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Review Article

Broken-Heart Syndrome (BHS)—Real or Imagined? Also Known as Takotsubo Syndrome (TS), Tako-Tsubo-Like Left Ventricular Dysfunction, and Takotsubo Cardiomyopathy (TCM). Investigation and Review; the Diagnosis and Treatment of Its Varied Manifestations

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Abstract

Takotsubo syndrome (TS) can be fatal due to its associated complications. Moreover, at this time, studies on the long-term prognosis after surviving the initial TS episode are inconclusive. There seem to be no differences based on age or gender. A significantly lower survival at 3 years was noted compared to the general population.

It has been reported that 1–2% of Asian and Western (mainly Caucasians) populations with suspected acute coronary syndrome (ACS) receive a final diagnosis of TS. In the US, about 6,837 patients were diagnosed with TS in 2008, increasing to 17,864 in 2009. Currently, considering the US and the UK data, 50,000–100,000 patients may be affected annually by TS.

The commonly reported risk factors for TS are tobacco smoking, alcohol consumption, anxiety disorder, and dyslipidemia. Elderly patients are at a high risk for TS and related complications. More than 90% of patients with TS are older than 50 years (65 years by some estimates) with hypertension and other cardiovascular diseases as comorbidities. The TS mortality rate is significantly higher among men than women.

In the 1990s, researchers Sato and Dote characterized takotsubo syndrome as an acute neurogenic-stunned myocardium. Since ACS has similar clinical and electrocardiographic presentations as TS, it is crucial to note that the characteristic finding of TS includes regional left ventricular wall-motion abnormality associated with an atypical circumference to systolic left ventricular ballooning.

Also, nearly one-third of patients with TS may present with a right ventricular abnormality. In most cases, the acute attack of TS is preceded by emotional stressors, such as grief or the death of a loved one. Triggers of TS in specific patients include intracranial hemorrhage, sepsis, pregnancy, and intercourse.

TS demonstrates specific clinical findings in primary TS and secondary TS. In primary TS, the initial symptoms are cardiac conditions. In secondary TS, the cardiac conditions manifest in patients already hospitalized for other medical or surgical reasons. Secondary TS typically occurs in elderly, postmenopausal women hospitalized for other medical or surgical indications.

TS comprises a complex pathophysiology due to the body's response to a sudden increase in endogenous catecholamine levels. Genetic predisposition for TS focuses on the α1-, β1-, and β2-adrenergic receptors, GRK5, and estrogen receptor genes. Cardiac biomarkers, ECG, coronary angiography, ECHO, MRI, and radionuclide imaging are standard investigative tools in TS.

Although TS can resolve spontaneously, complications include acute heart failure, left ventricular outflow tract obstruction, mitral regurgitation, cardiogenic shock, arrhythmias, thrombi, pericardial effusion, ventricular wall rupture, and right ventricular involvement.

TS or broken heart syndrome is genuine, not simply a psychosomatic phenomenon that will wane with time or solely psychotherapy—having a specific pathophysiology and clinical features, which need to be addressed medically.

Keyword: *Congenital Heart Disease; Echocardiography; Device Closure of Septal Defect*

Abbreviations

ACS: Acute Coronary Syndrome; AMI: Acute Myocardial Infarction; ARB: Angiotensin II Receptor Blocker; AV: Atrioventricular; BB: Beta-Blocker; BHS: Broken Heart Syndrome; BNP: Brain-Type Natriuretic Peptide; CAD: Coronary Artery Disease; CTA: Computed Tomography Angiography; ECG: Electrocardiogram; ECHO: Echocardiography; EKG: Electrocardiogram; ECMO: Extracorporeal Membrane Oxygenation; HPA: Hypothalamic-Pituitary-Adrenal; LBBB: Left Bundle Branch Block; LV: Left Ventricular; LVEF: Left Ventricular Ejection Fraction; LVOTO: Left Ventricular Outflow Tract Obstruction; LVWMA: Left Ventricular Wall-Motion Abnormality; MI: Myocardial Infarction; MIBG: Iodine-123 Metaiodobenzylguanidine; MRI: Magnetic Resonance Imaging; NIS-USA: Nationwide Inpatient Sample in the US; NSTEMI: Non-ST-Segment Elevation Myocardial Infarction; NT-proBNP: N-Terminal Pro-B-Type Natriuretic Peptide; STEMI: ST-Elevation Myocardial Infarction; TS: Takotsubo Syndrome

Introduction

In the 1990s, Sato and Dote characterized broken heart syndrome (BHS) or takotsubo syndrome (TS) as an acute neurogenic-stunned myocardium. In the Japanese language, *tako* means octopus, and *tsubo* means pot [1–3]. BHS or TS is actual: the condition has a well-defined pathophysiological etiology, well-documented diagnostic criteria, and recognized treatment options.

The condition was first acknowledged in five patients presenting with clinical features of myocardial infarction (MI) in the absence of obstructive coronary artery disease (CAD). Although TS and acute coronary syndrome (ACS) have similar clinical and electrocardiographic presentations, the characteristic finding of TS includes regional left ventricular wall-motion abnormality (LVWMA) associated with an atypical circumference, leading to systolic left ventricular (LV) ballooning [1–3].

The distinctive LVWMA involves the region supplied by the coronary artery, and the apical, mid-apical, mid-ventricular, basal, or mid-basal areas may be affected. Resolution of ventricular dysfunction can result in reversing the symptoms within hours or weeks of pre-

sentation. In addition to the above-mentioned anatomical sites, focal or global involvement of the LV contractile tissue has been reported [4,5].

Discussion

Nearly one-third of patients with TS may present with right ventricular abnormality [6]. In most (~70%) cases, the acute attack is preceded by emotional stressors, such as grief or the death of a loved one [4,7].

Physical triggers include underlying diseases, such as intracranial hemorrhage and sepsis; physiological events, including pregnancy and intercourse, can also precipitate TS in specific patients [8].

Primary and secondary TS are subsets of the syndrome [9]. In primary TS, the initial presenting symptoms are cardiac conditions. In secondary TS, the cardiac conditions manifest in patients hospitalized for other medical or surgical reasons. Since its first description as a distinct medical condition, several reports regarding TS have been published internationally [2]. The condition has been reported in different ethnic groups; however, it is considered rare among the African American and Hispanic populations [10,11].

About 2% of patients with ACS are described as having TS [12]. Lack of knowledge regarding the disease could cause low actual prevalence, although improved awareness and easier access to specialized investigative approaches, such as coronary angioplasty, have led to enhanced diagnostic frequency [13,14].

Clinical categorization of TS

Primary TS

Patients with primary TS typically present with cardiac symptoms that may or may not be associated with identifiable triggers (both physical and emotional) [15–17]. Other comorbidities in such patients are not the reason for increased catecholamine levels. Management of the condition is based on complications.

Secondary TS

As mentioned earlier, secondary TS typically occurs in patients, especially elderly, postmenopausal women [17], already hospitalized for other medical or surgical conditions [15–17]. In these patients, the triggers include sudden overactivity of the sympathetic nervous system and subsequent increase in catecholamine levels. Treatment is principally aimed at managing the complications and precipitating factors.

Anatomical variants of TS

There are several anatomical variants of TS. The first documented TS case is considered the classical pattern—with characteristic LVWMA, apical and circumferential midventricular hypokinesia, and basal hypercontractility. In the classical pattern, at the end of systole, the LV appears like a *takotsubo* (an octopus pot with a narrow neck and round lower part), leading to apical ballooning. The majority (50–80%) of patients with TS demonstrate apical dysfunction [18–20].

The two other common variants, in addition to the classical pattern, are the inverted takotsubo (or the basal variety; the "nutmeg" or the "artichoke" variety) and the mid-LV MLV abnormality. In both variants, the LV dysfunction appears to affect several cardiac areas in a circumferential pattern in the absence of CAD. TS with biventricular apical dysfunction without the apical tip and the isolated right ventricular TS are other rare manifestations of the disease [21–23]. The affected LV segments have a variable recovery trend. Moreover, affected individuals are susceptible to recurrence with a different anatomical variant of the condition, affecting other LV segments [23,24].

Epidemiology of TS

About 1–2% of Asian and Western (mainly Caucasians) populations with suspected ACS receive a final diagnosis of TS [25,26]. Per the Nationwide Inpatient Sample in the US (NIS-USA), about 6,837 patients were diagnosed with TS in 2008 [27], increasing to 17,864 in 2009 [28]. During 2008–2009, most affected patients were women (89%), with a mean age of 66.9 ± 30.7 years [28].

Currently, 50,000–100,000 patients may be affected annually both in the US and the UK. The commonly reported risk factors for TS are tobacco smoking, alcohol consumption, anxiety disorder, and dyslipidemia.

Gender predisposition in TS

The condition is predominantly described in postmenopausal women. Per the German TS registry, among the 324 patients with TS, 91% were women (mean age, 68 ± 12 years), and 9% were men (mean age, 66 ± 12 years). Although demographic and presenting symptoms are similar between the genders, the absence of precipitating factors or the presence of emotional triggers is more common among women [29].

Physical stressors, such as shock and high troponin levels, are more commonly reported in men with TS. Per the NIS-USA, the TS mortality rate is significantly higher among men than women (8.4% vs. 3.6%, $P < 0.0001$), indicating the increased frequency of secondary TS in this population [28].

Age predisposition in TS

Elderly patients are at a high risk of TS and related complications. More than 90% of patients with TS are older than 50 years [27–30]. Per the Takotsubo Italian Network, patients with TS are typically older than 65 and have hypertension and other cardiovascular diseases as comorbidities. These statistics infer that the elderly population is at an increased risk of complications and mortality rates from TS [31].

Pathophysiology of TS

The pathophysiology of TS is a complex phenomenon, reflecting the integrated and systemic physiological cardiovascular response to a sudden increase in endogenous catecholamine levels [32,33]. Catecholamine levels can be disrupted when the brain and hypothalamic-pituitary-adrenal (HPA) axis do not adequately regulate the amount of the hormone released into the system in response to stress.

The cardiovascular system—involving the myocardium, coronary arteries, and the peripheral vessels—reacts to the sudden increase in circulating catecholamine levels, leading to TS. The serum catecholamine is significantly higher in patients with TS than in patients with acute MI (AMI). Also, the level may be considerably higher than the baseline values in the same patient [34]. There have been iatrogenic cases of TS following the administration of sympathomimetic drugs, such as dobutamine, during stress echocardiography [34].

Several vascular and myocardial hypotheses have been put forth to explain the characteristic features of TS and the responses of the cardiovascular system to stress. As such, none of them have been established equivocally, implicating more than one factor and mechanism in the etiology of the syndrome.

Genetic predisposition in TS

Stress is an influential precipitating factor of TS. Specific genetic characteristics could predispose an individual to TS. Although not primarily considered a genetic cardiomyopathy, several studies have investigated the contribution of genes to TS etiology [35,36]. The α1-, β1-, and β2-adrenergic receptors, GRK5, and estrogen receptor genes have been implicated, albeit arguably [35,36]. A conspicuous limiting factor of the genetic studies was the limited sample sizes.

Clinical findings of TS

Primary TS

Postmenopausal women with an immediate past episode of severe emotional or physical stress are typically examined for TS. In some cases, the diagnosis is established with the background of anxiety or acute panic attack [27,29]. However, it may also affect those with no history of stress. These patients are usually younger. About 30–35% of the case reports and case series reports have identified the absence of an identifiable triggering factor in these individuals [27].

The typical presenting symptoms are acute-onset chest pain of cardiac origin, respiratory distress, and palpitation; in severe cases, syncope due to tachyarrhythmias or cardiac shock may occur. Patients typically describe the symptoms as increasing chest tightness and pressure radiating from the chest to the neck and finally to the head, anxiousness, and impending sense of doom.

Prompt clinical evaluation, 12-lead electrocardiogram (ECG), echocardiography (ECHO), and immediate coronary angioplasty aid in diagnosis. In patients with stable disease, mainly those with typical TS features, as revealed by echocardiography, computed tomography angiography (CTA) is considered [37]. Cardiac imaging and assessment of cardiac markers help exclude AMI and support a TS diagnosis.

Secondary TS

TS (in this case, secondary TS) can be precipitated in acute medical and surgical scenarios, even during specific elective non-cardiac procedures. It can also manifest following the administration of dobutamine during stress echocardiography. Importantly, clinicians must be aware of the various presenting features of TS under different clinical settings.

Summary of primary and secondary TS

TS can often be fatal, primarily due to associated complications. The majority of the complications are identified on post-mortem examination of patients with confirmed TS. However, the diagnosis of TS remains elusive in sudden cardiac death in non-hospitalized patients with normal heart and coronary arteries [38]. These cases are of medico-legal importance, mainly when death occurs during restraint in police custody or psychiatry wards.

Investigation of TS

Cardiac biomarkers

Cardiac troponin, as determined by a conventional assay, is increased in > 90% of the patients with TS. However, serum troponin or creatinine kinase level is disproportionately low concerning cardiac dysfunction [30].

In the acute phase of TS, brain-type natriuretic peptide (BNP) or N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels are constantly elevated, indicating the extent of damage to the ventricular wall-motion [39].

Evidence regarding biomarkers in the development and manifestation of TS is limited. However, the diagnostic importance of BNP and NT-proBNP measurement compared to the measurement of troponin in suspected acute cases of TS is well established. High BNP and NT-proBNP levels are considered essential for TS diagnosis. NT-proBNP is regarded as a valuable prognostic marker; a low NT-proBNP level at admission indicates a favorable prognosis and has been incorporated in the risk stratification criteria for TS.

Serum catecholamines (adrenaline, noradrenaline, and dopamine), neuropeptide-Y, and serotonin levels are also likely to be elevated in TS; however, these markers are not tested in conventional clinical settings [34].

Moral., *et al.* (2009) referred to several studies indicating that catecholamine levels at admission are characteristically high (at least 2–3 times from the baseline value) in patients with TS than in those with AMI [40], although a few studies have reported otherwise.

In one specific study, the researchers pointed out that the circulating micro-RNA levels served as a significant marker in TS [40]. The finding suggests a different pathogenesis for TS and the potential for the development of new diagnostic tests.

Electrocardiogram (ECG)

Abnormal electrocardiogram (ECG) findings are common, especially in the acute phase of TS (in > 95% of the patients) [30,41]. Worsening of serial ECG findings, especially of the QT interval, is vital for risk stratification and differentiating TS from ST-elevation myocardial infarction (STEMI). However, ECG alone is not adequate to differentiate TS from STEMI [42,43].

Acute-phase ECG abnormalities include elevation of ST segment, depression of ST segment, new onset of left bundle branch block (LBBB), Q waves, deep and widespread inversion of the T wave, and prolongation of the QT segment within 24–48h of symptom onset [42,43].

In patients with delayed presentation, inversion of the T wave and QTc prolongation in the absence of ST-segment elevation is noted. Pronounced QTc prolongation may predispose patients to torsades de pointes and ventricular fibrillation [29].

TS is differentiated from STEMI, in which QTc prolongation is rarely seen. ECG findings can be normal in a small proportion of patients with TS. Thus, careful evaluation of the condition is indicated.

Coronary angiography

Clinical presentation of TS is similar to STEMI and non-ST-segment elevation myocardial infarction (NSTEMI), and coronary angiography is used to exclude these conditions. Characteristically, the epicardial coronary arteries function normally and remain unobstructed in patients with TS. However, in elderly patients, co-existing coronary artery disease (CAD) can also be present. In such cases, it must be decided if CAD alone has caused LV dysfunction. Several studies have reported co-existing CAD in 10% of the patients with TS [44,45]. CAD may not precipitate TS; however, heart failure cannot be ruled out in acute onset.

An intravascular ultrasound study revealed that plaque rupture and intracoronary thrombosis are rare in TS [46]. Ventriculography should be performed for confirmation of TS diagnosis, especially during the acute stage. The reason for this investigation is that wall-motion abnormalities might recover completely, and diagnosis missed if ventriculography is delayed.

In TS, the characteristic wall-motion abnormality includes apical and mid-wall hypokinesis (from which the name "Takotsubo" is termed). However, it should be noted that apart from the classical pattern of wall-motion abnormality, other patterns of wall-motion abnormalities can occur in TS.

Echocardiography (ECHO)

Transthoracic Doppler echocardiography (ECHO) should ideally be the first non-invasive diagnostic test in suspected cases of TS. ECHO can evaluate LV morphology, its function, and wall-motion abnormality, if any. It can also detect complications, such as mitral regurgitation, right ventricular involvement, thrombus formation, and cardiac rupture (in extreme cases). This approach can be used to monitor the course of the disease [47].

In the acute phase of TS, the main echocardiographic findings include a large area of dysfunctional myocardium extending beyond the supplying area of a single coronary artery and symmetrical abnormalities affecting the mid-ventricular regions in the anterior, inferior, and lateral walls in a circumferential pattern [47].

Per the Takotsubo Italian Network, left ventricular ejection fraction (LVEF), the severity of the mitral regurgitation, and age > 75 years are independent risk factors for significant complications associated with TS [48].

Magnetic resonance imaging (MRI)

Magnetic resonance imaging (MRI) of the heart reveals characteristic anatomical defects typical for TS and helps distinguish the condition from other cardiac conditions. It also helps elucidate the cause of and pathophysiological changes associated with TS [49].

This diagnostic approach also helps assess left and right ventricular function and the characteristic LVWMA. In many patients with TS, the right ventricle is also affected with or without LV involvement [49]. Moreover, cardiac MRI is a better diagnostic tool than ECHO to detect apical LV thrombi; MRI is beneficial when ECHO is unclear, especially in patients with apical akinesia [49].

Depending on availability, cardiac MRI must be performed in all patients with suspected TS, especially during the acute phase (during the initial seven days of presentation). If availability is limited, MRI should be reserved for indeterminate cases. Thus, MRI plays an indispensable role in confirming the diagnosis, assessing the recovery, monitoring during the follow-up period, and excluding other cardiac conditions that mimic TS symptoms.

Computed tomography angiography (CTA)

Coronary artery occlusion and coronary stenosis must be excluded before confirming the diagnosis of TS. Computed tomography angiography (CTA) can also be performed to diagnose TS with symptoms mimicking MI [10,16].

Radionuclide imaging

The role of radionuclide imaging in the diagnosis and management of TS remains unexplored. In the absence of cardiac MRI, myocardial perfusion scintigraphy helps exclude infarction in some instances [50,51]. Iodine-123 meta-iodo-benzyl-guanidine (MIBG) is used in radionuclide imaging to assess the myocardial nerve terminal activities and detect pheochromocytoma (both of adrenal or ectopic origin).

When performed in the acute phase, MIBG uptake is reduced in the affected myocardial areas, consistent with the sympathetic nervous system's disrupted functioning [50,51]. The sympathetic disturbance may persist for months; thus, the MIBG uptake study can help confirm delayed TS presentation (beyond the acute phase).

Complications of TS

The condition resolves spontaneously without any long-term sequelae in most patients. However, growing evidence suggests that long-term complications arise in nearly 52% of patients with TS [48,49]. The commonly reported complications are described as follows.

Acute heart failure

Systolic heart failure is the most common complication in the acute phase of TS, affecting 12-45% of the patients [10,16,48,49].

Left ventricular outflow tract obstruction

In the acute phase of TS, about 10–25% of the patients may develop LV outflow tract obstruction (LVOTO), with a pressure gradient of 20–140 mmHg, along with mitral regurgitation [10,16,48]. In some patients, the complication may resolve spontaneously [10,16].

Mitral regurgitation

Mitral regurgitation is a fatal TS complication, affecting about 14–15% of affected patients [10,16]. Once the LV function returns to normal, mitral regurgitation also normalizes. However, recovery is delayed in patients with acute onset of mitral regurgitation with TS [50,52].

Cardiogenic shock

Acute-onset LV dysfunction can lead to cardiogenic shock in about 4–20% of the patients. The shock may be precipitated in the presence of other co-existing cardiac conditions, such as acute mitral regurgitation, LVOTO, and involvement of the right ventricle. Co-existing cardiogenic shock can increase TS mortality rate by 17–30% [10,16,50,52].

Arrhythmias

Arrhythmias are a common TS complication. New-onset atrial fibrillations are detailed in 5–15% of patients with TS [16]. In rare cases, ventricular arrhythmias can also occur weeks after the initial TS attack despite the normalization of LV function. Other arrhythmia-related complications of TS include bradycardia, atrioventricular (AV) block, and asystole [16].

Thrombi

In about 2–8% of patients, there may be a thrombus in the akinetic apex, further complicating the condition by precipitating cerebrovascular stroke and arterial embolism [16,53]. Diagnostic cardiac MRI is the preferred modality to identify apical thrombus in the acute phase, usually within 2–5 days after the attack. As such, prophylactic anticoagulant therapy, especially in high-risk patients, is recommended.

Pericardial effusion

Acute-onset pericardial effusion is expected during the recovery phase of TS, whereas pericardial tamponade is rare [54].

Ventricular wall rupture

Although life-threatening complications, such as rupture of the ventricle or perforation of the interventricular septum, are rare, they can occur in > 1% of patients with TS [16,55]. Typically, such complications occur within 2–8 days after the acute attack [55].

Right ventricular involvement

In severe cases, both the right and left ventricles can be affected (18–34%). Increasing age, lower LVEF, and pleural effusion could serve as the precipitating factors [16].

Prognosis of TS

Data on long-term prognosis after surviving the initial TS episode are meager and conflicting. In two studies exploring the long-term survival of patients with TS, there were no differences based on age or gender [56,57]. However, two other studies summarized that patients with TS had a significantly lower survival at 3 years than the general population [16,56,57].

The SWEDEHEART registry described similar 3-year mortality rates between NSTEMI and STEMI control subjects. These findings are in line with findings from the INTER-TAK registry [16,58]. TS mortality rates are typically higher in the initial 4 years after the first attack [58].

The majority of the patients recover rapidly after the initial attack; however, physiological malfunctioning may persist after macroscopic recovery of cardiac contractility in some patients. Specific patients may have persistent chest pain, respiratory distress, and palpitation, possibly due to increased sympathetic activity [58].

Despite the recovery of coronary artery and ventricular functions, it is essential to assess cardiac function regularly to reassure the patient and coordinate treatment decisions.

Monitoring, using a 24-h Holter ECG, reveals cardiac arrhythmia or sinus tachycardia. The 24-hour ambulatory blood pressure measurement identifies sudden and short-lasting hypertensive episodes. However, long-term follow-up studies for TS are lacking, warranting extensive research [58].

Management of TS

Treatment of precipitating or predisposing conditions

TS is often precipitated by physical stressors, including medical or surgical conditions, such as intracranial hemorrhage, chronic obstructive pulmonary disease, and pheochromocytoma [16,59]. Many studies have supported these findings [10,16]. Co-existing medical and surgical indications could be the reason for increased mortality among patients with TS [60]. In patients with undiagnosed pheochromocytoma, repeat TS attacks are common [10,16]. Competent diagnosis and appropriate management of precipitating diseases and other co-existing conditions are of utmost importance to improve prognoses and prevent subsequent attacks in affected patients.

Acute stage

TS involving LVWMA typically demonstrates spontaneous resolution within weeks from onset. Thus, in the acute stage of the disease, supportive therapy and complications management are mainstays [10,16,61].

There are no approved and established guidelines for managing TS. In patients with mild disease, supportive therapy can be augmented with beta-blockers or aspirin [62]. In patients with co-existing congestive heart disease, conventional heart failure drugs, such as angiotensin-converting enzymes (ACEs), angiotensin II receptor blockers (ARBs), beta-blockers (BBs), and diuretics are preferred [10,16,62]. As such, beta-blockers deserve special mention as they theoretically have a protective action against cardiac rupture [62,63].

Other co-existing cardiac conditions, such as arrhythmias, should be managed with anti-arrhythmic drugs [10,16]. Thromboembolism is a serious TS complication [63]. For TS with apical ballooning and LV thrombi or a co-existing embolism, anticoagulant drug therapy is advised for 2-3 months or until the LVWM abnormality is resolved, as confirmed by ECHO [63].

Cardiogenic shock

Cardiogenic shock is a fatal complication of TS [10,16]. It is essential to identify if the LVOTO or primary pump failure has caused hypotension in the presenting patient [64].

For LVOTO with mitral regurgitation, catecholamines, such as adrenaline, noradrenaline, dopamine, and ionotropic drugs (e.g., isoproterenol), are contraindicated. Diuretics and nitroglycerines are also contraindicated due to the risk of LVOTO deterioration. In the case of TS associated with LVOTO, intravenous fluid administration and parenteral beta-blocker therapy are advocated [65].

In the event of primary pump failure, extracorporeal membrane oxygenation (ECMO) or LV assist device may facilitate recovery [10,16]. Catecholamine-based inotropes must be avoided in primary pump failure, but non-catecholamine inotropic agents, such as levosimendan and pimobendan, can be beneficial [66].

Treatment after discharge

Published literature reveals a lack of randomized trials for long-term therapy for TS. Data obtained from observational studies suggest that ACE inhibitors and ARBs may increase survival up to one year after the initial TS attack. Such benefits are not reported following the use of beta-blockers [10,16].

In TS patients with thromboembolism, warfarin therapy should be maintained until resolution of wall-motion abnormality. Moreover, it is vital to manage precipitating conditions and other co-existing diseases to enhance survival and prevent future TS episodes.

Besides cardiologists, emergency medicine specialists and critical care specialists will likely confront TS as affected people often seek emergency care—except for secondary TS when the symptoms appear in an already-hospitalized patient. Despite the detailed role of psychological stress in the precipitation of TS, there is sparse research supporting the role of psychiatrists in managing these patients [67].

Conclusion

Researchers Sato and Dote, in the 1990s, characterized takotsubo syndrome (or broken heart syndrome) as an acute neurogenic-stunned myocardium. ACS has similar clinical and electrocardiographic presentations as TS. However, the characteristic finding of TS is regional LVWMA associated with an atypical circumference, leading to systolic LV ballooning.

Nearly one-third of patients with TS present with right ventricular abnormality [6]. In most cases, the acute attack is preceded by emotional stressors, such as grief or the death of a loved one. Triggers of TS in specific patients include intracranial hemorrhage, sepsis, pregnancy, and intercourse.

Primary and secondary TS are subsets of the syndrome. In primary TS, the initial symptoms are cardiac conditions. In secondary TS, the cardiac conditions manifest in patients already hospitalized for other medical or surgical reasons. Secondary TS typically occurs in elderly, postmenopausal women hospitalized for other medical or surgical indications.

About 1–2% of Asian and Western (mainly Caucasians) populations with suspected ACS receive a final diagnosis of TS. In the US, about 6,837 patients were diagnosed with TS in 2008, increasing to 17,864 TS-diagnosed patients in 2009. Currently, 50,000–100,000 patients may be affected annually in the US and the UK. The commonly reported risk factors for TS are tobacco smoking, alcohol consumption, anxiety disorder, and dyslipidemia. The TS mortality rate is significantly higher among men than women.

Elderly patients are at a high risk of TS and related complications. More than 90% of patients with TS are older than 50 years (65 years by some estimates), having hypertension and other cardiovascular conditions as comorbidities.

TS's pathophysiology is a complex phenomenon, reflecting the integrated and systemic physiological cardiovascular response to a sudden increase in endogenous catecholamine levels. Genetically, the α1-, β1-, and β2-adrenergic receptors, GRK5, and estrogen receptor genes have been implicated. TS demonstrates specific clinical findings in primary TS and secondary TS.

Investigation of TS includes cardiac biomarkers, ECG, coronary angiography, ECHO, MRI, and radionuclide imaging. Although TS can resolve spontaneously, complications include acute heart failure, left ventricular outflow tract obstruction, mitral regurgitation, cardiogenic shock, arrhythmias, thrombi, pericardial effusion, ventricular wall rupture, and right ventricular compromise.

Examinations into the long-term prognosis after surviving the initial TS episode are inconclusive at this time. However, there appear no differences based on age or gender, and a significantly lower survival at 3 years was noted compared to the general population. Importantly, TS can often be fatal due to its associated complications. TS is a definite and significant medical condition in need of diagnosis and

treatment. TS may not necessarily diminish over time if left untreated or if soley treated with psychotherapy. Takotsubo syndrome (also known as tako-tsubo-like left ventricular dysfunction, takotsubo cardiomyopathy, or broken heart syndrom) has a specific pathophysiology and clinical features.

Conflict of Interest Statement

The authors declare that this paper was written in the absence of any commercial or financial relationship that could be construed as a potential conflict of interest.

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