A comprehensive literature review of the epidemiology, diagnosis and management of Takotsubos cardiomyopathy syndrome

Abstract
Takotsubos cardiomyopathy is reported at an increasing frequency. Though it considered a diagnosis of exclusion it remains a pathology requiring focused investigation and tailored management. Despite its prevalence most clinicians do not seem to have a good grasp on the diagnosis and the management of this condition. There have been a large number of publications reporting the various aspects of this condition. Though a noxious emotional event seems to be the most commonly associated trigger, there are a large number of additional triggers that have been described. There are widely accepted diagnostic criteria. Different investigational modalities have different yields in supporting or excluding the diagnosis. The clinical course and the prognosis too can have significant variety. As far as the management strategy is concerned there is no widely accepted pathways published as yet. Clinicians are guided by the clinical condition and the circumstances of the event to decide on the optimal management strategy. We have attempted in this detailed review to collate as much published material as possible to give the clinician reader a sound global insight into this important cardiac condition.

Key words: Takotsubos Cardiomyopathy (TC), Acute coronary syndrome (ACS), Left ventricular (LV), Right ventricular (RV), Coronary artery disease (CAD), Acute myocardial infarction (AMI)

Introduction
Takotsubos Cardiomyopathy (TC) is defined as a non-ischaemic cardiomyopathy, characterized by a sudden reversible weakening of the myocardium and can be triggered by a physical or an emotional stress. TC is a disorder that is commonly confused with acute coronary syndrome (ACS) and is a well recognized cause of acute heart failure and ventricular arrhythmias. TC syndrome was first recognized by Sato H and colleagues [1] ~ 23 yrs ago in the Japanese population due to its characteristic pathological wall motion abnormality resulting in a LV geometry that resembles a Japanese jar used for trapping the squids (tako) with a round bottom and narrow necked (tsubo). TC syndrome is also known by other terms such as transient left ventricle apical ballooning syndrome (TLVABS), stress-induced cardiomyopathy (SIC), broken heart syndrome (BHS) or neurogenic stunned myocardium (NSM). Ceblin and Hirch et al., in 1980 [1] and Dote K et al., in 1991 were among the first who described this acute stress cardiomyopathy (ASC) syndrome in the Japanese population [2], whereas, Desmert WJ and colleagues (1998 – 2001) [3] were the first who described this cardiac syndrome of transient “apical ballooning” in the Caucasian population. Later, since 2001 – 2004 TC syndrome has gained a world-wide recognition with reported cases from all across the world, including Australian population [4], [5]. The worldwide incidence of TC is not accurately known due to its broad clinical spectrum and evolving diagnostic criteria. It is currently estimated that ~ 2% of all patients presenting with an initial diagnosis of an ACS with or without ST segment elevation may in fact have TC syndrome [6]. Studies have demonstrated a seasonal variation in the onset of TC characterized by increased cases...
during the summer months, contrary to the well-known winter peak of ACS [7]. However, it parallels that of ACS in that there is increased frequency in the morning, and patients are more likely to present on a monday [8], [9].

**Types**

TC is broadly classified into LV and RV dysfunction. LV dysfunction is further classified into four different subtypes include classic type (apical variant), reverse type (inverted type), mid-ventricular type and localized type.

**The classic type (apical variant):** accounts for ~60% cases [10], [11] is characterized by LV mid and apical segment akinesis, with hyperkinesia of the base, resembling a traditional Japanese octopus trap jar ("Tako-Tsubo"). Suggested anatomic and physiologic factors that might be responsible for the occurrence of classic type are differences in its anatomical sympathetic innervation and its enhanced responsiveness of to abrupt rise in circulating catecholamines [12]. In addition, as the apical LV lacks a three-layered myocardium, therefore, it loses its elasticity after excessive expansion and being a border zone of the perfusion area of major coronary vessels it is prone to delay of functional recovery from a global dysfunction [13], [14].

**The reverse type (inverted type):** affects significantly younger people [15] and presents with LV basal hypokinesis with preserved LV apical function.

**The mid-ventricular type:** accounts for ~40% [10] is characterized by transient LV mid-segment akinesis but preservation of LV apical segment [17]. **The localized type:** is characterized by any other segmental LV dysfunction with clinical characteristics similar to takotsubo-like LV dysfunction. **The RV type of dysfunction:** although much rarer is characterized by involvement of the distal segment of the RV with sparing of the base [18].

![Figure 1: Four types of Takotsubos Cardiomyopathy [19]](image)

**Trigger factors**

TC is a heterogeneous condition and its exact aetiology remains uncertain to date but has a unique feature that it has is a preceding emotional or physical trigger and it varies among patients. It is possible that trigger factors can be absent, unidentifiable, or overlapping.

The most well known and documented trigger factors for TC the so called ‘stressful events’ probably related to catecholamine surge are hypoglycaemia [20], phaeochromocytoma [21], pneumothorax [22], subdural hematoma [23], subarachnoid haemorrhage [24], sepsis and respiratory failure [25], anaphylaxis [26], news of the death [27], death of a close relative or a loved one [28], public speaking, or non-cardiac surgery [11], earthquakes [29], alcohol withdrawal [30], opiate withdrawal [31] and seizure [32]. In addition exposure to cocaine [29] or beta-agonist drugs even in routine clinical dose can elicit TC [33]. The reported distribution of emotional and physical triggers varies among patient cohorts, in a study Caucasians more frequently had an emotional stress as a trigger (63.8% vs. 28.6% p = 0.000) while Asians most commonly had no preceding stress (42.9% vs. 2.1% p = 0.000) [34].

**Pathogenesis**

Among the various pathophysiological mechanisms that have been proposed to describe the sympathetically mediated transient segmental LV dysfunction are endogenous
catecholamine-induced myocardial stunning [12], multi-vessel epicardial coronary vasospasm [35] and cardiac microvascular and endothelial dysfunction [36]. Inflammation such as myocarditis [3] and cardiotropic viruses [37] have also been postulated, but there is a paucity of evidence for these [38] and none have so far been successfully isolated [39]. Emotional stress-related surge in serum catecholamines seems to play a major role in the pathogenesis. In a study TC patients during their acute presentation had 2 to 3 times higher serum catecholamines levels than those who had acute myocardial infarction (Kilip class III) and 20 times higher than normal adults and these serum levels remained significantly elevated for more than a week in patients with TC [28]. Few theories are postulated that endogenous catecholamine surge can cause transient apical sympathetic dysfunction due to exposure of highly trabeculated LV apex to elevated endogenous catecholamines [40] and also by inducing paradoxical negative ionotropic effect, even in the presence of normal perfusion [12]. Whereas, atypical variant of TC the mid ventricular type could be related to the deviation in the distribution of adrenergic receptor density in the LV [10]. Alteration of the balance between the positive and negative inotropic effects of catecholamines on the myocardium, potentially leading to myocardial dysfunction in TC.

The hypothesis that transient epicardial coronary artery vasospasm causing ischemia as an underlying mechanism for transient reversible segmental LV myocardial stunning [115] has not been confirmed, and vasospasm has only been noted in case reports of individual patients. Furthermore, provocative substances, such as acetylcholine or ergonovine, have failed to induce a recurrent TTC pattern. Therefore, raises several doubts about this hypothesis.

There is inconclusive evidence from imaging studies such as nuclear medicine scan, PET scan, doppler transthoracic echocardiography, or coronary angiography to support that pronounced and reversible endothelial and coronary microvascular dysfunction directly or indirectly can impair myocardial perfusion to plays a role in TC [41]. It is clear that no single mechanism has been conclusively demonstrated to hold true for TC including its subtypes and possibly multifactorial elements may be in play.

**Clinical Presentation**

**Age:** Demographically there are significant differences in the age of initial presentation among TC patients and ACS patients. In a study age at initial presentation of TC patients was more than any type of acute myocardial infarction (60 to 86 yrs vs 44 to 75 yrs) [42]. The classic (apical) variant of TC tends to occur in the older age people whereas the reverse type (Inverted tako-tsubo) is more common in younger age people [43].

**Gender:** TC is much more common in women than men [13], [5] typically identified in women [44] and postmenopausal women (~90% of the cases) [4]. TC has been reported to occur in men as well and the figures are quoted as between 8% to 32 % [45], [46], [47], [48].

**Ethnics:** The epidemiology of TC reveals several ethnic trends. In a study Asians and Caucasians were chosen for comparison since they made up the majority of cases whose race was known (97.2%) [34]. TC tends to be more predominant in Asians (57.2%), with Caucasians (40%) being the second most common group [34].

**Cardiovascular risk factors:** The well known major cardiovascular risk factors for coronary artery disease and the coronary artery disease itself may co-exist in patients with TC particularly among older age people and postmenopausal women but their overall strong association is debated. **Coronary artery disease (CAD):** The left anterior descending artery (LAD) supplies the anterior wall of the LV in the majority of patients. If this artery also wraps around the apex of the heart, it may be responsible for blood supply to the apex and the
inferior wall of the heart. It was noted by some researchers that there could be a correlation of this anatomic variant with TC [49] but other researchers have shown that this anatomical variant is not common enough to explain its association with TC [42] and as an aborted acute myocardial infarction and plaque rupture [50] in the LAD cannot induce a multiregional left ventricular (LV) segmental wall motion abnormality might suggest TC. Furthermore, recent intravascular ultrasound (IVUS) studies also found no evidence of culprit lesions in the LAD [51]. But it should be noted that the presence of one does not rule out the other. Co-existence of angiographic documented coronary artery disease has been reported in separate series of 10% to 63% of TC patients [52]. Smoking: Is smoking a risk for TC is not known. In various studies TC patients had a frequency of smoking between 8% to 28% of cases [53], [11], [45], [54], [46],[48], [55],[56], [47]. Hypertension: It is not clear whether hypertension presents an actual risk factor for TC. A history of hypertension was found to vary between 33-76% among TC cases [57], [11], [4], [58], [59], [34], [60],[45], [54], [46], [48], [55], [47]. Diabetes: Although, Insulin resistance is associated with high levels of serum catecholamines, the aetiology of impaired glucose metabolism in this condition remains unclear [40]. In some studies diabetes was present in 6% to 28% of cases of TC [60], [45], [54], [46], [48], [55], [47]. Dyslipidemia: Whether hyperlipidemia is a risk factor for TC is unknown. Although, in some studies a history of dyslipidaemia was seen in 17% to 23% cases of TC [11], [45], [54], [48], [55], [47]. Obesity: What is the association of overweight and obesity with TC is uncertain. In a study a history of being overweight (BMI 25-30) was noted in 51% of cases and obesity (BMI > 30) was noted in 19% of TC cases [45]. Genetics: Studies have suggested the possibility of a familial etiology in TC [61] but a comprehensive DNA sequence analysis failed to show any association between functional variants of genes encoding the beta 1, beta 2, and alpha 2c adrenergic receptors modulating cardiac response to catecholamine and familial TC [62]. Presenting symptoms: The clinical picture typically includes symptoms associated with acute coronary syndrome [63], ST elevation MI [27] and acute heart failure. The most common presenting symptoms are chest pain (68%) and dyspnea (17%) [57], [60]. Palpitations (most likely ventricular in origin) and syncope have also been reported. Less commonly patients have presented with cardiogenic shock and out-of-hospital cardiac arrest (ventricular fibrillation in ~ 1.5%) [27], [11]. However, an episode of TC can occur with non-specific symptoms and signs and have been discovered incidentally during hospitalisation because of an abnormal ECG or elevated cardiac biomarkers, further clinical investigation help confirm or exclude TC. Acute Complications Several acute complications reported in TC includes hypotension, LV systolic dysfunction, cardiogenic shock, mitral regurgitation, LV apical thrombus, LV free wall rupture, ventricular septal perforation, arrhythmias and death. Hypotension: Although severe hypotension and shock occur commonly during acute stages of TC. It is multifactorial, may occur as a result of decrease in stroke volume (SV) secondary to LV systolic dysfunction [11], significant mitral regurgitation (MR) due to systolic anterior motion (SAM) of the mitral valve (MV) and dynamic LV outflow tract obstruction (LVOTO) [64]. Systolic left ventricular failure (LVF): Systolic heart failure with or without pulmonary edema is frequently seen. In a review of TC patients 45% cases had acute left ventricular failure (LVF) and Killip class II, III, and IV left ventricular failure was seen in 43%, 9%, and 47% cases respectively [65]. Cardiogenic shock with its corresponding high mortality is a rarer complication [11],[66]. Mitral regurgitation (MR): TC may be associated with acute mitral regurgitation of variable magnitude, which is
often transient [67], [55]. In a typical apical variant of TC acute reversible mitral regurgitation (MR) may be related to systolic anterior motion (SAM) of the mitral valve and left ventricular outflow tract obstruction (LVOTO) [68]. The degree of mitral regurgitation (MR) usually decreases significantly within the first 72 hours of presentation [69], but there may be persistent SAM of mitral valve even after normalization of LV systolic function [69].

Left ventricular outflow tract obstruction (LVOTO): Transient dynamic left ventricular outflow tract obstruction (LVOTO) is relatively common [11]. In a typical apical variant, especially in women, smaller left ventricular size, hypercontractility of the base while compensating for LV apical akinesis [38] and thickening of the mid ventricular septum [70] may predispose to the development of LVOTO. Dynamic LVOT has been associated with acute reversible mitral regurgitation (MR), reversible systolic anterior motion (SAM) of the mitral valve [67] and hemodynamic instability [71] but it can be asymptomatic in ~ 20% of patients [5]. LV apical thrombus: In a typical apical variant, during acute phase, reduced blood flow in the LV apex along with persistent apical LV systolic dysfunction can predispose to LV apical thrombus [66] and systemic embolization. The incidence has been quoted as ~ 8% [72] and in two systematic reviews of 2008 and 2010, occurrence of a LV apical thrombus was reported as high as in patients with acute myocardial infarction. In almost all of these studies, LV thrombus was successfully treated by anticoagulation [73].

Left ventricular free wall rupture: LV free wall was observed in TC patients who had higher systolic and diastolic blood pressure and higher fluctuations of intra-cardiac pressure [74]. A total of eleven case reports of LV free wall rupture were identified in 2009 MEDLINE systematic review. Ventricular septal perforation: Ventricular septal perforation has been demonstrated in TC a rare complication with a high mortality.

Arrhythmias: During acute and subacute phases of TC, there is a risk of catecholamine-mediated arrhythmias such as torsade de pointes, especially among those who have pre-existing QT interval prolongation [75]. However, ventricular tachycardia and fibrillation are uncommon [76]. Death: many studies report a good long term prognosis for patients who overcome the acute phase of TC and their risk of sudden death is low [77].

Diagnosis

Diagnostic criteria: There are several suggested diagnostic criteria available for diagnosing TC, the Modified Mayo Clinic Criteria (MMCC)[40] is one of the most commonly used however others exist (Abe and Konoda [63], Segovia Cubero [96]and the Kawai [97]). The MMCC inclusion criteria that must be met are 1) transient akinesis or dyskinesis of the left ventricular apical and mid-ventricular segments with regional wall-motion abnormalities extending beyond a single epicardial coronary artery territory, 2) absence of obstructive coronary artery disease or angiographic evidence of acute plaque rupture and 3) new electrocardiographic abnormalities (either ST – segment elevation or T-wave inversion) or elevated cardiac biomarkers (troponin). Patients are excluded if they have had 1) recent significant head trauma, 2) intra-cranial haemorrhage, 3) pheochromocytoma, 4) obstructive epicardial coronary artery disease, 5) myocarditis and 6) hypertrophic cardiomyopathy.

The modalities used in the diagnostic workup include cardiac biomarkers (myoglobin, CK, CK-MB, Troponin, BNP and pro-BNP, circulating microRNAs), serum norepinephrine, inflammatory markers (white cell count, CRP, hs-CRP), electrocardiography, echocardiography, coronary angiography, cardiac CT angiography, myocardial perfusion scans, cardiac magnetic resonance imaging and cardiac positron emission tomography scanning.
**Cardiac biomarkers:** Both creatinine kinase MB fraction (CK-MB) and troponin (Tn) are elevated in the setting of membrane leak caused by acute myocardial necrosis, whereas the production and release of BNP is related to ventricular distention with or without myocyte necrosis. There can be a large discrepancy between the area of myocardium affected and peak level of troponin T during acute phase of TC. In acute phase of the apical variant of TC, creatine kinase (CK), creatine kinase-muscle brain (CK-MB) and troponin are only mildly elevated than would be expected in AMI. In the reverse variant of TC levels of CK-MB and troponin-I are significantly higher than in patients with typical apical or mid-ventricular variant [46]. In a study, elevated cardiac troponin T at admission was one of the independent predictor of acute heart failure [60]. Cardiac **brain natriuretic peptide (BNP)** levels are often higher compared to patients with AMI [78]. Higher and persistent elevation of cardiac BNP and N-terminal pro-hormone BNP levels can correlate both the extent of catecholamine elevation and the severity of LV systolic dysfunction [79]. In a study, receiver operator characteristic curve analysis of the elevated cardiac biomarkers [80] and a recent study described a signature of four **circulating miRNAs** as a robust biomarker to distinguish TC from AMI patients, significant up-regulation of stress and depression related microRNAs suggests a close association of TC with neuropsychiatric disorders [81], but no specific biomarkers exist for the diagnosis of TC.

**Serum norepinephrine:** Elevation in serum norepinephrine level is non-specific and is not helpful in the diagnosis of TC [82].

**Inflammatory markers:** Elevation in white blood cell count, CRP, hs-CRP seen in TC patients is often non-specific and is not useful for the diagnosis of TC. In a study, during acute phase of TC elevated levels of hs-CRP and low LV ejection fraction were independent risk factors for death or cardiogenic shock [83].

**Electrocardiography:** ECG can help to investigate suspected TC or ACS. The ECG findings are variable and cannot reliably differentiate between the two. It may help to quantify LV dysfunction and guide initial treatment [84], [85].

![Figure 2: Receiver operator characteristic curve analysis of the elevated cardiac biomarkers to help distinguish TC from AMI](image)

![Figure 3: ROC curve analysis for the combination of four micro-RNAs resulting in enhanced specificity and sensitivity to distinguish TC form healthy subjects (74.2, 78.6%, respectively) and AMI controls (96.8, 70.4%, respectively)](image)
Figure 4: Prevalence of ST-segment elevation, T-wave inversion, and Q-wave in patients with TC [86].

ECG appeared in two forms i.e., ST-segment elevation and T-wave inversion. Where ST-segment elevation appeared first mainly in the precordial leads, the T-waves appear peaked followed by diffuse and often giant T-wave inversion which persisted from several days to several weeks and disappeared thereafter. There were no reciprocal changes in limb leads. The Q-waves were reversible and disappeared over time. Where T-wave inversion appeared first and persisted without ST-segment elevation, had pronounced QTc intervals prolongation. There was no atrioventricular block and significant arrhythmia event [86]. ST-segment depression in lead aVR and the absence of ST-segment elevation in lead V1 is more useful for identifying TC [87]. The ST segment deviations in TC are usually less pronounced in comparison to ST-segment elevation myocardial infarction and are exhibited more frequently in Asians than whites [34]. These ECG findings typically do not correspond to a typical coronary artery distribution [88]. Early ST segment and T-wave abnormalities at admission and their evolution in the first few days have not been shown to correlate with the magnitude of LV dysfunction or clinical outcome.

Coronary angiography and LV angiography: Coronary angiography is the gold standard for excluding obstructive coronary artery disease or angiographic evidence of acute plaque rupture or thrombotic occlusion and identifying TC and its subtypes with an early LV angiographic wall motion abnormalities of a typical apical variant, reverse or inverted type, mid-ventricular type, and a focal type LV dysfunction that do not correspond to a typical coronary artery distribution.

Differentiation between TC and ACS on coronary angiography may also be difficult as patients with TC tends to demonstrate abnormalities such as non-critical atherosclerotic lesions of < 50% of the luminal diameter [5] an unusual left anterior descending artery (LAD) anatomy such as “wrap-around” LAD [89] supplying an extensive vascular territory as well as disrupted atherosclerotic plaques in the LAD [90].
Cardiac CT angiography: CT coronary angiography may be a valuable and safe diagnostic tool for confirming the presence or absence of obstructive coronary artery disease [92] and also for assessment of LV systolic function particularly in patients with relatively few coronary risk factors. So therefore, helps discrimination of acute TC from ACS. It is a good modality in patients with a suspicion of recurrent TC, who has undergone prior evaluation via cardiac catheterization during their initial admission within a short period of time.

Echocardiography: Transthoracic echocardiography cannot reliably differentiate between LV dysfunction from TC and coronary artery occlusion. However, the findings of persistent LV wall motion abnormalities after the first day in the face of normal coronary arteries and gradual improvement of LV function within a week of the initial presentation, and complete normalization of LV function and wall motion abnormalities within ~ 4 – 8 weeks suggest a diagnosis of TC. However, recovery of LV function is variable and rarely can take longer than expected. Transthoracic contrast echocardiography, during acute phase of TC can detect, classify and quantify LV dyskinesia in a typical variant [5] and subtle right ventricular (RV) apical dyskinesia [93]. Dobutamine stress echocardiography may be used to classify typical and atypical TC. Transthoracic echocardiography can guide initial management of haemodynamically unstable TC patients particularly those with significantly reduced LV ejection fraction, acute reversible mitral regurgitation (MR) related to systolic anterior motion (SAM) of the mitral valve [11] & LV outflow tract obstruction (LVOTO) [53] and LV apical thrombus. Transesophageal echocardiography may provide better anatomic details that may direct repair or replacement of the mitral valve especially when significant MR persists even after resolution of LVOTO. Doppler echocardiography, regional strain echocardiography and time-volume curves from 3-dimensional echocardiography may offer good visualization of the regional wall motion abnormalities in TC patients with higher diagnostic sensitivity. The serial transthoracic doppler echocardiography-coronary flow reserve (CFR) in the distal part of the left anterior descending coronary artery, using intravenous adenosine infusion [94] showed transient coronary microcirculation dysfunction in parallel with LV wall-motion abnormality during the acute phase and recovery during
chronic phase does suggest a role of coronary microcirculatory dysfunction in the pathogenesis of TC.

Figure 6: (a,b,c) TTE images of the patient demonstrating LV systolic apical ballooning (arrows) and LV outflow tract obstruction. (d,e) TTE (4-chamber view) during d systole and e diastole shows basal and midventricular segmental hypokinesis but preserved apical segmental function during systole.

Cardiac single photon emission CT (SPECT): Serial gated SPECT phase imaging with 99mTc-sestamibi or tetrafosmin, 99mTc-PYP, 123 I-BMIPP & 201Thallium and 123 I-MIBG & 201Thallium is used to evaluate cardiac perfusion and metabolic activity. 99mTc-sestamibi or tetrafosmin coronary blood flow imaging during acute phase (3 – 5 days) of classic TC shows reversible myocardial dysfunction with a transient fixed perfusion defect that cuts across several coronary vascular territories even though there is no coronary artery disease along with LV apical ballooning and dyskinesia, followed by normalization of perfusion and function during chronic phase (~ 4 – 8 weeks). However, the recovery period is variable [95]. 99mTc-PYP SPECT imaging during acute phase of TC might represent LV apical and mid plane myocardium stunning caused by coronary microcirculation perfusion mismatch [95]. 123 I-BMIPP-201Thallium fatty acid metabolism-perfusion mismatch [95] and 123 I-MIBG-201Thallium [12] sympathetic innervations-perfusion mismatch occurs in parallel with LV apical and mid plane myocardium stunning during acute phase of TC, although myocardial fatty acid metabolism and sympathetic nervous system impairment is more adversely affected than perfusion, these abnormalities usually improves gradually during chronic phase [96], but may persist even after normalization of apical and mid plane perfusion.

Cardiac positron emission tomography (PET) scan: Serial cardiac 82rubidium PET and 201Thallium PET [97] as well as quantification of microcirculatory disturbance with rest & hyperemic myocardial blood flow (MBF) using 82rubidium PET [98] and coronary flow reserve (CFR) using 13nitrogen PET [99] demonstrate a reversible apical and mid plane dysfunction with a transient fixed metabolic-perfusion mismatch during acute phase of TC which do not correspond to the territory of a single coronary artery distribution followed by complete reversibility of the perfusion, microcirculatory and metabolic defect during chronic phase suggest TC as an underlying cause. In this mismatch, metabolic impairment is more extensive and severe than perfusion, therefore, suggests catecholamine-induced metabolic disorder as a possible underlying mechanism of TC secondary to cyclic-adenosine-
monophosphate mediated intra-myocardial calcium overload which decreases myocyte viability or ischemic-reperfusion phenomena [100]. Quantitative cardiac PET scan such as MBF and CFR can be helpful in distinguishing TC from ischemic cardiomyopathy [98], [99] and also in assessment of extent of ventricular dysfunction [97]. The 11C hydroxyephedrine sympathetic nervous system imaging using 13nitrogen PET can demonstrate LV apical innervations-perfusion mismatch [101].

**Cardiac magnetic resonance imaging (CMRI):** Cardiac MRI can provide diagnostic and prognostic information in TC by the use of T2 STIR sequence, cine balanced turbo echo gradient and contrast-enhanced sequence by ruling out acute myocardial infarction or myocarditis. In T2 STIR sequence MRI the most characteristic finding seen in acute phase of TC (< 3 days) is the location of ventricular edema which is not related to a vascular territory of coronary arteries, and distributed in both the apical and mid planes of the LV, the signal intensity decreases and completely resolves in many cases during chronic phase (> 4 weeks).

![Cardiac MRI of myocardial edema in a representative patient with Takotsubos Cardiomyopathy](image)

The cine balanced turbo echo gradient demonstrates the presence of a transient reversible apical akinesis which produces ballooning morphology along with hyperkinesis of the base of LV characteristic of TC, both apical & mid plane akinesis and basal plane hyperkinesis can produce a dynamic obstruction in the LV outflow tract with associated systolic anterior motion of the anterior mitral valve leaflet. An apical clot in the LV can be also seen.

![Cardiac MRI of 4 distinct ballooning patterns in Takotsubos Cardiomyopathy and at 3-Month Follow-up](image)
Images for each ballooning pattern are representative examples from a patient included in the study. A-C, Vertical long-axis views. A (left panel), asterisks indicate pericardial effusion. Middle panel, yellow arrowheads indicate the area of apical akinesia. B (middle panel), yellow arrowheads indicate the area of mid left ventricular (LV) akinesia. C (middle panel), yellow arrowheads indicate the area of basal akinesia. D, Horizontal long-axis view. Asterisks indicate bilateral pleural effusion at acute presentation. Middle panel, yellow arrowheads indicate apical LV akinesia and black arrowheads indicate right ventricular (RV) apical akinesia [45].

The contrast-enhanced sequence MRI shows no segmental LV perfusion defects in TC, whether or not focal or patchy late gadolinium enhancement (LGE) is seen in TC is debated as studies has reported its presence as well its absence. In a recent prospective study of acute phase of TC patients there was no evidence of LGE when SI threshold cut-off of 5 SD was used [45]. Cardiac MRI with adenosine can detect and quantify microcirculatory disturbance, which may prove useful in the management of TC [102].

Figure 9: Cardiac MRI of necrosis/fibrosis in a representative patient with Takotsubos Cardiomyopathy

Myocardial fibrosis was quantified, B, by selecting a region of interest in nonenhancing healthy myocardium (blue contour) and setting automated computer detection to 3 SDs (left) and 5 SDs (right) above the mean of healthy myocardium to identify fibrosis. Computer-aided signal intensity analysis detected positive late gadolinium enhancement (LGE) more than 3 SDs above the mean (red overlay), but no significant LGE more than 5 SDs above the mean was present (red contour=subendocardial border; green contour=subepicardial border of the myocardium) [45].

Treatment

There are no randomised controlled trials on the management of TC. During initial acute phase of TC, management is based on clinical judgment and electrocardiography and often mirrors that of ACS. Those presenting with ST segment elevation will often be managed with either fibrinolysis or primary percutaneous coronary intervention (PCI) and if they present
with non ST segment elevation or no ECG changes but has a troponin elevation are treated with aspirin and heparin initially and often undergoes early coronary angiography. Once the diagnosis of TC is established then management is aimed at relieving symptoms and close monitoring for treating complications.

**Acute systolic heart failure (~20%)**: during acute phase of TC [11] includes aspirin, a cardioselective beta-blocker, angiotensin converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) and diuretics [27], [65], [58]. To date no randomized trials have assessed the benefit or optimal dose and duration of medical therapy in TC. Aspirin is used initially, but later can be discontinued unless there is coexisting coronary atherosclerosis. Beta-blocker use is advocated for patients with abnormal response to excessive catecholamine [103]. Beta-blockers may also help to reduce the Left ventricular outflow tract obstruction (LVOTO) [58] but contraindicated in acute severe heart failure with reduced ejection fraction, hypotension and bradycardia. Initiation of ACEIs or ARBs therapy before discharge is reasonable and later discontinued once there is complete recovery of left ventricular systolic function. Diuretics are effective in most cases at treating signs of congestive failure and fluid overload.

**Hypotension and cardiogenic shock**: require evaluation of LV systolic dysfunction, LV outflow tract obstruction and mitral valve dysfunction by echocardiography and cardiac catheterization to initiate appropriate management. In cardiogenic shock without LVOTO treatment includes volume resuscitation, inotropes if required and placement of intra-aortic balloon pump if there is no response to initial medical therapy. In cardiogenic shock with moderate-to-severe LVOTO and SAM of mitral valve treatment includes cautious administration of short acting beta-blockers to decrease contractility and increase LV cavity size [27], [14], [104], [40], [105]. If beta-blockers are not tolerated, then alpha-agonist may be used with great caution and insertion of intra-aortic balloon pump rather than isotropic therapy which may exacerbate LVOTO [5], [106]. A prospective study of TC patients who had low LVEF (<35%) showed that levosimendan was a safe and feasible option. Vasodilators, such as nitrates, which may worsen LVOTO, therefore, should be avoided. In cardiogenic shock with severe LVOTO and SAM of mitral valve treatment includes administration of pure alpha-adrenergic agonist, such as phenylephrine with extreme caution [40], [58] and insertion of intra-aortic balloon pump if no response to initial medical therapy.

**Arrhythmias**: atrial fibrillation, ventricular tachycardia, and ventricular fibrillations may respond to beta-blockers and magnesium [58]. There is no specific treatment proposed for prolongation of QT interval and torsades de pointes.

**Cardio-embolic stroke**: there are no specific guidelines for the use and duration of anticoagulation therapy to prevent thromboembolism in TC patients with severe apical ballooning and reduced LVEF and management of an LV apical thrombus which can occur in 2–5% of cases is based on guidelines described in cases of AMI. Subcutaneous low molecular weight heparin during the acute phase until ventricular function recovers may help prevent apical thrombus formation and oral anticoagulation should be initiated and continued until the thrombus resolves.

**Concomitant coronary artery disease**: is present, than aspirin and statins therapy should be considered.

**Severe emotional stress and Recurrence**: It is not known clear how anxiolytic drugs can avoid a severe emotional stress which can precipitate TC [58]. The efficacy of chronic beta-blocker therapy with the aim of reducing the likelihood of a recurrent episode is unclear. Long-term beta-blockers may be used in order to reduce the recurrence rate [65].
Prognosis
The clinical course of TC remains uncertain, but its natural history is usually benign and long-term survival is similar to that of the general age-matched population [107]. Symptoms generally resolve early and ECG abnormalities, elevated cardiac biomarkers and LV regional wall motion abnormalities disappear in ~4 – 8 weeks, although the ECG can take longer to normalize [108], [109]. The in-hospital mortality (~1 – 3%) [110] and the long-term cardiac mortality is low [111]. In-hospital mortality is influenced by systolic heart failure with LVEF <40% and increases substantially in patients who’s hospital course is complicated by pulmonary edema, cardiogenic shock, atrial or ventricular arrhythmias, ventricular septal defect, free wall rupture, apical thrombus and recurrent hospitalizations [27], [34], [11], [112].

The recurrence of chest pain has been reported in ~30% of patients [107]. Recurrence of TC is infrequent ~3.5 – 10%, and often associated with specific triggering factors [113], [114], [57]. Time to recurrence is between 3 months to 13 years. Risk of death remain high in the year following diagnosis of TC and then it drops substantially during the subsequent years [33].

Conclusions
During recent years more and more cases have been recognized around the world and as a result our knowledge about TC has grown, but much is still unknown about its pathophysiology, diagnosis, management and clinical course. Therefore, further studies are needed for our better understanding to improve its management and clinical outcome.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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