Balkan Med J 2024;41:442-57

Takotsubo Syndrome: An International Expert Consensus Report on Practical Challenges and Specific Conditions (Part-2: Specific Entities, Risk Stratification and Challenges After Recovery)

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Received: 18-Sep-2024 **Accepted:** 26-Sep-2024 **Available Online Date:** 17-Oct-2024 • **DOI:** 10.4274/balkanmedj.galenos.2024.2024-9-99

Available at www.balkanmedicaljournal.org

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Cite this article as: Yalta K, Madias JE, Kounis NG, Y-Hassan S, Polovina M, Altay S, Mebazaa A, Yilmaz MB, Lopatin Y, Mamas MA, Gil RJ, Thamman R, Almaghraby A, Bozkurt B, Bajraktari G, Fink T, Traykov V, Manzo-Silberman S, Mirzoyev U, Sokolovic S, Kipiani ZV, Linde C, Seferovic PM. Takotsubo Syndrome: An International Expert Consensus Report on Practical Challenges and Specific Conditions (Part-2: Specific Entities, Risk Stratification and Challenges After Recovery). Balkan Med J.; 2024; 41(6):442-57.

ABSTRACT

Takotsubo syndrome (TTS) still remains as an enigmatic phenomenon. In particular, long-term challenges (including clinical recurrence and persistent symptoms) and specific entities in the setting of TTS have been the evolving areas of interest. On the other hand, a significant gap still exists regarding the proper risk-stratification of this phenomenon in the short and long terms. The present paper, the second part (part-2) of the consensus report, aims to discuss less well-known aspects of TTS including specific entities, challenges after recovery and risk-stratification.

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'This part of the consensus report (part-2) focuses on certain specific entities, risk-stratification and challenges after recovery in patients with TTS.'

1. SPECIFIC ENTITIES IN PATIENTS WITH TTS

1.1. Apical ballooning due to an intraventricular gradient: Mechanically-triggered TTS

- Mechanistic and clinical implications

In clinical practice, sudden intraventricular obstruction might be associated with substantial intraventricular pressure and myocardial wall tension due to afterload mismatch leading to consequent myocardial stunning, and might also have pathogenetic implications in the setting of TTS presenting with an apical ballooning pattern.[1-12] This form of TTS may be termed "mechanically-triggered TTS". Characteristically, it is generally encountered in female patients with a small left ventricular (LV) cavity and increased interventricular septal (IVS) thickness [including those with hypertrophic cardiomyopathy (HCM) and hypertensive heart disease].[3-12] Accordingly, previous case reports demonstrated apical ballooning pattern mostly in the setting of obstructive HCM.[13-22] Notably, a significant intraventricular gradient [midventricular or left ventricular outflow tract (LVOT) obstruction (MVO or LVOTO) may be already evident on TTS admission or may be provoked by challenge tests including dobutamine stress echocardiogram (DSE) (or exercise stress echocardiogram)].[3-7] By gross definition, a LVOT gradient of > 30 mmHg signifies LVOTO while a gradient of > 50 mmHg usually denotes a significant LVOTO.[1,7] Importantly, existing severe hypertrophy usually mitigates myocardial wall tension, and prevents the evolution of apical ballooning.[7,8] Accordingly, this form of TTS mostly arises in the setting of modest hypertrophy.[7,8,12] Accordingly, HCM patients with an apical ballooning pattern were previously reported to have significantly lower myocardial hypertrophy at the basal anterior IVS segment (15.2 ± 2 mm) compared with those without ballooning.[12] Hypertrophy was modest or absent in other segments in these patients.[12] In this context, a previous study describing four cases with a mechanically-triggered TTS suggested that dynamic MVO together with adrenergic discharge might lead to a classical apical ballooning pattern in susceptible patients including those with IVS thickening and sigmoid septum.[3] Importantly, all the cases reported in this study had a mean mid-IVS thickness of 13 mm at end-diastole, and also had a physical trigger (including heavy exercise and major surgery).[3] Accordingly, it was suggested by the authors that adrenergic discharge might still play a pivotal role in the evolution of TTS due to an intraventricular gradient.[3] This notion has been largely based on clinical findings that iatrogenically triggered severe MVO in the absence of extreme adrenergic discharge (due to postoperative dehydration and DSE) generally does not progress to TTS evolution.[3] Therefore, catecholamine-mediated subendocardial vasoconstriction (and hence; ischemia) in the apical territories (on top of catecholamine-mediated intraventricular obstruction) was suggested as a prerequisite for the evolution of mechanically-triggered TTS.[3]

However, there have been cases of mechanically-triggered TTS without an overt physical or emotional stressor as well.[4,5] This implies that this phenomenon might have a purely mechanical basis in the absence of adrenergic discharge in certain patients.[4,7] In this context, a substantially higher mechanical obstruction may be necessary for the generation of apical stunning.[7] In clinical practice, a portion of TTS cases may not have an identifiable emotional or physical trigger (namely spontaneous TTS).[6,7,23,24] In some of these cases, purely mechanical factors may play a pivotal role in TTS evolution, and pre-existing myocardial disease including HCM should be further explored in these cases.[7,11,12] Importantly, mitral valve elongation (and mitral-septal contact) was recently suggested to have a pivotal role in the evolution of LVOT gradient (and hence; should not be regarded as a passive abnormality secondary to LVOT gradient and Venturi effect) in patients with mechanically-triggered TTS.[1,7,9,12] Since heightened intraventricular pressure may significantly facilitate the evolution of myocardial rupture in the setting of TTS,[25] it may also be suggested that evolution of this ominous complication may be more likely in this form of TTS. Moreover, mechanically-triggered TTS might be particularly associated with acute mitral regurgitation (MR) and pulmonary hypertension (HT) that might result in pulmonary edema and/or hemodynamic compromise.[5,7,12,15] Mechanistically, acute MR, to a large extent, seems to be a primary phenomenon associated with abnormalities of the mitral valve apparatus in the setting of mechanically-triggered TTS. In contrast, acute MR in the setting of neurogenic TTS seems to be a secondary phenomenon due to a variety of factors including SAM (associated with systolic motion of the annular ring due to basal hypercontaction pattern, etc.) and valvular tethering (due to LV dysfunction and dilatation).[25-27]

Notably, not all HCM patients with a sudden intraventricular gradient present with an apical ballooning pattern. In a database of HCM (comprising 1519 patients), this phenomenon was observed only in 0.9% of the HCM population.[12] Therefore, there might exist an inherent proclivity for mechanically-triggered apical ballooning in certain HCM patients. Accordingly, apical geometric alterations associated with enhanced circumferential wall stress (leading to relative increases in diameter and myocardial thinning) was previously suggested to be associated with a predisposition to apical ballooning.[10,28] Therefore, such geometric changes involving the apex[10,28] on top of impaired sarcomeric energy utilization in patients with HCM may potentially reduce the threshold for apical ballooning during episodes of heightened intraventricular pressure largely through an exaggerated supply-demand mismatch.[12]

On the other hand, it may not be so easy to differentiate between a mechanically-triggered TTS due to sudden LVOTO and a classical neurogenic TTS complicated by LVOTO.[1,7,12] First of all, it is of paramount importance to confirm or exclude pre-existing myocardial conditions including HCM and hypertensive heart disease with various diagnostic modalities. Even though basic modalities including echocardiogram generally detect an overt HCM (before or following the TTS episode), cardiac magnetic resonance imaging (MRI) (and endomyocardial biopsy in rare instances) serves as an important adjunctive modality,[1] particularly in the setting of ambiguous morphological features (borderline hypertrophy and mild abnormalities). Furthermore, cardiac MRI also demonstrates the presence and extent of myocardial fibrosis and has prognostic implications in the setting of HCM.[1] On the other hand, neurogenic TTS denotes the widely-recognized TTS pattern primarily emerging due to the direct impact of catecholamines on myocardium.[1,7] Interestingly, patients with neurogenic TTS may also harbor increased IVS thickness, small LV cavity, septal bulge and small LVOT area as by-stander entities that might serve as risk factors for acute LVOTO.[10,12,25] In other words, these risk factors may create a particular predisposition to LVOTO in the setting of a particular TTS episode presenting with a basal hypercontraction pattern.[10,12,25,29] However, LVOTO in the context of neurogenic TTS may be relatively lenient.[7] In contrast, LVOTO in the setting of mechanically-triggered TTS generally appears to be more substantial and unrelenting,[1,4,12] and may persist following the complete recovery of apical ballooning.[1,8] As mentioned previously, structural changes including papillary muscle abnormalities and elongation of mitral leaflets are generally evident in patients with a mechanically-triggered TTS.[1,7,12] Notably, failure to provoke any significant LVOTO or MVO with challenge tests[12] [following the complete recovery of apical ballooning and mitigation of intraventricular gradient (if any)] may suggest a neurogenic TTS episode[8] (that might or might not have been complicated by a transient LVOTO) in patients with HCM or hypertensive heart disease. Importantly, challenge tests including DSE should be performed following complete TTS recovery[3] due to the detrimental impact of adrenergic agents on the disease course.[7,24] Finally, the severity and location of LVOTO may also be quantified with invasive gradient measurement in both TTS forms particularly in patients undergoing coronary angiogram (CAG).[1] Technical details of invasive gradient measurement are discussed elsewhere.[1] Since echocardiographic evaluation may potentially underestimate the severity of an existing intraventricular gradient in the setting of low cardiac output conditions [such as severe heart failure (HF)],[13] use of invasive techniques may demonstrate a higher diagnostic accuracy in this context. **Figure 1** demonstrates a proposed diagnostic algorithm that might aid in the differentiation between mechanically-triggered and neurogenic TTS episodes in patients with HCM (or hypertensive heart disease) presenting with an apical ballooning pattern.

- Management strategies:

Urgent and long-term management strategies have important implications in the setting of mechanically triggered TTS. β-blockers appear to be of paramount importance in the urgent settings.[1,12] Propranolol was previously demonstrated to improve apical wall motion abnormalities through mitigation of MVO in the context of TTS.[6] Mitigation of intraventricular gradient may at least improve hemodynamic compromise due to mechanical factors (including acute MR) even if it fails to abort WMAs immediately in this context. β-blockers may also be used to reverse the dobutamine-provoked MVO[5] in patients undergoing DSE for diagnostic purposes. In general, β-blockers (mostly metoprolol and esmolol), alpha agonists including phenylephrine and fluid therapy (in the absence of severe pulmonary edema) may significantly reduce intraventicular gradient regardless of whether this gradient serves as the trigger or consequence of apical ballooning.[1,7,12,29,30] Temporary mechanical circulatory support may be occasionally necessary in those with persistent hemodynamic compromise.[1,7] As expected, inotropes, agressive diuretic therapy and intraaortic balloon pump should be avoided in any form of intraventricular obstruction.[1,7] In cases who can not be weaned from mechanical circulatory support, urgent surgical reconstruction (septal myectomy ± mitral valve shortening) should be considered.[1] Bail-out use of alcohol septal ablation was also previously reported in this context.[15]

Finally, preventive measures including avoidance of triggers (such as dehydration, hypotension, prolonged standing potentially provoking intraventricular gradient due to enhanced myocardial contractility and decreased preload and/or afterload) seem to be necessary for the prevention of apical ballooning in the long term. Notably, use of β-blockers in the long-term, besides significantly alleviating LVOTO, may also augment LV systolic performance through improvement of certain parameters including global longitudinal strain in patients with HCM.[30] Agents including disopyramide and novel myosin ATPase inhibitors may also arise therapeutic options for the management of LVOTO in the context of HCM.[7,12] Surgical reconstruction (or alcohol septal ablation) may be of significant benefit in cases with a recalcitrant severe intraventricular gradient or recurrent episodes of apical ballooning particularly in the context of HCM.[1,7,9,12] Of note, certain clues including irreversible ballooning, wall thinning and substantial late gadolinium enhancement (LGE) on cardiac MRI in the apical region along with a recalcitrant intraventricular gradient might suggest an existing true aneurysm rather than reversible apical ballooning in those with HCM and MVO.[2] Finally, it also seems possible that sudden intraventricular obstruction in TTS patients with an apical ballooning pattern, rather than arising as an exclusive phenomenon in a small subset of patients, may serve as the fundamental yet; subtle mechanism of apical ballooning, and hence; may arise as an

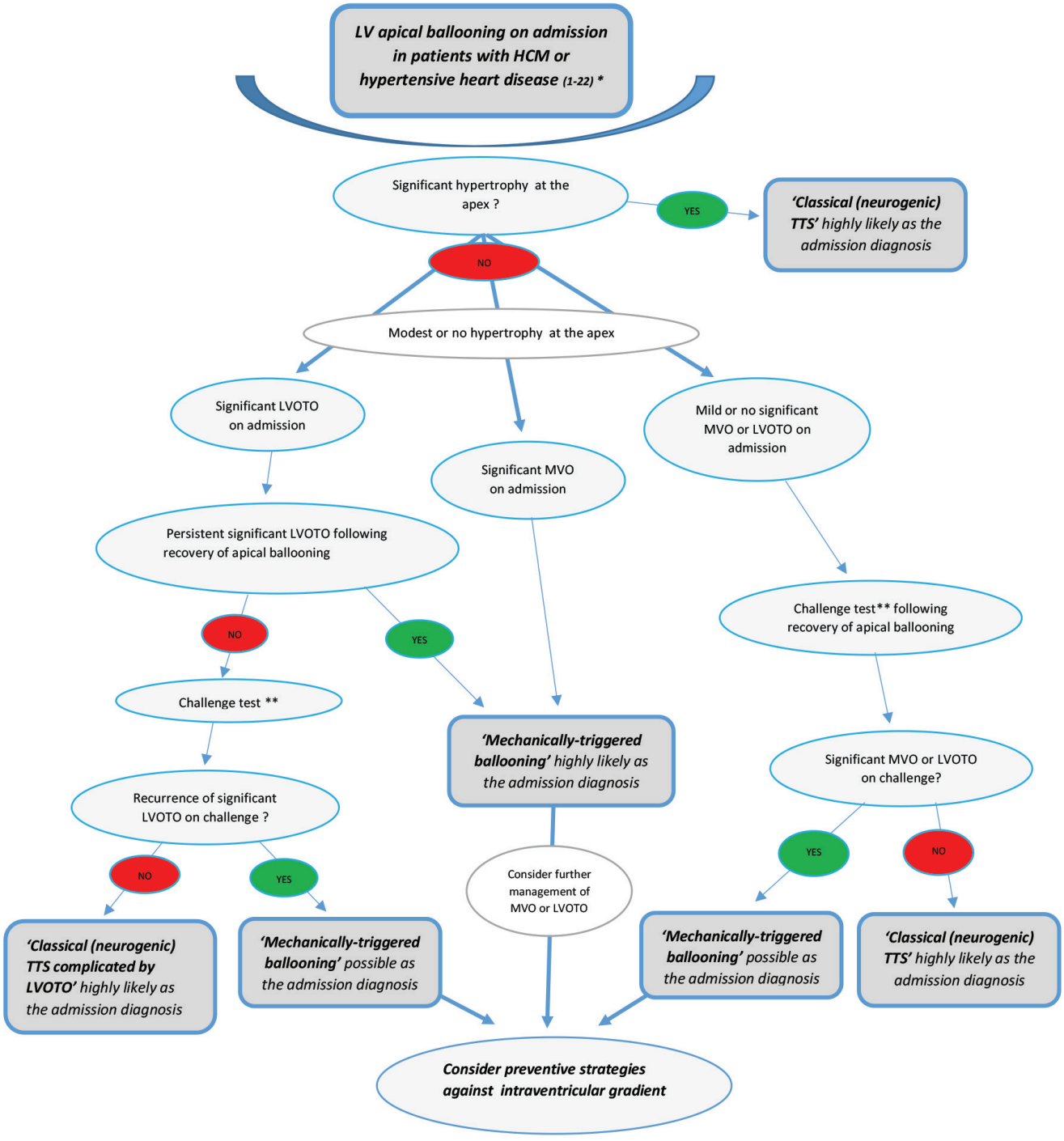

FIG. 1. A proposed algorithm for the differentiation between mechanically-triggered and neurogenic TTS episodes in patients with HCM (or hypertensive heart disease) presenting with an apical ballooning pattern.
TTS, Takotsubo syndrome; HCM, hypertrophic cardiomyopathy; LVOTO, left ventricular outflow tract obstruction; MVO, midventricular obstruction.
*: Morphological features of HCM may not be evident on initial echocardiogram in certain cases. Accordingly, some patients with a history of apparently neurogenic TTS were diagnosed as having HCM on follow-up raising the possibility of a previous mechanically-triggered TTS episode.[1] Cardiac magnetic resonance imaging (and rarely endomyocardial biopsy) may be necessary to establish the HCM diagnosis in patients with borderline features on echocardiogram.[1] Exclusion of HCM or hypertensive heart disease may, to a large extent, rule out a mechanically-triggered TTS episode. Nevertheless, challenge tests may be necessary in certain cases with ambiguous features.
**: Mostly dobutamine or exercise echocardiogram.

alternative theory in TTS pathogenesis.[9] However, this needs to be explored in future studies.

KEY POINTS

- Acute rises in intraventicular gradient (LVOTO or MVO) may lead to apical ballooning in patients with HCM or hypertensive heart disease usually in the absence of significant apical hypertrophy.
- Intraventricular gradient may serve as an obscure TTS trigger in a portion of patients with a spontaneous TTS episode.
- It seems crucial to identify LVOTO as the consequence or cause of apical ballooning in the setting of HCM or hypertensive heart disease.
- Challenge tests including DSE may have diagnostic value, and may be performed to provoke intraventicular gradient following recovery of apical ballooning in those with HCM or hypertensive heart disease.
- Urgent surgical relief of intraventricular gradient may be rarely necessary in high-risk patients with mechanically-triggered TTS who remain unresponsive to medical therapy.
- Preventive measures against intraventricular gradient may potentially reduce the risk of recurrent apical ballooning in these patients.

1.2. Coronary slow flow phenomenon on invasive coronary angiogram: Mechanisms and clinical implications in patients with TTS

Coronary slow flow (CSF) phenomenon is defined as the delayed opacification of the distal epicardial coronary system on CAG in the absence of obstructive coronary artery disease (CAD). The angiographic criteria used to define CSF is thrombolysis in myocardial infarction-2 (TIMI-2) flow and the corrected TIMI frame count (CTFC) of > 25 frames. CSF is considered a surrogate for an existing coronary microvascular dysfunction (CMVD), which is prevalent across a broad spectrum of cardiovascular diseases including TTS.[31,32] Other invasive techniques used to study the coronary microcirculation are TIMI myocardial perfusion grade, coronary flow reserve, index of microcirculatory resistance, and hyperemic microvascular resistance. Many studies have revealed invasive including CSF or non-invasive signs of CMVD in patients with TTS.[32] Among studies, which have enrolled a larger number of TTS patients, CSF was observed in 18% to 40% of patients.[33,34] Worth mentioning is that not all patients had CSF in all 3 vessels, some of them had CSF in only 2 vessels, other had in only one vessel[32] distribution. It has been reported that CSF is more prevalent and pronounced in the left anterior descending artery (LAD) distribution in TTS.[32,35] A previous study reported that CTFC in TTS patients was significantly higher exclusively in LAD compared with controls, and no difference in the CTFC was observed in left circumflex or right coronary arteries.[35] Of importance, studies have shown that TTS patients with CSF exhibit worse clinical presentation, and suffer a higher rate of in-hospital complications and long-term all-cause mortality.[33,34] This indicates that CSF in TTS patients may serve as an additional prognostic index and help in risk stratification and hence better management in the acute stage of the disease.[36] Otherwise, the CSF phenomenon and other invasive signs of CMVD in TTS is transient and significantly improve or normalize in parallel with the improvement and normalization of LV wall motion abnormalities.[32]

Some investigators hold the opinion that CMVD is the primary cause of TTS. However, the body of evidence challenging this hypothesis is substantial. More than half of the patients with TTS have no signs of CMVD. Such a severe degree of CMVD that causes ST segment elevation is supposed to elicit substantial troponin elevation and extensive myocardial infarction, yet this is not the fact in TTS.[32] Other arguments against this hypothesis are detailed elsewhere.[32] Others hold the opinion that sympathetic hyperactivity following stressful events may result in hyperactivation of the local cardiac sympathetic nerve terminals and norepinephrine spillover causing myocardial stunning and microvascular coronary vasoconstriction. This hypothesis is the most plausible pathogenetic mechanism of myocardial stunning in TTS, but concomitant microvascular vasoconstriction may be an epiphenomenon, which occurs only in some and not all patients. According to some expert opinions, myocardial pathological changes may cause compression of the microcirculation. Myocardial edema secondary to catecholamine induced inflammatory changes may compress the microvascular system.[32] However, not all patients with TTS develop myocardial edema. The most plausible cause of compression of microcirculation is the severe myocardial stunning (cardiac cramp) evidenced by the development of contraction bands, which is an important histopathological finding in TTS. This mechanism is discussed in details elsewhere.[32] This myocardial compression mechanism in this context also explains why CSF pattern is more prevalent and pronounced in LAD (**Figure 2**). Accordingly, this notion is based on the anatomical fact that the myocardial territory perfused by LAD, besides harboring intramyocardial resistance vessels (microcirculation), also has intramyocardial conductance vessels-septal branches (macrocirculation) and segments with myocardial bridging that can also be compressed by the TTS-induced cardiac cramp (**Figure 2**).

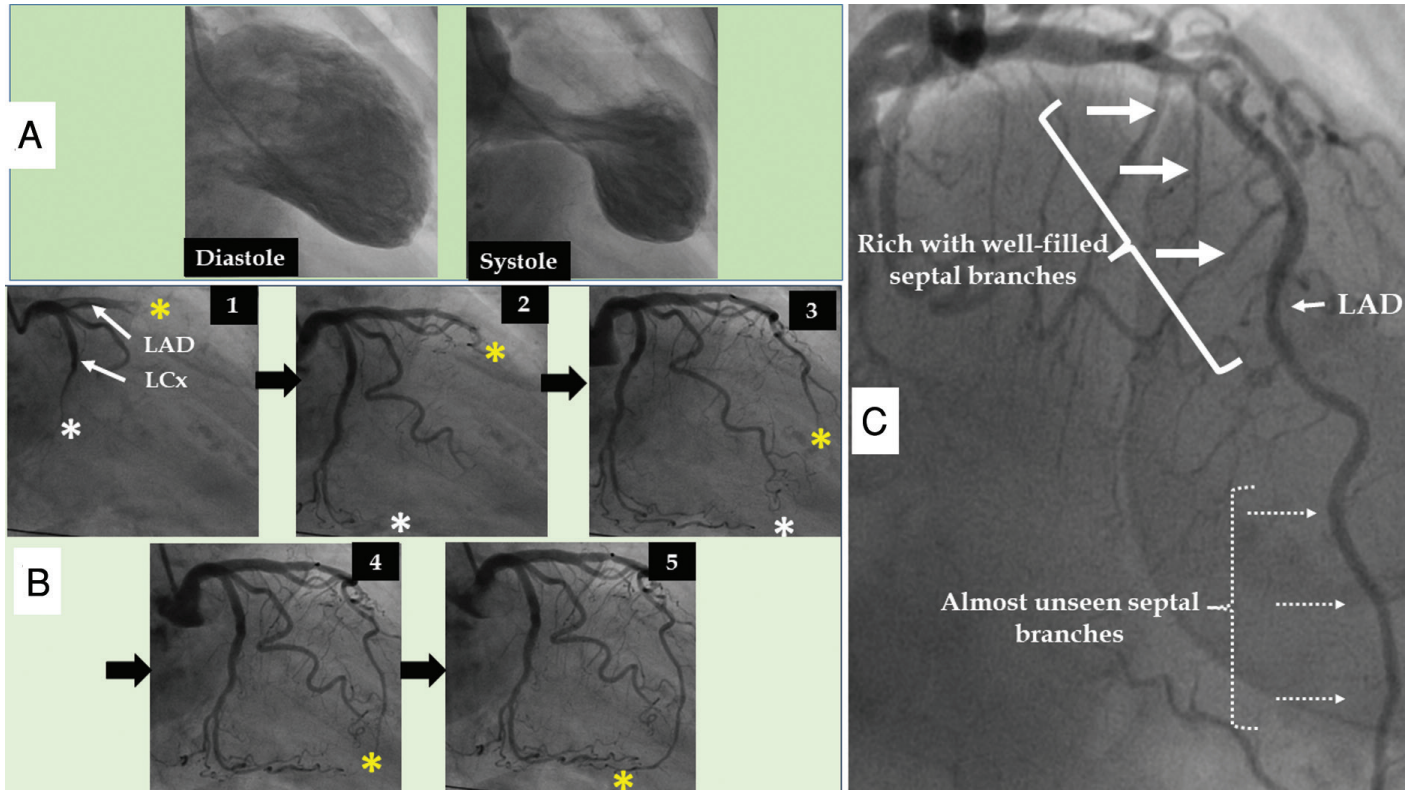

FIG. 2. (A) Invasive left ventriculogram in a female patient with mid-apical pattern of TTS. (B) left coronary angiogram (CAG) in the caudal projection demonstrating marked coronary slow flow (CSF) (yellow asterix) in the left anterior descending artery (LAD) compared with near- normal coronary flow pattern (white asterix) in the left circumflex artery. (C) Left CAG in the right cranial projection demonstrating LAD with its septal branches. The septal branches from the proximal LAD segment are clearly visible (thick white arrows), while the septal branches from the distal half of the LAD (thin dotted black arrows) within the affected left ventricular (LV) segment are not visible (or barely visible) due to the compression imposed by the stunned LV mid-apical segment (cardiac cramp). Compression of the septal arteries also contributes to the CSF pattern in the LAD.

KEY POINTS

- CSF may occur in up to 40% of patients with TTS and may indicate a severe index presentation with a higher long-term all-cause mortality.
- CSF may be observed in all-three, two or only one coronary artery, and is more prevalent and pronounced in LAD distribution.
- CSF in TTS is transient, and improves or normalizes in parallel with normalization of the LV dysfunction.
- CSF is most likely to be secondary to the myocardial stunning in TTS, and may also be an epiphenomenon.

1.3. Rapid morphological transition

- Definition and incidence

Rapid morphological transition may be defined as the migration of WMAs between different myocardial territories during a single TTS episode, and has been very rarely reported so far.[37-42] This form of rapid WMA transition was also termed as "fast wandering TTS" previously.[38] As expected, rapid morphological transition may be potentially overlooked particularly when the initial cardiac imaging is performed following the established transition.[37,41] Therefore, this TTS phenomenon may be particularly underdiagnosed in late presenters[37] and possibly in those undergoing infrequent serial echocardiographic evaluation during their hospital stay. Theoretically, multiple morphological transitions during a single TTS episode[37] and post-discharge transitions may be posssible as well. Incidence of this phenomenon is currently unknown among TTS patients.

- Pathophysiological and clinical aspects

On the other hand, pathophysiological and clinical implications of rapid morphological transition remain to be established in patients with TTS.[37] There have been a variety of suggested speculations regarding its pathogenesis. First, extreme levels of adrenergic discharge may be potentially associated with this phenomenon.[37] Accordingly, TTS due to pheochromocytoma was previously reported to present with a rapid transition from a

regional to a global pattern that might be regarded as a gradual deterioration of WMAs in response to excess catecholamine toxicity.[42,43] Second, transition of WMAs from the mid-apical to mid LV territory was also previously reported.[41] In this setting, apex (the worst affected territory due to the incremental sympathetic abnormalities from the base to the apex) was suggested to recover more quickly (compared with mid regions) due to a decline in catecholamine levels suggesting that a graded TTS recovery might emerge as a rapid transition pattern.[41] Third, it was also speculated recently that a rapid morphological transition might not arise just as a coincidental entity, and might serve as a protective mechanism against mechanical complications of TTS.[37] For instance; an impending LVOT gradient may be prevented with a morphological transition from the apex to other territories.[37] Finally, rapid morphological transition might denote an actual TTS recurrence following the quick recovery of an initial TTS episode involving a different myocardial territory. However, the above mentioned notions should be regarded as speculations regarding the pathogenesis of this phenomenon. Finally, nuclear imaging modalities might uncover persistent abnormalities in sympathetic nerves and glucose metabolism[44,45] in the recently affected and quickly normalized territories, and might support the diagnosis of TTS with a rapid morphological transition.

KEY POINTS

- Rapid morphological transition denotes migration of WMAs between different territories during a single TTS episode.
- Pathogenetic and clinical implications of this mysterious phenomenon are currently unknown.

2. CHALLENGES IN RISK STRATIFICATION: DO WE NEED FURTHER TOOLS AND MARKERS?

Risk-stratification in TTS has been quite challenging due to its unique characteristics and variability in presentation patterns.[46,47] There are some challenges of particular interest in the overall risk-stratification with inconsistencies regarding risk-markers in various studies possibly due to their methodological diversities.[48]

First, potential heterogeneity in age, gender, and comorbidities complicates the development of a one-size-fits-all risk stratification model in the setting of TTS. Comorbid conditions such as HT, diabetes, chronic kidney disease or mental health disorders can influence the clinical course of TTS and complicate the risk stratification process. Besides, there is large interobserver variability particularly in the diagnosis and classification of TTS.[47] This variability affects the consistency and reliability of risk-stratification.

Second, similarities of TTS to acute coronary syndromes (ACSs) in clinical presentation, including symptoms, electrocardiogram (ECG) changes, and elevated cardiac biomarkers[24] makes differentiating TTS from ACS quite challenging. As mentioned in the part-1 of the consensus report, even CAG might not clearly differentiate TTS from ACSs as there might be overlapping syndromes potentially hampering proper risk-stratification.

Third, clinical course of TTS may be substantially unpredictable compared with similar conditions, and can vary from a benign disease with a complete recovery to fatal cardiogenic shock or to complicated long term course with HF, arrhythmias, thromboembolism. This variability makes it challenging to predict outcomes accurately.

Fourth, lack of specific biomarkers remain a significant limitiation. Although, there exist specific patterns, there are no pathognomonic biomarkers for TTS.[46] This not surprisingly complicates risk stratification based on laboratory findings. Significant psychological and emotional triggers are integral part of the syndrome however assessing and quantifying these triggers are inherently subjective and challenging, complicating the risk stratification process. It is important to remember that inherent tendency could designate future recurrences.

However, thanks to international collaborations, the diagnostic criteria for TTS have evolved over time, narrowing potential inconsistencies in diagnosis and risk stratification, though, addressing these challenges requires a multifaceted approach, including the development of more precise diagnostic criteria, improved biomarkers, comprehensive registries to collect long-term data, and personalized risk assessment tools that consider the diverse factors influencing TTS outcomes.

Recently, the German and Italian Stress Cardiomyopathy (GEIST) score was suggested for the prediction of in-hospital complications in patients with TTS in 2019.[49] The GEIST score was developed using data from two registries and included variables like male sex, history of neurologic disorder, RV involvement, and LVEF [male sex: 20 points, history of neurologic disorders: 20 points, RV involvement: 30 points, and LVEF was included as a variable, with points deducted based on the LVEF value (decimal values between 0.15 and 0.70)]. It provided risk stratification into three groups: Low risk, intermediate risk, and high risk, based on the score points assigned to each variable. The study found that patients with in-hospital complications had significantly higher long-term mortality rates compared to those without complications, emphasizing the importance of early risk stratification in TTS patients. Besides, the GEIST score was externally validated in the Spanish Registry for

Takotsubo Cardiomyopathy, showing good accuracy in predicting in-hospital complications. These contributions highlight the development and validation of a practical risk prediction tool for identifying TTS patients at different risk levels for in-hospital complications and long-term outcomes.

The InterTAK Prognostic Score remains as one of the critical tools.[50] The score itself assigns 15 points to TTS secondary to neurologic disorders, 9 points to TTS secondary to physical activities, medical conditions, or procedures, 8 points to Age > 70 years, 7 points to systolic blood pressure (SBP) < 119 mmHg on admission, 6 points to left ventricle ejection fraction (LVEF) ≤ 45 % on admission, diabetes mellitus and male gender, 4 points to heart rate > 94 bpm on admission and 3 points to TTS without an identifiable triggering factor. Herein, ≤ 15 points puts the patient into low risk category for up to 6 years, 16-22 points into intermediate, 23-28 high and ≥ 29 points into very high risk.

Taken together, there are widely recognized high-risk features including advanced age, male sex, physical stressors (including sepsis, cancer, etc.), low SBP, pulmonary edema, reduced LVEF, biventricular involvement, LVOTO, MR, presence of mural thrombi, co-existing CAD, persistent ST-segment elevation, significant QT interval prolongation.[46,49-52] Importantly, it should be borne in mind that TTS was found to demonstrate an excess long-term mortality (with mortality rates similar to or even higher than acute myocardial infarction) in previous large scale studies and clinical registries.[52-55] Of note, risk stratification of TTS is a challenging but an evolving area of interest. Interestingly, clinical and ECG algorithms using artificial intelligence may significantly aid in this context.[51]

On the other hand, further strategies on top of established markers are still needed for more accurate risk-stratification of TTS. Among the promising strategies, evaluation of advanced echocardiographic [including deformation analysis in the left atrium, LV and right ventricle (RV) using speckle tracking, echocardiographic particle imaging velocimetry for the assessment of intracardiac blood flow patterns] and cardiac MRI parameters (deformation analysis, T1-T2 mapping, LGE), evaluation of myocardial ^{123}I metaiodobenzylguanidine uptake, stress activity on neuroimaging (through quantification of activity of certain stress-related areas including amygdala, etc. using flurodeoxyglucose), pericoronary fat attenuation index on computed tomography, coronary flow patterns (including CSF on CAG), systemic inflammation [including the ratio of neutrophil/lymhocyte and interleukins (IL) including IL-6 and IL-10] and neoplastic markers (including carcinoembryonic antigen and cancer antigen-19.9) as well as genetic mutations [involving adrenergic receptors, estrogen receptor 1 and Bcl-2-associated athanogene 3 may aid in further risk-stratification of TTS not only in the short-term (in-hospital outcomes) but also in the long-term (TTS recurrence, mortality after discharge].[33,34,36,52,56-69]

Notably, certain stress markers including copeptin (C-terminal provasopressin) have prognostic implications in the setting of various cardiovascular conditions.[70,71] Persistent elevation of endogenous stress as quantified by serum copeptin might denote delayed recovery and arrhythmogenesis in the setting of TTS.[71] In this context, the ratio of serum copeptin/NT-proBNP was previously suggested to serve as a marker of absolute endogenous stress with prognostic implications.[71] Finally, radiomics is a promising strategy based on extraction of extensive quantitative data from medical images.[68] It allows analysis of pixels and their relationships based on mathematical formulas,[68] and consequently extracts texture characteristics that are imperceptible by the human eye.[68] Radiomics may serve as an advanced prognostic tool in the setting of TTS. Moreover, combination of radiomics with artificial intelligence may further improve its prognostic accuracy in this setting.[68] However, the above-mentioned promising strategies should be tested in further clinical studies. **Figure 3** demonstrates a summary of established and promising risk markers in patients with TTS.

KEY POINTS

- Clinical course of TTS may be relatively unpredictable compared with similar conditions.
- Potential heterogeneity in clinical features hampers proper risk-stratification.
- Advanced imaging modalities (including MRI, neuroimaging) and certain markers (genetic, inflammatory, neoplastic) have yielded promising results. However, their prognostic value still need to be fully established in the short and long terms.

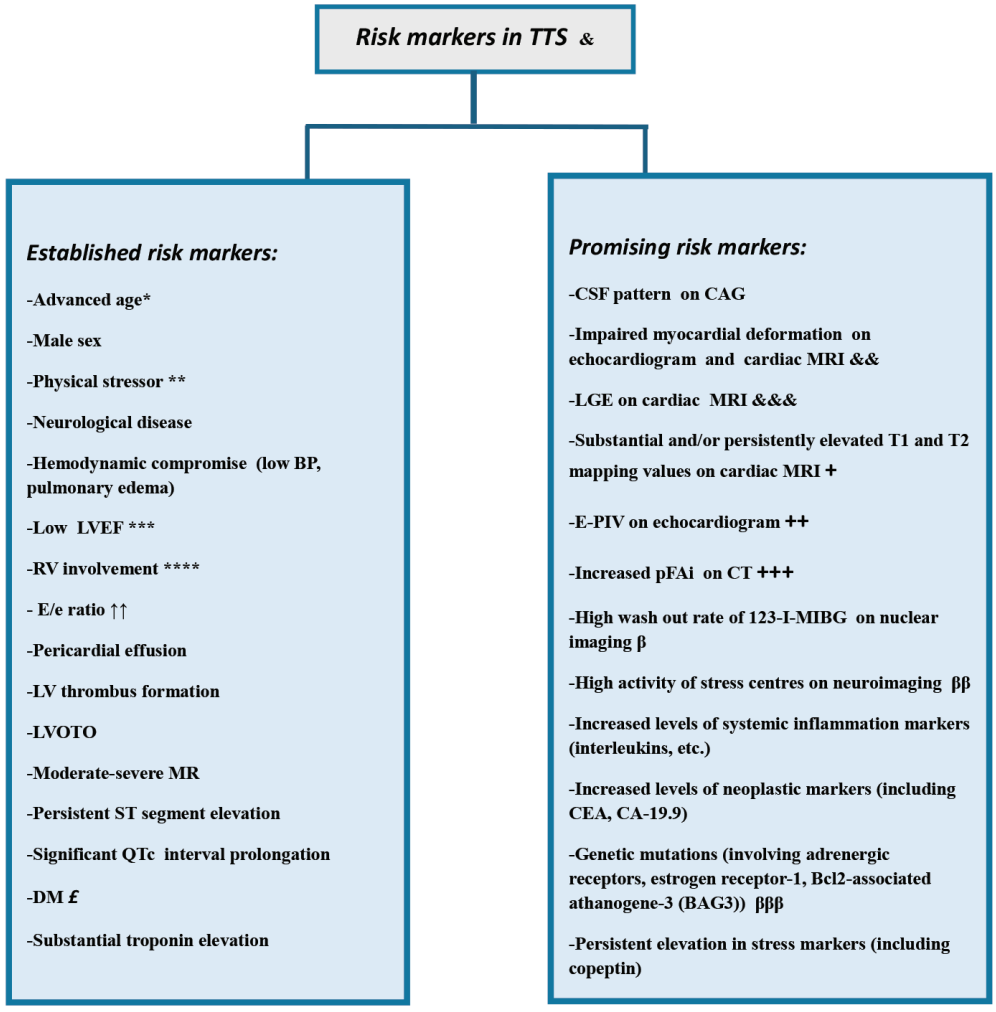

FIG. 3. A summary of established and promising risk markers in patients with TTS.

TTS, Takotsubo syndrome; CSF, coronary slow flow; CAG, coronary angiogram; LVEF, left ventricular ejection fraction; RV, right ventricle; BP, blood pressure; LVOTO, left ventricle outflow tract obstruction; MR, mitral regurgitation; DM, diabetes mellitus; LA, left atrium; MRI, magnetic resonance imaging; E-PIV, echocardiographic particle imaging velocimetry; pFAi, pericoronary fat attenuation index; CT, computed tomography; MIBG, metaiodobenzylguanidine; IL, interleukin; CEA, carcinoembryonic antigen; CA, carbohydrate antigen.

&: The listed risk markers are based on references[33,34,36,45,46,48,49,50-52,56-69,71,85,86]

**: Definition of advanced age varies in reports. It is mostly regarded as an age of > 70 years[46,50] or > 75 years.[47]*

***: Physical stressors are more likely to be associated with atypical TTS variants includind midventricular and basal TTS.[46]*

****: Definition of high-risk LVEF also varies in various reports (LVEF < 30%[46] or ≤ 35%[47] or ≤ 45%[50]). LVEF is also incorporated into certain risk scores (including the GEIST score) as a variable with decimal values (ranging between 0.15 and 0.70).[49]*

*****: May manifest as "reverse McConnell"s sign.[45]*

£: Even though DM was reported as an independent predictor of long-term mortality,[46] and was included in the interTAK prognostic score that predicts short and long term outcomes,[50] it might paradoxically exert a protective effect against TTS recurrence.[73]

&&: Impaired left ventricular global longitudinal strain (LV-GLS) and left atrial deformation were reported to be associated with in-hospital complications and mortality.[52,56,57] Persistent abnormalities in LV-GLS might be associated with poor exercise tolerance following TTS recovery.[52] Impaired LV-GLS, RV GLS and dysfunctional left atrium on feature tracking MRI were reported as markers of long-term mortality.[52,59,68]

&&&: A relatively low-intensity LGE may be present in a subset of TTS patients.[85,86] In this context, LGE was suggested to be associated with a higher incidence of cardiogenic shock and delayed recovery.[86] However, LGE was reported to disappear within 12 months.[85]

+: Higher native T2 values (extracellular water) were suggested to be associated with ECG changes, acute complications and delayed recovery.[52,68] Persistently elevated native T1 values (fibrosis, infiltration) might be associated with exercise limitation on exercise testing and delayed recovery.[52,68]

++: E-PIV reflects intraventricular energy dissipation (which is impaired in the setting of poor LV functions). However, E-PIVmay be relatively preserved in TTS compared with AMI. Its prognostic significance in TTS remains to be established.[52]

FIG. 3. Continued

+++: pFAi was suggested as an idependent predictor of cardiac mortality in the setting of non-obstructive CAD.[58] Patients with TTS were reported to have higher pFAi values compared with control subjects.[52] However, its prognostic significance in TTS needs to be established.[52]

β: High wash out rates in ^{123}-I-MIBG appear to be associated with excessive sympathetic activation. and might denote delayed TTS recovery and complications.[60]

ββ: A high amygdala activity at baseline [as measured with 18-flurodeoxyglucose (^{18}F-FDG) positron emission tomography/computed tomography, (PET/CT)] may independently predict TTS[67] and possibly its recurrences.[52]

βββ: Patients with TTS were reported to have an higher incidence of Arg389Gly variation in β1 receptors compared with healthy controls. However healthy controls had an higher incidence of Gln27Glu variation in β2 receptors.[63] BAG-3 is upregulated in cardiomyocytes as a protective mechanism in response to adrenaline. An existing g2252c polymorphism in the BAG3 3′-untranslated region (3′-UTR) potentially ends up with inhibition of binding of miR- 371a-5p leading to an altered response to adrenaline due to impaired BAG-3 upregulation in patients with TTS.[64] Genetic mutations may account for familial clustering of TTS and TTS recurrences.[52,63]

3. CHALLENGES AFTER TTS RECOVERY

3.1. TTS recurrence

- Risk factors and clinical aspects

There is nothing that looms above more distressingly in patients who have suffered an episode of TTS, than the fear of a TTS recurrence;[72] indeed, in the layman's conceptualization, it is incomprehensible/frightening, that one could suffer a "heart attack" in the absence of a "blockage of the heart's blood perfusing vessels". The pathogenesis of TTS is still elusive, and thus its TTS recurrence is mechanistically equally unexplainable. Nevertheless, there are certain risks (female sex, postmenopausal state, emotional/physical stresses, cancer, neurological/psychiatric illnesses) that predispose to TTS and its recurrence. Data on TTS recurrence derive from TTS registries[73,74] and patient cases and case series from the reported world literature.[75,76] However, absence or short follow-up of patients, who have suffered a TTS episode, misdiagnosis, and underreporting, suggests that the TTS recurrence rate is higher than currently reported.[72] Indeed, many episodes of seemingly first TTS presentations are recurrent TTS episodes, with previous TTS occurrences, misdiagnosed as cases under the broad rubric of "ACSs".[72,76] The rates of TTS recurrence reported in the literature vary between 1.5% and 5% after a TTS episode.[72-75]

Risks for TTS recurrence appear to be the same as the ones associated with a first TTS episode, although severe LV dysfunction during the initial TTS event, younger age in female patients, neurological/psychiatric disorders, and HT, appear to predispose patients to TTS recurrence.[73,74,76,77] Physical and/or emotional triggers are either different or the same for the initial TTS and recurrent TTS episodes.[73,74,76] The phenotypic morphological presentation (e.g., apical, mid-ventricular, reverse, focal) are either the same or may differ between index TTS or recurrent TTS episodes;[73,74,76] regarding the latter, it has been previously hypothesized that the myocardial territory involved in the first TTS episode may be "protected" in the subsequent TTS recurrence, via some mechanism reminiscent of "ischemic preconditioning", thus leading to a different myocardial segment being involved in the TTS recurrence than in the original TTS episode. Multiple TTS recurrences have been encountered, with many, several years apart.[72,76] Of interest is that patients who have suffered a TTS episode in the setting of a non-invasive/invasive procedures, anesthesia/surgery may not suffer a TTS recurrence, under the same "triggering/predisposing" circumstances, compounding further the complexity surrounding the pathophysiologic milieu of risks/predisposing factors/triggers, initiating/maintaining the TTS cascade.[78]

Diagnosing an index episode of TTS and subsequent TTS recurrence requires a high index of suspicion (with the latter providing advantages), and it requires a holistic assessment of patients presenting with chest pain, dyspnea, arrhythmias, syncope, HF, and cardiogenic shock. Many such patients are treated for hours or days as cases of ACS, with CAG providing the differentiation between ACS and TTS. However, it should be kept in mind that patients with TTS are not immune to preceding or subsequent to TTS presentation ACS episodes, and indeed some may have both an ACS and TTS, during a particular clinical encounter, with one precipitating the other. What is encouraged herein is an "out of the beaten path" attitude, unlike the notion that only CAG will provide the answers; accordingly, even before CAG, one should engage in an inquiry about the presence/absence of risk factors, gender of the patient, possible physical/emotional triggers/comorbidities, frequent auscultation and implementation of point of care ultrasound assessment, using portable/hand-held devices, to evaluate for evidence of LV regional contraction abnormalities and transient/persistent MR and/or LVOTO. **Tables 1, 2** demonstrates risk factors and clinical features of TTS recurrences, respectively.

- Management strategies

Management of TTS and TTS recurrence is not specific and is based on the pharmacological LV assist device armamentarium, employed for patients with ACS and all other cardiovascular maladies. Reassurance and psychological/psychiatric counseling for patients who have suffered TTS to allay their fears about a future TTS recurrence is paramount. Of particular importance is the handling of patients who had a previous TTS episode while undergoing particular procedures, which need to be repeated, where sedation and psychological support often has been found effective in preventing a TTS recurrence. There are no specific medications which have been found to prevent TTS recurrence,

TABLE 1. Risk Factors for TTS Recurrence.

Emotional/physical stresses[72-77] (However, patients occasionally may safely withstand repeat procedures/anesthesia/surgery, which have previously triggered TTS[78]
Female sex[72-77]
Postmenopausal state[72-77]
Neurological/psychiatric illnesses[72-77]
Cancer[72-77]
Hypertension[72-77]
Severe left ventricular dysfunction during the initial TTS episode[73-77]
Diabetes mellitus may exert a protective effect for TTS recurrence[73]

TTS, Takotsubo syndrome; ACS, acute coronary syndrome; references are included in parentheses.

TABLE 2. Clinical Features of Recurrent TTS.

- TTS recurrence is underdiagnosed (i.e., mild cases, misdiagnosed as ACS, no or short follow-up) and underreported in the literature[72-75]
- Some cases in the literature diagnosed as 1st episode(s), represent in reality recurrent TTS, since previous episodes of TTS, have been misdiagnosed as ACS[72,76]
- TTS recurrences, occasionally many years apart, occur[72,76]
- Physical and/or emotional triggers are either different or the same for the initial and recurrent TTS episode(s)[73,74,76]
- The phenotypic morphological variants are either the same or different in the index and recurrent TTS episodes[73,74,76]
- A protection of a previously involved with TTS myocardial territory, has been occasionally observed in TTS recurrence[72]

TTS, Takotsubo syndrome; ACS, acute coronary syndrome; references are included in parentheses

although angiotensin converting enzyme inhibitors/angiotensin receptor blockers (with more invariance) and β-blockers (with some variance) after discharge from a TTS episode have been associated with reduced TTS recurrence rates;[72,75,77] most clinicians currently employ both, after episodes of TTS/TTS recurrence, with proper management of all other comorbidities.

KEY POINTS

- Patients with an index episode of TTS can suffer one or more recurrent TTS episode(s), shortly after their discharge to 5, 10, or even 20 years, thereafter.
- Triggers for TTS episode(s) can be the same or different than the one which had precipitated the index TTS episode.
- Female sex, postmenopausal state, HT, cancer, severe LV dysfunction during the index TTS episode and neurological/psychiatric disorders were reported as risk factors. Diabetes may have a protective role.
- Morphological phenotypes (i.e., apical, mid-ventricular, reverse) may be the same, but frequently differ, from the index TTS episode.
- Patients should be reassured following their index TTS episode, be provided with psychological/psychiatric counseling, treated with angiotensin converting enzyme inhibitors/angiotensin receptor blockers/β-blockers, and have all their comorbidities properly managed.

3.2. Persisting symptoms following TTS recovery: Potential mechanisms and clinical implications

Despite common perception that TTS is a benign, self-limiting condition, newer data suggest that patients may have persistent myocardial functional/structural abnormalities, associated with limiting symptoms and poor prognosis. Indeed, prospective data suggest that after the acute phase, TTS patients experience similar rates of adverse cardiovascular events (9.9% per year) and mortality (5.6% per year) compared to individuals with ACS.[79] Prognosis is particularly poor when TTS was triggered by physical stressors (trauma, acute illness, infections, neurological disorders) and in individuals with evidence of persistent myocardial dysfunction.[46,80]

Several mechanisms have been purported to explain the persisting symptoms and functional impairment in TTS. Cardiac MRI has documented slowly resolving global myocardial oedema, which persisted > 3 months following the acute phase in symptomatic patients with prior TTS without MRI evidence of myocardial fibrosis (i.e. LGE).[81] The extent of myocardial oedema was associated with increased total LV mass, regional contractile abnormalities and elevated levels of catecholamines and natriuretic peptides.[81] A study employing radionuclide magnetic resonance spectroscopy and imaging also revealed severe global myocardial oedema, associated with significant impairment in myocardial energetics with incomplete resolution of both abnormalities 4 months after the acute event.[82] Moreover, multiparametric cardiac MRI, combined with the assessment of inflammatory mediators, suggested signs of myocardial inflammatory infiltration and low-grade systemic inflammation that persisted for at least 5 months after the acute event.[83] Findings of an echocardiographic study suggested that, despite normalization of global LV ejection fraction and volumes, patients with prior TTS demonstrated regional LV systolic and diastolic deformation abnormalities that persisted months after

the acute event.[84] Although earlier studies indicated the absence of myocardial fibrosis (i.e. LGE on cardiac MRI) as a hallmark of TTS, later findings revealed that LGE can be detected, and that LGE-positive patients have longer recovery times compared to those without myocardial fibrosis.[85,86] RV involvement was also implicated in worse clinical course during the acute phase and prolonged recovery.[87]

Prolonged and incomplete recovery has clinical implications, leading to persistent symptoms and functional limitations. Some patients continue to experience anginal pain, exertional dyspnoea, poor exercise tolerance, palpitations, anxiety, and depressive reactions for many months following the acute phase.[88] An observational study revealed that 88% of patients experienced symptoms consistent with HF > 12 months after index event and demonstrated signs of impaired exercise tolerance (decreased peak VO_2) on cardiopulmonary stress exercise testing.[89] Persisting symptoms, combined with anxiety/depression, increase the risk of TTS recurrence, despite apparent recovery of LV function.[73]

Specific, evidence-based strategies for the management of patients with TTS are currently lacking. In an observational study, the use of renin-angiotensin-system inhibitors after the acute phase was associated with improved 1-year survival and lower rates of recurrence.[79] Despite catecholamine excess being implicated in both acute and late manifestations of TTS, treatment with beta-blockers was not association with improved outcomes, but may ameliorate palpitations due to cardiac arrhythmia.[79] Patients with persisting symptoms and objective evidence of HF (elevated natriuretic peptide levels, congestion and documented cardiac dysfunction) should receive guideline recommended HF medications.[90]

KEY POINTS

- After the acute phase, a subset of patients with TTS may experience persistent myocardial functional/structural abnormalities, associated with limiting symptoms and poor prognosis.
- Objective evidence of prolonged myocardial oedema, impaired cardiac energetics, myocardial and systemic inflammation and more severe global and regional contractile abnormalities have been associated with persisting symptoms.
- There is no evidence-based therapies available for TTS, but patients should receive guideline-recommended medications if diagnosed with HF.

4. CONCLUSION

TTS may present with a variety of specific entities that need to be further established. In particular, sudden intraventricular gradient was previously described in patients with TTS. From a pathogenetic perspective, this phenomenon, besides being regarded as a complication of TTS, may also have the potential to directly trigger apical ballooning in susceptible subjects lagely through a variety of mechanisms including afterload mismatch. This form of mechanically-triggered ballooning pattern appears to be pathophysiologically different from the classical neurogenic stunning, and has important diagnostic, therapeutic and prognostic implications. Another phenomenon, CSF on invasive CAG, has been relatively frequent in patients with TTS. Among the various speculated mechanisms, compression of microcirculation by the stunned myocardium seems to be the most plausible one. Importantly, CSF may also have prognostic implications. Finally, rapid morphological transition has been a very rare phenomenon with poorly understood implications in patients with TTS.

On the other hand, TTS may be associated with particular challenges after its full recovery. One such challenge is the clinical recurrence emerging even several years after the index event. However, there has been no proven strategy to effectively prevent TTS recurrences. Interestingly, despite full recovery of systolic functions on imaging modalities, some patients may suffer persistent symptoms largely attributable to the residual functional and structural myocardial abnormalities (including impaired myocardial energetics, myocardial inflammation, etc.). Importantly, persistent symptoms may also be associated with an adverse prognosis in patients with TTS. Finally, risk-stratification of TTS in the short and long terms still poses a significant challenge, and requires further strategies. In this context, harnessing promising markers and tools (including markers of systemic inflammation, advanced cardiac imaging, neuroimaging, etc.) on top of conventional strategies may improve risk-stratification. However, this should be tested in further studies.

Author Disclosures: Mehmet Birhan Yılmaz: Institutional fee from Novartis, Bayer, Amgen, Astra Zeneca, Boehringer Ingelheim, Novo Nordisk, Albert Health., Robert J Gil: Speaker bureau/honoraria/travel grants/proctorship fees: Novartis, Pfizer, Servier, Astra Zeneca, Medtronic, Philips, Amgen, Abdallah Almaghraby: Speaker bureau/honoraria/travel grants/proctorship fees: Boehringer Ingelheim, Astra Zeneca, Novartis., Biykem Bozkurt: Abbott, Abiomed, Amgen, Astra Zeneca, Bayer, Boehringer Ingelheim, Cardurion, Daiichi Sankyo, Janssen, Novo Nordisk, Renovacor, Respicardia/Zoll, Roche, Salubris Pharmaceuticals, Sanofi-Aventis, Vifor., Gani Bajraktari: Speaker bureau/honoraria/travel grants: Krka, Novartis, Alkaloid, Bosnalijek. Vassil Traykov: Speaker bureau/honoraria/travel grants/proctorship fees: Boehringer Ingelheim, Novartis, Pfizer, Servier, J&J, Astra Zeneca, Medtronic, Abbott, Biotronik, Cecilia Linde: Research support from the Swedish Heart Lung Foundation, Swedish Society of Science, Stockholm County Council, consulting fees from AstraZeneca, Roche Diagnostics, speaker honoraria from Novartis, Astra, Bayer, Vifor Pharma and Medtronic, and Impulse Dynamics and serves on advisory boards for Astra Zeneca. The other authors did not declare any disclosures

Authorship Contributions: Concept- K.Y., J.E.M., N.G.K., S.Y.H., M.P., S.A., A.M., M.B.Y., Y.L., M.A.M., R.J.G., R.T., A.A., B.B., G.B., T.F., V.T., S.M.S., U.M., S.S., Z.V.K., C.L., P.M.S., Design- K.Y., J.E.M., N.G.K., S.Y.H., M.P., S.A., A.M., M.B.Y., Y.L., M.A.M., R.J.G., R.T., A.A., B.B., G.B., T.F., V.T., S.M.S., U.M., S.S., Z.V.K., C.L., P.M.S., Supervision- K.Y., J.E.M., N.G.K., S.Y.H., M.P., S.A., A.M., M.B.Y., Y.L., M.A.M., R.J.G., R.T., A.A., B.B., G.B., T.F., V.T., S.M.S., U.M., S.S., Z.V.K., C.L., P.M.S., Fundings- K.Y., J.E.M., N.G.K., S.Y.H., M.P., S.A., A.M., M.B.Y., Y.L., M.A.M., R.J.G., R.T., A.A., B.B., G.B., T.F., V.T., S.M.S., U.M., S.S., Z.V.K., C.L., P.M.S., Materials- K.Y., J.E.M., N.G.K., S.Y.H., M.P., S.A., A.M., M.B.Y., Y.L., M.A.M., R.J.G., R.T., A.A., B.B., G.B., T.F., V.T., S.M.S., U.M., S.S., Z.V.K., C.L., P.M.S., Data Collection or Processing- K.Y., J.E.M., N.G.K., S.Y.H., M.P., S.A., A.M., M.B.Y., Y.L., M.A.M., R.J.G., R.T., A.A., B.B., G.B., T.F., V.T., S.M.S., U.M., S.S., Z.V.K., C.L., P.M.S., Analysis or Interpretation- K.Y., J.E.M., N.G.K., S.Y.H., M.P., S.A., A.M., M.B.Y., Y.L., M.A.M., R.J.G., R.T., A.A., B.B., G.B., T.F., V.T., S.M.S., U.M., S.S., Z.V.K., C.L., P.M.S., Literature Review- K.Y., J.E.M., N.G.K., S.Y.H., M.P., S.A., A.M., M.B.Y., Y.L., M.A.M., R.J.G., R.T., A.A., B.B., G.B., T.F., V.T., S.M.S., U.M., S.S., Z.V.K., C.L., P.M.S., Writing- K.Y., J.E.M., N.G.K., S.Y.H., M.P., S.A., A.M., M.B.Y., Y.L., M.A.M., R.J.G., R.T., A.A., B.B., G.B., T.F., V.T., S.M.S., U.M., S.S., Z.V.K., C.L., P.M.S., Critical Review- K.Y., J.E.M., N.G.K., S.Y.H., M.P., S.A., A.M., M.B.Y., Y.L., M.A.M., R.J.G., R.T., A.A., B.B., G.B., T.F., V.T., S.M.S., U.M., S.S., Z.V.K., C.L., P.M.S.

Peer Review: Servet Altay is a member of the Editorial Board of the Balkan Medical Journal. However, he was not involved in the editorial decision of the manuscript at any stage.

Conflict of Interest: The authors declare that they have no conflict of interest.

Funding: The authors declared that this study received no financial support.

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