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Clinical Characteristics and Outcomes of Takotsubo Cardiomyopathy

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Abstract

Takotsubo cardiomyopathy (TC) is a transient, reversible form of cardiomyopathy which predominantly affects post-menopausal women and is an important differential diagnosis of acute coronary syndrome. It is characterised by normal (or near-normal) coronary arteries, regional wall motion abnormalities that extend beyond a single coronary vascular bed, and often proceeded by a stressful event. The pathophysiologic mechanism is complex and remains to be elucidated. There is increasing awareness among physicians about TC and hence, more cases are being reported. The diagnosis of TC has important clinical implications in the management at presentation and afterward. In this review, we discuss the demographics, clinical features, prognosis and management of this cardiomyopathy.

Keywords: Takotsubo cardiomyopathy; Apical ballooning syndrome; Stress cardiomyopathy; Acute coronary syndrome

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Introduction

Takotsubo cardiomyopathy (TC) (also known as apical ballooning syndrome or stress-induced transient left ventricular dysfunction) is a recently recognised condition which closely mimics the presentation of acute coronary syndrome. It is characterised by acute but rapidly reversible left ventricular (LV) dysfunction in the absence of obstructive coronary disease. TC was first described in a case series of 5 Japanese patients in 1991.[1] The condition was named on the basis of similarities between the appearance of the LV in systole and the round-bottomed narrow-necked Japanese fishing pot used for trapping octopus (Figure 1, movie). The prevalence of TC is reported to be 1% to 2.5% in patients presenting with acute coronary syndrome (ACS) and 12% in women presenting with anterior ST-elevation myocardial infarction (STEMI).[2,3] Concepts about the demographics, clinical characteristics, pathogenesis, prognosis and management of this reversible form of cardiomyopathy are still evolving. The purpose of this article is to provide an up-to-date review of the clinical characteristics and outcomes of this condition.

Diagnostic Criteria

Researchers at the Mayo Clinic proposed a diagnostic criteria in 2004,[4] which have been modified in 2008.[5]

1) transient hypokinesis, akinesis, or dyskinesis in the left ventricular mid segments with or without apical involvement; regional wall motion abnormalities that extend beyond a single epicardial vascular distribution; and frequently, but not always associated with a stressful trigger;
2) the absence of obstructive coronary disease or angiographic evidence of acute plaque rupture;
3) new ECG abnormalities (ST-segment elevation and/or T-wave inversion) or modest elevation in cardiac troponin; and
(4) the absence of phaeochromocytoma and myocarditis. Japanese investigators[6] have recently presented revised diagnostic guidelines; however, the modified Mayo Clinic criteria are still commonly used.

Clinical Features

Patient Characteristics

TC represents an estimated 1% to 2.5% of patients presenting with an ACS.[2,3] The condition tends to occur in postmenopausal women after a stressful event.[7-10] In a systematic review, women accounted for 82% to 100% of patients with an average age of 62 to 75 years, although cases have been reported in individuals aged 10 to 91 years.[3]

Clinical Presentation

Chest pain and dyspnoea are the two common presenting symptoms in TC.[11-13] Pulmonary oedema, cardiac arrest, cardiogenic shock, and serious ventricular arrhythmias have been reported.[7,14-16]

A unique feature of TC is a preceding emotional or physical stressor, although in some cases, precipitant stressors have not been identified. We have previously reported in a cohort of 100 patients with TC the presentation was preceded by a physical or emotional stressor in two-thirds of our patients, but in the remaining third there was no identifiable pre-event stressor despite specific enquiry after the diagnosis was made.[17]

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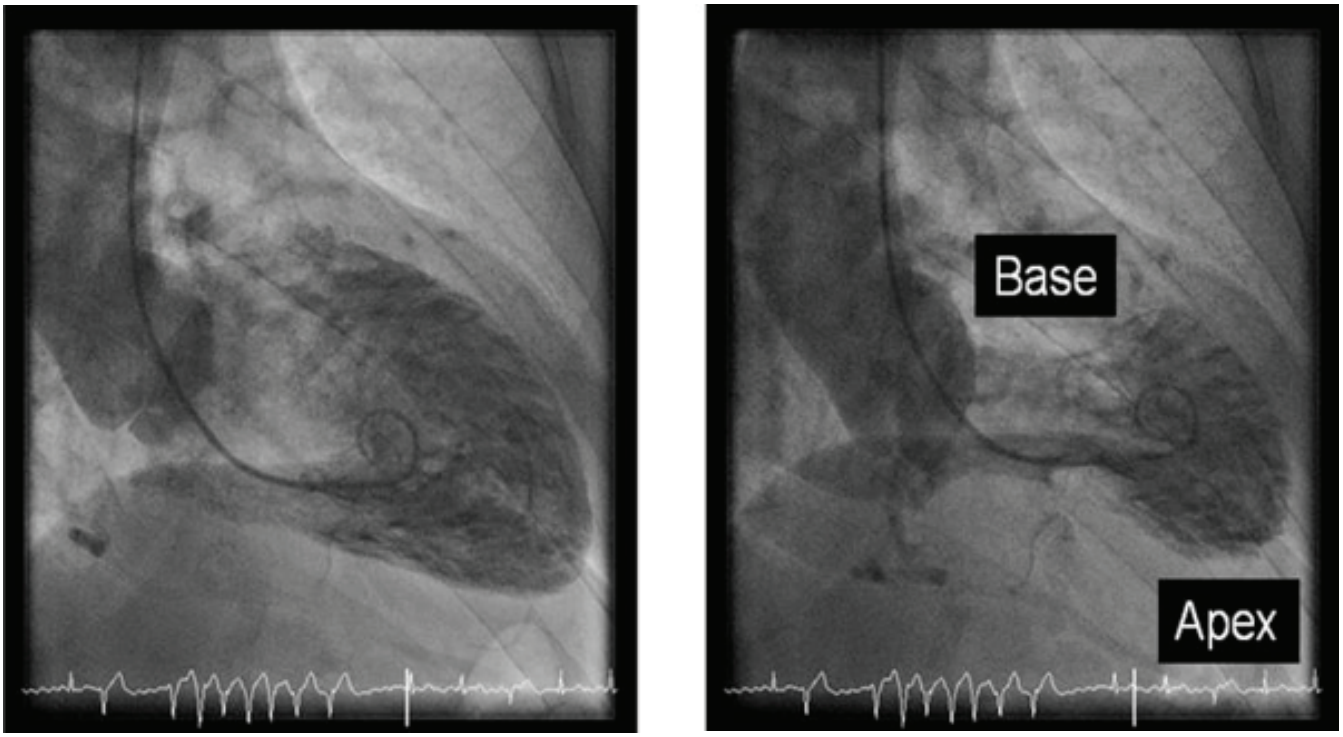

Figure 1. In Takotsubo cardiomyopathy, left ventriculogram during the acute phase typically shows apical akinesis and basal hypercontractility.

Therefore, in women presenting with suspected acute coronary syndromes the absence of an identifiable stressor does not preclude a diagnosis of TC. We have also demonstrated that the clinical characteristics, the rate of in-hospital events, and the long-term prognosis were similar in those with and without an identifiable trigger. In particular, the ECG and severity of LV dysfunction at presentation and the extent of myocardial necrosis measured by troponin level were similar.[17] Thus the presence of an emotional or physical trigger did not identify a subgroup of patients at greater risk of acute complications and long-term recurrence. This finding is consistent with a prior European report[10] and suggests that there is a common underlying pathophysiology, regardless of the precipitating cause. Templin et al [18] recently compared 1750 patients from the Takotsubo International Registry with TC with matched controls who had an ACS. They reported that emotional triggers were not as common as physical triggers, and almost 30% had no identifiable trigger. Younger patients with physical triggers and acute neurologic or psychiatric diseases had an increased risk of in-hospital complications. Since physical triggers are associated with sicker patients such as those in intensive care unit, it is possible that these patients might have worse outcomes. However, further studies are required to address this issue.

Recent studies suggest a predisposing influence of psychiatric disorders, psychosocial stress and type D personality[19] in the pathogenesis of TC. Two extensive overviews of American TC cohorts found that anxiety and chronic stress were both associated with significantly higher odds of developing TC.[20,21] Depression has also been reported to be associated with higher odds of developing TC[21] Templin et al[18] recently reported a higher prevalence of neurologic or psychiatric disorders in patients with TC with 42.3% had received a diagnosis of a psychiatric illness, with half of such illnesses identified as affective disorders. This is consistent with a previous report that found an increased prevalence of premorbid psychiatric diagnoses, particularly anxiety disorders in TC patients.[22] Further studies are needed to confirm the associations of the psychosocial attributes, personality traits, and chronic life stress in TC patients. If chronic psychiatric conditions were confirmed to play a role in its pathophysiology, it would be important to clearly identify and treat them with a view to preventing recurrence.

Pathophysiology

The aetiology of TC is currently unknown. Several hypotheses have been proposed including catecholamine excess and spasm of the epicardial and/or microvascular coronary circulation. We have previously reported evidence that the coronary artery distribution and the frequent finding of apical sparing make the coronary spasm hypothesis less likely. [23] Recent evidence suggests that patients with TC have increased vascular reactivity and impaired endothelial function.[24] It has also been hypothesised that the distal LV may be selectively vulnerable to myocardial stunning.[14]

The reason for the apparent female predisposition for TC is also unexplained but may be related to gender differences in myocardial sensitivity to catecholamine toxicity and subsequent intramyocyte calcium overload.[25,26] A deficiency in oestrogen activity may have a role, as suggested by the higher incidence in post-menopausal women and the evidence of oestrogen supplementation attenuating TC in an animal model.[27] However, many questions remain on the exact pathophysiological mechanism involved in this condition which will warrant further studies.

Diagnostic Method and Imaging Techniques

Cardiac Biomarkers

The troponin levels, a measure of myocardial necrosis are generally elevated at presentation.[3,7,28,29] Usually, the biomarker levels peak within 24-hour after presentation, but the levels are markedly lower than would be expected on the basis of the extent

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of wall motion abnormalities and electrocardiogram findings. This is supported by the fact that the observed myocardial necrosis in TC is modest and in the range typically seen in non ST-segment elevation myocardial infarction (NSTEMI).[17]

Plasma cardiac brain natriuretic peptide (BNP) levels are also elevated in TC patients compared to patients with myocardial infarction.[28] A recent study demonstrated up to a threefold increase in patients with TC compared to STEMI patients.[30] In a study of patients with TC, those with concomitant acute heart failure were compared against those without acute heart failure; the two groups did not demonstrate a significant difference in BNP levels.[31] Hence, there are no specific markers exist for the diagnosis of TC to date.

Electrocardiogram

At presentation TC typically mimics an acute myocardial infarction (AMI) and the initial electrocardiogram (ECG) exhibits ST-segment elevation in about a third of patients.[3,32,33] It has been well described that TC patients commonly demonstrate ECG changes similar to those seen with anterior STEMI.[4] to 50% of TC patients in other series.[7,34,35] Several ECG features of TC have been reported which may help to differentiate TC from an ACS. These include absence of reciprocal changes, absence of abnormal Q-waves, absence of ST-segment elevation in lead V1, progressive QTc interval prolongation and widespread T-wave inversion (TWI).[36-38]

Our group has recently published the largest cohort (n=100) published to date in Australasia and one of the largest cohorts internationally, evaluating ECG differences between TC and patients with myocardial infarction.[34] Compared with STEMI patients TC patients with ST-segment elevation on admission ECG had less prominent ST-segment elevation, less reciprocal ST-segment depression and no abnormal Q-waves. By Day 2 all STEMI patients had pathological Q-waves but none of the TC patients.

We demonstrated that NSTEMI patients had more ST-segment depression but less TWI on admission when compared with TC patients with non-ST segment elevation (NSTE-TC) on ECG. The most striking finding in our cohort was the consistency of evolution of widespread and deep TWI in NSTE-TC patients (Figure 2). By Day 2 >70% patients had TWI in at least half of the leads on ECG and >80% had at least one T-wave inverted ≥2 mm. The good sensitivity and specificity of peak TWI ≥ 3 mm and TWI in 6 or more leads on Day 2 suggest that these 2 ECG criteria could possibly be used to differentiate between NSTE-TC and NSTEMI.

Given the consequences of missing the diagnosis of a STEMI the diagnostic accuracy of ECG criteria are insufficient to reliably distinguish patients with TC from patients with STEMI at admission. On the other hand, our data suggest that ECG may be most useful in pointing to a possible diagnosis of TC on Day 1 or 2 in those presenting like NSTEMIs.[34] The evolution over the first 2 days of widespread TWI, particularly if at least six of the 12 standard leads are involved, should alert clinicians to a possible diagnosis of TC.

Progressive QTc prolongation is frequent in TC.[3,38] Despite the long QT interval, torsades de pointes or ventricular tachycardia is rarely reported. [39,40]

Coronary angiography and left ventriculography

Coronary angiography is necessary for definitive differentiation between TC and ACS. The absence of obstructive coronary artery disease or evidence of acute plaque rupture has been

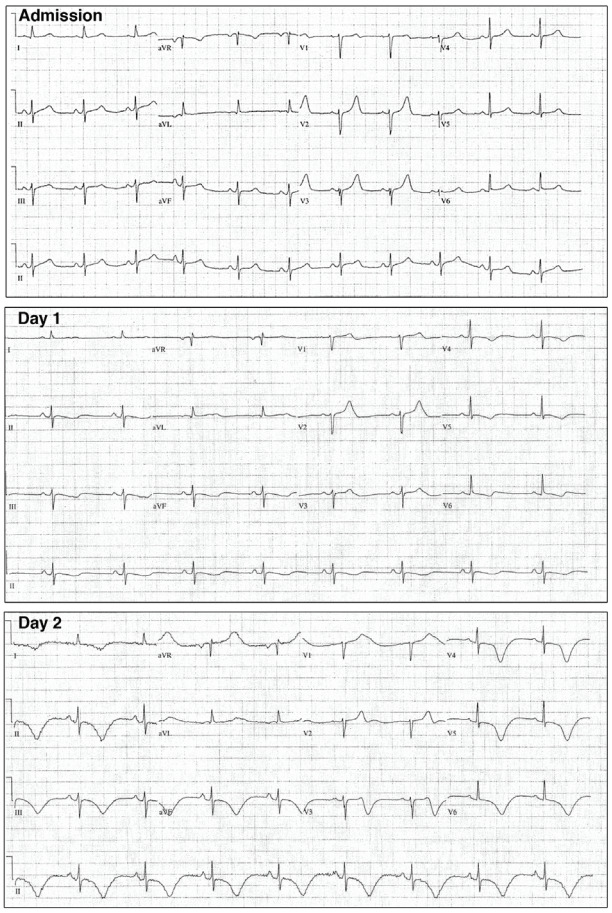

Figure 2. Electrocardiograms of a patient with non ST-segment elevation Takotsubo cardiomyopathy demonstrating progressive T-wave inversion and QTc prolongation.

proposed as a diagnostic criterion.[4] However, some patients may present with bystander coronary disease, where the stenosis are insufficient to explain the degree of wall motion abnormalities and left ventricular dysfunction. A recent case series of 97 Japanese patients with TC noted 10% incidence of incidental coronary artery disease (>75% stenosis of a major epicardial coronary artery).[41] Another series described 7 patients with TC had concomitant coronary artery disease with at least 1 epicardial coronary artery stenosis of 50% or more.[42] Thus, the presence of coronary artery disease does not exclude the diagnosis of TC. Left ventriculography performed at the time of coronary angiography, in a patient with suspected ACS but without obstructive coronary artery disease, is useful to investigate whether the patient has TC. The distribution of wall motion abnormality on the left ventriculogram is similar to that described below for echocardiography, with the added advantage that more minor degrees of apical sparing can be recognised.[23]

Echocardiography

Echocardiography is the non-invasive imaging modality of choice for assessing TC owing to its widespread availability and contributes to the increased detection and reported incidence in contemporary clinical practise.[43] During the acute phase, echocardiography detects extensive wall motion abnormalities usually extending beyond the territory of distribution of a single coronary artery. Classically, the apical or mid-ventricular segments (or both) of the left ventricle are akinetic. Other patterns of left ventricular wall motion abnormality have been reported including mid-ventricular akinesis with apical sparing[44] and basal akinesis with mid-ventricular and apical sparing.[45]

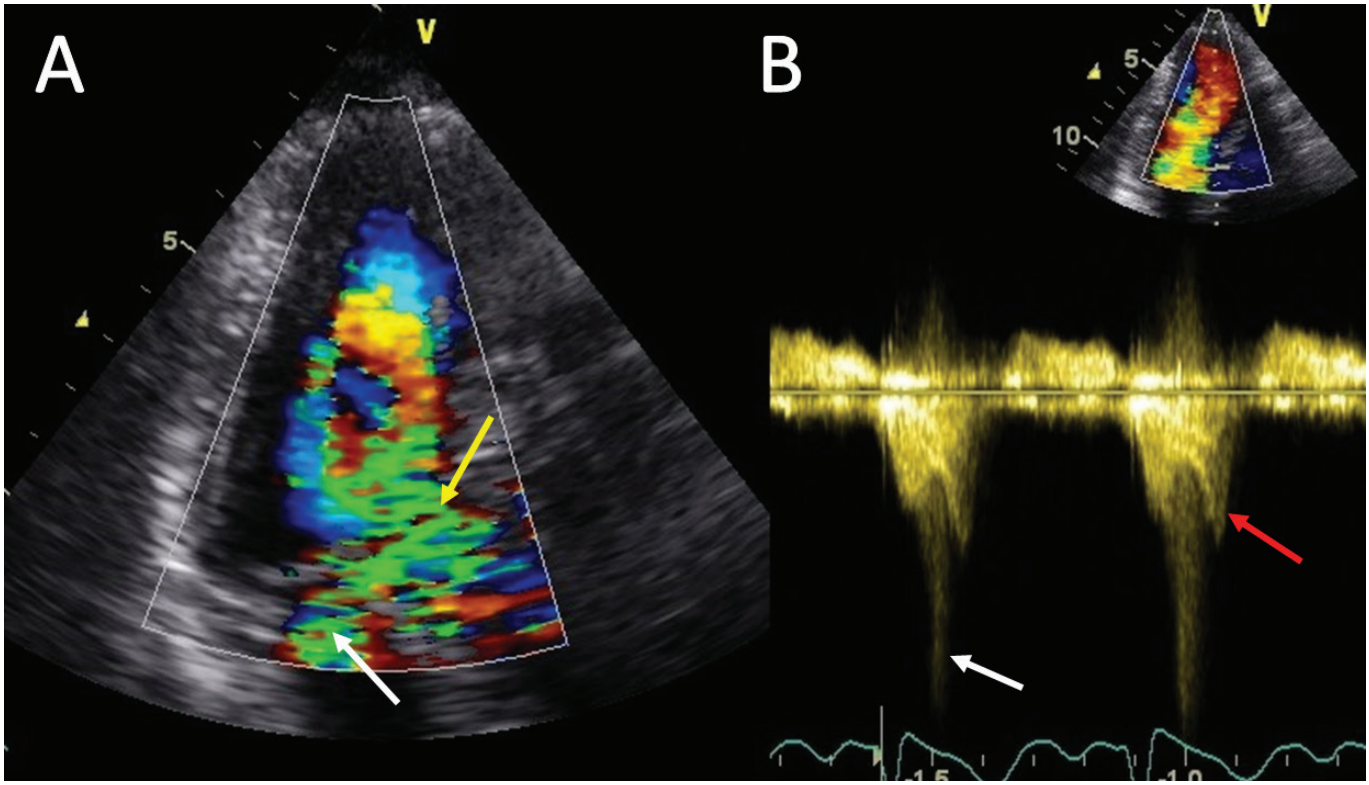

Figure 3. Echocardiogram (A) during the acute phase of Takotsubo cardiomyopathy showed left ventricular outflow tract obstruction (yellow arrow) with dynamic mitral regurgitation (white arrow). On colour Doppler (B), there was late systolic Dagger shape appearance consistent with dynamic obstruction (red arrow). The white arrow showed the signal of mitral regurgitation.

Echocardiography also plays an important role in the early detection of severe potential complications such as right ventricular involvement, left ventricular outflow tract (LVOT) obstruction due to systolic anterior motion (SAM) of the mitral valve (Figure 3), significant mitral regurgitation (MR), apical thrombus formation and ventricular rupture.[2,43,46,47] In addition, it is used at follow-up to confirm recovery of LV function. Normalisation of LV function and wall motion abnormalities generally takes approximately 4-8 weeks, however, there are cases which show longer recovery time.[4,9]

Cardiac Magnetic Resonance Imaging

Cardiac magnetic resonance (CMR) provides detailed cardiac anatomical information and may help to distinguish TC from other acute cardiac syndromes, and provides additional insights into the pathophysiology of the condition. CMR can accurately visualise regional wall motion abnormalities to identify the different variants of LV wall motion abnormality patterns seen in TC. CMR provides complete views of the RV and is helpful in TC cases with RV involvement. In an MRI study, biventricular involvement was observed in 42% of TC patients, a group that tended to have a worse outcome and longer hospitalisation compared to patients with only LV involvement.[48]

A unique feature of CMR is tissue characterisation of acute myocardial changes observed in TC patients. The characteristic finding on short T1 inversion recovery CMR images in TC patients is oedema of the hypokinetic myocardium, showing high signal intensity with a diffuse or transmural distribution. The oedema is restricted to the parts of the ventricle showing the wall motion abnormality and not restricted to a single coronary artery territory. These features aid in distinguishing TC from AMI and acute myocarditis. The oedema in AMI is usually subendocardial or transmural and always coherent with a vascular distribution, and in acute myocarditis is frequently mid myocardial or subepicardial, and often seen in the inferolateral LV segments.[49] The pathophysiological mechanism underlying the development of myocardial oedema remains unclear.

Typically, late gadolinium enhancement (LGE) is absent in TCC both acutely and at follow-up, and the absence of LGE is an important criterion to differentiate TC from AMI.[50,51]

However, while some studies have reported no LGE, others have demonstrated its presence.[52,53] In the largest MRI study to date, minute focal or patchy non-ischaemic LGE was seen in 9% of patients with TC when a threshold of 3 standard deviations above the mean signal intensity for normal myocardium was designated as significant enhancement.[48]

Usually the LGE will be absent at follow-up. Rarely small apical transmural apical LGE persists at follow-up.[53] A small study based on 15 patients with TC who had LV biopsies suggested that LGE may be transient and related to patchy myocardial fibrosis. [54]

Computed Tomography Coronary Angiography

Computed tomography coronary angiography (CTCA) can rule out high-grade coronary stenoses and also exclude pulmonary embolism and acute aortic diseases in patients with acute chest pain.[55,56] However, there are only a few case reports describing the role of CTCA in the acute setting of TC.[57,58] CTCA may be an alternative to invasive coronary angiography to rule out high-grade coronary stenoses in the appropriate clinical setting, particularly in women who have experienced a recent emotional or physical stressor, and echocardiogram and ECG findings suggestive TC.

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In-hospital Complications

Despite its favourable long-term prognosis and low in-hospital mortality (1% to 3%),[4,59] TC is not considered a benign condition because of the occurrence of life-threatening complications during the acute phase, related to haemodynamic instability (e.g. acute heart failure and cardiogenic shock) in a substantial proportion of patients.[9,60] Nearly one fifth of the patients in our cohort had pulmonary oedema at admission and there was a subset of patients who were critically ill at presentation.[17] Apart from one patient who died of cardiogenic shock, all patients with pulmonary oedema, including those requiring intubation and/or intra-aortic balloon pump, fully recovered, and at late follow-up had normalisation of LV function. Age, gender, presence of a stressor, ST-segment elevation on ECG, troponin level, and moderate-severe MR during the acute phase did not identify a subgroup of patients at greater risk of complicated in-hospital course. However, more severe LV impairment during the acute phase was associated with more in-hospital complications. Our findings were similar to a European study[9] where the extent of wall motion abnormalities was a significant univariate predictor of in-hospital events. Templin et al[18] recently reported almost 22% of TC patients had serious in-hospital complications with rates equal to or higher than those of patients with ACS. They found that in-hospital death occurred more frequently among men than among women. Furthermore, TC patients also had severe complications including ventricular tachycardia, ventricular thrombus and ventricular rupture.

Arrhythmias such as atrial fibrillation (AF), ventricular tachycardia (VT), and ventricular fibrillation (VF) are not rare in TC and are likely attributable to high levels of circulating catecholamines. One series reported life-threatening ventricular arrhythmia in over 8% of patients with stress cardiomyopathy.[61] Another study found that arrhythmias are present in nearly one-quarter of patients with TC and have adverse impact on short-term outcomes such as mortality, length of stay and cost of care.[62] AF was the most common form of arrhythmia. Life threatening arrhythmia like VT, VF and sudden cardiac arrest were also observed, but at a low frequency and the exact pathophysiology for occurrence of these arrhythmias is unknown. In our cohort of 100 patients,[17] 7 patients presented with new atrial arrhythmias. Five patients presented with ventricular arrhythmias: 3 patients presented with ventricular fibrillation arrest and two patients had ventricular tachycardia. One patient presented with torsades. Two patients presented with AV block.

Mechanical complications including LV free wall rupture and ventricular septal defects have been reported in TC but are rare. Apical LV thrombus formation and subsequent thromboembolism can occur.[13]

Treatment

There is no consensus about the appropriate treatment of patients with TC but there is a marked increase in prescribing aspirin, beta-blocker, ACE inhibitors and statins on discharge which would be consistent with what would be expected to be seen in treatment after an ACS. Intra-aortic balloon pump can be used to support the haemodynamic state in cardiogenic shock with or without LVOT obstruction.[63] The use of catecholamines as intotropic agents should be considered carefully in this situation, since catecholamines excess may play an important role in this condition and LVOT obstruction can be worsened. Levosimedan has been suggested,[64,65] although clinical data are limited to date. Beta-blockers have been advocated in the treatment of TC and they could be potentially helpful in preventing recurrence given that beta-blockers inhibit the sympathoadrenal system which is thought to be involved in the pathophysiology of TC. However, there are only a small number of case studies suggesting efficacy of these strategies and no randomised clinical trials.[66,67] Trials with long-term follow-up are required to address the optimal treatment and duration of treatment in patients with TC.

Prognosis

The prognosis of patients discharged after TC is generally favourable with a low mortality rate and a low recurrence rate. Comprehensive follow-up of 100 TC patients for a mean of 4.4+4.6 years at the Mayo Clinic showed a recurrence rate of 11.4%.[8] The study showed a mortality rate of 16%, which was similar to an age- and sex-matched local population. Our study showed similar findings with a good long-term prognosis with a low mortality rate and low rate of recurrence during a follow-up of six years.[17] On the other hand, Sharkey et al[9] have demonstrated that the risk for all-cause mortality was greater among TC patients compared to an age- and gender-matched population. The risk of death was greatest in the year following the diagnosis of TC and then decreased considerably in the ensuing years. The deaths reported in the study were related to non-cardiac causes and the recurrence rate was reported at 5%. Templin et al[18] in the largest cohort to date have recently reported a substantial rate of death and major adverse cardiac and cerebrovascular events in TC patients during a long-term follow-up of 10 years with a rate of death from any cause of 5.6% per patient-year and the rate of major adverse cardiac and cerebrovascular events of 9.9% per patient-year. The substantial risk for adverse events in patients with TC suggests that this condition may not be a benign disease. Further studies are needed to clarify these conflicting results.

Conclusion

Takotsubo cardiomyopathy is a recently recognised novel form of heart failure that is precipitated by sudden, unexpected emotional distress which predominantly affects post-menopausal women. The pathophysiological mechanisms are probably complex, and the abnormal catecholamine dynamics related to emotional distress seems to play a major role in the pathogenesis of this cardiomyopathy, rendering TC a type of neurocardiological disorder that manifests as an acute but reversible heart failure. Takotsubo cardiomyopathy is not rare and heightened awareness of this cardiomyopathy will likely lead to a higher reported incidence. The diagnosis of TC has important implications for clinical management at presentation and afterward. The long-term prognosis is generally favourable; however, a small subset has potentially life-threatening complications during the acute presentation. Further research is warranted to more precisely explore and understand the pathophysiology of this cardiomyopathy, characterise and identify those patients at risk, and develop strategies for treatment and prevention of this condition.

Declarations of Interest

The authors declare no conflicts of interest.

Acknowledgements

The authors state that they abide by the “Requirements for Ethical Publishing in Biomedical Journals”.[68]

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