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REVIEW

Autonomic neurocardiogenic syndrome is stonewalled by the universal definition of myocardial infarction

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Abstract

Myocardial infarction (MI) is defined as myocardial cell death due to prolonged myocardial ischemia. Clinically, troponin rise and/or fall have become the "defining feature of MI" according to the universal definition of MI (UD-MI). Takotsubo syndrome (TS) and TS-related disease conditions also cause troponin elevation with typical rise and/or fall pattern but through a mechanism other than coronary ischemia. By strict application of the clinical diagnostic criteria for type-1 MI, type-2 MI, type-3 MI, and MI with non-obstructive coronary arteries according to the UD-MI including the fourth one published recently, TS and most of the 26 other causes of troponin elevation mentioned in the fourth UD-MI may erroneously be classified as MI. The existing evidence argues for the case that TS by itself is not a MI. Hyper-activation of the autonomic-sympathetic nervous system including local cardiac sympathetic hyper-activation and disruption with nor-epinephrine churn and spillover is the most probable cause of TS. This autonomic neuro-cardiogenic (ANCA) mechanism results in myocardial "cramp" (stunning), the severity and duration of which depend on the degree of the sympathetic-hyperactivation and nor-epinephrine spillover. The myocardial cramp may squeeze the cytosolic free troponin pools causing mild to moderate troponin elevation in TS and TS-related disease conditions. This ANCA syndrome, which has hitherto been enveloped by the UD-MI over more than one decade, may occur in acute, recurrent, and chronic forms. In this critical review, the controversies of UD-MI, evidence for ANCA syndrome, and a hypothetical mechanism for the troponin elevation in ANCA syndrome are provided.

Key words: Universal definition; Myocardial infarction; Takotsubo; Myocardial stunning; Cardiac cramp; Autonomic neurocardiogenic syndrome; Heart failure; Chronic kidney diseases

Core tip: The fourth universal definition of myocardial infarction (MI) needs

reconsideration. Type 2 MI and MI with non-obstructive coronary arteries are not evidence-based. Autonomic neuro-cardiogenic (ANCA) syndrome is the second important cause of troponin elevation after acute coronary ischemia. Troponin release in ANCA syndrome is most probably due to cardiac cramp squeezing the cardiomyocyte causing mild to moderate release of troponin from the cytosolic free pool. ANCA syndrome may occur in an acute form as in takotsubo syndrome. The syndrome may also occur in recurrent or a chronic form as in chronic heart failure with acute exacerbations, and chronic kidney diseases.

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INTRODUCTION

Myocardial infarction (MI) is defined as myocardial cell necrosis due to protracted myocardial ischemia. Cardiac troponin (cTn) rise and/or fall have been regarded as the "defining feature of MI" according to the universal definition of MI (UD-MI). The fourth UD-MI classified non-procedure-related MI into type-1 MI (T1MI), type-2 MI (T2MI), and type-3 MI (T3MI)[1]. In addition, the term MI with non-obstructive coronary arteries (MINOCA) has been introduced to include patients from both T1MI and T2MI[1] and other causes of troponin elevations with non-obstructive coronary arteries. Regrettably; no efforts have been made to elucidate mechanisms other than ischemic causes of cTn elevation. Almost all cTn elevations have been described as MI as seen in T1MI, T2MI, T3MI, and MINOCA. Moreover, the definitions and the criteria of different types of MI are full of controversies. By strict application of the clinical criteria for the 3 types of MI (Table 1), most of the patients who suffer takotsubo syndrome (TS), TS-related disease conditions (described below) and even other non-ischemic conditions as myocarditis will be incorrectly diagnosed as MI. Most of the researchers agree that TS is not an ischemic heart disease[2,3]. Even the authors of the fourth UD-MI acknowledge that not all patients included in different types of MI have ischemic heart disease[1]. Consequently, it is justified to raise the question, whether all the non-ischemic causes of cTn elevations should be classified as MI? In this critical review, the controversies of the UD-MI and the confusions, which the terms T1MI, T2MI, T3MI, and MINOCA have caused, are explained. In addition, substantial evidences for the autonomic neuro-cardiogenic (ANCA) involvement and the mechanism by which it causes cTn elevation in TS and TS-related disease conditions is highlighted. Evidence for the contention that the ANCA syndrome may occur in acute form as TS and TS-related conditions and in recurrent or chronic forms as in undiagnosed pheochromocytoma, chronic heart failure (CHF) with acute exacerbations, and chronic kidney diseases (CKD) is also provided.

CONTROVERSIES OF THE FOURTH UNIVERSAL DEFINITION OF MYOCARDIAL INFARCTION

According to the fourth UD-MI, the pathogenesis of T1MI is coronary plaque rupture/erosion with occlusive or non-occlusive thrombus[1]. This implies that invasive coronary angiography (CAG) and in some cases intravascular imaging such as intravascular ultrasound or optical coherence tomography should be performed to confirm the diagnosis of T1MI. Strangely, the clinical diagnostic criteria of T1MI in the fourth UD-MI do not mandate invasive CAG (or, as an alternative, non-invasive coronary computed tomography angiography) in all cases (Table 1). This is clear from registry studies, which strictly adhere to the use of the UD-MI. In a study by Baron *et al*[4], 12841 (24.1%) of 53342 classified as T1MI were treated conservatively without performing CAG. How could the authors be convinced of plaque rupture with occlusive or non-occlusive thrombus in such huge numbers of patients when invasive CAG, intravascular ultrasound or optical coherence tomography were not performed, and when TS has an almost identical clinical presentation as that of T1MI[2,5,6]? In addition, according to the fourth UD-MI, the pathogenesis of T2MI is due to

Table 1 Diagnostic criteria for type 1, type 2, and type 3 myocardial infarction according to the fourth universal definition of myocardial infarction

Criteria for type 1 MI, type 2 MI, type 3 MI according to the fourth universal definition of myocardial infarction[1]
Type 1 MI
Detection of a rise and/or fall of cTn values with at least one value above the 99th percentile URL and with at least one of the following:
Symptoms of acute myocardial ischaemia
New ischaemic ECG changes
Development of pathological Q waves
Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology
Identification of a coronary thrombus by angiography including intracoronary imaging or by autopsy
Type 2 MI
Detection of a rise and/or fall of cTn values with at least one value above the 99th percentile URL, and evidence of an imbalance between myocardial oxygen supply and demand unrelated to coronary thrombosis, requiring at least one of the following:
Symptoms of acute myocardial ischaemia
New ischaemic ECG changes
Development of pathological Q waves
Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischaemic aetiology
Type 3 MI
Patients who suffer cardiac death, with symptoms suggestive of myocardial ischaemia accompanied by presumed new ischemic ECG changes or ventricular fibrillation but die before blood samples for biomarkers can be obtained, or before increases in cardiac biomarkers can be identified, or MI is detected by autopsy examination

MI: Myocardial infarction; ECG: Electrocardiogram; cTn: Cardiac troponin; URL: Upper reference limit.

imbalance between myocardial oxygen supply and demand unrelated to coronary thrombosis[1]. The diagnosis of supply and/or demand imbalance is a very subjective one and based rather on guesswork than on scientific evidence and hitherto this hypothesis has not been confirmed. Furthermore, after so many years, the investigators of UD-MI have not been able to confirm MI by endomyocardial biopsy or cardiac magnetic resonance (CMR) imaging in most of the patients deemed to have T2MI[7]. The highly varied reported incidence of "T2MI "across the studies from 1.6% to 29.6% is an indication for that not all clinicians believe in this diagnosis[7,8]. T2MI is really a figment of imagination. By the strict application of the criteria for both "T1MI" and "T2MI", the diagnosis of TS and other non-ischemic causes of troponin elevation would almost disappear[8]. Interestingly, even some co-authors of the fourth UD-MI agree entirely with the above-mentioned controversies and confusion, which T2MI have caused. Collinson and Lindahl[7] also believe that the term T2MI is confusing and not evidence-based. They have appropriately described T2MI as the "chimera of cardiology". Moreover, the authors have stated that "T2MI has always been defined by what it is not rather than what it is", and that "T2MI as defined according to the UD-MI is a mixed bag of patients, in whom the pathophysiology is different and, in fact in many cases, is unknown". They have concluded that "T2MI should be abandoned and replaced with secondary "myocardial injury"[7]; it is perhaps worth to mention, that secondary myocardial injury is also not appropriate

The fourth UD-MI has also introduced the term MINOCA, which might have aggravated the state of confusion for all these types of MI. According to the European society of cardiology (ESC) position paper[3] (Table 2), the most common causes of MINOCA are plaque rupture or erosion, coronary artery spasm, thrombo-embolism, spontaneous coronary artery dissection (SCAD), TS, unrecognized myocarditis, and other forms of T2MI (Table 2). In principle, this implies that almost all the conditions causing troponin elevation and included in MINOCA are regarded as MI, because the MI in MINOCA stands for myocardial infarction. Despite all the criteria, the definition, and causes of MINOCA (Table 2), the authors of the ESC position paper acknowledge that cardiac troponin is "organ specific" and not "disease specific" and that elevated cardiac troponin is not necessarily indicative of acute MI but reflects "myocardial injury". Interestingly, in 2013 when John F Beltrame[9] introduced the term MINOCA instead of myocardial infarction with normal coronary arteries, he stated that an important first step in the assessment of patients with apparent MINOCA is to exclude the causes of non-ischemic of troponin elevations such as pulmonary embolism, acute or chronic renal failure, acute on chronic heart failure, myocarditis, "cardiomyopathies" (infiltrative, takotsubo, and peripartum), stroke, septic shock, acute respiratory distress syndrome, acute trauma (including iatrogenic),

severe burns, chemotherapeutic agents and strenuous exercise. This contrasts the ESC reported causes of MINOCA[3].

Furthermore, most of the MINOCA patients who were investigated by CMR imaging have shown no signs of MI. Collste *et al*[10] reported normal CMR imaging in 102 of 152 patients (67%) with myocardial infarction with normal coronary arteries. Bière *et al*[11] reported on CMR imaging findings in 131 patients with MINOCA. There was late gadolinium enhancement (LGE) consistent with MI in only 34 patients (26%). LGE consistent with myocarditis in 47 patients (36%) and there was no LGE in 50 patients (38%). Interestingly, 20 patients with TS were excluded in that study. If TS patients would have been included in that study, only 22.5% of patients with MINOCA in that study would have MI; 77.5% had not MI. In a review of 16 CMR studies (CMR undertaken within 6 wk) in patients with MINOCA, Pasupathy *et al*[12] reported CMR findings of MI in 24%, myocarditis in 38%, TS in 16% and no significant abnormality in 21%. Consequently 76% of patients with MINOCA had no MI. Recently, Hausvater *et al*[13] reported on 292 patients with MINOCA pooled from three prospective cohort studies and found that 81% of patients had no CMR signs of MI. All these studies confirm that most patients included in MINOCA have no MI.

Interestingly, most of the patients who fulfill the criteria of "NOCA in MINOCA" have no MI[13] and some of those who fulfill the criteria of "MI in MINOCA" have obstructive coronary arteries (OCA) and not NOCA[14]. One real example for such controversy and the confusion which MINOCA causes is elaborated in Figure 1 and 2. TS and SCAD are 2 conditions among the causes of MINOCA according to the ESC position paper. Most of the patients with pure TS have no MI but have "NOCA" as in Figure 1. The reverse is true in patients with SCAD where most of the patients with SCAD have MI and have obstructive coronary artery disease (CAD), consequently no "NOCA" as illustrated in Figure 2. Why should TS be included under MINOCA when TS per se is not a MI?[2,6] Or why should SCAD be included under MINOCA whilst most of the cases with SCAD have obstructive CAD[15,16]? In VIRGO study[17], 61 of 299 (20%) MINOCA patients had SCAD where 51% of SCAD patients had ST-elevation MI (STEMI) ECG changes, which also indicates OCA and not NOCA. In a recent large study, 29.7% of 750 patients with SCAD had STEMI, which usually indicate a total coronary occlusion due to SCAD[14]. In the same study, the median angiographic stenosis in patients with SCAD was 79.0% (65%-100%)[14]. The most probable explanation for the classification of SCAD patients under MINOCA is that the diagnosis of SCAD is frequently missed by coronary interventionalists[15]. In conclusion almost 80% of patients in different MINOCA studies have no MI, and half of patients with MI have OCA and not NOCA; consequently only 10% of patients included in MINOCA studies fulfill the criteria of both MI and NOCA.

OTHER ESSENTIAL FINDINGS IN PATIENTS CLASSIFIED AS T2MI AND MINOCA ARGUING AGAINST MI

Patients with "T2MI" and MINOCA are predominantly women, have more co-morbidities, show smaller extent of "myocardial necrosis" and more normal coronary arteries[1,3,18]. These findings are also characteristic features encountered in patients with TS[2,6]. Recently, Nordenskjöld *et al*[19] in a study on MINOCA patients reported that lower level of total cholesterol was among the independent predictors for significant increase in major adverse cardiovascular events and long-term mortality. This finding contrasts the known confirmed evidence in large studies that the hyper-cholesterolemia is an important risk factor for coronary artery disease and that lowering of total cholesterol and LDL reduces the cardiovascular risk in both primary and secondary settings. Because of this, the authors used the term "cholesterol paradox" in MINOCA patients. One conceivable explanation for the "cholesterol paradox" may be the associated co-morbidities such as malignancy and chronic critical illnesses which may act as predisposing factors for TS and that these chronic co-morbidities may explain the lower cholesterol as well as the increased major adverse cardiovascular events and mortality in MINOCA patients. Consequently, the cholesterol paradox in MINOCA patients argues against MI in MINOCA patients. The same group of investigators[20] reported on the medical therapy for secondary prevention and long-term outcome in patients with MINOCA and found a neutral effect of dual anti-platelet therapy, arguing against an athero-thrombotic coronary cause of MINOCA. Despite mild-moderate troponin elevation in T2MI and MINOCA, the mortality in T2MI is significantly higher than T1MI during a mean follow up period of 3.2 years in one study[21]. The high mortality in that study was attributed mainly to the non-cardiovascular causes of death[21]. Furthermore, most of the patients with T2MI or MINOCA have no MI on CMR imaging[10-13,22].

Table 2 Diagnostic criteria and causes of myocardial infarction with non-obstructive coronary arteries

Diagnostic criteria and causes for myocardial infarction with non-obstructive coronary arteries according to the ESC working group position paper[3]

Diagnostic criteria:

The diagnosis of MINOCA is made immediately upon coronary angiography in a patient presenting with features consistent with an acute myocardial infarction, as detailed by the following criteria:

(1) AMI criteria

(a) Positive cardiac biomarker (preferably cardiac troponin) defined as a rise and/or fall in serial levels, with at least one value above the 99th percentile upper reference limit

(b) Corroborative clinical evidence of infarction evidenced by at least one of the following:

Symptoms of ischaemia

New or presumed new significant ST-T changes or new LBBB

Development of pathological Q waves

Imaging evidence of new loss of viable myocardium or new RWMA

Intracoronary thrombus evident on angiography or at autopsy

(2) Non-obstructive coronary arteries on angiography:

Defined as the absence of obstructive CAD on angiography, (*i.e.* no coronary artery stenosis ≥ 50%), in any potential infarct-related artery. This includes both patients with:

This includes both patients with:

Normal coronary arteries (no stenosis < 30%)

Mild coronary atheromatosis (stenosis > 30% but < 50%).

No clinically overt specific cause for the acute presentation:

At the time of angiography, the cause and thus a specific diagnosis for the clinical presentation is not apparent

Accordingly, there is a necessity to further evaluate the patient for the underlying cause of the MINOCA presentation

Causes

Plaque rupture or erosion

Coronary artery spasm

Thromboembolism

Coronary dissection

Takotsubo syndrome

Unrecognized myocarditis, and

Other forms of type-2 myocardial infarction

CAD: Coronary artery disease; ESC: European society of cardiology; MINOCA: Non-obstructive coronary arteries; RWMA: Regional wall motion abnormality; LBBB: Left bundle branch block; AMI: Acute myocardial infarction.

EVIDENCE FOR THE AUTONOMIC NEUROCARDIOGENIC (ANCA) SYNDROME AND ITS ROLE IN CAUSING TROPONIN ELEVATION

Signs of hyperactivation of sympathetic nervous system and cardiac sympathetic disruption has been reported in different cardiac diseases as CHF, CKD complicated by heart failure, and TS. ANCA syndrome is a continuum of syndromes with a constellation of clinical presentation, repolarization ECG changes, troponin elevation, left ventricular wall motion abnormality (LVWMA), and histopathological findings. TS has played a pivotal role and has paved the path to an understanding of this broad continuum of ANCA manifestation, which may occur in acute, recurrent and chronic forms. The evidence for that is discussed below.

TAKOTSUBO SYNDROME

TS, also known as neurogenic stunned myocardium, is now a recognized acute cardiac disease entity[2,5]. The term takotsubo (tako = octopus, tsubo = a pot) was introduced by Sato and Dote in 1990 and 1991 to describe the left ventricular silhouette during systole in patients with clinical features of MI but no obstructive coronary artery disease[23,24]. This acute syndrome has clinical and electrocardiographic features resembling that of an acute coronary syndrome (ACS). The main defining feature of TS is the regional LVWMA with a unique circumferential pattern resulting

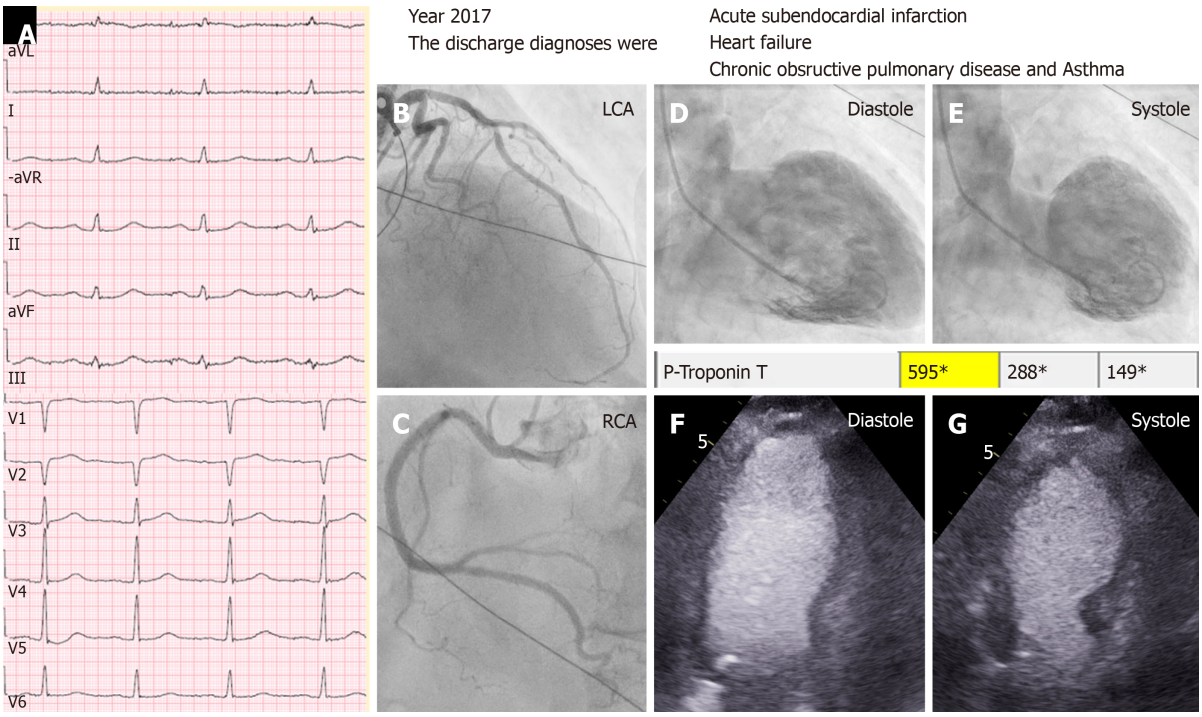

Figure 1 A case of midventricular takotsubo syndrome discharged under diagnosis of myocardial infarction. A typical mid-ventricular takotsubo syndrome triggered by an emotional stress in a 79-years-old man with chronic co-morbidities in the form of chronic obstructive pulmonary disease and carcinoma of urinary bladder. The case was incorrectly diagnosed as type 2 myocardial infarction according to the universal definition of myocardial infarction as seen in the discharge diagnosis. A: Electrocardiogram during admission; B: Left coronary artery shows moderate stenosis in the left anterior descending artery, which cannot explain the circumferential mid-ventricular left ventricular wall motion abnormality; C: Normal right coronary artery (RCA); D and E: Contrast left ventriculography during diastole and systole showing mid-ventricular ballooning pattern. There was modest elevation of troponin T (595 ng/L); F and G: Echocardiography during diastole and systole confirming the left ventriculography finding of mid-ventricular ballooning.

in a conspicuous ballooning of the left ventricle during systole[2,6]. The LVWMA extends beyond the coronary artery supply regions and is transient with almost complete resolution of ventricular dysfunction in hours to weeks[2,6]. The LVWMA may be localized to the apical, mid-apical, mid-ventricular, basal or mid-basal segments of the left ventricle[5]. Focal and global LVWMA has also been reported[25-27]. The right ventricle may be involved in about 30% of the patients with TS[28]. The syndrome is preceded by a trigger factor in more than two thirds of patients[25]. Emotional trigger factors as death of a close relative or acute grief may trigger the syndrome and hence the term broken heart syndrome[29]. Myriads of physical triggers (Figure 3), extending from serious diseases as acute sepsis, subarachnoid hemorrhages to the most physiological processes as pregnancy and sexual intercourse, may also trigger the syndrome[30,31].

TS is a typical example of a disease entity causing troponin elevation with a typical rise and/or fall pattern as that of MI but is not a MI by itself. However, the existing criteria for "T1MI, T2MI, T3MI, and MINOCA" (Tables 1 and 2) may submerge and classify TS as a MI as illustrated in Figure 1. This is also applied on patients with TS-related syndromes *i.e.*, syndrome which have the same pathogenesis of TS described below.

EVIDENCE FOR THAT TAKOTSUBO SYNDROME IS NOT A MI

TS has a clinical presentation, electrocardiographic changes and troponin elevation pattern like that of an ACS. However, invasive CAG is normal in most cases of TS[2,32]. Cardiac image studies (echocardiography, contrast left ventriculography, and CMR imaging) usually disclose LVWMA which extends beyond the coronary artery supply territory especially when the LVWMA involves only the mid-ventricular segments or the basal segments[5]. There is great discrepancy between the extensive LVWMA and the modest troponin elevations, which argues against significant necrosis seen in MI[6]. The CMR imaging may also show edema corresponding to the segments with LVWMA but there is no late gadolinium enhancement (LGE) in most of the cases, a

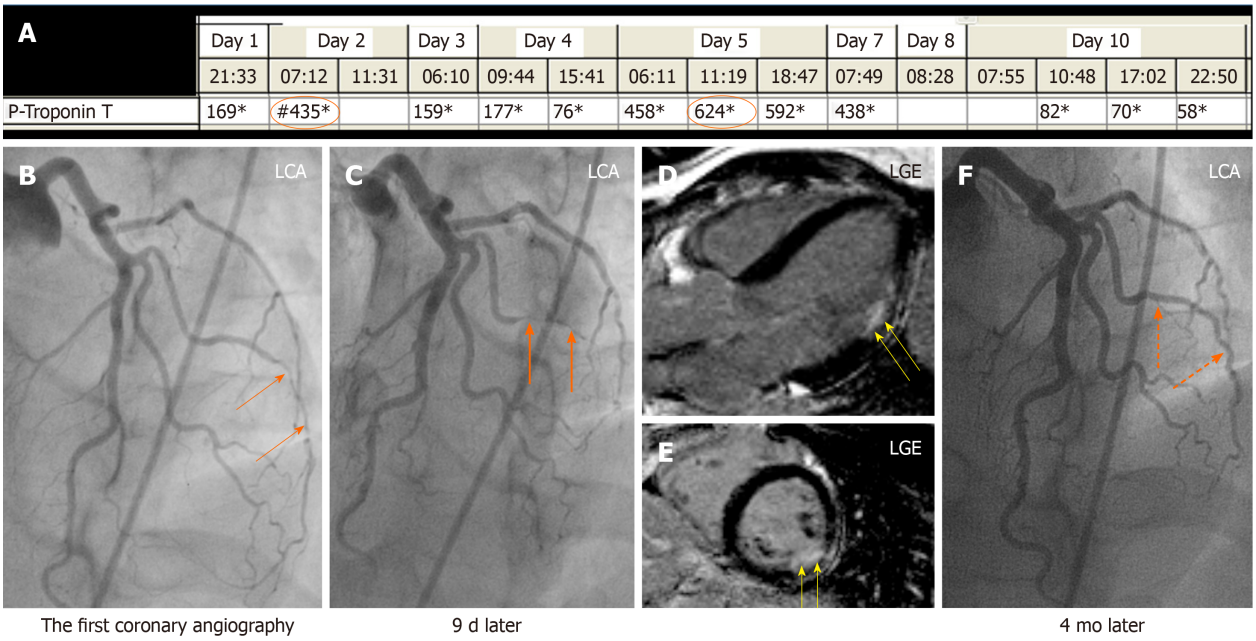

Figure 2 A case of obstructive coronary artery disease due spontaneous coronary artery dissection. A 35-years-old female patient with a spontaneous coronary artery dissection (SCAD) of the diagonal artery with documented myocardial infarction (MI) by cardiac magnetic resonance imaging and obstructive coronary artery stenosis. A: Recurrent troponin elevation with a rise and/or fall pattern (orange circles); B: A diagonal artery with a peripheral stenosis (thin orange arrows); C: Proximal propagation of diagonal artery narrowing during repeated left coronary artery angiography 9 d later (thick orange arrows); D and E: Cardiac magnetic resonance imaging shows MI corresponding to the diagonal artery supply territory (yellow arrows); F: Follow up left coronary artery angiography 4 mo later reveals complete resolution of the diagonal artery lesion consistent with SCAD (broken orange arrows). Consequently, this patient has documented MI caused by obstructive coronary artery disease due to SCAD. LGE: Late gadolinium enhancement; LGA: Left coronary artery.

finding argues against MI[5]. CMR imaging, if done early during TS, may reveal LGE in the affected hypokinetic segments in about one third of cases[33]. However, the signal intensity of LGE in TS is less than that of MI and myocarditis and the LGE is patchy in appearance and in some cases described as myocarditis[34,35]; chemical (neuro-mediated by norepinephrine) myocarditis may be a feature of TS[36] and may explain the patchy LGE findings in TS; it is usually reversible (neurogenic stunning). Moreover, the most important sign, which challenges MI in TS, is the histopathological finding of contraction band necrosis, which is distinct from coagulation necrosis seen in MI[37].

However, one confounding factor is that ACS irrespective of its cause (atherothrombotic coronary artery disease, SCAD, coronary spasm, or coronary embolism) as any other physical stress may also trigger TS[38]. Furthermore, TS may also be complicated by acute MI due to coronary embolism secondary to left ventricular thrombus, which may itself be a complication of TS[39]. In such cases, the patients will have features of both MI and TS[39].

OTHER DISEASE CONDITIONS INVOLVED IN TROPONIN ELEVATION

Apart from the atherosclerotic plaque disruption with thrombosis as a cause of troponin elevations, 26 other disease conditions mentioned in the fourth UD-MI may cause troponin elevation[1]. The list may be longer if other causes of troponin elevations are added such as pheochromocytoma and paraganglioma[31,40]. TS is mentioned as only one of the 26 disease conditions, which may cause troponin elevation. However, with critical analysis, most of the remaining 25 other mentioned conditions causing troponin elevations may act or have been reported as a trigger factor for TS as sepsis and infectious diseases[41], stroke and subarachnoid hemorrhage[42], chemotherapeutic agents[26], acute critical diseases[43], strenuous exercise, pulmonary embolism, coronary spasm, acute coronary syndrome including SCAD[2,32,38], chronic obstructive pulmonary disease with acute exacerbation, bradycardia and AV-block, and many others[2,32]; an example for that is given in figure 3. Some other conditions mentioned causing troponin elevation may be a complication of TS as coronary embolism, brady-arrhythmias, tachy-arrhythmias, hypotension and shock[2,32,39]. Consequently, it would be reasonable to conclude that

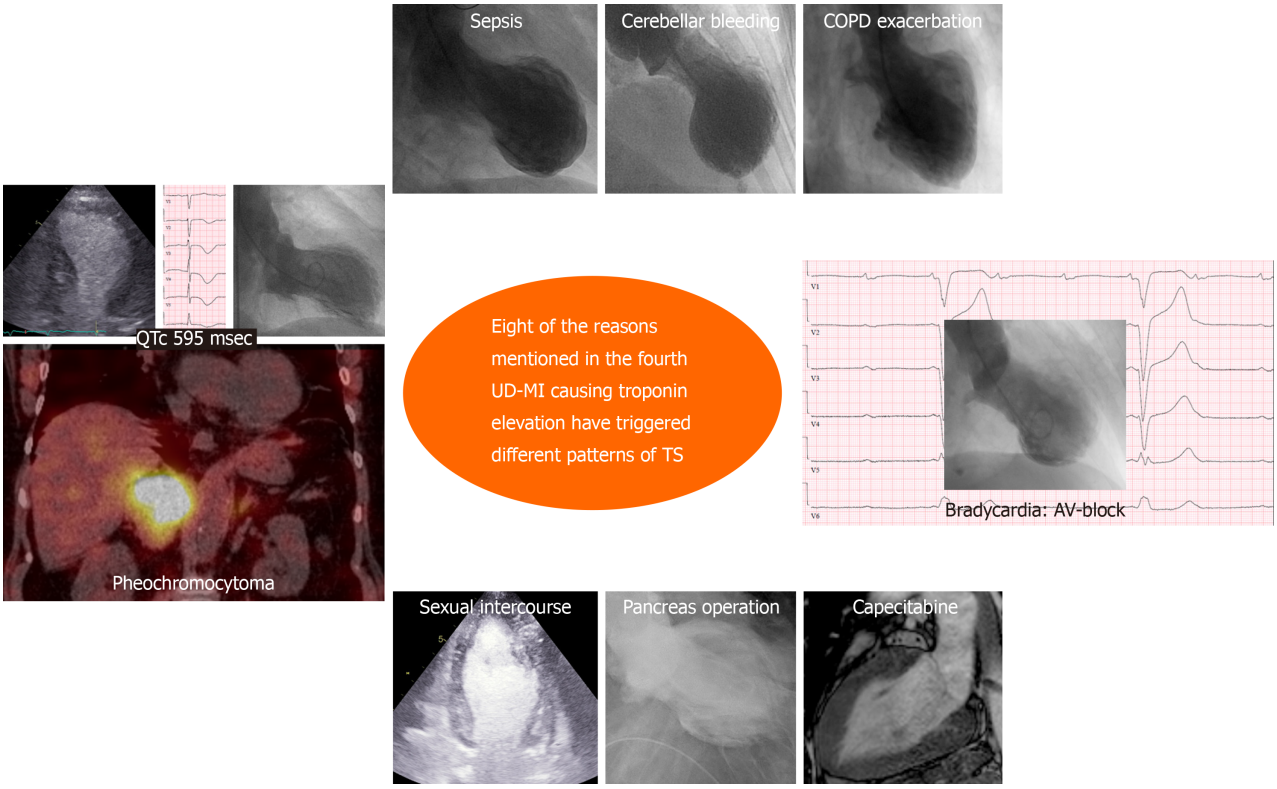

Figure 3 Eight clinical conditions causing troponin elevation have triggered different patterns of takotsubo syndrome. Most of the reasons for troponin elevation mentioned in the fourth universal definition of myocardial infarction have been reported to trigger takotsubo syndrome. In this figure, 8 of the mentioned reasons (pheochromocytoma, sepsis, cerebellar bleeding, chronic obstructive pulmonary disease with acute exacerbation, heart block, capecitabine, pancreas operation, and strenuous physical exercise in the form of sexual intercourse) triggering different ballooning's pattern of takotsubo syndrome are demonstrated.

most of the disease conditions mentioned that cause troponin elevation is directly or indirectly associated to TS or TS-related syndromes discussed below. The mechanism of troponin elevation will be the same as that of TS[5,44,45].

TS-RELATED DISEASE CONDITIONS

In addition to the distinctive circumferential LVWMA, TS have also other characteristic features namely: The repolarization ECG changes[46]; modest troponin elevation with a rise and/or fall pattern; patchy LGE or myocarditis like changes on CMR imaging[33]; and the contraction band necrosis on histopathological examination[37]. However, all the afore-mentioned constellations of findings are not always found in TS. Many of the clinical diseases reported to cause troponin elevations, as among others stroke, subarachnoid hemorrhage[42], sepsis[41], chronic obstructive pulmonary diseases[2], and pheochromocytoma[40] have been reported to trigger TS. However, the same clinical condition may cause repolarization ECG changes, troponin elevations, chemical (norepinephrine) myocarditis on CMR imaging, or contraction band necrosis alone or in combination without any LVWMA[42]. One plausible explanation for the absence of LVWMA in TS-related conditions may be the swift reversibility of LVWMA, which can occur within minutes, hours, or days in some cases of TS[6]. Typically, among patients with acute subarachnoid hemorrhage[42], up to 70% may show left ventricular diastolic dysfunction. In 67%, ECG changes may be present including repolarization abnormalities, in 30% troponin elevation[47], and only near 20% LVWMA. Consequently, substantial numbers of patients with subarachnoid hemorrhage may be complicated by repolarization ECG changes and troponin elevation without LVWMA. The same pattern of findings is seen in pheochromocytoma-and paraganglioma-induced acute cardiac disease[31,40,48]. During the last 10 -15 years, dozens of cases of pheochromocytoma-triggered TS have been reported[40]. For more than 50 years, cases of pheochromocytoma-induced acute "focal myocarditis", confirmed by either endomyocardial, autopsy[49], or by CMR imaging[35] have been reported. Critical analysis of some of these reports shows that those patients have features consistent with TS also[35]. As late as 2018, Khattak *et al*[35] reported on a case

with pheochromocytoma and CMR imaging findings consistent with acute myocarditis at the basal segments of the left ventricle. However, the ECG findings and the hypokinesis of the basal segments with cardiac image studies (echocardiography and CMR) argue strongly for inverted TS. CMR imaging may show patchy LGE in about one third of patients with TS[33]. Cases of pheochromocytoma-induced chest pain and ECG findings of MI have also been reported[50-52]. Analysis of some of those cases reveals findings consistent with TS. In 1983, McGonigle *et al*[51] reported on a case of "recurrent MI" in a patient with pheochromocytoma. During one admission, the patient had reversible marked ST elevation and the coronary arteries were normal. Left ventriculography revealed discrete left ventricular apical "aneurysm" with thrombus in the aneurysmal sac. This case can justifiably be deemed as recurrent TS triggered by pheochromocytoma with our current knowledge about TS[31]. Cases of reversible pheochromocytoma-induced cardiomyopathy with features consistent with global TS have also been reported[31]. Cases of pheochromocytoma-induced hypercontracted sarcomere and contraction band necrosis as that seen in TS has also been reported[53]. A similar pattern of ECG changes, troponin elevations, LVWMA, or histopathologic findings of contraction band necrosis, alone or in different combination is seen in other diseases reported to trigger TS as sepsis[41,43,54,55]. Consequently, substantial numbers of disease conditions may cause a continuum of manifestation as troponin elevation, ECG repolarization changes, and other features seen in TS without causing LVWMA; all driven by the same pathophysiology of TS described below and these conditions are coined here as TS-related conditions.

RECURRENT AND CHRONIC ANCA SYNDROME (RECURRENT AND CHRONIC TS)

The recurrence rate of TS has ranged from 0 to 22%[25,56]. In patients with pheochromocytoma- and paraganglioma triggered TS, a recurrence rate of 17.7% has been reported[31,40], which is most probably due to undiagnosed pheochromocytoma where the trigger factor remains and result in recurrent TS[31]. These repeated TS episodes may lead to permanent myocardial damages resulting in "pheochromocytoma induced cardiomyopathy[57]. There are two other clinical conditions, which may cause mild to moderate troponin elevation in a chronic form and they are decompensated CHF[58] and CKD[59]. Acute exacerbation of CHF is a well-known cause of troponin elevation. Critical review of the sequence of events occurring in decompensated CHF reveals events resembling that happen in TS but in chronic form[58,60]. In both TS and decompensated CHF, there are evidences for the local cardiac sympathetic disruption and norepinephrine seethe and spillover triggered by a physical stress or an emotional trigger in TS and by multiple trigger factor in decompensated CHF. This sympathetic disruption causes a unique circumferential LVWMA resulting in a conspicuous ballooning of the LV in TS; worsening of LVWMA in CHF causes remodeling of the LV and changing the LV geometry from ellipsoid to spherical shape[58]. The LVWMA is transient in TS and the worsening of the LVWMA in CHF is also reversible when properly treated. Both conditions are characterized by modest elevation of the cardiac troponins and marked elevation of NT-pro- BNP. The difference between the two conditions is that the above-mentioned sequence of events occurs acutely in TS and chronically with acute exacerbation in CHF[2,58]. Consequently, chronic ANCA with acute exacerbation may be the main pathogenesis for the increased morbidity and mortality in patients with decompensated CHF irrespective of the underlying cause of heart failure[58].

The second chronic condition which may cause chronic troponin elevation is CKD[59]. Heart failure and cardiovascular death are common in patients with CKD and extremely prevalent in patients undergoing dialysis[59]. Evidences supporting the occurrence of sympathetic over-activity in patients with dialysis and non-dialysis dependent CKD[59] are substantial. Several studies have also been reported on reversible segmental LVWMA consistent with myocardial stunning in association with dialysis especially hemodialysis[61]. In the literature, the most acceptable underlying cause for the myocardial stunning in CKD is "demand myocardial ischemia", which has never been confirmed. However, the repeated reversible myocardial stunning and the occurrence of cardiac sympathetic overactivation disruption in patients with CKD can be compared to that occurring in acute TS where the acute circumferential pattern of myocardial stunning is most probably caused by the local cardiac sympathetic disruption and norepinephrine seethe and spillover[5,45].

EVIDENCES FOR HYPERACTIVATION OF AUTONOMIC (SYMPATHETIC) NERVOUS SYSTEM IN TS AND TS-RELATED SYNDROMES

Evidences for the involvement of the autonomic nervous system including local cardiac sympathetic system in the pathogenesis of TS and TS-related conditions are substantial[6,45] and include: (1) The profound suffering that arises from bereavement and induces myocardial stunning in an individual reflects the feeling and the degree of sadness of that individual for the loss of another. This highly argues for the extreme sympathetic stimulation of the myocardium likely mediated via the neurocardiogenic cause of TS[45]. (2) Acute brain diseases and injuries or brain death is a well-recognized trigger factor of TS[42,45] indicating that TS is a neuro-cardiac disease. (3) The prevalence of diabetes mellitus is low in patients with the first episode of TS[62]. Remarkably, the prevalence of diabetes in patients with TS recurrence is also significantly lower compared to those without TS recurrence[63]. Autonomic neuropathy as a complication in patients with diabetes mellitus may lead to brain-heart disconnection and may have protective cardiac effects in situations with powerful emotional or physical stress factors[62]. (4) Signs of cardiac sympathetic denervation assessed by 123 meta-iodobenzylguanidine (^{123}I-MIBG) scintigraphy is detected in patients with TS[64]. The principal ^{123}I-MIBG scintigraphic findings are reduced regional uptake of the ^{123}I-MIBG in the hypokinetic/akinetic left ventricular segments and augmented washout rate of ^{123}I-MIBG[64]. (5) One of the characteristic electrocardiographic changes in TS is sympathetic T-wave changes in the form of T-wave inversion and prolongation of the corrected QT-interval[46]. Patients with TS and long QTc may suffer life threatening arrhythmias as torsade's de pointe and asystole, ventricular tachycardia, ventricular fibrillation, usually in the subacute phase of the disease[65]. Remarkably, the sympathetic nervous system plays also a central role in the pathogenesis of the congenital long QT syndrome (LQTS). Physical manipulations of the stellate ganglia have produced dramatic ventricular irritability arrhythmia in LQTS and removal of the left stellate ganglion normalized the electrocardiographic abnormalities[66]. A distinct regional pattern of impaired cardiac sympathetic function, assessed by ^{123}I-MIBG scintigraphy, is identified in the majority of symptomatic LQTS patients[67]. Interestingly, the episodes of arrhythmias in congenital LQTS are often associated with, if not precipitated by a physical or an emotional[66] as that in some patients with TS. (6) Increased nor-epinephrine levels in the coronary sinus have been demonstrated in patients with TS, suggesting increased local myocardial nor-epinephrine release from the cardiac sympathetic nerve terminals[68]. Intracranial disease processes including subarachnoid haemorrhage and brain death are well-recognised physical trigger factor for TS. Increased myocardial interstitial, but not plasma, nor-epinephrine release have been proved after brain death induction in pigs[69]. The local myocardial nor-epinephrine spill-over may explain the focal myocarditis changes seen in some patients with TS; focal myocarditis in TS has been confirmed both by endomyocardial biopsy[70] and even in the form of patchy LGE by CMR imaging[33,35]. (7) One of the vital and consistent histopathological changes in TS are the hypercontracted sarcomeres and contraction bands[37]. In a baboon model of catastrophic cerebral insult, Novitzky *et al*[71] demonstrated that contraction band necrosis could be prevented by cardiac denervation (cardiac sympathectomy) but not by vagotomy. (8) A remarkable finding in 2 of the 3 cases with successful heart transplantation of donor heart afflicted by TS was the documentation of a rapid resolution of LVWMA occurred at the accomplishment of heart transplantation; the simultaneous surgical sympathectomy in association with the donor cardiectomy may have resulted in relief of the myocardial stunning (cardiac cramp) caused by disinhibition of the cardiac sympathetic tone during donor brain death[5]. (9) Templin *et al*[72] have recently demonstrated evidence for hypoconnectivity of the central brain regions associated with autonomic function and regulation of the limbic system in patients with TS. The investigators deemed that those findings suggest that autonomic-limbic integration might play an important role in the pathophysiology and contribute to the understanding of TS. And (10) The LVWMA in TS has a characteristic systematized pattern. It affects the ventricular myocardium circumferentially with a sharp transition between the normal or hyperkinetic myocardium and the stunned myocardium[5,73]. The heart is densely innervated with sympathetic nerves, which are distributed on a regional basis. The pattern of LVWMA in TS appears to follow the anatomical sympathetic innervation from the left and right stellate and caudal ganglia[5,74]. The left ventricular systolic dysfunction after subarachnoid haemorrhage was studied in 30 patients by Zaroff *et al*[75]. The authors observed that many of regional wall motion patterns did not follow a coronary artery supply territory but correlated with the distribution of the myocardial sympathetic

nerve terminals providing an indirect evidence for a neuro-mediated mechanism of myocardial injury[75]. This circumferential pattern of LVWMA is congruent with cardiac nerve distribution[76,77]. Details of further evidence for the local cardiac sympathetic nervous system involvement in TS is described elsewhere[5,6,44,45]. For these reasons, it will be plausible to coin TS and TS-related disease conditions as ANCA syndrome.

MECHANISM OF TROPONIN ELEVATION IN ANCA SYNDROME (INCLUDING TS)

The cardiac specific isoforms, cardiac troponin T and cardiac troponin I, are components of the troponin complex. This consists of proteins attached to the myofibrils of the contractile apparatus in cardiomyocytes, but 6% of cardiac troponin T and 3% of cardiac troponin I exist in an unbound free form in the cytosol[78]. The discussed mechanisms of troponin elevation in the literature are: Myocardial ischemia, inflammatory and immunological processes, trauma, drugs and toxins.

Some investigators believe that troponin elevation indicates myocardial injury. However, troponin elevation in association with exercise and even during walking[78], no delayed gadolinium enhancement in the CMR imaging in the almost two thirds of patients with TS[2] and in patients classified having so called "T2MI" or "MINOCA"[10-13] argue against myocardial injury in every patient with troponin elevation. Exocytosis of the early releasable unbounded cytosolic troponin free pool into the blood stream from hypercontracted cardiomyocytes by neuro-adrenergic stimuli may be the most probable cause of elevated cardiac troponin values in TS and TS-related disease conditions *i.e.*, ANCA syndrome. There are findings in TS that may support the exocytosis mechanism of troponin release (Figure 4). The LVWMA in TS has the characteristic features of myocardial stunning[5], where the myocardium is in a state of cardiac cramp[79], which may cause release of the troponin through squeezing the unbound cytosolic troponin free pool[79,80]. This may explain the only mild-moderate elevation of troponin in all TS and TS-related disease conditions and even in decompensated CHF with acute exacerbation and CKD.

The evidence for the myocardial cramp in TS is discussed in details elsewhere[5] and will be briefed here: The systo-diastolic compression of the left anterior descending artery segments with myocardial bridging during the acute and sub-acute stages of TS and the relief of the diastolic compression during recovery of the LVWMA argues for the fact that the myocardial stunning in TS is in a cramp state[79] (Figure 5). The evidence of slow flow in the coronary arteries especially in the left anterior descending artery may indicate the increased microvascular resistance to the coronary flow caused by rigid stunned myocardium[5] (Figure 6). The valve-like hyperactive motility of the basal segments of the left ventricle in the mid-apical or mid-ventricular TS pattern and the slingshot-like motion of the apical segments in the apical sparing TS pattern is partially attributed to the stiff and rigid hypo-/akinetic involved segments in TS[5,80]. One of the important and consistent histo-pathological changes in TS is the presence of contraction bands and hyper-contracted sarcomeres[37]. This morphologic histopathologic alteration seems to constitute a spectrum, with mere hypercontraction at one end to cardiac rupture at the other. The hypercontracted sarcomeres may squeeze the unbound cytosolic troponin causing mild-moderate troponin elevation. In advanced and repeated episodes of TS, it may lead to necrosis where the cardiomyocyte dies in tonic state. A typical condition for recurrent TS is that occurring in undiagnosed pheochromocytoma and paraganglioma[31,40], and for repeated myocardial stunning is that occurring in CKD[59].

PROPOSAL FOR THE DIAGNOSIS OF MYOCARDIAL INFARCTION AND THE MAIN CAUSES OF TROPONIN ELEVATION

Because of the reasons mentioned above about the different types of MI, the currently used classification of MI needs urgent reassessment. Consequently, to diagnose MI and its differential diagnoses, the following investigations are required: Detection of a rise and/or fall of cTn values with at least one value above the 99th percentile upper normal limit, clinical presentation (cardiac signs and symptoms), ECG changes, invasive CAG findings, and cardiac imaging studies such as: Echocardiography, left ventriculography, and in some cases CMR imaging. The working diagnosis should concentrate on the following main causes of troponin elevations: (1) Coronary

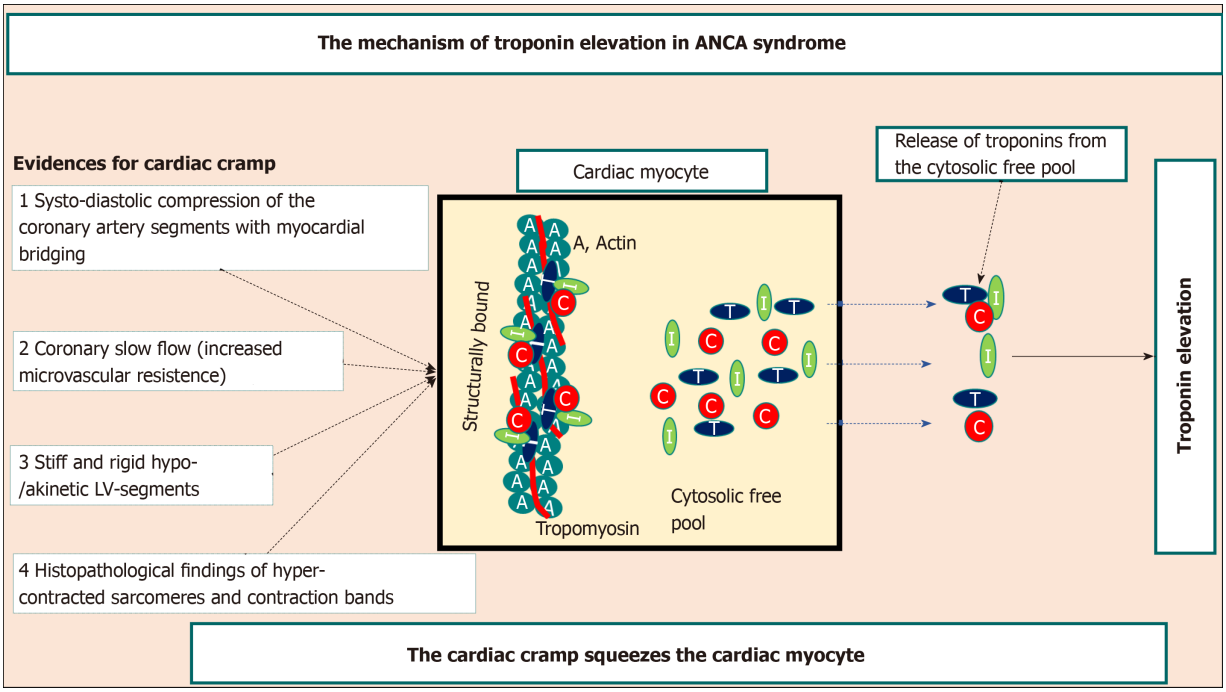

Figure 4 Mechanism of troponin elevation in autonomic neurocardiogenic syndrome. Illustration of the hypothetical mechanism of troponin release in autonomic neurocardiogenic syndrome including takotsubo syndrome and takotsubo-related conditions. The systo-diastolic compression of a coronary artery segment specially left anterior descending artery with myocardial bridging, the coronary slow flow due to increased microvascular resistance, the stiff and rigid myocardial stunning, and the hyper-contracted sarcomeres indicate that the affected myocardium in autonomic neurocardiogenic syndrome including takotsubo syndrome is in a state of cardiac cramp. This cardiac cramp may squeeze the cardiac myocyte causing release of troponins from the cytosolic free pool resulting in mild-moderate troponin elevation as demonstrated in the figure. C: Troponin C; I: Troponin I; T: Troponin T; ANCA: Autonomic neurocardiogenic.

ischemic mechanism and consequently MI (caused by coronary atherothrombotic changes, SCAD, coronary thrombo-embolism, epicardial coronary spasm, myocardial bridging with coronary compression, percutaneous coronary intervention-related, or coronary artery bypass graft surgery-related); (2) ANCA causes of troponin elevation (TS and TS-related disease conditions). The research should be concentrated on neurocardiogenic diseases, which has been disregarded and regrettably to say blocked by the UD-MI for many years; (3) Inflammatory and toxic cell destruction; and (4) Other miscellaneous causes.

CONCLUSION

The clinical criteria for the diagnosis of MI according to the fourth UD-MI document show controversial aspects. T2MI and MINOCA are not evidence-based. Most of the cases included under MINOCA have no MI and some of those with MI have missed obstructive instead of nonobstructive coronary arteries. In addition, the UD-MI have blocked thoughts to search for mechanisms other than coronary ischemia that may cause troponin elevation. The clinical diagnostic criteria of T1MI, T2MI, T3MI, and MINOCA need to be revised categorically. ANCA caused troponin elevation is probably the second most common cause of troponin elevation after acute coronary ischemia. The mechanism of troponin elevation in ANCA syndrome is most probably due to cardiac cramp squeezing the cardiomyocyte causing mild to moderate release of troponin from the cytosolic free pool. ANCA syndrome may occur in an acute form as in TS or TS-related disease conditions. The syndrome may also occur in a recurrent or a chronic form as in undiagnosed pheochromocytoma, CHF with acute exacerbations, and in CKD. A proposal for the diagnosis of MI and its differential diagnosis and the main causes of troponin elevation is provided.

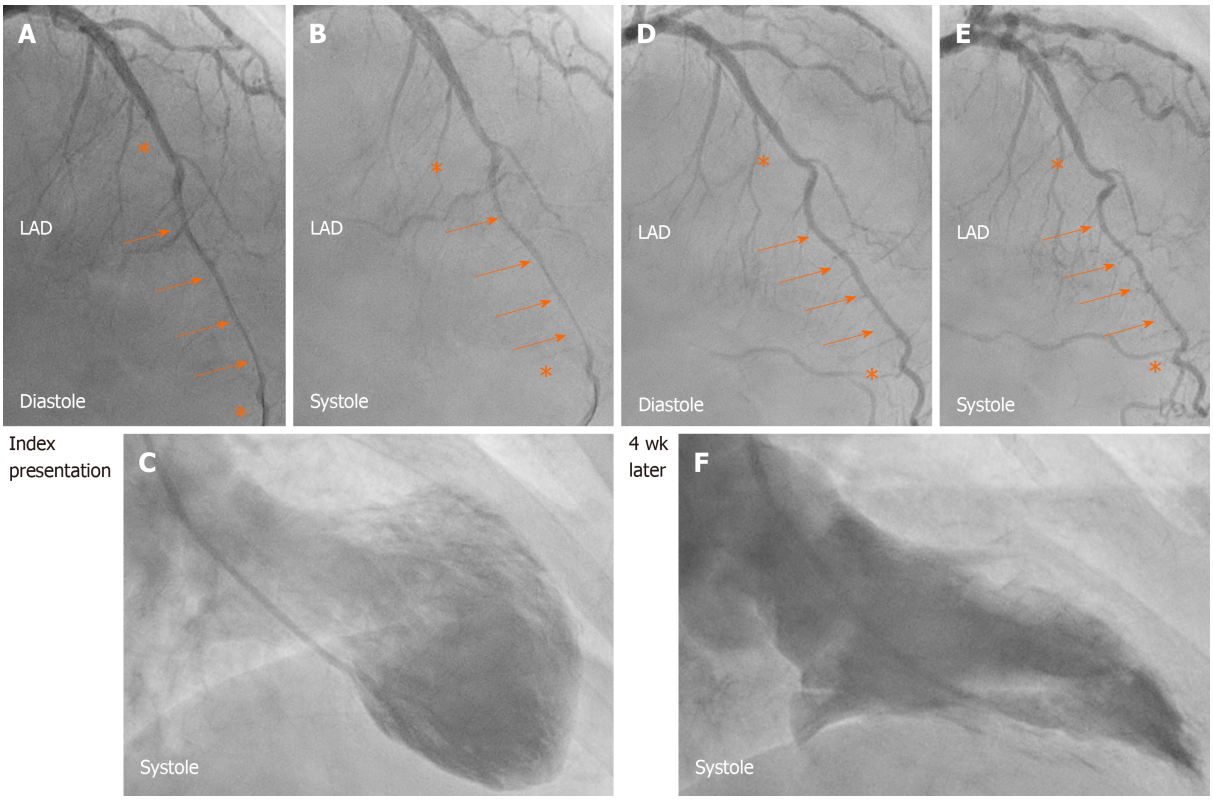

Figure 5 Systo-diastolic compression of a coronary artery segment with myocardial bridging. A, B, and C: Left anterior descending artery (LAD) during diastole (A) and systole (B) in the acute stage of takotsubo syndrome (TS) in a patient where contrast left ventriculography revealed mid-apical pattern of TS (C). During the acute stage of the disease: Note the diastolic and systolic compression of a segment of LAD with myocardial bridging (orange arrows) bordered by normal segments (Asterix) before and after the segment with myocardial bridging. D, E, and F: Four weeks later, there was complete relief of LAD compression during diastole (D, orange arrows) and only mild systolic compression (E, orange arrows) after normalization of left ventricular function (F). This indicates that the stunned myocardium was in a cramp state during the acute-subacute stage of TS. LAD: Left anterior descending artery.

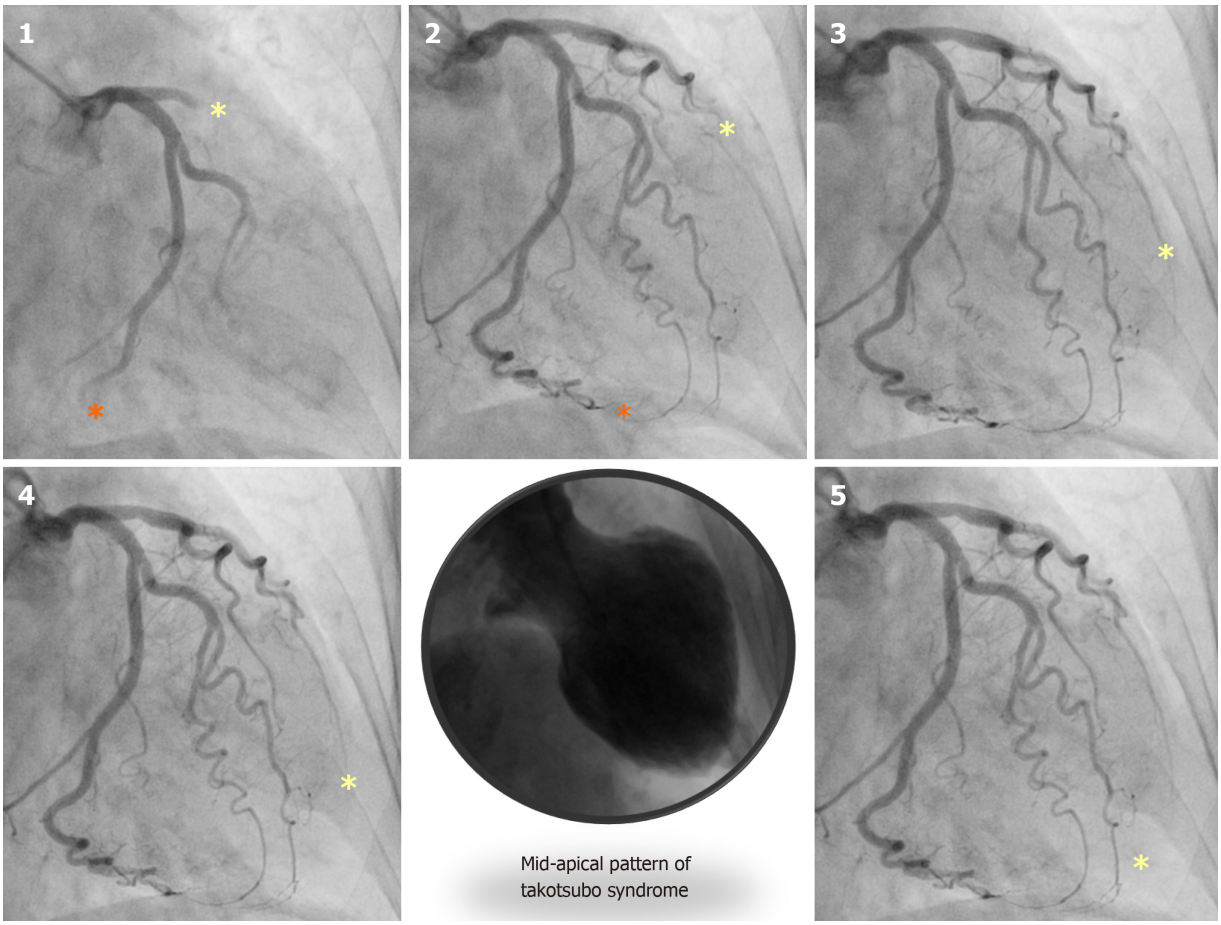

Figure 6 Slow flow in the left anterior descending artery in a patient with takotsubo syndrome. A case of mid-apical ballooning pattern of takotsubo syndrome (middle, lower panel) showing the marked slow flow in the left anterior descending artery (yellow Asterix) compared to left circumflex artery (orange Asterix) in panel 1 to 5.

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MINIREVIEWS

Cardiovascular magnetic resonance in myocardial infarction with non-obstructive coronary arteries patients: A review

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Abstract

The diagnosis of myocardial infarction with non-obstructive coronary arteries (MINOCA) necessitates documentation of an acute myocardial infarction (AMI), non-obstructive coronary arteries, using invasive coronary angiography or coronary computed tomography angiography and no clinically overt cause for AMI. Historically patients with MINOCA represent a clinical dilemma with subsequent uncertain clinical management. Differential diagnosis is crucial to choose the best therapeutic option for ischemic and non-ischemic MINOCA patients. Cardiovascular magnetic resonance (CMR) is able to analyze cardiac structure and function simultaneously and provides tissue characterization. Moreover, CMR could identify the cause of MINOCA in nearly two-third of patients providing valuable information for clinical decision making. Finally, it allows stratification of patients with worse outcomes which resulted in therapeutic changes in almost half of the patients. In this review we discuss the features of CMR in MINOCA; from exam protocols to imaging findings.

Key words: Cardiovascular magnetic resonance; Acute coronary syndrome unobstructed coronaries; Acute myocardial infarction; Acute myocarditis; Takotsubo cardiomyopathy

Core tip: Cardiovascular magnetic resonance (CMR) plays a key role in myocardial infarction with non-obstructive coronary arteries (MINOCA) patients. A CMR study protocol to evaluate MINOCA patients should include evaluation of cardiac structure

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and function and tissue characterization with evaluation myocardial injury. With this approach CMR could identify the cause of MINOCA in nearly two-third of patients (acute myocardial infarction, acute myocarditis, takotsubo syndrome and other causes) providing valuable information for clinical decision making and allows stratification of patients with worse outcome.

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INTRODUCTION

The diagnosis of myocardial infarction with non-obstructive coronary arteries (MINOCA) necessitates documentation of an acute myocardial infarction (AMI) according to the universal definition, non-obstructive coronary arteries, using invasive coronary angiography (ICA) or coronary computed tomography angiography (CCTA) and no clinically overt cause for AMI[1]. Possible causes of MINOCA include ischemic diseases such as coronary plaque - with less than 50% stenosis-rupture or erosion, coronary embolism, coronary dissection and microvascular coronary spasm or myocardial disorders such as myocarditis, Takotsubo (TS) and other cardiomyopathies, and finally non-myocardial disorders such as pulmonary embolism[2]. Historically patients with MINOCA represent a clinical dilemma with subsequent uncertain clinical management[1,3,4]. Differential diagnosis is crucial to choose the best therapeutic option for ischemic and non-ischemic patients[5]. A recent study stated that cardiovascular magnetic resonance (CMR) could identify the cause of MINOCA in 74% of cases[3]. Therefore, since CMR is able to analyze cardiac structure and function simultaneously and provides tissue characterization, it "should be a mandatory test[6]" to evaluate the patients, providing valuable information for clinical decision making.

Moreover, a study[7] showed that the CMR allows stratification of patients with worse outcomes which resulted in therapeutic changes in almost half of them. In particular, a CMR confirmation or exclusion of myocardial infarction (MI) allows tailored medical therapy, including secondary prevention and avoiding the use of antiaggregant therapy and the subsequent bleeding risks[3]. Furthermore, CMR can promptly identify many underlying conditions responsible for MINOCA, such as acute or chronic myocarditis, TS and other cardiomyopathies. A summary of the causes of MINOCA that can be identified by CMR is shown in Figure 1. In this review is discussed the features of CMR in MINOCA, from exam protocols to imaging findings.

CMR STUDY PROTOCOL

In MINOCA patients the CMR study should be performed within 7 d from symptom onset in order to prevent false negative results or underestimation of the disease extent[8]. It should also be underlined that the examination should not be performed too early, but at least 24 h after disease onset, to avoid too early or overt signs of pathology. Furthermore, in case of negative CMR but with clinical evidence of myocardial involvement, it may be useful to repeat the test between 1 and 2 wk after the initial study to make the correct diagnosis[9].

A CMR study protocol to evaluate MINOCA patients should include evaluation of cardiac structure and function with cine imaging, presence and pattern of myocardial edema with T2-weighted short-tau inversion recovery (T2w-STIR) image and presence and pattern of myocardial injury with late-gadolinium enhancement (LGE) imaging. Moreover, the use of new semiquantitative tissue characterization techniques, T1 and extracellular volume (ECV) and T2 mapping are recommended, due to their excellent sensitivity, specificity and diagnostic accuracy in detection of myocardial damage[10].

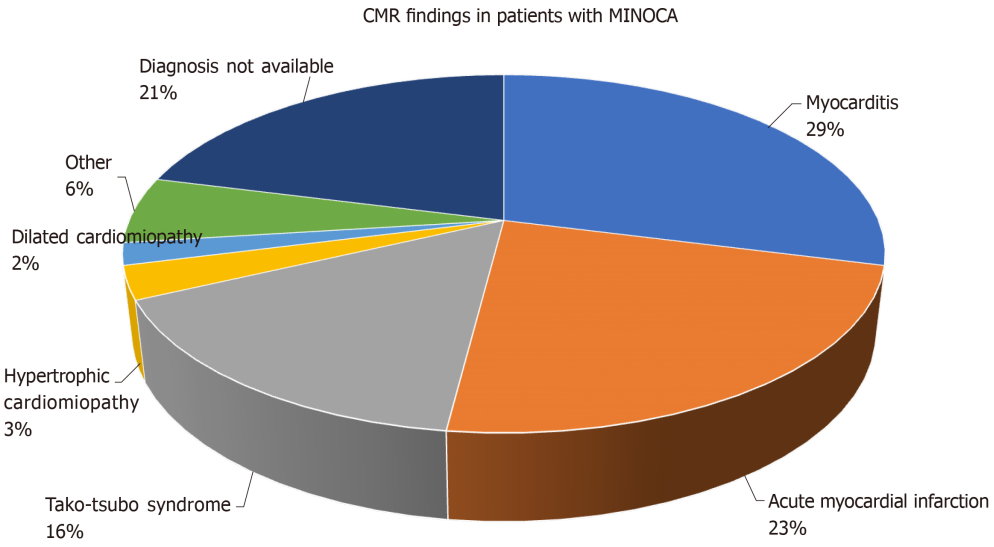


Figure 1 Cardiovascular magnetic resonance findings in patients with myocardial infarction with non-obstructive coronary arteries. Adapted from Pasupathy S *et al*[13]. CMR: Cardiovascular magnetic resonance; MINOCA: Myocardial infarction with non-obstructive coronary arteries.

AMI

The AMI criteria for MINOCA are defined by the "Fourth Universal Definition of Myocardial Infarction": (1) Clinical signs of ischemia; (2) Abnormal cardiac troponin value; and (3) at least one of: Symptoms of cardiac ischemia, electrocardiogram (ECG) changes (ischemic or development of Q-waves), imaging evidence of and ischemic pattern or identification of coronary thrombus by ICA or autopsy[11]. The diagnosis of MINOCA requires non obstructive coronary arteries on ICA or CCTA (no stenosis ≥ 50%)[12]. MINOCA patient characteristics differ from those of other AMI and coronaropathic patients because they are younger, more often female with fewer traditional cardiovascular risk factors[13].

In the absence of relevant coronary arteries disease, myocardial ischemia may be triggered by a disorder of epicardial arteries and/or malfunction in the microcirculation. Many atherosclerotic plaques show positive-outward remodeling with high risk features such as a lipid-core and a thin fibrous-cap. In this plaque, the intermittent and partial thrombosis produces distal embolization, with potential superimposed vasospasm, which may be responsible for MINOCA. Sometimes these alterations are not visible on ICA, in this sense, the use of techniques such as intravascular ultrasound (IVUS) that allow direct visualization of the vessel wall can play a key role in evaluation of the lesion[14]. In addition, an assessment with IVUS helps to predict future events based on the evaluation of plaque characteristics. Thrombosis may be a trigger to AMI in plaque disruption, coronary artery spasm, or in the absence of these conditions may be the cause of MI. Hereditary or acquired thrombotic disorders can give coronary thrombosis. Spasm of the coronary arteries may theoretically lead to AMI pathogenesis. It represents hyper-reactivity of the vascular smooth muscle to endogenous vasospastic agents, but can also happen in the presence of exogenous vasospastic agents (*e.g.*, cocaine or methamphetamines). In accordance with this, a recent study reported a rate of positive provocative tests in 46% of patients with MINOCA[15]. Positive testing was associated with an increased rate of death from any cause and cardiac death during follow up[15]. Calcium channel blockers and nitrates can be used to treat patients with vasospastic angina.

Spontaneous coronary artery dissection is a rare cause of AMI that is characterized by non-traumatic and non-iatrogenic displacement of the coronary arterial wall with the development of a false lumen filled with intramural hematoma. Dissection may not always be evident on ICA, resulting in the diagnosis of MINOCA and coronary artery intramural hematomas accounting for 25% of MI in women under the age of 50[16]. It is still unclear why coronary dissection occurred. However, fibromuscular dysplasia is present in other vascular beds in most cases when screening is performed: Changes in intima-media composition due to hormones, pregnancy and delivery have also been implicated.

CMR imaging is a key diagnostic tool to be employed in MINOCA patients with suspected AMI (Figure 2). Imaging for contractile function is important to localize the area of injury and to evaluate the biventricular function and volume. Myocardial

edema is evaluated on T2w-STIR images and LGE allows for myocardial damage localization and gives insight into mechanisms. An area of LGE in the subendocardium (or a transural extension) indicates an ischemic cause of injury, but it does not specify the particular mechanism of ischemia, while a non-ischemic appearance of LGE (mesocardial or subepicardial localization) speaks in favor of other myocardial disorders such as myocarditis and other cardiomyopathies. Dastidar *et al*[3] reported that CMR, as a noninvasive imaging technique, can diagnose 3 out of 4 patients with MINOCA presentation; the strongest predictors of mortality are CMR diagnosis of cardiomyopathy and presence of ECG changes with ST-segment elevation.

ACUTE MYOCARDITIS

The term acute myocarditis refers to an inflammatory condition. Inflammation of the myocardium may occur as a result of exposure to external antigens such as viruses, bacteria, protozoa, drugs, toxins or as an autoimmune condition. While historically enteroviruses and coxsackievirus B were the most common identified pathogens, parvovirus B19 and human herpesvirus 6 are currently the most frequent myocarditis related infections[17]. CMR is indicated for patients with new onset or persisting symptoms suggestive of myocarditis (dyspnea, orthopnea, palpitations, chest pain, effort intolerance), in case of recent or ongoing myocardial injury (ventricular disfunction, ECG abnormalities, increase in troponin) or if viral etiology is suspected with no evidence of coronary stenosis on CCTA or ICA[9].

The clinical spectrum of myocarditis is wide and can be divided in three distinctive patterns[18]: (1) Infarct-like pattern, characterized by chest pain, fever, ST segment elevation on ECG and troponin rise; (2) Cardiomyopathic pattern with symptoms of left ventricle (LV) disfunction and heart failure (New York Heart Association class III or IV) without ECG, serologic or other systemic abnormalities; and (3) Arrhythmic pattern presenting with sudden ventricular arrhythmia without evidence of systemic infection/inflammation.

According to European Society of Cardiology Working group statement, the gold standard for myocarditis diagnosis is endomyocardial biopsy (EMB) after the exclusion of coronary heart disease[19]. However, latest guidelines on diagnosis and treatment of acute and chronic heart failure recommend CMR as a Class I procedure for the identification of myocarditis in patients with heart failure[20] and EMB remains recommended in patients with elevated troponin values and deterioration of cardiac impairment after maximal medical therapy. The use of CMR (Figure 3) prior to EMB could reduce false negatives due to incorrect sampling; furthermore CMR can provide information related to prognosis in patients affected by acute myocarditis and is an essential tool to rule out many possible conditions in case of MINOCA[1,2,16,21]. Moreover, it must be underlined, as recently reported[8] that the typical feature of a patients with a positive CMR for infarct-like myocarditis is a young male with chest pain, ECG alteration and remarkable myocardial necrosis enzyme surge, and in such cases the biopsy may not even be performed.

A recent metanalysis reported a prevalence of myocarditis up to 33% in MINOCA patients[13]. In case of MINOCA it is therefore mandatory to perform CMR and it has been reported that its systematic use in those patients led to a significant increase in detection rate of myocarditis[22].

In 2009 an expert consensus formulated the Lake Louise Criteria (LLC) for diagnosis of myocarditis with CMR[9] As reported above, the CMR protocol used in these patients consisted in evaluation of: (1) Presence and pattern of myocardial edema with T2w-STIR images: (a) Patchy areas of high signal intensity; (b) Subepicardial or septal layer of high signal intensity; (c) Transmural high signal intensity (consistent with but not specific for myocardial inflammation); and (d) Global high signal intensity evaluated through the T2-ratio technique; (2) Evaluation of hyperemia and capillary leakage through the evaluation of myocardial early gadolinium enhancement ratio that explore the regional vasodilation as an integral feature of tissue inflammation; and (3) Presence and pattern of necrosis and fibrosis with LGE imaging: (a) Patchy areas of enhancement; (b) Subepicardial or septal layer of enhancement; and (c) Transmural enhancement (consistent with but not specific for myocardial inflammation).

The above-mentioned tissue characterization criteria are evaluated in parallel to the cardiac structure and function with cine imaging for the presence of LV dysfunction with regional or global systolic disfunction and pericardial effusion which were considered supportive criteria, neither necessary nor sufficient for diagnosis. In patients with infarct-like myocarditis the systolic function is often preserved and the

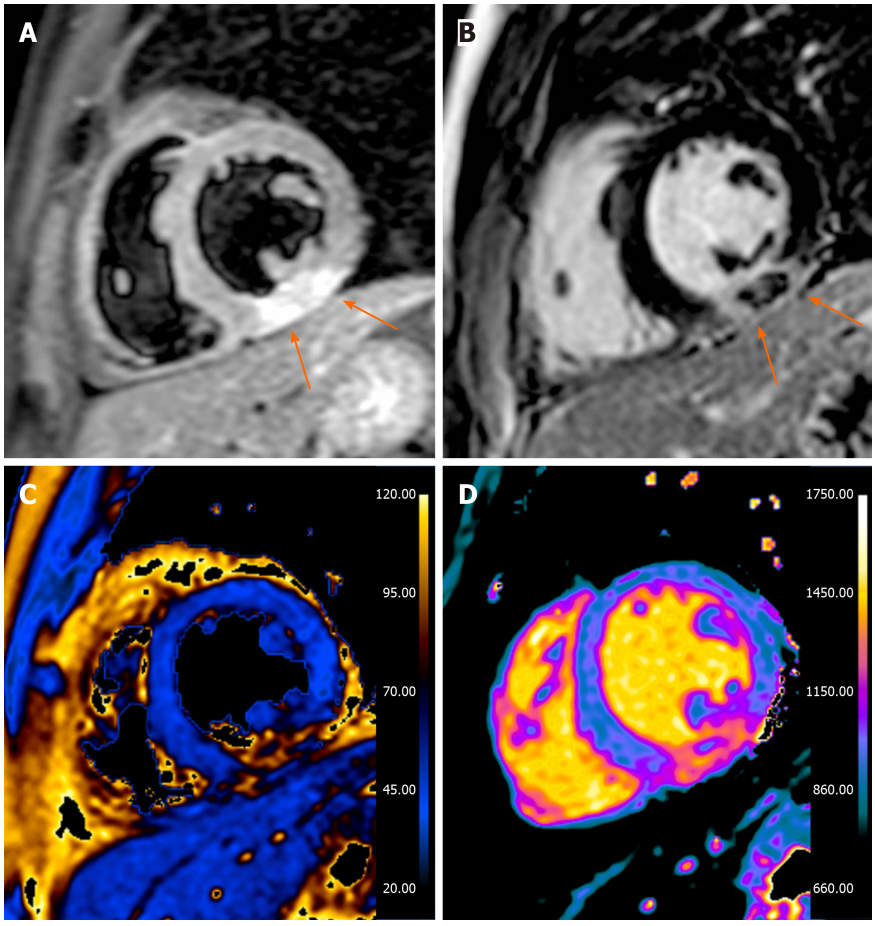


Figure 2 Thirty-three years old male presented with acute chest pain, nonspecific short-tau wave abnormalities, increased troponin values and negative invasive coronary angiography. A: Short axis T2-weighted short-tau inversion recovery image, a transmural hyperintense areas with central hypointensity is seen in the inferior wall (arrows); B: Late gadolinium enhancement image: the hypointense areas correspond with areas of microvascular obstruction and is thought to represent myocardial hemorrhage (arrows); C: T2 map; D: T1 map. The cardiovascular magnetic resonance study is in accordance with acute myocardial infarction with sign of microvascular obstruction and hemorrhage.

presence of segmental kinetics alterations are rare[23]. The use of advanced techniques for the analysis of myocardial deformation such as CMR feature tracking technique has been reporting promising results and could identify even subclinical myocardial dysfunction[24], but requires further confirmation in larger and prospective studies[25] in order to establish its diagnostic and prognostic role.

According to LLC, CMR findings are consistent with myocarditis if at least 2 out of 3 of the previous criteria are present, with a diagnostic accuracy of 78%[9]. A 2018 meta-analysis evaluating 22 acute myocarditis studies pointed out that using the full LLC criteria resulted in an Area under the curve (AUC) of 0.81 and individual parameter analysis resulted in 0.80 for increased T2 ratio/signal, 0.78 for early gadolinium enhancement and 0.87 for LGE[26].

However, the performance of LLC has also been discovered to be heavily dependent on clinical presentation: CMR sensitivity with classic LLC has been demonstrated to be higher in patients with infarct-like pattern (80%) compared with cardiomyopathic pattern (57%) and arrhythmic pattern (40%)[27].

Recently new semiquantitative tissue characterization technique have been developed. The mapping techniques can derive T1 and T2 relaxation time and allow ECV calculation. These techniques provide a good accuracy equals or better than traditional sequences in diagnosis of acute myocarditis[28], in particular the reported AUC for T1 mapping was 0.95, for T2 mapping was 0.88 and for ECV 0.81.

Based on these consideration, at the end of 2018, Ferreira *et al*[29] (Table 1) released updated LLC according to which the diagnosis of myocarditis can be made using a "two out of two" approach in presence of myocardial edema evaluation on T2w-STIR images /T2-mapping and non-ischemic myocardial injury assessment on T1-mapping, ECV or LGE. The presence of pericarditis and LV wall motion abnormalities are still present as supportive criteria.

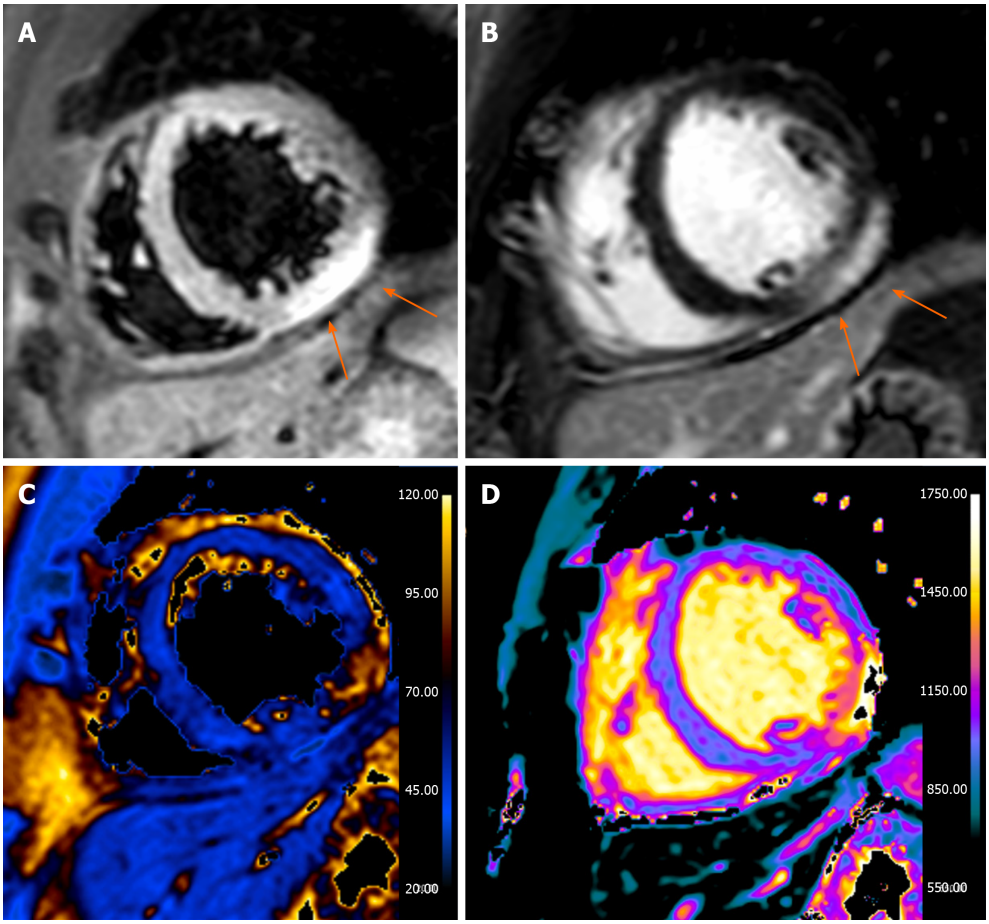


Figure 3 Thirty-seven years old male presented with acute chest pain, increased troponin values and negative invasive coronary angiography. A: A short axis T2-weighted short-tau inversion recovery image, a subepicardial and hyperintense areas is seen in the infero-lateral wall (arrows); B: Late gadolinium enhancement image with evidence of the same alteration (arrows); C: T2 map; D: T1 map. The cardiovascular magnetic resonance study is in keeping with acute myocarditis.

The prognosis of patients with "infarct-like" myocarditis is dubious: Some authors[30] reported an association between the infarct-like pattern and major cardiovascular events, while others[23] stated a positive evolution with a good prognosis. However, the presence of LV dysfunction at baseline and of LGE predicts patients at high risk of adverse events[31]. There are not yet consistent data on the prognostic role of mapping technique, mainly due to recent introduction in clinical practice.

TAKOTSUBO SYNDROME

Takotsubo syndrome affects about 2.5% of patients presenting with troponin-positive acute coronary syndrome (ACS)[32-35]. The term was firstly introduced in 1990 by Sato *et al*[36] and it derives from the Japanese word for octopus trap, which resembles the shape that LV assumes at the end of systole. During the last years a number of different names have been used in literature including "apical ballooning syndrome", "broken heart syndrome", "stress cardiomyopathy", and "ampulla cardiomyopathy".

Initially regarded as a benign condition, this syndrome is still a poorly recognized heart disease, with severe complications such as death, and a prognosis that does not differ from ACS[33]. There is a gender-difference in its incidence, and post-menopausal women are the most affected (80%-90%)[33]. Symptoms are similar to acute myocardial infarction (i.e. acute chest pain, dyspnea or syncope), and can be caused by a variety of physical or emotional triggers. Several pathophysiological mechanisms have been hypothesized, including plaque disruption, multivessel spasm, baroreflex abnormalities and catecholamine surge, with proof of evidence confirming this latter to play a key role in the myocardial injury[37].

Different diagnostic criteria have been proposed for TS (Table 2); LV dysfunction associated with wall motion abnormalities not limited to a specific coronary artery

Table 1 Cardiovascular magnetic resonance diagnostic criteria for acute myocarditis

	Original Lake Louise Criteria	2018 Lake Louise Criteria update
Main criteria	2 out of 3	2 out of 2
	T2-weighted imaging: Regional high T2 signal intensity or global T2 signal intensity ratio ≥ 2.0 in T2 weighted images	T2-based imaging: Regional high T2 signal intensity or global T2 signal intensity ratio ≥ 2.0 in T2 weighted images or regional or global increase of myocardial T2 relaxation time
	Early gadolinium enhancement signal intensity ratio myocardium/skeletal muscle of ≥ 4.0	T1-based imaging: regional or global increase of native myocardial T1 relaxation time or extracellular volume or areas with high signal intensity in a nonischemic distribution pattern in gadolinium enhancement images
	Late gadolinium enhancement: areas with high signal intensity in a nonischemic distribution pattern	
Supportive criteria (not necessary nor sufficient for diagnosis)	Pericardial effusion	Pericardial effusion or High signal intensity of the pericardium in late gadolinium enhancement, T1- or T2-mapping
	Left ventricular wall motion abnormality	Systolic left ventricular wall motion abnormality

Adapted from Ferreira *et al*[29].

territory is the most common[38]. As well as echocardiography and left ventriculography, CMR is able to identify LV wall motion abnormalities, and provides a more comprehensive assessment of right ventricle (RV) motility[39,40]. The most common presentation of TS is LV apical akinesia with preserved function of the remaining segments, which causes the typical "apical ballooning" appearance. Mid-ventricular type, basal or inverted type, focal variants, and isolated or concomitant RV akinesia have also been described but with lower frequency[6]. Wall motion abnormalities are reversible and complete recovery of systolic function has been demonstrated at 3 months follow-up[41].

Thanks to its high spatial resolution and three-dimensional image acquisition, CMR (Figure 4) represents a widely established method to non-invasively assess myocardial tissue, within a scanning time of 30 min[42]. Histologically, patients with TS typically present contraction bands, interstitial edema and mononuclear inflammatory response, which differs from the polymorphonuclear and lymphocytic inflammation seen respectively after myocardial infarction and myocarditis[43].

On CMR myocardial edema can be visualized by means of T2w-STIR images or assessed either on T1- or T2-mapping sequences, with increased values in both ballooning and non-ballooning segments[38]. Moreover, T2*-weighted imaging after injection of ultrasmall superparamagnetic particles of iron oxide has shown a diffusely increased myocardial uptake during the acute phase of TS, confirming the pathophysiologic role of tissue-resident myocardial macrophages and keeping with the theory of a catecholamine-mediated myocardial injury in TS[44,45].

Myocardial edema and inflammatory changes usually resolve without any myocardial scarring and with complete functional recovery at 3 months follow-up[41]. Usually no LGE is seen in TS patients, despite a few studies have shown subtle enhancement in akinetic segments, likely due to transient myocardial edema and delayed gadolinium washout[46,47]. However, these subtle changes should not be considered as a sign of myocardial necrosis.

In conclusion, wall motion abnormalities with matching myocardial edema distribution, and absent/subtle LGE represent the findings that allows CMR for providing a confident diagnosis of TS in patients with high serum troponin levels, and for differentiating this entity from myocardial infarction and myocarditis[48].

NEGATIVE CMR

Accordingly to a recent systematic review[49], the fourth finding at CMR per frequency (26% of cases) in case of MINOCA is the absence of wall motion abnormalities, edema or LGE. It has been known that the LGE technique has a necrosis detection threshold of about 1 g[50]. Therefore, patients with normal CMR may have either a limited necrosis or a necrosis spread over a wide area of myocardium, such that it is not highlighted. The doubt that in this subtype of patients the necrosis should be actually less extensive also comes from the fact that such patients often have lower peak troponin values at the onset of symptoms[51].

Vasospastic angina, coronary artery disease or coronary embolism may have

Table 2 International Takotsubo Diagnostic Criteria (InterTAK Diagnostic Criteria)[8]

No.	International Takotsubo Diagnostic Criteria
1	Transient left ventricular dysfunction (hypokinesia, akinesia, dyskinesia), manifests as apical ballooning or mid-ventricular, basal or focal wall motion abnormality, which usually extend beyond a single epicardial vascular distribution. Right ventricular involvement can be present
2	A mental, physical or mixed cause can precede the event of Takotsubo syndrome but this is not necessary
3	Takotsubo syndrome can be caused by neurological conditions (*e.g.* subarachnoid hemorrhage, stroke/transient ischemic attack, or seizures) as well as pheochromocytoma
4	Electrocardiogram changes (elevation or depression of the ST-segment, inversion of the T-wave and prolongation of the QTc); however, there are unusual cases without electrocardiogram changes
5	Elevation of cardiac biomarkers (troponin and creatine kinase)
6	Significant coronary artery disease could also be present in Takotsubo syndrome
7	Exclusion of acute myocarditis, in this case cardiovascular magnetic resonance is recommended
8	The pathology is common in postmenopausal women are predominantly affected

normal CMR findings; in these cases, IVUS may help to determine the underlying ischemic cause[52]. Moreover, another cause that must be considered when the CMR is negative is myocarditis; although diagnostic accuracy in patients with infarct-like presentation is the highest among the subtypes of myocarditis presentation, it does not reach 100%[27]. Finally, the possibility of pulmonary thromboembolism should not be ignored.

All in all, the number of negative CMR in MINOCA patients could be reduced in the near future with the introduction of new mapping techniques that seem promising and able to increase the sensitivity and specificity[10] and this will be of vital importance to the management of these patients, which is still a dilemma for clinicians.

OTHER CAUSES OF MINOCA

In a small percentage of MINOCA patients the results of CMR is hypertrophic cardiomyopathy (HCM) dilated cardiomyopathy (DCM) and other causes such as pericarditis and amyloidosis.

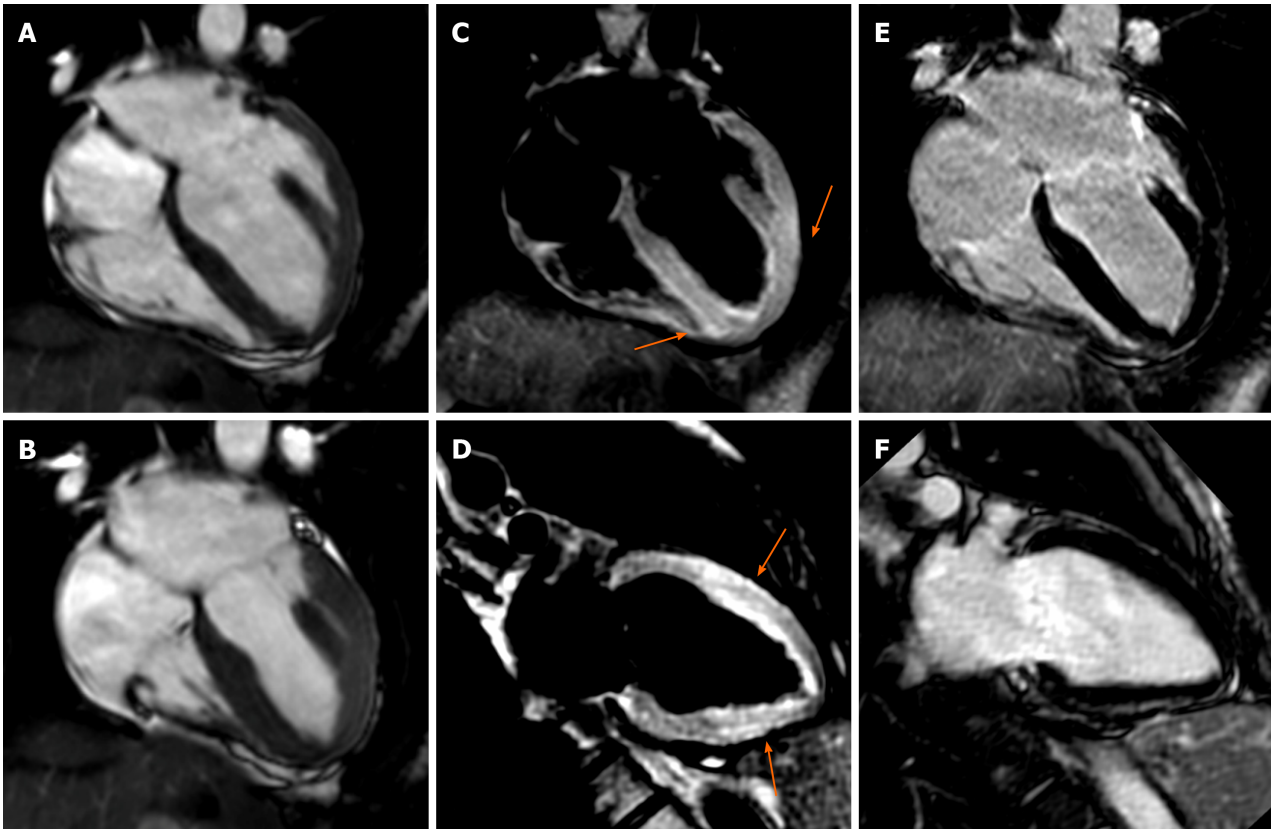
Hypertrophic cardiomiopathy

Coronary microvascular dysfunction is a common characteristic of HCM, even in the absence of symptoms and several studies indicated that patients with HCM had an impaired coronary flow reserve that may lead to cardiac ischemia. Microvascular disfunction in patients with HCM may be caused by several mechanisms such as structural abnormalities of small vessels, inadequate capillary density, fibrosis, myocyte disarray, and increased LV end-diastolic pressure[53,54].

In an acute setting, HCM patients present with increased ventricular myocardial thickness and could have hyperintense myocardial areas at T2w-STIR images, altered first pass perfusion and/or presence of LGE. The T2 alteration are likely to be associated with edema and may represent acute ischemic damage due to microvascular dysfunction. In addition, the presence of edema has been related to ventricular arrhythmias[55]. Moreover, first pass perfusion defects are related to microvascular disfunction and in association to the presence of LGE (*i.e.*, scar) that seems to be a marker of increased risk of non-sustained ventricular tachycardia episodes as a prognostic factor[56]. Concerning other mechanism that may cause ischemic insults, intramural coronary course has to be mentioned, however the impact of an intramural course of the coronary arteries on the clinical outcome of patients with HCM is unclear[57].

Dilated cardiomiopathy

Even if traditionally considered a "non ischemic" pathology, many studies have reported abnormalities of myocardial perfusion with moderate or severe adverse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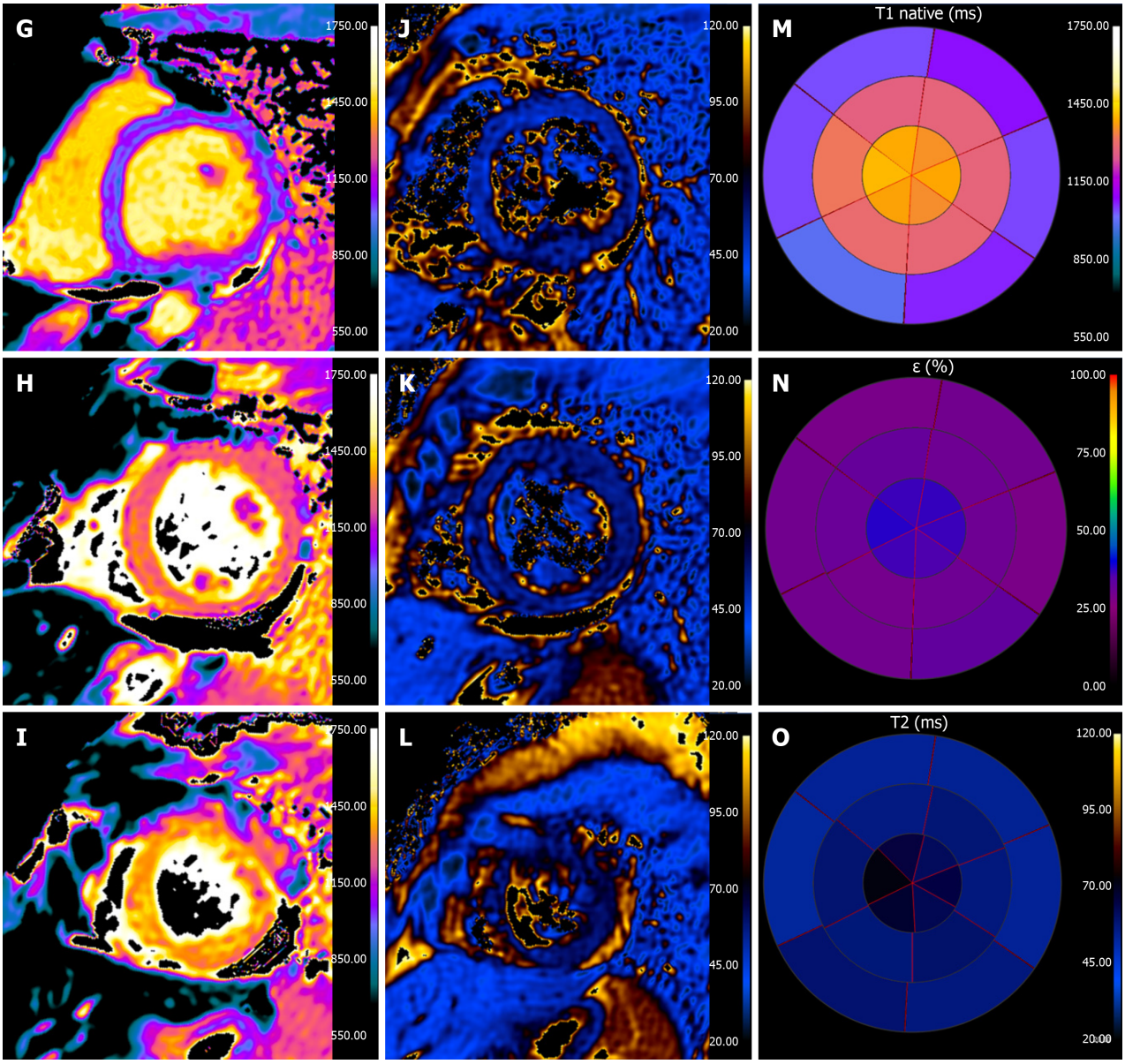

Figure 4 Thirty eight years old female presented with acute chest pain, increased troponin values and negative coronary angiogram. A and B: Diastolic and systolic 4-chamber cine-SSFP images: there is a minimum "apical ballooning" appearance with a relative left ventricle apical akinesia with preserved function of the remaining segments, which causes the typical "apical ballooning" appearance; C and D: T2-weighted short-tau inversion recovery images with evidence of myocardial edema in apical segments (arrows); E and F: Ate gadolinium enhancement images without presence of areas of increased signal intensity; G-I: T1-map; J-L: T2-map. M-O: T1 native, extracellular volume and T2 mapping bull's eye, there is a marked increase in values in the apical segments (T1 mapping: 1350 ms; extracellular volume: 38%, T2 mapping: 70 ms). The cardiovascular magnetic resonance images are in keeping with Takotsubo syndrome.

remodeling in DCM. A patient with DCM presents a dysfunction, stretched and enlarged ventricle with or without areas of LGE (*i.e.*, fibrosis). The typical pattern of DCM fibrosis is midwall and some research groups highlighted its prognostic value[58,59]. However, the pathophysiologic basis of midwall fibrosis are not completely understood, perfusion and microvascular abnormalities are thought to be implicated[60].

A previous study[61] found that stress and rest myocardial blood flow (MBF) in patients with DCM was decreased in LGE segments relative to others, indicating an association between abnormal perfusion and myocardial fibrosis. Such results indicate that fibrosis segments may exhibit microvascular anomalies, exemplified by the failure to increase MBF under stress, while impaired perfusion may merely represent decreased demand secondary to a reduced number of myocytes. However, if these pathological findings may drive to the development of an acute ischemic pathology, it is still unknown.

Amyloidosis

Amyloidosis is a restrictive cardiomyopathy resulting from deposition of abnormal

protein in the cardiac tissue[62]; the typical outcome of these patients is a diastolic dysfunction with heart failure symptoms and arrhythmias. However, some authors[63,64] highlighted a different aspect of cardiac amyloidosis: The presence of small vessel disease (intramural coronary artery), which led to fatal myocardial infarction. From a pathological point of view, a study on transplanted hearts demonstrated that the deposition of amyloid at the coronary artery level is frequent (over 90%), although it usually involves adventitia and vasa vasorum[65]. Therefore, most patients with primary systemic amyloidosis and cardiac involvement have obstructive intramural coronary amyloidosis; this finding is associated with microscopic ischemic changes demonstrating that myocardial ischemia may occur in these patients.

Pericarditis

Pericarditis may mimic myocardial infarction because of clinical presentation (chest pain may be sometimes difficult to be distinguished from ischemic pain, also because of myocardial involvement), cardiac enzyme elevations and ECG alterations. Based on its definition, in pericarditis coronary arteries must be unobstructed but they can be interested by contiguity from the inflammatory process[66]. A patient with acute pericarditis on CMR had thickening of the pericardium associated with effusion. The pericardium is hyperintense on T2w-STIR images and this is associated with LGE[67].

CONCLUSION

This review describes a summary of the main pathologies in which CMR makes it possible to do a differential diagnosis by providing therapeutic and prognostic information, underlining the importance of this imaging technique in MINOCA patients.

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ORIGINAL ARTICLE

Observational Study

Diagnostic and treatment utility of echocardiography in the management of the cardiac patient

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Abstract

BACKGROUND

Echocardiograms are an incredibly useful diagnostic tool due to their lack of harmful radiation, the relative ease and speed with which they can be performed, and their almost ubiquitous availability. Unfortunately, the advantages that support the use of echocardiography can also lead to the overuse of this technology. We sought to evaluate the physician perceived impact echocardiography has on patient management.

AIM

To evaluate the physician perceived impact echocardiography has on patient management.

METHODS

Surveys were distributed to the ordering physician for echocardiograms performed at our institution over a 10-wk period. Only transthoracic echocardiograms performed on the inpatient service were included. Surveys were distributed to either the attending physician or the resident physician listed on the echocardiogram order. The information requested in the survey focused on the indication for the study and the perceived importance and effect of the study. Observational statistical analysis was performed on all of the answers from the collected surveys.

RESULTS

A total of 103 surveys were obtained and analyzed. The internal medicine (57%) and cardiology (37%) specialties ordered the most echocardiograms. The most

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common reason for ordering an echocardiogram was to rule out a diagnosis (38.2%). Only 27.5% of physicians reported that the echocardiogram significantly affected patient care, with 18.6% reporting a moderate effect, and 30.4% reporting a mild effect. A total of 19.6% of physicians stated that there was no effect on patient management. Additionally, 43.1% of physicians reported that they made changes in patient management due to no change having occurred in the disease, 11.8% reported that changes in management were based on the recommendation of a specialist, and only 9.8% reported that further imaging was ordered due to the results of the echocardiogram. The majority of physicians (67.6%) considered an echocardiogram to be "somewhat essential" in the management of adult inpatients, with only 15.7% considering it "essential".

CONCLUSION
The majority of physicians surveyed report the echocardiogram had only a mild effect on management with only 27.5% reporting a significant effect. However, the majority of physicians (83.3%) perceived an echocardiogram to be somewhat or entirely essential for management. Only 9.8% reported the echo led to further imaging. These insights into ordering physician reasoning should help guide better definition of the optimal and ideal use of echocardiography.

Key words: Echocardiogram; Utilization; Cardiology; Inpatient; Survey; Management

Core tip: The echocardiogram is a useful tool used by cardiologists to manage patients. However, its practicality and availability may result in the overuse of echocardiography in situations where it is not warranted. Such overuse may result in exhaustion of resources and reduced efficiency. Our survey of physicians who ordered an echocardiogram sheds light on the true and perceived usefulness of the echocardiogram in an inpatient setting. The results illustrate physicians' perception of echocardiography as somewhat or entirely essential for patient management, despite a proportion of reported mild or no effect on patient management.

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INTRODUCTION

A transthoracic echocardiogram (TTE) is a commonly utilized imaging modality in the inpatient setting. TTE is a useful and convenient tool to evaluate patients who have or are at risk of having cardiovascular disease. The lack of harmful radiation, the relative ease and speed with which they can be performed, and their almost ubiquitous availability make TTE central to the diagnostic armamentarium in cardiac patients. Unfortunately, the advantages that support the use of echocardiography can also lead to its overuse. Appropriate use guidelines have been developed by medical organizations to counteract this overuse, however, despite this, several studies have shown evidence that echocardiograms continue to be over-utilized[1,2].

A nationwide study of hospitals in the United States found that the use of inpatient echocardiography has been continually increasing at an average rate of 3% annually for over a decade. It was also noted that the use of TTE has approximately doubled between 1999 and 2008[1,2]. The trend has continued with TTE use increasing between 5% and 8% annually and this has led to the creation of the appropriate use criteria (AUC) for echocardiography in 2007, and their update in 2011 with subsequent criteria for echocardiography now included under the umbrella of the Multimodality Cardiac Imaging AUC[3,4]. The rapid increase of TTE utilization brings the question of whether TTE is being overused or possibly being applied in inappropriate situations. Multiple published reports have suggested that echocardiograms may be performed with decreased clinical utility and may not have a clinical effect on the management of

a patient[5-8]. We sought to evaluate the TTE-ordering physician's perceived impact echocardiography has on patient management.

MATERIALS AND METHODS

Data was collected by distributing surveys to physicians who ordered TTEs at our institution during a 10-wk period. Surveys were distributed to the ordering physician at our facility over a 2-month period. Surveys were distributed to either the attending physician or the resident physician listed on the echocardiogram order. Only echocardiograms ordered in an inpatient setting were included. Surveys were not distributed to the physician if the echocardiogram had been ordered more than ten days previously to assure recall of the patient circumstances by the ordering physician. The physician's perception of the utility of TTE in standard clinical practice was assessed by surveying physicians at all levels of training who ordered a TTE for their hospitalized patients. The information requested in the survey is summarized here and the full survey is shown in Figure 1: (1) Why the echocardiogram had been ordered; (2) Who had ordered the imaging study and their level of training; (3) The extent to which it affected the patient's treatment; (4) The type of effect it had on the patient's treatment (*e.g.*, treatment was altered or remained the same due to the results of the echocardiogram); (5) How likely the ordering physician was to order an echocardiogram in the future; and (6) What the ordering physician considered the most important possible finding in an echocardiogram. Observational statistical analysis was performed on all of the answers from the collected surveys.

RESULTS

A total of 103 surveys were obtained and analyzed. Surveys were distributed to multiple hospital departments. The majority of the echocardiograms (57%) were ordered by the internal medicine physicians, followed by cardiologists (37%) (Figure 2). The most common reason for a physician ordering an echocardiogram was to rule out a diagnosis (38.2%) and to evaluate a known cardiac condition (22%) (Figure 3A). However, 19.6% of physicians stated that there was actually no effect on patient management (Figure 3B). Additionally, 30.4% of physicians reported a mild effect, 18.6% declared a moderate effect, and only 27.5% of physicians reported that the echocardiogram significantly affected patient care. Almost half (43.1%) of physicians reported that they altered their patient management due to no change having occurred in the disease based on echo findings, 11.8% reported that changes in management were based on the recommendation of a specialist, and only 9.8% reported that further imaging was ordered due to the results of the echocardiogram. The study also reveals that the majority of physicians (67.6%) considered an echocardiogram to be "somewhat essential" in the management of adult inpatients, with only 15.7% considering it "essential", and 14.7% chose not to answer this question.

DISCUSSION

In response to the dilemma of echocardiography overuse, the AUC for echocardiography was developed in collaboration with The American College of Cardiology Foundation and the American Society of Echocardiography. The initial AUC for echocardiography[1,2] rated indications as: "appropriate", "inappropriate", or "uncertain". The more recent statements include echocardiography evaluated under the multimodality imaging criteria[3,4] and rank indications as "appropriate", "may be appropriate", and "rarely appropriate". Generally, inappropriate use for the echocardiogram is rated in clinical cases where routine testing provided no change in clinical status or did not change management. Appropriate use was identified in clinical scenarios when the echocardiography result provided a change in clinical management or when used for initial diagnosis when there is a change in clinical status[9].

Studies evaluating the correlation between TTE use, AUC, and its clinical impact have shown various findings. In a retrospective study conducted in an academic medical center, 535 consecutive TTEs were reviewed. The study reported that although 9 in 10 TTEs were appropriate by AUC, less than 1 in 3 TTEs actually resulted in an active change in patient care, with nearly half resulting in the continuation of the current clinical care plan[10]. Other studies[5-8] have shown similar

Thank you so much for accepting to participate in our anonymous survey. We are interested in better understanding the impact echocardiograms have on physician decisions.

Which department are you a part of?

(a) Internal medicine
(b) Family medicine
(c) Surgery
(d) Ob/Gyn
(e) PM&R
(f) Emergency medicine
(g) Traditional rotating internship
(h) Cardiology

What is your level of training?

(a) PGY1
(b) PGY2
(c) PGY3
(d) > PGY3
(e) Fellow
(f) Attending 0-5 yr experience
(g) Attending 0-5 yr experience
(h) Attending > 10 years experience

What is your initial purpose for ordering an echocardiogram on your patient? Please check all that apply.

(a) To evaluate a known cardiac condition
(b) To rule out a diagnosis
(c) To confirm a suspected diagnosis
(d) To assess an acute change in a patient's status
(e) The management of decision has been left up to the consultant and will follow as per consultant

How did this particular study aid in the medical management of your patient? Please check one.

(a) No effect on medical management
(b) Mild effect on management
(c) Moderately affected management
(d) Significantly affected my management
(e) Request was made by consultant

In what way did the results of the echocardiogram change management for your patient?

(a) No change in management
(b) Change in management showing normal or no change in disease
(c) Change was based on consultant's clinical judgement and sub-specialist
(d) Further imaging was ordered such as a nuclear stress test, exercise stress test, etc.
(e) The results has no effect on management since the results were inconclusive

After reviewing the results of the echocardiogram for this patient, what is the likelihood of you ordering this particular type of study again?

(a) Extremely likely, it is an essential test
(b) Very likely
(c) Likely
(d) Not likely

What is the most important finding that you look for in an echocardiogram?

(a) Ejection fraction
(b) Valvular pathology
(c) Pericardial disease
(d) Right heart disease
(e) Diseases of the aorta

In your opinion, how essential is an echocardiogram in the overall management of adult inpatient?

(a) Essential, it should be part of a routine admission
(b) Somewhat essential, may order it depending on patient presentation
(c) Not essential in evaluating my patients that are admitted
(d) Do not have an opinion

Thank you for your participation!

Figure 1 Survey distributed to ordering physicians. Ob/Gyn: Obstetrics and gynecology; PM&R: Physical medicine and rehabilitation; PGY: Postgraduate year.

results and this leads to the revelation that while AUC may be useful to guide the choice to pursue a TTE, physician perception of the possibility of the presence of indications supported by the AUC may not necessarily correlate to the change in management expected and therefore still lead to overutilization of TTE due to the various reasons that make TTE so easy to order.

This realization is supported by our study showing that the majority of physicians surveyed stated that the echocardiogram only had a mild effect on management. However, the majority of physicians perceived an echocardiogram to be somewhat or entirely essential to the management of adult inpatients. Echocardiography is a useful test which easily provides a plethora of useful data about the cardiac patient in the inpatient setting as assessed by the ordering physicians. Perhaps instead of trying to limit TTE use, more efforts should allow for the implementation of bedside point of care echocardiography which can be more easily learned and implemented and be performed in a more time and cost-efficient manner.

While the majority of physicians perceived that the TTE resulted in a change in patient management in some way, 19.6% of survey results reported no effect on patient management. This finding highlights the importance of increased optimization of proper echocardiography use. Improvement of the appropriate use of clinical resources will offer increased high-quality healthcare and better utilization of hospital resources for patients who appropriately need the test.

Similar findings have been supported by other studies. In the study by Matulevicius *et al*[10], out of their 535 consecutive TTEs, 31.8% resulted in an active change in care; 46.9% a continuation of current care; and 21.3% no change in care. By 2011 AUC, 91.8% of TTEs were appropriate; 4.3% inappropriate; and 3.9% uncertain.

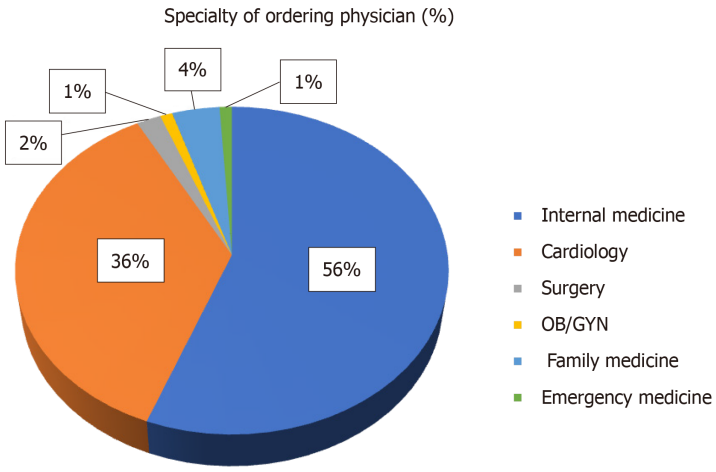

Figure 2 Specialty of ordering physician. OB/GYN: Obstetrics and gynecology.

Although 9 in 10 TTEs were appropriate by 2011 AUC, fewer than 1 in 3 TTEs resulted in an active change in care, nearly half resulted in a continuation of current care, and slightly more than 1 in 5 resulted in no change in care. The low rate of active change in care (31.8%) among TTEs mostly classified as appropriate (91.8%) highlights the need for a better method to optimize TTE utilization to use limited healthcare resources efficiently while providing high-quality care[10].

The present study is limited by the relatively small number of patients and its population of a single hospital rather than a multi-facility population with a larger sample size. There are also the given limitations of the survey study type which may include factors such as dishonesty, skipped questions, difficult questions and lack of conscientious answers.

While the AUC may reduce inappropriate studies, it still may result in unnecessary studies since 19.6% of cases did not change management. With the increased aging of our population and the rising cost of healthcare, improper utilization of resources must be identified and addressed. Systems of review, assessment, and action to change based on review, can limit inappropriate and unnecessary TTE performance. The employment of structured referral systems for TTE and an easily accessible and comprehensive checklist of appropriate indications as well as the focus by medical societies and the bodies responsible for regulating training programs for physicians of different medical specialties, will likely improve appropriate use of echocardiograms. While this improvement will expectedly improve efficiency and allow for correct employment of the use of echocardiography, our study shows that the actual versus the perceived usefulness of the echocardiogram in an inpatient setting usually does not correlate. Our results highlight the discrepancy of physicians' perception of echocardiography as somewhat or entirely essential for patient management, despite a proportion of reported mild or no effect on patient management. Because of this mismatch, it may therefore be better to allow for the implementation of bedside point of care echocardiography which can more easily be learned and implemented and be performed in a better time and cost-efficient manner while still providing essential patient information.

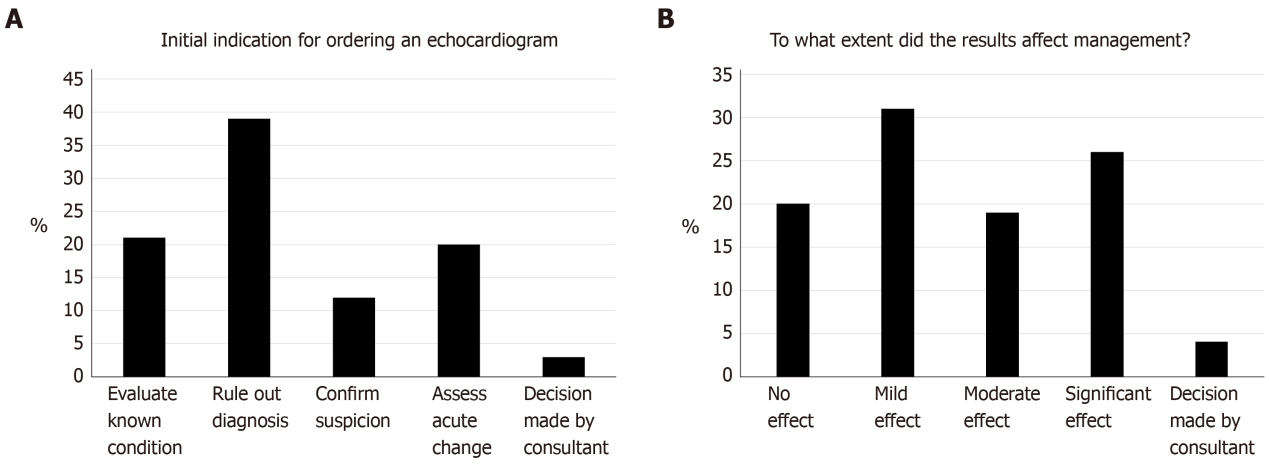

Figure 3 Indication for ordering an echocardiogram and range of effect of the results on management. A: Indication for ordering an echocardiogram; B: Range of effect of the results on management.

ARTICLE HIGHLIGHTS

Research background

The transthoracic echocardiogram (TTE) is a cardiovascular imaging tool that is used by doctors and hospitals to evaluate patients in various settings. The TTE is an incredibly useful tool due to the ability to examine the heart non-invasively, as well as the efficiency and lack of risk. Due to its usefulness and ease, it has been known to be overused. This has been recognized by the appropriate use criteria (AUC) and therefore guidelines have been created to limit its overuse. However, it has been perceived that the echocardiogram is still being overused in many settings despite the guidelines.

Research motivation

The topic of this study is to evaluate the perceived impact the TTE has on inpatient management. The overuse of this tool is an example of inappropriate usage of healthcare resources and can lead to improper patient care. Improving utilization of this tool will optimize patient care.

Research objectives

The objective of this study is to better understand the perceived impact that the TTE has on patient management that leads to its continued overuse.

Research methods

This observational study was conducted by distribution of surveys to physicians at an academic institution. The survey was completed by physicians of multiple hospital departments, who ordered a TTE within a 10 wk period in the inpatient setting. The survey requested information on the perceived importance and impact the TTE had on clinical management.

Research results

The most common reason for a physician ordering a TTE was to rule out a diagnosis and to evaluate a known cardiac condition. A total of 19.6% of physicians stated that there was no effect on patient management, 30.4% of physicians reported a mild effect, 18.6% declared a moderate effect, and only 27.5% of physicians reported that the echocardiogram significantly affected patient care. Almost half of physicians reported that they altered their patient management due to no change having occurred in the disease based on TTE findings, 11.8% reported that changes in management were based on the recommendation of a specialist, and only 9.8% reported that further imaging was ordered due to the results of the echocardiogram. The majority of physicians considered an echocardiogram to be "somewhat essential" in the management of adult inpatients, with only 15.7% considering it "essential", and 14.7% chose not to answer this question.

Research conclusions

This study reveals that there are a substantial number of physicians who order TTE without proper use despite the AUC guidelines. Many physicians stated in our study that the TTE had only a mild or no effect on patient management but is still perceived to be somewhat or entirely essential to patient care. While the AUC guidelines expectedly did limit an amount of inappropriate use of the TTE, this study better illustrates the actual utility of the TTE after the criteria is implemented. This lack of correlation calls for a new process of TTE utilization review of patient management for inpatient care.

Research perspectives

This study revealed the importance of increased optimization of proper echocardiography use.

Future research should explore bedside point of care echocardiography which can be performed more efficiently while still providing proper patient management.

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SYSTEMATIC REVIEWS

Intra-procedural arrhythmia during cardiac catheterization: A systematic review of literature

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Author contributions: Shaik FA participated in the development of the proposal to research on the topic, performed literature search and review, and wrote the draft of the manuscript, reviewed, edited and approved the manuscript; Slotwiner DJ participated in the supervision of the research on the topic, reviewed and edited the manuscript. Gustafson GM participated in the research on the topic, reviewed, edited and approved the manuscript; Dai X initiated and supervised the research on this topic, originated the manuscript concept, participated in literature search and review, wrote and revised the manuscript as a senior author.

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Abstract

BACKGROUND

Cardiac catheterization is among the most performed medical procedures in the modern era. There were sporadic reports indicating that cardiac arrhythmias are common during cardiac catheterization, and there are risks of developing serious and potentially life-threatening arrhythmias, such as sustained ventricular tachycardia (VT), ventricular fibrillation (VF) and high-grade conduction disturbances such as complete heart block (CHB), requiring immediate interventions. However, there is lack of systematic overview of these conditions.

AIM

To systematically review existing literature and gain better understanding of the incidence of cardiac arrhythmias during cardiac catheterization, and their impact on outcomes, as well as potential approaches to minimize this risk.

METHODS

We applied a combination of terms potentially used in reports describing various cardiac arrhythmias during common cardiac catheterization procedures to systematically search PubMed, EMBASE and Cochrane databases, as well as references of full-length articles.

RESULTS

During right heart catheterization (RHC), the incidence of atrial arrhythmias (premature atrial complexes, atrial fibrillation and flutter) was low (< 1%); these arrhythmias were usually transient and self-limited. RHC associated with the development of a new RBBB at a rate of 0.1%-0.3% in individuals with normal conduction system but up to 6.3% in individuals with pre-existing left bundle branch block. These patients may require temporary pacing due to transient CHB. Isolated premature ventricular complexes or non-sustained VT are common during RHC (up to 20% of cases). Sustained ventricular arrhythmias (VT and/or VF) requiring either withdrawal of catheter or cardioversion occurred infrequently (1%-1.3%). During left heart catheterizations (LHC), the incidence of ventricular arrhythmias has declined significantly over the last few decades, from

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1.1% historically to 0.1% currently. The overall reported rate of VT/VF in diagnostic LHC and coronary angiography is 0.8%. The risk of VT/VF was higher during percutaneous coronary interventions for stable coronary artery disease (1.1%) and even higher for patients with acute myocardial infarctions (4.1%-4.3%). Intravenous adenosine and papaverine bolus for fractional flow reserve measurement, as well as intracoronary imaging using optical coherence tomography have been reported to induce VF. Although uncommon, LHC and coronary angiography were also reported to induce conduction disturbances including CHB.

CONCLUSION
Cardiac arrhythmias are common and potentially serious complications of cardiac catheterization procedures, and it demands constant vigilance and readiness to intervene during procedures.

Key words: Catheterization; Coronary angiography; Percutaneous coronary intervention; Ventricular fibrillation; Ventricular tachycardia

Core tip: Cardiac catheterization is the most performed invasive procedure in the current healthcare system. Cardiac arrhythmias are common complications during the procedure. This review demonstrated a 0.14%-0.3% incidence of transient right bundle branch block during right heart catheterization in normal individuals, and a significantly higher risk of complete heart block (up to 6.3%) for individuals with pre-existing left bundle brunch block. Potentially life-threatening ventricular arrhythmias requiring either withdrawal of catheter or cardioversion could occur at the rates of 1%-1.3%. The incidence of significant arrhythmias during left heart catheterization has reduced by about 10 folds in the past half century, from 1.1% to 0.1%. Coronary interventions, as well as intracoronary imaging and measuring fractional flow reserve, carry increased risk of malignant arrhythmias, including up to 1% incidence of ventricular fibrillations. Constant telemetry monitoring is essential during cardiac catheterization.

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INTRODUCTION

Cardiac catheterization procedures performed in the cardiac catheterization laboratory (CCL) often include right heart catheterization (RHC); left heart catheterization (LHC); and coronary angiography with or without intra-coronary interventions. Cardiac catheterization is one of the most commonly performed procedures in the modern healthcare system. In 2014, there were more than 1 million inpatient diagnostic cardiac catheterizations and 480000 coronary angiography performed in the United States alone[1]. Given the nature of the intracardiac or intracoronary instrumentation as part of the cardiac catheterization procedure, cardiac arrhythmias are common and often unavoidable. We systematically reviewed the published literature to provide a comprehensive overview of the incidence rates, impact on outcomes and potential approaches to minimize the risk of cardiac arrhythmias during cardiac catheterization procedures.

Catheter-induced cardiac arrhythmias during RHC may occur as soon as the catheter tip enters the right atrium, and while advancing through the right atrium, right ventricle, right ventricular outflow tract and the pulmonary artery. Observed arrhythmias include supraventricular arrhythmias [premature atrial contraction, supraventricular tachycardias (SVTs, including atrial fibrillation (AF), atrial flutter)], ventricular arrhythmias, premature ventricular contractions (PVCs), non-sustained or sustained ventricular tachycardia (NSVT or VT) and ventricular fibrillation (VF), as well as various conduction disturbances, such as right bundle branch block (RBBB)

and complete heart block (CHB), especially in the setting of pre-existing left bundle branch block (LBBB)[2,3].

LHC studies typically include measuring the left ventricular pressures and performing left ventriculography with catheters crossing the aortic valve and positioned in the left ventricle, in addition to performing coronary artery angiography. Depending on the coronary angiographic findings, a percutaneous coronary intervention (PCI) may subsequently be performed. In addition, intravascular imaging such as intravascular ultrasound (IVUS) or optimal coherence tomography (OCT) may be used to examine coronary artery anatomy. Fractional flow reserve (FFR) may be applied to assess the hemodynamic significance of a coronary artery stenosis. This review summarizes arrhythmic complications of these procedures. Recently developed structural heart interventional procedures, *i.e*. transcatheter valvular therapies for valvular disease, often involve rapid pacing and have a potential to cause significant injury to the conduction system. Arrhythmias associated with structural heart interventions are not included in this review.

MATERIALS AND METHODS

We screened the titles and abstracts of studies against predefined terms, using PubMed, EMBASE and Cochrane databases (Table 1). The title and available abstracts of all returned articles were reviewed to identify relevant articles for a full-length review and follow-up of their references. We synthesized the following review according to the procedure and arrhythmia types. Meta-analysis was not performed due to the tremendous heterogeneity in inclusion criteria, equipment used in cardiac catheterization, and the arrhythmia definitions among reported studies.

RESULTS

Cardiac arrhythmic during RHC

RHC may be performed in the CCL, at the bedside of intensive care unit (ICU) or in the operating room. The majority of published studies on arrhythmias during RHC were about RHC procedures performed in the ICU or operating room settings. There have been no head-to-head comparisons about the incidence rates of significant arrhythmias or conduction disturbances during RHC performed in the ICU, operating room and CCL settings. The differences of arrhythmias occurring during RHC using different types or sizes (5 French *vs* 7 French) of balloon tipped catheters was not studied either.

Catheter-induced conduction disturbance during RHC

Right sided conduction disturbances, whether transient or permanent were observed infrequently (less than 1%) during RHC, which rarely resulted in the requirement of permanent pacemakers[4-7]. Damen *et al*[2] reported 2 catheter-induced RBBB during 1400 RHCs (0.14%). Ranu *et al*[8] retrospectively reviewed charts of 349 patients who underwent RHC and discovered that only 1 patient developed CHB (0.3%) required the removal of the pulmonary artery catheter and insertion of a temporary transvenous pacing wire for 36 hours until the patient recovered normal conduction. CHB could occur during RHC in patients with pre-existing LBBB[4,9-12]. In the setting of pre-existing LBBB, Damen found 1 out of 16 patients with LBBB experienced transient CHB requiring temporary pacing (6.3%)[2]. Morris *et al*[10] reported 82 procedures in the ICU setting, during which 7 French balloon-tipped flow directed catheters were used in patients with LBBB, and there was no occurrence of CHB. Based on this, the investigators recommended against routine placement of temporary transvenous pacing wires during RHC in patients with LBBB. The incidence of conduction disturbances during RHC which is performed routinely in the CCL for heart failure, pulmonary hypertension or cardiogenic shock has not been well documented.

Catheter-induced ventricular arrhythmia during RHC

During RHC, both advancing and withdrawing the balloon tipped catheter through the right atrium, right ventricle or pulmonary artery (PA) may cause arrhythmias[2,13,14]. Since the initial report of the improved design of the flexible, balloon-tipped, flow-directed catheter for RHC or a PA catheter placement by Swan and Ganz, it has been universally adopted in clinical practice. In Swan *et al*[15,16]'s initial experience and some subsequent experiences in the CCL, the risk of ventricular arrhythmia was minimal. However, during RHC or PA catheter placement at the bedside in the ICU or OR settings, there were higher rates of various degrees of

Table 1 Terms describing cardiac catheterization procedures and arrhythmias used in the combination for database search

Terms of procedures	Terms of arrhythmias
Cardiac catheterization	Cardiac arrhythmia
Left heart catheterization	Tachycardia
Right heart catheterization	Tachyarrhythmia
Pulmonary artery catheter	Ventricular fibrillation
Swan-Ganz catheter	Bradycardia
Coronary angiography	Heart block
Percutaneous coronary intervention	Conduction delay
Percutaneous transluminal coronary angioplasty	Bundle branch block

ventricular arrhythmias such as singlet PVCs, runs of couplets, consecutive PVCs, VT (non-sustained or sustained) and VF, as high as 85% in some reports (Table 2). All the published reports on ventricular arrhythmias related to RHC were single center studies with either retrospective or prospective designs. There are no uniform definitions in reporting the types of arrhythmias. Table 2 provides the most complete list of published data on the incidence of ventricular arrhythmias during RHC. Most of the observations confirmed that ventricular arrhythmias observed during RHC are generally short-lived and self-limited[17].

Severe life-threatening arrhythmias, such as sustained VT and VF can occur during RHC but are very rare[19]. Wennevold *et al*[3] reported that only 2 VT and 2 VF episodes occurred during more than four thousand RHC (< 0.1%) performed from 1947 to 1963 (before the design of balloon tipped Swan-Ganz catheter). The incidence of sustained VT or VF, requiring anti-arrhythmia treatment either by medication or cardioversion, is relatively low (0.26%[19], 1%[20], 1.5%[21] , 4.7%[17,22-28]). Bergmann *et al*[19] reported that no episodes of VT and 1 episode of VF requiring defibrillation occurred out of 380 RHCs (0.3%) performed for patients with severe aortic stenosis undergoing transcatheter aortic valve replacement. However, Gwak *et al*[13] reported a 2% incidence rates for VT or VF episodes requiring either withdrawal of the catheter or defibrillation, in their prospective observation of 100 PA catheter placements in the OR for liver allograft transplant recipients.

Cardiac arrhythmias during LHC, coronary angiography and intervention

Ventricular arrhythmias during LHC and coronary interventions: Much attention was paid to the occurrence of malignant ventricular arrhythmias – VF, VT and ventricular arrest/asystole (VA) during the early decades of coronary artery angiography (CAG). There were many reports from experienced single centers as well as multicenter registries detailing ventricular arrhythmias. Table 3 provides a comprehensive list of published reports of incidence rates of malignant ventricular arrhythmias during CAG. Gau *et al*[29] reported an unusually high incidence rate of VF (12%) in their single center study of 75 cases of selective CAG. Excluding this outlier, the median reported incidence rates of ventricular arrhythmias during diagnostic CAG is 0.9% with a range of 0.1% to 1.7%. Taken together the published data reported total of 163090 cases with 1260 incidences of malignant ventricular arrhythmias that resulted in an accumulated incidence rate of 0.77%. In the period of 1960s, ventricular arrhythmias occurred at the rate of 1.1% in CAG in the reported series (134 incidences in 11747 cases); in the 1970s, the rate was 1.0% (738 events in 73097 cases); in the 1980s, 0.8% (216 events in 26231 cases); and in the 1990s, 0.6% (136 events in 24142 cases). More recently, there were two reports from the same institute in China that included more than 18365 and 27798 diagnostic CAG respectively, using 4 or 5 French catheters. Due to the potential overlap of cases in these two reports, only the later report which included the larger sample size was included in our cumulative calculation. The incidence rate of VF was reported to be 0.1%. The temporal trends show that the incidence rates of malignant ventricular arrhythmias during diagnostic CAG have steadily declined from 1.1% to as low as 0.1% in contemporary practice (Table 3). Figure 1 provides a graphic view of the trend of reported incidence rates of VT/VF.

Percutaneous transluminal coronary angioplasty (PTCA) or percutaneous coronary intervention (PCI) has become the most commonly used approach to revascularize obstructive coronary artery disease both in stable ischemic conditions and acute myocardial infarctions. Ventricular arrhythmias are commonly encountered during PCI. In an early study of 1500 PTCA cases, Dorros *et al*[30] reported an incidence rate of

Table 2 List of studies reported the incidence rate of ventricular arrhythmia during right heart catheterization

Year	Number RHC	Types of arrhythmia	Incidence rate, *n* (%)	Setting	Study design	Procedural Outcomes	Ref.
1979	73	VA (> 1 PVCs in 4 beats)	27 (36.9)	OR	Prospective Randomized	All self-limited	Shaw *et al*[58]
1981	320	Overall	36 (16.4)	ICU	Prospective Observational	3 VTs: Treatment	Sise *et al*[20]
		VA not treatment	33 (10)				
		VA required treatment	3 (1)				
1981	60	PVCs	29 (48)	ICU	Retrospective Observational	2 VTs: Treatment 1 VF: Mortality	Sprung *et al*[56]
		VT	20 (33)				
1982	107	VT (> 3 cPVCs, > 150 pbm)		OR	Prospective Randomized	All self-limited	Salmenpera *et al*[60]
		Lidocaine	8/53 (15)				
		Placebo	10/54 (19)				
1982	150	Advanced VA	80 (53)	ICU	Prospective Observational	3 VTs: Treatment 2 VFs: Mortality	Sprung *et al*[17,56]
		Salvos (3-5 cPVCs)	45 (30)				
		NSVT (6-30 cPVCs)	30 (20)				
		VT (> 30 cPVCs)	5 (3)				
		VF	2 (1.3)				
1983	67	Advanced VA	42 (63)	ICU	Prospective Randomized	All self-limited	Sprung *et al*[59]
		Lidocaine ppx	18/31 (58)				
		placebo	24/36 (67)				
1983	528	PVCs	58 (11)	ICU	Prospective Observational	8 VTs: Meds	Boyd *et al*[21]
		VT	8 (1.5)				
		VF	0				
1985	56	Advanced VA	7 (12.5)	ICU	Prospective Observational	All self-limited	Iberti *et al*[22]
1985	250	PVCs	162/250 (64.8)	OR	Prospective Observational	All self-limited	Damen *et al*[14]
		VT (> 3 cPVC > 100 bpm)	11/250 (4.4)				
		VF	0				
1986	1400	Overall	880/1400 (62.9)	OR	Prospective Observational	All self-limited	Damen *et al*[2]
		PVCs	838/1400 (59.9)				
		VT (> 3 cPVC > 100 bpm)	42/1400 (3)				
		VF	0				
1986	142	Overall	64 (45)	ICU	Prospective Observational	All self-limited	Patel *et al*[55]
		Benign (singlet PVCs)	24 (16.9)				
		Malignant[1]	40 (28.1)				
1989	68	Overall	55 (80.9)	OR	Prospective Observational	All self-limited	Keusch *et al*[57]
		Benign (1-2 PVCs)	30 (44.1)				
		Malignant[2]	25 (36.8)				
2007	100	PAC insertion		OR	Prospective Observational	All self-limited	Gwak *et al*[13]
		Overall	70 (70)				
		Benign	33 (33)				
		Malignant[3]	37 (37)				
2012	139	Overall	76/139 (54.7)	OR	Prospective Randomized	All self-limited	Pipanmekaporn *et al*[28]
		Benign (1-2 PVCs)	58 (41.7)				
		Severe (≥ 3 PVCs)	28 (20.1)				
2013	380	VT	0	Hybrid CCL	Retrospective Observational	DCCV	Bergmann *et al*[19]
		VF	1 (0.26)				
2017	174	Overall	149/174 (85.6)	OR	Prospective	All self-limited	Satol *et al*[23]

Multiple PVCs ≥ 2	78/174 (44.8)	Observational

[1]Malignant definition: Premature ventricular contractions (PVCs) with couples or > 3 consecutive PVCs.
[2]Malignant definition: PVC couples, or ≥ 3 consecutive PVCs with heart rate > 120 bpm).
[3]Malignant definition: ≥ 3 consecutive PVCs with heart rate > 100 bp. RHC: Right heart catheterization; VA: Ventricular arrest (asystole); OR: Operating room; ICU: Intensive care units (including medical ICU, surgical ICU and cardiac ICU); PVC: Premature ventricular contractions; VT: Ventricular tachycardia; PAC: Pulmonary artery catheter; VF: Ventricular fibrillation; CCL: Cardiac catheterization laboratory; cPVCs: Consecutive PVCs; DCCV: Direct current cardioversion; NSVT: Non-sustained VT.

1.6% of VF and 0.5% of sustained VT required intervention. Subsequent reports of the rate of ventricular arrhythmias from both single center experiences and registries ranged from 0.84% to 4.3%[31-36]. Addala *et al*[31] have so far reported the largest single center cohort, with more than 19000 PTCA cases and 164 events of VF (0.84%). Based on the published data (255 events in 23882 PTCA cases), the cumulative incidence rates of VF/VT during PTCA in patients with stable or unstable angina was calculated to be 1.1%. Mehta *et al*[35] and Har *et al*[36] both reported a higher incidence of VF during primary PCI for ST-elevation myocardial infarction (STEMI), 4.3% and 4.1% respectively (Table 3). Available data in the literature suggests that the incidence rates of ventricular arrhythmias during PCI in patients with stable and acute coronary artery disease have been relatively constant in the past two decades of practice. NCDR CathPCI registry® and ACTION registry® did not collect information about intra-procedural arrhythmias during diagnostic CAG and PCI until the newest version of data collection form (version 5) for CathPCI registry® was implemented in July 2018.

Without timely termination, malignant ventricular arrhythmias could be life-threatening. Intrinsic build-in telemetry monitoring by trained staff in CCL has proven to be effective. In the reported series, the episodes of VT/VF during diagnostic LHC and CAG left minimal impact on long term outcomes. Gau *et al*[29] reported that all 9 episodes of VF in their first 75 CAG experiences (12% incidence rate) were successfully defibrillated without impacts on outcomes. Others reported the same successful immediate restoration of normal rhythm from intra-procedural VF/VT episodes without adverse sequelae during the hospitalization[30,31,37-39]. The prognosis of patients with stable coronary artery disease was more governed by the status of CAD and left ventricular dysfunction and other comorbidities, rather than the occurrence of VT/VF during the procedure[40].

Whether ventricular arrhythmias in the setting of acute myocardial infarctions have an impact on outcomes has been a controversial question. Mehta *et al*[35] reported that the occurrence of VT/VF during primary PCI did not influence PCI success, in-hospital or one-year outcomes, compared to patients who did not have intra-procedural ventricular arrhythmias. However, Har *et al*[36] recently found that, compared to patients without ventricular arrhythmias, the occurrence of intra-procedural VF/VT requiring cardioversion during primary PCI for STEMI was associated with increased early post-MI mortality (12.0% *vs* 0.5% in-hospital mortality, and 24.1% *vs* 3.6% of 30 days mortality); but not late mortality.

Atrial tachy-arrhythmia in LHC and coronary interventions: Bourassa *et al*[37] reported a 0.17% atrial tachy-arrhythmia (AF and SVT) in 5250 CAG cases in their single center study. Balloon inflation during PTCA was found to increase P wave dispersions and as well as the maximum duration of P waves[41]. which may result in increased risk of AF. There are no recent studies reporting atrial tachy-arrhythmias during LHC and coronary interventions.

FFR measurement and intravascular imaging related arrhythmias: Park *et al*[42] reported their first intracoronary adenosine-induced AF during FFR measurement. The patient required hospitalization, and amiodarone administration which led to sinus conversion, and a medical regimen for thromboembolic event prophylaxis. More seriously, there were a total of 7 cases of intracoronary adenosine induced VF during FFR have been reported in the literature[43-45]. Various doses (from 96 mcg to 360 mcg and 480 mcg) of intracoronary adenosine boluses were delivered right before the VF occurred. Shah *et al*[45] reported the incidence rate of VF during FFR was 0.9% (3 cases in 326 FFR cases). They postulated that the large volume of adenosine/saline solute injection (up to 30 cc/injection) might have contributed to the induction of VF by causing ischemia. By increasing the adenosine concentration and reducing the volume of injection with a similarly high dose of adenosine, Shah reported the avoidance of VF. The overall rate of intracoronary adenosine-induced VT/VF during FFR measurement is unknown. There is no reported case of intravenous adenosine induced VF. Intracoronary papaverine is also used to induce maximum hyperemia in FFR measurement. It was well known that use of intracoronary papaverine during FFR may prolong QT interval and induce polymorphic VT and VF[46-49]. The risk of

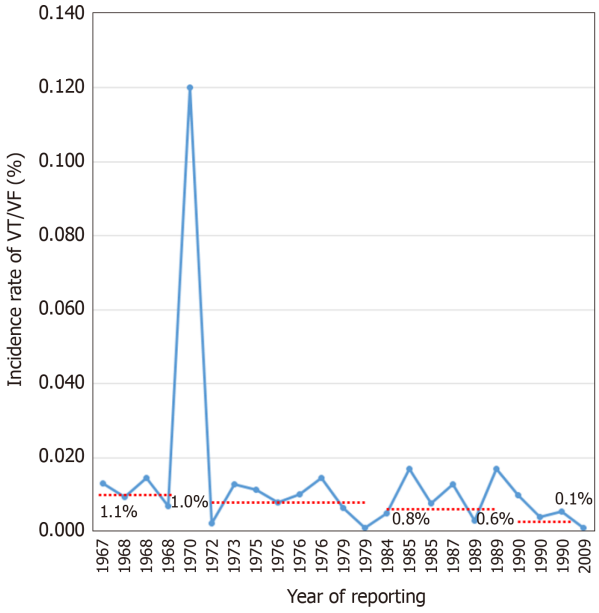

Figure 1 Graphic view of reported incidence rates of ventricular tachycardia / ventricular fibrillation during coronary angiography. Gau *et al*[29] reported in 1970, an outlier with high incidence of ventricular fibrillation (VF) in their early experience of 75 cases of coronary angiography (CAG). Excluding the outlier, other reported VF/ventricular tachycardia (VT) incidence rates were consistently low with median 0.9%, (range 0.1% to 1.7%). Total reported CAG cases excluding the 75 cases in Gau *et al*[29] were 163015, and total VF/VT cases 1251, with the incidence rate of 0.8%. VF: Ventricular fibrillation; VT: Ventricular tachycardia.

polymorphic VT (torsade de pointes) and VF has been reported to be around 1.2%-1.3%[48,50].

The potential risk of cardiac arrhythmias, especially malignant ventricular arrhythmias associated with intravascular imaging such as IVUS and OCT, has been reported to be 1.1% (5 out of 468 cases). VF rate was reported in a multicenter evaluation of the safety of OCT[51]. However, transient chest pain and electrocardiographic changes (QRS widening/ST segment depression/elevation) have been observed in 47.6% cases[52].

Brady-arrhythmias and conduction disturbances during LHC and coronary angiography: The risk of conduction disturbances is low during procedures performed *via* femoral artery approach and higher when using a radial artery approach. One study reported the incidence of symptomatic sinus bradycardia in patients undergoing trans-radial coronary angiography to be as high as 4.3%[53]. In almost all cases, the heart rate returned to normal with adjustment of catheter or atropine administration without residual consequences[53,54]. The etiology of this phenomenon is unclear. Perhaps catheter stimulation or stretch of subclavian, brachiocephalic arteries or ascending aorta may induce a vasovagal reaction.

DISCUSSION

Arrhythmias during right heart catheterization

Conduction disturbances were recognized during the very early practice of intracardiac catheterization[27]. It was anticipated that advancing catheters through the ventricle, would irritate the right bundle branch and its fascicular branches and might lead to transient or even permanent injuries. Fortunately the incidence of conduction abnormalities as well as ventricular arrhythmias is low and the long term implications are relatively negligible.

Pre-disposing risk factors associated with the increased incidence of ventricular arrhythmias, in particular the risk of VT or VF requiring intervention during RHC, include myocardial infarctions, septic shock[55], pre-existing cardiac conditions[17], use of a guidewire to assist PA catheter advancement[56], prolonged procedural time and presence of valvular diseases[23,55]. Recent studies suggested that positioning the patient in the head-up and right lateral position while passing right heart catheters would allow the catheter to easily enter the right ventricular outflow tract and thereby, reduce the incidence of severe arrhythmias[28,57]. Intravenous lidocaine

Table 3 Incidence rate of arrhythmia in coronary angiography and percutaneous coronary interventions

Year	Tachyarrhythmias required interventions					Bradycardias, asystole, and conduction disturbance (%)	Procedure types	Study designs (incidence/ total subjects)	Ref.
	Ventricular arrhythmia				Atrial arrhythmia (%)				
	VF (%)	VT (%)	VA (%)	Overall (%)					
1967	1.3	N/R	N/R	1.3	N/R	N/R	CAG	Single center (Sones) 84/6400	McGuire *et al*[85]
1968	1.33	N/R	N/R	1.33	N/R	N/R	CAG	Meta-analysis (5/535; 22/1500)	Takaro *et al*[86]
1968	0.7	0	0	0.7	N/R	N/R	CAG	Multicenter, CASS registry 23/3312	Ross *et al*[87]
1970	12	0	0	12	N/R	N/R	CAG	Single center 9/75	Gau *et al*[29]
1972	0.22	0	0	0.22	0	0.22%	CAG	Single center 1/445	Green *et al*[88]
1973	1.28[1]			1.28	N/R	N/R	CAG	Multicenter, survey; 600/46904	Adams *et al*[89]
1975	1.14	0	0	1.14	N/R	N/R	CAG	Single center, 4/351	Shah *et al*[90]
1976	0.36	0.11	0.32	0.8	0.19	0.24	CAG	Single center 19/5250 VF; 6/5250 VT; 17/5250 VA	Bourassa *et al*[37]
1976	1.01	N/R	N/R	1.01	N/R	0.46	CAG	Single center 11/1094	Nitter-Hauge *et al*[91]
1976	1.5	N/R	N/R	1.5	N/R	N/R	CAG	Single center 22/1500	Pridie *et al*[92]
1979	0.63	0	0	0.63	0	4.3	CAG	Multicenter registry 48/7553	Davis *et al*[93]
1979	0.11	0	0	0.11	0	0	CAG	Single center 10/10000	Vijay *et al*[38]
1983	1.6	0.5	0	2.1	N/R	N/R	PTCA	Registry 24/1500 VF; 8/1500 VT	Dorros *et al*[30]
1984	0.5[1]			0.5	N/R	N/R	CAG	Single center 39/7915	Nishimura *et al*[39]
1985	1.7			1.7	N/R	N/R	CAG	Single center 66/3906	Lehmann *et al*[94]
1985	0.78[a]			0.78	N/R	N/R	CAG	Single center 63/8081	Murdock *et al*[95]
1987	1.28	N/R	N/R	1.28	N/R	N/R	CAG	Single center 26/2025	Arrowood *et al*[96]
1989	0.27	0	0.03	0.3	0	0.03	CAG	Single center 11/3656	Armstrong *et al*[97]
1989	1.7[1]		0	1.7	N/R	N/R	CAG	Single center 11/648	Lehmann *et al*[98]
1990	1			1.0	N/R	N/R	CAG	Single center, 2 cohorts	Missri *et al*[64]
	0.4			0.4	N/R	N/R	CAG	Renografin-76 (20/2000) *vs* Isovue-370 (8/2000)	
1990	0.54			0.54	N/R	N/R	CAG	Multicenter, CASS registry (108/20142)	Epstein *et al*[40]
1991	2.06			2.06	N/R	N/R	PTCA	Single center, (19/922)	Brennan *et al*[32]
1991	0.4	0.8	0	1.2	0	0	PTCA	Iopamidol (6/507, 1.2%) Single center, double blinded, RCT	Lembo *et al*[33]
	0.7	2.0	0	2.7	0	0		Diatrizoate (15/551, 2.7%)	
2002	2.1	0	0	2.1	N/R	N/R	PTCA	Single center 19/905	Huang *et al*[99]
2004	4.3			4.3	N/R	N/R	PTCA	Multicenter, PTCA (133/3065, PAMI study, STEMI	Mehta *et al*[35]

2005	0.84	N/R	N/R	0.84	N/R	N/R	PTCA	Single center, (164/19497)	Addala *et al*[31]
2008	0.08	0.05	0	0.13	N/R	N/R	CAG	Single center 24/18365	Chen *et al*[100]
2009	0.1	N/R	N/R	0.1	N/R	N/R	CAG	Single center 27/27798 (radial 0.076%, femoral 0.147%)	Chen *et al*[101]
2017	4.1		N/R	4.1	N/R	N/R	PCI	Multicenter, APPROACH trial, 158/3814 STEMI	Har *et al*[36]
Summary	Total reported CAG cases: 163090; total of 1260 with overall VT/VF/VA rate 0.77% for diagnostic CAG. Total reported non-AMI PTCA cases: 2388; total of 255 VT/VF with VT/VF rate 1.1% for PTCA.								

[1]Ventricular fibrillation and sustained ventricular arrhythmias were reported together. VF: Ventricular fibrillation; VT: Ventricular tachycardia; VA: Ventricular arrest (asystole); CAG: Coronary arteriography or angiography; PTCA: Percutaneous transluminal coronary angioplasty; PCI: Percutaneous coronary intervention; RCT: Randomized controlled trial; STEMI: ST segment elevation myocardial infarction. N/R: Not reported.

administration before the catheter enters the right ventricle for prophylaxis of ventricular arrhythmias was tested, but its use remains controversial[58-60]. Due to the fact that the majority of catheter-induced ventricular arrhythmias are benign, self-limited, and rarely required medical or cardioversion, prophylactic lidocaine is not recommended during RHC.

Arrhythmias during left heart catheterization

The belief that the selective injection of contrast medium into coronary arteries would result in asymmetrical hypoxia, electrical imbalance, and invariantly ventricular arrhythmias was disproved by the pioneer of coronary arteriography, Dr. Sones Jr[61,62]. However, the fear of fatal ventricular arrhythmias related to coronary angiography persists. Due to the proximity of catheters, wires and other equipment to the ventricular walls during LHC, ventricular arrhythmias will unavoidably occur despite the advancement of techniques, reagents and equipment. Direct stimulation with wires and catheters of the ventricular myocardial tissues may disturb local electric activities and introduce myocardial contractions which lead to PVCs in singlets, couples or runs continuously for various lengths. Therefore, advancing equipment into the left ventricular chamber leading to frequent PVCs, non-sustained ventricular tachycardia (NSVT) with cPVCs ≥ 3 beats or ventricular tachycardia (cPVCs ≥ 30 beats) are common, up to 80% in our catheterization laboratory at New York Presbyterian Queens (Shaik *et al* manuscript in preparation). These ventricular arrhythmias are usually terminated by catheter manipulations (withdrawal, repositioning *etc*.) without significant impact on hemodynamics. Malignant ventricular arrhythmias, such as sustained VT, VF and ventricular arrest or standstill could occur but are much less common. These malignant ventricular arrhythmias usually cause hemodynamic compromise and require immediate interventions, *i.e*. chest wall compression, cardioversion and possibly the administration of a pharmacological agent. These malignant ventricular arrhythmias are also the topic of many case reports throughout recent decades. Understanding their potential causes, contributing factors, and approaches to minimize the risk as well as preparing to manage them when they occur are one of the core subjects of training in the interventional cardiology community.

Causes and contributing factors of ventricular arrhythmias during LHC and approaches to minimize the risk

The more than 10 folds decrease in incidence rate of malignant ventricular arrhythmias during CAG and LHC is the result of half a century's clinical and translations research. It is generally accepted that ischemic changes of myocardium, toxicities of contrast medium[63-66], and mechanical stimulations of myocardial tissue by catheter and wires, contribute to the occurrence of ventricular arrhythmias. Individual patients' vulnerability or susceptibilities to ventricular arrhythmias, often influenced by electrolyte derangement, pre-existing prolongation of QT interval, small caliber coronary arteries, or the severities and acuities of coronary artery disease, also play important roles. Furthermore, the operators' experience and approach in performing the LHC and coronary intervention also dictate outcomes (Table 4).

Atrial tachy-arrhythmia in LHC and coronary interventions

Contrary to RHC, LHC is performed *via* a retrograde approach. There is no direct contact of instruments with atrial structures. Direct stimulation of the atrium causing arrhythmia is rare during LHC and coronary interventions. Thus, the findings of our

Table 4 Known risk factors for ventricular tachycardia / ventricular fibrillation during coronary angiography and percutaneous coronary intervention and approaches to mitigate the risk

Risk factors	Approaches to mitigate risk
Catheter wedging coronary ostium, damping pressure causes ischemia and stagnation of contrast medium[32].	1 Smaller caliber catheter to avoid damping
	2 Catheters with sideholes to avoid damping
	3 Dis-engage catheter, clear contrast before next injection to minimize ischemia
	4 Avoid prolonged injection or large amount CM injection
Contrast medium toxicity[33,64,97]	1 Use non-ionic, low osmolar contrast
Non-ionic CM has lower risk than ionic CM	2 Eliminating calcium-binding additive in CM
Low osmolarity CM has lower risk than high Osmolarity CM	3 Use electrolytes optimized CM
Calcium-binding additive in CM increase the risk of VT/VF	
Catheter or wire tip irritation of LV[88]	1 Meticulously manipulating equipment
	2 More practice
High risk in RCA and bypass graft CAG[99]	Pay more attention to avoid or minimize ischemia during procedure
Direct injection into conus branch leading to VF[102,103]	Early recognition of conus branch engagement and avoid injection or abort injection
Increased risk of VF/VT in patients with severe CAD and cardiomyopathy	1 Pre-procedural workup to understand the risk
	2 Meticulous procedural technique
	3 Operators training and competency
	4 Close monitoring
	5 Early reperfusion therapy
Acute myocardial infarction and primary PCI patients have high risk of VF/VT	6 Consider mechanic circulatory support for AMI patients with cardiogenic shock or extensive CAD with severely reduced EF (high risk patients with high risk CAD)

CM: Contrast medium; VT: Ventricular tachycardia; VF: Ventricular fibrillation; LV: Left ventricular; CAG: Coronary angiography; CAD: Coronary artery disease; RCA: Right coronary artery; PCI: Percutaneous coronary intervention; EF: Ejection fraction.

literature review are not surprising.

FFR measurement and intravascular imaging related arrhythmias during LHC and coronary interventions

In symptomatic patients with moderate coronary artery stenosis, guidelines supported by robust clinical evidence recommend the use of FFR to guide the clinical decision making process[67]. The risk of arrhythmias during FFR measurement involves instrumentation of the coronary arteries with guidewires, catheters and contrast medium, as well as the pro-arrhythmic effects[68] of adenosine, which is the most commonly used agent to induce maximum hyperemia[69]. Intravenous infusion of adenosine at 140 mcg/kg/min or intracoronary bolus injection at the doses of 60 mcg, 120 mcg, up to 480mcg, are generally safe and well tolerated, largely owing to its very short half-life. Adenosine induced transient sinus bradycardia, AV block, and sinus tachycardia are common and expected physiologic effects on the heart rhythm. Adenosine-induced arrhythmias and conduction disturbance are short-lived and self-limited without the need of special treatment. The current gold standard for FFR studies is to use intravenous adenosine to induce hyperemia, especially when taking into consideration the reported risk of severe ventricular arrhythmias which using intracoronary adenosine and papaverine. However, head-to-head safety data is not available.

Because OCT involves high volume contrast injections to disperse blood components during image acquisition the incidence of ventricular arrhythmias is higher. This may cause chest pain, electrocardiographic changes and even ventricular arrhythmias – all three of which have been reported in the literature. There are no particular concerns regarding IVUS studies causing ventricular arrhythmias.

Brady-arrhythmias and conduction disturbances during LHC and coronary angiography

Brady-arrhythmias have been recognized since the very early experiences and are relatively common during LHC and coronary angiography[70].Direct toxicity of contrast medium and stimulation of chemoreceptors, other vasovagal reactions induced by pain and anxiety, *etc.* were the proposed mechanisms of these

arrhythmias[70-72].Lately, with the growing popularities of trans-radial catheterization, coiling of the catheters and direct stimulation of the aortic arch and carotid sinus receptors was also noted to cause sinus bradycardia[54].

An infrequent yet significant conduction disturbance associated with LHC and CAG is LBBB and/or CHB. As opposed to the right bundle, the trunk of the left bundle is generally short and immediately divides into two fascicles. The left bundle branch is also broadly distributed over the left septal surface in a diffuse fanlike structure. To some extent, these anatomic features of the left bundle protect it from mechanical damage during catheter instrumentation of the left ventricle. Some patients, however, may have anatomic variations, which include a left bundle that extends undivided for 20 mm or more, making the left bundle vulnerable. Shimamoto *et al*[73] reported 3 patients, without any known conduction abnormalities or evidence of infarction prior to LHC, who developed LBBB, without a change in heart rate during coronary angiography. Of these patients, only one eventually developed a permanent LBBB and none had significant complications. The recognition of the possibility of developing LBBB is particularly important when patients have pre-existing right bundle branch and/or fascicular blocks, which could potentially require permanent pacemaker implantation if persistent CHB occurs[74-76]. Furthermore, the His bundle travels through the membranous septum in immediate proximity to the posterior sinus of Valsalva and runs just under the left ventricular endocardium. It is thus, anatomically vulnerable to mechanical trauma during LHC and CAG. A single touch of these structures by the catheter tip may cause intra-His bundle injury resulting in CHB[75,77-80].

Understanding the risk factors for development of brady-arrhythmias and conduction disturbances during LHC and CAG helps the operator to be prepared should these arrhythmias occur and compromise hemodynamics, which will require either administration of atropine and other drugs, and/or emergent transvenous pacing. However, given the low incidence as well as relatively rapid recovery in most of the cases, prophylactic temporary transvenous pacing as performed earlier in practice[79] is no longer recommended. In recent years, there has been a growing interest in using coronary catheters and guidewires for left ventricular pacing in order to reduce resource utilization and avoid the risks of transvenous wire placement[81-84].

In conclusion, diagnostic RHC, LHC, CAG, and coronary interventions are the most commonly performed invasive cardiac procedures. This systematic literature review demonstrated a 0.14%-0.3% incidence of transient RBBB during RHC in normal individuals, with a significantly higher risk of CHB (up to 6.3%) requiring temporary or permanent pacing for individuals with pre-existing LBBB. Isolated PVCs or non-sustained VT which do not require specific treatment are common (approximately 20% incidence rate in most of the reports) during RHC. Potentially life-threatening ventricular arrhythmias (sustained VT and/or VF) requiring either withdrawal of catheter or cardioversion also occur but at much lower rates (1%-1.3%). The incidence rate of diagnostic LHC and CAG causing arrhythmias has reduced 10 fold in the last half century from 1.1% to 0.1% (in modern era) due to an improved procedural techniques, better training, improved contrast medium, and equipment. Coronary interventions as well as hemodynamic assessment with FFR and intracoronary imaging (especially OCT) continue to carry an increased risk of introducing malignant arrhythmias with up to 1% incidence rate of VF requiring shocks. Rigorous and constant monitoring, and readiness to intervene are essential for the modern cardiac catheterization facility.

ARTICLE HIGHLIGHTS

Research background

Cardiac Catheterization is one of the most commonly performed procedures in the modern health care system. Given the nature of intracardiac and intracoronary manipulation of catheters during the procedure, arrhythmias are common, and potentially consequential. Understanding the incidence, risk factors and strategies to mitigate the risk bears clinical significance.

Research motivation

There are sporadic reports on the topics of intra-procedural arrhythmias during cardiac catheterization. We systematically reviewed published literature, analyzed the incidence rate, temporary trends, and predictors of atrial and ventricular arrhythmias during left and right heart cardiac catheterization. We also discussed factors and approaches to reduce arrhythmias and improve the safety of the procedures.

Research objectives

The goal of this study is to provide a comprehensive overview of the incidence rates and impact on short- and long-term outcomes of arrhythmias during cardiac catheterization, as well as

understand approaches to minimize the risk of malignant arrhythmias during cardiac catheterization.

Research methods
We systematically searched PubMed, EMBASE and Cochrane databases with a combination of comprehensive terms related to cardiac catheterization procedures and various cardiac arrhythmias, then carefully reviewed and synthesized the data by types of procedure and arrhythmias.

Research results
We found a 0.14-0.3% incidence of transient right bundle branch block during right heart catheterization (RHC) in normal individuals, and a significantly higher risk of complete heart block (up to 6.3%) requiring temporary or permanent pacing for individuals with pre-existing left bundle branch block (LBBB). Isolated premature ventricular contraction or non-sustained ventricular tachycardia (VT) which do not require specific treatment are common (approximately 20% incidence rate) during RHC. Potentially life-threatening ventricular arrhythmias (sustained VT and/or ventricular fibrillation) requiring either withdrawal of catheter or cardioversion also occur but at lower rates (1.0%-1.3%). The incidence rate of diagnostic left heart catheterization and coronary angiography causing arrhythmias has significantly reduced from 1.1% to 0.1% in the last half century. However, invasive coronary intervention and hemodynamic assessment including optical computed tomography and fractional flow reserve continue to possess a significantly higher risk.

Research conclusions
Cardiac arrhythmias are common during cardiac catheterization. While the majority of arrhythmias are benign and self-limited, complete heart block in the presence of pre-existing LBBB and ventricular tachycardia during RHC could be consequential requiring interventions. As the improvement of reagents, equipment and techniques, the incidence rate of serious arrhythmias such as ventricular tachycardia/fibrillation during LHC has significantly decreased, but it continues to require constant intra-procedural monitoring and readiness to intervene.

Research perspectives
As cardiac catheterization procedure continues to serve as essential diagnostic and therapeutic tool for patients, intra-procedural cardiac arrhythmias occur at relatively low incidence rates. Understanding the types of arrhythmias, associated risk factors and the strategies to monitor and mitigate the risk continue to be essential for patient safety and procedure success. It continues to require close surveillance and exploration of best practice to minimize the risk.

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CASE REPORT

Tale of fat and fib — cardiac lipoma managed with radiofrequency ablation: A case report

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Abstract

BACKGROUND

Cardiac lipoma and lipomatous hypertrophy of interatrial septum (LHIS) are very rare disorders with distinct pathological features. While cardiac lipoma is a well-circumscribed encapsulated tumor of mature adipocytes, LHIS is due to entrapment of fat cells in the interatrial septum during embryogenesis. Although a biopsy is the definitive diagnostic test, these disorders can be differentiated by a cardiac magnetic resonance imaging (MRI). Treatment of LHIS is not warranted in asymptomatic patients. In symptomatic patients, surgical resection is the only recommended treatment, which has shown to improve good long-term prognosis.

CASE SUMMARY

A 63-year-old Caucasian woman with past medical history significant for hypertension, hypothyroidism, right breast ductal cell carcinoma treated with mastectomy and breast implant, platelet granule disorder, asthma requiring chronic intermittent prednisone use, presented to the outpatient cardiology office with recent onset exertional dyspnea, palpitations, weight gain and weakness. Initial workup with electrocardiogram and holter monitor did not reveal significant findings. During the subsequent hospitalization for community acquired pneumonia, the patient developed symptomatic paroxysmal atrial fibrillation. Transthoracic echocardiogram showed a right ventricular mass. A biopsy was not pursued given the high risk of bleeding due to platelet granule disorder. Cardiac MRI showed characteristic features consistent with cardiac lipoma and LHIS. Prednisone was discontinued. Genetic testing for arrhythmogenic right ventricular dysplasia and 24-h urine cortisol test was negative. As multiple attempts at rhythm control failed with sotalol and flecainide, pulmonary vein isolation and right atrial isthmus radiofrequency ablation were done. She is in follow-up with symptomatic relief and no recurrence of atrial fibrillation for 10 mo.

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CONCLUSION
Benign fatty lesions in heart include solitary lipoma, lipomatous infiltration and lipomatous hypertrophy of interatrial septum. Although transvenous biopsy provides a definitive diagnosis, Cardiac MRI is superior to computed tomography and aids in differentiating benign from malignant lesions. Surgical excision of cardiac lipoma along with capsule and pedicle removal generally prevents recurrence, but with our patient's unusual tumor features and comorbidities proscribed a surgical approach. Symptom management with antiarrhythmics and ablation techniques were successfully utilized.

Key words: Cardiac lipoma; Lipomatous hypertrophy of interatrial septum; Atrial fibrillation; Radiofrequency ablation; Case report

Core tip: Cardiac lipoma and lipomatous hypertrophy of interatrial septum are rare causes of atrial arrythmias. The clinical presentation for cardiac lipomas usually varies from absence of symptoms to dyspnea, palpitations, dizziness, decreased exercise tolerance, thromboembolism, and sudden death. Surgery is usually warranted in symptomatic individuals. We describe a very first co-existing case of unresectable cardiac lipoma and lipomatous hypertrophy of interatrial septum presenting with atrial fibrillation and managed with cardiac radiofrequency ablation.

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INTRODUCTION

Cardiac lipomas constitute approximately 10% of benign cardiac tumors. They are most commonly noted in interatrial septum (IAS) followed by the right atrium and left ventricle[1]. Lipomas involving the IAS should be differentiated from lipomatous hypertrophy of interatrial septum (LHIS) as they both have similar features on imaging except for the characteristic sparing of fossa ovalis in LHIS. In addition, the interatrial septal thickness of > 2 cm is considered diagnostic for LHIS. Cardiac lipoma and LHIS typically have a benign course with asymptomatic subjects[2]. In symptomatic patients, the clinical symptoms and outcome vary depending on the tumor size and location[3]. Differentiating cardiac tumors is essential for symptomatic patients as treatment and prognosis vary[2]. Although biopsy provides a definitive diagnosis, cardiac magnetic resonance imaging (MRI) was found superior to computerized tomography (CT) and aids in differentiating several lesions[4]. Surgical excision remains the main modality of treatment in cardiac lipoma and LHIS cases. Complete removal of the lipoma with capsule and pedicle ensures prevention of recurrence[5]. Here, we report a woman presenting with intractable arrhythmias resulting from unresectable cardiac lipoma and LHIS, who was successfully managed with cardiac radiofrequency ablation.

CASE PRESENTATION

Chief complaints

A 63-year-old Caucasian woman presented to the outpatient cardiology office with dyspnea on exertion and weakness.

History of present illness

Patient presented with recent onset dyspnea on exertion and weakness for 1-2 wk. Review of systems was positive for palpitations, fatigue and weight gain, but negative for chest pain, syncope, fever and cough.

History of past illness
Past medical history included hypertension, hypothyroidism, right breast ductal cell carcinoma treated with mastectomy and breast implant, platelet granule disorder, asthma requiring chronic intermittent prednisone use.

Physical examination
Physical examination revealed a regular pulse of 72/min, blood pressure 138/95 mmHg and body mass index 26.7 kg/m^2. Cardiac examination revealed normal heart sounds without murmur or gallop. Her lungs were clear to auscultation. Bilateral trace pitting edema was noted at her ankles.

Laboratory examinations
Electrocardiogram (EKG) showed normal sinus rhythm with right bundle branch block (RBBB), unchanged from prior EKG. Thirty-day event monitoring showed 3 episodes of isolated supraventricular ectopics which represented < 0.1% of the total beat count. During hospitalization for community-acquired pneumonia, the patient developed symptomatic paroxysmal atrial fibrillation (AF) (Figure 1).

Imaging examinations
Transthoracic echocardiogram showed a right ventricular (RV) mass, preserved RV function and a preserved ejection fraction of 60%-65%. A biopsy was not pursued given the high risk of bleeding due to platelet granule disorder. Cardiac MRI showed LHIS as well as well-defined capsular mass along the epicardial surface of RV free wall diffusely infiltrating the myocardium and mediastinal lipomatosis (Figure 2). No early or late enhancement of mass with gadolinium contrast was seen, suggesting a benign cardiac lesion. The characteristic features of the lesions in RV and IAS on fat suppression of the imaging provided a diagnosis of cardiac lipoma and LHIS respectively.

Further diagnostic work-up
Genetic testing for arrhythmogenic right ventricular dysplasia (ARVD) and 24-h urine cortisol test was negative.

MULTIDISCIPLINARY EXPERT CONSULTATION

Sanjeev Goyal, MD, Assistant Professor, University of Massachusetts Medical School, Department of Cardiology, Saint Vincent Hospital
For diagnosis of the lesion identified on transthoracic echocardiogram, Biopsy is more definitive but given the history of severe bleeding due to underlying platelet granule disorder and the patient's reluctance to undergo surgical procedures, Patient needs to undergo cardiac MRI for diagnosis of the lesion.

Brian B Ghoshhajra, MD, Department of Radiology, Massachusetts General Hospital
Cardiac MRI showed well-defined capsular mass along the epicardial surface of RV free wall diffusely infiltrating the myocardium and mediastinal lipomatosis. There is diffuse infiltration of the mass into the right ventricular myocardium without frank invasion of extracardiac structures. The mass is homogeneously hyperintense on T1 and demonstrates signal drop on fat-saturated sequences. No early or late enhancement of mass with gadolinium contrast was seen suggesting a benign cardiac lesion. There is also lipomatous hypertrophy of the interatrial septum. The characteristic features of the lesions in right ventricle and interatrial septum on fat suppression of the imaging provided a diagnosis of cardiac lipoma and LHIS respectively.

Sanjeev Goyal, MD, Assistant Professor, University of Massachusetts Medical School, Department of Cardiology, Saint Vincent Hospital
Patient was provided referral to cardiothoracic surgery for surgical resection of the cardiac lipoma. She failed to follow-up, refused any surgical interventions and opted for medical management.

FINAL DIAGNOSIS

The final diagnosis of the presented case is atrial fibrillation in the setting of cardiac lipoma and LHIS.

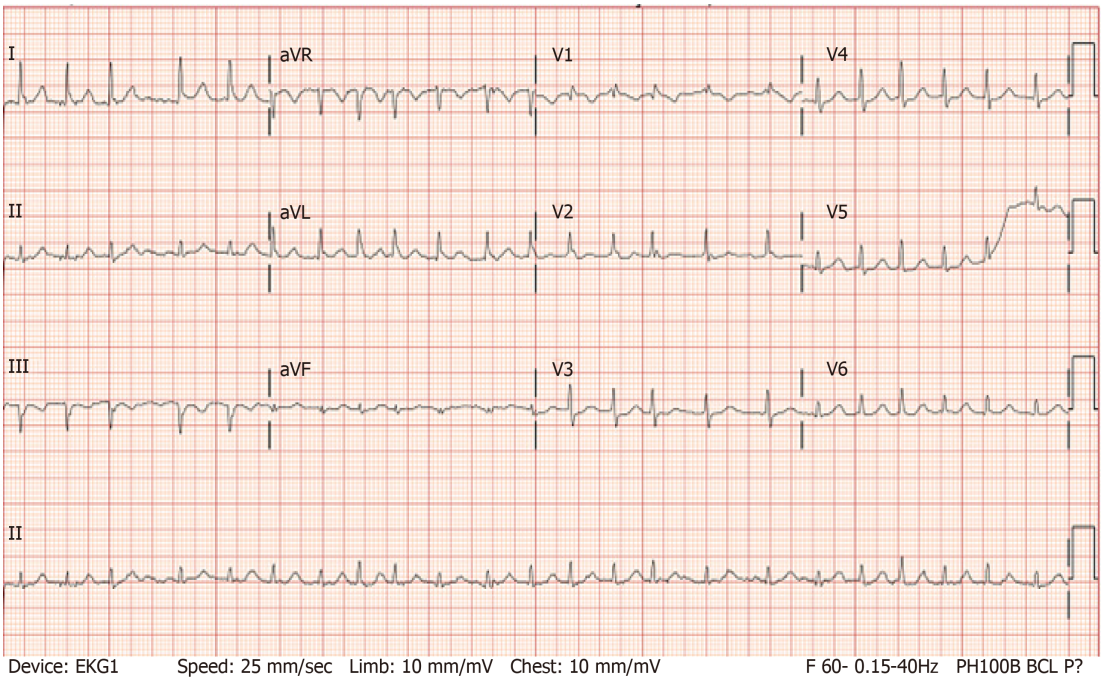

Figure 1 Electrocardiogram showing atrial fibrillation with rapid ventricular response.

TREATMENT

Prednisone was discontinued. Multiple attempts at rhythm control of her symptomatic paroxysmal AF failed with sotalol and flecainide. As the mass could not be resected, pulmonary vein isolation and right atrial isthmus radiofrequency ablation were done.

OUTCOME AND FOLLOW-UP

Post-procedure, EKG showed normal sinus rhythm with RBBB. She is in follow-up with no recurrence of AF for 10 mo along with no symptoms. Recent thirty-day event monitoring also showed no significant record of AF.

DISCUSSION

We describe an interesting case of a 63-year-old non-obese woman presenting with intractable AF most likely due to cardiac lipoma and LHIS. These clinical entities are very rare and a simultaneous presentation in a single patient, to the best of our knowledge, was never reported. Lam *et al*[6] reviewed 12485 autopsies performed over a 20-year period and reported a 0.056% prevalence of primary cardiac tumors and cardiac lipoma represented an even smaller fraction[6]. Most patients with cardiac lipoma are asymptomatic; however, the clinical features of cardiac lipoma vary from dyspnea to palpitations, dizziness, decreased exercise tolerance, thromboembolism, and sudden death. An atypical presentation including fever of unknown origin, hypertension, and epistaxis have been noted[3]. A transthoracic echocardiogram performed in our patient for palpitation and decreased exercise tolerance showed the intracardiac masses. Although transvenous biopsy would be the next step in management, high risk of bleeding[7] given the presence of platelet granule release disorders warranted a different approach in our patient. Cardiac MRI is superior to CT and aids in differentiating cardiac masses including both benign and malignant[4]. The characteristic fat saturation in MRI imaging suggested that the lesion mainly comprised of fat tissue with the differentials including lipoma, liposarcoma, ARVD, and LHIS. As malignant lesions have a more heterogeneous appearance with avid contrast enhancement, cardiac MRI findings of homogenous mass without contrast enhancement suggested a benign lesion in our patient. Given lack of liposarcoma features on MRI and a negative ARVD genetic test, the cardiac tumor in right ventricle was diagnosed as a lipoma. Interestingly, the fatty tissue in IAS was

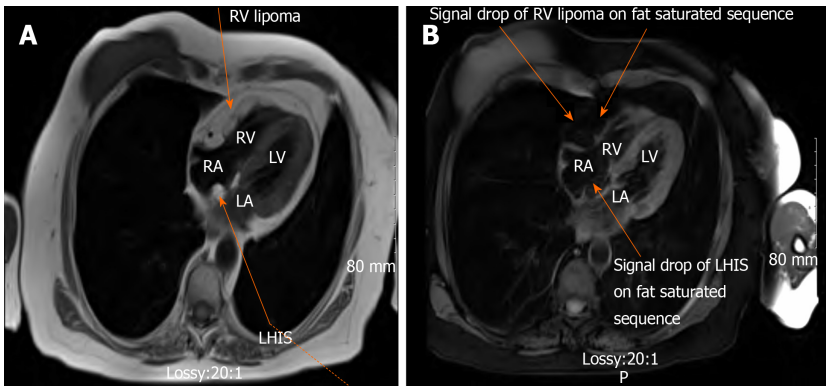

Figure 2 Cardiac magnetic resonance imaging. A: Axial section T1 weighted imaging showing (a) well-defined capsular homogenous mass along the epicardial surface of right ventricular, diffusely infiltrating the myocardium without frank invasion of adjacent structures (b) lipomatous hypertrophy of interatrial septum; B: Axial section T1 weighted imaging showing signal drop on fat saturated sequence of cardiac lipoma in right ventricular. RV: Right ventricular; LHIS: Lipomatous hypertrophy of interatrial septum.

diagnosed as LHIS due to its characteristic dumb bell shape form and sparing of fossa ovalis[8].

Lipomas are benign encapsulated fatty lesions with unclear etiologies[1]. A study done by Italiano *et al*[9] showed that solitary lipoma is associated with chromosome 12 gene rearrangements, where an abnormality in HMGA2-LPP fusion gene was noted. Multiple lipomas are associated with certain genetic disorders such as familial multiple lipomatosis, Gardner syndrome, adiposis dolorosa, and acquired conditions such as chronic corticosteroid use and chronic alcohol use (Madelung disease)[10]. Deep-seated lipomas should be differentiated from liposarcoma, because lipomatous malignancy commonly occurs at sites deeper than the subcutaneous region. Our patient did not have any of the above-mentioned conditions except for chronic low dose corticosteroid use. Taillé *et al*[11] reported a case of corticosteroid-induced mediastinal lipomatosis and increased risk of mediastinal hemorrhage on anticoagulant therapy with steroids. Sorhage *et al*[12] described a case with regression of multiple symmetric mediastinal lipomatosis with discontinuation of corticosteroid. Prednisone was discontinued to prevent further progression and associated complications[13].

LHIS, although has fatty deposits, it is a separate entity from lipoma with variable pathology[1]. Heyer *et al*[14] showed an LHIS incidence of 2.2% by multi-slice CT. Higher prevalence of LHIS has been observed in patients with advanced age, atrial arrhythmias, obesity. It is unclear whether the presence of LHIS increased the risk of atrial arrhythmias. Nonetheless, postulated mechanisms for cardiac arrhythmias in LHIS include concomitant coronary artery disease, conducting pathway defects from LHIS, and fibrosis of myocardium from fat deposition[15]. Due to the rarity of the condition, no definitive medical treatment is suggested. Zeebregts *et al*[15] recommended surgical resection in LHIS patients with altered hemodynamic function leading to congestive heart failure, and those with life-threatening rhythm abnormalities[15].

The long-term prognosis for asymptomatic lipomas is good, but symptomatic lipomas, if left untreated are known to have a grim prognosis. Cardiac lipomas following successful surgical excision have a favorable long-term prognosis[5]. Most commonly noted post-operative complications with cardiac lipoma excision include arrhythmias, pneumonia and bleeding. In addition, cardiac lipoma may recur[16,17]. With our patient's unusual tumor features and location in addition to, several comorbidities, surgical resection was proscribed and symptom management with antiarrhythmics showed only limited success. Due to the failure of medical management, ablation provided symptomatic relief and restoration of sinus rhythm for 10 mo post-procedure. With our case demonstrating a successful treatment and no symptom recurrence on follow-up, techniques like transthoracic puncture ablation, radiofrequency ablation *etc*. as the mainstay of treatment should be investigated further to avoid surgery and its risks. To the best of our knowledge, this is the first reported case of cardiac lipoma and LHIS successfully managed with radiofrequency ablation.

CONCLUSION

Cardiac lipoma and LHIS are the infrequent causes of atrial arrhythmias. Cardiac MRI is highly diagnostic in differentiating these lesions and should be considered as a reliable method for diagnosis prior to biopsy. Cardiac lipomas are typically treated with surgical excision due to favorable long-term prognosis. With our patient showing resolution of symptoms with cardiac ablation, we recommend further research in assessing the benefits and risks of various treatment modalities in the management of these lesions.

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CASE REPORT

Exercise-induced torsades de pointes as an unusual presentation of cardiac sarcoidosis: A case report and review of literature

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Abstract

BACKGROUND

Sarcoidosis is a rare multisystem disease characterized histologically by non-caseating granuloma formation in the affected organ. While cardiac sarcoidosis is found on autopsy in up to 25% of sarcoidosis cases, it is still underdiagnosed and is associated with a poor prognosis. Although the etiology of sarcoidosis remains unclear, an antigen triggered exaggerated immune response has been hypothesized. Early detection and prompt management of cardiac sarcoidosis remains pivotal.

CASE SUMMARY

A 60-year-old female, with pulmonary sarcoidosis in remission, presented to the cardiology outpatient clinic for evaluation of weeks-long dyspnea on moderate exertion (New York Heart Association class II) that was relieved by rest. Submaximal exercise stress test showed multifocal ventricular extrasystoles, followed by a self-limiting torsades de pointes. Cardiac magnetic resonance imaging showed nondilated and normotrophic left ventricle with basoseptal and mid-septal dyskinesis. The magnetic resonance imaging-derived left ventricular ejection fraction was 45%. Delayed enhancement showed patchy transmural fibrosis of the septum and hyperenhancement of the papillary muscles, all in favor of extensive cardiac involvement of sarcoidosis. A double-chamber implantable cardiac defibrillator was implanted, and methylprednisolone (12 mg/d) and methotrexate (12.5 mg/wk) treatment was initiated. Follow-up and implantable cardiac defibrillator interrogation showed episodes of asymptomatic nonsustained ventricular tachycardia and an asymptomatic episode of

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nonsustained ventricular tachycardia ending by the first antitachycardia pacing run.

CONCLUSION
Along an extensive review of the literature, this unusual case report highlights the importance of early detection of cardiac involvement of sarcoidosis, in order to avoid potential complications and increase survival.

Key words: Sarcoidosis; Cardiac sarcoidosis; Torsades de pointes; Ventricular tachycardia; Immunotherapy; Case report

Core tip: Cardiac sarcoidosis (CS) remains an underdiagnosed illness bearing a poor prognosis. While a number of reviews in the literature have tackled the treatment of CS, no published guidelines and only consensus publications of global experts' opinions are available for the diagnosis. Our objective with this case report and literature review was to consolidate the available literature for a better delineation of the diagnosis and treatment of CS.

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INTRODUCTION

In 1869, Dr. Jonathan Hutchinson introduced the modern description of cutaneous sarcoidosis[1]. The name "sarcoidosis" was bestowed in 1899 by Dr. Boeck, for its sarcoid nature according to its derivation from sarcoma cells[2]. Dr. Bernstein was the first to recognize cardiac involvement in 1929 [known as cardiac sarcoidosis (CS)], and in 1952, Drs. Longcope and Freiman reported myocardial involvement in 20% of 92 autopsy cases of sarcoidosis[3].

Today, sarcoidosis is known to be more common in younger adults, with African-Americans having 3- to 4-fold increased risk for the disease (as compared to Caucasian); the overall prevalence ranges between 4.7 and 64 per 100000 population[4,5]. While the etiology of sarcoidosis remains unclear, it has been hypothesized that it is possibly precipitated by an antigen triggering an exaggerated immune response, leading to granuloma formation in different organs[6]. This response mainly affects – but is not limited to – the lungs, skin, eyes, and lymph nodes.

Cardiac involvement is diagnosed clinically in as few as 5% of sarcoidosis cases[7], and most of those cases come from Japan. CS is clinically silent in 20%-25% of those diagnosed and isolated in two-thirds of patients. For all, it bears a poor prognosis[5,8]; accounting for up to 85% of deaths from sarcoidosis[9], mainly secondary to ventricular arrhythmias[10]. Unfortunately, to date, there are no existing reliable standard references to diagnose CS.

The guidelines for the diagnosis of CS published by the Japanese Ministry of Health and Welfare are not systematically endorsed and, compared to imaging techniques, have reduced sensitivity and specificity[11]. The Heart Rhythm Society (HRS) released a more contemporary expert consensus statement for the diagnosis of CS[10], which was revised in 2017 by Terasaki *et al*[11]. We report herein the diagnosis and treatment of an unusual presentation of CS *via* an exercise-induced torsades de pointes (TdP) in a patient with known pulmonary sarcoidosis.

CASE PRESENTATION

Chief complaints

A 60-year-old Caucasian female patient consulted our cardiology outpatient clinic for

complaint of dyspnea on moderate exertion (New York Heart Association class II) which had lasted for the past few weeks, and which she reported was relieved by rest.

History of present illness

The patient estimated that her symptoms started a couple of weeks prior to presentation and reported increasing frequency in the last couple of days. She denied any chest pain, palpitations, orthopnea, lower leg edema, paroxysmal nocturnal dyspnea, change in weight, or syncope.

History of past illness

The patient is a nonsmoker, known to have a 10-year history of type 2 diabetes mellitus, essential arterial hypertension, dyslipidemia, and untreated asymptomatic stable pulmonary sarcoidosis (diagnosed 5 years prior, according to mediastinal lymph node biopsy findings). Her past medical history also included resected epidermoid carcinoma of the tongue. A coronary angiography given 5 years prior showed a 40%-50% mid-left anterior descending artery stenosis.

Her routine medications included bisoprolol (2.5 mg/d), acetylsalicylic acid (80 mg/d), atorvastatine (10 mg/d), metformin (850 mg twice/d), gliquidone (15 mg/d), and dulaglutide (1.5 mg/wk).

Personal and family history

There was no family history of sudden cardiac death, and the patient denied any recent severe illness or respiratory symptoms. A recent abdominal and thoracic computed tomography (CT) scan revealed several infracentimetric mediastinal and hilar lymph nodes.

Physical examination

On physical examination, the patient showed no signs of distress. The vital signs displayed temperature of 37.2 °C, blood pressure of 130/70 mmHg, heart rate of 50 beats/min, and oxygen saturation of 97% on room air. There was no jugular vein distention nor carotid bruit. Peripheral pulses were present and equal. No skin lesions were noted. The heart rate was regular, with an occasional premature beat. The first and second heart sounds were heard, and no murmurs, rubs or gallops were noted. The lung and abdomen exams were unremarkable. There was no lower leg edema.

Laboratory examinations

Laboratory work-up (Table 1) was remarkable for an elevated level of glycated hemoglobin, normal levels of potassium and cardiac ultrasensitive troponin, and normal thyroid findings. Angiotensin converting enzyme levels were also within normal range. Notable finding on electrocardiogram was a regular sinus rhythm with prolonged PR interval and a QTc at 450 ms (Figure 1).

Imaging examinations

Initial cardiac ultrasound showed basal-septal akinesia, with a globally preserved left ventricular systolic ejection fraction by the modified Simpson method, normal left and right chamber sizes, and a normal tricuspid aortic valve associated with a trace insufficiency. The ascending aorta measured 41 mm. No other abnormalities were found.

Further diagnostic work-up

A submaximal exercise stress test reaching 67% maximal predicted heart rate for the patient's age stopped due to multifocal ventricular extrasystoles followed by a self-limiting TdP at 2 min, with no syncope or chest pain (Figure 2). The maximal blood pressure was 152/70 mmHg, and the recovery was notable for multiple multifocal ventricular extrasystoles.

We ordered an increase in the patient's bisoprolol (from 2.5 mg to 5 mg) and stopped the dulaglutide. The patient was admitted to the hospital for a diagnostic coronary angiography, which showed a stable 40%-50% mid-left anterior descending plaque. Cardiac continuous monitoring showed several ectopic supraventricular beats along abundant polymorphic ventricular extrasystoles and intermittent type I second degree atrioventricular block (Mobitz I).

A cardiac electrophysiology study was undertaken, inducing a poorly-tolerated, sustained monomorphic ventricular tachycardia (at a rate of 240 beats/min) and terminated by a burst (Figure 3).

Cardiac magnetic resonance imaging (CMR) showed nondilated and normotrophic left ventricle with basoseptal and mid-septal dyskinesis. The MRI-derived left ventricular ejection fraction was 45%. Delayed enhancement showed patchy transmural fibrosis of the septum and hyperenhancement of the papillary muscles, all

Table 1 Laboratory work-up on presentation

Test	Results	Reference range
Hematology		
White blood cells	6.6	4.2-11.4 × 10^3/mm^3
Hemoglobin	12.7	11.8-15.6 g/dL
Hematocrit	40.5	35.3%-46.1%
Platelets	275	174-402 × 10^3/mm^3
Biochemistry		
Sodium	140	132-145 mmol/L
Potassium	4.3	3.5-5.1 mmol/L
Magnesium	0.94	0.6-1.1 mmol/L
Calcium	2.27	2.1-2.55 mmol/L
Urea	25	15-50 mg/dL
Creatinine	0.68	0.2-1.2 mg/dL
HbA1c	6.7	4.0%-6.0%
Angiotensin converting enzyme	35	20-70 U/L
Cardiac markers		
Creatinine kinase MB	2.8	0.0-5.0 ng/mL
Troponin I (HS)	3	0-15 pg/mL
Cytometry markers		
CD4/CD8 ratio	2.78	1.20-2.40
CD3-16+56+ lymphocytes	8.3	5%-15%
CD19 (pan B) lymphocytes	13.40	5%-20%
Thyroid panel		
TSH	1.45	0.35-4.95 mU/L
Free T4	1.03	0.70-1.48 ng/dL

HbA1c: Glycated hemoglobin; HS: High sensitivity; MB: Myocardial band; MDRD: Modification of diet in renal disease; TSH: Thyroid stimulating hormone.

in favor of extensive cardiac involvement of sarcoidosis (Figure 4). A whole-body positron emission tomography (PET)/CT scan showed no myocardial uptake.

FINAL DIAGNOSIS

Based on CMR and malignant arrhythmia, a CS with pulmonary sarcoidosis in remission diagnosis was made.

TREATMENT

A double-chamber implantable cardiac defibrillator (ICD) was implanted for secondary prevention despite an ejection fraction of 45%, and the patient was started on methylprednisolone (12 mg/d) and methotrexate (12.5 mg/wk).

OUTCOME AND FOLLOW-UP

Regular ICD interrogation showed episodes of asymptomatic nonsustained ventricular tachycardia and an asymptomatic episode of nonsustained ventricular tachycardia ending by the first antitachycardia pacing run (Figure 5).

DISCUSSION

Pathophysiology

Although known to be a systemic inflammatory disease, the etiology of sarcoidosis

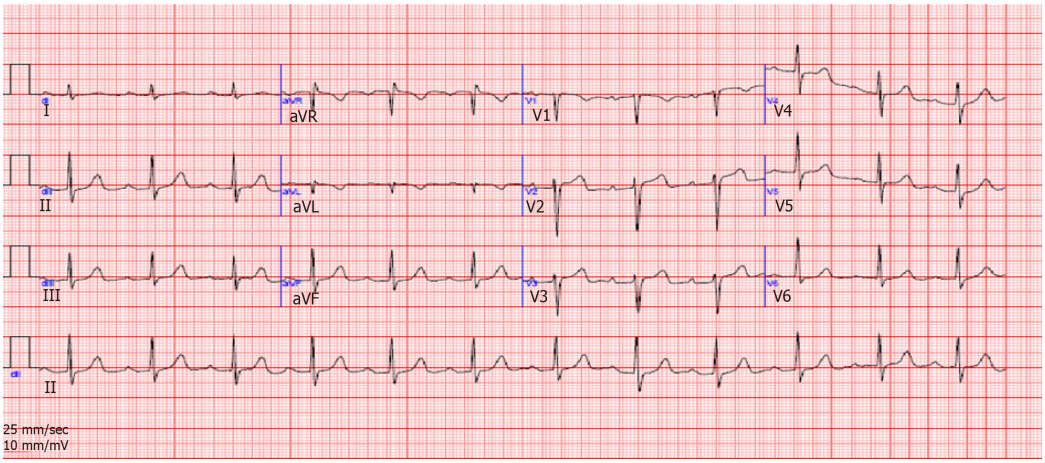

Figure 1 Resting electrocardiogram on presentation, showing first degree atrioventricular block and QTc at 450 ms.

remains unclear; infectious and environmental agents have been suggested as potential factors triggering a T helper (Th) cell-induced granuloma formation, which can later either resolve or progress to fibrosis[10]. Studies have begun to define the pathogenic processes of sarcoidosis. Early in the course of the disease, exposure to the culprit antigen activates phagocytes and CD4-positive T cells, with a Th1 profile secreting interleukin-2 and interferon-γ. Later on, the cytokine profile shifts towards a Th2 cell response, exerting an anti-inflammatory effect and creating scarring[12-14].

Three successive histological stages lead to CS - edema, granulomatous infiltration, and fibrosis, the latter of which is responsible for the characteristic post-inflammatory scarring[15]. These scaring zones can involve any portion of the heart (the pericardium, the myocardium, and the endocardium), with the myocardium being the most frequently affected by far. The left ventricular free wall is the predominant site of involvement, followed by the basal part of the ventricular septum and the right ventricular free wall[3,16]. From a histological standpoint, the typical granulomas characterizing sarcoidosis are noncaseating and consist of aggregates of epithelioid histiocytes, with minimal inflammation and large multinucleated giant cells. Advanced cases, however, develop a fibrotic reaction, causing permanent tissue damage.

Genetic factors have also been implicated in CS, with monozygotic twins being more likely to develop the disease. A Case Controlled Etiologic Sarcoidosis Study also concluded that first-degree relatives with sarcoidosis had a 5 times higher relative risk of developing the disease than control groups[17]. Finally, the HLA–DQB1*0601 type has been reported as associated with CS[18].

Clinical presentation

CS presentation ranges from asymptomatic conduction abnormalities and congestive heart failure to fatal ventricular arrhythmias. While the most important predictor of mortality is the left ventricular ejection fraction[12], the severity of the disease is not proportional to the number of granulomas[15]. In a retrospective study by Chapelon-Abric *et al*[19], CS was observed most commonly in the setting of severe multivisceral disease, presenting unusual clinical and imaging cardiac signs. Complete heart block is one of the most common findings in patients with CS, occurring mostly at a younger age and in 30% of patients[3], with either normal or reduced left ventricular ejection fraction. Complete atrioventricular block and bundle branch block occur in 23%-30% and 12%-32% of CS cases respectively[13]. These manifestations are caused by the involvement of the basal septum affected by scar tissue, granulomas, or ischemia in the conduction system secondary to involvement of the nodal artery.

Sudden death caused by ventricular arrhythmias or complete heart block account for up to 65% of CS deaths[3] and represent the initial presentation in 40% of patients. As is the case with our patient, ventricular tachycardia is also the most common reported arrhythmia noted in CS[3,20,21], with an incidence of 23%[9]. To the best of our knowledge, there has been no report of TdP. Arrhythmia mechanisms are postulated to be secondary to sarcoid granulomas becoming foci for abnormal automaticity or serving to disperse ventricular activation[14,22]. The healing of granulomas prompted by corticotherapy provides a substrate for reentrant arrhythmias to create a slow conduction zone in and around the scar area[23]. Active inflammation may also play a role in promoting monomorphic ventricular tachycardia due to reentry, either by

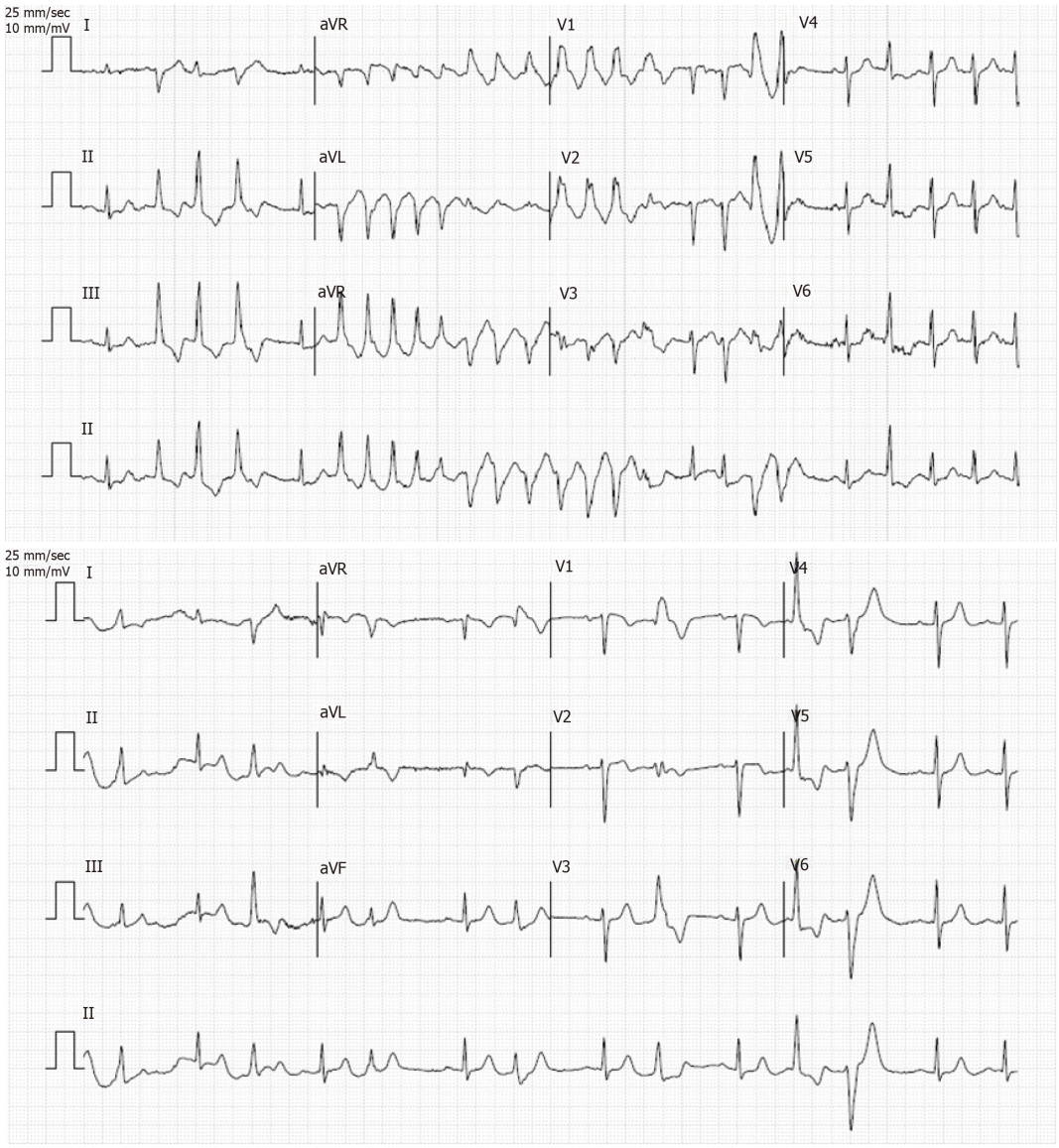

Figure 2 Exercise stress test, showing multifocal ventricular extrasystoles and torsades de pointes.

triggering it with ventricular ectopy or by slowing conduction in diseased scarred tissue[23,24].

Supraventricular arrhythmias may also occur but are less common (15%-17%) and are mostly the result of atrial dilatation or pulmonary involvement. Congestive heart failure, with features of dilated cardiomyopathy, is another common presenting feature[14,25] and accounts for 25%-75% of cardiac deaths in patients with CS. Another rare presentation is acute sarcoid myocarditis, characterized by high-degree atrioventricular block, malignant ventricular arrhythmias, and congestive heart failure[26].

Poor outcome is also associated with pulmonary hypertension secondary to extrinsic compression of pulmonary arteries by enlarged lymph nodes or cor pulmonale (occurring in patients with pulmonary sarcoidosis and hypoxic vasoconstriction secondary to CS)[13].

Diagnosis

Laboratory tests are generally nonspecific and, hence, nondiagnostic for sarcoidosis as illustrated in our case. A panel of tests, however, may support a clinical suspicion; these findings include anemia, elevation of sedimentation rate, and hypercalcemia secondary to the uncontrolled synthesis of 1,25-dihydroxyvitamin D3 by macrophages[27]. Serum angiotensin converting enzymes are often elevated (60%) and are useful for monitoring response to therapy[16,28,29]. Similarly, troponin levels, which might be elevated at presentation, usually normalize within 4 wk of steroid treatment initiation. Both levels were within normal ranges for our patient.

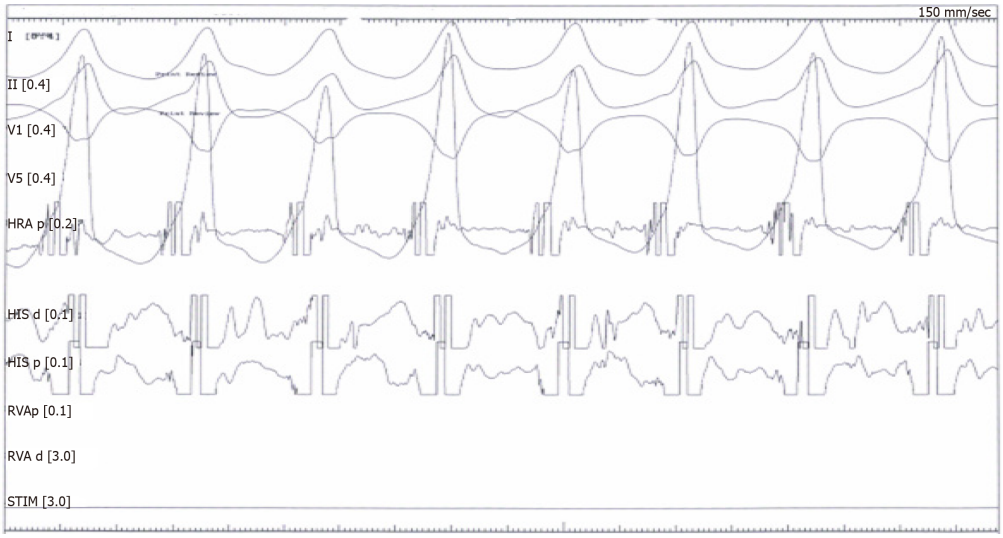

Figure 3 Cardiac electrophysiology study, showing a sustained induced ventricular tachycardia.

Nonspecific electrocardiogram changes are found in as many as 50% of patients with sarcoidosis, with or without clinical cardiac involvement[16]. QT dispersion on surface 12-lead electrocardiogram may be a predictor of sudden cardiac death[30]; carvedilol has been reported to significantly decrease the QT dispersion[31]. CS should be excluded in young patients with a high-degree atrioventricular block not explained by any coronary or hereditary cause[16] and in patients with a fragmented QRS or bundle-branch block pattern[32].

Transthoracic echocardiography, although useful for the assessment of the left ventricular systolic or diastolic function, lacks specificity in most of the CS cases. In CS, the spectrum of two-dimensional echocardiographic abnormalities include abnormal septal thickening or thinning, dilation of the left ventricle, systolic and diastolic dysfunction of the left ventricle, and regional wall motion abnormalities[5,16]. Thinning of the basal anterior septum in a young patient with dilated cardiomyopathy, although uncommon, is highly suggestive of CS[33]. Findings of left ventricular systolic dysfunction and left ventricular dilatation are predictors of mortality in CS and an ICD is recommended for primary prevention when left ventricular ejection fraction < 35%. When compared with age- and sex-matched groups, patients with CS were found to have an impaired global longitudinal strain[34,35].

Nonspecific cardiomegaly is often present on chest X-ray of patients with CS; if pulmonary involvement is also present, hilar adenopathy and/or pulmonary parenchymal changes can be noted, prompting performance of a CT scan. High-resolution CT scan is particularly sensitive for the detection of pulmonary involvement, whereas standard contrast-enhanced CT may be better for delineation of mediastinal and hilar lymphadenopathy[36]. Due to its high spatial and soft tissue resolution, CMR imaging allows for a noninvasive detection of scarring, biventricular dysfunction, edema, and myocardial perfusion defects. CMR relies on identifying areas of mid-wall and subepicardial late gadolinium enhancement, which corresponds to fibrosis as noted with our patient. Additional findings on CMR include thinning of the ventricular wall[5] and, on T2-weighted sequences, presence of edema and global or regional ventricular dysfunction[13]. According to Smedema *et al*[37], CMR sensitivity and specificity were respectively 100% and 78% in the diagnosis of cardiac involvement in patients with CS, who had been diagnosed using the Japanese Ministry of Health and Welfare guidelines[16].

Nuclear imaging provides an effective mean for assessing myocardial perfusion and inflammation. The fibro granulomatous lesions in the myocardium display segmental areas of decreased uptake. Thallium 201 or technetium 99m sestamibi are used most. Dipyridamole is able to differentiate between CS and coronary artery disease. This effect, termed "reverse distribution", may be due to possible microvascular vasoconstriction in CS, where myocardial perfusion abnormalities are reversible after pharmacological dilation[13].

PET is also used to identify CS and assess its severity. As such, it has emerged as a particularly useful tool for the follow-up of patients with CS. PET has the advantage of being applicable to patients with pacemakers or ICDs. The 18F-fluorodeoxyglucose (FDG) radiopharmaceutical – a glucose analog that is generally useful in

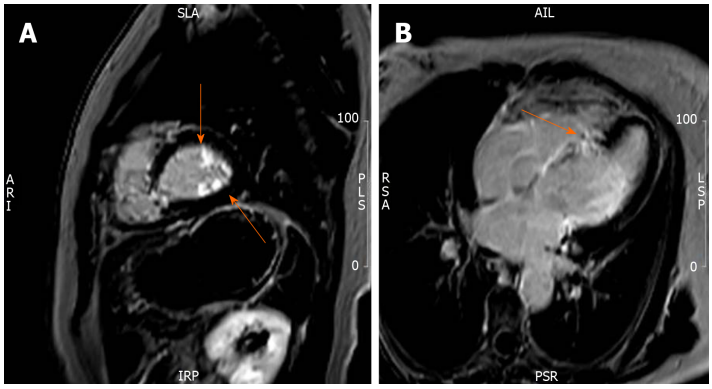

Figure 4 T1-weighted cardiac magnetic resonance image with delayed enhancement. A: Hyperenhancement of the papillary muscles (arrows); B: Patchy transmural fibrosis of the septum (arrow).

differentiating between normal and active inflammatory lesions – accumulates in inflammatory cells that have a higher metabolic rate and rate of glucose utilization[5]. FDG was also found to have higher binding ability than either thalium-201 or gallium-67[12].

Finally, endomyocardial biopsy in CS has low sensitivity due to the focal nature of the disease but may be necessary in cases of negative extracardiac biopsy yields. In order to increase sensitivity, electrophysiological or image-guided biopsy procedures are now recommended[38,39].

Prognosis

The prognosis of patients with symptomatic CS was found to be limited to 5 years[3,12], while more recent studies report up to 50% survival at 5 years[26,40]. Whether this is due to earlier detection of the disease or advances in therapy is still unknown. Independent predictors of mortality are New York Heart Association functional class, left ventricular end diastolic diameter, and sustained ventricular tachycardia.

Guidelines

In 2014, the first international guidelines for the diagnosis of CS were published by experts chosen by the HRS[10]. In 2017, Terasaki *et al*[11] published revised guidelines for the diagnosis of CS (Table 2).

Management

Despite the paucity of data and controversy about its clinical efficacy, most experts recommend treatment of CS by corticosteroid therapy to control the inflammation, prevent fibrosis, and protect against any deterioration of the cardiac function[16,29]. The optimal doses of corticosteroids and how to best assess response to therapy also remain unknown, with no significant difference in survival curves for patients treated with a high initial dose *vs* a low initial dose[41,42]. Corticosteroid treatment may halt the progression of the disease but does not prevent ventricular arrhythmias[29]. Treatment was shown to be beneficial for CS patients with preserved left ventricular ejection fraction but did not show improvement of patients with a severely reduced left ventricular ejection fraction[43]. Ballul *et al*[44] recently suggested that the use of high-dose corticosteroids along with immunotherapeutic agents was associated with a better outcome. Treatments with methotrexate, azathioprine, cyclophosphamide, and infliximab have been studied but there is no evidence of superiority for any[19,45].

Antiarrhythmic treatment and β-blockers are also often needed in the management of CS. While β-blockers increase the risk of atrioventricular block, amiodarone increases the risk of restrictive lung disease; therefore, the use of these agents should be weighted. Class Ic drugs are usually avoided because of their inherent risk of structural heart disease[46].

Ablation of ventricular arrhythmias produces modest outcome, reflecting the extensive scarring of the myocardium in most CS. As such, ablation is considered as a final step in cases with refractory disease[16,29]. Recent studies have shown that catheter ablation of refractory ventricular tachycardia is a safe and effective approach and can decrease the arrhythmia burden by 88.4%[14,47].

Given these limitations and the fact that limited data is present for risk stratification for sudden cardiac death, implantation of an ICD is a class I indication for secondary prevention and should be considered as primary therapy for patients with CS with low ejection fraction and/or ventricular arrhythmias induced upon electrophy-

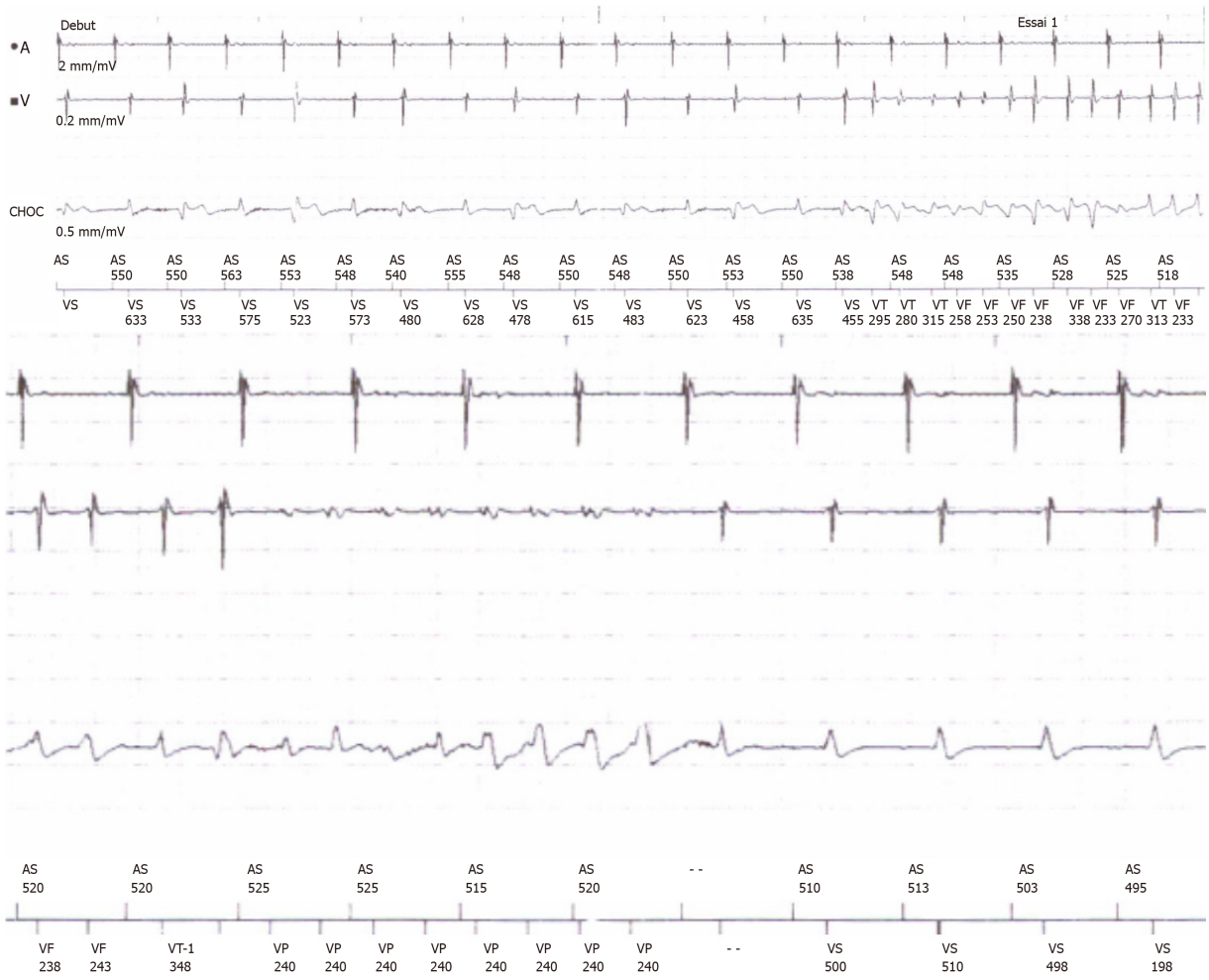

Figure 5 Episode of nonsustained ventricular tachycardia during implantable cardiac defibrillator interrogation stopped by an antitachycardia pacing run.

siological study[29]. Inappropriate ICD shocks were reported in one-third of patients with CS and ICD implanted for primary or secondary prevention due to supraventricular arrhythmias[48]. The indications for permanent pacing are similar to those in patients without CS. There was a class I indication for ICD and the occurrence of VT during follow-up confirmed its need.

Cardiac transplantation is reserved for end-stage disease patients refractory to therapy. The major indications for cardiac transplantation are resistant ventricular tachyarrhythmias and severe heart failure in young patients. Recurrent disease in a transplanted patient, although rare under low-dose corticosteroids and immunosuppressive therapies, can occur[49].

Screening

Although all patients with extra-CS should be referred for cardiac evaluation, the routine use of advanced cardiac imaging remains limited to symptomatic patients. Although these imaging modalities appear to be lacking in diagnostic value for minor disease, the HRS expert consensus states that screening for CS by CMR and/or FDG-PET/CT is recommended for patients with biopsy-proven extra-CSA with signs or symptoms of cardiac involvement or patients with no prior history of sarcoidosis but with unexplained high-degree atrioventricular block or sustained ventricular tachyarrhythmia of unknown etiology.

To the best of our knowledge, the presentation of CS by TdP has not yet been reported in the literature. For our case, the work-up by cardiac echography was nondiagnostic. Given the high suspicion for CS, CMR and PET/CT were used to confirm the diagnosis. A sustained ventricular tachycardia was noted on cardiac electrophysiology, which led to the implantation of an ICD. Ultimately, the patient was treated by an intermediate dose of corticotherapy and methotrexate, a choice of treatment based on the patient's co-morbidities. We hypothesized that the ventricular arrhythmia seen with our patient was secondary to a substrate due to myocardial inflammation and/or a scar-related reentry. The patient showed an advanced AV

Table 2 Summary of the 2017 new guidelines for the diagnosis of cardiac sarcoidosis

Diagnosis of cardiac sarcoidosis follows one of two pathways:
Histological diagnosis
Cardiac biopsy specimens demonstrating noncaseating epithelioid cell granuloma.
Clinical diagnosis
When extracardiac granulomas are found along with clinical findings strongly suggestive of cardiac involvement; or when the patient shows clinical findings strongly suggestive of pulmonary or ophthalmic sarcoidosis; at least two of the five characteristic laboratory findings of sarcoidosis; and clinical findings strongly suggestive of cardiac involvement
Clinical findings that satisfy the following strongly suggest the presence of cardiac involvement:
(1) More than two major criteria are met, OR
(2) One major criterion and two or more minor criteria are met
Major criteria:
Advanced atrioventricular block or malignant ventricular arrhythmia
Basal thinning of the ventricular septum or abnormal wall anatomy
Positive cardiac gallium uptake
Left ventricular contractile dysfunction
LGE on CMR showing delayed contrast enhancement of the myocardium
Minor criteria:
Abnormal ECG findings
Perfusion defects detected by myocardial perfusion scintigraphy
Interstitial fibrosis by endomyocardial biopsy
Laboratory findings
(1) Bilateral hilar lymphadenopathy
(2) High serum angiotensin-converting enzyme level or elevated serum lysozyme levels
(3) High serum soluble interleukin-2 receptor levels
(4) Significant tracer accumulation in 67Ga citrate scintigraphy or 18F-FDG PET
(5) A CD4/CD8 ratio of > 3.5 in broncho-alveolar lavage fluid

CMR: Cardiovascular magnetic resonance; ECG: Electrocardiogram; FDG: Fluorodeoxyglucose; LGE: Late gadolinium enhancement; PET: Positron emission tomography.

block, which could be attributed either to her underlying disease or her γ-blocker. The borderline QTc we observed was hypothesized to be secondary to her medications.

CONCLUSION

CS, although uncommon, should be considered in patients with extra-cardiac disease or unexplained cardiomyopathy, especially in young patients. Despite recent advances in cardiac imaging, CS still remains a challenge to diagnose and available guidelines are limited to expert's recommendations. The clinical spectrum of CS is highly variable, ranging from conduction abnormalities and tachyarrhythmias to heart failure. Early diagnosis of the disease is crucial for maximizing survival following therapy. FDG-PET/CT and CMR are pivotal elements of the diagnosis, given that other modalities present a lower sensitivity. Due to the high risk of sudden cardiac death, ICD implantation must be considered early in the disease due to the high risk of tachyarrhythmias. Steroid therapy, although lacking randomized clinical trials, remains the cornerstone of the medical treatment. Alternative treatments include methotrexate, azathiorpine, infliximab, and antimalarial drugs. Close follow-up is mandatory during treatment.

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