

# World Journal of *Cardiology*

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2014-2017

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physical exercise as a non-pharmacological tool in the treatment of hypertension. This paper draws attention to the possible role of physical exercise as an adjunct non-pharmacological tool in the management of resistant hypertension. A few studies have investigated it, employing different methodologies, and taken together they have shown promising results. In summary, the available evidence suggests that aerobic physical exercise could be a valuable addition to the optimal pharmacological treatment of patients with resistant hypertension.

**Key words:** Exercise training; Resistant hypertension; Blood pressure; Non-pharmacological; Cardiovascular disease

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**Core tip:** Taken together, the available evidence indicates that, unless there is a contraindication to performing physical exercise, patients with resistant hypertension should be encouraged to engage in regular aerobic physical exercise in addition to the optimal pharmacological treatment.

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### Abstract

Hypertension is a very prevalent risk factor for cardiovascular disease. The prevalence of resistant hypertension, *i.e.*, uncontrolled hypertension with 3 or more antihypertensive agents including 1 diuretic, is between 5% and 30% in the hypertensive population. The causes of resistant hypertension are multifactorial and include behavioral and biological factors, such as non-adherence to pharmacological treatment. All current treatment guidelines highlight the positive role of

### RESISTANT HYPERTENSION

Arterial hypertension (defined as blood pressure > 140/90 mmHg) is the most important risk factor for cardiovascular events and end-stage renal disease<sup>[1]</sup>. In the general population, arterial hypertension has a prevalence of 30%-45%<sup>[1]</sup>. The control of blood



pressure is essential to avoid cardiovascular events in primary and secondary prevention<sup>[1]</sup>. In an important percentage of subjects, arterial hypertension is not controlled ( $< 140$  and  $90$  mmHg) with a strategy to correct lifestyle behavior and three antihypertensive drugs in high doses, including a diuretic<sup>[1,2]</sup>, and is defined as resistant hypertension. Some authors suggest that resistant hypertension should be diagnosed in those who meet the criteria of blood pressure control with the use of four antihypertensive drugs<sup>[2]</sup>. Several studies found that the prevalence of resistant hypertension in the hypertensive population is between 5% and 30%<sup>[1]</sup>. So, it is essential that the diagnosis of resistant hypertension is well defined in order to exclude false resistant hypertension<sup>[3]</sup>. Normally, arterial hypertension is defined by office blood pressure obtained by an electronic oscillometric device, called casual blood pressure. Ambulatory blood pressure is another way to measure blood pressure. Ambulatory blood pressure is superior to casual blood pressure in the diagnosis<sup>[1]</sup> and the cardiovascular events prognosis<sup>[4,5]</sup>.

Blood pressure shows circadian rhythm; it is higher in the morning after waking (morning surge), declines during the day and in a more pronounced way during the night with sleeping (nighttime dipping)<sup>[6]</sup>. In relation to cardiovascular events prognosis, several studies have shown that nighttime blood pressure is superior to daytime blood pressure<sup>[4,7]</sup>. In patients with resistant hypertension, the absence of nighttime dipping is more prevalent than in patients with nonresistant hypertension and it is associated with higher cardiovascular events<sup>[6]</sup>. Ambulatory blood pressure also makes the exclusion of the alert reaction (difference between casual blood pressure and day blood pressure determined by ambulatory blood pressure) possible, which is one of the causes of false resistant hypertension or pseudo resistant hypertension<sup>[3]</sup>. In pseudo resistant hypertension, blood pressure is not controlled in office behavior but has normal values in ambulatory blood pressure. Nonadherence to the prescribed treatment is another cause of false resistant hypertension<sup>[5]</sup>.

Resistant hypertension is associated with higher organ damage and cardiovascular events and a worse renal prognosis<sup>[1]</sup>. Resistant hypertension can be caused by obesity, excessive alcohol ingestion, high salt intake and obstructive sleep apnea<sup>[5]</sup>. Secondary hypertension can be the cause of resistant hypertension<sup>[8]</sup>. Secondary causes of hypertension include hyperaldosteronism, obstructive sleep apnea, renal artery stenosis and pheochromocytoma<sup>[9]</sup>. Hyperaldosteronism is the most common secondary cause of hypertension; nonetheless, many newly diagnosed hypertensive patients<sup>[10]</sup> and resistant hypertension patients<sup>[11]</sup> can have undetected primary aldosteronism. So, in studies looking for the impact of lifestyle changes on blood pressure of patients with resistant hypertension, it is recommended to

assess at least the plasma aldosterone-renin ratio even if the serum potassium level is normal<sup>[9]</sup>. The treatment of arterial hypertension implies changes in lifestyle attitudes, namely regarding exercise habits<sup>[8]</sup>. Recently, a prospective, blinded, randomized, sham-controlled trial assessing the effect of renal denervation or a sham procedure on ambulatory blood pressure monitoring measurements 6 mo post-randomization failed to demonstrate a benefit of renal artery denervation on reduction in ambulatory blood pressure<sup>[12]</sup>. However, recently several predictors of blood pressure response in the SYMPLICITY HTN-3 trial were identified, which could at least partially explain the results of the trial<sup>[13]</sup>; among the predictors are the total number of ablation attempts, baseline office SBP  $\geq 180$  mmHg, prescription of an aldosterone antagonist at baseline, and age  $< 65$  years in age<sup>[13]</sup>. This information is significant for designing future studies in this field.

## EXERCISE TRAINING AND RESISTANT HYPERTENSION

The cardioprotective benefits of exercise training in those with cardiovascular diseases include the modification of traditional cardiovascular risk factors, the improvement of exercise tolerance, myocardial and peripheral perfusion, cardiac function, arterial stiffness, autonomic function, endothelial repair, as well as the mitigation of endothelial dysfunction and low-grade vascular wall inflammation, and, most importantly, the reduction of morbidity and mortality<sup>[14-25]</sup>. Indeed, it is widely accepted that exercise training is a polypill with several beneficial effects, including antihypertensive effects. Indeed, exercise is able to induce a decrease of 5-7 mmHg in systolic blood pressure in patients with hypertension<sup>[26]</sup>. Nonetheless, the antihypertensive effects of exercise in patients with cardiovascular disease are often underestimated because the analysis is frequently made without assessing the influence of the baseline blood pressure on the effects of exercise training. We showed<sup>[17,27]</sup> in previous studies that if cardiovascular disease patients with high and low blood pressure at baseline are considered together, an exercise training intervention has no effect on blood pressure. But, if the analysis is conducted dividing patients into two subgroups on the basis of baseline blood pressure (pre-hypertension/hypertension vs normotension), exercise training significantly decreases systolic blood pressure<sup>[17,27]</sup>. An interesting aspect of exercise for patients with hypertension is that they could benefit from the antihypertensive effect of aerobic exercise after just three exercise sessions. Additionally, the duration of the exercise sessions can be as short as 10 min and the intensity of exercise can be relatively low (40% to  $< 60\%$   $\text{VO}_2$  peak)<sup>[26]</sup>. The exercise prescription recommendation of the American College of Sports Medicine for those with high blood pressure

is to perform 30 min of continuous or accumulated aerobic exercise of moderate intensity (40%-60% of VO<sub>2</sub> Reserve) per day, on most, preferably all, days of the week<sup>[28]</sup>. The aerobic exercise could be supplemented by resistance exercise<sup>[28]</sup>.

The management of resistant hypertension includes lifestyle interventions that aim to reduce sodium intake and increase the levels of daily physical activity<sup>[29]</sup>. Nonetheless, there are few studies evaluating the effects of lifestyle interventions, including physical exercise in patients with resistant hypertension. The potential of aerobic physical exercise as an adjunct non-pharmacological therapeutic tool to manage resistant hypertension was recently addressed in three studies<sup>[30-32]</sup>.

Dimeo *et al.*<sup>[30]</sup> first showed that patients with a reduced responsiveness to medication do not necessarily have reduced responsiveness to non-pharmacological therapies, *i.e.*, aerobic physical exercise, to lower blood pressure. The authors conducted a randomized trial encompassing fifty patients with resistant hypertension on an exercise training program, consisting of walking on a treadmill 3 times per week for 8 to 12 wk. Initially, the duration of the sessions was 30 min (interval training until the fifth week) and then was gradually increased to 30, 32 and 36 min of continuous training. Dimeo *et al.*<sup>[30]</sup> observed a  $6 \pm 12$  and  $3 \pm 7$  mmHg reduction in ambulatory systolic and diastolic daytime ambulatory blood pressure, respectively. More recently, Guimarães *et al.*<sup>[31]</sup> confirmed these positive results using a different exercise approach. They enrolled 32 patients in a heated water exercise program or to a control group. The heated water exercise program was performed three times per week for 12 wk and consisted of callisthenic exercises (*i.e.*, exercises performed in a rhythmic, systematic way using the body weight for resistance) against water resistance and walking inside a pool with controlled temperature (30°C-32°C). After 12 wk, the exercise program group showed a decrease in 24 h systolic (from  $137 \pm 23$  to  $120 \pm 12$  mmHg) and diastolic blood pressure (from  $81 \pm 13$  to  $72 \pm 10$  mmHg), daytime systolic (from  $141 \pm 24$  to  $120 \pm 13$  mmHg) and diastolic blood pressure (from  $84 \pm 14$  to  $73 \pm 11$  mmHg), and nighttime systolic (from  $129 \pm 22$  to  $114 \pm 12$  mmHg) and diastolic blood pressure (from  $74 \pm 11$  to  $66 \pm 10$  mmHg). This reduction in blood pressure is of great importance as higher ambulatory blood pressure predicts cardiovascular morbidity and mortality in resistant hypertensive patients<sup>[33]</sup>.

Concern for safety must come first in all that prescribe or supervise exercise. Thus, patients with resistant hypertension should consult a physician prior to engagement in exercise training, particularly vigorous intensity exercise<sup>[34]</sup>. The progression of intensity of aerobic exercise should be gradual to enhance compliance; slow progression of frequency and intensity of resistance exercise is also

encouraged to avoid injuries. Isometric exercise is not recommended. In patients with poorly controlled blood pressure, vigorous intensity exercise should be discouraged or postponed until appropriate drug treatment has been instituted and blood pressure lowered<sup>[34]</sup>. It seems prudent to keep systolic blood pressures at  $\leq 220$  mmHg and/or diastolic blood pressures  $\leq 105$  mmHg during exercise<sup>[35]</sup>. It is also important to know that in some patients,  $\beta$ -blockers and diuretics have an adverse impact on thermoregulatory function and could cause hypoglycemia<sup>[35,36]</sup>. Additionally, patients treated with calcium channel blockers,  $\beta$ -blockers and vasodilators should stop exercise gradually as they have an increased likelihood of hypotension post exercise<sup>[35,36]</sup>. Hence, it is important to monitor the room temperature during exercise, use the Borg scale as an adjunct to heart rate to monitor exercise intensity, and extend the cool down period.

## FUTURE PERSPECTIVES

The above-mentioned results are promising and provide good perspectives for the future. Nonetheless, more studies enrolling a large number of patients are clearly needed to reinforce the role of physical exercise associated with antihypertensive medication in the control of blood pressure in patients with resistant hypertension. Future studies are also warranted to disclose the mechanisms responsible for the positive effects of exercise. Several mechanisms, none of them definitive, have been proposed to explain the benefits of exercise training in these patients, including the decrease of sympathetic and the increase of vagal nerve activity, the improvement of the sensitivity of the baroreceptor reflex, the improvement of endothelial function and arterial stiffness, the decrease in the concentration of rennin, angiotensin II and aldosterone, and the reduction of renal sympathetic outflow. These aspects seem to merit close attention in future studies.

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## Cardiac remodeling and physical training post myocardial infarction

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the course of post-MI myocardial remodeling and improve cardiac function. This review summarizes the present state of knowledge regarding the effect of post-MI exercise training on infarcted hearts. Due to the degree of difficulty to study a viable human heart at both protein and molecular levels, most of the detailed studies have been performed by using animal models. Although there are some negative reports indicating that post-MI exercise may further cause deterioration of the wounded hearts, a growing body of research from both human and animal experiments demonstrates that post-MI exercise may beneficially alter the course of wound healing and improve cardiac function. Furthermore, the improved function is likely due to exercise training-induced mitigation of renin-angiotensin-aldosterone system, improved balance between matrix metalloproteinase-1 and tissue inhibitor of matrix metalloproteinase-1, favorable myosin heavy chain isoform switch, diminished oxidative stress, enhanced antioxidant capacity, improved mitochondrial calcium handling, and boosted myocardial angiogenesis. Additionally, meta-analyses revealed that exercise-based cardiac rehabilitation has proven to be effective, and remains one of the least expensive therapies for both the prevention and treatment of cardiovascular disease, and prevents re-infarction.

**Key words:** Post-myocardial infarction; Exercise training; Myocardial remodeling; Angiotensin II ; Fibrosis

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### Abstract

After myocardial infarction (MI), the heart undergoes extensive myocardial remodeling through the accumulation of fibrous tissue in both the infarcted and noninfarcted myocardium, which distorts tissue structure, increases tissue stiffness, and accounts for ventricular dysfunction. There is growing clinical consensus that exercise training may beneficially alter

**Core tip:** After myocardial infarction, the heart undergoes extensive myocardial remodeling through the accumulation of fibrous tissue in both the infarcted and noninfarcted myocardium, which distorts tissue structure, increases tissue stiffness, and accounts for ventricular dysfunction. There is growing clinical consensus that exercise training may beneficially alter the course of post-myocardial infarction (MI) myocardial remodeling and improve cardiac function. This review



summarizes the present state of knowledge regarding the effect of post-MI exercise training on infarcted hearts.

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## INTRODUCTION

Myocardial infarction (MI) is the major cause of heart failure in the adult American population<sup>[1]</sup>. Annually, 1.5 million Americans suffer from MI, with just over one-third of all cases inflicting serious heart disease and death. Because of this, post-MI treatments have become the major focus of research. There is growing clinical consensus that exercise training may beneficially alter the clinical course of post-MI myocardial remodeling and improve cardiac function<sup>[2,3]</sup>. Exercise training in post-MI patients with left ventricle (LV) systolic dysfunction has been recommended as a useful adjunct to the existing medical therapy, not only to attain symptomatic and functional improvement but also to prevent the progression of LV dysfunction and its attendant morbidity and mortality<sup>[4,5]</sup>. Significant improvements in exercise capacity were noted with no major complications in patients with moderate or severe LV dysfunction<sup>[4,6,7]</sup>. Post-MI training reverses skeletal muscle metabolic derangements<sup>[8,9]</sup>, increases maximal cardiac output<sup>[6,10,11]</sup> and improves the quality of life in these patients. Exercise training also improves in myocardial perfusion, independent of regressive changes in coronary lesions<sup>[12]</sup>. The improvement in myocardial blood flow of the infarcted area, even late after acute infarction, may lead to a consistent recovery of both regional and global LV function. Patients with MI experienced an exercise training-induced improvement in myocardial oxygenation and LV function<sup>[13]</sup>.

In recent years, cardiac rehabilitation (CR) has become a multi-disciplinary and multi-faceted intervention aimed at restoring well-being and impeding disease progression in patients with heart disease<sup>[14]</sup>. This complex intervention involves a variety of therapies, including risk factor education, psychological input, and drug therapy. Nevertheless, international clinical guidelines have consistently identified exercise-based CR as an essential element of therapy.

Despite guidelines recommending the use of CR programs for patients with MI, participation in these programs continues to be low; in fact, it has been reported that only 10% to 20% of patients who survive an acute MI participate in an exercise-

based secondary prevention CR program<sup>[15]</sup>. Indeed, the reason for such low participation is likely multifactorial; additionally, conflicting results regarding the efficacy of experimental research and the absence of large randomized controlled trials with respect to re-infarction likely serve as additional barriers<sup>[3]</sup>. Therefore, we reviewed the evidence and the mechanisms by which post-MI exercise improves morbidity and mortality, as obtained by means of experimental and clinical studies.

## POST-MI LV REMODELING

LV remodeling is the process by which ventricular size, shape, and function are regulated by mechanical, neurohormonal, and genetic factors<sup>[16,17]</sup>. After acute MI, the abrupt increase in volume overload induces a unique pattern of remodeling in the infarct zone and bordering non-infarct myocardium. The oxygen deprived myocardium experiences a localized inflammatory response *via* neurohormonal activation mediated in part by the migration of neutrophils, monocytes and macrophages<sup>[16]</sup>. Hypotension and the subsequent decrease in cardiac output stimulate temporary circulatory hemodynamic compensatory mechanisms including increased sympathetic nervous system, renin-angiotensin-aldosterone system (RAAS), and natriuretic peptide activity<sup>[18]</sup>.

The induction of cardiomyocyte hypertrophy is a key process during post-MI remodeling that offsets increased volume over load, attenuates progressive dilation, and stabilizes contractile function; thus, post-MI myocyte hypertrophy initially serves as an adaptive, cardiac-preserving response<sup>[7,17]</sup>. However, over time, chronic neurohormonal activation, myocardial stretch, RAAS activity, and various paracrine and autocrine factors continue to promote eccentric, pathological hypertrophy, progressively deteriorating LV function to the point of failure. Interestingly, compelling evidence has shown that post-MI exercise favorably influences the course of LV remodeling, which accordingly, has attracted much attention<sup>[19]</sup>.

## EFFECT OF POST-MI EXERCISE

### TRAINING ON RAAS AND MYOCARDIAL REMODELING

Circulating angiotensin II (Ang II) is markedly increased following MI. Ang II is a potent stimulant in pathologic myocardial remodeling both as a circulating hormone and as an autocrine/paracrine mediator produced in response to hemodynamic overload<sup>[20]</sup>. Ang II plays a major role in vasoconstriction and aldosterone release. This peptide also serves as a growth factor and stimulates fibrous tissue formation in various<sup>[21-23]</sup>. Ang II is also generated in the infarcted heart and regulates tissue structure in an autocrine and paracrine manner. All the components for Ang

II generation including angiotensinogen, renin, and angiotensin converting enzyme (ACE), are present in the infarcted heart<sup>[24,25]</sup>. Locally generated Ang II stimulates transforming growth factor- $\beta$ 1 (TGF- $\beta$ 1) synthesis, which, in turn, enhances proliferation and collagen generation of myofibroblast, and leads to cardiac fibrosis<sup>[26]</sup>. Pharmacological intervention with ACE inhibitor or AngII receptor antagonist significantly attenuates cardiac fibrosis, and improves cardiac function and survival<sup>[27,28]</sup>.

Acute physical exercise stimulates renin release and activates renin-angiotensin system<sup>[29,30]</sup> with an elevation of aldosterone<sup>[31]</sup>, whereas chronic exercise training attenuates renin-angiotensin system at resting condition<sup>[32]</sup>. A study on patients with MI has demonstrated that the resting plasma Ang II reduced by 26% after 4 mo of exercise training<sup>[32]</sup>. The reduction in plasma Ang II was accompanied with 32% reduction in aldosterone, 30% reduction in vasopressin, and 27% reduction in atrial natriuretic peptide. An animal study using a pacing-induced heart failure in rabbits also revealed exercise training-induced attenuation of resting plasma Ang II<sup>[33]</sup>.

In a previous study<sup>[34]</sup>, we systematically examined the effect of exercise training on RAAS using a rat-MI model. Rats performed a moderate intensity exercise training on a rodent treadmill 1 wk after MI 5 d/wk for 8 wk at 16 m/min, 50 min per session. Our results showed that exercise training significantly attenuated circulating renin, ACE, Ang II, and aldosterone compared with sedentary rats with MI. Rats in exercise groups had similar LV end-diastolic diameters (LVEDd) compared with their sedentary counterparts and tended to have smaller LV end-systolic diameters (LVESd), and percent fractional shortening in exercise rats was significantly higher than in sedentary rats. These findings suggest that exercise training normalizes the circulating RAAS and improves LV function without compromising LV dilation.

In a similar study<sup>[35]</sup>, we further evaluated the effect of post-MI exercise training on myocardial fibrosis, cardiac function, and factors inducing adverse remodeling. For the first time, changes caused by exercise training were investigated in type I and III collagen, matrix metalloproteinase (MMP-1), tissue inhibitor matrix metalloproteinase (TIMP-1), TGF- $\beta$ 1, Ang II receptor type 1 (AT1), and ACE at both gene and protein levels after MI. Our results indicated exercise training significantly attenuated the expression of TIMP-1 at both gene and protein level and improved balance between MMP-1 and TIMP-1 (imbalance between the two appear to be responsible for the increased MMP activity observed in congestive heart failure). Training also lowered expression of AT1 receptor protein and reduced ACE mRNA expression as well as ACE binding. In addition, training significantly decreased collagen content, thereby resulting in attenuated cardiac fibrosis.

Lastly, exercise training preserved cardiac function.

Ang II receptor blockade has been widely used to alleviate detrimental effects associated with elevated RAAS<sup>[36,37]</sup>. In a subsequent study<sup>[38]</sup>, we investigated the effect of combined exercise training along with AngII receptor blockade on post-MI ventricular remodeling in rats. Losartan (an Ang II receptor antagonist) treatment (20 mg/kg per day) was initiated 1-wk post-MI, and administered *via* gastric gavage for 8 wk. The results indicated significantly decreased levels of TIMP-1 in mRNA and protein expression in both trained and losartan treated groups. Exercise trained groups exhibited attenuated expression of AT1 receptor protein, and decreased ACE binding. These findings revealed that exercise training after MI provided beneficial effects on post-MI cardiac function and LV remodeling by the alteration of specific gene and protein expressions that regulate myocardial fibrosis, whereas the combination of both exercise training and losartan treatment improved the effects<sup>[35,38]</sup>. Tables 1 and 2 summarize both human and animal studies on post-MI physical training.

## EARLY VS LATE PHASE POST-MI EXERCISE

Post-MI remodeling has been arbitrarily divided into two phases: the early phase, which lasts up to 72 h, and the late phase, lasting beyond 72 h<sup>[17]</sup>. Generally, adaptive responses that preserve stroke volume are invoked during the early stage, whereas late remodeling primarily involves hypertrophy and alterations in LV architecture in an attempt to distribute increased wall stresses more evenly. Differences in function between adjacent and remote non-infarcted regions are greatest at one week after anterior MI, and persist for a minimum of six months post-MI<sup>[39]</sup>; it is during this six-month period that systolic function decreases drastically, as the LV undergoes progressive dilatation, eccentric hypertrophy, and the lengthening of non-infarcted segments<sup>[17]</sup>. Thus, the question of when to begin exercise and at what intensity has proven elusive. Nevertheless, recent evidence offers novel insights and indeed provides an answer to some questions, although, as quality research often does, asks several more.

To date, several studies in humans reported contradictory effects of training on LV remodeling after MI<sup>[4,6,7,40-45]</sup>. However, careful inspection of these studies indicate that after small MI, exercise has no detrimental effect<sup>[7,41]</sup>, or even improves<sup>[4,43,44,46]</sup> LV geometry and function, independent and irrespective of whether exercise was started late (1 year)<sup>[4,44]</sup> or early (< 2 mo)<sup>[7,41,43]</sup> after MI. Conversely, in patients with large MI (encompassing 35% to 50% of LV mass), exercise had either no<sup>[42]</sup>, or a beneficial<sup>[4]</sup>

**Table 1** Summary of physical training protocols and outcomes in selected human studies

| Ref.  | Type of exercise   | Exercise intensity  | Exercise duration   | Exercise frequency | Training period | Assessment  | Outcome   |
|---|--|---|---|--------------------|-----------------|---|---|
| Braith <i>et al</i> <sup>[32]</sup><br>1999                   | Treadmill walk   | 40%-70% of peak oxygen uptake (VO <sub>2</sub> )          | Started with 10-20 min as tolerated and increased to 30-45 min by the 10 <sup>th</sup> wk | 3 times/wk         | 4 mo            | Plasma RAAS   | Reduced Resting AngII, Aldosterone, vasopressin, and atrial natriuretic peptide |
| Myers <i>et al</i> <sup>[143]</sup><br>2001                   | Outdoor walking at an elevation of 3500 ft, in addition to cycling | 60%-70% of peak VO <sub>2</sub>                           | Two 1-h sessions of walking, 45 min of cycling  | 5 times/wk         | 2 mo            | Post-exercise oxygen uptake kinetics  | High-intensity training did not result in a faster recovery of oxygen debt      |
| La Rovere <i>et al</i> <sup>[144]</sup><br>2002 <sup>1</sup>  | Graded exercise (cycling, calisthenics)                            | Adjusted to 75% of the heart rate at peak VO <sub>2</sub> | 30 min  | 5 times/wk         | 1 mo            | BRS, LVEF   | BRS improved by 26%, while LVEF remained unchanged                              |
| Marchionni <i>et al</i> <sup>[145]</sup><br>2003 <sup>2</sup> | Cycling  | 70%-85% of max heart rate                                 | 1 h   | 3 times/wk         | 6 mo            | Total work capacity, health-related quality of life   | Improved total work capacity and health-related quality of life                 |
| Zheng <i>et al</i> <sup>[146]</sup><br>2008 <sup>1</sup>      | Bicycle ergometer  | 75% of peak heart rate                                    | 30 min  | 3 time/wk          | 6 mo            | HR recovery, time to reach anaerobic threshold, left ventricular end-diastolic diameter, left ventricular ejection fraction | Exercise training prevented ventricular remodeling to a certain extent          |
| Giallauria <i>et al</i> <sup>[46]</sup><br>2013               | Bicycle ergometer  | 60%-70% of peak VO <sub>2</sub>                           | 30 min  | 3 times/wk         | 6 mo            | dipyridamole rest gated myocardial perfusion single photon emission computed tomography                                     | Improved peak oxygen consumption, myocardial perfusion and LV function          |

<sup>1</sup>Exercise was part of a comprehensive secondary prevention program; <sup>2</sup>Combination study consisting of Home and Hospital/group participants. RAAS: Renin-angiotensin-aldosterone system; LVEF: Left ventricular ejection fraction; BRS: Baroreflex sensitivity.

effect on ejection fraction (EF) and LV volumes but only when started late after MI. However, when exercise after large MI is initiated at a time when LV remodeling is still ongoing (3 to 4 mo after MI), the majority of studies reported that exercise has either no<sup>[6,7,41]</sup>, or even a detrimental<sup>[40,47]</sup> effect on LV volume and EF.

Similarly, experimental research using rat models of MI suggests that exercise initiated late (> 3 wk) after moderate to large MI does not aggravate<sup>[45,48]</sup>, or even blunts<sup>[49-51]</sup> LV dilation and hypertrophy. Contrarily, exercise started < 1 wk after moderate to large MI resulted in variable outcomes with beneficial<sup>[52]</sup>, no<sup>[53,54]</sup>, or detrimental<sup>[55,56]</sup> effects on LV remodeling. Therefore, these rodent studies further evidence the concern that early exercise after MI may further exacerbate LV remodeling. Importantly, there are a number of concerns with the methodology of these studies. First, exercise experimental studies conducted late after MI predominately used treadmill running<sup>[45,48-50]</sup>, whereas early exercise studies used swimming<sup>[51-55]</sup>. Since swimming is not a habitual activity for rats, this type exercise mode may markedly elicit both psychological and physiological stress to the animals, which potentially offsetting the beneficial effects of exercise compared to treadmill running<sup>[57,58]</sup>.

Amazingly, in a recent study of evaluating 8-wk

of volunteer exercise, de Waard *et al*<sup>[59]</sup> reported remarkable data addressing the question of exercise training 24 h after MI. As opposed to most humans, mice like to run, and will do so seemingly endlessly when presented the opportunity. During the first week after induction of MI, recovering mice slowly titrated up their daily running activity, reaching distances similar to their sham-operated counterparts towards the end of the study, thus, suggesting that early post-MI exercise training may have positive effect in post-MI recovery and myocardial remodeling. Authors reported that exercise had no effect on survival, MI size, or LV dimensions, but improved LV fractional shortening from 8% ± 1% to 12% ± 1%, LV dP/dt<sub>P30</sub> from 5295 ± 207 to 5794 ± 207 mmHg/s, and reduced pulmonary congestion. Additionally, this study also provided novel information regarding myocardial Ca<sup>2+</sup> handling after MI, debunking the previously held notion that exercise sensitizes myofilaments to the effects of Ca<sup>2+</sup><sup>[59]</sup>. A study from our group<sup>[34]</sup> systematically examined the timing effect of post-MI exercise training. Rats started exercise training at either 1 wk or 6 wk after MI on a treadmill for 8 wk. Rats in exercise groups had similar LVEDd compared with their sedentary counterparts and tended to have smaller LVESd, and percent fractional shortening (%FS) in exercise rats was significantly higher than

**Table 2 Summary of physical training protocols and outcomes in selected animal studies**

| Ref.  | Type of exercise                      | Exercise intensity                             | Exercise duration                 | Exercise frequency | Training period | Assessment   | Outcome  |
|---|---------------------------------------|--|-----------------------------------|--------------------|-----------------|--|--|
| Hashimoto <i>et al</i> <sup>[76]</sup> 2004 | Treadmill running                     | 10 m/min                                       | 60 min                            | 5 d/wk             | 6 wk            | Myosin heavy chain isoforms, cardiac wall measurements                 | Exercise training resulted in a significant increase of $\alpha$ -MHC expression in both anterior and posterior wall, ensuring a beneficial role in the remodeling of the heart  |
| Xu <i>et al</i> <sup>[35]</sup> 2008        | Treadmill running                     | 16 m/min @ 5% grade                            | 50 min                            | 5 d/wk             | 8 wk            | TIMP-1, AT1, ACE, collagen volume fraction, MMP                        | Early exercise training after MI reduces TIMP-1 expression, improves the balance between MMPs and TIMPs, and mitigates the expressions of ACE and AT1 receptor, thus attenuating myocardial fibrosis and preserving cardiac function |
| De Waard <i>et al</i> <sup>[59]</sup> 2007  | Voluntary treadmill exercise training | N/A  | N/A                               | 5 d/wk             | 8 wk            | LV fractional shortening, $Ca^{2+}$ sensitivity, PLB, SERCA            | Voluntary exercise improved LV and cardiomyocyte shortening, attenuates global LV dysfunction  |
| Wan <i>et al</i> <sup>[34]</sup> 2007       | Treadmill running                     | 16 m/min @ 5% grade                            | 50 min                            | 5 d/wk             | 8 wk            | Echo and RAAS  | Exercise training improved cardiac function and attenuated RAAS. Early and late exercise training had similar beneficial results   |
| Xu <i>et al</i> <sup>[106]</sup> 2010       | Treadmill running                     | 16 m/min @ 5% grade                            | 50 min                            | 5 d/wk             | 8 wk            | SOD, GPx, MnSOD  | Exercise training combined with Ang II receptor blockade reduced oxidative stress  |
| Yengo <i>et al</i> <sup>[147]</sup> 2012    | Treadmill running                     | 15% grade, speed increased from 13 to 24 m/min | Progressively increased to 60 min | 6 d/wk             | 10 wk           | Collagen concentration, non-reducible collagen cross-linking in the RV | Exercise training normalized the observed increase in cross-linking, and favorably modifies heart extracellular matrix   |

RAAS: Renin-angiotensin-aldosterone system; MHC: Myosin heavy chain; TIMP-1: Tissue inhibitor matrix metalloproteinase; AT1: AngII receptor type 1; ACE: Angiotensin converting enzyme; MMP: Matrix metalloproteinase; SOD: Superoxide dismutase; GPx: Glutathione peroxidase.

in sedentary rats. These finding suggest that exercise training does not cause LV dilation and preserves LV function.

## POST-MI EXERCISE AND MYOCARDIAL CONTRACTION

$Ca^{2+}$  handling abnormalities can largely explain depressed myocyte contractility in the remodeled myocardium, whereas abnormalities in myofilament function are less well understood. Previously, it was reported in pigs that impaired pump function three weeks after MI could also be attributed to decreased maximal isometric tension in skinned cardiomyocytes in areas remote from the ischemic border zone; as it turns out, the impairment occurred in the context of increased  $Ca^{2+}$  sensitivity of the myofilaments<sup>[60]</sup>. As a result, the authors attributed the increased post-MI  $Ca^{2+}$  sensitivity to reduced protein kinase A-mediated troponin I (TnI) phosphorylation<sup>[60]</sup>. Similarly, increased myofilament  $Ca^{2+}$  sensitivity has also been reported in end-stage human heart failure, mediated by decreased TnI phosphorylation.

Although experimentally challenging, investigators from the de Waard study were able to construct a full pCa-force relationships in isometrically contracting myocytes<sup>[59]</sup>, which differs from previous studies relying on simultaneous measurements of FS% and  $Ca^{2+}$  fluorescence in unloaded myocytes to estimate

myofilament  $Ca^{2+}$  sensitivity. Although a much simpler experimental approach, there are various problems associated with this method. First, maximal developed tension cannot be assessed in unloaded myocytes, and any changes in developed tension are ignored when estimating  $Ca^{2+}$  sensitivity. Secondly, basal sarcomere length is much shorter in unloaded myocytes (1.8 vs 2.2), and cannot be controlled; therefore, even a slight change in basal sarcomere length would confound the result, which in turn, has prompted investigators to wrongly conclude that exercise increases myofilament sensitivity<sup>[51]</sup>. Thus, data from de Waard *et al*<sup>[59]</sup> reveals that voluntary exercise training in mice early after MI normalizes myofilament dysfunction, which likely occurred in response to the exercise-induced improvement in unloaded shortening of isolated intact cardiomyocytes, as the  $Ca^{2+}$  transient amplitude was not found to be altered by exercise. Furthermore, basal  $Ca^{2+}$  was reduced by exercise, altogether suggesting that exercise decreases myofilament  $Ca^{2+}$  sensitivity.

Dysregulation of cardiac  $\beta$ -adrenergic receptor ( $\beta$ -AR) signaling represents another important factor leading to the pathological LV remodeling and the progression to heart failure. In the failing myocardium, adverse changes in  $\beta$ -AR signaling are mainly attributed to  $\beta_1$ -AR downregulation and desensitization/uncoupling of both  $\beta_1$  and  $\beta_2$ -AR's. It has been reported that exercise after MI increases



$\beta_1$ -AR, as evidenced by a 48% increase in  $\beta_1$ -AR protein, and a 36% increase in cAMP levels, and improves  $\beta$ -AR signaling<sup>[59,61]</sup>, which in turn, may also contribute to improvement in myocardial contractility in patients with MI.

Myosin heavy chain (MHC) acts as the chemical-mechanical transducer of motion in muscle fibers by converting energy from ATP into the sliding myofilaments<sup>[62]</sup>. The isoform  $\alpha$ -MHC elicits two to three times faster actin-activated ATPase activity and actin filament sliding velocity than the isoform MHC- $\beta$ <sup>[63,64]</sup>. Thyroid hormone (TH) has profound effects on the cardiovascular system, and is known to critically regulate the expression of MHC isoforms in the myocardium<sup>[65]</sup>; in fact, in the absence of TH, the  $\alpha$ -MHC gene is not transcribed<sup>[62]</sup>. Triiodothyronine ( $T_3$ ), the active cellular form of TH, mediates its actions upon binding to thyroid hormone receptors (TRs)<sup>[66,67]</sup>.

After MI,  $T_3$  levels are significantly reduced in patients<sup>[68]</sup>; similarly, decreased serum concentrations of TH have also been observed in patients with chronic heart failure (CHF), which, in part, attributes to impaired cardiac function<sup>[69]</sup>. In experimental post-MI rat models, following the decrease of serum  $T_3$ , significant downregulation of  $\alpha$ -MHC and the concomitant upregulation of MHC- $\beta$  are observed in the LV non-infarcted myocardium, along with changes in TR isoforms at the mRNA level<sup>[68,70,71]</sup>. These, in addition to other MI-induced alterations in cardiac phenotype, are thought to further contribute to the progressive nature of LV systolic dysfunction, and have been associated with poor prognosis<sup>[62,63,72,73]</sup>. Interestingly, endurance exercise has been reported to favorably reverse MHC  $\alpha$ - to  $\beta$ -cardiac isoform shifts after MI at both gene and protein levels<sup>[74,75]</sup>, which in turn, may be associated with preserved cardiac functioning, attenuated LV remodeling, and increased myofibril function<sup>[76]</sup>. Recent evidence by our group<sup>[75]</sup> indicated that post-MI exercise training significantly increase cardiac expression of  $\alpha$ -MHC and decrease cardiac expression of MHC- $\beta$  without changing serum  $T_3$  levels. Similarly, unpublished data from our group recently revealed that moderate-intensity treadmill exercise training markedly increased TR $\alpha$ -1 and TR $\beta$ -1 nine weeks after MI. Thus, it is likely that favorable changes in TH target gene transcription may be due to exercise-dependent upregulation of TR isoforms. Nevertheless, studies with experimental models of LV dysfunction and preliminary clinical investigation of patients with CHF reported that the TH analog 3,5-diiodothyropropionic acid elicits improvements in both systolic and diastolic LV function, accompanied by an increase in cardiac output and improved lipid profile<sup>[77]</sup>. Thus, it is conceivable that the combination of exercise combined with TH treatment could potentiate beneficial results, and warrants further investigation.

## POST-MI OXIDATIVE STRESS AND EXERCISE TRAINING

Reactive oxygen species (ROS) including superoxide ( $O_2^-$ ), hydroxyl ( $OH^\cdot$ ), and peroxynitrite ( $ONOO^-$ ), have an unpaired electron<sup>[78]</sup>. These ROS serve as signaling molecules when in low concentrations; however, they elicit harmful oxidative stress when produced in excess<sup>[79]</sup>. ROS can directly damage the lipids of cell membranes, proteins and both nuclear and mitochondrial DNA resulting in serious or mortal cellular injury<sup>[80]</sup>. However, the toxicity associated with the excessive ROS can be prevented by antioxidant defense systems that provide a healthy cellular environment. Living cells have both enzymatic and non-enzymatic defense mechanisms to balance the multitude of oxidative challenges presented to them. The enzymatic antioxidant system includes superoxide dismutase (SOD), catalase and glutathione peroxidase (GPX)<sup>[81]</sup>. SOD catalyzes the dismutation of superoxide ( $O_2^-$ ) to hydrogen peroxide ( $H_2O_2$ ). Catalase and GPX further metabolize  $H_2O_2$  to water and oxygen. The non-enzymatic group includes a variety of biologic molecules, such as vitamins E and C<sup>[81,82]</sup>. Oxidative stress is enhanced by an unbalance between elevated ROS production and diminished antioxidant system.

Excessive oxidative stress has been observed in the myocardium of patients with CHF<sup>[83,84]</sup>. Heart failure subsequent to myocardial infarction is associated with oxidative stress in both infarcted and noninfarcted myocardium<sup>[83,85,86]</sup>. Researchers have identified a membrane-based NAD(P)H oxidase as a major source of  $O_2^-$  in the heart<sup>[87]</sup>. An elevated NAD(P)H oxidase expression has been observed in the infarcted rat heart and the extent of NAD(P)H oxidase elevation is negatively correlated with the deteriorated hemodynamic function and ventricular remodeling of the heart<sup>[88]</sup>. Furthermore, progressive decrease in antioxidant enzymes, SOD, catalase<sup>[89]</sup>, and glutathione (an antioxidant)<sup>[90]</sup> has also been observed in the infarcted rat heart. These observations suggest that the impaired antioxidant system and/or augmented ROS promote oxidative stress, contributing to the adverse remodeling and dysfunction of the infarcted heart<sup>[91]</sup>.

There is growing evidence that chronic exercise training adaptively bolsters the activity of protective antioxidant enzymes such as catalase, SOD, GPX<sup>[92]</sup>, glutathione reductase (GR)<sup>[93]</sup>, and antioxidant glutathione content<sup>[94,95]</sup> in skeletal muscles of healthy animals. Nine-weeks of treadmill training markedly elevated manganese-SOD (Mn-SOD, an isozyme of SOD) activity and its protein content both at rest and after an acute exercise bout in the soleus muscle of rats<sup>[96]</sup>. In contrast, the muscle Mn-SOD gene expression of untrained rats was significantly decreased after an acute bout of exercise<sup>[96]</sup>. Exercise



training also resulted in significant increase in SOD activity in the LV of normal rats<sup>[97,98]</sup>. These findings suggest that muscles have the capacity of responding to training in such a manner as to enhance antioxidant system and reduce the accumulation of ROS resulting from enhanced metabolic activity.

In patients with CHF, exercise training enhanced GPX and catalase activities, and mitigated lipid peroxidation in skeletal muscles<sup>[99]</sup>. Exercise training also downregulated both gene expression and activity of pro-oxidant NAD(P)H oxidase, and decreased vascular generation of ROS in human arterial tissue<sup>[100]</sup>.

Inconsistent findings have been reported on the effect of post-MI exercise training on ROS and antioxidants. Yamashita *et al.*<sup>[101]</sup> and Brown *et al.*<sup>[102]</sup> reported that exercise training resulted in an increase in myocardial SOD content along with improved recovery from ischemia-reperfusion injury. Others, however, reported that exercise training increased cardioprotection without amplifying myocardial SOD content<sup>[103,104]</sup> and only certain cardiac antioxidant enzyme activities (*i.e.*, SOD) were enhanced in the exercise trained animals<sup>[97,101,105]</sup>. The variation in the findings of these studies may be due to the differences in the intensity and duration of exercise regimens. A study from our group<sup>[106]</sup> demonstrated that exercise training increased MnSOD gene expression after MI regardless of losartan treatment. In addition, exercise training together with losartan treatment remarkably enhanced the enzymatic activity of catalase, suggesting an additive effect of exercise training and Ang II receptor blockade treatment. But exercise training did not enhance myocardial glutathione peroxidase activity. Our data also revealed that post-MI exercise training notably attenuated MI-induced elevation of plasma thiobarbituric acid reactive substances (TBARS, a marker of lipid oxidation) although cardiac TBARS was not altered.

It has been documented that Ang II stimulates NAD(P)H oxidase activity, which promotes ROS production<sup>[107,108]</sup>. Thus, exercise training may improve antioxidant capacity and attenuate oxidative stress by attenuating RAAS<sup>[35,38,106]</sup>.

## MYOCARDIAL APOPTOSIS AND EXERCISE TRAINING

Loss of cardiomyocytes is an important mechanism in the development of myocardial remodeling and cardiac failure<sup>[109]</sup>. After MI, apoptotic cardiomyocyte death occurs in the infarcted myocardium as well as the surviving portions of the heart<sup>[110,111]</sup>. Myocyte apoptosis not only occurs at early phase (7 d) of MI<sup>[112,113]</sup>, but also progresses to late phase (up to 6 mo) in myocardium remote from the area of ischemic damage<sup>[114,115]</sup>, contributing to CHF<sup>[116]</sup>. ROS have proven to be powerful mediators of myocyte

apoptosis<sup>[117,118]</sup>. Treatment of cardiac myocytes with O<sub>2</sub><sup>-</sup> or H<sub>2</sub>O<sub>2</sub> induces apoptosis, suggesting a mechanism of ROS as an initial pathogenic event<sup>[119]</sup>. Enhanced pro-apoptotic Bax expression coexists with oxidative stress and apoptosis in the infarcted heart<sup>[120]</sup>, whereas oxidative stress activates pro-apoptotic enzymes, caspase-9 and caspase-3, resulting in cardiac apoptosis and ventricular dysfunction<sup>[117]</sup>. *In vivo* studies have demonstrated that long-term treatment with the antioxidants, probucol or pyrrolidine dithiocarbamate, attenuates oxidative stress and myocyte apoptosis within noninfarcted myocardium in rats<sup>[121,122]</sup>.

Siu *et al.*<sup>[98]</sup> demonstrated that endurance training downregulated the expression of caspase and Bax, and upregulated Bcl-2 (an anti-apoptotic gene product) in both skeletal and cardiac muscles of healthy rats. These anti-apoptotic effects were associated with elevated protein content of Mn-SOD. A clinical study also revealed that exercise training attenuated skeletal muscle apoptosis along with improved antioxidant capacity in patients with CHF<sup>[99]</sup>. Accordingly, the data are consistent with the idea that an increased antioxidant capacity and attenuated oxidative stress from exercise training may be involved in reducing pro-apoptotic genes, suggesting that exercise training may attenuate the extent of apoptosis in muscles. However, the influence of post-MI exercise training in myocardial apoptosis remains to be elucidated.

## POST-MI EXERCISE AND CARDIAC ANGIOGENESIS

After myocardial infarction (MI), the adequate growth of new capillaries and arterioles, or angiogenesis, represents a critical process in the development of compensatory hypertrophy in the remaining non-infarcted myocardium<sup>[123]</sup>. Although compensatory angiogenesis can be observed in both the ischemic and infarcted heart, previous studies have demonstrated that angiogenesis may be inadequate<sup>[124,125]</sup>; in fact, recent evidence suggests that impaired angiogenesis may lead to maladaptive LV remodeling, promoting the transition from adaptive cardiac hypertrophy to LV dilation and dysfunction<sup>[61,126]</sup>.

Exercise, through increased vascular shear stress, potentiates a powerful angiogenic stimulus<sup>[127]</sup>. The pro-angiogenic effect of exercise has previously been demonstrated in healthy swine hearts<sup>[128]</sup>. A study conducted by Leosco *et al.*<sup>[61]</sup> reported that exercise induced a significant increase of capillary density in lateral border and remote zones to the infarct site, but not in the area close to the infarcted site. One of our recent studies (unpublished data) confirms that post-MI exercise training induced about 1.5-fold increase in capillary density in the septum

and left ventricle compared to non-exercised heart, suggesting that exercise promotes capillary growth in non-infarcted areas of severely decompensated hearts.

A number of studies clearly demonstrate that exercise activates vascular endothelial growth factor (VEGF) dependent angiogenic pathways<sup>[129-131]</sup>, which represent critical molecular mechanisms by which exercise triggers angiogenesis<sup>[130]</sup>. In addition, exercise-induced upregulation of VEGF in patients with heart failure has also been documented<sup>[132]</sup>. Recently, experimental studies have revealed that exercise reactivates angiogenic signaling by increasing VEGF and eNOS phosphorylation by Akt in the heart, increases coronary vascular network and density, and enhances myocardial blood perfusion. Evidence of endothelial dysfunction in peripheral resistance arteries post-MI has also been observed in both experimental and clinical studies<sup>[133,134]</sup>, which likely contributes to arterial dysfunction<sup>[135,136]</sup>; in this regard, post-MI exercise has been shown to reverse arterial dysfunction by virtue of restored production of nitric oxide (NO) in the endothelial vessel wall mediated by adaptive changes in eNOS, its activation by Akt, and by reduced NAD(P)H oxidase-generated ROS scavenging of NO<sup>[137]</sup>.

## EXERCISE-BASED CR IN PATIENTS WITH HEART DISEASE

Previously, four meta-analyses<sup>[138-141]</sup> of the effects of exercise-based interventions in patients with coronary heart disease reported a statistically significant benefit in patients receiving exercise therapy compared with usual medical care, with a reduction in total and cardiac mortality ranging from 20% to 32%. However, randomized controlled trials (RCT) have generally been small and often of questionable methodological quality, raising concerns that the effect of exercise-based CR may be overestimated. In 2004, Taylor *et al.*<sup>[142]</sup> aimed to update the systematic review of the effects of exercise-based CR in patients with coronary heart disease, addressing previous concerns regarding the applicability of this evidence to routine practice.

For the analysis, over 5000 articles were retrieved from a number of search sources, and only 425 full papers were considered for possible inclusion. Studies were excluded for various reasons including nonrandomized design, inappropriate patient groups, inappropriate intervention, the control group received an exercise intervention, inappropriate outcomes, inadequate follow-up, and preliminary results only available in abstract form. After identification of duplicate publications, only 48 eligible studies remained, and were still of poor methodological quality.

Although exercise-based CR was associated with

a significant reduction in all-cause mortality and total cardiac mortality, there was no significant difference with respect to re-infarction<sup>[142]</sup>. Conversely, a recent meta-analyses conducted in 2011 consisting of 34 RCTs ( $n = 6111$ ) found that patients randomized to exercise-based CR had a significantly lower risk of re-infarction, cardiac mortality, and all-cause mortality<sup>[3]</sup>. In a stratified analysis, treatment effects were consistent regardless of study periods, duration of CR, or time beyond the active intervention<sup>[3]</sup>. Additionally, Exercise-based CR had favorable effects on cardiovascular risk factors, including smoking, blood pressure, body weight, and lipid profile<sup>[143]</sup>.

## CONCLUSION

Most of the human and animal studies demonstrated that post-MI physical exercise training results in positive effect on myocardial remodeling. These beneficial effects include improved cardiac function, mitigated interstitial myocardial fibrosis, and enhanced physical capacity. As a result, physical exercise training provides good prognosis and improves the quality of life of MI patients. The current literature revealed the mechanism of physical training-induced improvement in post-MI cardiac remodeling. Physical training attenuates renin<sup>[29,30]</sup>, ACE, Ang II, and aldosterone<sup>[31,34]</sup>. The attenuation of Ang II, in turn, reduces cardiac fibrosis<sup>[34]</sup> and aldosterone secretion<sup>[32,34]</sup>, which may ease MI-induced plasma expansion. Physical training also improves the balance between MMP-1 and TIMP-1, which, in turn, reduces cardiac stiffness *via* regulation of collagen accumulation<sup>[38]</sup>. Studies show that physical training significantly improves  $\beta$ -adrenergic receptor, cAMP<sup>[59,61]</sup>, and favorably reverses MHC  $\alpha$ - to  $\beta$ -cardiac isoform shifts<sup>[74,75]</sup>, attributing to improvement in myocardial contractility. In addition, post-MI physical training may enhance antioxidant enzyme capacity and attenuate oxidative stress<sup>[97,101,105]</sup>. It is important to note that the existing studies have only investigated the effects of *endurance* exercise on post-MI remodeling; therefore, the effects of post-MI resistance training have yet to be systematically examined to identify a better exercise mode. Furthermore, although majority of the research has shown that post-MI exercise training improves cardiac remodeling and function, the suitable exercise intensity, duration, and the time to start training are yet to be optimized to provide clinically relevant information regarding the pathophysiology of post-MI recovery through physical training.

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## Percutaneous left atrial appendage closure: Technical aspects and prevention of periprocedural complications with the watchman device

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### Abstract

Transcatheter closure of the left atrial appendage has been developed as an alternative to chronic oral anticoagulation for stroke prevention in patients with atrial fibrillation, and as a primary therapy for patients with contraindications to chronic oral anticoagulation. The promise of this new intervention compared with warfarin has been supported by several, small studies and two pivotal randomized trial with the Watchman Device. The results regarding risk reduction for stroke have been favourable although acute complications were not infrequent. Procedural complications, which are mainly related to transseptal puncture and device implantation, include air embolism, pericardial effusions/tamponade and device embolization. Knowledge of nature, management and prevention of complications should minimize the risk of complications and allow transcatheter left atrial appendage closure to emerge as a therapeutic option for patients with atrial fibrillation at risk for cardioembolic stroke.

**Key words:** Atrial fibrillation; Stroke prevention; Left atrial appendage; WATCHMAN® device; Complications

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**Core tip:** Left atrial appendage (LAA)-Occlusion was developed as an alternative to chronic anticoagulation therapy in patients with nonvalvular atrial fibrillation. In two large randomized trials the principal concept of LAA-occlusion has been demonstrated to be noninferior to coumadine therapy, in longterm follow up being even superior to oral anticoagulation in terms of efficacy

and some safety issues like bleeding complications. However the procedure is complex and knowledge of nature, management and prevention of complications should minimize the risk of the procedure and allow transcatheter left atrial appendage closure to emerge as a therapeutic option for patients with atrial fibrillation at risk for cardioembolic stroke.

Möbius-Winkler S, Majunke N, Sandri M, Mangner N, Linke A, Stone GW, Dähnert I, Schuler G, Sick PB. Percutaneous left atrial appendage closure: Technical aspects and prevention of periprocedural complications with the watchman device. *World J Cardiol* 2015; 7(2): 65-75 Available from: URL: <http://www.wjgnet.com/1949-8462/full/v7/i2/65.htm> DOI: <http://dx.doi.org/10.4330/wjc.v7.i2.65>

## INTRODUCTION

Stroke is one of the leading causes of death and disability worldwide. Approximately 25% of all strokes have a cardioembolic origin. More than 90% of all left atrial thrombi in patients with non-rheumatic atrial fibrillation (AF) originate in the left atrial appendage (LAA)<sup>[1,2]</sup>. Oral anticoagulation therapy with the vitamin K antagonist warfarin including all its well-known limitations is standard for the prevention<sup>[3]</sup>. Only about 55% of patients with AF, who are indicated for warfarin therapy, are really treated, however these patients are only about 67% of the time in the therapeutic range<sup>[4,5]</sup>. Several major recent trials have demonstrated the superiority of the new oral anticoagulants Dabigatran, Rivaroxaban and Apixaban as compared to standard therapy with warfarin<sup>[6-8]</sup>. Nevertheless, even with these new agents bleeding complications were substantial and in part comparable to that observed with warfarin except for intracranial bleedings being less. A certain amount of patients discontinued drug therapy prematurely for adverse events, mainly gastrointestinal reasons for example in dabigatran patients.

Several studies have been conducted focusing on the development of novel therapeutic tools to prevent AF-related strokes as an alternative to medical treatment. The technique which has arguably shown the most promise is the percutaneous (transcatheter) occlusion of the LAA from systemic circulation.

Three different devices specifically designed for occlusion of the LAA have been clinically evaluated: the Percutaneous LAA Transcatheter Occlusion system (PLAATO®), (ev3, Plymouth, MN), the WATCHMAN® system (Boston Scientific Corp., Natick, MA, United States), and the AMPLATZER® Cardiac Plug (St. Jude Medical, Inc., St. Paul, MN, United States) (Figure 1). Although safety and feasibility of the PLAATO device was demonstrated in several small

non-randomized studies, the device was withdrawn from the market for commercial reasons. But even with the PLAATO device we have learned that there are specific complications associated with the implantation procedure such as device embolizations and cardiac tamponade<sup>[9-11]</sup>. Initial experience with the AMPLATZER® cardiac plug (ACP) has been published recently from a registry containing 132 successfully implanted devices<sup>[12]</sup>. To date, only the WATCHMAN® device has demonstrated superiority in long term follow up compared with chronic warfarin therapy in randomized, controlled trials<sup>[12-14]</sup>. In Europe, the latter two systems are approved for implantation, whereas in the United States both systems are under FDA investigation for potential approval. Despite being a lesser invasive procedure (than surgical ligation of the LAA), transcatheter LAA closure has been associated with potentially serious complications due to the necessity of transseptal puncture, manipulation of stiff wires and guide catheters in the left atrium and the release of the device in the LAA.

The following review highlights the potential procedural complications of transcatheter LAA closure with the Watchman-Device and discusses their nature, management and prevention.

## IMPLANTATION PROCEDURE

Before starting the procedure transesophageal echocardiography (TEE) has to be performed as the gold standard for thrombus detection within the LAA (Figure 2). Thrombi have been reported to be present in the LAA in 8%-15% of patients with AF lasting greater than 48 h<sup>[15]</sup>. Understanding the anatomy of the LAA is also critical for procedural safety. To facilitate successful implantation, width and depth of the LAA as well as number and position of different lobes are important to know. Studies have shown that the width of the LAA orifice can vary from 15-35 mm and length from 20-45 mm<sup>[16]</sup> with various anatomical configurations.

### Patient preparation

Implantation of the LAA closure devices should be usually performed under conscious sedation or even general anaesthesia. This is necessary to reduce unintended movement of the patient to avoid perforation of the LA/LAA and for tolerance of TEE, which is crucial for guidance of the procedure with the Watchman-Device. Usually a combination of midazolam and propofol is used, although alternative regimens may be possible. Implantation of the device is performed *via* the right femoral vein through a transseptal puncture with a small sheath in the femoral artery for pressure control or even management of air embolism as outlined below, which might not be mandatory.



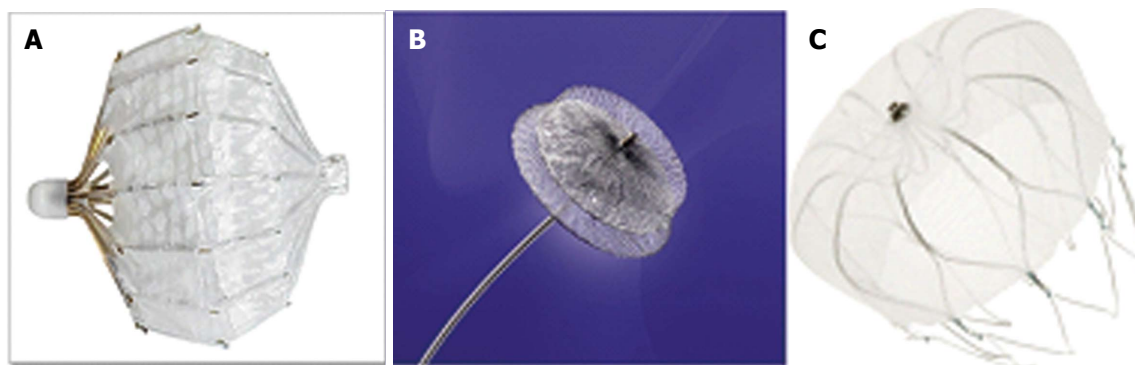


Figure 1 Devices for percutaneous occlusion of the left atrial appendage. A: PIAATO® device; B: Amplatzer® cardiac plug; C: Watchman® device.

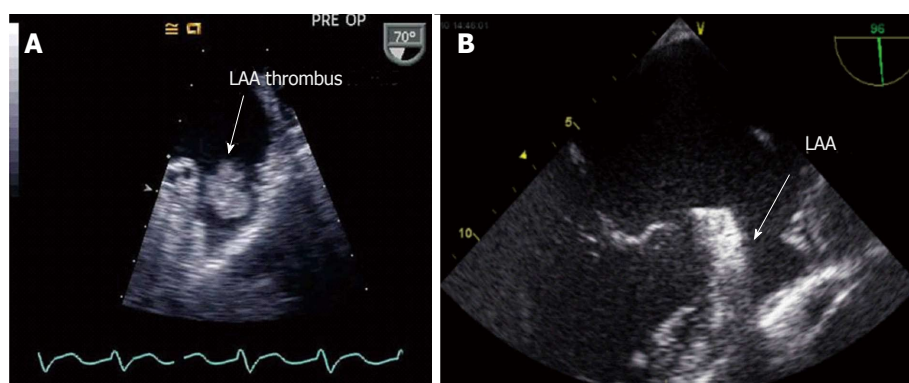


Figure 2 Left atrial appendage. A: With thrombus; B: Without thrombus. LAA: Left atrial appendage.

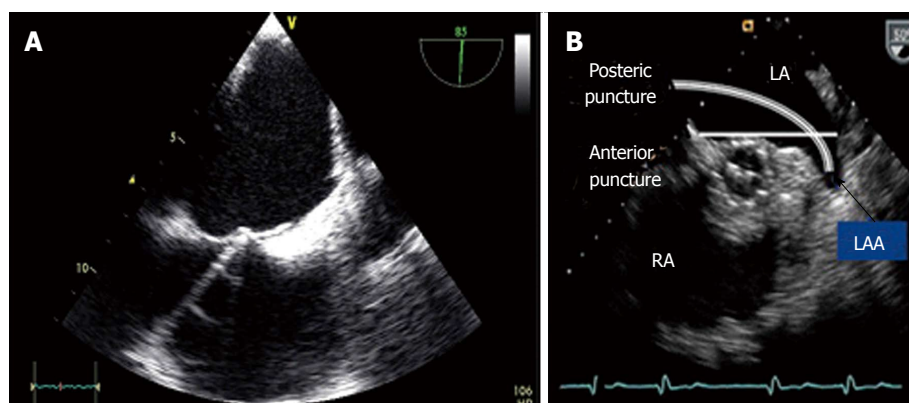


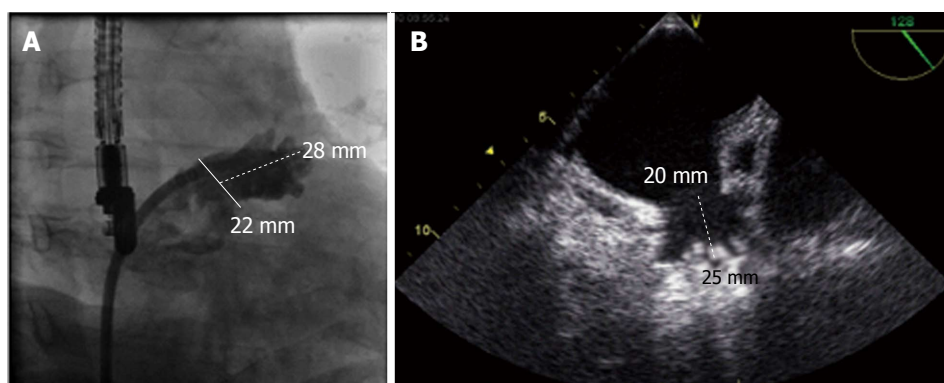
Figure 3 Echocardiography in transseptal puncture. A: Tenting of transseptal needle at the middle part of the atrial septum; B: Access sheath passing through the atrial septum within left atrium. LAA: Left atrial appendage.

### Transseptal puncture

Transseptal puncture is described elsewhere<sup>[17]</sup>. Transseptal puncture should be ideally performed under pressure control and with TEE and fluoroscopic guidance. To enhance successful implantation of the LAA closure device the site of transseptal puncture should be at the posterior atrial septum. The more anterior or inferior the LAA is located, the higher transseptal puncture should be performed. The more cranial the axis of the LAA, the more inferior puncture site should be. This can be easily controlled by TEE in the bicaval view (90°) for cranio-caudal

orientation and in the 45° view for anterior/posterior direction (Figure 3). Anterior puncture of the septum likewise going through an open PFO should be avoided due to the impossibility to turn the guiding catheter adequately to an anterior located axis of the LAA. An atrial septal defect may be used having enough space for turning the guide. After successful transseptal puncture heparin is given using a dosage of 100 U/kg body weight to achieve an ACT between 200 and 300 s. Heparin could be applied already before transseptal puncture, which, however might lead to an increased risk of bleeding during the





**Figure 4** Measurement of the left atrial appendage during implantation procedure. A: After angiography (RAO 25°, caudal 20°)-measurement of ostium size (22 mm) and depth (28 mm); B: Echocardiographic measurement at around 135° of ostium size (20 mm) and depth (25 mm).

transseptal procedure.

### Device implantation

Device implantation has been described previously<sup>[18]</sup> After exchange of the transseptal sheath over a stiff wire located best in the left upper pulmonary vein, the guiding catheter can be introduced. Wire positioning in the LAA with a loop may be also possible, however there is some risk of perforation. Two different curved sheaths (single and double curve) are available for implantation of the Watchman® device. For the Watchman device in more than 90% of patients the double curved sheath is used. To avoid undersizing of the LAA, the mean filling pressure of the left atrium should be in the high normal range (> 10 mmHg). For Watchman implantation a 4 or 5 French standard Pigtail catheter should be placed through the sheath. By turning the guiding catheter counter clockwise the pigtail can be advanced into the LAA under TEE and fluoroscopic guidance. The access sheath is then advanced slowly and carefully over the pigtail catheter into the LAA, thus at least reducing the risk of perforation. The marker bands on the access sheath of the Watchman® Device will help to determine the landing zone of the cover of the device at the site of the left atrium. The most suitable projections for angiographic visualization of the LAA seem to be RAO 30° with caudal 25° and cranial 20° for measurement of the orifice width and length of the LAA (Figure 4). Ideally the angiographic measurements will match the echocardiographic measurements in different angles from 0° to 135°, although they may vary by several mm depending on calibration methods.

Devices should be prepared according to the instructions for use. Careful flushing of the device and retrograde bleeding out of the access sheath is essential to avoid air embolism. Slight pressure on the patient's abdomen will increase venous pressure thus increasing backflow of blood through the sheath. A saline pressure infusion over the side branch of the guiding cath may be helpful.

### Implantation of the watchman device

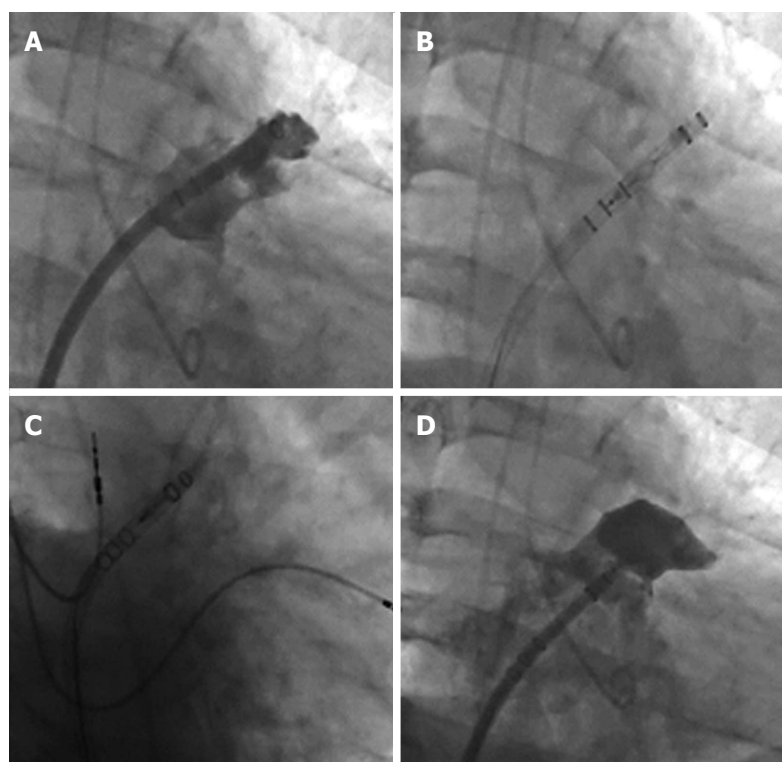
The Watchman device should be advanced in the sheath until the marker of the device catheter matches the most distal marker on the access sheath. The next step is to pull back the access sheath over the device until device catheter and access sheath are connected. At this point the device should remain in position and forward pushing of the device must be strictly avoided in terms of the risk of LAA injury or perforation with subsequent cardiac tamponade. The device is deployed by retracting the sheath and device catheter simultaneously while the device is held in place. Small amounts of contrast injections may help to visualize the relation between the tip of the device and the LAA wall during deployment (Figure 5).

Once the device is deployed within the LAA, correct positioning of the Watchman device at the LAA ostium must be demonstrated by echocardiography and angiography (Figure 6). To avoid embolism of the Watchman Device, there are four release criteria that should be evaluated before release: Position, Anchor, Size and Seal (PASS).

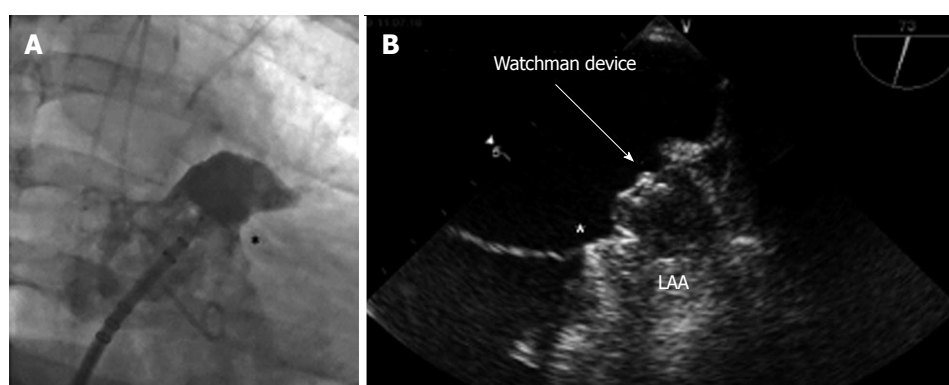
**Position:** To confirm that the device is properly positioned, ensure that the plane of maximum diameter of the device is at or just distal to the orifice of the LAA.

**Anchor:** To confirm the device is anchored in place, withdraw the access sheath/delivery catheter assembly 1-2 cm from the face of the device. After injecting a small puff of contrast gently retract and push the deployment knob to see the combined movement of the device and the LAA tissue.

**Size:** To confirm the correct device size, measure the plane of the maximum diameter of the device using TEE in the 4 standard views 0, 45, 90, and 135 degrees, ensuring the threaded insert is visible. The device size should be 80%-92% of the nominal diameter.



**Figure 5** Deployment of a Watchman® device (fluoroscopic views). A: Deployment sheath in correct position; B: Watchman device loaded within the sheath before deployment; C: Watchman device deployment; D: Watchman device completely deployed within the LAA. LAA: Left atrial appendage.



**Figure 6** Optimal position of the Watchman device within the left atrial appendage. A: Angiographic view (RAO 25° caudal 20°); B: Echocardiographic view. Indicates inferior transition from left atrial appendage to LA (star).

**Seal:** Using colour Doppler, ensure that all of the lobes are distal of the device and are sealed. If there is a gap visible between the wall of LAA and the device with more than 3 mm, the device should be repositioned.

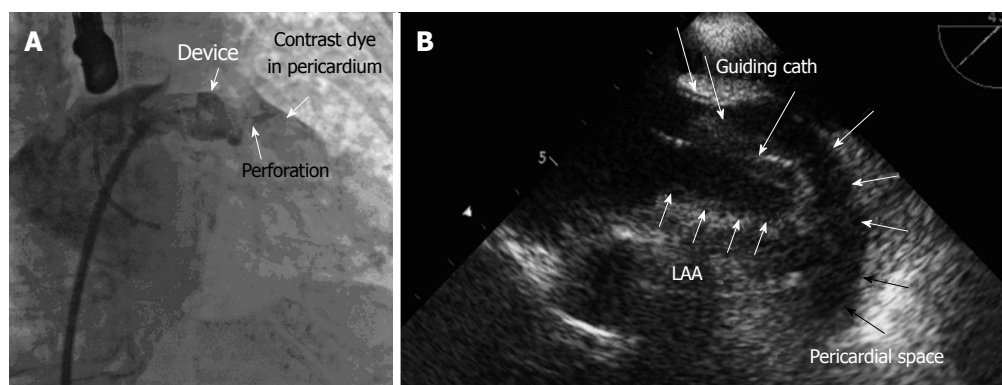
## PREVENTION AND MANAGEMENT OF COMPLICATIONS

### Pericardial effusion

Pericardial effusion as acute/subacute cardiac tamponade or as an asymptomatic effusion is one of the most serious complications in LAA-occlusion procedures<sup>[12,19]</sup>. The transseptal puncture itself<sup>[19]</sup>,

manipulation of stiff wires, guiding catheters and the device itself within the left atrium and the thin-walled LAA, as well as too aggressive movement of the device during stability testing may result in LAA wall injury leading to pericardial effusions.

In the Protect AF trial<sup>[12]</sup>, the rate of pericardial effusion occurring within 7 d of Watchman implantation was 4.5%, 3.3% of patients required pericardiocentesis. These complications are mainly observed at the beginning of the learning curve and became less frequent with more experience<sup>[12]</sup>. In the CAP registry, where experienced operators implanted Watchman® devices after the randomized trial was completed, the rate of pericardial effusions decreased to 2.2%<sup>[20]</sup> and could be held in the same



**Figure 7** Pericardial effusion. A: Angiographic view; B: Echo view. LAA: Left atrial appendage.

range in the PREVAIL-trial with adequate training of new operators<sup>[21-23]</sup>.

Several techniques to avoid pericardial effusions are: (1) TEE guidance and pressure monitoring to ensure a safe transseptal puncture at the correct site before advancing the sheath; (2) use of a 4 or 5 F. pigtail catheter inside the access sheath or a looped wire in the LAA to facilitate a safe movement of the guiding into the LAA; (3) slow and careful movements of the catheter and device manipulation within the left atrium; and (4) stability (tug-) testing after device implantation should be performed under TEE-control and fluoroscopy with injection of small amounts of contrast dye.

Cardiac tamponade with hypotension requires an aggressive approach with pericardiocentesis and reversal of anticoagulation (Figure 7). In case of recurrent tamponade, surgery is needed. Therefore early detection of an effusion by TEE is very important before hemodynamic deterioration arises from cardiac tamponade. Though most pericardial effusions occur early, subacute and late effusions are also possible. Therefore monitoring over a period of 48 h including 6 h close heart rate and pressure control and performance of trans-thoracic echocardiography at least before discharge to rule out pericardial effusion and to proof stable position of the device is recommended. Subacute effusions may arise from the anchors of the devices due to the thickness of only 0.5-0.8 mm of myocardial tissue of the LAA. If the effusion results in tamponade, pericardiocentesis and sometimes surgery is required. In case of late pericardial effusions also inflammatory processes may play a role, probably due to chronic injury of the hooks to the pericardium. In these cases anti-inflammatory therapy with non-steroidal antirheumatics like ASA, ibuprofen, diclofenac or even steroid therapy may be required at least for a certain period of time.

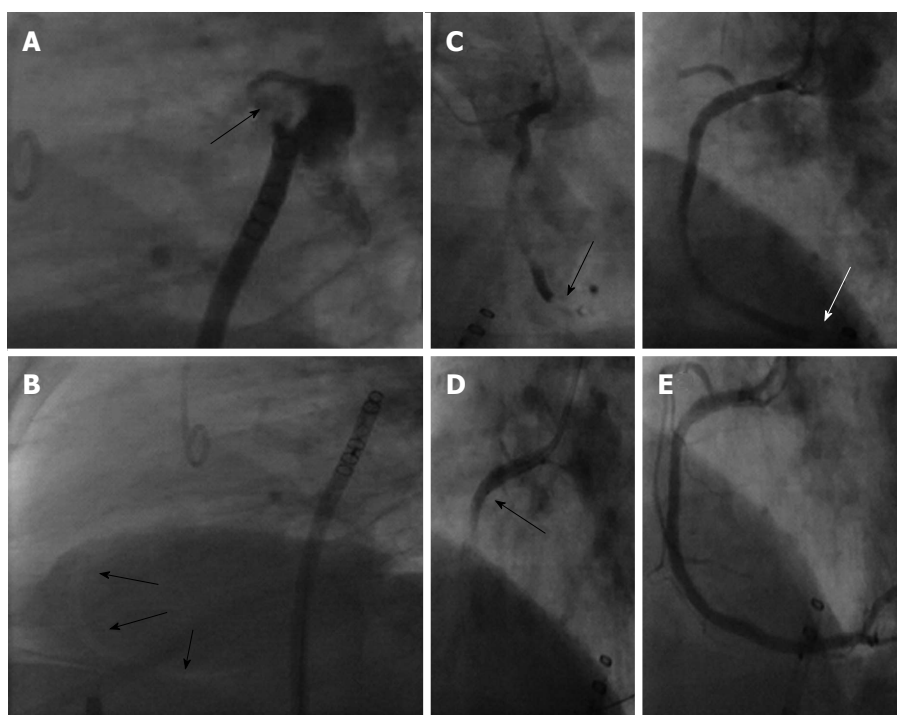
### Air embolism

Air embolism is frequently a clinically silent event. However, acute coronary ischemia, stroke, hypotension, cardiac arrest and/or death are all possible outcomes.

Holmes *et al*<sup>[12]</sup> report, that 5 of 449 patients with implantation of a Watchman® device suffered from a periprocedural stroke. The most common cause was air embolism, which is usually short-lived. Air emboli may enter the left atrium due to accidental injection of air, trapped air despite of flushing of the catheter or by air intrusion driven by a gradient between atmospheric and intracardiac pressure with a deep inspiration of the patient<sup>[24]</sup>. Therefore the left atrial pressure should be increased to normal or slightly high mean pressure using saline infusions. High pressure infusion through the side arm of the guiding catheter conversely can even lead to air embolism due to the Venturi-effect when opening the stop cock.

The management of air embolism is largely supportive. Hyperbaric oxygen has been shown to be of benefit in up to 80% of cases of cerebral air embolism, but controlled trials have not been performed yet<sup>[25]</sup>. However, as cerebral air embolism is mostly short-lived, there are usually no sequelae to be expected in longterm follow up.

Air embolism to the coronary circulation is most common in the right coronary artery because of the anterior position of the ostium (Figure 8). It often resolves within several minutes. However, marked ST-segment elevation, hypotension and ventricular arrhythmias may result, leading to cardiogenic shock. Aspiration of the air with an aspiration device (e.g., EXPORT Catheter, Medtronic Inc. Minneapolis, MN, United States) or rigorous contrast dye injection into the coronary artery may be helpful in selected cases (Figure 8). In this case the arterial access may be helpful to advance a right coronary catheter quickly to the aortic root or even having a right coronary diagnostic catheter already in place during transseptal puncture to mark the aortic root. Also Trendelenburg position is recommended; as air trapped anywhere within the heart (e.g., the LAA) might be dislodged leading to another air embolism. If there is a large amount of air within the left or right atrium, the LAA or in the ascending aorta, this may also be aspirated through the sheath or *via* a coronary multipurpose or right coronary catheter.



**Figure 8 Air embolism.** A: Air bubble within the left atrial appendage; B: Right coronary artery (RCA) filled with air (bright shadows); C: RCA with large air bubble; D: Placement of a aspiration catheter (EXPORT, Medtronic) within the RCA; E: RCA after successful aspiration of air bubbles without filling defect. LAA: Left atrial appendage

Aspiration of air should be performed before catecholamines are given for pressure management. This can protect from air movement into the brain circulation.

#### **Thrombus formation during device implantation**

During the procedure an activated clotting time of about 250 s should be aimed at using heparin and continuous flushing of the guiding catheter is recommended to avoid thrombus formation within the catheter. In case of new thrombus formation in the LAA, the operator must decide if it is prudent to continue the procedure. If a good position of the delivery sheath has been achieved, implantation might be possible, especially if it is deemed to be more dangerous to retract the device and sheath. The membrane of the device, once deployed, is able to catch a thrombus in the LAA.

If the sheath has not yet been maneuvered into the LAA, aspiration of blood and possible thrombus through the side port should be attempted followed by removal of the sheath for an outside flushing.

If thrombus formation is observed outside the access sheath in the left atrium, the only option is to withdraw the sheath back into the right atrium applying pressure on both proximal carotid arteries to minimize the risk of cerebral thromboembolism followed by close neurological monitoring.

#### **Early device embolization**

Percutaneous closure of the LAA may be complicated by immediate or late device embolization. Device

embolization occurs in about 0.2% of cases with the Watchman® device (Figure 9)<sup>[12]</sup> Selection of patients with favorable LAA morphology and appropriate device sizing are crucial to prevent embolization. Negative predictors are: large LAA ostial size, use of undersized devices, short LAA length for the Watchman and unusual LAA morphologies.

The Watchman-Device must be fully expanded and compressed by at least 10%-30% of its original size. If the device is too deep in the LAA and therefore not fully expanded, the device must be partially recaptured and repositioned. If the device is too proximal, a complete recapture and exchange of the device is necessary.

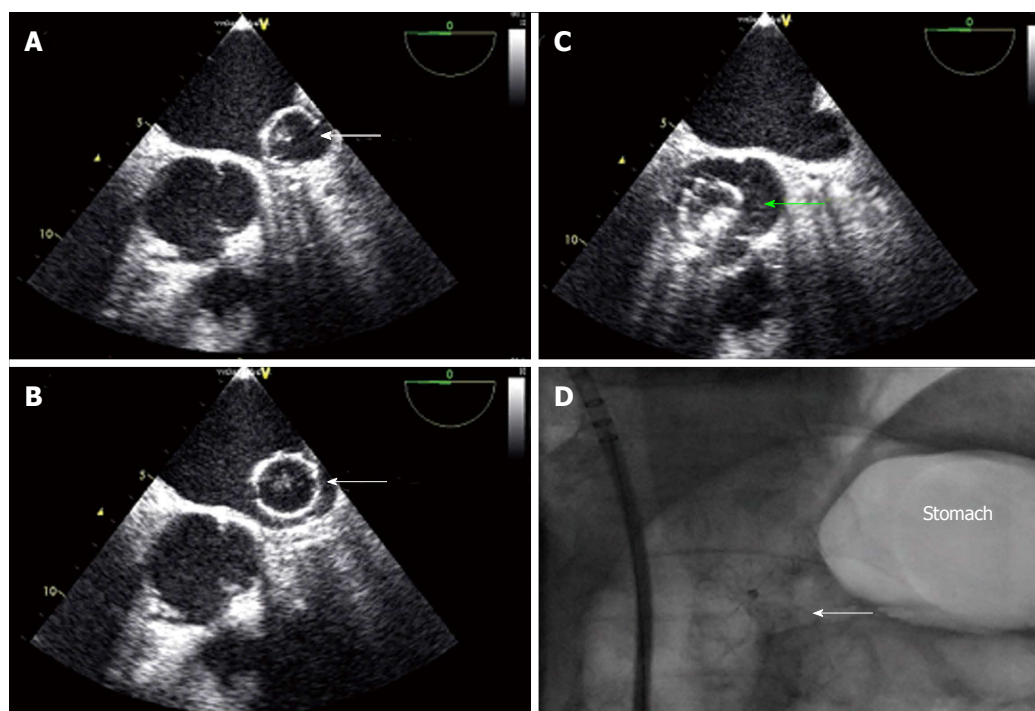
The above mentioned Device release criteria should be fulfilled before release.

#### **Late device embolization**

Routine post procedural TTE to exclude a new or expanding pericardial effusion and as a screen for device embolization is mandatory one to two days after implantation, even if the patient is asymptomatic<sup>[12,14]</sup>. The best way to visualize a LAA-occluder is from subxiphoidal. If the device cannot be seen, we recommend fluoroscopy to confirm correct position of the device.

Embolized devices that are found in the left atrium or left ventricle may be safely moved antegradely across the mitral and aortic valve by using coronary catheters. Snaring of devices within the heart itself is challenging and dangerous. However, retrieval from the descending aorta using a snare or biopptome





**Figure 9** Device embolisation of watchman-device. A: Within the left atrial appendage immediately after release (arrow indicates device); B: Embolisation from the left atrial appendage; C: Passage of the aortic valve; D: Device within the lower thoracic aorta after embolization.

through an appropriately sized retrieval sheath (min. 14 Fr.) (Figure 10) is both safer and more feasible. In rare cases of embolisation of larger devices, surgical retrieval might be necessary even through the groin. Therefore, close collaboration with cardiac/vascular surgery ensures open access retrieval, if the percutaneous maneuver fails.

## PROCEDURAL FOLLOW UP AND MEDICAL TREATMENT TO AVOID COMPLICATIONS

To avoid thrombus formation on the device for the Watchman® device, aspirin 100 mg/d and warfarin (INR goal 2-3x normal) should be administered until 45 d TEE control according to the PROTECT AF-trial<sup>[12]</sup>. If the device is still in position, the LAA occluded and no or minimal flow (residual jet < 5 mm) around the device, oral anticoagulation can be stopped and clopidogrel 75 mg/d should be added up to 6 mo after implantation. After another TEE-control aspirin alone should be administered lifelong at least according to the actual study results, though there are some centers that even stop aspirin therapy after three to six months. However, there are no data about long term results without any antiplatelet therapy. Within the Protect AF trial, patients having a residual gap < 5 mm were not likely to develop more stroke/TIA than patients without a gap, as a recent publication by Viles-Gonzalez was able to demonstrate<sup>[26]</sup>. If the 45 d TEE demonstrates a jet

> 5 mm, warfarin must be continued with another TEE after 3 mo. If there is no change, the implant is deemed to have failed and the patient should remain on chronic oral anticoagulation therapy. If the gap has decreased to < 5 mm, therapy can be changed to ASA and clopidogrel.

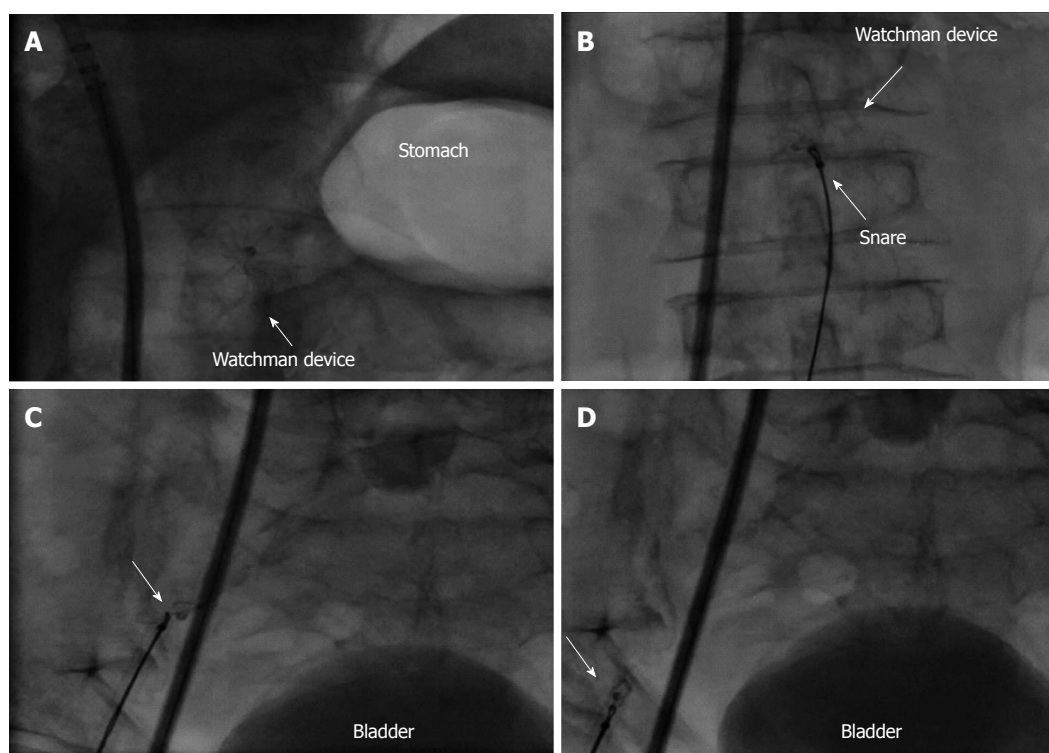
In case of absolute or relative contraindications for warfarin therapy, another regimen recommends to give ASA and Clopidogrel immediately after implantation for 6 mo followed by ASA alone, which was similar effective in a small registry trial called ASAP<sup>[27]</sup>. If ASA could be even stopped at 6 mo or some time later is not clear yet. There are no data really supporting continuation or discontinuation of ASA lifelong except the experience of PROTECT AF.

In some cases, thrombus formation on the device may be detected by TEE (Figure 11). In these cases, low molecular weight heparin or oral anticoagulation should be restarted for another 4-8 wk. A repeat TEE will direct further treatment as described above.

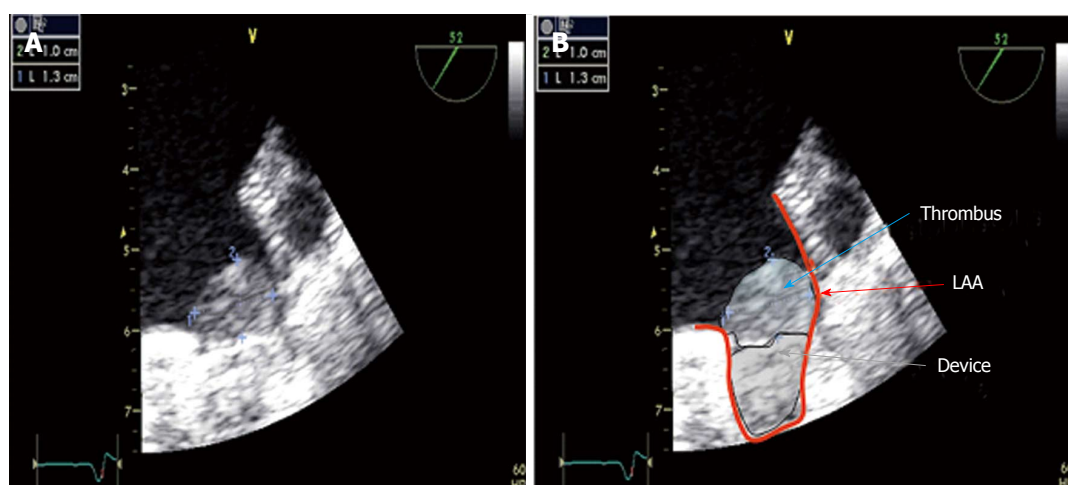
## CONCLUSION

Percutaneous closure of the left atrial appendage has been shown to be feasible with promising results in terms of reducing the rate of stroke and hemorrhagic complications, and has become an alternative therapy to standard anticoagulation therapy in patients with atrial fibrillation in Europe and other countries. The actual accepted indications for the use of LAA-occlusion therapy to be considered is published in an EHRA/EAPCI expert consensus statement<sup>[28]</sup>.





**Figure 10 Device retrieval after embolization.** A: Watchman device within the lower thoracic aorta after embolization; B: Snaring of the Watchman device with a goose neck snare 20 mm; C: Retraction of the device into the right arteria iliaca; D: Device retracted into a large (14 Fr.) sheath.



**Figure 11 Thrombus formation (1.0 cm x 1.3 cm) 45 d after implantation on a Watchman device (A) and schematic view: Thrombus, device and left atrial appendage are highlighted (B).**

Main indications are real contraindications for oral anticoagulation even for NOACs, patient refusal despite adequate information about different anticoagulation modalities, increased risk for bleeding due to a high HASBLED-score, need for prolonged triple therapy for example after coronary stenting, increased bleeding risk not reflected by the HASBLED-score and severe renal failure as a contraindication to NOACs. An individual risk benefit evaluation for each patient should be performed. FDA-approval may be expected in the beginning of the year 2015.

As a new invasive procedure, transcatheter LAA closure has several device- and procedure-specific complications, mainly pericardial effusions with or without tamponade, air embolism with subsequent stroke or device embolization. To minimize these complications, the procedure should be performed only by operators experienced in transseptal puncture and structural heart interventions. Additionally, TEE guidance by an experienced echocardiographer is important to ensure a complication-free and successful procedure. Profound knowledge of the

nature, management and prevention of complications is essential to optimize the outcome of transcatheter LAA closure.

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## Flecainide: Current status and perspectives in arrhythmia management

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polymorphic ventricular tachycardia associated both with ryanodine receptor and calsequestrin mutations. We herein review the current clinical data related to flecainide use in clinical practice and some concerns about its role in the management of patients with coronary artery disease.

**Key words:** Flecainide; Class IC antiarrhythmic drugs; Atrial fibrillation; Ventricular tachycardia; Proarrhythmia

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**Core tip:** Flecainide acetate is recommended as one of the first line antiarrhythmic drugs in patients with atrial fibrillation and/or supraventricular tachycardias for the restoration and maintenance of sinus rhythm. Based on the Cardiac Arrhythmia Suppression Trial study results, flecainide is contraindicated for patients with structural heart disease due to high proarrhythmic risk. Recent data support the role of flecainide in preventing ventricular tachyarrhythmias in patients with catecholaminergic polymorphic ventricular tachycardia associated both with ryanodine receptor and calsequestrin mutations.

### Abstract

Flecainide acetate is a class IC antiarrhythmic agent and its clinical efficacy has been confirmed by the results of several clinical trials. Nowadays, flecainide is recommended as one of the first line therapies for pharmacological conversion as well as maintenance of sinus rhythm in patients with atrial fibrillation and/or supraventricular tachycardias. Based on the Cardiac Arrhythmia Suppression Trial study results, flecainide is not recommended in patients with structural heart disease due to high proarrhythmic risk. Recent data support the role of flecainide in preventing ventricular tachyarrhythmias in patients with catecholaminergic

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### INTRODUCTION

Flecainide acetate is a class IC antiarrhythmic agent that was first synthesized in 1972. Its development began in 1966 in an attempt to generate new fluorinated anesthetic organic agents with the substitution of a trifluoroethoxy group on the aro-



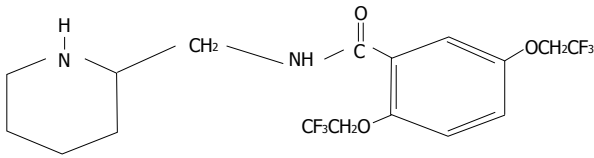


Figure 1 Chemical structure of flecainide acetate.

matic ring in the place of the amine group (Figure 1)<sup>[1]</sup>. The clinical efficacy of flecainide was confirmed by the results of several clinical trials, both in animals and humans<sup>[2-6]</sup>. Oral use of flecainide was approved in 1984 from the Food and Drug Administration for the suppression of sustained ventricular tachycardia since study results showed about 90% efficacy without significant adverse events<sup>[7]</sup>. However, safety data from 1330 patients between 1980 and 1985 demonstrated that flecainide use was associated with increased proarrhythmic events in patients with severe cardiac disease primarily in those who were starting therapy with high-dose<sup>[8]</sup>.

The publication of the Cardiac Arrhythmia Suppression Trial (CAST) study in 1989, which was designed to investigate the efficacy of class I antiarrhythmic agents moricizine, encainide or flecainide in patients after myocardial infarction with reduced ejection fraction and frequent ventricular ectopic beats, resulted in a major revision of the role of these antiarrhythmic drugs<sup>[9]</sup>. Thus, while flecainide suppressed ventricular ectopy in those patients, a threefold increase of arrhythmic death was recorded compared to placebo<sup>[9]</sup>. Based on CAST results, flecainide nowadays is not recommended for patients with structural heart disease and coronary artery disease. However, it is recommended as one of the first line therapies for pharmacological conversion as well as maintenance of sinus rhythm in patients with atrial fibrillation and/or supraventricular tachycardias without structural heart disease<sup>[10]</sup>. This review aims to present the existing data regarding the use, effectiveness and safety of flecainide in current clinical practice of arrhythmia management.

## CLINICAL PHARMACOLOGY OF FLECAINIDE

### Pharmacodynamics

Orally administrated flecainide is administrated twice daily and is absorbed rapidly without any significant interactions with food or antacid. Its bioavailability is around 90%, indicating no significant first pass effect through the liver. In normal subjects, plasma peak levels are reached after 2-3 h and steady state levels within 3-5 d. The half-life of flecainide ranges from 7 to 23 h and seems to be unaffected by dose<sup>[11,12]</sup>. Patients with ventricular ectopic beats have a longer half-life (mean 20 h) compared with normal subjects, mainly due to reduced renal function<sup>[13]</sup>. Flecainide

levels are higher in cardiac tissues compared to plasma<sup>[14]</sup>. Two major metabolites, the active meta-O-dealkylated flecainide and its inactive lactam, are produced by hepatic oxidative metabolism *via* cytochrome CYP2D6 and CYP1A2. Both flecainide and metabolites are excreted mostly in urine, so patients with impaired renal function require close monitoring and dose reduction. Approximately 30% of flecainide is excreted unchanged into the urine<sup>[13,14]</sup>. It should be pointed that the antiarrhythmic efficacy of flecainide is closely correlated to the QRS duration. Therapeutic plasma levels range between 0.2 and 1.0 mg/mL and higher values are associated with toxic cardiac effects, such as bradycardia or conduction abnormalities<sup>[15]</sup>. The recommended starting dose in patients without renal insufficiency and paroxysmal supraventricular tachycardia or paroxysmal atrial fibrillation is 50 mg *bid* and may be increased in increments of 50 mg *bid* until efficacy is achieved (maximum recommended dose 300 mg/d). In patients with ventricular tachycardia and no contraindications for flecainide administration, the starting dose is 100 mg *bid* and the maximum recommended dose is 400 mg/d. Attention should be paid in patients concomitantly receiving amiodarone, although rare to encounter, who may require a dose reduction about 50%<sup>[11]</sup>. Additionally, caution is needed prior to but also following drug initiation, to exclude concomitant electrolyte disturbances, especially hypokalemia. In patients with severe hepatic insufficiency, flecainide administration should be carefully considered and monitoring of drug levels in plasma may be required<sup>[12]</sup>.

### Electrophysiological properties

As mentioned above flecainide belongs to the class IC antiarrhythmic agents which produce a potent and selective blockade of the cardiac fast inward sodium ( $\text{Na}^+$ ) current resulting in conduction slowing<sup>[11]</sup>. A high affinity for open-state  $\text{Na}^+$  channels and the slow unbinding kinetics from these channels during diastole has been described, explaining the slowing of the recovery time during the cardiac diastole and the prolongation of refractoriness<sup>[11,12]</sup>. Moreover, flecainide inhibits opening of potassium channels, especially the rapid component of the delayed rectifier  $\text{K}^+$  current ( $\text{I}_{\text{Kr}}$ ), prolonging the action potential duration (APD) in ventricular and atrial muscle fibers. In opposite, in Purkinje fibers, flecainide causes a shortening in the APD due to the  $\text{Na}^+$  channel blockade<sup>[16-18]</sup>. Recent data suggest that flecainide blockades ryanodine receptor opening, thus reducing spontaneous sarcoplasmic reticulum  $\text{Ca}^{2+}$  release, which potentially results in afterdepolarization and triggered activity<sup>[19,20]</sup>. Therefore, flecainide has been used for the therapy of catecholaminergic polymorphic ventricular tachycardia (CPVT), which is an inherited arrhythmogenic disease with mutations of either the

cardiac ryanodine receptor or calsequestrin that can cause sudden cardiac death<sup>[21]</sup>.

Regarding the impact of flecainide in the intra-cardiac intervals, flecainide increases the AH interval (15%-22%) and the HV interval (25%-50%), thus slightly slowing both intra-atrial and atrioventricular nodal conduction<sup>[22,23]</sup>. In patients with evidence of dual atrioventricular node pathway physiology, flecainide has shown to prolong mainly the retrograde refractoriness of the fast pathway<sup>[22]</sup>. Also, in patients with accessory atrioventricular pathways, flecainide can cause complete retrograde pathway block especially in patients with refractoriness more than 270 ms at baseline, although potentially decreases both anterograde and retrograde refractory periods<sup>[24]</sup>. Additionally, flecainide does not seem to affect normal sinus node function but in patients with sinus node dysfunction an increase of the corrected sinus node recovery time and the sinoatrial conduction time have been reported<sup>[25,26]</sup>. Finally, patients with implanted cardiac rhythm devices (pacemakers or internal cardiac defibrillators) and concomitant flecainide treatment may experience an increase in the pacing thresholds<sup>[25]</sup>.

All the above mentioned electrophysiological properties of flecainide are deflected in the twelve lead surface electrocardiogram with an increase in PR, QRS and QT intervals duration. The QTc interval is not significantly increased since most of QT prolongation is due to the QRS widening<sup>[11,22]</sup>. During exercise, flecainide usually shortens QTc interval<sup>[27]</sup>.

#### **Proarrhythmic and inotropic effects of flecainide**

It is well known that class IC antiarrhythmic drugs may potentially be associated with proarrhythmia, either as atrial flutter with 1:1 atrioventricular conduction or ventricular tachyarrhythmia. Flecainide can convert atrial fibrillation into atrial flutter, potentially resulting in a rapid tachycardia with more than 200 bpm in case of 1:1 atrioventricular conduction<sup>[28]</sup>. The reported rate of this proarrhythmic effect is 3.5% to 5.0% and has been associated with high adrenergic conditions<sup>[29]</sup>. Drugs with atrioventricular nodal blockade properties, such as  $\beta$ -blockers, verapamil and diltiazem, should be administered concomitantly in order to lower the risk.

Ventricular tachycardias due to proarrhythmic effect seem to be rare in patients without structural heart disease, electrolyte disturbances and coronary artery disease. Ventricular proarrhythmia manifests either as monomorphic or polymorphic tachycardia not only early but also late after the initiation of therapy according to the results of CAST study<sup>[9]</sup>. The incidence of ventricular proarrhythmia in patients receiving flecainide for acute cardioversion of atrial fibrillation was reported in a systematic review to be less than 3%<sup>[30]</sup>.

Flecainide exerts a negative inotropic effect

and therefore is contraindicated in patients with congestive heart failure, coronary artery disease and reduced ejection fraction. In this population flecainide significantly reduces stroke volume index and left ventricle ejection fraction and increases right atrial and pulmonary capillary wedge pressures<sup>[31,32]</sup>. Even in patients with normal ejection fraction, oral administration of flecainide can slightly reduce the ejection fraction. Intravenous administration of flecainide (2 mg/kg) in healthy subjects was associated with a reduction in cardiac output and stroke volume during the first 90 min after dosing<sup>[33]</sup>. These hemodynamic effects are related to the reduced  $\text{Na}^+$  and  $\text{Ca}^{2+}$  entry into the myocardial cells. Moreover, as discussed above, flecainide has proved to blockade the ryanodine receptor opening and its interaction with the  $\text{Ca}^{2+}$  diastolic waves<sup>[34]</sup>.

#### **Mechanism of action of flecainide in maintenance of sinus rhythm and cardioversion in patients with atrial fibrillation**

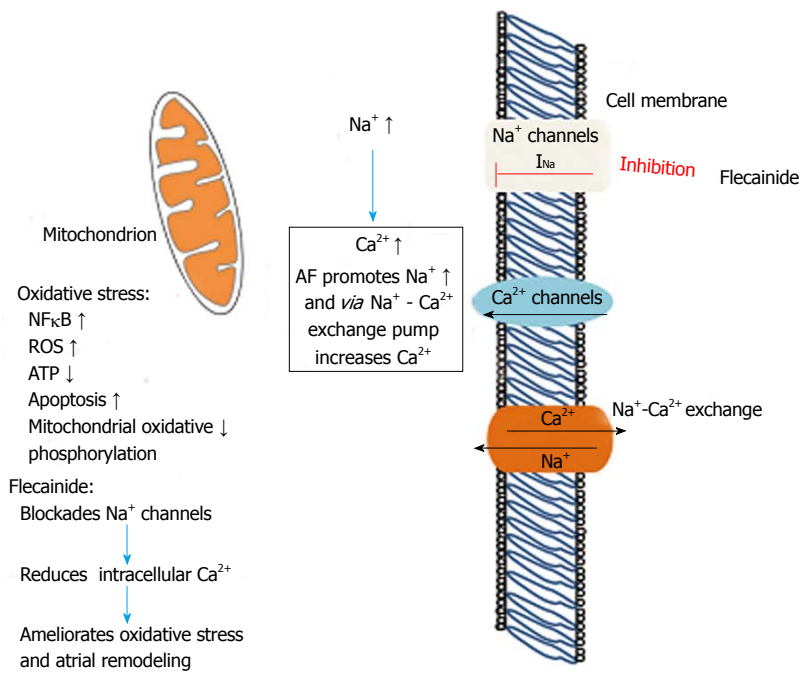
It is well known that atrial fibrillation causes both electrical and structural remodeling in atrial myocardium. Flecainide has proven its efficacy in the cardioversion of atrial fibrillation in sinus rhythm in both human and animal trials causing a shortening of the APD and prolongation of atrial refractoriness in a rate-dependent manner. Trial data have shown that the slow conduction properties of flecainide could result in a significant reduction of atrial wavelength so that atrial fibrillation cannot be maintained<sup>[34,35]</sup>.

Atrial fibrillation has been associated with significant structural changes in the atria which subsequently cause remodeling of the myocardial fibers and mitochondrial dysfunction due to oxidative stress<sup>[34]</sup>. Several inflammatory adhesion molecules associated with oxidative stress and subsequent myocardial ischemia, such as nuclear factor kappa  $\beta$  (NF $\kappa$ B), reactive oxygen species and glycogen, impair the cellular physiology enhancing apoptotic process and cellular protein decomposition<sup>[36]</sup>. Rapid atrial activation encountered during atrial fibrillation results in intracellular  $\text{Ca}^{2+}$  accumulation, thus promoting ischemia and cellular dysfunction. This process is facilitated by the high transient intracellular  $\text{Na}^+$  concentration during tachycardia, which accentuates the entry of  $\text{Ca}^{2+}$  via the  $\text{Na}^+/\text{Ca}^{2+}$  exchanger (Figure 2). Flecainide attenuates the intracellular  $\text{Ca}^{2+}$  accumulation by blocking  $\text{Na}^+$  channels, thus reducing oxidative stress process and further atrial remodeling<sup>[37]</sup>.

## **CLINICAL TRIALS**

#### **Acute conversion of atrial fibrillation of recent onset**

The efficacy of flecainide, both oral and intravenous formulation, in terminating recent-onset atrial fibrillation has been evaluated in several studies (Table 1) and is affected from the study design



**Figure 2 Mechanism of flecainide action during atrial fibrillation by inhibition of Na<sup>+</sup> channels which reduces intracellular Ca<sup>2+</sup> accumulation and reduces oxidative stress and mitochondrial dysfunction.** AF; Atrial fibrillation; I<sub>Na</sub>: Fast inward Na<sup>+</sup> current; ROS: Reactive oxygen species; NFκB: Nuclear factor kappa β; ATP: Adenosine triphosphate.

**Table 1 Reversion rate of recent-onset atrial fibrillation to sinus rhythm in clinical trials evaluating the conversion efficacy of oral or intravenous flecainide**

| Clinical trial                               | Patients in flecainide arm | AF duration | Formulation  | Reversion rate                                    |
|--|----------------------------|-------------|--|---|
| Capucci <i>et al</i> <sup>[38]</sup>         | 22 patients                | ≤ 7 d       | Single oral dose (300 mg)                                | 8 h → 91%<br>24 h → 95%                           |
| Donovan <i>et al</i> <sup>[39]</sup>         | 51 patients                | ≤ 3 d       | <i>iv</i> (2 mg/kg-max 150 mg)                           | 1 h → 57%<br>6 h → 67%                            |
| Donovan <i>et al</i> <sup>[40]</sup>         | 34 patients                | ≤ 3 d       | <i>iv</i> (2 mg/kg-max 150 mg)                           | 2 h → 59%<br>8 h → 68%                            |
| Boriani <i>et al</i> <sup>[41]</sup>         | 69 patients                | < 8 d       | Single oral dose (300 mg)                                | 1 h → 13%<br>3 h → 57%<br>8 h → 75%               |
| Martínez-Marcos <i>et al</i> <sup>[42]</sup> | 50 patients                | ≤ 2 d       | <i>iv</i> (2 mg/kg followed by 1 mg/kg at 8 h if not SR) | 1 h → 58%<br>8 h → 82%<br>12 h → 90%              |
| Romano <i>et al</i> <sup>[43]</sup>          | 138 patients               | ≤ 3 d       | Intravenous  | 1 h → 73%<br>3 h → 80%<br>6 h → 86%<br>24 h → 90% |

AF: Atrial fibrillation; SR: Sinus rhythm.

characteristics and the time intervals from drug initiation to assessment of reversion rate<sup>[38-42]</sup>.

Several randomized controlled clinical trials have also compared the efficacy of flecainide to other antiarrhythmic agents in acute conversion of recent-onset atrial fibrillation. Capucci *et al*<sup>[38]</sup> found that a single oral loading dose of flecainide was significantly more efficient than intravenous amiodarone within 8 h but not at 24 h. In a randomized, double-blind trial, intravenous flecainide was also shown to result in earlier reversion of recent onset atrial fibrillation to sinus rhythm as compared to intravenous amiodarone<sup>[40]</sup>. In accordance, Martínez-Marcos *et al*<sup>[42]</sup> found that a significantly higher proportion of patients reverted to sinus rhythm when treated with intravenous flecainide as compared to intravenous

amiodarone and propafenone, although the difference in reversion rate with intravenous propafenone reached statistical significance at 12 h but not at 8 h following treatment onset<sup>[42]</sup>. On the other hand, Romano *et al*<sup>[43]</sup> found a significantly higher efficacy of intravenous flecainide compared to intravenous propafenone in acute conversion of recent onset atrial fibrillation at 1, 3 and 6 h, although no difference was evident at 24 h. Finally, in a comparative study, Boriani *et al*<sup>[41]</sup> evaluated the conversion efficacy of different antiarrhythmic drug protocols and reported that oral flecainide had a similar conversion rate to oral propafenone.

#### Prevention of atrial fibrillation recurrences

**Continuous treatment:** The long-term safety and

efficacy of continuous treatment with flecainide for prevention of atrial fibrillation recurrences has been studied extensively in comparison to either placebo or other antiarrhythmic agents (Table 2). However, the majority of the trials published in the literature are hampered by methodological limitations, such as open-label design, small sample size, suboptimal follow-up and underestimation of AF burden mainly due to inability to document asymptomatic or short-lasting arrhythmia bouts. In the context of these limitations, oral flecainide has been demonstrated to be superior to placebo<sup>[44-48]</sup>, and similar to quinidine<sup>[49,50]</sup>, sotalol<sup>[48]</sup> and propafenone<sup>[51,52]</sup> in preventing AF recurrences. The clinical efficacy of flecainide in the maintenance of sinus rhythm has been proved in a meta-analysis of 60 trials showing that 65% of patients were responders to short term treatment and 49% in the long term treatment<sup>[53]</sup>. In terms of safety, flecainide is better tolerated than quinidine<sup>[46,50]</sup>, and is associated with a lower rate of adverse events as compared to propafenone<sup>[51,52]</sup>.

Special emphasis should be placed in two trials, the PITAGORA<sup>[54,55]</sup> and the FLEC-SL trial<sup>[56]</sup>. The PITAGORA trial was a multicenter, prospective, single-blind randomized trial which aimed to compare amiodarone with class IC antiarrhythmic agents (propafenone and flecainide) when administered as prophylactic treatment for sinus rhythm maintenance among pacemaker recipients with sinus node disease and history of atrial fibrillation<sup>[54]</sup>. The maintenance daily doses of tested antiarrhythmic agents were 200 mg amiodarone, 450-750 mg propafenone and 200 mg flecainide. The main strength of the study was the ability to quantify the frequency and burden of both symptomatic and asymptomatic atrial fibrillation episodes *via* pacemaker diagnostics. However, the primary endpoint of the study was not related to AF burden *per se* but was a composite endpoint defined as time to the first occurrence of one of the following adverse events: death, hospitalization for AF or heart failure, atrial cardioversion or AAD change owing to failure of AF prophylaxis or adverse events<sup>[54]</sup>. In terms of the incidence of this endpoint, flecainide and propafenone proved to be non-inferior to amiodarone<sup>[55]</sup>. Furthermore, when flecainide and propafenone, as single agents, were compared with amiodarone, only flecainide satisfied the criterion for noninferiority. Post-hoc analysis of arrhythmia burden data demonstrated that amiodarone and class Ic agents demonstrated similar efficacy in preventing arrhythmic episodes > 10 min, or > 1 d, with a trend in favor of amiodarone for prevention of episodes lasting more than a week<sup>[55]</sup>.

The Flec-SL trial is the largest, prospective randomized clinical trial testing the efficacy of oral antiarrhythmic treatment for prevention of atrial fibrillation recurrence, with a meticulous follow-up and endpoint assessment<sup>[56]</sup>. The aim of the study

was to evaluate whether short-term (4 wk) flecainide treatment is non-inferior to long-term (6 mo) treatment following cardioversion of persistent atrial fibrillation. The tested hypothesis was based on the concept that provision of antiarrhythmic protection until completion of reverse atrial electrical remodeling might provide a long-term effect with an enhanced safety profile due to reduced drug exposure. In total, 635 patients were randomly assigned in three treatment arms (placebo vs short-term vs long-term oral flecainide treatment). Patients were followed up for 6 mo with daily telemetric electrocardiograph recordings and Holter ECGs when atrial fibrillation was noted in more than two consecutive telemetric recordings. The primary outcome measure of the study was time to first recurrence of persistent atrial fibrillation or death from any cause. Based on the study results, in the per-protocol population 46% of patients receiving short-term treatment presented a recurrence of persistent AF as compared to 39% in the long-term treatment group. Additionally, short-term treatment with flecainide was superior to placebo but failed to demonstrate non-inferiority as compared to long-term treatment. However, short-term treatment demonstrated about 80% of the 6-mo effect of long-term treatment, supporting that the former could be considered a viable treatment option in patients with infrequent AF recurrences or increased risk of proarrhythmia.

**Pill-in-the-pocket strategy:** The safety and feasibility of treatment with a single oral dose of either flecainide (200-300 mg) or propafenone (450-600 mg) on an outpatient basis, for termination of recent onset atrial fibrillation was validated in a pivotal trial including 268 patients without severe heart disease and a previously successful in-hospital treatment<sup>[57]</sup>. The tested "pill-in-the-pocket" strategy was successful in 94% of arrhythmic episodes (equally effective for both propafenone and flecainide), while in 84% of patients the treatment was effective during all the arrhythmic episodes. The mean conversion time to sinus rhythm was about 2 h, while only one case (0.6%) of atrial flutter with rapid ventricular rate was reported. Furthermore, the implemented treatment approach resulted in significant reduction of hospitalizations and visits to the emergency rooms.

The pill-in-the-pocket strategy can be used in symptomatic patients with infrequent recurrences of atrial fibrillation. Patients with sinus node dysfunction causing bradycardia and patients with bradycardia or syncope due to atrioventricular conduction defects may not be considered candidates for the pill-in-the-pocket strategy. Prerequisites for the safe implementation of this strategy are the initial in-hospital testing of its efficacy and safety as well as careful screening of candidate patients to rule



**Table 2 Flecainide for prevention of atrial fibrillation recurrences - Randomized controlled clinical trials**

| Clinical trial                          | Patient population   | Compared treatments  | Endpoint of AF recurrence   | Results   | Comments   |
|---|--|--|---|---|--|
| Steinbeck <i>et al</i> <sup>[44]</sup>  | 45 patients<br>Paroxysmal AF                                       | Quinidine + digoxin<br>Flecainide + digoxin<br>Digoxin     | AF recurrence at 12 mo  | Flecainide and digoxin superior to other regimens and safer than quinidine and digoxin  | Quinidine is practically not used any more for sinus rhythm maintenance  |
| Anderson <i>et al</i> <sup>[45]</sup>   | 64 patients<br>Paroxysmal AF                                       | Flecainide (median daily dose: 300 mg)<br>Placebo          | Patients without AF recurrences<br>Time to first AF recurrence<br>Time interval between AF recurrences                      | Flecainide superior to placebo<br>Five-fold increase in time to first recurrence<br>Four-fold increase in time interval between attacks<br>Significantly increased percentage of patients free of AF recurrences<br>Adverse cardiac events in 11% of patients during flecainide therapy | Transtelephonic monitoring<br>Double-blind randomized crossover trial (8-wk observation period)<br>Daily flecainide dose > 300 mg in 29% of patients                                     |
| van Wijk <i>et al</i> <sup>[49]</sup>   | 26 patients<br>Paroxysmal AF                                       | Flecainide (200-300 mg daily)<br>Quinidine (1.0-1.5 daily) | AF recurrence during 3-mo follow-up period  | Flecainide superior to quinidine in the lower dosing regimen<br>Flecainide similar efficacy to quinidine in higher dosing regimen   | 20% discontinuation rate with higher quinidine dosing regimen<br>FU with 24-h Holter at the end of each month  |
| van Gelder <i>et al</i> <sup>[46]</sup> | 81 patients<br>Persistent AF/flutter                               | Flecainide<br>Placebo                                      | AF recurrence at 12 mo  | Flecainide superior to placebo in preventing arrhythmia recurrences   | Difficult to treat patients (mean AF duration: 12 mo)  |
| Pietersen <i>et al</i> <sup>[47]</sup>  | 43 patients<br>Paroxysmal AF/flutter                               | Flecainide (300 mg/d)<br>Placebo                           | AF recurrence at 3 mo   | Flecainide superior to placebo in preventing arrhythmia recurrences<br>Adverse effects in 74% of patients treated with flecainide   | Tolerable adverse events in flecainide group (only 2 withdrawals)<br>One episode of sudden death   |
| Carunchio <i>et al</i> <sup>[48]</sup>  | 66 patients<br>Paroxysmal AF                                       | Flecainide<br>Sotalol<br>Placebo                           | AF recurrence at 1, 3, 6 and 12 mo  | Flecainide similar efficacy to sotalol and superior to placebo  |  |
| Aliot <i>et al</i> <sup>[51]</sup>      | 97 patients<br>Paroxysmal AF/flutter                               | Flecainide (100-300 mg/d)<br>Propafenone (600-1200 mg/d)   | AF recurrence at 12 mo  | Flecainide similar efficacy to propafenone<br>Treatment discontinuation rate lower with flecainide (38% vs 53%, $P = 0.079$ )   | Multicenter, randomized, open-label study<br>One episode of sudden death in the propafenone group  |
| Chimienti <i>et al</i> <sup>[52]</sup>  | 200 patients<br>Paroxysmal AF                                      | Flecainide (200-300 mg/d)<br>Propafenone (450-900 mg/d)    | Palpitation recurrence on days 15, 30, 90, 180, 270, and 360  | Flecainide similar efficacy to propafenone<br>Similar rate of adverse cardiac and noncardiac events   | Multicenter, open label, randomized, parallel study<br>Suboptimal follow-up of AF recurrence   |
| Naccarelli <i>et al</i> <sup>[50]</sup> | 239 patients<br>Paroxysmal AF                                      | Flecainide (100-300 mg/d)<br>Quinidine                     | AF recurrence at 12 mo  | Flecainide similar efficacy to quinidine<br>Flecainide better tolerated than quinidine  | Multicenter, open label, randomized, parallel study<br>Self-reporting of symptomatic AF recurrences (diary recording)  |
| Gulizia <i>et al</i> <sup>[54]</sup>    | 176 pacemaker recipients with sinus node disease and paroxysmal AF | Class I AAD (flecainide or propafenone)<br>Amiodarone      | Primary endpoint: time to first occurrence of death, atrial cardioversion, cardiovascular hospitalization, or change of AAD | Class I AADs non-inferior to amiodarone in terms of the primary endpoint.<br>Similar efficacy in freedom from AT recurrences based on post-hoc analyses   | One patient experienced sudden cardiac death in flecainide group<br>Capability of continuous rhythm monitoring by pacemaker<br>AF recurrence and burden not included in primary endpoint |
| Kirchhof <i>et al</i> <sup>[56]</sup>   | 635 patients<br>Persistent AF                                      | Short-term flecainide<br>Long-term flecainide<br>Placebo   | Time to first recurrence of persistent atrial fibrillation or death from any cause  | Flecainide superior to placebo<br>Short-term flecainide not non-inferior to long-term   | Largest, prospective randomized clinical trial<br>Meticulous follow-up   |

AF: Atrial fibrillation; AAD: Antiarrhythmic drug; AT: Atrial tachycardia.

out underlying structural heart disease. However, it should be noted that in-hospital testing should include only oral formulations of antiarrhythmic agents, since tolerance to intravenous administration of flecainide or propafenone has not been shown to predict adverse events during out-of-hospital self administration of these drugs<sup>[57]</sup>.

## RECOMMENDATIONS FOR FLECAINIDE USE IN ATRIAL FIBRILLATION - ESC GUIDELINES

Based on the guidelines of the European Society of Cardiology, *iv* flecainide (2 mg/kg over 10 min)

is recommended for cardioversion of recent onset AF (duration less than 48 h) when pharmacological cardioversion is preferred and there is no structural heart disease (Class I A recommendation). In selected patients without significant structural heart disease, the pill-in-the-pocket strategy (single dose of 200-300 mg) should be considered if previously tested in a medically secure environment (Class II a recommendation). Flecainide is also recommended for long-term rhythm control in patients without significant underlying heart disease (Class I A recommendation)<sup>[10]</sup>.

### **Ventricular tachycardias**

**Ventricular tachycardias in patients with underlying heart disease:** The role of flecainide in the treatment of ventricular tachycardias among patients with underlying heart disease has been formulated mainly by the results of the CAST trial<sup>[1]</sup>. This multicenter, randomized, placebo-controlled trial was conducted to evaluate whether suppression of asymptomatic or mildly symptomatic ventricular arrhythmias after myocardial infarction with antiarrhythmic drugs (flecainide, encainide or moricizine) would result in reduction of arrhythmic mortality. Eligible patients had prior myocardial infarction (6 d to 2 years), ventricular arrhythmias ( $\geq 6$  ventricular extrasystoles per hour or ventricular tachycardia runs less than 15 beats) and impaired ventricular function (ejection fraction  $\leq 0.55$  if recruited within 90 d of the myocardial infarction, or  $\leq 0.40$  if 90 d or more after the myocardial infarction). Flecainide was not given to patients with an ejection fraction below 0.30. It should be highlighted that 789 of 1498 patients included in the study had ejection fraction  $\geq 0.40$ <sup>[23]</sup>. The treatment arms of flecainide and encainide were prematurely discontinued after a mean follow-up of 10 mo due to a significantly increased risk of arrhythmia-related (2.64; 95%CI: 1.60-4.36) and all-cause mortality (2.38; 95%CI: 1.59-3.57)<sup>[1]</sup>.

As regards the role of flecainide in patients with ventricular tachycardia without structural heart disease, type IC antiarrhythmic drugs seem to be useful in patients with right ventricular outflow ventricular tachycardia<sup>[58]</sup>.

**Catecholaminergic polymorphic ventricular tachycardia:** Accumulating data have verified that flecainide inhibits the cardiac ryanodine receptor open state, thus directly targeting the molecular defect responsible for diastolic calcium release, delayed afterdepolarizations, and triggered arrhythmias in CPVT<sup>[33,59]</sup>. Case reports and series have reported that flecainide may prove useful in preventing ventricular tachyarrhythmias in patients with CPVT associated both with ryanodine receptor and calsequestrin mutations<sup>[21,60]</sup>. Van der Werf *et al*<sup>[61]</sup> reported the clinical experience from several international centers

on the efficacy and safety of flecainide treatment in CPVT. The role of flecainide (median daily dose 150 mg in responders) was evaluated in 33 genotype-positive CPVT patients on optimal tolerated conventional treatment using as primary outcome measure the reduction of ventricular arrhythmias during exercise testing<sup>[61]</sup>. In total, 76% of patients had either a partial or complete suppression of exercise-induced ventricular arrhythmias by flecainide while no patient experienced worsening of exercise-induced ventricular arrhythmias<sup>[61]</sup>. Flecainide has also been shown to be effective in reducing ventricular arrhythmias during exercise testing and preventing arrhythmia events during long-term follow-up in patients with genotype-negative CPVT<sup>[62]</sup>. Marai *et al*<sup>[63]</sup> recently reported that the combination of flecainide and  $\beta$ -blockers can completely suppress exercise-induced ventricular arrhythmias and prevent recurrent ICD shocks in patients with calsequestrin-associated CPVT and high-risk features despite treatment with  $\beta$ -blockers.

## **PRACTICAL ASPECTS OF FLECAINIDE USE**

The following practical considerations should be kept in mind in the management of patients under flecainide treatment: (1) performance of exercise stress test before treatment initiation to assess the presence of underlying coronary artery disease; (2) screening of candidates for sinus and atrioventricular node disease; (3) performance of regular ECG monitoring upon treatment initiation and upon dose titration. In case of QRS prolongation more than 25% as compared to baseline value, flecainide dosage should be halved and if QRS is not normalized thereafter it should be discontinued; (4) performance of exercise stress testing under flecainide treatment to assess increased risk of proarrhythmia, especially in the presence of slight QRS prolongation at rest. Flecainide exerts use-dependent properties and a potential minor or modest increase in QRS duration at rest may increase dramatically during exercise-related rapid heart rate; (5) control of pacing threshold in pacemaker recipients, especially if pacemaker-dependent. Flecainide may increase the pacing threshold occasionally to a significant extent; and (6) concomitant use of agents with negative dromotropic effect is recommended to avoid one-to-one atrioventricular conduction and very rapid ventricular rates, if atrial fibrillation is converted to atrial flutter.

## **IS THERE ANY ROOM FOR FLECAINIDE IN CORONARY ARTERY DISEASE PATIENTS?**

The main precaution for flecainide administration is to rule out the presence of "structural" heart disease

and/or ischemic cardiomyopathy in order to avoid the associated increased risk of proarrhythmia. This caveat was mainly formulated on the basis of the CAST results which demonstrated that flecainide is associated with increased mortality when administered in patients with prior myocardial infarction. In this trial more than half of the enrolled patients had an ejection fraction > 40% and it is noteworthy that the hazard ratio of AAD therapy versus placebo for arrhythmic death was similar in patients with ejection fraction < 0.40 as compared to those with ejection fraction  $\geq$  0.40. Furthermore, the presence of a non-Q wave myocardial infarction was the only variable which significantly interacted with encainide or flecainide for prediction of arrhythmic or all cause mortality (hazard ratio 7.9 in non-Q wave myocardial infarction patients as compared to 1.8 in those with Q-wave myocardial infarction)<sup>[57]</sup>. Therefore, it seems prudent to contraindicate flecainide treatment among patients with prior myocardial infarction (either Q or non-Q wave) even if left ventricular ejection fraction is preserved. Furthermore, flecainide administration should be precluded in the presence of myocardial ischemia since the latter increases the risk of proarrhythmia.

However, the group of coronary artery disease patients, with preserved ejection fraction, no prior myocardial infarction and no evidence of ischemia represents a grey zone where there is absolute paucity of data regarding safety of flecainide treatment. According to the 2012 update of the ESC guidelines for the management of atrial fibrillation<sup>[10]</sup>, flecainide can be used in patients with “minimal structural heart disease”, but it cannot be used in patients with coronary artery disease. Two main issues can be raised from these recommendations. Firstly, there is no commonly accepted and well established definition of “minimal structural heart disease”. Secondly, there are no data supporting an increased proarrhythmic risk of flecainide among coronary artery disease patients in the absence of underlying scar and myocardial ischemia. Besides, even the definition of coronary artery disease may be obscured by the widespread use of advanced imaging techniques which may actually identify patients with coronary lesions but in low arrhythmic risk. Meanwhile, decision making in similar cases is not supported by solid evidence and all available treatment options, including catheter ablation in atrial fibrillation patients, should be taken into account.

Taking into consideration the limited therapeutic modalities that are currently available for the patients with coronary artery disease and atrial fibrillation, it is obvious that new studies need to be undertaken aiming to evaluate the safety of old antiarrhythmics, like flecainide, in the wide spectrum of patients with coronary artery disease, that we treat today. Nowadays, it is quite common to treat patients with

stable coronary artery disease who have preserved left ventricular ejection fraction, lack of symptoms and absence of detectable myocardial ischemia. Flecainide and other antiarrhythmics may be useful in the management of these patients, who remain vulnerable to atrial fibrillation and have limited access to invasive management of atrial tachyarrhythmias.

Finally, there is one more unsolved issue in the area of antiarrhythmic therapy in patients with ischemic heart disease. There is lack of evidence for the potential benefit from flecainide treatment in patients with implantable cardioverter defibrillators (ICDs) who have “minimal heart disease” and present symptomatic arrhythmias, refractory to sotalol and/or amiodarone. Although there is no available evidence to support this hypothesis, given that ICDs ameliorate the proarrhythmic risk, flecainide may be an alternative treatment. Unfortunately, due to medical and economic restraints, the aforementioned hypotheses have not been properly addressed in the scheme of a specifically designed randomized clinical trial.

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## Retrospective Study

# Cardiac and non-cardiac causes of T-wave inversion in the precordial leads in adult subjects: A Dutch case series and review of the literature

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**Author contributions:** Said SAM, Bloo R, de Nooijer R and Slootweg A treated patients and collected material and clinical data from patients; Bloo R performed the assays; de Nooijer R analysed data; Said SAM wrote the paper; all authors approved the final version of the manuscript.

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**Informed consent:** All study participants provided verbal informed consent.

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## Abstract

**AIM:** To describe the electrocardiographic (ECG) phenomena characterized by T-wave inversion in the precordial leads in adults and to highlight its differential diagnosis.

**METHODS:** A retrospective chart review of 8 adult patients who were admitted with ECG T-wave inversion in the anterior chest leads with or without prolongation of corrected QT (QTc) interval. They had different clinical conditions. Each patient underwent appropriate clinical assessment including investigation for myocardial involvement. Single and multimodality non-invasive, semi-invasive and invasive diagnostic approach were used to ascertain the diagnosis. The diagnostic assessment included biochemical investigation, cardiac and abdominal ultrasound, cerebral and chest computed tomography, nuclear medicine and coronary angiography.

**RESULTS:** Eight adult subjects (5 females) with a mean age of 66 years (range 51 to 82) are analyzed. The etiology of T-wave inversion in the precordial leads were diverse. On admission, all patients had normal blood pressure and the ECG showed sinus rhythm. Five patients showed marked prolongation of the QTc interval. The longest QTc interval (639 ms) was found in the patient with pheochromocytoma. Giant T-wave inversion ( $\geq 10$  mm) was found in pheochromocytoma followed by electroconvulsive therapy and finally ischemic heart disease. The deepest T-wave was measured in lead V<sub>3</sub> (5 ×). In 3 patients presented with mild T-wave inversion (patients 1, 5 and 4 mm), the QTc interval was not prolonged (432, 409 and 424 msec), respectively.

**CONCLUSION:** T-wave inversion associated with or without QTc prolongation requires meticulous history taking, physical examination and tailored diagnostic

modalities to reach rapid and correct diagnosis to establish appropriate therapeutic intervention.

**Key words:** T-wave inversion; Coronary angiography; Pulmonary computed tomography angiography; Magnetic resonance imaging; Differential diagnosis

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**Core tip:** Myriad of clinical conditions have been described in association with T-wave inversion in the anterior precordial leads. T-wave inversion associated with or without corrected QT prolongation may be encountered in a variety of clinical conditions. In the reversible (dynamic) types such as vascular coronary, cerebral and pulmonary disorders; metabolic disturbances and acute adrenergic stress cardiomyopathy; resolution of T-wave inversion may occur after days, weeks, months or years following the index event. Tailored diagnostic approach should be conducted avoiding overuse of diagnostic methods. Specific tailored therapeutic interventions were undertaken when high index of clinical suspicion was raised towards certain disease entity.

Said SAM, Bloo R, de Nooijer R, Slootweg A. Cardiac and non-cardiac causes of T-wave inversion in the precordial leads in adult subjects: A Dutch case series and review of the literature. *World J Cardiol* 2015; 7(2): 86-100 Available from: URL: <http://www.wjgnet.com/1949-8462/full/v7/i2/86.htm> DOI: <http://dx.doi.org/10.4330/wjc.v7.i2.86>

## INTRODUCTION

T-wave inversion is found in 1% of patients admitted to the coronary care unit<sup>[1]</sup> and in 14% of patients presented with unstable angina<sup>[2]</sup>. It has been stated that T-wave inversion in right precordial leads is relatively rare (0.5%) in the general population and not associated with adverse outcome<sup>[3]</sup>. The tendency to inversion of T-wave declines with increasing age. Normally in females, the T-wave in V<sub>3</sub> may be shallowly inverted. But in adult males, it is considered pathologic if the T-wave is inverted in V<sub>3-6</sub><sup>[4]</sup>. The T-wave in V<sub>1</sub> may be inverted normally at any age and in V<sub>2</sub> it is sometimes normally negative<sup>[5]</sup>.

Generally, the T-waves are negative in leads aVR, V<sub>1</sub> and III. Giant T-wave inversion in the precordial leads are seen in different pathologies, such as anterior myocardial wall ischemia in patients with acute coronary syndrome, apical hypertrophic cardiomyopathy, cerebral and pulmonary disorders and post-pacing or tachyarrhythmia states.

The definite diagnosis in the presence of inverted T-wave can usually be assessed by meticulous history taking including family history of sudden

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cardiac death or arrhythmias, physical examination as well as appropriate non-invasive, semi-invasive or invasive diagnostic investigations. This current review, will focus on T-wave inversion in the anterior chest wall leads and discuss its differential diagnosis with emphasis on the non-coronary non-cardiac disorders.

Diagnostic approach should be tailored according to the clinical presentation, medical and family history. We present a Dutch case series of eight patients with T-wave inversion in the precordial leads due to different etiologies and the literature is briefly reviewed.

## MATERIALS AND METHODS

The study was reviewed and approved by the Hospital Group Twente, Institutional Review Board. All study participants provided verbal informed consent.

Eight representative adult patients were identified and evaluated. In all patients, physical examination, electrocardiography and transthoracic echocardiography (TTE) were routinely performed. When necessary for adequate clarification of the clinical presentation, tailored diagnostic methods were undertaken in the individual patient at the clinician's discretion [TTE,  $n = 8$ ; coronary angiography "coronary angiography (CAG)",  $n = 7$ ; magnetic resonance imaging "magnetic resonance imaging (MRI)",  $n = 3$ ; perfusion-ventilation scan,  $n = 2$ ; computed tomography "computed tomography (CT)" abdomen,  $n = 1$ ; CT brain,  $n = 1$ ; CT thoracic aorta,  $n = 1$ ; <sup>123</sup>Iodine-metaiodobenzylguanidine (MIBG) scan,  $n = 1$  and DOPA- positron emission tomography (PET),  $n = 1$ ].

### Diagnostic criteria

The diagnostic criteria included presentation with T-wave inversion in the anterior chest leads on the admission ECG.

### Definitions

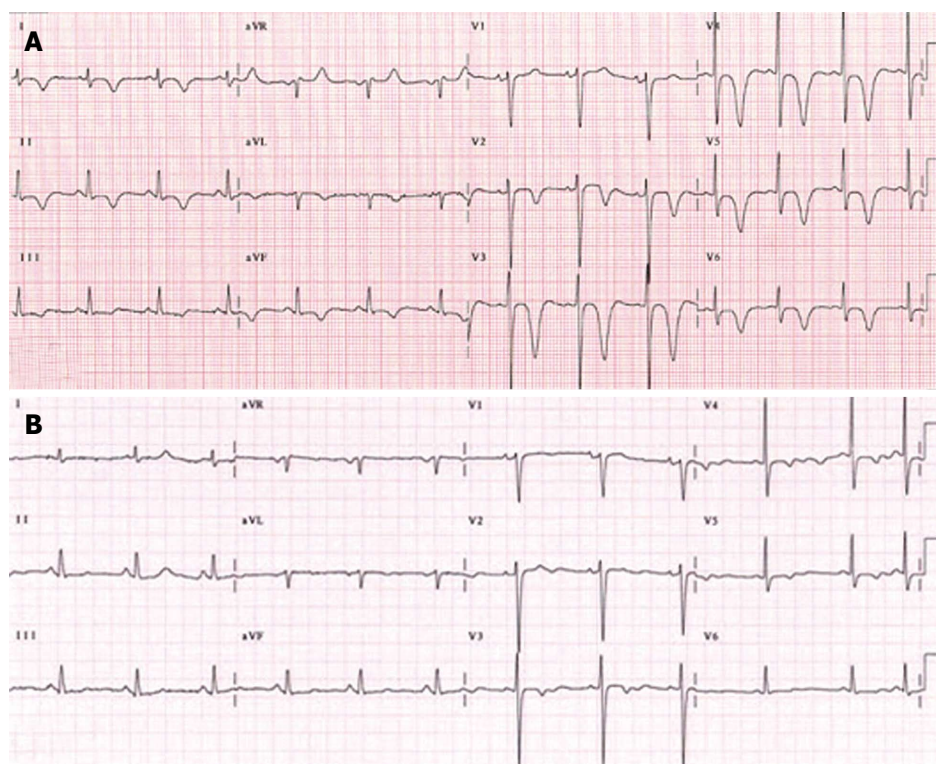
**Electrocardiography:** The admission ECGs were analyzed using standard criteria for measurements of T-wave axis, T-wave amplitude and QT interval. ECGs were analyzed for the presence of Left ventricular hypertrophy (LVH) using the Sokolow criteria<sup>[6]</sup>.

**T-wave negativity:** was defined as a voltage of giant negative T-wave  $\geq 10$  mm in any of the leads<sup>[7-9]</sup>, deep  $\geq 5$  mm<sup>[8]</sup> and mild 1-3 mm<sup>[8]</sup>.

**Corrected QT prolongation:** Corrected QT (QTc) interval for heart rate was performed in V<sub>2</sub> and was defined as QTc  $> 450$  msec. according to Bazett<sup>[10]</sup> and Ahnve<sup>[11]</sup>.

Measured serum biomarkers were creatine kinase and cardiac troponin T.





**Figure 1 Patient 1.** A: An electrocardiographic (ECG) tracing, illustrating the negative T-wave in the precordial leads V<sub>2-6</sub>, of a 51-year-old-female patient presented with palpitation following electroconvulsive therapy for her depression. In 2001, she underwent catheter ablation for atrioventricular nodal reentry tachycardia. She complained of palpitation after a shock of electroconvulsive therapy for treatment of depression. Post-electroconvulsive therapy, the ECG showed giant T-wave inversion in the precordial leads. The cardiac enzymes were minimally raised. Takotsubo cardiomyopathy is suggested due to emotional stress and electrical shock. Transthoracic echocardiography demonstrated apical hypokinesia and basal normokinesia with trivial valvular regurgitation without massive pericardial effusion. The estimated right ventricular systolic pressure was 35 mmHg. Coronary angiography and cardiac magnetic resonance imaging demonstrated normal findings. Medical treatment with beta blocker was initiated and the symptoms disappeared and (B) the ECG returned to base line in 2 wk time. The antidepressant drug was not discontinued.

**Transthoracic echocardiography:** Left ventricular (LV) wall thickness as well as septal thickness were measured according to the established standards and guidelines of the American College of Cardiology/American Heart Association/European Society of Cardiology<sup>[12,13]</sup>. LVH was defined as a LV wall thickness > 13 mm.

**Radionuclide studies: Radionuclide imaging and positron emission tomography:** One patient (patient 7) underwent <sup>123</sup>I-MIBG and dihydroxyphenylalanine-Positron Emission tomography (DOPA-PET) scanning. In 2 patients, pulmonary perfusion/ventilation scintigraphy were performed.

**Computed tomography:** Abdominal, cerebral and thoracic aorta CT scanning were performed in one patient each.

Pulmonary computed tomography angiography (PCTA) was performed in one patient.

Coronary angiography contrast angiography was performed in standard views *via* the femoral approach.

**Follow-up:** Follow-up was obtained by direct contact

with patients, their physicians or by chart review.

### Statistical analysis

No statistical data are available.

## RESULTS

A total of 8 adult patients presented with chest pain and negative T-wave in the anterior chest wall leads on the admission ECG were identified (Figures 1-8).

### Clinical features

On presentation, the blood pressure was normal in all patients and all were in sinus rhythm (Table 1). Cerebral pathology was excluded by the absence of neurological signs. No neurological deficits were found.

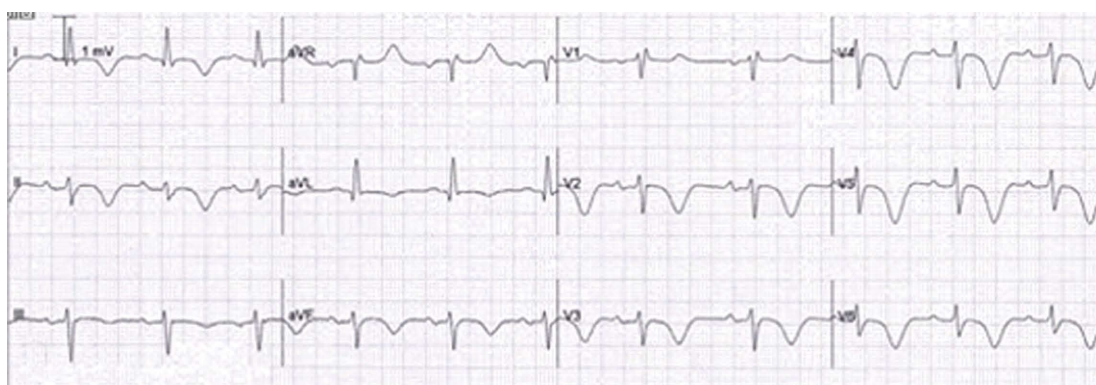
All patients had on physical examination no neurological abnormalities. One patient known with a previous transient ischemic attack showed a complete recovery. Of the 8 patients, one presented with abnormal rest ECG, three with chest pain, one with palpitation, one with fatigue, one with left abdominal pain and psychomotor agitation and one with out-of-hospital cardiac arrest (OHCA).

None of the patients, except one (patient 8)





**Figure 2 Patient 2.** An electrocardiographic (ECG) tracing, illustrating the negative T-wave with minimal ST segment elevation in the precordial leads V<sub>1-4</sub>, of a 82-year-old-female patient presented with acute coronary syndrome due to non ST elevation myocardial infarction. Her previous medical history included hormonal substitution for hypothyroidism, ablatio retinae, polymyalgia rheumatica, arterial hypertension, mild concentric left ventricular hypertrophy, aortic valvular stenosis with a peak gradient of 18 mmHg and mild aortic regurgitation grade 2/4. In 2011, analysis with ambulatory ECG recording for a syncopal attack revealed no abnormalities. Transthoracic echocardiography demonstrated apicoinferior hypokinesia. The patient was treated medically and remained free of symptoms. Her maintenance drug therapy consisted of BB, aspirin (ASA), clopidogrel, Angiotensin- II antagonist, prednisolon, diuretic and statin.



**Figure 3 Patient 3.** An electrocardiographic (ECG) tracing, illustrating the negative T-wave in the precordial leads V<sub>2-6</sub>, of a 72-year-old-woman who underwent 6 mo earlier direct current electric cardioversion for persistent atrial fibrillation. Her concomitant medical history includes temporal arteritis, carotid endarterectomy and cluster headache. She presented with abnormal rest ECG during out-patient follow-up. Her spouse died 2 wk prior to presentation. The cardiac markers were minimally elevated. The diagnosis of Takotsubo cardiomyopathy was strongly suggested as the emotional stress may have been the trigger. Transthoracic echocardiography depicted biventricular normokinesia with hypertrophic LV. Pulmonary perfusion-ventilation scintigraphy, Coronary angiography and cardiac MRI were all normal. She did well on pharmacological treatment with oral vit K antagonist, class 3 antiarrhythmic drug, anti-depressive drug and diuretics. The ECG alterations returned to baseline over a 6 mo period.

performed endurance sports activities all had no family history of sudden cardiac death or arrhythmias.

### Electrocardiography

The admission ECGs were analyzed using standard criteria for measurements of T-wave amplitude and QTc interval. Giant T-wave inversion ( $\geq 10$  mm) was found in the patients with pheochromocytoma (20 mm) followed by electroconvulsive therapy (15 mm) then ischemic heart disease (10 mm). Deep T-wave inversion ( $\geq 5$  mm) was detected in three and mild (1-3 mm) in two of the patients. The deepest T-wave was measured in lead V<sub>3</sub> (5 ×), V<sub>4</sub> (2 ×) and V<sub>2</sub> (1 ×). Epsilon wave was present in one patient with arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D) (patient 8) (Figure 8B). Electrocardiographic criteria for left ventricular hypertrophy was found in 4 patients (patients 2, 3, 6 and 7).

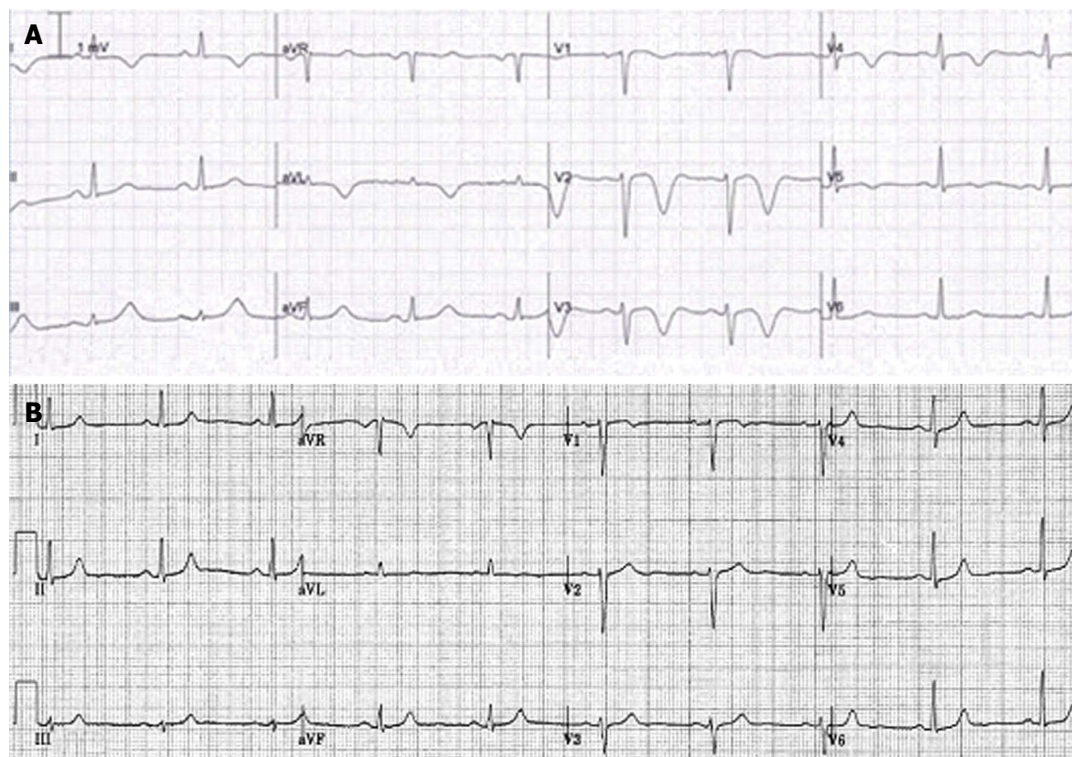
In 3 patients diagnosed with pulmonary embolism

(PE) (patient 5), LVH (patient 6) and ARVC/D (patient 8) presented with mild T wave inversion (1, 5 and 4 mm), the QTc interval was not prolonged (432, 409 and 424 msec), respectively.

### Corrected QT prolongation

Corrected QT prolongation defined as QTc > 450 msec. measured in lead V<sub>2</sub>. The corrected QT interval exceeded 450 ms in 5 (452-639) with a mean of 530 ms and it was not prolonged in 3 (409, 424 and 432 ms) of the patients. The amplitude of the inverted T-wave varied significantly with the maximum negative T-wave amplitude ranging from one to 20 mm. A gradual complete resolution of the T-wave inversion and QT prolongation occurred in 5 of the patients.

Other ECG findings were as follow: two patients (patients 2 and 3) showed first degree AV block, one patient (patient 8) revealed microvoltage in the standard and limb leads, negative T wave in I and



**Figure 4 Patient 4.** A: An electrocardiographic (ECG) tracing, demonstrating negative T wave in the precordial leads V<sub>2-5</sub>, of a 69-year female patient with past medical history of transient ischemic attack two years previously, presented with interscapular pain. She had no emotional or physical stress. Normal results were found on transthoracic echocardiography, perfusion-ventilation scintigraphy, Coronary angiography and cardiac MRI. Brain CT scan revealed mild cerebral atrophy and minimal ischemic changes; B: The ECG showed spontaneous regression in 2 mo time. The etiology of the negative T wave inversion remains undetermined. Her medical regimen included aspirin, beta blocker, statin and diuretic.



**Figure 5 Patient 5.** An electrocardiographic (ECG) tracing, showing negative T wave in the precordial leads V<sub>1-3</sub> and S<sub>1</sub> Q<sub>3</sub> T<sub>3</sub>, of a 55-year obese male patient without antecedent medical history presented with chest pain and minimally elevated serum cardiac biomarkers. Transthoracic echocardiography revealed dilated and hypokinetic RV with pulmonary hypertension and distended inferior caval vein. Coronary angiography was normal and pulmonary CT angiography confirmed the clinical diagnosis showing massive bilateral pulmonary embolism with central and peripheral localization. A continuous positive airway pressure was implemented for newly detected severe obstructive sleep apnea syndrome. He was successfully treated with medical regimen and on follow-up he became asymptomatic and the abnormal ECG findings gradually disappeared.

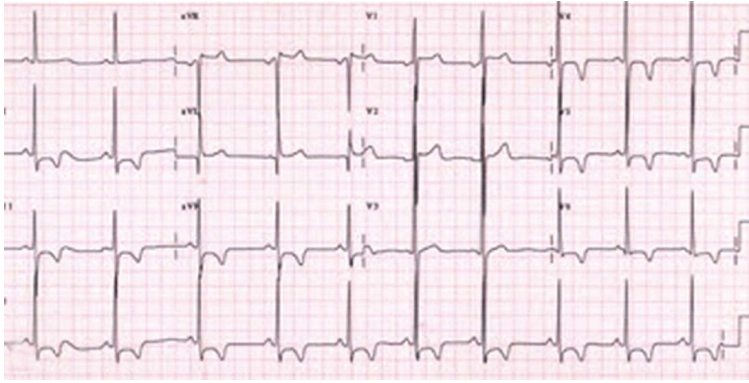
aVL in 2 patients (patients 4 and 7), negative T wave in leads I, II, III, aVL and aVF in (patients 1 and 3), negative T wave in II, III and aVF without (patient 5) or with (patient 6) ST segment depression.

#### Serum biomarkers

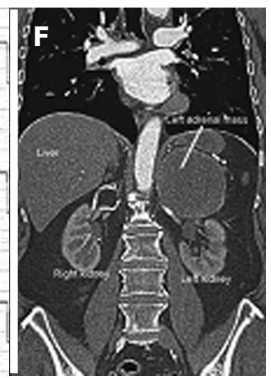
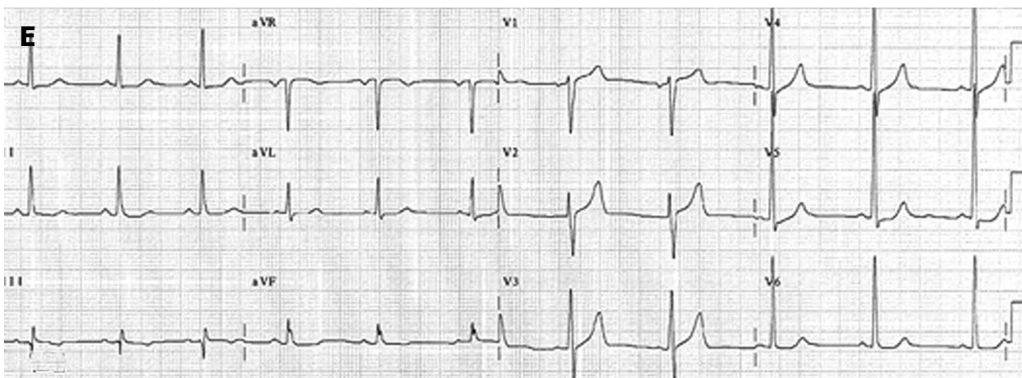
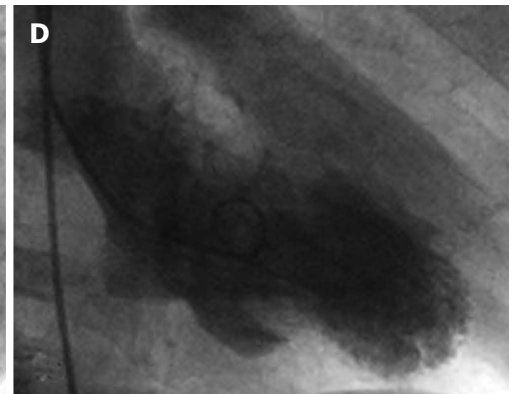
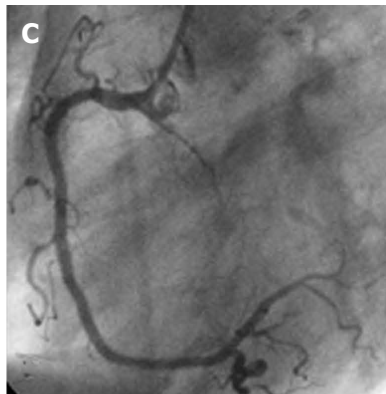
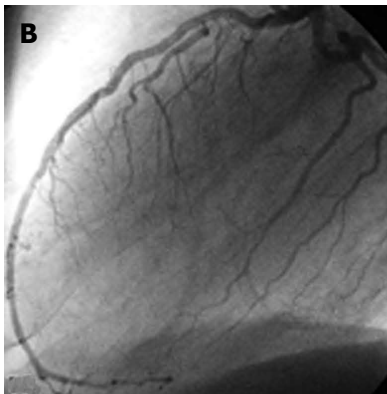
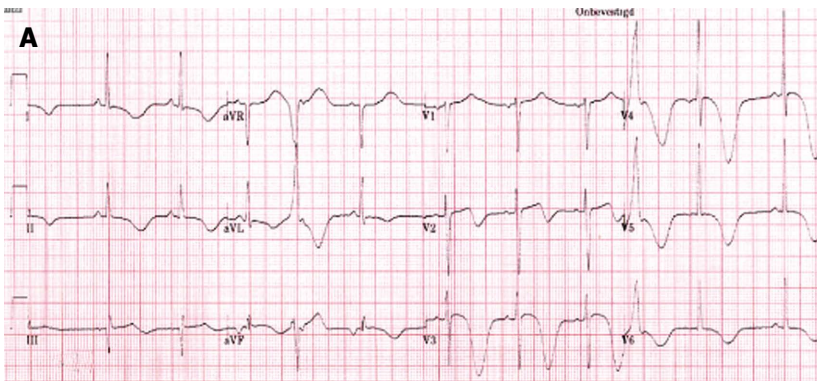
Cardiac troponin T were assessed. Myocardial infar-

ction was ruled out in 7 patients. One (patient 2) with non ST elevation myocardial infarction (NSTEMI) showed typical biomarker rise and fall course with markedly elevation of troponin level. Mild elevation of troponin value was found in 4 patients (patients 3, 4, 5 and 7). No elevation was detected in 3 patients (patients 1, 6 and 8).

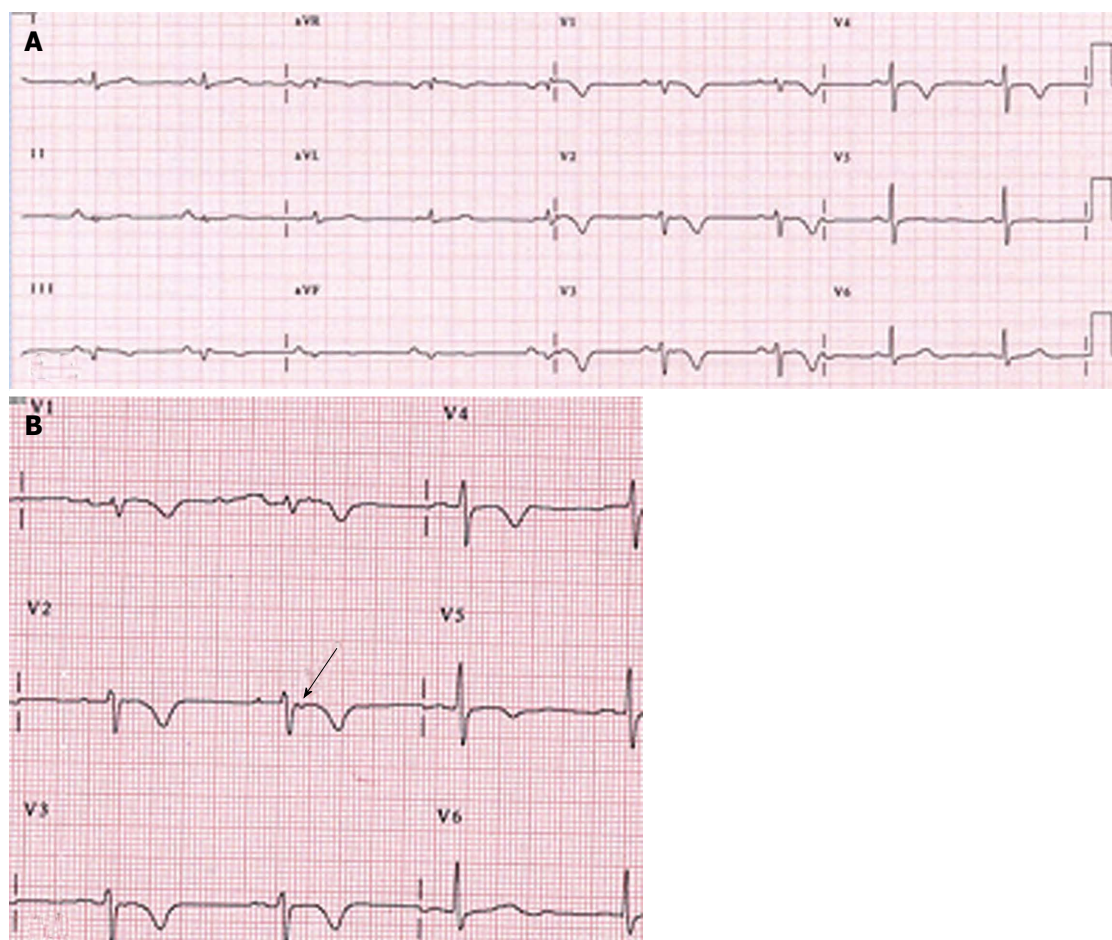




**Figure 6 Patient 6.** An electrocardiographic (ECG) tracing, showing voltage criteria for left ventricular hypertrophy with ST depression and negative T wave in the precordial and inferior leads V<sub>3-6</sub>, of a 52-year female patient with non-obstructive hypertrophic cardiomyopathy (thickness of septum 20 mm and posterior wall of 24 mm without septal anterior movement or obstruction of outflow tract). Normal coronary arteries were found on coronary angiography. She refused genetic counseling and invasive intervention. She was treated medically with beta blocker.



**Figure 7 Patient 7.** A: An electrocardiographic (ECG) tracing, showing giant T wave inversion in the precordial leads V<sub>2-6</sub>, of a 76-year Caucasian male with a past medical history of an old inferior myocardial infarction, percutaneous coronary intervention of the right coronary artery (RCA) and left anterior descending coronary artery, acutely presented with left abdominal pain, psychomotor unrest, diaphoresis and blood pressure difference between the right and left arm. Acute aortic dissection was excluded as well as recurrent MI. Coronary angiography frame of (B) the left coronary artery and (C) the RCA depicting no significant stenosis of the arterial tree. Serum cardiac markers were slightly elevated. Echocardiographic (hypokinesia of the mid and apical regions and hyperkinesia of the basal segments) findings and (D) ventriculography (apical ballooning) were all compatible with Takotsubo cardiomyopathy; E: Base line ECG. The abdominal ultrasound and (F) CT demonstrated a pheochromocytoma in the left adrenal region which was confirmed with 123I-MIBG scan and dihydroxyphenylalanine-Positron Emission tomography and proved by pathological results. Plasma and urine metanephrin and normetanephrin were highly elevated. After removal of the hormonally active tumor, the patient became symptom free and the ECG normalized. The medical treatment continued including calcium reentry blocker, beta blocker, aspirin, angiotensin converting enzyme inhibitor, statin and an  $\alpha$ -blocker.



**Figure 8 Patient 8.** Electrocardiographic (ECG) tracing, demonstrating negative T-wave in the precordial leads V1-5, microvoltage in the standard leads and an Epsilon wave (arrow) which can be appreciated on magnification of ECG lead V2, of a 73-year-old man, amateur marathon runner after successful resuscitation for OHCA due to ventricular fibrillation. His coronary angiography and transthoracic echocardiography were normal. Genetic counseling revealed mutation 1238C > A (Tyr616X) in the plakophilin2 gen, compatible with AC. He refused implantable cardioverter defibrillator implantation and remained on medical treatment including class III antiarrhythmic drug. He was advised to refrain from marathon running and other strenuous exercise.

### ***Transthoracic echocardiography***

Transthoracic echocardiography was performed in all patients. Mild and moderate tricuspid regurgitation was detected in 6 (patients 1, 3, 4, 5, 6 and 7) and one (patient 2) of the patients, respectively. In 3 patients (patients 2, 3 and 7) trivial aortic regurgitation was present. Mild and moderate mitral regurgitation was demonstrated in 4 (patients 3, 4, 5 and 7) and 3 (patients 1, 2 and 6) patients, respectively. Dilatation of the right ventricle (RV) was demonstrated in one patient (patient 8). In five patients (patients 1, 2, 3, 4 and 5) the estimated RV systolic pressure was 35, 28, 35, 32 and 59 mmHg, respectively. Echocardiographic criteria for LVH was found in 4 patients (patients 2, 3, 6 and 7). Apical hypokinesia was detected in two patients (patients 1 and 7).

### ***Cardiac magnetic resonance imaging***

Cardiac magnetic resonance imaging was performed in three patients (patients 1, 3 and 4). All had normal findings.

### ***Pulmonary computed tomography angiography***

Pulmonary computed tomography angiography was performed in one patient (patient 5). Tailored individual diagnostic investigation was performed. In 2 patients (patients 3 and 4), pulmonary perfusion/ventilation scintigraphy were performed and pulmonary embolism was ruled out.

### ***Computed tomography***

Abdominal CT scan was performed in one which revealed an abdominal mass in the left adrenal region, a CT scan of the thoracic aorta excluding acute aortic dissection (patient 7) and brain CT scan in another (patient 4) showing mild atrophy and minimal ischemic changes.

### ***Radionuclide imaging and positron emission tomography***

One patient (patient 7) underwent <sup>123</sup>I-MIBG scan and DOPA-PET scanning. This revealed MIBG uptake in the left adrenal region and a solitary lesion was detected at the left adrenal area with central necrosis



**Table 1** Demographic features, clinical presentations, diagnostic modalities and management

| Case/<br>gender/<br>age | Clinical<br>presentation                                  | ECG (SR)<br>T-wave<br>inversion   | QTc<br>(msec) | Associated disorders   | TTE   | Diagnostic<br>modalities   | Management   | Condition   |
|-------------------------|---|---|---------------|--|---|--|--|---|
| 1-F51                   | Palpitation   | 15 mm in<br>V <sub>2-6</sub>  | 452           | AVNRT<br>Depression  | Apical<br>hypokinesia                                     | TTE<br>CAG<br>MRI  | MM   | Post-ECT. TTC<br>(electrical stress)                |
| 2-F82                   | Chest pain  | 10 mm in<br>V <sub>1-4</sub>  | 484           | Mild AS PG 18 mmHg   | Apicoinferior<br>hypokinesia<br>LVH                       | TTE  | MM   | NSTEMI  |
| 3-F72                   | Abnormal<br>rest ECG                                      | 5 mm in<br>V <sub>2-6</sub>   | 553           | PAF 2011<br>Temporal arteritis<br>Carotid endarterectomy<br>Cluster headache | LVH   | TTE<br>CAG<br>PV scan<br>MRI   | MM   | TTC (emotional stress,<br>spouse died 2 wk earlier) |
| 4-F69                   | Inter-<br>scapular pain                                   | 9 mm in<br>V <sub>2-5</sub>   | 520           | TIA 2010   | Normal  | TTE<br>CAG<br>PV scan<br>MRI<br>CT brain   | MM   | Undetermined  |
| 5-M55                   | Chest pain  | 1 mm in<br>V <sub>1-3</sub><br>S <sub>1</sub> Q <sub>3</sub> T <sub>3</sub> | 432           | -  | Dilated<br>hypokinetic<br>RV<br>ePAP 75-80<br>mmHg<br>LVH | TTE<br>CAG<br>PCTA   | MM   | Pulmonary embolism                                  |
| 6-F52                   | Fatigue   | 5 mm in<br>V <sub>3-6</sub>   | 409           | -  | LVH   | TTE<br>CAG   | MM   | HCM   |
| 7-M76                   | Left<br>abdominal<br>pain and<br>psychomotor<br>agitation | 20 mm in<br>V <sub>2-6</sub>  | 639           | IMI 1990<br>PCI RCA 1990 and 2004<br>PCI LAD 1991                            | Apical<br>Hypokinesia<br>LVH                              | TTE<br>CAG<br>CT thoracic aorta<br>Ultrasound<br>abdomen<br>CT abdomen<br>123I-MIBG DOPA-<br>PET Pathology | Surgical left<br>adrenalectomy<br>MM   | TTC.<br>Pheochromocytoma<br>(hormonal stress)       |
| 8-M73                   | VF, OHCA  | Epsilon V <sub>2</sub><br>4 mm in<br>V <sub>1-5</sub>                       | 424           | Negative family history  | RV dilatation   | TTE<br>CAG<br>Genetic counseling   | MM, AAD<br>Refused ICD<br>implantation<br>Advise to<br>refrain from<br>strenuous<br>exercise | ARVC/D  |

AAD: Antiarrhythmic drug; ARVC/D: Arrhythmogenic right ventricular cardiomyopathy/dysplasia; AS: Aortic valvular stenosis; AVNRT: Atrioventricular nodal reentry tachycardia; BB: Beta blocker; CAD: Coronary artery disease; CAG: Coronary angiography; ECT: Electroconvulsive therapy; MM: Medical management; CRB: Calcium reentry blocker; CT: Computed tomography; ePAP: Estimated pulmonary artery pressure; F: Female; HCM: Hypertrophic cardiomyopathy; IMI: Inferior myocardial infarction; LAD: Left anterior descending coronary artery; LVH: Left ventricular hypertrophy; M: Male; MRI: Magnetic resonance imaging; NSTEMI: Non ST elevation myocardial infarction; OHCA: Out of hospital cardiac arrest; PAF: Persistent atrial fibrillation; PCI: Percutaneous coronary intervention; PCTA: Pulmonary computed tomography angiography; PET-CT: Positron emission tomography-computed tomography; PG: Peak gradient; PV scan: Perfusion-ventilation scan; RCA: Right coronary artery; RV: Right ventricle; SR: Sinus rhythm; TIA: Transient ischemic attack; TTC: Takotsubo cardiomyopathy; TTE: Transthoracic echocardiography; VF: Ventricular fibrillation; ECG: Electrocardiographic.

with DOPA-PET scanning.

### Coronary angiography

Seven patients underwent selective contrast angiography which revealed non-obstructive coronary artery disease in one patient and normal coronary arterial tree in 6 patients.

**Follow-up:** Follow-up was obtained by direct contact with patients, general practitioner, their physicians or by chart review.

## DISCUSSION

In middle-aged subjects, T-wave inversion in the

precordial leads is relatively rare in the general population occurring in 0.5% (54/10899)<sup>[3]</sup> of the subjects. T-wave inversion in the anterior chest wall leads is relatively common in children and adolescents<sup>[9]</sup> but infrequently found in healthy adults and is considered as "normal variants"<sup>[4]</sup>. This pattern is more common in young females and young adults (1%-3%)<sup>[14,15]</sup>. The prevalence was associated with gender difference, which was higher (0.9%) in women than in men (0.1%)<sup>[3]</sup>.

### Primary and secondary T-wave abnormalities

Primary T-wave abnormalities (ischemia or injury) are due to alterations in myocardial cellular electrophysiology and secondary T-wave abnormalities

(bundle branch block or ventricular Hypertrophy) are subsequent to alterations of sequence of ventricular activation.

### **Differential diagnosis of T-wave inversion**

In the 1960s of last century, Jacobson and Schrire described the differential diagnosis of T-wave inversion that included heart block, ischemic heart disease, bradycardia, right ventricular hypertrophy, right bundle branch block, metabolic disturbances, changes during diagnostic coronary angiography and cerebral disturbances<sup>[16]</sup>. Nowadays, the current differential diagnosis of T-waves inversion has expanded including, besides the abovementioned citations of Jacobson and Schrire, LV anterior wall ischemia, acute central nervous system disorders, acute adrenergic stress (Takotsubo cardiomyopathy "TTC")<sup>[17,18]</sup>, pulmonary edema<sup>[19,20]</sup>, antiarrhythmic drug effects<sup>[21]</sup>, pulmonary embolism<sup>[22]</sup>, cardiac memory secondary to transient tachycardia<sup>[8]</sup>, post-ventricular pacing states<sup>[23]</sup>, idiopathic<sup>[24]</sup> or in relation to cocaine use<sup>[25,26]</sup>. In a recent review, reversible or permanent inverted T-waves were found in 38% of patients with congenital coronary artery-ventricular multiple micro-fistulas (MMFs)<sup>[27]</sup>. Hence, congenital MMFs may be included in the differential diagnosis of anterior chest wall T-wave inversion.

### **Transient and permanent T-wave inversion**

Transient T-wave inversion may occur in the following conditions: Acute coronary syndrome<sup>[1]</sup>, cardiac memory T-wave<sup>[8,23]</sup>, cardiogenic non-ischemic pulmonary edema<sup>[19]</sup>, gastroenteritis<sup>[28]</sup>, post maxillofacial surgery<sup>[29]</sup>, subarachnoid hemorrhage<sup>[30]</sup>, electroconvulsive therapy<sup>[31-33]</sup>, Takotsubo cardiomyopathy<sup>[18,34]</sup>, pheochromocytoma<sup>[35]</sup> and indeterminate origin<sup>[24]</sup>. On the other hand, permanent T-wave inversion may accompany a variety of disorders associated with LV or RV cardiomyopathy such as apical hypertrophic cardiomyopathy (AHCM)<sup>[4,7,36,37]</sup> and arrhythmogenic right ventricular cardiomyopathy/dysplasia<sup>[38-41]</sup>.

### **Non-coronary cardiac and non-cardiac disorders**

Several non-coronary cardiac and non-cardiac disorders have been associated with the development of T-wave inversion. Among the Non-coronary cardiac disorders: are pericarditis, myocarditis, cardiac metastasis, athletic heart syndrome, AHCM<sup>[4]</sup>, hypertrophic cardiomyopathy<sup>[37]</sup>, post-tachycardia and right ventricular pacing (cardiac memory)<sup>[8,23]</sup>.

### **Non-coronary non-cardiac disorders**

Non-coronary non-cardiac disorders (T-wave wide asymmetric and associated with prolonged QT interval) include severe brain injury (subarachnoid hemorrhage "SAH", intracranial hemorrhage)<sup>[30,42]</sup>, traumatic head injury, maxillofacial surgery<sup>[29]</sup>, bilateral carotid endarterectomy, after vagotomy, cocaine

abuse<sup>[43]</sup>, flecainide use<sup>[21]</sup>, pheochromocytoma<sup>[44]</sup> and gastrointestinal emergencies (perforated ulcer, acute pancreatitis and acute cholecystitis)<sup>[28,45-48]</sup>.

### **Prognosis**

In the middle-aged population, inverted T-wave in the right precordial leads V<sub>1-3</sub> was associated with good prognosis in contrast to inverted T-wave in leads other than V<sub>1-3</sub> which predicted adverse outcomes such as increased risk of hospitalization due to congestive heart failure and coronary artery disease<sup>[3]</sup>. Migliore *et al*<sup>[49]</sup>, stated that inverted shallow asymmetric T-wave with the descending limb longer than the abruptly ascending limb seen in middle-aged women are not associated with cardiac disease.

### **Transient T-wave inversion**

**Acute coronary syndrome<sup>[1]</sup>:** T-wave inversion in the precordial leads have been reported since 1982 as narrow, sharp, and symmetrical waves; the so called "coronary type" reflecting high-grade stenosis of the proximal left anterior descending coronary artery due to regional delay in ventricular repolarization as generally found in ischemic heart disease<sup>[50,51]</sup>. In this condition, T-wave inversion may persist for days or weeks.

**Cardiac memory pattern:** Memory T wave was first presented by Chatterjee *et al*<sup>[52]</sup>, in 1969 in 94% of patients with intermittent right ventricular pacing. Transient T-wave inversion occurring after conversion to sinus rhythm from tachycardia or artificial pacing which is caused by abnormal ventricular activation. This pattern of transient T-wave inversion in the precordial leads is associated with tall T-wave in leads I and aVL and are common in patients with permanent pacemakers or ensue after recovery from ventricular or supraventricular tachycardia<sup>[23]</sup>. It is a diagnosis of exclusion. This pattern of T-wave inversion in RV pacing is caused by dyssynchronous LV activation and involvement of potassium ion channels are postulated to be the key issues in its pathogenesis<sup>[53]</sup>.

**Electroconvulsive therapy:** ECT may induce ECG changes with simultaneous echocardiographic regional wall motion abnormalities especially when arterial blood pressure and heart rate are markedly elevated<sup>[54]</sup>. It has been reported that transient T wave inversion Occurs in 4% of the patients undergoing ECT<sup>[55]</sup>. Transient T-wave inversion, not associated with cardiac abnormalities, has been reported due to increased sympathetic stimulation associated with ECT<sup>[31,32]</sup>. Conversely, Tuininga reported two cases of T-wave inversion following ECT with significant obstructive coronary artery disease requiring anti-anginal therapy and percutaneous coronary intervention<sup>[33]</sup>. It was recommended that

further investigation to rule out significant coronary artery disease should be performed especially in patients with cardiovascular risk factors. Moreover, transient T-wave inversion has been reported after electroconvulsive therapy but not following transthoracic direct current electrical cardioversion for treatment of atrial fibrillation<sup>[56]</sup>. In representative case (patient 1), the findings of CAG and cardiac MRI were normal.

**Cardiac sarcoidosis:** Cardiac sarcoidosis (CS) is a systemic inflammatory disease with unknown etiology characterized with non-caseating granulomas in multiple organ systems and may be associated with negative T-wave in the anterior precordial leads.

**Subarachnoid hemorrhage:** In the 1960s, electrocardiographic changes mimicking myocardial ischemia and infarction associated with spontaneous intracranial hemorrhage have been reported<sup>[57]</sup>. Reversible T-wave abnormalities accompanied with prolongation of QT interval were found in 32% of patients with SAH<sup>[30]</sup>. ECG changes and arrhythmias occurred within the first 48 h after SAH<sup>[43,58]</sup>. The postulated pathogenesis is cardiomyocytolysis due to excessive sympathetic stimulation. Possible mechanisms<sup>[30]</sup> are autonomic neural stimulation from the hypothalamus and elevated levels of circulating catecholamine. The care of patients with subarachnoid hemorrhage has improved dramatically over the last few decades. These gains are the result of improved microsurgical, endovascular, and medical management techniques. This intensive management subjects patients to multiple radiographic studies and thus increased radiation exposure. Thus, tailored diagnostic modalities are required for early and correct establishment of the diagnosis. This to avoid over exposure to ionizing radiation and other invasive procedures. T-wave abnormalities in patients suffering SAH are subsequent to TTC secondary to elevated levels of circulating catecholamine and excessive sympathetic stimulation<sup>[29]</sup>.

**Pulmonary embolism:** Acute pulmonary embolism may occasionally result in reversible deep T-wave inversion with QT interval prolongation<sup>[59]</sup>. T-wave inversion associated with PE was first described in 1938 by Love *et al.*<sup>[60]</sup>. T-wave inversion in the precordial leads have been noticed in a moderate-size PE<sup>[61]</sup>, partially occlusive<sup>[22]</sup> and non-occlusive<sup>[23]</sup> PE. Precordial T-wave inversion was the most common abnormal ECG finding (68%), this anterior wall ischemic pattern was found in 85% of massive PE and in 19% of mild-moderate PE followed by S1 Q3 T3 pattern detected in 54% of the patients<sup>[62]</sup>. The proposed mechanisms include RV strain and decreased perfusion of LV anterior wall caused by hypotension consequent to pulmonary embolism<sup>[63]</sup>. The above mentioned findings were present in the

patient with PE (patient 5).

Diagnostic workup for T-wave inversion should always focus on the most likely causes and patient individually tailored diagnostic program should be followed. This to avoid and to limit unnecessary radiation exposure including diagnostic invasive cardiac catheterization.

**Pulmonary edema:** T wave inversion in the precordial leads has rarely been reported: Possible postulated mechanisms are: an acute rise in the cardiac sympathetic tone either *via* an increased sympathetic discharge from the central nervous system or through subendocardial ischemia due to elevated wall stress, high end-diastolic pressure and decreased coronary arterial blood flow and the electrical heterogeneity in the ventricular wall<sup>[19]</sup>.

**Pheochromocytomas:** Pheochromocytomas are catecholamine secreting tumours that arise from the chromaffin cells of the adrenal gland. Biochemical diagnosis is established by measuring plasma free metanephrins or nor-metanephrin levels. Localization of the tumour is reached by performing computed tomography or magnetic resonance imaging scans and specifically using metaiodobenzylguanidine scan. The latter is considered the gold standard. Finally, it is confirmed by histopathologic examination<sup>[64]</sup>. Occasionally, pheochromocytoma may resemble acute coronary syndrome<sup>[35,65]</sup>. Pheochromocytoma-related cardiomyopathy has incidentally been reported with inverted takotsubo contractile pattern<sup>[45]</sup>. In patient No. 7, diagnosed with pheochromocytoma (Figure 7F) presented with chest pain and psychomotor agitation, showed periodic fluctuations of blood pressure and ECG abnormalities mimicking acute coronary syndrome (Figure 7A) without significant obstructive coronary artery disease (CAD) on his CAG (Figure 7B and C).

Pheochromocytomas are rare neuroendocrine tumours with a highly variable clinical presentation but most commonly presenting with bouts of headaches, sweating, palpitation and hypertension. Imaging techniques such as CT or MRI and functional assessments using <sup>123</sup>I-MIBG are applied to localize biochemically active tumors. In our patient (patient 7), full recovery occurred after left adrenalectomy was successfully performed in an academic hospital. The deepest T-wave inversion (Figure 7A) was found in this patient.

**Takotsubo cardiomyopathy:** TTC in relation to neurohormonal active adrenal tumor pheochromocytoma or after pulmonary resection for bilateral non-small cell lung neoplasms has rarely been reported<sup>[45,66]</sup>. TTC accounts for 2% of total hospital admissions for suspected acute coronary syndrome<sup>[67]</sup>. It Accounts for approximately 1% of admissions for suspected acute myocardial

infarction in Japan<sup>[68]</sup>. Satoh *et al*<sup>[69]</sup> and Dote and associates first described this syndrome in Japanese patients<sup>[70]</sup>. In 2001, Tsuchihashi *et al*<sup>[17]</sup> reported on cardiomyopathy with apical ballooning mimicking acute myocardial infarction (MI) without obstructive epicardial CAD, 97% of patients demonstrated T-wave inversion in the precordial leads with female predominance (86%). They observed that in 70% of the subjects there was a preceding heavy psychological or physical stress<sup>[17]</sup>. While the pathogenesis of TTC is not fully understood and remains to be elucidated, several hypotheses, including multivessel epicardial coronary artery spasm, storm of catecholamine excess and coronary microvascular disorder have been proposed<sup>[17,71,72]</sup>. In a comparison between patients with acute MI and heart failure and patients admitted with a LV systolic dysfunction after sudden emotional stress (95% female subject), Wittstein *et al*<sup>[18]</sup>, found CAD in only 5% in the latter group with significantly higher plasma catecholamine levels suggesting a relation between an exaggerated sympathetic stimulation and transient LV dysfunction<sup>[18]</sup>. The following criteria are required for establishing the diagnosis TTC; transient LV systolic dysfunction frequently emerging following a stressful trigger, not associated with significant obstructive CAD, novel ECG changes with ST-segment elevation or T-wave inversion usually accompanied with slightly elevation of cardiac markers and no signs of myocarditis and pheochromocytoma<sup>[73-75]</sup>. Occasionally, in the hyperacute phase of TTC, transient J wave may precede T-wave inversion<sup>[72]</sup>. Diagnostic work-up may include history, ECG, echocardiography, CAG, ventriculography and less frequent Cardiac magnetic resonance imaging<sup>[76]</sup>. Cardiac MRI has been useful to differentiate stress TTC from anterior ST-Elevation MI with segmental wall necrosis, by absence of late enhancement in the former condition on delayed image sequence. Other pivotal MRI findings for the diagnosis of TTC are diffuse edema of the left ventricular apical or mid wall associated with akinesia or hypokinesia and absence of perfusion defects<sup>[34]</sup>. Furthermore, T2-weighted MRI delineated the ECG characterizations (dynamic negative T waves and QTc prolongation) in TCC, resembling the ischemic-like Wellens' ECG pattern, correlating with the apicobasal gradient of myocardial edema, reflecting the edema-induced transient apicobasal inhomogeneity<sup>[77]</sup>. Recently, positron emission tomography computed tomography has been used to differentiate takotsubo cardiomyopathy TTC from acute coronary syndrome<sup>[78]</sup>. TTC may occur subsequent to aneurysmal subarachnoid hemorrhage<sup>[79]</sup>. The relation between TTC and SAH is well known. Many reports have shown the reversible pattern of T-wave inversion associated with SAH<sup>[29,78]</sup>.

**Athletic heart:** In 1899, Henschen<sup>[80]</sup> described

cardiac enlargement in cross-country skiers. Several ECG changes have been observed in athletes engaged in high intensity dynamic endurance sport activities which may mimic pathological and structural heart diseases. Among others, T-wave inversion in the precordial leads and relative bradycardia were reported<sup>[81]</sup>. Echocardiographic features of athletic left ventricular hypertrophy may include mild concentric LVH, mild LV dilatation, normal diastolic filling and normal systolic function<sup>[82]</sup>. It is important to distinguish between physiological adaptive ECG changes and pathological ECG abnormalities to prevent unnecessary distress<sup>[83,84]</sup>. Regression of LVH occurs when athletes decide to decondition. Some authors consider this adaptation of endurance sports athletic heart as pathologic since LVH regresses on cessation of endurance training in a similar response to a successful treatment of aortic stenosis or arterial hypertension<sup>[85]</sup>.

### **Permanent T-wave inversion**

Arrhythmogenic right ventricular hypertrophy was first described by Dalla Volta *et al*<sup>[86]</sup> in 1961 in Italy and it was brought comprehensively under attention by Frank *et al*<sup>[87]</sup> in 1978. They reported individuals with extending fibro-fatty non-ischemic changes of the right ventricle. Sudden death may be the first sign of disease<sup>[88]</sup>. Prevalence is 1/5000 individuals<sup>[89]</sup>. They have an autosomal dominant or recessive mode of inheritance with incomplete penetrance. ARVC/D affects mainly the right ventricular myocardium characterized with progressive fibro-fatty replacement and infiltration of the RV myocardium and is considered a major cause of sudden arrhythmic death. Recently, involvement of the left ventricle at a later stage may be associated with severe manifestation and carry a worse prognosis<sup>[90]</sup>. It has been suggested by Gallo *et al*<sup>[91]</sup> and others for the implementation of a broader term as arrhythmogenic cardiomyopathy (AC)<sup>[91,92]</sup>. In AC, two major criteria or one major and 2 minor criteria are required to establish the diagnosis<sup>[38]</sup>. T wave inversion may be the first presentation<sup>[3]</sup>. Recently, in 2010, the revised task force criteria and guidelines for the clinical diagnosis of AC have been updated and T-wave inversion in the right precordial leads V<sub>1-3</sub> or beyond was upgraded to a major criterion, in subjects > 14 years of age in the absence of complete right bundle branch block<sup>[93]</sup>, as was found in patient No. 8. The 12-lead ECG demonstrated abnormal changes in 90% of the cases with T-wave inversion in V<sub>1-3</sub> and sometimes across V<sub>6</sub> as the most common finding<sup>[38]</sup>. Right precordial T-wave inversions were present in 48%-85% of suspected subjects and Epsilon wave (terminal notch in the QRS complex due to slowed intraventricular conduction) was found in 8%-33% of patients with AC<sup>[38-40]</sup> as was the case in patient No. 8. In subjects with AC, global and or regional dysfunction and structural



alterations may be detected by echocardiography, angiography, radionuclide scintigraphy or MRI. Cardiac MRI has a high negative predictive value with sensitivity of 100% and specificity of 87%<sup>[94]</sup>. Mutations in the genes responsible for coding of connecting proteins, called desmosomes are the culprit. In the Dutch population, a founder mutation of p.Arg79X in plakophilin-2 (PKP2) gen with the same desmosome gene mutation in AC has been described<sup>[95]</sup>. Analysis of DNA in patient No. 8, showed a mutation of plakophilin-2 gen (1248C>A Tyr 616X). Rarely, cardiac sarcoidosis may mimic AC<sup>[96]</sup>.

**Apical hypertrophic cardiomyopathy**<sup>[4,7,36,37]</sup>: It is also called (Yamaguchi syndrome) and is considered a rare variant of hypertrophic cardiomyopathy. In the majority of cases (93%) of AHCM, negative T-wave in the precordial leads is the most frequent finding<sup>[7]</sup>. Its prevalence (15%) in Japan is high in comparison to the United States (3%)<sup>[97]</sup> and in Europe (< 5%)<sup>[98]</sup>. Giant negative T-wave exceeding 10 mm is found in 47% of patients with AHCM<sup>[7]</sup>. Typical findings were first described by Sakamoto in 1976<sup>[99]</sup> and Yamaguchi *et al.*<sup>[100]</sup> in 1979. In the retrospective study of Eriksson *et al.*<sup>[7]</sup>, T-wave inversion was found in (98/105) 93% of the patients. Apical wall thickness of 15 mm was based on TTE or MRI measurements. The T-wave inversion is permanent without tendency for recovery. The permanent ECG features of AHCM are among others giant negative T waves in the precordial leads, ST depression and negative U waves in II, III, aVF, V4-V6, a prolonged QTc and tallest R wave in V4; however, these permanent features may vary over time<sup>[101]</sup>.

Awareness of the differential diagnosis of T-wave inversion in the precordial leads will help trainees and physicians to discern different entities and will prevent some patients from undergoing unnecessary invasive investigations and procedures. Tailored individual diagnostic investigation was performed and specific diagnostic tools were undertaken when high index of clinical suspicion was raised towards a certain disease entity.

## COMMENTS

### Background

Myriad of clinical conditions have been described in association with T-wave inversion in the precordial leads. T-wave inversion associated with or without corrected QT prolongation may be encountered in a variety of clinical conditions.

### Research frontiers

In patients with T-wave inversion in the precordial leads, tailored diagnostic approach should be conducted avoiding overuse of diagnostic methods. Specific tailored diagnostic modalities and directed therapeutic interventions may be undertaken when high index of clinical suspicion is raised towards certain disease entity.

### Innovations and breakthroughs

This study is a retrospective analysis of patients presented with T-wave inversion in the anterior chest leads. The T-wave inversion may be accompanied with or without QTc prolongation. Classification has been made into reversible and

irreversible types to facilitate its differential diagnostic approach.

### Applications

Awareness of the differential diagnosis of T-wave inversion in the precordial leads will help trainees and physicians to discern different entities and will prevent some patients from undergoing unnecessary invasive investigations and procedures.

### Peer-review

In this paper, authors report the various clinical conditions of patients with T wave inversion in the anterior chest wall leads. This review article is interesting and very educational.

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## Pulmonary arterial dissection in a post-partum patient with patent ductus arteriosus: Case report and review of the literature

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without an obvious rise in pulmonary artery pressure and reviewed the relevant literature.

**Key words:** Pulmonary dissection; Patent ductus arteriosus; Pregnancy; Echocardiography; Computed tomography

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**Core tip:** A 26-year-old female patient was admitted to our clinics with sudden dyspnea and chest discomfort one hour after giving birth to twins by vaginal delivery. Dilated main pulmonary artery and dissection flap extending from main pulmonary artery to left pulmonary artery were found in echocardiographic examination, there after, pulmonary dissection was confirmed by a computed tomography and the patient underwent surgery. In summary, in this report, we described a very rare case of pulmonary artery dissection in a pregnant patient with a previously un-diagnosed Patent ductus arteriosus without an obvious rise in pulmonary artery pressure and reviewed the relevant literature.

### Abstract

Pulmonary arterial dissection is an uncommon but usually a deadly complication of chronic pulmonary hypertension. A 26-year-old female patient was admitted to our clinics with sudden dyspnea and chest discomfort one hour after giving birth to twins by vaginal delivery. An echocardiography was performed with a pre-diagnosis of pulmonary embolism. However, echocardiographic examination revealed a dilated main pulmonary artery and a dissection flap extending from main pulmonary artery to left pulmonary artery. In summary, in this report, we described a very rare case of pulmonary artery dissection in a pregnant patient with a previously un-diagnosed patent ductus arteriosus

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### INTRODUCTION

Pulmonary arterial dissection is an uncommon but usually a deadly complication of chronic pulmonary hypertension. However, with the development of diagnostic and therapeutic interventions in recent

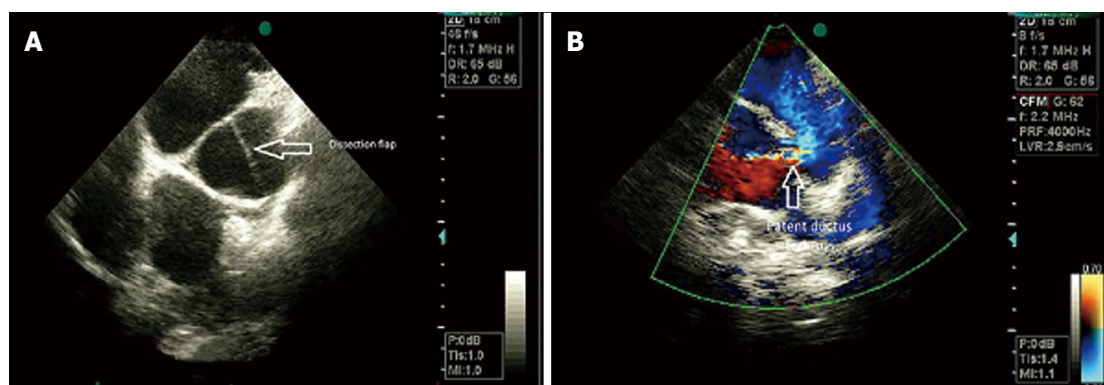


Figure 1 Echocardiographic views of pulmonary dissection (A) and patent ductus arteriosus (B).

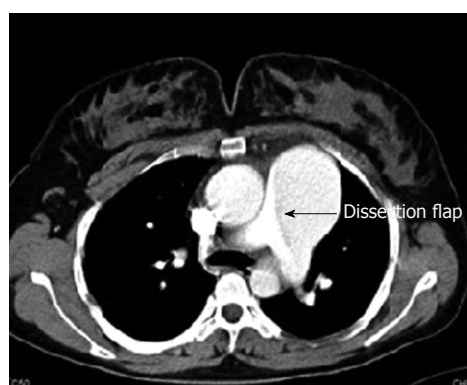


Figure 2 Computed tomography views of pulmonary dissection.

years, a few reports in surviving patients with pulmonary artery dissection have been reported<sup>[1]</sup>.

Patent ductus arteriosus (PDA) is a congenital anomaly caused by a failure to close of a fetal vessel which connects the pulmonary artery directly to the ascending aorta after birth. A rare but lethal complication of PDA is pulmonary artery dissection and dissection usually occurs as a result of chronic pulmonary arterial hypertension associated with PDA and is typically seen in patients with Eisenmenger's syndrome<sup>[2-5]</sup>. In this report, we described pulmonary artery dissection in a pregnant patient with a previously un-diagnosed PDA without an obvious rise in pulmonary artery pressure.

## CASE REPORT

A 26-year-old female patient was admitted to our clinics with sudden dyspnea and chest discomfort one hour after giving birth to twins by vaginal delivery. She had no previous medical history. On physical examination, her blood pressure was 100/60 mmHg and pulse rate was 125/min. The ECG was consistent with sinus tachycardia. An echocardiography was performed with a pre-diagnosis of pulmonary embolism. However, echocardiographic examination revealed a dilated main pulmonary artery and a dissection flap extending from main pulmonary

artery to left pulmonary artery (Figure 1A). Besides, in suprasternal and parasternal views, a PDA was observed (Figure 1B). Moderate tricuspid regurgitation was present with a peak continuous wave velocity 2.7 m/s. A thorax computed tomography examination was then performed which showed the dissection flap and the false lumen in the main pulmonary artery (Figure 2). The patient underwent emergent surgery after clarifying the diagnosis. A Dacron graft was positioned in the main pulmonary artery and the PDA was closed. She was discharged from the hospital at the 12<sup>th</sup> post-operative day. She was in a good clinical condition and asymptomatic at her regular polyclinic controls.

## DISCUSSION

PDA is a congenital heart disease resulting from the postnatal closure defect of the ductus arteriosus. It represents 5%-10% of all congenital heart diseases, with a female-to-male ratio of 2:1. Delayed treatment may lead to certain complications including pulmonary hypertension, Eisenmenger's syndrome, congestive heart failure, and infective endarteritis. Though rare, pulmonary artery dissection may also be included in the above list of complications.

Posing a high mortality risk, pulmonary artery dissection results from congenital heart diseases, pulmonary hypertension and cardiac interventions<sup>[1]</sup>. Right heart endocarditis, amyloidosis, trauma and severe atherosclerosis may also result in pulmonary artery dissection<sup>[6]</sup>. The most common cause is pulmonary hypertension associated with congenital heart disease. Interestingly, in our case, the patient did not have pulmonary hypertension.

The main pulmonary artery is involved in 80% of the pulmonary artery dissection cases. However, isolated cases with right or left pulmonary artery involvement can also be seen. Localized small dissections are rare. Because rupture causes cardiogenic shock and sudden death, diagnosis is rare in the living subject and pulmonary artery dissection is frequently detected in autopsy<sup>[5]</sup>. Khattar *et al*<sup>[1]</sup> stated that only

8 (12.6%) out of 63 cases were diagnosed to have pulmonary artery dissection while living, and that 34 (53.9%) of the cases had congenital heart disease<sup>[1]</sup>. In our case report, pulmonary dissection was reliably diagnosed by transthoracic echocardiography, and thereafter the diagnosis was confirmed by computed tomography examination.

Pulmonary artery dissections usually occur in patients with medial degeneration and pulmonary arterial dilatation due to chronic increases in pulmonary arterial pressures<sup>[7-10]</sup>. Medial degeneration is a common cause of weakened pulmonary arterial wall and dilatation of the vessel and if intravascular pressure and shear stresses increase due to pulmonary hypertension, intimal tear may develop and cause dissection in the arterial wall. In our case, we thought that pregnancy predisposed the patient to dissection due to weakening of the connective tissue and pulmonary dissection occurred during difficult twin labour which increases venous return and blood pressure in the already dilated pulmonary bed due to PDA.

In aortic dissection, the false lumen usually extends distally and develops a re-entry site. However, in pulmonary dissection, the false lumen usually ruptures causing sudden death of the patient<sup>[7-10]</sup>. Cardiac tamponade due to rupture seems to be the most common mechanism of death in case of pulmonary dissection<sup>[10]</sup>. We were lucky because our patient survived this serious clinical situation.

For the first time in literature, we reported a very rare case of pulmonary dissection after giving birth to twins. Presence of PDA without an obvious increase in pulmonary arterial pressures made us think that a transient increase in venous return and pressure during labour caused the dissection to occur. With the development of new imaging techniques providing high quality images in acceptably short time intervals, this mortal disease has become to be diagnosed before death. Moreover, successful repair of pulmonary dissection with surgery has been reported in recent reports including ours. In conclusion, the success of early diagnosis and surgical intervention in pulmonary dissection necessitates an increased awareness of this highly mortal condition.

## COMMENTS

### Case characteristics

A post-partum patient with sudden dyspnea and chest discomfort after giving birth was admitted.

### Clinical diagnosis

Tachycardia and a systolic murmur were found on physical examination.

### Differential diagnosis

Pulmonary embolism, aortic dissection.

### Imaging diagnosis

Echocardiography and computed tomography were used for the diagnosis of patent ductus arteriosus and pulmonary dissection.

### Treatment

Surgical treatment for pulmonary dissection and patent ductus arteriosus closure was performed.

### Related reports

Few reports are present about pulmonary dissection in the literature and this is the first report regarding the presence of pulmonary dissection in a post-partum patient without an obvious rise in pulmonary arterial pressures.

### Experiences and lessons

An increased awareness of pulmonary dissection with a view to early diagnosis and corrective intervention is necessary in selected cases.

### Peer-review

It is an excellent work.

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## Coronary stenting with cardiogenic shock due to acute ascending aortic dissection

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**Author contributions:** Hanaki Y, Yumoto K and Kato K designed the report; Hanaki Y, Yumoto K and Fukuzawa T performed percutaneous coronary intervention; Aoki H analyzed IVUS findings; I S analyzed CT findings; Watanabe T collected the patient's clinical data; Hanaki Y and Yumoto K wrote the paper.

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### Abstract

A 65-year-old man developed chest pain under cardiogenic shock. Coronary angiography revealed severe stenosis from the ostium of the left main coronary artery (LMCA) to the left anterior descending artery (LAD). Intravascular ultrasound (IVUS) identified a large hematoma that originated from the aorta and extended into the LAD, thereby compressing the true

lumen. Type A aortic dissection (TAAD) that involved the LMCA was diagnosed by IVUS. Coronary stenting was performed *via* the LMCA to the proximal LAD, which resulted in coronary blood flow restoration and no further propagation of dissection. Elective surgical aortic repair was performed 2 wk after the stenting. LMCA stenting under IVUS guidance is effective for prompt diagnosis and precise stent deployment in patients with cardiogenic shock due to TAAD with LMCA dissection.

**Key words:** Aortic dissection; Left main coronary artery; Myocardial infarction; Intravascular ultrasound; Coronary artery stenting

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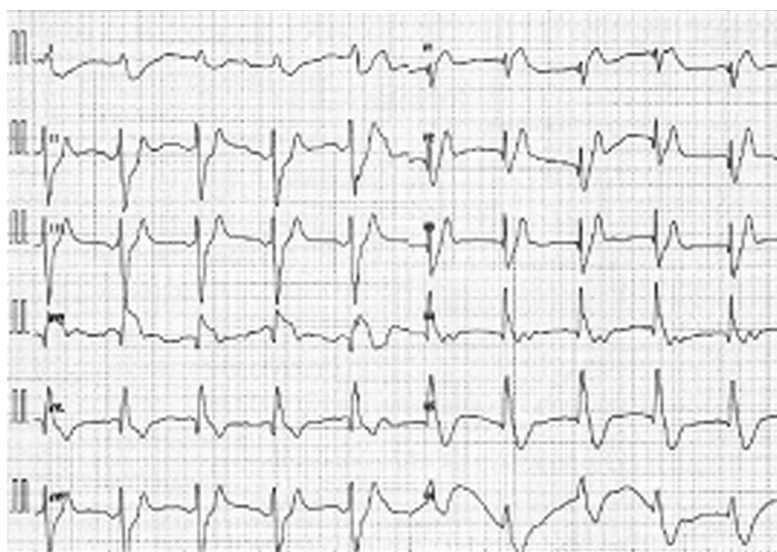
**Core tip:** Type A aortic dissection (TAAD) involving the left main coronary artery (LMCA) is a rare but potentially lethal condition. However, the precise diagnosis of TAAD prior to the treatment of acute myocardial infarction is difficult, and percutaneous intervention for LMCA obstruction secondary to TAAD is often complicated. This case report represents successful LMCA stenting under intravascular ultrasound (IVUS) guidance in a patient with cardiogenic shock due to TAAD with LMCA dissection. This procedure, particularly in terms of the use of IVUS, may be effective for rapid hemodynamic stabilization in patients in critical condition.

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### INTRODUCTION

Acute myocardial infarction (AMI) concomitant





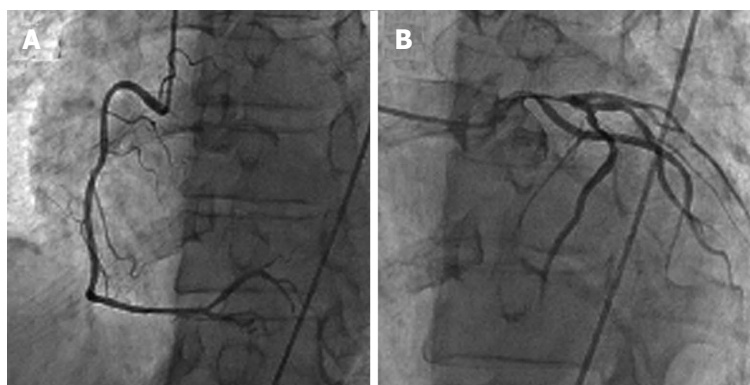
**Figure 1** Electrocardiogram on admission. Electrocardiogram shows an idioventricular rhythm with wide QRS complexes. A clear ST elevation is shown in lead aVR.

with acute type A aortic dissection (TAAD) is associated with a high hospital mortality rate despite improvements in TAAD surgical outcomes<sup>[1-3]</sup>. In particular, TAAD involving the left main coronary artery (LMCA) is a rare but lethal condition associated with low output syndrome, which results from extensive myocardial necrosis regardless of whether an aortic repair surgery is successful. Early coronary revascularization should be performed to minimize cardiac dysfunction<sup>[3]</sup>. The treatment of dissected coronary arteries with stent implantation achieves prompt and adequate myocardial blood flow and helps prevent extensive myocardial damage. However, an accurate diagnosis of TAAD prior to treatment for AMI is difficult, particularly in patients with hemodynamic instability<sup>[4,5]</sup>. Furthermore, percutaneous coronary intervention for LMCA obstruction due to TAAD is a complicated procedure unless the mechanism of the LMCA obstruction has been clarified<sup>[6]</sup>. Here, we describe a case of successful coronary intervention under intravascular ultrasound (IVUS) guidance in a patient with shock due to an unusually localized TAAD with LMCA obstruction.

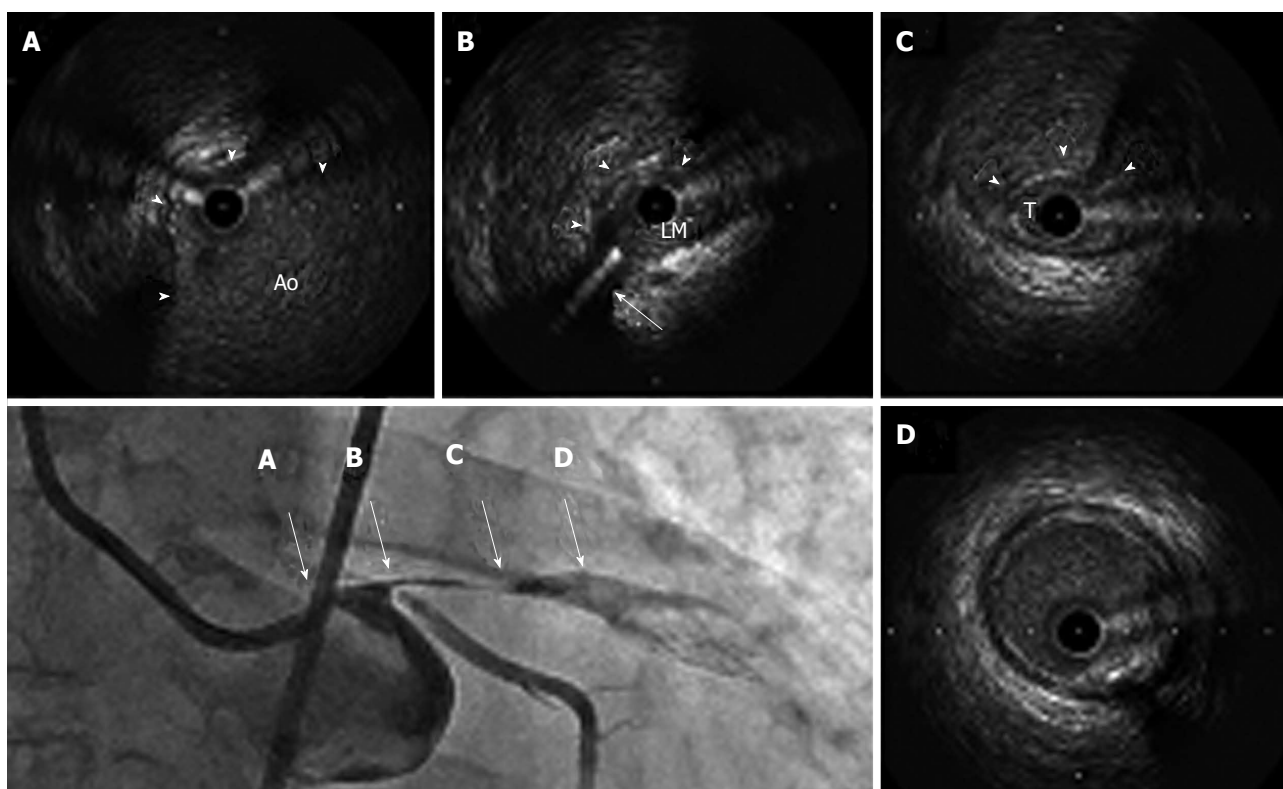
## CASE REPORT

A 65-year-old man was admitted due to sudden-onset chest pain accompanied with cold sweats. The patient had previously undergone a drug-eluting stent implantation in the left anterior descending artery (LAD) 5 years earlier to treat stable angina. His hypertension and hyperlipidemia were well controlled with medication, and he had continued dual antiplatelet therapy (DAPT) since the stent implantation. The patient was transported by ambulance to our hospital within an hour of onset, and his status on arrival included an unmeasurable blood pressure below 60 mmHg and a heart rate of 50 beats/min. The initial electrocardiogram

demonstrated bradycardia with an idioventricular rhythm, wide QRS complexes, and ST elevation in the lead aVR (Figure 1). Transthoracic echocardiography (TTE) revealed marked left ventricular dysfunction and a left ventricular ejection fraction of < 30% based on visual estimation. No aortic intimal flap, severe aortic regurgitation, or pericardial effusion was observed. The patient was immediately transferred to the cardiac catheterization laboratory because of ongoing myocardial ischemia and hemodynamic instability. An intra-aortic balloon pump was immediately inserted into the left femoral artery, and coronary angiography was performed from the right femoral artery without difficulty. The right coronary artery did not exhibit stenosis or collateral vessels. The left coronary artery exhibited severe stenosis from the ostium of the LMCA to the proximal LAD, which involved the ostium of the left circumflex artery (LCX) with TIMI grade 1 flow (Figure 2). Coronary intervention was subsequently performed. Run-through NS guidewire (Terumo, Tokyo, Japan) and SION guidewire (Asahi Intecc, Aichi, Japan) were inserted into the LAD and LCX, respectively. To confirm the wire position and evaluate the LMCA obstruction, IVUS (ViewIT, Terumo, Tokyo, Japan) was performed with quick pull-back. The IVUS revealed a large hematoma that originated from the aorta and extended into the LMCA and LAD (Figure 3A-C). The true lumen was compressed by the false lumen throughout the LAD immediately prior to the bifurcation of the diagonal branch (Figure 2D). A large intramural hematoma that involved the ostium of the LCX (Figure 3B) continued into the aortic wall in accordance with the double contour image in the coronary angiogram (Figure 3). We diagnosed an LMCA obstruction due to TAAD; thus, we decided to place a stent for immediate restoration of the coronary blood flow followed by aortic surgery. A 4.0- × 22.0-mm bare metal stent (Integrity; Medtronic, Minnesota, United States) was deployed *via* the



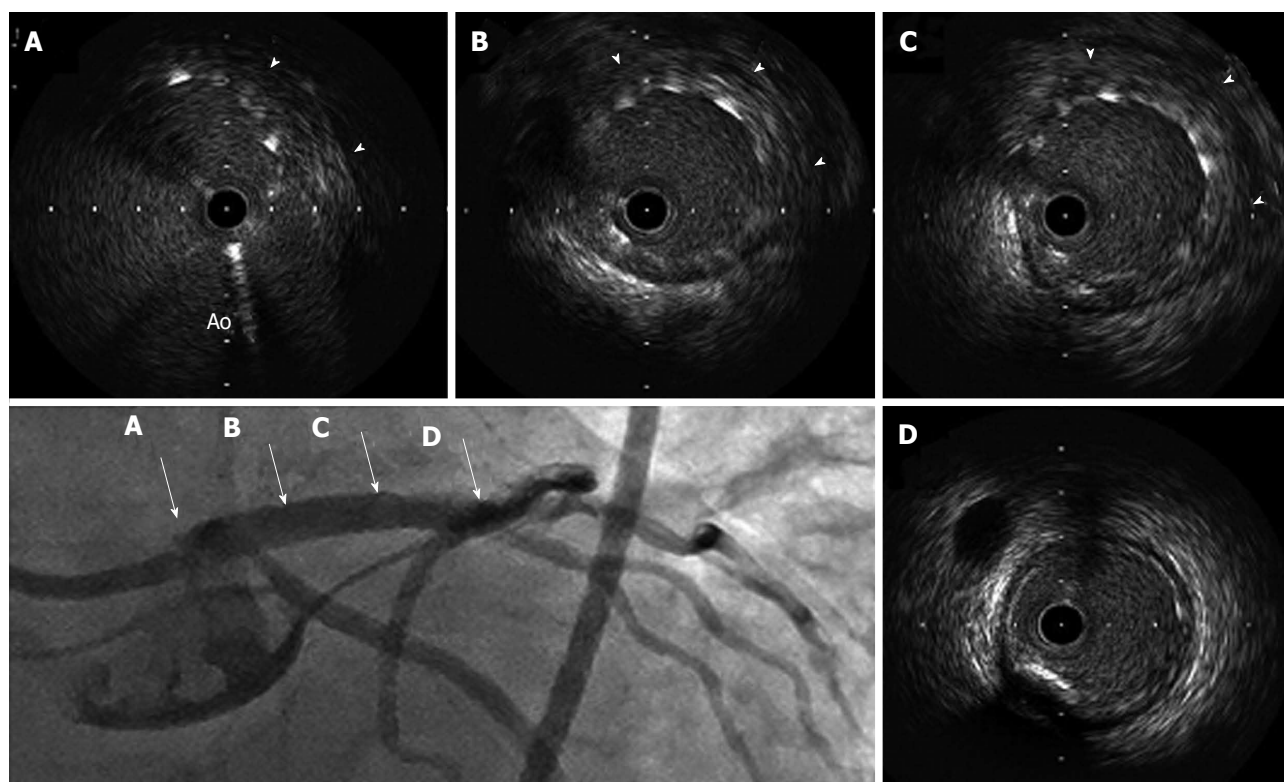
**Figure 2 Urgent coronary angiography.** A coronary angiography of RCA reveals no stenosis (A), but there is severe stenosis from the ostium of the left main coronary artery to the LAD with TIMI grade 1 flow (B). RCA: Right coronary artery; LMCA: Left main coronary artery; LAD: Left anterior descending artery; TIMI: Thrombolysis in myocardial infarction.



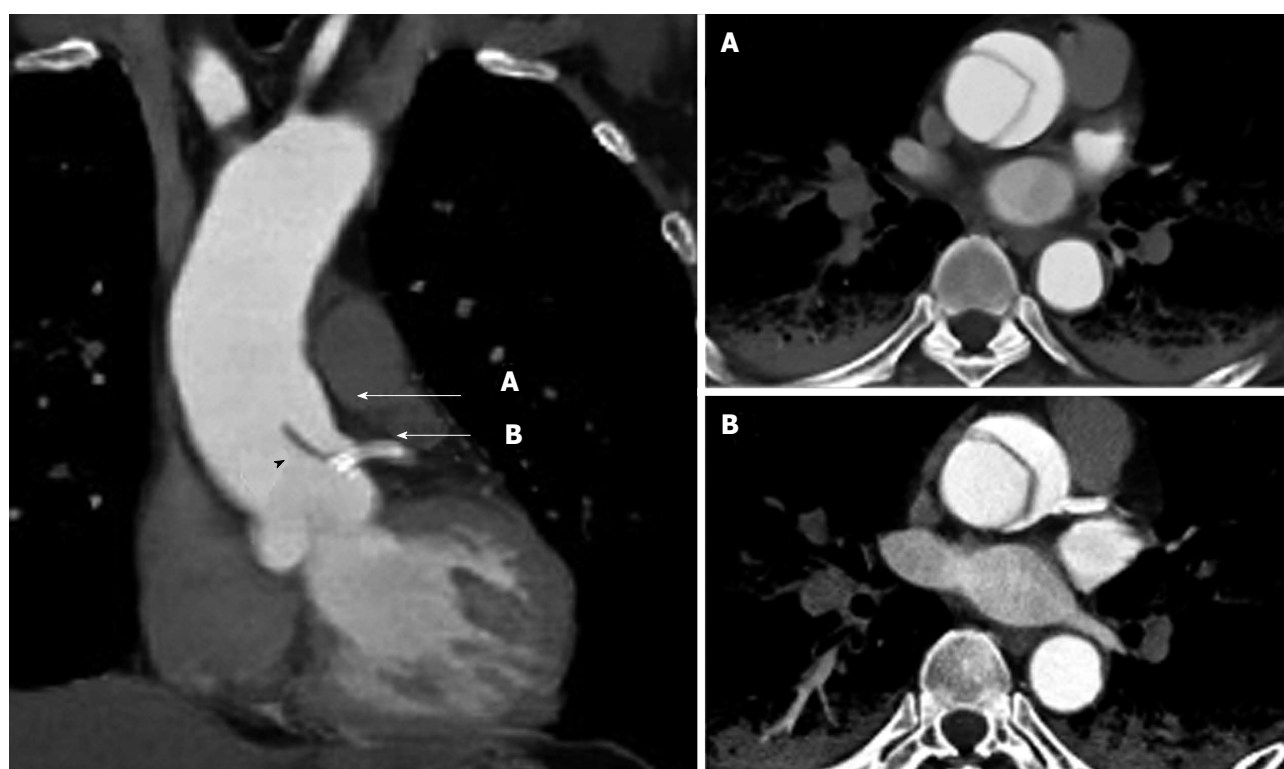
**Figure 3 Coronary angiography and intravascular ultrasound findings prior to stent implantation.** IVUS shows compression of the true lumen from the LMCA ostium to the LAD by a large false lumen. A: The large hematoma (arrowhead) eviscerates into the aorta (Ao); B: The false lumen (arrowhead) compresses the LMCA (LM), including both the LAD and LCX ostium. The arrow indicates the guidewire in the LCX; C: The large false lumen (arrowhead) compresses the true lumen (T) in the proximal LAD; D: The false lumen disappears before the bifurcation of the diagonal branch. Scale measures in 1 mm. IVUS: Intravascular ultrasound; LCX: Left circumflex artery; LAD: Left anterior descending artery.

LMCA through the LAD across the LCX ostium with satisfactory restoration of coronary blood flow. IVUS confirmed that the implanted stent appeared well-expanded and completely sealed the false lumen. No propagation of the false lumen into the distal LAD or the ostium of the LCX was observed (Figure 4). The patient's hemodynamic failure and symptoms improved immediately after stenting. We removed the intra-aortic balloon pump immediately after hemodynamic stabilization because of the potential exacerbation of TAAD. Contrast-enhanced computed tomography (CT) following the coronary intervention revealed a localized retrograde dissection of the ascending aorta that extended to the ostium of the

LMCA (Figure 5). The implanted stent protected the LMCA ostium from TAAD. Marked lung congestion was present. The following day, the patient's maximum creatine kinase and creatine kinase-myocardial band levels were 16190 and 829 IU/L, respectively. The DAPT comprised aspirin (100 mg/d) and clopidogrel (75 mg/d). An elective ascending aortic repair surgery was performed pending improvement of congestive heart failure under continued DAPT 2 wk after coronary stenting. Ascending aortic replacement with an interposition vascular prosthesis graft was performed; coronary artery bypass grafting (CABG), which included the left internal thoracic artery (LITA) to the distal portion of the LAD and a



**Figure 4** Coronary angiography and intravascular ultrasound findings after stent implantation. The implanted stent appears to be well expanded and completely seals the false lumen. There was no evidence of distal propagation of the false lumen or a flow limitation of the LCX. A: The hematoma (arrowhead) in the aorta is well covered by the stent; B, C: Implanted stent completely sealed the hematoma (arrowhead); D: No extension of the hematoma beyond the stent. Scale bars represent 1 mm.



**Figure 5** Contrast-enhanced computed tomography after coronary stenting. The sagittal view (left image) reveals the localized dissection of the ascending aorta that extends to the left main coronary artery ostium. The implanted coronary stent (arrow) protects against the intrusion of the dissection flap (black arrowhead) into the left coronary artery. Ascending aortic dissection is clearly visible in the horizontal view (right images) in accordance with A and B in the sagittal view.



**Table 1** Previously reported cases of coronary stenting for left main coronary artery due to acute ascending aortic dissection

| Ref.                                 | Patient (age/sex) | Hemodynamic status | Timing of diagnosis | Diagnostic modality | Timing of operation | CABG | Outcome   |
|--------------------------------------|-------------------|--------------------|---------------------|---------------------|---------------------|------|-----------|
| Saxena <i>et al</i> <sup>[7]</sup>   | 56 Male           | Unstable           | During PCI          | Aortogram           | < 24 h              | -    | Alive     |
| Ohara <i>et al</i> <sup>[8]</sup>    | 67 Male           | Unstable           | After PCI           | CT                  | Not performed       | -    | Dead      |
| Barabas <i>et al</i> <sup>[9]</sup>  | 74 Male           | Stable             | During PCI          | Aortogram           | < 24 h              | +    | Alive     |
| Ravandi <i>et al</i> <sup>[17]</sup> | 86 Male           | Unstable           | During PCI          | Aortogram           | Not performed       | -    | Uncertain |
| Imoto <i>et al</i> <sup>[18]</sup>   | 71 Male           | Unstable           | Before PCI          | CT                  | 3 d later           | -    | Alive     |
| Cardozo <i>et al</i> <sup>[19]</sup> | 68 Male           | Stable             | During PCI          | Aortogram           | Not performed       | -    | Dead      |
| Camero <i>et al</i> <sup>[20]</sup>  | 52 Female         | Unstable           | After PCI           | TEE                 | < 24 h              | -    | Alive     |
| Present case                         | 65 Male           | Unstable           | During PCI          | IVUS                | 14 d later          | +    | Alive     |

PCI: Percutaneous coronary intervention; CABG: Coronary artery bypass graft; CT: Computed tomography; TEE: Transesophageal echocardiogram.

saphenous vein graft (SVG) to the middle portion of the LCX, was performed at the surgeon's discretion. Intraoperatively, an intimal tear in the ascending aorta with the false lumen that extended to the ostium of the LMCA was identified without an intimal rupture or aortic valvular destruction. Satisfactory restoration of the intracoronary stent for the left coronary artery and wide patency of the ostia of the left and right coronary arteries were visibly confirmed at the time of surgery. The intraoperative bleeding volume was 1230 mL, which necessitated a blood transfusion of 650 mL. The patient was discharged 51 d after admission. The physical status at the one-month follow-up visit was characterized as New York Heart Association class 1 despite a high concentration of brain natriuretic peptide (400 pg/mL: normal range < 20 pg/mL). The TEE demonstrated reduced antero-septal wall motion; however, the overall ejection fraction recovered to 50%. A follow-up coronary angiography 6 mo after discharge revealed that the left coronary artery maintained excellent blood flow without in-stent restenosis. The SVG was patent; however, the LITA revealed shrinkage as a non-functional bypass.

## DISCUSSION

AMI with TAAD is associated with a high risk of extensive and irreversible myocardial damage and hemodynamic instability, which leads to high mortality regardless whether the surgical repair is successful<sup>[1,2]</sup>. TAAD that involves the LMCA is associated with a particularly high incidence of preoperative cardiopulmonary arrest and high operative mortality<sup>[3]</sup>. Postoperative low output syndrome due to extensive myocardial damage from AMI involving the LMCA is a major concern in surgical management. Although stent implantation in the treatment of dissected coronary arteries achieves immediate restoration of coronary blood flow and prevents extensive myocardial damage, the confirmation of the correct diagnosis and the performance of the optimal treatment procedure remain challenging<sup>[7-9]</sup> (Table 1).

AMI with shock might be overlooked as an

underlying factor of TAAD<sup>[4]</sup>. The diagnosis of TAAD with concomitant AMI is difficult because TAAD may be hidden in patients in critical condition. The present patient did not have back pain or a widened mediastinum on the chest X-ray obtained for suspected TAAD. Furthermore, the TTE revealed no evidence of localized TAAD. Although early revascularization should be strongly considered for patients with AMI secondary to cardiogenic shock<sup>[10]</sup>, subsequent thrombolytic therapy and/or coronary intervention can be complicated in patients with underlying TAAD<sup>[5]</sup>. CT is recommended as the first line of investigation for patients with suspected TAAD. However, CT imaging is more time consuming for critical shock patients with an ST segment elevation myocardial infarction<sup>[11]</sup>. TTE is also useful; however, it is a limited screening technique for the quick diagnosis of TAAD because of the unavoidable operator dependency, reduced image resolution, and limited field of view<sup>[12]</sup>. The IVUS findings in the present case enabled the determination of the precise diagnosis of TAAD with typical findings of coronary artery compression<sup>[13,14]</sup>.

Although coronary stenting is helpful in patients with TAAD, it remains challenging because of technical difficulties. The technical issues regarding coronary stenting include the navigation of the guidewire through the true lumen. IVUS imaging can be used to detect the orifice of the dissection, confirm the correct wire placement in the true lumen, and assist in the determination of the precise stent position, size, and length in a short time. Inappropriate ballooning or stenting that fails to completely seal the dissection might propagate the false lumen to the distal or proximal region. Repeated contrast injections should also be avoided because the extension of the dissection may result in the deterioration of the patient's condition<sup>[15]</sup>.

Imoto *et al*<sup>[3]</sup> reported that preoperative cardiopulmonary arrest and myocardial ischemia, particularly of the left coronary artery territory, negatively affected the survival outcomes in patients undergoing surgery for TAAD with coronary artery dissection. Early coronary intervention *via* stent implantation effectively prevents postoperative low cardiac output



syndrome. Several bridge approaches to surgery have consequently been developed to facilitate early coronary intervention and reduce the extent of myocardial cell necrosis.

The timing of surgical repair for TAAD after coronary stenting is important. A delay in surgical repair may lead to the propagation and rupture of the aortic dissection. Prompt intervention can serve as a bridge approach to gain time for critically unstable patients prior to definitive surgery. In contrast, perioperative stent thrombosis is a serious complication that is associated with a significant increase in mortality, particularly in LMCA stenting. This complication is caused by antiplatelet therapy discontinuation and a surgery-induced prothrombotic situation. DAPT is necessary after coronary artery stenting, particularly in the acute phase. Hansson *et al.*<sup>[16]</sup> studied the association of antiplatelet therapy with bleeding complications and mortality in patients undergoing operations for TAAD. The patients with ongoing platelet inhibition had significantly larger intraoperative and postoperative bleeding volumes; furthermore, the patients on DAPT had high 30-d mortality rates. In the present case, surgical aortic repair was performed after 2 wk while DAPT was continued. The duration of DAPT may be shortened, thus reducing bleeding during aortic surgery, by using a large bare metal stent with IVUS guidance to confirm the proper stent apposition. However, premature cessation of DAPT is likely to induce critical stent thrombosis. The addition of CABG is encouraging even after successful recanalization with stenting during the preparation for stent thrombosis after aortic surgery<sup>[3]</sup>. The optimal timing of surgical repair, the duration of DAPT and the efficacy of CABG addition after coronary artery stenting have not been established (Table 1).

LMCA stenting prior to the surgical repair of TAAD with LMCA dissection could be effective for an immediate improvement in hemodynamic instability. We emphasize the use of IVUS during the treatment of AMI because LMCA obstruction is necessary to exclude the presence of TAAD.

## COMMENTS

### Case characteristics

A 65-year-old male with a history of sudden-onset chest pain with hemodynamic instability.

### Clinical diagnosis

The shock status, peripheral coldness and electrocardiogram indicated a severe myocardial infarction with hemodynamic instability.

### Differential diagnosis

Coronary artery disease with or without coronary atherosclerosis, for example coronary spasm, thrombosis, or Takotsubo cardiomyopathy.

### Laboratory diagnosis

The cardiac enzyme levels were extremely elevated after the catheter procedure, with the following results: WBC 21.6 k/uL; AST 1706 U/L; LDH 2945 U/L; CK 16190 U/L; CK-MB 829 U/L; and D-dimer 10.18 µg/mL.

### Imaging diagnosis

The intravascular ultrasound (IVUS) findings during coronary intervention revealed a large hematoma that originated from the aorta and extended into the left main coronary artery (LMCA) and left anterior descending artery. An enhanced computed tomography scan revealed a localized retrograde dissection of the ascending aorta that extended to the ostium of the LMCA.

### Pathological diagnosis

No specimen materials were collected.

### Treatment

The patient was treated with a percutaneous coronary intervention and surgical procedure.

### Related reports

Type A aortic dissection (TAAD) involving the LMCA is rare; however, there are a few case reports of the efficacy of LMCA stenting prior to surgical repair for immediate improvement in hemodynamic instability.

### Experiences and lessons

The use of IVUS during acute myocardial infarction secondary to LMCA obstruction is effective for not only achieving appropriate stenting but also excluding the presence of TAAD.

### Peer-review

A well-written and interesting case report nicely outlining management strategy of acute myocardial infarction secondary to involvement of left main coronary artery by type A acute aortic dissection.

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