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Review Article

Clinical insights and management strategies in Takotsubo cardiomyopathy: a comprehensive review

Akansha Arewar¹, Suraj Dhankikar¹, Smruti Besekar², Marvel Bhosle^{3*}, Diptesh Besekar⁴

¹East State Tennessee University, TN, USA

²Department of Pharmacology, JNMC, Sawangi, Wardha, Maharashtra, India

³Division of Criminology and Forensic Science, Karunya Institute of Technology and Sciences, Coimbatore, Tamil Nadu, India

⁴MOIL Limited Nagpur, Maharashtra, India

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*Correspondence:

Dr. Marvel Bhosle,

Email: marvelbhosle@karunya.edu

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ABSTRACT

Takotsubo cardiomyopathy (TCM) is characterized by transient left ventricular dysfunction typically triggered by stressors, presents diagnostic challenges resembling acute coronary syndrome (ACS). This comprehensive review synthesizes diverse triggers (stress, illness, therapies), diagnostic complexities (variability in criteria, imaging modalities), and management strategies (supportive care, tailored medications). Despite favourable outcomes with reversible ventricular dysfunction, heightened risks in specific cohorts (e.g., malignancies, post-PCI) underscore the need for refined diagnostic criteria and optimized therapies. Prospective studies are essential to enhance understanding and management of TCM, aiming to improve clinical outcomes and patient care.

Keywords: Takotsubo cardiomyopathy, Broken heart syndrome, Stress cardiomyopathy, Broken heart syndrome, Management strategies

INTRODUCTION

Broken heart syndrome, also known as Stress cardiomyopathy, TCM, recurrent TCM, or Apical ballooning syndrome, is a cardiac condition typically precipitated by high-stress situations or intense emotions. Additionally, it can be triggered by severe physical illnesses or surgical procedures. While this syndrome is usually transient, some individuals may experience lingering discomfort even after their heart has physically recovered. There are different types of syndromes such as apical, mid-ventricular, basal, and focal. Apical is the most common type, affecting the lower half of the heart.¹ Mid-ventricular affects the middle section of the heart's lower chambers, while basal affects a higher area. Focal, the rarest type, involves a smaller area forming a noticeable bulge on the heart. Broken heart syndrome, occurring in approximately 2% of individuals seeking medical attention

for a suspected heart attack, disproportionately affects people assigned female at birth (AFAB), constituting around 89% of reported cases.² This susceptibility is particularly pronounced post-menopause, with the mean age range for occurrences falling between 58 to 77 years old. One hypothesis posits that estrogen, a hormone, acts as a protective factor for the heart against the potentially deleterious effects of stress-induced hormone release. As estrogen levels decline with age, individuals AFAB may become more vulnerable to the impact of sudden stress on the heart. Symptoms of broken heart syndrome can manifest within minutes to hours following a stressful event.³ The release of stress hormones can temporarily stun the heart muscle, leading to symptoms resembling those of a conventional heart attack.

Common signs and symptoms of broken heart syndrome include sudden and severe chest pain (angina) and

shortness of breath. Additionally, weakening of the left ventricle of the heart is a primary indication. Other associated symptoms may include irregular heartbeats (arrhythmias), low blood pressure (hypotension), heart palpitations, and fainting (syncope).⁴

Upon seeking medical attention, a healthcare provider will conduct a thorough physical examination and review your medical history. Following this initial assessment, they may recommend several diagnostic tests to confirm the presence of broken heart syndrome. These tests typically include a blood test to assess specific enzymes released from damaged heart muscle cells, an electrocardiogram (EKG) to record the heart's electrical activity, and coronary angiography to visualize the coronary arteries and rule out a heart attack, as broken heart syndrome does not involve blocked arteries.⁵ Additionally, imaging tests such as echocardiography, chest X-ray, and heart MRI may be performed to assess the heart's structure and function, identify any abnormalities, and pinpoint areas of damage. A ventriculogram, involving the injection of dye into the heart's left ventricle followed by X-rays, may also be conducted to evaluate the heart's pumping efficiency. These diagnostic procedures collectively help healthcare providers accurately diagnose broken heart syndrome and develop an appropriate treatment plan. While there is no definitive cure for broken heart syndrome, known as TCM, most individuals achieve a full recovery with appropriate medical intervention. Treatment typically involves the use of medications aimed at managing symptoms and supporting cardiac function. These medications may

include aspirin to improve circulation and prevent blood clot formation, ACE inhibitors or ARBs to lower blood pressure and reduce inflammation, beta-blockers to regulate heart rate, and diuretics to alleviate fluid buildup. In rare cases where the heart requires additional support in pumping function, interventions such as an intra-aortic balloon pump or left ventricular assist device may be necessary. Overall, with the proper medical management, most individuals with broken heart syndrome can expect a favourable prognosis and eventual recovery.⁶

This review is conducted on the cases of broken heart syndrome to analyze and document diverse clinical presentations, diagnostic approaches, and management strategies of TCM, highlighting its association with various triggers such as emotional stress, physical illness, and medical procedures.

The study aims to enhance understanding of TCM's pathophysiology, diagnostic challenges, and therapeutic interventions, emphasizing the importance of tailored medical care to improve patient outcomes.

LITERATURE REVIEW

In this review, author has included relevant articles that were suitable for the study, and define the rationale of the review. The articles were obtained from the free-access databases such as PubMed, Web of Science, Google Scholar, and selected cases were screened for the relevancy of the study.

Table 1: The characteristic of the studies included in the review.

Author	Demographic details and chief complaints	Laboratory/ radiographic findings	Diagnosis
Afana et al ⁷	66-year, female 2-day history of nausea and epigastric pain	WBC-15,400/uL, cardiac troponin level-19 ng/mL, brain natriuretic peptide level-1,403 pg/mL, creatinine level-3.2 mg/dL, lactate level-8.9 mmol/L, ECG-0.5-mm ST-segment elevation in leads III, aVF; PR depression in leads II, III, aVF; and PR elevation in lead aVR. Right-sided heart catheterization-right atrial pressure of 11 mmHg, a mean pulmonary artery pressure of 25 mmHg, a pulmonary capillary wedge pressure of 22 mmHg, and a substantially reduced fick cardiac output and index of 2.43 L/min and 1.55 L/min/m ² , respectively. Radiographic findings: USG showed an apparently solid mass in right upper quadrant, characterized on CT as a 111.5-mm right adrenal mass	Diagnosis: pheochromocytoma-induced TCM
Zadok et al ⁸	44-year, female History of heart transplantation of 5 months due to idiopathic non-ischaemic, non-dilated cardiomyopathy. She was asymptomatic after HTx, and describes a significant and emotional dispute with her spouse the preceding day.	WBC- 5,00 K/ μ L, Hb-11.3 g/dl, normal range elevated creatinine-2.1 mg/dl, natriuretic peptide (NT)-pro-BNP level-2917 pg/mL, cardiac troponin T-52 ng/l cyclosporine level-362 ng/mL, coronary angiography-Normal, hemodynamic measurements via jugular vein-Normal myocardial histological examination-Normal (no sign of acute cellular or antibody-mediated graft rejection). Repeated troponin T and NT pro-BNP levels were 23 ng/mL and 3839 pg/mL	The diagnosis of Takotsubo syndrome was made in a 5-month heart-transplanted patient.

Continued.

Author	Demographic details and chief complaints	Laboratory/ radiographic findings	Diagnosis
Stepien et al⁹	Case 1: 76-year, female history arterial hypertension and hypercholesterolemia was admitted with suspicion of ACS. Two years before she underwent resection of hormone receptor-positive left breast cancer followed by the adjuvant hormone therapy with tamoxifen Case 2: 75-year, female History of arterial hypertension, hypercholesterolemia, impaired fasting glucose and obesity, was also admitted with suspicion of ACS. She had a history of radical hysterectomy with appendages due to intermediate-risk endometrial cancer followed by adjuvant radiotherapy 5 days a week for three weeks	Case 1: Isoenzyme MB of creatine kinase-75 IU/l, troponin I-9.85 ng/ml, coronary angiography-normal epicardial segments, with narrow distal part of left anterior descending artery, left ventricular (LV) angiography and transthoracic echocardiography (TTE)-abnormal ballooning of apical segments with decreased ejection fraction up to 40% and hypertrophic intraventricular septum with obstruction of left ventricular outflow tract. Myocardial perfusion scintigraphy-irreversible defect of technetium-99m uptake in apex and small reversible defect in periapical segments. Case 2: ECG-admission we found left axis deviation, PQ interval lasted 0.2 s and inversed T wave in V2-6 leads, isoenzyme MB creatine kinase-19 U/l, troponin T concentration-0.178 ng/mL, coronary angiography-normal, slightly tortuous epicardial arteries	Direct relationship between TCM and adjuvant hormone therapy with tamoxifen or pelvic radiotherapy
Lu et al¹⁰	69-year, female With repeated episodes of chest tightness located over the area of the xiphoid process during exertion and at rest in the last week before presentation. Past medical history revealed erosive gastritis	Troponin I-14.00 pg/mL myoglobin-54.3 ug/l pro-B-type natriuretic peptide (Pro-BNP) level-269.0 pg/ml, total cholesterol-(TC) 5.98 mmol/l, low-density lipoprotein cholesterol (LDL-C) level- 3.85mmol/l. The ECG showed sinus rhythm-normal cardiac chamber size; the left ventricular ejection fraction (LVEF) was 73%	TTK followed by percutaneous coronary intervention
Patel et al¹¹	73-year Caucasian women medical history (PMHx) of esophageal dysmotility, gastroesophageal reflux disease (GERD), lymphocytic colitis, chronic obstructive pulmonary disease (COPD), essential hypertension (HTN), hyperlipidemia (HLD), neuropathy, and depression presented with substernal pleuritic chest pain and lightheadedness that began 2 hours after an uncomplicated outpatient upper and lower endoscopy	Hemoglobin level-11.5 g/dl B-type natriuretic peptide level-2900 pg/ml ECG-T-wave inversions and ST elevations, indicating ACS. TTE-apical hypokinesis, Left heart catheterization-nonobstructive CAD with a left ventriculogram of 45% and diffuse wall hypokinesis, confirming TCM.	TCM following an upper and lower endoscopy.

The demographic details reveal that broken heart syndrome predominantly affects older females, often with a significant medical history. The common chief complaints include chest pain, tightness, and symptoms suggestive of ACS. Emotional or physical stressors frequently precede the onset of symptoms, as observed in several cases.

Elevated cardiac biomarkers, particularly troponins and natriuretic peptides, are consistent findings across cases, indicating myocardial injury. ECG changes such as ST-segment elevation and T-wave inversions mimic those of ACS, complicating the diagnosis. Imaging modalities, including TTE and coronary angiography, typically show

transient LV dysfunction and absence of significant coronary artery disease, which are hallmarks of broken heart syndrome.

DISCUSSION

The cases presented in this review emphasize the diverse clinical presentations, underlying triggers, and diagnostic challenges associated with TCM, also known as broken heart syndrome. Despite its transient and reversible nature, TC can precipitate significant acute cardiac events and complications, necessitating a multidisciplinary approach for optimal patient outcomes.

Pheochromocytoma and TCM

The case highlights a rare yet clinically significant association between pheochromocytoma and TC, where the patient experienced cardiogenic shock. Elevated catecholamine levels due to pheochromocytoma can lead to severe myocardial stress, resulting in TC. This case underscores the importance of considering pheochromocytoma in the differential diagnosis of TC, particularly in patients presenting with abdominal symptoms and hemodynamic instability. Comprehensive diagnostic approaches, including biochemical testing and imaging, are crucial for accurate diagnosis. The management of pheochromocytoma-induced TC involves stabilization with supportive measures and pharmacotherapy, followed by surgical intervention to address the underlying tumor.⁷

TCM post-heart transplantation

The second case illustrates the occurrence of TC shortly after heart transplantation, a rare and complex scenario. The early post-transplant period is characterized by significant physiological changes, including potential rapid sympathetic re-innervation, immunosuppressive therapy, and emotional stress. This case emphasizes the need for heightened clinical awareness and consideration of TC in post-heart transplant patients presenting with acute cardiac dysfunction. Understanding the interplay between sympathetic stimulation, immunosuppressive treatment, and the patient's unique physiological status is crucial for appropriate diagnosis as well as the management.⁸

Association with neoplastic diseases and oncological therapy

The third case series document the co-occurrence of TC with neoplastic diseases, specifically in patients undergoing tamoxifen hormone therapy and pelvic radiotherapy. While the direct causal relationship between oncological therapies and TC is not well established, these cases highlight the increased cardiovascular risk in cancer patients. The InterTAK registry indicates that TC patients with malignancy require more acute cardiac care and experience higher in-hospital complications and long-term mortality. These findings underscore the importance of a thorough cardiovascular assessment in cancer patients and careful consideration of the risks and benefits of continuing anticancer therapy in TC survivors.⁹

Challenges in diagnosing takotsubo syndrome post-PCI

The fourth case discusses the diagnostic challenges of TC following percutaneous coronary intervention (PCI). Emotional distress, coupled with the invasive nature of PCI, can trigger TC, complicating the clinical picture with overlapping symptoms of myocardial infarction. This case underscores the importance of utilizing multiple diagnostic modalities, including echocardiography and cardiac

magnetic resonance imaging (CMR), to differentiate TC from other cardiac conditions. Early identification and tailored management strategies are crucial to mitigate morbidity and mortality associated with post-PCI TC.¹⁰

TCM post-endoscopy

The final case highlights TC triggered by an outpatient endoscopy procedure, emphasizing the condition's association with various medical interventions and procedures. Differentiating TC from ACS is essential, as management strategies differ significantly. Utilizing diagnostic criteria, including transient left ventricular dysfunction, new ECG abnormalities, and elevated cardiac biomarkers, is vital for accurate diagnosis. Supportive care, risk stratification, and close monitoring form the cornerstone of TC management, with a focus on reversible left ventricular dysfunction over time.¹¹

Overall, the studies highlight TCM's diverse triggers (stress, illness, therapies), diagnostic challenges (similarities to ACS, need for advanced imaging), and management strategies (supportive care, tailored medications). It emphasizes favorable outcomes with reversible ventricular dysfunction but underscores risks in specific patient groups (e.g., concurrent malignancies, post-PCI). Ongoing research aims to improve diagnostic precision and optimize treatment approaches for better patient outcomes.

Limitations of the study on TCM include its predominantly retrospective nature, which limits causal inference and introduces potential biases. Small sample sizes and focus on specific patient demographics reduce the generalizability of findings. Variability in diagnostic criteria and imaging modalities across studies complicates the comparability and accuracy of TCM diagnosis. Outcome variability and potential publication bias towards severe cases further underscore the need for larger, prospective studies with standardized protocols to better characterize TCM and refine clinical management approaches.

CONCLUSION

In conclusion, TCM manifests through diverse triggers including emotional stress, physical illnesses, and medical treatments, presenting diagnostic challenges akin to ACS. Effective management involves tailored therapies and vigilant monitoring, with most patients experiencing reversible ventricular dysfunction and favourable outcomes over time. However, heightened risks in specific patient cohorts necessitate continued research to refine diagnostic criteria and optimize therapeutic strategies, aiming to enhance clinical outcomes and quality of care for individuals affected by this complex cardiac condition.

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