Cardiovascular Revascularization Medicine 20 (2019) 153–166

Contents lists available at ScienceDirect

Cardiovascular Revascularization Medicine

Review

Takotsubo syndrome: State-of-the-art review by an expert panel – Part 2

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ARTICLE INFO

Article history:
Received 14 November 2018
Accepted 14 November 2018

Keywords:
Takotsubo
Heart failure
Catecholamine

ABSTRACT

In part 2 of this two-part manuscript on takotsubo syndrome (TTS), we discuss typical biomarkers (particularly excess catecholamines and what kinds of electrocardiographic information operators should look for) and numerous complications the syndrome can cause. This consensus paper is the result of a multinational effort aiming to summarize the current state of the art on TTS. Several novel and unique sections are emphasized in this document, including the current state of the art on genetics of takotsubo syndrome, microRNAs (miRs), racial differences, role of cardiac spectroscopy and intracoronary imaging, as well as mechanical circulatory support.
New structured algorithms are also proposed to aid clinicians in the decision-making process as well as future directions for research given the current lack of evidence-based medical approaches.

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Abbreviations: ACS, acute coronary syndrome; BNP, B-type natriuretic peptide; CRP, C-reactive protein; LV, left ventricle/ventricular; MACE, major adverse cardiac events; miRs, microRNAs; RV, right ventricle/ventricular; STEMI, ST-elevation myocardial infarction; TIMI, Thrombolysis in Myocardial Infarction; TTS, takotsubo syndrome.

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https://doi.org/10.1016/j.carrev.2018.11.016
1553-8389/

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1. Workup

1.1. Biomarkers

As patients with TTS and ACS commonly present with similar symptoms, distinguishing one disease from the other remains a challenge in the clinical setting [1].

Although several biomarkers have been proposed for the differential diagnosis of TTS, currently there is no specific and sensitive biomarker for TTS (Table 1).

1.2. Brain natriuretic peptide (BNP) and N-terminal-pro-BNP (NT-proBNP)

TTS is associated with severe LV dysfunction, and subsequently, brain natriuretic peptides, i.e., BNPs, NT-proBNPs, rise within the first few hours after the onset of symptoms, in response to myocardial stretch [1,2]. NT-proBNP levels correlate with plasma catecholamine levels as well as the wall motion score index and LV ejection fraction. As a consequence, BNP levels are higher in patients with typical TTS vs. atypical TTS, i.e., mid-ventricular-, inverted- or focal TTS [2].

Table 1
Biomarkers. Laboratory diagnostic tests to distinguish TTS and ACS/AMI.

Natriuretic peptides	BNP, NT-proBNP
Markers of myocardial necrosis	troponin I, troponin T, hsTn, myoglobin, CK, CK-MB
Catecholamines	metanephrine, normetanephrine
Other biomarkers	copeptin, sST2, sLOX-1, IMA
MicroRNAs	miR-16, miR-26a, miR-1, miR-133a
Relative elevation of different Biomarker assays	NT-proBNP/TnT, BNP/TnT, BNP/CKMB, BNP/TnI, NT-proBNP/myoglobin, hs-TnT/CKMB, copeptin/NT-proBNP

ACS = acute coronary syndrome; AMI = acute myocardial infarction; BNP = Brain natriuretic peptide; NT-proBNP = N-terminal proBNP; sLOX-1 = soluble lectin like oxidized LDL receptor-1; CK-MB = Creatine kinase-MB fraction; sST2 = soluble suppression of tumorigenicity-2.

1.3. Troponin (Tn), Creatine kinase (CK), CK-MB

Although autopsy specimens are not characterized by the histological features of infarction, serum troponin levels are usually positive in the acute course of TTS [3]. Troponin levels are relatively low as compared to the extent of myocardial dysfunction peaking earlier in TTS than ACS (6 h vs. 12 h) [4,5].

Although a vast body of literature describes higher markers of cardiac necrosis in ACS when compared to TTS on admission, the last report from the largest InterTAK Registry did not reveal significant differences in troponin levels. Interestingly, no differences were noted in Tn levels between patients with typical and atypical TTS [2]. Recently, the hs-TnT/CKMB ratio has been presented as a potential novel, readily available parameter to distinguish TTS from MI [6].

1.4. Catecholamines and other biomarkers

Despite the widely recognized pathophysiological role of catecholamine excess in TTS, its diagnostic role remains uncertain. Although initial reports showed markedly higher plasma catecholamine levels at presentation in TTS vs. acute myocardial infarction [7], recent studies have demonstrated similar plasma normetanephrine, metanephrine and cortisol levels as well as normal 24-hour urine catecholamine values in both subsets [8]. On the other hand, soluble lectin-like oxidized LDL receptor-1 (sLOX-1) elevation has been found comparable to troponin rise in ACS and essentially lower in the non-ACS setting

comprising TTS patients [8]. The soluble suppression of tumorigenicity-2 (sST2) can be an additional predictive value for TTS in patients with normal TnI. Thus, a combination of sST2 and cTnI may be useful to predict TTS in patients referred for invasive diagnostics due to the prior diagnosis of ACS. Last but not least, copeptin, a novel sensitive biomarker of endogenous stress response, was markedly elevated in TTS vs. AMI.

1.5. MicroRNAs (miRs)

MicroRNAs (miRs) are a class of highly conserved, small noncoding mRNA transcribed as regions of longer RNA molecules that can be as long as 1000 nt [9].

MiRs are implicated in regulating diverse cellular processes, such as proliferation, differentiation, development, and cell death [9]. MiRs are considered to act as intracellular endogenous RNAs controlling gene expression at a posttranslational level. In some pathological conditions, miRs in the systemic circulation may reflect tissue damage [9]. Interestingly, their tissue- and cell-specific expression profile can directly reflect the status of the disease. Recent studies have revealed the role of miR in a variety of basic biological and pathological processes, and as sensitive biomarkers in some conditions, for instance, cardiac hypertrophy, heart failure, acute hind-limb ischemia, myocardial infarction, and coronary artery disease.

In 2013, Jaguszewski et al. proposed a unique signature of circulating miRs (miR-1, miR-16, miR-26a, and miR-133a) as a biomarker suitable for confirming the diagnosis of an acute TTS, and for distinguishing TTS from acute MI, thus suggesting a different etiology for both conditions [10]. Interestingly, the up-regulation of stress and depression biomarkers (miR-16 and miR-26a) suggests a close connection between TTS and neuropsychiatric disorders. A down-regulation of endothelin-1 (ET-1)-regulating miR-125a-5p and increased ET-1 plasma levels stresses the potential mechanistic hypothesis of microvascular spasm in TTS [10]. The field of circulating miRs is expanding rapidly and holds great promise to become an important diagnostic tool to differentiate TTS from myocardial infarction.

1.6. Detailed electrocardiographic information

The classic evolutionary electrocardiographic changes that have been described in TTS include transient ST segment elevation, most commonly in anterior leads, followed by development of diffuse T-wave inversion involving most leads, as well as prolongation of the corrected QT interval [11].

These ECG changes are similar to those seen in patients with anterior STEMI [12].

The prevalence of ST elevation has been described with a wide variability, with a prevalence from 11% to 100% [11].

Four ECG phases have been described in TTS: Phase 1, initial ST elevation; Phase 2, initial T-wave inversion after ST elevation from days 1 to 3; Phase 3, transient improvement in T-wave inversion in the subacute period; Phase 4, second deeper T-wave inversion persisting for several months (Fig. 1).

T-wave inversion is the most prevalent ECG abnormality after 24 h, reaching a plateau between days 2 and 30; with 17% of patients having residual T-wave inversion up until 1 year.

It has been reported than African-Americans more commonly present with diffuse T-wave inversions and QTc prolongation, which is more consistent with a non-STEMI picture. The most common ECG abnormalities in Hispanics include T-wave inversions, followed by ST elevations and ST depressions [13,14].

Several detailed ECG findings in TTS include more frequent ST elevations in inferior leads, with a percentage ranging from 30 to 50% [15]; ST depression in aVR (also known as ST elevation in -aVR); and a longer maximal QTc interval with normalization by day 14. TTS has been less frequently associated with ST elevation in V1 or with pathologic Q waves, with a prevalence of 10%, with complete resolution by one month.

In TTS patients presenting with ST elevations, the ST elevations are less prominent than in STEMI, and there tends to be absence of reciprocal ST depression [13].

TTS has previously been associated with transient attenuation of the amplitude of QRS complexes when compared to a prior ECG, or low voltage QRS on admission ECG [16].

Some authors have attempted to develop a systematic approach to differentiate TTS from acute coronary syndrome using ECG criteria. Frangieh et al. reported that patients with ST depression in aVR and ST elevation in anteroseptal leads or ST elevation in inferior leads or concomitant T-wave inversion in any lead without ST elevation in V1 was 98–100% specific for TTS, with a sensitivity of 8–14% [17]. When ST depression was present in V2 to V4 or the inferior leads, with associated ST elevation in aVR, there was ⩾95% specificity for acute coronary syndrome.

Mugnai et al. reported that the combination of lack of ST elevation in lead V1, absence of abnormal Q waves, and ST depression in aVR identified TTS with a specificity of 95% and positive predictive value of 85.7% [18].

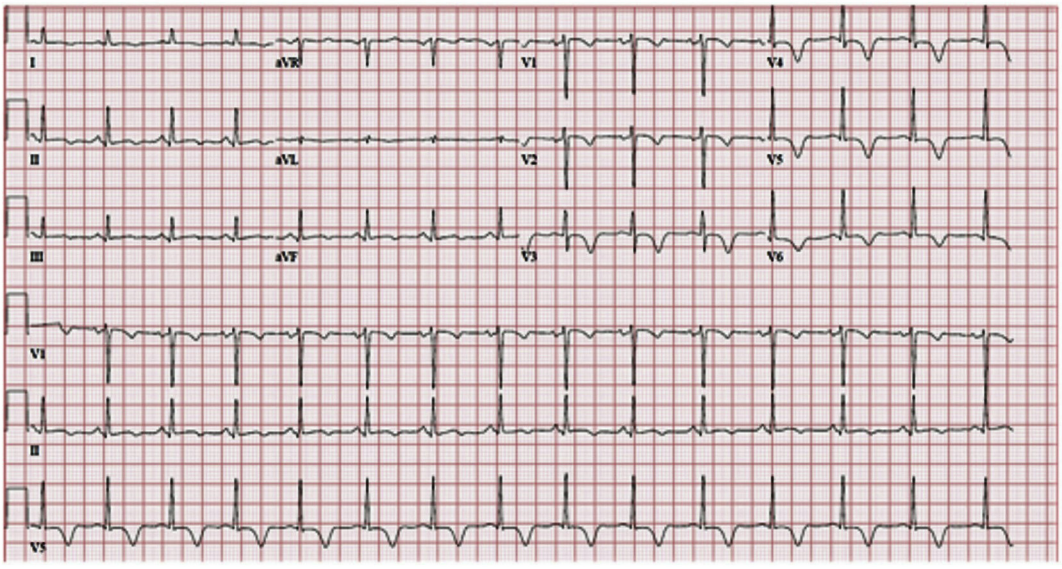

Fig. 1. 12 lead electrocardiogram with deep T wave inversion of a 62-year-old African American woman with TTS.

1.7. Transient reduction of the amplitude of the QRS complexes

The full array of the electrocardiogram (ECG) changes, pertaining particularly to repolarization and associated with all forms of acute coronary syndromes (ACS), have been encountered in patients with all topographic variants of TTS; thus, ST-segment elevations and depressions, and inverted and upright T-waves in various groups of ECG leads have been described [19,20]. In reference to changes in the QRS complexes, q- and Q-waves have been noted in patients with TTS early in the clinical course, abolished in subsequent ECGs. Review of ECGs of published TTS cases has disclosed that often the voltage amplitude of the QRS complexes is low (<5 mm in the limb leads and <10 mm in the precordial leads) (lQRS), or in case reports of patients with ≥2 ECGs, a transient attenuation of the QRS complexes (attQRS) is occasionally appreciated (Fig. 2). Previous work has shown that peripheral edema, particularly anasarca, of various etiologies, is associated with reversible attQRS, attributed to a decrease in the electrical impedance of the edematous body volume conductor [21].

Indeed edematous states affect the heart itself, via the compromise of its venous and lymphatic systems, in association with the edema apparent in the periphery [22]. TTS is characterized by transient appearance of myocardial edema (ME), documented in serial cardiac magnetic resonance imaging [23].

The above was the impetus to systematically explore the published literature of the association of TTS and the ECG attQRS. In a meta-analysis involving a total of 368 patients with TTS, lQRS was found in 91.5% of 200 patients with TTS and one ECG, with a distribution of 49.0, 42.8, 51.0, 52.0, and 46.9% in lead aVR, and inferior, anterior, lateral, and high lateral ECG lead groups, respectively, and attQRS as seen in 93.5% of 168 patients with TTS and ≥2 ECGs, with a distribution of 78.3, 74.5, 60.1, 70.7, and 74.5% in lead aVR, and inferior, anterior, lateral, and high lateral ECG lead groups, respectively [16].

1.8. Role of iodine-123 meta-iodo-benzyl-guanidine (mIBG)

Iodine-123-metaiodobenzylguanidine (^{123}I-mIBG) is a radioactive tracer that is analogue to noradrenaline in regard to presynaptic uptake, storage, and release [24,25] and ^{123}I-mIBG scintigraphy can therefore be used to visualize cardiac sympathetic nerve activity in vivo. It is unlikely that mIBG will have a clinical indication for assessing patients with TTS, but the modality may be used to investigate the underlying pathophysiology of the TTS. Several studies have investigated mIBG imaging in patients with TTS, and the results are uniform. Overall cardiac sympathetic activity appears increased [24,26,27], but ^{123}I-mIBG uptake is reduced in the akinetic regions of the left ventricle when compared to the surrounding contracting myocardium.

Thus, TTS is clearly associated with increased cardiac sympathetic activity, and the typical regional impairment of ^{123}I-mIBG uptake may be caused by excess adrenergic activity that leads to akinesia and sympathetic axon terminal damage in the vulnerable middle to apical myocardium. The main limitation to the published studies is that all patients inherently were examined after the onset of TTS; therefore, it cannot be ruled out that the observed increase in cardiac sympathetic activity observed with ^{123}I-mIBG scintigraphy is an adaptive mechanism rather than the underlying cause of the syndrome.

1.9. Optical coherence tomography

Intravascular imaging using optical coherence tomography (OCT) or intravascular ultrasound (IVUS) may help us either elucidate some of the pathophysiological mechanisms behind TTS or understand the natural history of the disease in terms of recovery (some patients fully recover ejection fraction while others do not). The following findings have been reported in the literature: Virtual histology IVUS evaluation of the left anterior descending coronary artery in patients with transient left

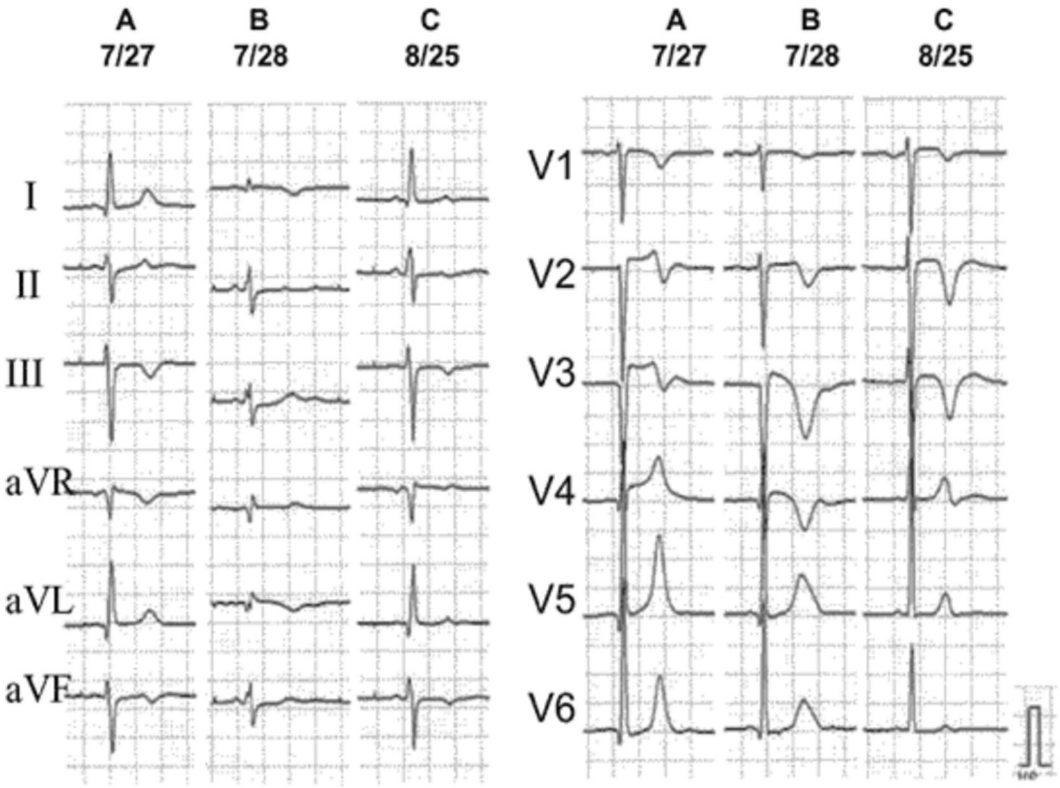

Fig. 2. Transient attenuation of the QRS complexes in a patient with TTS: ECGs on days 1, 2, and at 30-day follow-up of a 59-year-old woman with TTS following an epileptic seizure. Comparison of the ECG B with the ECGs A and C, reveals transient attenuation of the QRS complexes in the 6 limb and V1 and V2 leads.
(Reproduced and adapted from Sakuragi S et al. Heart Vessels 2007; 22:59–63, with the permission of Springer.)

ventricular ballooning syndrome found that there were 7 ruptured plaques, VH-TCFAs were found in 8 patients, 6 patients had a necrotic core >25%. The authors of this paper concluded that vulnerable plaques are observed in patients with TTS and even implied that the syndrome may be related to the natural course of atherosclerotic plaque development [28].

In another similar study, but using only IVUS grayscale in a limited number of patients, the authors did not find any plaque rupture; positive remodeling or intracoronary thrombus were absent in patients suffering from this disease [28].

There have been also reports using OCT (Fig. 3). In 23 consecutive patients, OCT in LAD to LMT was performed. Sixteen patients showed atherosclerotic plaque in the LAD or both LAD and LMT. Predominant fibrocalcific plaque: 52%, lipid rich plaque: 30.4%, TCFA: 26.1% were found, but ruptured plaque and intracoronary thrombi were not observed [29]. Some other isolated case reports using OCT did not find plausible explanations related to TTS [29,30].

There have been reports showing either no atherosclerosis or advanced CAD concomitantly at the time of the event; whether this is anecdotal or related to the disease needs further investigation.

1.10. Angiography data

In TTS, the epicardial coronary arteries are typically normal and unobstructed. The initial set of criteria proposed by researchers from the Mayo Clinic for the diagnosis of TTS required the absence of obstructive CAD. However, these criteria were later modified, and the authors acknowledged that patients with obstructive CAD may also develop TTS [11]. Patients with TTS can have coexisting CAD, as reported by Templin et al. in the largest International Takotsubo Registry, a consortium of 26 centers in Europe and the United States including 1750 patients with TTS, 15.3% of patients with TTS had evidence of significant coexisting coronary artery disease on angiography [31]. This finding shows that the presence of CAD is not an exclusion criterion for the diagnosis of TTS.

Differentiating TTS from acute coronary syndrome in an individual patient can be a difficult task. This is particularly true in cases where the LAD is involved (Fig. 4). In cases with acute plaque rupture, thrombus formation, and coronary dissection, the role of ACS is clear. Recently, Chou et al. reported that 8% of patients with TTS diagnosis had been overlooked for spontaneous coronary artery dissection (SCAD) on careful review of coronary angiography [32].

Plaque rupture with subsequent transient thrombotic coronary occlusion by a fast-dissolving clot is one of the proposed pathogenic mechanisms in TTS. In subsequent studies of TTS patients who underwent IVUS, some degree of CAD was found. Those studies conclude that coronary lesion in the LAD causing an aborted MI was not the primary underlying cause of TTS and that nonobstructive CAD and TTS could coexist without sharing a direct causal association [28].

OCT in these patients has revealed a high prevalence of atherosclerotic plaques, including a considerable number of highly vulnerable

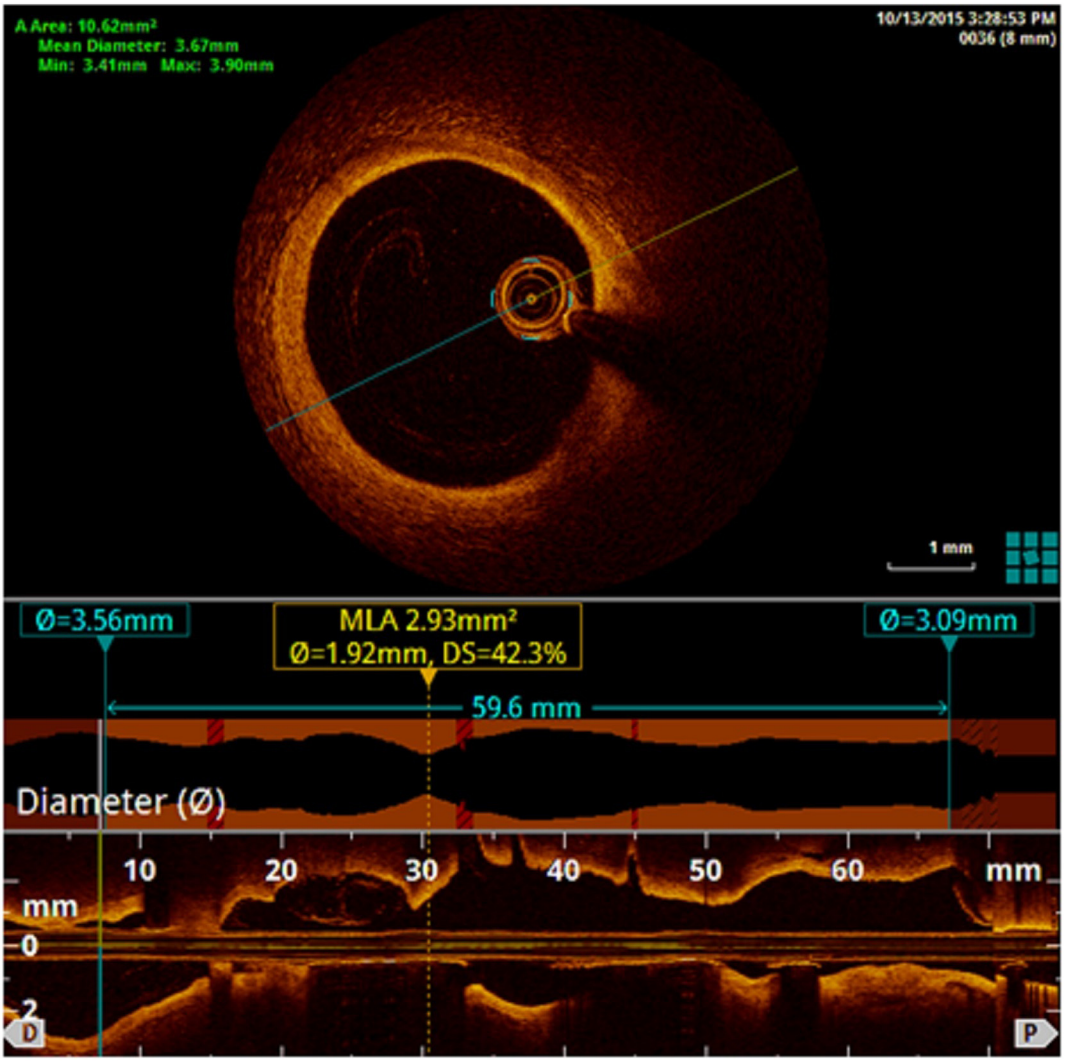

Fig. 3. OCT of TTS patient – coronary artery wall without evidence of significant plaque.

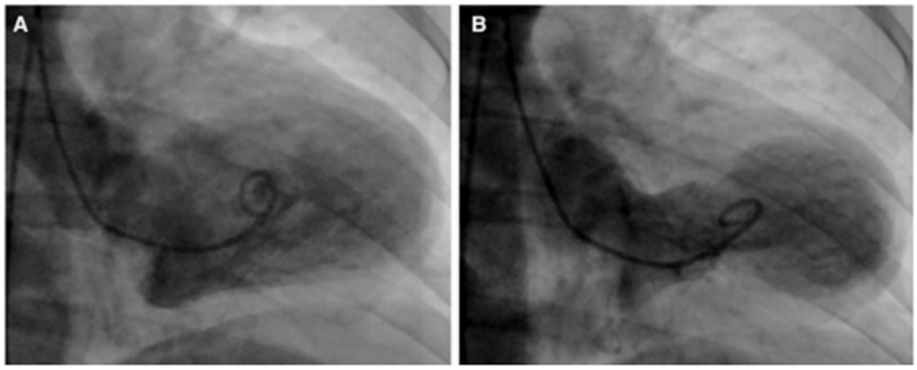

Fig. 4. Typical apical ballooning illustrated in the end-diastolic (A) and end-systolic (B) images from left ventriculography. (Courtesy Dr. Eitel et al. in Eitel I et al. J Am Heart Assoc. (2016).)

thin-cap fibroatheromas. However, ruptured plaques or intracoronary thrombi were not observed and are therefore most likely not the underlying mechanism of TTS [29].

1.11. MRI

Cardiac magnetic resonance (CMR) presents excellent anatomical information, enabling proper diagnosis and follow-up (Fig. 5) [33]. The diagnostic criteria for TTS using CMR have been proposed by Eitel et al. [34]; the absence of late gadolinium enhancement (LGE) in TTS is useful for differentiating TTS from myocardial infarction and other myocarditis. LGE exhibits the differences in the volume of distribution of gadolinium between the normal and diseased myocardium. However, clinicians should keep in mind that minor LGE can be found in patients with TTS. It has been reported that minor LGE is present in approximately 9% of patients with TTS when LGE is defined at a cutoff

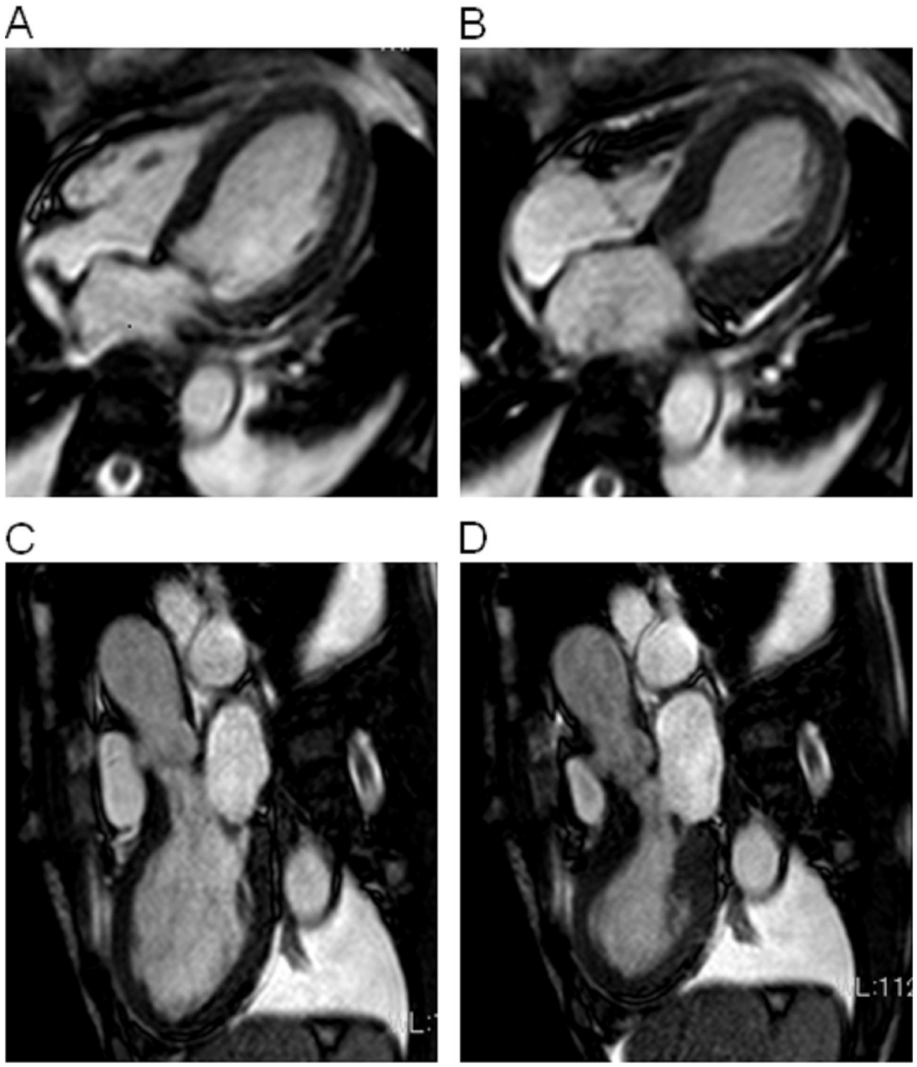

Fig. 5. Typical apical ballooning during the systolic period in the patient with TTS. Cine CMR (4-chamber view A-diastole, B-systole; 2-chamber C-diastole, D-systole).

value of >3 SD above the mean; however, none of those reveals evidence of LGE with a cutoff value of >5 SD above the mean [33].

CMR is useful to provide the accurate diagnosis for TTS and helpful to rule out acute coronary syndrome and myocarditis (Table 2).

Myocardial edema should be assessed before taking LGE images. Corresponding to the wall motion abnormality, high T2 signal intensity is usually observed in patients with TTS, without increasing ventricular mass or accompanying wall motion thickness [35]. The existence of myocardial edema is thought to be the presence of myocardial injury and inflammation. This edema, the finding of T2 high intensity, is gradually resolved after the wall motion is normalized (Fig. 6) [36].

CMR can provide not only the assessment of wall motion variabilities but also the calculation of extracellular volumes using T1 mapping technique [23]. This technique would be beneficial to observe specific phenomenon in TTS because of rapid increasing extracellular matrix in the myocardium. T2 mapping technique would be a promising option to quantity the volume of myocardial edema, although this new method has not been fully established in patients with TTS.

Volumetric CMR is valuable as three-dimensional modality to identify various cardiac function beyond the structure alone. Although the usefulness of the two- or three-dimensional speckle tracking echocardiography is clearly demonstrated [37,38], tracking technique using CMR is still for research use. Apical thrombus is often identified in patients with TTS; thus, CMR, including cine CMR and early gadolinium enhancement sequence, is useful to detect a thrombus.

1.12. Echocardiographic findings – systolic and diastolic mechanics cardiomyopathy

The acute depression in left ventricular ejection fraction brings no surprise that the strain and deformation of the entire left ventricle are profoundly abnormal. Perhaps the most extreme finding is the fact that the early propping twist disappears completely in the acute stage. This early motion occurs during isovolumic contraction and is directed clockwise at the apex and counterclockwise at the base (thus opposite to the normal direction of movement to follow during systole, like an athlete throwing a discus who first turns to the right before spinning leftward to throw). However, significant mechano-temporal alterations characterizing both systole (global longitudinal strain and apical circumferential strain, $p < 0.01$ for both; LV twist, twist rate, and torsion, $p < 0.0001$ for all) and diastole (untwist rate and time to peak untwisting, $p < 0.001$ for both) persist at 4-month follow-up compared with control subjects, despite normalization of LV ejection fraction and volumes. These findings show that there is a both a reduction in the amplitude of twist and untwist of the heart as well as a delay in the timing of these processes during the cardiac cycle [37].

Although the changes are subtle enough to allow a normal or near normal ejection fraction during this convalescent stage, they do affect the overall left ventricular twist, which has the potential to impact the stroke volume of these patients. It remains unknown at this stage whether this recovery is simply more protracted than initially assumed or if it is exhausted and results in a new clinical phenotype that remains to be defined. Nevertheless, the EF normalization remains clinically useful in consolidating the diagnosis at follow-up.

2. Complications

2.1. Acute heart failure syndrome

Acute heart failure syndrome in patients with TTS is unique in that it is completely reversible, usually one to four weeks after the triggering event. Patient symptoms may range from shortness of breath with or without pulmonary edema to cardiogenic shock, with the latter quite rare [39,40].

The prevalence of acute heart failure is reported in case series ranging from 12 to 45% followed by left ventricular outflow obstruction (10–25%), mitral regurgitation (14–25%), and cardiogenic shock (6–20%). This transient heart failure manifests with elevated brain natriuretic peptide (BNP) and elevated left ventricular end diastolic pressure (LVEDP) [41,42].

Upon presentation, patients can be risk-stratified into low- versus high-risk based upon several factors. Low-risk patients' ejection fraction is >45% and usually requires no treatment. High-risk patients, in addition to an ejection fraction <45%, may have right ventricular involvement contributing to low output syndrome and shock [4,43,44].

The mechanisms contributing to acute heart failure syndrome are complex and include both systolic and diastolic dysfunction. Elderly hypertensive patients with pre-existing septal hypertrophy may develop a dynamic left ventricular outflow tract obstruction (LVOTO) and further worsening of symptoms. Systolic anterior motion of the mitral valve increases mitral regurgitation as well as worsening of the LVOTO. In up to one-third of cases, right ventricular involvement has been reported, contributing to a marked decrease in left ventricular pre-load, low cardiac output syndrome, and possible shock. In addition to increasing tricuspid regurgitation, right ventricular involvement is associated with an increase in-patient mortality [31].

With chest pain as the most common symptom in TTS, the excellent temporal and special resolution found with newer coronary computed tomography angiography (CCTA) may provide evidence of lack of obstructive CAD, thus confirming the diagnosis. CMR provides addition diagnostic and prognostic information, including extent of right ventricular involvement, mitral regurgitation, LVOTO, SAM, and left ventricular thrombus.

Table 2
Differences in CMR features of TTS acute myocardial infarction and acute myocarditis (quoted with permission).

	Takotsubo syndrome	Myocardial infarction	Myocarditis
Site of wall motion abnormality	Concentric mid- and apical LV wall	Follows expected epicardial coronary artery distribution	Usually global unless regional edema/LGE is severe
Myocardial edema	Typically transmural in a concentric mid and apical LV wall distribution	Subendocardial or transmural at sites of wall motion abnormalities	Subepicardial, mid-myocardial or transmural
Left ventricular impairment	Yes: typically impaired ejection fraction with elevated indexed end systolic volume	Yes: typically impaired ejection fraction with elevated indexed end systolic volume	Yes, but may show only mild/borderline low normal ejection fraction
Right ventricular impairment	>33% of patients	May be seen, particularly if right coronary artery territory involved	Rarely impacts on right ventricular function
LGE	Maybe (10–40%)	Yes	Often
Site of LGE	Concentric transmural mid and apical LV wall	Typically subendocardial or transmural in recognized epicardial coronary artery distribution	Mid-myocardial or subepicardial in a focal non-coronary artery distribution
Type of LGE	Low-intensity LGE	Bright LGE	Low-intensity or Bright LGE
Microvascular obstruction	No	Maybe	No
Resolution at 3 months	Yes	No	Potentially but may show residual myocardial fibrosis and impairment

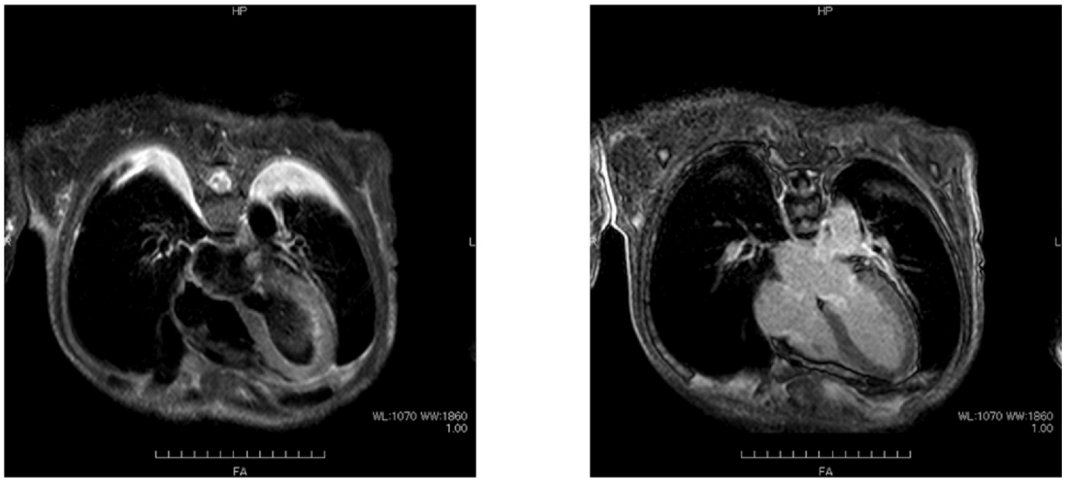

Fig. 6. Left side; myocardial edema. T2-weighted 4-chamber view showing slight transmural signal hyperintensity in the mid apical segments of left ventricle. Right side, the absence of late gadolinium enhancement in the patient with TTS was documented by CMR 4-chamber view.

On admission, 86.5% of patients had a reduced EF. The National Inpatient Sample (NIS) from 2007 to 2012 collected data on 22,005 patients with a primary diagnosis of TTS and 31,942 patients with a secondary diagnosis of TTS, making this the largest TTS registry of hospitalized patients in the United States. In this cohort, 64% reported hypertension, 4% presented with either cardiogenic shock or cardiac arrest, and 2.8% were treated with an intra-aortic balloon pump (IABP) [1,4,40,45]. There is a lack of prospective randomized clinical trials to clarify treatment protocols and guide therapy.

2.2. Arrhythmias in patients with takotsubo syndrome

Patients with TTS often have sinus tachycardia, although sinus bradycardia or other bradyarrhythmias are occasionally noted, suggesting an underlying vagal effect. Also, multiple atrial and ventricular premature beats, sinus node dysfunction (SND), asystole, paroxysmal supraventricular tachycardia (PSVT), atrial fibrillation (AF), nonsustained and sustained ventricular tachycardia (VT) (both monomorphic and polymorphic torsades de pointes (TdP)), ventricular fibrillation (VF), ventricular asystole, pulseless electrical activity, sudden cardiac death (SCD), and right and left bundle branch blocks are noted. AF was diagnosed in 4.7% of patients with TTS [46], but occasionally it was not clear whether this represented a new AF. SND and atrioventricular nodal dysfunction were reported in 1.3% and 2.9% of cases [46], but often details are lacking. The combined incidence of sustained VT and VF was 3.4%, with potentially threatening ventricular arrhythmias (VA) and SCD occurring in 1.1% and 0.9%, respectively [46]. In a large database of patients with TTS, arrhythmias were noted in 26%, with AF/atrial flutter seen in 8.8%, PSVT in 0.8%, and life-threatening VA in 4.2% of cases. The issue occasionally arises whether VT/VF is a complication of, or the trigger for, TTS [47]. Arrhythmias in patients with TTS tend to adversely influence the hospital course and outcome, and use of β-blockers for tachyarrhythmias to counter the excessive sympathetic discharge may play a preventive/ameliorating/therapeutic role, although proof is lacking.

AF in patients with TTS is associated with older age, fewer emotional triggers, higher incidence of cardiogenic shock, lower left ventricular ejection fraction (LVEF), prolonged hospital stay, and higher long-term mortality [48]. AF is an independent determinant of outcome, even after adjustment for clinical variables, left ventricular function, and cardiogenic shock, and thus it should be employed upon its emergence for risk stratification of patients with TTS [48].

Long-term anticoagulation following a transient episode of AF in the course of TTS should be considered, as is done currently for AF in association with other cardiac illnesses.

Both transient and persisting CHB [49,50] have been reported in association with TTS. Permanent pacemakers (PPM) have been implanted in patients with persisting CHB, with or without prior electrophysiologic evaluation [50]. Temporary pacing is often necessary in the acute/subacute phase of the illness to manage the CHB and the associated bradycardia, which in the presence of a prolonged QTc predisposes patients to TdP [51]. Temporary pacing should have preference over the employment of isoproterenol infusion for CHB, other atrioventricular conduction abnormalities, or SND. Occasionally, CHB is transient and does not need temporary or PPM. Notably, implantation of a PPM has led to TTS, triggered by the associated stress.

Compared to arrhythmias encountered in the setting of AMI, VA, including VT, VF, and SCD, are less frequent in TTS, even in patients with prolonged QTc [46,52]. Regardless, continuous telemetry monitoring of patients with TTS for at least 3 days, or longer when QTc is >500 ms, is recommended [53]. To prevent TdP in patients with TTS and prolonged QTc, a form of acquired long QT syndrome, one should avoid QTc prolonging drugs, evaluate for hypokalemia and hypomagnesemia, manage bradycardia, and consider predisposing congenital/genetic long QT syndromes [53]. Magnesium is recommended for the prevention/treatment of TdP, and β-blockers should be avoided, or discontinued, until the prolongation of the QTc is resolved. Implantation of cardioverter-defibrillators (ICD) should follow consideration of persistence of QTc prolongation and bradycardia, and clinical presentation with SCD. Indeed, occasionally, TTS follows resuscitated SCD, with documentation of sustained VT, VF, or TdP, suggesting that the VA had triggered the TTS [54] rather than being its complication, and in such patients, ICD implantation is mandatory. Whether patients who had VT, VF, and TdP, in the course of TTS, should receive an ICD needs to be handled on a case-by-case basis [52,53].

2.3. Thromboembolic events

The incidence and clinical significance of thromboembolic events in TTS has not yet been sufficiently established. Data documenting these events are scarce; however, a recent in-depth analysis of existing references reveals the common occurrence of intra-ventricular thrombus among these patients, thus signifying a potential relevance [55,56].

The incidence of ventricular thrombus formation and stroke varies between 2.5%–8% and 1%–5%, respectively [31,56].

Right ventricular involvement, apical TTS form, and elevated troponin I levels might be positive predictors of thromboembolic events in TTS [55].

There are many inherent difficulties in diagnosing intraventricular thrombus formation and its peripheral embolization in TTS. Two-

dimensional echocardiogram and transesophageal echocardiogram remain the gold standard.

2.4. In-hospital mortality

In-hospital mortality is 3–5%, greater in males, and remarkably similar to that of patients with acute myocardial infarction due to obstructive CAD [44]. Cardiac-related in-hospital death is usually attributable to intractable cardiogenic shock or cardiac arrest [40,57].

In those with cardiac arrest, anoxic brain injury is an important influence on outcome. Rarely, takotsubo-related death is consequent to left ventricular free wall rupture or ventricular septal perforation [58].

Predictors of in-hospital mortality include hemodynamic instability (cardiogenic shock, use of catecholamine drugs), age >70 years, physical illness trigger, male gender, and cardiac arrest [31]. More than 80% of in-hospital deaths occur in those with a co-existing critical illness, most commonly subarachnoid hemorrhage, acute respiratory failure, sepsis, and ischemic stroke [31].

Examination of large data sets, segregating patients into those with TTS as either a primary or secondary event (in the context of an accompanying major illness), has revealed short-term mortality to be 2–3 times greater in the secondary event category, likely reflecting the importance of co-morbid conditions in determining ultimate outcome [31,59]. Importantly, even those with profoundly reduced LV ejection fraction and cardiogenic shock may experience complete normalization of LV contractile function [60].

3. Management

3.1. Role of Levosimendan and short-acting beta blockers

Levosimendan may be occasionally preferred in patients with acute heart failure over other inotropes because of lower oxygen consumption and acute myocardial depression. Its use, however, is limited to those patients with impaired systolic function, without left ventricular outflow tract obstruction and with systolic arterial pressure ≥90 mm Hg. Clinical data showed safety and feasibility of this treatment in patients with TTS [61]; Levosimendan infusion should be performed preferably for 24 h at an infusion rate of 0.1 μg/kg/min without loading dose. Invasive hemodynamic and ECG monitoring should be performed during infusion and at least for the following 48 h due to a minimal risk of hypotension and/or arrhythmias [62].

In the presence of elevated intraventricular gradients and hemodynamic impairment, patients with TTS and left ventricular outflow obstruction may benefit from the infusion of beta-blockers (BB). Although selective and non-selective BB have been proven to reduce intraventricular gradient [61], experimental data showed an increasing density of β2 adrenergic receptors from the base to the apex and a potential higher concentration of β1-adrenergic receptors in basal left ventricular segments [4,63]; therefore, β1 cardio-selective BB could be preferred. Short-acting BB like esmolol, a beta-1 cardio-selective with a short half-life (9 min) is a potential therapeutic option that could be stopped quickly in case of hemodynamic worsening [63]; the treatment usually requires invasive hemodynamic monitoring.

3.2. Mechanical circulatory support

Approximately 9–15% of patients with TTS develop cardiogenic shock [31,45], and 4–9% have cardiac arrest or need cardiopulmonary resuscitation (CPR), respectively [31,45]. Catecholamines are generally avoided in patients with TTS, given their role in TTS pathogenesis and the risk of inducing or aggravating LVOTO [60]. Mechanical circulatory support (MCS) should be evaluated early in patients with TTS and cardiogenic shock (Fig. 7) [4], although there is no reason for MCS in TTS patients without shock.

Currently there are four different percutaneous MCS systems: Intra-aortic balloon pump (IABP), TandemHeart, extracorporeal membrane oxygenation (ECMO), and microaxial pumps (i.e., Impella™, Abiomed). As TTS is a transient acute heart failure syndrome per definition [11], MCS is used in a bridge-to-recovery strategy. TTS hemodynamics are characterized by already severely increased filling pressures in the absence of shock [31], probably due to stunning-related impairment of myocardial relaxation and compliance.

IABP reduces afterload in systole and increases coronary blood flow during diastole. IABP is potentially harmful in patients with TTS, as deflation of the intra-aortic balloon during systole may increase the transaortic gradient [1] and thereby induce or aggravate LVOTO. If used, it is mandatory to perform emergent bedside echocardiogram to assess for the presence of LVOTO prior to IABP implantation.

IABP has been used in TTS with shock [64] and after CPR [65]. Upgrade to ECMO has been reported due to LVOTO [66] or lack of efficacy [67,68].

3.2.1. TandemHeart

TandemHeart drains blood from the left atrium and returns it to the iliac artery toward the aorta, like an ECMO with a left atrial cannula. TandemHeart is not as widely used as ECMO and Impella and requires transseptal cannulation. Nonetheless, left atrial unloading appears attractive for facilitating myocardial recovery. There is one published report on the successful use of TandemHeart in a patient with TTS [69].

3.2.2. ECMO

Venoarterial ECMO drains blood from the right atrium and reinfuses oxygenated and decarboxylated blood to the femoral artery [70]. This massive right-to-left shunt reduces preload and enhances end-organ perfusion at the cost of increased afterload. The latter may impede myocardial recovery and aggravate mitral regurgitation and pulmonary edema during LVOTO. ECMO is well-established for interhospital transfer and broadly available. There are several reports on ECMO in TTS, primarily for TTS with shock [71]. ECMO is effective for bridging right ventricular failure during TTS. ECMO delivers circulatory and respiratory support, and accordingly, ECMO has been used in patients with TTS and CPR, either after ROSC [72] or in refractory arrest [73]. ECMO has been used successfully without anticoagulation for a short period of time, such as in patients with TTS after polytrauma [74].

3.2.3. Impella

Impella drains blood from the left ventricle and expels it in the aortic root, thus providing antegrade transaortic blood flow. It drains blood during systole and diastole, thereby effectively unloading the left ventricle and contributing to myocardial recovery. Both the 2.5 variant [75] and the CP variant [76] have been used for bridge-to-recovery in TTS. Mechanistically, Impella appears to be the most meaningful support form in most TTS cases, and effectively bridges LVOTO and reduces associated mitral regurgitation. Notwithstanding the very positive experience in infarction-related shock and positive initial experience in TTS, controlled studies on Impella support in TTS are urgently needed.

3.3. Dilemma of ACE inhibitors

ACE-inhibitors (ACEi) are the first-line treatment in subjects with left ventricular systolic dysfunction; however, their role in patients with transient left ventricular obstruction as observed in TTS is not clear. In one of the largest populations of patients with TTS, subjects in treatment with ACEi or angiotensin-receptor blockers (ARBs) showed at 1-year follow-up a 1-year mortality rate nearly one-fourth of those not treated with such classes of drugs [31].

The study, however, was observational, and a meta-analysis of observational studies previously failed to reach statistical significance when the hypothesis was that ACEi could reduce the recurrence of TTS (odds ratio 0.42, 95% confidence interval 0.08–2.36). A meta-

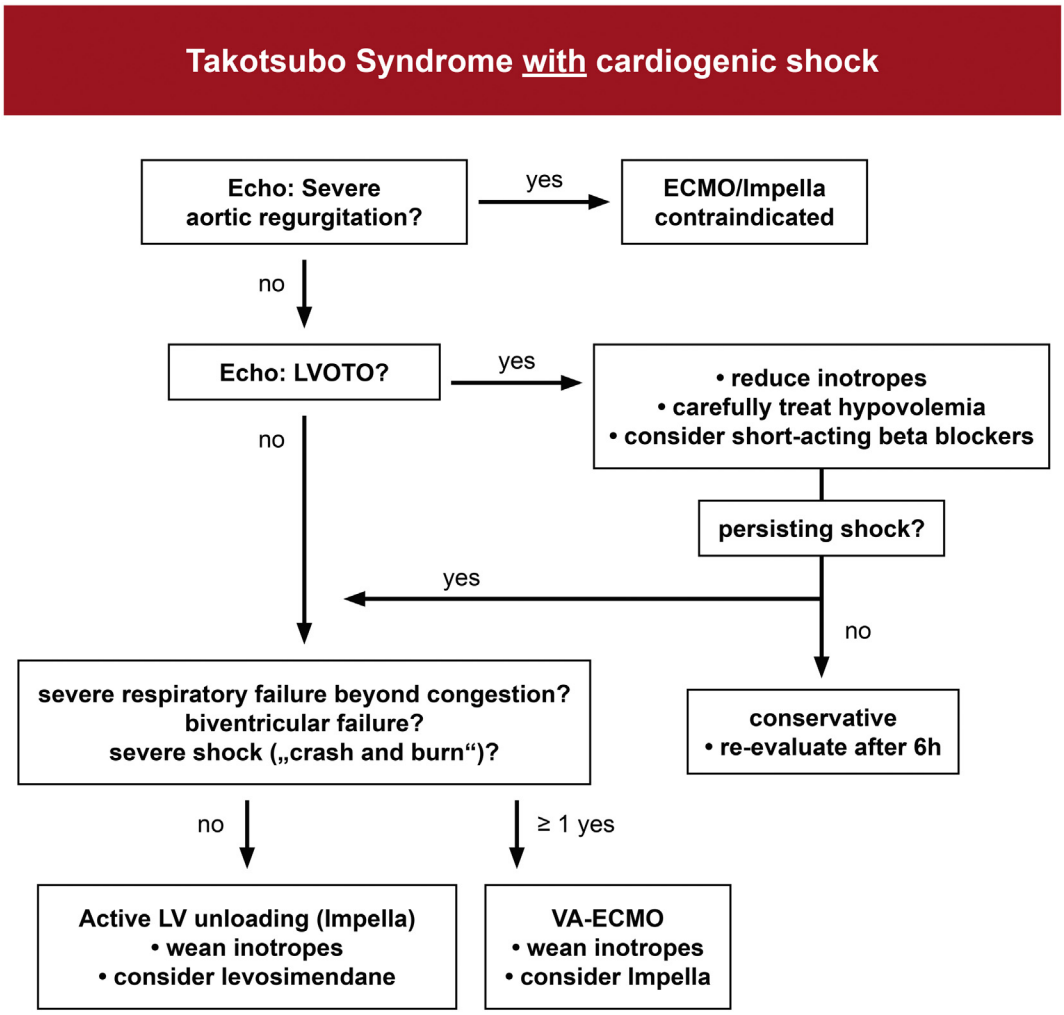

Fig. 7. Proposed criteria for mechanical circulatory support in TTS with shock.

regression by Singh et al. analyzed the effect of drug treatment on recurrence of TTS; the study, after a comprehensive search of four major databases for original research studies, recruiting ≥5 participants with ≥3 months of follow-up published in English language that reported data on recurrence in patients with TTS, included 31 cohorts (1664 patients) with a mean follow-up of 24.5 months [59,77]. The authors found that recurrence rates were independent of ambulatory utilization of BB, but inversely correlated with ACEi/ARB prescription [77,78]. The same data were subsequently reanalyzed, now weighted for populations' size, in a meta-regression analysis. Brunetti et al. have shown that recurrence of TTS is less frequent among TTS patients who have higher rates of treatment with ACEi/ARB [77,78].

However, these data should be interpreted with caution since this does not necessarily imply that ACEi may prevent recurrence of TTS. It is conceptually possible that some TTS patients or cohorts may have received more frequent and careful outpatient medical care were more compliant with guideline-directed medical therapy and therefore had lower rates of TTS recurrence.

Interestingly, statistical analysis of previously published data seems to suggest the hypothesis that rates of recurrence are lower in populations treated with combination of ACEi-BBs [77,78].

3.4. Role of long-term beta blockers

Chronic administration of BB for the prevention of TTS recurrence has been commonly used based on the speculation that, by opposing the actions of catecholamines, BB could prevent or attenuate clinical severity of a TTS recurrence. However, no study has proven any clear benefit at long-term follow-up so far. Templin et al., in a registry of 1750 patients, showed comparable death rates at 1 year whether or not patients with TTS are treated with BBs [1]; a meta-analysis including 8 studies and 511 patients found no difference in terms of recurrence rate between patients given BBs and those who were not [74]. Even the severity of TTS is not affected by pretreatment with low doses of BB [79]. Randomized controlled trials are surely warranted in order to clarify the real efficacy of BB at long term (Fig. 8).

3.5. Is there any role for aspirin alone or dual antiplatelet therapy?

TTS patients are frequently started on single or dual antiplatelet therapy on the basis of suspected acute coronary syndrome. However, to date, there are no randomized clinical trials on antithrombotic medication and respective duration.

Catecholamines can stimulate platelet activation, leading to transient thrombosis and microvascular endothelial dysfunction. As previously reported, TTS patients may have disproportionally high levels of catecholamines during a psychologically or emotionally stressful event; therefore, in theory, single or dual antiplatelet therapy could potentially decrease the risk of future cardiac events [4,31]. Recently published data show that single antiplatelet therapy with aspirin or dual with aspirin plus clopidogrel may reduce major adverse cardiovascular events during hospitalization [80]. In the International Takotsubo Registry, 67% of TTS patients were discharged on aspirin, and antithrombotic therapy, including aspirin, P2Y12 antagonists or oral anticoagulation,

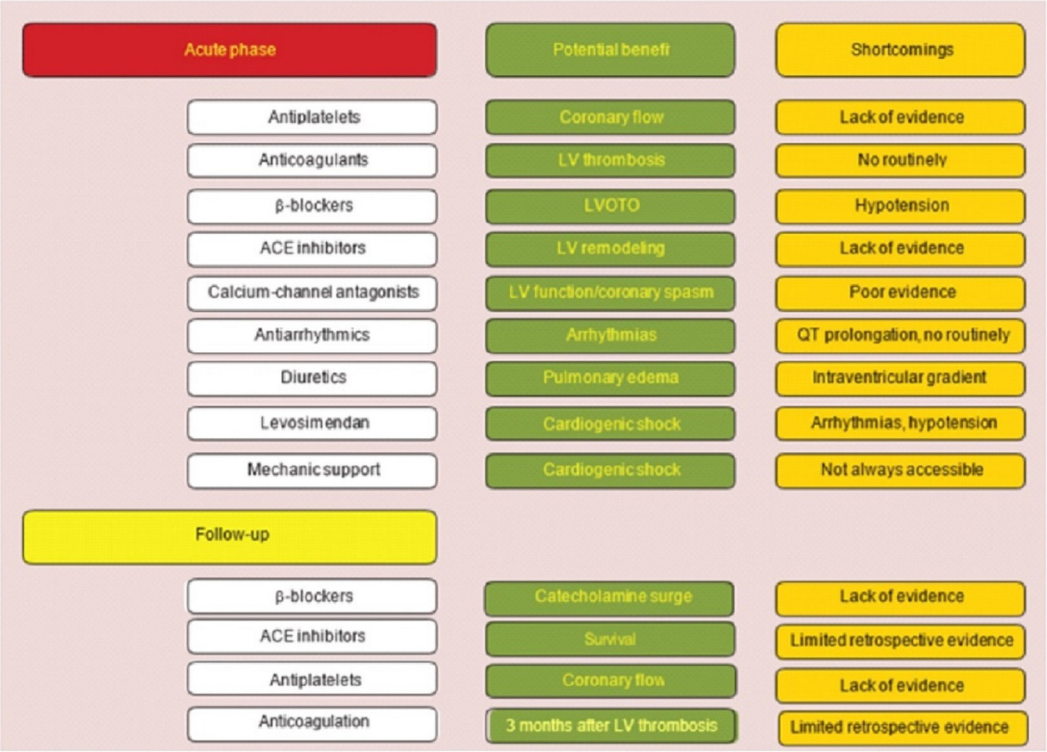

Fig. 8. Potential benefit and field of application of main therapeutic options in TTS during the acute phase and at follow-up.
(Modified from Brunetti ND, Santoro F et al. Therapy of TTS: present shortcomings and future perspectives. Future Cardiol. 2016;12 (5):563–72.)

was recommended in >80% of the patients [31]. TTS patients appear to have low bleeding rates; therefore, some authors advocate that they may benefit from short-term antiplatelet therapy, particularly those with significant LV dysfunction and until wall motion abnormalities improve [80].

In a recent subanalysis of the Intertako Registry, recurrence of TTS and MACE were not influenced by use of aspirin [1,66]. Similarly, aspirin did not reduce the risk of TTS recurrence or MACE among those discharged without BB and ACE-inhibitors [81].

3.6. Long-term prognosis: Cardiac and non-cardiac mortality

Recently published data suggest that TTS is not associated with a favorable prognosis [1]. The correlation of TTS with a bevy of complications as compared to ACS highlights a similar outcome in each scenario.

The large InterTAK-Registry reported a 5.6% mortality per patient year [1].

The recurrence rate of TTS has been reported to be up to 12% in a mean follow-up of four years [77], which might be affected by a variable pattern. It has been reported that male gender, reduced ejection fraction, old age and high Killip score are associated with a poor long-term prognosis [43,82–84]. The discussion pertaining to the prognostic impact of diabetes mellitus is still unclear. While some reports suggested an adverse outcome among diabetic TTS patients, which could potentially be attributed to long-term diabetes-associated complications, other studies have postulated a possible protective effect and lower event rates in TTS patients with diabetes mellitus [84].

Recent reports have suggested a high rate of non-cardiovascular long-term mortality in TTS, which could possibly be linked to malignancies [43].

3.7. Role of psychological distress

Psychological distress (anxiety and depression) clearly plays an important role both in the onset of TTS and in the aftermath of an acute episode. Retrospective, registry-based studies consistently report a higher prevalence of psychological distress in TTS patients compared to controls. The prevalence of anxiety and mood disorders in TTS patients was 13% and 9%, respectively, in a systematic review of registry-based studies from North America, Europe, Asia, and Australia ($n = 1109$) [85]. In the International Takotsubo Registry ($n = 1750$, 90% women), women with TTS had a greater prevalence of anxiety (10% vs. 1%) and depression (20% vs. 8%) compared to age- and sex-matched historical MI controls [31]. A large observational study involving >20,000 patients from the National Inpatient Samples found a higher prevalence of anxiety disorders in TTS (9%) compared to both MI patients (3.4%) and controls hospitalized with joint injuries (3.7%), while the prevalence of depression was 15%, 7%, and 12%, respectively [86]. Taken together, these findings suggest that anxiety and possibly depression are likely predisposing factors for the onset of TTS, particularly for the primary form of this condition. Anxiety and depression could predispose to the onset of TTS risk by affecting the magnitude of the catecholamine discharge following exposure to a stressor. In fact, both anxiety and depression have been associated with excessive reactivity to emotional stress and decreased catecholamine re-uptake.

In contrast, information on psychological distress after an acute episode and the role of distress in increasing the risk of TTS recurrence is scarce. A prospective study conducted in women with a first episode of TTS found that TTS women had significantly higher psychological distress (Hospital Anxiety and Depression scores), perceived stress, and post-traumatic stress disorder symptoms (scores on the Impact of Events Scale-Revised) compared to MI or healthy controls 4 weeks after discharge [84,87–89]. PTSD symptoms remained significantly higher in TTS women even after adjustment for confounding variables ($p < 0.05$ vs. MI and < 0.01 vs. healthy controls). The only other study that examined the psychological sequelae of TTS reported an increase in depressive symptoms in TTS compared to a group of MI patients 1 year after the acute event. The presence of PTSD symptoms in the aftermath of an acute episode suggests that women with a first episode of

TTS may be at risk for poor psychological adjustment and, possibly, future recurrences.

4. Treatment of psychological distress

To our knowledge, no studies have yet examined whether the use of anxiolytics or antidepressants could prevent the onset of a first TTS episode or their role in the treatment of distress after an acute episode. The prescription of medications to treat depression or anxiety (i.e., serotonin/norepinephrine uptake inhibitors, tricyclic antidepressants, SSRIs) appears contraindicated based on data suggesting that the use of these and other drugs that decrease catecholamine reuptake can actually increase the risk of occurrence of TTS [88–90], possibly by increasing the release of catecholamines during an acute episode.

While psychotherapy, counseling, and stress reduction approaches are reasonable and viable options for these patients, the systematic prescription of antidepressants and anxiolytics cannot be recommended, also in consideration of the lack of data on the benefit of antidepressants and anxiolytics in the prevention of a first TTS episode or future recurrences. Such treatments should be decided on an individual basis, with careful consideration of the risks and benefits involved.

5. Recurrence of TTS

Experience with TTS recurrence is inherently limited by the infrequency of the condition itself and incomplete long-term follow-up. Initial studies, with 2–4 years follow-up, noted a recurrence rate of 1–2% per year [39]. More recently, a meta-analysis of 31 takotsubo cohorts (1664 patients, mean follow-up 2 years) yielded an annual recurrence rate of 1.5%, cumulative incidence of 5% at 6 years, and average age at recurrence of 66 years [59,82]. These are likely underestimates given the difficulty in systematically tracking this diverse population over a number of years [59]. Recurrence is associated with the magnitude of LV systolic dysfunction, measured by ejection fraction, at initial event [59,82]. At recurrence, the triggering event, i.e., physical or emotional, may differ from the index event [40,83,91].

Recurrence onset may be as early as 3 weeks, or as late as several years, after the initial event. Inexplicably, in recurrent TTS, the LV ballooning pattern may differ, for example with apical ballooning during the initial event and mid-ventricular ballooning during the second event. Multiple takotsubo events (six) in the same individual have been encountered [40,82].

Current information suggests regional LV contraction and global ejection fraction recover promptly and completely during recurrence, similar to that of the index event [40,59,82,84,87]. Nonetheless, other measures of cardiac function remain abnormal for an extended time post-event, including LV global longitudinal strain, LV diastolic function, left atrial emptying volume, and NT-proBNP level [36,40]. Histologic studies have shown microscopic foci of contraction bands [4,66]. Low-intensity late gadolinium enhancement on CMR has been demonstrated in about 10% of cases, corresponding to an increase in myocardial type 1 collagen staining [92].

Recurrent TTS events could lead to a cumulative, delayed cardiac injury process, although no reports of late deterioration of LV systolic function or heart failure have yet emerged [92].

Both initial and recurrent TTS events have been reported in patients receiving beta-blocker therapy, usually administered for co-existing systemic hypertension [31,40,82]. Contemporary analyses have revealed 20–25% of TTS patients were receiving beta-blocker drugs at the time of their initial event, and 40% at the time of a second episode. Consistent with this observation, a meta-analysis found no benefit of drug therapy for prevention of TTS recurrence [74]. At this time, there is no evidence that pharmacologic therapy is effective for prevention of TTS recurrence.

6. Conclusion

This paper is the result of a multinational crowdsourcing effort aiming to provide the current state of the art on takotsubo syndrome. Several experts in the field contributed to it.

Important spikes of TTS cases have been consistently reported over the past few years. It is still unclear if the growing numbers reflect an increasing awareness of this acute heart failure syndrome by clinicians or if it is in fact a true rise in its incidence. Nonetheless, multiple aspects of this syndrome are still unknown or not completely understood. Moreover, our current knowledge is mostly based on case reports and relatively small cohorts. Since individual health facilities may see a small number of TTS cases per annum, it is crucial to establish national and international TTS registries. These networks will enable us to better understand this specific syndrome and improve the accuracy of identifying the disease and its prognosis.

Declarations of interest

Milosz Jaguszewski, MD, FESC, has received lecture honoraria from St. Jude Medical.

Dana Dawson, DM, FRCP, DPhil, FESC, has a research agreement with Philips Healthcare and holds an MTA with AMAG Pharmaceuticals.

L. Christian Napp, MD, received lecture honoraria from Abiomed, Maquet and Cytosorbents, consultant fees from Bayer, and traveling or congress support from Abbott, Abiomed, Bayer, Biotronik, Boston Scientific, Lilly, Medtronic, Merit Medical, Pfizer, Servier, and Volcano.

Kathy Hebert, MD, MPH, is an employee of GE Healthcare.

Takashi Akasaka, MD, has received lecture fees and research funds from Kowa Pharmaceutical Co. Ltd.

Ron Waksman, MD, received honoraria from Abbott Vascular, Amgen, Boston Scientific, Chiesi, Medtronic and Philips Volcano, and consulting fees from Biosensors, Biotronik, Corindus, Lifetech Medical and Pi-Cardia LTD. He is on the advisory boards of Abbott Vascular, Amgen, Boston Scientific, Medtronic, Philips Volcano and Pi-Cardia LTD, is a consultant for Abbott Vascular, Amgen, Biosensors, Biotronik, Boston Scientific, Corindus, Lifetech Medical, Medtronic, Philips Volcano and Pi-Cardia LTD, received grant support from Abbott Vascular, Biosensors, Biotronik, Boston Scientific, Chiesi and Edwards Lifesciences, and is an investor in MedAlliance.

All other authors have no conflicts of interest to disclose.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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