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Review article

Cardiogenic shock in Takotsubo syndrome: Insights into phenotype-tailored management

Shock cardiogénico secundario a síndrome de Takotsubo: tratamiento individualizado según el fenotipo hemodinámico

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ABSTRACT

Takotsubo syndrome (TTS) is an acute and reversible condition that mimics acute coronary syndromes but occurs in the absence of coronary disease. Cardiogenic shock in TTS (CS-TTS) represents its most severe complication, affecting up to 25% of the cases and multiplying by six by six in-hospital mortality. CS-TTS is heterogeneous, arising from multiple and often overlapping mechanisms. Beyond classical pump failure due to severe systolic dysfunction, distinct phenotypes include dynamic left ventricular outflow tract obstruction (LVOTO) with mitral regurgitation, isolated or combined right ventricular failure, and rare mechanical complications. Additionally, vasoplegic and mixed shock can further expand the hemodynamic spectrum. Phenotype recognition guides therapy: pure pump failure may require cautious short-term inotropes or unloading mechanical support; LVOTO-mediated shock contraindicates catecholamines and favors cautious volume, pure vasopressors, and short-acting β-blockers; vasoplegia requires vasopressors; RV failure needs inotropes and preload optimization. Prospective phenotype-guided trials are urgently needed.

Palabras clave:
Síndrome de Takotsubo
Shock cardiogénico
Miocardiopatía de estrés
Bajo gasto cardíaco
Obstrucción del tracto de salida del ventrículo izquierdo
Inotrópicos
Vasopresores
Soporte circulatorio mecánico
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Revisión

RESUMEN

El síndrome de Takotsubo (TTS) simula un síndrome coronario agudo, en absencia de enfermedad coronaria significativa. El shock cardiogénico en el TTS (CS-TTS) afecta hasta el 25%, sextuplicando la mortalidad intrahospitalaria. El CS-TTS es heterogéneo, pudiéndose deber a mecanismos diferentes: insuficiencia de bomba por disfunción sistólica severa, obstrucción dinámica del tracto de salida del ventrículo izquierdo (LVOTO), insuficiencia mitral, insuficiencia ventricular derecha, y raras complicaciones mecánicas. Estados de shock vasoplégico y mixto pueden se pueden superponer. La identificación del fenotipo permite dirigir el tratamiento: el fallo de bomba puro requiere inótropicos o descarga mecánica, mientras que la presencia de LVOTO contraindica los inotrópicos. La afectación del ventrículo derecho se puede beneficiar de optimización de la precarga e inótropicos. Son necesarios ensayos prospectivos que evalúen tratamientos guiados por fenotipo hemodinámico.

Introduction

Takotsubo syndrome (TTS), also known as stress cardiomyopathy or broken heart syndrome, was first documented in Japan in 1990.[1] Typically induced by an identifiable emotional or physical stressor, it presents as an acute, transient form of segmental left ventricular dys-

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function that closely mimics acute coronary syndrome but occurs in the absence of complicated obstructive coronary artery disease.[2–4] The main pathophysiological hypothesis implicates massive sympathetic nervous system activation and subsequent catecholamine-induced myocardial injury as the central mechanism.[5]

Despite increasing recognition of its clinical relevance over the past three decades, TTS remains largely unexplored in randomized clinical trials, and no specific management guidelines have been established. Much of the current evidence on TTS epidemiology, clinical presentation, pathophysiology, and prognosis comes from observational studies based on data from large multicenter registries, such as the InterTAK (international), GEIST (German-Italian-Spanish), RETAKO (Spanish), and Chi-TTS (Chinese) registries.[6–9]

Cardiogenic shock (CS), characterized by end-organ hypoperfusion and tissue hypoxia due to reduced cardiac output, is the most severe TTS complication, affecting up to one in five patients and worsening both short- and long-term outcomes.[10–12] CS in the context of TTS (CS-TTS) results from a complex interplay of reversible neurohormonal, microvascular, and mechanical mechanisms, often manifesting in distinct yet overlapping hemodynamic phenotypes and demanding tailored, physiology-driven management strategies.[4,13,14]

This review synthesizes contemporary evidence on CS-TTS, with a focus on its epidemiology, underlying mechanisms and management strategies. By integrating data from registries, pathophysiological insights, and emerging prognostic tools, we provide a framework for more precise diagnosis, individualized treatment, and improved patient outcomes in this heterogeneous clinical entity.

Clinical predictors and risk stratification in CS-TTS

TTS accounts for 1–4% of all presentations clinically mimicking acute coronary syndrome.[15] Among patients with TTS, 5–17% develop CS,[11,14,16,17] although higher rates are reported in series that also include milder shock phenotypes without overt end-organ hypoperfusion.[18]

Demographic profile

While the typical age at TTS presentation is in the mid-to-late 60 s, patients with CS-TTS are, on average, 5–10 years younger than patients without shock.[19] Younger age, particularly <50 years, is associated with a higher incidence of CS, especially in men.[20,21] Women account for about 90% of the general TTS population but are less represented among those who develop CS, comprising about 80–85% of CS-TTS cases.[22] Across international registries and meta-analyses, male sex consistently emerges as a strong and independent predictor of CS development, with a frequency of up to 16% in men versus 6% in women.[22] Pooled data also show increased risk of both CS and in-hospital mortality in men.[23] However, once CS is established, sex-related differences in short- and long-term outcomes largely disappear after adjusting for comorbidities and severity, suggesting that the excess risk observed in male individuals is driven more by baseline vulnerability and triggering mechanisms than by intrinsic differences in prognosis within the CS subset.[24]

Comorbidities

Beyond demographic factors, several baseline comorbidities confer increased susceptibility to the development of CS in TTS. Classical risk factors such as arterial hypertension and diabetes mellitus, although less frequent in the general TTS population compared to classical cardiovascular cohorts, have a higher prevalence among patients who develop CS-TTS. Other comorbidities that confer an elevated risk of CS in TTS include chronic heart failure and atrial fibrillation,[25] as well as non-cardiac conditions such as neurological and psychiatric disorders,[26] chronic pulmonary disease, chronic kidney disease, and malignancies.[27]

Triggers

Regarding the nature of precipitating trigger, physical trigger, such as acute medical illness, surgery, or trauma, are associated with higher CS rates compared to the more typical emotional stressors.[28–30]

Early diagnostic predictors

Several early clinical and diagnostic findings can help identify patients at elevated risk. On the electrocardiogram (ECG), the characteristic abnormalities consist of repolarization changes and rhythm disturbances, with greater severity in patients who develop CS. ECG evolution typically progresses from initial ST-segment elevation to diffuse T-wave inversion, accompanied by QT-interval prolongation. QT-duration >490 ms has been proposed as cutoff for predicting ventricular arrhythmias.[31]

Echocardiographically, a lower left ventricular ejection fraction at admission is a strong predictor of CS, with values $<35\%$ indicating particularly high risk.[32] Atypical (non-apical) ballooning patterns are also associated with a higher incidence of CS.[6] CS-TTS is more often accompanied by left ventricular outflow tract obstruction (LVOTO), systolic anterior motion (SAM)-mediated mitral regurgitation (MR), right ventricular involvement, and intraventricular thrombus formation, mechanisms that can individually or collectively contribute to the development and persistence of CS.[33,34]

Laboratory tests in TTS typically show a modest elevation of troponin with a disproportionately high N-terminal pro-B type natriuretic peptide (NT-proBNP). In CS-TTS, both troponin and NT-proBNP are significantly higher, with median NT-proBNP ~8800 pg/mL vs ~2300 pg/mL in patients without shock.[17,35] Elevated white blood cell counts and a high neutrophil-to-lymphocyte ratio, further indicating systemic inflammation, also correlate with shock risk and worse in-hospital outcomes.[36]

Risk stratification and prognosis

Risk stratification in CS-TTS must integrate clinical, echocardiographic, and laboratory information to guide triage and therapy. The Society for Cardiovascular Angiography and Interventions (SCAI) shock staging system has been validated in TTS cohorts and reliably stratifies risk: higher stages (C–E) are associated with progressively greater in-hospital and 1-year mortality, providing a pragmatic framework for therapeutic escalation decisions.[18] Independent predictors of shock include male sex, physical (non-emotional) triggers, QTc prolongation, reduced left ventricular ejection fraction and the presence of intraventricular pressure gradients; these variables are incorporated in TTS scores developed in German and Italian cohorts.[8],16

Reported in-hospital mortality rates of CS-TTS are 23–32%, roughly sixfold higher than in TTS without shock, with most fatalities occurring within the first 24 h.[11,18] In fact, shock is the strongest independent predictor of both short- and long-term all-cause and cardiovascular mortality. In-hospital complications such as malignant ventricular arrhythmias, cardiac arrest, acute kidney injury and major bleeding are more frequent in CS-TTS.[16,24] Higher vasoactive-inotropic scores correlate with increased short- and long-term mortality, and concomitant respiratory illness and advanced age (>75 years) identify patients at especially high risk.[37,38]

Beyond the acute phase, TTS carries a non-trivial long-term risk of death and adverse events, with mortality rates comparable to those seen in age- and sex-matched acute coronary syndrome cohorts. Physical trigger, older age, comorbidities (notably cancer and neurological disorders), and delayed recovery of left ventricular function (>10 days) are associated to worse long-term outcomes.[16,39,40]

Shock mechanisms and hemodynamic phenotypes

While the main pathophysiological theory in TTS centers on excessive local sympathetic stimulation causing direct myocyte toxicity and abnormal β-adrenergic receptor signaling, particularly affecting the apical myocardium, the reason why only a subset of patients progress to hemodynamic collapse remains unclear. Left ventricular systolic dysfunction (pump failure), causing severely reduced cardiac output and tissue hypoperfusion, is the hallmark of CS-TTS. However, shock can result from a multifactorial and overlapping set of mechanisms (Fig. 1), which include dynamic LVOTO; SAM of the mitral valve and subsequent MR; right ventricular failure; arrhythmias; and, although rare, mechanical complications, such as left ventricular free-wall rupture or ventricular septal defect. Moreover, vasoplegic or mixed shock components, often driven by autonomic dysregulation and systemic inflammation, may further exacerbate circulatory failure.[14]

The following sections explore each of these mechanisms, highlighting their interplay and clinical implications for CS-TTS diagnosis and tailored management.

Pump failure

Left ventricular pump failure is the hallmark shock mechanism in TTS and may occur alone or in combination with other contributory factors. It results from acute, typically reversible, systolic dysfunction characterized by impaired contractility and shortened systolic time, leading to reduced cardiac output and end-organ hypoperfusion, as well as elevated left ventricular end-diastolic pressure and pulmonary congestion. Echocardiographic findings typically include a diminished left ventricular outflow tract velocity-time integral and elevated E/e′ ratios. Hemodynamic studies demonstrate rightward-shifted pressure-volume loops, prolonged relaxation, and inefficient myocardial energetics, occasionally with preserved stroke volume despite overall impaired function.[41] In pure pump failure, pulmonary artery catheterization demonstrates increased pulmonary capillary wedge pressure, low cardiac index, and elevated peripheral vascular resistance.[41,42] A notable complication in some cases of severely depressed contractile function is the formation of intraventricular thrombus, likely due to stagnant flow within akinetic or dyskinetic ventricular segments, increasing the risk of embolic events.[43,44]

LVOTO and SAM-MR

Another potential contributor to hemodynamic compromise in TTS is LVOTO, which results from hypercontractility of the basal segments, a feature observed in both the typical apical ballooning pattern and in less frequent midventricular variants. During ventricular systole, basal hyperkinesis narrows the left ventricular outflow tract, creating a dynamic pressure gradient that limits forward stroke volume. LVOTO should be suspected in patients with hypotension or pulmonary congestion that appears disproportionate to the degree of left ventricular systolic dysfunction. It is more frequent in patients with small left ventricular cavity and can be exacerbated by increased septal thickness. LVOTO has been reported in 7–33% of unselected TTS series and in about one-fifth of CS-TTS.[16,34]

The diagnosis is established by transthoracic echocardiography, with color Doppler showing flow acceleration (Supplemental Video 1) and continuous wave Doppler typically demonstrating a late-peaking ("dagger-shaped") velocity profile. Peak gradients >30–40 mmHg, either at rest or with provocation (i.e. Valsalva maneuver), are considered diagnostic in most series, and gradients >50 mmHg are classified as severe. LVOTO is a dynamic phenomenon, highly sensitive to loading conditions, with gradients increasing when preload or afterload falls, or when contractility is enhanced.[17,33,41]

In addition, basal hypercontractility often causes SAM of the anterior mitral leaflet toward the interventricular septum, impairing full leaflet coaptation. SAM can cause significant MR, usually posteriorly directed, which increases left atrial pressure, aggravates pulmonary congestion, and further compromises hemodynamics. Other contributors to MR include geometric distortion of the subvalvular apparatus due to apical ballooning and volume overload. Severe MR has been reported in up to 16% of patients with CS-TTS, and in up to 40% of those with LVOTO. The coexistence of LVOTO and MR can markedly amplify CS-TTS severity, underscoring the importance of systematic echocardiographic assessment in suspected cases.[33,34]

Right ventricular failure

Right ventricular failure, although infrequent in TTS cases, is linked to higher rates of shock, in-hospital complications, and adverse long-term outcomes, representing a high-risk phenotype. In CS-TTS cohorts, overt right ventricular failure is reported in 5–6%, whereas subclinical right ventricular involvement detected by imagining occurs in up to one third of cases.[45] Acute right ventricular failure should be suspected when hypotension and low cardiac output appear to be disproportionate to the degree of left ventricular dysfunction, particularly in the presence of systemic venous congestion signs such as elevated jugular venous pressure, hepatomegaly, or peripheral edema. Diagnosis is based on transthoracic echocardiography, which may reveal right ventricle dilation, sometimes with biventricular ballooning, and reduced systolic function, evidenced by decreased tricuspid annular plane systolic excursion, reduced free-wall strain, or diminished radial contractility. Isolated right ventricular TTS leading to CS has also been described. Early recognition is crucial to guide fluid management and initiate targeted therapeutic strategies.[45–47]

Arrhythmias

Up to 10% of TTS cases present with life-threatening arrhythmias, which tend to cluster at presentation or within the first 48–72 h of hospital admission.[25] Ventricular repolarization anomalies, manifested on the ECG as a prolonged QT-interval, constitutes the electrical substrate for polymorphic ventricular tachycardia (torsades de pointes) and, potentially, subsequent ventricular fibrillation and sudden cardiac arrest. Bradyarrhythmias, which may further predispose to malignant ventricular arrhythmias, are reported in around 5% of TTS patients.[48,49] Arrhythmia occurrence is associated with higher in-hospital mortality and often requires prompt antiarrhythmic intervention or device-based therapies.[50]

Mechanical complications

Although rare (e.g., 0.2% prevalence in the InterTAK registry), mechanical complications of TTS, most notably left ventricular free-wall rupture and, more rarely, ventricular septal rupture (Supplemental Video 2), are among its most catastrophic events, with mortality rates approaching two-thirds in reported cases.[51] These ruptures often lead to hemopericardium and cardiac tamponade or, in the case of septal rupture, acute left-to-right shunt, both typically resulting in abrupt hemodynamic collapse. Registry data highlight that rupture usually occurs within the first few days of presentation, most often in elderly women with apical ballooning, persistent ST-segment elevation, and elevated cardiac biomarkers. Despite pericardial drainage and urgent surgical repair being the definitive therapy, outcomes remain poor, underscoring the need for early recognition and vigilance in high-risk patients.[51–53]

Vasoplegic and mixed shock phenotypes

In TTS, shock is not always purely cardiogenic. A subset of patients presents with a vasoplegic shock phenotype, characterized by profound systemic vasodilation and hypotension disproportionate to the degree of

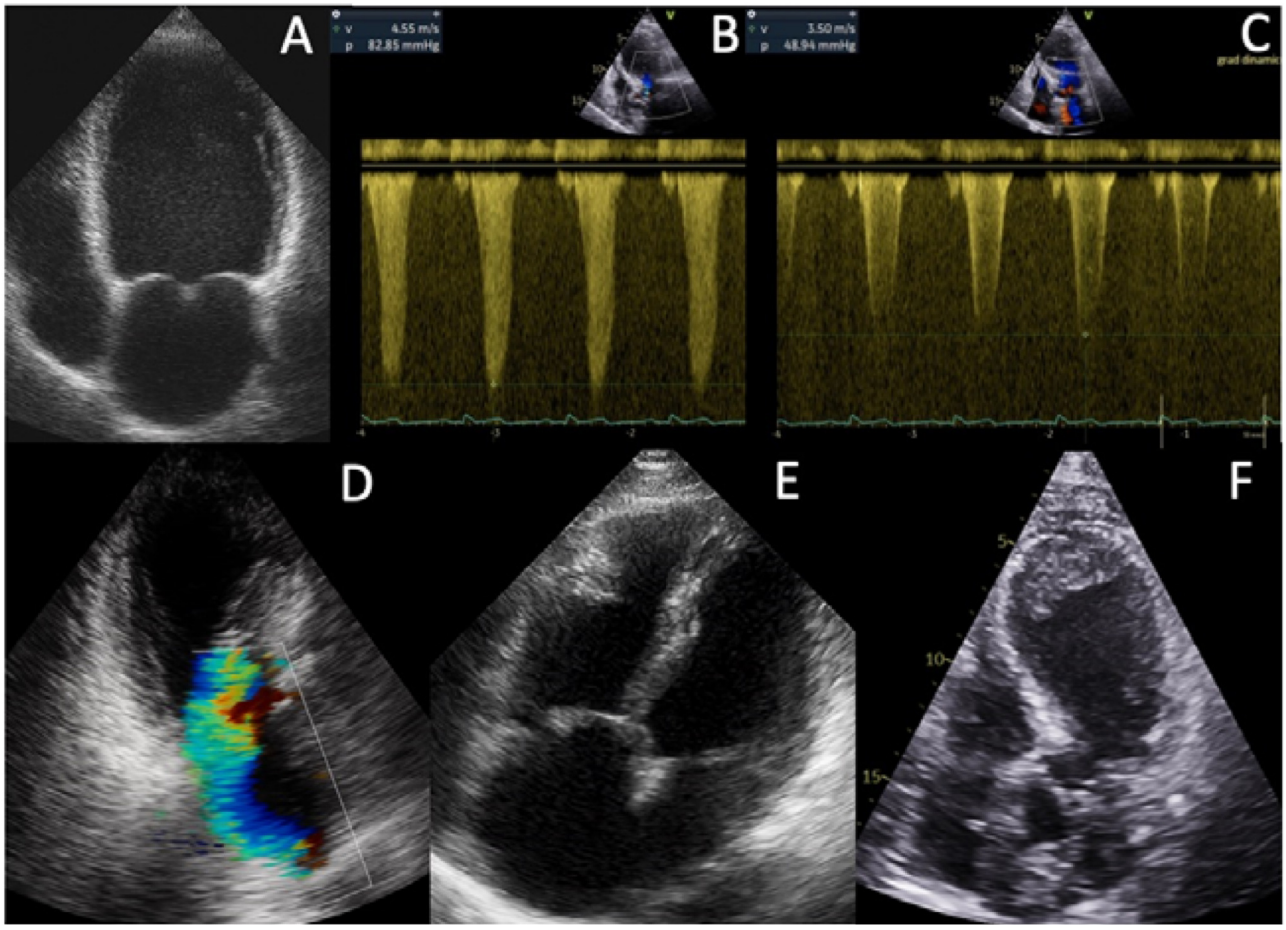

Fig. 1. Cardiogenic shock phenotypes in Takotsubo syndrome. Pure pump failure secondary to acute-onset left ventricular dysfunction (Panel A). Left ventricular outflow tract obstruction (Panel B) and its improvement flowing phenylephrine administration (Panel C). Mitral regurgitation secondary to systolic anterior movement of the anterior mitral leaflet (Panel D). Right ventricular dilatation secondary to acute right ventricular failure (Panel E). Other mechanisms of shock and hemodynamic collapse include bradyarrhythmias and tachyarrhythmias, and mechanical complications, such as free wall rupture and ventricular septal defect. A notable complication in some cases of severely depressed contractile function is the formation of intraventricular thrombus, likely due to stagnant flow within akinetic or dyskinetic ventricular segments, increasing the risk of embolic events (Panel F).

left ventricular systolic dysfunction. This state is thought to arise from catecholamine-mediated endothelial and microvascular injury, nitric oxide-driven vasodilation, and natriuretic peptide-associated vasodilatory effects, and it may coexist with only modest impairment of pump function.[41] Clinical clues include warm extremities, wide pulse pressure, low filling pressures, limited response to inotropes, and blunted response to vasopressors. Importantly, intercurrent conditions, particularly systemic infections, which may also serve as physical triggers for TTS, can exacerbate or precipitate vasoplegia. Also, in patients with preceding cardiac arrest, vasoplegia may be part of the post-cardiac arrest syndrome.[54]

Vasoplegia can occur in isolation or in combination with a significant cardiogenic component, producing a mixed shock state with both low cardiac output and low systemic vascular resistance. This combination requires simultaneous treatment of pump failure and vasodilation, often with temporary mechanical circulatory support (MCS) alongside vasopressors.[37]

Management

The management of CS-TTS is primarily supportive, centered on rapid hemodynamic assessment, early exclusion of obstructive coronary artery disease, and the delivery of therapy tailored to the prevailing pathophysiological phenotype (Table 1).[14,55] Optimal care should be embedded within a structured multidisciplinary framework, ideally through dedicated shock teams, to facilitate early phenotyping and coordinated decision-making. High-risk TTS patients and those with established shock should be admitted to a cardiac intensive care unit, where continuous multisystem monitoring allows for rapid recognition of evolving hemodynamic phenotypes, early detection of complications, and timely escalation of therapy.[18,34] Close surveillance should include ECG telemetry, invasive arterial pressure monitoring, bedside clinical reassessment, and serial laboratory surveillance, including lactate, arterial blood gases, electrolytes, renal and liver function, cardiac biomarkers, and indices of tissue perfusion.[56] The overarching priorities in this setting are: 1) exclude competing causes of acute ventricular dysfunction, most importantly obstructive coronary artery disease, reviewing coronary angiography if needed; 2) prompt recognition of the prevailing pathophysiological phenotype; 3) restoration and maintenance of adequate tissue perfusion; 4) prevention or early treatment of potential complications.

Cardiac imaging plays a central role in the acute phase: transthoracic echocardiography is the cornerstone for assessing biventricular systolic function, detecting LVOTO, quantifying MR, identifying pericardial effusion or mechanical complications, and screening for intraventricular thrombus.[17,57] Transesophageal echocardiography should be performed without delay in cases of inadequate transthoracic window, clinical-hemodynamic discordance, or unexplained hemodynamic instability. Imaging should be repeated at short intervals to track functional recov-

Table 1
Cardiogenic shock in Takotsubo syndrome: hemodynamic phenotype-guided approach.

Prevailing pathophysiological phenotype	Fluid management	Vasoactive and inotropic drugs	MCS	Avoid
Pure pump failure	Volume depletion	Inotropes Consider vasodilators	Consider mAFP, V-A ECMO	Vasoconstrictors
LVOTO	Volume expansion	Phenylephrine; vasopressin Esmolol	Consider mAFP, V-A ECMO	Inotropes, vasodilators IABP
Vasoplegia	Volume expansion	Vasopressors: phenylephrine, vasopressin, norepinephrine	Low benefit from MCS	Vasodilators
Right ventricular failure	Volume optimization	Inotropes Inhaled pulmonary vasodilators	Early consider V-A ECMO	mAFP, IABBP Positive pressure ventilation

Cardiogenic shock in Takotsubo syndrome: hemodynamic phenotype-guided approach. IABP indicates intraaortic balloon pump; LVOTO, left ventricular tract obstruction; mAFP, microaxial flow pump; MCS, mechanical circulatory support; V-A ECMO, veno-arterial extracorporeal membrane oxygenation.

ery or deterioration and to guide therapeutic decisions, including the timing and modality of MCS.[33,58]

When noninvasive findings are inconclusive, particularly in the presence of suspected mixed cardiogenic and vasoplegic physiology, invasive hemodynamic monitoring with a pulmonary artery catheter should be considered, as it provides definitive measurements of filling pressures, cardiac output, and systemic vascular resistance, enabling more precise titration of fluid therapy and vasoactive drugs.[59]

Respiratory care

Respiratory care in CS-TTS should be adapted to the severity of respiratory failure and the underlying hemodynamic status. Pulmonary congestion resulting from elevated ventricular end-diastolic pressures is the primary cause of respiratory failure. However, pneumonia, an important potential TTS trigger or complication, must be excluded. Initial management includes supplemental oxygen therapy, progressing to high-flow nasal cannula or noninvasive ventilation in patients without indications for airway protection. Invasive mechanical ventilation is indicated in cases of refractory hypoxemia, airway protection, or severe hemodynamic instability. Positive end-expiratory pressure must be cautiously titrated, given that positive-pressure ventilation may reduce venous return and afterload, potentially exacerbating LVOTO and impairing cardiac output. This consideration is particularly critical in case of right ventricular failure, where positive pressure should be minimized.[14,60,61]

Volume assessment and fluid management

Assessment of intravascular volume status is fundamental in CS-TTs management. While some patients might benefit from cautious fluid administration, others are at risk of exacerbating pulmonary congestion and hemodynamic compromise with volume expansion. Traditional clinical evaluation remains essential, including careful assessment of jugular venous pressure, peripheral perfusion, and auscultation for pulmonary crackles, as well as central venous pressure. Volume status assessment should be guided by focused echocardiographic evaluation of left ventricular cavity size and inferior vena cava dynamics, although the latter must be interpreted with caution in mechanically ventilated patients with altered intrathoracic pressures. Dynamic parameters such as stroke-volume variation or pulse-pressure variation can inform about fluid responsiveness, particularly in ventilated patients with sinus rhythm. Functional maneuvers such as passive leg raising with corresponding changes in velocity-time integral of the left ventricular outflow tract can aid in real-time assessment of preload reserve. Serial monitoring of lactate levels and urine output further supports evaluation of end-organ perfusion.[34,62,63]

Loop diuretics, primarily intravenous furosemide, are the mainstay for managing pulmonary congestion by reducing left ventricular filling pressures. Their use, however, requires careful titration and clinical judgment, especially in patients in whom excessive volume depletion might exacerbate LVOTO. In such scenarios, hemodynamic reassessment should be frequent, and management adapted accordingly. Diuretics should never be administered indiscriminately but rather within a framework of ongoing monitoring to balance decongestion with maintenance of adequate preload. Similarly, fluid therapy in this setting demands a conservative, physiology-driven approach. Fluid challenges should be reserved for patients demonstrating clear evidence of preload responsiveness or those with clinical features of vasoplegia accompanied by low filling pressures. Each fluid bolus must be immediately reassessed, ideally utilizing dynamic indices or echocardiographic parameters, to avoid inadvertent fluid overload in patients prone to congestion or with marked left ventricular dysfunction. Excessive fluid administration can rapidly worsen pulmonary edema and hypoxaemia, aggravating clinical status.[34,64]

Renal replacement therapy is useful when renal dysfunction progresses despite optimized medical management, particularly in the context of oligo-anuria with refractory fluid overload. In hemodynamically unstable patients, continuous renal replacement therapy modalities are preferred as they allow gradual fluid removal and metabolic control, minimizing the risk of precipitous haemodynamic deterioration.[14]

Vasoactive and inotropic drugs

The pharmacologic management of CS-TTS is uniquely challenging, as the same catecholaminergic surge that precipitates myocardial stunning can be amplified by vasoactive therapy. For this reason, drug selection must be strictly adapted to the prevailing hemodynamic phenotype.

Patients without LVOTO

In cases with severe pump failure without LVOTO, vasoactive and inotropic therapy can be cautiously employed to restore perfusion. Observational registries describe frequent use of dobutamine and, less commonly, phosphodiesterase-III inhibition with milrinone. Importantly, there is no evidence that the initiation of these drugs induces LVOTO.[34] Nevertheless, catecholamine exposure has been repeatedly associated with worse outcomes in TTS, plausibly reflecting both indication bias (sicker patients receive more drugs) and amplification of

sympathetic toxicity; thus, doses and duration should be minimized.[37,60] Non-adrenergic inotropy with levosimendan has been reported as an alternative in selected patients without LVOTO, especially in patients who are beta-blocked or have insufficient response to diuretics. However, supporting data remain limited, and its vasodilatory profile together with the long elimination half-life of its active metabolites mandate special caution.[60,65,66]

Patients with LVOTO

In patients with LVOTO, therapeutic priorities are essentially reversed compared to pure pump failure. Catecholamines and inodilators, by increasing basal contractility and lowering afterload, can steepen the intraventricular gradient and precipitate or worsen obstruction, leading to hemodynamic collapse. First-line management relies on short half-life β-blockade (e.g., intravenous esmolol) to attenuate basal hyperkinesis, combined with cautious volume expansion to increase preload and enlarge cavity size. These measures typically reduce both the gradient and SAM of the mitral valve. If hypotension persists, vasopressors that increase afterload without enhancing contractility can be used: phenylephrine is generally preferred, while norepinephrine may be considered in mixed phenotypes but requires careful titration due to its β-1 activity.

Real world series show that patients with LVOTO often present in more profound shock and therefore receive vasoactive drugs more frequently. In such cases, therapy should be delivered under continuous echocardiographic monitoring, using the lowest effective doses, with prompt weaning once gradient decreases, and rapid escalation to mechanical support when pharmacologic measures fail. Supporting this, a recent multicenter study[34] demonstrated that catecholamine use in CS-TTS, particularly in the presence of LVOTO, was independently associated with higher in-hospital and 1-year mortality. In contrast, patients treated with non-catecholaminergic strategies, including β-blockade, cautious fluid expansion, and early mechanical support, achieved more favorable outcomes, underscoring the need for strict phenotype-guided management and caution against indiscriminate adrenergic stimulation in this high-risk subgroup.

Vasoplegic phenotypes

Shock profiles with a vasoplegic component mandate vasopressors to restore tissue perfusion. Norepinephrine is the pragmatic first-line agent in pure vasoplegia because of its potent α-1 adrenergic agonist effect, with modest β-1 support. However, in the setting of basal hypercontractility or known LVOTO, a pure α-agonist (phenylephrine) is preferable. Vasopressin can serve as a catecholamine-sparing adjunct. All vasoactive therapy should be titrated to the lowest effective dose and reassessed frequently to avoid unmasking or worsening LVOTO.[37]

Right ventricular failure

Right ventricle involvement denotes a high-risk subgroup requiring meticulous preload and afterload management. Besides volume optimization, restoration of sinus rhythm in setting of supraventricular arrhythmias can markedly enhance right ventricle filling and stroke volume. When contractile support is necessary, short-acting inotropes (dobutamine, milrinone) may improve right ventricle systolic function. Inhaled pulmonary vasodilators (nitric oxide, prostacyclins) can reduce right ventricle afterload, with low risk of systemic hypotension. Prompt correction of hypoxaemia, acidosis and anemia, close echocardiographic monitoring, and early escalation to right ventricle-targeted MCS strategies are essential.

Mechanical circulatory support

The role of MCS in CS-TTS remains insufficiently defined, with available evidence limited to observational registries and case series. Nonetheless, phenotype-guided selection is critical, and timely escalation may be life-saving.

Devices providing direct ventricular unloading with minimal afterload increase, such as microaxial flow pumps, align well with the catecholamine-mediated stunning of TTS by improving forward flow, lowering wall stress, and permitting early initiation of β-blockade while minimizing the need for inotropes. Multicenter experiences report hospital survival around 80 % in such patients. In cases complicated by LVOTO and severe MR, microaxial flow pumps have been reported not only to maintain systolic blood pressure but also to attenuate intraventricular gradients and reduce mitral regurgitation, providing a mechanistic advantage over other devices.[67]

Veno-arterial extracorporeal membrane oxygenation (V-A ECMO) is the preferred option for profound or biventricular shock, or when concomitant respiratory failure is present. Registry data suggest hospital survival in CS-TTS supported with V-A ECMO of 85–90%, consistent with the reversible nature of the syndrome. Importantly, the afterload augmentation induced by ECMO may play a beneficial role in patients with LVOTO, as it raises aortic pressure, enlarges cavity size, and reduces both the intraventricular gradient and SAM, thereby stabilizing hemodynamics. Conversely, in patients with severe systolic dysfunction but no LVOTO, the same afterload increase may cause left ventricular distension and pulmonary congestion.[68,69]

By contrast, the utility of the intraaortic balloon pump (IABP) is more nuanced. While it can modestly improve cardiac output and reduce wall stress, its afterload-lowering effect may worsen LVOTO. A recent large multicenter registry showed that IABP use in CS-TTS was not associated with reduced short- or mid-term mortality, raising doubts about its role in this setting.[70] Nevertheless, its relative availability, ease of implantation, and lower cost explain why it remains widely used in clinical practice despite these limitations.

Overall, observational data suggest that early escalation to unloading strategies may facilitate faster ventricular recovery and better outcomes, whereas reliance on pharmacological therapies alone, particularly catecholamines, is associated with higher mortality.[68,71] Given the scarcity of randomized evidence, careful bedside imaging, invasive hemodynamic monitoring, and phenotype-based selection remain the cornerstones for guiding MCS in CS-TTS.

Conclusions and future directions

CS-TTS is a heterogeneous syndrome that requires rapid phenotype recognition and physiology-tailored therapy. In predominant pump-failure, cautious short-term inotropes may be used, with early consideration of mechanical unloading. In patients with LVOTO, the priority cautious volume expansion, phenylephrine for afterload support if required; inotropes and afterload-reducing strategies should generally be avoided. Pure vasoplegia requires carefully titrated vasopressors, while right-ventricular involvement denote a high-risk phenotype demanding precise hemodynamic optimization and often early MCS. Currently, most evidence comes from observational registries; thus, contemporary care must integrate bedside imaging, invasive monitoring, and individualized escalation, while prospective studies are urgently needed to define optimal phenotype-specific strategies. Improving outcomes in CS-TTS will not come from universal algorithms, but from accurate recognition of the hemodynamic phenotype and truly personalized support.

Importantly, most available evidence in TTS derives from observational registries, with inherent limitations related to selection bias and heterogeneity in management, underscoring the need for prospective, phenotype-guided trials, particularly in CS-TTS. Upcoming expert consensus and clinical practice guidelines should explicitly address this high-risk scenario. Priorities include standardized phenotyping and rigorous evaluation of supportive strategies. Several randomized trials, such as BROKEN-SWEDEHEART (Optimized Pharmacological Treat-

ment for Broken Heart [Takotsubo] Syndrome, NCT04666454),[72] CIT, (Cyclosporine in Takotsubo Syndrome, NCT05946772),[73] and β-TAKO (Beta-Blockers in Takotsubo Syndrome Study, NCT06509074),[74] are underway.

CRediT authorship contribution statement

Conceptualization: MT and AU. Writing – Original draft preparation: MT, FGS. Writing – Reviewing and Editing: MT, FGS, LA, and AU. Supervision: AU.

Declaration of Generative AI and AI-assisted technologies in the writing process

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Declaration of competing interest

None.

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