


Takotsubo Syndrome: Cardiotoxic Stress in the COVID Era

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Abstract

Takotsubo syndrome (TTS), also known as stress cardiomyopathy and broken heart syndrome, is a neurocardiac condition that is among the most dramatic manifestations of psychosomatic disorders. This paper is based on a systematic review of TTS and stress cardiomyopathy using a PubMed literature search. Typically, an episode of severe emotional or physical stress precipitates regions of left ventricular hypokinesis or akinesis, which are not aligned with a coronary artery distribution and are out of proportion to the modest troponin leak. A classic patient with TTS is described; one who had chest pain and dyspnea while watching an anxiety-provoking evening news program on the coronavirus disease 2019 (COVID-19) pandemic. An increase in the incidence of TTS appears to be a consequence of the COVID-19 pandemic, with the TTS incidence rising 4.5-fold during the COVID-19 pandemic even in individuals without severe acute respiratory syndrome coronavirus 2 infection. Takotsubo syndrome is often mistaken for acute coronary syndrome because they both typically present with chest pain, electrocardiographic changes suggesting myocardial injury/ischemia, and troponin elevations. Recent studies report that the prognosis for TTS is similar to that for acute myocardial infarction. This review is an update on the mechanisms underlying TTS, its diagnosis, and its optimal management.

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 On April 2, 2020, a 56-year-old woman with a history of hypertension and migraines presented with acute neck and jaw tightness with dyspnea while watching an evening news program highlighting the coronavirus disease 2019 (COVID-19) pandemic. She admitted to feeling extremely anxious and frightened by the reports and associated images of the COVID-19 pandemic. She presented to the hospital 17 hours after symptom onset; her initial blood pressure was 96/57 mm Hg, and the electrocardiogram (ECG) in the emergency department revealed ST and T-wave abnormalities suggesting acute coronary syndrome (ACS) (Figure 1A). The initial troponin-I level was 1.91 ng/mL, and the N-terminal prohormone of brain natriuretic peptide (NT-proBNP) level was 3261 pg/mL. Urgent cardiac catheterization revealed normal coronary arteries without stenosis or coronary dissection. The echocardiogram revealed a left ventricular (LV) ejection fraction (LVEF) of 39%, with extensive akinesis in the apical

and mid LV segments with hyperkinesis of the basal segments (Figure 1B and C), dynamic LV outflow tract obstruction (LVOTO) with a peak gradient of 51 mm Hg, and systolic anterior motion of the mitral leaflets. Symptoms resolved during the first few hours of hospitalization, and no arrhythmias occurred. She received a diagnosis of Takotsubo syndrome (TTS) and was discharged with prescription of metoprolol and apixaban. A follow-up echocardiogram 1 month later was entirely normal, with LVEF 75% and resolution of all previous anomalies including wall motion abnormalities, systolic anterior motion, and dynamic outflow tract gradient.

Coronavirus disease 2019 continues to infect millions of people around the world, with catastrophic rates of morbidity and mortality. These adverse physical health effects are compounded by social, economic, and cultural disruptions that in conjunction have markedly increased levels of psychological stress and anxiety worldwide.¹ During the COVID-19 pandemic, the incidence of TTS

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ARTICLE HIGHLIGHTS

- Takotsubo syndrome (TTS) is a stress-mediated syndrome that results from catecholamine-induced metabolic myocardial stunning.
- Although considered benign and self-limited, TTS has a prognosis similar to acute coronary syndrome.
- Treatment strategies to support patients with acute TTS and improve prognosis are outlined.
- Presently, no therapy has been proven to prevent the recurrence of TTS.

has risen 4.5-fold (Figure 2).² All the patients in the study by Jabri et al² who received a diagnosis of TTS during the pandemic had negative reverse transcription–polymerase chain reaction test results for COVID-19. Thus, the reported increase in TTS during the pandemic in this Cleveland Clinic study has been presumably caused by increased emotional stress, not physiological stress due to severe acute respiratory syndrome coronavirus 2 infection.² However, acute severe acute respiratory syndrome coronavirus 2 infection has also been reported to cause TTS.³

This paper is based on a systematic review of TTS and stress cardiomyopathy using a PubMed literature search. Takotsubo syndrome has become a relatively common diagnosis within cardiovascular physician practices. It is characterized by transient LV systolic and diastolic dysfunction in the absence of a culprit coronary artery lesion, usually with a concomitant mid LV and apical wall motion abnormalities.^{4,5} Also known as broken heart syndrome, apical ballooning syndrome, and stress cardiomyopathy, TTS was first described in Japan in 1990.⁶ Because of the similarities in presenting symptomatology, ECG findings, and troponin elevations, TTS often mimics ACS.⁴ The original association and characteristic hallmark of this disease process, however, is its frequent association with psychosocial stress (PSS) and the lack of obstructive coronary artery disease to explain the clinical presentation.

Stress, both PSS and physiological stress, can disturb normal neurohormonal cardiac regulation and is not only the usual cause of

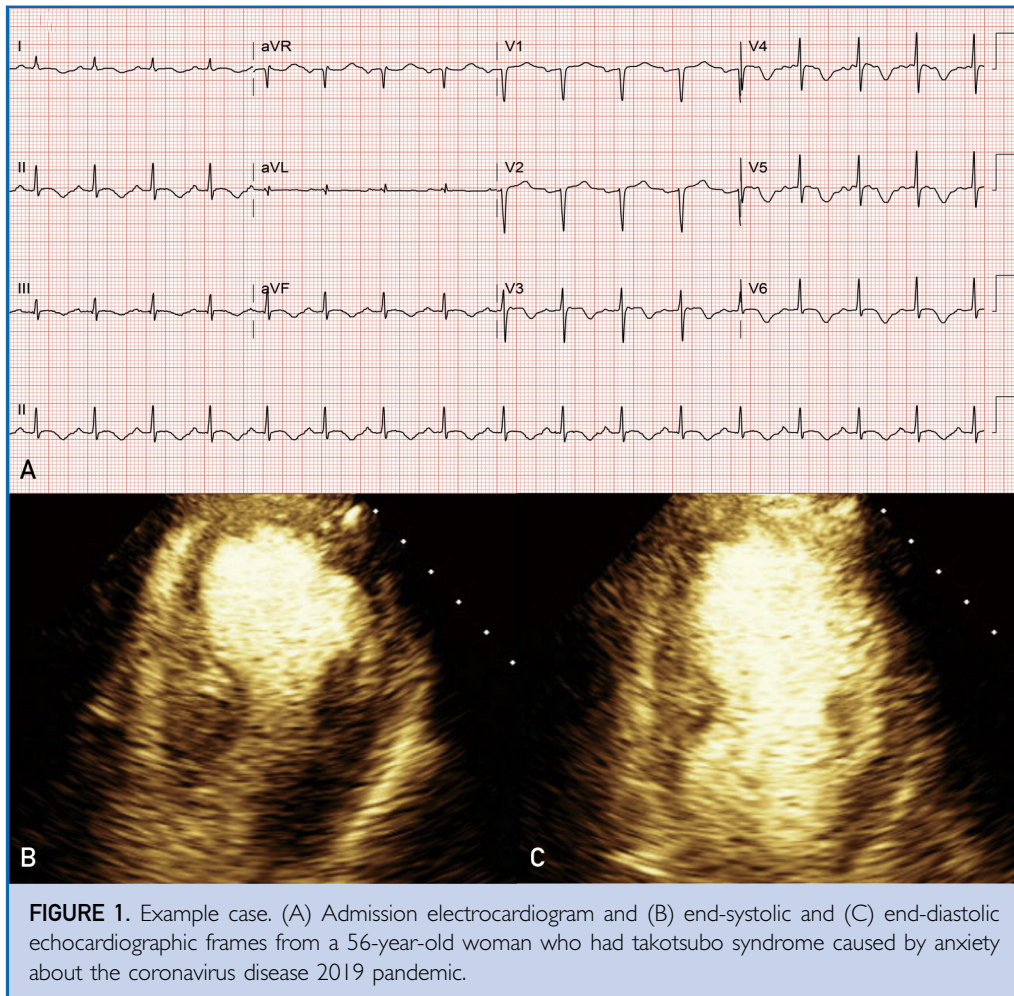
TTS but also the third most potent risk factor for acute myocardial infarction (MI).^{7,8} Since its initial description, the association of TTS with PSS has been a fundamental aspect of the syndrome, as attested to by the large proportion of patients with TTS who have received a diagnosis of a concomitant acute psychosocial stressor, neurological or psychiatric disorder.^{5,9} Takotsubo syndrome is a prototypical psychosomatic disorder in which excessive adrenergic tone from either endogenous or exogenous sympathomimetic amines and other neurohormonal derangements overwhelm myocardial homeostasis, causing acute LV dysfunction (Figure 3).^{10,11} This can result in hemodynamic instability, atrial and ventricular arrhythmias, acute heart failure (HF), and even shock due to acute LV dysfunction and profound vasodilation.⁴

Studies report serious in-hospital adverse events in 20% of patients with TTS, with estimates of in-hospital mortality of about 2.0% to 5.6%¹² and rates of major adverse cardiovascular and cerebrovascular events (MACCEs) ranging from 5% to 10%.^{5,13} However, the true global burden of TTS remains uncertain, stemming from a lack of physician awareness, difficulty in diagnosis, atypical and variable presentations, and resemblance to ACS.

RECOGNIZING TTS

Over the past 3 decades, the predominantly affected demographic has remained women, who comprise 85% to 90% of cases.^{5,13,14} Women older than 55 years have a 5-fold higher incidence of developing TTS than do those younger than 55 years, and women have a 10-fold higher risk than do men.¹⁵⁻¹⁷

Despite making up only 0.02% of hospitalizations, TTS is thought to account for about 2% of all suspected ST-segment elevation MIs (STEMIs) and up to 10% of suspected STEMIs in women.^{16,18-20} This overlap is due to the clinical resemblance of the 2 conditions; 76%, 47%, and 8% of patients with TTS are admitted for symptoms of chest pain, dyspnea, and syncope, respectively.⁵ As awareness has increased, so has the rate of TTS diagnosis, growing from 0.16% in 2005 to 2.2% of all MIs in 2012.²⁰

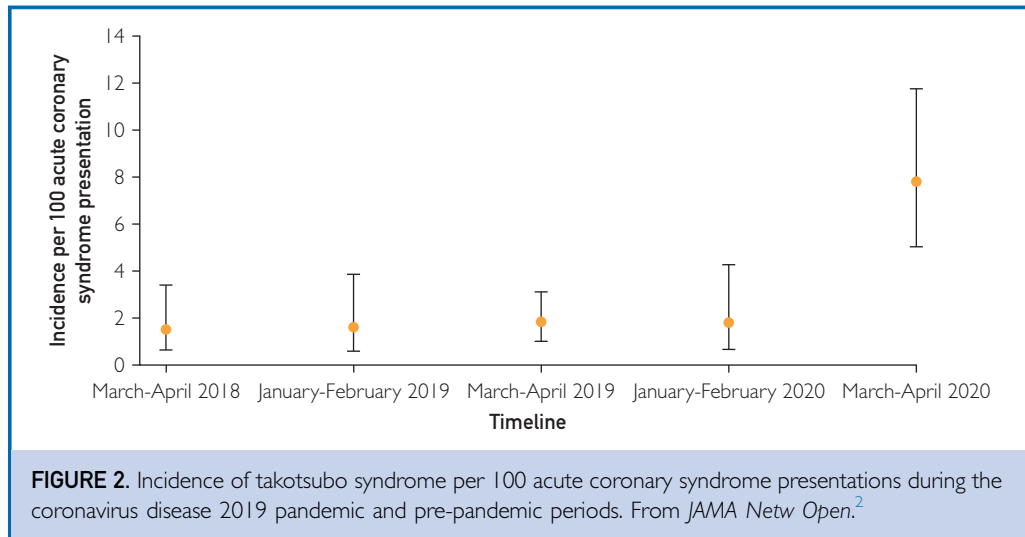


CLINICAL FINDINGS

Most TTS cases involve the apical and mid-ventricular segments—which often mimic STEMI because of left anterior descending coronary artery occlusion.^{5,21} In a meta-analysis of 4500 patients with TTS, most presented with an abnormal ECG, including 44% with ST-segment elevation and 15% with ST-segment depression²¹; progressive QT interval prolongation was also common.²² Among patients with TTS, 91% exhibit attenuation of ECG voltage (due to transient myocardial edema), with return to normal voltage by 1 month.²³ T-wave inversion is also commonly seen in TTS and is paradoxically associated with a reduced risk of ventricular tachycardia and ventricular fibrillation.²⁴ Less surprisingly, patients with TTS who have a rhythm

other than sinus rhythm are at increased risk of MACCEs.²⁴

Troponin elevations are present in about 90% of patients with TTS and reach a mean peak value of 1.1 ng/mL.⁵ Although initial troponin levels are similar in patients with ACS and patients with TTS, the subsequent levels climb 6-fold in patients with ACS as compared with only 1.8-fold in patients with TTS. Because of the ambiguous clinical presentation of TTS, generally in the context of troponin elevations and ST and/or T wave changes suggesting ischemia or MI, coronary angiography is often required for distinguishing TTS from ACS.²⁵ A minority (15%) of patients with TTS will have occlusive coronary artery disease on angiography, but usually this does not explain the distribution of wall motion



abnormalities.⁵ A well-described feature of TTS, however, is that striking wall motion abnormalities and degree of LV dysfunction are out of proportion to the troponin elevation and do not correspond to a typical coronary artery distribution.^{4,26} Cardiac magnetic resonance imaging (MRI) may be required to differentiate between ACS, TTS, and other potential etiologies such as myocarditis.^{23,27} Indeed, cardiac MRI is arguably the “criterion standard” for the diagnosis of TTS owing to its ability to reveal characteristic myocardial edema and no late gadolinium enhancement. By way of comparison, MRI in acute MI typically reveal late gadolinium enhancement in a typical coronary distribution.^{23,27}

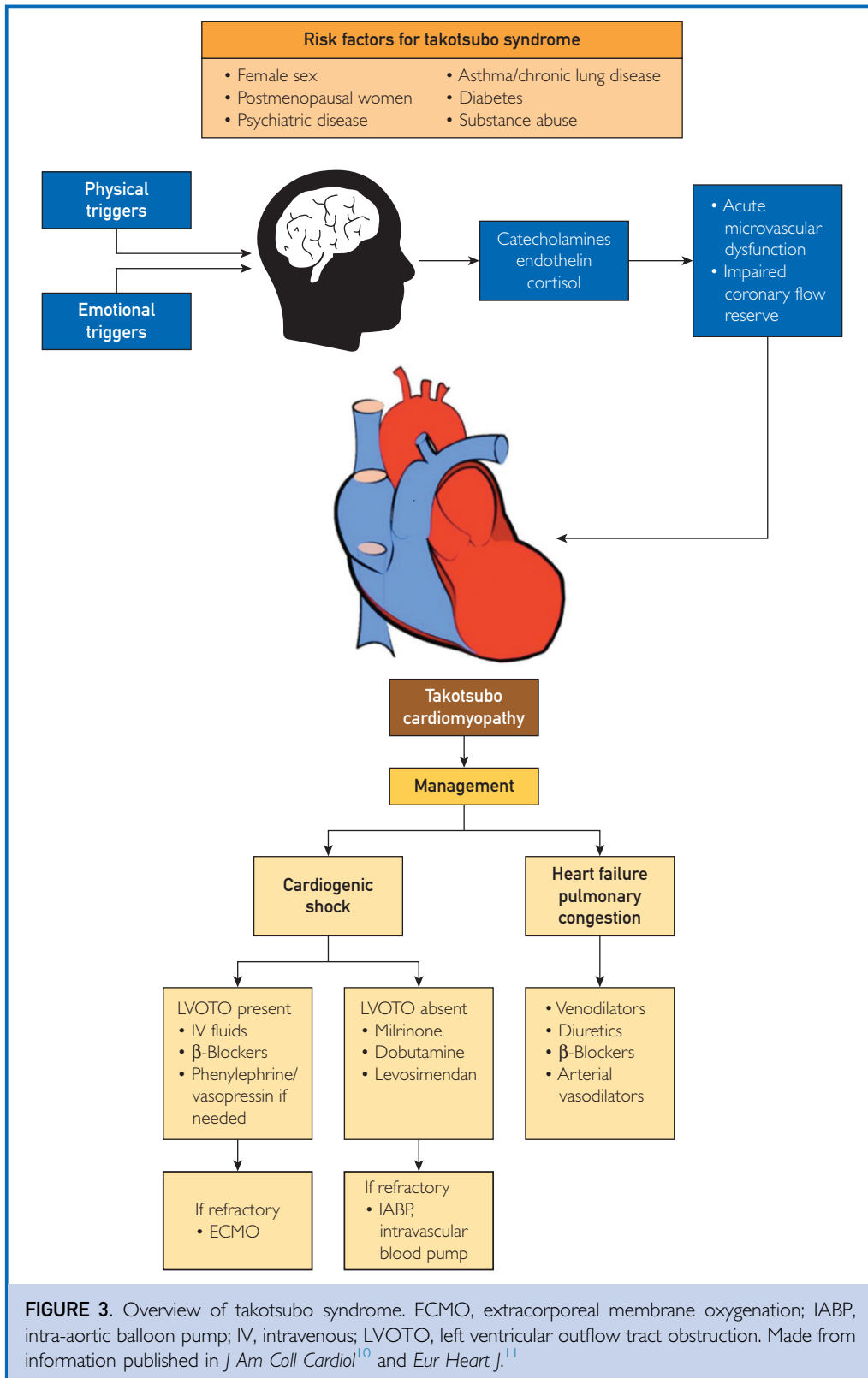
Takotsubo syndrome is considered to be a unique reversible form of LV systolic and diastolic dysfunction. Reduced LVEF is noted in 90% of patients with TTS with a mean LVEF of 40%; elevated LV end-diastolic pressure is present in 93% of patients.⁵ Wall motion abnormality involving apical and mid-apical segments is most common, making up 82% of cases.⁵ Midventricular TTS is present in 14%, with basal and focal TTS accounting for 2.2% and 1.5%, respectively.⁵ The rise in NT-proBNP level associated with TTS is comparable to that seen with decompensated HF.²⁸ Moreover, peak NT-proBNP levels in TTS are correlated with the severity of LV systolic dysfunction as well as the degree of sympathetic overactivation and long-term prognosis.²⁹

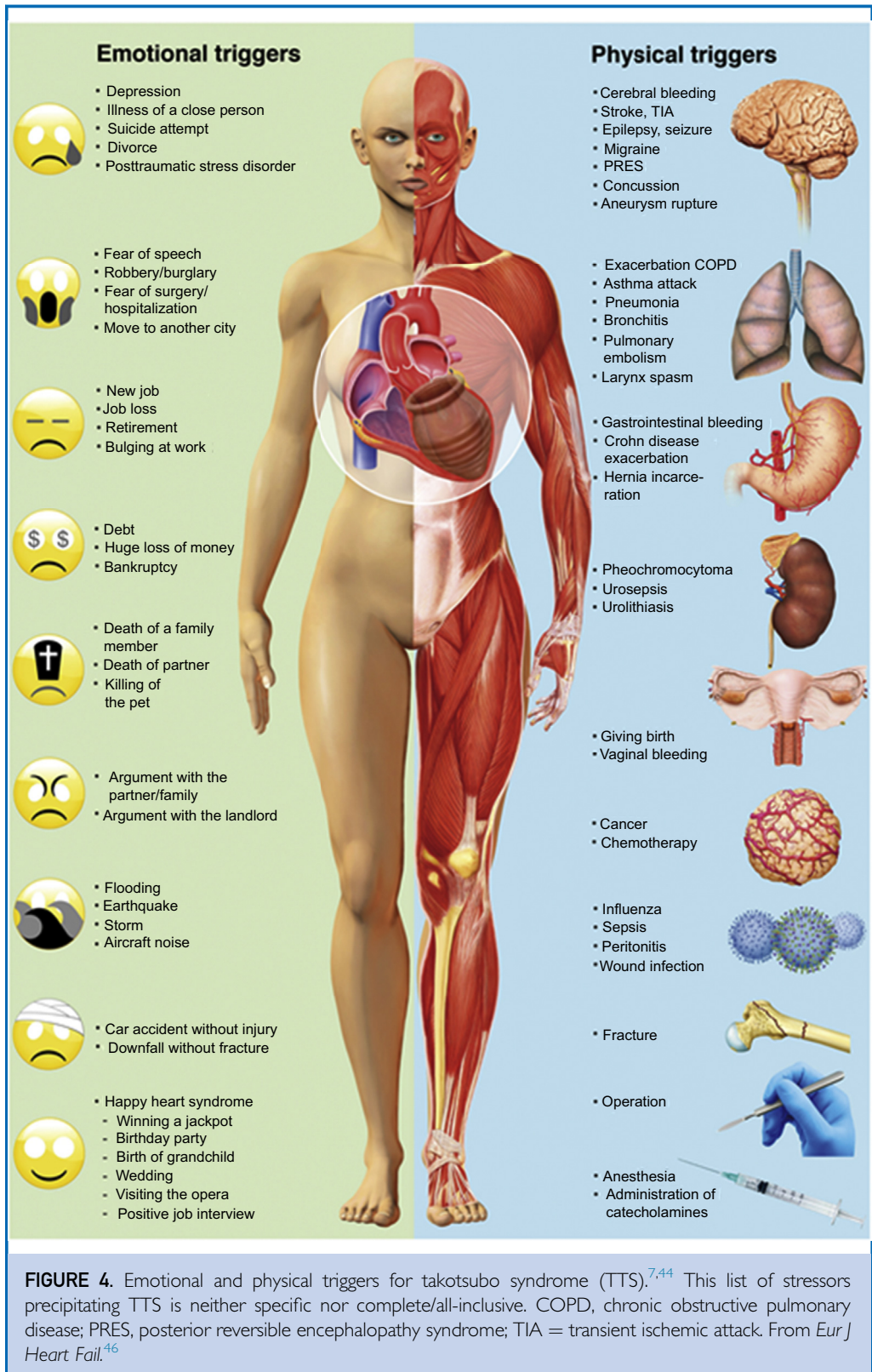
PATHOGENESIS OF TTS

Currently, the leading hypothesis is that TTS is a stress-mediated syndrome that results from catecholamine-induced metabolic myocardial stunning. The stress response produces a reduction in vagal tone in combination with elevated levels of catecholamines, endothelin, and cortisol.^{30,31} As observed with pheochromocytoma and with the therapeutic or recreational use of sympathomimetic amines such as amphetamines, elevated blood levels of catecholamines can be cardiotoxic.⁷

With high levels of adrenergic tone, endomyocardial biopsies reveal a pattern of contraction band necrosis, which results from myocardial catecholamine overload—an injury pattern also seen in TTS.³² Catecholamine elevations in these patients are not only substantially above baseline but approximately 2-fold above those recorded in cases of acute MI.³³ Various reports have found that sympathomimetic amines including intravenous epinephrine or dobutamine, amphetamines and oral agents for attention-deficit hyperactivity disorder, intranasal cocaine, and even inhaled β -agonist bronchodilators can trigger LV wall motion abnormalities and symptoms characteristic of TTS.^{32,34} Serotonin norepinephrine reuptake inhibitors can also trigger TTS, probably because they increase levels of norepinephrine and dopamine.³⁵

Catecholamines and endothelin are powerful vasoconstrictors of the coronary microvasculature.^{36,37} This sympathetically driven



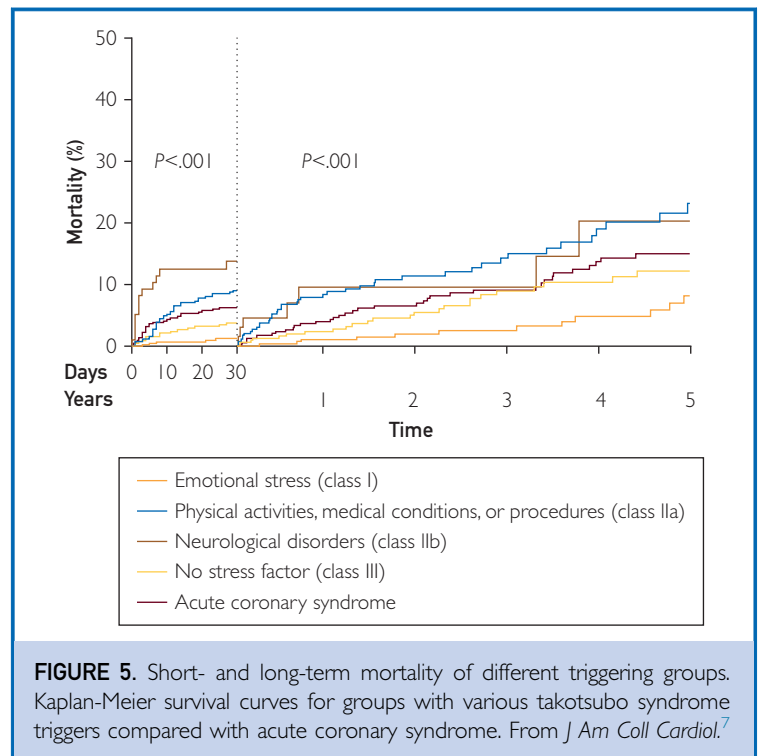


vasculopathy likely plays a role in pathogenesis, as virtually all patients with TTS have endothelial dysfunction and apoptosis on the microvascular level.³⁸ It is postulated that the myocardial stunning of TTS is due in large part to the direct effects of the catecholamine surge and associated free radicals in combination with sympathetically induced microcirculatory dysfunction.³⁹ This is supported in human cases and animal models of TTS in which LV dysfunction increases proportionally to the degree of sympathetic hyperactivity and oxidative stress.^{39,40} This results in a transient regional impairment of myocardial metabolism of free fatty acids and glucose, resulting in myocyte stunning that causes systolic and diastolic dysfunction.

The pathogenesis of TTS begins with a coronary vasculitis, which leads to vascular extravasation of fluid and infiltration of neutrophils and monocytes into myocardial tissue.⁴¹ The central mechanism is aberrant post-receptor β -2 signaling, with consequent activation of nitric oxide synthase and formation of peroxynitrite—a potent oxidant that damages DNA and impairs myocardial metabolism.⁴¹⁻⁴³ This in turn leads to hypotension, which is often a major issue early in the course of TTS and can be life-threatening. Although HF in TTS has been assumed to be a form of cardiogenic shock, it may be more accurately considered “vasodilatory shock.”^{41,43}

STRESS TRIGGERS OF TTS

One-third of patients with TTS report an emotional stressor, another one-third report a preceding physical stressor, and the final third have no apparent trigger.²¹ Studies report that chronic anxiety and/or depression are twice as common in patients with TTS compared with patients with ACS (70% vs 36%).^{44,45} In comparison to the general population, patients with TTS are significantly more likely to be living alone (52% vs 24%), to be divorced (20% vs 2%), to have a history of substance abuse, or to have experienced previous emotional or physical abuse.⁴⁵ Female patients with TTS are more likely to report a preceding emotional trigger, whereas male patients are more susceptible to physical triggers.⁵ These physical stressors can be virtually any condition or activity known to induce physiological stress (Figure 4).^{7,46}



A study using functional MRI analyzed the connectivity of central brain regions associated with the regulation of autonomic nervous and limbic systems.⁴⁷ Patients with TTS had reduced resting state functional connectivity within these central networks that are the chief mediators of emotional processing and the stress response.⁴⁷ Systemically, patients with TTS have increased levels of miR-16 and miR-26a, which are 2 microRNAs previously known to be up-regulated in neuropsychiatric conditions.³⁷ Thus, evidence supports the concept that myocardial stunning in TTS may be related in part to an individual's abnormal processing of stress.^{10,11}

IS TTS BENIGN AND REVERSIBLE?

Although TTS has generally been viewed as a relatively benign condition, recent data indicate that it can be a life-threatening illness with substantial morbidity and mortality. Indeed, both short- and long-term prognoses are not better than those associated with ACS.⁷ Takotsubo syndrome can be classified as “primary”—the stress cardiomyopathy symptoms are primary reason for patient's presentation or “secondary”—a serious

underlying illness precipitates TTS.⁴⁶ The classic patient with primary TTS, such as the woman presented in this review, with an emotional trigger and transient LV dysfunction tends to have a more favorable prognosis.⁷ In contrast, patients with secondary TTS caused by acute neurological disorders (eg, intracranial hemorrhage, seizure, and head trauma) or physical stressors (eg, acute illness, major surgery, and severe injuries), or presenting with higher levels of troponin and NT-proBNP, have a significantly worse prognosis (Figure 5).⁷ Cancer is another common cause of secondary TTS, and it is also associated with an adverse prognosis.⁴⁸ The International Takotsubo Registry reported higher in-hospital mortality rates in male patients with TTS and those 50 years or younger or 75 years or older, with a lower mortality rate noted in the age group of 50 to 75 years.¹²

Recent studies report that patients with TTS have reduced survival compared with the general population.^{13,21,49,50} The International Takotsubo Registry, the largest TTS database to date, estimated the 1-year mortality rate to be 5.6% and the rate of MACCEs 9.9%.⁵ A different study reported the in-hospital mortality rates of 2% to 4%, 3% to 5%, and 5% to 7% for patients with TTS, non-STEMI, and STEMI, respectively.³¹ In contrast, a study of 572 patients found that compared with patients with STEMI, patients with TTS had a significantly higher 4-year mortality rate (25% vs 15%, respectively) despite no significant mortality differences between these 2 groups at 28 days and 1 year.⁵¹

During the acute phase of TTS, 22% of patients suffer in-hospital complications, which can include cardiopulmonary arrest and death.⁵ The most common lethal complication is cardiogenic/vasodilatory shock. Other adverse effects include arrhythmias, LV thrombus formation, and cerebrovascular accident.⁹ Acute hemodynamic instability can result from dynamic LVOTO due to the hypokinetic/akinetic apical and mid-ventricular segments adjacent to hyperdynamic myocardial segments at the base of the LV. This physiology can also result in systolic anterior motion of the anterior mitral leaflet and mitral regurgitation.

Acute neurological disease, a physical trigger, older age, extensive apical ballooning, initial troponin levels 10 times the upper

limit of normal, LVEF less than 45%, increased LV filling pressures, and moderate or severe mitral regurgitation have all been associated with a worse TTS prognosis.^{5,11,21} N-Terminal prohormone of brain natriuretic peptide may serve as a particularly useful biomarker for prognostication, as the degree of elevation is directly correlated with the level of sympathetic overactivation and systolic LV dysfunction.²⁹ In-hospital TTS also carries with it reduced survival as compared with out-of-hospital TTS, probably owing to serious antecedent comorbidities.⁵²

Recovery from TTS can be slow, with persistent abnormalities on echocardiography and cardiac MRI, prolonged NT-proBNP elevation, impaired quality of life, and even long-term myocardial fibrosis in up to 10% of patients with TTS. Patients with TTS are at risk for a repeat episode of stress-induced cardiomyopathy; the largest study reported a recurrence rate of 1.8% per patient-year.^{4,5}

MANAGEMENT

There are no randomized controlled trials defining optimal therapy for TTS. Currently, the mainstay of treatment is simply to monitor closely and support patients with TTS through the dangerous acute phase. Mild TTS cases presenting with venous congestion and no evidence of low cardiac output or hypotension can be treated with venodilators, diuretics, and arterial vasodilators such as angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, neprilysin inhibition, hydralazine, and β -blockers.¹⁰ The major contributors to mortality in the initial days after presentation are systemic embolization and cardiogenic shock. Up to 11% of the patients with TTS develop cardiogenic/vasodilatory shock within the first 72 hours of admission and 20% to 25% develop LVOTO.^{11,53,54} The contributing factors to the development of shock include a sudden loss of regional LV contraction with a drop in the LVEF by 30% to 40%, LV stroke volume reduced by 40%, and cardiac output by 25%.^{49,55,56} Concomitant transient right ventricular dysfunction occurs in approximately one-third of patients with TTS and is associated with a greater likelihood of hypotension and hemodynamic instability. These patients may require intravascular volume expansion for blood pressure support.

Although treatment with fluid and an anti-coagulant may be indicated, the use of catecholamines to treat cardiogenic shock is not recommended because of the catecholaminergic origin of myocardial stunning and injury in TTS. This could hypothetically be worsened by exogenous catecholamine administration, leading to increased LVOTO and delayed spontaneous recovery. In a case series of 114 patients, those receiving catecholamines had a higher in-hospital mortality (28 % vs 3%), 30-day mortality (51% vs 17%), and long-term mortality (81% vs 39%).⁵⁷ In patients with cardiogenic shock and LVOTO, intravenous fluids, short-acting β -blockers, and LV assist device should be considered, whereas in those with shock due to primary pump failure, LV assist device, early use of extracorporeal membrane oxygenation, and levosimendan, a calcium sensitizer and noncatecholamine inotrope, may be beneficial.^{11,58} An intra-aortic balloon pump can be useful in selected patients with refractory shock, particularly in those without LVOTO.⁴⁶

β -Blockers must be approached with caution in the acute phase of TTS as they are contraindicated in decompensated HF. However, they may provide benefit in those presenting with dynamic LVOTO.⁵⁹ Although long-term β -blockers might theoretically prevent the recurrence of TTS, data are lacking. In fact, a third of patients taking a β -blocker had a recurrence of TTS.⁵ Evolving data suggest that treatment with an angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker is associated with improved 1-year survival and reduced risk of recurrence.¹¹

α_1 -Agonists such as phenylephrine or vasopressin can be considered in patients with hemodynamically significant LVOTO and hypotension to support blood pressure and without increasing inotropy and chronotropy.^{10,46,54} Ivabradine, a sodium current inhibitor, may be an option for refractory tachycardia management, though no data on its effect on TTS outcome are available.⁶⁰

Given the relationship of TTS with psychological stress and psychiatric disorders, these factors should be addressed and treated when present. The potential benefits of psychiatric medications, counseling, and cognitive behavioral therapy for patients with TTS have yet to be documented.

FUTURE DIRECTIONS

More research is needed to understand the pathophysiological mechanisms and treatment options for TTS. Improved strategies to prevent recurrence are also paramount, as the recurrence of TTS is estimated at 10% over 4 years. Better detection algorithms are also needed because many cases of TTS probably go undiagnosed. More data are needed to understand potential long-standing derangements of LV function and complications after presentation with TTS.

Abbreviations and Acronyms: ACS = acute coronary syndrome; COVID-19 = coronavirus disease 2019; ECG = electrocardiogram; HF = heart failure; LV = left ventricle or ventricular; LVEF = left ventricular ejection fraction; LVOTO = left ventricular outflow tract obstruction; MACCE = major adverse cardiovascular and cerebrovascular event; MI = myocardial infarction; MRI = magnetic resonance imaging; NT-proBNP = N-terminal prohormone of brain natriuretic peptide; PSS = psychosocial stress; STEMI = ST-segment elevation myocardial infarction; TTS = Takotsubo syndrome

Potential Competing Interests: The authors report no competing interests.

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