Takotsubo syndrome: aetiology, presentation, and treatment

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Learning Objectives

- To understand postulated hypotheses about the pathophysiology of takotsubo syndrome.

- To obtain knowledge on clinical presentation and the examination findings of takotsubo syndrome, which is helpful in differentiating between takotsubo syndrome and acute coronary syndrome.

- To learn the general strategy for the treatment of takotsubo syndrome based on the limited evidence.
1. Introduction

In the clinical setting, takotsubo syndrome (TTS) is one of the most important diseases that must be accurately differentiated from acute coronary syndrome (ACS) to enable appropriate follow-up and medical management. The prevalence of TTS is estimated to be approximately 2-3% in all patients presenting with suspected ACS. However, it may be underestimated because knowledge of diagnostic criteria is often incomplete, such as the possible coexistence of coronary artery disease (CAD). According to the widely-used Mayo Clinic Diagnostic Criteria modified in 2008, incidental obstructive CAD, not related to the wall motion abnormality may be an inclusion criterion for the diagnosis of TTS. However, this fact has been cited only as a footnote in a paper by Prasad and colleagues. In addition, atypical variants are not very well recognised by physicians, which may contribute to the underestimation of TTS. In 2015, the International Takotsubo Registry (www.takotsubo-registry.com), which is the largest systematic database on patients suffering from TTS, revealed novel data pertaining to TTS which aided to the understanding of this enigmatic disease. This review summarises current knowledge on the aetiology, presentation, and treatment of TTS.

2. Aetiology

The exact aetiology of TTS is still unknown but several hypotheses are considered relevant for its pathophysiology. A number of observational clinical studies and pre-clinical models have helped to illuminate how the cardiovascular system responds to sudden extreme stress. These studies frequently provide a simplified and reductionist approach to a complex situation; therefore, it is important to note that a full understanding of this response is
incomplete. A critical factor in determining the quality of the observational studies is the timing, as the cardiovascular response following sudden and extreme stress evolves over seconds, minutes, hours, and days. Combining myocardial, coronary, systemic vascular, adrenal, the hypothalamic-pituitary-adrenal axis, and neural responses results in a complex picture of integrated physiological and biological systems.

**Vascular responses**

**Multivessel vasospasm**

Many of the initial TTS cases from Japan reported multivessel coronary vasospasm in patients during acute presentation. It is possible that in some patients multivessel coronary vasospasm could solely contribute to the phenotype of acute ischaemic stunning. An additional effect of high circulating catecholamine levels and/or high acute after-load from peripheral vasospasm may also be a contributing factor resulting in acute apical dysfunction, a pattern that is not observed through ischaemia alone. However, in the majority of acute cases vasospasm is not observed and when provoked in follow-up studies, it is not clear if this is causative or an epiphenomenon in the aftermath of a catecholamine surge. Factors, which are not consistent, include initiation by vasodilatory catecholamines, other anatomical variants where circumferential dysfunction cannot be explained by multivessel vasospasm alone, and endomyocardial biopsies that do not show ischaemic changes.

**Aborted acute myocardial infarction**

Intravascular ultrasound (IVUS) studies during acute presentation TTS in patients are limited and inconsistent. However, for those that have been reported, coronary arteries free of
atheroma or plaque rupture have generally been reported.\textsuperscript{11} A retrospective analysis of coronary anatomy in a cohort of TTS patients showed no increased frequency of wrap-around LAD anatomy.\textsuperscript{12} The circulating microRNA profile showed significant differences between acute myocardial infarction (MI) and TTS patients supporting a different pathophysiological entity, with a link to both neuropsychiatric physiology and the endothelin axis.\textsuperscript{13} Together with the epidemiology regarding seasonal and diurnal presentation patterns, and the prevalent demographic, evidence strongly suggests that TTS is not the result of acute atherosclerotic plaque rupture.\textsuperscript{5}

\textit{Myocardial causes}

\textit{Direct catecholamine-mediated myocardial stunning}

A number of clinical observations and pre-clinical studies suggest that high levels of catecholamines play a causative role in TTS. Wittstein and colleagues measured circulating catecholamine levels in the blood of a cohort of TTS patients and reported levels that were 10-20 times higher than normal, and higher than matched patients with acute left anterior descending (LAD) artery occlusion and ST Segment Elevation Myocardial Infarction (STEMI),\textsuperscript{14} although others could not replicate this finding. Clinical conditions associated with high catecholamine levels, including phaeochromocytoma,\textsuperscript{15} acute subarachnoid haemorrhage with sympathetic storm,\textsuperscript{16} and acute thyrotoxicosis,\textsuperscript{17} have been reported to cause TTS. Perhaps the most robust evidence is from the cohorts of patients reported where TTS was triggered by administration of adrenaline or dobutamine, either for medical reasons or by accident.\textsuperscript{18} The plausibility of the catecholamine hypothesis has also been supported by experimental data. Several models have been reported where acute and reversible apical or
basal dysfunction in more than one coronary territory has been triggered by acute administration of high dose adrenaline or isoproterenol.\textsuperscript{19,20} These pre-clinical studies have their limitations but provide supportive evidence to the growing portfolio of clinical studies. They also permit elucidation of some of the pathophysiology and biology.

One hypothesis is based on the observed opposing apical-basal gradients of sympathetic nerve endings and β-adrenergic receptors (βARs) in mammalian hearts (Figure 1). A consistent finding across species including humans is a gradient of sympathetic nerve endings in the mammalian heart, with the highest in the atria and basal ventricular myocardium, and the lowest in the apical myocardium.\textsuperscript{21} To compensate for this innervation gradient, there appears to be a reverse βAR gradient on the myocardium, with the highest βAR density in the apical myocardium, and a lower βAR density towards the basal myocardium.\textsuperscript{19} This has been demonstrated in the healthy hearts of various mammals but to date this has not been proven in humans.\textsuperscript{6} These gradients provide balanced responses to sympathetic neural and circulating catecholamines under resting conditions. During extreme stress, the apical myocardium may be more sensitive to high levels of circulating catecholamines due to higher βAR density.\textsuperscript{22} Pharmacological studies have demonstrated that catecholamines demonstrate different inotropic responses via the β1AR and β2AR during dose-response studies, which may be relevant to an understanding of the cardiac responses to extreme stress in TTS. Whilst both adrenaline and noradrenaline elicit positive inotropic responses via the β1AR-Gs pathway, these hormones behave differently when activating the β2AR. The latter comprises ~20% of βARs on healthy human hearts. Noradrenaline stimulates a positively inotropic response via β2ARs at all doses studied. In contrast, adrenaline activates the positive inotropic β2AR-Gs pathway whilst at low and medium range doses. However, at higher doses it initiates a
molecular switch to the β2AR-Gi pathway, which is negatively inotropic. This could explain why at higher levels of stress or following injection of high adrenaline doses, the apical myocardium with the highest density of βARs, is initially hypercontractile for the first few minutes and then progressively becomes hypokinetic. Excess activation of β1AR-Gs and β2AR-Gs pathways is cardiotoxic, promoting necrosis and apoptosis via high levels of oxidative stress and calcium overload. However, adrenaline-mediated activation of β2AR-Gi is cardioprotective, activating anti-apoptotic survival pathways to limit the degree of acute myocardial injury in response to the catecholamine storm.

Endomyocardial biopsy studies from patients during the acute phase of TTS support activation of the pro-survival pathways PI3K and akt, which can be activated by βAR-Gi signalling. These acute gene expression changes have returned to normal levels at follow-up and not activated in samples from acute ischaemic myocardium. This would correlate with the relatively low troponin release observed for the degree of dysfunctional myocardium during the acute phase, and the recovery with limited infarction compared to acute coronary occlusion, which initiates the same extent of acute left ventricular impairment. Indeed, in experimental models that blocked the cardioprotective Gi signalling pathway mortality was increased following acute catecholamine administration.

Oestrogen and cardiovascular stress responses

Oestrogen regulates sympathetic tone via central actions and βAR expression both in the myocardium and vasculature, and contributes to a tonic-relative suppression of βAR expression in women during their reproductive years. This sympatholytic effect of oestrogens is lost following the menopause, with heightened myocardial and vascular responses to βAR
agonists. This may partly explain why TTS is most commonly observed in postmenopausal women. \(^{27}\)

Recent studies suggest that the peripheral vascular responses may also be relevant to myocardial dysfunction and the importance of ventricular-arterial coupling. In the initial seconds following intravenous adrenaline administration, both humans and animals show an acute hypertensive response, often with extremely high systolic and diastolic aortic pressure. In the following minutes and hours, hypotension may develop in the context of acute heart failure. \(^{19}\) In patients with hypotension during acute TTS, some show paradoxical peripheral vasodilatation in addition to acute ventricular failure and this correlates with dysfunctional peripheral sympathetic nerve regulation in the aftermath of the catecholamine storm. Rodent model studies have also reported varied apical and basal variants in response to differing afterload scenarios initiated and manipulated pharmacologically. \(^{28}\) Whilst these studies have their limitations e.g., non-physiological catecholamines and delayed timing of assessment, they contribute to an understanding of the complex pathophysiology in TTS.

In summary, according to the etiology of TTS, these hypotheses are still being investigated but there is no proven pathophysiological mechanism to explain the clinical features of both typical and atypical variants of TTS.

3. Clinical Presentation and Diagnosis

3.1. Clinical features

TTS occurs predominantly in post-menopausal women but can also occur in younger women, men, children, and even in newly born babies. The International Takotsubo Registry
demonstrated that 89.8% of women were affected with a mean age of 66.8 years.\textsuperscript{4} Deshmukh et al. reported that women have an almost 9-fold higher risk of developing TTS compared to men; furthermore women older than 55 years had a 4.8-fold higher risk when compared with women younger than 55 years.\textsuperscript{29} Interestingly, male patients in Asia have a higher prevalence of TTS than male Caucasians.\textsuperscript{30}

A preceding emotional or physical stressor is a typical feature of TTS, and approximately two-thirds of patients have identifiable preceding stressors (Figure 2).\textsuperscript{31,32} Emotional stressors are usually associated with negative life events, such as death of a beloved one, disasters, bullying or financial loss. Recently, Ghadri et al. revealed that TTS is not only provoked by negative stressors but can also be precipitated by positive, joyous events; this entity has been described as the ‘happy heart syndrome’.\textsuperscript{33} A patient suffering from TTS is no longer the classic “broken-hearted” patient as the disease can be triggered by positive emotions, too. It is important that clinicians are aware of this fact.

A variety of physical stressors have been reported, including acute critical illness, respiratory failure, central nervous system disorders and iatrogenic factors such as surgery, exercise tests,\textsuperscript{34} or dobutamine stress echocardiography,\textsuperscript{35} or electroconvulsive therapy.\textsuperscript{36} Yerasi et al. reported that TTS patients with a preceding medical illness experience an unfavorable outcome compared to those with an emotional stressor.\textsuperscript{37} This is not surprising because patients with a physical stressor are usually treated for a variety of underlying diseases (including subarachnoid haemorrhage, surgery, cancer, and sepsis) and are “more ill”. However, this result needs careful interpretation because almost all in-hospital deaths were associated with the underlying medical illness and not exclusively with a cardiac cause.

Of note, the absence of a preceding trigger does not exclude TTS, since it has recently
been shown that one-third of patients have no identifiable stressors.\textsuperscript{31}

Summers et al. reported that TTS patients are more likely to have chronic anxiety disorder or a family history of psychiatric disease compared to a general population.\textsuperscript{38} Data from the International Takotsubo Registry revealed that more than half of all TTS patients had an acute, former, or chronic neurologic disorder, such as seizure, intracranial bleeding and stroke, or psychiatric disorder, such as affective, anxiety, and adjustment disorder, and the incidence was significantly higher than that of age- and gender-matched patients with ACS.\textsuperscript{4} In addition, it has been reported that stress- and depression-related miRNAs were significantly up-regulated in patients with TTS.\textsuperscript{13} These results indicate that patients with neuropsychiatric disorders may be susceptible for the development of TTS. Other important co-morbidities are pulmonary diseases, malignancies, chronic kidney diseases, and thyroid diseases are also common comorbidities in TTS.\textsuperscript{39}

Ghadri et al. reported differences in the clinical features between typical and atypical types of TTS.\textsuperscript{40} Patients with atypical TTS were younger at the age of onset, had more frequent ST-segment depression, less pronounced reduction in LVEF, and lower BNP values on admission and more often neurologic disorders. Furthermore, patients with atypical TTS were more likely to have compared with those of typical TTS. This finding suggests that neurologic disorders may alter patient susceptibility in response to a triggering stressor leading to morphologic changes in the heart. Outcomes are comparable between typical and atypical TTS, suggesting that both variants of the condition require careful follow-up.\textsuperscript{40}

3.2. ECG

Abnormal findings of ECG resembling ACS are present on admission in most TTS patients,
although a minority of TTS patients present with a normal ECG. In the typical time course of TTS, ST-segment elevation is observed at onset, followed by deep and widespread T-wave inversion with significant QT prolongation, and an abnormal Q wave may be observed after 24–48 h.\textsuperscript{41} If presentation is delayed, giant T-wave inversion with QT prolongation without ST-segment elevation may be observed. Madias et al. reported that 8.6% of TTS patients experienced ventricular fibrillation or torsades de pointes (TdP), and prolongation of the corrected QT interval was significantly associated with the occurrence of ventricular arrhythmias.\textsuperscript{42}

ECG findings during the acute phase of the disease may be helpful in distinguishing TTS from STEMI. Recently, Frangieh et al. defined specific ECG criteria for the differentiation between TTS and MI. These novel criteria may differentiate between TTS and AMI, regardless of STEMI or NSTEMI (Figure 3).\textsuperscript{43}

3.3. Laboratory studies

Biomarkers of myocardial injury, such as creatine kinase, creatine kinase-MB, and troponin are elevated in most TTS patients. However, the extent of these biomarkers are disproportionately low when compared to the extent of wall motion abnormality.\textsuperscript{4} During the acute phase of TTS, serum cardiac brain natriuretic peptides (BNP or NT-proBNP) are often notably elevated compared to patients with ACS.\textsuperscript{44} Nguyen et al. reported that BNP and NT-proBNP were substantially elevated during the first 24 h after the onset of TTS. Slow and incomplete resolution was observed during 3 months and the peak NT-proBNP level correlated with the severity of wall motion abnormality.\textsuperscript{45} Other studies found that elevated BNP was associated with delayed recovery of wall motion abnormality\textsuperscript{46} or poor clinical
outcomes in TTS patients.

Jaguszewski et al. identified a signature of four circulating miRNAs (miR-16, miR-26a, miR-1, and miR-133a) related to the stress response as novel and robust biomarkers for differentiating between patients with TTS and those with STEMI. These miRNAs may have the potential as future diagnostic biomarkers for TTS.  

### 3.4. Invasive Imaging

Patients with a suspected diagnosis of TTS should immediately undergo coronary angiography to exclude ACS and to confirm the diagnosis of TTS unless there is a contraindication. In most patients with TTS, epicardial coronary arteries are normal and unobstructed. However, bystander CAD can be found incidentally, because most TTS patients are quite old and often have several risk factors for CAD. As aforementioned, the revised Mayo Clinic Diagnostic Criteria do not exclude patients with incidental CAD which does not cause the wall motion abnormality. The prevalence of incidental CAD in TTS patients has been reported to be approximately 10-15%. Recently, in a database of patients with a TTS diagnosis, Chou et al. reported that 8% of patients had been overlooked for spontaneous coronary artery dissection (SCAD) upon careful review of coronary angiography. Thus, coronary angiography should be closely scrutinized for subtle signs of SCAD to avoid misdiagnosis in patients with suspected TTS.

Once causative CAD is excluded, left ventriculography including pressure measurements (LVEDP etc.) should be performed. Left ventriculography is important for correct classification of the TTS type. Four different patterns of TTS have previously been reported (Figure 4). Although apical ballooning is the classic and most common type (80%), variant
forms such as mid-ventricular and basal type have been demonstrated. The mid-ventricular type has been shown to be present in approximately 4-40% of TTS patients. The basal type is rare and only evident in 1-3% of all TTS. Focal types occur in 1.5-7%.

To differentiate between TTS and aborted MI, biplane left ventriculography is more useful than single plane, if it can be performed. Regional wall motion abnormality extending beyond a single epicardial coronary artery distribution is one of the most important feature distinguishing TTS from CAD. However, it may be difficult in some patients especially for the focal type because the area of wall motion abnormality in this type of TTS is limited and nearly identical to a single branch distribution. In this regard, biplane left ventriculography provides more information on wall motion and is helpful in confirming an accurate diagnosis.

3.5. Non-invasive Imaging

Echocardiography is useful in the diagnosis of TTS in the emergency department and also in the clinical course of the disease. In typical TTS, circumferential wall motion abnormality can be detected in the short axis view of the mid LV. Echocardiography is also valuable in detecting potential complications of TTS, such as LVOTO, acute mitral regurgitation, right ventricular (RV) involvement, or apical thrombus. Follow-up echocardiography is mandatory to confirm complete recovery.

CMR can accurately visualize regional wall motion abnormality in both the LV and RV, which helps to distinguish TTS from other cardiac diseases. CMR may be superior to echocardiography in evaluating the RV and detection of apical thrombus especially in patients with obesity or chronic obstructive pulmonary disease. However, in our experience CMR is
often not well-tolerated by the acute patient.

A CMR study has shown that RV involvement can be present in 34% of TTS patients and is associated with a longer and more severe clinical course of disease. Ahtarovski et al. used serial CMR to demonstrate that recovery of LV diastolic function was delayed compared with that of systolic function in TTS patients. One of the characteristic CMR findings of TTS is myocardial oedema, showing high signal intensity in T2-weighted images, which is located in the area consistent with wall motion abnormality. In TTS, myocardial oedema is usually located transmurally. In contrast, in patients with acute myocarditis, myocardial oedema is frequently located in the middle layer of the ventricular wall or subepicardial region and often seen in the infero-lateral wall of the LV. These differences may permit differentiation of TTS from acute myocarditis. Classically, the absence of obvious late gadolinium enhancement (LGE) is an important criterion of TTS. However, it remains controversial whether small amounts of LGE may be present in some TTS patients. In this regard it has been shown that minute focal or patchy LGE can be detected in approximately 9% of TTS patients when a threshold of 3 standard deviations (SDs) above the mean signal intensity for normal myocardium is applied as significant enhancement. Yet, no patients have been shown to have evidence of LGE using a threshold of 5 SDs, which is commonly used for defining LGE in MI and myocarditis.

Different nuclear imaging techniques have been used to evaluate TTS. Myocardial perfusion imaging during the acute phase demonstrates normal or mildly reduced uptake in the dysfunctional segments. Normalization of uptake occurs in association with wall motion recovery. Ghadri et al. reported that microcirculatory function including hyperemic myocardial blood flow and coronary flow reserve detected by positron emission tomography
(PET) with N-13-NH$_3$ were globally reduced in the entire LV.$^{64}$ In contrast, PET with F-18 fluoro-deoxy-glucose shows abnormal glucose metabolism in the area matching the distribution of wall motion abnormality.$^{64,65}$ Other metabolic imaging with iodine-123-β-methyl-p-iodophenyl penta-decanoic acid demonstrated abnormal fatty acid metabolism in the same area. These metabolic defects often exceed the area of perfusion defect.$^{65}$ Myocardial sympathetic nerve activity imaging with iodine-123-meta-iodobenzylguanidine detects sympathetic denervation, persisting for several months even when contraction has been normalized.$^{66}$

4. Treatment

4.1. Therapy in the acute phase

There are no randomized clinical trials on the specific treatment of TTS. Table 1 shows a list of results of different studies regarding treatment in TTS.$^{4,67-71}$ Current treatment strategies during the acute phase are mainly supportive aiming to reduce life-threatening complications. For a long time it was thought that the prognosis of patients with TTS is favorable. However, serious cardiac complications during the acute phase occurs in approximately 20% of TTS patients, which is comparable to ACS.$^4$ Predictors for a poor outcome include physical triggers, acute neurologic or psychiatric diseases, high troponin levels, and a low ejection fraction on admission (Figure 5). Recently, Lyon et al. proposed a risk stratification system for in-hospital complications of TTS.$^{72}$ All patients with TTS should be ECG monitored for at least 24 h. Furthermore, ECG monitoring should be considered in patients with QTc prolongation due to increased risk of ventricular arrhythmias.$^{42}$

In TTS patients complicated by cardiogenic shock, it is important to determine whether
haemodynamically significant LVOTO exists. If LVOTO is present, inotropic agents should be immediately discontinued to avoid further obstruction because LVOTO in TTS patients is associated with basal hypercontractility. In such patients without severe heart failure, short-acting intravenous β-blockers would be reasonable. On the other hand, in TTS patients complicated by cardiogenic shock without LVOTO the use of catecholamines such as inotropes should be considered carefully because catecholamines are thought to be associated with the pathogenesis of TTS. Levosimendan may be a useful alternative in terms of a catecholamine-sparing positive inotrope, but its role is controversial because of limited robust evidence. Therefore, early consideration of mechanical support is reasonable in patients with low cardiac output. Regarding novel mechanical support devices, such as a microaxial blood pump, this may be useful as a bridge-to-recovery in TTS patients complicated by cardiogenic shock. The advantage of such therapy is that the afterload is not increased by such therapy. In TTS patients with refractory shock, extracorporeal membrane oxygenation (ECMO) and temporary LV assist devices (LVAD) should be considered, if there are no contraindications.

In TTS patients with congestive heart failure, the standard therapies such as diuretics or nitroglycerine can be carefully used to reduce pre-load. Angiotensin-converting enzyme inhibitors (ACEI) or angiotensin II receptor blockers (ARBs) may also be an option when wall motion abnormality and impaired LVEF is present. Isogai et al. unexpectedly found that β-blocker use during the acute phase of TTS had no beneficial effect on in-hospital mortality in patients with or without LVOT obstruction. Intraventricular thrombus is a known complication of TTS especially in patients with severe apical ballooning and reduced LV ejection fraction, which occurs in approximately 2-5% of patients. Some experts have
recommended that prophylactic anticoagulation should be considered to prevent apical thrombus formations, following embolic events in all TTS patients until LVEF recovery.\textsuperscript{76,77} As previously mentioned, 8.6\% of TTS patients experienced ventricular fibrillation or TdP and prolongation of the corrected QT interval was significantly associated with the occurrence of ventricular arrhythmias.\textsuperscript{42} In this regard, QT-extending medications should be avoided. The effectiveness of temporary ventricular pacing at a high rate\textsuperscript{78} or intravenous magnesium\textsuperscript{79} to prevent its recurrence has been described. Whether an implantable cardioverter defibrillator (ICD) is required for secondary prevention in TTS patients complicated by ventricular arrhythmias during acute phase is not known but the reversible nature of TTS suggests that systematic ICD implantation may not be needed. LifeVest TM may be an alternative for patients with TTS and arrhythmia until full recovery is achieved.

\textbf{4.2. Therapy non-acute phase}

Beta-blockers are intuitively the most logical pharmaco-therapy for prevention of TTS recurrence. This may protect against stressful triggers and subsequent catecholamine surges. In fact, \(\beta\)-blockers are the most common prescribed medication in patients with TTS upon discharge. However, recently it has been demonstrated that the use of \(\beta\)-blockers in patients with TTS after discharge, did not have a beneficial effect on mortality after one year of follow-up.\textsuperscript{4} In addition, two meta-analyses failed to show a benefit of \(\beta\)-blockers in preventing recurrence of TTS.\textsuperscript{70,71} It is possible that \(\beta\)-blockers might be useful for preventing recurrence of TTS in selected patients especially those with persistent anxiety and elevated sympathetic tone. On the other hand, the use of ACEI or ARBs during the chronic phase after the initial event of TTS was associated with reduced recurrence rate of TTS\textsuperscript{71} or improved
survival at 1 year follow-up. Reduction of sympathetic activity through the renin-angiotensin system or the anti-inflammatory effect on myocardium may explain these results. As mentioned previously, oestrogens may play a role in the pathogenesis of TTS. Thus, oestrogen supplementation may be an intriguing concept for preventing recurrence of TTS. However, no trials have been so far performed. At present, this therapy may not be recommended, given the known risk of oestrogen supplementation, such as increased risk of venous thromboembolism.

In patients with multiple, recurrent TTS triggered by emotional stressors or suffering from neuropsychiatric disorders, the psychological response to emotionally stressful triggers may be a therapeutic target. Psychological counseling or anti-anxiety drugs may be beneficial for preventing recurrence of TTS.

5. Future directions

TTS has been increasingly recognized among clinicians worldwide, yet the exact pathophysiological mechanisms are still unknown. The International Takotsubo Registry and other studies have demonstrated that TTS has a much more diverse clinical presentation than initially appreciated and the short- and long-term outcome is not benign. Further research is needed to clarify the pathophysiology to help guide clinical decision-making and development of novel therapeutic strategies for those at risk of mortality, acute complications or chronic cardiac symptoms. Current knowledge may help for precise diagnosis of TTS and to optimize clinical management during both the acute and chronic phase. However, large-scale randomized controlled trials are needed to obtain more robust evidence for optimal treatment of TTS. In parallel with these clinical approaches, it is necessary to clarify the exact pathophysiology, which can rapidly facilitate systematic management strategies for TTS.
Key Points

- The prevalence of takotsubo syndrome (TTS) may be underestimated because knowledge of diagnostic criteria is often incomplete.

- The exact aetiology of TTS is still unclear, but catecholamines may play a central role.

- A preceding emotional or physical stress is a typical feature of TTS, and positive life events can provoke TTS. However, obvious triggers cannot be identified in one third of TTS patients.

- The novel criteria using electrocardiography on admission can differentiate between TTS and acute coronary syndrome (ACS) with high specificity and positive predictive value.

- In TTS patients, bystander coronary artery disease can be found incidentally, because most of TTS patients are quite old.

- Although apical ballooning is classic and the most common, variant forms such as mid-ventricular, basal and focal type have been demonstrated.

- Cardiac magnetic resonance imaging can provide not only functional but also pathological information of the myocardium. Thus, it is useful to differentiate between TTS and other myocardial disease, such as myocarditis.
The International Takotsubo Registry reveals that serious cardiac complications during hospitalization occur in 20% of TTS patients, which is comparable to ACS.

Predictors for an in-hospital worse outcome include physical triggers, acute neurologic or psychiatric diseases, high troponin levels, and a low ejection fraction on admission.

β-blockers may not be beneficial for both acute and chronic treatment of TTS.

In TTS patients complicated by cardiogenic shock, intra-aortic balloon pump is not any more recommended, but novel mechanical support device, such as microaxial blood pump, may be useful as a bridge-to-recovery.
Figure legends

Figure 1. Schematic of the difference in sympathetic innervation and β-adrenoceptor density of the myocardial regions.

The opposing apical-basal gradients of sympathetic nerve endings and β-adrenergic receptors may relate to the pathogenesis of TTS. Figure adapted from Lyon AR et al.\textsuperscript{22} with copyright permission.

Figure 2. Stressors associated with takotsubo syndrome (TTS).

Emotional and physical stressors can trigger TTS. Emotional stressors do not only include negative life events but also very joyous moments, which can trigger TTS. Physical stressors can be associated with every organ system. Figure adapted from Schlossbauer SA et al.\textsuperscript{32} with copyright permission.

Figure 3. Algorithm for the differential diagnosis of takotsubo syndrome (TTS) and ST-elevation myocardial infarction (STEMI) / non ST-elevation myocardial infarction (NSTEMI).

These criteria can clearly differentiate between TTS and acute coronary syndrome (ACS) with high specificity and positive predictive value. STe, ST-segment elevation; STD, ST-segment depression; TTS, takotsubo syndrome. *100% specificity and 100% positive predictive value; †More than 2 leads out of 3 in II-III-aVF; ‡More than 4 leads out of 6 in (V1-V2-V3-V4-V5-V6); ×More than 2 leads out of 3 in (V1-V2-V3). Figure from Frangieh AH et al.\textsuperscript{43} with copyright permission.
Figure 4. Different takotsubo types

Left ventriculography in the right anterior oblique projection during diastole (upper row) and systole (middle row) shows the 4 different wall motion patterns of TTS: apical, midventricular, basal, and focal. The bottom row demonstrates the schema of wall motion abnormalities. Blue dashed lines indicate affected regions. LVEF, left ventricular ejection fraction. Figure from Ghadri JR et al.\textsuperscript{40} with copyright permission.

Figure 5. Predictors of in-hospital complications in takotsubo syndrome (TTS).

Univariate (A) and Multivariate (B) analysis for in-hospital complications in TTS. Multivariate analysis demonstrated physical triggers, acute neurologic or psychiatric diseases, high troponin levels, and a low ejection fraction on admission as being independent predictors of a poor outcome. Black: statistically significant predictors, grey: not significant. BNP, brain natriuretic peptide; C.I., confidence interval; LVEF, left ventricular ejection fraction; OR, odds ratio; ULN, upper limit of the normal range. Figure from Templin C et al.\textsuperscript{4} with copyright permission.
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