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EDITORIAL

- 1 Is there a role for ischemia detection after an acute myocardial infarction?
Peteiro J, Bouzas-Mosquera A

REVIEW

- 7 Diagnosis and treatment of heart failure with preserved left ventricular ejection fraction
Henning RJ
- 26 Radial artery access site complications during cardiac procedures, clinical implications and potential solutions: The role of nitric oxide
Coghill EM, Johnson T, Morris RE, Megson IL, Leslie SJ

ORIGINAL ARTICLE

Observational Study

- 35 Impact of training specificity on exercise-induced cardiac troponin elevation in professional athletes: A pilot study
Wedin JO, Nyberg NS, Henriksson AE
- 44 Prognostic impact of body mass index on in-hospital bleeding complications after ST-segment elevation myocardial infarction
Ingremau D, Grall S, Valliet F, Desprets L, Prunier F, Furber A, Bière L

CASE REPORT

- 55 Phrenic nerve displacement by intrapericardial balloon inflation during epicardial ablation of ventricular tachycardia: Four case reports
Conti S, Bonomo V, Taormina A, Giordano U, Sgarito G
- 67 *Salmonella typhimurium* myopericarditis: A case report and review of literature
Jin D, Kao CY, Darby J, Palmer S

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Is there a role for ischemia detection after an acute myocardial infarction?

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Abstract

Coronary angiography and eventual revascularization have become the most common approaches for patients with acute coronary syndromes. Ischemia detection in this scenario is usually regarded as unnecessary for most of the patients. In fact, current guidelines recommend complete revascularization for patients with multivessel disease in the context of ST-elevation myocardial infarction, although it is in contrast with previous recommendations. However, some recent data suggested that ischemia could have a role for the decision of revascularization in these patients. The CROSS-AMI study randomized patients with ST-elevation myocardial infarction treated with primary angioplasty and who also had multivessel disease to a complete anatomic revascularization of the non-infarct related artery lesions *vs* subsequent revascularization of the non-infarct related artery lesions only if ischemia was demonstrated by stress echocardiography. The main findings were that only 30% of the patients in the ischemia arm needed a second revascularization and that the outcome was similar in both arms. Regarding non-ST-elevation acute coronary syndrome, coronary angiography is in general warranted for most of the patients. However, recent long-term published studies on patients randomized to an invasive or less aggressive approach based on ischemia detection have found no differences in outcome. The ultimate study in non-ST-elevation acute coronary syndrome comparing ischemia detection with an invasive approach is pending. Therefore, ischemia detection might have a role for stratifying these subjects. This is particularly true in the current era of imaging of high quality and sensitivity, last generation stents, radial access and modern antithrombotic therapy.

Key words: Ischemia; Acute myocardial infarction; Stress echocardiography; Coronary angiography; Stents

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Core tip: Coronary angiography and eventual revascularization have become the most

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common approaches for patients with acute coronary syndromes. Ischemia detection in this scenario is usually regarded as unnecessary for most of the patients. However, some recent data suggested that it could have a role in the decision-making process, particularly after ST-elevation acute myocardial infarction in the presence of multivessel disease but also after non-ST-elevation acute coronary syndrome.

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INTRODUCTION

Coronary angiography and eventual revascularization have become the most common approaches for patients with acute coronary syndromes. Although ischemia detection is usually regarded as unnecessary for most of these patients, some recent data suggested that it could have a role in the decision-making process.

ST-elevation myocardial infarction (STEMI) with multivessel disease

The best treatment for STEMI is to rapidly open the infarct-related artery (IRA), which is better achieved by angioplasty^[1]. However, having done this, patients may still have significant coronary stenoses in up to 40% to 60% of the cases. These patients likely have higher atherosclerotic burden with increased risk, and it is not clear how to prevent their risk. Also, these patients may have worse left ventricular function.

In the last years several studies have dealt with the issue of multivessel disease (MVD) after STEMI treated with primary angioplasty, and these studies have been changing the guidelines ever since. Thus, guidelines in 2013 recommended exclusive treatment of the IRA^[2] reserving treatment of MVD just in cases of cardiogenic shock or persistent ischemia (indication IIa-class B), whereas the last guidelines recommend routine revascularization of MVD before hospital discharge (indication IIa-class A)^[3].

The PRAMI^[4] and CvLPRIT^[5] studies randomized patients with STEMI and MVD disease to an IRA-only strategy *vs* complete revascularization and reported better outcome with the complete revascularization strategy.

Further studies like the PRIMULTI^[6] and the ACUTE-COMPARE^[7] randomized STEMI and MVD disease patients to an IRA-only revascularization strategy *vs* a complete revascularization strategy based on ischemia, as detected by flow reserve-guided (FFR) < 0.80. Both studies demonstrated that the functional strategy was better than the mere revascularization of the IRA.

Recently, the CROSS-AMI study, using a completely different design, randomized patients with STEMI treated with primary angioplasty and who also had MVD to a complete anatomic revascularization of the non-infarct related artery (non-IRA) lesions *vs* subsequent revascularization of the non-IRA lesions only if ischemia was demonstrated by stress echocardiography^[8,9]. The main findings of this study were that only 30% of the patients in the ischemia arm needed a second revascularization and that the outcome was similar in both arms. In fact, there were 22 events in the complete revascularization arm and 21 in the ischemia-guided arm [14.3% *vs* 13.8%; hazard ratio (HR) = 1.06, 95% confidence interval (CI): 0.58-1.92, *P* = not significant]. **Figure 1** shows the Kaplan-Meier event-free survival curves for both arms and Video 1 to 3 are examples of two patients randomized to the stress-guided strategy. Of note, most of the stress echocardiography studies were performed using peak treadmill exercise, a very sensitive modality^[10,11]. This study therefore showed that ischemia detection has indeed a role for avoiding procedures and saving costs in this scenario.

These results are not completely surprising because revascularization based on ischemia has led to better prognosis than revascularization based on anatomy as reported in the FAME study, where ischemia was investigated by FFR^[12]. The investigators found that measurement of FFR in patients with multivessel coronary artery disease who were undergoing percutaneous coronary intervention with drug-eluting stents significantly reduced the rate of the composite end point of death, nonfatal myocardial infarction, and repeat revascularization. Also, Escaned *et al*^[13] recently reported similar results, such that the use of functional assessment based on FFR/iFR led to a 25% reduction in the use of stents.

Additional studies on this subject are ongoing. For instance, the FULL-REVASC

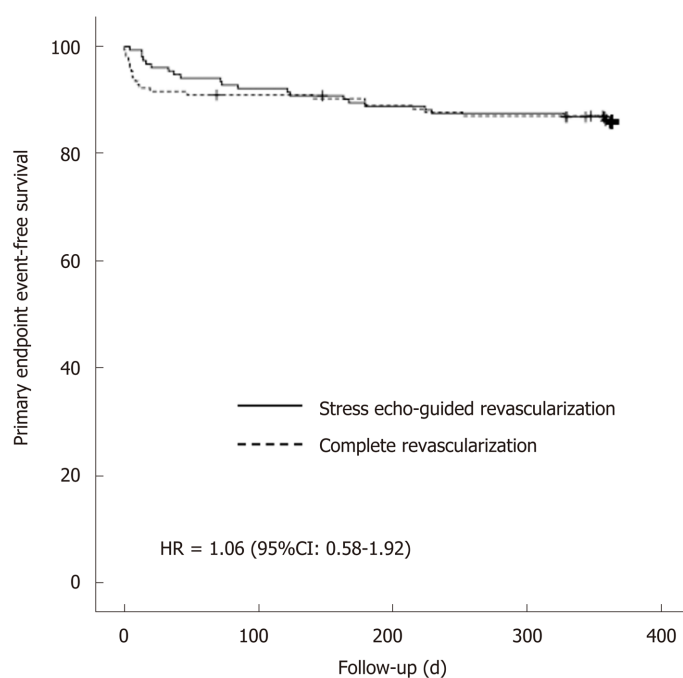


Figure 1 Kaplan-Meier event-free survival curves for patients with ST-elevation myocardial infarction treated with primary angioplasty and multivessel disease according to management with complete revascularization vs stress echo-guided revascularization (CROSS-AMI study). This figure is adapted from Calviño-Santos *et al*.^[8]. HR: Hazard ratio; CI: Confidence interval.

study will randomize patients with STEMI and MVD to an initial conservative management of non-IRA lesions *vs* FFR-guided revascularization of non-culprit lesions during hospitalization (<https://www.ucr.uu.se/fullrevasc/>).

However, as it is clear from above, the optimum study would be one with three arms comparing conservative management of non-IRA stenoses, complete anatomic revascularization and ischemia/FFR-guided revascularization. Meanwhile, it is worth stating that the current approach in our center for patients with STEMI and multivessel coronary artery disease is based on ischemia.

NON-ST-ELEVATION ACUTE CORONARY SYNDROME

In patients with non-ST-elevation acute coronary syndrome who do not have recurrence of chest pain, signs of heart failure or abnormalities in the initial or subsequent electrocardiography and increase in (preferably high-sensitivity) cardiac troponin level, a non-invasive stress test (preferably with imaging) for inducible ischemia is recommended before deciding on an invasive strategy. This recommendation has been clearly stated in the last guidelines on the issue^[14].

Therefore, when there is troponin elevation, a coronary angiography is currently warranted. However, in the last decades there has been a lot of discussion on this matter, and several studies have focused on the comparison between an invasive and functional strategy for patients with non-STEMI or unstable angina. A Cochrane review^[15] joining all studies published between 2001 and 2012 and including almost 9000 patients found that there was no significant differences in mortality [risk ratio (RR) = 0.87; CI: 0.64-1.18] or in the composite of mortality and non-fatal myocardial infarction (RR = 0.93; CI: 0.71-1.2). Less hard end-points like myocardial infarction (RR = 0.79; CI: 0.63-1), refractory angina (RR = 0.64; CI: 0.52-0.79) and rehospitalization (RR = 0.77; CI: 0.63-0.94) were lower with the invasive strategy. In contrast, complications of angiography or revascularization like bleeding or procedure-related myocardial infarction were higher in the invasive arms (RR = 1.73, CI: 1.2-2.31; and RR = 1.87, CI: 1.47-2.37). Therefore, the conclusion of this meta-analysis was that in patients with non-ST-elevation acute coronary syndrome, a conservative strategy based on clinical risk for recurrent events is the preferred management strategy. However, it is worth stating that the use of stents was lower (50% to 88% of the patients), and the use of coronary artery by-pass was higher (up to 10% to 41% of revascularizations). Also, antiplatelet therapy was less developed. On the other hand, functional testing consisted of just exercise electrocardiography for most of the

patients.

In this regard, the only old study that clearly observed a superiority of a functional approach in patients with non-STEMI was the VANQUISH trial^[16]. Unlike other conceptually similar studies, the conservative strategy of the VANQUISH was in fact a “conservative aggressive strategy” as almost half of the patients in this arm underwent coronary angiography. Another key point was that almost all patients in the conservative arm were studied by treadmill exercise with myocardial perfusion imaging, which is a very sensitive technique, or by dipyridamole myocardial perfusion imaging in case of the inability to exercise. Although the VANQUISH trial was a pre-stent study, these aspects may explain the superiority of the conservative strategy over the invasive strategy regarding both the primary end-point ($P = 0.007$) and all-cause death ($P = 0.004$).

Some of these studies comparing invasive and conservative approaches have long term follow-up. Fox *et al*^[17] published the joint results of the fast revascularization during instability in coronary artery disease (FRISC-II), randomized intervention trial of unstable angina 3 (RITA-3) and invasive *vs* conservative treatment in unstable coronary syndromes (ICTUS) at 5 years, demonstrating superiority of an invasive strategy for the combination of cardiovascular death and myocardial infarction (HR = 0.8, CI: 0.71-0.93, $P = 0.002$), which was driven for myocardial infarction occurrence (HR = 0.77; CI: 0.65-0.90, $P = 0.001$); the difference in cardiovascular mortality did not reach statistical significance (HR = 0.83, CI: 0.68-1.01, $P = 0.068$). However, these differences were at expense of the results of the FRISC-II and RITA-3 studies, as in the ICTUS study there were no significant differences between arms.

We were curious what the differences between the ICTUS study and the other studies were. Crucial differences were that the percentage of angiographies in the conservative arm of ICTUS reached up to 53% of the patients, and all patients in the conservative arm were studied by a sensitive imaging technique (both characteristics similar to the older VANQUISH study). Table 1 depicts these differences between studies. In fact, the ICTUS trial at 10 years demonstrated an excess of the combined event (death or myocardial infarction) in the invasive arm as compared to the conservative arm (HR = 1.30, CI: 1.07-1.58, $P = 0.009$)^[18]. In addition, both the RITA-3 at 10 years and the FRISC-II at 15 years, which were studies that had shown better performance of an invasive strategy in the first years, found no significant differences in mortality between arms at longer-term follow-up^[19,20]. Therefore, given these results, it is not surprising that some experts have advocated for a fair study comparing the two strategies in a current era of imaging of high quality and sensitivity, last generation stents, radial access and modern antithrombotic therapy^[21].

The use of exercise electrocardiography testing in most of the conservative arms of the above-mentioned studies (if performed) should be considered as an important limitation. The superiority of modern techniques of imaging like stress echocardiography^[10,11], magnetic resonance or myocardial perfusion imaging would likely make a difference for stratification of these patients.

CONCLUSION

In patients with acute myocardial infarction and MVD, ischemia detection may be useful for clinical decisions. In non-ST elevation myocardial infarction or acute coronary syndrome, the ultimate role of ischemia detection for clinical decision making process in the current era of modern imaging and new drugs and stents is pending.

Table 1 Main differences between the invasive vs conservative treatment in unstable coronary syndromes, randomized intervention trial of unstable angina 3 and fast revascularization during instability in coronary artery disease studies

	FRISC-II	RITA-3	ICTUS
Year	1999	2002	2005
Inclusion criteria: Raised troponin	No	No	Yes
Functional imaging in the conservative arm	-	No (exercise ECG testing)	Yes (exercise with MIBI-SPECT)
Interventionism in the conservative arm	7%	16%	53%
Stents, invasive arm	61%	88%	88%

ICTUS: Invasive vs conservative treatment in unstable coronary syndromes; RITA-3: Randomized intervention trial of unstable angina 3; FRISC-II: Fast revascularization during instability in coronary artery disease; ECG: Electrocardiography.

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Diagnosis and treatment of heart failure with preserved left ventricular ejection fraction

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Abstract

Nearly six million people in United States have heart failure. Fifty percent of these people have normal left ventricular (LV) systolic heart function but abnormal diastolic function due to increased LV myocardial stiffness. Most commonly, these patients are elderly women with hypertension, ischemic heart disease, atrial fibrillation, obesity, diabetes mellitus, renal disease, or obstructive lung disease. The annual mortality rate of these patients is 8%-12% per year. The diagnosis is based on the history, physical examination, laboratory data, echocardiography, and, when necessary, by cardiac catheterization. Patients with obesity, hypertension, atrial fibrillation, and volume overload require weight reduction, an exercise program, aggressive control of blood pressure and heart rate, and diuretics. Miniature devices inserted into patients for pulmonary artery pressure monitoring provide early warning of increased pulmonary pressure and congestion. If significant coronary heart disease is present, coronary revascularization should be considered.

Key words: Diastolic heart failure; Myocardial stiffness; Incomplete left ventricular relaxation; Echocardiographic heart failure criteria; Pulmonary artery pressure monitoring; Drug treatment

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Core tip: Three million people in United States have heart failure with normal left ventricular systolic function but abnormal diastolic function due to increased myocardial stiffness. These patients are often elderly women with hypertension, ischemic heart disease, atrial fibrillation, obesity, diabetes mellitus, renal disease, or obstructive lung disease. The annual mortality rate of these patients is 8%-12% per year. The diagnosis is based on history, physical examination, laboratory data, echocardiography, and, when necessary, by cardiac catheterization. These patients often require weight reduction, an exercise program, aggressive control of blood pressure and heart rate, and diuretics. If significant coronary heart disease is present, coronary revascularization should be considered.



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INTRODUCTION

Heart failure is a clinical syndrome, characterized by symptoms of breathlessness and easy fatigability, and signs of fluid retention, such as elevated jugular venous pressure, pulmonary crackles, and ankle edema, that result from the impaired ability of the heart to maintain a cardiac output that meets the metabolic needs of the body. Currently, nearly six million people in the United States have heart failure and require 30.7 billion dollars per year for health care^[1]. Moreover, the healthcare costs for treating patients with heart failure in the United States are projected to increase to \$70 billion in 2030^[2].

Approximately 50% of the patients with heart failure have normal, or near-normal left ventricular (LV) systolic heart function with a LV ejection fraction $\geq 50\%$ and a LV end-diastolic volume index $< 97 \text{ mL/m}^2$. These patients are described as having heart failure with preserved ejection fraction (HFpEF). However, these patients have abnormal LV diastolic function with incomplete LV relaxation due to increased myocardial stiffness. This form of heart failure is becoming the dominant form of heart failure among older adults in the United States and in Europe due, in part, to the increasing longevity of the population. By the year 2020, 8% of the United States and European population older than 65 years of age will have HFpEF^[3].

Although most physicians have only recently become aware of HFpEF, the first description of HFpEF was in 1966 when “presbycardia” with decreased elasticity of the heart, also known as “senile heart disease”, was first described in elderly individuals^[4]. Currently, the most common patients with HFpEF are elderly women with comorbid conditions, such as hypertension with LV hypertrophy (60%-80%), ischemic heart disease (35%-70%) that may be occult, atrial fibrillation (15%-65%), obesity (32%-46%), diabetes mellitus (20%-45%), renal disease (51%-58%), and obstructive lung disease (24%-30%)^[5,6]. In addition, women as they age develop greater systemic arterial and LV stiffness than men which results in concentric LV myocardial remodeling and HFpEF.

The systemic arterial and ventricular stiffness in HFpEF is amplified by the coexistence of hypertension, chronic renal disease, and diabetes mellitus. With an increase in arterial stiffness, the pressure wave ejected from the LV is reflected back to the heart, thereby increasing LV afterload, decreasing diastolic ventricular function, and increasing the hydraulic work and myocardial oxygen requirements of the heart. These hemodynamic effects lead to decreased ventricular diastolic function, increased ventricular diastolic filling pressures, decreased coronary flow reserve, and pulmonary vascular congestion. As a result, patients experience shortness of breath.

Heart disease with preserved ejection fraction is a heterogenous syndrome with multiple different conditions that can contribute to the syndrome. Understanding and targeting the pathological conditions that contribute to this syndrome may have greater patient benefit than targeting the final pathway of cardiac dysfunction alone. The specific conditions that can contribute to HFpEF are listed in Table 1 which is adapted in part from^[7,8].

Patients who are hospitalized because of HFpEF have complication rates that are similar to those patients with heart failure and reduced ejection fraction (HFrEF), including similar rates of cardiac arrest, acute coronary syndromes, renal insufficiency and failure, and admission to critical care units^[9]. Despite similar rates of in-hospital complications in the two groups, patients with HFpEF are less likely to receive cardiology consultation while in the hospital than patients with HFrEF.

Table 2 compares the clinical characteristics of patients with HFpEF with patient with HFrEF and is adapted in part from^[10,11].

The annual mortality rate of patients with HFpEF is approximately 8% per year but increases to approximately 10%-12% per year among patients older than 70 years of age^[11-13]. The prognosis of patients after the first hospitalization for HFpEF is poor with one-year mortality rates as high as 25% among older patients and five-year mortality rates of 24% to 54%^[14]. Thirty percent of the patients with HFpEF die of noncardiac causes, compared with 17% of patients with HFrEF, due to the presence of one or more comorbid conditions. In this regard, the predictors of death among

Table 1 Conditions that contribute to heart failure with preserved ejection fraction

Obesity
Hypertension
Coronary artery disease
Atrial fibrillation
Diabetes mellitus
Chronic obstructive pulmonary disease
Obstructive sleep apnea
Anemia

patients with HFpEF include advanced age, increased systolic blood pressure, atrial fibrillation, a prior cerebral vascular event, renal insufficiency or other major organ dysfunction with sepsis^[14,15].

PATHOPHYSIOLOGICAL MECHANISMS IN HFpEF

LV diastolic dysfunction in individuals with HFpEF is characterized by increased diastolic ventricular stiffness, which slows LV relaxation, increases LV diastolic filling pressures and limits cardiac output^[16,17]. Different pathophysiologic mechanisms are hypothesized to contribute individually or in combination to LV diastolic dysfunction in patients with HFpEF. The current hypotheses include: (1) Cardiomyocyte titin hypophosphorylation; (2) Vascular endothelial cell inflammation and dysfunction; (3) Abnormal calcium homeostasis; (4) Increased ventricular matrix formation; and (5) Obesity.

CARDIOMYOCYTE TITIN HYPOPHOSPHORYLATION

Resting tension in cardiomyocytes is highly dependent on titin, which is a large sarcomeric protein that functions as a “molecular spring” which stores energy during ventricular contraction and releases energy during ventricular relaxation. Consequently, titin contributes to early myocardial diastolic recoil and late myocardial diastolic distensibility^[18]. A shift in titin isoform expression from the compliant N2BA to the stiff N2B isoform, hypophosphorylation of the N2B isoform, and lower overall phosphorylation of titin increases the resting tension of cardiomyocytes and contributes to increased LV myocardial stiffness and diastolic dysfunction^[18-21]. Consequently, manipulation of the phosphorylation state of titin and the titin isoforms represents a therapeutic target for the treatment of patients with HFpEF.

INFLAMMATION

Obesity, hypertension, diabetes mellitus, chronic obstructive pulmonary disease, chronic kidney disease, and anemia in patients can induce an inflammatory state with increased circulating C reactive protein, interleukin 1 (IL-1) receptor-like 1 protein, growth differentiation factor 15, IL-6, tumor necrosis factor- α , and pentraxin 3^[22-24]. See **Figure 1**. Inflammation of the coronary microvascular endothelium produces free oxygen radicals and vascular cell adhesion molecules that attract circulating leukocytes to the microvascular which secrete transforming growth factor- β (TGF- β). TGF- β converts myocardial fibroblasts to myofibroblasts, which increase myocardial collagen deposition and cause interstitial fibrosis. Inflammatory free oxygen radicals also reduce nitric oxide (NO) bioavailability, and increase peroxynitrite (ONOO⁻), which reduces protein kinase G (PKG), which can increase cardiomyocyte stiffness, promote hypophosphorylation of titin, accelerate pro-hypertrophic signaling in cardiac myocytes and enhance diastolic dysfunction^[17,21,25].

In addition, systemic inflammation decreases the vasodilator response of the coronary microvascular to acetylcholine and reduces renal blood flow and the ability of the kidneys to excrete sodium and water with resultant progressive expansion of intravascular volume^[3]. Systemic inflammation also affects the lungs and skeletal muscle by contributing to pulmonary hypertension, muscle weakness and sarcopenia^[3]. However, therapies to date that reduce systemic inflammation and/or

Table 2 Clinical characteristics of patients with heart failure with preserved ejection fraction and heart failure and reduced ejection fraction

	HFpEF	HFrEF
Sex	Women (62%)	Men (60%)
Age (yr)	74	70
Obesity	41.4%	35.5%
Diabetes mellitus	45%	40%
Hypertension	77%	69%
Chronic kidney disease	56%	45%
Coronary artery disease	50%	59%
Prior myocardial infarction	24%	36%
LV remodeling	Concentric	Eccentric
LV ejection fraction	≥ 50%	< 40%
Atrial fibrillation in hospitalized patients	65%	53%
Ventricular dysrhythmias	3%	11%
Hospitalizations for heart failure	Increasing	Decreasing
Therapies that decrease mortality	None at present time	Beta-Blockers, ACE inhibitors, biventricular pacemakers, coronary revascularization

HFpEF: Heart failure with preserved ejection fraction; HFrEF: Heart failure and reduced ejection fraction; LV: Left ventricular.

improve or increase vascular endothelial function, such as statins, angiotensin receptor blockers, and phosphodiesterase-5 inhibitors have proven ineffective in improving the morbidity or the mortality of patients with HFpEF.

CARDIOMYOCYTE CALCIUM-HANDLING ALTERATIONS

High circulating concentrations of the free oxygen radical peroxynitrite in patients with HFpEF increase cardiomyocyte protein phosphatase 2A activity, which decreases cardiomyocyte phospholamban phosphorylation, reduces sarcoplasmic reticulum Ca^{2+} uptake, and increases cardiomyocyte diastolic cytosolic Ca^{2+} . In addition, abnormal cardiomyocyte sodium-calcium exchange and also calcium leak from the sarcoplasmic reticulum increase cardiomyocyte diastolic cytosolic calcium concentrations, which increases cardiomyocyte resting tension in HFpEF patients due to a delayed inactivation of actin-myosin crossbridges^[26,27]. However, reductions in cardiomyocyte calcium overload with ranolazine to date have not significantly improved myocardial relaxation and diastolic dysfunction^[28]. Nevertheless, abnormal calcium homeostasis is a potential therapeutic target for the treatment of patients with HFpEF.

INCREASED EXTRACELLULAR MATRIX FORMATION

Myocardial biopsies from patients with HFpEF, especially patients with hypertension and HFpEF, show an increase in the collagen volume fraction and an increase in myocardial fibrosis in comparison with patients without heart failure^[29,30]. In this regard, Inflammation can cause the release of TGF- β from fibroblasts and monocytes/macrophages, which induce the differentiation of fibroblasts into collagen-producing myofibroblasts, while simultaneously decreasing matrix metalloproteinase (MMP)-1 and the tissue inhibitor of (MMP)-1^[17,31,32]. In addition, endothelin-1, angiotensin II, platelet-derived growth factor, and connective tissue growth factor govern fibroblast activation/differentiation and represent potential therapeutic targets in the treatment of patients with HFpEF^[33].

Myocardial collagen synthesis can also be increased during the female menopause where decreased circulating estrogen is associated with activation of the renin-angiotensin-aldosterone system^[34]. Collagen expansion of the myocardial extracellular matrix, and especially an increase in the collagen type 1 fibers and the amount of crosslinked collagen, has an adverse effect on myocardial mechanical, electrical, and microvascular function and contributes to decreased diastolic function in HFpEF. Myocardial fibrosis also decreases myocardial capillary density, coronary perfusion reserve, and myocardial energy production^[33]. Studies of anti-fibrotic agents, such as

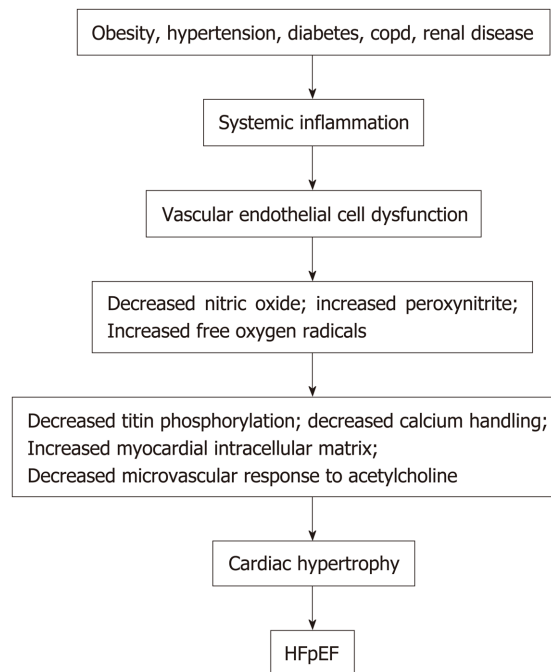


Figure 1 Factors that contribute to heart failure with preserved ejection fraction. COPD: Chronic obstructive pulmonary disease; HFpEF: Heart failure with preserved ejection fraction.

Pirfenidone and also valsartan/sacubitril, in the PIRouETTE trial, the Parallax and the PARAGON-HF trials will help to determine in patients with HFpEF whether significant regression of fibrosis in the myocardium can occur and can be associated with improvement in diastolic ventricular function.

MICROVASCULAR DYSFUNCTION

Exercise studies of patients with HFpEF implicate LV stiffness and impaired exercise vasodilation and raise the possibility that the impaired diastolic reserve in these patients may be related to coronary microvascular dysfunction. In an autopsy study of 124 patients with HFpEF compared with 104 age-matched control patients, HFpEF patients had a median of 961 coronary microvessels/mm² vs 1316 vessels/mm² in controls^[31,35]. In addition, patients with HFpEF had more severe coronary artery disease with 65% of patients with ≥ 1 coronary vessel with $> 50\%$ diameter stenosis versus 13% in controls^[34]. The vascular changes in the HFpEF patients were associated with heavier hearts with a median weight of 538 g with 9.6% myocardial fibrosis versus 335 g with 7.1% fibrosis in controls^[35]. In addition, the myocardial fibrosis increased with decreasing microvascular density. However, cardiomyocyte size and LV hypertrophy are important determinants of the coronary microvascular density in adults and the role of cardiomyocyte size and LV hypertrophy in the determination of microvascular density in HFpEF requires further investigation.

OBESITY

Adipocytes synthesize cell-signaling molecules which include leptin, nerilysin and aldosterone which play a role in systemic inflammatory processes, cardiac fibrosis, and sodium and water retention^[36]. In this regard, obesity can lead to cardiac fibrosis and increased ventricular diastolic stiffness through: (1) Leptin secretion from adipose tissue which induces cardiac fibrosis through galectin-3, TGF- β and connective tissue growth factors^[37]; (2) Activation of beta2-adrenergic receptors which can enhance the synthesis of proinflammatory cytokines such as IL-6^[38]; (3) Increased activity of neprilysin from adipocytes, which by degrading endogenous natriuretic peptides promotes plasma volume expansion, loss of the anti-aldosterone action of endogenous natriuretic peptides, and cardiac fibrosis^[39]; and (4) Aldosterone secretion, in direct proportion to body mass, which increases collagen synthesis by cardiac fibroblasts^[40].

Together these mechanisms can cause myocardial fibrosis and also cause sodium

retention with plasma volume expansion. In addition, increased intramuscular fat decreases the supply of oxygen to working muscles and can impair oxidative metabolism in the skeletal musculature and, in this manner, contributes to the decreased functional capacity experienced by patients with HFpEF^[5,41]. **Figure 1** summarizes the different factors that can contribute to HFpEF.

DIAGNOSIS

The diagnosis of HFpEF in patients is based on the history, the physical examination, the laboratory data, the echocardiogram, and, when necessary, by cardiac catheterization.

The chest radiograph in patients with HFpEF often shows the presence of cardiomegaly and also evidence of pulmonary congestion. The electrocardiogram shows nonspecific ST-T wave changes although ECG evidence of myocardial ischemia or prior myocardial infarction may be present. Atrial fibrillation is frequently present on the ECG^[42]. Plasma brain natriuretic peptide (BNP) or N-terminal pro-BNP (NT-proBNP) are often mildly increased with BNP > 100 pg/mL or NT-proBNP > 300 pg/mL. The concentrations of these peptides are less than the concentrations in patients with HFrEF^[43]. Nevertheless, a BNP measurement > 100 pg/mL or a NT-proBNP > 300 pg/mL are independent predictors of adverse cardiovascular events in patients with HFpEF^[44]. Currently, the measurements of natriuretic peptides and troponins are recommended for the diagnosis and the prognosis of patients with heart failure, and the measurements of suppression of tumorigenicity 2, a marker of systemic inflammation, and galectin-3, a marker of cardiac fibrosis, are recommended for additional patient risk stratification and prognosis^[45,46].

Echocardiography is a very useful noninvasive technique in the diagnosis of patients with HFpEF and often demonstrates the presence of LV hypertrophy or concentric LV remodeling with a LVEF that is $\geq 50\%$ and a LV volume index that is $< 97 \text{ mL/m}^2$. Left atrial enlargement is oftentimes present with a left atrial volume index $> 34 \text{ mL/m}^2$ in patients who are not in atrial fibrillation. Common echocardiographic indices of significant diastolic dysfunction are listed in **Table 3** which is adapted in part from^[47-49].

However, echocardiographic determined E/A and E/e' ratios should not be used in isolation in assessing patients, but rather the ratios should be used in conjunction with the patient's clinical characteristics and laboratory data to accurately diagnose LV diastolic dysfunction and HFpEF^[50]. In this regard, echocardiographic studies of 745 patients with HFpEF in the I-PRESERVE study reported that the LV end-diastolic volume was within normal limits in $> 95\%$ percent of the patients, LV hypertrophy or concentric remodeling was present in 50 to 60 percent, LV diastolic dysfunction (mild to severe) was present in $> 70\%$ percent, and left atrial area enlargement was present in $> 65\%$ percent of patients^[51].

Recently a scoring system has been developed to facilitate the diagnosis of HFpEF in patients with dyspnea and distinguish these patients from patients with non-cardiac causes of dyspnea^[52]. The scoring system uses 6 clinical and echocardiographic characteristics (H2FPEF: Heavy, Hypertension, Atrial Fibrillation, Pulmonary Hypertension, Elderly, LV filling Pressure) that are obtained in the evaluation of patients with unexplained exertional dyspnea to determine the probability of HFpEF. Patients with score high s of 6 to 9 have a probability of HFpEF $> 90\%$. Conversely, patients with low scores of 0 to 1 have a probability of HFpEF $\leq 23\%$. Patients at intermediate probability with H2FPEF scores of 2 to 5 require additional testing to determine the cause of dyspnea. **Table 4** lists the H2FPEF scoring system and is adapted from^[52].

CARDIAC MAGNETIC RESONANCE (CMR)

In patients with HFpEF, the myocardial extracellular matrix can be determined with CMR T1 mapping and is a predictor of LV myocardial stiffness and LV diastolic dysfunction. Excessive extracellular matrix deposition is a major contributor to the impaired cardiac relaxation and cardiac stiffness that are the hallmarks of HFpEF. Moreover, the CMR detection of myocardial extracellular matrix can precede the clinical diagnosis of HFpEF and correlates with patient myocardial biopsy specimens and hospitalizations for heart failure or death from cardiovascular causes^[48,53-56].

In 410 patients with HFpEF or at risk for HFpEF, CMR determinations of increased myocardial extracellular volume (ECV) as an estimate of myocardial fibrosis were strongly associated with hospitalizations for heart failure or death during the

Table 3 Echocardiographic indices of diastolic dysfunction

1. The ratio of the mitral blood flow velocity into the LV in early diastole (the E wave) to peak blood flow velocity in late diastole caused by atrial contraction (the A wave), or the E/A ratio, ≥ 2 . The normal E/A is approximately 0.8. However, tachycardia, atrioventricular block, and left bundle branch block can lead to fusion of E and A waves, and ambiguity in diastolic function assessment.
2. Increased left atrial pressure measured by early mitral blood flow velocity across the mitral valve (E wave) to the early diastolic velocity (e') of the lateral mitral annulus, or E/ e' ratio. An E/ e' ratio 10 = mild and E/ e' ratio > 14 = significant LV dysfunction. If the lateral mitral annulus e' velocity is not quantifiable, the septal mitral annular e' velocity can be used. In this case, the E/ e' is increased if the ratio is > 15 .
3. Lateral mitral annular e' velocity < 10 cm/s or septal e' mitral annular velocity < 7 cm/s.
4. Pulmonary artery systolic pressure > 35 mmHg indicative of pulmonary arterial hypertension. Pulmonary artery systolic pressure = $4 \times (\text{peak tricuspid regurgitation velocity})^2 + \text{estimated right atrial pressure}$. These criteria should not be used in patients with significant pulmonary disease.
5. An echocardiographic determination of global longitudinal strain of -16.05 ± 2.16 . This measurement can separate patients with HFpEF from patients with hypertension and normal controls in whom the global longitudinal strain measurements are -18.58 ± 2.84 and -19.59 ± 1.49 , respectively.

HFpEF: Heart failure with preserved ejection fraction.

subsequent four years^[56]. In this investigation, myocardial ECV was more strongly associated with outcome than age, LV mass, atrial fibrillation, or previous myocardial infarction. See [Table 5](#) which is adapted from^[56] and information kindly provided by Erik Schelbert, MD.

CMR determined ECV measurements provide risk stratification for HFpEF during the ensuing four years. Patients with ECV $> 30\%$ had decreased event-free survival during the subsequent four years.

However, the ECV fraction can be normal in as many as one-third of patients with HFpEF, which demonstrates the pathophysiological variation in this syndrome and the necessity to utilize the patient's history, the physical examination, laboratory data, echocardiography, and, if necessary, cardiac catheterization in order to establish the diagnosis.

HEART CATHETERIZATION

For patients for whom the probability of HFpEF remains intermediate after history, physical examination, natriuretic peptide determinations, and echocardiography have been performed, invasive hemodynamic assessment of cardiac filling pressures, with provocative stress maneuvers such as exercise, is useful to make or exclude the diagnosis of HFpEF.

Right heart catheterization

Many patients with HFpEF have normal right and LV end-diastolic pressures at rest, when measured either invasively or non-invasively. In these patients, right heart catheterization measurements of pulmonary artery wedge pressure, cardiac output, and oxygen extraction during exercise are valuable tools in the diagnosis of patients with dyspnea due to HFpEF. During submaximal exercise, patients with HFpEF display pulmonary artery wedge pressures > 25 mmHg or an increase of 7 ± 3 mm Hg above the resting measurement, and pulmonary artery systolic pressures ≥ 45 mmHg in contrast to patients with noncardiac dyspnea^[57,58]. With exercise, older patients with HFpEF demonstrate a marked rise in arteriovenous oxygen content difference of 10.8 ± 1.8 , driven by enhanced oxygen extraction, and lower increments in cardiac output in comparison with younger patients with HFpEF^[5,59]. This is especially true in older women who have small LV chambers and rely on heart rate increases to meet the cardiac output demands of exercise.

Left heart catheterization and coronary artery angiography

Community-based studies show that coronary heart disease (CAD) is common in HFpEF, and is present in 40% to 60% of patients with HFpEF^[60-62]. Patients with CAD are more likely to be men and to have CAD risk factors, including hypertension, diabetes, hyperlipidemia, and tobacco use^[63]. However, symptoms of angina and heart failure are similar in patients with and without CAD, as are measures of cardiovascular structure, function, and hemodynamics. Nevertheless, HFpEF patients with CAD experience a fourfold greater decline in EF over time compared with patients without CAD^[63]. The presence of CAD is associated with worse outcome in HFpEF, which appears to be independent of other predictors. In a study of elderly patients with a mean age of 72 years, patients with HFpEF and CAD have a 1-2-year mortality rate of 20%^[63]. In these patients, coronary revascularization is associated with a decrease in mortality and with outcomes that are not different from patients

Table 4 Heart failure preserved ejection fraction scoring system: Heart failure with preserved ejection fraction

Clinical characteristic	Clinical measurement	Points awarded
Heavy	Body mass index > 30 kg/m ²	Two
Hypertension	Two or more hypertensive medications	One
Atrial fibrillation	Paroxysmal or persistent	Three
Pulmonary hypertension by echocardiogram	Pulmonary artery systolic pressure > 35 mmHg	One
Elderly	Age > 60 yr	One
LV filling pressure by echocardiogram	Echocardiographic e/e' > 9	One

with HFpEF without CAD^[62,63]. Consequently, patients with HFpEF should be subcategorized according to the presence or absence of CAD. If significant coronary artery disease is present, the patients should be evaluated for coronary revascularization^[62,63].

TREATMENT

Patients with HFpEF and major obstructive coronary artery disease should be treated with coronary artery revascularization. In addition, since many hospitalizations and deaths in patients with HFpEF are due to noncardiovascular causes such as chronic obstructive lung, chronic kidney disease, and diabetes, these disorders must be identified early in the clinical course and aggressively treated. In patients with NYHA class II and III heart failure and iron deficiency (ferritin < 100 ng/mL or 100 to 300 ng/mL if transferrin saturation is < 20%), intravenous iron replacement is reasonable to improve functional status and quality of life^[46].

GENERAL TREATMENT OF PATIENTS WITH HFpEF WITH OBESITY, HYPERTENSION, AND ATRIAL FIBRILLATION

Medical treatment in HFpEF patients with non-obstructive coronary artery disease includes weight reduction and control of blood pressure, heart rate, and fluid status. More than 80% of patients with heart failure with HFPEF, are overweight or obese and deconditioned. A caloric restriction diet is feasible and safe in older, obese patients with HFpEFs, and significantly improves patient dyspnea, peak oxygen consumption, and quality of life^[64]. Caloric restriction combined with endurance exercise, such as walking exercise for one hour three or more times per week, is additive and the combination can produce a 2.5 mL/kg/min increase in peak oxygen consumption and an increase in exercise capacity^[64]. Exercise training, such as can occur with a cardiac rehabilitation program, can also improve the maximum heart rate and the diastolic function of the LV as measured by the echocardiographic ratio of early to late mitral valve filling (E/A ratio) and the LV filling pressure E/e' ratio^[65]. Moreover, a decrease in body weight and an increase in peak oxygen consumption is strongly correlated with a decrease in the systemic biomarkers of inflammation in the body and is primarily attributable to increased peripheral microvascular and skeletal muscle function^[66].

Fifty-one percent of patients with HFpEF have hypertension, whereas among patients with HFrEF, hypertension is present in 41%^[67]. In a meta-analysis of 123 studies with 613815 hypertensive patients, a 10 mmHg decrease in systolic BP reduced the risk of heart failure complications by 28%, independently of the baseline BP or co-morbidity status^[68]. In this regard, diuretic drugs are effective for blood pressure control and for the prevention of volume overload. Analysis from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack (Allhat) Trial found that the diuretic chlorthalidone reduced the risk of HFpEF and the incidence of HFpEF hospitalizations among high-risk hypertensive patients when compared with lisinopril, amlodipine, and doxazosine^[69]. For patients whom are persistently hypertensive despite diuretic therapy, renin-angiotensin-aldosterone inhibition with an angiotensin converting enzyme inhibitor or an angiotensin receptor blocker are recommended for reduction in the blood pressure to ≤ 130/80 mmHg^[46]. In addition, mineralocorticoid antagonists, such as spironolactone or eplerenone, can play an important role in treatment of patients with HFpEF by limiting aldosterone, which is a volume retention and profibrotic hormone, and blood pressure. In the

Table 5 Survival after cardiac magnetic resonance determined extracellular volume determination

CMR ECV	Year one	Year two	Year three	Year four
ECV < 25%	95.8%	95.8%	95.8%	82.1%
25% ≤ ECV < 30%	95.5%	90.5%	87.6%	81.1%
30% ≤ ECV < 35%	88.0%	77.3%	69.6%	65%
35% > ECV < 40%	82.2%	74.3%	69.4%	61.7%
ECV ≤ 40%	40.0%	40.0%	40.0%	40.0%
Cardiac amyloid	47.1%	23.5%	0%	0%

CMR: Cardiac magnetic resonance; ECV: Extracellular volume.

Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) Trial, spironolactone reduced patient hospitalizations for heart failure, reduced the composite end-point of cardiovascular death, heart failure hospitalization, and aborted cardiac arrest in patients from the Americas but not patients from Russia and Georgia^[70]. Furthermore, two recent retrospective studies report that the long-term treatment with a mineralocorticoid receptor antagonist, such as spironolactone or eplerenone, and a beta-adrenergic receptor blocker drugs is associated with a reduction in the incidence of new-onset HFpEF in patients with hypertension^[9,71,72]. Consequently, the effective control of vascular volume and blood pressure in hypertensive patients can prevent patient progression to symptomatic HFpEF. However, while diuretics and antihypertensive medications can be effective in bringing about symptomatic relief, care must be taken to avoid hypotension and azotemia in patients with HFpEF.

Atrial fibrillation is present in 15% to as many as 41% of patients with HFpEF^[73]. The arrhythmia may be associated with increased fatigue and exertional intolerance, natriuretic peptide elevation, left atrial remodeling and an increase in the risk of death^[74,75]. The treatment includes identification and treatment of the causes of atrial fibrillation, such as poorly controlled hypertension, obstructive sleep apnea, diabetes mellitus, or thyrotoxicosis. Patients with atrial fibrillation, HFpEF, and sleep apnea should undergo a sleep study in order to determine whether the sleep apnea is predominantly obstructive or central in nature and patients with obstructive sleep apnea treated with continuous positive airway pressure^[46,76]. Anticoagulation is recommended for patients with a CHA2DS2 VAS score ≥ 2. Beta-adrenergic receptor blocking drugs or non-dihydropyridine calcium channel blocking drugs, such as verapamil or diltiazem, are suggested for rate control. Experience with atrial catheter ablation of atrial fibrillation in patients with HFpEF is limited. In a small, single center study, catheter ablation of atrial fibrillation improved diastolic function in patients who maintained sinus rhythm^[77]. Additional investigations of catheter ablation of atrial fibrillation in patients with HFpEF are necessary.

Recent clinical trials of sodium glucose cotransporter-2 inhibitors have shown promising effects on heart failure outcomes in patients with heart failure and diabetes mellitus. In the EMPA-REG Cardiovascular Outcome Event Trial in patients with type 2 diabetes mellitus, the sodium-glucose cotransporter-2 (SGLT2) inhibitor empagliflozin was associated with a reduction in major adverse cardiovascular endpoints and a significant reduction in heart failure hospitalizations^[78]. SGLT2 inhibitors, such as empagliflozin, promote glycosuria and diuresis by reducing glucose and sodium absorption in the proximal renal tubule, without activating the sympathetic nervous system. SGLT2 inhibitors also appear to decrease markers of inflammation^[79]. Additional studies of SGLT2 inhibitors in patients with HFpEF and diabetes mellitus are in progress.

In summary, inhibitors of the sympathetic nervous and renin-angiotensin-aldosterone systems should be considered in patients with HFpEF who have coronary artery disease, hypertension, and atrial fibrillation^[46]. Sodium glucose cotransporter-2 inhibitors should be considered in patients with HFpEF and type 2 diabetes mellitus^[78]. Patients with major obstructive coronary artery disease that contributes to heart failure should be evaluated for coronary artery revascularization^[62,63].

GENERAL PHARMACOLOGY TREATMENT OF PATIENTS WITH HFpEF

The pharmacologic therapy trials for LV dysfunction in patients with HFpEF with beta-adrenergic receptor blockers, calcium channel blocking agents, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, and nitrates are not consistent and, in general, have been neutral in decreasing patient mortality. This is, in part, due to differences in trial design and patient population heterogeneity with differences in heart failure etiologies or stages of disease. Recently, patients with LV ejection fractions between 41% and 49% have been categorized as heart failure with mid-range ejection fraction. Patients in this intermediate category match a phenotype that is closer to the clinical profile of HFrEF and have a higher risk of sudden cardiac death and cardiovascular death than patients with HFpEF. **Table 6** lists the major pharmacologic studies that have been performed in patients with HFpEF and patients with heart failure with mid-range ejection fraction. **Table 6** is adapted, in part, from^[80].

MEDICAL DEVICES

Patients with HFpEF and chronotropic incompetence are currently being tested with rate-adaptive atrial pacing (government trial NCT02145351). Patients with HFpEF can have normal resting left atrial pressures but develop marked increases in left atrial pressures and pulmonary hypertension with exercise due to a decrease in LV diastolic compliance. This is typically manifested as exertional dyspnea. Innovative medical devices, listed below, inserted into patients with HFpEF in clinical trials have shown some promise in improving patient symptomatology.

INTERATRIAL SEPTOSTOMY

An 8 mm unidirectional interatrial left to right shunt device in patients with HFpEF has been investigated to reduce left atrial pressure by 3 to 11 mmHg and provide symptomatic patient relief from dyspnea that is due to increased pulmonary venous pressure. In a randomized Reduce-Left Atrial Pressure in Heart Failure Trial I in 39 patients, the decrease in pulmonary wedge pressure during exercise and the improvement in workload corrected pulmonary capillary wedge pressure, exercise duration, and peak exercise workload compared to sham controls were numerically better in the treatment group but the differences from controls did not achieve statistical significance^[109,110]. A larger trial (REDUCE LAP-HF II Governmental Trial NCT03088033) is currently examining the effects of an interatrial septal device on clinical outcomes and quality of life. The long term effects of volume loading with this device and similar devices, such as the V Wave device (Governmental Trial NCT02511912) and the Atrial Flow Regulator (Governmental Trial NCT03030274), on right heart chambers and function, the pulmonary circulation, the cardiac rhythm, and the potential for paradoxical embolism in older patients who typically have HFpEF, require further investigation.

PULMONARY ARTERY PRESSURE MONITORING

The CHAMPION (CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in NYHA Class III Heart Failure Patients) Trial was a prospective, randomized controlled trial that investigated whether medical treatment based on daily pulmonary artery pressure monitoring would significantly reduce hospitalizations for heart failure treatment^[111]. A 15 mm electromechanical pressure sensor was permanently implanted by right heart catheterization into a branch of the right pulmonary artery of each patient and transmitted pulmonary artery pressures by radio signals to an internet web-based system that notified the patient's physician if the daily pulmonary pressure measurements were outside of a defined range. After 17.6 mo of follow-up, the hospitalization rate was 50% lower in patients where medical treatment decisions were made based on the pulmonary artery pressure measurements^[111]. Hemodynamic-guided management using PA pressure measurements appears to be a successful strategy to improve the outcome of patients with HFpEF. More recently, the HEMODYNAMICALLY GUIDED MANAGEMENT OF HEART FAILURE (Guide-HF Governmental Trial NCT03387813) Trial is examining the effects of pulmonary artery pressure monitoring on patient mortality

Table 6 Pharmacologic studies in heart failure with preserved ejection fraction

Ref.	Drug vs control	Drug half-life hours	Number patients	Duration	LVEF	Results
Beta-blockers						
Swedish Heart Failure Registry ^[81]	All BBs (prescribed at discharge)	6-h Atenolol; 12-19 h Nebivolol	8244	755 d	LVEF 49%-50% and LVEF > 50%	β -blockers decreased mortality but not combined all-cause mortality or hospitalizations
SWEDIC Trial ^[82]	Carvedilol	6-10 h	97	6 mo	LVEF \geq 40%	E/A ratio improved but no other measures of diastolic function
J-DHF Trial ^[83]	Carvedilol	6-10 h	245	38 mo	LVEF \geq 40%	Standard dose, but not low dose, carvedilol reduced; CV mortality and hospitalizations
COHERE Registry ^[84]	Carvedilol	6-10 h	4280	12 mo	LVEF > 40%	Carvedilol had no mortality benefit but decreased hospitalization
SENIORS ^[85,86]	Nebivolol	2.5-20 h	643	21 mo	LVEF > 35%	Nebivolol did not decrease CV hospitalizations or mortality
ELANDD Trial ^[87]	Nebivolol	2.5-20 h	116	21 mo	LVEF \geq 45%	Nebivolol did not increase exercise capacity
CIBIS-ELD Trial ^[88]	Bisoprolol vs Carvedilol	9-12 vs 6-10 h	250	3 mo	LVEF \geq 45%	Bisoprolol and carvedilol had no effect on established and prognostic markers of diastolic function
El-Refai <i>et al</i> ^[89]	Beta Blocker (bisoprolol, carvedilol, metoprolol, labetalol, and atenolol)	6-7 h (Atenolol); 9-12 h (Bisoprolol)	741	25 mo	LVEF \geq 50%	Beta blockers decreased mortality and HF rehospitalizations
β -PRESERVE ^[90]	Metoprolol succinate vs control	3-9 h	1200	24 mo	LVEF \geq 50%	Trial Results not available
OPTIMIZE-HF ^[91]	All BBs (prescribed at discharge)	6-7 h Atenolol 12-19 h Nebivolol	21149	3 mo	LVEF 40%-49% and \geq 50%	Beta blockers had no effect on mortality and rehospitalization
Calcium channel blockers						
Setaro <i>et al</i> ^[92]	Verapamil vs placebo	4.5-12 h	20	1 mo	LVEF \geq 45%	Verapamil increased exercise capacity clinicoradio-graphic score. No change in LVEF.
Hung <i>et al</i> ^[93]	Verapamil vs placebo	4.5-12 h	15	3 mo	Normal LVEF	Verapamil increased exercise time and LV diastolic function
ACE inhibitors						
Aronow <i>et al</i> ^[94]	Enalapril vs control (diuretics alone)	11 h	21	3 mo	LVEF \geq 50%	Enalapril increased exercise time and LVEF
PEP-CHF trial ^[95]	ACE inhibitor (perindopril) vs placebo	3-10 h with prolonged terminal elimination	207	12 mo	LVEF \geq 45%	Perindopril increased 6 min walk distance but did not decrease mortality
Angiotensin II receptor blockers						
I-PRESERVE ^[96]	Irbesartan vs placebo	11-15 h	4563	24 mo	LVEF \geq 45%	No decrease in hospitalization or mortality

CHARM-Preserved ^[97]	Candesartan <i>vs</i> control medication (ACE Inhibitor, BB, CCB)	9 h	3023	37 mo	LVEF ≥ 40%	Candesartan slightly decreased hospitalizations but did not decrease mortality
Angiotensin receptor blocker/nephrylysin inhibitors						
PARAMOUNT Trial ^[98]	Sacubitril/valsartan <i>vs</i> valsartan	11.5 h	301	3 and 8-9 mo	LVEF ≥ 45%	Sacubitril Valsartan reduced NT-proBNP
PARAGON-HF Governmental Trial NCT01920711	Sacubitril/valsartan <i>vs</i> valsartan	11.5	4300	57 mo	LVEF ≥ 45%	Sacubitril/valsartan not superior to valsartan alone in decreasing hospitalization or cardiovascular mortality
Ivabradine						
Kosmala <i>et al</i> ^[99]	Ivabradine <i>vs</i> placebo	11 h	61	7 d	LVEF ≥ 50%	Ivabradine increased exercise time, peak oxygen uptake, and decreased E/e'
EDIFY trial ^[100]	Ivabradine <i>vs</i> placebo	11 h	179	8 mo	LVEF ≥ 45%	No improvement in 6 min walk, E/e', or NT-proBNP
Statins						
Fukuta <i>et al</i> ^[101]	Standard HF therapy with a statin <i>vs</i> without a statin	2 h (lovastatin)-19 h (rosuvastatin)	137	21 mo	LVEF ≥ 50%	Statin therapy associated with reduced mortality
Ouzounian <i>et al</i> ^[102]	Standard HF therapy with a statin <i>vs</i> without a statin	2 h (lovastatin)-19 h (rosuvastatin)	6451	38 mo	LVEF ≥ 50%	Statins did not decrease morbidity or mortality in patients with HF without CAD
Animal model of heart failure (rats) ^[103]	Standard HF therapy with rosuvastatin <i>vs</i> without rosuvastatin	19 h	46	19 mo	Preserved EF	Statins had no benefit
Digoxin						
(DIG) trial ^[104]	Digoxin <i>vs</i> placebo	36-48 h	988	37 mo	LVEF ≥ 45%	Digoxin had no effect on all-cause and CV mortality, heart failure hospitalizations
Phosphodiesterase-5 inhibitors						
RELAX trial ^[105]	Sildenafil <i>vs</i> placebo	3-4 h	216	24 mo	LVEF ≥ 50%	No improvement in 6 min walk distance, clinical status, or peak O ₂ consumption
Nitrates						
NEAT-HFpEF trial ^[106]	Isosorbide mononitrate <i>vs</i> placebo	2.5-5.1 h	110	22 mo	LVEF ≥ 50%	No improvement in 6 min walk distance or NT-proBNP
INDIE-HFpEF ^[107,108]	Inhaled inorganic nitrite <i>vs</i> placebo	0.7 h	105	4 wk	LVEF ≥ 50%	No significant improvement in exercise tolerance, NY Heart Association Class, E/e', NT-proBNP
Governmental trial NCT02840799	Oral KNO ₃ <i>vs</i> KCL	1.2 h	26	1 mo	LVEF ≥ 50%	KNO ₃ trial is in progress

LVEF: Left ventricular ejection fractions; HF: Heart failure; EF: Ejection fraction.

from heart failure.

MECHANICAL CIRCULATORY ASSISTANCE

For patients with severe refractory HFpEF in whom medical therapies have provided

no benefit, mechanical circulatory support is being investigated to decrease LV filling pressures and pulmonary congestion and increase cardiac output. In this regard, a partial mechanical circulatory microdevice, which is inserted with a minimally invasive approach, directs blood from the left atrium into the subclavian artery^[112]. This system is reported to decrease pulmonary and left atrial pressures in patients with HFpEF. However, patients with HFpEF have small LV dimensions and further decreases in LV stroke volume may limit patient coronary and cerebral blood flow. Additional investigations are needed to evaluate whether this invasive therapy decreases patient morbidity and mortality.

FUTURE PERSPECTIVES

The specific etiologies of HFpEF, the mechanisms, the clinical manifestations, and the contributions of comorbidities to the morbidity and mortality of HFpEF must be fully identified in patients. Such identifications will be facilitated by the pursuit of clinical registries and large clinical trials that focus on collecting clinical, imaging, laboratory, and outcome data and treatments. Successful pursuit of these goals will ultimately permit the development of specific drugs and medical devices that will decrease the morbidity and mortality of HFpEF in patients.

SUMMARY

The American College of Cardiology, the American Heart Association and the Heart Failure Society recommend the following treatments for patients with HFpEF and symptoms and signs of heart failure (adapted from^[46,113]): (1) Treatment of hypertension in all HFpEF patients with angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers or beta-adrenergic receptor blocking drugs; (2) Treatment of patients with HFpEF with volume overload with diuretics; (3) In patients with HFpEF with increased BNP, creatinine < 2.5 mg/dL, glomerular filtration rate > 30 mL/min and potassium < 5 mEq/L, treatment with an aldosterone antagonist; (4) Control of heart rate with medications in patients with atrial fibrillation; (5) In patients with HFpEF and type 2 diabetes mellitus, treatment with a SGLT-2 inhibitor such as Empagliflozin should be considered; and (6) Treatment of patients with symptomatic obstructive coronary artery disease and myocardial ischemia that contributes to heart failure with coronary revascularization.

HFpEF BULLET POINTS

Introduction

Currently, 5.7 million people in the United States have heart failure and require 30.7 billion dollars per year for health care and medications.

50% of patients with heart failure have normal, or near-normal LV systolic heart function but abnormal LV diastolic function with incomplete LV relaxation due to increased myocardial stiffness. These patients have HFpEF.

The most common patients are elderly women with hypertension, ischemic heart disease, atrial fibrillation, obesity, diabetes mellitus, renal disease, or obstructive lung disease.

Patients who are hospitalized because of HFpEF have complication rates that are similar to those patients with HFrEF.

The annual mortality rate of patients is approximately 8% per year but increases to approximately 10%-12% per year among patients older than 70 years of age.

Pathophysiological mechanisms in HFpEF

Current hypotheses include: (1) Cardiomyocyte titin hypophosphorylation; (2) Vascular endothelial cell inflammation and dysfunction; (3) Abnormal calcium homeostasis; (4) Increased ventricular matrix formation; and (5) Obesity.

Clinical manifestations/diagnosis

The diagnosis is based on the patient's history and physical examination with the assistance of laboratory data, echocardiography, and, when necessary, by cardiac catheterization.

A scoring system facilitates the diagnosis of HFpEF in patient with dyspnea and distinguish these patients from patients with non-cardiac causes of dyspnea.

In patients with HFpEF, the myocardial extracellular matrix can be determined

with CMR T1 mapping and is a predictor of LV myocardial stiffness, LV diastolic dysfunction, and patient outcome.

HFpEF treatment

Since many hospitalizations and deaths in patients with HFpEF are due to non-cardiovascular causes such as chronic obstructive lung, chronic kidney disease, and diabetes, these disorders must be identified early and aggressively treated.

Patients with obesity, hypertension, and atrial fibrillation require weight reduction, an exercise program, and aggressive control of blood pressure and heart rate.

Patients with volume overload should be treated with diuretics.

Pharmacologic therapy trials with beta-adrenergic receptor blockers, calcium channel blocking agents, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, and nitrates have, in general, been neutral in decreasing patient mortality.

Medical treatment based on pulmonary artery pressure monitoring with a permanently implanted right pulmonary artery microsensor significantly reduces hospitalizations for treatment of heart failure. A clinical trial is currently examining the effects on patient mortality from heart failure.

If significant coronary artery disease is present and contributes to heart failure, the patient with HFpEF should be evaluated for coronary revascularization.

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Radial artery access site complications during cardiac procedures, clinical implications and potential solutions: The role of nitric oxide

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Abstract

Percutaneous coronary intervention for the treatment of coronary artery disease is most commonly performed in the UK through the radial artery, as this is considered to be safer than the femoral approach. However, despite improvements in technology and techniques, complications can occur. The most common complication, arterial spasm, can cause intense pain and, in some cases, procedural failure. The incidence of spasm is dependent on several variables, including operator experience, artery size, and equipment used. An anti-spasmodic cocktail can be applied to reduce spasm, which usually includes an exogenous nitric oxide (NO) donor (glyceryl trinitrate). NO is an endogenous local vasodilator and therefore is a potential target for anti-spasm intervention. However, systemic administration can result in unwanted side-effects, such as hypotension. A method that adopts local delivery of NO might be advantageous. This review article describes the mechanisms involved in radial artery spasm, discusses the advantages and disadvantages of current strategies to reduce spasm, and highlight the potential of NO-loaded nanoporous materials for use in this setting.

Key words: Radial artery; Cannulation; Spasm; Nitric oxide; Vasodilation; Nanoporous material

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Core tip: Radial access during interventional cardiology procedures is much safer than

manuscript

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femoral access although complications can still arise. However, the radial artery is more prone to spasm which can cause pain for the patient and lead to procedural failure. Current strategies to avoid spasm include administration of an anti-spasmodic cocktail. Several disadvantages towards the use of this “cocktail” leaves a gap in the industry for a new product to dilate the artery without any systemic effects.

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INTRODUCTION

Coronary artery disease is a major cause of mortality and morbidity worldwide^[1,2]. The underlying disease process, atherosclerosis, results in the accumulation of lipid plaque in the arterial intima. Atherosclerosis is triggered by endothelial dysfunction and can lead to reduced coronary blood flow, resulting in angina or myocardial infarction with a reduction in patient survival and quality of life^[3-5]. Treatments for occlusive coronary artery disease are divided into three major categories: Medical therapy alone, concomitant coronary artery bypass grafting, or concomitant percutaneous coronary intervention (PCI). PCI was introduced in 1977 by Grüntzig *et al*^[7] and is now the most common procedure used to treat diseased coronary arteries^[6], improving symptoms and reducing mortality in certain patients^[6,7].

There have been considerable technological advances in PCI since its inception, with the introduction of improved delivery equipment, intracoronary stents, improvement in stent design and introduction of anti-proliferation stent coatings, resulting in improved procedural success and patient outcomes. In the United Kingdom, PCI is most commonly performed through the radial artery (RA) because this is considered to be safer than the femoral approach. However, despite these developments, complications associated with PCI persist. These include vascular access site complications, coronary artery complications and procedure-related complications, such as embolism or renal dysfunction caused by radio-opaque contrast^[8]. The most common complications are related to the vascular access site.

This review article describes the mechanisms that are involved in RA spasm and discusses strategies to reduce spasm and improve outcomes, with a particular focus on the potential for novel nitric oxide (NO) materials in this setting.

PCI ACCESS SITES

Vascular access can be achieved via the femoral artery or, more recently, the RA^[9-11]. Although femoral artery access is still used, it has several disadvantages compared to the RA approach, including longer bed rest, difficult access through the tortuous aorta, the need for puncture site compression after the procedure, and vascular complications of arteriovenous fistula and haematoma^[9]. Furthermore, the femoral artery is an ‘end artery’ with limited alternative vascular pathways to contribute to lower limb perfusion. As a result, vascular complications can lead to limb loss^[12]. The RA approach was introduced in 1989 by Campeau *et al*^[13] and has been used increasingly for interventional and diagnostic cardiology over the last thirty years.

Studies have shown that, compared with the femoral approach, the radial method has reduced bleeding risk, earlier hospital discharge, lower cost, reduced haematoma formation, lower mortality and morbidity, and is preferred by most patients^[14-18]. However, it carries technical challenges, not least on account of the small RA diameter, which hinders instrument insertion and increases artery-instrument contact, heightening the risk of disruption to the endothelial surface, which increases the risk of spasm.

As the RA approach is becoming more commonly used, there is a greater need to reduce the risk of complications.

THE RADIAL ARTERY: ANATOMICAL AND PHYSIOLOGICAL CONSIDERATIONS

Anatomy

The RA runs along the lateral part of the front of the forearm beside the superficial branch of the radial nerve^[19,20]. Variation in the anatomy of the RA is less frequent in the distal forearm, where arterial cannulation is commonly performed^[18,19,21]. Arterial blood flow is provided to the hand through a dense anastomotic network of four arches created from the radial and ulnar arteries. The complexity of the anatomy of the RA ensures substantial collateral blood flow is instrumental in ensuring that cannulation (and occlusion) is generally well-tolerated.

The RA has a thick tunica media composed of mainly smooth muscle cells with a high density of $\alpha 1$ adrenoceptors (Figure 1). High density sympathetic innervation, coupled with a thick, muscular wall makes the RA highly susceptible to spasm; the predominance of α -adrenoceptors leads to rapid vasoconstriction in response to stress-induced local release of the catecholamine, noradrenaline^[22,23]. Anomalous radial artery anatomy and small artery diameter are major predisposing factors which can determine the development of spasm^[24]. During cannulation, spasm can cause the vessel to “clamp” onto the guide catheter, which can result in pain for the patient and procedural difficulty for the operator, limiting successful completion. Spasm then exacerbates friction between the arterial wall and the sheath, which acts to intensify the spasm and induce a positive feedback loop (Figure 1). This continuous cycle of events can lead ultimately to intimal tear and thrombus formation in the artery^[25,26]. Once catheters are inserted through a sheath, spasm can occur at other sites at any level from the RA to the subclavian artery^[26].

NO - a powerful endogenous local vasodilator and anti-platelet agent

NO is an endogenous biological signalling molecule that mediates a variety of biological functions in the cardiovascular, immune and nervous systems^[5]. NO mediates vasodilatation, cell proliferation and inhibition of platelet adhesion^[27-29].

The importance of NO in biological processes was first realised when it was identified as an endothelium-derived relaxing factor that is released by the vascular endothelium and mediates vasodilation. It has long been known that endogenous NO is reduced or absent in coronary arteries affected by atherosclerosis^[27,30]. NO is now recognised to play a critical role in pathologic processes that culminate in the development of atherosclerotic lesions. Endothelial dysfunction is one of the earliest processes identified in atherosclerosis development. The normal homeostatic function of the endothelium requires NO, which has decreased bioavailability in patients with developing atherosclerosis^[28]. Deficiency in NO generation or functional availability is a fundamental feature of atherosclerosis and many other processes associated with cardiovascular disease, including thrombosis, intimal hyperplasia and aneurysm^[28,29].

COMPLICATIONS FROM RADIAL ARTERY CANNULATION

Table 1 summarises the complications associated with radial artery cannulation.

Spasm

During RA cannulation, an early occurrence of RA spasm can result in difficulty to advance the sheath or guide catheter within the artery, or failure to cannulate altogether. RA spasm as a specific consequence of RA cannulation can occur at any stage of the procedure. Spasm at the end of the procedure can result in difficult and painful sheath removal. A report in 2004 indicated that severe spasm occurred in over 50% of patients that received transradial catheterization; incidence was inversely correlated with arterial diameter^[33]. However, most recent studies report a much lower rate (1%-34%)^[11,18,19,24,26,34-36], presumably due to improved technique. The large range in reported RA spasm incidence (Table 1) is likely due to a combination of factors, including sheath size, vessel size, procedural differences, experience of the interventionalist, and the different definitions of spasm^[24]. RA spasm is more common in females, smaller patients and patients with vaso-occlusive disorders such as diabetes^[22]. Spasm in the RA is generally temporary and resolves spontaneously, but more prolonged spasm can occur, leading to trapping of the catheter and increased risk of RA occlusion.

Other complications

It is out with the scope of this current review to discuss in detail other potential complications that can arise from RA cannulation, however their frequency is shown

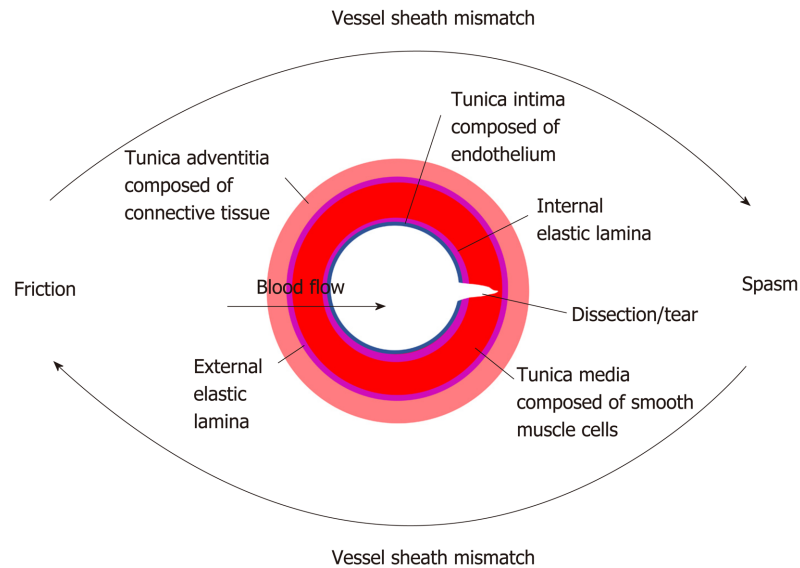


Figure 1 Composition of the radial artery. The thick layer of tunica media contributes to the increased incidence of radial artery spasm. Vessel sheath mismatch induces spasm and friction. Spasm promotes friction which in turn induces more spasm, creating a continuous loop. The increased friction and spasm can lead to dissection of the artery lining.

in **Table 1**. In summary, reported rates of RA occlusion vary greatly from 1%-3% to up to 19.7% (temporary occlusion)^[11,19,24,26,35-37]. Perforation or rupture of the artery is a rare complication that can lead to forearm haematoma^[24]. In the event that intervention is delayed, more serious complications, such as compartment syndrome, can occur^[26,36]. Pseudoaneurysm is an extremely rare complication in the RA approach (more common in transfemoral procedures) and occurs when an artery wall is injured, resulting in possible haemorrhage and haematoma in the surrounding tissue^[11,26]. RA cannulation can also cause direct damage to the endothelium, which can affect RA function^[38,39] impairing endothelium-dependent vasodilatory, anti-thrombotic and anti-mitogenic properties.

PREVENTING COMPLICATIONS

Administration of vasodilators, either alone or in an anti-spasmodic cocktail is the most common approach to prevention or management of spasm (**Table 2**). However, hydrophilic coatings and structural alterations of the sheaths are alternative strategies that are available^[32,37].

It is well recognised that RA spasm rates are lower in procedures conducted by experienced operators with good technique; patient preparation is recognised to be key to a successful procedure. Intraprocedural anticoagulation (usually heparin) is routinely administered to prevent thrombotic occlusion of the RA; the occlusion rate is inversely correlated to activated clotting time^[15]. In selected cases, sedatives such as short acting benzodiazepines can be used (or at least offered to patients) as a means of reducing the incidence of spasm. Low dose sedation (opioid/benzodiazepine) has been shown to reduce spasm (2.6% in treatment group *vs* 8.3% in control group)^[40].

Vasodilators, such as NO donor drugs and calcium channel blockers can be used alone, or in combination with other compounds, to form an anti-spasmodic radial “cocktail”, to prevent or reduce RA spasm^[26,28,32,34]. However, on account of the risk of systemic vasodilatory effects of spasmodic drugs used in this setting, there are side-effects associated with systemic hypotension and this approach is contra-indicated in patients with pre-existing hypotension^[15]. The use of a radial “cocktail” is based on the operator’s preference but is common practise in many units^[37].

Depending on the unit, the cocktail components and concentrations differ (**Table 2**), along with their reported effectiveness. The L-type calcium channel antagonist, verapamil is reported to be the most widely used agent for preventing spasm^[15,41]. Nitroglycerin [glyceryl trinitrate (GTN)] is also widely used in RA catheterisation. GTN is metabolised to release NO in smooth muscle, resulting in smooth muscle relaxation through activation of guanylate cyclase and increased cyclic guanosine monophosphate.

Table 1 Complications from radial artery puncture

Complication	Frequency (%)
Radial artery spasm ^[11,18,19,24,26,34-36]	1-34
Radial artery occlusion ^[11,19,24,26,35-37]	Up to 19.7
Haematoma ^[11,19,24,35]	Up to 14.4
Dissection ^[35,36]	Very rare (0.4)
Compartment Syndrome ^[26,36]	Very rare
Pseudoaneurysm formation ^[11,19,26,35,36]	Very rare up to 2.78
Infection ^[19,35]	Up to 3.4
Perforation ^[26,36]	Very rare

A recent review of individual drugs and drug cocktails found that the use of verapamil (5 mg) alone or in combination with GTN (100-200 µg) was effective at achieving a significant but modest reduction in the incidence of spasm (9% compared to 12% for placebo)^[41]. Despite these reported benefits of verapamil in this setting, there is concern about the negative chronotropic and inotropic effect of verapamil, especially in those patients with left ventricular dysfunction, hypotension and bradycardia. It has been suggested that verapamil may not necessarily be required by high-volume trans-radial-operators^[42]. GTN is thought to have a more favourable side-effect profile compared to verapamil and carries the additional benefit of inhibiting platelet aggregation. However, there are contraindications of GTN in certain patients (*e.g.*, severe aortic stenosis or severe hypotension^[15,42]).

Development of a prophylactic vasodilator, with effects entirely localised to the vasculature affected by spasm would be a distinct advantage.

Sheath type and materials

It has been suggested that the success rate of the RA approach is influenced by the ratio of sheath diameter to vessel diameter. The anatomy of the RA varies between patients, so vessel sheath mismatch is a potential issue^[37]. In clinical practice, operator experience and personal preference largely controls catheter selections^[15]. Operators will generally use the smallest sheath possible and therefore there is limited opportunity to further reduce sheath size. Several trials have evaluated the impact of different sheaths and catheters on occurrence of RA spasm. Several investigations have studied the impact of sheath length and coating, or the impact of sheath coating alone. In a study conducted by Rathore *et al*^[35], the application of 4 different introducer sheaths were examined: A long (23 cm) hydrophilic-coated, long uncoated, short (13 cm) hydrophilic-coated, and short uncoated. The results of this study showed that the hydrophilic sheath coating caused significantly less RA spasm (19% *vs* 39.9%) and patient discomfort (15.1% *vs* 28.5%), with no difference observed between long and short sheaths. Interestingly, RA occlusion was observed in 9.5% of patients, this was unaffected by sheath coating or length. One advantage of hydrophilic coatings is that larger sheaths can be used in smaller arteries^[37]. Similar results have been found in other studies, but despite these approaches and advancements, RA spasm continues to affect a sizable proportion of patients, even with experienced operators.

Opportunity for a novel approach

The application of a novel sheath coating could be advantageous in the cardiovascular setting, although the components of the coating would have to be carefully designed to produce the desired effect without any adverse systemic effects. A sheath design that dilates the vessel without the use of vasodilator drugs would not only minimise the risk of RA spasm, but also reduce the risk of any unintended side-effects of the drugs used. The application of NO to the sheath used in RA approach might provide the local dilating effects of NO with the potential to avoid any unwanted systematic effects. It would be essential that NO is delivered in appropriate quantities for a suitable time scale, to prevent adverse effects and optimise vasodilation. The use of a NO releasing coating of a sheath could prevent local vasospasm without prompting systemic vasospasm, reducing patient pain and anxiety. The delivery of NO through this mechanism could also inhibit any platelet aggregation prompted by catheterisation, preventing thrombosis during the procedure. Novel nanoporous materials such as metal organic frameworks (MOFs) or zeolites are excellent gas storage and release materials. Zeolites are inorganic, microporous materials often used for large-scale catalytic applications^[45,46]. MOFs are organic- inorganic crystalline

Table 2 Variations of anti-spasmolytic cocktail components

Ref.	Radial cocktail ingredients	Concentration	Drug class
Kiemeneij <i>et al</i> ^[32]	Verapamil	5 mg	Calcium channel blocker ¹
	Nitroglycerin	0.2 mg	Nitrate ²
Pancholy <i>et al</i> ^[44]	Nitroglycerin	0.2 mg	Nitrate ²
	Diltiazem	5 mg	Calcium channel blocker ¹
Hizoh <i>et al</i> ^[43]	Verapamil	5 mg	Calcium channel blocker ¹
He <i>et al</i> ^[23]	Heparin	2500 units	Anticoagulant ³
	Nitroglycerin	0.2 mg	Nitrate ²
	Verapamil	2.5 mg	Calcium channel blocker ¹
Ruiz-Salmerón <i>et al</i> ^[24]	Heparin with	5000 units	Anticoagulant ³
	Verapamil or	2.5 mg	Calcium channel blocker ¹
	Phentolamine	2.5 mg	Alpha-adrenergic antagonist ¹

¹Disrupts the movement of calcium through calcium channels, Causing vasodilation.

²Activates guanyl cyclase and increases cyclic guanosine monophosphate causing vasodilation;

³Inhibits coagulation, preventing thrombus formation.

microporous materials made up of organic spacers which connect metal ions^[47,48]. MOFs and zeolites have attracted interest for use in drug storage and delivery due to the ability to tune their structure and function^[45-48]. NO storage in both nanoporous materials has been studied extensively with very promising results. However, cytotoxicity of these compounds is yet to be examined in the cardiac setting.

Previous work examining NO-loaded zeolites showed evidence that these high capacity NO stores could inhibit platelet aggregation over several hours. NO release profiles could be easily tuned through manipulation of the metal ion, along with the composition and nature of the polymer used for production. Stability studies also found that NO-loaded zeolites were very stable in the absence of water, suggesting a long shelf life of months to years under vacuum^[46]. These data show promise for potential use in a sheath coating. More recent developments in NO storage materials have focused on the use of MOFs. MOFs have an advantage over zeolites due to the infinite number of possible frameworks that can be synthesised. This ability to fine-tune their structures provides an opportunity to alter chemical characteristics the suit the required function. Many MOF structures have been developed to store and release NO. Previous work has examined the capability of storage and release of NO in MOFs with different incorporated metal ions. The alteration of metal ions allows for the delivery of biologically active, but non-toxic levels of NO. It has been shown that the use of Ni²⁺ as a dopant can improve the NO release performance of a MOF (CPO-27), delivering an appropriate bio-active concentration of NO. The results from this study highlights a significant advance in the development of a NO storage and delivery compound^[47]. A 2017 study examined the release of NO from vascular catheters to prevent bacterial infection using a NO donor^[49]. Results showed inhibition of bacterial adhesion without any cytotoxic effects towards mammalian cells. Another study investigated the release of NO from a coronary stent using a NO donor^[50]. Results showed the promising positive effect of NO as a releasing agent to suppress or prevent restenosis and thrombosis. Authors proposed further investigations using other NO carriers or donors to further improve NO release pattern.

The tuneable nature of these materials could allow for an appropriate release of NO over a desired period thus excluding any toxic effects that may occur from overexposure of NO. The effects of the NO released should ensure a larger intraluminal diameter making the procedure safer and easier for the operator. The localised nature of the NO release should inhibit inflammation and thrombosis at the site of access without any adverse systemic effects. The development of these nanoporous materials has the potential for long-lasting, low level NO generation that mimics endothelial NO, with the potential to both inhibit spasm and prevent localised thrombosis. The use of a nanoporous material in the coating of a sheath could prevent local vasospasm without prompting systemic vasospasm, reducing patient pain and anxiety. Overall the procedure efficiency and effectiveness could be improved.

This application might not only benefit cardiac catheterisation, but other situations where catheter thrombosis or platelet aggregation can be problematic such as peripheral and central venous cannulae.

CONCLUSIONS

The use of the RA instead of the femoral artery has reduced complications at the time of coronary artery procedures. However, despite improvement in cannulation techniques, minimisation of sheath size, hydrophilic coatings and use of radial “cocktails” complications still occur, most commonly RA spasm, in a proportion of patients resulting in pain, procedural failure and RA damage. Novel approaches in sheath materials, perhaps to include NO releasing materials such as MOFs and zeolites might offer an exciting new target for improvement in outcomes.

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Observational Study

Impact of training specificity on exercise-induced cardiac troponin elevation in professional athletes: A pilot study

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Abstract

BACKGROUND

Release of cardiac biomarkers is common after strenuous endurance exercise, but data on intermittent exercise are scarce. It has not been investigated whether cardiac troponin elevation is influenced depending on the type of exercise that an athlete is adapted to perform. We hypothesized that intermittent but not continuous exercise induces cardiac troponin elevation in professional athletes adapted to high-intensity intermittent exercise.

AIM

To examine how training specificity impacts high-sensitivity cardiac troponin T (hs-cTnT) release.

METHODS

Nine professional floorball players participated in the study, which comprised two different exercise tests: a continuous incremental cycle ergometer test and a Yo-Yo Intermittent Recovery 2 (Yo-Yo IR2) test. Serial assessment of hs-cTnT was performed after the cycle ergometer test and the Yo-Yo IR2 test (baseline, 0, 2, 6, and 24 h).

RESULTS

No hs-cTnT elevation above the myocardial damage cutoff (≥ 14 ng/L) was shown after the cycle ergometer test, whereas hs-cTnT levels rose over the cutoff in three of nine participants after the Yo-Yo IR2 test. The hs-cTnT levels peaked at 6 h after both tests, but were significantly higher after the Yo-Yo IR2 test compared to the cycle ergometer test (median hs-cTnT concentration 10.6 ng/L vs 7.8 ng/L, $P = 0.038$). All levels returned to baseline within 24 h.

CONCLUSION

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In professional athletes adapted to high-intensity intermittent exercise, hs-cTnT was significantly elevated after intermittent but not continuous exercise. This principle of specificity training should be considered when designing future studies to avoid misinterpretation of hs-cTnT elevation.

Key words: Athlete; Exercise; Floorball; Sports medicine; Yo-Yo IR2 test; Myocardial injury; Cardiac troponin

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Core tip: Exercise-induced cardiac troponin elevation is common after continuous exercise, but the response to intermittent exercise is less investigated. Nine professional athletes adapted to intermittent exercise underwent serial assessment of high-sensitivity cardiac troponin T (hs-cTnT) after continuous exercise and intermittent exercise tests. The intermittent exercise test induced higher levels of hs-cTnT compared to the continuous exercise test. The peak hs-cTnT concentration was observed 6 h after the exercise tests. The principle of specificity training and timing of blood sampling should be considered when designing future studies to avoid misinterpretation of hs-cTnT elevation.

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INTRODUCTION

Cardiac troponin (cTn) is a highly specific biomarker of cardiac myocyte injury and necrosis^[1,2]. Asymptomatic elevation of cTn in athletes following strenuous and continuous-type endurance events is common^[3,4], but the mechanisms and clinical relevance are unknown^[5]. We previously reported that high-sensitivity cardiac troponin T (hs-cTnT) elevation occurs after floorball games with intra-individual reproducibility^[6]. cTn response to high-intensity intermittent exercise remains poorly examined and inconsistent due to assay differences and variability in sampling frequency and exercise mode^[7].

According to the training specificity principle, physical adaptations are related to exercise mode, duration, and frequency^[8]. Thus, an exercise routine similar to the competitive element is desirable. Continuous exercise tests are inadequate in intermittent team sports such as football^[9], whereas intermittent tests such as the Yo-Yo Intermittent Recovery (IR) test correlate with match performance^[10]. Despite this, little is known about the impact of the training specificity principle on cTn release. Looking at endurance athletes in a meta-analysis, Shave *et al*^[11] found a greater magnitude of cTn elevation after running than cycling. However, these results were based on earlier generation assays as well as single blood draws post-exercise that failed to detect late cTn peaks^[12].

Floorball is a popular Scandinavian intermittent team sport and among the fastest growing sports in Sweden^[13]. Depending on player position and time played, there are individual differences in physical effort and cardiac load during a game. Laboratory-based studies with exercise manipulations give a better understanding of how cardiac work influences the release of cTn^[14]. The use of standardized physical tests correlates with a defined physical effort and levels of cardiac biomarkers.

The aims of this study were to investigate the response of hs-cTnT to high-intensity intermittent exercise compared to continuous exercise in standardized settings, and to examine hs-cTnT release kinetics up to 24 h post-exercise.

MATERIAL AND METHODS

Participants and experimental design

Nine male elite floorball players were invited to participate in the study. The participants were screened for cardiovascular disease using the Lausanne Recommendations questionnaire, physical examination, two-dimensional echocardiography, and resting 12-lead ECG interpreted according to recommendations in athletes^[15]. All participants were informed in detail of the experimental procedures and gave their written consent for participation. The study was approved by the regional ethics committee, and all procedures adhered to the Declaration of Helsinki.

Two different types of standardized exercise tests, a cycle ergometer test and a Yo-Yo IR2 test, were carried out on different occasions with a 6-mo interval. All testing sessions were performed indoors in air-conditioned facilities with a set temperature of 20°C and a humidity of approximately 50%. The participants were instructed to avoid all physical activity 48 h prior to the tests. Venous blood samples were collected before the tests and 0, 2, 6, and 24 h after the tests to measure levels of hs-cTnT. Blood lactate levels were measured before and at different timepoints after the cycle ergometer test.

Cycle ergometer test

A cycle ergometer test was performed on a computer-controlled, mechanically braked cycle ergometer (Ergomedic 839; Monark, Vansbro, Sweden). The initial workload was set to 120 W and the resistance was increased 20 W every minute up to 300 W where, if reached, the participants pedaled until exhaustion. Pedal rate was kept constant at 60-65 revolutions per min. A 12-lead electrocardiogram (ECG), including heart rate (HR), was monitored throughout the test (Cardiolex EC Sense Software, Cardiolex, Solna, Sweden). No participant was asked to terminate prematurely due to adverse cardiovascular events, and the ECG gave no indication of ischemia or arrhythmias. All participants ($n = 9$) reported leg fatigue as the cause of termination.

Yo-Yo IR2 test

The participants completed a Yo-Yo IR2 test that consisted of repeated shuttle runs between a starting line and finishing line marked by cones 20 m apart. A third cone was placed 5 m behind the starting line. The running speed was dictated by beeps from a CD player, using the Team Beep Test Software 4.1 for PC (Bitworks Design, Cheltenham, United Kingdom). The initial speed was 13 km/h and increased progressively for each covered level; 2 km/h after the first level, 1 km/h after the second level, and then 0.5 km/h for the following levels. Between each running bout of 2 x 20 m, the participants had a 10 s period of active recovery jogging around the cone behind the starting line^[16]. A test supervisor was placed at each end line to ensure that the participants completed the full distance. When a participant first failed to complete a shuttle run in the designated time (*i.e.*, before the beep), a warning was given by the supervisor at the end line. When a participant failed to complete a shuttle run a second time or felt unable to complete another shuttle due to exhaustion, the test was terminated. The performance time was registered. HR was measured throughout the test using a Polar S810 HR monitor (Polar Electro Oy, Kempele, Finland).

Laboratory assays

Blood samples for plasma analysis were collected into 3.5 mL lithium heparin vacutainer gel tubes, and blood for analysis of blood lactate concentration was collected into 3 mL sodium heparin vacutainer tubes. The same experienced phlebotomist collected all blood samples, which were immediately transported to the laboratory for analysis. For quantitative measurement of plasma hs-cTnT, the Elecsys 2010 system (Roche Diagnostics GmbH, Mannheim, Germany) was used according to the manufacturer's instructions. The hs-cTnT assay had a limit of blank of 3 ng/L, a 5 ng/L limit of detection, and a 99th percentile myocardial damage cutoff point of 14 ng/L. The coefficient of variation (CV) was 7% at the cutoff level. Venous blood lactate levels were measured using an amperometric method on a Radiometer ABL825 Flex (Radiometer, Copenhagen, Denmark) according to instructions, with a total CV < 4% across the analytical range (0-30 mmol/L).

Statistical analysis

Continuous variables were calculated as median (interquartile range), and categorical data were expressed as absolute numbers with percentages. The highest achieved heart rate in the tests is referred to as peak HR. Differences between pre-exercise and post-exercise plasma hs-cTnT concentrations and differences in hs-cTnT concentration between exercise modes were assessed using paired Wilcoxon rank-sum test. Results were considered statistically significant when P values were < 0.05. All calculations were performed with IBM SPSS 23.0 (IBM, Armonk, NY, United States).

RESULTS

Cardiovascular screening showed no signs of cardiovascular abnormalities in the nine participants included in the study. Baseline characteristics of the participants are presented in [Table 1](#). There was no difference in training volume since all participants played for the same floorball team. The performance time was significantly longer in the cycle ergometer test than in the Yo-Yo IR2 test (10.1 min *vs* 7.4 min, $P = 0.018$). Median peak HR achieved in the Yo-Yo IR2 test (196 bpm) were significantly ($P = 0.021$) higher than that in the cycle ergometer test (190 bpm). The average HR was higher in the Yo-Yo IR2 test (171 bpm *vs* 159 bpm, $P = 0.008$). Baseline hs-cTnT concentrations and changes 0, 2, 6, and 24 h after completion of each exercise mode are shown in [Figure 1](#), [Table 2](#), and [Table 3](#). Median hs-cTnT concentration was significantly higher at 2 and 6 h post-exercise ($P = 0.028$ and $P = 0.038$, respectively) in the Yo-Yo IR2 test compared to the cycle ergometer test ([Table 2](#)).

Cycle ergometer test

All participants had normal baseline levels of hs-cTnT (< 14 ng/L) prior to the cycle ergometer test. Median values of hs-cTnT increased post-exercise but were below cutoff at all timepoints post-exercise ([Table 3](#)). The peak median hs-cTnT concentration of 7.8 ng/L was observed 6 h post-exercise, a significant ($P = 0.021$) increase from baseline. All concentrations normalized within 24 h post-exercise. The maximal individual value observed was 12.6 ng/L (6 h post-exercise), having increased 133% from baseline. The median percentage change in hs-cTnT compared to baseline peaked 2 h post-exercise (28% increase in hs-cTnT concentration).

Median concentration of lactate was within the reference interval (0.5–2.2 mmol/L) before the cycle ergometer test, increased significantly ($P < 0.001$) to 14.7 mmol/L immediately after the test, and returned within reference in all participants within 2 h post-exercise. A lactate concentration > 4.0 mmol/L indicated that the cycle ergometer test had an anaerobic character.

Yo-Yo IR2 test

All participants had normal hs-cTnT baseline levels (< 14 ng/L) prior to the Yo-Yo IR2 test. Increased median hs-cTnT levels was observed at all timepoints post-exercise, with the peak median concentration at 6 h post-exercise of 10.6 ng/L, a statistically significant increase from baseline ($P = 0.008$). Median values of hs-cTnT post-exercise were below cutoff at all timepoints post-exercise, but the 75th percentile value rose above the cutoff at 2 and 6 h post-exercise. All concentrations normalized within 24 h post-exercise, and the median value 24 h post-exercise (5.7 ng/L) was nonsignificant when compared to baseline ($P = 0.260$). Individually ([Figure 1](#)), a total of three of nine participants had hs-cTnT levels above cutoff at 6 h post-exercise. The highest individual value was observed 6 h post-exercise (22.6 ng/L) and corresponded to a 178% increase from baseline. The hs-cTnT median percentage change in hs-cTnT concentration was higher after the Yo-Yo IR2 test compared to the cycle ergometer test, 98% *vs* 28% at 2 h post-exercise and 107% *vs* 27% at 6 h post-exercise.

DISCUSSION

This is the first study to compare serial hs-cTnT release after two different standardized exercise modes in professional athletes adapted to high-intensity intermittent exercise. The primary finding was that hs-cTnT release among floorball players was significantly higher after completion of an intermittent test (Yo-Yo IR2 test) than after a continuous cycle ergometer test. Concentrations of hs-cTnT exceeded the 99th percentile cutoff in one-third (3 out of 9) of the participants after the intermittent test, but in none (0 of 9) after the continuous cycle ergometer test. Our findings support the theory that the training specificity principle impacts the release of cTns. These findings were observed in standardized settings and expand previous work from field-based studies. The results suggest that physicians must be aware that release of cTn commonly occurs following short high-intensity intermittent exercise, and not exclusively after long-term strenuous efforts.

In daily clinical practice, the results of laboratory tests assist in decision making. cTns are a cornerstone in the diagnosis of myocardial infarction (MI). In patients with signs of myocardial ischemia, acute MI is defined by one troponin concentration > 99 th percentile together with a rising or falling pattern^[2]. With increasing sensitivity of cTn assays, the rise or fall of cTn concentration in serial blood samples is important to differentiate acute from chronic myocardial injury^[17], but the magnitude of increase or decrease has not been determined. With high-sensitivity assays, even minor numerical changes above the 99th percentile cutoff arising from biological and/or

Table 1 Baseline characteristics of the 9 participants included in the study

Characteristics	Number/ Ratio
<i>n</i>	9
Male, %	9 (100)
Caucasian, %	9 (100)
Age, yr	24 (23-25)
Height, cm	184 (183-188)
Body weight, kg	82 (75-88)
BMI, kg/m ²	23.8 (23.5-24.8)
Training volume, h/wk	12 (12-12)
Resting HR, bpm	52 (49-58)
SBP, mmHg	120 (120-125)
DBP, mmHg	70 (70-80)

Values are presented as numbers (%) or median (interquartile range). BMI: Body mass index; HR: Heart rate; bpm: Beats per minute; SBP: Systolic blood pressure; DBP: Diastolic blood pressure.

analytical variations could prompt important clinical decisions. The reference change value (RCV) might aid the interpretation in such small cTn elevations, as it takes both analytical and biological variation into account. The RCV describes the maximum size of a difference that can occur by chance^[18]. Thus, a relative change in cTn that exceeds the RCV is considered clinically significant and may indicate acute myocardial necrosis. Vasile *et al.*^[19] found that, for the Roche hs-cTnT assay, short-term RCV over a 6 h period was 84%. Two other groups also evaluated the Roche hs-cTnT assay in healthy individuals and found lower RCV, 62% and 40% respectively^[20,21]. We found that the percentage change was significantly higher after the Yo-Yo IR2 test. The median percentage change 6 h post-exercise exceeded the upper RCV suggested in the studies mentioned above. This indicates that the change could be considered clinically significant. By the same reasoning, the percentage change in the cycle ergometer test could be explained by biological and/or analytical variation.

In the present study, the performance time was significantly longer in the cycle ergometer test. Therefore, it seems that differences in exercise times had no impact on hs-cTnT concentration. Also, peak lactate concentration in the cycle ergometer test was not different from the previously observed values in the Yo-Yo IR2 test^[10], indicating performance of similar high-intensity exercise in both tests. All participants reported leg fatigue as cause of termination in the cycle ergometer test, which might have restricted them from reaching higher HR^[22]. The results showed significantly higher average and peak HR in the Yo-Yo IR2 test, which indicates that a Yo-Yo IR2 test is more appropriate than a cycle ergometer test for assessment of cardiovascular demands among floorball players whereas cycle ergometer demands leg muscle strength.

cTn assays detect myocardial cell damage and necrosis^[1,2], but it is still debated to what extent exercise-induced cTn elevation is a physiological or pathological finding. As exercise-induced cardiac biomarker elevations mainly lack correlation to impaired left ventricular function, elevations have been interpreted as physiological^[5,23]. A prolonged and biphasic cTn release is indicative of release of structurally bound troponin from necrotic cardiomyocytes^[24]. Most studies report a small, transient leakage of cTn from the cytosolic pool, possibly because of affected sarcolemmal integrity caused by reversible ischemia^[25,26] or increased reactive oxygen species production^[27]. Mechanical stretch of cardiomyocyte integrins, a consequence of increased preload and afterload during exercise, has also been suggested as a cause of troponin release from living cardiomyocytes^[28]. Higher peak HR in the Yo-Yo IR2 test results in a greater cardiac output and thus ventricular strain could explain why we observed higher hs-cTnT levels. It has also been shown that skeletal muscle damage can cause increases in circulating levels of cTn. In patients with chronic skeletal muscle damage, elevation of noncardiac cTn can mimic an acute myocardial injury^[29,30]. It is therefore possible that skeletal rather than cardiac muscle is the source of circulating cTn found in the athletes participating in this study.

Serial blood specimen collection during the recovery period enables examination of post-exercise cardiac biomarker kinetics and is important to obtain a maximal concentration. In line with other studies recently reviewed by Baker *et al.*^[31], we observed an early peak of cTn elevation (6 h post-exercise), but it is possible that the

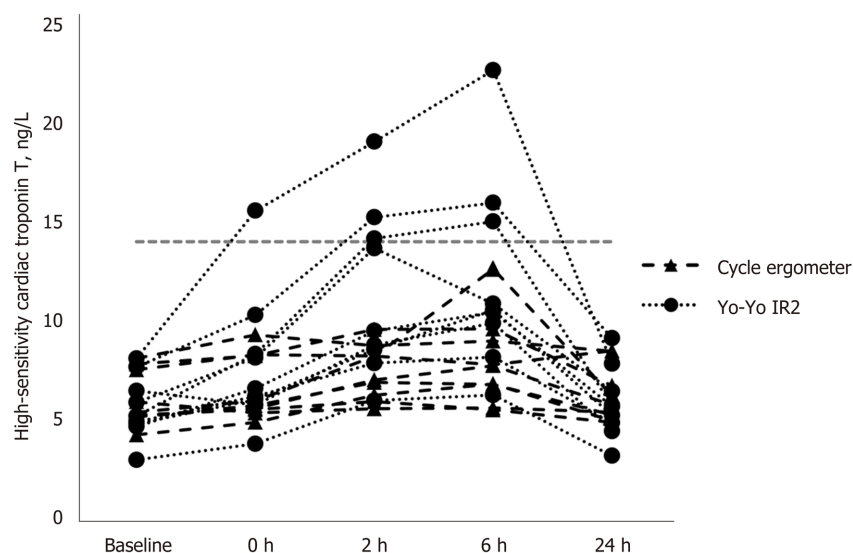


Figure 1 Individual baseline high-sensitivity cTn concentration and changes 0, 2, 6 and 24 h after completion of the cycle ergometer test and the Yo-Yo IR2 test.

true hs-cTnT peak was missed in our study. Therefore, a higher sample frequency during the first 6 h post-exercise could be considered in future studies. The small degree and rapid clearance of cTn elevation in the present study argue against myocardial injury and cardiomyocyte necrosis. Accordingly, it seems to reflect a physiological response to exercise. However, the intra-individual reproducibility first observed by Sahlén *et al*^[32], and recently supported in our previous study^[6], suggest that some individuals might be susceptible to exercise-induced cTn elevation. This phenomenon should be examined in future studies as it raises the question whether some individuals are susceptible to exercise-induced myocardial damage. This might be an important aspect to consider in the clinical significance of exercise-induced cTn release.

There are some limitations to consider when analyzing the results of this study. First, the sample size was small, and the results may not be applicable in a larger population. This study should therefore primarily be hypothesis-generating for future work. Nonetheless, we detected differences between exercise modes that could be interpreted as clinically relevant and beyond both biological and analytical variation. Second, pulse watches can overestimate HR^[33] but the pulse watch used in this study has been validated to ECG^[34]. However, future studies of similar rationale should aim to use ECG for a reliable comparison of HR. Third, we did not perform post-exercise assessment of cardiac structure and function with echocardiography, making the significance of post-exercise hs-cTnT elevation uncertain in this study group. Fourth, including a group of professional endurance athletes for comparison would add strength to the conclusion that troponin release is dependent on the training specificity principle.

In professional athletes adapted to high-intensity intermittent exercise, we found that hs-cTnT was significantly elevated after high-intensity intermittent but not after continuous exercise. The principle of specificity should be considered when designing future studies to avoid underestimating exercise-induced cTn elevation in athletes. Peak hs-cTnT concentration was observed after 6 h indicating that serial assessment post-exercise is important to observe maximum values. As the relevance of exercise-induced cTn elevation remains unclear, it should be cautiously interpreted in the clinical setting.

Table 2 Exercise test variables in the cycle ergometer test compared to the Yo-Yo IR2 test

	Cycle ergometer test	Yo-Yo IR2 test	P value
Performance time, min	10.1 (9.2-11.4)	7.4 (6.5-8.3)	0.018
Average HR, bpm	159 (151-161)	171 (169-176)	0.008
Peak HR, bpm	190 (181-191)	196 (190-197)	0.021

Values are presented as median (interquartile range). $P < 0.05$ calculated by the Wilcoxon rank-sum test is considered significant. HR: Heart rate; bpm: Beats per minute.

Table 3 Comparison of plasma levels of high-sensitivity cTn after the cycle ergometer test and Yo-Yo IR2 test

	Cycle ergometer test	Yo-Yo IR2 test	P value
Baseline	5.4 (5.2-7.7)	5.2 (4.8-7.1)	0.575
0 h	5.8 (5.5-8.3)	6.6 (5.9-9.3)	0.139
2 h	7.1 (6.1-8.5)	9.5 (8.2-14.7)	0.028
6 h	7.8 (6.2-9.3)	10.6 (9.1-15.5)	0.038
24 h	5.8 (5.2-7.6)	5.7 (4.7-7.2)	0.343

Values are presented as the median (interquartile range). $P < 0.05$ calculated by the Wilcoxon rank-sum test was considered significant.

ARTICLE HIGHLIGHTS

Research background

Release of biomarkers of myocardial damage such as cardiac troponins (cTns) is common after strenuous endurance exercise.

Research motivation

Although it is widely recognized that continuous exercise can induce release of cTns into the bloodstream, data on intermittent exercise are scarce. Furthermore, the principle of training specificity has never been investigated.

Research objectives

This study examined how training specificity impacts high-sensitivity cardiac troponin T (hs-cTnT) release.

Research methods

In this observational study, nine professional floorball players performed two different exercise tests: A continuous incremental cycle ergometer test and a Yo-Yo Intermittent Recovery 2 (Yo-Yo IR2) test. Serial assessment of hs-cTnT was performed after the cycle ergometer test and the Yo-Yo IR2 test (baseline, 0, 2, 6, and 24 h).

Research results

No hs-cTnT elevation above the myocardial damage cutoff (≥ 14 ng/L) was shown after the cycle ergometer test, whereas hs-cTnT levels rose over the cutoff in three of nine participants after the Yo-Yo IR2 test. The hs-cTnT levels peaked at 6 h after both tests, but were significantly higher after the Yo-Yo IR2 test compared to the cycle ergometer test (median hs-cTnT concentration 10.6 ng/L *vs* 7.8 ng/L, $P = 0.038$). All levels returned to baseline within 24 h.

Research conclusions

High-sensitivity cardiac troponin T was significantly elevated after intermittent but not continuous exercise.

Research perspectives

The principle of training specificity should be considered when designing future studies and sampling should continue at least 24 h post-exercise to avoid misinterpretation of hs-cTnT elevation.

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Observational Study

Prognostic impact of body mass index on in-hospital bleeding complications after ST-segment elevation myocardial infarction

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Abstract

BACKGROUND

ST-elevation myocardial infarction (STEMI) remains a major cause of mortality despite early revascularization and optimal medical therapy. Tailoring individual management by considering patients' specificities may help in improving post-STEMI survival.

AIM

To evaluate whether in-hospital bleeding complications may be involved in post STEMI prognosis among overweight patients.

METHODS

We prospectively included 2070 patients with a STEMI between January 2005 and December 2012 in the French observational cohort, "Registre d'Infarctus Maine-Anjou". Bleeding Academic Research Consortium (BARC) in-hospital bleeding complications were recorded.

RESULTS

Of 705 patients (35.3%) were presented as being of normal weight, defined as a body mass index (BMI) < 25 kg/m², 877 (43.9%) had a BMI between 25 and 30 kg/m² and 416 (20.8%) had a BMI ≥ 30 kg/m². One-year cardiovascular mortality was lower for BMI ≥ 25 kg/m² (5.3% and 7.1%) patients than for normal weight patients (10.8%) ($P = 0.001$). We found an interaction between the effect of BARC 3 on mortality and BMI groups. While a BARC 3 was related to a higher 1-year mortality in general (HR: 2.58, 95%CI: 1.44-4.64, $P \leq 0.001$), prognosis was even worse in normal weight patients (HR: 2.97, 95%CI: 1.61-5.5, $P < 0.001$) than for patients with a BMI ≥ 25 kg/m² (HR: 1.94, 95%CI: 1.02-3.69, $P = 0.041$).

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CONCLUSION

Normal weight patients presented higher rates of in-hospital bleeding complications and lower survival after a STEMI. Excess mortality might be due to greater vulnerability to bleeding amongst normal weight patients.

Key words: Myocardial infarction; Body mass index; Bleeding complications; Obesity paradox

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Core tip: There was an obesity paradox, with body mass index (BMI) ≥ 25 kg/m² ST-elevation myocardial infarction patients presenting better survival. Normal weight patients presented more in-hospital bleeding than others. In-hospital bleeding was related to 1-year cardiovascular mortality. Presenting a normal BMI increased the effect of bleeding on mortality.

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INTRODUCTION

The prevalence of overweight people in France [Body Mass Index (BMI) between 25 and 30 kg/m²] in 2012 was 32% and obesity rates (BMI greater than 30 kg/m²) were at 15% according to the “National Epidemiological Study on excess weight and obesity” (*ObÉpi*)^[1]. In the United States of America, the obesity rate more than doubled from 15% in 1980 to 34% in 2006^[2]. It is an independent risk factor for cardiovascular (CV) disease, conducive to the occurrence of ST-segment elevation myocardial infarction (STEMI)^[3].

Yet, increasingly, studies also suggest that obesity might also have a protective role in some chronic diseases once they are established, including coronary artery disease. Recent studies have demonstrated an “obesity paradox” after percutaneous coronary intervention, whereby overweight and obese patients seem to have better outcomes than normal weight individuals^[4]. There are multiple explanations. Obese patients may be more likely to receive full-dose guideline-based medical therapy during hospital admission and at discharge^[4]. They present greater coronary diameters^[5]. Thin patients may present higher rates of comorbidities such as cancer^[6], but also a higher rate of bleeding^[7].

In parallel, the unfavourable impact on the prognosis of bleeding complications after STEMI was recently highlighted in various studies. A meta-analysis based on 133597 patients presenting an acute coronary syndrome pointed to major bleeding as a strong predictor of in-hospital or 30-d death and acute myocardial infarction^[8]. Evaluating the relationship between bleeding events and BMI could explain the obesity paradox^[7]. The objective of this study is to evaluate the impact of BMI on the occurrence of bleeding complications and its further relationship with prognosis after a STEMI.

MATERIALS AND METHODS

Study population

We studied 2070 patients consecutively from the “Registre d’Infarctus Maine-Anjou” (RIMA) survey^[9]. We prospectively included all patients presenting with a STEMI in a Western region of France, in which the only available 24 h-7 d coronary angiography service was in Angers University Hospital. Patients were recruited between January 2005 and December 2012. Comparisons were carried out between 3 groups: Normal weight (BMI < 25 kg/m²) ($n = 705$, 35.3%), overweight (25 kg/m² \leq BMI < 30 kg/m²) ($n = 877$, 43.9%), and obese (BMI ≥ 30 kg/m²) ($n = 416$, 20.8%) (Figure 1).

Patients with missing weight or height data ($n = 28$), or a BMI < 18.5 kg/m² ($n = 44$)

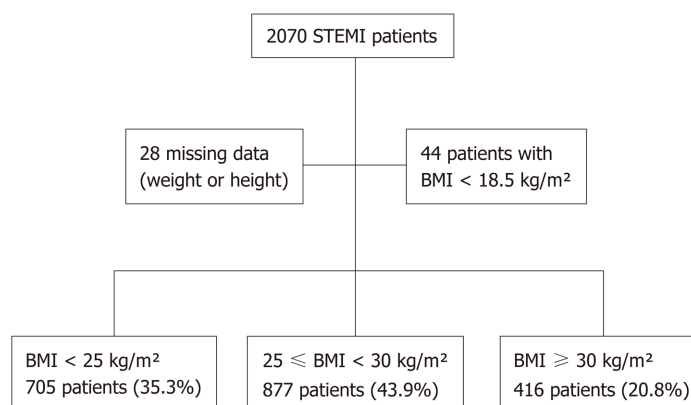


Figure 1 Flow chart. BMI: Body mass index; STEMI: ST elevation myocardial infarction.

were not considered for analysis. This study was carried out in accordance with the Declaration of Helsinki and the protocol was approved by the ethics committee of Angers University Hospital.

Study definitions

STEMI was defined as the presence of symptoms attributed to myocardial ischemia for at least 30 min accompanied with ST-segment elevation of ≥ 1 mm in at least two contiguous limb leads or ≥ 2 mm in precordial leads, or new or undetermined left bundle-branch block, as well as elevation of cardiac biomarkers^[10].

In-hospital bleeding complications were defined according to the Bleeding Academic Research Consortium (BARC)^[11] bleeding classification. The BARC classification identified STEMI patients at risk of 1-year mortality^[12]. We considered type 3 and 5 for analysis: BARC 3a was defined as haemorrhage (haematoma ≥ 4 cm at the site of vascular puncture, or gastrointestinal blood loss, or retroperitoneal bleeding verified by either ultrasound or computed tomography imaging, or intracranial bleeding^[10]) plus haemoglobin drop equal to between 3 g/dL and < 5 g/dL or any transfusion with bleeding; BARC 3b was defined as haemorrhage plus haemoglobin drop ≥ 5 g/dL, cardiac tamponade, haemorrhage requiring surgical intervention for control (excluding dental/nasal/skin/haemorrhoids) or haemorrhage requiring intravenous vasoactive agents; BARC 3c was defined as intracranial haemorrhage; BARC 5 bleeding was defined as fatal haemorrhage^[12].

Data collection

Data on demographics (age, sex, BMI), CV risk factors (smoker, diabetes history, hypertension, dyslipidaemia, family history of premature coronary vascular disease^[13], obstructive sleep apnoea), medical history (prior MI, stroke, peripheral vascular disease, renal failure, cancer) and admission characteristics (systolic blood pressure) were prospectively recorded for each patient at admission. The CRUSADE^[14] and HEMORR2HAGES^[15] bleeding risk scores were calculated based on the patient's initial characteristics.

We collected data concerning acute stage management, including thrombolytic use, time from symptom onset to first medical contact or to admission in the coronary angiography room, coronary angiogram findings [infarct location, vessel disease, puncture access, duration of the procedure and final thrombolysis in myocardial infarction (TIMI) flow], and the medical therapy given before and in the first 24 h after the first medical contact (antiplatelet therapy, antithrombotic therapy). Anticoagulants and their doses were mandated by a single protocol (see supplementary file). During the hospital stay, an echocardiography was obtained for the evaluation of left ventricular ejection fraction (LVEF) by the biplane Simpson method. Blood samples were collected to measure serum haemoglobin at admission and during hospitalisation to determine the haemoglobin drop, haematocrit and creatine phosphokinase peak. In-hospital complications were examined by two physicians and included death, bleeding event, transfusion, necrosis recurrence, heart failure and stroke. The 1-year follow-up for survival was available for all patients who were initially included.

Statistical analysis

Patient characteristics, in-hospital and 1-year events were compared relating to the BMI group. Continuous variables are expressed as the median (interquartile range).

Continuous variables were analysed using the Mann-Whitney *U*-test for 2-group comparisons and the Kruskal-Wallis test for 3-group comparisons. Qualitative variables were expressed as frequencies and percentages. The Pearson χ^2 test or Fisher's exact test were used to carry out comparisons between qualitative variables and in-hospital event rates.

Binomial logistic regression was carried out to determine correlates of in-hospital BARC 3 or 5 bleeding. The variables entered into the model were gender, age, history of hypertension, BMI, smoking, renal failure, puncture access, duration of the procedure, number of diseased vessel(s), final TIMI flow, creatine phosphokinase peak, LVEF and pre-use of antithrombotic K. Interactions between BMI and procedure duration and puncture access were evaluated.

Univariate Cox analysis was made to identify predictors of 1-year CV mortality. Overweight and obese patients were grouped for analysis, and variables demonstrating a $P < 0.05$ were included in an exploratory Cox proportional hazards model to assess 1-year CV mortality. Interactions between the effect of BMI groups and independent variables on mortality (BARC 3, in-hospital heart failure, history of cancer, stroke) were calculated and included in the multivariate model when significant. $P < 0.05$ was considered significant. Statistical tests were performed using SPSS software (Version 17; SPSS, Inc., Illinois, United States).

RESULTS

Baseline characteristics and initial management

Obese patients were younger than overweight and normal weight patients [respectively 61 (51, 74) years old *vs* 64 (53, 76) and 67 (53, 79)]. They presented more CV risk factors such as hypertension, diabetes, dyslipidaemia and obstructive sleep apnoea. The main characteristics are summarised in [Table 1](#). There was no difference in medical history and infarct characteristics among the three groups. There was less use of femoral access for obese patients (51.5%) than for the other groups (60.1% and 59.5%) ($P = 0.021$).

In-hospital events and bleeding

Among the population, 150 patients (7.5%) presented a BARC 3 or 5 bleeding event. These patients were older (70.2 ± 13.9 *vs* 64.1 ± 14.73 , $P < 0.001$) and the use of femoral access was higher (71.5% *vs* 56.6%, $P = 0.001$). Normal weight patients had higher rates of BARC 3 and 5 bleeding than overweight and obese patients (9.5% *vs* 6.2% and 6.2%, $P = 0.031$) ([Table 2](#)). Independent variables associated with in-hospital BARC 3 or 5 bleeding were duration of the procedure, puncture access and LVEF ([Table 3](#)). The other in-hospital outcomes were not different among the three groups.

Cardiovascular mortality

One-year CV mortality was significantly lower for BMI ≥ 25 kg/m² (5.3% and 7.1%) patients than for normal weight patients (10.8%) with $P = 0.001$ ([Table 2](#)). Independent variables associated with 1-year CV mortality were age, prior myocardial infarction, prior stroke, cancer, creatine phosphokinase peak, in-hospital heart failure and BARC 3 bleeding ([Table 4](#)). BMI was not an independent variable in this multivariate analysis although there was an interaction between BARC 3 and BMI (HR: 2.58, 95%CI: 1.44-4.64, $P = 0.001$), demonstrating BARC 3 bleeding to have a stronger clinical impact among normal weight patients (HR: 2.97, 95%CI: 1.61-5.5, $P < 0.001$) than for BMI ≥ 25 kg/m² patients (HR: 1.94, 95%CI: 1.02-3.69, $P = 0.041$) ([Figure 2](#)).

DISCUSSION

The 1-year cardio-vascular mortality of patients with BMI ≥ 25 kg/m² in the RIMA cohort was lower than for normal weight patients, yet BMI was not an independent predictor for mortality, while an in-hospital bleeding event was. We found a BMI ≥ 25 kg/m² to be related to the bleeding event have less of an effect on prognosis.

Population characteristics

The 416 patients in our study with BMI ≥ 30 kg/m² were younger, predominantly male and their prevalence of diabetes, hypertension and dyslipidaemia was higher. These are typical characteristics as identified in populations with acute coronary syndrome^[16], including STEMI^[17]. Nevertheless, there was no difference in regard of infarct location, reperfusion success, and LVEF.

Table 1 Baseline clinical characteristics according to body mass index

	Total <i>n</i> = 1998	BMI < 25 kg/m ² <i>n</i> = 705	25 ≤ BMI < 30 kg/m ² <i>n</i> = 877	BMI ≥ 30 kg/m ² <i>n</i> = 416	<i>P</i> value
Cardiovascular risk factors					
Age (yr)	64 (53-77)	67 (53-79) ^{ae}	64 (53-76) ^{ac}	61 (51-74) ^{ce}	< 0.001
Male	1485 (74.3)	493 (69.6) ^a	693 (79.0) ^{ac}	302 (72.6) ^c	< 0.001
Hypertension	986 (49.3)	308 (43.6) ^e	422 (48.2) ^c	257 (61.9) ^{ce}	< 0.001
Diabetes mellitus	492 (24.6)	134 (19.1) ^{ae}	211 (24.3) ^{ac}	147 (35.6) ^{ce}	< 0.001
Dyslipidaemia	1001 (50.1)	323 (45.8) ^{ae}	442 (50.8) ^{ac}	236 (57.0) ^{ce}	0.001
Smoker	708 (35.4)	261 (37) ^{ae}	299 (34.2) ^a	148 (35.8) ^e	0.006
Family history of coronary artery disease	442 (22.1)	134 (19.1) ^{ae}	210 (24.4) ^a	98 (24.0) ^e	0.032
Prior myocardial infarction	171 (8.6)	53 (7.5)	83 (9.5)	35 (8.5)	0.36
Obstructive sleep apnoea	22 (1.1)	0 (0.0) ^{ae}	10 (1.5) ^{ac}	12 (3.7) ^{ce}	< 0.001
History					
Stroke	86 (4.3)	34 (4.8)	37 (4.2)	15 (3.6)	0.4
Renal failure	59 (3.0)	21 (3.0)	29 (3.3)	9 (2.2)	0.52
Cancer	158 (7.9)	61 (8.7)	71 (8.1)	27 (6.5)	0.41
Clinical presentation					
Systolic blood pressure (mmHg)	139 (120-159)	135 (116-155) ^{ae}	140 (120-160) ^{ac}	141 (127-162) ^{ce}	< 0.001
HEMORR2HAGES score	1 (0-2)	1 (0-2)	1 (0-2)	1 (0-2)	0.09
CRUSADE score	24 (14-37)	29 (18-42) ^{ae}	21 (12-33) ^{ac}	18 (9-33) ^{ce}	< 0.001
Infarct characteristics					
Time from symptoms to first medical contact (h)	2.25 (1-5.5)	2.3 (1.2-5.7)	2 (1-4) ^c	2 (1-6) ^c	0.024
Time from symptoms to admission (h)	3 (1.9-6.5)	3.1 (2-6.3)	2 (1-6) ^c	3 (2-7) ^c	0.025
Anterior infarction	820 (41)	294 (41.6)	362 (41.3)	166 (40.2)	0.57
Multivessel disease	1003 (53)	356 (53.2)	433 (52.5)	217 (54.5)	0.75
Femoral access	1017 (57.5)	365 (59.5) ^e	463 (58.7) ^c	191 (51.5) ^{ce}	0.021
Duration of the angioplasty procedure (min)	39 (22-60)	40 (22-59)	38 (22-60)	40 (21-60)	0.8
Fibrinolysis	307 (15.4)	100 (14.1)	153 (17.4)	55 (13.3)	0.06
Final TIMI 3 flow	1508 (92.8)	527 (92.5)	670 (93.3)	314 (92.4)	0.7
LVEF (%)	50 (40-55)	47 (36-58)	49 (38-59)	48 (38-59)	0.09
Creatine phosphokinase peak (UI/L)	1404 (606-2675)	1374 (520-2565) ^e	1367 (626-2711)	1526 (728-2683) ^e	0.048
Prior medication					
Antivitamin K	62 (3.1)	21 (3)	29 (3.3)	12 (2.9)	0.91
In-hospital medication					
Aspirin	1964 (98.3)	696 (98.9)	863 (98.6)	408 (98.8)	0.95
Clopidogrel	1777 (88.9)	627 (89.1)	786 (89.9)	367 (88.9)	0.74
Prasugrel	223 (11.2)	75 (11.5)	95 (11.4)	53 (13.6)	0.48
Antivitamin K	35 (1.8)	13 (1.9)	12 (1.4)	10 (2.4)	0.4
LMWH	1481 (74.1)	511 (72.7)	671 (76.7)	302 (73.3)	0.06
UFH	454 (22.7)	166 (23.6)	180 (20.6)	108 (26.2)	0.06
LMWH + UFH	198 (9.9)	71 (10.1)	78 (8.9)	49 (11.9)	0.25
Bivalirudin (since 2010, for information)	136	55	55	26	0.41

Data given as number (%) or median (interquartile range).

^a*P* < 0.05 to compare body mass index (BMI) < 25 kg/m² with BMI between 25 kg/m² and 30 kg/m²;^c*P* < 0.05 to compare BMI between 25 kg/m² and 30 kg/m² with BMI ≥ 30 kg/m²;^e*P* < 0.05 to compare BMI < 25 kg/m² with BMI ≥ 30 kg/m². BMI: Body mass index; LVEF: Left ventricular ejection fraction; LMWH: Low molecular weight heparin; TIMI: Thrombolysis in Myocardial Infarction; UFH: Unfractionated heparin.

The obesity paradox

Bucholz *et al*^[18] studied 2334 patients with an infarction in the PREMIER registry. The 4-year mortality was 24.1% for normal weight patients, 17.2% for overweight patients and 12.4% for obese patients. The increase of 1 BMI point in the RICO cohort led to a reduction of 5% in the risk of death after one-year [OR: 0.95, (0.93-0.98), *P* < 0.001]^[19]. Despite a higher coronary risk, in-hospital and one-year mortality was lower for

Table 2 In-hospital and one-year events

	Total	BMI < 25 kg/m ²	25 ≤ BMI < 30 kg/m ²	BMI ≥ 30 kg/m ²	P value
	n = 1998	n = 705	n = 877	n = 416	
In-hospital events					
Duration of hospitalisation in intensive care (d)	5 (3-7)	5 (4-7)	5 (3-7)	5 (3-6)	0.21
Heart failure	417 (20.9)	153 (21.7)	176 (20.1)	89 (21.5)	0.56
Stent thrombosis	38 (1.9)	19 (2.5)	11 (1.3)	8 (1.9)	0.16
Atrial fibrillation	196 (9.8)	75 (10.6)	92 (10.5)	29 (7.0)	0.06
Stroke	39 (2.0)	14 (2)	19 (2.2)	6 (1.4)	0.65
Tamponade	22 (1.1)	10 (1.4)	7 (0.8)	5 (1.2)	0.56
Mortality	115 (5.8)	54 (7.6) ^{ac}	43 (4.9) ^a	18 (4.3) ^e	0.018
Cardiovascular mortality	112 (5.6)	54 (7.6) ^{ac}	40 (4.6) ^a	18 (4.3) ^e	0.013
In-hospital bleeding events					
Input Haemoglobin (g/dL)	14.4 (13.3-15.5)	14.1 (13-15.3) ^{ac}	14.6 (13.5-15.6) ^a	14.7 (13.5-15.7) ^e	< 0.001
Haemoglobin drop (g/dL)	1.9 (0.9-2.9)	2 (1-3.2) ^{ac}	1.7 (0.8-2.9) ^a	1.8 (0.9-2.7) ^e	0.016
Input haematocrit (%)	42.6 (39.6-45.5)	42 (38.9-44.9) ^{ac}	42.8 (40-45.8) ^a	43.3 (40.2-45.6) ^e	< 0.001
Haematocrit drop (%)	5.3 (2.8-8.4)	6.1 (3.1-9.3) ^{ac}	5 (2.6-8.1) ^a	4.9 (2.8-7.8) ^e	< 0.001
Haemorrhagic stroke	9 (0.5)	6 (0.8)	3 (0.3)	0 (0.0)	0.07
Gastrointestinal bleeding	25 (1.3)	12 (1.7)	8 (0.9)	5 (1.2)	0.45
Haematoma at the puncture site	138 (6.9)	56 (7.9)	58 (6.6)	24 (5.8)	0.22
Surgical repair of the haematoma	9 (0.5)	3 (0.4)	4 (0.5)	2 (0.5)	0.98
Use of amines in bleeding	33 (1.7)	18 (2.5)	10 (1.1)	6 (1.4)	0.13
Transfusion	82 (4.1)	42 (5.9) ^a	25 (2.9) ^a	15 (3.6)	0.011
Fatal bleeding (BARC 5)	9 (0.5)	6 (0.8)	2 (0.2)	1 (0.2)	0.17
BARC 3 or 5	146 (7.3)	67 (9.5) ^{ac}	54 (6.2) ^a	26 (6.2) ^e	0.031
One-year events					
Mortality	198 (9.9)	93 (13.1) ^{ac}	82 (9.4) ^{ac}	23 (5.5) ^{ce}	< 0.001
CV mortality	160 (8.0)	76 (10.8) ^{ac}	62 (7.1) ^a	22 (5.3) ^e	0.001

^aP < 0.05 to compare body mass index (BMI) < 25 kg/m² with BMI between 25 kg/m² and 30 kg/m²;

^cP < 0.05 to compare BMI between 25 kg/m² and 30 kg/m² with BMI ≥ 30 kg/m²;

^eP < 0.05 to compare BMI < 25 kg/m² with BMI ≥ 30 kg/m². BARC: Bleeding Academic Research Consortium; BMI: Body mass index; CV: Cardiovascular.

patients with BMI ≥ 25 kg/m².

Several theories have been developed to explain this phenomenon. One hypothesis is that thin patients are older and have more comorbidities than overweight patients, notably in term of higher prevalence of cancer. This hypothesis was developed by Witassek *et al*^[20] in the Swiss AMIS Plus registry. The prevalence of history of cancer among the three groups in the RIMA appeared to be similar, despite the fact that normal weight patients were older. Other explanations have been put forward, such as obtaining targeted and adapted therapeutic doses in overweight and obese patients, which was not the case for thin patients^[4,9], particularly regarding anticoagulants^[16].

In our study, factors conducive to 1-year cardio-vascular mortality were age, history of infarction or stroke; history of cancer, creatine phosphokinase peak, in-hospital heart failure, and a BARC 3 in-hospital haemorrhagic event. While BMI did not appear to be an independent factor for mortality *per se*, BMI was an effect modifier of the impact of haemorrhagic complications. Of note, bleeding events were more frequent among BMI < 25 kg/m² patients compared to others (Table 2).

Haemorrhagic complications

The prevalence for bleeding events varies in the literature from 3.9% in a GRACE-derived report^[21] to 22% in a STEMI cohort^[22]. In our study, we defined bleeding events by the BARC scoring system, which is robust and takes into account quantitative parameters such as a haemoglobin drop. Consequently, we reported a bleeding prevalence of 7.3% in the RIMA cohort; and we showed this prevalence to be higher among normal weight patients than among the other groups. Das *et al*^[17] found the same relationship in 49329 patients with STEMI, as already reported by other sources^[4,6,19,23-26]. The main location of bleeding events was at the puncture site.

Table 3 Predictor of Bleeding Academic Research Consortium 3 and 5 bleeding by univariate and multivariate analysis

	Univariate analysis	Multivariate analysis	Odds ratio (95%CI)
	P value	P value	
Male	0.001	0.19	
Age (per decade)	< 0.001	0.08	
Hypertension	0.001	0.18	
BMI < 25 kg/m ²	0.006	0.75	
Smoker	0.005	0.31	
Renal failure	0.032	0.77	
Radial puncture access	0.001	0.036	0.54 (0.3-0.96)
Duration of the procedure	< 0.001	0.004	1 (1-1.01)
Multivessel disease	0.003	0.76	
Final TIMI flow	0.005	0.46	
Creatine phosphokinase peak (per 500 UI/L)	< 0.001	0.15	
Left ventricular ejection fraction	< 0.001	0.017	0.97 (0.94-0.99)
Antivitamin K use before	0.016	0.48	

BMI: Body mass index; TIMI: Thrombolysis in myocardial infarction.

According to Hamon *et al*^[8], predictive factors for haemorrhagic complications are being female, low weight (BMI < 19 kg/m²), aged 75 or more, severe renal failure, history of stroke and uncontrolled arterial hypertension. Indeed, pharmacokinetics of anticoagulants may be driven by body composition, as patients with a lower ratio of lean body mass are exposed to supra-therapeutic dose of anticoagulants. Moreover, the management of antiplatelet therapy being mostly unadjusted to body weight, normal weight patients may receive relatively greater doses. In the present study, independent correlates to bleeding events were longer procedure duration, lower LVEF and a femoral puncture site. Of note, a femoral puncture site was responsible for higher rates of bleeding events BARC 3 or 5 (Figure 2). It should be noted that a femoral puncture site was responsible for higher rates of BARC 3 or 5 bleeding events (Table 3)^[27].

These bleeding complications are also associated with a more severe prognosis in normal weight patients than for other patients (Figure 2). The originality of this report was the evidence of lower prevalence and a poorer prognostic impact of bleeding complications in normal weight patients (Figure 3). Special concerns should be given to the management of antithrombotic therapies, including following drug requirements, stopping anticoagulants early after effective angioplasty^[28], avoiding changing anticoagulants several times^[29], and encouraging low-risk strategies when invasive management is uncertain^[30]. Even though the benefits of newer antiplatelet therapy is unquestionable in terms of prevention of stent thrombosis, a switch to clopidogrel – as soon as one month after angioplasty – may lower bleeding events^[31].

Limitations

However, there are limits to this real-life cohort study. It only included hospitalised patients, leading to a bias in the recruitment of survivors. The BMI is not the best criterion for evaluating abdominal obesity, our study did not include a measurement of the waist size and the waist-to-hip ratio, and did not take into account for confounders like chronic inflammatory disease or coagulation disorder in the database.

In conclusion, in the present study, we show in-hospital bleeding to be more prevalent amongst normal weight patients (BMI < 25 kg/m²) with greater impact on prognosis. Normal weight did not impact on one-year CV mortality *per se*, but increased the effect of bleeding on mortality. Here, we raise one explanatory hypothesis of the obesity paradox, with in-hospital bleeding in BMI ≥ 25 kg/m² patients related to lower impact on one-year mortality after STEMI.

Table 4 Predictor of one-year cardiovascular mortality by univariate and multivariate analysis

	Univariate analysis	Multivariate analysis	Hazard ratio (95%CI)
	<i>P</i> value	<i>P</i> value	
Male	< 0.001	0.5	
Age (per decade)	< 0.001	< 0.001	1.56 (1.31-1.87)
Hypertension	< 0.001	0.28	
BMI < 25 kg/m ²	< 0.001	0.5	
Smoker	< 0.001	0.62	
Diabetes mellitus	0.042	0.71	
Prior myocardial infarction	0.011	0.015	1.91 (1.13-3.22)
Stroke history	< 0.001	0.011	2.07 (1.17-3.64)
Renal failure	< 0.001	0.43	
Cancer	0.002	0.02	1.83 (1.09-3.06)
Radial puncture access	< 0.001	0.06	
Creatine phosphokinase peak (per 500 UI/L)	0.003	< 0.001	1.05 (1.03-1.07)
In-hospital heart failure	< 0.001	< 0.001	5.29 (3.44-8.13)
BARC 3 among BMI < 25 kg/m ²	< 0.001	< 0.001	2.97 (1.61-5.5)
BARC 3 among BMI ≥ 25 kg/m ²	< 0.001	0.041	1.94 (1.02-3.69)

BARC: Bleeding Academic Research Consortium; BMI: Body mass index; TIMI: Thrombolysis in myocardial infarction.

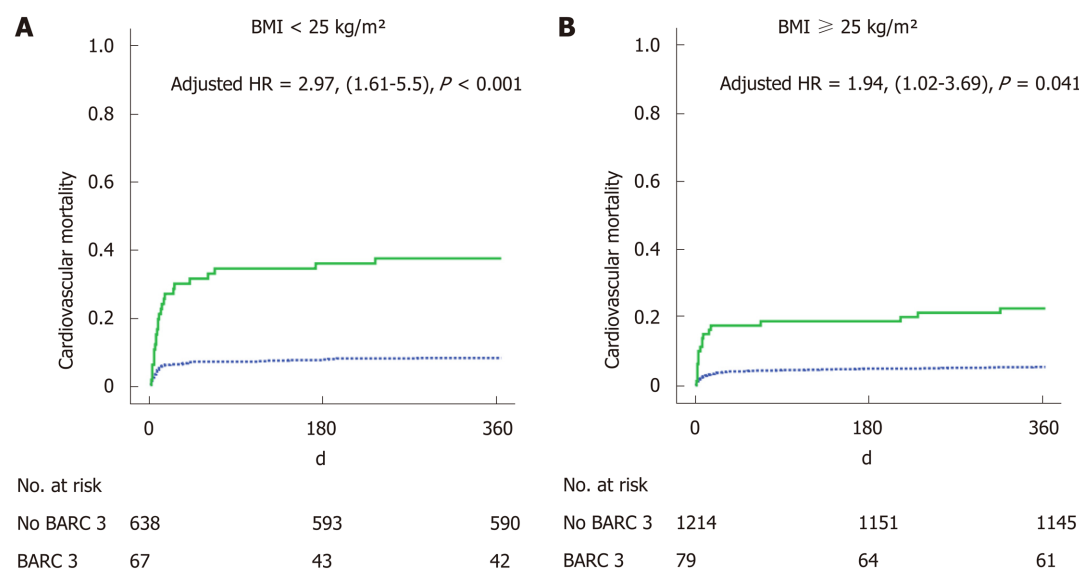


Figure 2 Time-to-event curves for the primary end-point. A: Occurrence of 1-year cardiovascular mortality according to Bleeding Academic Research Consortium (BARC) 3 in body mass index (BMI) < 25 kg/m² patients; B: Occurrence of 1-year cardiovascular mortality according to BARC 3 in BMI ≥ 25 kg/m² patients. BARC: Bleeding Academic Research Consortium; BMI: Body mass index; HR: Hazard ratio.

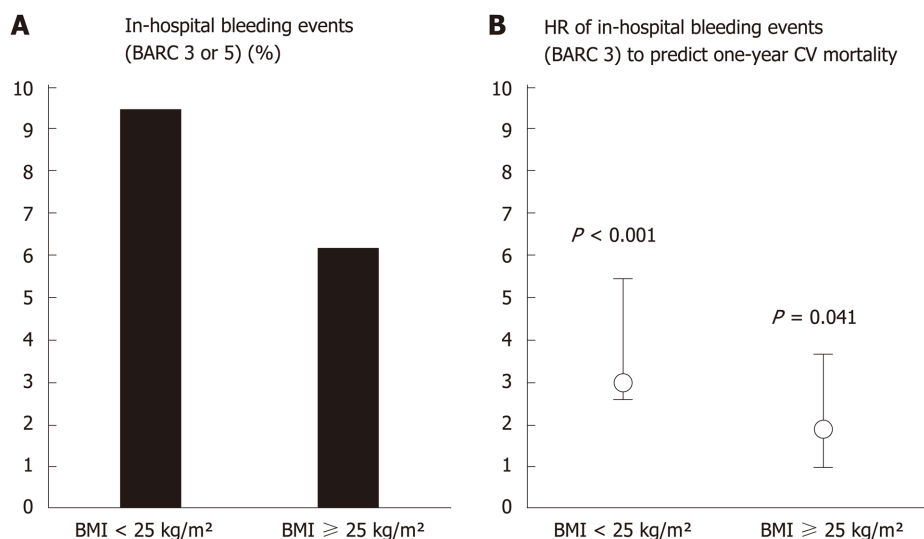


Figure 3 Bleeding events and prognosis. A: In-hospital bleeding events [Bleeding Academic Research Consortium (BARC) 3 or 5] prevalence; B: Hazard ratios (HR) of in-hospital bleeding event (BARC 3) to predict one-year cardiovascular mortality. *P* values for HR in each body mass index subgroup. BARC: Bleeding Academic Research Consortium; BMI: Body mass index; CV: Cardiovascular; HR: Hazard ratio.

ARTICLE HIGHLIGHTS

Research background

ST-segment elevation myocardial infarction (STEMI) remains a major cause of mortality despite early revascularization and optimal medical therapy. Tailoring individual management by considering patients' specificities may help in improving post-STEMI survival.

Research motivation

While overweight and obesity are correlated with common cardiovascular (CV) risk factors and outcomes, overweight and obese patients present better survival after suffering from myocardial infarction. This obesity paradox is not elucidated.

Research objectives

To assess whether the obesity paradox might be explained by bleeding events after a first STEMI.

Research methods

We studied 2070 patients consecutively from the "Registre d'Infarctus Maine-Anjou" survey, that prospectively included all patients presenting with a STEMI in a Western region of France, in which the only available 24 h-7 d coronary angiography service was in Angers University Hospital. Median age was 64 (interquartile range 53-77) years, 74.3% were male, 41% presented with anterior infarction and 81% underwent primary percutaneous coronary intervention. Outcomes were gathered during the year following MI. Bleeding Academic Research Consortium (BARC) 3 and 5 bleeding events were used to assess in-hospital bleeding complications. Cox regression analyses were performed to assess correlates for 1-year mortality.

Research results

One-year CV mortality was significantly lower for body mass index (BMI) ≥ 25 kg/m² (5.3% and 7.1%) patients than for normal weight patients (10.8%) with *P* = 0.001. Independent variables associated with 1-year CV mortality were age, prior myocardial infarction, prior stroke, cancer, creatine phosphokinase peak, in-hospital heart failure and BARC 3 bleeding. BMI was not an independent variable in this multivariate analysis although there was an interaction between BARC 3 and BMI (HR: 2.58, 95%CI: 1.44-4.64, *P* = 0.001), demonstrating BARC 3 bleeding to have a stronger clinical impact among normal weight patients (HR: 2.97, 95%CI: 1.61-5.5, *P* < 0.001) than for BMI ≥ 25 kg/m² patients (HR: 1.94, 95%CI: 1.02-3.69, *P* = 0.041).

Research conclusions

We show in the present study the role that in-hospital bleeding may play in the obesity paradox. Indeed, not only in-hospital bleeding events were lower among overweight patients, but also presented a weaker impact on 1-year CV mortality. The results of this study first suggest a need to adjust antithrombotic therapies in normal weight patients. Lowering doses to lower bleeding events must be balanced with anti-ischemic efficacy. Second, the reasons why intra-hospital bleeding presents a lower impact on overweight patients raise question and need further investigation.

Research perspectives

Randomized control trials are needed to better monitor anti-thrombotic therapies in STEMI patients. Beside age, gender and clinical presentation, BMI might be a valuable feature to assess.

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Phrenic nerve displacement by intrapericardial balloon inflation during epicardial ablation of ventricular tachycardia: Four case reports

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Abstract

BACKGROUND

Phrenic nerve (PN) injury is one of the recognized possible complications following epicardial ablation of ventricular tachycardia (VT). High-output pacing is a widely used maneuver to establish a relationship between the PN and the ablation catheter tip. An absence of PN capture is usually considered an indication that it is safe to ablate, and that successful ablation may be performed at adjacent sites. However, PN capture may impact the procedural outcome. Only a few cases have been reported in the literature that avoid PN injury by using different techniques.

CASE SUMMARY

Three patients with a previous history of myocarditis and one patient with ischemic cardiomyopathy underwent epicardial ablation for drug-refractory VT. Before the procedure, transthoracic echocardiogram, coronary angiogram, and cardiac magnetic resonance imaging were performed on all patients. Under general anesthesia, endo/epicardial three-dimensional anatomical and substrate maps of the left ventricle were accomplished. Before radiofrequency delivery, the course of the PN was identified by provoking diaphragmatic stimulation with high-output pacing from the distal electrode of the ablation catheter. In every case, a scar region with late potentials was mapped along the PN course. After obtaining another epicardial access, a second introducer sheath was placed, and a vascular balloon catheter was inserted into the epicardial space and inflated with saline solution to separate the PN from the epicardium. Once the absence of PN capture had been proven, radiofrequency was applied to aim for complete late potential elimination and avoid VT induction.

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CONCLUSION

PN injury can occur as one of the complications following epicardial VT ablation procedures, and may prevent successful ablation of these arrhythmias. PN displacement by using large balloon catheters into the epicardial space seems to be feasible and reproducible, avoid procedure-related morbidity, and improve ablation success when performed in selected centers and by experienced operators.

Key words: Catheter ablation; Epicardial access; Myocarditis; Nonischemic cardiomyopathy; Ventricular tachycardia; Phrenic nerve; Case series

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Core tip: Epicardial ventricular tachycardia ablation procedures are constantly increasing in number. Among the complications potentially carried by this approach, Phrenic nerve (PN) injury can be prevented using certain precautions. However, when ablation is at risk of being unsuccessful due to PN proximity, there are some helpful tips and tricks available. We herein present a case series of epicardial ablation of ventricular tachycardia, in which PN displacement was necessary to successfully eliminate the arrhythmia. This case series highlights the importance of an accurate definition of PN course, and reports upon the feasibility of PN displacement through use of a vascular balloon placed into the epicardial space.

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INTRODUCTION

Phrenic nerve (PN) injury is one of the recognized possible complications following catheter ablation procedures. Although uncommon, PN injury can result in permanent paralysis of the diaphragm. The symptoms of diaphragmatic palsies can vary from asymptomatic to cough, dyspnea, recurrent pneumonia, and severe respiratory dysfunction requiring mechanical ventilation. The severity of clinical presentation primarily depends upon the degree of PN injury and underlying lung capacity. PN injury has been reported after endocardial catheter ablation of atrial fibrillation^[1], atrial tachycardia^[2], inappropriate sinus tachycardia^[3], left-sided accessory pathways^[4], and epicardial ablation of ventricular tachycardia (VT)^[5-7]. In particular, the increasing number of epicardial VT ablations^[8] could increase the risk of PN injury, given that the left PN is in direct contact with the epicardial surface. The course of the PN is usually determined by eliciting diaphragmatic contraction through high-voltage output pacing, and which can be viewed using one of the available 3D electroanatomical mapping (3D-EAM) systems^[9]. Different techniques for avoiding PN injury have been reported, including introduction of air and/or saline into the pericardial space, or introduction of a deflectable sheath as well as different types of large balloons^[10]. We have reported our single-center experience of epicardial VT ablation procedures, where the use of a valvuloplasty balloon catheter successfully prevented PN injury.

CASE PRESENTATION

Electrophysiologic study and catheter ablation

After informed consent was obtained, three patients underwent epicardial ablation for drug-refractory VT under general anesthesia. Intracardiac catheters were inserted *via* the right and left femoral veins, and included a 6F decapolar catheter placed into the coronary sinus, a 6F quadripolar catheter placed into the right ventricular apex, a standard multipolar or a high-definition mapping catheter (LiveWire 2-2-2 or Advisor

HD Grid, Abbott, Medical, United States), an ablation catheter, and an intracardiac echo probe (AcuNav, Siemens). Invasive blood pressure was monitored from the right femoral artery. The EnSite Precision™ electroanatomical mapping system (Abbott Medical, United States) was used to create endo/epicardial geometries, substrates, and activation maps. Epicardial access was obtained by subxiphoid pericardial puncture, as described elsewhere^[11]. Once an epicardial map was obtained and the area of interest identified, a coronary angiogram was performed upon all patients in order to show the safety distance between the coronary arteries and the scar region. Then, in order to prevent PN injury, the course of the PN was identified by provoking diaphragmatic stimulation with high-output pacing from the distal electrode of the ablation catheter. The locations of PN capture were marked on the 3D-EAM. Considering the close relationship between the area of interest and the PN, we decided to displace the PN in order to increase its distance from the ablation catheter. We then obtained another epicardial access in order to insert a 12F introducer sheath with a hydrophilic coating (Sentrant, Medtronic) (Figure 1A and B). In every case, an 18 mm × 40 mm percutaneous transluminal balloon aortic and pulmonic valvuloplasty catheter (Nucleus-X, Braun Medical) was inserted and inflated with saline solution to separate the PN from the epicardium (Figure 2A and B). Finally, high-output pacing was repeated to reassess PN capture. Radiofrequency (RF) was delivered using a 3.5 mm open irrigated tip ablation catheter (FlexAbility SE, Abbott Medical, United States) and an Agilis EPI steerable epicardial sheath (Abbott Medical, United States). The energy setting was 40-50 W, 43 °C maximum temperature, 17 mL/min ablation catheter flow rate. Successful RF ablation was defined as the complete elimination of all LPs, and the inability to induce VTs with programmed stimulation. A final remap was performed to assess the complete elimination of LPs. After completion of RF delivery, the valvuloplasty balloon catheter was deflated and removed. PN capture was tested after ablation. Following the procedure, the absence of fluid in the pericardial space was confirmed by the intracardiac echo.

Patient 1

A 32-year-old woman with a prior history of myocarditis and a subcutaneous implantable cardioverter defibrillator (S-ICD) presented at the Emergency Department of our hospital after three syncope and S-ICD shocks. The 12-lead ECG showed a VT with a CL of 230 ms and right bundle inferior axis (RBIA) morphology (Figure 3). Echocardiogram showed a normal LV ejection fraction (LVEF) of 55%. Coronary angiogram showed no significant coronary artery disease. Cardiac magnetic resonance imaging (MRI) showed an LVEF of 50%. Moreover, MRI showed intramural and transmural late-gadolinium enhancement (LGE) in the basal anterolateral LV wall and sub-epicardial LGE in the mid-basal lateral wall (Figure 4). Electrophysiological (EP) study with 3D-EAM of the epicardium was performed as described above. In concordance with the MRI findings, we found a mid-basal lateral epicardial scar, and LPs were identified within the epicardial scar (Figure 5A and B). After the angiogram, high-output pacing was performed to assess PN capture. The scar region was along the PN course (Figure 6). Through the second epicardial access, we inserted another sheath and the valvuloplasty balloon in the epicardial space. Once the balloon was inflated in the epicardial space, high-output pacing was repeated without PN capture. RF was delivered along the scar region, aiming for complete LP elimination with no complications (Figure 7). Once the lesion set was considered complete, the valvuloplasty balloon was deflated and removed. Programmed ventricular stimulation was performed up to three extrastimuli without induction of ventricular arrhythmia. No VT were reported to have recurred within the 2 years of follow-up.

Patient 2

A 56-year-old woman with no previous cardiac history presented to our Centre with a hemodynamically-tolerated VT with an RBIA morphology and CL 320 ms (Figure 8). The VT was converted to sinus rhythm after an intravenous bolus of amiodarone. Transthoracic echocardiogram and coronary angiogram were both normal. However, the MRI showed a subepicardial scar in the basal lateral-posterolateral LV wall with LGE, which was compatible with myocarditis. During the EP study, the clinical VT was induced by programmed ventricular stimulation. At first, an endocardial ablation was attempted in the basal posterolateral LV, but it was unsuccessful. Therefore, we obtained epicardial access and, in concordance with the MRI findings, we found a basal posterolateral epicardial scar with LPs (Figure 9). As per the protocol, we performed a coronary angiogram that showed enough distance between the coronary arteries and the scar. We observed PN capture along the scar, and LPs were located along its course. Following the same procedural steps, we inserted the second epicardial sheath and the balloon facing the PN. Once the balloon was inflated, an

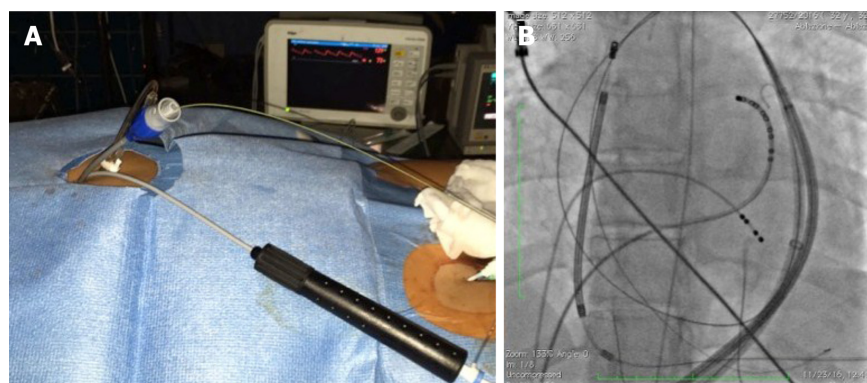


Figure 1 Epicardial access to insert a 12F introducer sheath with a hydrophilic coating. A: Secondary epicardial access and introduction of 12F introducer sheath with a hydrophilic coating; B: Fluoroscopy image of the second wire and introducer in the epicardial space.

absence of PN was noted and all LPs could be targeted and eliminated. After successful RF delivery, the balloon was deflated and removed. Programmed ventricular stimulation demonstrated no acute VT inducibility, and no VT recurrences have been documented within the 1-year follow-up.

Patient 3

A 46-year-old man with a previous history of myocarditis and implantable cardioverter defibrillator implantation was admitted to our Emergency Department because of intense palpitations lasting up to 2 h. The 12-lead ECG showed a hemodynamically-tolerated VT with an RBIA morphology and CL 300 ms. After ineffective intravenous amiodarone, VT was converted to sinus rhythm through the use of a 200J DC shock. Echocardiography showed an LVEF of 50%, and a coronary angiogram showed normal coronary arteries. Cardiac MRI showed a subepicardial scar in the basal lateral LV wall with sub-epicardial LGE in the mid-basal anterolateral wall. An endo-epicardial substrate map revealed a scar in the mid-basal lateral and posterolateral LV wall, with LPs along the border zone of the mid-basal posterolateral scar and along the mid-basal lateral wall (Figure 10). PN capture was documented along the scar and in the LP region. Once again, after obtaining secondary epicardial access, the balloon was inserted and positioned to avoid PN capture, and RF was delivered along the entire extension of the scar (Figure 11). The final remap showed no more signs of LPs, and programmed ventricular stimulation showed no VT inducibility. The patient had not reported any VT recurrences at the time of the 9-mo follow-up.

Patient 4

A 66-year-old man with a previous history of ischemic cardiomyopathy, implantable cardioverter defibrillator, and previous endocardial VT ablation was admitted to our Centre because of several ICD therapies noted during the remote monitoring follow-up. The 12-lead ECG showed normal sinus rhythm. Echocardiography showed an LVEF of 30%, and a coronary angiogram did not show new coronary artery lesions. An epicardial substrate map revealed a scar in the infero-postero-lateral mid-basal LV wall, with LPs along the border zone of the scar (Figure 12). PN capture was documented along the scar and in the LP region. The same approach was used to avoid PN injury (Figure 13). After obtaining secondary epicardial access, the balloon was inserted and positioned in order to avoid PN capture. Two slightly different morphologies of VT were induced by ventricular programmed stimulation, and RF was delivered with VT termination (Figure 14 and 15). The final remap showed no more LPs, and programmed ventricular stimulation showed no VT inducibility. The patient had not reported any VT recurrences at the time of the 3-mo follow-up.

DISCUSSION

PN injury is a recognized complication of catheter ablation procedures, and has been reported following ablation of atrial, supraventricular, and VT and with multiple ablation modalities including RF, cryoballoon ablation, and LASER^[1-7]. Particularly notable is the left PN that runs along the lateral LV wall before inserting in the diaphragm^[12]. Due to the left PN course and the increasing number of epicardial VT

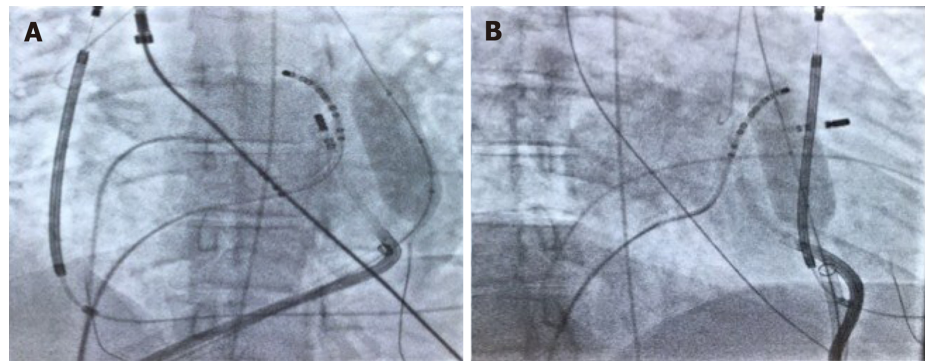


Figure 2 Patient 1: The vascular balloon was inflated to displace the phrenic nerve. A: Right anterior oblique 30 degrees; B: Left anterior oblique 30 degrees.

ablations, it will not be uncommon to deal with the potential risk of PN injury in the future. In order to avoid PN complications, a common precaution is to establish the proximity of the ablation catheter tip in relation to the PN course. This is typically performed using high-output pacing, and includes 3D tags into the EAM in order to create a visual representation of the distance between the tip of the ablation catheter and the PN course. However, ablation in an area close to the PN is sometimes necessary, and different techniques have been described to avoid PN injury, such as the introduction of air and/or saline into the pericardial space, or introduction of a second deflectable sheath and different types of large balloons. Table 1 summarizes all cases reported in the literature of epicardial VT ablation, in which PN was displaced using various types of large balloons in the pericardial space. Buch *et al*^[13] described the first case in 2007 in a 78-year-old patient with ischemic cardiomyopathy and drug-refractory VT originating from the epicardial posterosuperior aspect of the LV. They used an 18 mm × 40 mm dilatation catheter (Meditech, Boston Scientific) positioned close to the ablation tip obtaining PN displacement without complication^[13]. Biase *et al*^[10] reported a multicenter prospective comparison between methods for separating the PN from the epicardial surface. Interestingly, of the eight patients involved, the authors reported two cases of failure to prevent PN capture, and three cases of unsuccessful placement of the intrapericardial balloon. They found controlled “hydro-pneumopericardium” to be the best strategy for preventing PN injury during epicardial ablation^[10]. Kumar and colleagues reported the largest series. Five patients with nonischemic cardiomyopathy underwent epicardial VT ablation and effective PN displacement by using the vascular or the gastrointestinal balloon. The authors reported two complications among these patients, including a case of pleuro-pericardial fistula and moderate pericarditis, which was resolved after colchicine administration^[14]. One of the limitations of intrapericardial balloon placement is the inability to steer the balloon catheter, and the lack of support and stability. Fan *et al*^[5] found that in order to overcome these limitations, the use of a steerable outer sheath to guide balloon placement was necessary for additional support and stability^[5]. In this case series, the use of intrapericardial balloon placement was safely and successfully used to increase the distance between the PN and the ablation target area, thus eliminating PN capture with high-output pacing.

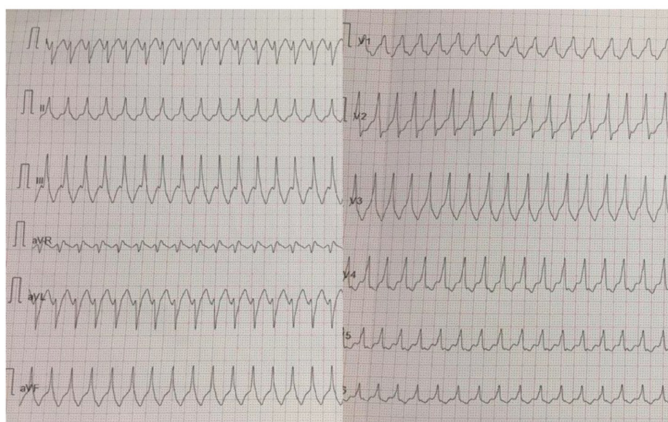
CONCLUSION

PN injury can occur as one of the complications following epicardial VT ablation procedures, and may prevent successful ablation of these arrhythmias. Although few cases have been reported in the literature, PN displacement through the use of different types of large balloon catheters in the epicardial space to separate the PN from the ventricular epicardium during epicardial VT ablation seems to be feasible and reproducible, can help to avoid procedure-related morbidity, and can improve ablation success when performed in selected Centers and by experienced operators.

Table 1 Reports published of various types of large balloons inserted into the pericardial space

Author	Number of cases	Procedure	Cardiomyopathy	Device used	Complications	Outcome
Buch E <i>et al</i> ^[13]	1	VT	ICM	18 mm × 40 mm (Meditech, Boston Scientific)	None	Arrhythmia-free at 10 mo
Biase <i>et al</i> ^[10]	2	VT	1 ICM - 1 NICM	25 mm × 40 mm (NA)	None	No VT at 9 ± 3 mo
Kumar <i>et al</i> ^[14]	5	VT	5 NICM	18 mm × 20 mm (NMT, Boston Scientific); 18-20 mm esophageal balloon (Hercules 3, Cook)	1 pleuro-pericardial fistula and pericarditis	No VT recurrence at median follow-up 13 mo
Fan <i>et al</i> ^[5]	1	VT	NICM	18 mm × 60 mm (Braun Medical)	None	No acute VT inducibility

VT: Ventricular tachycardia; ICM: Ischemic cardiomyopathy; NICM: Nonischemic cardiomyopathy.

**Figure 3** Patient 1: 12-lead ECG of ventricular tachycardia with a right bundle inferior axis morphology.**Figure 4** Patient 1: Cardiac magnetic resonance imaging showing intramural and transmural late-gadolinium enhancement in the basal anterolateral left ventricular wall and sub-epicardial late-gadolinium enhancement in the mid-basal lateral wall.

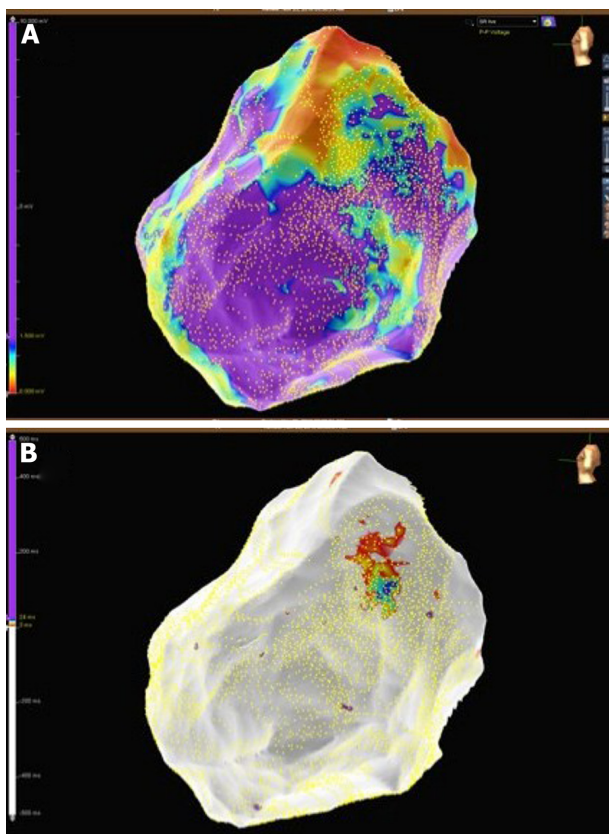


Figure 5 Patient 1: Mid-basal lateral epicardial scar and late potentials were identified within the epicardial scar. A: Epicardial substrate map showing a basal lateral scar in the left ventricle; B: Epicardial late potentials map at the border zone of the epicardial scar.

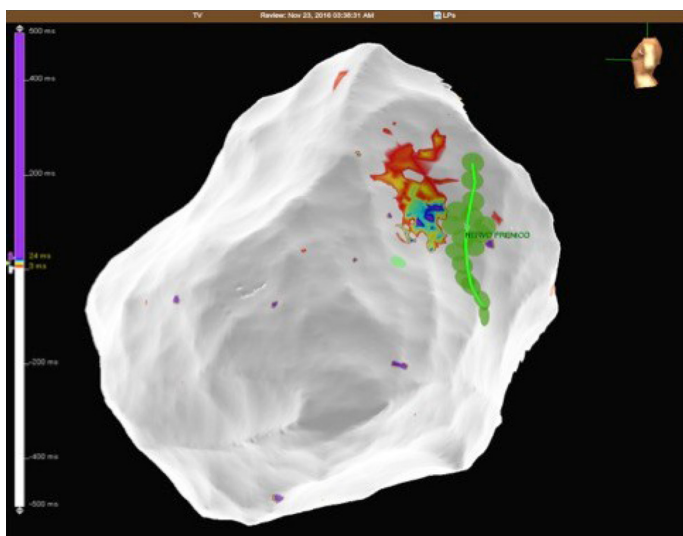


Figure 6 Patient 1: Epicardial late potentials map of the basal lateral segment of the left ventricle. The phrenic nerve course is represented with green dots.

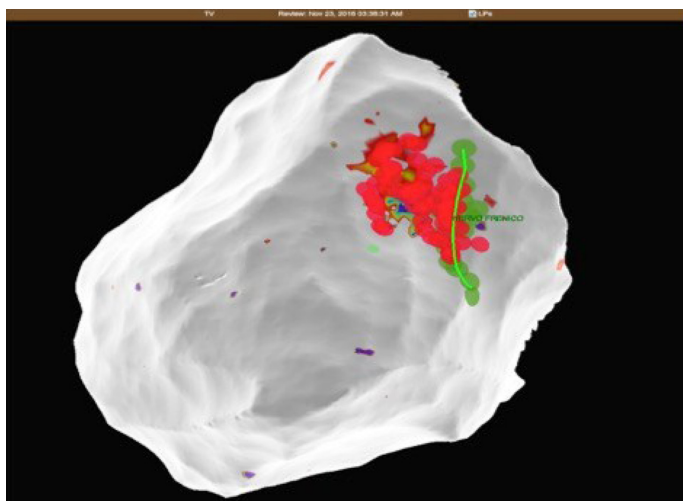


Figure 7 Patient 1: The close relationship between radiofrequency ablation points (red dots) and the phrenic nerve course (green dots and line).

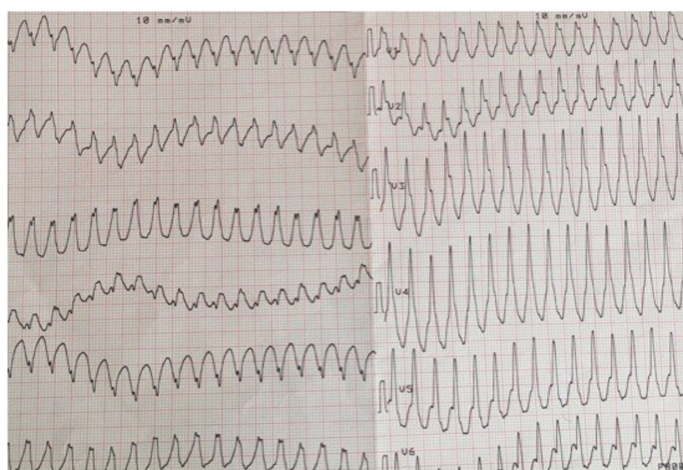


Figure 8 Patient 2: 12-lead ECG of ventricular tachycardia with a right bundle inferior axis morphology.

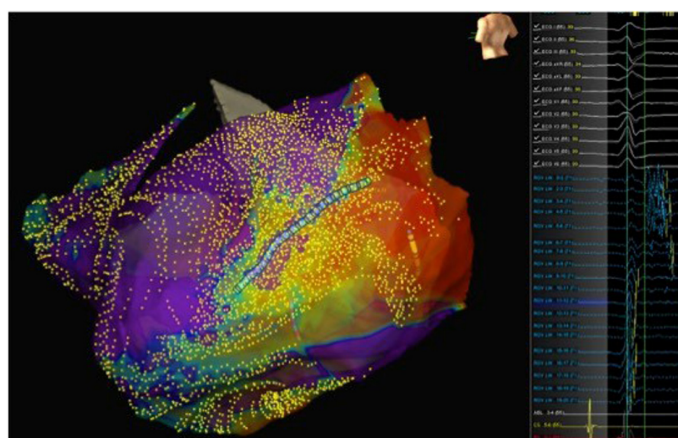


Figure 9 Patient 2: A basal posterolateral epicardial scar with late potentials. Left panel: Epicardial activation map showing late potentials on the posterolateral left ventricular wall; Middle panel: Late potentials mapped using the LiveWire mapping catheter; Right panel: Epicardial substrate map showing the basal posterolateral scar.

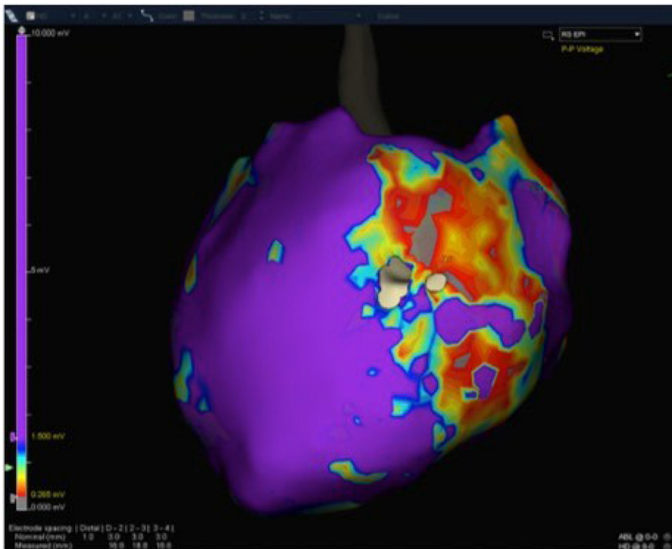


Figure 10 Patient 3: Epicardial substrate map showing a wide scar extending from the basal lateral to the mid-posterolateral left ventricle wall.

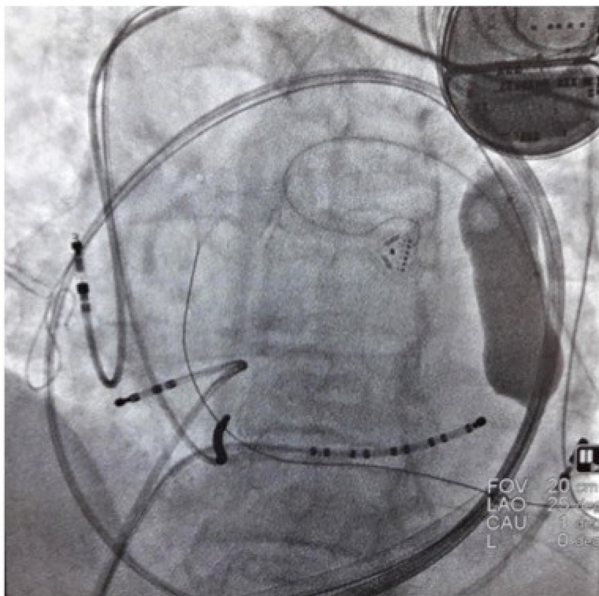


Figure 11 Patient 3: The vascular balloon has been inflated to displace the phrenic nerve (Left anterior oblique 35 degrees).

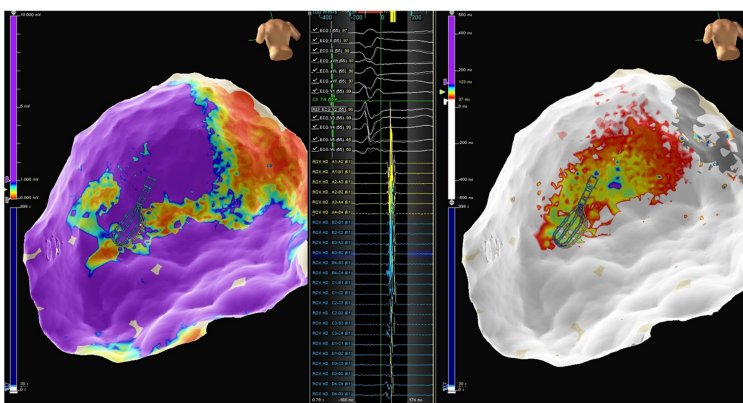


Figure 12 Patient 4. Left panel: Epicardial map showing an infero-postero-lateral mid-basal scar; Middle panel: Late potentials mapped using the Advisor HD Grid; Right panel: Epicardial activation map in sinus rhythm showing late potential around the superior aspect of the scar.

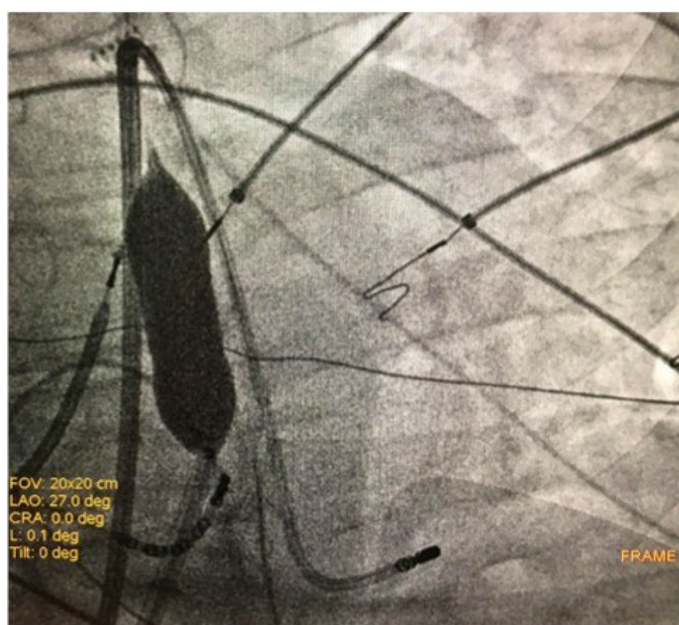


Figure 13 Patient 4: Inflation of the vascular balloon in the posterior epicardial space (Left anterior oblique 27 degrees).

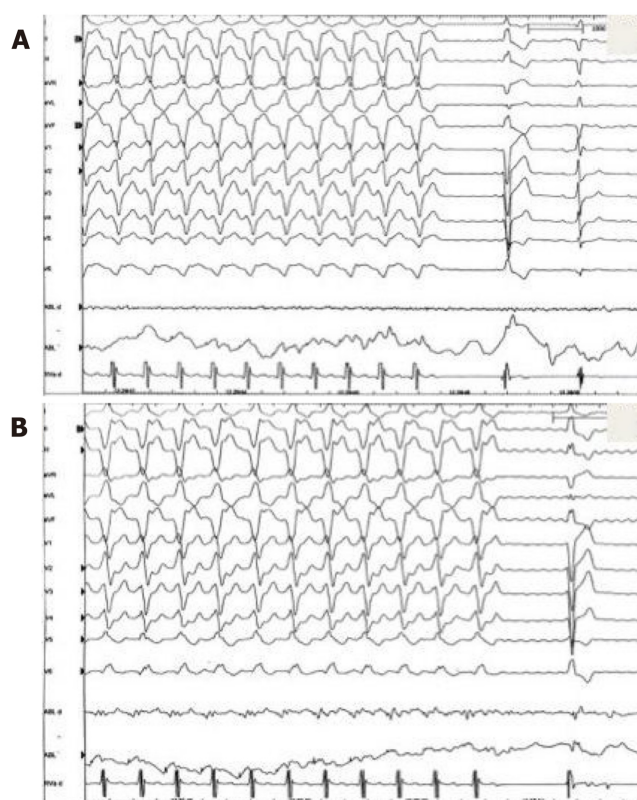


Figure 14 Patient 4: Two slightly different morphologies of VT were induced by ventricular programmed stimulation and radiofrequency was delivered with VT termination. A: First morphology of VT termination during radiofrequency delivery in the infero-lateral region; B: Second morphology of VT termination during radiofrequency delivery in the more inferior region. VT: Ventricular tachycardia.

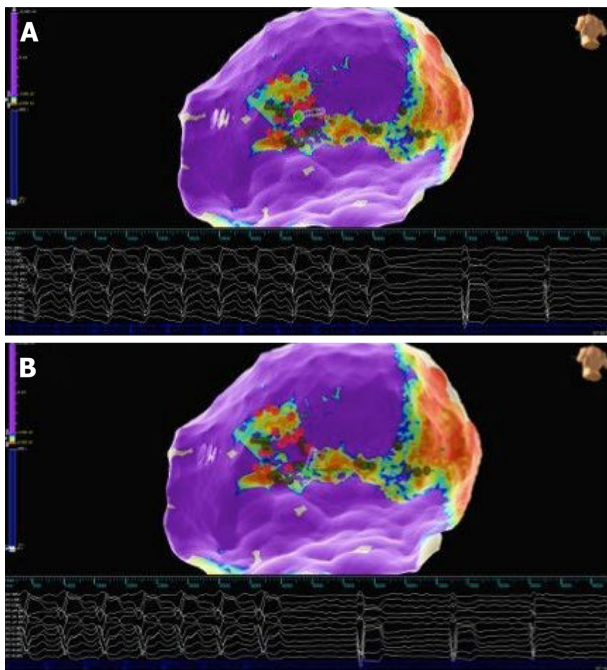


Figure 15 Patient 4: Epicardial substrate map. Red dots are tags of phrenic nerve capture areas. Green dot on the tip of the ablation catheter represents the tag of VT termination. A: First morphology of VT termination during radiofrequency delivery in the infero-lateral region; B: Second morphology of VT termination during radiofrequency delivery in the more inferior region. VT: Ventricular tachycardia.

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Salmonella typhimurium myopericarditis: A case report and review of literature

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Abstract

BACKGROUND

Non-typhoidal salmonella (NTS) is a rare, but well-established cause of myopericarditis. Presenting symptoms may be varied, however often revolve around the dual presentation of both myopericarditis and infectious diarrhoea. Given the rarity of NTS related myopericarditis, we conducted a systematic review of the literature, identifying 41 previously reported cases.

CASE SUMMARY

We present the case of an otherwise healthy 39-year old male, presenting with chest pain in the setting of documented *Salmonella typhimurium* infection. After further investigation with echocardiogram and laboratory blood tests, a diagnosis of NTS associated myopericarditis was made, and the patient received antibiotic treatment with an excellent clinical outcome. Overall, myopericarditis is rare in NTS. Although treatment for myopericarditis has not been well established, there are guidelines for the treatment of NTS infection. In our review, we found that the majority of NTS cases has been pericarditis (27/42, 64.3%), with an average age of 48.3 years, and 71.4% being male. The average mortality across all cases was 31%.

CONCLUSION

Myopericarditis is a rare, but potentially serious complication of NTS infection, associated with an increased morbidity and mortality.

Key words: *Salmonella typhimurium*; Pericarditis; Myocarditis; Myopericarditis; Non-typhoidal salmonella; Case report

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Core tip: Myopericarditis symptoms can be variable but generally presents with ischaemic sounding chest pain or pleuritic chest pain and cardiac biomarker elevation (troponin I and T). Non-typhoidal salmonella (NTS) generally presents as a non-bloody infectious diarrhoea. *Salmonella enterica* has multiple subtypes, with *Salmonella typhi* and *paratyphi* causing typhoid fever. However, there are a large number of NTS, which may include *Salmonella choleraesuis*, *enteritidis*, and *typhimurium*. Relevant investigations may consist of laboratory blood tests, electrocardiogram, echocardiography, coronary angiography, cardiac magnetic resonance imaging, cardiac biopsy, and faecal culture for *Salmonella*. *Salmonella* is a rare cause of myopericarditis; however, it should be considered when patients with symptoms of myocarditis or pericarditis present with a history of diarrhoea, abdominal pain and fever.

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INTRODUCTION

Myocarditis is defined as an inflammatory disorder of the myocardium, formally diagnosed on clinical biopsy, however many cases are often diagnosed clinically^[1]. Pericarditis, also inflammatory, is when the inflammation primarily involves the pericardial sac. Given their close anatomical relation, co-inflammation can occur as part of a syndrome known as myopericarditis, however, clinical manifestations are predominantly myocarditic or pericarditic^[2]. The aetiology of myopericarditis is varied, ranging from infections (viral being the most common), autoinflammatory conditions, neoplasms, trauma, metabolic and idiopathic^[3]. A rare, but potentially serious cause is as a sequelae of *Salmonella* infection.

Most cases of *Salmonella* myocarditis are associated with typhoid fever (*Salmonella typhi/paratyphi*), complicating up to 5% of all infections, and is well described in literature^[4]. We conducted a systematic review of all case studies and case series published on nontyphoidal salmonella (NTS) associated pericarditis and/or myocarditis from January 1970 to March 2019. Both authors (Jin D and Kao CY) searched on PubMed and EMBASE using the search terms “*Salmonella* AND myocarditis” and “*Salmonella* AND pericarditis”. PubMed was further searched for the combined MeSH values of “Myocarditis” as well as “*Salmonella* (excluding typhi and paratyphi)”. Paediatric and non-human cases were excluded. References of articles were then further reviewed. We aim to discuss a case NTS myopericarditis, as well as reviewing the relevant literature.

CASE PRESENTATION

Chief complaints

We report a case of a 39-year old male, with no previous medical history, presenting with *Salmonella typhimurium* myopericarditis.

Personal and family history

The patient initially presented to our emergency department (ED) with acute chest discomfort, on the background of a four-day history of persistent, watery diarrhoea, occurring three to four times per day. On Day 0 (four days prior to admission), he noticed diffused abdominal cramps, bloating, nausea without vomiting, and fever. There was no history of recent travel, however he had a seven-year-old daughter, who had a one-week history of the same symptoms which had resolved prior to the patient's presentation. There was no report of blood in the diarrhoea, which was beginning to decrease and form solid motions by Day 4.

However, it was during this stage (Day 4) that the patient noted central chest discomfort, described as a burning sensation, radiating to the axilla and neck, associated with diaphoresis and self-resolving shortness of breath. This was not exacerbated by exercise, however there was some relief with leaning forwards. He initially presented to his General Practitioner (GP), who organised for faecal cultures,

before referring onto ED.

Laboratory examinations

At presentation to ED, his observations were within normal limits, with no documented fevers or tachycardia. Physical exam was unremarkable. Serial electrocardiogram (ECG, [Figure 1](#)) revealed prominent ST elevation (> 2 mm in leads V2-V6, > 1 mm in II/aVF), as well as ST depression in aVR. Investigations revealed a white cell count (WCC) of $7.3 \times 10^9/L$, C-reactive protein (CRP) of 84 mg/L, as well as a Troponin I (Abbott Architect) of 14,757 ng/L and a creatinine kinase of 594 units/L. Other blood tests such as electrolytes, creatinine and liver function tests were unremarkable.

Imaging examinations

Chest X-ray showed mild cardiac enlargement, without signs of pulmonary oedema or pneumonia. Faeces microscopy and culture, along with blood cultures were taken, and the patient was admitted without specific antimicrobial treatment. An echocardiogram conducted the next day showed a trivial amount of pericardial fluid. There was no clinical or echocardiographic evidence of tamponade, ventricular dysfunction, or thrombus formation.

During Day 5, we were notified of a *Salmonella* species from the faecal culture organised by the GP. Treatment was commenced with 1 g of ceftriaxone daily. Later that night there was an associated, asymptomatic rise in the Troponin I from the previous nadir of 8,915 to 15,114 ng/L. Ceftriaxone was increased to 2 g daily, and the Infectious Diseases Unit were consulted. At this stage the repeat faecal culture also identified *Salmonella* species, with negative blood cultures at 48 h. Joint decision at this stage was made to change to azithromycin 500 mg daily for 5 d and to not initiate non-steroidal therapy, given that the initial presenting symptoms had fully resolved. There had been no clinical events of arterial or venous thrombus, combined with no significant echocardiography changes, therefore no anticoagulation was prescribed. After a further period of observation over 24 h, during which the troponin decreased to 11,327 ng/L, the patient was discharged home.

Post discharge, at Day 7, the initial presenting blood culture was positive for gram negative bacilli in one aerobic bottle, out of two sets, also identified as *Salmonella typhimurium*, however by this stage the patient was convalescing well at home.

FINAL DIAGNOSIS

Myopericarditis in the setting of *Salmonella typhimurium* gastroenteritis and bacteraemia.

TREATMENT

Two days of ceftriaxone 2 g IV daily followed by azithromycin 500 mg orally daily for 5 days.

OUTCOME AND FOLLOW-UP

Clinical and biochemical resolution of myopericarditis and *Salmonella typhimurium* infection. Patient well with no further complaints at routine one-month follow-up.

DISCUSSION

The presentation of NTS myopericarditis can be varied, but generally is divided into two categories, the symptoms of myopericarditis, and the diarrhoeal syndrome. Although the manifestations of myopericarditis are commonly a spectrum between myocarditis and pericarditis, there is often a predominance of one^[2]. Myocarditis typically presents with chest pain, often of a varied nature, and can be impossible to differentiate on history from ischaemic chest pain. Otherwise heart failure symptoms, flu-like symptoms, fatigue, palpitations, syncope, or even sudden cardiac death may be the presenting symptom^[5]. Pericarditis is associated with a pleuritic chest pain, often relieved by leaning forward, as well as fatigue, palpitations, dyspnoea, and potentially tamponade^[5]. The classic exam finding is the pericardial friction rub, often described as a scratching sound best heard over the left sternal edge. Purulent

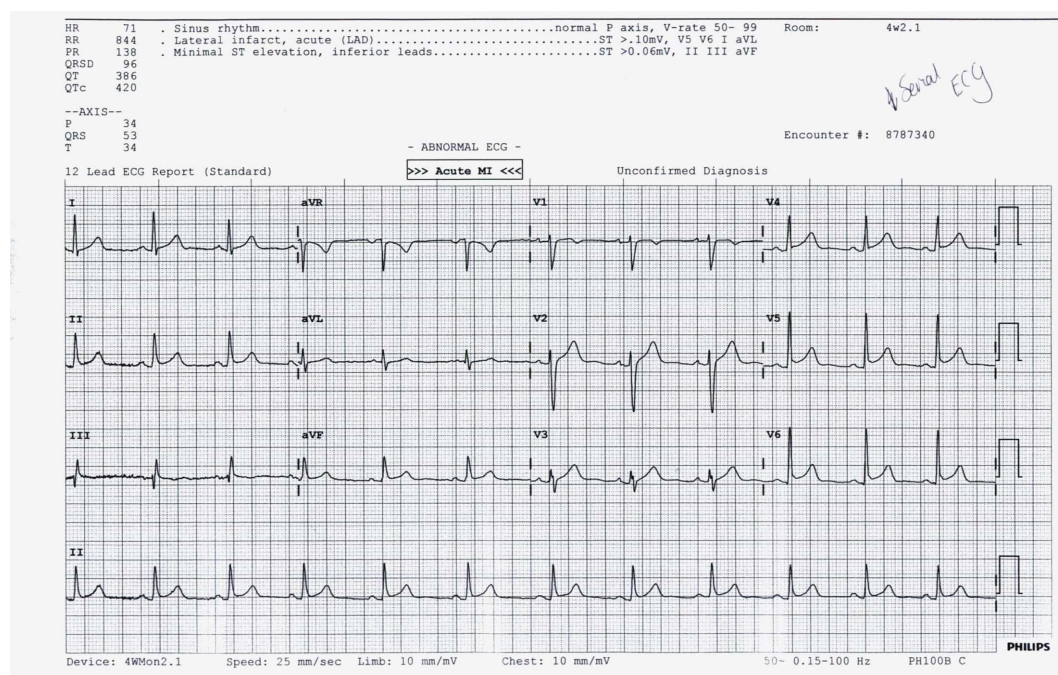


Figure 1 Electrocardiography from admission, showing diffuse ST elevation and mild ST depression in automatic voltage regulator.

pericarditis, a rare subset in the antibiotic era, should nevertheless be considered given its high morbidity and mortality. Presenting symptoms may include signs of pericarditis, especially if associated with sepsis or bacteraemia, with *Salmonella aureus* being the most commonly identified organism.

Investigations of relevance in myopericarditis include ECG, echocardiography, laboratory blood tests, biopsy, coronary angiography and cardiac magnetic resonance imaging. ECG changes are varied^[6], but typically involve diffuse ST elevation and PR depression, progressing to normalization of segments with subsequent T-wave inversion. However, given this can also manifest as focal ST elevation, combined with the fact that the pain can be ischaemic in nature, differentiation from acute coronary syndromes (ACS) is often required. This is most frequently done with interventional angiography, or more recently computed tomography coronary angiography. Aside from raised troponin, inflammatory markers such as WCC and CRP are often raised, however this has not been shown to help differentiate NTS as a cause^[7]. Echocardiography is another critical area of investigation, as this can help identify ventricular dysfunction, valvular incompetence and thrombus in myocarditis^[8], as well as the extent of pericardial involvement, ranging from completely normal to cardiac tamponade in pericarditis^[9]. Cardiac magnetic resonance imaging is another investigation that can be potentially used, as it can accurately assess inflammation in either the pericardium or myocardium, as well as help differentiate between ACS^[10]. Definitive diagnosis of myocarditis requires endocardial biopsy, however indication revolves around whether a biopsy result would change patient management, and thus is rarely conducted in those with normal or only mildly impaired ventricular function^[11]. Biopsy is most frequently performed in cases of fulminant heart failure, heart failure with rhythm disturbance, or when there is peripheral eosinophilia, suggestive of eosinophilic myocarditis.

The most recognised infection from *Salmonella* is typhoid fever, also known as enteric fever, caused by *Salmonella enterica* serotype Typhi (formerly *Salmonella typhi*), as well as *Salmonella paratyphi* (*Salmonella enterica* serotype *paratyphi*). Due to a nomenclature change, within *Salmonella* there are now two species; *bongori* and *enteric*^[12]. *Salmonella enterica*, which causes the majority of infections, contains 6 subspecies, of which the most clinically relevant is *Salmonella enterica* subspecies *enterica*. These are then further divided into serovars, with the most common including: *Salmonella choleraesuis*, *Salmonella enteritidis*, and *Salmonella typhimurium*. These organisms make up the group known as NTS.

NTS often manifests within 72 h of exposure to the offending pathogen and is usually associated with faecal-oral contamination. The most common presenting symptoms by far is gastroenteritis^[13], associated with watery, non-bloody diarrhoea, abdominal cramps, nausea and vomiting, as well as fever.

In our review of the literature (Table 1), we found 42 reported cases of NTS (Table

2), with 9 myocarditis, 6 myopericarditis and 27 cases of pericarditis. Overall, we found that *Salmonella enteritidis* was the most common organism, representing 18 (42.9%) of all reported cases, with *Salmonella typhimurium* at 31.7%. Males consisted 71.4% of the cases, and the average age of patients was 48.3 years. In the case studies that we have identified, the overall mortality rate was 31%, and up to 77.8% in myocarditis cases, compared to 14.8% in pericarditis. Tamponade was the most commonly reported complication, especially in pericarditis, at 54.3%, whilst ventricular rupture was the most commonly reported complication of myocarditis. However, this is limited by both reporting and publication bias, and by the fact that most deaths and myocarditis cases occurred earlier in time, prior to modern diagnostic techniques and treatment.

The mainstay of therapy in treating the inflammation and pain associated with myopericarditis is non-steroidal anti-inflammatory drugs (NSAIDs)^[6]. However when there is a predominant myocarditic component, NSAIDs are often reconsidered, as animal models show increased inflammation and mortality in viral myocarditis^[14]. Corticosteroids are also potentially used, but should only be considered in cases of ongoing uncontrolled inflammation, as there is minimal data to recommend its routine use, and there is association with recurrent myocarditis^[15]. Anticoagulation can be considered in specific patients, similar to the indications in non-ischaemic dilated cardiomyopathy^[16]. These would be if there were new onset AF, clinical or radiographical evidence of arterial or venous thromboembolism, thrombus formation on the echocardiogram, or significant ventricular dysfunction. If treatment was indicated, evidence currently leans towards anticoagulation with warfarin or a Direct Oral Anti-Coagulant, as opposed to single-agent treatment with an antiplatelet^[17]. If there are concurrent symptoms of heart failure, routine heart failure treatment should be initiated, including diuretics, angiotensin converting enzyme inhibition, and extended release beta blocker treatment. Invasive treatment is often limited to coronary angiography when differentiating from ACS, as well as pericardiocentesis in the setting of large pericardial effusions with features suggestive of developing or frank cardiac tamponade.

Lastly, it is also important to treat the underlying *Salmonella* infection, however guidelines vary secondary to local antimicrobial susceptibility patterns. After clinical rehydration, current Australian guidelines^[18], recommend treatment with intravenous therapy initially, such as ceftriaxone (2 g IV daily), or ciprofloxacin (400 mg twice-daily), before an oral tail of ciprofloxacin/azithromycin, determined by the severity of the infection.

At this stage, there is very limited high-quality data on long-term prognosis and complications in patients diagnosed with myopericarditis^[3]. Nevertheless, it appears that survival rates in idiopathic and infectious myocarditis are overall quite favourable, especially the predominant pericarditis subtype^[19]. The main complications are the development or non-resolution of heart failure, cardiomyopathy, arrhythmias, and sudden cardiac death, especially if there is significant myocardial scarring. Routine follow up in the acute phase with echocardiography is recommended, especially if there are clinical or radiological signs of heart failure.

CONCLUSION

The presentation of NTS myopericarditis is varied, however it revolves around two main areas, the symptoms of myocarditis and pericarditis, as well as the infectious symptoms of diarrhoea accompanying *Salmonella* infection. Definitive diagnosis with biopsy is rarely undertaken, as this is usually a clinical diagnosis from the clinical history and examination, ECG, troponin and echocardiogram, as well as a stool culture for the NTS. There is a lack of consensus regarding the treatment of myopericarditis, however there are well established antibiotic guidelines for NTS. Although NTS is a rare cause of myopericarditis, given the severity of potential sequelae, remains a worthwhile consideration when patients present with symptoms of both infectious diarrhoea and myopericarditis.

Table 1 Non-typhoidal salmonella pericarditis and myocarditis

Author	Relevant medical history	Age and sex	Cardiac manifestation	Organism	Complications	Outcome
Bengtsson et al ^[20] , 1955	NA	50F	Myocarditis	<i>Salmonella typhimurium</i>	NA	Deceased
Bengtsson et al ^[20] , 1955	NA	51M	Myocarditis	<i>Salmonella typhimurium</i>	NA	Deceased
Sanders et al ^[21] , 1964	NA	62F	Myocarditis	<i>Salmonella choleraesuis</i>	Ventricular Rupture	Deceased
Shilkin et al ^[22] , 1969	SLE	61M	Myopericarditis	<i>Salmonella typhimurium</i>	Endocarditis	Deceased
Schatz et al ^[23] , 1973	NA	62M	Myopericarditis	<i>Salmonella typhimurium</i>	Tamponade	Deceased
Webster et al ^[24] , 1977	NA	19F	Myopericarditis	<i>Salmonella agona</i>	NA	Survived
Simonsen et al ^[25] , 1980	NA	24M	Myocarditis	<i>Salmonella typhimurium</i>	NA	Deceased
Götz et al ^[26] , 1983	NA	53M	Myocarditis	<i>Salmonella typhimurium</i>	NA	Deceased
Martínez-Martínez et al ^[27] , 1989	NA	60M	Myocarditis	<i>Salmonella enteritidis</i>	Mycotic aneurysms of aorta	Deceased
Burt et al ^[28] , 1990	NA	29M	Myocarditis	<i>Salmonella Heidelberg</i>	VF	Deceased
Dunbabin et al ^[29] , 1990	Chemotherapy	52F	Pericarditis	<i>Salmonella Dublin</i>	Tamponade	Deceased
Doig et al ^[30] , 1991	NA	36F	Pericarditis	<i>Salmonella enteritidis</i>	Tamponade	Survived
Clesham et al ^[31] , 1993	NA	45M	Pericarditis	<i>Salmonella enteritidis</i>	Tamponade	Survived
Li et al ^[32] , 1993	NA	22F	Pericarditis	<i>Salmonella enteritidis</i>	NA	Survived
Yang et al ^[33] , 1995	NA	54F	Pericarditis	<i>Salmonella typhimurium</i>	NA	Survived
Victor et al ^[34] , 1997	NA	71M	Pericarditis	<i>Salmonella enteritidis</i>	NA	Survived
Kiuchi et al ^[35] , 1998	ITP (prednisolone)	39M	Pericarditis	<i>Salmonella enteritidis</i>	Tamponade	Survived
Badawi et al ^[36] , 2002	NA	48M	Pericarditis	<i>Salmonella typhimurium</i>	NA	Survived
Pace et al ^[37] , 2002	NA	65M	Pericarditis	<i>Salmonella enteritidis</i>	Tamponade	Survived
Salavert et al ^[38] , 2002	NA	61M	Pericarditis	<i>Salmonella arizonae</i>	Tamponade	Survived
Candel et al ^[39] , 2003	HIV	37M	Pericarditis	<i>Salmonella Derby</i>	NA	Survived
Yoshioka et al ^[40] , 2003	NA	40M	Pericarditis	<i>Salmonella enteritidis</i>	NA	Survived
Arruvito et al ^[41] , 2004	Arthritis (steroids)	75M	Pericarditis	<i>Salmonella enterica</i>	Tamponade	Deceased
Can et al ^[42] , 2004	NA	42M	Pericarditis	<i>Salmonella typhimurium</i>	NA	Deceased
Fernández Guerrero et al ^[43] , 2004	SLE (prednisolone and azathioprine)	23F	Pericarditis	<i>Salmonella typhimurium</i>	Tamponade	Survived
Fernández Guerrero et al ^[43] , 2004	NA	66M	Myopericarditis	<i>Salmonella enteritidis</i>	NA	Survived
Hoag et al ^[44] , 2005	HIV	47F	Pericarditis	<i>Salmonella arizonae</i>	Tamponade	Survived
Górecki et al ^[45] , 2008	RA (steroids) ESRF (on HDx)	64M	Pericarditis	<i>Salmonella enteritidis</i>	Tamponade	Survived
Sahu et al ^[46] , 2008	Hodgkin's lymphoma	23M	Pericarditis	<i>Salmonella typhimurium</i>	NA	Survived
Takamiya et al ^[47] , 2008	CD4/CD8 depression (ratio = 0.81)	65M	Pericarditis	<i>Salmonella enteritidis</i>	NA	Survived
Hibbert et al ^[48] , 2010	NA	25M	Myopericarditis	<i>Salmonella enteritidis</i>	NA	Survived
Tseng et al ^[49] , 2010	ESRF	66M	Pericarditis	<i>Salmonella enterica</i>	Tamponade	Survived
Tseng et al ^[49] , 2010	ESRF	82M	Pericarditis	<i>Salmonella enteritidis</i>	Tamponade	Deceased

Ortiz et al ^[50] , 2014	SLE (prednisolone)	62M	Pericarditis	<i>Salmonella enteritidis</i>	Tamponade	Survived
Chand et al ^[51] , 2015	NA	67M	Pericarditis	<i>Salmonella enteritidis</i>	Tamponade	Survived
Zaman et al ^[52] , 2015	NA	67M	Myopericarditis	<i>Salmonella enteritidis</i>	Tamponade	Survived
Dawar et al ^[53] , 2017	NA	46F	Pericarditis	<i>Salmonella typhimurium</i>	NA	Survived
Kuo et al ^[54] , 2017	Adult onset Still's disease (methylprednisolone / prednisolone)	30F	Pericarditis	<i>Salmonella enteritidis</i>	Tamponade	Survived
Suzuki et al ^[55] , 2017	NA	31M	Pericarditis	<i>Salmonella arizonae</i>	Tamponade	Survived
Ezad et al ^[56] , 2018	NA	29F	Myocarditis	<i>Salmonella typhimurium</i>	NA	Survived
Sundbom et al ^[57] , 2018	NA	22M	Myocarditis	<i>Salmonella enteritidis</i>	NA	Survived
Saddler et al ^[58] , 2019	Crohn's disease (Infliximab)	57M	Pericarditis	<i>Salmonella enterica</i>	Tamponade	Survived

NA: Not applicable; SLE: Systemic lupus erythematosus; ESRF: End-stage renal failure; HIV: Human immunodeficiency virus; RA: Rheumatoid arthritis; ITP: Idiopathic thrombocytopenic purpura; M: Male; F: Female.

Table 2 Summary of non-typhoidal salmonella ca

Cardiac Manifestation (Cases)	Organisms (Number of cases)	Mortality
Myocarditis (9)	<i>Salmonella typhimurium</i> (5) <i>Salmonella enteritidis</i> (2) <i>Salmonella choleraesuis</i> (1) <i>Salmonella Heidelberg</i> (1)	77.8% (7/9)
Myopericarditis (6)	<i>Salmonella enteritidis</i> (3) <i>Salmonella typhimurium</i> (2) <i>Salmonella agona</i> (1)	33.3% (2/6)
Pericarditis (27)	<i>Salmonella enteritidis</i> (13) <i>Salmonella typhimurium</i> (6) <i>Salmonella arizonae</i> (3) <i>Salmonella enterica</i> (3) <i>Salmonella Derby</i> (1) <i>Salmonella Dublin</i> (1)	14.8% (4/27)
Total (42)	<i>Salmonella enteritidis</i> (18) <i>Salmonella typhimurium</i> (13) <i>Salmonella arizonae</i> (3) <i>Salmonella enterica</i> (3) <i>Salmonella agona</i> (1) <i>Salmonella choleraesuis</i> (1) <i>Salmonella Derby</i> (1) <i>Salmonella Dublin</i> (1) <i>Salmonella Heidelberg</i> (1)	31% (13/42)

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