Takotsubo syndrome: Unraveling the mystery behind its triggers (Review)

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Abstract. Takotsubo syndrome (TTS) is a clinical condition characterized by left ventricular dysfunction, clinically mimicking acute coronary syndrome. Despite significant advancements in understanding TTS, more questions about its underlying pathological mechanisms remain unresolved. The present review offered current data on the underlying pathological mechanisms of TTS, including central nervous system structural and functional alterations, sympathetic nervous system overstimulation, excessive catecholamine secretion, shifts in adrenergic receptors (ARs) distribution and balance, hormone influences, epicardial vasospasm, endothelial dysfunction and genetic predispositions. For example, stressors from physical or emotional triggers induce central neurohumoral activation by influencing the hippocampus and amygdala, which results in excessive local or systemic secretion. This catecholamine surge affects the myocardium by altering cellular metabolism, disrupting signaling pathways and impairing endothelial function. The regional myocardial effects are influenced by the modified ARs distribution and the density of autonomic innervation, which are pivotal in the onset of TTS. These insights suggest potential therapeutic strategies, including cognitive behavioral therapy, endothelin A antagonists and β-blockers. However, the complex interplay of these factors in TTS onset remains poorly understood. Further research is essential to elucidate the intricate mechanisms and interactions underlying this syndrome, paving the way for improved prevention and treatment approaches.

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Contents

1. Introduction

Takotsubo syndrome (TTS) is characterized by distinctive regional wall systolic dysfunction in the left ventricle (LV), presenting as apical ballooning without the presence

of coronary artery disease (CAD). TTS was first described in 1990, in a patient initially suspected of having acute coronary syndrome (ACS) and now it is a pan-ethnic condition across ethnicities (1-4). It is difficult to quantify the TTS prevalence, due to its frequent underdiagnosis and transient cardiac phenotype. However, following increasing recognition, TTS is now reported to account for 1-4% of all patients with ST-elevation myocardial infarction (STEMI) along with electrocardiography (ECG) changes and increased cardiac biomarkers (5-8). Moreover, angiography reveals unobstructed coronary arteries (UCA) and systolic LV apical ballooning. There is a significant female preponderance in TTS prevalence, with nearly 90% of cases occurring among women (9-12). TTS predominantly manifests in middle to late adulthood, particularly in individuals >50 years and postmenopausal women (13). Physical triggers are more common than emotional triggers, with the latter being more prevalent in women and the former in men (9,14).

Possible pathophysiological mechanisms associated with the development of TTS mainly include structural and functional alterations in the central nervous system (CNS), sympathetic nervous system (SNS) overstimulation, surges in catecholamine secretion, changes in the distribution of adrenergic receptors (ARs), hormonal influences, epicardial vasospasm, endothelial dysfunction and genetic predispositions. However, the interactions among these factors and their specific roles in the pathogenesis of TTS remain unclear. The present review aimed to summarize the clinical features of TTS and its underlying pathophysiological mechanisms. Additionally, it explored the prognosis and clinical implications of TTS, as well as targeted interventions for managing the condition. By elucidating the complex interplay of various factors that contribute to TTS, the present review provided practical insights for clinicians to improve their ability to identify, diagnose and manage patients with TTS. At the same time, it offered recommendations for future research directions, encouraging collaboration between academia and clinical practice to advance the understanding and effective treatment of TTS, while fostering interdisciplinary cooperation in the ongoing study of this syndrome.

2. TTS clinical features

Patients with TTS exhibit clinical manifestations overlapping with ACS, most commonly chest pain (75.9%) as the predominant presenting symptom, followed by dyspnea (46.9%) and syncope (7.7%) during hospitalization (9,12,15). Particularly in males, it may present as cardiogenic shock and cardiac arrest (10,16,17). Moreover, some TTS cases occur in asymptomatic patients, presenting solely with ECG abnormalities, characteristic imaging findings and elevated troponin levels (18,19). The most prevalent abnormalities observed in ECGs of patients with TTS are ST-segment elevation, T-wave inversion, left bundle branch block (20,21). Other ECG findings, including J wave during the superacute phase, fragmented QRS complexes and low voltage QRS complexes, have also been reported in some studies (22-25). Common complications associated with patients with TTS include hypotension, cardiogenic shock, left ventricular outflow tract obstruction (LVOTO), mitral regurgitation and systemic thromboembolism (26).

While TTS may initially be suspected based on clinical and ECG characteristics, it is confirmed through the typical features on the left ventriculogram, cardiac magnetic resonance imaging (cMRI), transthoracic echocardiogram (TTE) and unobstructed coronary angiography. The most common and widely recognized manifestation of TTS is the apical ballooning variant, often referred to as the typical presentation of TTS. Other 'atypical' types of TTS include mid-ventricular, basal and focal wall motion patterns (6,21,27). Recently, a fifth variant of TTS has been proposed, where the mid-ventricle is hyperdynamic, while the apex and base are either akinetic or hypokinetic, known as reverse apical ballooning (28). The right ventricle may also be involved in up to one-third of patients with TTS and, in rare cases, may be the only myocardial chamber affected (27,29,30).

Numerous diagnostic criteria for TTS have been proposed (31). The developed International Takotsubo (InterTAK) Diagnostic Criteria provide universally accepted standards for diagnosing TTS (6). Additionally, the InterTAK Diagnostic Score, derived from clinical and ECG parameters, was designed to facilitate the early and accurate differentiation of TTS from ACS (6,8). Of patients with TTS ~7% develop atrial fibrillation (AF), 3% experience ventricular embolic or thrombi events and 10% of cases present with ventricular arrhythmias during acute and convalescent phases (32-34). Distinguishing between TTS and ACS poses a challenge, particularly in patients exhibiting heart wall motion abnormalities. Avoiding misdiagnosis is crucial in clinical presentation and clinicians should be vigilant in identifying subtle differences (35-38) (Table I). Given that the epidemiology of TTS has been well-characterized, current research priorities should focus on delineating its underlying pathological mechanisms to develop targeted interventions, as schematically summarized in Fig. 1.

3. Pathophysiological mechanisms of TTS

Although the underlying mechanisms of TTS remain elusive, several hypotheses have been proposed, including the overstimulation of the SNS (10,11,39,40), excessive catecholamine secretion (40-42), ARs modulation (40,43-46), epicardial vasospasm or dysfunction (47-52), endothelial dysfunction (53-57), CNS structural and functional alterations (6,9,58-62), hormone-mediated changes (9,10,53,63,64) and genetic predispositions (65-68) (Fig. 2).

Structural and functional alterations in the CNS. There are anatomical structural differences in the brain between patients with TTS and healthy controls (69,70). Studies have shown that neurological and psychiatric comorbidities are more prevalent in patients with TTS compared with those with ACS (9,59). Patients with depression and/or anxiety demonstrate functional and structural adaptations in most brain regions, which can predict the presence of TTS (71). During TTS episodes, stress-related structures in the brain undergo anatomical and neurophysiological changes, indicating that stress-induced alterations in the CNS may activate the SNS, leading to TTS (72). During the acute phase of TTS, changes in the volume of the frontal lobe region, insula, anterior cingulate cortex and amygdala occur (73). Whole-brain

Table I. Differentiation of TTS with ACS based on clinical presentation.

Clinical presentation	TTS	MI with obstructive coronary arteries	MI with non-obstructive coronary arteries
Clinical Features	Acute chest pain or dyspnea; stressors (other illnesses or psychiatric illness)	Acute chest pain; cardiovascular risk factors; imbalance between supply and demand of myocardial oxygen; tachycardia or hypotension; concomitant illness; complications	Acute chest pain; clinical evidence of myocardial infarction
Blood	Moderate cardiac troponin elevation [on admission for Patients with TTS without malignancy: 1.04 μg/l (range: 0.35-3.65); on admission for Patients with TTS without atrial arrhythmias 2.6±4.3 μg/l; marked BNP and CRP elevation [on admission for patients with TTS without malignancy: BNP: 268 ng/l (range: 82-986), CRP: 10 mg/l (range: 1-28); on admission for patients with TTS without atrial arrhythmias: BNP: 592±860 ng/l; CRP: 32±57 mg/l	Marked cardiac high-sensitivity cardiac troponin T elevation (0.618 μg/l, range: 0.15-2.346); Moderate NT-ProBNP: 133.2±127.8 ng/l and CRP: 7.94±25.0 mg/l elevation measured at 3-months follow-up	Elevated troponin (0.18 μg/l, range: 0.069-0.467)
ECG	Widespread ST-segment and T wave abnormality; QTc prolongation (late)	Territorial ST-segment or T wave abnormality	Ischemic changes
Echocardiography	Temporary LV regional wall motion abnormality based on the subtypes of TTS (apical, basal, focal)	Normal or persistent LV impairment; regional wall motion abnormality	Normal or persistent LV impairment; regional wall motion abnormality
MRI	No persistent LGE, elevated T1/T2	LGE-infarct pattern; elevated native T1/T2; regional wall motion abnormality cement-infarct pattern	LGE; Regional wall motion abnormality
Angiography	Normal or non-obstructive CAD; apical ballooning on left ventriculography	Obstructive CAD	Normal or non-obstructive CAD; evidence of acute plaque rupture

TTS, Takotsubo syndrome; ACS, acute coronary syndrome; MI, myocardial infarction; MRI, magnetic resonance imaging; LGE, late gadolinium enhancement; CAD, coronary artery disease; LV, left ventricle; BNP, B-type natriuretic peptide; CRP, C-reactive protein.

network analysis confirmed the specificity of central brain structures related to the limbic/autonomic nervous system, showing reduced resting-state functional connectivity, which is therefore important in TTS (74). Growing evidence highlights the importance of the brain-heart axis in the pathophysiology of TTS (58,75-78). Emotional stress can impair neuronal norepinephrine reuptake, leading to elevated local catecholamine levels that amplify sympathetic neural signaling in the heart. This heightened sympathetic activity may trigger symptom development and increase the risk of adverse cardiac events (79,80). Stress triggers the amygdala, hypothalamus and cingulate gyrus activation, innervating the locus coeruleus (the brain's primary center for norepinephrine synthesis). This activation propagates through noradrenergic neurons to engage the hypothalamic-pituitary-adrenal axis, leading to elevated epinephrine and norepinephrine secretion from adrenal medullary chromaffin cells (60,81). These mechanisms likely play a key role in the increased vulnerability to myocardial stunning and contractile dysfunction in patients with TTS.

Single-photon emission computed tomography (SPECT) imaging in the acute phase of TTS has demonstrated increased cerebral blood flow (CBF) in the basal ganglia, brainstem and hippocampus, accompanied by a notable decrease in the prefrontal cortex (61). Moreover, injury to the insular cortex has been identified as a predominant feature in patients with acute ischemic stroke and is linked to the onset of TTS (18). Given the amygdala's pivotal role in stress

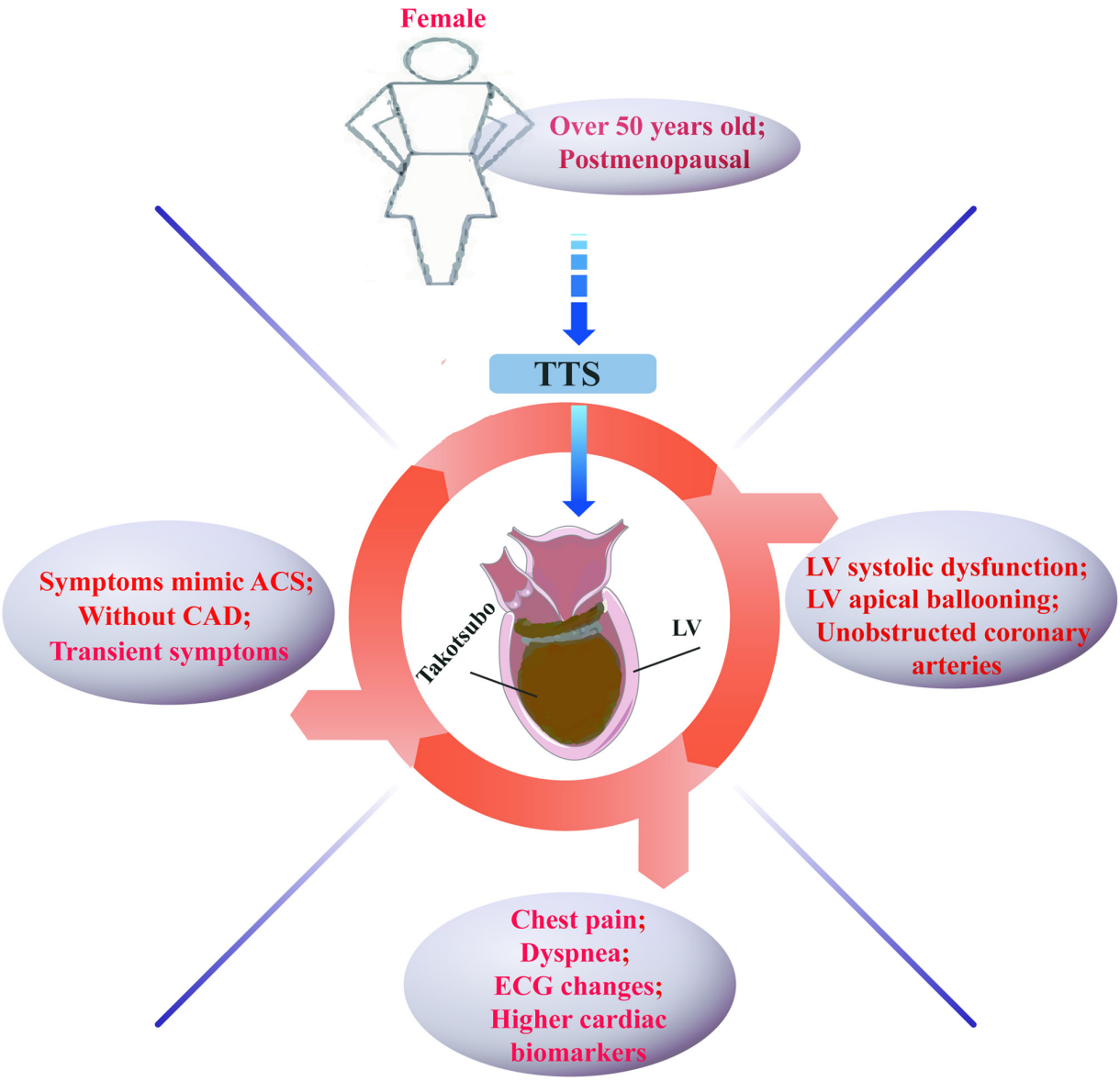

Figure 1. Epidemiology and clinical features of TTS. TTS, Takotsubo syndrome; ACS, acute coronary syndrome; CAD, coronary artery disease; LV, left ventricle; ECG, electrocardiography.

response regulation, 18F-fluorodeoxyglucose positron emission tomography/computed tomography (18F-FDG PET/CT) has demonstrated that elevated baseline amygdala activity is linked to a higher risk of developing TTS (82).

Studies have reported morphological differences in cerebral MRI findings of patients with TTS, including reduced cortical thickness in the left and right anteroventral insula and both cingulate cortices, reduced gray matter volume in the amygdala and diminished structural connectivity within the limbic system, when compared with healthy controls (62). In another study, these findings in patients with TTS were corroborated, revealing reduced gray matter volume in the right subcallosal cortex, right middle frontal gyrus and right insular cortex by the anatomical and resting-state functional MRI (73). However, it remains uncertain whether these changes are a consequence or a cause of TTS.

In summary, structural anatomical abnormalities and functional alterations in cerebral metabolism and perfusion are key contributors to TTS. Using advanced cerebral functional and anatomical imaging techniques, along with biomarker profiling, offers valuable insights into the potential causative role of CNS changes in TTS. However, it remains to be determined whether these CNS changes act as primary drivers of TTS or are secondary phenomena induced by the triggering stimulus affecting the CNS.

SNS overstimulation. Given the preceding physical or emotional stress triggers, SNS overstimulation underpins a common pathogenesis following TTS (6,9,53,83). Heart rate variability, a surrogate of autonomic tone, is markedly depressed during the acute phase, particularly within 48 h of admission. This reduction gradually improves during the subacute phase and typically normalizes within 3 months in the chronic phase (84). A study by Vaccaro *et al* (85) demonstrated through direct muscle microneurography assessments that TTS cohorts exhibit markedly elevated SNS activity

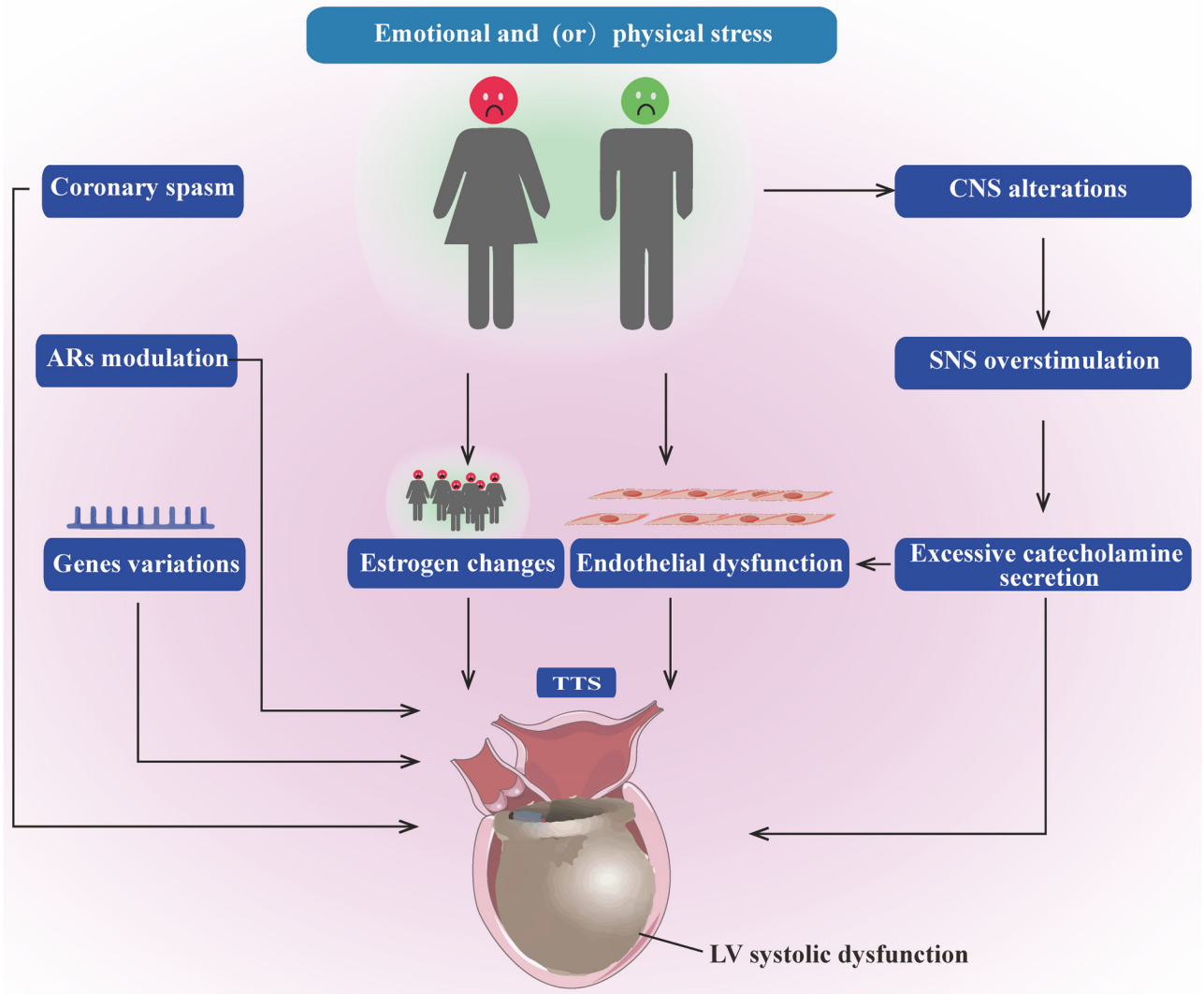

Figure 2. Underlying mechanisms of TTS. The underlying mechanisms of TTS are predominantly triggered by emotional or physical stress and encompass structural and functional alterations in the CNS, overstimulation of the SNS, excessive catecholamine secretion, modulation of ARs, epicardial vasospasm or dysfunction, endothelial dysfunction, hormone-mediated changes and genetic predispositions. TTS, Takotsubo syndrome; CNS, central nervous system; SNS, sympathetic nervous system; ARs, adrenergic receptors; LV, left ventricle.

and reduced spontaneous baroreflex control compared with controls. Myocardial iodine-123 metaiodobenzylguanidine (123I-MIBG) studies using planar imaging and SPECT have suggested functional alterations in presynaptic sympathetic neurotransmission in patients with TTS (86). These findings provide a potential pathophysiologic explanation for the observed impairment of LV function in TTS.

While physical or emotional stressors are common experiences, SNS overstimulation alone does not account for why only a small subset of individuals exposed to these stressors go on to develop TTS. The brain-heart axis remains a hot topic that requires further exploration and may hold the key to a deeper understanding of the pathophysiology of TTS (21). Pheochromocytomas and paragangliomas, primary endocrine disorders characterized by heightened SNS activation and episodic excessive catecholamine release, can induce a phenocopy of TTS. This further supports the concept of overstimulation of SNS as a critical mechanism in TTS (87-89). A stressful event initiates the activation of the sympathetic nervous system, resulting in the secretion of catecholamines. This suggests that catecholamines play an important role in the occurrence and development of TTS.

Excessive catecholamine secretion. The findings indicate that certain individuals may possess a specific predisposition to developing TTS in response to a catecholamine surge (90). Compared with myocardial infarction (MI) patients, individuals with TTS exhibit elevated levels of circulating plasma dopamine, epinephrine and norepinephrine, underscoring the significance of heightened catecholamine release and SNS stimulation in the pathogenesis (41). Due to epinephrine's short plasma half-life and the delay between symptom onset and medical presentation, the peak catecholamine levels may be much higher than those measured retrospectively (46).

Histopathological and microscopic analyses, including light and electron microscopy, reveal morphological alterations and structural deterioration similar to those observed in conditions of severe catecholamine excess. This excess is known to induce microcirculatory dysfunction and direct cardiotoxicity (91,92). Cardiomyocytes differentiated from

induced pluripotent stem cells derived from somatic cells of patients with TTS exhibit enhanced β1-AR signaling and heightened catecholamine-dependent responses, highlighting key mechanisms of the TTS phenotype. Notably, these cellular responses are predominantly mediated through β1-AR signaling in TTS. Excessive catecholamines play a direct role in the development of myocardial contraction band necrosis, which is a pathological characteristic of TTS (60,93). During the fight-or-flight response, the swift release of catecholamines markedly elevates heart rate and contractility via the activation of the cAMP-dependent protein kinase A (cAMP-PKA) signaling pathway dependent on β-adrenergic receptors (β-ARs) (94). Catecholamines secreted by the sympathetic nervous system bind to β-ARs, stimulating the activation of cAMP-PKA in cardiomyocytes. Increased PKA activity enhances Ca^{2+} cycling and increases myocardial contractility; therefore, dysregulation of the PKA signaling pathway may be a pathogenic mechanism leading to TTS cardiomyopathy (94). Epinephrine enhances ACE activity and inhibits ACE2 activity through the α1-adrenergic receptor/Gq/PKC signaling pathway, thereby triggering the release of Ang II (95).

Additionally, the phosphatidylinositol 3-kinase/protein kinase B signaling pathway may be activated by elevated catecholamine levels, a mechanism essential for myocardial cell survival and protecting cardiomyocytes from apoptosis (60,96). 123I-MIBG imaging reveals reduced myocardial activity at the mid-ventricle and apex of patients with TTS on SPECT imaging, alongside elevated systemic circulating catecholamines, reinforcing the hypothesis of catecholamine-induced myocardial stunning (7,42,97). Icariin primarily prevents ISO-induced TTS-like heart failure in rats by maintaining the dynamic balance of the reactive oxygen species (ROS) system, promoting the activity of antioxidant components and inhibiting the expression of Toll-like receptor 4/NF-κB signaling pathway proteins (98). This highlights the important role of catecholamines and their mechanisms of action in the occurrence and development of TTS, as well as emphasizing the potential therapeutic role of icariin in regulating oxidative stress and inflammatory responses.

Despite the compelling findings mentioned, the literature reveals a disparity, as several studies have not consistently shown markedly elevated circulating catecholamine levels in TTS compared with the controls (49,97,99-101). A study by Madhavan *et al* (102) indicated that plasma concentrations of metanephrine and normetanephrine showed no significant differences. These negative findings were further supported by a study showing that 86.4% of patients with TTS had normal plasma levels of metanephrine and normetanephrine (103). These findings challenge the notion that TTS is solely driven by a systemic catecholamine surge. A likely explanation is localized catecholamine release with rapid reuptake or the initial surge being missed due to delayed sample collection.

Additional considerations include the expression of catecholamine biosynthetic enzymes in myocardial cells. Specific enzymes facilitate the local synthesis of approximately one-third of cardiac adrenaline in the heart. There is evidence of differential localization of phenylethanolamine N-methyltransferase (a marker for adrenergic cells), an enzyme involved in adrenaline biosynthesis, within the myocardium (104-106). Catecholamine-producing enzymes are primarily concentrated in the left heart, with a distinct distribution pattern from the base to the apex of the LV myocardium (105,107). This distribution supports the hypothesis that localized myocardial catecholamine excess may play a key role in the pathogenesis of TTS, even when systemic catecholamine levels are not elevated (108). Localized catecholamine release from intrinsic cardiac stores, through autocrine or paracrine mechanisms, may overload ARs in specific regions of the heart, contributing to the regional myocardial dysfunction characteristic of TTS.

Local ARs distribution differences. It has been hypothesized that the regional differences in myocardial contractility observed in TTS could be explained by variations in the myocardial ARs distribution. A potential systemic catecholamine excess could activate myocardial ARs, leading to positive inotropy and subsequent myocyte death through PKA activation (109). These include ARs-mediated injury, direct catecholamine toxicity, epicardial vasospasm and an increased cardiac workload (60,110). Functionally, this manifests as transient apical LV ballooning. The apical-basal gradient in β_2-ARs explains the differential regional myocardial responses (40).

Another proposed mechanism for TTS involves a shift in high circulating epinephrine-induced intracellular signal trafficking in ventricular cardiomyocytes. Supranormal levels of epinephrine intensely activate the β1-AR and β2-ARs Gs pathway, changing the Gs adenyl-cyclase pathway to β2-AR Gi signaling (111-113). The shift of Gi signaling offers protection by exerting anti-apoptosis and anti-arrhythmia, safeguarding the LV myocardium from catecholamine excess (40). This Gi signaling subsequently triggers the activation of the p38 MAPK pathway, leading to a negative inotropic effect. This effect is likely mediated through the elevation of sodium-calcium ion exchangers and the suppression of L-type calcium channel currents, which together decrease myofilament sensitivity (114,115).

Studies have revealed regional differences in the density of acetylcholinesterase (AChE)-positive nerves and tyrosine hydroxylase (TH)-positive autonomic nerve endings across the LV. The basal region of the ventricle exhibits a 40% higher density than the apical zone. Additionally, TH-positive nerves are more abundant than AChE-positive nerves in the ventricle (45). The increased density of β2-ARs in the apical myocardium is proposed to compensate for the lower SNS endings of apical LV (46). The regional variation of β2-ARs density from base to apex in the LV may explain the differential myocardial response to increased systemic or local catecholamine excess, thereby accounting for the onset of various TTS phenotypes (46).

Vascular spasm formation. The coexistence of CAD and TTS is not mutually exclusive. Angiographic findings in most patients with TTS reveal smooth, UCA or minimal non-obstructive plaques. Early theories suggested that TTS might originate from acute plaque rupture, with subsequent spontaneous thrombus resolution or recanalization facilitated by anti-platelet therapy before angiographic evaluation. However, optical coherence tomography imaging has failed to demonstrate ruptured plaques or intracoronary thrombi in the left anterior descending coronary artery, suggesting these

changes in the coronary are unlikely to be the primary mechanism of TTS (116).

Recently, MI with non-obstructive coronary arteries (MINOCA) as a new topic has gained increasing attention. A cohort study identified distinct characteristics differentiating patients with TTS from those with MINOCA. Patients with TTS tend to be older, predominantly female and more likely to have a history of psychiatric conditions. Furthermore, they exhibited higher in-hospital mortality and complication rates but experienced fewer major adverse cardiovascular events than MINOCA patients (117).

Epicardial coronary spasm has been proposed as a potential mechanism underlying TTS. In a clinical study of 30 patients diagnosed with TTS accompanied by LV dysfunction without significant CAD, spontaneous multivessel coronary spasm was observed in three patients during angiography. Additionally, multivessel coronary spasm was provoked in six patients by administering acetylcholine or ergonovine (49). Coronary spasms, either at baseline or during acetylcholine provocation, have been observed in Patients with TTS (50-52). In animal models, norepinephrine does not induce a TTS phenotype, whereas epinephrine and isoprenaline do. This distinction arises because norepinephrine, unlike epinephrine, has minimal impact on β1-ARs or β2-ARs Gi signaling (40).

Endothelial dysfunction. Studies have shown an increase in spasms of both large and small coronary arteries during the occurrence of TTS, indicating that TTS is associated with coronary endothelial dysfunction (60,95,118,119). Endothelial dysfunction may represent an important pathophysiological link between stress and myocardial dysfunction in TTS (120). Female patients with TTS have been observed to have a higher likelihood of a history of migraine or Raynaud's disease, suggesting vascular or endothelial dysfunction (53,54). In healthy individuals, mental stress has been shown to affect flow-mediated (FMD), endothelium-dependent vasodilation, as assessed by high-resolution ultrasound of the radial artery (55). Patients with TTS exhibited transiently impaired brachial artery FMD in the acute phase compared with those with STEMI and healthy controls. However, within 1-3 weeks, FMD in patients with TTS improved markedly, indicating reversible endothelial dysfunction (57).

In a study, 16 female patients with acute TTS demonstrated elevated thrombolysis in MI (TIMI) frame counts across the three major coronary arteries, despite the absence of obstructive CAD (121). Elesber *et al* (122) reported that among 42 consecutive female patients with TTS, 29 exhibited an abnormal TIMI myocardial perfusion grade (TMPG), an angiographic index of myocardial perfusion. Patients with abnormal TMPG exhibited higher peak troponin levels than those with normal TMPG. Similarly, ECG findings, including deep T-wave inversion or ST elevation, were more frequently observed in patients with abnormal perfusion. This effect reflects abnormal microvascular perfusion. Similarly, the vasodilatory capacity, marked by a transient reduction in coronary flow reserve, was diminished in acute TTS, as evaluated using transthoracic Doppler echocardiography (123).

Increased production of ROS reduces the availability of nitric oxide (NO) in the cardiovascular system and elevated catecholamine release leads to endothelial dysfunction, which further leads to transient impairment of myocardial contractility (56). Excessive catecholamines may lead to endothelial dysfunction in TTS through Ang II and SK4-related signaling pathways (95). Endothelial dysfunction can be prevented by endothelin (ET)-A receptor antagonist following mental stress (55). ET exhibits potent, long-lasting vasoconstrictor effects, indicating it is relevant to spasm (124). Jaguszewski *et al* (58) reported that a markedly elevated ET-1 plasma level may contribute to microvascular spasms and they also identified downregulation of miR-125a-5p, a regulator of ET-1 expression, in patients with TTS. Exosomal miR-126-3p, derived from endothelial cells, contributes to ion channel dysfunction by inhibiting RGS3 signaling in cardiomyocytes, providing insights into the mechanisms by which endothelial dysfunction affects cardiomyocytes (125). Furthermore, biopsied coronary microvessels from patients with TTS showed evidence of microvascular endothelial cell apoptosis (126). The infusion of ACh and dobutamine in the coronary arteries reveals that microvascular dysfunction is commonly present in patients with TTS. These findings may help explain the reduced coronary flow reserve and microvascular blood flow observed in TTS.

Hormone influence. Women constitute nearly 90% of TTS cases, with the vast majority occurring postmenopause, as evidenced by data from the InterTAK Registry, a consortium of 26 centers across the United States and Europe (9,10). This pronounced disparity in sex, coupled with the significant increase in TTS incidence during postmenopausal years, suggests that the biological decline in estrogen levels may heighten susceptibility to TTS. However, the occurrence of TTS despite exogenous hormone use in some patients indicates that estrogen deficiency alone is unlikely to be the primary factor in its pathophysiology (53).

Estrogen has been shown to modulate contractile function and provide cardioprotection. In the absence of estrogen, ovariectomized female rats exhibit an upregulation of β1-AR and L-type Ca^{2+} channel proteins, alongside a reduction in Na^{+}-Ca^{2+} exchange proteins. Estrogen supplementation restores the levels of these proteins to those observed in Sham-operated controls (127). Similarly, estrogen supplementation in ovariectomized rats has been shown to reduce c-fos mRNA expression, a marker of cellular activation, in the paraventricular hypothalamic nucleus, LV and adrenal glands. Additionally, it mitigates emotional stress-induced cardiac dysfunction by attenuating hypothalamus-sympathetic-adrenal outflow from the CNS to target organs (64).

Estrogen supplementation increases the levels of atrial natriuretic peptide and heat shock protein 70, both of which play key roles in providing cardioprotective effects (60). Furthermore, it reduces β1-AR levels, thereby mitigating myocardial necrosis caused by sympathetic overactivity during myocardial ischemia (128). This protective effect is further supported by studies showing that norepinephrine induces less forearm vasoconstriction in women compared with men, a difference attributed to greater β2-ARs sensitivity in women (129). Additionally, TTS has been prevented in a rat model through estrogen supplementation or the combined use of α- and β-ARs (64,130).

Case-control studies challenging the estrogen theory suggest that patients with TTS do not differ markedly from STEMI cohorts or population controls in terms of parity, years since menopause, menopausal status, or history of oophorectomy. Notably, hormone replacement therapy was more prevalent in TTS cohorts than in controls, suggesting that although TTS is more prevalent in postmenopausal women, estrogen deficiency alone is unlikely to be the primary or sole factor contributing to the development of the condition (53).

Overall, it is suggested that sex hormone profiles alone are insufficient to fully explain the underlying mechanisms of TTS. While a clear sex bias exists in TTS cases, the central pathophysiological role of estrogen remains unproven. Nonetheless, estrogen may still play a contributory role in increasing susceptibility to the syndrome.

Genetic predisposition. The involvement of underlying genetic mutations in causing or predisposing individuals to TTS remains uncertain. In certain cases, patients with TTS develop a dilated cardiomyopathy (DCM) phenotype, characterized by incomplete recovery of left ventricular ejection fraction (LVEF) during the convalescence phase. Moreover, reports of familial TTS cases suggest genetic predisposition in some individuals who develop the condition (65,66,131). Genes variations in BAG3, APOE, ADRB1, MFGE8, GRK5, ALB, APOB, SAA1, A2M and C3 may predispose certain individuals to a higher risk of developing TTS compared with others (67,68).

One study by Zaroff *et al* (132) suggested that ARs polymorphisms, particularly in β1-ARs and β2-ARs, are linked to increased troponin release and reduced LVEF. These polymorphisms have been identified as contributing factors to the heightened risk of cardiac abnormalities observed in patients with SAH. However, whole-exome sequencing study shows similar functional adrenergic polymorphisms in patients with TTS compared with population control (133). Unlike genetic forms of DCM, there is no definitive evidence of a systematic Mendelian inheritance pattern in TTS. Instead, it is more likely that genetics, alongside other risk factors, contributes to an increased susceptibility to TTS when interacting with epigenetic influences (Fig. 3).

4. TTS prognosis and clinical implications

TTS is generally viewed as a benign, short-term and self-resolving condition, with the majority of patients regaining LVEF spontaneously in wide-ranging interval within a few days to weeks (134,135). The annual recurrence rate of TTS is 1.0%, while some studies have reported a higher recurrence rate of 5% (136,137). Age, physical stressors and atypical ballooning patterns are markedly associated with the long-term mortality of TTS (136,137). TTS triggered by physical factors may present with a worse prognosis in terms of mortality, as reported in studies comparing different triggers, with observed increases in both short-term and long-term mortality (138,139). Male patients exhibited a threefold increase in mortality rate and major adverse cardiovascular and cerebrovascular events, alongside a higher susceptibility to underlying critical illnesses, which further contributed to elevated mortality (9). Long-term clinical outcomes in patients with coronary artery dissection are markedly worse compared with those in women with TTS, primarily driven by readmissions related to cardiac disease (140). Meta-analysis of case reports examining endogenous (pheochromocytomas and paragangliomas) and exogenous (externally administered catecholamines) catecholamine-induced TTS found that complications, including pulmonary edema, circulatory and respiratory failure, cardiogenic shock, arrhythmias (such as ventricular tachycardia, cardiac arrest, electro-mechanical dissociation and LVOTO, metabolic acidosis, multiple organ failure and thromboembolism, occurred in up to 68.2% of patients (12,136).

There were no significant differences in cardiovascular survival, as evidenced by a 17% 4-year mortality rate, when compared with age- and sex-matched populations (90). Regional wall motion abnormalities may occasionally be associated with the systolic anterior motion of the mitral valve or chorda, leading to mid-cavity or LVOTO. This obstruction can cause hypotension and intravenous propranolol has proven effective in managing dynamic obstruction in Patients with TTS (141). In rare instances, severe LV wall stress caused by apical ballooning resulted in free wall rupture, as reported in several case studies (142-145).

An observational study indicated that physical triggers could act as an independent predictor for TTS, with patients experiencing higher mortality rates than those with ACS during long-term follow-up. Conversely, patients with TTS triggered by emotional stress demonstrated more favorable outcomes compared with patients with ACS (138,146). Male patients exhibited higher mortality rates than females, a difference attributed to their higher prevalence of in-hospital critical illnesses (147). Patients with global LV ballooning experience higher complication rates than those with apical ballooning (12). The InterTAK Prognostic Score is a useful clinical tool with high specificity and sensitivity for predicting both short- and long-term mortality in patients with TTS (148). A study by Elesber *et al* (90) reported a recurrence rate of 11.4% within four years of the initial presentation, with chest pain being the most frequently observed recurring symptom during follow-up. Meta-analyses by Hassan and Falhammar (12) suggested a higher recurrence rate of 16.6%, specifically in patients with TTS induced by pheochromocytomas and paragangliomas. Comorbid psychiatric and neurological disorders have been recognized as independent predictors of recurrence. Notably, 34.8% of patients who experience recurrent TTS exhibit different LV ballooning patterns compared with their initial onset (59).

Studies indicate that patients with TTS may develop persistent subclinical cardiac dysfunction, characterized by impaired cardiac deformation indices, compromised cardiac energetic status and elevated native T1 mapping values, even after apparent recovery of LVEF and normalization of serum biomarkers following the acute episode (149-151). In some cases, cMRI reveals persistent right ventricular myocardial edema in patients with TTS even after a 4-month follow-up, which may lead to microscopic fibrosis (149,152). A clinical trial by Scally *et al* highlighted an ongoing inflammatory response in the acute phase of TTS, as evidenced by cMRI showing greater enhancement with ultrasmall superparamagnetic iron oxide particles in both non-ballooning and ballooning LV myocardial segments (153,154). These findings point to a myocardial macrophage-mediated cellular

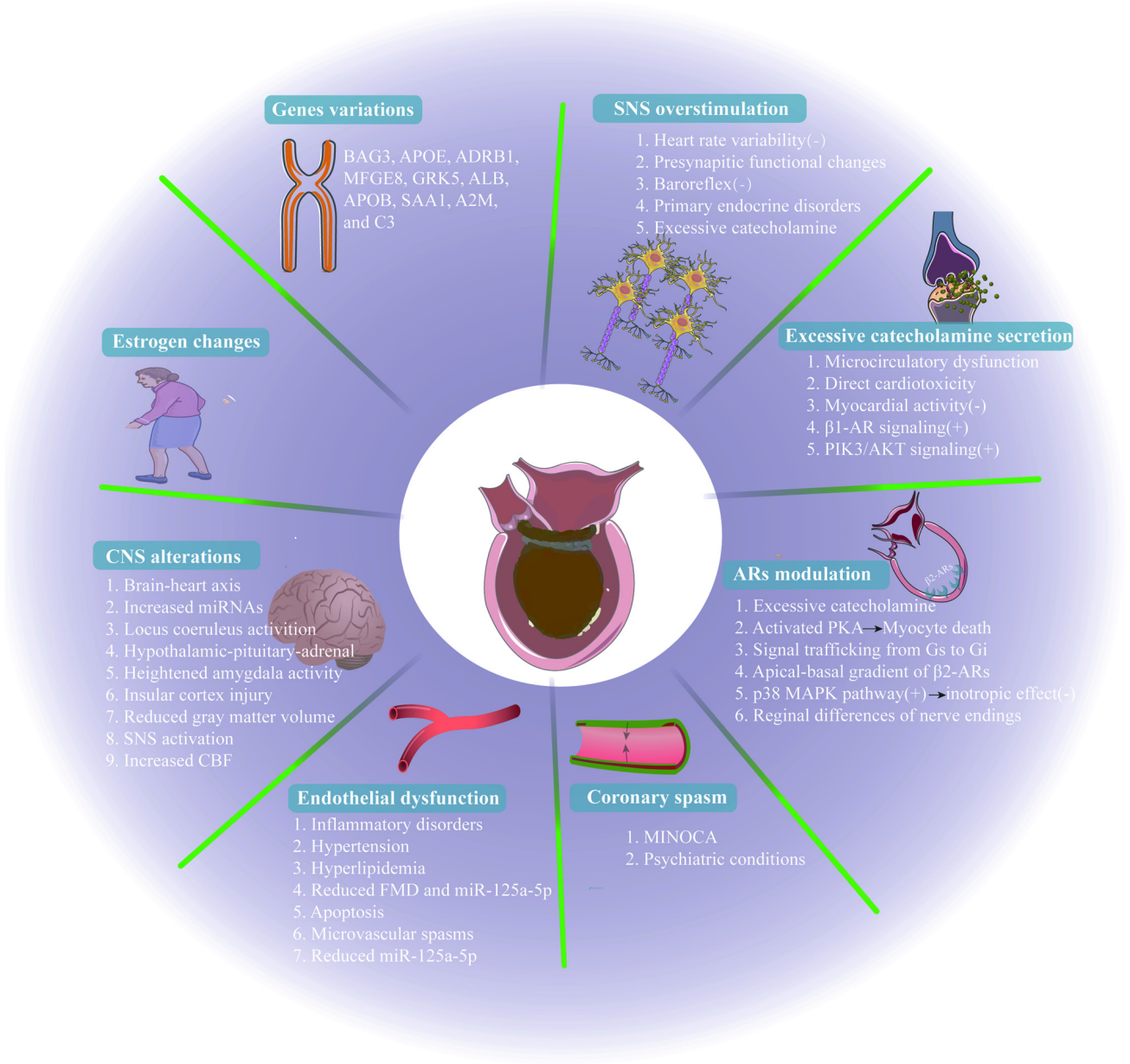

Figure 3. The potential pathophysiological mechanisms of TTS. Current pathological mechanisms underlying TTS, encompass CNS structural and functional alterations, SNS overstimulation, excessive catecholamine secretion, ARs distribution and balance shifts, hormonal influences, epicardial vasospasm, endothelial dysfunction and genetic predispositions. TTS, Takotsubo syndrome; CNS, central nervous system; SNS, sympathetic nervous system; ARs, adrenergic receptors; CBF, cerebral blood flow; FMD, flow-mediated; MINOCA, MI with non-obstructive coronary arteries; LV, left ventricle.

inflammatory response. Moreover, such activity is linked to elevated serum levels of IL-6, chemokine (C-X-C motif) ligand 1 (and classical $CD14^{++}CD16^{-}$ monocytes, which persist for at least five months post-follow-up compared with control subjects. This suggests the presence of a systemic humoral inflammatory component in TTS, indicative of a low-grade chronic inflammatory state (153) (Fig. 4).

5. Targeted interventions for TTS

Given the association between TTS and neuropsychiatric disorders, therapeutic strategies targeting the CNS have been proposed (9). Cognitive behavioral therapy (CBT), which is known to reduce amygdala activity, may help prevent TTS (155). However, the excessive amygdala response observed in some patients could present challenges in managing anxiety reactions triggered during CBT, potentially limiting its effectiveness (156). However, this area remains largely unexplored and warrants further investigation.

The effect of medical therapy on long-term outcomes following acute TTS remains uncertain. Due to the lack of reliable evidence-based support for TTS, some medical teams have adopted treatment strategies widely recognized in the management of myocardial infarction, such as β-blockers and angiotensin-converting enzyme inhibitors (ACEI), in an effort to improve patient outcomes. While β-blockers might theoretically reduce the effects of catecholamines on β2-ARs due to the hypothesized role of localized or systemic catecholamine release, some patients still develop TTS despite prior β-blocker use and a significant proportion experience recurrent episodes

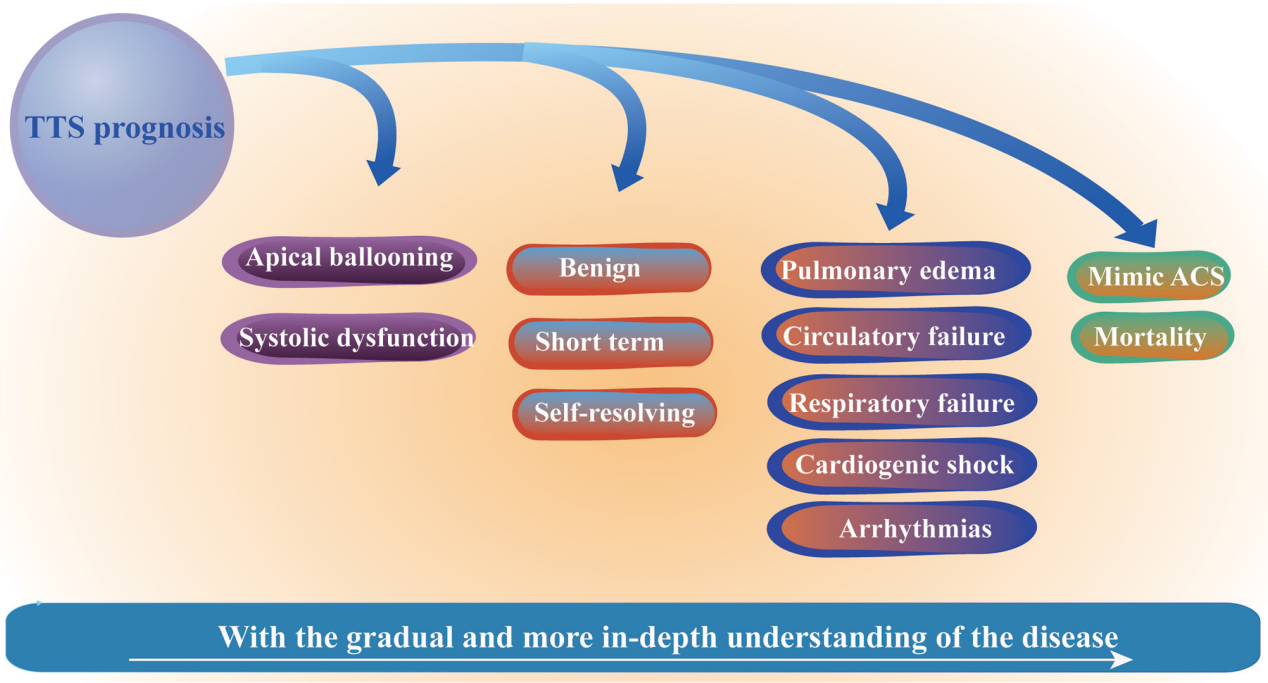

Figure 4. TTS prognosis and clinical implications. Illustration of the natural course of TTS and factors influencing patient outcomes. Initial triggers such as emotional or physical stress, the role of cardiovascular complications and comorbidities during the acute phase are associated with clinical prognosis. TTS, Takotsubo syndrome; ACS, acute coronary syndrome.

while on the medication (9), indicating that β-blockers are not effective in treating TTS. Notably, the β-blocker therapy was not associated with lower TTS recurrence during follow-up and no association was observed between the use of β-blockers at discharge and left ventricular ejection fraction recovery (157). The observational nature of the study limits the conclusions to hypothesis generation.

Furthermore, an observation study by Isogai *et al* (158), employing logistic regression and instrumental variable analysis, found no significant benefit of early β-blockers use in reducing 30-day in-hospital mortality among patients with TTS compared with the control group. Large registries have suggested that angiotensin receptor blockers or ACEI, rather than β-blockers, improve survival in patients with TTS with impaired LV function and are linked to risk of recurrence (9,159). Long-term treatment with RAS inhibitors after TTS episodes is not associated with lower mortality rates (160).

Evidence suggests that myocardial abnormalities may persist beyond the acute phase of TTS, potentially driven by a cellular and humoral inflammatory response (153). The potential of anti-inflammatory medications to modulate this response, prevent heart failure and improve long-term outcomes has gathered significant interest (161). However, this hypothesis remains unproven and requires rigorous validation through randomized clinical trials.

In 2.2% of 541 consecutive patients with TTS enrolled in a multicenter international registry, ventricular thrombi were identified based on clinical features and echocardiographic data obtained (162). Anticoagulation therapy is administered to patients with an elevated risk of thromboembolism or those with a pre-existing thrombus. A 3-month course of anticoagulation has been shown to fully resolve all cases of LV apical thrombi (162).

Although most patients with TTS do not have flow-limiting CAD, aspirin is often prescribed at discharge to reduce the risk of future thrombotic events and potentially improve prognosis (163). However, current evidence does not demonstrate a reduced risk of major adverse cardiovascular events in patients with TTS at 30-day or 5-year follow-up (164). A systematic meta-analysis and review reinforce these findings, revealing that antiplatelet therapy in patients with TTS does not markedly reduce the risk of recurrence, shows no clear benefit in improving long-term outcomes and may even have detrimental effects (165).

Some patients with TTS develop cardiogenic shock during hospitalization, necessitating inotropic or vasopressor support to stabilize blood pressure and ensure adequate end-organ perfusion. However, the administration of exogenous catecholamines, reflecting higher grades of circulatory and cardiac compromise in patients with TTS, has been linked to increased short-term and long-term mortality (166). A case series by Santoro *et al* (167,168) reported that intravenous infusion of the calcium sensitizer Levosimendan is both safe and feasible, accelerating recovery for patients with TTS (167,168). Moreover, a multicenter registry by Santoro *et al* (169) suggested that β-blockers, such as esmolol infusions, may benefit a subset of patients with TTS who develop acute LVOTO by reducing systemic blood pressure and intraventricular pressure gradients. In LVOTO patients, using inotropic agents is contraindicated, as these can exacerbate LVOTO. Extracorporeal membrane oxygenation (ECMO), used as a rescue therapy for severe refractory cardiogenic shock, is a viable option for mechanical circulatory support in select patients with TTS experiencing cardiogenic shock (170,171). Ghadri *et al* (20) provide a practical and valuable treatment algorithm for managing patients

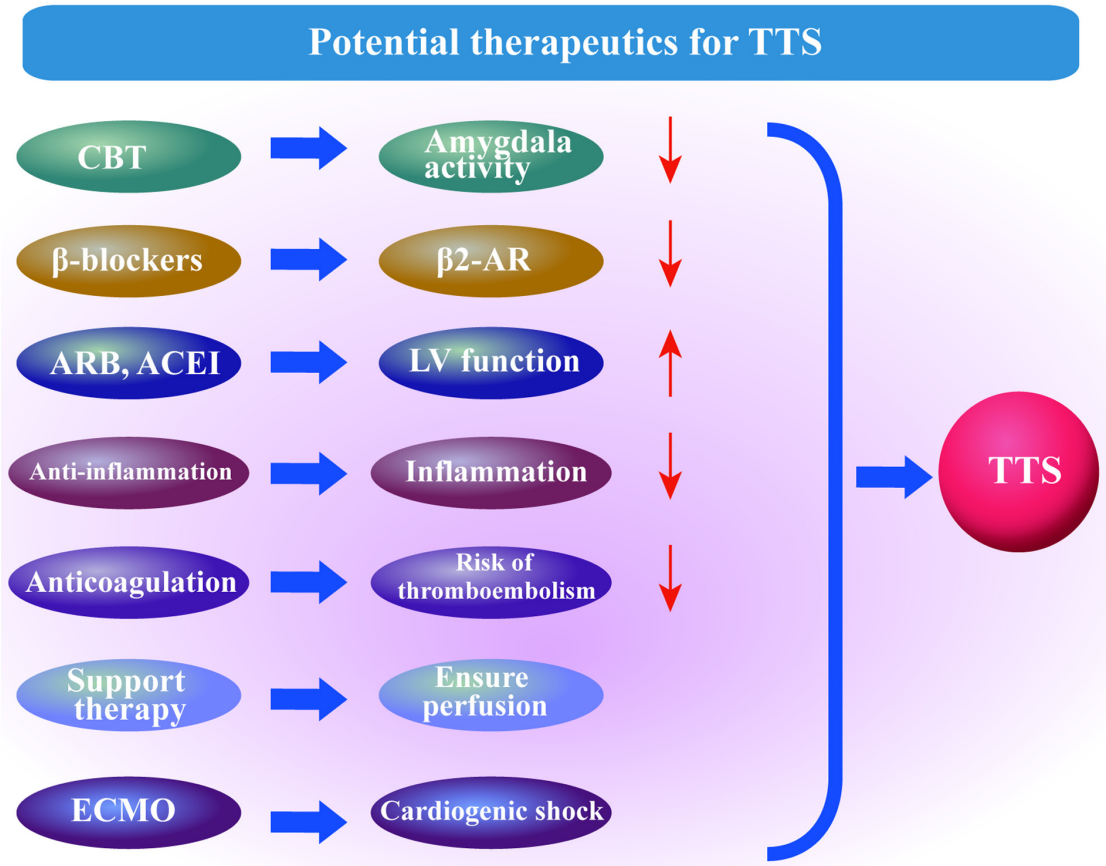

Figure 5. Overview of potential therapeutic approaches for TTS. Representation of therapeutic strategies for TTS, emphasizing pharmacological interventions, stress management and supportive care. Highlighted treatments include β-blockers, ACEI and therapies targeting SNS regulation alongside emerging approaches for managing severe complications. TTS, Takotsubo syndrome; ACEI, angiotensin-converting enzyme inhibitors; SNS, sympathetic nervous system; ARB, angiotensin-converting enzyme inhibitors/Angiotension II receptor blockers; CBT, cognitive behavioral therapy; ECMO, extracorporeal membrane oxygenation; LV, left ventricle.

with TTS (Fig. 5). Treatment strategies for TTS should integrate evidence-based medical evidence with individualized assessment. Current research still presents many unresolved questions. Future studies should focus on validating the efficacy of existing therapies and exploring novel treatment approaches through high-quality randomized controlled trials (RCTs).

6. Conclusion

The precise mechanisms underlying TTS remain unclear, but emerging evidence suggests a complex interplay of neurophysiological, metabolic and vascular factors. Emotional and physical stressors appear to motivate a neurologically altered SNS substrate, both structurally and functionally, which triggers cascades involving intra-synaptic, local, or systemic catecholamine surges, altered myocardial ARs signaling and metabolic disruption, all of which coincide with endothelial dysfunction. These processes collectively disrupt regional myocardial wall motion abnormalities, influenced by autonomic innervation density and ARs distribution. Despite advances in cardiac imaging, TTS remains underdiagnosed due to delays in echocardiography, limited access to cMRI and delayed angiography. At later stages of TTS, diagnostic markers and therapeutic interventions may become less effective, underscoring the urgency for improved strategies. Further investigation is required to clarify how these intricate mechanisms interplay and lead to the various TTS phenotypes. Larger clinical datasets with prolonged longitudinal follow-up are essential for determining why some patients experience recurrent TTS while others do not, why LVEF recovery is incomplete in certain cases and whether guideline-recommended heart failure therapies genuinely enhance short- or long-term outcomes.

Future research on TTS should prioritize the elucidation of its complex mechanisms, the advancement of diagnostic tools, the innovation of therapeutic strategies and the fostering of interdisciplinary collaboration. To deepen our understanding of TTS pathophysiology, studies should investigate the role of the CNS in modulating sympathetic overactivation and its downstream effects on myocardial function, using advanced techniques such as single-cell RNA sequencing to uncover heterogeneity in myocardial cell responses. In terms of diagnostic advancements, the development of machine learning algorithms for AI-driven imaging analysis could enable the detection of TTS-specific patterns, such as apical ballooning, while differentiating TTS from other cardiomyopathies. Therapeutically, RCTs are urgently needed to evaluate the efficacy of β-blockers, calcium channel blockers and ET-A antagonists in mitigating catecholamine-induced

cardiotoxicity. Integrating engineering and AI technologies, such as quantum computing, could uncover hidden patterns in TTS pathogenesis and treatment outcomes. These studies would improve our understanding of the underlying pathophysiological mechanisms of disease and its natural progression and complication rates, addressing the limitations of smaller observational TTS cohorts. By addressing these research directions, TTS can transition from an enigmatic condition to a manageable, personalized disease, ultimately enhancing survival rates and quality of life for affected patients.

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Availability of data and materials

Not applicable.

Authors' contributions

XF, YY, ZH, PL and GY wrote the original draft and conceived the study. LZ, BZ and DZ performed visualization and reviewed the original draft. YL and GC categorized and organized the literature. XF, PL and GY conducted project administration and acquired funding. All authors read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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