Tako-tsubo cardiomyopathy: The "broken heart syndrome"

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CLINICAL POINTS

- Tako-tsubo cardiomyopathy (TCM) is a clinical mimic of acute myocardial infarction (MI) and usually presents with chest pain and dyspnoea. Studies estimate that TCM accounts for 1-2% of acute MI hospital admissions.
- The condition is most common in postmenopausal women, and two-thirds of cases are preceded by an identifiable physically or psychologically stressful event.
- Non-specific findings on electrocardiogram and cardiac enzyme assays similar to MI are associated with TCM. "Ballooning" of the left ventricle on systolic ventriculogram is pathognomonic of the condition.
- Management is usually supportive, although complications are managed as they arise. There is a potential role for chronic beta-blockade and ACE-inhibition on discharge.
- TCM usually resolves spontaneously, has a low mortality rate and recurs in less than 10% of individuals.

ABSTRACT

Tako-tsubo cardiomyopathy is a recently described clinical entity which classically presents as an acute coronary syndrome. Key features include "ballooning" of the left ventricle, patent coronary arteries, non-specific electrocardiogram changes and elevated cardiac enzymes. This condition clinically mimics acute myocardial infarction and is believed to account for at least 1-2% of patients admitted to hospital with this diagnosis. The typical patient with tako-tsubo cardiomyopathy is a postmenopausal woman presenting with acute onset of chest pain and dyspnoea, who has recently experienced a profoundly stressful physiological or psychological event. Catecholamines are implicated in the pathophysiology of this condition, although their precise role is the subject of much debate. Currently, routine investigations are not specific for tako-tsubo cardiomyopathy and it should be considered as a diagnosis of exclusion. Relative to myocardial infarction, the prognosis of tako-tsubo cardiomyopathy is excellent; the mortality rate is low, fewer than 10% of patients experience a recurrence of the condition and recovery is generally spontaneous with minimal intervention. Herein, the aim of this review is to provide an overview of tako-tsubo cardiomyopathy by examining its pathophysiology and clinical characteristics.

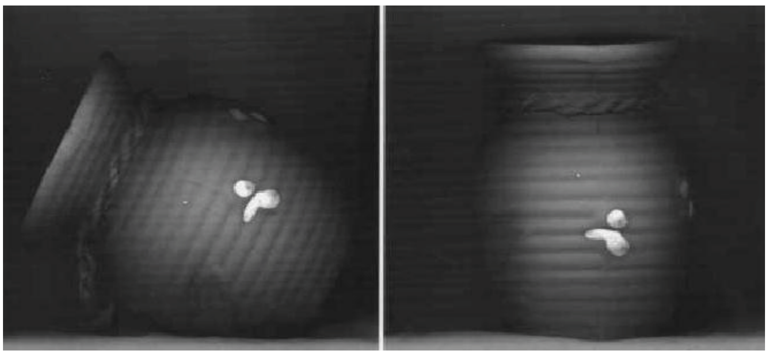


Figure 1: A tako-tsubo. This is a device used by Japanese fishermen to capture octopuses. Reproduced with permission[29].

INTRODUCTION

First described in 1991[1], tako-tsubo cardiomyopathy (TCM) is a discrete, transient cardiomyopathy which clinically mimics acute myocardial infarction (MI). The syndrome is defined by its clinical characteristics: dyskinesia of the mid and apical segments of the left ventricle, normal or non-significantly stenotic coronary arteries, abnormal electrocardiogram (ECG) findings and moderately elevated cardiac enzymes. A patient with TCM typically presents with acute chest pain and dyspnoea, temporally associated with an acute psychologically or physically stressful event. The precise nomenclature of TCM remains controversial; the condition is also referred to as transient left ventricular apical ballooning syndrome, stress cardiomyopathy and "broken heart syndrome". A "tako-tsubo" is a pot used by Japanese fishermen to capture octopuses and resembles the "ballooned" appearance of the left ventricle observed in TCM (Figure 1).

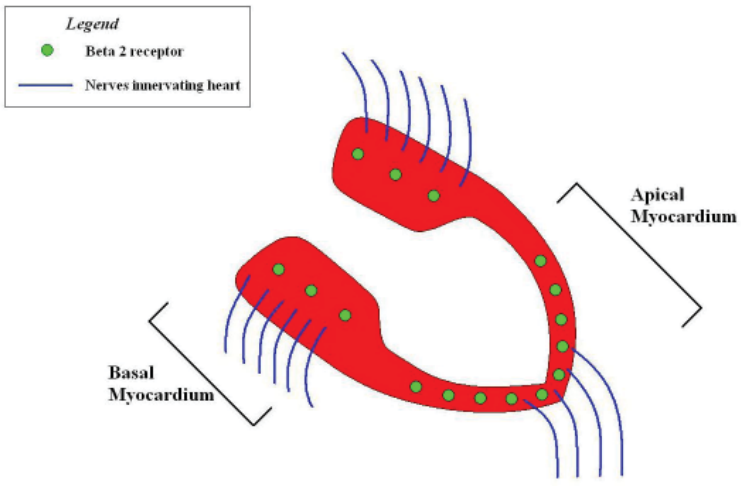
Current studies estimate that TCM is responsible for 1-2% of admissions for acute MI[2,3,4]. American Heart Association data reports that approximately 732,000 Americans are discharged

with a primary diagnosis of acute MI each year[5]. Therefore, it may be surmised that TCM accounts for at least 7,000-14,000 hospital discharges per year in the United States. Similarly, ESRI (HIPE) data suggests that TCM is responsible for 60-121 hospital discharges from Irish hospitals per year[6].

TCM shows a marked preponderance for females[7], with women accounting for 89% of patients. The mean age ranges from 58-75 years and <3% of patients are under the age of 50 years[7,8,9]. A stressful triggering event is readily identifiable in two-thirds of cases[9,10]. Classical emotional triggering events include major medical diagnoses[11], confrontational arguments[12], unexpected death of a friend or relative, gambling losses and domestic abuse[7]. Examples of reported physical stressors include demanding work or exercise[13], administration of EpiPen[14] and non-cardiac surgery[9,15]. One interesting study[16] reported a rise in incidence of TCM following the Central Niigita Prefecture earthquake in Japan in 2004. In the four weeks preceding the earthquake, only one case of TCM was reported, whereas 25 cases of TCM were confirmed in the four weeks following the incident.

By considering TCM as a differential diagnosis of acute MI, patients may be rendered a diagnosis with an extremely good prognosis and less significant emotional burden. Indeed, both the recurrence and mortality rates for TCM are extremely low relative to MI and it generally resolves spontaneously with minimal or supportive therapy. There is conflicting evidence regarding how to differentiate TCM from acute MI using routing investigations in the acute setting. Emerging research is focused on identifying findings on routine investigations which are specific for TCM and elucidating the underlying pathophysiological mechanisms. An increased understanding and awareness of this unique condition is necessary to improve diagnostics and optimize management. The aim of this introductory review, therefore, is to present the pathophysiology of TCM as it is currently understood and to provide an overview of the clinical aspects of this increasingly recognised clinical entity.

Figure 2: Illustration of the densities of Beta-2 receptors and sympathetic nerve fibres in the apical and basal myocardium. A comparable dilation is seen at the apex relative to basal contraction ("ballooning"). This is due to the greater density of beta-2 receptors at the apex and the greater density of sympathetic fibres at the basal myocardium. Thus, serum catecholamines have a more pronounced effect at the apex, causing a localised relative negative inotropic effect.



PATHOPHYSIOLOGY

The precise pathological mechanism of TCM has yet to be identified[5]. Although several hypotheses have been proposed, the Catecholamine Hypothesis is the most widely accepted. Therefore, a detailed overview of this theory will be provided, in addition to a synopsis of the salient points of alternative theories underlying TCM.

CATECHOLAMINE (NEUROHUMORAL) HYPOTHESIS

Catecholamines are released from the adrenal glands and some presynaptic neurons during episodes of stress, exercise or other "fight or flight" reactions.

Raised serum total catecholamine levels of up to 3600 pg/L have been reported in TCM[17] (normal level <250 pg/L[18]). This catecholamine excess has been implicated in the pathogenesis of so-called myocardial "stunning"[17], proposed as the cause of apical ballooning of the left ventricle which is pathognomonic of the syndrome. The neurohumoral hypothesis postulates that a complex interplay between neural (related to nervous system) and humoral (pertaining to elements in blood) factors is responsible for the manifest features of TCM[19].

Norepinephrine and epinephrine exert their effects on the heart primarily through β_1 and β_2 adrenergic receptors (the ratio of β_1:β_2 in the heart is approximately 4:1[20]). Binding at these receptors normally results in activation of a cascade of signalling molecules beginning with G_s, which results in a positive inotropic effect (more forceful contraction of heart muscle)[21]. While this normal pathway is preserved at the β_1 receptor, extremely raised catecholamine concentrations result in a switch at the β_2 receptor from a G_s to a G_i pathway

(probably via phosphorylation of the β_2 receptor[22]). The G_i pathway results in negative inotropy and is believed to act as a protective mechanism against myocyte apoptosis. It is proposed that as serum catecholamine levels rise, a greater proportion of β_2 receptors transduce signals through the G_i pathway causing an increasingly negative inotropic effect. Meanwhile, the stress response in the central nervous system (sympathetic response) results in both positive chronotropy (increased rate of contraction) and positive inotropy.

In the human heart, the density of sympathetic nerve fibers is approximately 40% higher in the basal myocardium than in the apical myocardium[23] (Figure 2). Conversely (extrapolated from a canine model), the apical myocardium has a greater concentration of β receptors than the basal myocardium[24]. Thus, neural input has a greater effect in the basal myocardium and receptor-mediated effects are greater in the apical myocardium. Functionally, this suggests that the negative inotropic effect produced by transduction from the β_2 receptor in the presence of raised cathecholamines is relatively larger in the myocardium at the apex of the heart. This mildly counteracts the sympathetic overdrive, leading to relatively weaker contractions in the apical than in the basal myocardium – a local humoral response at the apex resisting the generalized positive inotropy. This provides a possible explanation for the characteristic takotsubo-like ventricular changes of basal contraction and apical ballooning.

In the presence of raised serum catecholamines, cardiac myocytes undergo oxidative stress and some may apoptose (though less than encountered in MI). Since both TCM and MI share the feature of myocyte apoptosis, this may explain their similar ECG and biochemical findings. Moreover, as this apoptotic phenomenon is present to a lesser degree in TCM, this may explain why these abnormalities are less marked and observed for a shorter period of time.

Additional support for catecholamine involvement in TCM includes the finding that β blockers such as propranalol have also been effective in preventing certain stress-induced cardiac pathology[25]. Furthermore, in some cases of phaeochromocytoma (a catecholamine-secreting adrenal gland tumour), a similar pattern of apical ballooning has been observed[26].

Inflammatory Hypothesis

This hypothesis postulates that catecholamine excess directly causes cardiac inflammation and apoptosis, which in turn gives a picture of heart failure[27]. This arose from the detection of elevated non-specific inflammatory markers such as C-reactive protein (CRP)[28], as well as the observed infiltration of inflammatory cells into the myocardium in TCM[29]. Catecholamines can cause apoptosis via cyclic AMP-mediated calcium overload[30], serving also as a potential source of oxygen-derived free radicals[31]. The significance of raised inflammatory markers has been disputed and is currently believed to be an epiphenomenon as CRP levels reach a peak several days after presentation.

Coronary Flow Impairment Hypothesis

Coronary flow impairment was one of the earliest pathophysiological hypotheses of TCM. This theory postulates that increased sympathetic activity from stress induces coronary artery spasm and vasoconstriction[32], resulting in transient ischaemic myocyte apoptosis. Recently, many studies using acetylcholine or ergonovine to induce coronary artery vasospasm during angiography have yielded inconclusive results[7]. However, further research has indicated that microvascular spasm may result in impaired blood supply to discrete areas of the myocardium and reversible myocardial dysfunction[33].

Myocyte Metabolism Hypothesis

Having observed that coronary microcirculation may be markedly impaired in the early stages of TCM[33], researchers sought to elucidate whether abnormalities of myocyte metabolism similar to those seen in acute MI are also present. Under aer-

Mayo Clinic Diagnostic Criteria for TCM
Each of the following criteria must be satisfied for the diagnosis of TCM:
1) Transient hypokinesis, akinesis, or dyskinesis of the left ventricular mid segments with or without apical involvement; the regional wall motion abnormalities extend beyond a single epicardial vascular distribution; a stressful trigger is often, but not always present.
2) Absence of obstructive coronary disease or angiographic evidence of acute plaque rupture.
3) New electrocardiographic abnormalities (either ST-segment elevation and/or T-wave inversion) or modest elevation in cardiac troponin.
4) Absence of phaeochromocytoma and myocarditis.

▲ **Table 1:** Mayo Clinic Diagnostic Criteria for Tako-tsubo Cardiomyopathy (TCM)[8]

obic conditions, the normal myocardium utilises fatty acids (via β oxidation) as 70-80% of its energy source. In TCM, fatty acid oxidation is significantly impaired with only a slight decrease in perfusion[34]. This disproportionate impairment was confirmed in multiple studies, usually involving reduced uptake of iodine-123-BMIPP radioisotope tracer into myocytes and is thought to be consistent with a mildly ischaemic picture[34].

Clinical Presentation and Diagnostic Criteria

Clinically, TCM is essentially indistinguishable from acute MI with reversible left ventricular dysfunction. In a systematic review by Gianni et al[7], cardiac-type chest pain and dyspnoea were reported as cardinal symptoms in 67.8% and 17.8% of TCM patients, respectively. Nevertheless, patients may present with more serious complications, such as cardiogenic shock (4.2%) and/or ventricular fibrillation (1.5%)[5]. Mild to moderate congestive cardiac failure is frequent and due to the reduction in stroke volume, hypotension may occur, though syncope is uncommon[8]. Rarely, patients may present with sudden cardiac death syndrome[35].

To assess a patient with the above clinical picture for the presence of TCM, the Mayo Clinic has proposed several diagnostic criteria[36] (Table 1).

Investigations

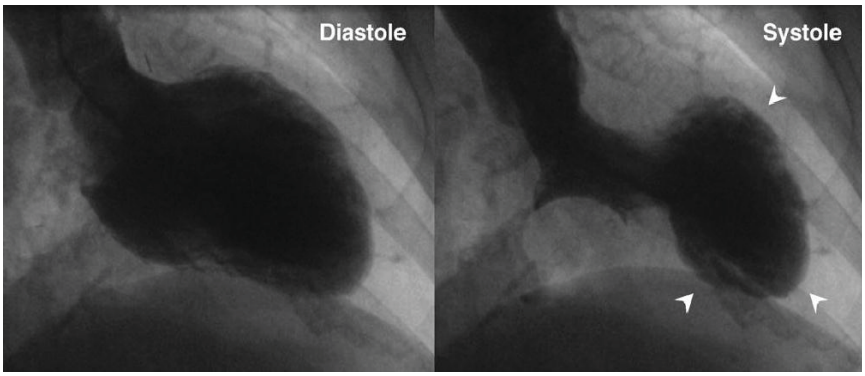
Electrocardiogram Findings

The most commonly observed abnormality on the electrocardiogram (ECG) is ST-segment elevation which mimics ST-elevation MI (STEMI)[15]. Few identified features distinguish STEMI from TCM on ECG, with some papers denying that discriminatory features exist[37]. However, a growing evidence base suggests that certain fine characteristic features may be useful. In a cross-sectional retrospective record review of low power (n=26) by Ogura et al[38], ST-elevation was quantitatively measured in patients with TCM and acute anterior MI. There was a statistically significant (p=0.008) difference in the level of ST-elevation in leads V_{1-3} in patients with acute anterior MI (11.04+/-7.35millimetres) than with TCM (4.33+/-3.10mm). In leads V_{4-6} the ST-segment elevation was also marked but similar in both conditions (p=0.56): MI (7.73+/-6.10mm) versus TCM (6.44+/-4.69mm). Most notable, however, was the difference noted in the ratio of ST-segment elevation in leads V_{4-6} to leads V_{1-3} ($STeV_{4-6}$:$STeV_{1-3}$): MI (0.56+/-0.57mm) versus TCM (1.55+/-0.53mm), which is statistically significant (p=0.0004). Thus, while ST-elevation is present in both conditions, it was found in this study to be quantitatively greater in MI. In practical terms, the ratio of elevation in V_{4-6}:V_{1-3} has the potential to be a specific marker for TCM and requires further investigation in a study of higher power.

Other changes which may prove useful in distinguishing TCM from acute anterior MI include the absence of ST-segment depression in inferior leads[39] and resolution of QT-interval prolongation and T-wave inversion over 4-6 months[40,41]. Pathological Q waves may be less common in patients with TCM than in patients with acute MI[38].

Cardiac Imaging

Transthoracic echocardiography and ventriculography are useful tools in detecting wall motion abnormalities typically seen in TCM, specifically hypokinesis or dyskinesis of the mid or apical portions of the left ventricle. Subsequent "ballooning" of the left ventricle may be observed and is considered to be pathognomonic of the syndrome (Figure 3). Similar regional wall motion abnormalities are seen in the right ventricle in approximately 30% of patients who tend to be sicker and are more likely to develop congestive cardiac failure[42,43]. However, visualisation of the true anatomical apex can be difficult in acutely ill patients[8]. It is worth noting that the characteristic wall motion abnormalities involve myocardium supplied by branches of both the left and right coronary arteries[44]. In studies by Wittstein et al[17], Bybee et al[45] and Tsuchihashi et al[15], left ventricular ejection fraction (LVEF) at presentation of TCM was markedly reduced (to an average of 20%, 39% and 41%, respectively). Full recovery was the trend in each of these trials; follow-up LVEF values were measured at



▲ **Figure 3:** **The characteristic appearance of TCM on ventriculogram. Diastolic and systolic freeze frames from a left ventriculogram of a patient with classic TCM. This illustrates hyperdynamic basal contraction but akinesis of the mid and apical segments of the left ventricle. Reproduced with permission[8].**

an average of 60%, 60% and 64%, respectively (within the normal healthy range of 62.3+/-6.1%)[46].

Unlike typical patients with acute coronary syndromes, angiographically normal or mildly atherosclerotic coronary arteries are usually seen on emergency coronary angiography in patients with TCM[7,9].

Laboratory Studies

In TCM, cardiac biomarkers tend to be modestly raised relative to the levels observed in MI. Sharkey et al[47] found the mean peak Troponin T titre to be elevated in 95% of TCM patients at 0.64+/-0.86 ng/ml, but lower than in those with left anterior descending coronary artery occlusions (3.88+/-4.9 ng/ml). As would be expected, patients demonstrating left heart failure were noted to have elevated serum brain natriuretic peptide (BNP) levels. Further, serum catecholamines have been noted to be two to three times higher than in patients with acute MI[17].

Management and Prognosis

Optimal management of TCM has yet to be established. The initial management should therefore be that of myocardial ischaemia until a diagnosis of TCM is made. Management would include continuous ECG monitoring, administration of aspirin and IV heparin and β-blockade are indicated. Discontinuation of all medications except for β-blockade and supportive fluids is recommended once the diagnosis of TCM is established[8]. Complications should be treated as they arise. Congestive cardiac failure complicates 20% of TCM cases[7] and as with acute MI, mechanical (e.g. free wall rupture and mitral regurgitation) and arrhythmic complications (both atrial and ventricular) may occur. Given the excess of catecholamines, it is sensible to avoid catecholamine vasopressors in treating hypotension[9,48]. Anticoagulation is advisable in the presence of severe left ventricular systolic dysfunction, with warfarin maintenance until function recovers. Mayo Clinic guidelines suggest a role for chronic β-blockade in reducing the likelihood of recurrences and for ACE-inhibitors on discharge[8].

Complete recovery is seen in virtually all patients within 4-8 weeks[8,15,17,48] and recurs in less than 10% of patients[10]. In a four-year follow-up study of 70 TCM patients in Rhode Island, among three deaths in the cohort, only one was reported to be due to cardiovascular morbidity[49]. This further reinforces the low mortality rate reported by other studies[8,48]. Overall, long-term survival is similar to that of the general age-matched population[10].

Conclusion

As evidenced by phrases such as "scared to death" and "dying of a broken heart", TCM seeped into popular culture long before it was recognised and afforded a name. As TCM is further unmasked, its implications are becoming better understood. Improving diagnostics is incentivised not only by the opportunity to offer patients a diagnosis with an excellent prognosis and more tolerable treatment, but also to reduce unnecessary expenditure by shortening inpatient stays and avoiding costly interventions. This unique syndrome should be included in the differential diagnosis of any patient presenting with suspected acute MI. Currently, there is significant international interest in TCM, as reflected by the exponential growth in the number of publications in recent years. As the evidence evolves, enthusiasm for research into this disease has reached new heights and the prognosis will continue to improve.

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