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Current Clinical Perspectives on Takotsubo Syndrome: Comprehensive analysis of Diagnosis, Management, and Pathophysiology

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Abstract

Takotsubo syndrome (TTS), commonly referred to as stress-induced cardiomyopathy or broken heart syndrome, is a disorder characterized by acute left ventricular (LV) failure and apical ballooning that tends to occur due to extreme psychological or physical stress. Mainly affecting postmenopausal women, it has great similarities with other cardiac conditions like acute coronary syndrome. However, it has characteristic and distinct pathophysiology and disease progression. A wide range of diagnostic methods can be used, ranging from radiologic imaging to important biomarkers and biochemical analysis. These include cardiac magnetic resonance imaging, coronary angiography, echocardiography, echocardiogram, and inflammatory and cardiac biomarkers. There is a significant role for catecholamines in diagnosis. Key features include transient LV dysfunction and characteristic apical ballooning on imaging. The etiology involves a catecholamine surge leading to myocardial toxicity and microvascular dysfunction. Risk factors include age, sex, and stress, with additional associations such as pheochromocytoma and certain thyroid disorders. Management focuses on supportive care and pharmacological interventions, including beta-blockers, angiotensin converting enzyme inhibitors, and anticoagulants. Despite a good short-term prognosis, this condition can lead to severe complications and even sudden cardiac death. Long-term prognosis varies, with factors like reduced LV ejection fraction as well as old age affecting outcomes. This review summarizes the most updated information and is crucial for understanding TTS's diagnostic and therapeutic strategies. This review underlines the pathophysiology, risk factors, management strategies, and importance of nutritional management. Future research is recommended for improving diagnostic and therapeutic strategies, emphasizing early and accurate detection to mitigate risks and enhance patient outcomes.

Keywords: Takotsubo syndrome, cardiomyopathy, stress-induced cardiomyopathy, broken heart syndrome, cardiology, left ventricular dysfunction

INTRODUCTION

Takotsubo syndrome (TTS) is a relatively rare but potentially life-threatening cardiac event. Characterized as an acute dysfunction of the left ventricular (LV) caused by dilation of the apex of the LV and the proximal myocardium.^[1] TTS is often known as stress-induced cardiomyopathy or broken heart syndrome. In recent years, it has gained attention due to its

life-threatening complications and mortality potential. It is often associated with extreme emotional stress, which could result in severe LV impairment.^[1] It often mimics the symptoms of acute coronary syndrome (ACS), making it important to have an accurate differential diagnosis. The most common manifestations of TTS are angina and dyspnea which worsens with exertion.^[2,3] In terms of electrocardiogram (ECG) findings, TTS mimics the findings of ST-elevated ACS. The diagnosis is

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often made by coronary angiography, which excludes coronary artery disease (CAD). Echocardiography findings show a great dilation of the left ventricle, which resembles a Japanese octopus trap or takotsubo.^[2,4] The exact etiology of TTS remains unclear to date. However, it is linked to high levels of chronic stress or cases dealing with the sudden loss of a close person.^[3] Drugs like angiotensin-converting enzyme inhibitors are seen to be giving promising results in terms of long-term prognosis. Other pharmacologic interventions like dual antiplatelet therapy are also beneficial treatment options.^[2,5] This review provides in-depth and recent information about these management strategies. This review aims to provide the most recent updates on TTS and address gaps in the current literature.

1. Epidemiology

TTS was first described in 1990. It was observed to develop in any age group among males or females of any ethnicity. Approximately 90% of the patients were female, and 80% were aged >50 years. Surprisingly, this syndrome is also reported in children. TTS is more prevalent in women than men by 10%.^[6-8] However, studies in Japan have found that TTS is more common in men in Japan.^[9-11]

The exact reason why females are more prone to TTS is still not known but studies indicate that a low estrogen level in postmenopausal females can be the reason, as estrogen is essential in the regulation of sympathetic functioning and microvascular flow from the endothelial mechanisms. Some studies suggest an increase in sympathetic nervous system activity with age, especially in females, and that cardiac stimulation is enhanced because of an imbalance in neuronal norepinephrine homeostasis. As females age, there is a significant decrease in vagal tone and sensitivity of the baroreflex together with an associated rise in sympathetic activation causing the susceptibility of the myocardium to increase the levels of catecholamines.^[8,12] From the data on TTS from different regions of the world according to National Institutes of Health reports 85-90% of the patients are females within the age group 65-70 years old. The probability of TTS recurrence ranges from 0% to 22%. Studies suggest a link between pheochromocytoma and TTS, as it has a 17.7% recurrence rate due to undiagnosed pheochromocytoma. The yearly rate of recurrence was seen to be 1.5% and the incidence of recurrence was increased by 1.2% at 6 months and 5% by 6 years.^[13] Increasing anxiety and stress levels experienced in the Western populations resulted in a higher prevalence of TTS. During the coronavirus disease-19 (COVID-19) pandemic, the incidence of TTS has increased by 2 to 3 folds due to social isolation, stress, financial crisis, anxiety, and quarantine compared to before COVID-19.

2. Pathogenesis

The pathogenesis of TTS is complex and yet not entirely known. Several processes have been proposed as potential causes of TTS, such as sympathetic overactivity accompanied by elevated catecholamine levels, coronary spasm, microvascular dysfunction, reduced estrogen levels, inflammation, or compromised myocardial fatty acid metabolism.^[14] However, it is believed that several processes play a role in TTS growth. Up to two-thirds of patients report experiencing preceded emotional or physical stress. This stressor includes natural disasters, death of a loved one, financial issues, previous surgery, trauma, and conditions associated with the central nervous system. This results in an excess of catecholamine being released, causing a catecholamine surge.^[15] This condition is characterized by a shift in β -2-adrenoceptor signaling from Gs to Gi, resulting in negative inotropy and LV contractile dysfunction. This condition is called stimulus trafficking. The alpha-adrenergic receptors in the coronary vasculature's smooth muscle cells are activated by both norepinephrine and epinephrine, resulting in coronary vasoconstriction. These spasms can reduce blood flow to the myocardium, mimicking myocardial infarction (MI). Immediate coronary vasospasm occurs in 5-10% of patients, indicating that most do not experience it.^[8] A previous study showed abnormally high levels of plasma catecholamines and stress-related neuropeptides in individuals with TTS compared with Killip class III ACS patients.^[16] This suggested a connection between TTS and excessive catecholamine levels. The catecholamine surge leads to a cascade of events, starting from direct myocardial toxicity and microvascular and coronary artery dysfunction. Among the emitted catecholamines, only a small amount enters the bloodstream. The majority of it is sent straight to the myocardium's adrenoceptor by the sympathetic nerve endings, which release it into the nerve terminals. Catecholamine enters myocardial cells through β -adrenergic receptors and triggers a pathway that increases calcium influx, leading to cellular damage and toxicity.^[15]

Catecholamines and endothelin predominantly cause vasoconstriction in the coronary microvasculature through α 1-receptors and endothelin receptor type A. This indicates that acute microcirculatory disruption may play a significant role in TTS. Numerous non-invasive and invasive techniques have confirmed that coronary microvascular abnormalities could be responsible for TTS pathogenesis. However, whether microvascular dysfunction is the primary cause or secondary is still unclear.^[17] Studies have suggested that perfusion of the myocardium examined while angiography is more compromised in patients with TTS than in patients with ST-segment elevation MI (STEMI) who show cardiac reperfusion. At the same time, it is less compromised than in patients with STEMI showing obstruction of microvasculature.^[18] Microcirculatory dysfunction was prevalent during the acute phase of cardiomyopathy, and

microvascular damage was as severe as that in STEMI patients. Similarly, there have been reports of increased thrombolysis in MI (TIMI) frame counts and aberrant grades of TIMI myocardial perfusion. A quantitative coronary flow evaluation using the TIMI frame count (TFC) demonstrated prolonged corrected TFC in either the left anterior descending (LAD) artery alone or in all three coronary arteries.^[19-21]

As estrogen provides a cardioprotective effect, a decrease in estrogen levels has been found to increase the susceptibility of cardiac myocyte to catecholamines.^[10,22] This may be seen to be more prevalent among females. TTS associated with pheochromocytoma is a known but rare event. It is part of the Paraganglioma family of tumors and causes the gland to produce an excessive number of catecholamines. Studies have suggested rare cases of TTS after stroke. According to a study, 0.1% of patients develop TTS after 4 weeks following stroke.^[23] Thyrotoxicosis can have adverse effects in the cardiovascular system. Takotsubo cardiomyopathy may present as a symptom of thyroid storm, possibly due to elevated levels or increased sensitivity to catecholamines.^[24-26] Studies have contributed to understanding how the cardiovascular system responds to unexpected severe stress. It is observed that normal myocardial tissue generates most of its energy from fatty acid metabolism and 10% from glucose metabolism. TTS appears to be moving away from fatty acid metabolism toward glucose.^[27] Inflammation is another mechanism that has drawn attention. Findings from cardiac magnetic resonance imaging (MRI) show myocardial edema, necrosis, and fibrosis. Microvascular dysfunction, evidenced by prolonged TIMI frame count and abnormal coronary flow patterns, contributes to the pathogenesis of the disease. TTS can also represent aborted MI, where imaging techniques like intravascular ultrasound (IVUS) and optical coherence tomography (OCT), have revealed underlying atherosclerotic plaques and coronary vasospasm.^[28-31]

3. Risk Factors

Strong evidence indicates that TTS is caused by extreme mental or physical stress. Other predisposing factors like cardiovascular risk factors, also play a role.^[32] Risk factors include age, gender, diabetes mellitus, lung diseases, and even chronic kidney disease. These factors are associated with recurrence or even death in TTS.^[33] Additionally, the risk of TTS increases with age >55 years, smoking, alcohol abuse, and anxiety. Cannabinoid use, including non-dependent cannabis, is linked to increased Traditional Chinese medicine risk, affecting cardiovascular function. Marijuana use is associated with transient LV ballooning and significant morbidity, contributing to the complexity and prognosis.^[34] Comorbidities such as obesity, hypertension, dyslipidemia, psychological disorders, and malignancies. Other associated

conditions include neurologic and thyroid diseases. Some surgeries and interventions can also increase the risk of developing TTS. In some cases, immediate postoperative use of epinephrine and dobutamine as well as atrioventricular valve surgery. Although rare, precise and personalized risk assessment plans should be made for such patients.^[32,34] TTS is less likely to recur if managed properly. Compared with individuals with no recurrence of TTS, those with recurrent TTS were more likely to have no clear stressful trigger at admission. Stroke, although with a lesser prevalence among patients with TTS based on a study, was observed to be associated with TTS. According to a study, these individuals were seen to be having a significantly higher risk of stroke and death.^[35,36] Sudden cardiac death (SCD) is also seen to be associated with TTS as the most severe complication among patients with TTS. TTS patients have a greater risk for SCD because they have extended QT intervals, which may result in torsades de pointes, as well as other ECG abnormalities including diffuse negative T-waves and larger QRS complexes. Bradyarrhythmias, existing comorbidities, associated CAD or vasospasm, significant LV dysfunction, and sympathomimetic consumption.^[37] TTS tends to involve psychological disorders such as depression and nervousness. Cognitive-behavioral therapy combined with cardiovascular rehabilitation may be more effective in improving mental health and reducing negative thinking than cardiac rehab alone. Ongoing research, such as PLEASE (NCT04425785), is investigating the beneficial effects of regimented fitness and mental health programs.^[38] Hypertension is common in patients with recurrent TTS. Being overweight and having chronic kidney disease are linked to a worse prognosis, whereas hyperlipidemia is linked to fewer problems; data are limited. The influence of diabetes mellitus on TTS prognosis is yet unknown, indicating the need for additional research to better understand these interactions.^[39,40]

TTS is a prominent variant of MI with non-obstructive coronary arteries (MINOCA) and is affected by a variety of risk factors. Severe angina, defined as two or more occurrences within 24 hours, is an independent predictor of TTS in patients with MINOCA. Furthermore, mental stress and psycho-emotional problems play an important role in TTS development. Other significant risk factors include age >55 years, anxiety, and underlying cardiovascular disease. Comorbidities, such as hypertension, diabetes, and chronic renal disease, can increase the risk of TTS. Furthermore, cardiac MRI combined with biomarkers and ECG anomalies can help identify TTS within MINOCA instances. Pulmonary embolism has also been identified as a possible cause of MINOCA, with some cases matching TTS.^[41-44]

Recent research suggests a complex link between myocarditis and TTS. Myocarditis may cause TTS and is also a defining

hallmark of this condition. The inflammatory theory in TTS is supported by evidence of transitory apical wall thickening caused by cardiac edema and catecholamine spillover. Some researchers contend that cardiac inflammation in TTS may be a result of mechanical disruption rather than a primary trait. Despite their different pathologies, patients with TTS tend to be older, have a larger female preponderance, and have a higher fatality rate than patients with myocarditis. The association between TTS and myocarditis is still being investigated, with some studies indicating that many myocarditis patients may be TTS.^[20,45-47]

4. Diagnosis Using Radiological Imaging and Electrocardiography

TTS can be diagnosed with a combination of many clinical evaluations. One of them is imaging, which is also performed so that we can exclude other heart conditions like ACS, immediately.

4a. X-Ray

An X-ray commonly displays apical ballooning, which is a reversible condition associated with TTS. At systole, the left ventricle's center and apex expand out, referred to as apical ballooning, whereas the area above, known as the base, shrinks normally. The design resembles a Takotsubo pot used to collect octopuses.^[48]

4b. Electrocardiography

Inverted T-waves are seen in both the limb and precordial leads, a frequent feature of TTS with apex balloon-like dilation. Potential ECG abnormalities include ST-segment elevation, ST-segment depression, left bundle branch block, and prolonged QT interval. TTS can occasionally present with normal ECG findings, but our data indicate that it resembles ischemia in the anterior distribution.

Initially, the ECG changes resembled a lot of ACS. These are ST elevations, inverting T-waves, and left bundle branch blocks. ST elevation and T-wave inversion are not specifically localized in this case. Certain ongoing alterations can be categorized as follows: stage 1 involves ST deviation, stage 2 involves progressive T-wave inversion and QTc prolongation, and stage 3 comprises gradual resolution of T-wave and QTc alterations over several weeks or months. Ventricular arrhythmias, including torsade de pointes, can occur in the hyperacute phase. They are often associated with prolonged QTc but not necessarily related to it. TTS often presents with less prominent ST elevation and more diffuse T-wave inversions, making it challenging to distinguish from ACS solely based on ECG findings. Over time, beyond the acute phase, TTS often involves the resolution of ST elevation, as well as broad and deep T-wave inversions, which are frequently linked with QT prolongation. Although transient Q-waves may occur, but they are infrequent.^[50]

4c. Echocardiography

Echocardiographic imaging of a patient with TTS may reveal mitral valve alterations. These are LV outflow tract (LVOT) obstruction and systolic anterior motion (SAM). The hallmark pattern involves akinesia at the apex of the heart, followed by akinesia at the base. This apical ballooning trend may resemble LAD-distribution ischemia. The images also show SAM and turbulence across the LVOT, which indicates LVOT obstruction. Echocardiography can assess the severity, location, and nature of wall motion anomalies in TTS. Approximately 20% of individuals with apical-to-mid-cavity ballooning and basal hyperkinesis experienced increased LVOT blockage. Contrast drugs can help distinguish wall motion anomalies and detect LV thrombus, which can occur abruptly or later. Other advanced techniques, such as speckle-tracking echocardiography, indicate that the left ventricle's twist indices are aberrant, as are deformations. Cardiac deformation indicators that remain abnormal during recovery suggest heart failure with preserved ejection fraction.^[51,52]

4d. Cardiac Magnetic Resonance

On MRI, four distinct patterns of abnormal movement and ballooning were observed. The apical is the most common ventricle, followed by the biventricular, midventricular, and basal. Cardiac MRI using gadolinium contrast helps differentiate TTS from acute MI and myocarditis. TTS does not show late gadolinium enhancement, revealing fibrosis, unlike MI or myocarditis. A characteristic thin transmural band of fibrosis can be detected at the junction of the hyperkinetic base and dyskinetic apex or mid-cavity, both acutely and at follow-up. Cardiac magnetic resonance (CMR) can accurately detect right ventricular involvement and identify left and right ventricular thrombi. This method is frequently used to visualize minor pericardial effusions. On CMR, TTS is characterized by severe myocardial edema, which gradually diminishes over 5-6 months throughout recovery.^[52,53]

4e. Coronary Angiography and Left Ventriculography

Coronary angiography is performed to confirm whether the patient has MI or not because takotsubo cardiomyopathy can mimic this disease. This phenomenon should be considered when individuals present with sudden chest pain and other STEMI-like symptoms but coronary angiography shows a normal or non-obstructive coronary artery. ST segment elevation on ECG and associated symptoms are indicators of myocardial ischemia, which requires prompt assessment with a cardiologist. Coronary angiography may be normal; however, CAD does not rule out the diagnosis of TTS. TTS diagnosis is often accomplished after coronary angiography, which may show normal or non-obstructive CAD. There may be less acuteness in TTS presentations, such as with non-

specific ECG findings or elevated biomarkers, which can make physicians avoid performing coronary imaging. In cases where cardiac catheterization is not feasible or safe, defining the coronary anatomy using noninvasive angiography is recommended for suspected TTS. In patients with TTS, CAD, which occurs in approximately 15% of cases, requires a link between angiography findings and wall motion anomalies. Left ventriculography is another important imaging technique that typically shows mild LV end-diastolic pressure elevation with mild to moderate ballooning of the cardiac apex, suggesting a possible case of TTS. Modern intravascular imaging techniques, such as OCT and IVUS, may rule out plaque rupture, which is not characteristic of TTS. The majority of cases present with apical or midventricular dyskinesia and basal sparing as a hallmark of TTS. Other forms include reverse or mid-ventricular presentations, isolated right ventricular involvement, and focal LV participation.^[52,54,55] The modified Mayo Clinic diagnostic criteria are used when a patient is suspected of having an acute MI but cardiac catheterization reveals no coronary blockage, as mentioned in Table 1.^[56,57]

5. Diagnosis Using Hormonal Analysis and Biomarkers

TTS is usually diagnosed either primarily or secondary to coronary heart disease. The therapeutic implications of recovery time are uncertain; however, developing data suggest that full recovery may be slower and less complete than originally thought. Apart from radiologic imaging, certain biomarkers and hormonal analyses are important to consider. These contain certain cardiac biomarkers, inflammatory biomarkers, brain natriuretic peptide (BNP), and catecholamines to name some.^[51]

5a. Cardiac and Inflammatory Biomarkers

Along with ECG findings, TTS is associated with an increase in certain biomarkers, indicating myocardial damage. Creatine kinase is elevated in approximately 56% of patients with TTS. Cardiac Troponin is almost universally elevated in TTS because of the greater sensitivity of contemporary assays. The troponin levels were modest, peaking at approximately 60 times the upper limit of normal (ULN). In patients with

acute STEMI, troponin levels can be elevated up to 400 times the ULN. This pattern can also be observed during non-STEMI. Troponin-ejection fraction product (TEFP) is another method for differential diagnosis. If TEFP is 250 or higher, it correctly identified STEMI 95% of the time and non-STEMI cases (like TTS) 87% of the time, with an overall accuracy of 91%. This makes TEFP a reliable tool for accurate diagnosis in clinical settings.^[55]

5b. Brain Natriuretic Peptide Levels

BNP levels were higher in TTS than in STEMI. These levels may indicate the extent of myocardial dysfunction and damage. These levels may increase for months after the acute case. NT-proBNP levels are notably higher in patients with the apical variant than in those with the atypical variant. This difference may indicate more significant acute LV enlargement and myocardial stretching.^[52,55]

5c. The Role of Catecholamines in Takotsubo Syndrome

Plasma catecholamine levels for epinephrine, norepinephrine, and dopamine are found to be 2-3 times higher in TTS than in individuals having Killip class III acute heart failure after MI and about 7-34 times higher than normal ranges. Not all studies consistently reported elevated catecholamine levels as it was not one of the primary reliable biomarkers to indicate TTS.^[29,55]

6. Management and Postdischarge Follow-up

The overall aim of management is to stabilize the patient and prevent recurrence. This can be achieved through comprehensive and personalized cardiac risk assessment. Initial management of TTS involves supportive care that aims to address the triggers. It is combined with pharmacological interventions, such as β -blockers, ACE inhibitors, and angiotensin receptor blockers (ARBs). ACE inhibitors and ARBs are suggested for their potential benefits in improving LV function and reducing cardiovascular mortality.^[10,58] However, the effectiveness of β -blockers in decreasing mortality or recurrence remains debatable. Inotropes are favored vasopressors in individuals with complex conditions, particularly those with LVOT obstruction, with β -blockers being the safer choice. For individuals at high risk of thromboembolism, anticoagulation therapy is indicated, often beginning with low-molecular-weight heparin and progressing to oral anticoagulants for up to 3 months. In cases of cardiogenic shock, mechanical support devices should be considered immediately. Although the future outlook is generally good, with a majority of patients regaining LV function, ongoing treatment necessitates regular monitoring and follow-ups.^[3,59]

Post-discharge follow-up is usually indicated within 1 month to check for any residual abnormalities using ECG and

Table 1: Revised Mayo Clinic criteria for the diagnosis of Takotsubo syndrome^[57]

	Criteria
1	Transient dyskinesia of the left ventricle midsegment
2	Regional wall motion abnormalities beyond a single epicardial vascular distribution
3	Absence of obstructive coronary artery disease or acute plaque rupture
4	New electrocardiographic abnormalities or modest troponin elevation
5	Absence of pheochromocytoma and myocarditis

echocardiogram, with subsequent visits within 3 to 6 months depending on the patient’s recovery. Patients at high risk or with chronic symptoms may benefit from cardiopulmonary exercise testing and annual examinations. Statins are recommended in patients with CAD. Moreover, aspirin with antiplatelet drugs may reduce major cardiovascular events, but their impact on TTS-specific outcomes is unknown. Hormone therapy, notably estrogens, and novel medicines such as angiotensin-neprilysin receptor inhibitors, SGLT2 inhibitors, and novel mineralocorticoid receptor antagonists are all being investigated for their potential role in TTS management. Multidisciplinary management is essential for managing difficult situations involving psychiatric problems, cancer, or other major illnesses.^[4,59-61]

6a. Nutritional Management for Patients with Takotsubo Syndrome

A personalized dietary plan for managing TTS should be provided that includes many important factors. In general, this plan aimed to individualize dietary adjustments based on both physical and emotional factors that specifically affected each patient. Sodium restriction to prevent fluid retention, with a focus on reducing salt intake and avoiding processed foods. Incorporating heart-healthy spices, herbs, and phenol-rich fruits like red, purple, and citrus fruits can provide beneficial antioxidant benefits. Limiting fructose intake to 25-30 g per day is important to prevent excessive uric acid production, which can affect cardiovascular health. Probiotics and prebiotics, such as those found in fermented dairy products, support gut health and aid in the elimination of toxins. The management of fat intake is crucial. Emphasizing the intake of polyunsaturated fats while avoiding trans fats and minimizing cooking methods that produce harmful advanced glycation end products is one of the most important nutritional recommendations. Maintaining electrolyte balance through potassium-rich diets is essential, and regular monitoring advised.^[39,61-64]

6b. Schematic Algorithm for the Management of Takotsubo Syndrome

The schematic diagram of TTS management provides an organized way to diagnose and manage it, as shown in Figure 1. The findings highlight the importance of early detection of symptoms and other associated presentations. Using various diagnostic techniques, such as coronary angiogram and echocardiography, a physician can differentiate TTS from other conditions with similar presentations. Using this scheme, physicians can implement appropriate therapeutic modalities for both hemodynamically stable and unstable patients. It also addresses long-term care as well as related complications.^[15,65,66]

7. Prognosis

The prognosis of TTS is no longer as positive as it was once due to multiple complications and mortality-related conditions. Patients with TTS have a lower LV ejection fraction. An LV ejection fraction (LVEF) below %35 at admission has been identified as a predictor of both short- and long-term outcomes.^[67] However, some studies have found that LVEF 35% was an independent predictor of mortality among patients with TTS.

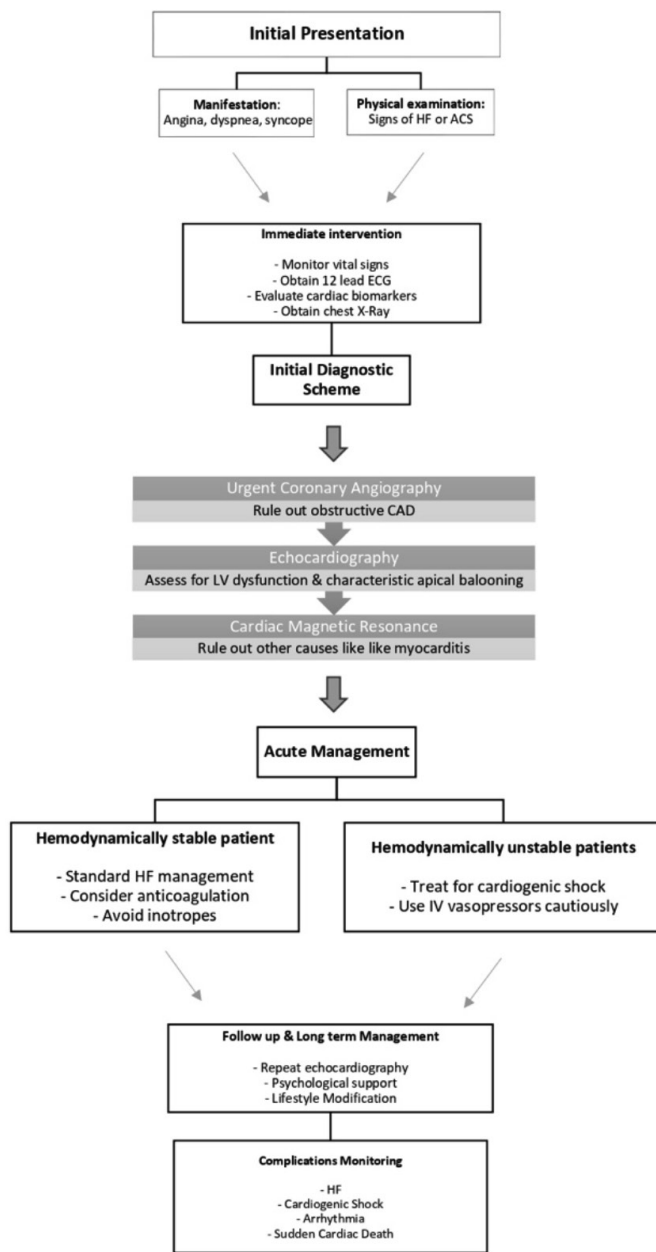


Figure 1: Schematic algorithm for the management of Takotsubo syndrome
 ACS: Acute coronary syndrome, CAD: Coronary artery disease, HF: Heart failure, IV: Intravenous, LV: Left ventricle, ECG: Electrocardiogram

Recently, the registry on TTS database, which was launched by a Spanish research group, discovered that cardiogenic shock is associated with both short- and long-term prognoses among these patients.^[68,69] Reduced systolic blood pressure upon admission is considered a prognostic indication.^[65] Furthermore, in multivariate studies, elderly age remained an independent prognostic factor. This disease is induced by a decrease in β -1 adrenergic receptor density. The increasing prevalence of mitral regurgitation (MR) in elderly patients requires particular medical attention. MR in these patients usually occurs due to the SAM of the mitral anterior leaflet, anchoring by papillary muscle displacement, and regional or global ventricular dysfunction. Some studies have identified long-term prognosis for patients with TTS. These patients had a similar long-term mortality rate as those with ACS. In addition, TTS that is typically caused by stress has a good short- and long-term outlook. In terms of prognosis, TTS requires a personalized treatment strategy and follow-up. Patients were seen to have the same in-hospital mortality rate as those with ACS, but patients with TTS had a higher survival rate post-discharge.^[70-73]

CONCLUSION

TTS is a complex cardiac event often misdiagnosed as ACS. Mainly seen to affect women in the postmenopausal age, it can be triggered due to severe stress, leading to transient LV dysfunction. The exact pathogenesis is not known. The proposed mechanisms involve catecholamine surges, microvascular dysfunction, and estrogen deficiency. Diagnosis requires imaging, such as echocardiography and cardiac MRI, along with biomarkers. TTS management focuses on supportive care, stressor management, and medications like ACE inhibitors and beta-blockers. TTS can lead to serious complications and even death. Future research should refine diagnosis, management protocols, and prevention strategies to improve prognosis and overall quality of life.

Footnotes

Authorship Contributions

Concept: H.S.W., Design: H.S.W., H.V., S.C., S.H., P.G., V.F., Data Collection or Processing: H.S.W., H.V., S.C., S.H., P.G., V.F., Analysis or Interpretation: H.S.W., H.V., S.C., S.H., P.G., V.F., Literature Search: H.S.W., H.V., S.C., S.H., P.G., V.F., B.S., A.A.P., Writing: H.S.W., H.V., S.C., S.H., P.G., V.F., B.S., A.A.P.

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REFERENCES

- Ralston SH, Penman ID, Strachan MWJ, Hobson R. Davidson's Principles and Practice of Medicine E-Book. Elsevier Health Sciences. 2018.
- Salamanca J, Alfonso F. Takotsubo syndrome: unraveling the enigma of the broken heart syndrome?-a narrative review. *Cardiovasc Diagn Ther.* 2023;13:1080103-1103.
- Sattar Y, Siew KSW, Connerney M, Ullah W, Alraies MC. Takotsubo syndrome: A Comprehensive Review. *Cureus.* 2020;12:6556.
- Canavero I, Rifino N, Bussotti M, Carrozzini T, Potenza A, Gorla G, *et al.* The Octopus Traps of Takotsubo and Stroke: Genetics, Biomarkers and Clinical Management. *J Pers Med.* 2022;12:1244.
- K Komamura, M Fukui, T Iwasaku, S Hirofani, T Masuyama. Takotsubo cardiomyopathy: Pathophysiology, diagnosis and treatment. *World J Cardiol.* 2014;6:602-9.
- Merchant EE, Johnson SW, Nguyen P, Kang C, Mallon WK. Takotsubo Cardiomyopathy: A Case Series and Review of the Literature. *West J Emerg Med.* 2008;9:104-11.
- Takotsubo cardiomyopathy: symptoms, causes, and treatment | NORD [Internet]. [cited 2024 Sep 1]; Available from <https://rarediseases.org/rare-diseases/takotsubo-cardiomyopathy/>
- Y-Hassan S, Tornvall P. Epidemiology, pathogenesis, and management of takotsubo syndrome. *Clin Auton Res.* 2018;28:53-65.
- Sharkey SW, Maron BJ. Epidemiology and Clinical Profile of Takotsubo Cardiomyopathy. *Circ J.* 2014;78:2119-28.
- Matta AG, Carrié D. Epidemiology, Pathophysiology, Diagnosis, and Principles of Management of Takotsubo Cardiomyopathy: A Review. *Med Sci Monit.* 2023;29:93020.
- Akashi YJ, Nef HM, Lyon AR. Epidemiology and pathophysiology of Takotsubo syndrome. *Nat Rev Cardiol.* 2015;12:387-97.
- Singh T, Khan H, Gamble DT, Scally C, Newby DE, Dawson D. Takotsubo Syndrome: Pathophysiology, Emerging Concepts, and Clinical Implications. *Circulation.* 2022;145:1002-19.
- Assad J, Femia G, Pender P, Badie T, Rajaratnam R. Takotsubo Syndrome: A Review of Presentation, Diagnosis and Management. *Clin Med Insights Cardiol.* 2022;16:11795468211065782.
- Ahmad SA, Brito D, Khalid N, Ibrahim MA. Takotsubo Cardiomyopathy. StatPearls. Treasure Island (FL): StatPearls Publishing; 2024.
- Ghadri JR, Wittstein IS, Prasad A, Sharkey S, Dote K, Akashi YJ, *et al.* International Expert Consensus Document on Takotsubo Syndrome (Part I): Clinical Characteristics, Diagnostic Criteria, and Pathophysiology. *Eur Heart J.* 2018;39:2032-46.
- Wittstein IS. Cardiac arrest and Takotsubo syndrome. *Eur Heart J.* 2019;40:2152-4.
- Vitale C, Rosano GM, Kaski JC. Role of Coronary Microvascular Dysfunction in Takotsubo Cardiomyopathy. *Circ J.* 2016;80:299-305.
- De Caterina AR, Leone AM, Galiuto L, Basile E, Fedele E, Paraggio L, *et al.* Angiographic assessment of myocardial perfusion in Tako-Tsubo syndrome. *Int J Cardiol.* 2013;168:4717-22.
- Kim SY, Yoon JH, Lee SH. Takotsubo-Like Severe Left Ventricular Dysfunction After Cesarean Delivery in a 28-Year Old Woman. *Korean Circ J.* 2011;41:101-4.
- Khalid N, Iqbal I, Coram R, Raza T, Fahsah I, Ikram S. Thrombolysis In Myocardial Infarction Frame Count in Takotsubo Cardiomyopathy. *Int J Cardiol.* 2015;191:107-8.
- Khalid Ahmed S, Gamal Mohamed M, Abdulrahman Essa R, Abdelaziz Ahmed Rashad Dabou E, Omar Abdulqadir S, Muhammad Omar R. Global reports of takotsubo (stress) cardiomyopathy following COVID-19

- vaccination: A systematic review and meta-analysis. *Int J Cardiol Heart Vasc.* 2022;43:101108.
22. Kalra R, Wasir AS, Bhavsar AS, Singh VP, Padwal MK. Takotsubo Cardiomyopathy: Narrative Review With Relation to COVID-19. *Indian Journal of Clinical Cardiology.* 2022;3:198-206.
 23. Buckley BJR, Harrison SL, Lane DA, Hill A, Lip GYH. Stroke–heart syndrome: mechanisms, risk factors, and adverse cardiovascular events. *Eur J Prev Cardiol.* 2024;31:23-6.
 24. Dong F, Yin L, Sisakian H, Hakobyan T, Jeong LS, Joshi H, *et al.* Takotsubo syndrome is a coronary microvascular disease: experimental evidence. *Eur Heart J.* 2023;44:2244-53.
 25. Mohamed AA, Basaran T, Othman MH, Andersen NH, Bonnema SJ. The association between Takotsubo cardiomyopathy and thyrotoxicosis: A systematic review. *Endocrine.* 2022;78:418-28.
 26. Waqar A, Jain A, Joseph C, Srivastava K, Ochuba O, Alkayali T, *et al.* Cardioprotective Role of Estrogens in Takotsubo Cardiomyopathy. *Cureus.* 2022;14:22845.
 27. Baltzer Nielsen S, Stanislaus S, Saunamäki K, Grøndahl C, Banner J, Jørgensen MB. Can acute stress be fatal? A systematic cross-disciplinary review. *Stress.* 2019;22:286-94.
 28. Scally C, Abbas H, Ahearn T, Srinivasan J, Mezincescu A, Rudd A, *et al.* Myocardial and Systemic Inflammation in Acute Stress-Induced (takotsubo) Cardiomyopathy. *Circulation.* 2019;139:1581-92.
 29. Lyon AR, Rees PCS, Prasad S, Poole-Wilson PA, Harding SE. Stress (Takotsubo) cardiomyopathy: A novel pathophysiological hypothesis to explain catecholamine-induced acute myocardial stunning. *Nat Clin Pract Cardiovasc Med.* 2008;5:22-9.
 30. Kuo BT, Choubey R, Novaro GM. Reduced estrogen levels during menopause may predispose women to takotsubo cardiomyopathy. *Gend Med.* 2010;7:71-7.
 31. Eitel I, von Knobelsdorff-Brenkenhoff F, Bernhardt P, Carbone I, Muellerleile K, Aldrovandi A, *et al.* Clinical characteristics and cardiovascular magnetic resonance findings in stress (takotsubo) cardiomyopathy. *JAMA.* 2011;306:277-86.
 32. Pelliccia F, Parodi G, Greco C, Antonucci D, Brenner R, Bossone E, *et al.* Frequency of comorbidities in takotsubo syndrome: an international collaborative systematic review including 1109 patients. *Am J Med.* 2015;128:654.11-19.
 33. Lau C, Chiu S, Nayak R, Lin B, Lee MS. Survival and risk of recurrence of takotsubo syndrome. *Heart.* 2021;107:1160-6.
 34. Kim YS, Lim JY. Risk factors for Takotsubo syndrome following cardiac surgery: A case–control study. *J Card Surg.* 2021;36:2767-73.
 35. Jessen N, Andersen JA, Tayal B, Østergaard L, Andersen MP, Schmidt M, *et al.* Takotsubo syndrome and stroke risk: A nationwide register-based study. *Int J Cardiol.* 2023;392:131283.
 36. Fernández-Cordón C, Núñez-Gil IJ, Martín de Miguel I, Pérez-Castellanos A, Vedia O, Almenro-Delia M, *et al.* Takotsubo Syndrome, Stressful Triggers, and Risk of Recurrence. *Am J Cardiol.* 2023;205:58-62.
 37. Manolis AA, Manolis TA, Melita H, Manolis AS. Takotsubo Syndrome and Sudden Cardiac Death. *Angiology.* 2023;74:105-28.
 38. Wells A, Reeves D, Capobianco L, Heal C, Davies L, Heagerty A, *et al.* Improving the Effectiveness of Psychological Interventions for Depression and Anxiety in Cardiac Rehabilitation: A Single-Blind, Parallel, Randomized, Controlled Trial of Group Metacognitive Therapy. *Circulation.* 2021;144:23-33.
 39. Khalid S, Khalid A, Maroo P. Risk Factors and Management of Takotsubo Cardiomyopathy. *Cureus.* 2018;10:2626.
 40. Liang L, Feng L, Zheng X, Wu Y, Zhang C, Li J. Effects of dialectical behavior group therapy on anxiety and depression among medical students under the normalization of epidemic prevention and control of the COVID-19 epidemic: a randomized study. *Ann Palliat Med.* 2021;10:10591-9.
 41. Mantzouranis E, Leontsinis I, Sakalidis A, Sarrou M, Vlachakis P, Fragoulis C, *et al.* Severe angina increases the probability of Takotsubo syndrome diagnosis among MINOCA patients. *European Heart Journal.* 2023;44(Suppl 2).
 42. Pais JL, Izquierdo Coronel B, Galán Gil D, Espinosa Pascual MJ, Martínez Peredo CG, Awamleh García P, *et al.* Psycho-emotional disorders as incoming risk factors for myocardial infarction with non-obstructive coronary arteries. *Cardiol J.* 2018;25:24-31.
 43. Joseph NR, Fu S, Ivanova V, Biederman R, Nguyen V. Myocardial Infarction With Nonobstructive Coronary Arteries (Minoca) Manifesting As Atypical Takotsubo Syndrome. *Journal of the American College of Cardiology.* 2020;75:3409.
 44. Jolobe OMP. Pulmonary Embolism a Potential Cause of Myocardial Infarction With Nonobstructive Coronary Arteries. *Am J Med.* 2019;132:672.
 45. Khalid N, Ahmad SA, UmerAffan, Chhabra L. Takotsubo cardiomyopathy and myopericarditis: Unraveling the inflammatory hypothesis. *Int J of Cardiol.* 2015;196:168-9.
 46. Kwan AC, Navarrette J, Botting P, Chen MT, Wei J, Merz CN, *et al.* Mortality Risk of Takotsubo Syndrome Versus Myocarditis. *J Am Heart Assoc.* 2022;11:025191.
 47. Y-Hassan S. Myocarditis in takotsubo syndrome: may be a trigger and/or a feature. *Int J Cardiol.* 2015;199:154.
 48. Takotsubo cardiomyopathy (broken-heart syndrome) [Internet]. Harvard Health2010 [cited 2024 Sep 1]; Available from <https://www.health.harvard.edu/heart-health/takotsubo-cardiomyopathy-broken-heart-syndrome>
 49. Takotsubo cardiomyopathy electrocardiogram review [Internet]. [cited 2024 Sep 1]; Available from <https://www.healio.com/cardiology/learn-the-heart/ecg-review/ecg-topic-reviews-and-criteria/takotsubo-ecg>
 50. Singh T, Khan H, Gamble DT, Scally C, Newby DE, Dawson D. Takotsubo Syndrome: Pathophysiology, Emerging Concepts and Clinical Implications. *Circulation.* 2022;145:1002-19.
 51. Zghyer F, Botheju WSP, Kiss JE, Michos ED, Corretti MC, Mukherjee M, *et al.* Cardiovascular Imaging in Stress Cardiomyopathy (Takotsubo Syndrome). *Front Cardiovasc Med.* 2022.
 52. Singh T, Khan H, Gamble DT, Scally C, Newby DE, Dawson D. Takotsubo Syndrome: Pathophysiology, Emerging Concepts, and Clinical Implications. *Circulation.* 2022;145:1002-19.
 53. Takotsubo cardiomyopathy | Radiology Case | Radiopaedia.org [Internet]. [cited 2024 Sep 1]; Available from <https://radiopaedia.org/cases/takotsubo-cardiomyopathy-1>
 54. Foster T. Takotsubo cardiomyopathy | Radiology Case | Radiopaedia.org [Internet]. Radiopaedia [cited 2024 Sep 1]; Available from <https://radiopaedia.org/cases/takotsubo-cardiomyopathy-6>
 55. Scantlebury DC, Prasad A. Diagnosis of Takotsubo cardiomyopathy. *Circ J.* 2014;78:2129-39.
 56. Boyd B, Solh T. Takotsubo cardiomyopathy: Review of broken heart syndrome. *JAAPA.* 2020;33:24-29.
 57. Takotsubo Syndrome [Internet]. American College of Cardiology [cited 2024 Sep 1]; Available from <https://www.acc.org/Latest-in-Cardiology/ten-points-to-remember/2020/03/30/12/17/http%3a%2f%2fwww.acc.org%2fLatest-in-Cardiology%2ften-points-to-remember%2f2020%2f03%2f30%2f12%2f17%2fTakotsubo-Syndrome>
 58. Bietry R, Reyentovich A, Katz SD. Clinical Management of Takotsubo Cardiomyopathy. *Heart Fail Clin.* 2013;9:177-86.
 59. Jha S, Zeijlon R, Enabtawi I, Espinosa AS, Chamat J, Omerovic E, *et al.* Electrocardiographic predictors of adverse in-hospital outcomes in the Takotsubo syndrome. *Int J Cardiol.* 2020;299:43-8.

60. Matta A, Delmas C, Campelo-Parada F, Lhermusier T, Bouisset F, Elbaz M, *et al.* Takotsubo cardiomyopathy. *Rev Cardiovasc Med.* 2022;23:38.
61. Campos MTF de S, Valente FMQ, Araújo RMA, Bressan J. Mourning and Takotsubo cardiomyopathy: neuroendocrine implications and nutritional management. *Rev Assoc Med Bras (1992).* 2018;64:952-9.
62. Li P, Li C, Mishra AK, Cai P, Lu X, Sherif AA, *et al.* Impact of malnutrition on in-hospital outcomes in takotsubo cardiomyopathy. *Nutrition.*2022;93:111495.
63. Olson S. Nutritional Interventions for Preventing and Treating Stress Cardiomyopathy. *Rupa Health* 2024.
64. Read "Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids" at NAP.edu [Internet]. [cited 2024 Sep 1]. Available online: <https://nap.nationalacademies.org/read/10490/chapter/1>
65. Lyon AR, Bossone E, Schneider B, Sechtem U, Citro R, Underwood SR, *et al.* Current state of knowledge on Takotsubo syndrome: a Position Statement from the Taskforce on Takotsubo Syndrome of the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail.* 2016;18:8-27.
66. Templin C, Ghadri JR, Diekmann J, Napp LC, Bataiosu DR, Jaguszewski M, *et al.* Clinical Features and Outcomes of Takotsubo (Stress) Cardiomyopathy. *N Engl J Med.* 2015;373:929-38.
67. Citro R, Radano I, Parodi G, Di Vece D, Zito C, Novo G, *et al.* Long-term outcome in patients with Takotsubo syndrome presenting with severely reduced left ventricular ejection fraction. *Eur J Heart Fail.* 2019;21:781-9.
68. Almendro-Delia M, Núñez-Gil IJ, Lobo M, Andrés M, Vedia O, Sionis A, *et al.* Short- and Long-Term Prognostic Relevance of Cardiogenic Shock in Takotsubo Syndrome: Results From the RETAKO Registry. *JACC Heart Fail.* 2018;6:928-36.
69. Böhm M, Cammann VL, Ghadri JR, Ukena C, Gili S, Di Vece D, *et al.* Interaction of systolic blood pressure and resting heart rate with clinical outcomes in takotsubo syndrome: insights from the International Takotsubo Registry. *Eur J Heart Fail.* 2018;20:1021-30.
70. Izumo M, Nalawadi S, Shiota M, Das J, Dohad S, Kuwahara E, *et al.* Mechanisms of Acute Mitral Regurgitation in Patients With Takotsubo Cardiomyopathy: an echocardiographic study. *Circ Cardiovasc Imaging.* 2011;4:392-8.
71. Ghadri JR, Kato K, Cammann VL, Gili S, Jurisic S, Di VD, *et al.* Long-Term Prognosis of Patients With Takotsubo Syndrome. *J Am Coll Cardiol.* 2018;72:874-82.
72. JL Looi, M Lee, MW Webster, AC Toy, JA Kerr. Postdischarge outcome after Takotsubo syndrome compared with patients after ACS and those without prior CVD: ANZACS-QI 19. *Open Heart.* 2018;5:000918.
73. El-battrawy I, Ansari U, Lang S, Behnes M, Schramm K, Fastner C, *et al.* Impact of left ventricular function management on the prognosis of Takotsubo syndrome. *Eur J Clin Invest.* 2017;47:477-85.