



A Comprehensive Literature Review of the Epidemiology, Diagnosis and Management of Takotsubo Cardiomyopathy Syndrome

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Authors' contributions

This work was carried out in collaboration between the two authors. Both authors together managed the literature searches, wrote all drafts and the final version of the manuscript and both authors read and approved the final manuscript.

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ABSTRACT

Takotsubo cardiomyopathy is reported at an increasing frequency. Though it is 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 published reports on 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 others that have been described. There are widely accepted diagnostic criteria based on clinical and investigational findings. 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.

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1. INTRODUCTION

Takotsubo 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) or acute myocardial infarction (AMI) and is a well recognized cause of acute heart failure and ventricular arrhythmias.

Sato and colleagues first described TC syndrome 23 years ago in Japan [1]. The name was due to the characteristic pathological wall motion abnormality and left ventricular (LV) geometry that resembles a Japanese jar used for trapping octopus (Tako) with a round bottom and narrow neck (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 Hirsch, in 1980 [2] and Dote et al., in 1991 were also among the first who described this acute stress cardiomyopathy (ASC) syndrome [3], whereas, Desment and colleagues (1998–2001) [4] were the first to describe this cardiac syndrome of transient “apical ballooning” as a case series in a Caucasian population. Later, (between 2001–2004) TC syndrome gained global recognition with cases reported from all across the world [5,6]. The worldwide incidence of TC is not accurately known due to its broad clinical spectrum and evolving diagnostic criteria. It is currently estimated that approximately 2% of all patients presenting with an initial diagnosis of an ACS with or without ST segment elevation may in fact have TC syndrome [7]. Studies have demonstrated a seasonal variation in the presentation of TC characterized by increased frequency during the summer months, contrary to the well-known winter peak of ACS [8,9]. Paralleling the diurnal pattern of ACS there is increased frequency of presentations in the morning, and also on Mondays [9,10].

2. TYPES

TC is broadly classified into LV and right ventricular (RV) dysfunction. LV dysfunction is further classified into four different subtypes called classic type (apical variant), reverse type

(inverted type), mid-ventricular type and localized type.

2.1 The Classic Type (Apical Variant)

This accounts for close to 60% cases [11,12]. It is characterized by akinesis of the mid and apical LV segment, with hyperkinesia of the base, resembling a traditional Japanese octopus trap jar (“Tako-Tsubo”). One proposed mechanism that might explain the pathophysiology of the classic type relates to the differences in the anatomical sympathetic innervation of the LV and its enhanced responsiveness to an abrupt rise in circulating catecholamines [13]. The apical LV lacks a three-layered myocardium; therefore, it loses its elasticity after excessive expansion. This region falls in the border zone of the perfusion areas of major coronary vessels, hence it is prone to delayed functional recovery after global ischaemia [14,15].

2.2 The Reverse Type (Inverted Type)

This type seems to affect younger people [16] and presents with LV basal hypokinesia with preserved apical function [17].

2.3 The Mid-ventricular Type

This type accounts for less than 40% cases and [11] is characterized by transient LV mid-segment akinesis but preservation of contractility in the LV apical segment [18].

2.4 The Localised Type

This type is characterized by any other segmental localised LV dysfunction with clinical characteristics similar to TC syndrome.

2.5 The RV Type of Dysfunction

Although much rarer this type is characterized by the involvement of the distal segment of the RV with sparing of the base [19].

Based on LV appearance on imaging TC can be described according to the four types as depicted in (Fig. 1) [20].

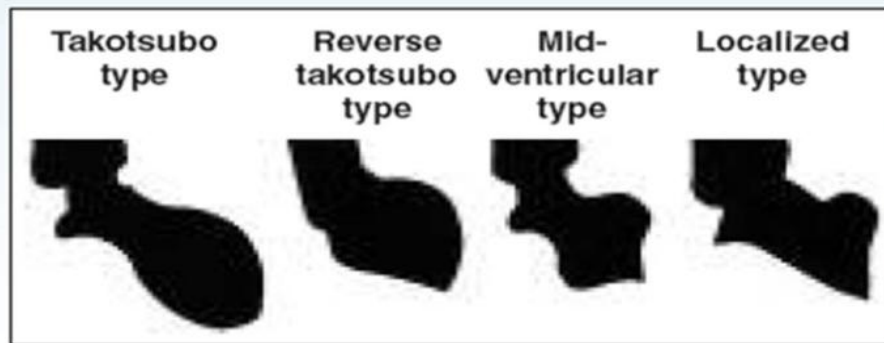


Fig. 1. Schematic diagrams depicting the four types of Takotsubos Cardiomyopathy [20]

3. TRIGGER FACTORS

TC is a heterogeneous condition and its exact aetiology remains uncertain. Its unique attribute is the preceding emotional or physical trigger, which nevertheless varies between patients. It is possible at times for the trigger factors to be absent, unidentifiable, or even overlapping.

Among the most well known and documented trigger factors for TC that can cause probable or definite catecholamine surge are hypoglycaemia [21], pheochromocytoma [22], pneumothorax [23], subdural hematoma [24], subarachnoid haemorrhage [25], sepsis and respiratory failure [26], anaphylaxis [27], bereavement [28], public speaking [29], non-cardiac surgery [12], earthquakes [30], alcohol withdrawal [31], opiate withdrawal [32] and seizure [33]. In addition exposure to cocaine [30] or beta-agonist drugs even at standard clinical doses can elicit TC [34]. 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% $p=0.000$) [35].

4. 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 [13], multi-vessel epicardial coronary vasospasm [36] and cardiac micro-vascular and endothelial dysfunction [37]. Myocarditis [4], particularly due to cardiotrophic viruses [38] has also been implicated, but with paucity of evidence [39] and no pathogen has so far been successfully

isolated [40]. Emotional stress-related surge in serum catecholamines seems to play a major role in the pathogenesis of TC. In one study TC patients during their acute presentation had 2 to 3 times higher serum catecholamines levels than in those who had acute myocardial infarction with heart failure (Killip class III) and 20 times higher than in normal adults. The serum catecholamines levels remained significantly elevated for more than a week in patients with TC [29]. One theory explains that endogenous catecholamine surge causes a transient apical sympathetic dysfunction in the highly trabeculated LV apex [41] and causes profound hypokinesis by inducing paradoxical negative inotropic effect, despite the presence of normal perfusion [13]. The atypical variant of TC, the mid ventricular type could be explained by the deviation in the distribution of adrenergic receptor density in the LV [11]. An imbalance in the positive and negative inotropic effects of catecholamines on the myocardium, may lead to the segmental myocardial dysfunction in TC.

The hypothesis of transient epicardial coronary artery vasospasm related ischemia as the causative mechanism for transient reversible segmental LV myocardial stunning [3] has not been conclusively proven, and vasospasm has been noted in only a few published case reports [3]. Furthermore, provocative substances, such as acetylcholine and ergonovine, have failed to induce TC pattern in a predictable manner in experimental models. Therefore, the above factors raise several doubts about this hypothesis.

There is no conclusive evidence from imaging studies such as nuclear medicine scan, Doppler transthoracic echocardiography, or coronary angiography to support that pronounced and reversible endothelial and coronary

microvascular dysfunction and impaired myocardial perfusion play a definitive role in TC [42].

Another hypothesis is that it is due to stunning triggered by cellular mechanisms in the apical myocardium in response to enhanced circulatory adrenergic drive that is quite distinct to stunning due to transient ischaemia [43]. The cellular mechanism of this response is considered to represent switching of epinephrine signalling through the pleiotropic β_2 -adrenergic receptor (β_2 AR) from canonical stimulatory G-protein-activated cardiostimulant to inhibitory G-protein-activated cardiodepressant pathways explaining the negative inotropic effect on the cardiac apex [44].

It is clear that no single pathogenic mechanism has been conclusively demonstrated to hold true for TC including its subtypes and hence it is possible that multifactorial elements may be at play.

5. CLINICAL PRESENTATION

5.1 Age

There is significant difference between the age of initial presentation of TC patients and ACS patients. In one study the age of initial presentation of TC patients was significantly higher than that of ACS [45]. The classic (apical) variant of TC tends to occur in older people whereas the reverse type (Inverted TC) is more common among the young [46].

5.2 Gender

TC is significantly more common in women than men [13,5,47] and particularly so in the postmenopausal age group (approximately 90% of the cases occurred in post menopausal women) [4]. But however, TC has been reported in men too but at a lower frequency; 8% to 32 % of the cases [48-51].

5.3 Ethnicity

The prevalence of TC has some ethnicity related patterns. TC has been reported more often among Asian and Caucasian populations [35]. Prevalence of TC was highest among Asians (57.2%), followed by Caucasians (40%) according to the published reports [35].

5.4 Cardiovascular Risk Factors

Coronary artery disease and/or its known risk factors may co-exist in patients presenting with TC particularly among those of the older age cohort. But however a strong association between the two remains contentious.

5.5 Coronary Artery Disease (CAD)

The left anterior descending artery (LAD) supplies the anterior wall of the LV in the majority of the patients. If this artery happens to wrap around the apex of the heart, it may be responsible for the blood supply to the apex and the apical-inferior wall of the LV. It was noted by some researchers that there could be a correlation of this anatomic variant with TC [52]. But other researchers since have negated this suggestion as weak and inconclusive [42]. It is clear that an aborted acute myocardial infarction of a "wrap-around" LAD territory is not able to bring about the multi vessel – territory segmental wall motion abnormality of TC [53]. Furthermore, recent intravascular ultrasound studies also found no evidence of culprit lesions in the LAD [54] that are consistently associated with TC. But it should be noted that the presence of one does not rule out the other. Co-existent, angiography-documented coronary artery disease has been reported in 10% to 63% of TC patients [55]. However most workers define TC as acute cardiac syndrome without significant coronary stenosis [56].

5.6 Smoking

If smoking is a risk for TC is not known. In various studies TC patients had a frequency of smoking between 8% to 28% [12,45,48-51,57-59].

5.7 Hypertension

It is not clear whether hypertension is an actual risk factor for TC. Prevalence of hypertension was found to vary between 33-76% among TC cases [60,12,5,61,62,35,63,48,57,49,51,58,50].

5.8 Diabetes

Although, Insulin resistance is associated with high levels of serum catecholamines, the association of impaired glucose metabolism to this condition remains unclear [41]. In the published studies diabetes was present in 6% to 28% of cases of TC [48-51,57,58,62].

5.9 Dyslipidemia

Whether hyperlipidemia is a risk factor for TC is unknown. Although, in the published studies a history of dyslipidaemia was seen in 17% to 23% cases of TC [12,48,50,51,57,58].

5.10 Obesity

The association between TC and obesity remains unclear. In one series a history of being overweight (BMI 25-30) was noted in 51% of cases and obesity (BMI > 30) in 19% of cases [46].

5.11 Genetics

Some studies have suggested the possibility of a familial association to TC [64] 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 a familial type TC [65].

6. PRESENTING SYMPTOMS

The typical clinical picture is often similar to that of acute coronary syndrome [66], especially ST elevation MI [28] and acute heart failure. The two most common presenting symptoms are chest pain (68%) and dyspnoea (17%) [60], [63]. 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 was noted in 1.5%) [28,12]. However, TC can also present with non-specific symptoms and signs and diagnosed incidentally during hospitalisation for an abnormal ECG or elevated cardiac biomarker profile.

7. ACUTE COMPLICATIONS

The acute complications reported in TC include hypotension, LV systolic dysfunction, cardiogenic shock, mitral regurgitation (MR), LV apical thrombus, LV free wall rupture, ventricular septal perforation, arrhythmias and death.

7.1 Hypotension

Severe hypotension and shock could occur during the acute stages of TC. It may occur as a

result of reduced stroke volume (SV) secondary to LV systolic dysfunction [12], significant MR, systolic anterior motion (SAM) of the mitral valve (MV) and the associated dynamic LV outflow tract obstruction (LVOTO) [67].

7.2 Systolic Left Ventricular Failure (LVF)

Systolic heart failure with or without pulmonary oedema has been described in TC. In a review of TC patients 45% cases had acute LVF; Killip class II, III, and IV LVF was seen in 43%, 9%, and 47% cases respectively [68]. Cardiogenic shock with its corresponding high mortality is a much rarer complication [12,69].

7.3 MR

TC may be associated with acute MR of variable magnitude and this is often transient [70], [58]. In a typical apical variant of TC acute reversible MR may be related to SAM of the MV that contributes to LVOTO [71]. The degree of MR usually decreases significantly within the first 72 hours of the presentation [72], but there may be persistent SAM of MV even after normalization of LV systolic function [72].

7.4 LVOTO

Transient dynamic LVOTO is relatively common [12]. In a typical apical variant, especially in women with a smaller left ventricular size, hypercontractility of the base while compensating for LV apical akinesis [39] and thickening of the mid ventricular septum [73] may predispose to the development of LVOTO. Dynamic LVOTO has been associated with acute reversible MR, reversible SAM of the MV [70] and hemodynamic instability [74]. But it can be asymptomatic in 20% of patients [6].

7.5 LV Apical Thrombus

In a typical apical variant, during the acute phase, stagnant blood in the LV apex along with persistent apical LV akinesis can predispose to LV apical thrombus formation [69] and potential systemic embolization. The incidence of this has been quoted as approximately 8% [75] and in two systematic reviews in 2008 and 2010 occurrence of a LV apical thrombus was reported to be similar in frequency to that of acute MI. In almost all of these studies, LV thrombus was successfully treated with anticoagulation [76].

7.6 LV Free Wall Rupture

Though quite uncommon, LV free wall rupture was observed in TC patients who had higher systolic and diastolic blood pressure and higher fluctuations of intra-cardiac pressure [77].

7.7 Ventricular Septal Perforation

Ventricular septal perforation has been demonstrated in TC as a rare complication with a high mortality [78,79].

7.8 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 [80]. However, ventricular tachycardia and fibrillation are uncommon [81].

7.9 Death

Many studies report a good long term prognosis for patients who overcome the acute phase of TC and the risk of sudden death is low [82].

8. DIAGNOSIS

8.1 Diagnostic Criteria

There are several proposed and well-accepted criteria available for diagnosing TC; the Modified Mayo Clinic Criteria (MMCC) [41] remain the most commonly used however others too exist [66,83,84]. The MMCC inclusion criteria are 1) transient akinesis or dyskinesia of the LV 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).

Exclusion criteria include- 1) recent significant head trauma, 2) intra-cranial haemorrhage, 3) pheochromocytoma, 4) obstructive epicardial coronary artery disease, 5) myocarditis and 6) hypertrophic cardiomyopathy.

The elements and modalities helpful in the diagnostic workup include cardiac biomarkers

such as myoglobin, creatinine kinase (CK) MB fraction of CK (CK-MB), Troponin (Tn), Brain natriuretic peptide (BNP) and N-terminal(NT) pro-BNP, circulating microRNAs, serum norepinephrine level, circulating inflammatory markers (white cell count, CRP, hs-CRP), electrocardiography, echocardiography, coronary angiography, cardiac CT angiography (CTCA), myocardial perfusion scan, cardiac magnetic resonance imaging (CMRI) and cardiac positron emission tomography (CPET) scanning.

9. CARDIAC BIOMARKERS

Both the CK-MB and Tn levels are elevated in the setting of acute myocardial necrosis. The release of BNP is related to ventricular distension with or without myocyte necrosis. There can be a lack of correlation between the area of myocardium affected and peak level of Tn during the acute phase of TC. In the acute phase of the apical variant of TC, CK-MB and Tn levels are only mildly elevated. The levels seen are much less than that seen in AMI. In the reverse variant of TC levels of CK-MB and Tn-I are significantly higher than in patients with typical apical or mid-ventricular variant [48]. In one study, elevated cardiac Tn level at admission was an independent predictor of acute heart failure [63]. Generally cardiac BNP levels are often higher in TC compared to AMI [85]. Higher and persistent elevation of cardiac BNP and NT pro- BNP levels correlate with the extent of catecholamine elevation and the severity of LV systolic dysfunction [86]. One published study demonstrated that the receiver operator characteristic curve analysis of the elevated cardiac biomarkers (Fig. 2) could help distinguish between TC and AMI [87]. A recent study described the signature of four circulating mRNAs as a robust biomarker to distinguish TC from AMI patients (Fig. 3); significant up-regulation of stress and depression related mRNAs suggests a close association of TC with neuropsychiatric stressors [88]. Nevertheless no specific biomarker has been described as diagnostic of TC.

10. SERUM NOREPINEPHRINE

Though present in the acute setting, elevation in serum norepinephrine level is non-specific and is not helpful in the diagnosis of TC [89].

11. INFLAMMATORY MARKERS

Elevation in white blood cell count, CRP and hs-CRP seen in TC patients is often non-specific and 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 observed to be independent risk factors for death or cardiogenic shock [90].

12. ELECTROCARDIOGRAPHY

ECG changes are seen in both suspected TC as well as ACS. However the ECG findings are

variable and cannot reliably differentiate between the two pathologies [91,92].

ECG changes appear in three forms (Fig. 4); ST-segment elevation, T- wave inversion and rarely non-permanent Q wave formation [93]. Often ST-segment elevation appears first, mainly in the precordial leads, the T-waves appear peaked followed by diffuse and often giant T-wave inversion, and could persist from several days to several weeks and disappear thereafter. No reciprocal changes were observed in the limb leads. The Q-waves were reversible and disappeared over time.

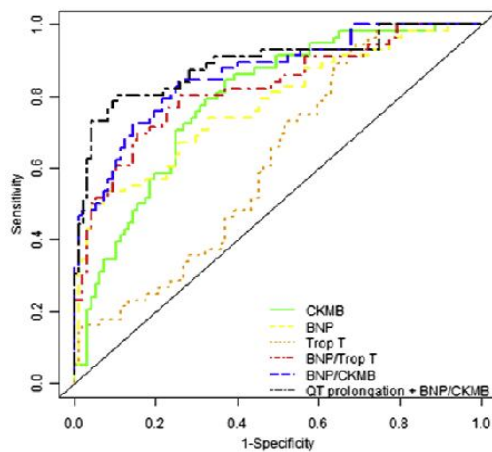


Fig. 2. Receiver operator characteristic curve analysis of the elevated cardiac biomarkers to help distinguish TC from AMI [87]

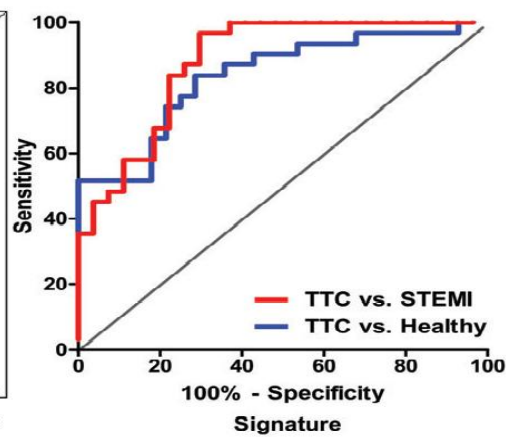


Fig. 3. ROC curve analysis for the combination of four micro- RNAs resulting in enhanced specificity and sensitivity to distinguish TC from healthy subjects (74.2, 78.6%, respectively) and AMI controls (96.8, 70.4%, respectively) [88]

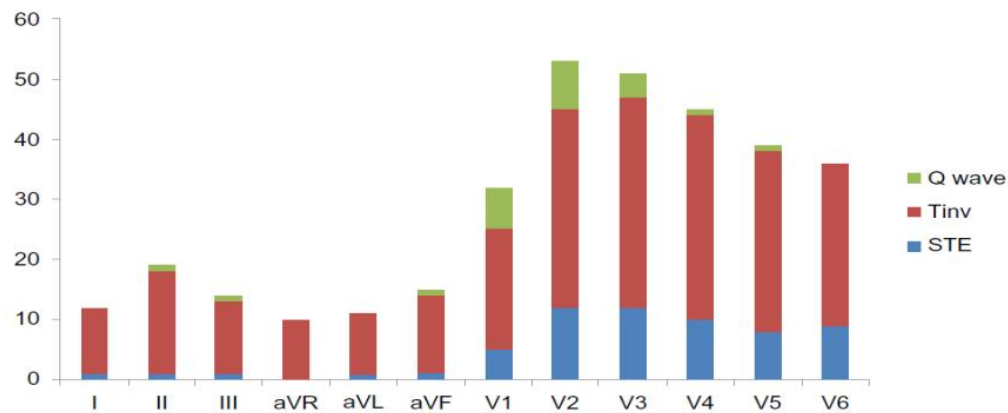


Fig. 4. Prevalence of ST-segment elevation, T-wave inversion, and Q-wave in patients with TC [93]

When T-wave inversion appeared first and persisted without ST-segment elevation, there was pronounced QTc interval prolongation. There are no atrioventricular block and significant bradyarrhythmia events described [93]. ST-segment depression in lead aVR and the absence of ST-segment elevation in lead V1 are more useful ECG markers for identifying TC [94]. The ST segment deviations in TC are usually less pronounced in comparison to ST-segment elevation MI and are exhibited more frequently in Asians than in Whites [35]. These ECG findings typically do not correspond to a singular coronary artery distribution [95]. 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 the clinical outcome.

13. 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. LV angiography is useful for identifying TC and its subtypes with the early LV wall motion abnormalities of characteristic nature.

Differentiation between TC and ACS on coronary angiography may also be difficult as patients with TC some times tend to demonstrate abnormalities such as non-critical atherosclerotic lesions of < 50% luminal diameter coronary stenosis [6], or “wrap-around” LAD [96] supplying an extensive vascular territory with disrupted atherosclerotic plaques [97]. Normal coronary angiography together with ballooning of the left ventricle on ventriculography is hallmark of TC [98].

14. CTCA

CTCA may be a valuable and less invasive diagnostic tool for demonstrating the presence or absence of obstructive coronary artery disease [99] and assessing LV systolic function, particularly in patients with relatively few or no coronary risk factors. So therefore, it can help distinguish acute TC from ACS. It could be useful in investigating the coronary anatomy in patients who present with recurrent TC who have had normal invasive angiography in the past.

15. TRANSTHORACIC ECHOCARDIOGRAPHY (TTE)

TTE can show the apical hypokinesis (ballooning) with increased basal contractility in the classic form as well as basal hypokinesis with preserved apical contraction in the reverse form [100]. TTE 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 with the 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 highly likely diagnosis of TC. However, recovery of LV function is variable and rarely can take longer than expected. Contrast TTE, during acute phase of TC can detect, classify and quantify LV dyskinesia in a typical variant and also help detect subtle RV apical dyskinesia [101]. Dobutamine stress echocardiography may be used to distinguish between typical and atypical TC. TTE can guide the initial management of haemodynamically unstable TC patients particularly those with significantly reduced LV ejection fraction, acute reversible MR related to SAM of the MV [12] & LVOTO [56] and/or LV apical thrombus.

Transesophageal echocardiography may provide better anatomic details that may be useful in deciding on repair or replacement of the MV especially when significant MR persists even after the resolution of LVOTO. Doppler echocardiography, regional strain echocardiography and time-volume curves from 3-dimensional echocardiography may offer good assessment of the regional wall motion abnormalities in TC patients enhancing the 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 [102] has shown transient coronary microcirculation dysfunction in parallel with LV wall-motion abnormality during the acute phase. The recovery of this CFR during chronic phase does suggest a possible role-played by coronary microcirculatory dysfunction in the pathogenesis of TC.

16. CARDIAC SINGLE PHOTON EMISSION CT (SPECT)

Serial gated SPECT phase imaging with ^{99m}Tc-Sestamibi or tetrafosmin, ^{99m}Tc-PYP, ¹²³I-BMIPP & ²⁰¹Thallium and ¹²³I-MIBG & ²⁰¹Thallium has used to evaluate cardiac perfusion and metabolic activity. ^{99m}Tc-Sestamibi or tetrafosmin coronary blood flow imaging during post-acute phase (within 3–5 days of the onset) 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. It can also show the initial LV apical ballooning and dyskinesis, followed by normalization of perfusion and function during the chronic phase (after 4–8 weeks). However, the recovery period could be variable [101].

^{99m}Tc-PYP SPECT imaging during acute phase of TC could show LV apical and mid plane myocardium stunning caused by coronary microcirculatory perfusion mismatch [97]. ¹²³I-BMIPP-²⁰¹Thallium fatty acid metabolism-perfusion mismatch [103] and ¹²³I-MIBG-²⁰¹Thallium [13] sympathetic innervations-perfusion mismatch occurs in parallel with LV apical and mid plane myocardium stunning during acute phase of TC. Although the myocardial fatty acid metabolism and sympathetic nervous system impairment is more adversely affected than perfusion, these abnormalities usually improves gradually during the chronic phase [81]; but it may still persist even after normalization of apical and mid plane perfusion.

17. CPET SCAN

Serial cardiac ⁸²rubidium PET and ²⁰¹Thallium PET [82] as well as quantification of microcirculatory disturbance with rest & hyperaemic myocardial blood flow (MBF) using ⁸²rubidium PET [104] and CFR using ¹³nitrogen PET [105] demonstrate a reversible apical and mid plane dysfunction with a transient fixed metabolic-perfusion mismatch during acute phase of TC. These abnormalities do not correspond to the territory of a single coronary artery distribution. These changes are followed by complete reversal of the perfusion, microcirculatory and metabolic defects during chronic phase suggesting the diagnosis TC. In this picture of mismatch, the metabolic impairment is more extensive and severe than

that of perfusion. This phenomenon therefore, suggests catecholamine-induced metabolic disorder as a possible underlying mechanism of TC orchestrated by cyclic-adenosine-monophosphate mediated intra-myocardial calcium overload which decreases myocyte viability [106]. Quantitative CPET scan such as MBF and CFR can be helpful in distinguishing TC from ischemic cardiomyopathy [102,103]. It can also assist in the assessment of the extent of LV dysfunction [101]. The ¹¹C hydroxyephedrine sympathetic nervous system imaging using ¹³nitrogen PET can demonstrate LV apical innervations-perfusion mismatch [107].

18. CMRI

CMRI 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 oedema (Fig. 5) which is not related to a specific singular vascular territory, and distributed in both the apical and mid planes of the LV. The signal intensity decreases and completely resolves in many cases during the chronic phase (> 4 weeks) [48].

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. Both apical & mid plane akinesis and basal plane hyperkinesis can produce a dynamic LVOTO with associated SAM of the anterior MV leaflet. An apical clot in the LV can be also seen. Changes in the LV function in the acute setting and then in 3 months on follow up can be well demonstrated on MRI for all 4 types of TC [48].

The contrast-enhanced sequence MRI shows no segmental LV perfusion defects in TC, and whether or not focal or patchy late gadolinium enhancement (LGE) is seen in TC is debated as studies have 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 (Fig. 6) [48]. CMRI with adenosine can detect and quantify microcirculatory disturbance, which may prove useful in the management of TC [108].

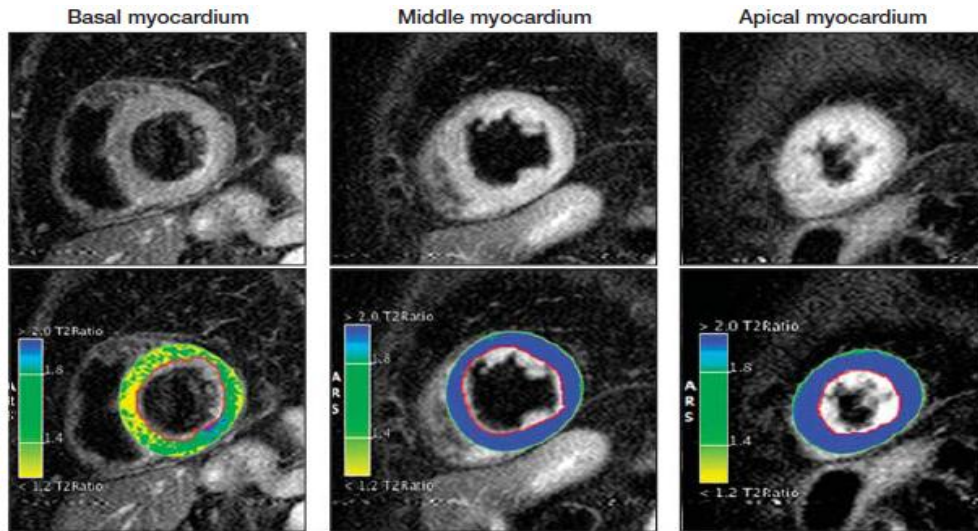


Fig. 5. CMRI of myocardial oedema in a representative patient with TC T2-weighted images (short-axis view) demonstrating normal signal intensity (SI) of the basal myocardium but global oedema of the mid and apical myocardium. Computer-aided SI analysis (bottom row) of the T2- weighted images with color-coded display of relative SI normalized to skeletal muscle (blue indicates an SI ratio of myocardium to skeletal muscle of ≥ 1.9 or higher, indicating oedema; green/yellow indicates a normal SI ratio of ≤ 1.9) confirm the presence of global mid and apical oedema. Outlines of regions of interest are manually drawn around the myocardium (red contour - subendocardial border; green contour - subepicardial border) and within the skeletal muscle (contour not shown) [48]

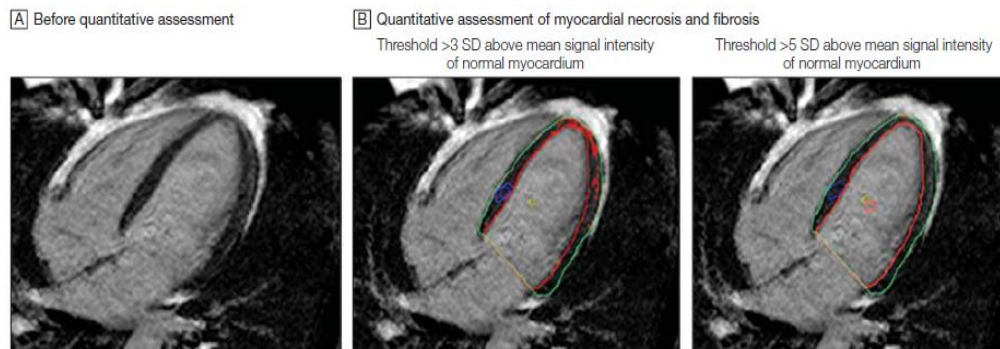


Fig. 6. Cardiac MRI of necrosis/fibrosis in a representative patient with TC myocardial fibrosis was quantified by selecting a region of interest in non-enhancing healthy myocardium (blue contour) and setting automated computer detection to 3 SDs (left) and 5 SDs (right) above the mean of healthy myocardium 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 (red contour=sub-endocardial border; green contour=sub-epicardial border of the myocardium) [48]

19. TREATMENT

Evidence base for the best therapeutic strategy for TC is slim. At the initial presentation of TC, the management is dictated by the clinical

assessment and often mirrors that of ACS. Those presenting with ST segment elevation are often managed with either fibrinolysis or urgent catheterisation as per the standard STEMI pathways and available facilities. Those

presenting with other ECG changes suggestive of coronary ischaemia with or without biomarker elevation are treated with anti-platelet therapy and anticoagulation with early catheterisation. Once coronary disease is excluded and the diagnosis of TC is established the management is aimed at relieving symptoms, maintaining haemodynamic stability and oxygenation together with close monitoring for acute complications.

Acute severe systolic LVF of TC [12] is treated with aspirin, a cardioselective beta-blocker (only if there is no pulmonary congestion), angiotensin converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) (only if not hypotensive) and diuretics (when there is congestive features) [28,68,61]. This too remains an evidence free zone. 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 [109]. Beta-blockers may also help to reduce the LVOTO [58] but are contraindicated in acute severe VF with reduced ejection fraction, pulmonary oedema, hypotension and bradycardia. Initiation of ACEIs or ARBs therapy before discharge is reasonable and later discontinued once there is complete recovery of LV 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, LVOTO and MR 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 MV there is a case for cautious administration of short acting beta-blockers to decrease basal segment hyper-contractility and increase LV cavity size [28,15,41,110,111]. If beta-blockers are not tolerated, an alpha-agonist may be used with great caution. This could be further assisted by the insertion of intra-aortic balloon pump. Inotropic therapy may exacerbate LVOTO, hence relatively contraindicated [5,112]. A prospective study of TC patients who had low LVEF (<35%) showed that levosimendan therapy was a safe and feasible option. Vasodilators, such as nitrates may worsen LVOTO, therefore, should

be avoided. In cardiogenic shock with severe LVOTO and SAM of MV, treatment with pure alpha-adrenergic agonist, such as phenylephrine with extreme caution may be beneficial [41,61]. Insertion of intra-aortic balloon pump is indicated in this setting if there is no response to initial medical therapy.

20. ARRHYTHMIAS

Atrial fibrillation, ventricular tachycardia, and ventricular fibrillations may respond to beta-blockers and magnesium infusion [61]. There is no specific treatment proposed for the prolongation of QT interval and Torsades de pointes. Conventional therapeutic modalities should be administered in the case of Torsades.

21. CARDIO-EMBOLIC STROKE

there are no specific guidelines on the choice of agent and optimal duration of anticoagulation therapy to prevent thromboembolism in TC patients. Management of LV apical thrombus (which can occur in 2–5% of cases) is similar to that after an apical AMI. Subcutaneous low molecular weight heparin during the acute phase until ventricular function recovers may help prevent apical thrombus formation and in the case of established thrombus, oral anticoagulation should be initiated and continued until the it resolves.

22. CONCOMITANT CORONARY ARTERY DISEASE

If present aspirin and statins therapy should be considered. Revascularisation should be guided by the clinical indications.

23. SEVERE EMOTIONAL STRESS AND RECURRENCE

It is not known if anxiolytic drugs could prevent severe emotional stress which can precipitate recurrent TC [61]. The efficacy of chronic beta-blocker therapy for the prevention of recurrent episodes is unclear. Long-term beta-blockers may be of benefit in some cases for secondary prevention [68].

24. PROGNOSIS

The clinical course of TC remains uncertain, but on most occasion its natural history is usually benign and long-term survival is similar to that of

the general age-matched population [113]. Symptoms generally resolve early and ECG abnormalities, elevated cardiac biomarkers and LV regional wall motion abnormalities disappear within approximately 4–8 weeks. However the ECG changes can take longer to normalize [114,115]. The in-hospital mortality can be between 1%– 3% [116] but the long-term cardiac mortality is low [117]. In-hospital mortality is influenced by systolic heart failure with LVEF <40% and increases substantially if complicated by pulmonary oedema, cardiogenic shock, atrial or ventricular arrhythmias, ventricular septal defect, free wall rupture, apical thrombus and recurrent hospitalizations [12,28,35]. The recurrence of chest pain has been reported in 30% of patients [110]. The syndrome has been described as a completely reversible form of heart failure [118]. Recurrence of TC is infrequent and can vary between 3.5%–10%, and often associated with specific trigger factors [60,119,120]. Time to recurrence could vary from 3 months up to even 13 years. According to one published series, if associated with aforementioned complications, the risk of in hospital mortality can be as high as 5% and interestingly in this series, a high non cardiac (mostly cancer related) was observed in the year following the index episode. But however it then dropped substantially during the subsequent years [34]. Though considered to have a benign prognosis overall in the long-term TC may sometimes represent an underlying impairment of health and wellbeing in a minority of the patients.

25. FUTURE DIRECTION

Recent work has demonstrated the desensitisation effect of protein β -arrestin of the catecholaminergic activation of the adrenal-cardiac axis in the setting of heart failure [121]. This may play a potential role in the pathogenesis and the clinical course of TC. By Managing the β -arrestin mediated signalling in the adrenal-cardiac axis one could improve the clinical outcomes in patients with TC and heart failure [122]. More work in this arena may offer effective future therapeutic options in this setting.

26. CONCLUSION

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 remains still unknown about its pathophysiology, diagnosis, management and

clinical course. Therefore, further studies are needed for the better understanding of this condition to improve its management and clinical outcomes.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Sato H, Tateishi H, Uchida T, et al. Takotsubo type cardiomyopathy due to multivessel spasm. In: Kodama K, Haze K, Hon M, editors. Clinical aspect of myocardial injury: From ischemia to heart failure. Kagaku Hyoronsha; Tokyo. 1990;56–64.
2. Cebelin MS, Hirsch CS. Human stress cardiomyopathy. Myocardial lesions in victims of homicidal assaults without internal injuries. *Hum Pathol.* 1980;11(2):123-32.
3. Dote K, et al. Myocardial stunning due to simultaneous multivessel coronary spasms: A review of 5 cases. *J Cardiol.* 1991;21(2):203-14.
4. Desmet WJ, Adriaenssens BF, Dens JA. Apical ballooning of the left ventricle: first series in white patients. *Heart.* 2003;89(9):1027-31.
5. Bybee KA, et al. Clinical characteristics and thrombolysis in myocardial infarction frame counts in women with transient left ventricular apical ballooning syndrome. *Am J Cardiol.* 2004;94(3):343-6.
6. Sharkey SW, et al. Acute and reversible cardiomyopathy provoked by stress in women from the United States. *Circulation.* 2005;111(4):472-9.
7. Parodi G, et al. Incidence, clinical findings, and outcome of women with left ventricular apical ballooning syndrome. *Am J Cardiol.* 2007;99(2):182-5.
8. Spencer FA, et al. Seasonal distribution of acute myocardial infarction in the second National Registry of Myocardial Infarction. *J Am Coll Cardiol.* 1998;31(6):1226-33.
9. Citro R, et al. Chronobiological patterns of onset of Tako-Tsubo cardiomyopathy: A multicenter Italian study. *J Am Coll Cardiol.* 2009;54(2):180-1.
10. Manfredini R, et al. Monday preference in onset of takotsubo cardiomyopathy. *Am J Emerg Med.* 2010;28(6):715-9.

11. Kurowski V, et al. Apical and midventricular transient left ventricular dysfunction syndrome (tako-tsubo cardiomyopathy): Frequency, mechanisms, and prognosis. *Chest*. 2007;132(3):809-16.
12. Gianni M, et al. Apical ballooning syndrome or takotsubo cardiomyopathy: A systematic review. *Eur Heart J*. 2006;27(13):1523-9.
13. Owa M, et al. Emotional stress-induced 'ampulla cardiomyopathy': Discrepancy between the metabolic and sympathetic innervation imaging performed during the recovery course. *Jpn Circ J*. 2001;65(4):349-52.
14. Tsuchihashi K, et al. Transient left ventricular apical ballooning without coronary artery stenosis: A novel heart syndrome mimicking acute myocardial infarction. *Angina Pectoris-Myocardial Infarction Investigations in Japan*. *J Am Coll Cardiol*. 2001;38(1):11-8.
15. Villareal RP, et al. Anteroapical stunning and left ventricular outflow tract obstruction. *Mayo Clin Proc*. 2001;76(1):79-83.
16. Ramaraj R, Movahed MR. Reverse or inverted takotsubo cardiomyopathy (reverse left ventricular apical ballooning syndrome) presents at a younger age compared with the mid or apical variant and is always associated with triggering stress. *Congest Heart Fail*. 2010;16(6):284-6.
17. Van de Walle SO, et al. Transient stress-induced cardiomyopathy with an "inverted takotsubo" contractile pattern. *Mayo Clin Proc*. 2006;81(11):1499-502.
18. Cimarelli S, et al. Nuclear medicine imaging of takotsubo cardiomyopathy: Typical form and midventricular ballooning syndrome. *J Nucl Cardiol*. 2008;15(1):137-41.
19. Kurisu S, et al. Takotsubo-like transient biventricular dysfunction with pressure gradients. *Intern Med*. 2005;44(7):727-32.
20. Shimizu M, Kato Y, Masai H, Shima T, Miwa Y. Recurrent episodes of Takotsubo-like transient apical ballooning occurring in different regions: A case report. *J Cardiol*. 2006;48:101-107.
21. Saito Y. Hypoglycemic attack: A rare triggering factor for takotsubo cardiomyopathy. *Intern Med*. 2005;44(3):171-2.
22. Kassim TA, et al. Catecholamine-induced cardiomyopathy. *Endocr Pract*. 2008;14(9):1137-49.
23. Akashi YJ, Sakakibara M, Miyake F. Reversible left ventricular dysfunction "takotsubo" cardiomyopathy associated with pneumothorax. *Heart*. 2002;87(2):E1.
24. Ohtsuka T, et al. Images in cardiovascular medicine. Neurogenic stunned myocardium. *Circulation*. 2000;101(17):2122-4.
25. Kono T, et al. Left ventricular wall motion abnormalities in patients with subarachnoid hemorrhage: Neurogenic stunned myocardium. *J Am Coll Cardiol*. 1994;24(3):636-40.
26. Park JH, et al. Left ventricular apical ballooning due to severe physical stress in patients admitted to the medical ICU. *Chest*, 2005. **128**(1): p. 296-302.
27. Vultaggio, A., et al., Tako-Tsubo-like syndrome during anaphylactic reaction. *Eur J Heart Fail*. 2007;9(2):209-11.
28. Bybee KA, et al. Systematic review: Transient left ventricular apical ballooning: a syndrome that mimics ST-segment elevation myocardial infarction. *Ann Intern Med*. 2004;141(11):858-65.
29. Wittstein IS, et al. Neurohumoral features of myocardial stunning due to sudden emotional stress. *N Engl J Med*. 2005;352(6):539-48.
30. Watanabe H, et al. Impact of earthquakes on takotsubo cardiomyopathy. *JAMA*. 2005;294(3):305-7.
31. Suzuki K, et al. An atypical case of "Takotsubo cardiomyopathy" during alcohol withdrawal: Abnormality in the transient left ventricular wall motion and a remarkable elevation in the ST segment. *Intern Med*. 2004;43(4):300-5.
32. Sarcon A, et al. Takotsubo cardiomyopathy associated with opiate withdrawal. *QJM*. 2014;107(4):301-2.
33. Stollberger C, Wegner C, Finsterer J. Seizure-associated takotsubo cardiomyopathy. *Epilepsia*. 2011;52(11):e160-7.
34. Sharkey SW, et al. Natural history and expansive clinical profile of stress (takotsubo) cardiomyopathy. *J Am Coll Cardiol*. 2010;55(4):333-41.
35. Donohue D, Movahed MR. Clinical characteristics, demographics and prognosis of transient left ventricular apical ballooning syndrome. *Heart Fail Rev*. 2005;10(4):311-6.

36. Inoue F, et al. So-called "ampulla" cardiomyopathy associated with coronary vasospasm compared with acute myocardial infarction showing similar abnormal left ventricular wall motion: Two case reports. *J Cardiol.* 2002;39(1):29-38.
37. Sadamatsu K, et al. Coronary microvascular abnormality in the reversible systolic dysfunction observed after noncardiac disease. *Jpn Circ J.* 2000;64(10):789-92.
38. Bahlmann E, et al. Tako-Tsubo cardiomyopathy (apical ballooning) with parvovirus B19 genome in endomyocardial biopsy. *Int J Cardiol.* 2007;116(1):e18-21.
39. Ibanez B, et al. Takotsubo syndrome: A Bayesian approach to interpreting its pathogenesis. *Mayo Clin Proc.* 2006;81(6):732-5.
40. Eshtehardi P, et al. Transient apical ballooning syndrome-clinical characteristics, ballooning pattern, and long-term follow-up in a Swiss population. *Int J Cardiol.* 2009;135(3):370-5.
41. Dorfman TA, Iskandrian AE. Takotsubo cardiomyopathy: State-of-the-art review. *J Nucl Cardiol.* 2009;16(1):122-34.
42. Abe Y, et al. Assessment of clinical features in transient left ventricular apical ballooning. *J Am Coll Cardiol.* 2003;41(5):737-42.
43. Lyon AR, Rees P, Prasad S, et al. Stress (Takotsubo) cardiomyopathy-a novel pathophysiological hypothesis to explain catecholamine-induced acute myocardial stunning. *Nat Clin Pract Cardiovasc Med.* 2008;5:22-29.
44. Paur H, Wright PT, Sikkell MB, et al. High levels of circulating epinephrine trigger apical cardiodepression in a β_2 -adrenergic receptor/ G_i -dependent manner; *Circulation.* 2012;126:697-706.
45. Inoue M, et al. Differentiation between patients with takotsubo cardiomyopathy and those with anterior acute myocardial infarction. *Circ J.* 2005;69(1):89-94.
46. Mansencal N, et al. Relationship between pattern of tako-tsubo cardiomyopathy and age: From midventricular to apical ballooning syndrome. *Int J Cardiol.* 2010;138(1):e18-20.
47. Prasad A, et al. Incidence and angiographic characteristics of patients With apical ballooning syndrome (takotsubo/stress cardiomyopathy) in the HORIZONS-AMI trial: An analysis from a multicenter, international study of ST-elevation myocardial infarction. *Catheter Cardiovasc Interv.* 2014;83(3):343-8.
48. Eitel I, et al. Clinical characteristics and cardiovascular magnetic resonance findings in stress (takotsubo) cardiomyopathy. *JAMA.* 2011;306(3):277-86.
49. Song BG, et al. The clinical characteristics, laboratory parameters, electrocardiographic, and echocardiographic findings of reverse or inverted takotsubo cardiomyopathy: Comparison with mid or apical variant. *Clin Cardiol.* 2011;34(11):693-9.
50. Parodi G, et al. Natural history of takotsubo cardiomyopathy. *Chest.* 2011;139(4):887-92.
51. Citro R, et al. Differences in clinical features and in-hospital outcomes of older adults with tako-tsubo cardiomyopathy. *J Am Geriatr Soc.* 2012;60(1):93-8.
52. Ibanez B, et al. Tako-tsubo syndrome associated with a long course of the left anterior descending coronary artery along the apical diaphragmatic surface of the left ventricle. *Rev Esp Cardiol.* 2004;57(3):209-16.
53. Haghi D, et al. Takotsubo cardiomyopathy is not due to plaque rupture: An intravascular ultrasound study. *Clin Cardiol.* 2010;33(5):307-10.
54. Delgado GA, et al. An angiographic and intravascular ultrasound study of the left anterior descending coronary artery in takotsubo cardiomyopathy. *Am J Cardiol.* 2011;108(6):888-91.
55. Kurisu S, et al. Prevalence of incidental coronary artery disease in tako-tsubo cardiomyopathy. *Coron Artery Dis.* 2009;20(3):214-8.
56. Cortadellas J, et al. Acute cardiac syndromes without significant coronary stenosis: Differential features between myocardial infarction and apical-ballooning syndrome. *Coron Artery Dis.* 2011;22(6):435-41.
57. Takashio S, et al. Usefulness of SUM of ST-segment elevation on electrocardiograms (limb leads) for predicting in-hospital complications in patients with stress (takotsubo) cardiomyopathy. *Am J Cardiol.* 2012;109(11):1651-6.
58. Haghi D, et al. Incidence and clinical significance of mitral regurgitation in Takotsubo cardiomyopathy. *Clin Res Cardiol.* 2010;99(2):93-8.

59. Nunez-Gil IJ, et al. Electrocardiographic criteria in takotsubo cardiomyopathy and race differences: Asians versus Caucasians. *J Am Coll Cardiol.* 2010;56(17):1433-4; author reply 1434.
60. Pilgrim TM, Wyss TR. Takotsubo cardiomyopathy or transient left ventricular apical ballooning syndrome: A systematic review. *Int J Cardiol.* 2008;124(3):283-92.
61. Pernicova I, et al. Takotsubo cardiomyopathy: A review of the literature. *Angiology.* 2010;61(2):166-73.
62. Regnante RA, et al. Clinical characteristics and four-year outcomes of patients in the Rhode Island Takotsubo Cardiomyopathy Registry. *Am J Cardiol.* 2009;103(7):1015-9.
63. Madhavan M, et al. Acute heart failure in apical ballooning syndrome (takotsubo/stress cardiomyopathy): Clinical correlates and Mayo Clinic risk score. *J Am Coll Cardiol.* 2011;57(12):1400-1.
64. Ikutomi M, et al. Takotsubo cardiomyopathy in siblings. *Heart Vessels.* 2014;29(1):119-22.
65. Handy AD, Prasad A, Olson TM. Investigating genetic variation of adrenergic receptors in familial stress cardiomyopathy (apical ballooning syndrome). *J Cardiol.* 2009;54(3):516-7.
66. Seth PS, et al. A syndrome of transient left ventricular apical wall motion abnormality in the absence of coronary disease: A perspective from the United States. *Cardiology.* 2003;100(2):61-6.
67. Wu KC, et al. Late gadolinium enhancement by cardiovascular magnetic resonance heralds an adverse prognosis in nonischemic cardiomyopathy. *J Am Coll Cardiol.* 2008;51(25):2414-21.
68. Prasad A, Lerman A, Rihal CS. Apical ballooning syndrome (takotsubo or stress cardiomyopathy): A mimic of acute myocardial infarction. *Am Heart J.* 2008;155(3):408-17.
69. Lee PH, et al. Takotsubo cardiomyopathy: A case of persistent apical ballooning complicated by an apical mural thrombus. *Korean J Intern Med.* 2011;26(4):455-9.
70. Parodi G, et al. Left ventricular apical ballooning syndrome as a novel cause of acute mitral regurgitation. *J Am Coll Cardiol.* 2007;50(7):647-9.
71. Izumo M, et al. Mechanisms of acute mitral regurgitation in patients with takotsubo cardiomyopathy: An echocardiographic study. *Circ Cardiovasc Imaging.* 2011;4(4):392-8.
72. To AC, et al. Resting systolic anterior motion of mitral valve apparatus: association with apical ballooning syndrome. *Circ Heart Fail.* 2008;1(1): 84-5.
73. Merli E, et al. tako-tsubo cardiomyopathy: New insights into the possible underlying pathophysiology. *Eur J Echocardiogr.* 2006;7(1):53-61.
74. Brunetti ND, et al. Ventricular outflow tract obstruction, systolic anterior motion and acute mitral regurgitation in tako-tsubo syndrome. *Int J Cardiol.* 2008;127(3):e152-7.
75. Haggi D, et al. Incidence and clinical significance of left ventricular thrombus in tako-tsubo cardiomyopathy assessed with echocardiography. *QJM.* 2008;101(5):381-6.
76. de Gregorio C. Cardioembolic outcomes in stress-related cardiomyopathy complicated by ventricular thrombus: A systematic review of 26 clinical studies. *Int J Cardiol.* 2010;141(1):11-7.
77. Kumar S, et al. Cardiac rupture in takotsubo cardiomyopathy: A systematic review. *Clin Cardiol.* 2011;34(11):672-6.
78. Mariscalco G, Cattaneo P, Rossi A, et al. Tako-tsubo cardiomyopathy complicated by ventricular septal perforation and septal dissection. *Heart and Vessels.* 2010;25(1):73-75.
79. Sakai K, Ochiai H, Katayama N, et al. Ventricular septal perforation in a patient with takotsubo cardiomyopathy. *Circ J.* 2005;69:365-67.
80. Denney SD, Lakkireddy DR, Khan IA. Long QT syndrome and torsade de pointes in transient left ventricular apical ballooning syndrome. *Int J Cardiol.* 2005;100(3):499-501.
81. Vivo RP, Krim SR, Hodgson J. It's a trap! Clinical similarities and subtle ECG differences between takotsubo cardiomyopathy and myocardial infarction. *J Gen Intern Med.* 2008;23(11):1909-13.
82. Mathew B, Villarreal D. Two unusual cases of takotsubo cardiomyopathy presenting with sudden cardiac death. *Am J Med Sci.* 2009;337(6):473-5.
83. Ito K, et al. Assessment of takotsubo cardiomyopathy (transient left ventricular apical ballooning) using ^{99m}Tc-tetrofosmin, ^{123I}-BMIPP, ^{123I}-MIBG and ^{99m}Tc-PYP myocardial SPECT. *Ann Nucl Med.* 2005;19(6):435-45.

84. Kurisu S, et al. Myocardial perfusion and fatty acid metabolism in patients with tako-tsubo-like left ventricular dysfunction. *J Am Coll Cardiol.* 2003;41(5):743-8.
85. Ahmed KA, Madhavan M, Prasad A. Brain natriuretic peptide in apical ballooning syndrome (takotsubo/stress cardiomyopathy): Comparison with acute myocardial infarction. *Coron Artery Dis.* 2012;23(4):259-64.
86. Nguyen TH, et al. N-terminal pro-brain natriuretic protein levels in takotsubo cardiomyopathy. *Am J Cardiol.* 2011;108(9):1316-21.
87. Randhawa MS, et al. Diagnostic utility of cardiac biomarkers in discriminating Takotsubo cardiomyopathy from acute myocardial infarction. *J Card Fail.* 2014;20(1):2-8.
88. Jaguszewski M, et al. A signature of circulating microRNAs differentiates takotsubo cardiomyopathy from acute myocardial infarction. *Eur Heart J.* 2014;35(15):999-1006.
89. Akashi YJ, et al. Reversible left ventricular dysfunction "takotsubo" cardiomyopathy related to catecholamine cardiotoxicity. *J Electrocardiol.* 2002;35(4):351-6.
90. Lee JW, et al. Clinical characteristics and prognostic factors of stress-induced cardiomyopathy. *Korean Circ J.* 2010;40(6):277-82.
91. Castillo RAM, Ruiz-Bailen MM, Aguilar LR. Takotsubo cardiomyopathy-a clinical review. *Med Sci Monit.* 2011;17(6):135-47.
92. Zeb M, et al. Takotsubo cardiomyopathy: A diagnostic challenge. *Postgrad Med J.* 2011;87(1023):51-9.
93. Namgung J. Electrocardiographic findings in takotsubo cardiomyopathy: ECG evolution and its difference from the ECG of acute coronary syndrome. *Clin Med Insights Cardiol.* 2014;8:29-34.
94. Kosuge M, Kimura K. Clinical implications of electrocardiograms for patients with anterior wall ST-segment elevation acute myocardial infarction in the interventional era. *Circ J.* 2012;76(1):32-40.
95. Ogura R, et al. Specific findings of the standard 12-lead ECG in patients with 'Takotsubo' cardiomyopathy: Comparison with the findings of acute anterior myocardial infarction. *Circ J.* 2003;67(8):687-90.
96. Kurisu S, et al. Tako-tsubo-like left ventricular dysfunction with ST-segment elevation: A novel cardiac syndrome mimicking acute myocardial infarction. *Am Heart J.* 2002;143(3):448-55.
97. Ibanez B, et al. Tako-tsubo transient left ventricular apical ballooning: Is intravascular ultrasound the key to resolve the enigma? *Heart.* 2005;91(1):102-4.
98. Bashir A, et al. Imaging features in takotsubo cardiomyopathy. *BMJ Case Rep;* 2013.
99. Hara T, et al. Noninvasive detection of Takotsubo [corrected] cardiomyopathy using multi-detector row computed tomography. *Int Heart J.* 2007;48(6):773-8.
100. Kepez A, Yezildag O, Erdogan O, et al. Takotsubo cardiomyopathy in a patient with lung adenocarcinoma. *Heart Views.* 2012;13(3):107-110. DOI: 10.4103/1995-705X.102154.
101. Haghi D, et al. Right ventricular involvement in takotsubo cardiomyopathy. *Eur Heart J.* 2006;27(20):2433-9.
102. Meimoun P, et al. The coronary flow reserve is transiently impaired in takotsubo cardiomyopathy: A prospective study using serial Doppler transthoracic echocardiography. *J Am Soc Echocardiogr.* 2008;21(1):72-7.
103. Yoshida T, et al. A pathophysiologic study of tako-tsubo cardiomyopathy with F-18 fluorodeoxyglucose positron emission tomography. *Eur Heart J.* 2007;28(21):2598-604.
104. Hasbak P, et al. Preserved myocardial blood flow in the apical region involved in takotsubo cardiomyopathy by quantitative cardiac PET assessment. *J Nucl Cardiol.* 2012;19(1):169-71.
105. Feola M, et al. Reversible impairment of coronary flow reserve in takotsubo cardiomyopathy: A myocardial PET study. *J Nucl Cardiol.* 2008;15(6):811-7.
106. Bolli R, Marban E. Molecular and cellular mechanisms of myocardial stunning. *Physiol Rev.* 1999;79(2):609-34.
107. Prasad A, Madhavan M, Chareonthaitawee P. Cardiac sympathetic activity in stress-induced (takotsubo) cardiomyopathy. *Nat Rev Cardiol.* 2009;6(6):430-4.
108. Deetjen AG, et al. Value of gadolinium-enhanced magnetic resonance imaging in patients with tako-tsubo-like left ventricular dysfunction. *J Cardiovasc Magn Reson.* 2006;8(2):367-72.
109. Prasad A. Apical ballooning syndrome: An important differential diagnosis of acute myocardial infarction. *Circulation.* 2007;115(5):e56-9.

110. Kyuma M, et al. Effect of intravenous propranolol on left ventricular apical ballooning without coronary artery stenosis (ampulla cardiomyopathy): Three cases. *Circ J.* 2002;66(12):1181-4.
111. Hurst RT, et al. Takotsubo cardiomyopathy: A unique cardiomyopathy with variable ventricular morphology. *JACC Cardiovasc Imaging.* 2010;3(6):641-9.
112. Brenner ZR, Powers J. Takotsubo cardiomyopathy. *Heart Lung.* 2008;37(1):1-7.
113. Elesber AA, et al. Four-year recurrence rate and prognosis of the apical ballooning syndrome. *J Am Coll Cardiol.* 2007;50(5):448-52.
114. Madhavan M, Prasad A. Proposed mayo clinic criteria for the diagnosis of takotsubo cardiomyopathy and long-term prognosis. *Herz.* 2010;35(4):240-3.
115. Stollberger C, Finsterer J, Schneider B. Transient left ventricular dysfunction (takotsubo phenomenon): Findings and potential pathophysiological mechanisms. *Can J Cardiol.* 2006;22(12):1063-8.
116. Bybee KA, Prasad A. Stress-related cardiomyopathy syndromes. *Circulation.* 2008;118(4):397-409.
117. Song BG, et al. Clinical characteristics, ballooning pattern, and long-term prognosis of transient left ventricular ballooning syndrome. *Heart Lung.* 2010;39(3):188-95.
118. Akashi YJ, et al. Takotsubo cardiomyopathy: A new form of acute, reversible heart failure. *Circulation.* 2008;118(25):2754-62.
119. Previtalli M, et al. Clinical characteristics and outcome of left ventricular ballooning syndrome in a European population. *Am J Cardiol.* 2011;107(1):120-5.
120. Cherian J, et al. Recurrence of stress-induced (takotsubo) cardiomyopathy. *Cardiology.* 2007;108(2):144-6.
121. Barthgate-Siryik A, Dabul S, Pandya K, et al. Negative impact of β -arrestin-1 on post-myocardial infarction heart failure via both cardiac and adrenal-dependent neurohormonal mechanisms. *Hypertension.* 2014;63:404-412
122. Santulli G. Adrenal signalling in heart failure - something more than a distant ship's smoke on the horizon. *Hypertension.* 2014;63:215-216

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