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**Review Article**

# Takotsubo cardiomyopathy: a rare neuro-cardiological entity with its challenges

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## ABSTRACT

Takotsubo cardiomyopathy (TCM) is a type of neuro cardiological disorder that evince as acute but reversible heart failure. On the whole, it occurs by stress-related cardiomyopathy which illustrates the heart-brain connection. It was first discovered in 1990, by a Japanese cardiovascular specialist. That's the beginning of this heart disease in gaining worldwide acceptance as an independent disease entity. TCM is entirely different from acute myocardial infarction as usually occurs in postmenopausal elderly women due to emotional or physical stress. It is characterized by transient hypokinesis of the left ventricular apex. However, there are complications too that need to be addressed. Some reports of serious TCM include hypotension, thrombosis involving LV apex, heart failure, and ventricular rupture. It is also suggested that coronary spasms, myocarditis, and coronary microvascular dysfunction might contribute to the pathogenesis of TCM. But in total, its pathophysiology is unclear. In this review article, we review the pathogenesis and etiology of this rare complex disorder along with its clinical features, findings, challenges in diagnosis, and a comprehensive discussion on the same.

**Keywords:** Takotsubo cardiomyopathy, Left ventricular apex, Stress, Myocarditis, Postmenopausal

## INTRODUCTION

The postmenopausal elderly women who present with a background of unanticipated, sudden emotional, and physical stress are mainly subjected to Takotsubo cardiomyopathy (TCM). Emotional stress mainly acts as a trigger for transient left ventricular apical ballooning.[3] Takotsubo cardiomyopathy, a neuro-cardiological disease, is named so because, during the symptoms and signs of spasms and acute myocardial infarction presenting without any coronary artery stenosis, the heart appears to be a Japanese octopus fishing pot called a takotsubo (Figure 1). In this illness, left ventricular dysfunction is mainly seen which recovers within a few weeks.[2] It is also known by some other names which include broken heart syndrome, stress-related cardiomyopathy, Ampulla cardiomyopathy, and transient LV apical ballooning syndrome.[1]

Many cases have demonstrated reversible left ventricular dysfunction. Iga et al reported a case of reversible left ventricular dysfunction associated with pheochromocytoma in which the takotsubo appearance

was first described, although they did not use the term takotsubo. Later in 1990, Sato et al described this reversible cardiomyopathy as tako-tsubo - like left ventricular dysfunction and was used in Japan. In other places, the phenomenon was called apical ballooning or stress cardiomyopathy.[2]–A major earthquake that took place on 23 October 2004, in Niigata prefecture, Japan led to a diagnosis of Takotsubo cardiomyopathy among 16 patients. Among them were 15 women and 1 man with an average age of 71.5 years. This incidence, therefore, revealed that Takotsubo Cardiomyopathy can occur among elderly women living near the epicenter.[3]

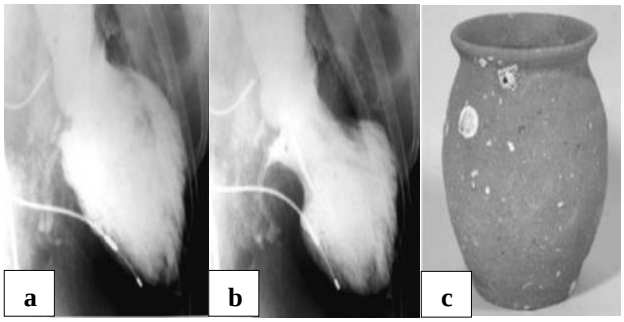


**Figure 1: Right anterior oblique projection of the left ventriculogram (a) end-diastolic phase; (b) end-systolic phase), the basal segments exhibit hypercontraction, particularly at the end-diastolic phase, while the large region surrounding the apex exhibits akinesis; (c) an image of an actual takotsubo, which is a Japanese device that has been used for a very long time to catch octopuses and has a thin neck and a spherical bottom.**

### *Epidemiology*

TCM cases are increasing rapidly nowadays while the same was considered extremely rare until the past 20 years.[1] Currently, more than 5000 studies have aroused concern about this topic. Based on these back-dated studies, patients suspected of acute coronary syndrome accounted for approximately 2% of all the patients diagnosed with TCM.[7,8] Additionally, 90% of TCM patients were postmenopausal women.[9,10] There is a very rare chance for children or young adults to be affected since the average age of TCM patients was 68 years.[11,12] Few reports indicated fewer men who were inpatients were diagnosed with TCM and it was reported that physical stress was the major reason for the progress of the disease.[13] The number of patients with TCM has increased manifold, especially since 2001 because, it probably accounts for approximately 1-2% of all cases of acute myocardial infarction.[2]

## METHODS

### *Search strategy and selection criteria*

References for this comprehensive review were taken by searches of PubMed, Google scholar, Scopus, and Cochrane library between January 1975 and September 2022, and references from relevant articles. The search terms "Takotsubo cardiomyopathy", "left ventricular apex", "postmenopausal", "myocarditis", and "stress" were used. There were no language restrictions.

**Table 1: Inclusion and exclusion criteria.**

| Inclusion criteria | Exclusion criteria |
|---|---|
| **Studies in adults and geriatric populations** | Studies in pediatric population |
| **Published literature Reviews, meta-analyses, cohort studies, systematic reviews, and randomized controlled trials** | Case studies |
| **Papers in the English Language** | Papers not in the English language |
| **Papers selected from the previous 50 years** | Papers published over 50 years ago |
| **Papers relevant to the subject of discussion** | Papers irrelevant to the subject of discussion |

## DISCUSSION

### *Pathophysiology*

The exact cause and pathophysiology of TCM are still unknown.[1] Many hypotheses have been given regarding this disease. The most accepted theories were that of catecholamine-induced cardiotoxicity and microvascular dysfunction.[1,33] Wittstein et al in his recent study revealed that the plasma levels of epinephrine were critically elevated in TCM patients because emotional stress was its major precipitating factor. His study also indicated that the concentration of serum catecholamine was 2-3 folds higher in TCM than in myocardial infarction patients.[34] In addition, other studies also substantiate this theory further by exogenous administration of catecholamine and pheochromocytoma, which results in similar features of TCM.[35,36] During stressful conditions excessive amounts of catecholamines are released by the sympathetic nervous system. This situation could result in intracellular calcium overload and cardiac dysfunction through the $B_1$-adrenoreceptor signal transduction pathway.[37] The main cause of ventricular dysfunction and catecholamine cardiotoxicity is calcium overload in myocardial cells.[38] Conditions with high catecholamine levels also affected the $B_2$-adrenoreceptor. This results in myocyte injury due to calcium leakage because of hyperphosphorylation of the ryanodine receptor.[39] Despite that, cardiotoxicity caused major changes in myocardial features with contraction band necrosis, inflammatory cell infiltration, and fibrosis.[40]

Recently a review study revealed that there is a higher prevalence of TCM when physical stress is triggered than that an emotional stress. However, it should be noted that

the absence of an isolated trigger should not be excluded while diagnosing this disorder. Since a large number of major causes for this disorder is remained unclear till now and it is also believed that TCM may manifest a wide variety of features, symptoms, and causes. Among the patients of TCM, the features of microvascular dysfunction were constantly demonstrated.[41] The features of this syndrome include the impairment of endothelium-dependent vasodilation, excessive vasoconstriction, and abnormality of myocardial perfusion.[42] Going further into these features, a study by Uchida et al revealed that through myocardial biopsy, apoptosis of endothelial cells was shown.[43]

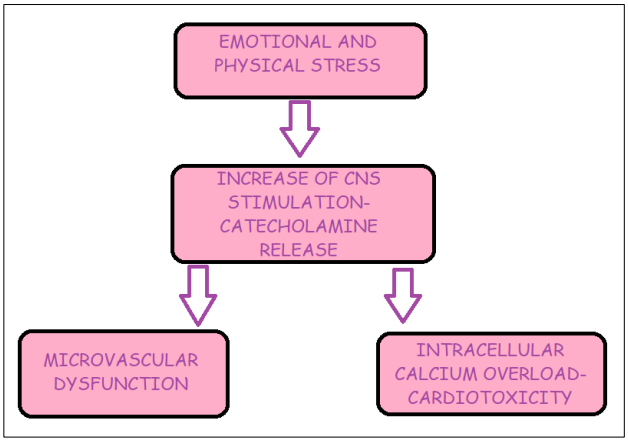


**Figure 2: Mechanism of Takotsubo cardiomyopathy.**

***Risk factors***

Moving on to the risk factors, the risk factors of TCM include majorly emotional or physical stress, estrogen deficiency, and a few genetic factors too. The majority of TCM patients are postmenopausal females. According to research by Ueyama et al, rats who had ovariectomy after being exposed to stressful situations showed worse LV function than rats that received estrogen supplementation.[44] The transcription of cardioprotective genes like heat shock protein and atrial natriuretic peptide may also be amplified by estrogen, protecting against cardiotoxic substances such as catecholamines, calcium excess, and oxidative stress.[44,45] Emotional stress is also a crucial triggering element in the development of TC. Stress stimulates the sympathetic nervous system, which has been associated with the incidence of TC.[46] Genetic factors have also been implicated in the incidence of TC. According to one study, individuals with TC carry the L41Q polymorphism of the G protein-coupled receptor (GRK5) more frequently than the control group.[47] The GRK5 L41Q polymorphism responds to catecholamine stimulation and reduces the response of b-adrenergic receptors. Furthermore, Mediterranean and Asian women are more vulnerable to this disorder.[48,49]

Several emotional or psychological stresses have been identified as initiating the start of TC, with structures in the central and autonomic nervous systems mediating these reactions.[50] Stressors activate the brain, raise cortisol levels, and increase catecholamine bioavailability. In the acute phase of TC, circulating epinephrine and norepinephrine produced by adrenal medullary chromaffin cells, as well as norepinephrine released locally from sympathetic nerve terminals, are greatly enhanced. This process, which has a functional counterpart in transient apical left ventricular ballooning, causes myocardial damage via a variety of mechanisms including direct catecholamine toxicity, and adrenoceptor-mediated damage. Other risk factors, such as estrogen deficiency, may also play a role, presumably through endothelial dysfunction, as previously indicated.[4]

Numerous research has examined whether multivessel epicardial spasm during angiography occurs spontaneously or is provoked. During coronarography, only a small number of individuals (three out of 212 patients, 1.4%; 95% CI: 0.5-4.1%; range: 0-10%) exhibited spontaneous multivessel epicardial spasm. To assess inducible coronary spasms, several researchers utilized provocative procedures like acetylcholine or ergonovine infusions, with mixed findings. After receiving an infusion of a provocative drug, 24 out of the 84 patients who were assessed (28.6%, 95% CI: 20.0-39.0%) had a multivessel spasm. However, outcomes in several series that ranged from 0% to 100% differed greatly. Only findings from Japan, where vasospastic ischemia may be more prevalent, should be taken into account. Both spontaneous and induced cardiac spasms were rare (1.8 and 27.7%, respectively).

Utilizing echocardiography with a Doppler guidewire or contrast, Abe et al assessed the coronary microcirculation. Despite being based on a small number of patients, their results seem to indicate that anomalies in the coronary microcirculation do not significantly contribute to the condition. Kurisu et al discovered that 28 patients with transient LV apical ballooning syndrome had substantially greater TIMI frame counts, a validated indicator of coronary blood flow, than controls both during the acute period and follow-up. Bybee et al evaluated coronary angiograms done at the time of admission and verified similar findings. They also compared 16 age- and gender-matched controls without coronary atherosclerosis but who had coronary angiography prior to valve surgery to 16 patients with this disease to assess the TIMI frame counts in those individuals. They discovered that the mean TIMI frame counts were significantly higher compared to controls and that all patients with transient LV apical ballooning syndrome had significantly abnormal TIMI frame counts in one or more epicardial coronary vessels. Ten patients also had significantly abnormal TIMI frame counts in the distribution of all three major epicardial vessels. These researchers hypothesized that this anomaly may be important in the development of this disease and concluded that their results were suggestive of widespread coronary microvascular dysfunction. It is not yet apparent, though, whether microvascular dysfunction is the syndrome's fundamental cause or just a byproduct.

Four studies that assessed the plasma levels of catecholamines and their metabolites discovered that 26 of the 35 patients they studied had high norepinephrine concentrations (74.3%, 95% CI: 57.9-85.8%; range: 50-100%). For instance, Wittstein et al compared the plasma catecholamine concentrations of seven controls hospitalized for acute MI with Killip class III on presentation with those of 13 patients with transitory LV apical ballooning syndrome.[6] They discovered that individuals with transient LV apical ballooning syndrome had catecholamine levels that were two to three times greater than normal. Four investigations used single photon emission computed tomography to assess myocardial perfusion (SPECT). These studies' findings indicated mild to severe myocardial ischemia. Therefore, Abe et al observed that there was reduced radioisotope absorption at the LV apex in 11 of 13 patients (85%) who underwent resting technetium-99m tetrofosmin tomographic myocardial imaging during the acute period. According to Ito et al, myocardial perfusion as measured by SPECT imaging was decreased right away after hospital admission but significantly improved after 3-5 days. They saw the nuclear imaging results showing lower myocardial perfusion in the absence of obstructive coronary lesions as compelling proof that the coronary microcirculation was impeded as the syndrome's underlying cause. In four investigations, fifteen individuals underwent endomyocardial biopsy; none of these samples revealed myocarditis. Additionally, all individuals who were examined lacked viral antibodies.[5]

***Diagnosis***

The four parts of the widely used Mayo clinic TC diagnostic criteria are as follows: the presence of stress elicitation; the absence of substantial coronary artery disease; transient hypokinesis, dyskinesis, or akinesis in LV segments with or without apical involvement; aberration in regional wall motion transcending a single vascular distribution; recent electrocardiographic (ECG) abnormalities (ST-segment elevation and/or T-wave inversion) or significantly elevated blood cardiac troponins; and absence of pheochromocytoma or myocarditis.[23]

A more accurate method of detecting TC will benefit from the use of diagnostic modalities combinations such as ECG, cardiac biomarkers, echocardiography, coronary angiography, and cardiac magnetic resonance (CMR) imaging. The majority of recent abnormalities on the ECG, such as ST-segment elevation, are indicative of ACS, particularly in the anterior leads (56%) and T-wave inversion (39%). QT-prolongation, ventricular tachycardia (VT), ventricular fibrillation (VF), and torsade de pointes are further ECG abnormalities that might manifest.[24] Furthermore, research by Kosuge et al discovered that TC could be detected with 91% sensitivity, 96% specificity, and 95% accuracy when combined with ST-segment depression in aVR and the lack of ST-segment elevation in V1.[25] Additionally, as demonstrated by other studies, the ECG should show no reciprocal changes, Q waves, and a ratio of ST elevation in leads V4-6 to V1-3 that is greater than 1, as well as the absence of ST depression or subsequent inferior ST elevation, in order to distinguish between anterior MI and TC.[26]

In accordance with ECG results, TC also exhibits higher cardiac biomarker levels indicative of myocardial dysfunction.[27] 90% of patients had increased troponin levels, which are frequently misdiagnosed as ACS.[28] However, unlike to ACS, the greatest troponin level would typically be less than 1ng/ml. Additionally, it has been discovered that B-type natriuretic peptide (BNP) and N-terminal pro-BNP (NT-proBNP) are commonly elevated up to 3–4 times greater compared to individuals with ACS.[29] According to one study, significantly increased levels of these biomarkers were linked to decreased ejection fraction (EF) and raised plasma catecholamine levels rather than pulmonary congestion or pulmonary capillary wedge pressure, indicating the pathophysiology of TC and its severity.[29]

Apical ballooning of the LV during echocardiography is the pathognomonic finding of TC. It was noted that 75% of patients had this particular morphology.[19] Mid-LV akinesis was observed to cause a ballooning pattern in 25% of patients' morphologies, with no disruption of basal or apical contraction.[30,31] In this example, it was also possible to find an impaired LVEF with characteristic systolic anterior motion (SAM). CMR is crucial imaging research that can offer more compelling proof of TC. The right ventricular (RV) involvement that CMR might demonstrate helps to distinguish it from other cardiomyopathies.[32] But because it can be challenging to tell the difference between TC and ACS, coronary angiography may play a crucial part in TC diagnosis. Angiograms of the coronary arteries can more precisely demonstrate normal coronary arteries or little atherosclerosis. If there are no contraindications, a myocardial biopsy may also be carried out, primarily to reveal interstitial infiltrates with mononuclear cells, leukocytes, macrophages, cardiac fibrosis, and contraction bands. Inflammatory response and contraction bands exhibit various characteristics in TC and MI, and they may reveal coagulation necrosis in situations when coronary arteries are blocked.[2]

***Treatment***

The primary focus of TCM treatment during the acute period is symptom management. For patients with hemodynamic instability, in addition to cardiopulmonary circulatory support and continuous veno-venous hemofiltration, intra-aortic balloon pump equipment is necessary.[14-16] Because of the elevated levels of catecholamines in the blood, there is debate concerning the usage of cardiac stimulants.[17] However, 20% to 40% of TCM patients also utilize cardiac stimulants.[18,19] Because of its inotropic action and vasodilator effect, levosimendan could be advantageous.[20,21] Anticoagulant use is possible,

at least up until the restoration of systolic function. Treatment with a beta-blocker or beta-adrenoceptor agonists like phenylephrine and volume augmentation should be taken into consideration for patients with significant LV outflow tract blockage and hemodynamic compromise. Calcium channel blockers can be utilized to lower the pressure gradient in the LV outflow tract. In these situations, it is crucial to avoid using nitrites or inotropic medications as a kind of therapy. The use of calcium channel blockers like verapamil or diltiazem is advised for patients with suspected vasospasm.[22]

Patients who have hemodynamic stability are frequently treated with diuretics, ACE inhibitors, and beta-blockers. Patients with LV apex loss should receive anticoagulant medication until the apex's contractility is restored in order to lower the risk of thrombosis unless there is a clear contraindication. Although it is appropriate to treat patients with -blockers and ACE inhibitors throughout the ventricular recovery phase, there is little agreement on the long-term therapy of TCM. However, there is little evidence to back up the continued use of these medications to increase survival rates or prevent TCM recurrence. Physicians may think about stopping these medications after LV function returns to baseline.[1]

## CONCLUSION

An important alternative diagnosis for acute coronary syndrome is takotsubo cardiomyopathy. Normal (or almost normal) coronary arteries, regional wall motion abnormalities that go beyond a single coronary vascular bed, and frequently a triggering stressor are its distinguishing features. Mid- or basal left ventricular wall motion anomalies are becoming more and more recognized as variations of the typical left ventricular apical ballooning. Takotsubo cardiomyopathy is not uncommon, and more people becoming aware of this particular cardiomyopathy will probably increase the reported occurrence. Takotsubo cardiomyopathy diagnosis has significant effects on clinical care both during the presentation and subsequently. The long-term outlook is typically positive; nevertheless, a tiny proportion of cases initially present with potentially fatal complications. Although the pathophysiologic mechanism is unclear, catecholamine excess is most likely a key factor.[6]

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