP in migraine patients during the headache attack was similar to controls [2.29 ± 0.29 mL/(dL·min·μg), *P* < 0.02 *vs* M, *P* > 0.05 *vs* C].

In Figure 2, we report the dose response curves to
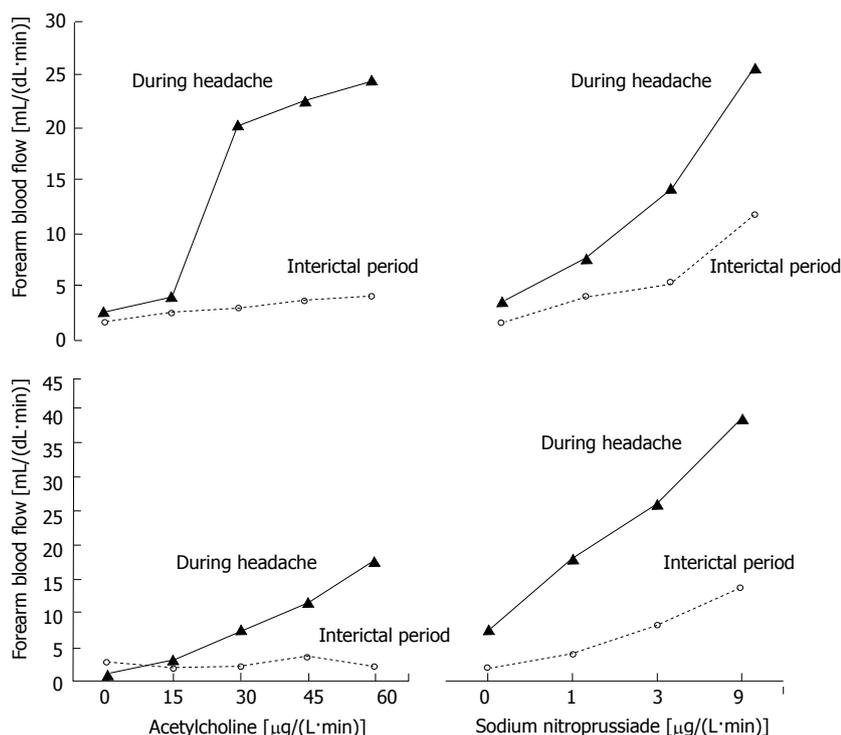
Figure 2 Individual forearm blood flow response to infusion of acetylcholine or sodium nitroprusside into the brachial artery in two patients with migraine studied during or free from headache.
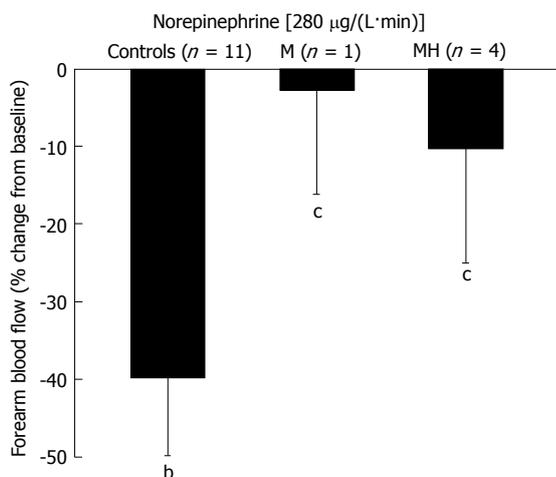
Figure 3 Forearm blood flow response to infusion of norepinephrine at the rate of 280 μg/L per minute into the brachial artery in patients with migraine during or free from headache, and control subjects. The patients with migraine were studied during the interictal period (group M) or the headache attack (group MH). Data (mean ± SE) were analyzed by paired *t* test *vs* baseline and unpaired *t* test among groups. [b]$P < 0.01$ *vs* baseline; [c]$P < 0.05$ *vs* controls.

Ach or NP infusions for the two patients who gave us a unique opportunity to study the phenomenon both during the interictal period and the headache attack. It is striking how potently the response to both Ach and NP was enhanced by the headache attack as compared with the basal response.

Figure 3 shows the data on the effect of NE infusion. FBF was reduced by 1.19 ± 0.17 mL/dL per minute by NE infusion in C (-40% ± 6%, $P = 0.001$ *vs* baseline). In

contrast, NE infusion was unable to elicit a vasoconstrictory response in migraine patients either when studied in the headache-free period or during the headache attack (-0.29 ± 0.23 and -0.66 ± 0.69 mL/dL per minute, accounting for a reduction by 3% ± 13% and 10% ± 15% in M and MH, respectively; $P > 0.05$ *vs* baseline and $P < 0.05$ *vs* C).

DISCUSSION

In the present study, we measured vascular reactivity in patients with migraine without aura either during the interictal period or during a headache attack. We confirm our previous finding that patients with migraine studied in the interictal period suffer from impaired vasodilation in response to acetylcholine and sodium nitroprusside. Furthermore, we extend our observation to the vasoconstrictory response to an adrenergic agonist and show that in these patients a defect in the response to NE also coexists. In addition, we studied a group of patients with migraine during the headache attack. Under these circumstances, the marked defect in vasodilation completely reverted, as documented by the normal responses to Ach and NP. In contrast, the vasoconstrictory response to the sympathetic agonist NE remained blocked.

Although patients with migraine during the headache-free period have a normal postural increase compared to control subjects, they are also characterized by a 50% reduction of absolute circulating NE levels in both supine and orthostatic position[12-14], suggesting an abnormal regulation of the sympathetic nervous system activity. Because in these patients NE intravenous administration

induces more prolonged elevation in blood pressure (BP) than in control subjects, an adrenergic receptor super-sensitivity was invoked[12]. In addition, the observation of greater and more prolonged BP response to phenyl-ephrine led to the conclusion that an alpha-adrenergic receptor increased sensitivity was implicated[15]. However, it must be considered that the intravenous administration of NE or phenylephrine does not trigger only the receptors localized in the vessel wall, but can potentially unleash more complex, systemic mechanisms. In addition, indirect data obtained by administering the beta-blocker propranolol to patients with migraine, suggested that beta receptors distribution in the radial artery might be abnormal[16]. To the best of our knowledge, the current study is the only one in which NE is directly infused into the brachial artery in patients with migraine. The agonist was infused locally in very small amounts that were unable to induce systemic perturbations of NE circulating levels, given its very short half-life. This is also supported by the lack of any change in FBF of the con-tralateral arm in control subjects or in systemic BP (data not shown). Therefore, under the current circumstances, any confounding involvement of indirect sympathetic mechanisms secondary to changes in circulating NE levels can be excluded, and the observed effects only reflect the direct action of NE on the forearm resistance vessels. It must be also stressed that NE stimulates both the alpha-receptors (vasocostrictory response) and the beta-receptors (vasodilatory response). Therefore, the response to NE infusion represents the net balance of two opposite forces. In normal subjects, however, the vasoconstrictory response clearly prevails, whereas in patients with migraine the resistance vessels are unable to respond to the sympathetic agonist. We cannot dis-sect whether the block of the vasoconstrictory response in migraine patients is due to a relative reduction of the NE effect through the alpha-receptors or an increase of the beta-receptor response or a combination of the two. Unfortunately, no information is available in the literature regarding the adrenergic receptor relative distribution in the cell membranes of peripheral arterial vessels.

Given the inability of VSMCs to relax in response to endothelial NO in the interictal period, were the va-soconstrictory ability of NE intact rather than severely impaired, patients with migraine would experience con-stantly raised vascular resistance and systemic hyperten-sion. Therefore, the defective NE-induced vasoconstric-tion observed in patients with migraine might represent a chronic hemodynamic adjustment to compensate for the reduced vasodilatory response to NO by the VSMCs. The hypothesis of a compensatory down-regulation of the vasoconstrictory response of VSMCs would be well in agreement with the generalized reduction of sympa-thetic nervous system activity previously reported in mi-graine patients[12].

We have previously demonstrated the presence of impaired vascular reactivity in patients with migraine dur-ing the interictal period, entirely attributable to VSMCs

dysfunction[4,5]. The impaired vasodilatory response to Ach was associated with normal NO production by en-dothelial cells. Moreover, the hemodynamic response to NP, a direct stimulator of VSMCs, was markedly im-paired. In the current study, we confirm the observation that in patients with migraine studied free from headache the response to Ach and NP is severely impaired. Data in the literature have provided divergent results, either when flow-mediated dilation or forearm perfusion technique associated with plethysmography or other approaches were used[17-23]. In previous studies, migraine patients have not been discriminated with regard to the presence of aura and different vascular beds (micro- *vs* macro-vascular and intra- *vs* extra-cranial) have been explored. The possibility exists that the two types of migraine might be characterized by a different vascular reactivity. Accordingly, the cardiovascular risk profile of the two types of migraine appears to be different, suggesting that the intimate mechanism of vascular function diverge and our findings lend support to the hypothesis that migraine without aura is not associated with dysfunction of the endothelial cells potentially triggering atherosclerotic pro-cesses[1,2,24-28].

In patients with migraine during the headache at-tack, basal FBF was similar to that measured off the pain attack and to that of control subjects. In contrast, the impaired vasodilation in response to the infusion of Ach and NP of the interictal period was fully restored. Taken together, our data indicate that the patients with migraine in the interictal period have a reduced sensitivity of their VSMCs to the NO released by the endothelial cells. In contrast, during the headache attack, the response to NO, as suggested by the NP infusion data, becomes similar to that measured in the controls, indicating a restored sensitivity of VSMCs. We have previously demonstrated that during Ach infusion in patients with migraine dur-ing the interictal period the release of NO is normal and that endothelial function is intact[4,5]. Interestingly, when in previous studies systemic nitroglycerin, an NO donor, was administered to patients with migraine, an approach used to induce headache in migraine patients or to mea-sure non-endothelial-mediated vasodilation, an increased sensitivity to NO was demonstrated in intra-and extra-cranial vessels[19-25]. Further studies are necessary to clarify the intriguing issue about the mechanisms that come into play during the migraine attack to redirect VSMC sensi-tivity towards normal.

Study limitations

A potential limitation of the current study is the small sample of patients studied during the headache attack. The forearm perfusion technique requires the cannula-tion of the brachial artery and, in general, this approach precludes the possibility to study large patients groups. In addition, it is quite hard to perform a forearm study that lasts several hours in patients who during the headache attack abstain from taking analgesics for the potential drug impact on vascular reactivity.

As compared with ultrasonographic techniques, such as the flow mediated dilation, the forearm technique bears much less variability. Indeed, the effects observed in our patients during the headache attack were very clear-cut, providing solid statistics despite the small sample. A final consideration is that we studied patients with spontaneous headache attack. This is a point of great strength of our work, since confounding factors linked to experimental stimuli used to trigger a headache attack were not operative.

In conclusion, patients with migraine without aura studied in the interictal period are characterized by VSMCs impaired ability to relax in response to NO and to contract in response to NE. We hypothesize that the two defects compensate for each other and this provides for the maintenance of normal vascular resistance and blood pressure homeostasis. In contrast, during the headache attack, due to mechanisms still unclear, the VSMCs regain their ability to respond to NO, but remain unresponsive to NE. Such differential effect of the migraine attack is not surprising, given that NO and NE activate different intracellular signaling pathways in VSMCs.

COMMENTS

Background
Migraine has been associated with an increased risk of cardiovascular events. However, authors have recently demonstrated that patients with migraine without aura, studied during the interictal period, do not present peripheral endothelial dysfunction, which is classically associated with a worse cardiovascular risk profile, but rather an abnormal relaxation of the vascular smooth muscle cells (VSMCs). It is unclear whether the inability of VSMCs to respond to vasodilators is an isolated abnormality or, rather, reflects a more complex hemodynamic alteration and whether persists during the headache attack.

Research frontiers
The demonstration that the vascular abnormality observed in migraine are not due to endothelial dysfunction, but rather to VSMCs impairment might result in novel therapeutic approachs. Furthermore, life style intervention useful to improve endothelial dysfunction might be ineffective to correct the defects in VSMCs dysfunction.

Innovations and breakthroughs
This is the first study to demonstrate that patients with migraine without aura studied in the interictal period are characterized by VSMCs impaired ability to relax in response to nitric oxide (NO) and to contract in response to norepinephrine (NE). Authors hypothesize that the two defects compensate for each other and this provides for the maintenance of normal vascular resistance and blood pressure homeostasis. In contrast, during the headache attack, due to mechanisms still unclear, the VSMCs regain their ability to respond to NO, but remain unresponsive to NE.

Applications
Elucidation of the vascular response in patients with migraine both free of and during the headache episode would be of great importance to the authors' understanding of the mechanisms involved in the pathogenesis of the disease and to better design appropriate therapeutic approaches.

Terminology
Vascular dysfunction is mainly attributable to endothelial dysfunction. In migraine patients without aura, the inability of VSMCs to respond to nitric oxide can be considered a novel mechanism of vascular dysfunction.

Peer review
The authors studied peripheral vascular function in patients with migraine without aura. the patients were studied both during and free of the headache attack. Vascular dysfunction in these patients involves both impairment of vasodilation and vasoconstriction, both due to an abnormal functioning of VSMCs. The results are very interesting.

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BRIEF ARTICLE

Low-dose CT coronary angiography using iterative reconstruction with a 256-slice CT scanner

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Abstract

AIM: To explore whether computer tomography coronary angiography (CTCA) using iterative reconstruction (IR) leads to significant radiation dose reduction without a significant loss in image interpretability compared to conventional filtered back projection (FBP).

METHODS: A consecutive series of 200 patients referred to our institution to undergo CTCA constituted the study population. Patients were sequentially assigned to FBP or IR. All studies were acquired with a 256-slice CT scanner. A coronary segment was considered interpretable if image quality was adequate for evaluation of coronary lesions in all segments ⩾ 1.5 mm.

RESULTS: The mean age was 56.3 ± 9.6 years and 165 (83%) were male, with no significant differences between groups. Most scans were acquired using prospective ECG triggering, without differences between groups (FBP 84% *vs* IR 82%; P = 0.71). A total of 3198 (94%) coronary segments were deemed of diagnostic quality. The percent assessable coronary segments was similar between groups (FBP 91.7% ± 4.0% *vs* IR 92.5% ± 2.8%; P = 0.12). Radiation dose was significantly lower in the IR group (2.8 ± 1.4 mSv *vs* 4.6 ± 3.0 mSv; P < 0.0001). Image noise (37.8 ± 1.4 HU *vs* 38.2 ± 2.4 HU; P = 0.20) and signal density (461.7 ± 51.9 HU *vs* 462.2 ± 51.2 HU; P = 0.54) levels did not differ between FBP and IR groups, respectively. The IR group was associated to significant effective dose reductions, irrespective of the acquisition mode.

CONCLUSION: Application of IR in CTCA preserves image interpretability despite a significant reduction in radiation dose.

Core tip: A consecutive series of 200 patients referred to our institution to undergo computer tomography coronary angiography (CTCA) were sequentially assigned to filtered back projection (FBP) or iterative reconstruction (IR). The percent assessable coronary segment was similar between groups. Radiation dose was significantly lower in the IR group. Image noise and signal density levels did not differ between FBP and IR groups. The IR group was associated to significant effective dose reductions, irrespective of the acquisition mode. Our findings suggest that application of IR in CTCA preserves image interpretability despite a significant reduction in radiation dose.

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INTRODUCTION

With a large body of evidence accumulated within the past decade, computer tomography coronary angiogra-

phy (CTCA) has earned a role in diagnostic algorithms of patients at intermediate risk of coronary artery disease[1-3]. However, the high effective radiation dose related to CTCA scans remains a limitation and has been the foundation of most of the criticisms received. Indeed, the recently published Prospective Multicenter Study on Radiation Dose Estimates of Cardiac CT Angiography I and II (PROTECTION I and II) reported a wide range of effective radiation doses according to the acquisition technique, therefore encouraging the application of dose reduction techniques such as prospective ECG-triggering, tube current modulation, and/or high pitch helical scanning[4,5].

In the past few years, iterative reconstruction (IR), an alternative to conventional image reconstruction filtered back projection (FBP), has gained interest in order to attempt to attenuate the increase in image noise related to tube current modulation and low tube voltage acquisitions[6]. IR has the ability to reduce image noise by iteratively comparing the images obtained to a modeled projection. Thus, it can be used to reconstruct images with similar image quality despite a significant reduction in tube current, resulting in a reduction in overall radiation dose. This has particular interest in CTCA studies in order to attempt to overcome the main limitation of the technique for cardiovascular purposes[7-11]. The aim of our investigation was to explore whether CTCA using IR can achieve a substantial effective dose reduction without a significant loss in image interpretability.

MATERIALS AND METHODS

The present was a single-centre, investigator-driven, observational, prospective study that aimed to explore whether IR of CTCA scans leads to a significant radiation dose reduction without impairment of image interpretability. For that purpose, a consecutive series of patients referred to our institution to undergo CTCA constituted the study population. Patients were assigned to FBP or, sequentially, to IR. Inclusion criteria included adult patients ($\geq$ 18 years), without a history of contrast related allergy, renal failure, or hemodynamic instability, that were referred to CTCA to exclude coronary artery disease. Baseline heart rate, arrhythmia, or body mass index did not impact the enrollment decision. Patients with pacemakers or implantable devices were excluded. The institution's Ethics Committee approved the study protocol, which complied with the Declaration of Helsinki, and written informed consent was obtained from all patients.

CTCA acquisition

All studies were acquired with a 256-slice CT scanner (Philips Healthcare, Cleveland). Patients with a heart rate of > 65 beats/min received 50 mg oral metoprolol one hour prior to the scan or 5 mg intravenous propralonol if needed in order to achieve a target heart rate of less than 60 bpm. A dual phase protocol with 70 mL of iobitridol (Xenetix 350^{TM}, Guerbet, France) followed by a 50-mL saline flush was injected through an arm vein after administration of 0.4 mg of sublingual nitroglycerin. A bolus tracking technique was used to synchronize the arrival of contrast at the level of the coronary arteries with the start of the scan. Scanning parameters were as follows. Rotation time 270 ms; tube voltage in FBP with body mass index (BMI) < 25 kg/m^2: 100 kV, BMI > 25 kg/m^2: 120 kV; tube voltage in IR with BMI < 20 kg/m^2: 80 kV, BMI 20-30 kg/m^2: 100 kV, BMI > 30 kg/m^2: 120 kV. Tube current was adjusted according to the scan protocol and BMI (range 170-1200 mA). Prospective ECG-triggering axial scanning was used when possible based on heart rate. ECG-based tube current modulation was performed for all helical studies.

CTCA analysis

Image analysis and coronary segment interpretability were assessed by consensus of two experienced level 3-certified coronary CTA physicians using dedicated software (Comprehensive Cardiac Analysis, Philips Healthcare) on a CT workstation (Brilliance Workspace, Philips Healthcare, Cleveland, OH, United States), blinded to the acquisition mode. A coronary segment was considered interpretable if image quality was adequate for evaluation of coronary lesions in all segments $\geq$ 1.5 mm.

Slice CT images were reconstructed preferably at end diastole using axial planes, multiplanar reconstructions, and maximum intensity projections at 1 mm slice thickness. Image noise and signal density for both FBP and IR (iDose^{TM}, level 5, Philips Healthcare) reconstruction algorithms were evaluated. The signal density and noise were evaluated using standardized regions of interest of 10 mm^2 within the aortic root at the level of the left main coronary artery on axial images, being the signal density defined as the mean Hounsfield units and the signal noise as the mean standard deviation of the signal density. Studies were evaluated using the previously reported 17-segment model, and effective dose radiation estimates were calculated using the dose-length product[12].

Statistical analysis

Discrete variables are presented as counts and percentages. Continuous variables are presented as mean $\pm$ SD, or median (25th, 75th percentile) for variables with non-Gaussian distribution. Comparisons between groups were performed using independent Student's t test, or χ^2 tests as indicated. We explored correlations between continuous variables using Pearson correlation coefficients. A two-sided P value of less than 0.05 indicated statistical significance. Statistical analyses were performed with the use of SPSS software, version 13.0 (Chicago, IL, United States).

RESULTS

A consecutive series of 200 patients referred to undergo CTCA constituted the study population (FBP, n = 100) and (IR, n = 100). The mean age was 56.3 $\pm$ 9.6 years

Table 1 Demographical characteristics, acquisition parameters, radiation dose and image quality			
	FBP	**IR**	***P* value**
Age (yr)	55.6 ± 9.1	56.0 ± 10.1	0.67
Male	85 (85)	80 (80)	0.35
Body mass index (kg/m^2)	27.2 ± 2.7	26.3 ± 3.4	0.03
Body mass index ⩾ 30	15 (15)	13 (13)	0.68
Heart rate (bpm)	58.3 ± 7.0	58.2 ± 6.4	0.88
Acquisition technique			
Prospective (axial)	84 (84)	82 (82)	0.71
Retrospective (helical)	16 (16)	18 (18)	
Tube voltage (kV)	119.0 ± 4.4	109.0 ± 10.4	< 0.0001
Percent 80-100 kV	5 (5)	54 (54)	< 0.0001
mAs in prospective	203.1 ± 15.4	195.7 ± 26.8	< 0.0001
mAs in helical	943.2 ± 119.5	870.1 ± 122.8	< 0.0001
Radiation dose (mSv)			
Total	4.6 ± 3.0	2.8 ± 1.4	< 0.0001
Prospective (axial)	3.4 ± 2.4	2.4 ± 0.7	< 0.0001
Retrospective (helical)	10.3 ± 3.9	5.2 ± 1.6	< 0.0001
Image quality			
Attenuation level (HU)	461.7 ± 51.9	462.2 ± 51.2	0.54
Image noise (HU)	37.8 ± 1.4	38.2 ± 2.4	0.20
Signal to noise ratio	12.2 ± 1.4	12.1 ± 1.4	0.28
Coronary assessment (%)	91.7 ± 4.0	92.5 ± 2.8	0.12

Data are expressed as absolute numbers (percentage) or mean ± SD. FBP: Filtered back projection; IR: Iterative reconstruction.

and 165 (83%) were male, with no significant differences between groups. The mean heart rate was 58.3 ± 7.0 bpm for the FBP group and 58.2 ± 6.4 bpm for the IR group (*P* = 0.88). Patients assigned to IR had a significantly lower body mass index (26.3 ± 3.4 kg/m^2 *vs* 27.2 ± 2.7 kg/m^2; *P* = 0.03), despite both groups had similar proportion of patients with BMI ⩾ 30 kg/m^2 (Table 1). Most scans were acquired using prospective ECG triggering, without difference between groups (FBP 84% *vs* IR 82%; *P* = 0.71).

A total of 3198 (94%) coronary segments were deemed of good diagnostic quality. The percent of assessable coronary segments was similar between groups (FBP 91.7% ± 4.0% *vs* 92.5% ± 2.8%; *P* = 0.12). Image noise (37.8 ± 1.4 HU *vs* 38.2 ± 2.4 HU; *P* = 0.20) and signal density (461.7 ± 51.9 HU *vs* 462.2 ± 51.2 HU; *P* = 0.54) levels did not differ between FBP and IR groups, respectively. The median effective radiation dose was 3.35 mSv (interquartile range 2.45-3.35). The IR group was associated to significant effective dose reductions, irrespective of the acquisition mode (helical or axial). Prospective scans with IR exhibited the least radiation doses (Table 1).

We found no significant relationships between radiation dose and the percent of interpretable segments (*r* = -0.01, *P* = 0.85). In turn, we found a significant, albeit weak, correlation between the effective radiation dose (mSv) and the signal to noise ratio (*r* = 0.25, *P* < 0.001), as well as between the mA and the signal to noise ratio (*r* = 0.31, *P* < 0.001).

DISCUSSION

In the past decade, CTCA has rapidly emerged as a non-invasive diagnostic tool with the ability to identify

obstructive coronary disease, and has gained a role in different risk stratification and diagnostic algorithms. Moreover, it has demonstrated a significant prognostic value independent of traditional risk factors and functional tests[13-17]. Notwithstanding, one of the main challenges of CTCA is the relatively high radiation dose related to the technique[18-20]. Several different strategies have been proposed in order to attempt to decrease effective radiation dose, including tube modulation and prospective (axial) scanning[21-24]. One of the latest developments aimed at lowering dose radiation is IR.

The main finding of our investigation was that compared to conventional FBP, IR in CTCA preserved image interpretability despite a significant reduction in radiation dose. Compared to FBP, IR achieved a 50% dose reduction in helical scans, and a 29% dose reduction in prospective scans, being these results within the range of previous findings in different populations[7]. Such significant reduction might be attributed to the fact that more than half of the IR scans were performed using low voltage (80-100 kV), whereas within the FBP group only 5% of the scans were performed using 100 kV.

Tube current reduction with FBP, a commonly used dose reduction strategy, leads to an increment in image noise. In turn, IR consists in synthesized projection data that are compared to real data in an iterative manner, resulting in a significant reduction of image noise[6]. By reducing image noise, IR allows tube current reduction and, consequently, effective dose reduction. This explains the significantly larger dose reduction in helical compared to axial scans using IR.

A number of limitations must be recognized. Despite patients were sequentially assigned to FBP or IR, randomization was not performed, leading to an expected significantly higher body mass index of FBP patients, although it should be stressed that no significant differences were observed regarding the number of obese patients (BMI ⩾ 30 kg/m^2). Furthermore, coronary angiography was not performed in order to evaluate the diagnostic accuracy of each technique; therefore our results should do not allow making assumptions in this regard and should be limited to the image interpretability.

Application of IR in CTCA preserves image interpretability despite a significant reduction in radiation dose, being this mainly attributed to the use of lower voltage scans.

COMMENTS

Background

In the past decade, computer tomography coronary angiography (CTCA) has rapidly emerged as a non-invasive diagnostic tool with the ability to identify obstructive coronary disease, and has gained a role in different risk stratification and diagnostic algorithms. Moreover, it has demonstrated a significant prognostic value independent of traditional risk factors and functional tests.

Research frontiers

Several different strategies have been proposed in order to attempt to decrease effective radiation dose, including tube modulation and prospective (axial) scanning. One of the latest developments aimed at lowering dose radiation is iterative reconstruction (IR).

Innovations and breakthroughs

The main finding of this investigation was that compared to conventional filtered back projection, IR in CTCA preserved image interpretability despite a significant reduction in radiation dose.

Applications

Application of IR in CTCA preserves image interpretability despite a significant reduction in radiation dose, being this mainly attributed to the use of lower voltage scans.

Peer review

In principle, it is a solid work on a state-of-the-art scientific topic. However, there are numerous minor typing errors as well as grammatical mistakes throughout the entire manuscript that need to be corrected prior to possible publication.

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CASE REPORT

Left ventricular myxoma: Missed *vs* metastatic

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Abstract

Left ventricular myxomas account for 2.5% of all cardiac myxoma cases. There are very few case reports on left ventricular myxoma (LVM) presented after complete surgical resection of left atrial myxoma. Here we report a case of a 58-year-old male presented to the hospital for transient limb weakness, numbness and dysarthria. Magnetic resonance image of the brain revealed multiple thromboembolic cerebrovascular accidents. Transthoracic echocardiogram (TTE) revealed a left atrial myxoma. It was resected completely with good surgical margins. After one and half year he started having dizziness, and transient right sided weakness. Computer tomography scan of the head revealed a progression of thromboembolic disease. TTE revealed a LVM that was confirmed by transesophageal echocardiogram. It was resected with good surgical margins 3 wk after recurrent cerebrovascular accident.

Key words: Left ventricular myxoma; Metastatic myxoma; Left atrial myxoma; Recurrent myxoma

Core tip: Left ventricular myxoma (LVM) after surgical resection of left atrial myxoma is very rare. Etiologies for recurrent LVM after left atrial myxoma resection are incomplete surgical resection, metastasis, totipotent multicentricity and missed. Here we are describing a case that was probably a metastatic LVM as it is uncommon statistically for it to be a recurrent myxoma in the left ventricle after complete resection from left atrium. If there is a progression of the cerebral hemorrhagic lesions it would confirm our diagnosis of the metastatic process.

INTRODUCTION

Left ventricular myxomas account for 2.5% of all cardiac myxoma cases. There are very few case reports on left ventricular myxoma (LVM) presented after complete surgical resection of left atrial myxoma.

CASE REPORT

A 58-year-old male with a past medical history of hypertension and diabetes went to see a primary care physician with complaints of multiple episodes of transient limb weakness, numbness and dysarthria lasting less than 1 h. A magnetic resonance image (MRI) of the brain was obtained revealing multiple bilateral, supra, infratentorial, cortical and sub-cortical infarctions in watershed areas consistent with multiple thromboembolic strokes. Upon admission to the hospital, routine lab work (complete blood count, complete metabolic profile, lipid panel, thyroid function tests, coagulation studies), and carotid doppler failed to reveal any significant abnormalities other than poorly controlled diabetes, and a serum cholesterol of 113 mg/dL. A transthoracic
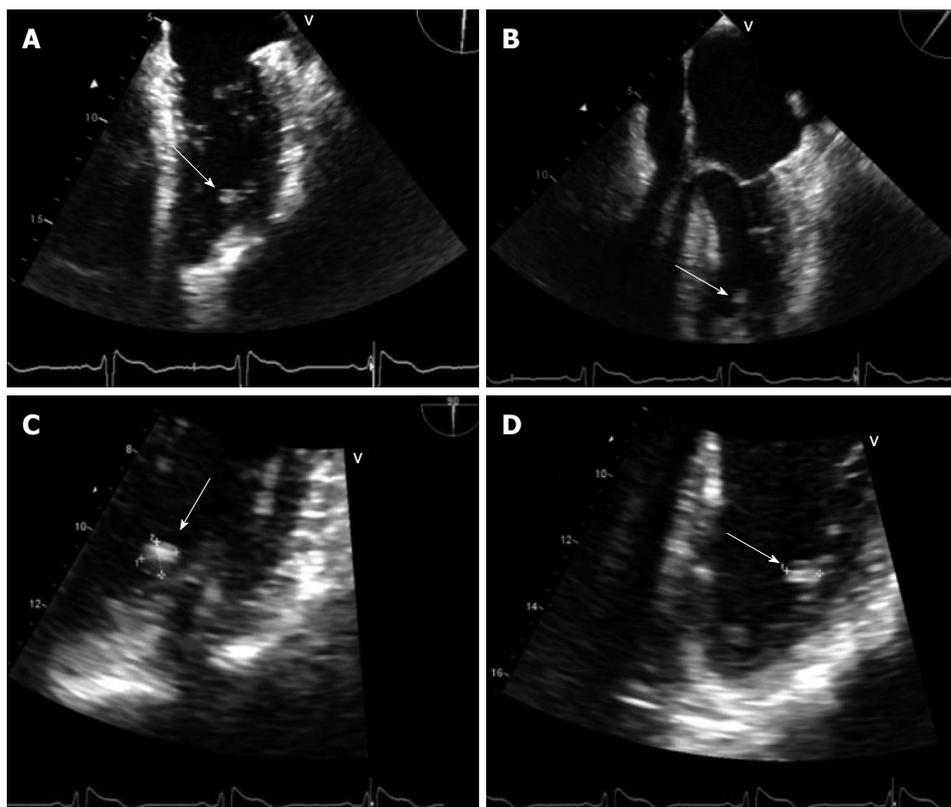
Figure 1 Transesophageal echocardiogram. A: Mid esophagus view of the transesophageal echo (TEE) revealing left ventricular myxoma; B: TEE, four chamber view showing Left ventricular myxom; C: Magnified view showing a myxoma, size 1 cm x 2 cm; D: Magnified view showing a myxoma of 1 cm in horizontal direction. Showing its close proximity to trabecular muscles.

echocardiogram (TTE) demonstrated a 3.5 cm homogenous mass in the left atrium with mild dilation and a normal left ventricle (LV). A pre-operative coronary angiogram failed to reveal any significant coronary artery disease. The left atrial mass was subsequently resected with good surgical margins and a small incidental patent foramen was successfully closed. Final pathology of the mass confirmed it to be a transparent myxoma. Patient was discharged home in stable condition and did well for few months without any major symptoms other than generalized weakness.

Nearly one year later the patient was diagnosed with generalized partial seizures following an episode of right-side weakness and was started on antiepileptic medication, which he refused to take. Over the next 2-3 wk he experienced two more episodes of right sided weakness associated with dizziness and admitted for non-adherence with medication. He then presented to our institution with near syncope and atypical chest pain. Routine cardiac evaluation was negative and he was discharged after 2 d. Later, he again presented to the emergency department, this time for intermittent right-sided weakness and transient dizziness. A computer tomography (CT) scan of the head revealed interval progression of thromboembolic disease. An MRI confirmed the CT scan findings; multiple small hemorrhagic lesions were subsequently identified and later confirmed by cerebral angiography. Multiple my-

cotic aneurysms were ruled out by blood cultures. TTE was performed and it revealed a 0.94 cm × 0.74 cm mass attached to lateral wall of LV. A transesophageal echo (TEE) then confirmed the presence of a mobile, round homogenous mass attached to the anterolateral wall of the LV (Figure 1). Three weeks after the recurrent cerebrovascular accident (CVA) the mass was resected. Initially, a left atrial and then aortic approach was attempted to locate and isolate the mass. Both approaches were unsuccessful. Eventually, an anterolateral approach located the mass buried in trabecular muscles of the posteroapical area without any valvular attachment. Excision was done without a difficulty. Pathology confirmed a LVM and the patient was discharged 1 wk later.

DISCUSSION

Primary cardiac tumors are rare and have an average incidence of 0.02%[1,2]. Of these, cardiac myxomas account for 88% of cases and are primarily benign in nature[3]. Myxomas constitute 0.23% of all the open heart surgical procedures[2]. The most common location for myxoma is the left atrium followed by the right atrium. A biatrial location is occasionally seen but all other locations are quite uncommon[3]. Myxomas found in the left ventricle account for only 2.5% of cases[3,4]. Myxomas are primarily sporadic while familial cases

constitute up to 10%[2]. Familial myxomas have unusual locations and recurrences, and some are associated with Carney's Complex (myxomas of the heart, and skin, spotty skin pigmentation, blue nevi, and endocrine over activity)[3].

Most myxomas are either asymptomatic or produce non-specific symptoms such as malaise, fatigue or heart failure symptoms. Embolic events are one of the major clinical presentations of myxomas. The risk of embolization is mostly determined by the morphology of the myxoma rather than its size. As in this case, semi-transparent polyploid myxomas carry a high risk for embolization compared to round myxomas[2]. Valvular myxomas carry high risk of embolization[2,5]. This variation in prevalence of emboli seen in published series can be explained by the fact that valvular myxomas carry a high risk of embolization compared to myxomas located elsewhere. Even though the final embolic destination is commonly the cerebrovascular territory other arterial territories such as the pulmonary or coronary circulation can be involved[1-4].

The other common mechanisms of symptom production with myxomas are mechanical obstruction and arrhythmias when cardiac conducting system is involved[1-4].

Most myxomas are diagnosed with TTE, but are often missed when located in unusual places. In this case, locating the LV myxoma was difficult both on TTE and intraoperatively was difficult due to its concealment by trabecular muscle. TEE and MRI are best studies for localizing and characterizing myxoma. In all cases of suspected myxomas TEE should be performed[3].

Surgical resection is the treatment of choice for myxomas and should be performed as early as possible as there is a risk of embolization. In the presence of a recent CVA, surgical resection may be delayed for up to 4 wk and should be performed on pump with systemic heparinization[6]. Even though surgical technique is changing constantly, resection should include clean surgical margins to reduce the likely of recurrence[7,8]. There are very few cases myxoma has recurred in the LV after the resection of the tumor in LA[7]. In this case the myxoma recurred in the LV one year after the initial resection. The index TTE and the initial surgery did not give reason to suspect a LV myxoma. Possible mechanisms for the LVM in this case are recurrence (incomplete surgical resection or new growth of reserve cell or implantation from original tumor), or missed during initial evaluation, or metastasis. During the index diagnosis, neither MRI nor TEE was performed thus raising the possibility of LV myxoma was initially missed. However, though limited, neither TTE nor cardiac cauterizations have identified any LVM.

Recurrent myxomas often grow faster than primary tumors and can occur in 3% of sporadic cases and 20% of familial cases[9]. Incomplete surgical margins is one of the major reason to have recurrences[7]. The tumor recurs near the original resection site in 85% of cases with an atrial location in 97%[7]. In this case initial sporadic myxoma had good surgical margins during the index surgical resection. The site of recurrence however, was LV making the recurrence secondary to incomplete resection much less likely. Metastatic seeding of myxoma cells is well described in the literature. The malignant nature of myxomas is defined based on growth rate behavior rather than histological features. Malignant myxoma may be identified by high interleukin 6 levels, presence of constitutional symptoms, elevated gamma globulins, and a high erythrocyte sedimentation rate (ESR) after complete resection of the tumor[9]. In this case, the patient reported some constitutional symptoms malaise and generalized weakness but lack of specificity of these symptoms and the failure to obtain a post-operative ESR make supporting malignant potential of the tumor problematic. Multiple cerebral hemorrhagic lesions (probably secondary to small aneurysms) were noted in this patient and may support the idea of metastatic process. A malignant nature may be confirmed in future if the tumor is subsequently found at other distant sites. We excluded the probability of familial disease by taking a good family history, and there were no signs or symptoms of Carneys Complex[9]. At this time, it is believed that this recurrent LV myxoma case is most likely due to a metastatic process. Careful follow up has been planned for this patient to monitor for recurrence of myxoma as well as any worsening of neurological symptoms.

Follow up echocardiography is required to evaluate for recurrence. It is highly crucial in familial cases and in those cases where good surgical margins cannot be achieved[6].

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CASE REPORT

Medical management of connector pin thrombosis with the Amplatzer cardiac plug left atrial closure device

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Abstract

Transcatheter closure of the left atrial appendage with the Amplatzer™ cardiac plug device and double antiplatelet treatment for 3 mo has become an alternative treatment for patients with atrial fibrillation at high embolism risk and contraindications for chronic oral anticoagulation. The inadequate implantation of the left atrial appendage closure device and the discontinuation of double antiplatelet therapy are well-known as factors related to device thrombosis. Nevertheless, device thrombosis after adequate implantation requiring surgical treatment or restarting chronic oral anticoagulation has been reported and can reach 15% of patients. The connector pin thrombosis of the Amplatzer™ cardiac plug, despite a good adherence to antiplatelet treatment, has been recently described as a potential mechanism for device thrombosis. Our clinical case reports the management of this condition for the first time, showing that the early detection of thrombotic complications by transesophageal echocardiography permits solving this serious complication with medical treatment only.

Core tip: Percutaneous closure of the left atrial appendage has become an alternative treatment for patients with atrial fibrillation and with contraindications for chronic oral anticoagulation. Recently, the first case of connector pin thrombosis of the Amplatzer™ cardiac plug device for percutaneous left atrial appendage closure was described. Our work describes the management of this serious problem for the first time.

INTRODUCTION

Transcatheter closure of the left atrial appendage (LAA) with the Amplatzer™ cardiac plug (ACP) device has become an alternative treatment for patients with atrial fibrillation (AF) at high embolism risk and with contraindications for chronic oral anticoagulation (OAC)[1,2]. The inadequate implantation of ACP and the discontinuation of double antiplatelet treatment (DAPT) are well-known as factors related to device thrombosis[1,3]. Furthermore, device thrombosis after adequate implantation, requiring surgical treatment or restarting chronic OAC, has been reported[4,5] and can reach 15% of patients[6]. The connector pin thrombosis of the ACP, despite a good adherence
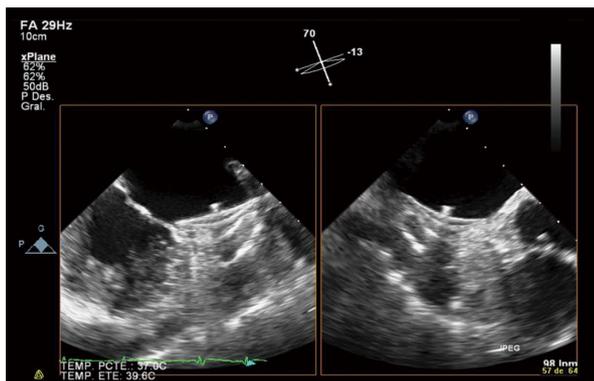
Figure 1　Forty-five day control. Transesophageal echocardiography two-dimensional X-plane processing, simultaneous visualization at 70° (left) and 13° (right). Successful Amplatzer™ cardiac plug implantation: completely covering the left atrial appendage ostium by the occluder disk and no evidence of device thrombosis.
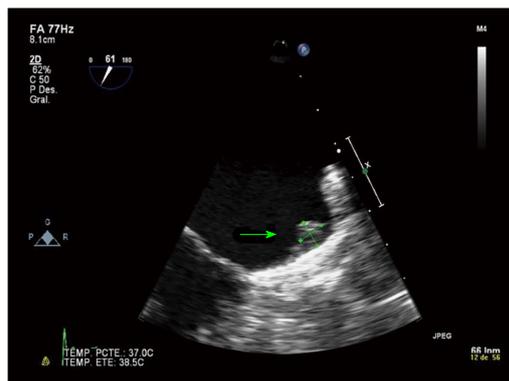
Figure 2　Four month control. Transesophageal echocardiography two-dimensional image. Adequate covering of the left atrial appendage ostium but little thrombus (7 mm × 7 mm) is observed at the top of the button of the Amplatzer™ cardiac plug.

Figure 3　Transesophageal echocardiography two-dimensional image. A: Control after 2 wk of intravenous sodium heparin treatment. Complete resolution of button thrombosis and correct device positioning; B: 6 mo control. Correct device positioning and absence of button thrombosis.

to antiplatelet therapy, has been recently described as a potential mechanism for device thrombosis[7]. The aim of this work is to describe the management of this serious complication after ACP device implantation.

CASE REPORT

A 79-year-old woman with ischemic heart disease, hypertension and diabetes mellitus presented with paroxysmal AF. The patient was under OAC because of a high embolism risk (CHADS2 score of 4 points) but had multiple admissions because of gastrointestinal bleeding (GIB) of unknown cause, despite an intensive etiological study. To avoid long-term OAC, a percutaneous closure of the LAA with a 26-mm ACP device was performed and the patient was discharged under DAPT (aspirin 100 mg and clopidogrel 75 mg) until the 6th month. The post procedural transesophageal echocardiography (TEE) and the 45 d TEE revealed correct device positioning and the absence of thrombosis of the ACP (Figure 1). The patient remained asymptomatic with the absence of any GIB. The 4 mo transthoracic echocardiography (TTE) demonstrated correct device positioning without thrombotic complications but the 4 mo TEE detected a thrombus

over the connector pin of the ACP despite the DAPT (Figure 2). Intravenous anticoagulation with heparin was started and TEE 2 wk later showed thrombosis resolution (Figure 3A). The patient continued with DAPT for two more months. The 6 mo TEE showed the absence of thrombus (Figure 3B), allowing the withdrawal of clopigrel. The 12 mo TTE confirmed the thrombus resolution and the patient remained uneventful, with no GIB or cardioembolic events after 2 years.

DISCUSSION

Four major points about thrombosis of the ACP could be drawn from our report. Firstly, the incomplete endothelization of the connector pin of the ACP during the initial 6 mo can contribute to the development of thrombosis of the ACP device. Our clinical case is in accordance with the first description of the connector pin thrombosis in correctly implanted ACP devices[7]. For that reason, a second generation of the ACP (ACP 2 or Amulet™) with a modified connector pin has been designed[8]. Secondly, the role of TEE and TTE in detecting device-related complications remains controversial[1]. The correct positioning can be detected with both techniques

but TEE is the only method that permits the correct diagnosis of residual or emerging device thrombosis. So, the strict monitoring with TEE is mandatory until the 6th month because of the considerable proportion of device thrombosis. Thirdly, recommended antiplatelet therapy for prevention of thrombotic events varies with the type of device used for transcatheter closure of the LAA. The ACP manufacturer recommends DAPT for 3 mo, based on porcine models[1], but button thrombosis in ACP successfully implanted devices in humans beyond 3 mo suggests the possibility of extending the DAPT until the 6th month with complete exclusion of thrombotic complications by TEE. For these reasons, we recommend a strict echocardiographic follow-up protocol in order to detect any thrombotic complication early (1 d, 45 d, 3 mo and 6 mo TEE and 12 mo TTE). Fourthly, the case illustrates the adequacy of our management of thrombotic complications of ACP. After ACP implantation, DAPT is administered and anticoagulation is stopped due to the contraindication of long-term OAC. If thrombotic complications are detected by a strict TEE monitoring during the follow-up, the early initiation of intravenous anticoagulation can remove the thrombus, preventing serious thrombotic complications if not detected early and avoiding the need of long-term OAC in patients at high risk of complications under OAC treatment.

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LETTERS TO THE EDITOR

Circle of Willis atherosclerosis, Alzheimer's disease and the Dean number

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Abstract

The important role of atherosclerosis in pathophysiology of Alzheimer's Disease has become evident. Mechanisms such as hyperlipidemia, inflammation, abdominal obesity and insulin resistance are important yet they may not fully explain the specific involvement of the Circle of Willis in these pathologies. The Circle of Wills is a complex geometrical structure which has several areas with different curvature as well as various branching angles of vessels composing the circle. The hemodynamics in this region should take into account the Dean number which indicates the influence of curvature on the resistance to blood flow. Thus, areas with various curvature and angles may have different hemodynamics and there are certain areas in the Circle of Willis that are more likely to develop atherosclerotic changes. Therefore, this could suggest the novel pathophysiological pathway resulting from the geometric peculiarities of the Circle of Willis. One of the directions of future research is to examine whether specific areas of the Circle of Willis are more likely to develop atherosclerotic changes compared to other ones. Selective areas of the Circle of Willis affected by atherosclerotic changes could indicate the primary role of atherosclerosis promoting Alzheimer's disease although other pathophysiological mechanisms suggesting the opposite direction should be also examined in prospective studies.

Core tip: The Dean number can become an important local pathophysiological mechanism that can help to explain the specific involvement of the Circle of Willis in atherosclerosis and Alzheimer's Disease as anatomically different parts of the Circle of Willis would exhibit various degree of the curvature which would predispose to Alzheimer's disease. This could possibly explain some sporadic cases of Alzheimer's disease in the presence of minimal damage from atherosclerosis as well as open up new avenues for prevention of sporadic Alzheimer's disease.

TO THE EDITOR

The important role of atherosclerosis in pathophysiology of Alzheimer's disease has become evident. Studies that examined an association between the Circle of Willis atherosclerosis, Alzheimer's disease and some other neurodegenerative conditions are examples of important research directions focused on probable influence of various vascular factors on Alzheimer's disease[1,2]. On the other hand, those studies suggest that these pathologies could share some common pathophysiological mechanisms that yet need to be investigated. Some of such mechanisms such as hyperlipidemia, inflammation, abdominal obesity and insulin resistance were described by authors as prob-
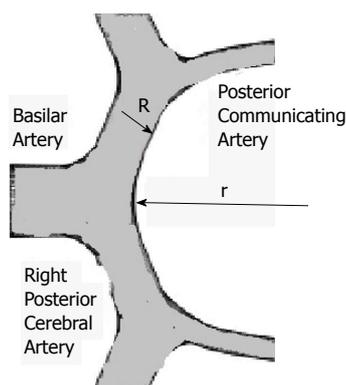
Figure 1 The Circle of Willis: The values of curvature (R and r).

able candidates[1,2]. However, although all these factors are very important, they may not fully explain the specific involvement of the Circle of Willis in these pathologies.

The Circle of Wills is a complex geometrical structure which has several areas with different curvature as well as various branching angles of vessels composing the circle. On the other hand, there are multiple anatomical variations of the Circle of Willis[3]. When a fluid runs through branching pipes a change of the its direction happens and similarly, when blood flows through the branching area in the Circle of Willis it changes direction. In general, taking into account that blood flow in the cardiovascular system is mostly laminar and the fact that branching areas of many arterial bifurcations have various angles, several hemodynamic factors (*i.e.,* radius of curvature of internal wall at branching area, Reynolds number, diameters of bifurcating vessels, *etc.*) should be taken into account[4]. One of them is the degree of curvature or the Dean number (Di). The Dean number indicates the influence of curvature on the resistance to blood flow[4,5]. If flow is laminar, then the Dean number is determined as:

$$D = 0.5\ Re\{[R(\frac{R}{r})^{1/2}]\}$$

Where Re indicates Reynolds number, R is a radius of the vessel, r is a radius of the curvature[4] (Figure 1).

Thus, areas with various curvature and angles may have different hemodynamics. For example, hemodynamics in the area where the degree of curvature is substantial could be described by the so called "hemodynamic shade" zone[6]. This zone can be characterized by a secondary flow and a boundary, therefore, there is a significant deterioration of mass exchange due to the attachment of stacks of erythrocytes (rouleaux) to the vascular wall[6]. This could deteriorate the permeability of the endothelium and decrease the rate of removal of various particles such as lipids and lipoproteins, which in turn can lead to the formation of lipid stripes directed along the blood flow and located in the "hemodynamic shade" of the original attached rouleaux. This could also explain why hyperlipidemia could be one of the non specific yet contributing pathophysiological mechanisms in the development of the Circle of Willis atherosclerosis. Therefore, there are certain areas in the Circle of Willis

that are more likely to develop atherosclerotic changes. As mentioned earlier, other factors such as hyperlipidemia or abdominal obesity should be taken into account as well.

Subsequently, with the development of atherosclerosis, vascular wall in the certain areas of the Circle of Willis (*i.e.,* with substantial curvature) becomes less elastic and more rigid. This could result in the deterioration in the cyclic changes in the vascular wall deformation produced by cardiac contractions, and, therefore, in the performance of a "deformation pump"[7]. The operating principle of this pump is in the cyclic creation of the boundary layer and its separation[7]. This deformation pump is important to consider as it could influence the dynamics of the regional brain extravascular extracellular fluid which was previously studied with regard to amyloid beta-protein, amyloid-beta building blocks for plaques and subsequent involvement in neurodegeneration[8]. Such consideration of regional brain extravascular extracellular fluid dynamics is also particularly important in light of the fact that certain waste products such as glutamate or calcium can accumulate there causing degradation of certain cellular components thus playing an important role in the pathogenesis of Alzheimer's disease[9,10]. A consideration of both the deformation pump and extravascular extracellular fluid could become an important link between Alzheimer's disease and atherosclerosis.

All this could suggest the novel pathophysiological pathway resulting from the geometric peculiarities of the Circle of Willis. One of the directions of future research is to examine whether specific areas of the Circle of Willis are more likely to develop atherosclerotic changes compared to other ones. Selective areas of the Circle of Willis affected by atherosclerotic changes could indicate the primary role of atherosclerosis promoting Alzheimer's disease. On the other hand, other pathophysiological mechanisms that could explore local factors (*i.e.,* the Dean number) and suggesting the opposite direction should be also examined in prospective studies. For example, anatomically "different" parts of the Circle of Willis (*i.e.,* narrowed branching areas) would exhibit various degree of the Dean number and this would predispose to Alzheimer's disease. This could possibly explain some sporadic cases of Alzheimer's disease in the presence of minimal damage from atherosclerosis in this area. More importantly, this would open up new avenues for prevention of sporadic Alzheimer's disease in the light of the fact that this is an emerging health concern in the elderly. In addition, certain rheological factors such as blood viscosity should be taken into account as a contributing pathophysiological mechanism as well. In conclusion, more studies are needed to examine the common pathophysiological mechanisms related to both Alzheimer's disease and various vascular pathologies. Such common pathophysiological pathways should take into account multiple factors such as hyperlipidemia, insulin resistance, certain local rheological and hemodynamic

factors as well as potentially new contributing factors established in future research.

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Contents

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EDITORIAL

Intravenous drug abuse and tricuspid valve endocarditis: Growing trends in the Middle East Gulf region

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Abstract

Traditionally, tricuspid valve endocarditis is uncommon in the Middle East region. However, recent global data indicate growing trends in the use of illicit drug abuse, specifically injectable heroin, in the Middle East Gulf region. The presence of many transit port services in the Middle East Gulf States has led to smuggling of substance abuse drugs in the region. The Middle East Gulf States, currently a transit market, are also becoming a growing consumer market in view of the increased substance abuse in the youth. However, there is a paucity of data with respect to the prevalence or incidence of tricuspid valve endocarditis in the region, probably due to underdiagnosis or underreporting. A high index of suspicion of tricuspid valve endocarditis is essential in patients with a history of intravenous drug abuse. This article reviews the epidemiology of illicit drug abuse in the Middle East Gulf region, as well as the diagnosis and treatment of tricuspid valve endocarditis, and calls for all physicians in the region to be vigilant while dealing with intravenous drug abuse.

Core tip: It is presumed that tricuspid valve endocarditis is uncommon in the Middle East region. However, recently published global data indicate growing trends in the use of illicit drug abuse in the Middle East Gulf region. The Middle East Gulf States, currently a transit market, are also becoming a growing consumer market in view of the consumption patterns of substance abuse in the youth. This article reviews the epidemiology of illicit drug abuse in the Middle East Gulf region as well as diagnosis and treatment of tricuspid valve endocarditis.

INTRODUCTION

Illicit drug abuse, including intravenous drug abuse (IVDA), is increasing in the Middle East Gulf region[1,2]. The existence of many transit port services in the Middle East Gulf States (Saudi Arabia, United Arab Emirates (UAE), Oman, Bahrain, Kuwait and Qatar) has contributed to smuggling of substance abuse drugs in the region[1,2]. The Middle East and Gulf, traditionally transit markets, are also increasingly becoming consumer markets in view of their geographical location and the young population of the region (60% below 15 years). As a direct consequence, this may have led to increasing correlates of drug abuse such as overdose, dependence, psychosis, suicide, road traffic accidents, cutaneous complications, thrombophlebitis of veins, myocardial infarction, pulmonary embolism, infective endocarditis

Figure 1 Map of Middle East Gulf States. UAE: United arab emirates.

(IE) specifically tricuspid valve endocarditis (TVE), pneumonia, pulmonary tuberculosis, septicemia, transmission of blood-borne infections (human immune deficiency virus (HIV)/hepatitis) and have also impacted on increased mortality due to overdose[2]. However, there is a paucity of data with respect to the incidence of tricuspid valve endocarditis in this region, probably due to underdiagnosis or underreporting. In addition, there is a lack of epidemiological studies documenting the burden of disease in terms of prevalence and related morbidity and mortality due to drug abuse in this region. This review article summarizes the epidemiology of illicit drug abuse in the Middle East Gulf Region (Figure 1) in relation to the diagnosis and treatment of TVE.

EPIDEMIOLOGY AND BURDEN OF ILLICIT DRUG ABUSE IN THE MIDDLE EAST GULF REGION

The commonly abused illicit substances can be broadly grouped as stimulants (amphetamines/methamphetamines/crystal meth/speed/captagon tablets/khat/3,4-methylenedioxy-N-methylamphetamine/ecstasy, lysergic acid diethylamide, cocaine/crack and cannabis/marijuana/ganja/hashish/bhang), hypnotics (barbiturates and methaqualones) and opiates (morphine, heroin/smack/brown sugar, opium, methadone). Among these, the most commonly injected drug is heroin[1]. However, morphine, amphetamines/methamphetamines, and cocaine are also common[1].

Globally, the United Nations Office on Drugs and Crime (UNODC), estimates that there were about 149-271 million people aged 15-64 years (3.3%-6.1%) who used an illicit drug at least once in 2009[1]. A large systematic review which included UNODC data reported 125-203 million people to be cannabis users, 15-39 million were opioid, amphetamine or cocaine users, and 11-21 million IVDAs[2]. The highest levels of use were in North America, Western Europe and Oceania. The

Middle East data suggested that 6-12 million (2.4%-4.8%) were cannabis users, 2-3 million were opioid users (0.8%-1.4%), 0.4-4 million were amphetamine users (0.2%-1.7%) and 0.04-0.6 million were cocaine users[2]. Opioid use, including heroin, had an estimated 12 to 21 million users globally. The highest rates of opioid use was reported in the Middle Eastern regions, where up to 1.4% of the population aged 15 to 64 had tried the drug at least once in 2009[2].

Data from the Eastern Mediterranean Regional Office of the World Health Organization suggest a prevalence of illicit drug use disorders at the rate of 3500 per 100000 population and that of injecting drug use to be 172 per 100000 population[3]. A report from UAE estimated that about 40% of all illegal drugs in the world are sold in the Gulf region[4]. The same report noted that the mean age of new drug abusers has dropped from 17-18 years to 10 years[4]. Most of the illicit drugs destined for African and European countries transited *via* the Gulf States, with significant leakage to the Gulf States[4]. In a report from Oman, quoting the Ministry of Health, 1521 drug misuse-related cases were reported in the period 2006-2011 and the most common mode of misuse was IVDA (66%)[5].

In 2002, a report from Al-Amiri Hospital in Kuwait estimated the presence of 18000-20000 drug users in this small Gulf State, the equivalent of 1% its total population[6]. Unemployment, excess disposable income, boredom and frustration were cited as important factors for the youth to take up drugs. In addition, drug dealers easily get couriers among the thousands of expatriate laborers entering Kuwait[6]. Another survey conducted among university students in Kuwait revealed that the total lifetime prevalence of illicit drug use was 14.4% and the most frequently used illicit substance was marijuana (11%)[7]. On multivariate logistic regression analysis, drug use was significantly associated with age, poor academic performance, high family income, being an only child in the family, divorced parents and graduation from a private high school[7].

TRICUSPID VALVE ENDOCARDITIS PATHOGENESIS

Right sided endocarditis accounts for 5%-10% of all IE and predominantly affects the tricuspid valve (TV)[8-10]. TVE commonly occur among IVDAs[11,12]. The cause for the increased prevalence of TVE in IVDAs is multifactorial. Frontera *et al*[10] suggested possible mechanisms which include: (1) recurrent episodes of particulate matter bombardment (drug solutions may contain particulate matter like talc) leading to damage of TV; (2) TV intimal damage, vasospasm (cocaine induced) and thrombus formation due to injected drugs; (3) increased right sided cardiac turbulence secondary to drug-induced pulmonary hypertension (buprenorphine); (4) increased expression of matrix molecules on the TV which are capable of binding microorganisms in IVDAs; (5) injection of large
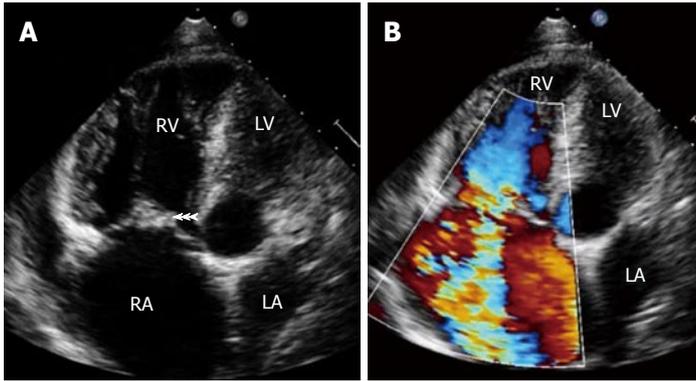
Figure 2 Transthoracic echocardiography showing (A) large vegetation attached to tricuspid valve leaflets (arrowheads) in a patient with intravenous drug abuse and septic pulmonary emboli. Note hugely dilated right atrium and right ventricle and (B) severe tricuspid regurgitation. RA: Right atrium; RV: Right ventricle; LA: Left atrium; LV: Left ventricle.

"bacterial loads" from contaminated drug solutions causing IE; and (6) IVDA-related "immune dysregulation" with or without coexistent HIV infection. In addition, poor injection hygiene (*e.g.*, lack of skin cleaning before injecting), injecting with unsterile needles, multiple needle sharing and injecting contaminated drug solutions which tends to introduce high bacterial loads.

WORLDWIDE INCIDENCE OF TVE

Among the published reports, the overall incidence of IE among IVDAs ranges from 1.5-20 per 1000 drug user per year[10]. In the United States, the incidence is estimated at 1.5 to 3.3 cases per 1000 person-years[12]. From the Western series, acute infection is responsible for 60% of all hospital admissions among IVDAs. Among these acute infections, TVE is implicated in 5%-15% of these cases[12,13]. It is also estimated that the incidence of IE in IVDAs is 2%-5% per year and is responsible for 5% to 10% of the overall death rate[14]. In the large multinational International Collaboration on Endocarditis-Prospective Cohort Study (ICE-PCS) evaluating 2781 patients with IE, 10% of the patients were IVDAs[15].

INCIDENCE OF TVE IN THE MIDDLE EAST

There are few published reports of IE from Middle East Gulf States. Among these studies, IVDA is reported in only 1 study. Even although the Middle East region has the highest prevalence of IVDA among all countries in the world[2], the incidence of TVE and IVDA is reported to be very low. This may be due to either underdiagnosis or underreporting. In a study from Oman published in 2003 and involving 90 patients with IE, there were no patients with TVE or with a history of IVDA[16]. This was similar to studies from Yemen (72 patients) and Kuwait (60 patients), with no involvement of TV or history of IVDA[17,18]. However, between 2006 and 2011, 7 cases of TVE with 3 of them reporting active IVDA were reported from Oman (personal communication). In a study from Saudi Arabia among 83 patients with IE, 4 cases of native TV involvement and 1 case of prosthetic TV involvement were reported, but with no mention of IVDA[19]. In a second study from Saudi Arabia, out of 47 cases of endocarditis, TV was affected in 3 patients

(6.4%), pulmonic valve in 2 patients and both pulmonic valve and TV in 1 patient (2.1%). In addition, 2 (4.3%) patients gave a history of IVDA[20]. A study from Lebanon also reported 7% (6/91) of patients with IE had TVE and no IVDA[21].

CLINICAL MANIFESTATIONS

The majority of IVDAs with TVE are young, between 20-40 years of age, and predominantly men (male:female ratio, 4 to 6:1)[12]. The most common presenting manifestations of TVE are persistent fever, bacteremia and multiple pulmonary emboli[9,11]. Respiratory symptoms are more common in TVE than left sided endocarditis. Dyspnea, pleuritic chest pain, cough and hemoptysis are the most common symptoms. Patients can present with metastatic abscesses in lungs that may lead to repeated episodes of dyspnea with hypoxemia and may mimic pulmonary embolism. However, left sided endocarditis in IVDAs is not uncommon and when any peripheral emboli or stroke occur, either left sided endocarditis or paradoxical embolism should be strongly suspected in patients with IVDA[11]. It is important to note that history and physical examination are not diagnostic of TVE in patients with IVDA. There is an absence of underlying heart disease in two-thirds of the patients. Symptoms and signs may be nonspecific. In about 65% of IVDAs with TVE, heart murmurs are not appreciated[11]. This is in view of normal or mildly elevated right ventricular pressures resulting in a low velocity less turbulent tricuspid regurgitation (TR) jet[11]. Generally, respiratory findings dominate the clinical, chest X-ray and computed tomography (CT) scan features. They can even mimic other respiratory infections like pulmonary tuberculosis[22].

DIAGNOSIS

The two most important diagnostic features of TVE in patients with IVDA are echocardiographic evidence of vegetation (Figure 2A) and the presence of septic embolic phenomena[11]. In addition, moderate to severe tricuspid regurgitation may be present (Figure 2B). In IVDAs with IE, TV is commonly involved in about 60%-80% of cases, with reported mortality of 5%-10%[9]. In a study of 105 IVDAs with IE, 86% were right sided and 14%

were left sided[11]. In IVDAs, both sides of the heart are usually involved simultaneously in 5% to 10% of cases[13]. TV vegetations generally grow to a larger size (> 2 cm) due to low pressure in right heart chambers and thus may mimic fungal endocarditis[11]. Vegetations may embolize and can be seen in the right ventricle or pulmonary artery or entrapped in the tricuspid chordal apparatus[11,22]. Transthoracic echocardiography (TTE) plays an important role in the diagnosis of TVE. Many IVDAs are young and generally have good echo windows, resulting in good high resolution images[11]. In addition, as the TV is relatively nearer to the transducer, excellent images can be obtained by TTE. TEE is indicated in patients with poor echo window or in those with initial negative TTE in whom there is high index of suspicion of TVE[11]. The diagnostic yield of TTE is comparable with that of TEE in IVDAs[23].

Duke's criteria have been predominantly applied for left sided endocarditis and have not been studied specifically in TVE. However, the two major criteria of typical echocardiographic features of TVE along with positive blood cultures with a typical organism should be regarded as diagnostic of TVE[11]. Blood culture is positive in a high proportion of TVE. When the culture is negative, it is usually due to prior antibiotic use or due to rare organisms such as Bartonella and HACEK organisms. The predominant organism of TVE in IVDAs is Staphylococcus aureus (60%-90%)[9-15]. Other organisms causing TVE are pseudomonas aeruginosa, other gram-negative bacilli, poly-microbial infections, fungi and group B streptococci[9-15]. In a study, the incidence of IE was 17% among all staphylococcal bacteremia patients and 46% among IVDAs[13]. In another study, 24% of IVDAs developed methicillin resistant staphylococcus aureus, of whom 41% developed IE[24]. Thus, in IVDAs, if patients develop staphylococcal bacteremia, nearly 50% of them go on to develop TVE. In another study among IVDAs presenting with fever to emergency departments, negative predictors of TVE were lack of skin infection, tachycardia, hyponatremia, pneumonia on chest radiograph, history of endocarditis, thrombocytopenia and heart murmur. The best criteria combination of lack of skin infection, tachycardia and cardiac murmur had a sensitivity and negative predictive value of 100%[25].

COMPLICATIONS

Septic pulmonary embolism in patients with TVE occurs in 75% to 100% of patients[26]. It may cause pulmonary infarction, pulmonary abscesses, bilateral pneumothoraces, mycotic aneurysms of pulmonary arteries, pleural effusions and empyema[9,11]. The chest X-ray may show pulmonary infiltrates or opacities in about 56% of radiographs at presentation[11]. Typical chest manifestations on CT scan due to emboli are pulmonary infiltrates, obstruction, nodules or wedge shaped opacities with or without cavitations and abscesses suggesting septic emboli, which are seen in 80% of such patients[9-14]. The use of large

proximal veins (femoral veins) in IVDAs may result in life-threatening septic deep venous thrombosis and pulmonary embolism[27].

Right heart failure is common due to acute pulmonary hypertension or severe TR or TV obstruction[9,11]. Large vegetations can cause tethering of the septal and lateral valve leaflets, causing the TV to remain open throughout systole and leading to severe TR. In addition, prolapse, perforation, right ventricular dilation and flail leaflet due to disruption can all lead to severe TR. Large vegetations can even protrude through patent foramen ovale into the left atrium[28]. Paravalvar abscess formation occurs infrequently. Hypoxemia and paradoxical embolism can occur due to right to left shunting through a patent foramen ovale[11].

MANAGEMENT AND PROGNOSIS

Uncomplicated TVE is successfully treated medically in 80% of patients, with only 20% needing surgical intervention[12,29]. The reason why TVE responds well to medical therapy is that right sided heart involvement, even when severe, often allows time for medical treatment because of the greater tolerance for TR and pulmonary embolization[29]. Hence, it is recommended to wait before surgical intervention if possible until sepsis resolves with antibiotic treatment[29]. Right sided involvement, younger age and lack of pre-existing heart disease or other underlying diseases have been thought to explain the better prognosis of Staphylococcus aureus endocarditis among IVDAs than in the general population.

In methicillin-sensitive staphylococcal aureus native-valve endocarditis, beta-lactamase-resistant penicillins, like flucloxacillin, oxacillin or glycopeptides (teicoplanin or vancomycin), combined with gentamycin (for 2 wk) is recommended[9]. In uncomplicated TVE, medical treatment should be continued for 4-6 wk[12]. However, IVDAs pose a unique challenge in the treatment as they are poor or non-compliant to medication and follow-up, get early self-discharge from hospital and may go back to injecting drugs again once discharged from hospital. This naturally leads to high rates of relapse and re-infection[30]. Given the low likelihood of adherence to a 4 wk course of antimicrobials among IVDAs, shorter courses of therapy, with a combination of β-lactam with or without an aminoglycoside (for 2 wk) have become an accepted standard[12,30]. However, in a few centers in highly selected IVDA IE patients, with appropriate counseling and monitoring, it was possible to treat with outpatient parenteral antibiotic therapy using peripherally inserted central catheter lines[31]. Poly-microbial endocarditis is more frequent in IVDA, which may need long-term suppressive therapy, specifically if fungal endocarditis is present[32]. The most important organisms in poly-microbial IE in IVDAs are: Staphylococcus aureus, Streptococcus pneumonia and Pseudomonas aeruginosa, as well as mixed cultures of Candida spp. and bacteria[33].

The European Society for Cardiology guidelines made

some recommendations for operative indications for TVE in the active stage. These recommendations are: (1) refractory right heart failure secondary to severe persistent TR; (2) IE caused by organisms which are difficult to eradicate (*e.g.*, persistent fungi) or bacteremia for at least 7 d despite adequate antibiotic therapy; and (3) TV vegetations > 20 mm which persist after recurrent pulmonary emboli with or without concomitant right heart failure[9]. Surgical options include vegetectomy, valvulectomy, valve repair/reconstruction with annuloplasty ring or replacement (either mechanical or bioprosthesis valves)[29,34]. A few authors opine that in IVDAs, vegetectomy and valve repair is preferred, avoiding artificial material and thus preventing prosthetic valve endocarditis[29,35,36]. If a valve replacement is done, some authors prefer a bioprosthesis valve as it could be better in terms of prognosis than a mechanical valve[36-38]. However, in a few studies, both mechanical and bioprosthesis valves have been successfully implanted in IVDAs with a similar 15 year survival (47.8% for mechanical *vs* 46.7% for bioprosthesis valves) and re-operation free survival (53% for mechanical *vs* 52% for bioprosthesis valves)[39,40].

Prognosis in TVE is generally good and in-hospital mortality is less than 10%[9-14]. Vegetation length > 20 mm and fungal etiology were found to be the main predictors of death in right sided IE in IVDAs[41,42]. In the ICE-PCS registry, 22% of TVE patients needed surgery and in-hospital mortality was 6%[15]. In patients with IE and HIV infection, there was higher total mortality at 2 mo, specifically in those with a CD4 count below 200 per microl[43,44]. In addition, any left sided involvement and age greater than 35 years are independently associated with mortality[45-47]. In a study, IVDAs with IE admitted to intensive care unit had very high mortality (27%), mainly due to sepsis and septic embolization[48]. In patients with repeated IVDA and endocarditis, the prognosis is poor and few authors are of the opinion that these patients should be offered valve replacement only once. If they develop a second episode of endocarditis, they should not be offered another valve replacement surgery[49,50].

CONCLUSION

In conclusion, recent reports indicate increasing trends in IVDA in the Middle East region. However, there is lack of reports about TVE, probably due to underdiagnosis or underreporting. TVE can mimic other respiratory diseases and may mislead in obtaining early diagnosis. A high index of suspicion of TVE is essential in patients with IVDA. In addition to already prevailing regulations and strict laws against drug trafficking in the Middle East Gulf region, programs to increase public awareness about the harmful effects of drug abuse are essential. Furthermore, a de-addiction drive among the youth in this region, anti-drug campaigns and the establishment of more rehabilitation centers are the need of the hour for eradicating this menace.

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MINIREVIEWS

Taurine supplementation in spontaneously hypertensive rats: Advantages and limitations for human applications

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Abstract

Taurine (2-aminoethanesulfonic acid) is a β-amino acid found in many tissues particularly brain, myocardium, and kidney. It plays several physiological roles including cardiac contraction, antioxidation, and blunting of hypertension. Though several lines of evidence indicate that dietary taurine can reduce hypertension in humans and in animal models, evidence that taurine supplementation reduces hypertension in humans has not been conclusive. One reason for the inconclusive nature of past studies may be that taurine having both positive and negative effects on cardiovascular system depending on when it is assessed, some effects may occur early, while others only appear later. Further, other consideration may play a role, *e.g.*, taurine supplementation improves hypertension in spontaneously hypertensive rats on a low salt diet but fails to attenuate hypertension on a high salt diet. In humans, some epidemiologic studies indicate that people with high taurine and low salt diets display lower arterial pressure than those with low taurine and high salt diets. Differences in techniques for measuring arterial pressure, duration of treatment, and animal models likely affect the response in different studies. This review considers both the positive and negative effects of taurine on blood pressure in animal models and their applications for human interventions.

Core tip: Many reports indicate that dietary taurine can reduce hypertension in humans and in animal models; however, the hypotensive effect of taurine supplementation depends on many factors. Taurine supplementation improves hypertension in spontaneously hypertensive rats on a low salt diet but fails to attenuate hypertension on a high salt diet. In humans, some epidemiologic studies suggest that people with high taurine and low salt diets display lower arterial pressure than those with low taurine and high salt diets. This review considers both positive and negative effects of taurine on blood pressure in animal models of hypertension to apply for human interventions.

INTRODUCTION

Hypertension is a risk factor for both acute and chronic adverse diseases, including stroke and cardiovascular disease[1,2]. Arterial blood pressure displays a diurnal variation, *i.e.*, it is elevated during active behavior periods and decreased during quiescent periods (*e.g.*, sleep)[3]. Thus, in humans, arterial pressure typically increases during the daytime and decreases during the nighttime[4]. In contrast, rats are generally nocturnal animals, and thus their diurnal rhythm is reversed, *i.e.*, their arterial pressures are elevated at night during active behavior, and decreased during the daytime[5]. Established hypertension is associated with decreased amplitude of diurnal arterial pressure variation, in that arterial pressure fails to decrease in the non-active period (*e.g.*, sleep), especially in older adults. In contrast, during the development of hypertension, the arterial pressure amplitude is typically greater than normal. Spontaneously hypertensive rats (SHR) display a circadian rhythm that is directly correlated with activity. However, in adult SHR compared to other strains, arterial pressure declines slowly in the morning (as the animals begin to sleep) and remains in the hypertensive range throughout the sleep period (mean arterial pressure > 110 mmHg)[5,6]. Further, high NaCl diets initially increase arterial pressure in the nighttime and more slowly increase daytime arterial pressure in both SHR and Wistar Kyoto rats (WKY; a normotensive control for SHR). This is especially evident after four nights of high NaCl treatment[5]. In addition, in SHR, high NaCl diets significantly increase daytime arterial pressure after a week of feeding, but they have little effect at that time point on daytime arterial pressures of normotensive WKY[5,7]. In the SHR on either a high or basal NaCl diet, sympathetic blockade greatly decreases arterial pressure rhythm, suggesting that the sympathetic nervous system contributes significantly to SHR hypertension, especially during its development[8,9].

Taurine (2-aminoethanesulfonic acid) is a non-protein, free amino acid found in many tissues particularly brain, myocardium, liver, muscle, and kidney[10-12]. Several lines of evidence indicate that dietary taurine can reduce hypertension in humans and in animal models[13]. For examples, dietary taurine attenuates hypertension in adult SHR[14] and deoxycorticosterone acetate and high NaCl (DOCA-NaCl) rats[15]. Sugar-induced hypertension can also be greatly blunted by dietary taurine and exacerbated by taurine deficiency[16]. Epidemiological studies indicate that people consuming high taurine diets display a low incidence of hypertension and other cardiovascular diseases[17]. Taurine supplementation was also reported to decrease systolic and diastolic blood pressure in young patients with borderline hypertension[18], but not in healthy men[19]. In addition, perinatal taurine exposure affects adult susceptibility to sugar-induced hypertension in rats[20-25].

De novo taurine synthesis is limited in rats and humans; therefore, dietary taurine is needed to maintain taurine in the body, which is especially important during developmental periods[11,12]. Intestinal taurine absorp-

tion is *via* high affinity sodium chloride-dependent active transport[26]. Thus, a high luminal sodium concentration accelerates intestinal taurine absorption, and high taurine transport increases sodium absorption into the blood. This complex relation has been suggested as the reason that in previous studies, taurine supplementation did not prevent NaCl-induced hypertension in SHR[27]. There are no experiments examining the effect of taurine on 24-h arterial pressure in animal models, and such information could elucidate the mechanisms underlying the failure of taurine to reduce arterial pressure in these models. This article reviews the advantage and limitation of taurine's antihypertensive action based on 24-h arterial pressure monitoring data in SHR.

24-H ARTERIAL PRESSURE DATA

In 1978, Nara *et al*[14] demonstrated that dietary taurine decreases hypertension in SHR. This finding is later supported by both experimental and epidemiological studies[13,17]. The effective dose of taurine has been between 1%-5% in drinking water for most of animal models of hypertension, and the duration of treatment has usually been more than 2 wk. For examples, Trachtman *et al*[28] demonstrate that 1% taurine in drinking water significantly decreases arterial pressure by 4 wk of treatment and reaches a maximum antihypertensive effect by 16 wk of treatment. Although taurine supplementation prevents hypertension in DOCA-NaCl sensitive rats, it does not blunt NaCl-sensitive aspects of hypertension in stroke-prone SHR[27]. However, this finding is based on acute arterial pressure measurements that were done during the normal sleep period (daytime), when the rat's arterial pressure is typically low.

To clarify the diurnal effect of taurine on arterial pressure, we did experiments in young SHR. At 7 wk of age, rats were anesthetized with isoflurane, and the abdominal aorta was exposed *via* a midline abdominal incision. After a segment of aorta below the renal artery was cleared, the flexible tip of the pressure sensing telemetry transmitter probe was inserted and secured to the vessel with tissue adhesive. The transmitter signal was then tested and the transmitter was surgically sutured to the abdominal wall. After surgically closing the wound, all rats were caged individually in clear cages and recovered on a basal NaCl diet (0.6%) for one week. Thereafter, the rats were fed a high NaCl diet (4.0%; w/w) and given 3% taurine in the drinking water (Taurine; *n* = 12) or water alone (Control, *n* = 7) for three weeks. This high NaCl diet has been commonly used to increase arterial pressure in SHR[27], and the 3% taurine in the drinking water has been used previously to attenuate hypertension in several animal models including SHR on a basal NaCl diet[13].

On a basal (0.6%) NaCl diet, both control and taurine-fed groups displayed a similar diurnal variation of mean arterial pressure, *i.e.*, mean arterial pressures were high at night but low in daytime, and they were not significantly different between groups (Figure 1). The high NaCl intake increased daytime and nighttime arterial pressures in both
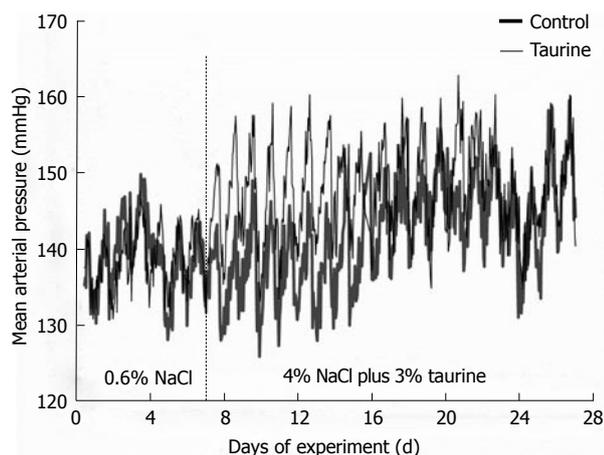
Figure 1 Group average, mean arterial pressures in control (thick line) and taurine (thin line) groups. The values were averaged from seven (control) and twelve (taurine) rats and the standard errors of means were not included to avoid confusion. Significant differences between groups (*P* < 0.05 by one-way analysis of variance and post hoc Duncan's multiple range test) were consistently observed in nighttime but not daytime mean arterial pressures from day 1 to day 9 of high salt treatment. The vertical dashed line at day 7 indicates the day that the high NaCl diet and taurine supplementation began.

groups, but with different time courses. Throughout the study, taurine had no effect on daytime arterial pressures (Table 1). In contrast, nighttime arterial pressures were significantly higher in the taurine (compared to control) group from the first to ninth night of treatment, but thereafter, taurine did not result in any significant difference in the high NaCl fed SHR for the remainder of the study. The arterial pressure analysis indicated that after starting a high NaCl diet, the taurine group displayed a rapid increase in mean nighttime arterial pressure within the first night, with arterial pressure approaching its maximum in the taurine-treated rats by night 2 (Figures 2 and 3). Thereafter, the nighttime mean arterial pressure of taurine group remained at nearly the same high level throughout the remainder of the study (3 wk).

These data confirm that taurine supplementation does not affect NaCl-induced daytime hypertension in the SHR, and thus, has little effect on mean average precision or on the eventual maximum level of arterial pressure in this model. Unexpectedly, the data also indicate that rather than being hypotensive or having no effect on arterial pressure in the SHR on a high NaCl diet, taurine supplementation accelerates the development of NaCl-sensitive hypertension during the nighttime.

ADVANTAGES AND LIMITATIONS OF TAURINE SUPPLEMENTATION

In most hypertensive rat and mouse models, a high (compared to basal or low) NaCl diet slowly increases nighttime arterial pressure after about 4 d of feeding, but the high dietary NaCl does not increase daytime arterial pressures until much later in these models[5,29,30]. This effect appears to be a consequence of the high dietary NaCl intake leading to Na^+ and fluid retention, especially dur-

Table 1 Noon and midnight mean arterial pressures in control (high salt alone, *n* = 7) and taurine (high salt plus taurine, *n* = 12) rats before and after treatment

Days of treatment	Control (mmHg)		Taurine (mmHg)	
	Noon	Midnight	Noon	Midnight
Before	128 ± 5	136 ± 4	133 ± 2	140 ± 2
1	129 ± 3	139 ± 4	136 ± 3	147 ± 2[a]
3	130 ± 3	140 ± 3	133 ± 2	150 ± 4[a]
7	138 ± 6	136 ± 4	147 ± 5	151 ± 3[a]
14	137 ± 6	143 ± 8	145 ± 2	152 ± 5
21	147 ± 5	149 ± 8	142 ± 3	148 ± 3

Data are mean ± SE; [a]*P* < 0.05 compared to midnight control by one-way analysis of variance and post hoc Duncan's multiple range test; No significant difference in noon mean arterial pressures between groups.
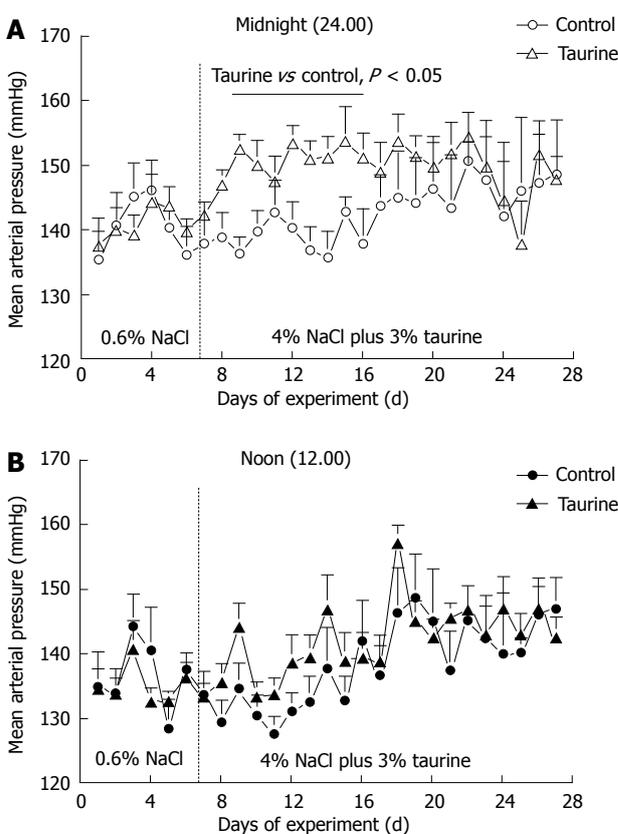
Figure 2 Group averages of mean arterial pressure in control (*n* = 7) and taurine (*n* = 12) treated groups at midnight (A) and at noon (B). The daytime mean arterial pressures were not significantly different between groups throughout the study. The vertical dashed line at day 7 indicates the day that the high NaCl diet and taurine supplementation began. Statistical comparisons were performed by one-way analysis of variance and post hoc Duncan's multiple range test.

ing the active period. This may be exacerbated by taurine supplementation if the taurine increases intestinal sodium absorption, which in SHR on a high NaCl diet may lead to increased NaCl-sensitive hypertension that offsets the normal hypotensive action of taurine.

The underlining mechanism for this effect likely relates to dietary NaCl and fluid retention that leads to increased sympathetic nerve activity, resulting in increased arterial vasoconstriction and cardiac output and ulti-
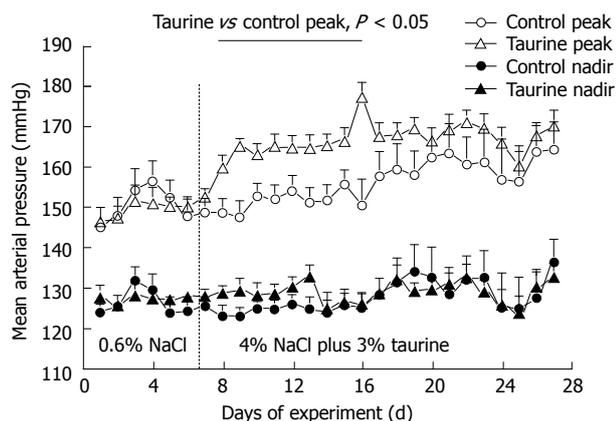
Figure 3 Peak (open symbols) and nadir (closed symbols) mean arterial pressures in control (*n* = 7) and taurine treated (*n* = 12) groups. The vertical dashed line at day 7 indicates the day that the high NaCl diet and taurine supplementation began. Statistical comparisons were performed by one-way analysis of variance and post hoc Duncan's multiple range test.

Figure 4 Possible pathways explaining the nighttime increase in arterial pressure after a combination of taurine supplementation and high salt diet in spontaneously hypertensive rats. CSF: Cerebrospinal fluid.

mately an increase in hypertension (Figure 4). Increased cardiac output significantly contributes to initial phase of essential hypertension, while increased total peripheral resistance sustains it[31,32]. In rats, 24-h measurements of plasma sodium concentration indicate that plasma Na^+ has a circadian rhythm that is opposite in phase to diurnal variation of mean arterial pressure[6]. Further, in SHR and WKY, a high NaCl diet increases daytime and nighttime plasma sodium levels, but in SHR compared to WKY on the high NaCl diet, the normal nighttime decrease in plasma sodium is greatly blunted, *i.e.*, plasma sodium remains high during the active phase[6]. This early failure of plasma Na^+ to decrease during the active period parallels the rise in nighttime arterial pressure in SHR.

Since intestinal taurine is absorbed *via* a high affinity sodium chloride-dependent active transport[26], high luminal sodium concentration can accelerate intestinal taurine absorption, and high taurine transport increases sodium absorption into the blood. This potentially causes an early increase in plasma Na^+. Further, in Dahl-NaCl sensitive rats, taurine supplementation alone increases sodium and fluid retention after a month on high NaCl diets[33]. It is likely that in the high taurine and NaCl fed SHR, taurine-facilitated Na^+ absorption and associated water absorption rapidly increase nighttime arterial pressure, which is already significantly elevated on the first night of high NaCl diet.

The increase in blood pressure in SHR on taurine and a high NaCl diet also may relate to altered brain control of sympathetic nervous system activity and a resulting increase in vasoconstriction. Huang *et al*[34] demonstrates that in SHR and Dahl-NaCl-sensitive rats, a high NaCl diet (8% NaCl) increases cerebrospinal fluid Na^+ concentration within a few days of treatment and 1-2 d before a rise in arterial pressure. This effect is not observed in WKY and Dahl-NaCl-resistance rats. Further, disruption of the hepatorenal natriuresis/diuresis pathway by hepatic denervation heightens nighttime hypertension in WKY rats[30], indicating that the nervous system normally
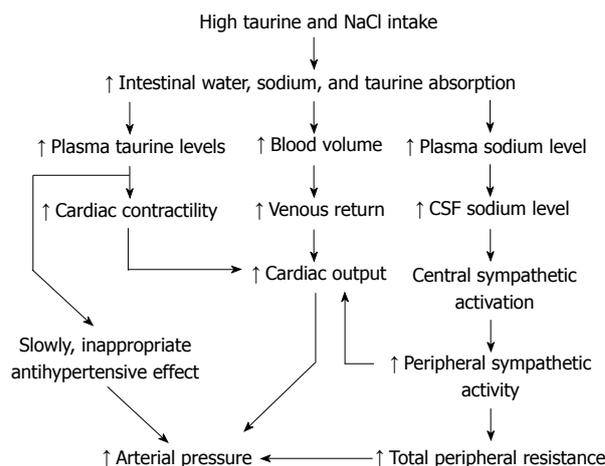
activates the hepatorenal reflex to reduce plasma Na^+ concentration by activating renal Na^+ excretion. This is particularly effective, since the receptors in the liver very quickly monitor the concentration of Na^+ that enters through the gut. Further, an abnormality in this feedback underlies NaCl and fluid retention observed in nephrotic syndrome[35]. These studies suggest that in SHR, high NaCl intake may lead to both peripheral and/or central increases in Na^+ concentration, leading to increased sympathetic nerve activity and increased arterial pressure. At least in its developmental phase, NaCl sensitivity in SHR appears to primarily result from sympathetic nervous system overactivity and not alterations in the renin-angiotensin system[7,36].

The hypertensive interactions between dietary NaCl and taurine may be mediated, in part, by taurine effects on Na^+ transport across the blood-brain barrier. As in the gut, taurine is transported across the blood-brain barrier by a Na^+-dependent, carrier-mediated mechanism[37]. SHR display low taurine content in brain[38,39] and heart[40]. In the SHR brain, taurine content is especially low in the hypothalamus and rostral ventrolateral medulla, both key areas that regulate cardiovascular function[41,42]. In SHR on a basal NaCl diet, long-term (but not short-term) taurine supplementation increases brain taurine levels to those of the WKY and decreases hypertension and related disorders, *e.g.*, cardiac hypertrophy and renal dysfunction. In SHR, the long-term taurine treatment is probably necessary because SHR display slow taurine transport across blood-brain barrier[37], thus decreasing taurine's ability to rapidly accumulate in the brain after acute treatment. In the short-term study, taurine supplementation may have increased cerebrospinal fluid Na^+ concentration in the high NaCl fed SHR before it is able to increase taurine concentration in the brain, leading to the early activation of the sympathetic nervous system[9,43].

In SHR on a basal NaCl diet, overactivity of both the sympathetic nervous system and the renin-angiotensin system contribute importantly to the development of

hypertension[7,36], and taurine supplementation reduces both mechanisms in SHR on a basal NaCl diet[13]. Sugar-induced hypertension is also maintained by overactivity of both the sympathetic nervous system and the renin-angiotensin system and is associated with mild insulin resistance[44]. Chronic treatment with taurine improves insulin sensitivity and reduces hypertension in these models of hypertension[16]. The hypotensive action of taurine in DOCA-NaCl rats is also related to inhibition of sympathetic nervous system activity[45]. In humans, taurine supplementation decreases plasma epinephrine levels in borderline hypertension, suggesting a sympathetic nervous system mechanism[18]. Further, epidemiological studies indicate an inverse relationship between taurine-rich diets and sympathetic nervous system activity in hypertension[17]. However, our 24-h arterial pressure study suggests that, while dietary taurine supplementation is antihypertensive in most hypertensive models, at least in SHR, the combination of high dietary NaCl and taurine supplementation causes an early acceleration in the development of NaCl-sensitive hypertension and does not lead to any reduction in arterial pressure at later time points. This indicates that further studies in animals and humans are needed to explore the interactions between dietary supplements and NaCl intake.

Taurine possess positive inotropic effects on cardiac muscle particularly in *in vitro* experiments (*i.e.*, an acute effect) and in taurine deficient animals[46-48]. These actions are related to taurine-increased calcium inward current and calcium release from sarcoplasmic reticulum. More taurine intake during the nighttime may increase plasma taurine (and likely cardiac taurine concentration), leading to increased cardiac contractility in the nighttime compared to the daytime. In subjects on high taurine and NaCl diets, this positive inotropic effect may increase the Starling's effect of increased venous return due to increased blood volume, leading to increased cardiac output and eventually increased arterial pressure.

CONCLUSION

Diets high in taurine prevent or decrease hypertension in many animal models of hypertension and in humans[13,17]. In SHR fed a basal NaCl diet, taurine supplementation significantly blunts the development of hypertension; however, taurine supplementation fails to decrease NaCl-induced hypertension in SHR. In contrast to our hypothesis that taurine supplementation lowers arterial pressure, taurine accelerates the hypertensive response to a high NaCl diet in this animal model. The taurine supplementation initially accelerates arterial pressure in SHR fed a high NaCl diet during the nighttime but not the daytime. After the initial 9 d of the high NaCl diet, taurine no longer increases nighttime arterial pressure above that displayed by non-treated SHR on the high NaCl diet. These data suggest that while taurine is generally beneficial to arterial pressure in hypertensive situations, dietary taurine supplementation may have early adverse effects when paired with a high NaCl diet.

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MINIREVIEWS

The importance of avoiding unnecessary right ventricular pacing in clinical practice

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Abstract

Symptomatic bradycardia is effectively treated with the implantation of a cardiac pacemaker. Although a highly successful therapy, during recent years there has been a focus on the negative effects associated with long-term pacing of the apex of the right ventricle (RV). It has been shown in both experimental and clinical studies that RV pacing leads to ventricular dyssynchrony, similar to that of left bundle branch block, with subsequent detrimental effects on cardiac structure and function, and in some cases adverse clinical outcomes such as atrial fibrillation, heart failure and death. There is substantial evidence that patients with reduced left ventricular function (LVEF) are at particular high risk of suffering the detrimental clinical effects of long-term RV pacing. The evidence is, however, incomplete, coming largely from subanalyses of pacemaker and implantable cardiac defibrillator studies. In this group of patients with reduced LVEF and an expected high amount of RV pacing, biventricular pacing (cardiac resynchronization therapy) devices can prevent the negative effects of RV pacing and reduce ventricular dyssynchrony. Therefore, cardiac resynchronization therapy has emerged as an attractive option with promising results and more clini-
cal studies are underway. Furthermore, specific pacemaker algorithms, which minimize RV pacing, can also reduce the negative effects of RV stimulation on cardiac function and may prevent clinical deterioration.

Core tip: A high amount of long-term right ventricular (RV) pacing produces ventricular dyssynchrony and clinical deterioration in patients with reduced left ventricular ejection fraction (LVEF). In this patient group, cardiac resynchronization therapy has been shown to improve clinical outcomes and should be considered before a conventional pacemaker. In subjects with normal LVEF, the deleterious effects of RV pacing is less clear; however, specific pacemaker algorithms that minimize RV pacing may improve clinical outcomes in selected patients. Future studies will help to better identify those at risk of suffering the negative effects of RV pacing and define the correct use of preventive therapeutic strategies.

INTRODUCTION

Cardiac pacing has greatly improved the prognosis of patients with symptomatic bradycardia, approximating that

Table 1 Summary of the major pacing and implantable cardioverter-defibrillator randomized trials that compared atrial (AAI or DDD) *vs* ventricular based pacing strategies

Ref.	Patients (*n*)	Follow-up (yr)	Pacing/ICD indication	Study groups	Endpoints	Results
Danish study[8] (1997)	225	5.5	SSS	AAI *vs* VVI	All-cause mortality, CV mortality, AF, stroke, HF, and AV block	Significant reduction in CV mortality, AF, stroke and HF in the AAI group
PASE[11] (1998)	407	1.5	SSS and AVB	DDDR *vs* VVIR	Quality of life, all-cause mortality[1], HF[1], and AF[1]	No overall difference in quality of life albeit moderate improvement in patients with SSS but not AVB in the DDDR group. No difference in mortality, HF or AF
CTOPP[9] (2000)	2568	6.4	SSS and AVB	DDD/AAI *vs* VVI(R)	Stroke, CV mortality, all-cause mortality[1], AF[1], and HF[1]	No difference in stroke, CV mortality, all-cause mortality or HF. Significant reduction in AF in the DDD/AAI group.
MOST[10] (2002)	2010	2.8	SSS	DDDR *vs* VVIR	All-cause mortality, stroke, AF[1], HF[1], QoL[1], pacemaker syndrome[1]	No difference in all-cause mortality, stroke. Significant reduction in AF, HF, and QoL in the DDDR group. 18.3% cross-over due to pacemaker syndrome in the VVIR group
UK-PACE[14] (2005)	2021	3	AVB	DDD(R) *vs* VVI(R)	All-cause mortality, AF[1], HF[1], stroke[1]	No difference in any of the endpoints
DANPACE[13] (2011)	1415	5.4	SSS	AAIR *vs* DDDR	All-cause mortality, AF[1], HF[1], stroke[1], need for pacemaker reoperation[1]	No difference in all-cause mortality, chronic AF, HF or stroke. Increased risk of paroxysmal AF and need for pacemaker reoperation (development of AVB) in the AAIR group
DAVID[7] (2002)	506	0.8	Primary and secondary prevention ICD	VVI 40 *vs* DDDR 70 ICD	Composite of hospitalization for HF and mortality	Prematurely interrupted due to increased occurrences of the composite endpoint in the DDDR 70 group
MADIT Ⅱ substudy[17] (2005)	1232	1.7	Primary prevention ICD	0%-50% *vs* 51%-100% VP	Composite of HF and mortality	Nearly two-fold increase in hospitalization for HF in the 51%-100% VP group

[1]Secondary endpoints. AF: Atrial fibrillation; AVB: Atrioventricular block; CV: Cardiovascular; HF: Heart failure; ICD: Implantable cardioverter-defibrillator; QoL: Quality of life; SSS: Sick sinus syndrome; VP: Ventricular pacing; VVI: Ventricular.

of the general population. However, animal and human studies have shown that RV pacing leads to abnormal electrical and mechanical activation patterns (dyssynchrony), which leads to impaired hemodynamic parameters and myocardial remodeling[1-5]. Large pacemaker and implantable cardiac defibrillator (ICD) trials have reported an association between long-term RV pacing and deterioration of cardiac structure and function, as well as increased risk of heart failure (HF), atrial fibrillation (AF) and death[1,6,7]. This has subsequently caused concerns about the potential deleterious clinical effect of long-term right ventricular (RV) pacing. As a result, several therapeutic strategies, such as alternative RV pacing sites, cardiac resynchronization therapy (CRT) and alternative pacemaker programming options/algorithms that minimize RV pacing have emerged. This review will outline the available evidence concerning the negative effects of long-term RV pacing and comment on how to minimize RV pacing, with a focus on CRT and specific pacemaker algorithms.

THE CLINICAL EVIDENCE OF THE NEGATIVE EFFECTS OF RV PACING

Patients without baseline heart failure

The large bulk of information regarding the negative effects of RV pacing in patients without baseline HF comes from large pacemaker randomized clinical trials (RCT) of elderly patients with mainly Sick sinus syndrome (SSS) that were designed to assess the difference between atrial (AAI or DDD) and ventricular-based pacing strategies[8-14]. In the single center Danish trial, 225 patients with SSS were randomized to either single chamber atrial pacing (AAI) or single chamber ventricular pacing (VVI)[8]. After a mean of 5.5 years of follow-up, a significant increase in total and cardiovascular mortality, HF and AF in the ventricle-based pacing group was reported. The authors also found that the VVI pacing led to increased dilatation of the left atrial diameter and reduced left ventricular (LV) fractional shortening. An assumption that conserving atrioventricular (AV) synchrony is beneficial was made and because of that, several RCTs that compared dual chamber (DDD) *vs* single chamber (VVI) pacing in elderly patients with SSS only[10,12], SSS and AV block[9,11], and AV block alone[14] were carried out. To the surprise of many, DDD pacing was not associated with a decrease in mortality or hospitalization for HF, although a reduction in AF and minor improvements in quality of life were observed in the same group. These results were later confirmed in a meta-analysis[15] that included the Danish trial[8] and 4 of the recently mentioned RCTs that compared DDD *vs* VVI pacing[9-11,14] (Table 1). With atrial-based pacing, there was no significant difference in

mortality (HR = 0.95, 95%CI: 0.87-1.03) or HF (HR = 0.89, 95%CI: 0.77-1.03), but a significant reduction in AF (HR = 0.81, 95%CI: 0.72-0.89) was observed[15].

One of the previously mentioned studies is The Mode Selection Trial in Sinus Node Dysfunction (MOST), which was a multicenter randomized study that randomized a total of 2010 patients with SSS to either VVIR or DDDR pacing[10]. Unexpectedly, after 33 mo of follow-up, a small but significant increased incidence of AF and hospitalization for HF in the DDD pacing group was reported, with no difference in all cause mortality between the two groups. When analyzing 1339 patients from the same study, the DDDR group received significantly more RV pacing than the VVIR group (90% *vs* 58%, respectively) and interestingly, the amount of RV pacing was a strong predictor for AF [HR = 1.36 (95%CI: 1.09-1.69) for each 25% increase in cumulative RV pacing] and HF hospitalization [HR = 2.99 (95%CI: 1.15-7.75) for > 40% of cumulative RV pacing][6]. On the contrary, the recent Danish Multicenter Randomized Trial on Single Lead Atrial Pacing *vs* Dual Chamber Pacing in Sick Sinus Syndrome (DANPACE) trial which included 1415 patients reported no difference in mortality, HF or chronic AF between DDDR or AAIR pacing[13] or the amount of RV pacing[16] after a mean follow-up of 5.4 years. Furthermore, there was a significant increase in paroxysmal AF and need for pacemaker reoperation, mainly due to the development of AV conduction disease in the AAIR group[13].

The conflicting results of the DANPACE trial[13] and the study limitations of the subanalyses from the older pacemaker trials, like patient heterogenicity (a minority presented clinical HF) and no echocardiographic evaluation, make it difficult to estimate to what extent long-term RV pacing causes clinical deterioration in patients without baseline HF. Although with the data available, it seems likely that most patients with normal LV function tolerate some degree of RV pacing without developing HF during long-term follow up.

Patients with reduced LVEF at baseline

The Dual Chamber and VVI Implantable (DAVID) trial[7] and a subanalysis of the Multicenter Automatic Defibrillator Trial II (MADIT II)[17] have provided strong evidence for the negative effects of RV pacing in patients with reduced baseline LVEF (Table 1). The DAVID trial was designed to study whether DDDR pacing with a lower rate limit at 70/min (DDDR 70) would decrease total mortality and hospitalization for HF when compared against VVI backup pacing with a lower rate of 40/min (VVI 40) through increased cardiac output and allowing higher doses of β-blocker therapy[7]. A total of 506 patients with standard indication for ICD implantation as secondary prevention but without indications for antibradycardia pacing were included in the trial, with an LVEF of 28% ± 8%. After a median follow-up of 8.4 mo, the study was prematurely interrupted due to more occurrences of the composite endpoint in the DDDR

70 group, largely driven by hospitalization for HF (1 year survival free of the composite endpoint: 73.3% for DDDR 70% and 83.9% for VVI 40; *P* = 0.02). Like in the MOST trial[10], a subanalysis of the DAVID trial[18] reported a continuous relationship between the percentage of RV pacing and the primary endpoint, with the most significant divergence of outcomes occurring with RV pacing > 40%. The results were further supported by the DAVID II trial[19], which randomized 600 patients with baseline characteristics similar to the DAVID trial to receive ICD implantation with either AAI pacing with a lower rate of 70/min or VVI 40. No difference in mortality or hospitalization for HF was observed after a mean follow-up of 2.7 years. Additional evidence comes from a subanalysis of the MADIT II trial[17], which randomized 1232 patients with previous myocardial infarction and LVEF < 30% to ICD plus optimal medical therapy *vs* medical therapy alone[20]. A significant 31% reduction in mortality risk was observed in the ICD arm but there was a worrisome trend towards more hospitalizations for HF in the ICD group and the subanalysis reported a nearly two-fold increased risk of hospitalization for HF in those who received > 50% of cumulative pacing. A recent report of the 8 years of follow-up of the patients with > 50% in the MADIT II trials reported mortality rates similar to the optimal medical therapy group, with the ICD group with a low percentage of RV pacing presenting a continued significant mortality benefit[21]. The MADIT II trial[20] results therefore illustrate how the clinical expression of the detrimental effects of RV pacing is the result of years of a high amount of RV pacing.

THERAPEUTIC OPTIONS TO AVOID UNNECESSARY RV PACING

Alternative RV pacing sites

The purpose of RV non-apical (RVNA) pacing is to take advantage of the specialized conduction system and thereby reduce ventricular dyssynchrony. Three main anatomical sites have been evaluated: right ventricular outflow tract (RVOT), intraventricular septum (IVS) and the His bundle. Overall, evidence from several small studies suggests that dyssynchrony is reduced and that LVEF is improved with RVOT[22], IVS[23] and His bundle[24] pacing, although negative results have also been reported[25]. Nevertheless, there is conflicting evidence regarding the clinical benefit of RVNA pacing in terms of exercise capacity or quality of life scores[23,25,26]. Furthermore, only one study evaluated whether RVNA pacing would result in prolonged survival benefit and failed to find such an association, although this endpoint was not powered properly[27]. Furthermore, a recent meta-analysis reported improved LVEF with RVNA pacing but no demonstrable clinical benefit when compared with RV pacing[28]. Large RCTs with statistical power to evaluate clinical endpoints are needed in order to establish whether RVNA pacing is an effective alternative to conventional RV apical pacing.

Table 2 Pacemaker algorithms that reduce right ventricular pacing

Reverse Mode Switch/RYTHMIQ™ (Boston Scientific, St. Paul, MN, United States)
 Atrial based pacing in AAI(R) with VVI backup (LRL minus 15/min) with the two modes operate independently from one another. If complete AVB occurs, ventricular paces will be delivered at backup VVI rate, asynchronous to the AAI rate. If 3 slow ventricular beats are detected in a window of 11 beats, AV conduction is considered blocked and switch to DDD (R) takes place. The algorithm will switch back to AAI if intact AV conduction is recuperated
Managed Ventricular Pacing™ (Medtronic, Minneapolis, MN, United States)
 Atrial based pacing (labeled as AAI(R)+) with switch to DDD(R) if AV block is detected, defined as 2/4 absent ventricular event. The algorithm checks for AV conduction at regular intervals and if present it will switch back to AAI(R)+
Ventricular Intrinsic Preference™ (St. Jude Medical, Sylmar, CA, United States)
 Intrinsic AV conduction is assessed by increasing AV delay at regular intervals (programmable AV extension of up to 200 ms; maximum AV delay 350 ms). If present, the longer AV delay will be maintained until a programmable number of cycles of absent ventricular sensed events (*i.e.*, continuous need for ventricular pacing), thus deactivating the algorithm
AV hysteresis (Biotronik, Berlin, Germany)
 Similar to Ventricular Intrinsic Preference™ (St. Jude)
AAISafeR™ and AAISafeR2™ (Sorin Group, Mirandola, Italy)
 Atrial based pacing in AAI (R). Abnormal AV intervals (> 350 ms if atrial sensed; > 450 ms if atrial paced) are monitored. Switch to DDD in response to any of the following:
  > 6 abnormal AV intervals ("first degree AVB")
  > 3/12 nonconducted atrial events ("second degree AVB")
  > 2 consecutive nonconducted atrial event ("advanced AVB")
  Ventricular pauses of 2–4 s (programmable)

AV: Atrioventricular; AVB: Atrioventricular block; LRL: Lower rate limit; VVI: Ventricular.

Table 3 Clinical studies of pacemaker algorithms that minimize right ventricular pacing

Study	Design	Pacing indication	Patients (*n*)	Follow-up (mo)	Outcomes
Sweeney *et al*[30]	Randomized, crossover MVP *vs* DDD(R)	SSS	181	1	Amount of pacing: MVP™: 4.1%; DDD(R): 73.8%
Murakami *et al*[29]	Randomized, crossover MVP *vs* Search AV+	SSS and AVB	127	1	Amount of pacing: MVP: 66.1%; Search AV+: 54.3% (patients with %RVP < 40) MVP: 57.5%; Search AV+: 38.6% (patients with %RVP < 10)
Olshansky *et al*[32]	RCT DDD(R) AVSH 60/min *vs* VVI 40/min (non-inferiority)	ICD[1]	1530	10.4	Trend towards a lower rate of death and hospitalization for HF in the DDD(R) AVSH group
Sweeney *et al*[33]	RCT Search AV+/MVP *vs* DDD(R)	SSS	1065	12	Amount of pacing: DDD(R): 99%; Search AV+/MVP: 9.1% Reduction in time to development of AF (primary endpoint) in the search AV+/MVP group No difference in hospitalization for HF or death (secondary endpoints)
Sweeney *et al*[36]	RCT MVP 60/min *vs* VVI 40/min (non-inferiority)	ICD[1]	1030	29	Prematurely interrupted due slightly more deaths and hospitalization for HF in MVP group

[1]Patients with an implantable cardiac defibrillator indication were included in the trial; AVB: Atrioventricular block; AVSH: AV Search Hysteresis (Medtronic); MVP: Managed Ventricular Pacing (Medtronic, Minneapolis, MS, United States); ICD: Implantable cardiac defibrillator; RCT: Randomized control trial; RVP: Right ventricular pacing; SSS: Sick sinus syndrome; VVI: Ventricular.

Pacemaker algorithms to reduce RV pacing

There are several pacemaker algorithms that permit prolonged AV intervals, all potentially capable of reducing RV pacing, and they can be divided into two large groups: (1) algorithms which periodically prolong the AV interval to search for, and if present, allow intrinsic AV conduction (AV hysteresis); and (2) algorithms that operate in a primary atrial pacing mode, with mode switch to secondary mode ventricular pacing (DDD) in case of significant loss of AV conduction[29-31] (Table 2). The most studied algorithm is probably the Managed Ventricular Pacing™ (MVP) (Medtronic, Minneapolis, MN, United States) that operates in primary atrial based mode labeled (AAI[R]+) with switch to secondary DDD[R] mode in the case of

loss of AV conduction occurring in 2 out of 4 atrial-atrial intervals[30]. In a short-term study without clinical endpoints with patients with SSS and various degrees of AV block, the MVP algorithm was reported to be significantly more effective in reducing the amount of RV pacing when compared to one AV hysteresis algorithm (66.1% *vs* 54.3% had < 40% of RV pacing, respectively)[29].

In terms of the potential clinical benefits associated with algorithms that minimize RV pacing, this has been evaluated by a few RCTs (Table 3). The Inhibition of Unnecessary RV Pacing With AVSH in ICDs (INTRINSIC RV) Study[32] was a multicenter non-inferiority trial which included 1530 patients with conventional indication for ICD implantation to dual chamber pacing

(DDDR mode with lower rate of 60) with AV Search Hysteresis™ (DDDR 60 AVSH) (Boston Scientific, St. Paul, MN, USA) or backup VVI 40 pacing. However, due to the worrisome results of the DAVID trial[7], eventually only 988 patients with < 20% RV pacing at 1 wk with DDDR 60 AVSH were randomized to the two programming modes. After a mean follow-up of 10.4 mo, non-inferiority of the primary endpoint, hospitalization for HF or total mortality had been met with a trend towards superiority for the primary endpoint in the DDDR 60 AVSH group. The DDDR AVSH 60 and VVI 40 groups presented with a mean RV pacing percentage of 10% and 3%, respectively. The results of the INTRISC RV study are reassuring since they suggests that in ICD recipients with a need for dual chamber pacing (*e.g.,* SSS and various degrees of AV block), the deleterious effects of long-term RV pacing as observed in the DAVID trial[7] can be avoided by the use of the AV hysteresis algorithm. However, since only those with < 20% of RV pacing were included in the trial, one should only consider the pacing algorithm in this patient profile and not in patients with high grade AV block who would expect to receive a significant amount of RV pacing (> 20%) despite the use of the algorithm. The Search AV Extension and Managed Ventricular Pacing for Promoting Atrioventricular Conduction (SAVE PACe) trial[33] assessed whether dual chamber pacing, using the Search AV+™ or MVP algorithms (Medtronic), decreases time to development of persistent AF compared with conventional dual chamber pacing (AV interval 120-180 ms) in patients with SSS and normal LVEF. After a follow-up of a mean of 1.7 years, significantly less patients in the minimal pacing group developed persistent AF (7.9% *vs* 12.7%, respectively, *P* = 0.004). However, no difference in the secondary endpoints, hospitalization for HF or mortality was found. As expected, the median percentage of atrial pacing was similar between the two groups but the amount of RV pacing in the conventional group was markedly increased when compared to the minimal pacing group (99.0% *vs* 9.1%). For the first time, a prospective association between a reduction in RV pacing and clinical benefit (freedom from AF) was reported. The results therefore support the use of algorithms that minimize RV pacing in patients with SSS.

Although the results are promising, the algorithms that minimize RV pacing may not be suitable in some patients. No large long-term trials with clinical endpoints have evaluated these algorithms in patients with high-degree AV block (although there is evidence that supports their short-term safety and effectiveness in reducing RV pacing)[34]. Furthermore, allowing severely prolonged AV intervals may lead to compromised cardiac output resulting from inefficient atrial systole and various degrees of diastolic mitral regurgitation[35]. The Managed Ventricular Pacing Versus VVI 40 Pacing Trial[36] compared dual chamber pacing with the MVP algorithm (with a lower rate of 60) and backup VVI 40 pacing in ICD patients. The trial was unexpectedly terminated early since non-

inferiority for the primary combined endpoint of HF events or total mortality could not be demonstrated, with a trend towards more primary endpoint events in the MVP. Interestingly, the subgroup analysis found that the increase in HF and mortality was largely contributed to by patients with a PR interval of ≥ 230 ms. Moreover, a subanalysis of the INTRINSIC RV study[37] reported on a J-shaped relationship between amount of RV pacing and the clinical event rate, with the best outcome for those with RV pacing between 10% and 19%. It therefore seems that a certain amount of RV pacing in those with impaired baseline AV conduction is necessary, although the equilibrium between low amounts RV pacing and preserved AV synchrony is not fully known. However, patients with normal or near normal AV conduction and the need for antibradycardia pacing are likely to benefit from the use of algorithms that minimize RV pacing.

Finally, sometimes pacemaker algorithms, like the ones previously discussed, may not work as expected. We recently evaluated the performance of the reverse mode switch™ (RMS) algorithm (Boston Scientific) which offers, like the MVP algorithm, primary atrial pacing AAI(R) mode with switch to DDD(R) secondary mode in the case of AV conduction loss, in a small retrospective study of 21 patients[38]. A large majority (84%) of the RMS episodes analyzed revealed an inappropriate switch to DDD(R) mode, mainly triggered by premature ventricular contractions (PVC). Therefore, our results suggest that patients with the RMS algorithm and high amounts of PVCs are paradoxically subject to an increased risk of unnecessary RV pacing through inappropriate RMS episodes. The results are also transferable to the newer but similar algorithm RYTHMIQ™ (Boston Scientific), given that the only difference between the two algorithms is the availability of the atrial tachycardia response feature in AAI(R) mode in RYTHMIQ.

Cardiac resynchronization therapy

It is well established that CRT improves ventricular dyssynchrony, LVEF, hospitalization for HF and mortality in patients with HF, prolonged QRS interval and NYHA class Ⅱ-Ⅳ and it has become a part of standard HF treatment[39,40]. Until recently, there was little data on the benefit of CRT in patients with a conventional indication for antibradycardia pacing; however, the results from the Biventricular Versus Right Ventricular Pacing in Patients with AV block (BLOCK HF) study[41] were recently published. It constitutes the first large scale RCT that assesses the clinical benefits of CRT compared to RV pacing in patients with LV systolic dysfunction (LVEF ≤ 50%) and AV conduction loss with a standard pacemaker indication but without conventional indication for CRT. A total of 691 patients, with mean QRS of 125 ms and 121 ms and mean LVEF 43% ± 7% and 33% ± 8% (CRT pacing and CRT-ICD groups, respectively) were randomized to RV pacing and CRT. The patients presented with first (19%), second (33%) and third degree (48%) AV block. After a mean of 37 mo of follow-up, CRT was

Table 4 Clinical studies of right ventricular pacing *vs* cardiac resynchronization therapy

Study	Design	Patient characteristics	Patients (*n*)	Follow-up (mo)	Baseline LVEF	LVEF in RV pacing	LVEF in CRT	Clinical benefit from CRT
Martinelli *et al*[42]	RCT multicenter	AVB	60	5 (crossover)	30.1% ± 9.2%	22.5% ± 8.1%	29.3% ± 6.9%[a]	Improved NYHA class and QoL
Yu *et al*[45]	RCT multicenter	AVB and SSS	177	12	61.6% ± 6.6%	54.8% ± 9.1%	62.2% ± 7%[b]	No difference in hospitalization for HF, exercise capacity or QoL
Curtis *et al*[41]	RCT multicenter	AVB	691	37	43% ± 7% (CRT-P) 33% ± 8% (DRT-D)	-	-	Reduction in composite endpoint (mortality, HF urgent care and LVESI)
Brignole *et al*[47]	RCT multicenter	AVN ablation	186	20	38% ± 14%	Increasing from baseline + 4.7%	Increasing from baseline +6.6% (NS)	Reduction in composite endpoint (death from HF, hospitalization for HF or worsened HF)
Doshi *et al*[49]	RCT multicenter	AVN ablation	184	6	46% ± 16%	41.1% ± 13%	46% ± 13%[a]	Improved exercise capacity No difference in QoL
Orlov *et al*[51]	RCT multicenter	AVN ablation	127	6	56.1% ± 9.4% (CRT group) 57.2% ± 7.5% (RVP group)	54.6% ± 11.5%	59.3% ± 7.7%[a]	No difference in NYHA class, exercise capacity or QoL

[a]$P < 0.05$; [b]$P < 0.001$ *vs* left ventricular function in right ventricle pacing; AVB: Atrioventricular block; AVN: Atrioventricular node; CRT-D: Cardiac resynchronization with implantable cardiac defibrillator; CRT-P: Cardiac resynchronization therapy pacing; NS: Non-significant; RVP: Right ventricular pacing; SSS: Sick sinus syndrome; QoL: Quality of life; LVEF: Left ventricular function; RV: Right ventricle; LVESI: Left ventricular end-systolic index; HF: Heart failure; RCT: Randomized controlled trial.

associated with a 26% risk reduction in the primary composite endpoint of all-cause mortality, HF-related urgent care and LV end-systolic index [HR = 0.74 (95% credible interval 0.60-0.90)] and a 27% risk reduction in all-cause mortality and HF-related urgent care [HR = 0.73 (95% credible interval 0.57-0.92)]. The findings from the BLOCK study therefore confirm the results from previous small studies[42] that CRT in patients with a pacemaker indication for AV block and a high degree of expected RV pacing and LV systolic dysfunction improves LV function and clinical outcomes. Furthermore, there is also data suggesting that patients with reduced LVEF and a reported high amount of long-term RV pacing may benefit from a device upgrade to CRT. For example, in a retrospective study, Fröhlich *et al*[43] reported inverse LV remodeling (LVEF and LV end-systolic and end-diastolic diameters) and improved NYHA functional class in patients with chronic RV pacing and reduced LVEF who received a CRT upgrade. A recent small RCT that included 50 patients with LV systolic dysfunction listed for routine pacemaker generator replacement with > 80% RV pacing in the preceding 12 mo found that an CRT upgrade was associated with improved LVEF, reduced N-terminal pro-B-type natriuretic peptide levels, exercise capacity and quality of life[44].

There is less evidence in favor of CRT in patients with normal LVEF. The Pacing to Avoid Cardiac Enlargement (PACE) study[45], which was a multicenter, double blind trial, randomized 177 patients with SSS or AV advanced block to receive either RV pacing (DDDR mode) or CRT. After 1 year of follow-up, the authors reported maintained LVEF and LV end-systolic volume (primary endpoints) in the CRT group but a reduction in these parameters in the RV pacing group. However, CRT did not improve the secondary clinical endpoints: 6

min walking test, hospitalization for HF or quality of life. It should be noted that no increased procedure-related complications were reported in the discussed studies, indicating that CRT is also a safe alternative to conventional RV pacing.

In AF patients with rapid ventricular rates who undergo catheter ablation of the AV node to create complete AV block due to irresponsiveness to pharmacological treatment, there is a high risk of suffering the detrimental effects associated with prolonged high density RV pacing, such as LV dyssynchrony, reduced LVEF and worsened HF symptoms[46]. Five small short-term RCTs studied the potential benefit of CRT compared to RV pacing in patients with AF and AV node ablation[47-51] and found improved LVEF and in some instances a reduction in hospitalization for HF. Thus, there is evidence that this group of patients would also benefit from CRT. Nevertheless, in asymptomatic individuals with AV node ablation for AF and normal LV function there is currently no evidence to support CRT. A list of some of the major clinical studies that compared CRT *vs* RV pacing is shown in Table 4.

A PRACTICAL APPROACH TO MINIMIZE UNNECESSARY RIGHT VENTRICULAR PACING IN CERTAIN PATIENT GROUPS

Data from subanalyses of ICD trials, including patients with reduced LVEF, suggests that > 40%-50% of RV pacing is associated with adverse clinical outcomes[17,18]. In addition, patients with reduced LVEF are at a significantly higher risk of suffering the negative clinical effects of RV pacing when compared to those with a normal cardiac function and most patients with normal LVEF
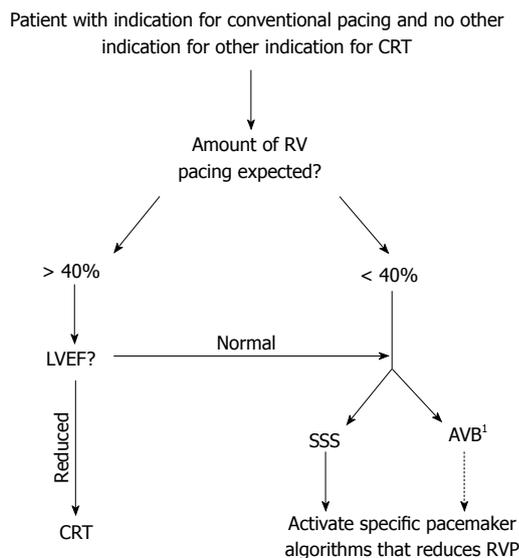
Figure 1 A schematic management plan of how to avoid unnecessary right ventricle pacing in a patient with an indication for conventional pacing and no other indication for cardiac resynchronization therapy. [1]No large scale trials have assessed the benefits and safety of the managed ventricular pacing algorithm in patients with high-grade AV block. AVB: Atrioventricular block; LVEF: Left ventricular ejection fraction; RVP: Right ventricular pacing; SSS: Sick sinus syndrome; CRT: Cardiac resynchronization therapy; RV: Right ventricle.

appear to tolerate some degree of chronic RV pacing[16,52]. It is therefore useful to stratify the patient with an indication for permanent cardiac pacing according to LVEF (reduced or conserved) and the likelihood of a high amount of RV pacing (high or low) (Figure 1). However, it may sometimes be difficult to estimate the latter although some more clear-cut scenarios also exist, such as patients with complete AV block (high risk) and patients with SSS and intact AV conduction (low risk).

Considering the available evidence, in a patient with a normal LVEF, a conventional pacemaker is currently the best option and unnecessary RV pacing should be avoided through appropriate device programming. This includes the correct selection of the pacing mode and also the lower rate limits (*e.g.,* VVI mode at 40 ppm in a patient with infrequent paroxysmal AV block), AV interval (*e.g.,* long AV intervals or AV hysteresis if there is no significant AV conduction loss) and the use of special algorithms aimed at minimizing RV pacing (if available). As discussed, several algorithms that all reduce the amount of RV pacing exists, although the MVP algorithm is the most studied with results indicating improvement in LV mechanics and also some clinical benefit[33,53]. However, there is currently insufficient evidence on the use of the MVP algorithm in patients with high grade AV block and in addition it may have a neutral or even negative effect when the PR interval is prolonged (> 230 ms)[36,54]. We therefore suggest that the MVP algorithm should only be used in those with SSS with no significant AV conduction disease (narrow QRS and PR interval < 230 ms).

If a patient presents with a reduced LVEF, with the results from the BLOCK HF study[41], there is now

strong evidence that CRT should be chosen over a conventional pacemaker in order to improve both LV reverse remodeling as well as clinical outcomes[41,42]. The recently published European guidelines on cardiac pacing and CRT thus recommend *de novo* CRT in patients with HF, reduced LVEF ($\leqslant$ 50%), bradycardia indication for pacing and an expected high percentage of RV pacing[39]. Furthermore, patients with reduced LVEF and planned AV node ablation for AF are likely to benefit from CRT[55]. Also, an important group of patients with indication for antibradycardia pacing also have a conventional indication for CRT and should obviously be offered this therapy[40]. Finally, there is presently not enough evidence to support the use of alternative RV pacing sites, such as RVOT, IVS and His bundle[28].

FUTURE DIRECTIONS AND UNSOLVED QUESTIONS

Despite the publication of a significant amount of evidence that has made us aware of the adverse pathophysiological mechanisms and clinical effects of prolonged RV pacing, as well as on the use of different strategies to overcome them, several questions remain unresolved. There is currently a lack of specifically designed studies that evaluate the potentially negative effect of long-term RV pacing in patients with normal LVEF. Most of the available information comes from old pacemaker trials aimed at evaluating atrial *vs* ventricular based pacing strategies in which echocardiography evaluation of LV function or percent RV stimulation was not always reported[8-11,14]. The conflicting results of the recent DANPACE trial[13], in which no association between the amount of RV pacing and clinical outcome was observed in patients with normal LVEF, further complicates the matter. Therefore, the extent of the negative effects of RV pacing in patients with normal LVEF and whether this is clinically relevant is at present debatable and future studies in this area are subsequently warranted. Other areas of future research include the indications and potential benefits of therapeutic strategies aimed at minimizing RV pacing such as specific algorithms, alternative pacing sites and CRT; however, several large scale trials are ongoing and the results will provide guidance for future clinical practice. The Biventricular Pacing for Atrioventricular Block to Prevent Cardiac Desynchronization (BIOPACE) study[56] is an international large randomized prospective mortality-driven trial that is comparing CRT *vs* conventional RV pacing in patients without a standard indication for CRT. Since patients with severely depressed to normal LVEF are being included, the results will not only help in defining the role of CRT in a wide range of patient characteristics but also provide information on the detrimental effects of RV pacing in those with normal LVEF. Finally, future large RCTs with long-term follow-up and clinical endpoints are currently evaluating the MVP algorithm and should provide important new information on its potential benefits[57,58].

CONCLUSION

In a significant number of patients, chronic RV pacing leads to negative effects such as reduced LV function and adverse cardiac remodeling, as well as increased incidence of HF, AF and death. Those with reduced LVEF and long-term high amount of RV pacing are at particular risk and there is now solid evidence that CRT improves LV function and clinical outcomes in this group. However, patients with normal LVEF seem to tolerate some degree of long-term RV pacing and thus the clinical relevance of the detrimental effects of RV pacing is less certain in these individuals. Appropriate pacemaker programming and the use of different pacemaker algorithms represent important methods to avoid unnecessary RV pacing in this patient group.

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BRIEF ARTICLE

Trend in prevalence of uncontrolled total serum cholesterol for cardio-cerebro-vascular disease in a mediterranean area, 1988/89-2008/09

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Abstract

AIM: To examine trends of uncontrolled total serum cholesterol, treatment and control in a Mediterranean region (Campania).

METHODS: We considered and compared the data collected as part of "Montecorvino Rovella Project" 1988-1989 and cross-sectional data from the two phases of the "VIP Project-Valle dell'Irno Prevenzione": 1998-1999 (1st phase) and 2008-2009 (2nd phase), in the 35-74-year-old-population.

RESULTS: Data show a reduction of mean cholesterolemia in the last twenty years of 7.3 mg/dL for men and unchanged values for women. In the three surveys the mean values for serum cholesterol are in men: 205.2 ± 47.1 mg/dL (1988/89), 200 ± 38.9 mg/dL (1998/99) and 197.9 ± 40.2 mg/dL (2008/09); in the women: 203.1 ± 42.5 mg/dL (1988/89), 198.9 ± 37.9 mg/dL (1998/99) and 203.3 ± 39.3 mg/dL (2008/09). Prevalence of uncontrolled high cholesterol $\geq$ 240 mg/dL for men decreased from 20.8% (1988/89) to 14.3% (1998/99) and 13.9% (2008/9), P = 0.002; for women the values decreased from 19.9% (1988/89), to 18.2% (1998/99) and 18.1% (2008/09), P = 0.007. Is statistically increased the number of patients treated and those treated to target.

CONCLUSION: Encouraging increases in awareness, treatment, and control of hypercholesterolemia occurred from 1988 through 2008. Nevertheless, control of hypercholesterolemia remains poor.

Core tip: Risk of cardiovascular disease (CVD) is directly related to blood cholesterol levels. CVD due to atherosclerosis is the foremost cause of premature mortality and of disability-adjusted life years in Europe, and is also increasingly common in developing countries. The objective of this study was to examine trends of high cholesterol, treatment and control in a Mediterranean region (Campania). Data show a reduction of mean cholesterol in the last twenty years of 7.3 mg/dL for men and unchanged values for women. Encouraging increases in treatment and control of hypercholesterolemia occurred from 1988 through 2008. However, control of hypercholesterolemia remains poor.

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INTRODUCTION

Coronary heart disease (CHD) is now the leading cause of death worldwide. It remains the major cause of premature death in Europe, even though CHD mortality has fallen considerably over recent decades in many European countries[1,2].

Raised serum total cholesterol is an important cardiovascular risk factor, which causes an estimated 4.4 million deaths every year worldwide[3,4]. Research from the World Health Organization highlights the importance of raised blood cholesterol as a risk factor for CHD. The World Health Report 2002[5] estimates that around 8% of all disease burden in developed countries is caused by raised blood cholesterol and that over 60% of CHD and around 40% of ischaemic stroke in developed countries is due to total blood cholesterol levels in excess of the theoretical minimum (3.8 mmol/L). Variations in diet, especially consumption of animal-based *vs* plant-based fats, adiposity, and use of drugs to lower cholesterol have led to differences in serum cholesterol concentrations across populations and over time[6-8]. Therefore, the focus on cardiovascular prevention must remain high. Our aim was to estimate trend in total serum cholesterol, in a Mediterranean area of southern Italy, in the last twenty years.

MATERIALS AND METHODS

We compared the results of three epidemiological surveys as far as cardiovascular risk factors are concerned, performed in Southern Italy, in a Mediterranean region (Campania), in two areas near the city of Salerno.

In particular we considered and compared the data collected as part of "Montecorvino Rovella Project"[9] (PMR) 1988-1989 and cross-sectional data from the two phases of the "VIP Project-Valle dell'Irno Prevenzione": 1988-1989 (first phase)[10] and 2008-09 (second phase).

In three investigations, a sample taken from people between 25-74 years (divided into 5 classes of age: 25-34, 35-44, 45-54, 55-64, 65-74) was studied. People were enlisted at random from the electoral rolls and subjected to blood tests after an overnight fast.

The methodology of data collection and conducting tests to which the population underwent during the three phases are standardized and comparable, they have been fully described in some other publications[9-11].

PMR and VIP were conducted by the same working group and the same coordinator. Areas over district level, are similar for geographic position, they both are about 20 km far from Salerno. Moreover the socio-economic status of the rural populations and their recent industrial development are similar.

PMR project design

PMR project had the following aims: to analyze the prevalence of cardiovascular risk factors in an area of the Campania region at the end of 1980s. This study was conducted between 1988 and 1989, inviting a randomized statistical sample to represent the area. Randomized samples included 1500 subjects, 300 (150 males and 150 females) for each decade. Only 1091 subjects (569 females and 522 males) were examined with a total participation of 72.7% (75.9% for females and 69.6% for males).

VIP project design

VIP project has the following aims: to conduct a program of cardiovascular prevention in a population of the Irno Valley controlled by Mercato S. Severino's Hospital, to know the physiological limits and biohumoral parameters of the resident population, to know the trend of the main cardiovascular risk factors in the area near Salerno. This study has collected epidemiological data on cardiovascular risk factors in two phases: 1998/99 and 2008/09. The "VIP Project" is a part of CINDI program, WHO study[12,13] and has contributed to the Global Burden of Metabolic Risk Factors of Chronic Diseases Collaborating Group[14]. Both surveys include 1200 subjects, 600 males and 600 females, age ranging from 25 to 74 years, randomized from the electoral rolls of the towns of Mercato S Severino and Baronissi, near Salerno, in Southern Italy. In a randomized way, we compiled three lists, each one of 120 subjects divided into decades of sex and age. The recruitment from the first list was realized by letter of invitation, in the case of impossibility or refusal, the subject was replaced by a person of the same age and sex from the second list and in the case of failure, someone from the third list. This type of procedure for the recruitment was suggested by the manual of the rules of monica project-monica cardiovascular diseases[15]. During all phases the subjects underwent to: (1) General examination; (2) Ecording of blood pressure; (3) Anthropometric measurements (weight, height, waist-hip ratio); (4) Electrocardiogram; and (5) Laboratory tests (total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, blood glucose, blood count, platelets, plasma insulin, fibrinogen, creatinine, C3).

Fasting venous blood was taken in the seated position without stasis after an overnight fast. The laboratory has always made use of quality control: Biorad (in 1988/89 and 1998/99) and VEQ (University Hospital of Bologna, Policlinico S. Orsola Malpighi) in 2008/09.

In particular, with regard to the parameters analyzed, cholesterol, HDL cholesterol, triglycerides were determined through an enzymatic method (Fixed-time to 500 nanometer) installed on Cobas-ABX (Roche, Milan Italy) automatic line.

A history, with a focus on cardiovascular disease, was performed by a physician who, through a questionnaire,

Table 1 Mean ± SD of cholesterol, high density-cholesterol, low density lipoprotein-cholesterol and triglycerides

	Age (yr)	Cholesterol (mg/dL)	HDL-C (mg/dL)	LDL-C (mg/dL)	Triglycerides (mg/dL)
Male	25-34	191.9 ± 41.6	45.1 ± 10.1	125.2 ± 35.5	114.6 ± 78.9
	35-44	206.8 ± 39.7	48.4 ± 12.5	131.3 ± 35	136.7 ± 77.3
	45-54	197.9 ± 40	55.7 ± 13.9	117.8 ± 34.6	122.2 ± 70.9
	55-64	195.6 ± 31.6	49.4 ± 12.6	120.2 ± 31.9	130.2 ± 62.7
	65-74	196 ± 45.5	52.4 ± 12.4	119.5 ± 39	118.9 ± 69.9
	25-74[1]	197.9 ± 40.2	50 ± 12.3	123.3 ± 34.9	124.9 ± 72.6
Female	25-34	201.1 ± 37.6	47.8 ± 11.4	131.0 ± 34.7	111.5 ± 71.7
	35-44	206.7 ± 41.4	52.5 ± 14.9	130.3 ± 37.7	119.6 ± 65.3
	45-54	203.7 ± 38.3	59.7 ± 13.7	120.9 ± 33.1	115.8 ± 72.7
	55-64	206.2 ± 38.8	52.4 ± 12.7	125.3 ± 34.2	142.6 ± 74.7
	65-74	195.6 ± 41.4	51.9 ± 12.4	119.8 ± 34.7	119.2 ± 67.1
	25-74[1]	203.3 ± 39.3	53.0 ± 13.1	126.1 ± 34.9	121.0 ± 70.5

[1]Data standardized to the European population. VIP Study 2008/09 (120 subjects by age group). HDL: High density lipoprotein; LDL: Low density lipoprotein.

Table 2 Percentiles of cholesterol, high density-cholesterol, low density lipoprotein-cholesterol and triglycerides (mg/dL) for both sexes

Percentiles	Cholesterol		LDL-C		HDL-C		Triglycerides	
	M	F	M	F	M	F	M	F
5°	136	137	70	70	32	34	47	49
25°	169	175	98	101	40	43	75.5	76
50°	196.5	201	121	123.5	49	52	105.5	104.5
75°	222	229.5	143	146.5	57	60	151	145
95°	267	270	189.5	182.5	72.5	79.5	256	235

M: Male; F: Female. HDL: High density lipoprotein; LDL: Low density lipoprotein.

also evaluated: the habit of cigarette smoking, physical activity, occupation, and level of education, the educational qualification of the partners, civil status, and regular use of pharmacological therapy.

Statistical analysis

Results are expressed as mean ± SD for continuous variables and as frequency distributions for the categorical ones. The data have been standardized using the direct method considering the European population standards of reference. To compare the means among the three groups, we used one-way analysis of variance and Bonferroni's test for the differences among the groups. χ^2 analysis was used to compare prevalences. $P < 0.05$ was considered significant.

RESULTS

Table 1 show age-specific levels of lipid pattern in the VIP Study 2008/09. The data from the previous surveys were published in a previous work[16]. Mean values of cholesterolaemia are higher in women, with a statistically significant difference ($P = 0.02$). The values of HDL are, in all decades, higher in females (except in the 65-74 years), with more marked differences for age groups 35-44 and 45-54 years.

The values of LDL cholesterol are similar between men and women: 123.3 ± 34.9 and 126.1 ± 34.9 ($P = $ NS) whereas for the age groups 25-34 and 55-64 years,

are higher in women. Regarding triglycerides mean values were found to be higher for men in the first three age groups but less in the last two decades. The highest values are recorded in the 35-44 years for male and in the 55-64 years for women. Table 2 shows the percentiles of lipidic pattern.

Figure 1 show age-specific levels of total serum cholesterol for PMR (1988/89) and two phases of VIP studies (1998/99 and 2008/09). The mean values (standardized to the European population) are in the male: 205.2 ± 47.1 (1988/89), 200 ± 38.9 (1998/99) and 197.9 ± 40.2 (2008/09); in the female: 203.1 ± 42.5 (1988/89), 198.9 ± 37.9 (1998/99) and 203.3 ± 39.3 (2008/09). Is evident a reduction of cholesterol in the last twenty years of 7.3 mg/dL for men and unchanged values for female. In both of sexes it is clear a reduction in cholesterol values after 45 years.

Table 3 shows prevalence of uncontrolled high cholesterol. The trend is decreasing for both men and women. The decrease was greater in men. Table 3 also shows the percentage of patients treated to target. The hypercholesterolemic to target increased, statistically significant, in both sexes.

DISCUSSION

Hypercholesterolemia is undoubtedly one of the major risk factors of cardiovascular disease. Knowing its trend is particularly important for prevention strategies and to
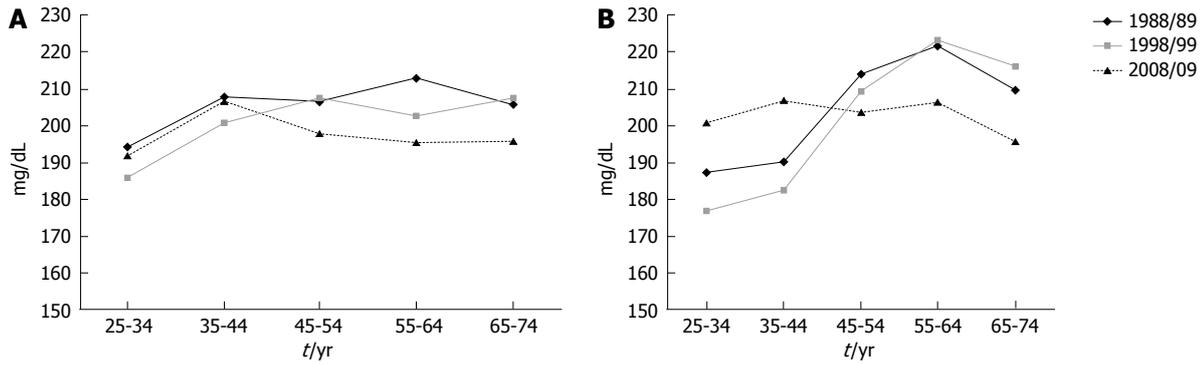
Figure 1 Cholesterolaemia between 25-74 years: 1988/89-2008/09. A: Male; B: Female.

Table 3 Prevalence of ipercholesterolaemia

	Group1 1988-89 (n = 522)	Group2 1998-99 (n = 600)	Group3 2008-09 (n = 600)	P value	1 vs 3	1 vs 2	2 vs 3
Male							
Uncontrolled high cholesterol (≥ 240 mg/dL)	20.80%	14.30%	13.9%	0.002	< 0.05	< 0.05	NS
Hypercholesterolemia	20.80%	16.40%	21.1%	NS			
Treated hypercholesterolaemia	-	2.50%	40.8%	0.000			
Treated to target	-	84%	91.0%	0.000			
Hypercholesterolaemia to target	-	12.80%	37%	0.000			
Female							
Uncontrolled high cholesterol (≥ 240 mg/dL)	19.90%	18.20%	18.1%	0.007	< 0.05	< 0.05	NS
Hypercholesterolemia	19.90%	18.90%	25.8%	NS			
Treated hypercholesterolaemia	-	7.90%	39.1%	0.000			
Treated to target	-	46.70%	80.2%	0.000			
Hypercholesterolaemia to target	-	3.70%	37%	0.000			

Data standardized to the European population; Men and women. Uncontrolled high cholesterol (≥ 240 mg/dL): Subjects with Cholesterolaemia ≥ 240 mg/dL, may or may not have been taking medication; Hypercholesterolemia: Subjects with cholesterol ≥ 240 + cholesterol-lowering therapy subjects; Treated hypercholesterolaemia: Treated/Hypercholesterolemia; Treated to target: Treated to target (cholesterol < 240 mg/dL)/all subjects treated; Hypercholesterolaemia to target: (Hypercholesterolemia < 240 mg/dL/subject with hypercholesterolemia). NS: Non-significant.

evaluate the effectiveness of interventions.

In Southern Italy, the cholesterol value, in the years between 1950 and 1960, was one of the lowest in the world[17]. Our country is the place where the practice of the Mediterranean Diet was born and developed. Successively, high consumption of saturated fats and low use of vegetable fibres that had as a consequence an increase of cholesterol until the beginning of 1990[18]. In those years, a greater attention to risk factors, the return to a more balanced nutrition, and use of statins have led to important change in the trend. Our data show a favorable trend, similar to that registered in other parts of the world, including North America and Western European countries[7,14,19,20]. We have observed a more favorable trend in the male population, consequence of a difference between the two sexes in percentage of treated hypercholesterolemic (48% in male and 39.1% in female) and in reaching an acceptable target (91% in male and 80.2% in female). This can be explained probably by considering a more direct drug intervention in the male population than in the female one. A therapeutic attitude more aggressive in men than in women is clearly described in the literature[21,22].

Another interesting observation is that, in the period before the statins, the cholesterol curves showed a reduction only after 65 years, due to the fact that subjects with high cholesterol die more easily[9]. Today, with statins, the distribution of cholesterol is reduced already after 45 years to stay then essentially unchanged.

Recently, the Global Burden of Metabolic Risk Factors of Chronic Diseases Collaborating Group has published the trend at national, regional and global cholesterol[14].

These data provide an interesting point of comparison to analyze the data of our study. Globally, mean total cholesterol changed little between 1980 and 2008, falling by less than 3.9 mg/dL per decade in both sexes. In our population the mean cholesterol was steadily declining in men (7.3 mg/dL) while substantially constant in women, with a decrease in the survey of the 1998/99 before recovering to the initial values. An exception is the age group 64-75 years, where there is a decrease of over 20 years, 14 mg/dL, and this is probably related to the increased use of statins in the population more adult. Doing an analysis for areas, total cholesterol decreased among high-income territories formed by Australia, North America, Western Europe, Central and Eastern Europe regional. The decreases were approximately 7.7 mg/dL per decade in both sexes. In the population of

the VIP Project we find a smaller reduction: 3.7 mg/dL per decade in men and non-reduction for women. Despite this, serum total cholesterol in 2008 was higher in high-income countries; the regional mean was 202.2 mg/dL for men (in our population are slightly lower: 197 mg/dL) and 201.8 mg/dL for female (the values of the VIP project are slightly higher: 203.3 mg/dL). It was lowest in sub-Saharan Africa at 157.45 mg/dL in men and 164.8 mg/dL for female. Thus, there is evidence of a trend in the reduction of cholesterol levels in many areas of the world, as confirmed by our data, but we must undoubtedly increase interventions (particularly in women) because this result could be more obvious. The intervention must be conducted in two directions: encourage healthy diets, with unsaturated fats and extending and optimizing therapy with statins in the population at greatest risk[23-25].

COMMENTS

Background

Coronary heart disease (CHD) is now the leading cause of death worldwide. Raised serum total cholesterol is an important cardiovascular risk factor, which causes an estimated 4.4 million deaths every year worldwide. Therefore, the focus on cardiovascular prevention must remain high. The aim was to estimate trend in total serum cholesterol, in a Mediterranean area of southern Italy, in the last twenty years. In particular the authors considered and compared the data collected as part of "Montecorvino Rovella Project " 1988-1989 and cross-sectional data from the two phases of the "VIP Project-Valle dell Irno Prevenzione": 1988-1989 (1st phase) and 2008-2009 (2nd phase). Data show a reduction of mean cholesterol in the last twenty years of 7.3 mg/dL for men and unchanged values for women. Is statistically increased the number of patients treated and those treated to target.

Research frontiers

Research from the World Health Organization highlights the importance of raised blood cholesterol as a risk factor for CHD. In Southern Italy, the cholesterol value, in the years between 1950 and 1960, was one of the lowest in the world. The authors' country is the place where the practice of the Mediterranean Diet was born and developed. Successively, high consumption of saturated fats and low use of vegetable fibres that had as a consequence an increase of cholesterol until the beginning of 1990. Successively, high consumption of saturated fats and low use of vegetable fibres that had as a consequence an increase of cholesterol until the beginning of 1990. In those years, a greater attention to risk factors, the return to a more balanced nutrition, and use of statins have led to important change in the trend. The data show a favorable trend, similar to that registered in other parts of the world, including North America and Western European countries.

Innovations and breakthroughs

The authors have observed a more favorable trend in the male population, consequence of a difference between the two sexes in percentage of treated hypercholesterolemics (48% in male and 39.1% in female) and in reaching an acceptable target (91% in male and 80.2% in female). This can be explained probably by considering a more direct drug intervention in the male population than in the female one. A therapeutic attitude more aggressive in men than in women is clearly described in the literature. Another interesting observation is that, in the period before the statins, the cholesterol curves showed a reduction only after 65 years, due to the fact that subjects with high cholesterol die more easily. Today, with statins, the distribution of cholesterol is reduced already after 45 years to stay then essentially unchanged.

Applications

There is evidence of a trend in the reduction of cholesterol levels in many areas of the world, as confirmed by our data, but the authors must undoubtedly increase interventions (particularly in women) because this result could be more obvious. The intervention must be conducted in two directions: encourage healthy diets, with unsaturated fats and extending and optimizing therapy with statins in the population at greatest risk.

Terminology

The World Health Report 2002 estimates that around 8% of all disease burdens

in developed countries is caused by raised blood cholesterol and that over 60% of CHD and around 40% of ischaemic stroke in developed countries is due to total blood cholesterol levels in excess of the theoretical minimum (3.8 mmol/L). Variations in diet, especially consumption of animal-based *vs* plant-based fats, adiposity, and use of drugs to lower cholesterol have led to differences in serum cholesterol concentrations across populations and over time.

Peer review

The authors are dealing with an interesting topic, as the regulation of risk factors and the related communities planning are the best way to fight cardiovascular disease. The objective of this study was to examine trends of uncontrolled serum total cholesterol, treatment and control in a Mediterranean region (Campania). Data show a reduction of mean cholesterol in the last 20 years of 7.3 mg/dL for men and unchanged valves for women. Encouraging increases in awareness, treatment, and control of hypercholesterolemia occurred from 1988 through 2008.

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BRIEF ARTICLE

Positive influence of aspirin on coronary endothelial function: Importance of the dose

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Abstract

AIM: To investigate the effects of different doses of aspirin on coronary endothelial function.

METHODS: The study included 139 Japanese subjects (mean age, 60 years; 53 women) with angiographically normal coronary arteries. Patients were distributed into Group I (n = 63), who was administered aspirin and Group II (n = 76), the control, who were not administered aspirin. Group I was further divided into Group I a (n = 50, low-dose aspirin, 100 mg) and Group I b (n = 13, high-dose aspirin, 500 mg). After a routine coronary angiography, acetylcholine (ACh; 3 and 30 μg/min successively) and nitroglycerin (NTG) were infused into the left coronary ostium over 2 min. The change in the diameter of the coronary artery in response to each drug was expressed as the percentage change from baseline values.

RESULTS: The patient characteristics did not differ between the two groups. The change in coronary diameter in response to ACh was greater in Group I than in Group II (P = 0.0043), although the NTG-induced coronary vasodilation was similar between groups. ACh-induced dilation was greater in Group I a than in Group I b (P = 0.0231). Multivariate regression analysis showed that a low-dose of aspirin (P = 0.0004) was one of the factors associated with ACh-induced dilation at 30 μg/min.

CONCLUSION: In subjects with angiographically normal coronary arteries, aspirin only had a positive influence on coronary endothelial function at the low dose of 100 mg. This improvement of coronary endothelial function may be involved in the preventive effect of aspirin against future coronary events.

Key words: Acetylcholine; Aspirin; Coronary endothelial function; Quantitative coronary angiography

Core tip: We investigated the effect of aspirin on coronary endothelial function. Patients were distributed into Group I, who were administered aspirin and Group II, which was the control group. Group I was divided into Group I a (low-dose aspirin) and Group I b (high-dose aspirin). Acetylcholine (ACh)-induced coronary dilation was greater in Group I than in Group II and was greater in Group I a than in Group I b. Multivariate regression analysis showed that a low-dose of aspirin was associated with ACh-induced coronary dilation. A Low dose of aspirin has a positive influence on coronary endothelial function.

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INTRODUCTION

Aspirin, an inhibitor of cyclooxygenase-1, helps prevent cardiovascular disease. However, its efficacy with respect to primary prevention of cardiovascular events remains controversial[1-6]. Although several studies have shown that primary prevention with aspirin has a positive effect on cardiovascular disease[1-3], others have not shown any such relationship[4-6]. Aspirin increases the risk of bleeding, particularly gastrointestinal bleeding[7]. In addition, the discrepancies in the effect of primary prevention with aspirin may depend on the cardiovascular risk of individual patients. These factors may contribute to the study findings reported for this population; therefore, aspirin may be effective in the primary prevention of cardiovascular disease if the degree of risk for cardiovascular burdens and gastrointestinal bleeding are appropriately assessed. The efficacy of aspirin in the secondary prevention of cardiovascular disease is, however, well established[8,9], and aspirin reduces reoccurrence in patients with established cardiovascular disease.

The dose of aspirin used to prevent cardiovascular disease ranges from 75 to 325 mg/d[8,10]. Aspirin inhibits the synthesis of thromboxane A2 in platelets and prostaglandin I2 in endothelial cells. Low-dose aspirin only inhibits thromboxane A2 in platelets, whereas high-dose aspirin inhibits both thromboxane A2 and prostaglandin I2[11]. Low-dose aspirin (approximately 81-162 mg) has been widely used as a preventive therapy against cardiovascular disease[10]. This preventive effect of aspirin may be primarily due to its prevention of thrombus formation, which is mediated by inhibition of platelet aggregation[11]. However, several studies have shown a favorable effect of aspirin on endothelial function[12-16], and there is some interest in the relationship between aspirin and endothelial function. To investigate the existence of such a relationship in the coronary arteries, and if one exists, to confirm whether this relationship depends on the dose of aspirin used, we investigated the effects of different doses of aspirin on coronary endothelial function in patients with angiographically normal coronary arteries.

MATERIALS AND METHODS

Study population

One hundred and thirty-nine Japanese patients who underwent coronary angiography to evaluate chest pain were included in this study. All had angiographically normal epicardial coronary arteries, normal left ventricular function (contrast ventriculographic ejection fraction; LVEF, $\geq 60\%$), and normal coronary flow reserve (CFR; > 2.0). We excluded patients with vasospastic angina, previous myocardial infarction, left ventricular hypertrophy, moderate-severe valvular disease detected using echocardiography, heart failure, or other serious diseases.

The patients were divided into two groups based on their aspirin intake: Group I consisted of 63 patients who took aspirin and Group II consisted of 76 patients who did not. The 63 patients in Group I were subdi-

vided into Group I a, consisting of 50 patients who took aspirin 100 mg/d, and Group I b, consisting of 13 patients who took aspirin 500 mg/d in Group I a, 32 patients had taken aspirin for a possible coronary artery disease before admission. The remaining 18 patients in Group I a and 13 patients in Group I b began taking aspirin on admission. All patients in Group I took aspirin for at least 2 d. Written informed consent was obtained from all patients before their entry into the study. The protocol was approved by the Ethics Committee of our institution.

Study protocol

All anti-anginal agents were discontinued at least 48 h before catheterization, except for sublingual nitroglycerin, which was withheld for 1 h before catheterization but was otherwise unrestricted. Diagnostic left heart catheterization and coronary angiography were performed using a standard percutaneous brachial approach. A 6F-guide catheter was introduced into the left main coronary artery. A 0.0014-inch Doppler flow guidewire (Volcano FloWire; Volcano Therapeutics Inc., Rancho Cordova, CA) was subsequently advanced through the guide catheter into the proximal segment of the left anterior descending coronary artery. The wire tip was positioned in a straight segment of the vessel to obtain a reliable flow-velocity signal.

After baseline control conditions were established, incremental doses of acetylcholine (ACh) were infused into the left coronary artery (3 and 30 μg/min) for 2 min with 5-min intervals between consecutive doses. After re-establishment of control conditions, nitroglycerin was intracoronarily infused at a rate of 200 μg/min for 1 min. Finally, adenosine triphosphate (20 μg) was infused. ACh and nitroglycerin (NTG) were directly infused into the left coronary ostium using an infusion pump (TE-311; Terumo, Tokyo, Japan) at a rate of 1 mL/min.

Coronary angiography was performed under controlled conditions and at the end of each drug infusion. Coronary blood flow (CBF) velocity was continuously monitored using a 12-MHz pulsed Doppler velocimeter (FloMap; Volcano Therapeutics Inc.). Arterial pressure, heart rate, and electrocardiogram were continuously monitored and recorded using a multichannel recorder (Polygraph 1600; Nihon Electric Corporation, Tokyo, Japan).

Quantitative coronary angiography

The method used for measuring the coronary diameter was previously described in detail[17-20]. The coronary segment 2 mm distal to the Doppler wire tip was selected for quantitative analysis. In each patient, the luminal diameters of selected segments of the left anterior descending coronary artery were measured by a single investigator blinded to angiographic and clinical data to determine the effects of the different drugs on epicardial coronary diameter. The luminal diameters were measured on an end-diastolic frame using a computer-assisted coronary angiographic analysis system (CAAS II /QUANTCOR; Siemens, Berlin and Munich, Germany).

Means of triplicate measurements of luminal diameter were used for analysis. Changes in coronary diameter in response to ACh and NTG infusions are expressed as the percentage change from the baseline measurement on the angiogram obtained before infusion. Intra- and inter-observer variability have previously been reported to be excellent[17].

Estimation of CBF and CFR

CBF was calculated as the product of CBF velocity and vessel diameter using the following formula: $\pi \times$ average peak velocity $\times 0.125 \times$ diameter^2. For CBF calculations, the internal diameter of the vessel at the location of the flow measurements (2 mm distal to the wire tip) was measured using the method described above. CFR was calculated as the ratio of CBF velocity after adenosine triphosphate infusion relative to baseline velocity.

Definition of coronary vascular function

As described previously[17,18,21-23], in the present study, we adopted the percent changes in epicardial coronary diameter in response to ACh and NTG infusions as the endothelium-dependent and -independent functions, respectively, of the coronary artery at the level of conduit vessels. When the ACh-induced changes in coronary diameter is reduced despite of preserved NTG-induced dilation, it is accepted that coronary endothelial dysfunction at the level of conduit vessel is present. In addition, we adopted the percent change in CBF in response to ACh infusion and CFR as the endothelium-dependent and -independent functions, respectively, of the coronary artery at the level of resistance vessels. When the ACh-induced increase in CBF is reduced despite of preserved CFR, it is accepted that coronary endothelial dysfunction at the level of resistance vessel is present.

Other parameters

Blood samples were drawn from each patient on the same day as coronary angiography after fasting. Total cholesterol, triglyceride, high-density lipoprotein -cholesterol, low-density lipoprotein -cholesterol, glucose, hemoglobin A1C, high-sensitive C-reactive protein (CRP), and fibrinogen levels were subsequently measured.

Statistical analysis

All data are expressed as mean ± SEM. Baseline characteristics of the two groups were compared using Student's unpaired *t* test or χ^2 analysis, as appropriate. Serial changes in hemodynamic variables and changes in coronary vasoreactivity in response to drug infusion were compared using a one-way analysis of variance. If the analysis of variance showed a significant difference between means, the level of significance was determined by contrast analysis. Serial percentage changes in the coronary vascular response to ACh infusion were compared between groups using a two-way analysis of variance. Univariate and multivariate regression analyses were also performed to identify factors associated with percent changes in coronary artery

Table 1 Characteristics of the patients (mean ± SE) *n* (%)

	Group I (*n* = 63)	Group II (*n* = 76)	*P* value
Age	60 ± 1	59 ± 1	NS
Men/women	40/23	46/30	NS
Body mass index (kg/m²)	24.6 ± 0.3	24.2 ± 0.3	NS
Coronary risk factors			
Smoking (%)	22 (35)	19 (25)	NS
Hypertension (%)	29 (46)	29 (38)	NS
Hypercholesterolemia (%)	23 (37)	30 (39)	NS
Diabetes mellitus (%)	9 (14)	6 (8)	NS
Medications			
Statins (%)	11 (17)	13 (17)	NS
ACI and/or ARB (%)	8 (13)	11 (14)	NS
LV ejection fraction (%)	70 ± 1	71 ± 1	NS

ACI: Angiotensin-converting enzyme inhibitor; ARB: Angiotensin II receptor blocker; LV: Left ventricular; NS: Not significant.

Table 2 Biochemical parameters (mean ± SE)

	Group I	Group II	*p* value
Total cholesterol (mg/dL)	210 ± 5	206 ± 5	NS
Triglyceride (mg/dL)	155 ± 10	144 ± 9	NS
HDL-cholesterol (mg/dL)	54 ± 2	52 ± 2	NS
LDL-cholesterol (mg/dL)	125 ± 5	125 ± 4	NS
Fasting blood sugar (mg/dL)	100 ± 2	98 ± 2	NS
Hemoglobin A1C (%)	5.5 ± 0.1	5.4 ± 0.1	NS
C-reactive protein (mg/L)	1.4 ± 0.4	2.1 ± 0.4	NS
Fibrinogen (mg/dL)	340 ± 21	350 ± 22	NS

HDL: High-density lipoprotein; LDL: Low-density lipoprotein; NS: Not significant.

diameter induced by ACh. A *P* value < 0.05 was defined as indicative of statistical significance.

RESULTS

Patient characteristics and biochemical parameters

The patient characteristics are detailed in Table 1. Age, sex, body mass index, frequency of coronary risk factors, medications, and LVEF were similar between the two groups. The patient characteristics between Groups I a and I b were also similar.

Data on the biochemical parameters are detailed in Table 2. The biochemical parameters did not differ between Group I and Group II; the parameters were also similar between Group Ia and Group I b.

Results of coronary vasoreactivity

The hemodynamic and coronary vasoreactivity findings are shown in Table 3. Hemodynamics were similar between the two groups, as were the baseline coronary artery diameter and CBF. Changes in coronary artery diameter in response to ACh infusion were reduced in Group II compared with those in Group I (*P* = 0.0043), whereas NTG-induced coronary dilation did not differ between the two groups (Figure 1 and Table 3). The increase in CBF in response to ACh infusion and CFR did

Table 3 Hemodynamics and angiographic results between groups I and II (mean ± SE)

	Group I	Group II	*P* value
Baseline mean BP(mmHg)	107 ± 2	104 ± 1	NS
Baseline heart rate (/min)	66 ± 1	67 ± 1	NS
Coronary diameter			
Baseline (mm)	3.22 ± 0.07	3.07 ± 0.06	NS
ACh at 3 μg/min (mm)	3.28 ± 0.07	3.07 ± 0.07	NS
(% change)	1.8 ± 0.9	0.1 ± 0.8	NS
ACh at 30 μg/min (mm)	3.26 ± 0.08	2.95 ± 0.07	0.0030
(% change)	1.2 ± 1.1	-3.9 ± 1.0	0.0008
Nitroglycerin (mm)	3.67 ± 0.07	3.51 ± 0.07	NS
(% change)	14.0 ± 1.1	15.1 ± 1.0	NS
Coronary blood flow			
Baseline (mL/min)	88.1 ± 3.7	81.9 ± 3.3	NS
ACh at 3 μg/min (mL/min)	131.3 ± 7.8	123.3 ± 7.1	NS
(% change)	50.0 ± 6.3	52.1 ± 5.7	NS
ACh at 30 μg/min (mm)	219.9 ± 21.4	194.8 ± 19.5	NS
(% change)	172.8 ± 33.2	142.6 ± 30.3	NS
Coronary flow reserve	3.4 ± 0.2	3.4 ± 0.1	NS

BP: Blood pressure; ACh: Acetylcholine; NS: Not significant.

**Table 4 Hemodynamics and angiographic results between groups I a and I b (mean ± SE)**

	Group I a (*n* = 50)	Group I b (*n* = 13)	*P* value
Baseline mean BP (mmHg)	108 ± 2	105 ± 3	NS
Baseline heart rate (/min)	67 ± 2	65 ± 3	NS
Coronary diameter			
Baseline (mm)	3.23 ± 0.08	3.14 ± 0.16	NS
ACh at 3 μg/min (mm)	3.32 ± 0.08	3.05 ± 0.17	NS
(% change)	2.4 ± 0.9	-0.6 ± 1.8	NS
ACh at 30 μg/min (mm)	3.32 ± 0.08	3.05 ± 0.17	NS
(% change)	2.6 ± 1.1	-3.8 ± 2.9	0.0123
Nitroglycerin (mm)	3.67 ± 0.08	3.65 ± 0.16	NS
(% change)	13.6 ± 1.1	15.4 ± 2.2	NS
Coronary blood flow			
Baseline (mL/min)	91.0 ± 4.6	76.8 ± 9.1	NS
ACh at 3 μg/min (mL/min)	137.7 ± 9.5	106.8 ± 18.7	NS
(% change)	53.4 ± 6.8	37.0 ± 13.4	NS
ACh at 30 μg/min (mm)	195.2 ± 15.9	188.6 ± 31.1	NS
(% change)	125.3 ± 16.2	141.9 ± 31.7	NS
Coronary flow reserve	3.4 ± 0.2	3.7 ± 0.3	NS

BP: Blood pressure; ACh: Acetylcholine; NS: Not significant.

Figure 1 Percentage changes in epicardial coronary artery diameter in response to acetylcholine infusion and nitroglycerin in Groups I and II. A: Greater changes in coronary artery diameter in response to acetylcholine infusion were observed in Group I (open circles) compared with Group II (black circles); B: Nitroglycerin-induced coronary dilation was similar between Groups I and II. Vertical bars represent SEM. ACh: Acetylcholine; NS: Not significant; NTG: Nitroglycerin.

using this value.

Factors responsible for coronary endothelial dysfunction

As noted above, statistically significant differences between the two groups were observed in the percentage change in coronary diameter induced by ACh infusion at a dose of 30 μg/min. Univariate analysis revealed that the presence or absence of aspirin ($P = 0.0002$), NTG-induced coronary dilation ($P = 0.0142$), and the increase in CBF in response to ACh infusion at a dose of 3 μg/min were associated with the change in coronary artery diameter response induced by ACh infusion at 30 μg/min; the mean blood pressure at baseline also showed a trend toward a positive association with the change in coronary artery diameter associated with ACh infusion at 30 μg/min ($P = 0.0888$). Multivariate regression analysis using these parameters demonstrated that low-dose aspirin ($P = 0.0004$), NTG-induced coronary dilation ($P = 0.0077$), and the increase in CBF induced by ACh infusion at a dose of 3 μg/min ($P = 0.0344$) were positively associated with the change in coronary artery diameter induced by ACh infusion at 30 μg/min, and that not taking aspirin ($P = 0.0387$) was negatively associated with this change ($r^2 = 0.212$; Table 5).

not differ between the two groups (Table 3).

The hemodynamic and coronary vasoactivity findings for the subgroups of Group I are shown in Table 4. Hemodynamics, coronary artery diameter, and CBF at baseline did not differ between Group I a and Group I b (Table 4). However, changes in coronary artery diameter in response to ACh infusion were reduced in Group Ib compared with those in Group I a ($P = 0.0231$). NTG-induced coronary dilation did not differ between the two groups (Table 4, Figure 2). The increase in CBF in response to ACh infusions or CFR did not differ between the two groups (Table 4). Statistically significant differences were observed in the percentage change in coronary diameter induced by ACh infusion at a dose of 30 μg/min, and the subsequent analyses were performed

Figure 2 Percentage changes in epicardial coronary artery diameter in response to acetylcholine infusion and nitroglycerin in Groups I a and I b. A: Greater changes in coronary artery diameter in response to acetylcholine (ACh infusion were observed in Group I a (open circles) than those in Group I b (gray circles); B: Nitroglycerin -induced coronary dilation was similar between Groups I a and I b. Vertical bars represent SEM. ACh: Acetylcholine; NTG: Nitroglycerin; NS: Not significant.

DISCUSSION

In the present study, we investigated the effects of different doses of aspirin on coronary endothelial function in patients with angiographically normal coronary arteries. We showed that the change in coronary artery diameter in response to ACh infusion was higher in patients who took aspirin than in those who did not take aspirin. However, NTG-induced coronary dilation, the increase in CBF in response to ACh infusion, and CFR were not significantly different between the two groups. In addition, among patients who took aspirin, the change in coronary artery diameter in response to ACh infusion was higher in those who took a low dose of aspirin (100 mg/d) than in those who took a higher dose of aspirin (500 mg/d). Multivariate regression analysis demonstrated that taking a low dose of aspirin was positively associated with ACh-induced coronary artery dilation and not taking aspirin was negatively associated with such dilation. These findings suggest that taking a low dose of aspirin has a positive influence on coronary endothelial function in patients with angiographically normal coronary arteries.

The preventive effect of aspirin against cardiovascular disease is mainly because of its inhibition of platelet aggregation, which is mediated by the inhibition of throm-

boxane A2 in platelets and prevention of thrombus formation[11]. However, there has been some interest in the relationship between aspirin and endothelial function[12-16]. Husain *et al*[12] reported that intra-arterial co-infusion of aspirin (1000 mg) restored ACh-induced microvascular endothelial dysfunction of the femoral vasculature in patients with coronary atherosclerosis and atherosclerotic burdens. In addition, Noon *et al*[13] showed that intra-arterial co-infusion of aspirin (600 mg) restored ACh-induced microvascular endothelial dysfunction of the forearm in hypercholesterolemic patients but not in control subjects. Monobe *et al*[14], Magen *et al*[15], and Furuno *et al*[16] have reported a relationship between aspirin and endothelial function using flow-mediated dilation (FMD) of the brachial artery. Monobe *et al*[14] reported that FMD was higher in hypercholesterolemic patients who took a low dose of aspirin (100 mg). Magen *et al*[15] reported that FMD was higher in hypertensive patients who took a low dose of aspirin (100 mg). Furuno *et al*[16] investigated the effects of various doses of aspirin on FMD in healthy male subjects and showed that aspirin had a positive influence even in healthy volunteers. Taking these studies into consideration, the effect of aspirin on endothelial function may, in part, depend on the severity of the atherosclerotic burden or on the dose of aspirin.

In the present study, we showed that aspirin has a positive influence on coronary endothelial function in patients with chest pain who have angiographically normal coronary arteries. When assessing coronary endothelial function, it is advantageous to simultaneously assess endothelial function at the level of both the conduit and resistance vessels[21,22]. In this study, aspirin only had a positive effect on coronary endothelial function at the level of the conduit vessels. In general, endothelium-derived nitric oxide (NO) and prostaglandin I 2 act as an endothelium-derived vasodilators, primarily in large vessels[24-26]; this may account for the effect of aspirin on coronary endothelial function being limited to the level of the conduit vessels.

With regard to the dose of aspirin administered, 75-325 mg/d and particularly, 75-162 mg/dare widely used in the clinical setting[8,10]. Although a high dose of aspirin is effective in preventing cardiovascular disease[8], bleeding increases as the dose of aspirin increases[27], and this may explain the widespread use of low-dose of aspirin. Theoretically, a high dose of aspirin inhibits both

Table 5 Multivariate analysis of variables influencing %change in coronary diameter induced by acetylcholine infusion

Variables	%change in coronary diameter induced by ACh 30 mg/min	
	t value	*P* value
Taking aspirin		
(+) at the low dose	3.61	0.0004
(-)	-2.09	0.0387
Nitroglycerin-induced dilation	2.71	0.0077
%increase in CBF at ACh 3 mg/min	2.14	0.0344
Mean blood pressure at baseline	1.79	0.0765

r^2 = 0.212. ACh: Acetylcholine; CBF: Coronary blood flow.

thromboxane A2 in the platelets and prostaglandin I 2 in endothelial cells; therefore, it is not unexpected that a high dose of aspirin has a negative influence on endothelial function. However, only one study has shown the relationship between the dose of aspirin administered and endothelial function[16]. Furuno *et al*[16] reported that the maximum effect of aspirin on endothelial function was observed at 162 mg/d, whereas the minimum effect was observed at 660 mg/d. In the present study, because a small number of patients took a high dose of aspirin, the multivariate regression analysis did not show that taking a high dose of aspirin led to a deterioration in endothelial function. However, in the subgroup analysis, the coronary endothelial function of patients who took a high dose of aspirin was significantly lower than that of patients who took a low dose. These results suggest that a low dose of aspirin is superior to a high dose of aspirin for improving endothelial function.

Several studies have examined possible mechanisms associated with the positive effect of aspirin on endothelial function[12,28-31]. Theoretically, a low dose of aspirin inhibits only thromboxane A2, which is an endothelium-derived, cyclooxygenase-dependent constricting factor, leading to vasodilation[12]. Furthermore, aspirin has a positive effect on endothelium-derived NO. Aspirin directly enhances NO synthesis in endothelial cells[28,29]; it delays the onset of endothelial senescence[30] and reduces oxidative stress[31]. These factors may contribute to aspirin-induced improvement of endothelial function. It is possible that vascular inflammation causes endothelial dysfunction[18], but aspirin has not been observed to have any influence on the assessment of high-sensitive CRP. Therefore, the anti-inflammatory effect of aspirin may not be involved in the mechanism through which aspirin exerts its positive effect on endothelial function.

The present study demonstrated that a low dose of aspirin had a positive effect on coronary endothelial function in patients with angiographically normal coronary arteries. However, this does not always imply that a low dose of aspirin should be administered for the primary prevention of cardiovascular disease. As mentioned above, there is no doubt that aspirin frequently causes gastrointestinal bleeding[27]; therefore, despite the positive effect of aspirin on coronary endothelial function, a low dose of aspirin should be used, particularly for primary prevention in consideration of the balance of atherosclerotic burden and bleeding risks.

There are several limitations to the present study. First, all patients in our study had chest symptoms and had undergone coronary angiography; thus, they may represent a specific group. Therefore, the results of the present study may not be representative of endothelial function in all patients. Second, the duration of aspirin intake was not consistent between the patients who took aspirin. This difference may have influenced the results, such as the high-sensitive CRP level. Third, the number of patients who took a high dose of aspirin was small, and this may also have influenced the results. However,

it was not ethically possible to increase the number of patients in this subgroup. Finally, we did not measure biochemical parameters and platelet function associated with aspirin. Therefore, we cannot report on the precise mechanisms by which aspirin had a positive influence on coronary endothelial function in the present study.

In conclusion, our findings suggest that only low-dose aspirin has a positive effect on coronary endothelial function in patients who have chest pain but angiographically normal coronary arteries. The favorable effect of aspirin on coronary endothelial function as well as the prevention of thrombus formation may be involved in the mechanisms responsible for the preventive effects of aspirin against cardiovascular disease.

COMMENTS

Background

Aspirin, an inhibitor of cyclooxygenase-1, helps prevent cardiovascular disease. This preventive effect of aspirin may be primarily due to its prevention of thrombus formation. In addition, several studies have reported a relationship between aspirin and endothelial function. However, it has not been fully elucidated whether aspirin has a positive influence on coronary endothelial function.

Research frontiers

Aspirin has a preventive effect against cardiovascular disease, mainly mediated by its anti-platelet effect. Clarifying the relationship between aspirin and endothelial function may reveal other mechanisms responsible for the preventive effect of aspirin against cardiovascular diseases.

Innovations and breakthroughs

The results showed that acetylcholine (ACh)-induced coronary artery dilation was higher in patients who took aspirin compared with patients who did not take aspirin, whereas nitroglycerin (NTG)-induced coronary artery dilatation and coronary blood flow increase in response to ACh or coronary flow reserve did not differ significantly between the 2 groups. Furthermore, aspirin-induced coronary artery dilation in response to ACh was higher in patients who took low-dose aspirin, compared with patients who took high-dose aspirin. These findings suggest that only low-dose aspirin has a positive effect on coronary endothelial function in such patients.

Applications

Aspirin should be used in primary prevention, but in consideration of the balance between atherosclerotic burden and bleeding risks because it can cause gastrointestinal bleedings. However, if taking aspirin, a low dose should be recommended for improving endothelial function.

Terminology

There are two components of coronary vascular functions: at the level of conduit vessels (epicardial coronary artery) and at the level of resistance vessels (microvascular coronary artery). In addition, there are two factors of coronary artery vasodilation: endothelium-dependent and -independent. In the present study, using quantitative coronary angiography and Doppler velocity measurements, the authors defined the percent changes in epicardial coronary diameter in response to ACh and NTG infusions as the endothelium-dependent and -independent functions, respectively, of the coronary artery at the level of conduit vessels, and the authors defined the percent change in coronary blood flow in response to ACh infusion and coronary flow reserve as the endothelium-dependent and -independent functions, respectively, of the coronary artery at the level of resistance vessels.

Peer review

The research is important in that it provides new evidence of aspirin effect on the endothelial function of the coronary artery. The experiments are well designed with good controls matched with age, gender, body mass index, coronary risk factors, medications, left ventricular function, as well as many biochemical parameters. The study also excluded many apparent heart diseases, making the sampled population more homogenous. Paper is well organized.

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BRIEF ARTICLE

Myocardial bridging analysis by coronary computed tomographic angiography in a Saudi population

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Abstract

AIM: To assess the incidence, location, morphology and clinical association of myocardial bridging in a Saudi population using coronary computed tomographic angiography (CCTA).

METHODS: A total of 350 CCTA of Saudi patients were included in this study (236 men, 114 women) with a mean age of 56.3 years. All patients were examined for appropriateness criteria of CCTA indications (typical chest pain, recent onset cardiomyopathy, left bundle branch block, *etc.*). The scans were retrospectively reviewed for the presence of myocardial bridging and any other pathological association.

RESULTS: Myocardial bridging was found in 89 of 350 (22.5%) patients. Most of the intramuscular segments were of the superficial type and found in the mid left anterior descending (LAD) (24.6%), followed by distal LAD (3.7%), diagonal branches (2%), ramus intermedius artery (1.4%) and obtuse marginal artery (0.8%). No myocardial bridging was detected in the right coronary or circumflex arteries. No significant differences were found between males and females ($P = 0.14$). Coronary artery atherosclerosis was found in 51 of 89 (57.3%) patients with MB. Atherosclerotic plaques were not detected in the intramuscular or distal segment of bridging arteries. Dynamic compression was observed in 35 (94.5%) patients with full encasement. No evidence of myocardial hypoperfusion was found in the territories supplied by the bridging arteries.

CONCLUSION: CCTA is excellent in analyzing myocardial bridging in a Saudi population and the results are comparable to other populations. However, finding the real incidence may need a large multicenter study.

Core tip: A great revolution has happened in imaging of coronary arteries with multi-detector computed tomography. Myocardial bridging is considered a benign anomaly, but in exceptional incidences, it is associated with clinical manifestations. By reviewing the current literature, there is no research studying the prevalence of myocardial bridging (MB) in a Saudi population. This study is considered the first to investigate the prevalence of MB in a Saudi population and its clinical significance in 350 patients. The study highlighted that coronary computed tomographic angiography offers an excellent way to detect and characterize MB and the national prevalence of MB and its anatomical and clinical findings in Saudi Arabia is comparable to worldwide prevalence.

INTRODUCTION

Myocardial bridging (MB) is an inborn abnormality. It occurs when a segment of a coronary artery or its major branch travels through the myocardium instead of on the surface of the myocardium, resulting in a tunneled arterial segment[1]. In an autopsy study, Ferreira *et al*[2] distinguished two types of MB: superficial bridges crossing the artery perpendicularly or at an acute angle towards the apex and deep bridges characterized by muscle bundles arising from the right ventricular apical trabeculae that cross the affected artery transversely, obliquely or helically before terminating in the interventricular septum[2]. The clinical outcome of patients with MBs has been considered benign when it is not associated with hemodynamic changes[3]. However, the relationship of MB and ischemia remains controversial. Myocardial bridging is considered clinically significant when it is associated with regional hemodynamic compression.

Atherosclerotic changes usually affect the segment immediately proximal to the myocardial bridge, whereas its occurrence in the tunneled coronary segment is still controversial[3-5].

Coronary angiography was considered the gold standard for the diagnosis of myocardial bridging[6,7]. However, it is an invasive procedure and requires a great deal of experience for its interpretation. Also, a superficial type of myocardial bridges may be missed on angiography.

Recently, coronary computed tomographic angiography (CCTA) has been introduced as a noninvasive imaging of the coronary arteries. CCTA is able to visualize the lumens of coronary arteries as well as their walls and the neighboring myocardium in any plane. The depiction rate of MB is greater with 64-section multi-detector computed tomography (MDCT) than with conventional coronary angiography; the higher prevalence of MB on MDCT is considered to be due to the inclusion of partial and full encasement on CCTA, the use of short-axis images obtained perpendicular to the long axis of the left anterior descending (LAD) for all analysis and measurement, and the consistently high image quality of MDCT. Coronary CT Angiography is able to visualize myocardial bridging in a more sensitive and comprehensive way than conventional coronary angiography, in which the diagnosis is not made by the direct visualization of the intramuscular course but the indirect finding of systolic compression of the coronary artery indicated by the milking effect[8,9]. Based on CCTA, Kim *et al*[9] classified myocardial bridging of LAD into three types. Type I is myocardial bridging with partial encasement with the artery within the interventricular gorge and in direct contact with left ventricular myocardium. Type II is myocardial bridging with full encasement of LAD by myocardium but without measurable overlying myocardium. Type III is myocardial bridging with full encasement of LAD by myocardium but with measurable overlying myocardium (> 0.7 mm)[9].

The objective of the present study is to assess the incidence of myocardial bridging, as well as their location and morphology, in Saudi patients by using CCTA and comparing the national results to the international worldwide published studies. The clinical association and pathological changes in relationship to myocardial bridging will be also assessed.

MATERIALS AND METHODS

The study was designed to be a retrospective observational study. A total of 350 Saudi Caucasian subjects were included in this study. Patients of other ethnic groups were excluded from the study. The patients included 236 men and 114 women, with an average age of 56.3 ± 11 years. The patients were examined for different clinical cardiac conditions (Table 1). All CCTA studies were done between January 2010 and February 2013. Written informed consent was taken from all patients included in the study. The ethics committee in the hospital approved the use of the clinical and imaging data.

Machines used for CCTA are dual-source 128-slice scanners (Siemens Definition Flash, Forchheim, Germany) and 64-slice CT scanners (Light Speed VCT, GE Healthcare, Waukesha, Wisconsin, United States). Briefly, the technique used for CCTA is as follows. Volumetric data set for the coronary arteries is acquired; the data set covers the entire heart from the proximal ascending aorta (approximately 1-2 cm below the carina) to the diaphragmatic surface of the heart. The scan is acquired in a single breath-hold during inspiration and starts with the injection of a nonionic contrast agent with a concentration of 300-400 mg I/mL at a flow rate of 4-6 mL/s. The total volume of contrast agent depends on the scan length, but typically 60-80 mL is injected, followed by a saline bolus (40-70 mL at 4-6 mL/s). Scanning delay was determined according to the test bolus technique and the region of interest was placed on the ascending aorta. The subjects were instructed to maintain an inspiratory breath-hold during which the CT data and ECG trace were acquired. Retrospective ECG-gated reconstructions were generated at best systolic and diastolic phases

Table 1 Clinical presentations of the patients *n* (%)

	Total patients	MB patients
Typical chest pain	32 (9.1)	6 (6.8)
Atypical chest pain	138 (39.4)	44 (49.5)
Known coronary artery disease	21 (6)	4 (4.5)
Valvular lesions	16 (4.5)	2 (2.3)
New onset of heart failure symptoms	39 (11.2)	8 (8.9)
Presence of risk factors	104 (29.8)	25 (28)

MB: Myocardial bridging.

Table 2 Location and incidence of myocardial bridge in different coronary arteries in Saudi patients *n* (%)	
Coronary artery	Patients
Mid LAD	68 (24.6)
Distal LAD	13 (3.7)
Diagonal	7 (2)
Ramus intermedius	5 (1.4)
Obtuse marginal artery	3 (0.8)
Left circumflex	0 (0)
Right coronary	0 (0)

LAD: Left anterior descending.

or any other phase of the R-R interval according to the situation. All patients included in this study were in sinus rhythm and were always pre-medicated with nitroglycerin (5 mg sublingually 1 min before the examination) to dilate the coronary arteries. The heart rate ranged between 50 and 78 BPM with a mean of 65 BPM. Most patients received beta-blockers to control their heart rate within this range, as metoprolol tartarate (5 mg/mL IV bolus) can be repeated according to HR (Beloc ampule, AstraZeneca).

Image reconstruction and interpretation
Two experienced readers certified with level III CCTA blindly interpreted the CCTA images for all patients. Interpretation started with the axial resource images, then other multiplanar reconstructions. If myocardial bridging was detected, the depth and length of the tunneled segment were measured. Myocardial bridge was defined as a segment of a coronary artery that courses through the myocardium. Coronary artery disease (CAD) was defined as coronary wall atheromatous change (calcified and non-calcified plaque) with or without luminal reduction. Hemodynamically significant stenosis was defined as equal or greater than 50% reduction of the lumen diameter[10].

Each involved coronary artery was assessed for the presence of atherosclerotic changes and the location of those changes in relationship to the tunneled segment. The exact anatomy of a normal coronary artery or a tunneled segment was identified in both axial and reformatted images in all planes. The tunneled segment is considered superficial or deep if the depth of the covering myocardium is ≤ 1 or > 1 mm respectively[11].

Superficial MB was further subdivided into complete and incomplete based on the full or partial encasement of the LAD within the left ventricular myocardium[9].

The relationship between length, thickness of the bridge, and severity of the stenosis in the coronary artery proximal to the bridge was studied. The coronary CTA findings were classified as the following: no atheromatous changes or luminal narrowing as normal; atheromatous changes without luminal narrowing as mild disease; atheromatous changes with insignificant stenosis as moderate disease; and atheromatous changes with significant stenosis as severe disease. Because the LAD is the most common artery involved with MB, we compared coronary CTA findings in subjects with myocardial bridge with other patients without bridging.

Statistical analysis
The SPSS software package was used for the statistical data analysis. In the descriptive statistical analysis, quantitative variables were expressed as mean ± SDs, whereas categorical variables were expressed as a percentage. Statistical significance was set at P value < 0.05.

RESULTS
All CCTA scans interpreted in this study were of a good image quality and all involved tunneled segments were assessable. Myocardial bridging was found in 89 of 350 (22.5%) patients. No significant differences were found between males and females ($P = 0.14$). The total intramuscular segment was 96; thus, in 7 patients, more than 1 intramuscular segment was found. Most of the intramuscular segments were in the LAD artery. No myocardial bridging was detected in the right coronary artery or proximal LAD. The coronary arteries involved are presented in Table 2.

The length of the intramuscular segments ranged from 6 to 24 mm (average 15 ± 7 mm). The mean diameter of the intramuscular segments was 3 ± 3 mm and 1.6 ± 0.5 mm for LAD and the remaining arteries, respectively. The diameter of the proximal segments was significantly larger than that of the intramuscular segment, 2.8 ± 0.5 mm for the LAD and 1.8 ± 0.6 mm for the remaining arteries ($P > 0.001$). The depth of the intramuscular segments ranged from 1 to 6.2 mm and the mean thickness was 2.3 ± 3.9 mm.

Two anatomical patterns of intramuscular segments were identified according to the depth and the course of the intramuscular segment of LAD: the superficial type [46 segments (61.3%)] in which the intramuscular artery had a superficial course along the interventricular septum (Figure 1) and was covered by a thin layer of tissue (< 1 mm thick) and the deep type [29 segments (38.6%)] in which the intramuscular segment penetrated the interventricular septum at a depth between 1 and 6.2 mm (Figure 2).

Imaging evidence of coronary artery atherosclerosis was found in 51 of 89 (57.3%) patients and in 41 of 261 (15.7%) patients without bridging. Atherosclerotic plaques were not detected in the tunneled or distal segment to myocardial bridging in any case. No evidence of myocardial hypoperfusion was found in the myocardial territories subtended by the tunneled coronary arteries.

In 81 patients with a LAD-myocardial bridge, atherosclerotic changes were found in 37 subjects (45.7%) and were consistently localized in the coronary segment proximal to the bridge. Dynamic compression was observed in two patients with partial encasement (5.5%) and 35 patients with full encasement (94.5%). The results indicated that dynamic compression occurred almost exclusively in myocardial bridging with full encasement. In patients with MB of other coronary arteries, significant atherosclerotic
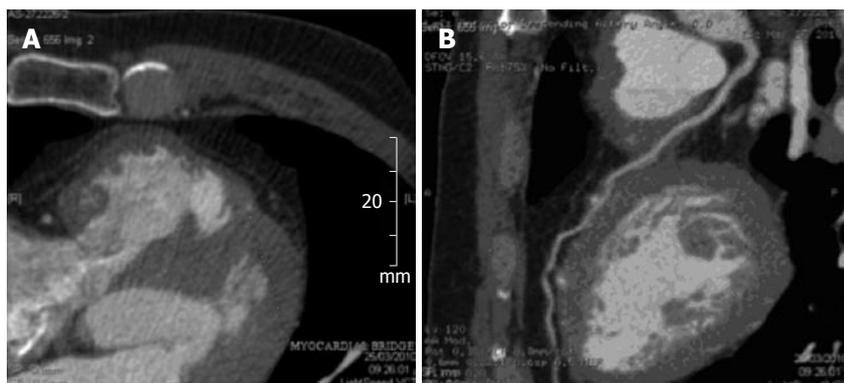
Figure 1 Coronary computed tomographic angiography in transverse axis (A) and long axis (B) show a thin layer of myocardium covering mid-left anterior descending (superficial myocardial bridging).
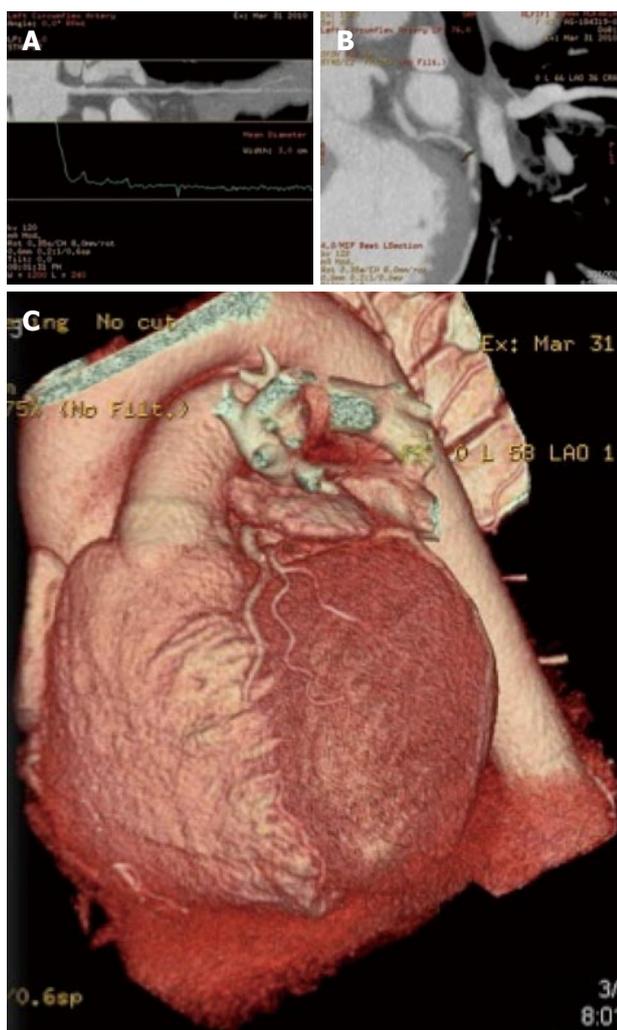
Figure 2 Curved multiplanar reconstruction (A), Sagittal image (B) and 3D- coronary computed tomographic angiography image (C) show thick myocardium covering mid-left anterior descending associated with luminal narrowing of the involved segment (deep myocardial bridging).

changes were detected in three with diagonal artery MB, in two patients with ramus intermediate artery MB, and in one patient with obtuse marginal artery MB.

DISCUSSION

Myocardial bridging is generally considered a benign

anomaly but in exceptional cases, it is associated with clinical manifestations. Coronary angiography was considered the gold standard for the diagnosis of myocardial bridging[6,7]. With the introduction of MDCT into clinical practice, a great revolution has happened in the imaging of coronary arteries and their diseases. By reviewing the current literature, there is no research studying the prevalence of MB in a Saudi population. This study is considered the first to investigate the prevalence of MB in a Saudi population and its clinical significance in a relatively big sample size (350 patients). There is a wide discrepancy in the reported prevalence of myocardial bridging between autopsy findings (average 33%, range 15% to 85%)[12,13] and those of conventional angiography (average 5%, range 0.5% to 16%)[14-23]. This discordance occurs because most patients with MB have unrelated overt symptoms that are rarely referred for CCA. Also, CCA is not sensitive enough to detect a milking effect (temporary occlusion of artery during systole) with superficial MB[16]. Recently with an apparent increase in the detection rates of MB, a prevalence as high as 44% has been found[23].

Multiple studies have reported myocardial bridging by coronary CTA, showing a wide range of frequencies. With the use of 16 slice CT frequencies of MB, 18.9% of 228 patients[24], 48.7% of 235 patients[25], 15.8% of 148 patients[26] and 8.7% of 276 patients[27] had MB , while frequencies of MB with 64 slice CT were 6.42%, 30%, 22.5%, 5.8%, 10.4%, 17%, 18.6%, 50%, 37%, 58%, 23%, 44% and 30.5%[9,11,28-38]. On the other hand, by dual source MDCT, Ou[39] detected 5.4% of 2530 patients with MB and the results by Hwang *et al*[7] showed 46% of 1275 patients with MB. The worldwide prevalence of MB (if we exclude the lower and higher results) ranges from 17%-40%[37]. In this study, the incidence of MB in Saudi patients is 22.5%, which lies within the worldwide prevalence range near its lower limit. Also, in the current study, there is no difference in prevalence of MB between male and female subjects. This observation is in agreement with other studies[40,41].

The exact course of the coronary arteries was easily recognized on reformatted MDCT in all our cases together with the consequences of myocardial bridging making it possible for the clinician to see the problem and start the management plan. The length and depth of myocardial bridging in the current study are in agreement

with the results of many studies[7,42]. In the vast majority of cases, angiographic localization of myocardial bridges is in the LAD[43]. Localization other than the LAD is extremely rare[14].

This study shows that the intramuscular course of coronary arteries most commonly involves the middle segment of LAD, followed by its distal segment, and no cases were reported to have MB of the proximal LAD, circumflex or right coronary arteries. These results are in contrast with Loukas *et al*[44] who demonstrated that the presence of myocardial bridges appeared to be related to coronary dominance and it goes with their results in detecting MB in LAD, diagonals, OM and RCA in descending order. On the other hand, Arjomand *et al*[45] reported the first case of myocardial bridging of the circumflex artery (mid-portion) association with acute myocardial infarction.

Also, Tuncer *et al*[46] reported a 63-year-old man with myocardial bridging of the left circumflex coronary artery with significant systolic narrowing at the mid segment after the first obtuse marginal branch.

The length of the intramuscular segments and their mean diameters were clearly determined by CCTA in the current study. The diameter of the proximal segments and the depth of the intramuscular segments were also evaluated. The results revealed a significant decrease in the diameter of the intramuscular segment compared with the adjacent proximal segment. Similar observations were reported in other literature[26,47]. These structural differences between intramuscular and epicardial segments and the reduced diameter of the intramuscular segments have been associated with the detection of atherosclerotic changes detected in our cases.

Depth criteria is not clear cut for the classification of MB into superficial or deep types depicted on CT. However, some research classified MB as superficial or deep depending on the thickness of the covering muscular layer, either $\leqslant 1$ mm or $\geqslant 1$ mm respectively[11]. In addition, superficial MB can be classified as complete or incomplete in accordance with the extent of the vessel encasement by the myocardium[9]. This subdivision of superficial MB into complete and incomplete types based on the full or partial encasement is in our study. The incidence of superficial MB (61.3%) was higher than that of the deep type (38.6%). Nearly the same results were illustrated by Hwang *et al*[7] as they found that the prevalence of superficial MB (66%) was higher than that of deep MB (34%). This study illustrated that dynamic compression was detected in two patients with partial encasement (5.5%) and 35 patients with full encasement (94.5%). The results indicated that dynamic compression occurred almost exclusively in myocardial bridging with full encasement, which is in concordance with Kim *et al*[9] who reported that dynamic compression occurred almost exclusively (97.5%) in patients with full encasement of the LAD coronary artery regardless of the presence of overlying muscle[9].

Atherosclerotic changes detected in our series are

limited exclusively to the arteries proximal to the deep-tunneled segments. No atherosclerotic changes were found in the superficial type of bridging, which can be explained by the lower shear stress that may contribute to atherosclerosis at proximal segment of MB, whereas higher shear stress may protect it from atherosclerosis at the tunneled segment of MB[48]. Another explanation is that due to the high-pressure gradient at the proximal segment, the local wall tension and subsequent endothelial dysfunction will enhance atherosclerotic changes in that segment[49]. This observation was in agreement with other investigators who reported that the tunneled segments are free of atheroma[50].

Duygu *et al*[51] found a significant positive correlation between hs-CRP and the percentage of atherosclerotic stenosis on the IVUS study of patients with stable angina pectoris and detected MB in LAD. They concluded that their results indicate the presence of low-grade inflammation in patients with an atherosclerotic lesion in bridged segments.

On the other hand, Duygu *et al*[52] studied 71 patients with MB diagnosed by coronary angiography and they concluded that a myocardial bridge may initiate the development of an atherosclerotic lesion or may facilitate progression of atherosclerosis in the proximal segment of the vessel. The risk of acute coronary syndrome rises when atherosclerosis is superimposed on MB.

Zoghi *et al*[53] studied 50 patients with MB in LAD on coronary angiography. All coronary artery segments were evaluated by IVUS and endothelial function was assessed with measurement of flow mediated dilatation in the brachial artery. They concluded that endothelial function is impaired in patients with MB and there is an increased tendency for atherosclerosis proximal to the bridge in MB patients.

However, our results do not agree with other studies showing that the atherosclerotic process occurs in the tunneled coronary segment with the same severity and frequency as the epicardial coronary segments[54].

Some studies showed that such instances of myocardial bridging are linked to clinical complications that include ischemia, acute coronary syndrome, coronary spasm, arrhythmia and sudden death, although in the vast majority of cases, myocardial bridging remains clinically silent[3,4,15,16]. Because dynamic compression occurs almost exclusively in myocardial bridging with full encasement, the incidence of myocardial bridging with full encasement is considered to be more meaningful in the clinical setting[55].

Finally, our results support the classic belief that myocardial bridging is a normal variant and has no clinical consequences as none of our patients required specific medical or invasive treatment for MB. These findings are supported by Kramer *et al*[56] and Nakanishi *et al*[23] who demonstrated that MB is an incidental finding associated with an excellent survival rate of 97% at 5 years. They postulated that the clinical significance of a MB appears to be related to the anatomic properties of a tunneled

segment of coronary artery, the presence of associated myocardial ischemia, and the presence of proximal and distal atherosclerotic disease. They concluded that medical treatment is the choice for symptomatic patients. Coronary stenting and surgery should be kept for resistant cases that have not responded well to medical therapy. Preoperative mapping of MB allows the surgeon to be ready to deal with myocardial bridging and this will shorten the surgery time and operative risks significantly.

Limitations of the study

This study is the first to investigate such a relatively large patient group in Saudi Arabia. However, this study has a few limitations, including that it is just a descriptive study; we do not compare CCTA with other techniques like coronary angiography for a radiation dose. Also, we did not correlate our results with the clinical outcome after treatment. These limitations can be avoided by including a wide spectrum of patients from different provinces of the country. Also, multicenter clinical studies of larger groups are required to determine the degree to which myocardial bridging is responsible for symptoms such as angina, myocardial infarction and life-threatening arrhythmias. Prospective multicenter studies of larger groups are definitely still required to determine the true national prevalence and whether myocardial bridging is responsible for cardiac symptoms or not.

In conclusion, the study shows clearly that CCTA offers an excellent non-invasive way to detect and characterize myocardial bridging. The national prevalence of MB in Saudi Arabia is comparable to worldwide prevalence. Also the anatomical and associated pathological findings of the tunneled arteries are similar to many other studies. However, multicenter clinical studies of larger groups are required to determine the real national incidence of MB, as well as the true clinical and physiological significance of myocardial bridging. However, it is still remains unclear which patients require further testing after the detection of myocardial bridging.

COMMENTS

Background

Myocardial bridging occurs when a segment of a coronary artery or its major branch travels through the myocardium instead of on the surface of the myocardium. Coronary computed tomographic angiography (CCTA) is able to visualize myocardial bridging in a more sensitive and comprehensive way than conventional coronary angiography. The prevalence of myocardial bridging varies widely between different studies.

Research frontiers

The current study assessed the incidence, location and morphology of myocardial bridging in Saudi patients by using CCTA and comparing the results to other international studies. The clinical association and pathological changes in relationship to myocardial bridging was also assessed.

Innovations and breakthroughs

This study highlighted the usefulness of CCTA as a non-invasive method to detect and characterize myocardial bridging. The incidence, location and clinical significance of myocardial bridging (MB) in Saudi patients do not differ from most of other populations.

Applications

CCTA is an excellent imaging modality to assess the real incidence and clinical

significance of myocardial bridging in Saudi patients.

Terminology

MB is an inborn abnormality. It occurs when a segment of a coronary artery or its major branch travels through the myocardium. CCTA is the use of CT imaging to visualize the courses, lumens and relationships of the coronary arteries.

Peer review

In this study, the authors retrospectively examined the incidence of myocardial bridges in Saudi people, as well as their location and morphology from 350 individuals with coronary CT angiography. This paper is the first to describe the prevalence and clinical significance of MB in Saudi patients.

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Contents

APPENDIX I-V Instructions to authors

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Coronary CT angiography: State of the art

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Abstract

Coronary computed tomography (CT) angiography has been recognized as the most rapidly developed imaging technique in the diagnosis of coronary artery disease due to the emergence and technological advances in multislice CT scanners. Coronary CT angiography has been confirmed to demonstrate high diagnostic and predictive value in coronary artery disease when compared to invasive coronary angiography. However, it suffers from high radiation dose which raises concerns in the medical field. Various dose-reduction strategies have been proposed with effective outcomes having been achieved to reduce radiation exposure to patients. This article provides an introduction and overview of the series of articles that will focus on each particular topic related to coronary CT angiography.

Key words: Coronary artery disease; Coronary computed tomography angiography; Radiation dose; Diagnostic value; Predictive value

Core tip: This article provides an overview of a series of articles that focus on individual topic highlight related to coronary computed tomography (CT) angiography. In particular, use of beta-blocker protocol, radiation dose measurements, dose-reduction strategies, diagnostic and prognostic value of coronary CT angiography will be described in detail in each series. Furthermore, potential applications of coronary CT angiography beyond luminal visualization and future directions will also be discussed.

CORONARY CT ANGIOGRAPHY

Over the last decade a great deal of interest has been focused on imaging and diagnosis of coronary artery disease (CAD) using coronary computed tomography (CT) angiography due to its less invasive nature and improved spatial and temporal resolution. With latest multislice CT scanners (64- and post-64 slice CT), coronary CT angiography has been reported to have high diagnostic value, and it can be used as a reliable alternative to invasive coronary angiography in selected patients[1-7]. In addition to the diagnostic value, coronary CT angiography has demonstrated the ability to assess coronary plaques in terms of morphology and plaque characterization, thus providing prognostic information for prediction of major adverse cardiac events[8-11].

Despite these promising reports and increasing studies available in the literature, coronary CT angiography suffers from a major limitation, which is high radiation dose. This has raised serious concerns in the medical field, as radiation-induced cancer is not negligible. Awareness of this issue plays an important role in ensuring that use of

coronary CT angiography is medically justified, and dose-reduction strategies are implemented whenever possible, while diagnostic image quality is still acceptable[12].

This series consists of 5 articles on the clinical applications of coronary CT angiography in CAD. Part I deals with beta-blocker administration protocol as beta-blocker is the most commonly used drug to achieve heart rate control during coronary CT angiography. It has become a routine protocol to use beta-blocker to slow down heart rate in patients with heart rate more than 70 beats/min prior to coronary CT angiography, thus, understanding the preparations and patient care is important for clinicians (in particular for those who are inexperienced in performing the coronary CT angiography) to effectively utilize this imaging technique.

Part II focuses on radiation dose measurements in coronary CT angiography. As mentioned above, coronary CT angiography is associated with high radiation dose, therefore, awareness of the basic dosimeters for dose measurement will help clinicians to understand the radiation risks. Part III is about dose-reduction strategies in coronary CT angiography. This part contributes to an overview of different dose-saving methods that are currently recommended in the clinical practice.

Part IV focuses on the diagnostic and prognostic value of coronary CT angiography in CAD. A systematic review of the literature on these two aspects will provide readers with updated information with regard to the current status of coronary CT angiography in terms of diagnostic accuracy and prediction of disease outcomes.

Part V is the last article of this series presenting information on the emerging diagnostic value of coronary CT angiography in CAD, which is entitled coronary CT angiography: beyond luminal visualization. In addition to the evaluation of coronary wall morphology and plaque assessment, coronary CT angiography is able to provide functional information such as assessment of myocardial ischemia which is available with dual-energy CT; hemodynamic analysis of coronary stenosis and plaque, as well as determination of patient-specific lesions (CT-derived fractional flow reserve) with use of computational fluid dynamics. This research area represents some novel applications of coronary CT angiography, although its applications are still at infancy.

In summary, this series provides a comprehensive coverage of different topics related to the coronary CT angiography in CAD, ranging from the patient preparation of heart rate control to dose measurements, dose reduction to the diagnostic and prognostic value. Finally, future research directions of coronary CT angiography are discussed and highlighted in the last part. We believe these articles contribute to improving our knowledge and understanding on coronary CT angiography and its corresponding clinical value.

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TOPIC HIGHLIGHT
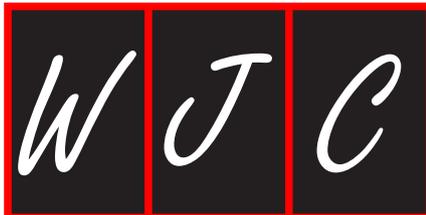
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Coronary CT angiography: Beyond morphological stenosis analysis

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Abstract

Rapid technological developments in computed tomography (CT) imaging technique have made coronary CT angiography an attractive imaging tool in the detection of coronary artery disease. Despite visualization of excellent anatomical details of the coronary lumen changes, coronary CT angiography does not provide hemodynamic changes caused by presence of plaques. Computational fluid dynamics (CFD) is a widely used method in the mechanical engineering field to solve complex problems through analysing fluid flow, heat transfer and associated phenomena by using computer simulations. In recent years, CFD is increasingly used in biomedical research due to high performance hardware and software. CFD techniques have been used to study cardiovascular hemodynamics through simulation tools to assist in predicting the behaviour of circulatory blood flow inside the human body. Blood flow plays a key role in the localization and progression of coronary artery disease. CFD simulation based on 3D luminal reconstructions can be used to analyse the local flow fields and flow profiling due to changes of vascular geometry, thus, identifying risk factors for development of coronary artery disease. The purpose of this article is to provide an overview of the coronary CT-derived CFD applications in coronary artery disease.

Core tip: Coronary computed tomography (CT) angiography is limited to the visualization of anatomical details of coronary artery tree, while computational fluid dynamics (CFD) overcomes this limitation by providing hemodynamic changes to the coronary artery due to presence of plaques. CFD has been increasingly used in the investigation of cardiovascular disease due to its ability of providing flow changes and variations. This article provides an overview of the clinical applications of coronary CT-derived CFD in coronary artery disease.

INTRODUCTION

Coronary artery disease (CAD) is the leading cause of death in advanced countries and its prevalence is increasing among developing countries[1]. Traditionally, diagnosis of CAD is performed by invasive coronary angiography which is considered the gold standard technique, since it has superior spatial and temporal resolution leading to excellent diagnostic accuracy. However, it is an invasive and expensive procedure associated with a small but distinct procedure-related morbidity (1.5%) and mortality (0.2%)[2]. Furthermore, invasive coronary angiography usually requires patients to stay for a short period in the hospital after the examination and this causes discomfort for the patients. Thus, a non-invasive technique for imaging and

Figure 1 3D volume rendering shows normal right and left coronary arteries with excellent demonstration of main and side branches.
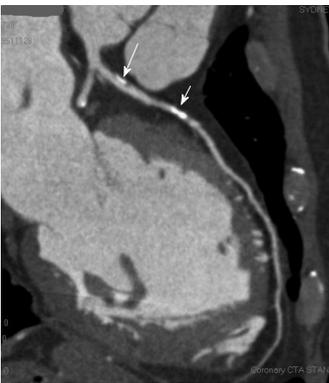
Figure 2 Curved planar reformation image shows significant stenosis of the left anterior descending coronary artery due to presence of plaques. The long arrow refers to the mixed plaque at the proximal segment of left left anterior descending (LAD), while the short arrow points to the calcified plaque at the proximal segment of LAD.

diagnosis of CAD is highly desirable.

Cardiac imaging has experienced rapid growth in recent years. Several techniques have been investigated for diagnosis and prognosis of patients with proven or suspected CAD. Although currently there is no less-invasive imaging modality that can replace invasive coronary angiography, the development of computed tomography (CT), magnetic resonance imaging (MRI), single photon emission computed tomography and positron emission tomography contribute to the detection and diagnosis of CAD less invasively when compared to the invasive coronary angiography[3-11].

Despite promising results achieved with these less-invasive modalities, the application is still limited to the visualization of anatomical details such as stenosis or occlusion, while the hemodynamic interference due to the presence of coronary plaques and subsequent flow changes cannot be assessed by traditional imaging techniques. Thus, identification of plaques that may cause cardiac events is of paramount importance for reducing the mortality and improving healthcare in patients suspected of CAD.

Computational fluid dynamics (CFD) enables analysis of hemodynamic changes of the blood vessel, even be-

fore the atherosclerotic plaques are actually formed in the artery wall. Therefore, to some extent, CFD allows for an early detection of atherosclerotic disease and improves understanding of the progression of plaques[12-14]. The purpose of this article is to provide an overview of the applications of CFD in the diagnosis of coronary artery disease based on coronary CT angiography examination.

CORONARY CT ANGIOGRAPHY VISUALIZATION OF CAD

Over the last decade a great deal of interest has been focused on imaging and diagnosis of CAD using coronary CT angiography due to its less invasive nature and improved spatial and temporal resolution (Figure 1). Moderate to high diagnostic accuracy was achieved with 64- or post-64 slice CT, owing to further technical improvements[15-19]. These studies have indicated that coronary CT angiography has high accuracy for the diagnosis of CAD and could be used as an effective alternative to invasive coronary angiography in selected patients (Figure 2).

In addition to the diagnostic value, coronary CT angiography demonstrates the potential to visualize coronary artery wall morphology, characterize atherosclerotic plaques and identify non-stenotic plaques that may be undetected by invasive coronary angiography (Figure 3). Studies have shown that coronary CT angiography demonstrates high prognostic value in CAD, as it is able to differentiate low-risk from high-risk patients, with very low rate of adverse cardiac events occurring in patients with normal coronary CT angiography, and significantly high rate of these events in patients with obstructive CAD[20-22].

According to the guidelines of the European Society of Cardiology, and the American College of Cardiology/American Heart Association, the decision to perform interventional procedures such as coronary angioplasty or bypass surgery should integrate anatomical information with a test that provides objective proof of ischemia[23,24]. Echocardiography is a multimodality imaging technique which allows accurate assessment of myocardial structure, function and perfusion. Stress echocardiography has become widely used for evaluation of patients with suspected or known CAD, and it has been reported to be a cost-effective and feasible modality in the diagnosis of CAD[25,26]. Although coronary CT angiography has been reported to provide potentially important additional information on myocardial perfusion and chronic myocardial infarction, a limited correlation between stenotic coronary disease and single photon emission computed tomography (SPECT) findings was noticed[27]. However, with the emergence of dual-energy CT (DECT), which offers fascinating new applications such as the mapping of the iodine distribution, acquisition of both anatomic and functional information is possible[28,29]. Early studies have reported that DECT had more than 90% diagnostic accuracy for detecting myocardial perfusion defect compared to myocardial perfusion SPECT imaging[29,30], although large patient cohorts are needed to confirm the potential application of DECT
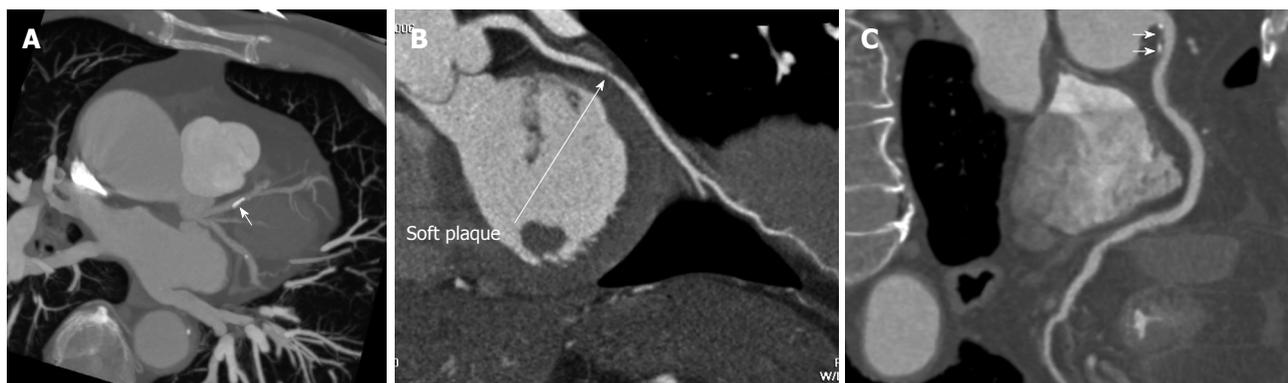
Figure 3 Characterization of coronary plaques on coronary computed tomography angiography. Coronal maximum intensity projection shows a calcified plaque (A, arrow) at the proximal segment of left coronary artery. A non-calcified plaque is present at the mid-segment of right coronary artery (B, arrow) on a curved planar reformation image. A mixed plaque is present at the proximal segment of right coronary artery (C, arrows) on a curved planar reformation image.

for both anatomic and myocardial perfusion assessment of CAD.

Coronary CT angiography provides excellent views of anatomical changes of the artery wall due to presence of plaques, thus enabling assessment of the degree of coronary stenosis. Coronary CT angiography claims to not only identify flow-limiting coronary stenosis, but also detect calcified and non-calcified plaques, measure atherosclerotic plaque burden and its response to treatment, and differentiate stable plaques from those that tend to rupture[31,32]. However, these expectations have not yet been met. In contrast, CFD enables analysis of hemodynamic changes of the blood vessel, thus improving our understanding of the progression of plaques formation and development of atherosclerosis.

COMPUTATIONAL FLUID DYNAMICS

CFD is a general term of all numerical techniques that are used to describe and analyse the flow of fluid elements at each location in certain geometry. The basic principle in CFD is that a complex geometry is separated into a large number of small finite elements. Those elements create a grid on which the equations describing the flow are analysed. The merit of CFD is developing new and improved devices and system designs, and optimization is conducted on existing equipment through computational simulations resulting in enhanced efficiency and lower operating costs[33]. However, CFD is still emerging in the biomedical field due to complexity of human anatomy and human body fluid behaviour. With high performance hardware and software easily available due to advances in computer science, biomedical research with CFD has become more accessible in recent years[34].

APPLICATIONS OF CFD IN CAD

Recently, CFD techniques have been increasingly used to study cardiovascular hemodynamics through simulation tools to assist in predicting the behaviour of circulatory blood flow inside the human body. Mechanical forces and intravascular hemodynamics can chronically affect and regulate blood vessels structure which induces a chronic inflammatory response in the arterial walls resulting in atherosclerosis[35,36]. Early CFD-based hemodynamic studies were conducted to represent *in vitro* conditions within restrictive assumptions[37-40]. Later reports demonstrated that CFD methods have the potential to enhance the data obtained from *in vivo* methods (CT or MRI) by providing a complete characterization of hemodynamic conditions (blood velocity and pressure as a function of space and time) under precisely controlled conditions (Figure 4)[41-44].

Knight *et al*[41] performed an analysis of the hemodynamic parameters including average wall-shear stress gradient, wall shear stress and oscillatory shear index obtained through a CFD study on the right coronary arteries of 30 patients. These parameters were correlated to each patient's specific plaque profile with aim of predicting the particular plaque location. Their results showed a statistically significant difference between average wall shear stress and oscillatory shear index in sensitivity and positive predictive value for the identification of atherosclerotic plaque sites in the right coronary artery. These findings further strengthen the theory that low shear stress is a contributor to the initiation of atherosclerosis.

In addition to the CFD analysis of main coronary arteries, impact of side branches on local wall shear stress should not be neglected. Wellnhofer *et al*[42] studied the impact of side branches on wall shear stress calculation in 17 patients and they concluded that side branches showed significant impact on coronary flow and wall shear stress profile in the right coronary artery. In contrast, Chaichana *et al*[43] investigated the influence of realistic coronary plaques on coronary side branches, based on a sample patient with coronary artery stenosis at the left coronary bifurcation. A direct correlation was found between coronary plaques and subsequent wall shear stress and wall pressure stress gradient changes in the coronary side branches (Figure 5). These research findings improve the understanding of the development of
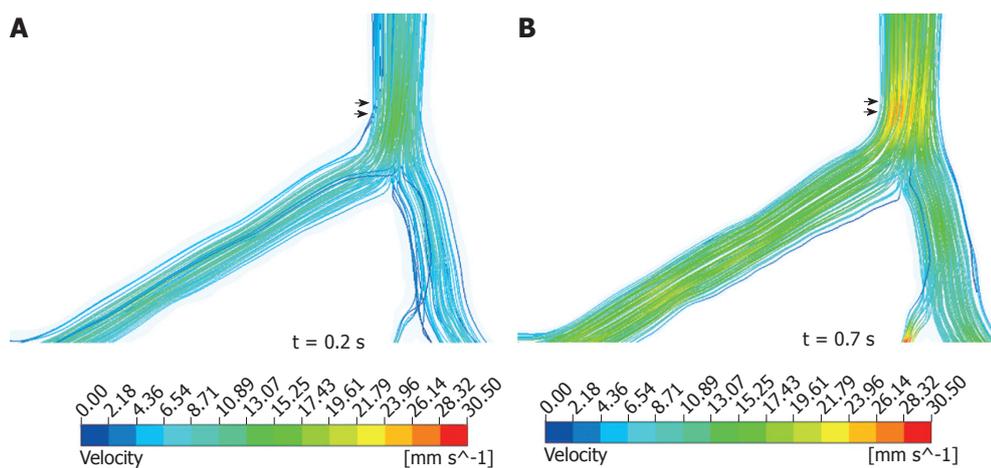
Figure 4 Local impact of flow velocity observed in a normal coronary model during systolic phase of 0.2 s (A) and diastolic phase of 0.7 s (B). Double arrows reveal high flow velocity locations at bifurcation in the left coronary artery model.
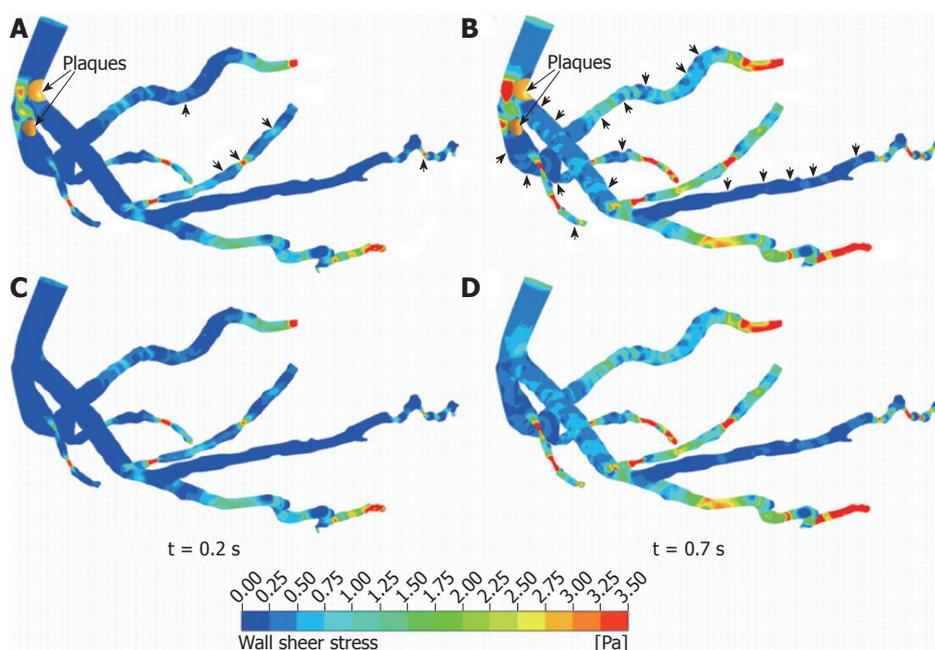
Figure 5 Computational fluid dynamics analysis of wall shear stress in 3D realistic models generated from coronary computed tomography angiography during systolic phase of 0.2 s and diastolic phase of 0.7 s. A, B: Coronary models with presence of plaques in the left anterior descending; C, D: Computational fluid dynamics analysis simulation in coronary models without presence of plaques. Arrows indicate the effect of plaques locations on wall shear stress changes in coronary side branches in the post-plaques-conditions.

atherosclerosis by exploring the hemodynamic effect of coronary plaques using CFD technique, although further studies based on a large cohort are required to verify these results.

Hemodynamic effect of left coronary angulation

The natural history of coronary plaque is dependent not only on the formation and progression of atherosclerosis, but also on the vascular remodelling response. If the local wall shear stress is low, a proliferative plaque will form. Local inflammatory response will stimulate the formation of so-called "vulnerable plaque" which is prone to rupture with superimposed thrombus formation. The vast majority of these inflamed high-risk vul-

nerable plaques cannot be detected by anatomic imaging and myocardial perfusion imaging. Since the progression and development of vulnerable plaque is associated with low wall shear stress and the presence of expansive remodelling, measurement of these characteristics *in vivo* will enable risk stratification for the entire coronary circulation[12,13,44]. Wong *et al*[45] simulated plaque locations in different angles involving ten patterns of plaques formation in the coronary artery wall, and they studied the effects of blood flow resistance through diseased coronary artery. Their proposed formation of the wall geometry has potential applications in the provision of reduction of flow estimates in angiography equipment and in situations where practical experimental measurement of the

A

B

120°

73°
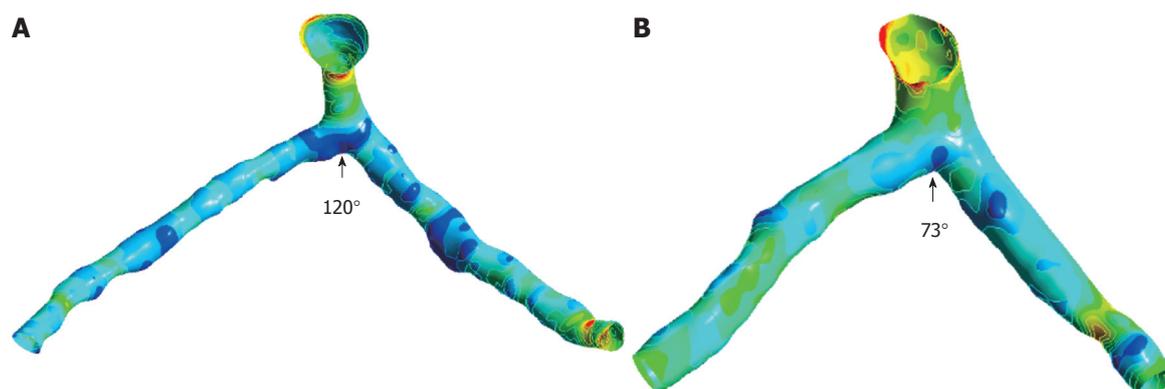
Figure 6 Wall shear stress gradient observed with different angles of the realistic left coronary artery models generated from coronary computed tomography angiography at peak systolic phase of 0.4 s. The arrows display the wall shear stress gradient distributions, with a large region of the low magnitude present at present at a 120° model (A) and a small region at a 73° model (B).

flow is unavailable.

The strong correlation between averaged low wall shear stress and the localization of atherosclerotic lesions in arterial bifurcations has been well established[12,46,47]. Rodriguez-Granillo *et al*[47] in their prospective study reported that atherosclerotic plaques located in the ostial left anterior descending coronary artery demonstrated larger plaque burden, maximal plaque thickness and low shear stress than those located in the distal left main coronary artery. Chaichana *et al*[48] in their recent study based on simulated and realistic coronary models showed a direct relationship between angulations of the left coronary artery and corresponding hemodynamic changes. Low wall shear stress and wall shear stress gradient was observed in the wide-angled models ranging from 75° to 120° when compared to the narrow-angled models ranging from 15° to 60°. Similarly, the magnitude of wall shear stress was significantly lower in the wide angulation models (120° and 110°) than that observed in the narrow angulation models (58°) which were generated based on patient's coronary CT images (Figure 6). This emphasises the potential risk of developing atherosclerosis at the left coronary bifurcation, although further studies are needed to validate these results in more realistic patient' data.

Hemodynamic effect of plaque location at the left coronary artery

Coronary plaque generally originates in the bifurcation region due to the angulations. The angulations cause a region of low wall shear stress, as confirmed by previous reports[48-53]. Medical imaging modalities such as intravascular ultrasound and coronary CT angiography have been commonly used to detect plaque locations in the left main coronary artery[54,55]. These imaging techniques provide valuable diagnostic information, such as assessment of plaque components and corresponding coronary lumen changes, however, they offer no tangible insight into the resultant hemodynamics. CFD provides an opportunity to predict the hemodynamic behaviour. Thus, the characterization of hemodynamic variations due to the various types of bifurcation plaque in the configurations can be

further explored with flow visualizations; this exceeds the traditional anatomical analysis of coronary stenosis or occlusion.

According to a recent study by Chaichana *et al*[56], various types of plaques were simulated in different positions of the left coronary artery to reflect the realistic distribution of coronary plaques, as shown in Figure 7A. The wall shear stress, velocity and pressure gradient were computed and compared using CFD method. Figure 7B shows hemodynamic effects corresponding to different types of plaque in the left coronary artery, with significant difference among these plaques, while Figure 7C demonstrates the pressure gradient variations in relation to the plaque locations. These findings indicate that extra plaque located in the left coronary artery may increase the risk of plaque rupture, although further studies are needed to analyse the realistic plaque at the coronary artery based on different configurations (concentric *vs* eccentric plaques) and compositions (calcified *vs* non-calcified plaques).

Coronary CT angiography-derived fractional flow reserve

A technique to reveal the culprit CAD during invasive coronary angiography is the fractional flow reserve (FFR) measurement using a pressure-sensing guiding wire. FFR is the gold standard assessment of the hemodynamic significance of coronary stenoses as it is a measurement of the functional severity of a stenosis based on the pressure changes over a lesion during maximal coronary hyperemia. FFR is defined as maximal blood flow in a stenotic artery as a ratio to normal maximal flow[57]. FFR is measured at the time of invasive coronary angiography. An FFR of 0.80 is used as a cut off value to determine coronary stenoses responsible for ischemia with an accuracy of more than 90%[58,59]. FFR has been shown to improve detection of lesions that cause ischemia when compared with coronary CT angiography stenosis, thus, reducing the rates of false positive lesions incorrectly classified by stenosis alone[60].

Computation of FFR$_{CT}$ is performed by computational fluid dynamics modelling after segmentation of coronary arteries and left ventricular myocardium. 3D
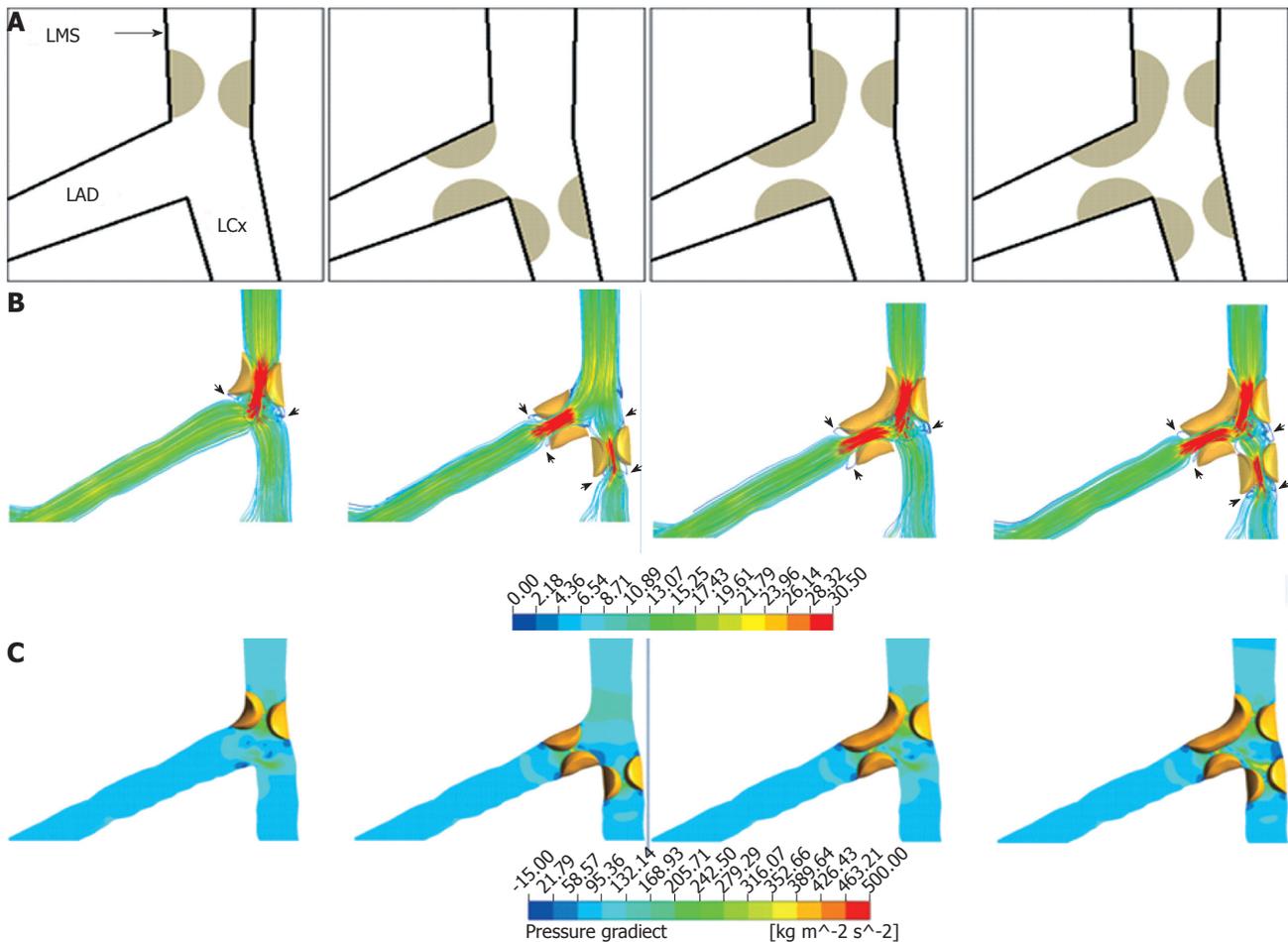
Figure 7 Computational fluid dynamics simulation of left coronary models with measurement of flow velocity and pressure gradient. A: Diagram shows characterization of the four different types of bifurcation plaques in the left coronary artery; B: The velocity patterns inside left bifurcation at effective plaque locations with these types of bifurcation plaques during the diastolic phase (0.7 s); C: The pressure gradient patterns inside left bifurcation at plaque locations with different types of bifurcation plaques during the systolic phase (0.2 s) (C). Arrows refer to the flow changes in the location of plaques. It is noticed that high velocity and high pressure gradient are present in the models with more plaques formed in the left coronary artery branches. LMS: Left main stem; LAD: Left anterior descending; LCx: Left circumflex.

blood flow simulations of the coronary arteries are performed with blood modelled as a Newtonian fluid using incompressible Navier-Stokes equations, with implementation of appropriate initial and boundary conditions to the models using a finite element method on a supercomputer. In order to ensure that the analysis reflects the realistic simulation *in vivo* conditions, realistic physiological boundary conditions are applied for 3D numerical analysis. The transient simulation is performed using accurate hemodynamic rheological and material properties, as described in previous studies[43,48]. Coronary blood flow is simulated under conditions modelling adenosine-mediated coronary hyperemia. The FFRCT ratio is obtained by dividing the mean pressure distal to the coronary stenosis by the mean aortic pressure, which can be measured during CFD simulations.

The FFR measurement was tested with coronary CT angiography and CFD technique and results are promising[61-63]. Min *et al*[61] in their multicenter study involving 252 stable patients with suspected or known CAD compared CT-derived FFR (FFRCT) with coronary CT angi-

ography and invasive coronary angiography for the diagnosis of hemodynamically significant coronary stenosis. Their results showed that FFRCT is considered a potentially promising non-invasive method for identification of individuals with ischemia. FFRCT plus CT improved diagnostic performance in terms of sensitivity and specificity when compared to CT alone. Similarly, Koo *et al*[62] in their DISCOVER-FLOW multicenter study further confirmed the usefulness of FFR derived from coronary CT angiography in the identification of ischemic coronary stenosis. On a per-vessel analysis (FFRCT was performed on 159 vessels in 103 patients), the diagnostic accuracy, sensitivity, specificity, positive predictive value and negative predictive value were 84.3%, 87.9%, 82.2%, 73.9%, 92.2%, respectively, for FFRCT, and were 58.5%, 91.4%, 39.6%, 46.5%, 88.9%, respectively, for coronary CT angiography. These findings together with others indicate that FFR computed from coronary CT angiography provides better diagnostic performance for the diagnosis of lesion-specific ischemia and offers incremental value for the depiction of the culprit lesion in CAD compared to

coronary CT angiography[62-65]. In addition to the assessment of coronary stenosis, FFR_CT could be further applied to evaluate the in-stent restenosis or for coronary artery bypass grafts, although reports are limited in these areas.

Despite the promising results of FFR_CT in the detection of flow-limiting coronary stenosis, this technique suffers from some limitations. In order to confirm the diagnostic accuracy of FFR_CT, it needs to be compared with the gold standard, FFR which is measured by invasive coronary angiography. Furthermore, coronary CT angiography is associated with high radiation dose, although dose-reduction strategies have been recommended to reduce radiation exposure to patients[15]. Currently, myocardial perfusion SPECT imaging remains a widely accepted technique for functional assessment of coronary artery disease[27].

SUMMARY AND CONCLUSION

Although many risk factors predispose development of atherosclerosis, it tends to develop at locations where disturbed flow patterns occur, suggesting that lesion-prone areas may be due to biomechanically related factors. Furthermore, regional hemodynamics such as flow velocity, wall shear stress and wall pressure have been regarded as other risk factors for developing coronary artery disease[66-69].

CFD has been increasingly used to analyse coronary artery hemodynamics and implicate atherosclerosis progression. CFD method applied to coronary CT angiography has enabled non-invasive assessment of lesion-specific ischemia by FFR_CT. Furthermore, these methods also assist prediction of changes in coronary flow and pressure from therapeutic procedures (e.g., percutaneous coronary intervention, coronary artery bypass graft)[70]. More research is being conducted on realistic in vivo coronary geometry models, and it is expected that research findings will provide potential valuable information for improving our understanding of the biomechanical pathophysiology of atherosclerosis and its complications.

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Beta-blocker administration protocol for prospectively ECG-triggered coronary CT angiography

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Core tip: This article provides the protocol of beta-blocker as guidance for prospective ECG-triggered coronary computed tomography angiography (CCTA). With the use of beta-blocker, patients' heart rate can be regulated and controlled to suit the protocol of prospective ECG-triggering CCTA. We believe that this article can give an insight on the management of beta-blocker administration in the coronary computed tomography protocol.

Abstract

The aim of this article is to discuss the protocol of beta-blockers that is commonly used for prospectively ECG-triggered coronary computed tomography angiography (CCTA). It is essential to ensure a low and regular heart rate in patients undergoing prospectively ECG-triggered CCTA for optimal visualization of coronary arteries. Although early generations of computed tomography-scanners are not applicable to be tailored according to patients' heart rate, a low and regular heart rate is possible to be achieved by the administration of medications according to the beta-blocker protocol. Beta-blocker can be safely administered to reduce patients' heart rate for CCTA examination if patients are screened for certain contraindications.

INTRODUCTION

Prospectively ECG-triggered coronary computed tomography angiography (CCTA) is increasingly used in the diagnosis of coronary artery disease (CAD) due to its very low radiation dose with acceptable image quality[1-3]. This technique not only provides comparable diagnostic accuracy to that of conventional approach, retrospectively ECG-gated CCTA, but also shows superior advantage in reducing radiation dose (up to 83%), which is significantly lower than that from retrospectively ECG-gated protocol[1-4]. However, in order to ensure that image quality is acceptable for clinical diagnosis, prospectively ECG-triggered CCTA is restricted to patients with low (heart rates less than 65 bpm) and regular (HR variability < ± 5 bpm) during the scan[1,2,5].

With the advancements of computed tomography (CT) technology, the latest generation of multislice CT scanners enables customization of the scanning protocol to tailor individual patient's condition such as using multiple heart-beat scanning modes or application of additional padding windows[5,6]. Thus, the prospectively ECG-triggered CCTA

Table 1 Beta-blocking agents

B-blockers	Selectivity	Partial agonist activity	Lipid solubility	Onset		Hemodynamic effect		Plasma half-life	Elimination's route
Generic name				Oral	IV	Oral	IV		
Acebutolol hydrochloride	β1	Yes	Low	1-2 h	No	> 24 h	No	3-4 h	Hepatic, renal
Atenolol	β1	No	Low	1 h	1-2 min	24 h	12 h	6-9 h	Renal
Betaxolol hydrochloride	β1	No	Low	24 h	No	> 24 h	No	12-22 h	Hepatic, renal
Bisoprolol	β1	No	Low	1-4 h	No	24 h	No	7-15 h	Hepatic, renal
Esmolol	β1	No	Low	No	1-4 min	No	5-10 min	4-9 min	Erythrocyte, renal
Metoprolol tartrate	β1	No	Moderate	1 h	5-10 min	5-8 h		3-7 h	Hepatic
Metoprolol succinate	β1	No	Moderate	2-3 h	No	24 h	No	3-7 h	Hepatic
Nadolol	None	No	Low	1-2 h	No	24 h	No	20-24 h	Renal
Pindolol	None	Yes	Moderate	1-2 h	No	24 h	No	3-4 h	Hepatic, renal
Propranolol hydrochloride	None	No	High	30 min	< 1 min	6-12 h	4-6 h	3.5-6 h	Hepatic

could be extended to more patients with variable heart rates. However, these protocols suffer from radiation dose which limits the widespread use of the prospectively ECG-triggering technique in cardiac imaging. Therefore, the use of beta-blockers is an option which is widely used in CCTA studies to reduce the heart rate to less than 65-70 bpm and to make the cardiac rhythm more regular[7].

All of the beta-blockers used in clinical practice are competitive pharmacologic antagonists. Drugs in beta-blocker group can be classified into subgroups on the basis of β1 selectivity, partial agonist activity, local anesthetic action and lipid solubility (Table 1)[7,8]. Most of the organ-level effects of beta-blockers are predictable blockade of the beta-receptor-mediated effects of sympathetic discharge. The clinical applications of beta-blockade are broad ranging from treating glaucoma to cardiovascular disease[8].

The applications of beta-blockers in cardiovascular disease treatment are of paramount importance, especially in the situations such as hypertension, angina and arrhythmias[8]. However, adverse cardiovascular effects such as bradycardia, atrioventricular blockade and heart failure may occur due to beta-blockade toxicity. Patient with airway disease may suffer severe asthma attacks. In addition, adverse effects of central nervous system include sedation, fatigue and sleep alterations might only occur with use of lipid soluble beta-blockers. Sexual dysfunction has been reported in some patients using the beta blockers[8,9].

It has been shown in clinical studies that Beta-blocking agents have a preferential effect on beta1 adrenoreceptors, mainly located in the cardiac muscle[8,10,11]. Beta-blockers lessen cardiac contractility and heart rates by blocking myocardial beta-receptors, and therefore prevent exercise-induced increase in oxygen demands by the heart[9]. Clinical pharmacology studies have confirmed that beta-blocking activity had enormous effect on the reduction in heart rate and cardiac output at rest and upon exercise, reduction of systolic blood pressure upon exercise, reduction of reflex orthostatic tachycardia and inhibition of isoproterenol-induced tachycardia[8,10,11]. Therefore, beta-blockers are recommended to be administered prior to CCTA scanning. The purpose of this article is to provide an overview of the use of beta-blockers administration protocol for prospectively ECG-triggered CCTA.

PATIENT PREPARATION

There are several common indications for prospectively ECG-triggered CCTA inclusive of the CAD indications and non-CAD indications. CAD indications are inclusive of evaluation of coronary arteries in patients with new-onset heart failure to assess etiology, symptomatic patients at intermediate preset probability of CAD, patients with a chest pain syndrome regardless of acute or chronic with interpretable stress test. In certain circumstances, CCTA is required although non-CAD detection indications are presented such as suspected pulmonary embolism or aortic dissection or aneurysm, assessment of complex congenital heart disease, suspected coronary anomalies in symptomatic patients, evaluation of pulmonary vein anatomy prior to atrial fibrillation radiofrequency ablation, evaluation of cardiac venous anatomy prior to biventricular pacing and evaluation of cardiac mass or pericardial condition when non-radiation imaging modalities are limited[12,13].

However, there are some contraindications to CCTA procedure which include pregnancy, severe anaphylactic contrast reaction, unable to comply with the scanning instructions such as fail to hold long breath-hold, renal insufficiency and clinically unstable patients[12,13]. In addition, identification to contraindicated drug must be clarified before undergoing CCTA procedure inclusive of the pre-scan nitroglycerine such as severe aortic stenosis, hypertrophic cardiomyopathy and phosphodiesterase-5 (PDE-5) inhibitor and beta-blockers[8,12]. For patients who are considered to undergo beta-blocker protocol, some guidelines have been suggested to avoid complications including screening contraindications to beta-blockers[7]. The contraindications include sinus bradycardia, which is defined as a heart rate of < 60 bpm with systolic pressure of less than 100 mmHg; allergic to beta-adrenergic antagonists or its constituents; decompensated cardiac failure; asthma on beta-agonist inhalers; active bronchospasm; second or third-degree of atrioventricular (AV) block[14-16]. Patients who are likely to have second- or third-degree AV block can be evaluated by generating a single-lead ECG strip[7].

Patient's vital signs and pulse are also monitored and documented upon arrival. In patients with a sinus rhythm with heart rate < 65 bpm, no beta-blockers are required and therefore, the patient can be prepared for CCTA ex-

amination. In patients with irregular rhythm or/and higher heart rate (> 65 bpm), the beta-blockers are given according to the protocol setting (Figure 1).

In addition, patients are required to follow all standard instructions for contrast-enhanced studies including fasting for at least 4 h prior to the scan, maintaining oral hydration with clear fluid up to 1 h before scan and need to hold metformin for a minimum of 48 h following the scan. Patients with non-severe anaphylactic contrast reaction in the past should receive pre-medication treatment to avoid the risk of current contrast reaction. A pre-medication protocol suggested as 50 mg of prednisone is administered orally 13, 7 and 1 h prior to scan with additional of 50 mg oral diphenhydramine (*Benadryl*) is taken 1 h prior to scan[12,17].

With regards to optimal heart rate control, caffeine product is not permitted within 12 h of CCTA. Moreover, severe hypotension can occur if PDE-5 inhibitors interact with nitrates. Therefore, patients are refrained from undertaking PDE-5 inhibitor drugs such as sildenafil (*Viagra*), vardenafil (*Levitra*) and tadalafil (*Cialis*) for at least 48 h before CCTA[12,18,19]. However, usual cardiovascular medications are advisable to be taken continuously.

ADMINISTRATION OF BETA-BLOCKERS AND OTHER ALTERNATIVE DRUG IN HEART RATE-LOWERING THERAPY

Several cardio selective beta-blockers are available with distinct pharmacokinetic profiles such as acebutolol hydrochloride, atenolol, betaxolol hydrochloride, bisoprolol, esmolol, metoprolol succinate and metoprolol tartrate. However, metoprolol tartrate (*Lopressor*) was selected due to its convenient method of administration, dosage form availability and cardioselectivity[7]. Unlike oral metoprolol tartrate, intravenous metoprolol dosage form is recommended due to its fast onset reaction (between 5 and 10 min) after administration. On the other hand, metoprolol tablets (oral) effect can only be seen within 1 hour after administration and the peak plasma concentrations are seen at 90 min. Although the onset reaction in both oral and IV routes differ significantly, the plasma half-life for metoprolol tartrate is similar in both oral and IV which ranges from 3 to 4 h in a healthy adult[7,15,16].

Oral pre-medication in heart rate-lowering therapy is another alternative to achieve lower heart rate prior to the CT scanning. Pre-medicating the patient with tablet metoprolol gives an advantage which may reduce the risk of being injected with IV of metoprolol. However, without proper scanning arrangement, the effect of the oral metoprolol might not be effective and other factors such as anxiety and nervousness may also increase the patients' heart rate on the day of the examination. Thus, administration of metoprolol intravenously is most commonly performed prior to the CT scanning due to its fast onset and clinically feasibility.

Most previous practices injected their first bolus of metoprolol once the patient is lying down supine on the CT examination table. Our practice suggests that first bolus administration of metoprolol (2.5 mg) is given before the patient is brought on the CT examination table; right after the IV line is set (pre-procedure). Then, the patient's heart rate is monitored at the designated area under supervision of medically authorized personnel. This aims to avoid interruption of the procedure workflow and the delay time for beta-blockers to respond.

Although beta-blockers helped in lowering the heart rate, they also have negative inotropic effect and could decrease left ventricular contractility which may affect the assessment of ventricular function[7]. However, ventricular function is only being evaluated by echocardiography or nuclear medicine studies and CCTA study is mainly performed for assessment of coronary arteries and degree of stenosis. Initially, two 2.5 mg doses of metoprolol are given with 5 min interval. Then two doses of 5 mg each are given 5 min apart with a total maximum dose of no more than 15 mg. Blood pressure and HR are monitored before each of the IV dose as stated in Figure 1. The beta-blockers' administration is conducted under the supervision of the radiologists or cardiologists. Blood pressure and continuous ECG monitoring should always be used when giving IV metoprolol.

Ivabradine is another attractive option to reduce patient heart rate for CCTA procedure[20]. Unlike metoprolol, ivabradine selectively inhibits if current in sinoatrial node cells that controls the spontaneous diastolic depolarization, resulting in the reduction of diastolic depolarization rate and heart rate[21,22]. Therefore, it is useful in patients in sinus rhythm, but not in other rhythms such as atrial fibrillation. Ivabradine lowers heart rate at concentrations that do not affect other cardiac ionic currents. Therefore, ivabradine has no other direct cardiovascular effect[20]. Therefore, the main pharmacodynamics of ivabradine in humans is a specific dose-dependent reduction in heart rate. Heart rate reduction is achieved approximately 10 beats/min (bpm) at rest and during exercise at the recommended dosage (no more than 10 mg/d) which leads to a reduction in cardiac workload and myocardial oxygen consumption[21]. Ivabradine has a relatively short half-life of around 2 h and is currently only available as an oral preparation.

HEART RATE CONTROL-LESS COMMONLY APPLIED IN 64- AND POST-64 CT

Heart rate control with use of medications is necessary in 4- and 16-slice CT, but less common in 64- and post-64 slice coronary CT angiography due to improvement in temporal resolution. Pache *et al*[23] in their early study showed that 64-slice CT has high diagnostic accuracy in the assessment of coronary artery bypass grafts, despite the presence of irregular or high heart rates. Recent tech-
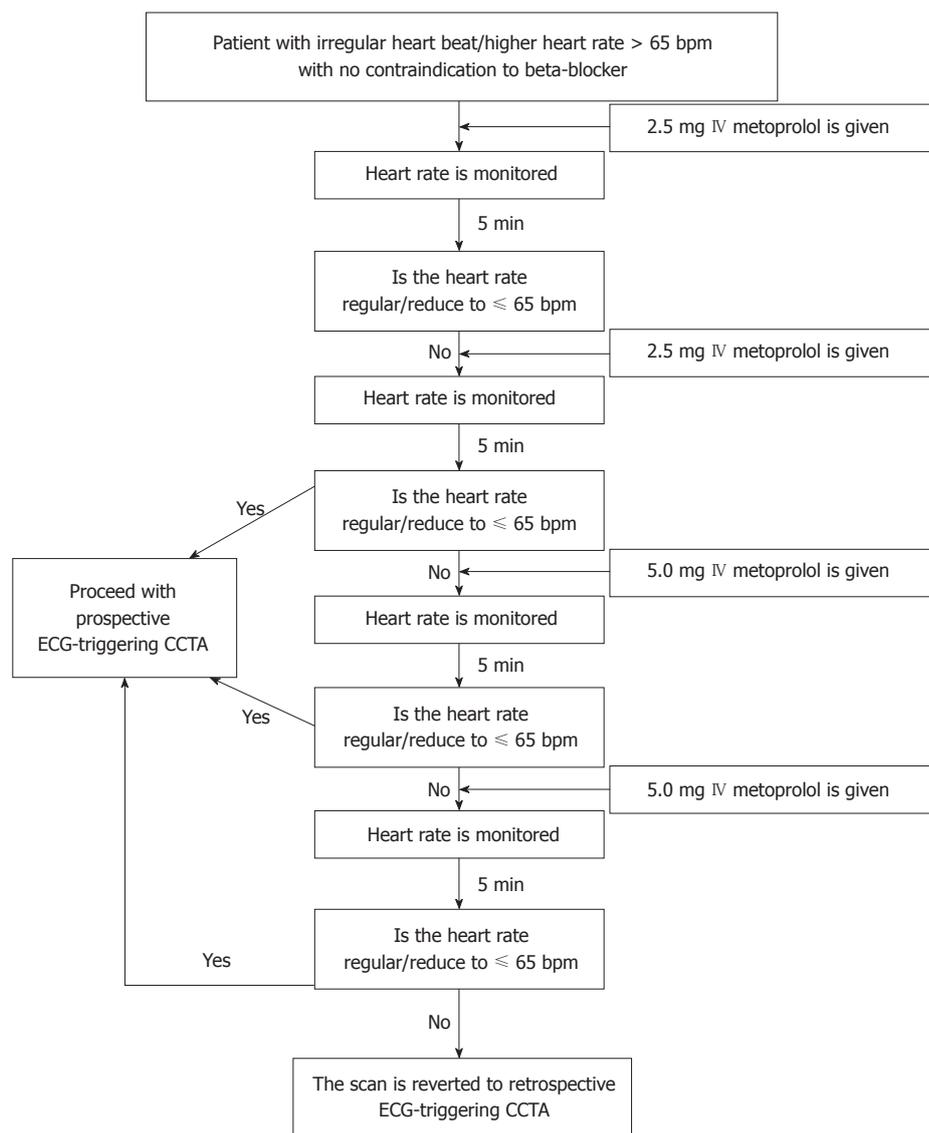
Figure 1 Flow chart showing the intravenous administration of metoprolol protocol in heart rate-lowering therapy. CCTA: Coronary computed tomography angiography.

nological developments with the introduction of dual-source CT and 320-slice CT have overcome the limitation of early generation of multislice CT as the temporal resolution was significantly increased, thus image quality and diagnostic value of coronary CT angiography was less dependent on heart rates[24,25]. It has been reported that dual-source coronary CT angiography shows improved diagnostic performance in patients with a wide range of different heart rates being included[26,27]. Expansion of multislice CT systems from a prototype 256-slice to a 320-slice system has allowed for acquisition of whole heart coverage in one gantry rotation. Studies have shown that 320-slice coronary CT angiography demonstrated high sensitivity and specificity at per-patient, per-vessel and per-segment analysis in patients with atrial fibrillation[28-30]. These results indicate that 320-slice CT has the potential to broaden the use of coronary CT angiography to more patients with high or irregular heart rates or those without responding well to the heart rate control.

POST-PROCEDURE CARE

All patients who are given IV metoprolol are observed for about 30 min once the scan is completed. If the patient presents with bronchospasm, an albuterol inhaler is given accordingly[7,31]. If the patient's heart rate drops to less than 45 bpm, administration of atropine is considered. However, if the patient is resistant to the atropine while the heart rate drops continuously, resuscitative measures and IV administration of beta-agonists need to be administered such as dopamine or epinephrine[7].

In general, beta-blockers are helpful in patients with irregular heart rate, either with premature atrial or ventricular contractions, supraventricular tachycardia and arrhythmias such as arterial fibrillation. With atrial fibrillation, the negative chronotropic and dromotropic effects of the beta-blockers lengthen the diastolic portion of the

cardiac cycle[7,8]. In prospectively ECG-triggered CCTA, X-ray exposure occurs during a small portion of the cardiac cycle typically centered at mid-diastole at 75% of R-R interval[1,6]. Therefore, increasing diastole by beta-blockers would improve CCTA image quality. Previous studies showed that the vessel visibility was achieved with the single-segment reconstruction in patients with low heart rates (< 65 bpm) and with multisegment reconstructions in patients with high heart rates (> 65 bpm)[32,33]. Moreover, the visibility of right coronary artery also has been shown to improve significantly with the administration of beta-blockers. The proportion of the cardiac cycle spent in diastole increases as the heart rate decreases. Therefore, use of beta-blockers is suggested to increase the diastolic phase in the cardiac cycle[34].

In conclusion, beta-blockers administration protocol has been discussed in this article with regard to is usefulness in preparing patient's heart rate for prospectively ECG-triggered CCTA. Since use of medication is essential to ensure that coronary CT angiography will provide excellent diagnostic images with few artifacts, understanding the mechanism of beta-blockers in cardiac imaging will contribute to the efficient use of coronary CT angiography technique in clinical diagnosis.

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Radiation dose measurements in coronary CT angiography

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Abstract

Coronary computed tomography (CT) angiography is associated with high radiation dose and this has raised serious concerns in the literature. Awareness of various parameters for dose estimates and measurements of coronary CT angiography plays an important role in increasing our understanding of the radiation exposure to patients, thus, contributing to the implementation of dose-saving strategies. This article provides an overview of the radiation dose quantity and its measurement during coronary CT angiography procedures.

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Key words: Coronary computed tomography angiography; Dose measurement; Dose quantity; Multislice computed tomography; Radiation dose

Core tip: Various dose parameters are used for measurement of radiation dose associated with coronary computed tomography (CT) angiography. It is important to be aware of the dose quantity and measurement in order to achieve the low-dose coronary CT angiography protocol. This article provides an in-depth review of the dose quantity and dose measurement parameters that are commonly used in coronary CT angiography.

INTRODUCTION

The introduction of latest multi-slice computed tomography (MSCT) technology has emerged as a useful diagnostic imaging modality for the noninvasive assessment of coronary artery disease. The recent advances in the spatial and temporal resolution with thinner detector widths and the low helical pitch values being required for data acquisition in cardiac computed tomography (CT), mainly in retrospective ECG-gating coronary CT angiography (CCTA) mode, however, resulted in increased radiation dose. Compared with plain film radiography, CT examination produces significant higher radiation dose, resulting in a marked increase in radiation exposure to patients. However, the main concern of exposure to ionizing radiation is the potential risk of radiation-induced cancer, and this has raised serious concerns in the literature[1].

Risks associated with radiation exposure are manifested as either deterministic or stochastic effects. Deterministic effects occur when the radiation dose reaches a threshold dose level. The threshold level in deterministic effects varies in different subjects and the damages are significantly related to the amount of dose received. Skin injury, hair loss and cataract are the examples of deterministic effects associated with radiation dose. For example, skin injuries range from skin erythema, moist desquamation, epilation, laceration to necrosis if the skin is exposed to radiation dose beyond the threshold level of 2 Gy[2]. On the other hand, stochastic

effects can be defined as an effect that occurs without any dose threshold. It happens at all time and the damages are not depending on the amount of dose received. Ionizing radiation-induced cancer and genetic changes belong to the stochastic effects. However, previous studies have reported that the increment of radiation dose could increase the chance of developing cancer[3].

Radiation dose estimates for cardiac CT examinations are best expressed as the CT volume dose index (CTDIvol), dose-length product (DLP) and effective dose (E). These parameters are precisely defined to allow comparisons of the radiation doses among different CT imaging protocols. The dose received by a patient from a given CT examination is commonly estimated using CTDIvol or DLP value available on the scanner console[4]. Other than CTDIvol, DLP and E, there were several radiation dose parameters widely used in CT study in order to measure or quantify the radiation dose of CT scanning procedure. Therefore, the purpose of this article is to provide an overview of the radiation dose quantity and its measurement during CCTA procedures.

RADIATION DOSE QUANTITY AND MEASUREMENTS

CT dose index

The fundamental radiation dose parameter in CT is the computed tomography dose index (CTDI). CTDI100 is a measured parameter of radiation exposure which is more convenient than the CTDI and it is regarded as the measurement of choice performed by medical physicists in the clinical setting. Initially, CTDI100 is measured by a 100-mm long pencil-shaped ionization chamber in two different cylindrical acrylic phantoms (16 and 32-cm diameter) which was placed at the iso-center of the CT scanner. Most manufacturers use a 16 cm phantom for head and 32 cm phantom for body examinations during CTDI calculation[5]. The CTDIw is the weighted average of the CTDI100 measurements at the center and the peripheral locations of the phantom. This parameter reflects the average absorbed dose over the two-dimensions (*x* and *y* dimensions) of the average radiation dose to a cross-section of a patient's body.

The CTDIvol is different from CTDIw where CTDIvol represents the average radiation dose over the volume scan (*x*, *y*, and *z* directions) while CTDIw represents the average exposure in the x-y plane only. CTDIvol is the weighted CTDI divided by the pitch, or CTDIvol = CTDIw/pitch and it is measured in mGy. The CTDIvol is now the preferred radiation dose parameter in CT dosimetry. CTDIvol is commonly used in clinical practice due to its accessibility to the radiologists and CT operators as it specifies the radiation intensity used to perform a specific CT examination and not to quantify how much radiation that each patient receives from the CT examination[6]. Rather than the dose to a specific patient, CTDIvol is a standardized index of the average dose delivered from the scanning series. CTDIvol is available to be displayed on the

control console. This allows the clinicians or operators to compare the radiation doses that patient receive from different imaging protocols. CTDIvol can also be used in turn to determine DLP.

Dose-length product

The dose-length product (DLP) is an indicator of the integrated radiation dose of an entire CT examination. The DLP is an approximation of the total energy a patient absorbs from the scan. It incorporates the number of scans and the scan width, *e.g.* the total scan length, while in contrast CTDIw and CTDIvol represent the radiation dose of an individual slice or scan. Therefore, DLP increases with an increase in total scan length or variables that affect the CTDIw (*e.g.* tube voltage or tube current) or the CTDIvol (*e.g.*, pitch). Because scan length is expressed in centimeters, the SI unit for DLP is mGy·cm. Similar to CTDIvol, DLP is also available on the operator's console.

Absorbed dose and equivalent dose

Absorbed dose is an amount of energy that is deposited in a unit of mass of matter (tissue). It is measured in gray (Gy) with 1 Gy equivalent to 1 joule per kilogram. Each type of ionizing radiation produces different biological effect. For instance, the biological effect on tissue which is exposed to 1 Gy α radiation is more harmful than 1 Gy of X-rays. This is because α particles are more heavily charged and slower than x-rays. Therefore, α particles lose much more energy along the travel path before reaching the target[7]. However, the quantity of equivalent dose is used to compare all types of ionizing radiation equally on the biological effect. Equivalent dose is measured in Sievert (Sv). Equivalent dose is obtained by multiplying the absorbed dose with the radiation weighting factor (Table 1).

Effective dose

The most important parameter in CT imaging is the effective dose (E), which is valuable in assessment and comparison of the potential biological risk of a specific examination. E is a sum of equivalent doses in organs of the body that are considered radiosensitive. It is a uniform whole-body dose that has the same nominal radiation risk of carcinogenesis and induction of genetic effects as any given non-uniform exposure[8]. Each organ in human body has different radiosensitivity with some organs more sensitive to the risk of damage than the others. E can be estimated by multiplying each equivalent dose by a relative organ with the tissue weighting factor related to the risk associated with that organ and summing overall exposed organ. International Commission on Radiological Protection (ICRP) publication 103 released in 2007 has recommended values for the tissue weighting factors with major changes different from the previously published ICRP publication 60[9,10] (Table 2).

The SI unit of estimating E is the sievert (Sv) or millisievert (mSv). The weighting factors used for individual

Table 1   Radiation weighting factor for various type and energy range

Type and energy range	Radiation weighting factor, W_R (ICRP-60)
Photons, all energy	1
Electrons, muons, all energy	1
Neutrons < 10 keV	5
10 eV-100 keV	10
> 100 keV-2MeV	20
> 2–20 MeV	10
> 20 MeV	5
Protons > 2 MeV	5
Alpha particles, fission fragments and heavy nuclei	20

Adapted from Ng *et al*[7]. ICRP: International Commission on Radiological Protection.

Table 2   Tissue weighting factor comparison between International Commission on Radiological Protection publication-103 and publication-60

Organs	Tissue weighting factor, W_T	
	ICRP-103	ICRP-60
Colon	0.12	0.12
Lung	0.12	0.12
Red bone marrow	0.12	0.12
Stomach	0.12	0.12
Breast	0.12	0.05
Gonads	0.08	0.20
Bladder	0.04	0.05
Liver/Oesophagus	0.04	0.05
Thyroid	0.04	0.05
Bone surface/skin	0.01	0.01
Brain	0.01	-
Salivary glands	0.01	-
Remainder tissues	0.12[1]	0.05[2]

Adapted from Ng *et al*[7]. [1]Remainder tissues in International Commission on Radiological Protection (ICRP)-103: adrenals, kidneys, muscle, small intestine, pancreas, spleen, thymus, uterus/cervix, prostate, extra-thoracic region, gallbladder, heart, lymphatic nodes and oral mucosa; [2]Remainder tissues in ICRP-60: adrenals, kidney, muscle, small intestine, pancreas, spleen, thymus, uterus, upper large intestine and brain.

tissues are based on a statistical analysis of the increase in the long-term incidence and mortality for cancer determined from a life span study of the survivors in Japan during the atomic bomb explosion[11-13]. Usually, tabular data of conversion coefficients are available to estimate E from entrance skin dose for radiography[14,15], from dose area product (DAP) for fluoroscopy[16,17], or from CTDI$_{vol}$ or DLP for CT[18]. The goal is to convert the higher radiation doses delivered to a small portion of the body into an equivalent uniform dose to the entire body that carries the same biological risk for causing radiation-induced fatal and nonfatal cancers.

The *E* can be estimated by multiplying the DLP with a conversion coefficient factor (*E*/DLP), *k* (mSv/mGy per centimetre). The *E*/DLP value of 0.026 or 0.028 mSv/mGy per centimetre was applied for coronary CT study since this value was likely to be more accurate for

estimation of radiation dose associated with cardiac CT compared to the chest CT (0.014 or 0.017 mSv/mGy per centimetre)[10,19,20]. If no dose-saving strategy is applied, it is estimated that effective doses of coronary CT angiography may reach up to 30 mSv in patients undergoing cardiac CT imaging, thus, there is potential risk of associated radiation-induced malignancy[21].

Gosling *et al*[20] compared the effective dose using the latest ICRP 103 tissue-weighting factors with that calculated with previously published chest conversion factors. Their results showed that the use of chest conversion factors (0.014-0.017) significantly underestimated the effective dose when compared to the dose calculated using the conversion factor of 0.028. A conversion factor of 0.028 would give a better estimation of the effective dose from prospectively ECG-triggered coronary CT angiography. Appropriate conversion factors are needed to accurately estimate effective dose. A conversion factor of 0.014 or 0.017 is commonly used in many cardiac CT studies to estimate the effective dose associated with coronary CT angiography, thus, this could lead to variations in the reported effective dose. As a result, the DLP or CTDI$_{vol}$ is recommended to compare the radiation exposure of coronary CT angiography[22].

Background equivalent radiation time
Background equivalent radiation time (BERT) is used to explain the dose to the general public without complicated scientific units, terminology or concepts. It converts the radiation dose to an equivalent period of natural background radiation in days, weeks, months or years to which the entire population is exposed every day from natural radioactive substance in the air, internal, terrestrial, cosmic and environment. For example, it is more likely for patient to easily understand that "your chest X-ray dose is about equal to 3 d of background radiation" rather than "you have received 0.02 mSv for your chest X-ray examination"[7]. BERT is not used to provide a high level of diagnostic accuracy, but to relieve anxiety about radiation by giving an understandable and satisfactory answer (Table 3)[23].

Entrance skin dose
Entrance skin dose is an amount of energy imparted per gram of tissue at the entrance surface. It is also known as surface absorbed dose (SAD). About 1 Gy is equal to 1 millijoule per gram of energy deposited by the X-rays. Entrance skin dose can be obtained by multiplying the radiation exposure measured in the air at the skin by a factor, f for the tissue. The f factor is a quantity of radiation dose exposure conversion measured in the air (coulomb per kilogram at the standard temperature and pressure) to an equivalent radiation dose absorbed in tissue (grays) at the same location. However, entrance skin dose is not an indicator to measure radiation risks except for skin erythema, but it is useful for organ dose calculation especially in a computer-based program that is involved with Monte Carlo simulations[14,15].

Table 3 Estimated effective doses for diagnostic medical exposures associated with background equivalent radiation time and life-time fatal cancer risks from National Radiological Protection Board

X-ray examination	Estimated effective dose (mSv)	BERT[1]	Fatal cancer risk per examination[2]
Limbs and joints (exclude hip)	< 0.01	< 1 d	1 in a few millions
Dental (single bitewing)	< 0.01	< 1.5 d	1 in a few millions
Dental (panoramic)	0.01	1.5 d	1 in 2 million
Chest (single PA)	0.02	3 d	1 in a million
Skull	0.07	1 d	1 in 300000
Cervical spine	0.08	2 wk	1 in 200000
Thoracic spine	0.7	4 mo	1 in 30000
Lumbar spine	1.3	7 mo	1 in 15000
Abdomen	0.7	4 mo	1 in 30000
Hip	0.3	7 wk	1 in 67000
Pelvis	0.7	4 mo	1 in 30000
Intravenous urography	2.5	14 mo	1 in 8000
Barium swallow	1.5	8 mo	1 in 13000
Barium meal	3	16 mo	1 in 6700
Barium follow-through	3	16 mo	1 in 6700
Barium enema	7	3.2 yr	1 in 3000
CT head	2	1 yr	1 in 10000
CT chest	8	3.6 yr	1 in 2500
CT abdomen/pelvis	10	4.5 yr	1 in 2000

Adapted from Ng *et al*[7]. [1]Natural background radiation based on Australia average = 2.4 mSv per year; [2]Appropriate lifetime risk for patients from 16-69 years old: paediatric = 2x; geriatric = 5x. BERT: Background equivalent radiation time.

Critical organ dose

Critical organ dose (COD) is more commonly reported in the literature for radiologic examinations. Critical organ dose refers to the energy deposited per unit mass to individual critical organs for which the radiosensitivity and radiation dose are high. Its unit of measurement is usually milligrays, which is equivalent to millijoules per kilogram. COD can be used to assess the risks of irradiation beyond cancer induction for certain organs; for example, other potential biological effects can include skin erythema, cataracts, fetal abnormalities, haematologic effects, vascular damage, and effects on the central nervous system.

Critical organ dose may be determined by other dose descriptors, such as entrance skin dose or dose area product, by using tables or software programs that are based on Monte Carlo calculations for standard patient sizes[14,15]. Also, the critical organ dose values for various organs, along with their corresponding weighting factors, can be used to calculate the effective dose[9,24]. In clinical practice, knowledge of organ doses and the carcinogenic sensitivity of certain organs can lead to better collimation and patient positioning to reduce the risks from exposure to radiation.

Diagnostic acceptable reference level

Diagnostic acceptable reference level is also known as diagnostic reference level (DRL). DRL values are published based on the nationwide evaluation of X-ray trends surveys[23,25]. The data values can be used as a reference point to ensure that all current clinical practice involving radiation in radiological investigations are safe. However, ESD, DAP, or CTDI$_{vol}$ values that are greater than those of DRL may be attributed to the patient's size, the complexity of the clinical case, equipment malfunctions, or suboptimal protocols. Some of the higher values may be unavoidable; however, many of the higher values can be avoided. When patient doses appear to be above those of DRL, especially when they are consistently higher, investigation and assessment are required. If suboptimal protocols or equipment deficiencies are the cause of the higher dose levels, necessary strategies must be undertaken to reduce the radiation dose.

Radiation dosimeter

Radiation dose in clinical practice can be measured accurately by using a dosimeter. There are a number of dose measurement tools with different methods being used to measure the radiation dose absorption. The value of absorbed dose is determined indirectly by measuring the radiation effect through ionization of air, fogging of photographic emulsion, thermoluminescence, scintillation and ionization of a semiconductor. However, the most commonly used method in radiation dosimetry is thermoluminescence dosimeter (TLD)[26].

Thermoluminescence phenomenon

Thermoluminescence is a condition where the light is emitted from a heated crystalline material which is made up of lithium fluoride (LiF) or calcium fluoride (CaF_2) phosphors. When the crystalline is exposed to the radiation, electrons in the crystal are pulled out from valence band to the conduction band by a small amount of energy. However, without enough energy, some of the electrons are trapped into one of the isolated levels provided by impurities in the crystal. It will remain immobilized at that state until energy is supplied to release it (usually by heat). Thus, the electrons leave a positive hole in the valance band. By heating the crystal, the trapped elec-
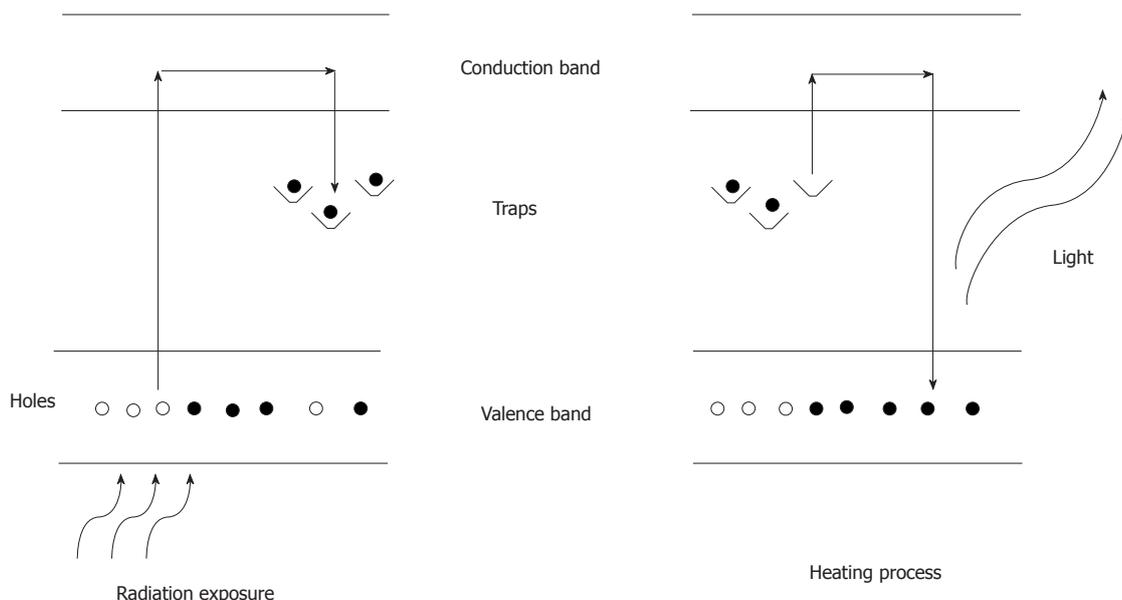
Figure 1 Process of light emission from the radiation exposure in the thermoluminescence phenomenon.

trons will elevate and return to the valence positive hole. A photon of visible light is emitted during the process of returning electrons from the trap to the valence band (Figure 1)[11]. The total light emitted is counted where the measurement for the number of trapped electron indicates the absorbed radiation. Surprisingly, it can be used even after a month of storage.

Several types of TLD are commercially available for a wide range of applications. For instance, LiF: Mg, Li₂B₄O₇, CaSO₄: Dy, Al₂O₃, CaF₂: Dy and CaF₂: Mn[27]. In diagnostic radiology, LiF: Mg, Ti or usually known as TLD-100 was chosen for dosimetry purposes in clinical radiation measurement. In fact, it was the first material used in diagnostic radiology and one of the most utilised materials when compared to others[28]. TLD with LiF: Mg, Ti material is chosen because of the physical shape which is small, light and convenient for local measurement during the radiological examinations. Apart from physical appearance, it is able to measure entrance surface absorbed dose at the reference point at specific organs without obscuring an image due to the radiolucency specification[27]. Moreover, it has high reproductive capability, thus it can be used repeatedly. The materials are sensitive to detect radiation exposure in a range between 10 μGy and 10 Gy, in addition to having a good linear relationship between thermoluminescence readout value and dose absorption up to 1 mrad.

CT dose measurement

Effective dose in CT can be easily estimated by a simple calculation through multiplying the DLP with a conversion coefficient factor (E/DLP). Huda, Ogden, and Khorasani in their study introduced a new approach to determine the E[8]. They suggested that E can be calculated from DLP by using ImPACT software package which is based on Monte Carlo simulation performed by the National Radiological Protection Board[29]. Yet, the accuracy of this system is undisputable when Huda, Ogden, and Khorasani compared those E calculations with other software packages like CT-expo and ImpactDose. As a result, there were approximately 5% differences between E/DLP values according to each software package and it was not statistically significant[8]. CT-Expo is a program run on Monte Carlo dosimetry data while ImpactDose is a personal computer based-program that calculates ED values for arbitrary scanning parameters and anatomic ranges[30]. However, the E values still can be calculated manually by multiplying the DLP values with the conversion coefficient factor in CT imaging based on individual organs and tissue weighting factors published by the ICRP 103[10,16,31]. Using CT dose reporting packages is an advantage because they are easy to use and produce quick results. However, it must be recognised that there are deviations between the different software packages, and users should understand this and be familiar with different terminologies used in order to provide accurate dose reporting for a consistent comparison[30].

In conclusion, it is important to be aware of the amount of radiation dose produced from cardiac CT scanning. The quantification of the radiation dose is a crucial issue that must be addressed by both practitioners and the operators in determining the correct and accurate dose measurement. With sufficient knowledge of radiation dose terminology and dose quantification, the understanding of radiation dose safety and radiation awareness will be accordingly increased when performing coronary CT angiography examinations. Various dose-saving strategies have been undertaken in the past decade to lower radiation exposure to patients who undergo coronary CT angiography, with effective dose ranging from 10 mSv to as low as 1 mSv. Details of these dose reduction techniques will be discussed in Part Ⅲ of this series.

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Coronary CT angiography: Dose reduction strategies

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Abstract

With the introduction of 64- and post-64 slice computed tomography (CT) technology, coronary CT angiography has been increasingly used as a less invasive modality for the diagnosis of coronary artery disease. Despite its high diagnostic value and promising results compared to invasive coronary angiography, coronary CT angiography is associated with high radiation dose, leading to potential risk of radiation-induced cancer. A variety of dose-reduction strategies have been reported recently to reduce radiation dose with effective outcomes having been achieved. This article presents an overview of the various methods currently used for radiation dose reduction.

Key words: Coronary artery disease; Coronary computed tomography angiography; Multislice computed tomography; Radiation dose; Dose reduction

Core tip: Various dose-reduction strategies of coronary computed tomography angiography have been discussed in this article with the aim of providing readers with a comprehensive summary of the effectiveness of these radiation reduction approaches.

INTRODUCTION

Coronary computed tomography angiography (CCTA) procedure has been known as an effective technique in non-invasive coronary artery assessment. With high accuracy in the detection of coronary artery disease, this makes CCTA accepted as a widely used diagnostic tool in cardiac imaging[1-4]. However, radiation dose of CCTA that has been reported in the literature is the greatest concern and varies a great deal depending on the scanning parameter settings. There are many factors influencing the overall radiation exposure including tube voltage, tube current, scan range, scanner geometry, the electrocardiogram (ECG)-gating application either prospective or retrospective ECG-gating, slice thickness and pitch value selection (for helical scan mode).

Most of the parameters are controlled, monitored and modulated by the computed tomography (CT) operator during the procedure in order to obtain an optimum image quality. Therefore, all factors need to be taken into consideration in minimizing the radiation exposure to achieve the goal of "as low as reasonably possible". Previous studies have also reported that standard CCTA procedure with the use of retrospective ECG-gated technique results in very high radiation dose, which ranged from 13.4 to 31.4 mSv[5-7]. This has raised serious concerns in the literature due to the potential risk of radiation-induced malignancy resulting from CCTA. Therefore, several dose-saving strategies have been introduced to deal with radiation dose issues, and

these techniques include anatomy-based tube current modulation[8,9], ECG-controlled tube current modulation[10,11], tube voltage reduction[12,13], a high-pitch scanning[14,15] and prospective ECG-triggered CCTA[16,17]. This article is written purposely to provide information about the strategies that could be used to further reduce the radiation dose to patient during CCTA procedure.

STRATEGIES FOR RADIATION DOSE REDUCTION IN CCTA

Anatomy-based tube current modulation

Tube current is an important element that is directly related to radiation dose and image quality. With rapid developments of CT technology, implementation of automatic tube current modulation allows significant reduction in radiation dose for CT examinations. In CT examination, automatic tube current modulation can be defined as a series of techniques that enable automatic adjustment of the tube current in x-, y-plane (angular modulation) or z-plane (z-axis modulation), according to the size and attenuation characteristics of the human body. The purpose of these adjustments is to achieve optimum image quality with low radiation dose. The term automatic tube current modulation is similar to automatic exposure-control that is commonly used in conventional radiography[18,19]. Anatomy-based tube current modulation is then divided into two modes namely angular modulation and z-axis modulation.

Angular modulation (x-y plane)

Since the shape of patients body is not symmetrical [anteroposterior (AP) *vs* lateral], angular-modulation techniques automatically adjust the tube current for each projection angle to the appropriate attenuation according to patient's anatomical structures. Without angular modulation, the tube current is held constant over the 360° rotation, regardless of the patient attenuation profile. The angular-modulation technique reduces tube current as a function of projection angles for low-attenuation projections (AP *vs* lateral projections). This technique calculates the modulation function from the online attenuation profile of the patient. The modulation function data are processed and sent to the generator control for further tube current modulation with a delay of 180° from the X-ray generation angle. In asymmetrical regions being scanned such as the shoulders in chest CT, the X-ray attenuation is substantially less in the AP than in the lateral direction. The radiation dose reduction could be achieved up to 90% with application of the angular-modulation technique[20]. Therefore, the technique of angular modulation helps in improving dose efficiency in the x- and y-axis by reducing radiation exposure in a particular scanning plane.

Z-axis modulation

The principle of z-axis-modulation technique is different from that of angular modulation. Unlike angular modulation, the z-axis modulation technique adjusts the tube current automatically to maintain a user-specified quantum

noise level in the image data. It provides a noise index to allow users to select the amount of X-ray noise that will be presented in the reconstructed images. Using a localizer radiograph, the scanner computes the tube current required obtaining images with a selected noise level. Hence, z-axis modulation attempts to make all images have a similar noise irrespective of patient size and anatomy. The noise index value is approximately equal to the image noise (standard deviation) in the central region of an image of a uniform phantom. However, the actual noise measured on the image by drawing a region of interest that will differ from the noise index selected for scanning. This is due to the fact that noise index settings only adjust the tube current, whereas the standard deviation is also affected by other parameters, including the reconstruction algorithm, the reconstructed section thickness (if different from the prospective thickness), the use of image space filters, variations in patient anatomy and patient motion, and the presence of beam-hardening artifacts.

The CARE Dose 4D protocol (Siemens, Medical Solutions, Erlangen, Germany) was then introduced in order to adapt the tube current to the patient's individual anatomy and modulate the tube current in the section with the lowest dose levels. Previous studies have shown that 20%-60% dose reduction was achieved depending on the anatomic region and patient habitus, with improved image quality[21]. Another study combining angular and z-axis modulation (3D Auto mA; GE Yokogowa Medical Systems, Tokyo, Japan) reported significant dose reductions (60%) in abdominal-pelvic CT examinations[22]. This technique uses a single localizer radiograph to determine patient asymmetry and appropriate angular and z-axis modulation for the patient. The investigators added noise (computer modification of original raw scan data to simulate lower tube current noise levels) to patients' scan data to produce images and calculate the radiation dose reduction.

A lower minimum tube current may result in reduced exposure to patients, which occasionally increases image noise in smaller patients scanned with a substantially reduced tube current. Generally, larger patients receive higher tube current with z-axis modulation if a fixed-tube-current technique used in order to maintain the selected image noise. In contrast, with automatic tube current modulation, the tube current is inconsistent throughout the scan and thus results in the diagnostic image quality with reduced radiation dose. The main limitation of automatic tube current modulation is the lack of uniformity between techniques developed by different vendors.

ECG-CONTROLLED TUBE CURRENT MODULATION

The idea of decreasing radiation doses associated with tube current modulation in CT stimulates manufacturers to improve the CCTA examinations. One of the most recently developed methods, CARE dose 4D by Siemens Medical Solutions, which combining the effects of angular and z-axis modulation techniques[23]. Virtually all ana-

tomic regions in the thorax, abdomen, and pelvis have benefited from these sophisticated techniques that result in considerable significant dose reduction[10,24].

However, the *z*-axis modulation principle in CARE dose 4D was not compatible with ECG pulsing. ECG-pulsed tube current modulation is the most significant improvement in minimizing radiation from CT technology and it is the only technique dedicated to cardiac imaging. ECG pulsing is performed online during cardiac CT examination which allows a decrease in radiation exposure of between 30% and 50%. The radiation dose is reduced by modulating the tube current output during the systolic phase[25]. Moreover, the algorithm for ECG-dependent dose modulation also represents a very effective tool for limiting radiation dose in the vast majority of patients undergoing cardiac CT studies.

In ECG-controlled tube current modulation technique, a high tube current with optimal image quality is applied only during the diastolic phase of the cardiac cycle, in which images are most likely to be reconstructed with minimal artifacts, while in the systolic phase, a low tube current (50% of normal tube current) is applied. Image reconstruction during cardiac CT examinations is usually performed in ventricular mid-diastole phase due to less cardiac motion that causes blurring of cardiac structures. Thus, high quality diagnostic images can be acquired during the diastolic phase[26]. However, this method totally depends on the patient's heart rate and requires a regular sinus rhythm in order to prevent poor image quality. Unfortunately, the ECG-controlled tube current modulation algorithm cannot be performed in the presence of arrhythmias such as premature extra beats. Thus, this algorithm may not be useful in patients with arrhythmias.

LOW TUBE VOLTAGE

Since radiation dose varies with the square of tube voltage, an application of lower tube voltage during CT data acquisition is another approach for radiation dose reduction. A previous study by Huda *et al*[27] showed that reducing the X-ray tube potential from 140 to 80 kVp at constant tube current decreased the radiation dose by a factor of about 3.4. Consequently, image contrast and image noise will definitely be increased because of fewer numbers of photons produced[27-29]. However, since the contrast-to-noise ratio (CNR) and signal-to-noise ratio are the key factor of CT image quality, noise is rather irrelevant if the level of contrast or amount of signals are too high[28]. The change in image contrast is dependent on the anatomic number (*Z*) of the structures being investigated. The image structure with high-anatomic-number becomes significantly more prominent than image of low-anatomic-number structures (soft tissue) in the application of low tube voltages[27].

It has been confirmed that diagnostic image quality was not affected by lower tube voltages in pediatric CT investigations. Similarly, in a phantom study by Siegel *et al*[29] showed that reduced beam energy in contrast-enhanced

pediatric CT decreased the radiation dose without affecting image contrast and image noise. Moreover, the inter-relationship between beam energy and tube output has been described by Boone *et al*[30] in the context of image noise characterization in CT techniques by using tube voltages of 80-140 kVp and tube currents of 10-300 mA. Provided the tube current-time product was appropriately adapted, radiation dose can be significantly reduced at lower tube voltage while CNR remained at a constant level. Cody *et al*[31] reported that the use of 80-kVp tube voltage resulted in beam-hardening artifacts and thus recommended the use of 100- to 120-kVp settings in pediatric patients. For non-cardiac CT studies with kilovoltage reduction, an increase of the tube current by 50% has been proposed to maintain image quality and to reduce the dose estimation concurrently[31]. However, a further increase in tube current is limited with the available standard protocols for cardiac CT scanning on the studied CT scanners. Therefore, a trade-off between dose saving and increased image noise has to be considered with current cardiac CT protocols.

Previous study compared the diagnostic image quality of the coronary artery segments in order to detect stenosis in various scan protocols[32]. In this qualitative analysis, no deterioration of image quality was detected in most of the scan protocols inclusive of the ECG-dose modulation and the 100-kVp tube voltage for both 16- and 64-slice CT scanners. The value of this analysis is only limited by a potential selection bias of the scanning protocols. Image obtained with 120-kVp scan protocol without ECG modulation (on patients with arrhythmia) are likely to present with more non-diagnostic coronary segments, even when no dose-saving algorithms were applied. However, the impact of dose-saving algorithms on the detection of calcified and non-calcified plaques remains unknown. Therefore, further studies are needed to investigate the balance between dose savings and maintained diagnostic image quality for CCTA investigations.

HIGH PITCH VALUE

With the recent advent of second-generation of dual-source, another low-dose technique has been introduced for cardiac CT which is high-pitch scanning mode[33]. This technique was successfully tested with dual-source 128-slice CT in retrospective ECG-gating protocol. In this technique, the data are acquired in a spiral mode while the X-ray table runs with a very high pitch of 3.4 equaling to a table feed of 46 cm/s. When this high-pitch mode is used, the entire heart is scanned within one single cardiac cycle, generally during the diastolic phase (75% R-R interval). The temporal resolution for this system is 75 ms, with the gantry rotation time of 280 ms and only quarter rotations for data reconstruction. Early reports on phantom studies have shown that the purpose of this scan mode is to deliver images of diagnostic quality at a low radiation dose. Moreover, two studies have successfully proved that feasibility of this high-pitch mode technique also in

patients by using the remodeled first generation of dual-source 64-slice CT scanners with effective dose less than 1 mSv[15,34]. Then, several recent studies also have reported similar results[35-37]. In addition to low dose aspect, high diagnostic accuracy has been achieved with the high-pitch dual-source CT[38].

In order to apply the high-pitch mode, several requirements must be fulfilled. Firstly, dual-source geometry is necessary in order to obtain the projection data by the second detector for gaps fill-up due to rapid table movement. In this way, the pitch can be increased up to 3.4 while allowing image reconstruction, although the limited field of view is covered by both detectors. A quarter rotation of data per measurement is used for image reconstruction, and each of the individual axial images has a temporal resolution of a quarter of the rotation time $t_{rot}/4$. Thus, the overlapping of radiation exposure can be avoided with the application of high pitch resulting in radiation dose reduction to the minimum level[39]. Secondly, a higher temporal resolution is essential to enable single cardiac cycle reconstruction without image distortion due to motion artifacts. Thirdly, patient's heart rate must be regular and consistent in order to obtain a good image quality. With used of high pitch mode, the examination table is accelerated to the maximum speed during data acquisition which is triggered by the R-peak of the heartbeat. The examination table could not be accelerated in an infinitely small time period; therefore, it has to be set in motion sufficiently earlier prior to scanning acquisition. Inconstant heart rates lead to inaccurate positioning of the data acquisition window, with data being acquired either too early (if heart rate decreases) or too late (if heart rate increases) in the cardiac cycle. Inconsistent heart rates would compromise image quality by stair-step artifacts.

Finally, high pitch mode requires patient with low heart rates (< 65 bpm). In order to obtain a motion-free artifact, CT data acquisition can possibly be performed during a single diastolic period if the patient heart rate is constantly lower than 65 bpm[39]. On the other hand, patients with high heart rates may not yield diagnostic image quality of the coronary arteries due to a narrow diastolic exposure of R-R interval window and therefore, tube current modulation is required for adjustment accordingly[35].

ITERATIVE RECONSTRUCTION METHODS

Alternative image reconstruction techniques such as iterative reconstruction have been used mainly in nuclear medicine studies[40,41]. In CCTA, iterative reconstruction such as adaptive statistical iterative reconstruction (ASIR) (GE Healthcare) has been introduced as a new reconstruction algorithm[42]. Iterative reconstruction is a method to reconstruct 2D and 3D images from measured projections of an object. However, unlike filtered back projection, iterative reconstruction starts with an initial estimate of the object which is subsequently improved in

a stepwise fashion by comparing the synthesized image to the one acquired with projection data and improving the previous estimation.

Moreover, iterative reconstruction reduces image noise by iteratively comparing the acquired image to a modeled projection. This reconstruction algorithm is used to help deal with one of the primary issues of dose and tube current reduction for CCTA. Since iterative reconstruction has been consistently associated with image quality improvement, especially improving CNR, it has the possibility of improving spatial resolution[43,44]. With faster computer technologies and adapted techniques, the use of iterative reconstruction for cardiac CT imaging has been increasingly studied and the reconstruction speed now allows its use in clinical practice. Iterative reconstruction has been shown to reduce noise, improve image quality and reduce radiation dose not only in body CT but in coronary CT. The ASIR technique was reported to provide about 27% of radiation dose reduction compared to that standard filtered back projection reconstruction[43]. In addition, image quality and the proportion of interpretable segments were also improved with the application of 40% or 60% ASIR in CCTA reconstruction compared to that filtered back projection reconstruction[43]. Another study using the similar reconstruction method with different nomenclature, namely iterative reconstruction in image space (IRIS) also resulted in significant reduction of image noise and improved subjective image quality[45]. However, the main limitation to its routine use is the high computational cost, which can be 100-1000 times higher than for filtered back projection[46].

Moreover, iterative reconstruction does not assume that the measured signal is free of noise due to x-ray photon statistics or electronic noise but rather uses more accurate statistical modeling during the reconstruction process[42]. This enables improved noise properties in the reconstructed images, while maintaining spatial resolution and other image quality parameters. The use of iterative reconstruction techniques is expected to increase in CT as computational processing improves and algorithms become more robust and easy to apply. Owing to more powerful iterative reconstruction algorithms are emerging, the impact of these techniques may show greater noise reduction and thereby permit further reductions in radiation exposure to patients.

PROSPECTIVELY ECG-TRIGGERED CORONARY CT ANGIOGRAPHY

Various strategies have been developed to reduce radiation exposure to patients, and prospectively ECG-gated CT coronary angiography is remained as the most important and effective in reducing the radiation dose which also called step-and-shoot mode. The step-and-shoot mode is characterized by turning on the x-ray tube only at a predefined time point of the cardiac cycle, usually in mid-diastole, while keeping the patient table stationary. The x-ray exposure time of this technique is short,
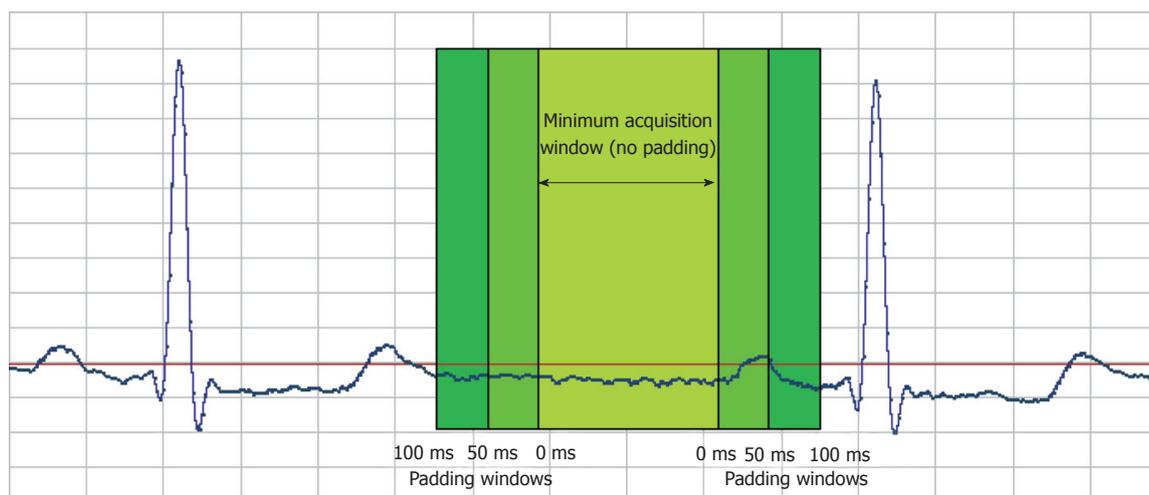
Figure 1 Use of extra tube-on time to acquire image data during additional cardiac phases. Padding turns tube on prior to minimum half-scan time and leaves it on afterwards. It is recommended in cases when heart rate varies during examination.

and thus, low radiation doses ranging between 1.2 and 4.3 mSv have been reported using various 64-slice and first-generation of dual-source 64-slice CT[32,47]. Most importantly, this low-dose step-and-shoot method is still being able to produce high diagnostic accuracy for the detection of coronary stenosis[32,48].

Unlike standard retrospective ECG-gating, where the tube output (in mA) is constant throughout the data acquisition during spiral CT which results in high radiation dose, prospective triggering is performed with sequential scans. In prospective triggering, the tube current is turned off for most of the scan period and is triggered by the ECG to be "on" only for a short period during diastole. Thus, this results in remarkable reduction in radiation dose[49]. With application of prospective ECG triggering, the radiation dose of CCTA can be reduced by up to 83% when compared to that standard retrospective ECG gating technique[47,49].

Prospectively ECG-triggered technique uses axial images and an incrementally moving table to cover the heart with minimal overlap of axial slices. Cardiac imaging with electron beam CT also uses prospective data acquisition triggered by ECG. Prospective triggered technique in cardiac CT is not new and it was actually being used in early 1980 by Dr. Godfrey Hounsfield with conventional single-slice CT[50]. It was recognized that CT image synchronization with heart diastolic phase was optimal for imaging the heart. Unfortunately, the findings were not being achieved when the patient heart rate increases.

When a 64-slice system is used, the scan is prescribed by using 3-5 incremental of 64 mm × 0.625 mm (40 mm) image groups which requires 2-4 incremental table translations of 35 mm. Thus, allow for 5 mm of overlap. The minimum interscan delay is approximately between 0.6 and 1.0 second which normally requires skipping a cardiac cycle between data acquisitions which results in one image acquisition per 2 cardiac R-R cycles[49]. However, the process will be faster with larger detectors (128-, 256- or 320-slice CT) being used. The detector width de-

termines the number of steps/scans to cover the entire heart and complete an examination. For instance, the dual-source 64-slice CT has a narrower detector array (32 mm × 2 mm × 0.6 mm = 38.4 mm per acquisition); thus, it takes more incremental steps (normally 4-5 cardiac cycles) to cover the heart and complete an examination than with the 320-row system (320 × 0.5 mm = 160 mm) which covers the heart in a single acquisition[51].

Prospectively ECG-triggered technique has a limited number of cardiac phases available for reconstruction. Therefore, mid-diastolic phase (75% of R-R interval) was always being selected for data acquisition for all subjects. In addition, by using add-on 'padding' will allow more cardiac phases for reconstruction. Padding technique is described as prolonging the acquisition window in order to allow the reconstruction to adapt with minor heart rate variations and to produce consistent image quality. Padding turns the X-ray tube on before and after the minimum or actual acquisition time (milliseconds) required. Available padding options with current software ranges from 0 to 200 ms (Figure 1). No padding is required for patient with stable heart rates and minimal heart rate variability. However, radiation dose also will increase with application of padding window due to expense of radiation exposure on the particular windows phase[24,49].

Other than adjusting prospective triggering parameters in order to adapt with high heart rates, application of β-blockade for heart rate control is also commonly used in CCTA to produce better results. However, precautions have to be taken in patients who are contraindicated to β-blockage agent. Alternatively, calcium channel blocker could be used in order to reduce the heart rate. The maximum of 15 mg of intravenous metoprolol (β-blocker) or 40 mg of intravenous diltiazem (calcium channel blocker) is recommended prior to the scan in order to control the heart rat[49,52].

The major drawback of prospective ECG triggering is that cardiac functional analysis is unavailable. Since pro-

Table 1 Dose reduction strategies and corresponding effectiveness in dose reduction in coronary computer tomography angiography

Techniques	Advantages	Pitfalls	Dose reduction
Tube current modulation: anatomy-based	Suitable for unsymmetrical body habitus	No apparent reduction in CCTA procedure due to homogeneity of the body thickness in the cardiac region	20%-60%[1]
Tube current modulation: ECG- controlled	Dedicated for cardiac imaging Modulates tube current output during systolic phase	Heart rate must be regular	30%-50%
Low tube voltage (kVp)	Image structure with high-atomic number becomes more prominent than that with low-atomic number	Beam hardening artifacts may occur May increase image noise which leads to suboptimal image quality	Up to 30%
High pitch value	Fast image acquisition Reduce motion artifacts	Patient heart rate must at < 65 bpm and regular Can only be performed on second generation of dual-source CT scanner	Up to 80%
Iterative reconstruction algorithms	Improve contrast-to-noise ratio and spatial resolution Reduce image noise	High computational cost	Up to 40%
Prospectively ECG- triggered CCTA	High sensitivity in the detection of CAD Tube current is only 'on' in a short period during diastolic phase	Limited number for cardiac reconstruction phases No cardiac functional analysis	Up to 83%

[1]Applied to the abdominal-pelvic region. CT: Computed tomography; CCTA: Coronary CT angiography; CAD: Coronary artery disease; ECG: Electrocardiogram.

spective technique acquires data during a limited portion of the cardiac cycle, it cannot be used to evaluate cardiac function. Both quantitative and qualitative functions, either global or regional, require images to be reconstructed throughout the entire cardiac cycle. If the clinical scenario or referring physician requires information about cardiac function, then retrospective gating must be undertaken. Heart rate variability is another limitation for the prospective ECG triggered technique. Heart rate variability of > 5 beat/min is considered not applicable for prospective triggering. Therefore, the scan has to be reverted into retrospective ECG gating technique if patients' heart rate elevated or heart rate variability does not meet the requirement after β-blocker has been given[49]. However, the prospective ECG triggered technique in patients with higher heart rates still produces diagnostic images. CT scanner with higher detector arrays is an alternative to obtain CCTA in patients with high or irregular heart rates. It has been reported that high diagnostic value could be achieved with 320-slice CT angiography in the diagnosis of CAD, with image quality independent of heart rate[51]. The improved temporal resolution (175 ms) and increased coverage scan value (160 mm) of 320-slice CT results in robust image quality within a wide range of heart rates; thus providing the opportunity to image patients with higher heart rates without requiring pre-examination beta-blockage[51].

CONCLUSION

Recent technological developments have led coronary CT to be used widely and the acceptable indications for CCTA imaging become broaden. However, despite the strength of CCTA, the potential risk of radiation- induced malignancy has received attention in scientific publications although it may be unproven. Therefore, appropriate referral of CT studies, lowering tube voltage, using tube current modula-

tion, increasing the pitch value, applying iterative reconstruction technique and implementation of prospective ECG-triggering CCTA enable CCTA to be performed at a low dose while preserving good image quality and diagnostic accuracy. Table 1 summarises above-mentioned dose-reduction strategies and corresponding effectiveness in the reduction of radiation dose associated with CCTA.

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Coronary CT angiography: Diagnostic value and clinical challenges

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Abstract

Coronary computed tomography (CT) angiography has been increasingly used in the diagnosis of coronary artery disease due to improved spatial and temporal resolution with high diagnostic value being reported when compared to invasive coronary angiography. Diagnostic performance of coronary CT angiography has been significantly improved with the technological developments in multislice CT scanners from the early generation of 4-slice CT to the latest 320- slice CT scanners. Despite the promising diagnostic value, coronary CT angiography is still limited in some areas, such as inferior temporal resolution, motion-related artifacts and high false positive results due to severe calcification. The aim of this review is to present an overview of the technical developments of multislice CT and diagnostic value of coronary CT angiography in coronary artery disease based on different generations of multislice CT scanners. Prognostic value of coronary CT angiography in coronary artery disease is also discussed, while limitations and challenges of coronary CT angiography are highlighted.

Core tip: Coronary Computed tomography (CT) angiography represents the technical evolution in cardiac imaging due to its high diagnostic value in coronary artery disease as a less invasive technique. Diagnostic performance of coronary CT angiography is significantly enhanced with the development of multislice CT scanners, ranging from 4-slice to 64- and post-64 slice scanners. This article provides readers with a comprehensive review of the diagnostic value of coronary CT angiography according to different generations of multislice CT, with limitations and challenges being addressed.

INTRODUCTION

Computed tomography (CT) scanner has rapidly evolved from single slice to multislice CT (MSCT) which started from 4-slice systems in 1998 to the latest 256-slice and 320-slice CT systems. With smaller detector size and faster gantry rotation speed, spatial and temporal resolutions of the 64- and post-64 MSCT scanners have enabled coronary artery imaging a feasible and reliable clinical test. The technological advancements from 16- to 320-slice systems have progressed in a relatively uniform fashion with improved longitudinal (z-axis) volume cov-

erage, decreased gantry rotation time, and smaller detector elements[1,2]. With the ability to acquire volume data, technological improvements in CT scanning also enable generation of 3D image processing such as multiplanar reformation, maximum intensity projection, surface-shaded display, and volume-rendering techniques, and these reconstructed visualizations have made coronary CT angiography (CCTA) an important component of medical imaging visualization in daily practice[3].

The purpose of this paper is to provide an overview of CCTA with a focus on the diagnostic accuracy and prognostic value in coronary artery disease. Technological developments of MSCT scanners are briefly discussed, while limitations and challenges of CCTA are highlighted.

TECHNOLOGICAL DEVELOPMENTS IN CCTA

Diagnostic performance of CCTA is closely related to technological improvements that occurred with each successive generation of MSCT scanners. The spatial and temporal resolution of MSCT scanners determine the diagnostic value of CCTA in coronary artery disease (CAD).

4-slice CT

In 1998, a 4-slice CT scanner was introduced by several manufacturers representing an obvious quantum leap in clinical performance[4,5]. Four detector "rows"corresponding to the 4 simultaneously collected slices fed data into four parallel data "channels", so that these 4-slice scanners were said to possess four data channels. These 4-slice scanners, however, were quite flexible with regard to how detector rows could be configured; groups of detector elements in the z-direction could be electronically linked to function as a single, longer detector, thus providing more flexibility in the section thickness of the four acquired slices[6,7]. Fundamental advantages of MSCT include substantially shorter acquisition times, retrospective creation of thinner or thicker sections from the same raw data, and improved three-dimensional rendering with diminished helical artifacts[4].

The main advantage is the increased volume coverage per unit time at high axial resolution and subsequent improved temporal resolution[4]. Four-slice scanners are the basic system for CCTA examination. With only 250 ms of temporal resolution from a gantry rotation of 500 ms CCTA with use of 4-slice CT requires longer longitudinal scan to cover the entire cardiac chamber and coronary arteries, thus, this may result in long breath-hold between 30 and 40 s which leads to breathing and motion artifacts, and also limits to patients with low heart rates[8].

16-slice CT

The installation of 16-slice CT scanners in 2002 provides 16 detector channels enabling simultaneously acquisition of 16 slices per gantry rotation[9]. In addition to simulta-

neously acquiring up to 16 slices, the detector arrays associated with 16-slice scanners were redesigned to allow thinner slices to be obtained as well. Note that in all of the models, the innermost 16 detector elements along the z-axis are half the size of the outermost elements, allowing simultaneous acquisition of 16 thin slices (from 0.5 mm to 0.75 mm thick, depending on the model and manufacturer). When the inner detectors were used to acquire submillimeter slices, the total acquired z-axis length and therefore the total width of the x-ray beam ranged from 8 mm for the Toshiba model to 12 mm for the Philips and Siemens scanners. Alternatively, the inner 16 elements could be linked in pairs for the acquisition of up to 16 thicker slices[10].

Sixteen-slice scanners have a slightly better spatial resolution and faster gantry rotation (420 ms) than that in 4-slice CT[11]. The major advantage of 16-slice scanners over 4-slice CT is the longer z-axis coverage (16 mm × 0.75 mm *vs* 4 mm × 1.0 mm), resulting in significantly shorter breath- hold and fewer motion artifacts[12-14]. The rotational speed of 16-slice scanners is only marginally faster, and adaptive multi-cycle reconstructions, which require a high number of detectors, cannot be applied because of heart rate variations. As a consequence of these factors, image quality with the 16-slice scanner is significantly improved, reducing the number of coronary segments with poor image quality[12-15].

CCTA became more clinically practical with 16-slice CT scanners using retrospective electrocardiogram (ECG) gating to capture cardiac motion plus the z-axis coverage[16]. However, cardiac motion and stair-step artifacts are the main challenge for this system. Therefore, there are a few steps that are suggested to overcome these problems, which include increasing the number of detector elements and the volume coverage along the z-axis of detector block. Moreover, increase in the sensitivity of detector material and application of iterative image reconstruction algorithms represents another approach to improve cardiac image quality[17,18]. During 2003 and 2004, manufacturers introduced different types of MSCT models with less than 16-slice scanners, but most commonly the introduction of more than 16-slice scanners represented the main direction for improving MSCT systems[9].

64-slice CT

The 64-slice CT was first introduced with a single x-ray source mounted opposite to a 64-detector-array in the gantry unit. With gantry rotation times down to 0.33 s for 64-slice CT (0.375 s for 16-slice CT), temporal resolution for ECG-gated cardiac imaging is again markedly improved. The increased temporal resolution of 64-slice CT has the potential to improve the clinical strength of ECG-gated cardiac examinations at higher heart rates, thereby reducing the number of patients requiring heart rate control. In contrast to previous studies, high diagnostic accuracy has been achieved despite the presence of calcified coronary plaques. In addition, using 64-slice
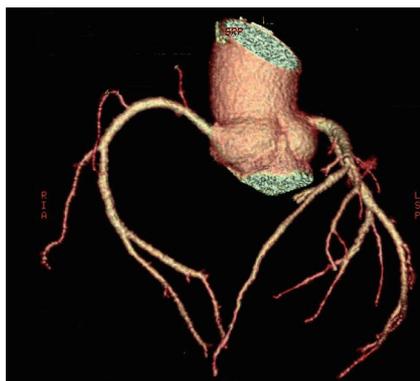
Figure 1 Three-dimensional volume rendering image acquired with 64-slice coronary computed tomography angiography demonstrates right and left coronary arteries without lumen stenosis.

CT the scanning time is reduced to less than 15 s, allowing a decreased breath-hold time, better utilization of contrast medium with fewer enhancements of adjacent structures and a lower dose of applied contrast medium. Improvement of image quality has also been reported in the visualization of all coronary artery branches with high sensitivity and specificity achieved (Figure 1).

The new-generation dual-source MSCT (Somatom Definition FLASH; Siemens Medical Solution, Forchheim, Germany) which was introduced in late 2008 is equipped with two 64-detector row units, each with an alternating focal spot. The 360° gantry rotation time is 280 ms, translating to a temporal resolution of approximately 75 ms when the scanner operates with both x-ray tubes collecting data at the same energy (Figure 2). The vendor has proposed a high-pitch prospectively ECG-triggered scanning acquisition[19,20]. In single-source 64-slice CT, the maximum pitch used in CCTA is roughly between 0.2 and 0.5 for gapless image reconstruction. The pitch can be increased up to 3.4 in dual-source Siemens Definition Flash systems. For CCTA, the typical phase window required for a diagnostic quality examination regarding motion artifact is 10% of the R-R interval. The pitch required for multiphase acquisition ranges from 0.2 to 0.5, depending on the heart rate[21].

With the high-pitch acquisition mode, only one phase is acquired, which gradually increases with the z-axis table translation. The influence on image quality for different clinical scenarios and heart rates is evaluated with the second generation dual-source CT. Achenbach *et al*[22] demonstrated the feasibility of this new scanning method using second-generation dual-source CT. However, slow and regular heart rates are the prerequisite for this acquisition protocol that is prospectively triggered by ECG signal and is anticipated to scan the entire heart in 270 ms, with a pitch of up to 3.4[22]. Another potential advantage of dual-source CT is tissue characterization with both detector systems operating at different tube voltages known as dual-energy CT (DECT). Although this has not been extensively studied to date, the two x-ray beams of different energy spectra in theory could better demonstrate
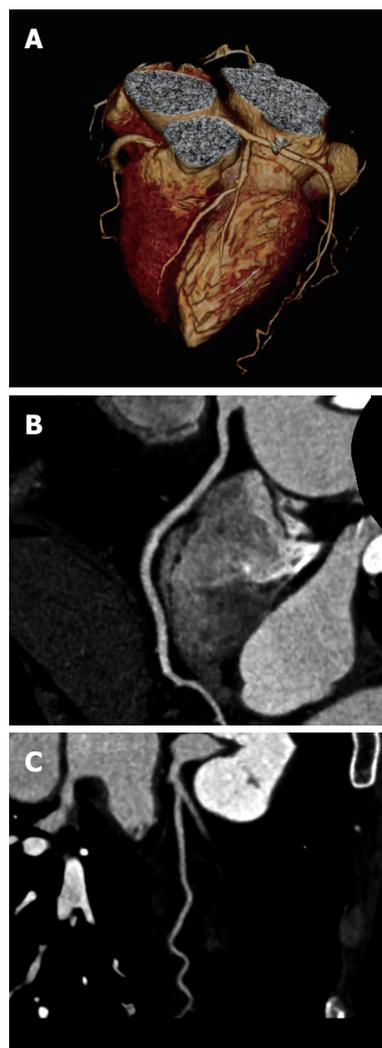
Figure 2 New-generation dual-source multislice computed tomography. A: 3D volume rendering image acquired with dual-source coronary computed tomography angiography shows excellent visualisation of normal left coronary artery and its side branches; B, C: Curved planar reformation clearly shows the anatomical structure of right and left coronary arteries.

varying attenuation characteristics of different tissues[23,24]. Studies have shown the feasibility of using DECT for myocardial perfusion imaging of CAD. Ruzsics *et al*[23] compared DECT with SPECT to evaluate the diagnostic performance of DECT for imaging coronary artery morphology and assessing myocardial blood supply. In a group of 36 patients with suspected or known CAD, over 90% diagnostic accuracy was achieved with DECT for detecting any type of myocardial perfusion defect observed on SPECT. Nagao *et al*[25] used iodine map that is available with DECT to detect alterations in coronary flow during adenosine stress and rest. This is the first non-invasive method to provide a functional assessment of coronary artery flow using cardiac CT, although further studies are needed to confirm these early results.

DECT cardiac imaging can also be achieved with a single X-ray tube. GE Healthcare's Discovery CT750 HD spectral imaging is based on fast kV switching-dynamic
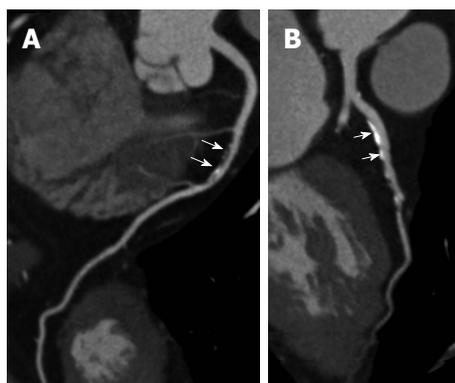
Figure 3 Electrocardiogram-triggered coronary computed tomography angiography. Prospectively ECG-triggered coronary computed tomography angiography shows a mixed plaque at the mid-segment of right coronary artery (A, arrows), and calcified plaques at the proximal segment of left anterior descending branch (B, arrows). ECG: Electrocardiogram.

switching between 2 different energy levels of X-rays from view to view during a single rotation[26]. This allows for demonstration of different material densities as scatter plots, histograms and region of interest, thus, enabling myocardial perfusion analysis of cardiac function. Despite these promising results, however, large patient cohorts are needed to confirm the potential application of a single protocol for anatomic and myocardial perfusion assessment of CAD. The diagnostic accuracy of CCTA has been reported extensively in the literature ranging from the earlier studies using retrospectively ECG-gated protocols to the recent reports comparing prospective ECG-triggering and retrospective ECG-gating. In retrospectively ECG-gated CCTA, several studies on different types and generations of MSCT scanners were carried out with overall results showing that CCTA had moderate to high sensitivity of 86%-99% and high specificity of 89%-100% in patients with suspected CAD. Image quality of coronary artery visualization was impaired and suboptimal in a number of cases with 4-slice CT as the unassessable coronary segments could be as high as more than 20%[27]. With 16-and 64-slice CT, thinner detector rows increased the spatial resolution and further shortened the total scan time, resulting in improved diagnostic value of CCTA[12,14,15]. In particular, a very high negative predictive value of over 95% (96%-99%) has been reported in these studies indicating that CCTA can be used as a reliable screening tool for CAD[28,29]. Moreover, multicenter studies were also conducted on 64-slice CT scanner to investigate the diagnostic accuracy of CCTA with different risks of CAD prevalence. The results showed that high sensitivity (94%), specificity (83%) and negative predictive value (99%) was achieved in high risk patients with CAD (68%). Similarly, high diagnostic accuracy was also presented in low risk of CAD with sensitivity, specificity and negative predictive value being 94%, 83% and 99% in 25% of CAD prevalence; 85%, 90% and 83% in 56% of CAD prevalence, respectively[30-32]. A study on the high-pitch mode with dual source CT also

resulted in high sensitivity, specificity and negative predictive value of 94%, 91% and 97% respectively[33]. Over the last few years, prospectively ECG-triggered CCTA is increasingly used in the diagnosis of CAD with promising results reported. The sensitivity (93.7%-100%), specificity (82.7%-97%) and negative predictive value (95%-98%) in the assessment of CAD were reported in multiple studies confirming the feasibility of this fast developing technique[28,29] (Figure 3).

128- and 256-slice CT

In late 2007, the 128-slice CT (Brilliance iCT; Philips Healthcare, Cleveland, OH) was introduced with a 128 mm × 0.625 mm detector row system with dual focal spot positions to double the number of slices within the 8-cm (width) z-axis gantry coverage. The iCT has a gantry rotation time of 270 ms, which translates to an approximate temporal resolution of 135 ms. Prospectively ECG-triggered CCTA typically covers the entire heart in two axial acquisitions over three heartbeats. During the diastole of the first heartbeat, the upper half of the heart is imaged. During the second heartbeat, the X-ray table translates 62.4 mm. Subsequently, the lower half of the heart is acquired during the diastole of the third heartbeat. The scanner is equipped with several radiation reduction capabilities, including a dynamic helical collimator and an adaptive axial collimator to reduce z-over scanning[34,35].

Second generation of 128-slice CT was introduced with dual-source which uses two x-ray tubes with opposing 64 detector arrays mounted 90° from each other. The main advantage of this system is that the temporal resolution is effectively halved because each x-ray tube/detector array system only needs to rotate half of the angle that would otherwise be required by a single-source system. The number of detector rows in the longitudinal axis (z-axis) and the number of slices of CT system are not interchangeable terms because multiple systems with an alternating focal spot allow the same z-axis coverage to be sampled twice, and thus the number of image slices generated is double the number of detector rows[20]. However, the volume coverage remains the same; for example, a 128-detector row scanner with two alternating z-focal spot positions can be referred to as 256-slice CT. It is important to specify the number of detector rows in z-axis, with or without alternating focal spot positions, and single versus dual source. A 128-slice dual-source CT also demonstrated high diagnostic accuracy of 93%, 94% and 97% corresponding to sensitivity, specificity and negative predictive value, respectively[33].

Most of the current studies using 128- and 256-slice CCTA focus on image quality and radiation dose reduction, while reports on the diagnostic performance are scarce[34-36]. Two recent studies have reported that 256-slice CCTA have high sensitivity (> 90% patient- and segment-based) and high diagnostic accuracy in patients with suspected CAD, with resultant very low radiation dose[37,38], althoughfurther research is needed to investigate the di-
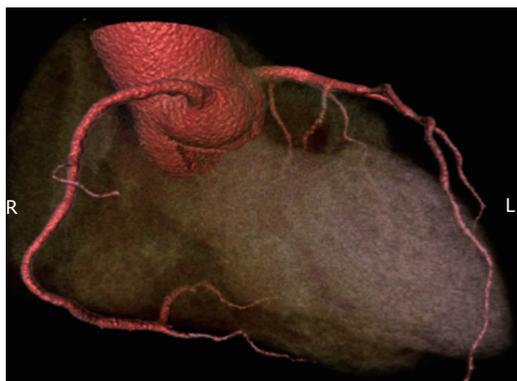
Figure 4 3D volume rendering image acquired with 320-slice coronary computed tomography angiography in a single heartbeat shows excellent visualisation of coronary arteries and side branches without artifacts.

agnostic performance of CCTA with use of these recent models based on a large cohort and multi-centre studies.

320-slice CT

This hardware (Aquilion One Dynamic Volume CT; Toshiba Medical System, Japan) currently has the largest z-axis detector coverage. It was released shortly after experiments with a 256-detector row CT prototype[39-41]. Each detector element is 0.5 mm wide, yielding a maximum of 16-cm z-axis coverage (Figure 4). This configuration allows three-dimensional volumetric entire heart imaging during the diastole of one R-R interval. In 320-detector row CT, the entire heart is imaged with temporal uniformity. Furthermore, if the x-ray beam is turned on for a longer period, the scanner can capture the heart over one or more cardiac cycles. This has been described as four-dimensional CT or volumetric cine imaging[42]. The temporal resolution of CT scanner reflects the ability to freeze cardiac motion, thus producing motion-free images. The 320-detector scanner has a standard temporal resolution of approximately 175 ms, half of the gantry rotation times. For patients with higher heart rate (> 65 bpm) and contraindications to β-blockers, multi-segment reconstruction can be used at the expense of higher radiation dose. For example, in two-segment reconstruction, data required for image reconstruction are acquired over two cardiac cycles. Therefore, only data from 90° rotation during each of the two cardiac cycles are used, improving the effective temporal resolution by a factor of 2[43].

Results using 320-slice CCTA are compared favourably to the studies using 64-slice and DSCT coronary angiography[44,45]. van Velzen *et al*[44] in their recent study reported sensitivity and specificity of 100% and 85% for 320-slice CCTA in 106 patients with acute chest pain admitted to the Emergency Department. Pellicia *et al*[45] in their prospective study consisting of 118 unselected consecutive patients with suspected CAD demonstrated the excellent results with 320-slice CT, with more than 90% of sensitivity, specificity, positive predictive value and negative predictive value achieved at the per-patient, per-

vessel and per-segment analysis. These results indicate that 320-slice CT has the potential to broaden the use of CCTA to more patients, such as patients with atrial fibrillation.

Two recently reported systematic reviews and meta-analyses further confirmed the high diagnostic accuracy of 320-slice CCTA[46,47]. These results also revealed that negative predictive value of CCTA was close to 100%, indicating the high value of 320-slice CCTA for excluding coronary artery stenosis. However, it has to be recognized that diagnostic performance of 320-slice CCTA is similar to that of 64- and 128-slice for the determination of ≥ 50% coronary artery stenosis due to its limited temporal resolution, despite improved extended z-axis coverage.

## DIAGNOSTIC VALUE OF CCTA: CURRENT STATUS AND CHALLENGES

Despite promising results having been achieved with CCTA in coronary artery disease, it suffers from some limitations which affect its diagnostic performance to some extent. Artifacts (motion-related or due to severe calcification) represent one of the common limitations, although this is less commonly seen in CCTA performed with latest post-64 slice CT. Heart rate comprises another issue which needs to be addressed in the cardiac imaging, and temporal resolution of CCTA is still inferior to that of invasive coronary angiography.

Artifacts

Imaging coronary arteries using coronary CT angiography requires high spatial and temporal resolution, good low-contrast resolution, intravascular contrast enhancement and a short scanning time. Image artifacts are always associated with the limitations of either temporal resolution, or noise or the reconstruction algorithm in the scanner system. Images artifacts are mainly demonstrated as blooming, streaks, partial volume and motion artifacts. All these artifacts can arise from technical, operator, and patient errors[48].

Stair-step artifact is the most common artifact that occurs in CCTA. Stair-step artifact occurs especially in patients with high heart rates, heart rate variability, and the presence of irregular or ectopic heart beats such as premature ventricular contractions and atrial fibrillation during image acquisition (Figure 5). It can be best recognized in a sagittal or coronal view. Therefore, beta-blockers should be used to lower the heart rate prior to the scan. Reducing this artifact is achieved by reconstructing the dataset at different phases of the cardiac cycle. In general, reconstructions for CCTA are performed in mid-diastole to late diastole (60%-70% of the R-R interval). However, because the duration of diastole decreases as the heart rate increases, an end-systolic phase reconstruction at 25%-35% of the R-R interval might be considered for image processing[48].
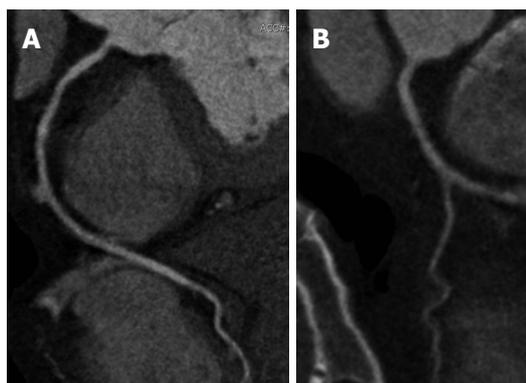
Figure 5 Prospectively electrocardiogram-triggered coronary computed tomography angiography and coronary arteries. Prospectively ECG-triggered coronary computed tomography angiography curved planar reformatted images show right (A) and left (B) coronary arteries with blurred borders due to motion artifacts. ECG: Electrocardiogram.

Heart rate

Heart rate variability is another limitation for the prospectively ECG-triggered technique. Heart rate variability of > 5 beats/minute is considered not applicable for prospective triggering. Therefore, the scan has to be reverted into retrospective ECG gating technique if patients' heart rate elevated or heart rate variability does not meet the requirement after β-blocker has been given[49]. However, precautions have to be taken in patients who are contraindicated to β-blockage agent. Alternatively, calcium channel blocker could be used in order to reduce the heart rate. The maximum of 15 mg of intravenous *metoprolol* (β-blocker) or 40 mg of intravenous diltiazem (calcium channel blocker) is recommended prior to the scan in order to control the heart rate[50,51].

However, the prospectively ECG-triggered technique in patients with higher heart rates still produces diagnostic images. CT scanner with higher detector arrays is an alternative option in patients with high or irregular heart rates. It has been reported that high diagnostic value could be achieved with 320-slice CCTA in the diagnosis of CAD, with image quality independent of heart rate[42]. The increased longitudinal coverage scan value (up to 160 mm) of 320-slice CT results in improved image quality within a wide range of heart rates; thus providing the opportunity to image patients with higher heart rates without requiring pre-examination beta-blockage[42,44,45].

Coronary CT angiography is most commonly performed in the spiral acquisition mode with continuous acquisition of data throughout the cardiac cycle. Multiple reconstruction parameters determine the quality of the reconstructed axial images. Images are usually reconstructed with a slice thickness of 0.5-0.6 mm, 50% overlap between images (0.4 mm increment), and a pixel matrix of 512 × 512. Although a thinner slice improves the resolution of the 3D dataset and the quality of reconstructed images, it comes at the cost of increased image noise, which can significantly limit the diagnostic assessment of the coronary arteries in patients with body mass index of greater than 30 kg/m^2[52].

Temporal resolution

In single-source CT, improved temporal resolution is obtained at the expense of limited spiral pitch and correspondingly increased radiation dose to the patient. For a single segment reconstruction, the table has to travel slowly in order to ensure that each z-position of the heart is visualized by a detector slice during each phase of cardiac cycle. Therefore, the patient's heart rate would determine the spiral pitch (if the heart rate goes up, the spiral pitch can be increased). Moreover, if multi-segment reconstructions are applied at higher heart rates to improve temporal resolution, the spiral pitch has to be reduced again. For example, each z-position of the heart has to be visualized by a detector slice during two consecutive heart beats in a 2-segment reconstruction; and three consecutive heart beats for a 3-segment reconstruction; and so on. In general, manufacturers of single-source CT scanners recommend an adaptive approach for ECG-gated cardiac scanning which the pitch of the ECG-gated spiral scan is kept constant at a relatively low value between 0.2 and 0.25. Therefore, more segments are used for image reconstruction at higher heart rates to improve temporal resolution[53,54].

Using a DSCT system, a temporal resolution of a quarter of the gantry rotation time is achieved, resulting in high temporal resolution of 75 ms, independent of the patient's heart rate. This shows a significant improvement in cardiac imaging. However, the temporal resolution is still inferior to that of invasive coronary angiography, which is 10 ms, therefore, aggressive approaches such as heart rate control with the use of beta-blockers are necessary in CCTA examinations.

Excellent spatial resolution of 0.4 to 0.5 mm is achieved with latest CT models, however, this is still not comparable to that of invasive coronary angiography, with spatial resolution being 0.1 and 02 mm. Although CCTA enables excellent visualization of main and side coronary arteries, identification and characterization of coronary plaques[55,56], differentiation of lipid-rich content from fibrous component with CCTA remains difficult and challenging due to overlap in the attenuation values of lipid and fibrous tissue[57].

Severe calcifications

Vessel calcification poses a serious challenge to the accurate assessment of coronary artery lumen. Calcium deposits have CT attenuation which is similar to metal density and thus overwhelm the density of other tissues in the same voxel. Beam hardening is due to the attenuation of low-energy X-ray by very dense structures such as calcium. A higher energy beam, causing a darker appearance that can be mistaken for plaque, therefore penetrates adjacent pixels. All these effects can be modified, but not eliminated, by the smaller voxel size produced by the 64-slice scanner. The efficacy of this scanner in ameliorating imaging difficulties is shown in an overall sensitivity of 95% and specificity of 90% for the detection of angiographically significant stenosis even in the
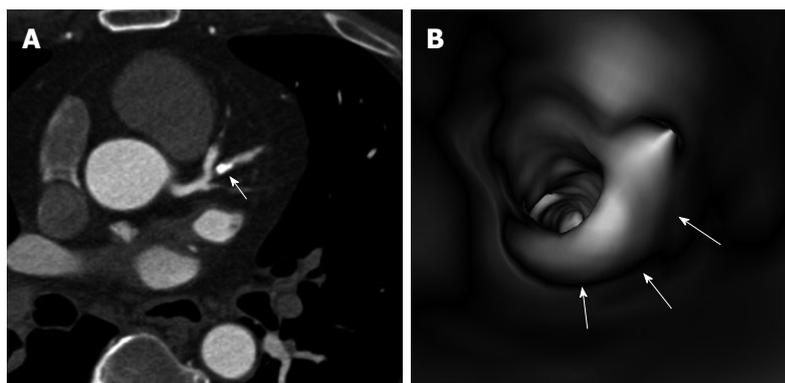
Figure 6 A severely calcified plaque is present in the left coronary artery (ramus intermedius) (A, arrow), with impression of more than 90% lumen stenosis on a 2D axial image. Corresponding 3D virtual endoscopy views shows the intraluminal protrusion sign due to presence of plaque (B, arrows), but with less than 60% lumen stenosis.

presence of high coronary calcium scores (Agatston score of > 400)[58] (Figure 6).

A study by Brodoefel *et al*[58] compared overall calcium burden and studies the effects of calcium on image quality and diagnostic accuracy. Their results showed that dual-source CCTA was affected by calcification in terms of image quality and diagnostic value. Furthermore, a total of 100 (8.1%) segments that were considered non-diagnostic because of abundant calcification suggest that calcium burden remains a fundamental problem of coronary CT angiography and is certainly not addressed by exclusive increase of temporal resolution. In fact, from the linear regression analysis[59], there is a persistent threshold for adequate image quality at an Agatston score around 400. This is supported by reports from Diederichsen *et al*[59] and Chen *et al*[60] who also concluded that the specificity of CCTA was decreased significantly in patients with high calcium score > 400. However, Stolzmann *et al*[61] stated in their study that CCTA had high diagnostic accuracy despite the presence of heavy calcifications with sensitivity and specificity being 99% and 99% in patients with median CAC score < 316, and 98% and 99% in patients with median CAC score > 316. Despite these promising results, further studies on 256- and 320-slice CT are needed to evaluate the diagnostic performance of CCTA in patients with high coronary calcium score.

PROGNOSTIC VALUE OF CCTA

CCTA allows for visualization and characterization of coronary plaques, thus, it can detect non-obstructive and non-calcified plaques as well as plaques with positive modelling, both of which play an important role in the pathophysiology of acute myocardial infarction and may be indicative of vulnerable plaques. Studies based on single centre experiences have demonstrated that CCTA provides prognostic information for predictive adverse cardiac events in patients with known or suspected CAD[62-65]. Ostrom *et al*[66] demonstrated a correlation between mortality and the number of involved vessels for both nonobstructive and obstructive coronary lesions. Min *et al*[67] reported that coronary

segments with presence of plaque, regardless of stenosis severity, had a particularly good correlation with patient survival.

Prospective large and multi-centre trials evaluating patients presenting to the emergency department with acute chest pain symptoms further confirmed the prognostic value of CCTA. In a 2-year follow-up of the ROMICAT trial, Schlett *et al*[68] evaluated the prognostic value of CCTA for major adverse cardiac events in 333 patients with a mean follow-up of 23 mo. Their results showed that in acute chest pain emergency patients, CCTA provided incremental prognostic value beyond clinical risk score in predicting major adverse cardiac events with absence of CAD leading to a 2-year cardiac events free warranty period, while coronary stenosis with regional wall motion abnormalities associated with highest risk of major cardiac events. Results from the international Coronary CT Angiography Evaluation For Clinical Outcomes: An International Multicenter Registry consisting of 20299 patients have further reaffirmed the predictive value of segmental plaque burden above and beyond the degree of stenosis[69]. A predictive score combining CCTA parameters with clinical information has been demonstrated to significantly improve prediction compared with well-established clinical risk scores.

CCTA REFERRAL

Identification of the exact role of CCTA in patients from different risk groups is clinically significant as this could lead to unnecessary examinations due to the fact that CT is an imaging modality with high radiation dose[70-72]. In addition, appropriate selection of CCTA is of paramount importance for physicians to choose CCTA as a gate-keeper for further diagnostic testing. **Performing CCTA before invasive coronary angiography is a cost-effective strategy in the management of patients without symptoms who have positive stress rest results.** Halpern *et al*[73] in their study reported that when a patient with an expected CAD prevalence of less than 85% is found to have a positive test result, CCTA is a less expensive alternative

to invasive coronary angiography. Thus, the use of CCTA in asymptomatic patients can avoid unnecessary invasive coronary angiography procedures. CCTA is considered to be of limited clinical value in the evaluation of symptomatic patients or the high pre-test probability group as the majority of these patients are likely to proceed to invasive coronary angiography, despite the negative CCTA findings[74,75]. In patients with a high pre-test likelihood for significant stenosis, functional evaluation, such as myocardial perfusion imaging, may be more relevant than CCTA to determine the need for revascularization.

SUMMARY AND CONCLUSION

There is increasing evidence to show that coronary CT angiography represents the most rapidly developed imaging modality in cardiac imaging. Coronary CT angiography has high diagnostic value in the diagnosis of coronary artery disease due to rapid advances in multislice CT scanners. Furthermore, coronary CT angiography has demonstrated incremental prognostic value beyond clinical risk factors and allows for a quantification of the risk associated with coronary plaque in coronary CT angiography. The current challenges in performing coronary CT angiography have made the imaging technique to improve by using latest CT technology which provides an attractive alternative to invasive coronary angiography in routine clinical practice. With further developments in CT technology, coronary CT angiography will continue to play an important role in the diagnostic evaluation of coronary artery disease and prediction of major adverse cardiac events.

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REVIEW

Coronary-cameral fistulas in adults: Acquired types (second of two parts)

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Abstract

Acquired coronary artery fistulas (CCFs) are infrequently detected during conventional coronary angiography. To delineate the characteristics of congenital (first part) and acquired (second part) CCFs in adults, a PubMed search was conducted for papers dealing with congenital or acquired CCFs. None of the publications describing patients with coronary-vascular fistulas were included. Papers dealing with pediatric subjects were excluded. From the world literature, a total of 243 adult patients were selected who had congenital (n = 159/243, 65%) and acquired (n = 84/243, 35%) CCFs. Among the acquired types (n = 72, 85.7%) were traumatic (iatrogenic (n = 65/72, 90%), accidental (n = 7/72, 10%) and (n = 12, 14.3%) spontaneously developing in relation to severe coronary atherosclerosis or myocardial infarction. A high incidence of spontaneous resolution of iatrogenic CCFs resulting from endomyocardial biopsy or following post-septal myectomy was reported. Spontaneous CCFs associated with myocardial ischemia or infarction resolved completely in 8% of the subjects. Early surgical intervention was the treatment of choice in acquired traumatic accidental CCFs. The congenital types are addressed in a previous issue of this journal (first part). In this review (second of two parts, part Ⅱ), we describe the acquired coronary-cameral fistulas.

Core tip: The literature addressing acquired coronary artery fistulas (CCFs) is reviewed. A detailed classification of acquired CCFs is attempted. Acquired coronary artery fistulas are subdivided into spontaneous and traumatic types. The traumatic fistulas encounter iatrogenic and accidental subtypes. The iatrogenic fistulas are secondary to non-surgical interventions (endomyocardial biopsy, permanent pacing and implantable cardioverter-defibrillator leads, radiofrequency cardioablation, baro-trauma and transseptal puncture) and cardiac surgical procedures (septal myectomy and other cardiac surgical procedures). Diagnosis of acquired CCFs is suspected by clinical history and recurrence of symptoms, occurrence of a new continuous machinery cardiac murmur and a palpable thrill. Watchful waiting and supportive medical management may be advocated in the majority of acquired CCFs. Acquired traumatic accidental CCFs are indications for emergent surgical procedures. Within this entity of CCFs, each subtype has its own specific characteristics such as age of the subjects, origin, termination of fistulas or mechanism

of injury and its specific treatment modality.

INTRODUCTION

Congenital coronary-cameral fistulas (CCFs) include solitary and coronary-ventricular multiple micro-fistulas. Congenital CCFs have been described in the first part of this review[1]. Acquired CCFs are rare disorders. In this part (second of two parts), we present the acquired traumatic iatrogenic, acquired traumatic accidental and spontaneously occurring CCFs[2-4]. The acquired types are defined as single or multiple, direct communications arising from one or more coronary arteries entering into one of the four cardiac chambers (right atrium (RA) and ventricle (RV) and left atrium (LA) and ventricle (LV)) elucidating arterio-venous or arterio-arterial connection, giving rise to left-right or left-left shunt, respectively. Acquired traumatic accidental CCFs as a result of penetrating chest injuries have been reported since 1935[5]. Acquired traumatic accidental fistulas usually occur when the continuity or the vicinity of a coronary artery is lacerated subsequent to severe blunt or sharp chest trauma.

Acquired traumatic accidental fistulas may develop secondary to exogenous injuries such as deceleration traumas[6] or sharp chest injuries[7] in civilian practice due to violence and physical assault[8-10] and warfare[11] situations during military combat[12]. On the other hand, acquired traumatic iatrogenic fistulas may occur following endogenous (intravascular or extra-vascular) diagnostic[13,14] or therapeutic interventions[15-17].

Furthermore, iatrogenic fistulas may be acquired secondary to surgical[3,18] or non-surgical interventions[19,20]. Rarely, CCFs may occur spontaneously in association with severe obstructive atherosclerotic lesions or myocardial infarction[21,4]. Diagnosis of acquired CCFs is suspected by clinical history and recurrence of symptoms, occurrence of a new continuous machinery cardiac murmur and a palpable thrill[8].

The entity of CCFs characterized by various manifestations and etiologies, congenital (first part) and acquired (second part), are discussed and the international literature is briefly reviewed. The acquired traumatic iatrogenic, acquired traumatic accidental and spontaneously developing types are presented.

LITERATURE RESEARCH

PubMed and Google Scholar were searched for the terms "coronary-cameral fistulas (CCFs)", "congenital" and "acquired" combined with "adult". The English and non-English medical literature were screened for both types of congenital (first of two parts, part 1) and acquired (second of two parts, part 2) CCFs in an adult population. The related articles shown on the side page were explored and references were checked for relevant papers, as illustrated in the flow diagram (Figure 1). The definition used for acquired traumatic iatrogenic acquired and traumatic accidental CCFs was adopted from a previous publication[22]. The following criteria were stipulated to include homogenous subsets for analysis: acquired traumatic accidental, acquired traumatic iatrogenic and spontaneous CCFs. Manuscripts were checked for completeness and a meticulous search was performed for recognition of fistula termination into any of the four cardiac chambers. Patients were tabulated according to the etiology, age, gender, clinical presentations, complications and management (Table 1 and Figure 2). Publications dealing with adult patients with congenital or acquired coronary-vascular fistulas were not included. Publications considering a pediatric population were excluded.

Definitions

Acquired traumatic (accidental or iatrogenic) coronary-cameral fistulas are secondary to exogenous or endogenous thoracic trauma, accidental (penetrating or non-penetrating) or iatrogenic (intravascular or extravascular, surgical or non-surgical diagnostic or therapeutic procedures). Furthermore, a direct communication occurs between one or more epicardial coronary arteries and a cardiac chamber, bypassing the myocardial capillary network, which was not present on a prior coronary angiographic study (when available) and not congenital in origin[22].

Iatrogenic coronary-cameral fistulas (surgical and non-surgical procedures) (Figure 3A) develop subsequent to surgical septal myectomy[3] or other cardiac surgical procedures (bypass grafting, valvular repair and surgery for congenital anomalies)[2,23,24]. The varieties of non-surgical interventions are caused by repeated endomyocardial biopsy[15,13], permanent pacing and ICD implantation[16,20] or electrophysiological procedures[17,25] and following barotrauma[19,26] or subsequent to vessel rupture after coronary stent placement[27].

Accidental coronary-cameral fistulas (penetrating and non-penetrating injuries) (Figure 3B) may occur due to sharp chest wounds such as shrapnel[11], stab wound[7] or gunshot[8], and blunt thoracic injury due to deceleration trauma (car and motorcycle accidents)[6,28].

Spontaneous CCFs are coronary-cameral fistulas, spontaneously emerging, associated with severe atherosclerotic lesions[29] or develop following myocardial infarction[4,21], resulting in direct communication between the culprit coronary artery and an adjacent cardiac chamber.

Descriptive analyses

Descriptive analyses were expressed as means and ranges and categorical data were presented as percentages.

RESEARCH

From the world literature, 243 adult patients were selected
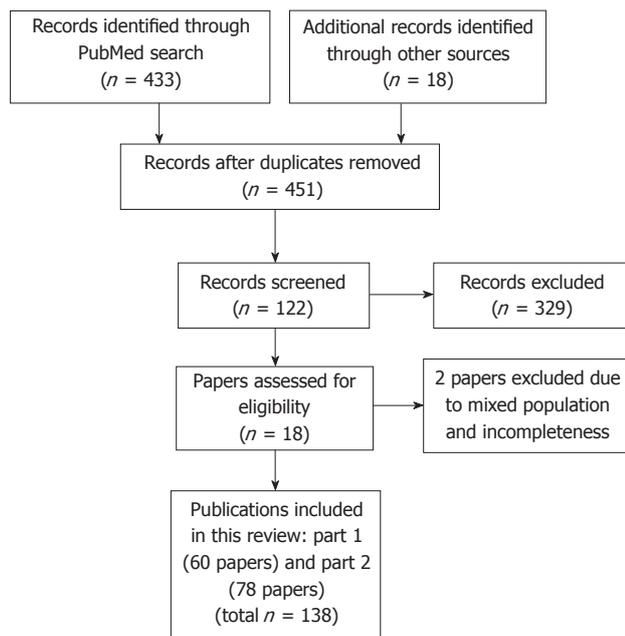
Figure 1 Flow diagram of literature search of coronary cameral fistulas in adult population.

with congenital (n = 159/243, 65%) or acquired (n = 84/243, 35%) CCFs. Among the reviewed subjects with acquired fistulas, (n = 65/84, 77.4%) were traumatic iatrogenic of origin, (n = 7/84, 8.3%) were traumatic accidental and (n = 12/84, 14.3%) presented with spontaneous occurrence of fistulas developing post-MI.

This review focuses on the different aspects with regard to etiology, clinical presentation and management of congenital (first part)[1] or acquired (second part) coronary-cameral fistulas (Table 1).

Summary of literature review (Figure 1): Acquired coronary artery fistulas are subdivided into spontaneous (n = 12/84, 14.3%) and traumatic (n = 72/84, 85.7%). The traumatic fistulas encounter iatrogenic (n = 65/72, 90%) and accidental (n = 7/72, 10%) subtypes. The iatrogenic fistulas are secondary to non-surgical interventions (endomyocardial biopsy, permanent pacing and implantable cardioverter-defibrillator (ICD) leads and radiofrequency cardio-ablation) and cardiac surgical procedures (septal myectomy and other cardiac surgical procedures).

Traumatic fistulas: (n = 72/84, 85.7%), acquired traumatic iatrogenic (n = 65/72, 90%), non-surgical interventions: (n = 40/65, 61%).

Acquired traumatic iatrogenic: Electrophysiological procedures (permanent pacing and ICD leads, transseptal puncture and percutaneous cardio-ablation procedures): These CCFs involve complications of permanent pacing and implantable cardioverter-defibrillator leads, transseptal puncture and electro-physiological procedures (n = 8/65, 12%)[14,16,17,20,23,25,30]. The data of 8 patients (5 male and 3 female) were analyzed. The mean age was 55.8 years (range 46-73). The termination sites were RA[14], LA[23], RV[16,20] and LV[17]. Regardless of their termination site, conservative medical management was sufficient to relieve symptoms in these acquired fistulas and spontaneous res-

olution occurring following RF cardio-ablation after 9-10 mo was observed[17,23].

Acquired traumatic iatrogenic (baro-trauma): These CCFs occur subsequent to non-surgical therapeutic interventions *e.g.*, baro-trauma. Subsequent to percutaneous coronary intervention (PCI) procedures, fistulous communications between the native left coronary artery and RV[19] or LV[26] were reported in 7 (n = 7/65, 11%) patients (5 males and 2 females) with a mean age of 66.6 (range 58-75). Moreover, these complications were described after PTCA of a distal anastomosis of a totally occluded venous graft[31]. The donor artery was the left anterior descending coronary artery (LAD) in most of the cases. As the shunt magnitude was trivial without hemodynamic consequences and spontaneous closure was observed, conservative medical management (CMM) was commonly employed.

Post-endomyocardial biopsy (EMB) following heart transplantation (n = 25/65, 38%): The iatrogenic fistulas occurred after repeated EMB[32] or interrelated[33] with the applied surgical procedure. The mean age was 50.8 years (range 43-64) with 22% female subjects.

Surgical procedures: 25/65 = 38%
Acquired traumatic iatrogenic after bypass surgery, valvular repair and surgical procedures for congenital heart anomalies: These CCFs occur subsequent to surgical procedures[2,18,34-36]. Five adult patients were selected (n = 5/65, 8%) with a mean age of 61 years (range 40-78). CCFs occurring after heart surgery were reported post-aortic valve[36] and mitral valve[35] replacement.

Acquired CCFs have been observed after surgical septal myectomy **(**SM**)** for hypertrophic cardiomyopathy (HCMP)(n = 20/65, 31%)[3,18,37-40]. Twenty patients were selected with a mean age of 45 years (range 32-74). Acquired CCFs following surgical intervention may occur after SM alone[39] or after combined aortic valve replacement and SM for hypertrophic cardiomyopathy[18]. The drainage site was always the LV. The majority were asymptomatic and disappeared spontaneously (78%). The management is usually a conservative medical strategy and percutaneous therapeutic embolization (PTE) was rarely needed to close the acquired fistula in a symptomatic patient[3].

Acquired traumatic accidental CCFs (n = 7/72, 10%)[6-8,28,41-43]: The mean age of the 7 reviewed male subjects was 24.1 years (range 17-38). CCFs occurred following penetrating (n = 3) or non-penetrating chest injuries (n = 4). They presented with chest pain, angina pectoris, palpitation, dyspnea, congestive heart failure and hemoptysis. The origin was the LAD (n = 4) and the right coronary artery (RCA) (n = 3). The CCFs terminated into the RA (n = 1), RV (n = 4) and LV (n = 2). All 7 reviewed patients were treated surgically. The surgical procedures included ligation and coronary artery bypass grafting, valvular repair and closure of ventricular septal defects. In three patients, reoperation was necessary for a complete repair.

Spontaneous fistulas
Spontaneously occurring: These are CCFs associated with
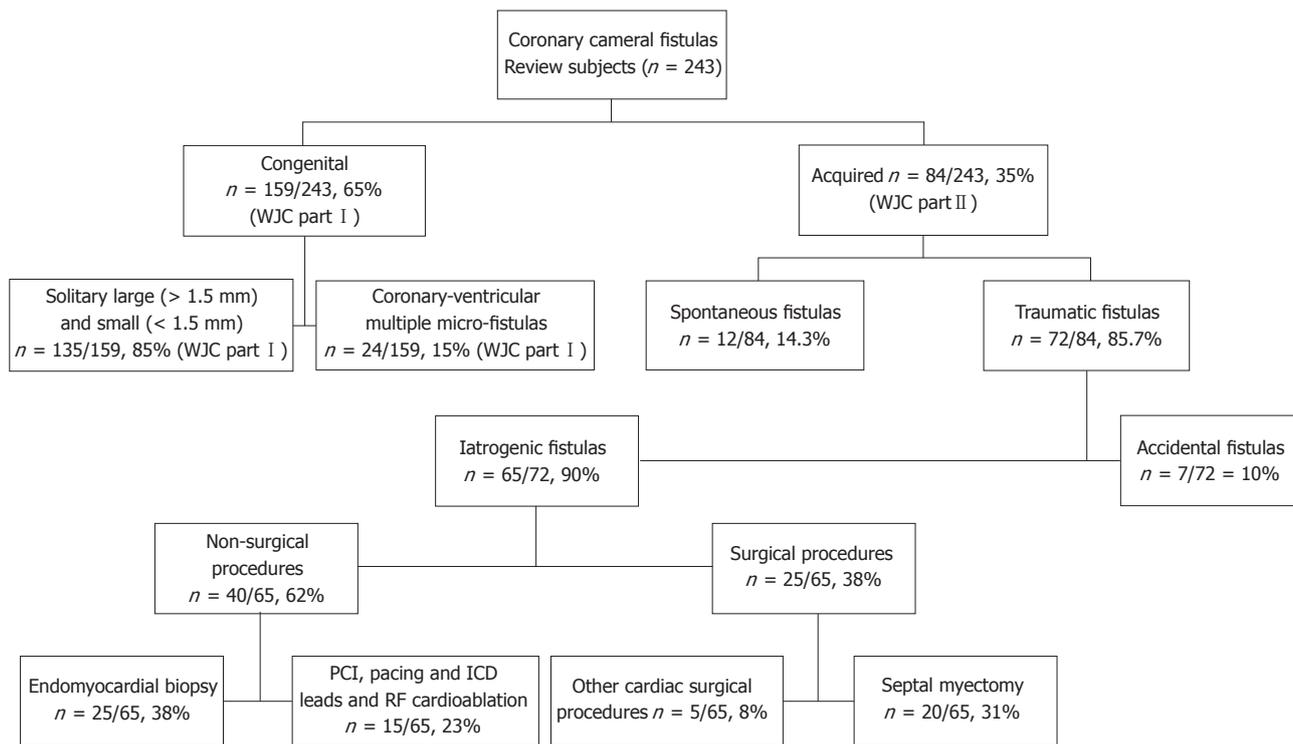
Figure 2 Schematic representation of review subjects with congenital and acquired coronary-cameral fistulas. ICD: Implantable cardioverter-defibrillator; PCI: Percutaneous coronary intervention; RF: Radiofrequency.
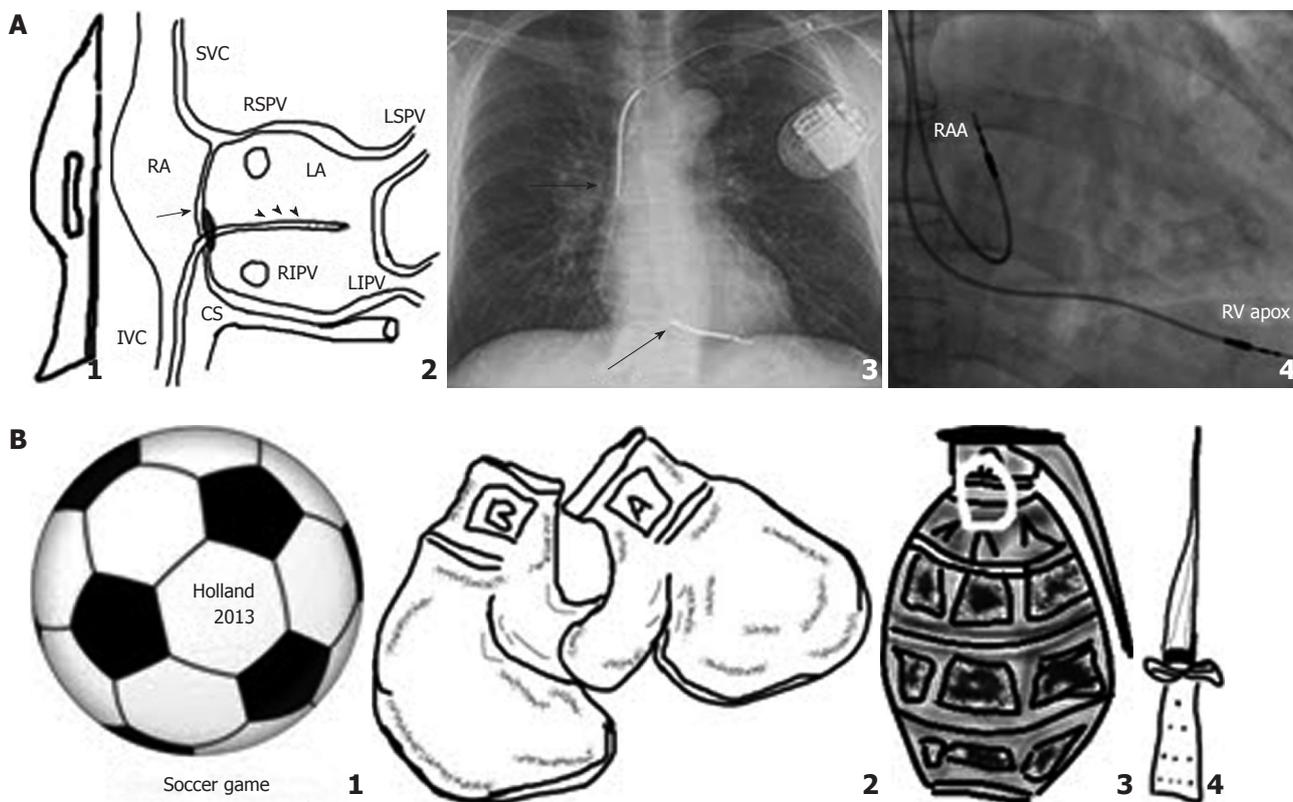
Figure 3 Schematic examples of some of the conditions, procedures and attributes involved in the development of (A) acquired traumatic iatrogenic and (B) acquired traumatic accidental coronary-cameral fistulas. A: 1: Surgical scalpel; 2: Radiofrequency cardio-ablation (arrow heads), and transseptal puncture (arrow); 3: ICD lead (arrows); and 4: Pacing leads; B: 1 Soccer game; 2 Boxing; 3: Shrapnel; and 4: Knife. CS: Coronary sinus; ICD: Internal cardioverter defibrillator; IVC: Inferior vena cava; LA: Left atrium; LIPV: Left inferior pulmonary vein; LSPV: Left superior pulmonary vein; RA: Right atrium; RAA: Right atrial appendage; RIPV: Right inferior pulmonary vein; RSPV: Right superior pulmonary vein; RV: Right ventricular; SVC: Superior vena cava.

Table 1 Fistula characteristics in congenital and acquired coronary cameral fistulas of 243 reviewed subjects

	Congenital CCFs n =159 (65%)		Acquired n = 84 (35%)					Spontaneous n = 12 (14.3%)
	Solitary CCFs and coronary artery-ventricular multiple micro-fistulas[1]		Traumatic CCFs n =72 (85.7%)					
			Iatrogenic CCFs n =65/72 (90%)				Accidental CCFs n =7/72 (10%)	
Sub-classification	Solitary 85%	MMFs 15%	Post-SM	After other cardiac surgery	Post-EMB	EP and PCI	Blunt or sharp chest trauma	post-MI or associated with severe coronary artery disease
Aetiology	Congenital 65%							
Female percentage	50%	63%	Unknown	20%	22%	33%	0%	0%
Mean age	46.2 (18-85)	62.7 (39-85)	45 (32-74)	61 (40-78)	50.8 (43-64)	60.8 (46-75)	24.1 (17-38)	61 (29-75)
Prevalence/incidence	135/159 (85%)	24/159 (15%)	20/65 (31%)	5/65 (8%)	25/65 (38%)	15/65 (23%)	10%	14.30%
Management	CMM 22%, SL 56%, PTE 22%	CMM 100%, incidentally ICD	CMM 11%, PTE 11% WW 40%,	CMM 40%, PTE 20%	CMM 73%	CMM	Surgical repair 100%	CMM 17%, SL 58%
Fistula characteristics								
Origin	Proximal segment	Mid- or distal segment	Septal perforators	LCA or RCA	RCA > LAD > Cx	LCA	RCA or LAD	RCA or LAD
Termination	Any cardiac chambers	LV > RV	LV	Any cardiac chambers	RV	Any cardiac chambers	RV or LV	RV or LV
Spontaneous resolution	Occasionally	Not reported	High rate	Not reported	High rate	Occasionally	Not reported	8%

CCFs: Coronary cameral fistulas; CMM: Conservative medical management; EMB: Endomyocardial biopsy; EP: Electrophysiological procedures; ICD: Implantable cardioverter-defibrillator; LA: Left atrium; LAD: Left anterior descending artery; LCA: Left coronary artery; LV: Left ventricle; MI: Myocardial infarction; MMFs: Coronary artery-ventricular multiple micro-fistulas; PCI: Percutaneous coronary intervention; PTE: Percutaneous therapeutic embolization; RA: Right atrium; RCA: Right coronary artery; RV: Right ventricle; SL: Surgical ligation; SM: Septal myectomy; WW: Watchful waiting follow-up.

severe atherosclerotic stenotic lesions or myocardial infarction ($n = 12/84$, 14.3%)[4,21,44-51]. Twelve male subjects with a mean age of 61 years (range 29-75) were selected. The RCA[21] ($n =4$) and LCA[44] ($n =8$) participated in the formation of the acquired CCFs. Acquired CCFs (LAD-LV fistula) were noticed following anterior MI[46] and complicating neovascularization of mural thrombus formation[51]. The right[47] ($n = 5$) lumen, right atrium ($n = 1$) and left atrium ($n = 3$) may be the site of cameral termination. Among these patients, spontaneous resolution occurred in ($n = 1/12$, 8%)[47], surgical ligation of the fistula was conducted in ($n = 7/12$, 58%) and CMM was implemented in ($n = 2/12$, 17%). Death was reported in one case[45] and the management was not reported in another[44].

COMMENTS

CCFs encompass a group of infrequently detected solitary or multiple *micro* or *macro* coronary cameral communications, either congenital[1] or acquired traumatic subsequent to accidental injuries[43], and iatrogenic secondary to surgical[3] or non-surgical interventions[15,16] that are increasingly recognized due to material sophistication and wide spread application of non-invasive and invasive angiographic imaging modalities[2,16,52]. CCFs may be subdivided into congenital and acquired types, the former making up the vast majority.

As was found in the current review, 35% of the subjects presented with an acquired type. In 1997, on reviewing the world literature 36% of the fistulas were found to have an acquired etiology[22].

Within this entity of CCFs, each subtype has its own specific characteristics, such as age of the subjects, origin, termination of fistulas or mechanism of injury and its specific treatment modality.

The precise incidence of acquired traumatic accidental CCFs is unknown due to a lack of data and literature has been essentially limited to case reports and small series of patients[43]. Acquired traumatic iatrogenic CCFs may occur due to trans-venous[16,20] or trans-arterial[19,26] endovascular diagnostic (endomyocardial biopsy) or therapeutic procedures (percutaneous coronary intervention and pacemaker implantation)[20,53]. In the current era, it is believed that technical developments, material sophistications, procedural refinements and the enhanced gain in experience have resulted in a great reduction or abolishing of acquired traumatic iatrogenic CCFs post percutaneous coronary intervention (PCI) and spontaneously developing post-MI[53,54].

Acquired iatrogenic CCFs may occur after heterogeneous causes of endogenous or exogenous traumas such as sharp[7,12] and blunt chest injury. Endogenous surgical or non-surgical trauma, such as baro-trauma after PCI[19,26,31,55], and following permanent endocardial ventricular pacing lead placement[20] may cause CCFs. Acquired accidental CCFs develop after non-penetrating[42] or penetrating thoracic injuries[7,56]. They may also occur after surgical septal myectomy[3] and radio-frequency cardio-ablation[17]. They are sometimes characterized by the appearance of a novel continuous cardiac murmur or by recurrence of symptoms[6,9,34].

Traumatic fistulas

Acquired traumatic iatrogenic CCFs (non-surgical): secondary to electrophysiological procedures (permanent pacing and implantable cardioverter-defibrillator (ICD) leads, transseptal puncture and radiofrequency cardio-ablation).

Etiology and incidence: They formed 12% of the traumatic fistulas. These are very rare complications of permanent pacing and ICD leads, transseptal puncture and electrophysiological procedures that have been observed. Only a few cases have been reported in the literature. Recently, Tamura *et al*[14] reported the occurrence of acquired iatrogenic CCFs between the Cx and the RA following transseptal puncture. Surgical[23,30] and non-surgical[17,25] electro-physiological interventions (*e.g.*, radiofrequency cardio-ablation) may lead to acquired CCFs. The potential risk of coronary vessel lesions during the cardio-ablation is associated with the close relationship between the RCA and Cx to the site of ablation on the atrioventricular annulus. After percutaneous radiofrequency ablation, in the majority of reviewed subjects, the origin of CCFs was the Cx[23,30,57].

Mechanism: Acquired traumatic iatrogenic CCFs develop secondary to mechanical and thermal injuries. The application of radiofrequency cardio-ablation may be complicated with the occurrence of a communication between an adjacent coronary artery and a cardiac chamber which is thought to result from thermal and mechanical injury[23,14,25]. Most of the reported acquired CCFs have

their exit to the RV, but outflow to the LA[30] and LV[17] have also been described.

Management and prognosis: Pharmacological or supportive therapy is sufficient to relieve symptoms in these acquired fistulas, and spontaneous resolution occurring after 9-10 mo has been reported[23,17]. In the current review, regardless of their termination site, they were all treated medically except two in whom spontaneous resolution occurred. Conservative management was advised for acquired CCFs entering the RV complicating endocardial active fixation of an ICD lead[16] and of permanent ventricular pacing leads[20].

Acquired traumatic iatrogenic CCFs secondary to baro-trauma

Etiology and incidence: They formed 11% of the iatrogenic fistulas. These coronary-cameral fistulas occur subsequent to baro-trauma (non-surgical therapeutic procedures). These complications have infrequently been reported in Asian[31] and Caucasian patients[26]. Subsequent to PTCA procedures, fistulous communications between the native left coronary artery and RV[19] or LV[26] have been reported. Moreover, these complications have been described after PTCA of a distal anastomosis of a totally occluded venous graft[31]. The donor artery was the LAD in most of the cases.

Mechanism: Several mechanisms are responsible, alone or together. It is thought to be based on mechanical injury to the vessel wall in the vicinity of a cardiac chamber, resulting in a direct communication. Moreover, they may occur due to subsequent rupture of a false aneurysm following PTCA, besides inappropriate wire tracking, artery-balloon size mismatch and involvement of calcified lesions with vessel wall cracking and curved segment[19,26,27,31,55].

Earlier reports documented acquired traumatic iatrogenic CCFs caused by baro-trauma that were associated with a high mortality rate (29%, 2 of the 7 reported cases in literature) which were published in the eighties and nineties. In 1996, Karim[55] reported the first case of an acquired iatrogenic fistula between RCA and RA, complicating stent placement in a tight lesion, after which it was rarely reported following vessel rupture after coronary stenting[27] or subsequent to coronary artery pseudo-aneurysm late post-stenting[53]. Not only acquired CCFs could occur between a coronary artery and a cardiac chamber following PCI procedure, but also it may develop after PCI to saphenous vein graft which was treated by a covered stent[58].

Management and prognosis: As the shunt magnitude was trivial without hemodynamic consequences and spontaneous closure was observed, CMM was commonly employed. Complete and spontaneous resolution of an acquired fistula complicating PCI occurring between a branch of the RCA and RV has been documented[59]. In the current era, such complications following PCI proce-

dures are rarely reported[53,54].

Acquired iatrogenic CCFs following endomyocardial biopsy in the heart transplant population

Etiology and incidence: They formed 38% of the iatrogenic fistulas. The reported angiographic prevalence varies from 2.8% to 23.2%[13,15,60-63]. Two decades ago, Sauer *et al*[64] reported an incidence of 80%. The majority of these CCFs have their origin from the RCA (52%), followed by the LAD (43%) and finally by the Cx (5%)[15]. They nearly all terminate into the RV[13,32,60,62,65]. Rarely, repeated endomyocardial biopsy induced a fistula from an atrial branch of the Cx to the LA[61].

Mechanism: They occur subsequent to arterial trauma with neovascularization during the phase of granulation and tissue organization at the biopsy site following frequent and repeated RV endomyocardial biopsies and in relation to the applied surgical techniques of cardiac implantation[13,15,61].

Management and prognosis: Spontaneous disappearance is a more common occurrence in biopsy-related CCFs. Spontaneous closure is reported to occur in post-biopsy CCFs in heart transplant patients with an estimated rate of 27%[15]. The majority demonstrate a benign evolution and non-surgical management is usually the treatment of choice due to lack of severe symptoms and small shunt magnitude[13,15,52]. However, in some symptomatic patients, closure of the fistula may be obtained surgically[32] or achieved by placement of a covered stent[65] or a detachable balloon[66] using percutaneous catheter techniques[65,66].

Surgical procedures

Acquired traumatic iatrogenic CCFs following surgical septal myectomy

Etiology and prevalence: They formed 31% of the iatrogenic fistulas. After surgical septal myectomy for hypertrophic cardiomyopathy, CCFs have been reported[3,18,37-40]. Asymptomatic acquired CCFs draining into the LV following surgical intervention may occur after SM alone[39] or after combined aortic valve replacement with SM for HCMP[18]. The prevalence of acquired post-SM CCFs varies from 19% to 23%[3,37].

Mechanism: The proposed mechanism of fistula formation after surgical SM for treatment of hypertrophic cardiomyopathy: It is postulated that they originate secondary to injury of one or more septal perforator branches of the left anterior descending coronary artery, resulting in a direct communication between the lacerated vessel and the left ventricular cavity[3,37-39].

Management and prognosis: Surgical or percutaneous interventions were rarely needed to close the acquired fistula in a symptomatic patient since spontaneous clo-

sure is reported to be very high, accounting for 78%[3]. With the introduction of alcohol septal ablation in 1994, acquired CCFs are currently not seen after percutaneous procedures for treatment of HCMP with an outflow gradient[67-69].

After other cardiac surgical procedures (coronary artery bypass grafting, valvular repair and surgery for congenital heart anomalies)

Etiology and incidence: These CCFs occur after aortic or mitral valvular replacement[34,35] or surgical procedures for congenital cardiac anomalies. Chiu *et al*[2] reported an incidence of 0.44% following surgery for tetralogy of Fallot, ventricular septal defect (VSD), double chamber RV and transposition of the great arteries with VSD. In the current review, the acquired traumatic iatrogenic fistulas (*n* = 5/65, 8%) developed subsequent to other cardiac surgical procedures.

Clinical presentation: The majority was asymptomatic but recurrence of congestive heart failure was reported. Audible continuous murmur or continuous Doppler flow on echocardiography was prevalent.

Mechanism: The postulated mechanisms were subsequent to right atrial artery injured at the site of access for cardiopulmonary bypass, damage to the precapillary arteriole of the circle of Vieussens[2], injury to the RCA at reoperation[35] or possibly secondary to hypoxia-induced angiogenesis[36]. Chiu *et al*[2] identified risk factors for acquired CCFs as re-do procedures and RV myocardial resection of hypertrophic muscle bundles in ventricular septal defect.

Management and prognosis: Watchful waiting follow-up and CMM were the strategies in all except a case described in 2004, by Mestre Barceló *et al*[34] who performed percutaneous occlusion using coated stent of an acquired iatrogenic CCF between LAD and RV.

Acquired traumatic accidental CCFs

Etiology and incidence: They formed 10% of the acquired traumatic fistulas. They occur secondary to penetrating and non-penetrating thoracic injuries and are infrequently reported[43,10]. The mean age was 24.1 years, which was found to be lower than the patients presented with congenital solitary CCFs (46.2) or congenital coronary artery left ventricular multiple micro-fistulas (62.7)[1].

Clinical presentation: Three presented with sharp and four with blunt chest traumas. Dyspnea, angina pectoris, chest pain, palpitation, congestive heart failure and hemoptysis were reported. Machinery cardiac murmur was audible in four, diastolic in one and holosystolic murmur in two of the patients.

Mechanism: Myocardial contusion, laceration and tissue damage in blunt chest trauma and secondary to transfer

of kinetic energy in case of gunshot wounds associated with penetrating and non-penetrating injuries were the suggested mechanisms.

Management and prognosis: The management of acquired accidental CCFs, whether subsequent to penetrating or non-penetrating injury, is always an emergent surgical intervention. In 1965, Jones and Jahnke described the first surgical repair of a traumatic CCFs[10].

As early as 1975, a few papers were published regarding CCFs, with twelve traumatic CCFs reported in the world's literature; the penetrating injuries were prevalent[70]. In 2000, Hancock Friesen *et al*[43] reviewed 28 patients, published between 1958-1998, with acquired accidental CCFs and added one of their own. All were surgically repaired. Origin from the RCA was twice as common as origin from the LAD. Five of them had blunt chest trauma and 24 were presented with sharp thoracic injury. Termination into right-sided atrial or ventricular cardiac chambers was prevalent. The first reported successful repair of a traumatic CCF was in 1965 by Jones *et al*[10]. Blunt trauma to the anterior chest wall may cause laceration of the RCA[42] or LAD[6,28], associated with or without myocardial contusion. Regardless of their origin, they usually communicate with the RV or RA due to traumas directed to the anterior chest wall[6,28,42,43] but they sometimes communicate with the LV cavity[41]. These CCFs usually manifest itself by the presentation of a new continuous cardiac murmur[71]. Early intervention was recommended, applying surgical ligation with[72] or without a coronary artery bypass graft (CABG) and direct repair from within a recipient chamber[8,43]. In the review of Haas *et al*[9], surgical repair was performed in all 19 patients with acquired traumatic accidental CCFs resulting from penetrating and non-penetrating chest injuries. Of these, 5 required reoperation due to recurrence of murmur after an interval varying from 24 h to 7 mo[8]. In our current literature review, the origin was equally distributed between the LAD and the RCA. All seven reviewed patients were treated surgically. Reoperation for complete repair was needed in three subjects. No spontaneous closure was observed among the reviewed subjects with acquired traumatic accidental CCFs.

Spontaneous CCFs
Spontaneously acquired CCFs as a result of severe stenotic lesions or myocardial infarction have been reported[4,21,29].

Etiology and incidence: They formed 14.3% (12/84) of the acquired fistulas. In the last century, reports have rarely been published incriminating myocardial ischemia or infarction for the occurrence of spontaneous CCFs[4,21]. Currently, such complications are rarely published. Two reports were cited in the literature of acquired CCFs secondary to anterior MI with a fistula entering into the RV[44] or LV[45]. Acquired CCFs were reported after anterior[44,45,48], inferior[4,21] or posterior MI[47,50]. They may also be associated with inferior[49] or anterior myocardial ischemia[73].

Mechanism: It has been postulated that an aberrant

pathway of newly developed collaterals, neo-vascularization of left ventricular mural thrombus formation post-MI, ruptures of localized micro-necrosis subsequent to destruction of the microvasculature or by reopening of the Thebesian vessels probably may lead to the fistula formation into the lumen of a cardiac chamber[4,45,47-50]. Furthermore, it has been suggested that as collaterals lose their way, acquired fistulas may develop following MI or in association with severe atherosclerotic obstructive lesions[74]. In contrast to congenital CCFs between the LAD and LV which may cause angina pectoris secondary to myocardial ischemia documented with myocardial perfusion test[75], acquired CCFs may develop and emerge secondary to MI or severe atherosclerotic lesions. The precise mechanisms by which congenital or acquired CCFs could enhance atherosclerosis are not yet known.

Management and prognosis: In the current review, the majority of patients (58%) were treated surgically. Angiographically documented spontaneous closure was seen in 8% and CMM was the treatment modality in 17% of subjects. One death (8%) secondary to intractable congestive heart failure occurred in a 63 year old Asian patient who developed CCF between LCA and LV following anterior MI.

Patients considered for the potential diagnosis of acquired CCFs: Although acquired CCFs are incidentally detected on routine CAG, the diagnosis should be expected, with a high index of suspicion, in subjects who develop new symptoms or show recurrence of symptoms or develop a novel cardiac murmur. Treatment is reserved for symptomatic patients with a hemodynamically significant shunt. Management of asymptomatic patients is controversial. In contrast to congenital CCFs, high spontaneous disappearance of the acquired CCFs has been reported. Watchful waiting and supportive medical management may be advocated in the majority of acquired CCFs. With amenable fistulous morphological anatomy, percutaneous therapeutic embolization or surgical closure may be applied. Acquired traumatic accidental CCFs are indications for emergent surgical procedures. Furthermore, indications for surgery, as suggested by Konno *et al*[76] and others for congenital types, are: large L-R shunt > 30%, ischemia or volume overload, pulmonary hypertension or congestive heart failure, the presence of an aneurysm, and infective endocarditis[77,78].

CONCLUSION

Acquired CCFs are infrequent coronary artery anomalies which are often asymptomatic and found incidentally on routine coronary catheter angiography. The majority of acquired CCFs are secondary to iatrogenic trauma resulting from various interventional surgical or non-surgical endovascular or extravascular procedures. Acquired traumatic accidental CCFs are associated with a younger age (between second and fourth decade of life) compared with congenital fistulas[1] or acquired iatrogenic

CCFs (fifth decade of life). They usually originate from the RCA or LAD and all end in the RV. Early surgical intervention is always indicated in these subjects. The termination site of acquired iatrogenic CCFs resulting from endomyocardial biopsy in post-heart transplantation subjects is nearly always the RV associated with reported high spontaneous resolution. The prevalence of acquired post-SM CCFs is also high and they possess the highest rate of spontaneous disappearance.

ACKNOWLEDGMENTS

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