Cellular and molecular mechanisms of arrhythmogenesis in Takotsubo syndrome (Review)

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Abstract. Takotsubo syndrome (TTS), an acute stress-induced heart failure, is frequently complicated by arrhythmias that significantly worsen prognosis. Despite advances in understanding its pathology, the electrophysiological basis of these arrhythmias remains incompletely elucidated. The present review synthesizes current evidence to explore the core electrophysiological mechanisms underlying arrhythmogenesis in TTS, including abnormal calcium handling, repolarization abnormalities, altered conduction and refractoriness due to structural remodelling, and autonomic nervous system imbalance. The corresponding clinical manifestations of ventricular arrhythmias, atrial arrhythmias and bradyarrhythmias were further delineated, and contemporary diagnostic and therapeutic strategies were discussed. By integrating clinical observations with experimental findings, the present review aims to bridge the knowledge gap between mechanistic insights and clinical practice. Finally, critical research gaps were highlighted and future directions were proposed, emphasizing the need for personalized medicine and novel therapeutic targets to improve arrhythmia management and patient outcomes in TTS.

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1. Introduction

Takotsubo syndrome (TTS) is an acute heart failure typically triggered by emotional or physiological stress, characterized by transient regional wall motion abnormalities of the left ventricle in the absence of obstructive coronary artery disease but may co-exist with acute coronary syndrome (ACS) (1). The clinical presentation of TTS mimics ACS, commonly featuring acute chest pain and/or dyspnea, electrocardiographic (ECG) abnormalities, and elevated serum troponin levels (2).

Although historically considered rare, the diagnostic rates of TTS have risen in recent years. It accounts for ~0.02% of hospitalizations, and ~1-3% of all patients and 5-6% of female patients presenting with ACS (3,4). TTS exhibits a sex disparity, predominantly affects women, who account for ~80-90% of all cases, with a typical onset between 65 and 70 years of age (5). While incidence in men shows no clear age-related trends, male patients often experience more severe in-hospital complications and a poorer prognosis. TTS incidence is low in children, with the youngest reported case being a preterm infant born at 28-week gestation (6).

Arrhythmias are the most common complication during the acute phase of TTS, predominantly featuring ventricular arrhythmias, atrial arrhythmias, and bradyarrhythmias (7-9). The presence of arrhythmias in TTS disrupts cardiac

contraction rhythms, reduces cardiac output, and exacerbates myocardial ischemia, leading to a poorer prognosis. Clinical studies have confirmed that the occurrence of arrhythmias is significantly associated with elevated in-hospital and one-year mortality in patients with TTS (10). Notably, arrhythmia profiles differ between TTS and ACS, which has direct implications for risk stratification and management. In a comparative cohort of 620 patients with TTS and 620 patients with myocardial infarction (MI), arrhythmias at presentation were more frequent in TTS (4% vs. 1%) (11). However, the subtype distribution differs: In a large retrospective study, atrial arrhythmias occurred in 9.1% of patients with TTS vs. 6.0% of patients with anterior MI, whereas ventricular arrhythmias were far less common in TTS (0.3% vs. 4.1%) (12). A nationwide analysis confirmed that ventricular arrhythmia risk in TTS is intermediate, higher than type 2 MI but lower than type 1 MI (13). Furthermore, the prognostic weight of ventricular arrhythmias appears greater in TTS (12). These differences underscore the need for TTS-specific arrhythmia risk assessment rather than extrapolation from ACS paradigms.

However, the mechanisms of arrhythmias in TTS remain poorly understood, posing a critical barrier to optimal management. The present review aims to explore these underlying mechanisms, discuss their direct implications for clinical management and patient prognosis, and outline promising future research directions. In contrast to some previous reviews that have mainly focused on clinical features, diagnostic criteria, or individual pathophysiological pathways (3,5,7,9,14), the present review provides an integrated, mechanism-oriented synthesis of arrhythmogenesis in TTS. It links cellular and molecular electrophysiological abnormalities to specific clinical arrhythmia phenotypes, risk stratification and therapeutic implications. Ultimately, the present review seeks to bridge the current knowledge gap and provides discussion for improving clinical outcomes in patients with TTS.

2. Methods

Published literature on PubMed was searched using the following terms: 'TTS', 'stress cardiomyopathy', 'apical ballooning syndrome', 'pathophysiological mechanisms of TTS', 'abnormal calcium handling', 'repolarization abnormalities', 'sympathetic overactivation', 'myocardial edema', 'TTS and fibrosis', 'microvascular dysfunction', 'inflammation', 'TTS and arrhythmias', 'TTS and ventricular arrhythmias', 'TTS and atrial arrhythmias', 'TTS and bradyarrhythmia' and 'diagnostic and treatment strategies for TTS'. Additionally, supplementary searches covering emerging research areas were performed, including 'TTS and genetics', 'TTS and microRNA', and 'TTS and risk stratification', to capture recent advances in these fields. The reference lists of included articles and relevant reviews were also manually screened to retrieve additional eligible publications.

Eligible study types comprised cohort studies, case series, basic experimental research, review articles, consensus documents and clinical guidelines. Studies investigating biomarkers, novel therapeutic targets, and research gaps pertaining to Takotsubo-associated arrhythmias were also included. Peer-reviewed articles published in English were prioritized and no restrictions were imposed on study design. Manual screening of reference lists from included articles and related reviews was performed to identify potentially relevant studies missed in the primary database search. The final literature search was completed on October 1, 2026.

3. Potential pathophysiology of TTS

Although the precise pathophysiology of TTS remains incompletely defined, several interrelated mechanisms are centrally implicated: sympathetic nervous system overactivation, myocardial injury and inflammation, and microvascular dysfunction (Fig. 1). These mechanisms may operate independently or synergistically to precipitate the onset of TTS (15-18). This section provides a concise mechanistic primer; the downstream electrophysiological consequences are detailed below.

Sympathetic nervous system overactivation. Excessive sympathetic activation is the most established pathogenesis for TTS, involving both massive catecholamine release and the cardiovascular system's response (19). Upon stress stimulation, the locus coeruleus and other stress-associated regions releases norepinephrine to activate the hypothalamic-pituitary-adrenal (HPA) axis, resulting in a significant rise in circulating catecholamines, which can induce TTS (20,21). Clinical data show that acute-phase catecholamine levels in patients with TTS can be 7- to 34-fold higher than normal, with ~70% of patients reporting a preceding stressor (22). Animal studies provided direct causal evidence that high-dose catecholamine infusion produces TTS-like myocardial changes (23-25). Furthermore, localized myocardial catecholamine release may explain cases in which systemic levels are normal despite clear signs of myocardial sympathetic overactivity (26).

The apical propensity of TTS is explained by a unique physiological gradient: β2-adrenergic receptor (β2-AR) density is highest in the left ventricular (LV) apex, whereas sympathetic innervation is most sparse in this region (24,27). This mismatch renders the apical myocardium exceptionally sensitive to circulating catecholamines. At critically high levels, epinephrine exerts a paradoxical negative inotropic effect on the apex, leading to the characteristic 'apical ballooning' observed in TTS (24). Beyond transient stunning, sustained β-AR overactivation promotes cardiomyocyte necrosis and apoptosis, leading to localized ventricular dysfunction. This direct injury is histologically substantiated in patients with TTS, whose endomyocardial biopsies reveal contraction band necrosis and interstitial mononuclear infiltrates (28).

The electrophysiological consequences of catecholamine overload, including the β2-AR/Gi switch, calcium handling abnormalities, and triggered activity, are detailed below.

Myocardial injury and inflammation. Oxidative stress and inflammation are critical components of TTS pathogenesis. During the acute phase, excessive catecholamines activate β-AR, leading to a surge of reactive oxygen species (ROS) that directly damages cardiomyocytes; significantly elevated superoxide levels have been observed in myocardial tissue from patients with TTS (29). Oxidative stress also impairs endothelial nitric oxide synthase (eNOS) function, reducing nitric oxide (NO) bioavailability and contributing to

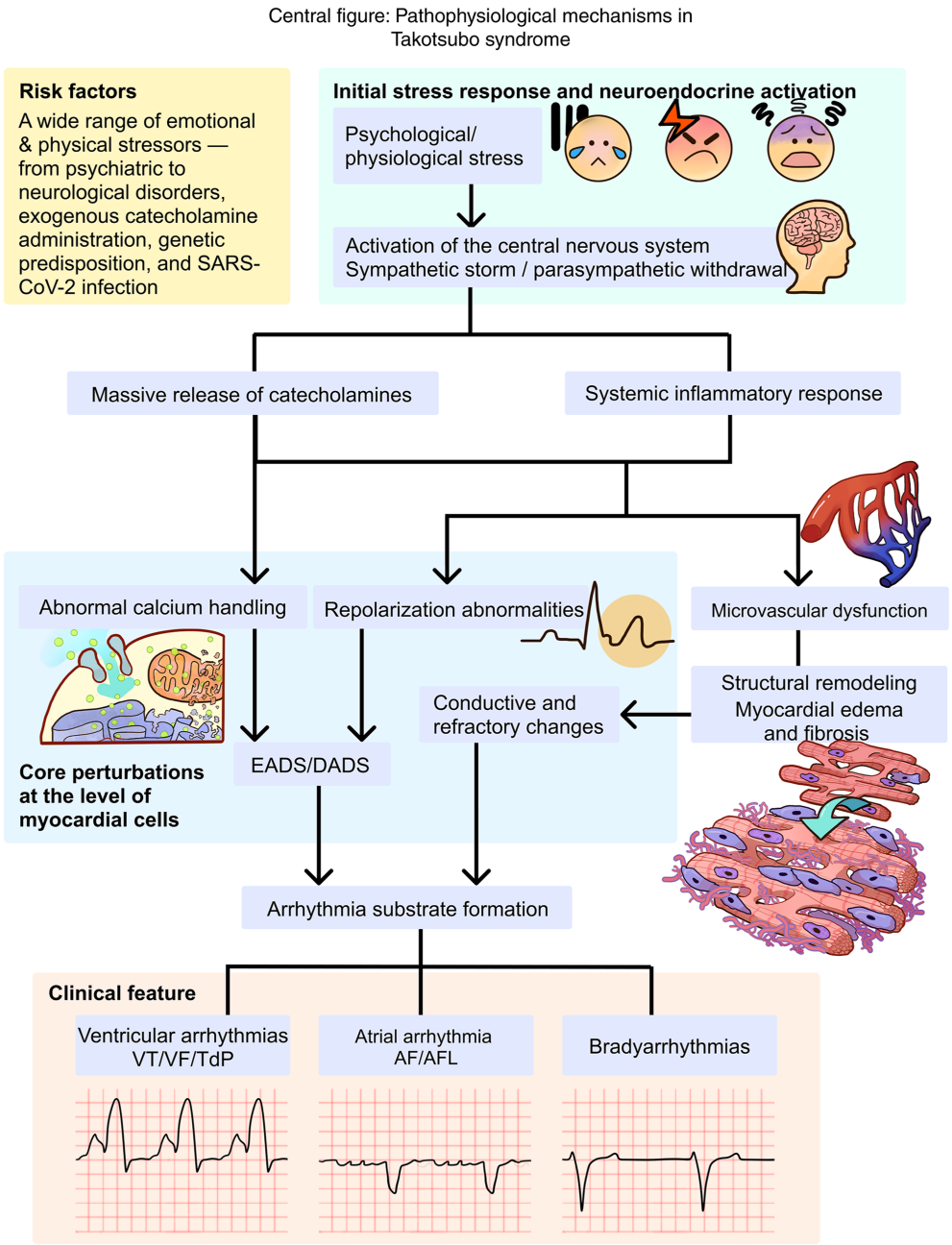


Figure 1. Pathophysiological mechanisms in Takotsubo syndrome. EADs, early afterdepolarizations; DADs, delayed afterdepolarizations; VT, ventricular tachycardia; VF, ventricular fibrillation; TdP, torsades de pointes; AF, atrial fibrillation; AFL, atrial flutter.

microvascular impairment (30). TTS is further characterized by inflammatory infiltration of myocardial macrophages, altered monocyte subset distribution, and elevated systemic proinflammatory cytokines (31,32). Persistently elevated serum interleukin-6 (IL-6) concentrations and a reduction in intermediate $CD14^+/CD16^+$ monocytes remain detectable after acute resolution (33). Elevated C-reactive protein (CRP) and white blood cell count further confirm a robust systemic inflammatory response in TTS (34). How these inflammatory and oxidative pathways translate into ion channel dysfunction and repolarization abnormalities is discussed below.

Microvascular dysfunction. Although coronary angiography typically shows no significant stenosis in patients with TTS, advanced assessments using cardiac magnetic resonance (CMR) and pressure-wire-based techniques have consistently revealed profound impairment in coronary microvascular function, reflected in elevated indices of microvascular resistance (35). It remains unclear whether such microvascular abnormalities precede TTS onset or arise as a consequence of the acute episode. Notably, myocardial catecholamine excess and microvascular dysfunction are increasingly viewed as complementary mechanisms. Stress-induced sympathetic hyperactivity may provoke local myocardial catecholamine overflow, triggering acute microvascular coronary vasoconstriction and myocardial stunning by activating α_1-adrenergic receptors (36). At the molecular level, excess norepinephrine stimulates ROS production, promoting the conversion of NO to peroxynitrite radicals and leading to eNOS uncoupling (37). This shifts eNOS activity from NO generation to

ROS production, thereby attenuating NO-mediated vasodilation and enhancing ET-1-mediated vasoconstriction. Another significant pathway linking catecholamines to microvascular impairment is RhoA/Rho kinase activation, which enhances vascular smooth muscle contraction by modulating calcium sensitivity and is implicated in coronary vasospastic susceptibility (38,39). The impact of microvascular dysfunction on conduction and refractoriness is addressed below.

4. Electrophysiological mechanisms of arrhythmia in TTS

The electrophysiological mechanisms underlying arrhythmias in TTS are not discrete, independent processes but rather constitute a highly integrated and self-perpetuating network. At the core of this network lies a common upstream driver, catecholamine excess and systemic inflammation, which simultaneously disrupts calcium homeostasis, alters ion channel function, impairs intercellular communication, and creates structural heterogeneities. These derangements do not operate in isolation; instead, they amplify one another through positive feedback loops, ultimately converging on two fundamental electrophysiological disturbances: Triggered activity and reentrant excitation. The following subsections dissect each of these interconnected mechanisms, with particular emphasis on their synergistic interactions and their cumulative impact on clinical arrhythmia phenotypes.

Abnormal calcium handling. Abnormal intracellular Ca^{2+} handling is a central electrophysiological mechanism linking the catecholamine surge of TTS to ventricular arrhythmia. In patients, this abnormality has been documented directly at the level of sarcoplasmic reticulum (SR) pump regulation: Endomyocardial biopsy specimens obtained during the acute phase show significantly reduced SERCA2a expression, an increased phospholamban (PLN)/SERCA2a ratio, dephosphorylation of PLN, and ventricular re-expression of sarcolipin, whereas NCX and RyR2 expression remain unchanged (40). This finding anchors and delimits the present section: It establishes that a Ca^{2+}-handling defect is present in human TTS myocardium, but the steps downstream of SR pump dysregulation, catecholamine-induced Ca^{2+} overload, the β2-AR signaling switch, and the generation of triggered activity, have not been directly demonstrated in human myocardium and rest predominantly on animal and cellular experiments.

The initiating event is catecholamine-induced Ca^{2+} overload. Supporting this, Bruns *et al* demonstrated that high-dose epinephrine infusion recapitulates the calcium overload phenotype of TTS in mouse model, leading to electrical instability and arrhythmogenesis (41). Excessive catecholamine stimulation triggers a cascade of downstream signaling events. The β2-AR switch from Gs to Gi coupling is the molecular trigger of this cascade. In an *in vivo* rat model, a high intravenous epinephrine bolus, but not norepinephrine, produced the characteristic reversible apical depression coupled with basal hypercontractility, an effect prevented by Gi inactivation with pertussis toxin pretreatment (24). β2-AR number and functional responses were greater in isolated apical cardiomyocytes compared with basal cardiomyocytes. This apical-basal β2-AR density gradient acts as a spatial amplifier, converting a uniform catecholamine surge into regionally heterogeneous electrical behavior. When circulating epinephrine reaches the critically high concentrations observed in TTS, the apical myocardium with higher β2-AR density, undergoes preferential Gi coupling, resulting in suppressed calcium transient amplitude and shortened action potential duration (APD) in the apex. By contrast, the basal myocardium, with lower β2-AR density, retains predominantly Gs-mediated signaling and exhibits preserved or enhanced contractility. This spatially discordant calcium handling creates a steep repolarization gradient between apex and base, which directly predisposes to reentrant arrhythmia (42).

A second, calcium-dependent route to arrhythmia arises from sympathetic co-transmission. Among the primary catecholamines, dopamine, norepinephrine and epinephrine (43), neuropeptide Y (NPY) is co-stored and co-released with norepinephrine from cardiac sympathetic nerves and acts through Y1 and Y2 receptors (44,45). Its upregulation in cardiac sympathetic nerves is sufficient to induce a TTS-like phenotype in experimental animals (46). In patients with ST-elevation MI, higher cardiac NPY release was associated with early ventricular tachycardia (VT) or fibrillation despite β-blockade, and in the corresponding isolated perfused rat heart NPY increased the amplitude and shortened the duration of the ventricular Ca^{2+} transient and significantly lowered the ventricular fibrillation (VF) threshold, effects prevented by the Y1 antagonist BIBO3304 but not by maximal β-blockade (47). Because NPY alters Ca^{2+} cycling and excitability rather than SR pump activity, this pathway is complementary to, rather than a continuation of, the β2-AR/Gi mechanism.

Simultaneously, catecholamine-driven ROS activate CaMKII, which enhances the L-type calcium channel (ICa-L) opening, promoting calcium influx and establishing a positive feedback loop that exacerbates calcium overload (48-50). Impaired SR function further exacerbates calcium handling abnormalities. Downregulated expression of SERCA2a and dephosphorylation of key phosphoproteins lead to reduced SR calcium uptake capacity (51). In TTS myocardium, reduced SERCA2a disrupts calcium recycling, leading to depleted SR calcium stores and impaired myocardial relaxation and contraction (40,52,53).

Sustained Ca^{2+} loading and impaired SR buffering converge on the generation of afterdepolarizations. Excessive RyR2 phosphorylation produces diastolic SR Ca^{2+} leak, and the resulting rise in cytosolic Ca^{2+} is extruded principally by the electrogenic Na^{+}/Ca^{2+} exchanger (NCX) in its forward mode, generating a transient inward current that depolarizes the membrane and produces delayed afterdepolarizations (DADs) (54); when DAD amplitude reaches threshold, a triggered action potential ensues. When APD is substantially prolonged, as it is in TTS, the repolarization phase of these potentials can be disrupted, generating early afterdepolarization (EADs) and initiating complex ventricular arrhythmias (55).

Taken together, the evidence supports a coherent but unevenly documented cascade. In human TTS myocardium, the abnormality is demonstrable at the level of SR Ca^{2+} pump regulation; the upstream β2-AR/Gi switch, NPY-dependent modulation of Ca^{2+} transients and NCX-mediated generation of DADs are established in animal, cellular and human cell

model preparations; and the clinical arrhythmic phenotype is linked to these mechanisms through repolarization markers such as corrected QT interval (QTc).

Repolarization abnormalities. QT interval prolongation and increased dispersion constitute the most prominent repolarization abnormalities in TTS, occurring in more than half of the patients (56). These ECG manifestations originate from dysregulation of multiple ion channels that induces APD prolongation, which may be closely associated with sympathetic overactivation and systemic inflammation.

Proinflammatory cytokines including tumor necrosis factor α (TNF-α) and IL-6 prolong APD and QT interval by reducing the transient outward potassium current (Ito) or enhancing ICa-L (18). Additionally, in human induced pluripotent stem cells-derived cardiomyocytes (hiPSC-CMs), high concentration of isoproterenol prolongs APD through increased ROS production, which enhances late sodium current and suppresses Ito (57). Sympathetic overactivation elevates intracellular cAMP levels via G protein-coupled receptor stimulation of adenylate cyclase, resulting in protein kinase A (PKA) activation (51). PKA subsequently phosphorylates ICa-L and RyR2, increasing calcium influx and prolonging APD (58).

Against this background of QT prolongation, both EADs and DADs are likely to arise, which trigger arrhythmogenesis. DADs can initiate premature ventricular complexes, which may deteriorate into VF or other lethal arrhythmias (59). Furthermore, diffuse electrical heterogeneity during repolarization results in non-uniform propagation of electrical activity across the myocardium, exacerbating transmural and regional repolarization dispersion. From a clinical perspective, QTc interval prolongation exceeding 470 milliseconds in men or 480 milliseconds in women is designated as long QT syndrome (LQTS) and signifies high arrhythmic risk in TTS (60). Although TTS-associated QT prolongation and congenital LQTS share similar ECG manifestations, their underlying mechanisms differ fundamentally. Congenital LQTS is typically caused by single-gene mutations in cardiac ion channel subunits, most commonly KCNQ1 (LQT1), KCNH2 (LQT2), or SCN5A (LQT3), leading to loss-of-function of IKs, IKr, or gain-of-function of late INa, respectively (61). By contrast, TTS-associated QT prolongation arises from an acquired, multifactorial process involving simultaneous dysfunction of multiple ion channels (reduced Ito, enhanced ICa-L, enhanced late INa) superimposed on structural remodeling (myocardial edema and interstitial fibrosis) and autonomic imbalance (18,32,57). This distinction has important clinical implications: Whereas congenital LQTS is a lifelong condition requiring genotype-guided therapy, TTS-associated QT prolongation is typically transient and resolves with recovery of ventricular function. Moreover, the multi-ion-channel nature of TTS-associated repolarization abnormalities means that targeting a single ion channel is unlikely to be effective; instead, management should focus on correcting the underlying catecholamine surge, inflammation and edema. A further distinction is that congenital LQTS predisposes to torsades de pointes (TdP) primarily through EADs arising from reduced repolarization reserve, whereas TTS-associated TdP may be driven by both EADs (from APD prolongation) and DADs (from calcium overload and spontaneous SR calcium release) (59,62). In TTS, QT prolongation and increased dispersion reflect the severity of repolarization disturbances, providing a reliable foundation for early clinical detection.

Ion channel remodeling. Repolarization reserve depends on the balance between inward and outward currents, and its reduction directly promotes EADs and TdP (63). Among the outward currents, the rapid delayed rectifier current (IKr) dominates human ventricular repolarization, and its loss is the commonest cause of drug-induced QT prolongation. In TTS, catecholamine-driven PKA phosphorylation and oxidative stress can reduce IKr, lowering repolarization reserve (64). The slow delayed rectifier current (IKs) is the principal sympathetic-sensitive repolarizing current and shows an apex-to-base expression gradient; failure of its sympathetic augmentation contributes to the aforementioned steep apical-basal APD dispersion, consistent with the neurohormonal regulation of IKs in heart failure (65). The inward rectifier current (IK1), which sets the resting membrane potential, is similarly destabilized by oxidative stress, and loss of IK1 facilitates afterdepolarizations (66). Under metabolic stress, ATP-sensitive potassium channels (IKATP) open as intracellular ATP falls, further shortening the action potential and destabilizing repolarization; in the context of TTS this mechanism is inferred from ischemia-reperfusion models rather than demonstrated directly, and no human data are available (63). In hiPSC-CMs, isoprenaline increased ICa-L, IKr and IKs while reducing INa and IK1, suggesting that the net effect of catecholamine excess on repolarization depends on the relative magnitude of these opposing changes (67,68).

Inward current remodeling is equally important. Enhanced late INa, driven by ROS and CaMKII activation, prolongs APD, promotes calcium overload through reverse-mode Na^+/Ca^{2+} exchange, and exacerbates repolarization lability. CaMKII also hyper-phosphorylates RyR2 at Ser2814, increasing channel open probability and producing the diastolic SR Ca^{2+} leak that underlies DADs (50). In hiPSC-CMs, toxic isoprenaline concentrations increase ROS, raise late INa and reduce the transient outward current (Ito), thereby prolonging APD and QT interval; β-estradiol attenuates these effects, which may partly explain the higher susceptibility of postmenopausal women (57). N-acetylcysteine abolishes the effects of isoprenaline on late INa and Ito, and H_2O_2 mimics them, confirming that these ion channel changes are ROS-dependent (56). Inflammatory cytokines such as TNF-α and IL-6 act in the same direction by suppressing Ito, IKr and IKs while enhancing ICa-L and INa, thereby contributing to APD and QTc prolongation (68).

The NCX extrudes one Ca^{2+} ion in exchange for three Na^+ ions and therefore generates a net inward current. In TTS, with the presence of calcium overload, NCX activity increases and the resulting forward-mode inward current contributes to the transient inward current underlying DADs and triggered activity (40). Because calcium released through phosphorylated RyR2 is removed from the cytosol largely by NCX, diastolic SR calcium leak and NCX activity are mechanistically coupled. However, it should be noted that a human biopsy study detected no changes in NCX or RyR2 expression in TTS myocardium, whereas increased NCX expression or activity has been reported in experimental models, suggesting

a potential discrepancy between human tissue data and model-derived findings.

Loss-of-function variants in SCN5A and in other arrhythmia-susceptibility genes have been reported in patients with TTS, suggesting that a pre-existing electrical substrate (Brugada syndrome, long-QT syndrome, or a subclinical channelopathy) may predispose to arrhythmia when challenged by a catecholamine surge (69-71).

Taken together, these changes indicate that repolarization abnormalities in TTS reflect a combined reduction of repolarization reserve rather than isolated QT prolongation.

Altered conduction and refractoriness. Myocardial edema and fibrosis are the primary manifestations of myocardial structural remodeling in TTS, significantly altering myocardial conduction properties. As introduced, microvascular dysfunction contributes to myocardial injury. CMR imaging typically reveals characteristic features of TTS, including myocardial edema, cellular injury, and the absence of late gadolinium enhancement (LGE), which helps distinguish TTS from acute MI (72). Neil *et al* (73) documented the persistent myocardial edema in affected segments for 3 to 4 months after acute TTS episode, noting that edema resolution follows a considerably longer time course than the recovery of ventricular contraction. Subsequent investigations have established that the evolution and resolution of ventricular repolarization abnormalities parallel the temporal course of LV edema, with both processes being closely associated with acute catecholamine release and inflammatory activation (74).

The temporal trajectory of myocardial edema and fibrosis has direct implications for arrhythmia risk in TTS. Migliore *et al* (75) proposed that myocardial edema serves as the substrate for life-threatening arrhythmias in reversible ventricular dysfunction of TTS, with edema creating differential zones of electrical conductivity that predispose to functional reentry. In the acute and subacute phases (first 72 h to ~1 month), arrhythmia risk is primarily edema-driven: Myocardial edema increases intercellular spacing, reduces gap junction density, and creates conduction delay zones that facilitate reentry (76,77). This is consistent with clinical observations that ventricular arrhythmias most commonly emerge within the first 72 h of hospitalization (10). As edema resolves over 3-4 months (78), the arrhythmia substrate shifts from edema-driven conduction heterogeneity to fibrosis-driven structural remodeling (79). Fazzini *et al* (80) demonstrated persistently increased extracellular matrix volume at 4-month follow-up on CMR, attributed to microscopic fibrosis by the time myocardial edema has subsided. This transition from an edema-predominant to a fibrosis-predominant substrate may explain why ventricular arrhythmias can persist into the recovery phase of TTS, particularly in cases of incomplete cardiac functional recovery or ongoing stress exposure.

It is important to clarify that the 'fibrosis' described in TTS is not classical replacement fibrosis. Current evidence indicates that TTS is not characterized by replacement fibrosis, and the absence of LGE is often used to support its diagnosis (77,80). However, a recent systematic review and meta-analysis reported that the overall frequency of LGE in TTS is 22.4%, with a significantly higher detection rate (40.7%) when CMR is performed within 3 days of symptom onset compared with after 3 days (3.9%) (81). Notably, LGE is rarely present at follow-up (1.7%), suggesting that the acute-phase LGE findings may reflect reversible myocardial injury rather than replacement fibrosis (81). The fibrosis process in TTS is more consistent with reactive/interstitial fibrosis, detected by elevated native T1 mapping and extracellular volume on CMR (79,80). This distinction is crucial because reactive interstitial fibrosis, unlike replacement fibrosis, may be reversible and does not necessarily represent irreversible myocardial injury. The development of microscopic fibrosis in TTS remains an area of active investigation, and the extent to which it contributes to long-term arrhythmic risk requires further study.

These pathophysiological factors promote interstitial fluid accumulation and increased intercellular spacing, ultimately reducing gap junction density and slowing conduction velocity. Moreover, cardiac conduction fibers demonstrate particular sensitivity to edema, inflammation, ischemia and catecholamine surges (82). Edematous myocardial regions form zones of conduction delay that facilitate reentry circuits and ventricular arrhythmias (83). At the molecular level, electrically active regions within fibrotic cardiomyocytes exhibit elevated excitation thresholds and reduced sodium channel density, most pronounced in the apical region. These alterations impede normal current conduction pathways, forcing myocardial conduction to adopt an irregular 'jumping' pattern. Consequently, ectopic conduction pathways increase susceptibility to conduction block and reentry arrhythmias (84).

In normal myocardium, APD remains relatively homogeneous across different regions. However, patients with TTS exhibit significant APD heterogeneity, particularly between the apical and basal regions of the left ventricle, largely due to structural alterations caused by myocardial edema and fibrosis (85). This spatial dispersion of repolarization is a key arrhythmogenic factor, and clinical studies have confirmed its association with VT and other rhythm disturbances. Notably, the spatial heterogeneity of sympathetic innervation creates a steep APD gradient between the LV apex and base, with differences reaching 80-120 ms. This pronounced dispersion establishes a functional substrate for reentrant circuits and facilitates the initiation of EADs and DADs.

Connexins, gap junctions and source-sink mismatch. Cell-to-cell electrical coupling is mediated by gap junctions composed mainly of connexin 43 (Cx43) in ventricular myocardium, with Cx40 and Cx45 contributing to specialized conduction tissue. Conduction velocity is proportional to gap-junction number and conductance, thus reduced Cx43 slows conduction and favours unidirectional block and reentry (86). In TTS, interstitial edema increases intercellular distance while inflammatory infiltration and oxidative stress impair gap-junction coupling; reduced or redistributed Cx43 has been described in TTS-like models and in human myocardial samples, and Cx43 dephosphorylation reduces junctional conductance (87). Connexin remodeling therefore links the structural changes of TTS (edema, inflammation and reactive interstitial fibrosis) to the conduction slowing that underlies reentry.

Conduction failure at the boundary between dyskinetic and preserved myocardium can also be explained by source-sink mismatch, the imbalance between the depolarizing current

delivered by the activation wavefront and the current required to excite the resting tissue ahead of it (88). Where excitable tissue is separated from source tissue by edema, fibrosis or low gap-junction coupling, the sink becomes disproportionately large and conduction fails, creating the conditions for unidirectional block and reentry. In TTS, the abrupt boundary between ballooning apical segments and hypercontractile basal segments reproduces this geometry, favours heterogeneous propagation, and provides a plausible substrate for the reentrant ventricular arrhythmias of the acute phase (89,90). A similar geometry underlies reentry in the border zone of MI and in other forms of structural heart disease, where surviving myocyte bundles separated by fibrosis, and the resulting zigzag course of activation, slow conduction and sustain reentry (91-93).

Autonomic imbalance. Autonomic imbalance, characterized by sympathetic overactivity and parasympathetic withdrawal, is increasingly recognized as an important mechanism in TTS. A neurocardiological study provided foundational evidence by examining structural and functional connectivity within autonomic brain networks of TTS survivors (94). The investigation identified significant alterations in brain regions governing autonomic nervous system, including the frontotemporal insula, amygdala and cingulate cortex, areas closely involved in emotional processing and autonomic control in patients with TTS (20,94). Additionally, functional magnetic resonance imaging revealed reduced thickness in the anterior ventromedial insular cortex and diminished amygdala gray matter volume in TTS (95).

Functionally, resting metabolic activity in the amygdala correlated with hematopoietic activity, arterial inflammation, and perceived stress levels, effectively predicting cardiovascular disease progression. This supports the role of the amygdala as a neuroanatomical link between psychological stress and cardiovascular events. Mechanistically, stress-induced activation of this central circuit promotes sympathetic outflow and HPA axis stimulation, elevating circulating catecholamines, glucocorticoids and inflammatory cytokines (96,97). These systemic changes concurrently increase heart rate and blood pressure while disrupting structural connectivity between key brain regions within autonomic networks (98).

Beyond the central autonomic network alterations, peripheral autonomic dysfunction is well-documented in TTS and provides clinically accessible correlates. Cardiac sympathetic denervation, assessed by 123I-metaiodobenzylguanidine (123I-MIBG) scintigraphy, has been consistently observed in patients with TTS. Akashi *et al* (99) demonstrated that 123I-MIBG myocardial scintigraphy in patients with TTS revealed a unique pattern of ventricular asynergy with evidence of cardiac sympathetic hyperactivity despite maintained coronary blood flow, strongly suggesting neurogenic myocardial stunning. A recent study using three-dimensional imaging in a TTS mouse model revealed a bimodal pattern of sympathetic nerve changes: Denervation during the acute phase, followed by re-innervation and subsequent denervation in the chronic phase (100). This phase-dependent sympathetic dysinnervation corresponds temporally with the evolution of arrhythmia risk, acute denervation contributes to electrical instability during the acute phase, while chronic denervation may facilitate reinnervation hypersensitivity and late arrhythmogenesis (100). Importantly, the persistence of 123I-MIBG uptake defects in patients with TTS, even after recovery of LV function, indicates that autonomic dysfunction outlasts the acute episode and may contribute to long-term arrhythmic risk. These peripheral markers of sympathetic dysinnervation complement the central autonomic findings and provide a clinically accessible tool for risk stratification in TTS.

The electrophysiological activity of ventricular myocardium is tightly regulated by the autonomic nervous system. Sympathetic input releases NPY, enhancing cardiomyocyte excitability, leading to calcium overload, shortening APD, and augmenting calcium transient amplitude. The spatial distribution of sympathetic fibers aligns with regional heterogeneities in ion channel expression, such as the apical-basal gradient of the slow delayed rectifier potassium current (IKs), enabling precise spatiotemporal control of ventricular depolarization and repolarization (101). By contrast, parasympathetic nerves innervate epicardial fat pads, releasing acetylcholine and vasoactive intestinal peptide to prolong APD via muscarinic receptors (102).

Under stress stimulation, patients with TTS exhibit sympathetic overactivation and parasympathetic suppression, ultimately leading to excessive release of neurotransmitters. These mediators directly modulate ion channel function in cardiomyocytes or indirectly influence electrophysiological stability by activating pro-inflammatory signaling pathways. Inflammatory cytokines, particularly IL-6, IL-1 and TNF-α, contribute to arrhythmogenesis by suppressing potassium current while enhancing sodium currents, collectively prolonging ventricular APD and causing QTC prolongation (62).

The parasympathetic nervous system, which modulates heart rate and myocardial excitability through the vagal nerve, exerts a protective antiarrhythmic effect under physiological conditions (103). Clinically, parasympathetic dysfunction is associated with QT interval prolongation and diminished heart rate variability, both of which are closely associated with elevated arrhythmia risk (104). Studies demonstrate significantly reduced parasympathetic activity and heart rate variability in patients with TTS (105). This loss of parasympathetic regulation may also disrupt the restorative role of vagal nerve during diastole, rendering myocardium more vulnerable to electrophysiological instability and triggered activity. Therefore, autonomic imbalance in TTS forms a critical link between psychogenic stress and cardiac electrophysiological disturbances. This dysregulation not only disrupts myocardial excitability and conduction but also markedly lowers the threshold for lethal arrhythmias. The aforementioned mechanisms of arrhythmogenesis in TTS are summarized in Fig. 2.

An integrated mechanistic framework for arrhythmogenesis in TTS. Taken together, the aforementioned pathways converge on a temporally ordered cascade rather than acting as independent mechanisms. The acute catecholamine surge initiates a common molecular core, excessive intracellular calcium, ROS and CaMKII activation that hyperphosphorylated RyR2 and the ICa-L, which then drives the aforementioned downstream electrophysiological abnormalities. This core is the point at

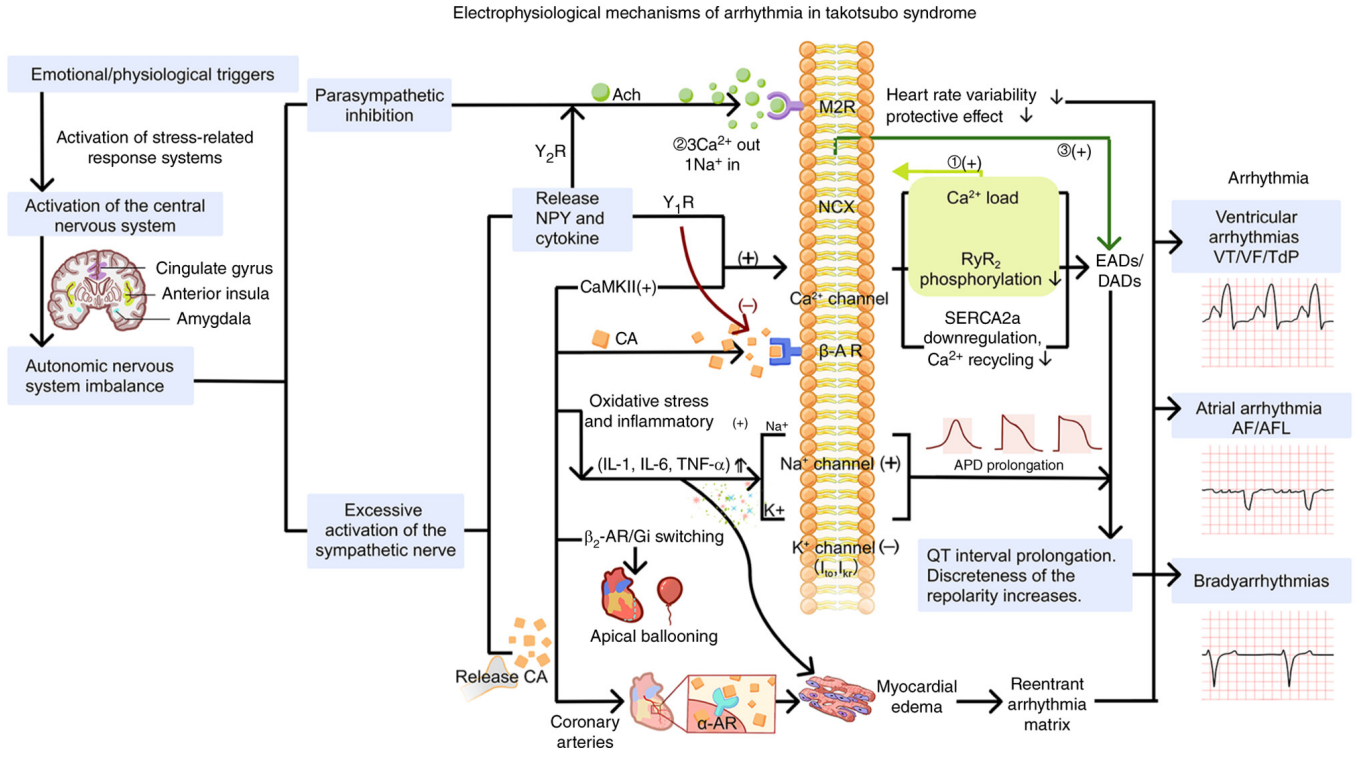


Figure 2. Electrophysiological mechanisms of arrhythmia in Takotsubo syndrome. A unified mechanistic framework connecting upstream triggers to downstream arrhythmia phenotypes is illustrated. NPY, neuropeptide Y; Y1R, Y1 receptors; Y2R, Y2 receptors; CA, catecholamines; IL-1, interleukin-1; IL-6, interleukin-6; TNF-α, tumor necrosis factor α; NCX, Na^+/Ca^{2+} exchanger; AR, adrenergic receptor; MR, M receptors; APD, action potential duration; I_{to}, transient outward potassium current; I_{kr}, rapidly activating delayed rectifier potassium channel current; EADs, early afterdepolarizations; DADs, delayed afterdepolarizations; VT, ventricular tachycardia; VF, ventricular fibrillation; TdP, torsades de pointes; AF, atrial fibrillation; AFL, atrial flutter.

which the diverse upstream pathways become electrophysiologically relevant, and it explains why calcium-handling, repolarization and conduction abnormalities in TTS are mechanistically linked rather than coincidental.

The initial trigger is transient, but arrhythmic risk extends well beyond the acute phase because inflammation, structural remodeling and autonomic imbalance amplify and sustain the substrate. Inflammation exacerbates the molecular core and directly modulates ion channels, prolonging APD and QT interval (43,56); myocardial edema, followed by reactive interstitial fibrosis, creates zones of conduction delay and APD dispersion that persist for months (75,78,81) and central autonomic network remodeling together with peripheral sympathetic dysinnervation modulates excitability throughout (46,99,105). These three systems convert a transient catecholamine insult into a sustained arrhythmic substrate.

The framework maps onto the clinical arrhythmia phenotypes. DAD-mediated triggered activity and EAD-driven repolarization lability underlie the ventricular arrhythmias (VT, TdP and VF) that cluster within the first 72 h (59,106); acute atrial inflammation and edema together with autonomic and hemodynamic changes provide the substrate for atrial fibrillation (AF) and flutter (107,108); and bradyarrhythmias reflect the parasympathetic surge and transient conduction-system dysfunction (10). The transition from an edema-predominant to a fibrosis-predominant substrate explains why arrhythmic risk can persist into the recovery phase (79,80). Because the pathways converge on a shared molecular core early in the cascade, interventions directed at the upstream trigger or at the core are more likely to be effective than those aimed at individual downstream ion channels.

Critical appraisal of the evidence: Strength, consistency and translational validity. The aforementioned mechanisms rest on evidence of unequal strength, graded on a four-level scheme: Strong (reproduced in independent human studies), moderate (limited human data or a single robust experimental model), emerging (preclinical observations or small series), and hypothetical (plausible but not demonstrated in TTS itself). Applying this scheme, the strongest support concerns the upstream trigger and the clinical phenotype. Circulating catecholamines are markedly elevated in patients with TTS (22), and high-dose epinephrine reproduces reversible apical dysfunction in intact animals (24,40). The association between QTc prolongation and malignant ventricular arrhythmias is reproducible across independent cohorts (8,55,60,106), with consistent clustering of events within the first 72 h (10,14). A Ca^{2+}-handling defect has also been documented directly in human TTS myocardium, albeit in a single biopsy series (40).

Several widely cited mechanisms, by contrast, rest on substantially weaker evidence. The β2-AR Gs→ Gi switch is well established in rodent models (24,42) but has not been demonstrated in human myocardium. Reactive interstitial fibrosis as a determinant of late arrhythmic risk rests on emerging evidence alone, because LGE is absent in most patients and its reported prevalence varies widely with imaging timing (81). Connexin remodeling and source-sink mismatch remain hypothetical in TTS: The underlying

electrophysiology is well characterized in ischemic and heart-failure models (86,88), but no conduction or mapping study in TTS has yet demonstrated such remodeling. Likewise, IKATP activation is inferred entirely from ischemia-reperfusion data (63).

The evidence is also not fully consistent. Proinflammatory cytokines prolong APD (18,57), whereas NPY shortens the ventricular Ca^{2+} transient and action potential (47), thus the net effect in the intact human heart remains unresolved; the role of PKA-dependent RyR2 hyperphosphorylation at Ser2808 is likewise debated, with some studies reporting no functional consequence (58). Systemic catecholamine concentrations also correlate poorly with the severity of wall-motion abnormality in some cohorts (22), and the reported prevalence of LGE ranges from ~2-40% depending on imaging timing (81), both of which temper the inferences that can be drawn, in particular, that fibrosis constitutes an arrhythmic substrate.

Finally, extrapolation from animals to patients requires explicit caveats: Rodent hearts differ in ion-channel expression and action potential morphology (most obviously in the dominance of Ito) and do not reproduce the apex-to-base heterogeneity of the human left ventricle; numerous experimental studies use supraphysiological catecholamine doses, and β-adrenoceptor subtype distribution differs between species; and the human central nervous system, whose emotional responses are central to the triggering of TTS, cannot be modelled in animals. Findings reproduced in human myocardial tissue (40) or in hiPSC-derived cardiomyocytes (57,68) therefore carry greater translational weight than rodent-only observations.

5. Clinical manifestations of arrhythmias in TTS

Ventricular arrhythmias. Although TTS is generally considered a self-limiting disease, it is associated with substantial short- and long-term mortality, largely attributable to life-threatening arrhythmias. These events occur in 4-14% of patients, most commonly during periods of QTc prolongation (14). Ventricular arrhythmias include VT, TdP and VF, typically emerging within the first 72 h of hospitalization. VT, categorized as sustained or non-sustained, accounts for ~1/3 of ventricular arrhythmic events (106).

Clinically, VT may present with palpitations, chest pain, dyspnea, dizziness and fatigue. A notable proportion of VT manifests as TdP, which is strongly associated with a QT interval exceeding 500 ms in TTS (109). Importantly, the absence of premonitory symptoms in some patients before VT onset complicates clinical detection and monitoring. In some cases, VT may persist for several minutes to hours. Without timely intervention, it can degenerate into VF, the most lethal arrhythmia in TTS. A retrospective study involving 114 patients with consecutive TTS identified QT interval prolongation as a significant predictor of life-threatening arrhythmias, particularly VF and/or tachycardia (110). Other independent risk factors for these fatal arrhythmias included increased dispersion of myocardial repolarization and a LV ejection fraction (LVEF) below 40% (111). Notably, ventricular arrhythmias may persist into the recovery phase of TTS, especially in cases of incomplete cardiac functional recovery or ongoing stress exposure. Therefore, close monitoring of both electrical stability and cardiac function remains essential throughout both the acute and convalescent stages of TTS.

Sudden cardiac death (SCD) is the most severe complication of TTS (106,110-112). A large case-control study revealed that among patients with TTS experiencing SCD, the initial recorded rhythm was almost equally distributed between VF (44.0%) and pulseless electrical activity (PEA) (42.9%), with VT (13.1%) accounting for a smaller proportion (106).

Analysis of resuscitation outcomes revealed that patients with VF as the initial rhythm have a relatively better prognosis, whereas those presenting with PEA face extremely poor survival rates (113). Recognition of these patterns provides crucial guidance for risk stratification and timely intervention in TTS.

Atrial arrhythmias. Atrial arrhythmias in patients with TTS primarily encompass atrial premature beats, atrial tachycardia, atrial flutter (AFL) and AF (67). Among these, AF is most prevalent, with its incidence increasing significantly with age (114). Patients with TTS developing AF commonly present with palpitations, dyspnea and acute heart failure.

Compared with other arrhythmias, AF is associated with poorer hemodynamic status, higher rates of cardiac arrest, and elevated levels of troponin and inflammatory markers (115). Clinical studies indicate that AF correlates with worse outcomes, including increased incidence of cardiogenic shock and longer hospitalization (107). The presence of AF often reflects underlying LV dysfunction characterized by reduced ejection fraction and left atrial enlargement. It may worsen clinical outcomes through several hemodynamic mechanisms. Notably, both systemic inflammation and LVEF have been identified as independent predictors of atrial arrhythmia onset, in-hospital mortality, and cardiovascular mortality in patients with TTS (108).

While AFL occurs less frequently than AF, it shows a stronger association with structural atrial abnormalities. Atrial myocardial inflammation and transient fibrosis may provide a substrate for AFL development. Clinically, AFL typically manifests with consistent atrial conduction delay, producing a rapid but regular atrial rhythm, often with more predictable episode patterns compared with AF. Although AFL in patients with TTS generally present with better rate control, persistent episodes can still lead to significant hemodynamic compromise (116).

Thromboembolic complications occur in ~12.2% of patients with TTS with atrial arrhythmias, with the LV apex being the most common site of thrombus formation (117). In patients with documented LV thrombus, oral anticoagulation is recommended for at least 3 months or until resolution of thrombus and recovery of myocardial contractility (118). Prophylactic anticoagulation may be considered in high-risk patients with severe LV dysfunction and extensive apical ballooning, although this recommendation is based on expert consensus. For patients with midventricular or basal ballooning patterns, routine prophylactic anticoagulation is not recommended.

In TTS, atrial arrhythmias are often a transient phenomenon of the acute phase, temporally linked to the catecholamine surge and acute inflammatory activation rather than to chronic structural remodeling (108). Patients with TTS and AF show higher levels of inflammatory markers, including elevated

CRP and white blood cell levels, than those without AF, suggesting that inflammation plays a key role in AF during an acute TTS event (119). Acute atrial stretch and inflammation may occur either as an indirect consequence of increased left filling pressure or as a direct consequence of high catecholamines at the atrial myocardium (16). This contrasts with AF in chronic heart failure, where the substrate is dominated by long-standing fibrosis, chamber enlargement, and electrical remodeling. Consequently, whereas anticoagulation in chronic heart failure is guided by validated risk scores (for example, CHA_2DS_2-VASc) applied to a persistent arrhythmia, anticoagulation decisions in TTS-associated AF must account for both the transient nature of the arrhythmia and the concurrent risk of LV thrombus formation related to apical ballooning and severe LV dysfunction. Current recommendations suggest that anticoagulation therapy should be individualized according to thromboembolic risk stratification using validated scoring systems, with additional consideration of TTS-specific risk factors such as apical ballooning, LVEF ≤30% and leukocytosis (120). The InterTAK Thrombus Risk Score may serve as a supportive tool for this purpose.

Bradyarrhythmias. A subanalysis of the international multicenter GEIST registry, which included 906 patients with TTS, demonstrated that bradyarrhythmias (asystole and/or AV block) were more frequently observed than ventricular tachyarrhythmias specifically before hospital admission (121). However, in the overall TTS population, bradyarrhythmias remain less common than tachyarrhythmias (incidence 1.3-2.5%); ventricular arrhythmias occur in 4-14% of patients and are often associated with prolonged QT interval and are a direct cause of sudden death in TTS (14). Sinoatrial node (SA) dysfunction typically presents as significant sinus bradycardia or sinus arrest, potentially leading to dizziness, presyncope or syncope (121). The underlying mechanism may involve myocardial ischemia or transient local dysfunction impairing SA node conduction and automaticity. In addition to SA node dysfunction, TTS can involve varying degrees of atrioventricular block, ranging from first- and second-degree (Type I or II) to third-degree atrioventricular block (AV block). While most patients with sinus bradycardia or AV block do not require specific intervention, temporary pacing may be necessary to restore rhythm during episodes of sinus arrest. However, in cases of persistent high-degree AV block or SA node dysfunction beyond the acute phase, permanent pacemaker implantation should be considered, as conduction disturbances may persist despite recovery of LV function (122).

ECG findings in TTS. ECG abnormalities in patients with TTS typically include ST-segment changes, QT interval prolongation and T-wave inversion (123). Data from the InterTAK registry provide the following distribution of initial ECG findings: ST-segment elevation (44%), ST-segment depression (8%), T-wave inversion (41%), and left bundle branch block (5%) (124). Similar to ACS, TTS exhibits characteristic temporal evolution on ECG: Initial ST-segment elevation (when present) typically resolves within hours, followed by progressive T-wave inversion and QT interval prolongation over subsequent days (125). These changes gradually normalize over days to weeks.

ST-segment changes of patients with TTS typically emerge within the initial hours of symptom onset, most frequently observed in leads I, II, III, aVF and aVR (126,127). The distribution of ST-segment elevation typically involves the anterior or inferior LV walls, suggesting regional myocardial stress. Conversely, ST-segment depression may reflect underlying myocardial ischemia, microvascular dysfunction, or transient myocardial impairment. Clinically, these ST-segment alterations closely mimic acute MI. For patients suspected of having acute anterior wall MI with ST-segment elevation in the anterior leads, the absence of ST-segment depression or ST-segment elevation in the inferior leads suggests TTS.

A prolonged QTc is observed in ~50-80% of patients with TTS, indicating significant repolarization disturbance and serving as a crucial predictor of malignant arrhythmias in patients with TTS (128). Clinical evidence confirms that QTc prolongation in patients with TTS elevates the risk of ventricular arrhythmias and SCD (129). Consequently, continuous ECG monitoring and avoidance of QT-prolonging medications are essential during acute management.

T-wave abnormalities constitute another fundamental ECG feature in TTS, manifesting as either inverted or prominently peaked T-waves (124). These changes indicate myocardial ischemia and electrical remodeling during the acute phase, with greater prominence often observed in patients with concomitant atrial or ventricular arrhythmias. Beyond electrophysiological responses, T-wave abnormalities reflect underlying ion channel dysfunction and cellular injury, offering insight into TTS pathophysiology.

6. Diagnostic and therapeutic approaches

Diagnostic tools. Diagnosing TTS remains challenging because its clinical presentation closely mimicking ACS. Current diagnostic approaches rely on a comprehensive assessment of ECG, advanced imaging and biomarker analysis.

Electrocardiography. ECG serves as the first-line screening tool for detecting arrhythmias and characteristic patterns in TTS, valued for its immediacy and accessibility. Typical ECG manifestations include acute ST-segment changes, significantly prolonged QT intervals, and deep inverted T waves (130). Particular attention should be paid to high-risk patterns such as the 'shark-fin' morphology (characterized by a QRS-ST-T wave fusion) or persistent ST-segment elevation, both of which correlate with adverse clinical outcomes and compromised short-term prognosis (131,132).

Imaging modalities. Imaging studies play an indispensable role in the diagnosis of TTS, including echocardiography, CMR and coronary angiography. Transthoracic echocardiography serves as the most accessible initial imaging tool, providing essential assessment of cardiac structure and function. Characteristic findings typically involve apical akinesia or hypokinesia with basal hypercontractility, creating the classic 'apical ballooning' morphology.

CMR offers superior tissue characterization and is particularly valuable in the subacute phase. T2-weighted images delineate the myocardial edema extent, which correlates with electrophysiological disturbances, while the absence of LGE helps exclude irreversible myocardial injury and supports the diagnosis of TTS (133-135). Although these techniques are

predominantly non-invasive, patients presenting with ACS-like symptoms typically require early coronary angiography to definitively exclude obstructive coronary artery disease. Combined with LV angiography, this approach remains the gold standard for confirming TTS and ruling out alternative diagnoses.

Biomarker profiles. Biomarker evaluation provides quantitative evidence for TTS. Evidence of myocardial injury is present in nearly all cases, with biomarkers of cardiac necrosis, including troponin I, troponin T and creatine kinase, elevated to levels comparable to those in patients with acute MI. However, these elevations often show incomplete correlation with either the magnitude of ST-segment deviation on electrocardiogram or the severity of clinical symptoms (136). Additionally, plasma concentrations of B-type natriuretic peptide increase substantially within ~24-48 h after symptom onset and are significantly higher in patients with TTS than in patients with ACS (137).

Previously, other factors such as microRNAs (miRNAs or miRs) are suggested to be biomarkers of TTS. For instance, miR-16 and miR-26a are significantly elevated in patients with TTS (138). These miRNAs are considered to enhance cardiac sensitivity to catecholamines by modulating calcium channel activity and G-protein signaling, thereby facilitating the characteristic apical akinesia with basal hyperkinesis. Concurrently, inflammation-associated miRNAs, including miR-15, miR-21 and miR-146a, are upregulated in the acute phase of TTS, correlating closely with the systemic inflammatory state (139). Moreover, recent research has identified endothelial cell-derived exosomal miR-126-3p as a direct contributor to arrhythmogenesis in TTS (140). These miRNAs serve not only as promising biomarkers for early diagnosis and risk stratification of TTS but also reveal a multi-level regulatory network that integrates neuroendocrine activation, inflammatory signaling and electrophysiological remodeling. The high-risk ECG, imaging, and biomarker features for arrhythmia stratification in TTS are summarized in Table I.

Management of arrhythmias. The management of arrhythmias in TTS is stratified into acute and long-term management, with therapeutic decisions tailored to arrhythmia type, hemodynamic status and patient comorbidities.

The emergency treatment for acute arrhythmias aims to stabilize hemodynamics, prevent further myocardial injury, and mitigate arrhythmic complications. For paroxysmal supraventricular tachycardia, intravenous adenosine effectively terminates episodes through transient atrioventricular nodal blockade (141). Pharmacological cardioversion of AF in patients without structural heart disease may be achieved with propafenone or ibutilide, whereas in patients with concomitant heart failure rate control is generally preferred over rhythm control in the acute phase, because of the QT-prolonging risk of class III agents (142,143).

In acute heart failure, nitroglycerin can reduce ventricular filling pressures and afterload; however, it is contraindicated in the presence of LV outflow tract obstruction (LVOTO) due to risk of exacerbating pressure gradients. Drugs that prolong the QT interval, particularly Group III antiarrhythmic agents such as amiodarone and sotalol, should be avoided in the acute phase of TTS, given the elevated risk of inducing TdP or other malignant ventricular arrhythmias (67). Beta-blockade and Group III antiarrhythmics should be used cautiously in patients with QTc prolongation due to the risk of further lengthening; short-acting agents (for example, esmolol) or temporary pacing (in concomitant bradycardia) may be considered instead (144).

Electrical cardioversion (ECV) serves as an alternative intervention for patients unresponsive to medical therapy or experiencing life-threatening arrhythmias. Non-synchronized defibrillation is indicated for VF or pulseless VT, whereas synchronized cardioversion is required for AFL, AF or hemodynamically stable VT to avoid triggering VF (145). Notably, specific arrhythmias such as TdP demand targeted management, including intravenous magnesium and electrolyte repletion, rather than conventional antiarrhythmic drugs or ECV alone.

The role of electrophysiology study (EPS) and catheter ablation in TTS remains limited but may be relevant in selected patients with recurrent arrhythmias during recovery. In the acute phase, EPS is rarely indicated because the arrhythmogenic substrate is dynamic and largely reversible (146). In patients with recurrent sustained monomorphic VT or VF beyond the acute phase, particularly those with persistent LGE on CMR or incomplete LV functional recovery, EPS may identify a fixed substrate amenable to ablation. For atrial arrhythmias, catheter ablation is not routinely recommended acutely because the substrate is transient and inflammation-driven; after recovery, it may be pursued according to standard AF indications once LV function has recovered and inflammation has resolved. Catheter ablation itself can rarely trigger TTS, with a systematic review of 18 patients reporting onset within 4 days and complications including VF and PEA; close monitoring for at least 1 week is therefore prudent, particularly in postmenopausal women. EPS may also help determine the level of block in persistent high-degree AV block and guide permanent pacemaker decisions (147).

Long-term management of TTS aims to prevent recurrence and reduce the risk of SCD. Pharmacotherapy for patients with TTS with LV dysfunction commonly includes β-blockers, ACE inhibitors/angiotensin receptor (ACEi/ARB) blockers, and diuretics as needed. Current guidelines recommend maintaining this regimen for at least 3 months or until recovery of LV function (148). Growing understanding of autonomic nervous system involvement in TTS pathophysiology has reinforced the role of β-blockers in long-term management. Raposeiras-Roubin *et al* (149) demonstrated that β-blocker therapy is associated with reduced mortality during follow-up. Carvedilol is generally preferred in clinical practice unless significant LVOTO is present, in which case β1-selective agents such as bisoprolol are recommended. However, it is important to note that no randomized controlled trials have yet conclusively established the benefit of β-blockers in reducing TTS recurrence or improving survival. The observation that 1/3 of patients experience recurrence despite β-blocker therapy suggests potential involvement of additional pathways. By contrast, data from the InterTAK registry indicate that ACEi/ARB therapy is associated with improved 1-year survival and lower recurrence rates (150). For patients with concomitant coronary artery disease, aspirin and statins should be incorporated.

Table I. High-risk ECG, imaging and biomarker features for arrhythmia risk stratification in TTS.

Domain	Parameter	Threshold/Feature	Risk association	Suggested action	(Refs.)
ECG	QTc interval	≥460 ms at admission	Predictor of in-hospital ventricular tachycardia and VF; associated with higher 1-year VA incidence and all-cause mortality	Continuous ECG monitoring; avoid QT-prolonging drugs	Multicenter cohort studies (8,60,144)
	QTc interval	>490 ms at admission	Highest sensitivity and specificity for polymorphic VT/VF (AUC=0.687)	Consider wearable cardioverter-defibrillator; intensive monitoring during first 72 h	Retrospective cohort (8,55)
	QTc interval	>500 ms	Strongly associated with TdP; designated as high-risk threshold in TTS	Temporary pacing if bradycardia-dependent TdP; avoid Group III antiarrhythmics	Expert consensus/ case series (109,128)
	Tpeak-Tend interval	Corrected global Tp-Te ≥108 ms at 48 h	Independent predictor of subacute VAs; superior to QTc (sensitivity 71%, specificity 72%)	Serial ECG at 48 h; consider as supplementary risk marker	Prospective observational study (8)
	Tpeak-Tend interval	Tp-Te > QTc	Superior to QTc in predicting 1-year ventricular arrhythmias	Integrate into risk assessment when QTc is borderline	Letter/secondary analysis (8,111)
Imaging	LVEF	≤30% on admission	Included in InterTAK Thrombus Risk Score; high-risk patients (score >3) had 11.3% event rate vs. 1.7% in low-risk	Anticoagulation consideration; intensive monitoring	InterTAK registry-derived score (118,120)
	LVEF	<40% during the acute phase	Independent risk factor for life-threatening ventricular arrhythmias (VT/VF) in the acute phase	Incorporate into acute-phase risk stratification; intensify ECG monitoring	Retrospective cohort (111)
	LVEF	<35% persistent beyond 3-6 months	Indication for individualized ICD consideration (after excluding reversible causes)	Reassess LVEF at 3-6 months; CMR for LGE assessment	Expert consensus (151)
	Apical ballooning pattern	Apical akinesia with basal hyperkinesia	Associated with higher QT prolongation and arrhythmia risk compared with midventricular/basal variants	More intensive monitoring; lower threshold for anticoagulation if LVEF ≤30%	Observational studies (62,120)
	Myocardial edema (CMR)	T2-weighted edema in acute phase	Correlates with extent of repolarization abnormalities; proposed substrate for life-threatening arrhythmias	CMR in subacute phase for substrate characterization	CMR T1/T2 mapping studies (74,75,133)
	LGE on CMR	Presence of LGE (any pattern)	Patients with LGE show worse clinical profile with higher in-hospital events	Consider as marker of worse prognosis; not routinely recommended for ICD decision	Retrospective CMR study (81,134)
	Right ventricular involvement	RV dysfunction on echocardiography or CMR	Associated with increased mortality and adverse outcomes in TTS	Incorporate into risk assessment; consider more intensive monitoring	Observational studies (84)

Table I. Continued.

Domain	Parameter	Threshold/Feature	Risk association	Suggested action	(Refs.)
Biomarker	Troponin peak	>7 μg/l (troponin I)	Independent predictor of ventricular arrhythmia in acute phase (P=0.04)	Serial troponin measurement; higher vigilance if peak exceeds threshold	Retrospective cohort (110,111)
	Troponin peak	Per 1 μg/l increase	Independent predictor of newly diagnosed atrial arrhythmias (OR 1.03, 95% CI 1.003-1.06)	Consider earlier anticoagulation assessment in patients with high troponin peak	Retrospective study (108,119)
	BNP/NT-proBNP	Elevated on admission (higher than ACS)	BNP peak predictive of in-hospital mortality (OR 1.00, 95% CI 1.000-1.001)	Serial BNP measurement; integrate into risk assessment	Observational study (108,137)
	CRP	Elevated peak level	Independent predictor of newly diagnosed atrial arrhythmias (OR 1.006, 95% CI 1.001-1.01)	Monitor inflammatory markers; consider as adjunctive risk marker	Retrospective study (108,119)
	Leukocyte count	Elevated peak level	Predictor of in-hospital mortality (OR 1.095, 95% CI 1.034-1.16)	Routine CBC monitoring; integrate into risk assessment	Observational study (108,120)

AA, atrial arrhythmia; ACS, acute coronary syndrome; AUC, area under the curve; BNP, B-type natriuretic peptide; CBC, complete blood count; CMR, cardiac magnetic resonance; CRP, C-reactive protein; ECG, electrocardiogram; ICD, implantable cardioverter-defibrillator; LGE, late gadolinium enhancement; LVEF, left ventricular ejection fraction; OR, odds ratio; RV, right ventricle; TdP, torsades de pointes; Tp-Te, Tpeak–Tend; TTS, Takotsubo syndrome; VA, ventricular arrhythmia; VF, ventricular fibrillation.

Integrated management should address psychiatric comorbidities commonly associated with TTS. Patients with depression or anxiety may benefit from psychocardiology rehabilitation, though evidence regarding the efficacy of antidepressant medications in this population remains limited and controversial.

Implantable cardioverter-defibrillator (ICD) implantation is generally discouraged in TTS because of the reversible nature of cardiac dysfunction and the low rate of appropriate device therapy during follow-up. In selected high-risk cases, such as those with persistent LVEF <35% beyond 3-6 months despite optimal medical therapy, recurrent malignant arrhythmias beyond the acute phase, or concomitant structural heart disease, ICD implantation may be considered on an individual basis (151). The management for arrhythmias in TTS is summarized in Table II.

7. Future directions and research gaps

Mechanism studies. In recent years, the contribution of genetic predisposition to arrhythmia susceptibility in TTS has gained increasing research attention. Increasing evidence suggests that TTS does not follow a monogenic inheritance pattern but is influenced by a polygenic architecture, in which multiple rare and common variants contribute to individual vulnerability (152). However, a definitive genetic marker panel for TTS remains to be established.

It is important to note that most genetic studies in TTS to date have focused on susceptibility to the syndrome rather than on genetic determinants of arrhythmia risk during or after the acute episode. Case reports and small series have described rare variants in genes such as RYR2, CASQ2, SCN5A and TTN in patients with TTS complicated by malignant ventricular arrhythmias (84,86,153,154). These observations suggest that an underlying arrhythmogenic substrate may modulate arrhythmic risk in a subset of patients. However, systematic studies specifically designed to identify genetic predictors of arrhythmia in TTS are lacking, and no common genetic variant can currently be considered a robust or clinically actionable marker for arrhythmia risk stratification (155).

Future large-scale genomic studies, including genome-wide association studies and whole-exome sequencing in multi-ethnic cohorts, are warranted to identify novel genetic risk loci and with a specific focus on arrhythmia-related phenotypes. Furthermore, research on elucidating gene-environment interactions, particularly how specific genetic backgrounds modulate responses to emotional and physical stressors, and how these interactions contribute to the striking sex differences observed in TTS epidemiology can be prioritized.

Therapeutic innovations. Current evidence remains insufficient to guide standardized treatment for TTS, highlighting a critical need for further research in this area.

Personalized and biomarker-guided strategies. Personalized treatment tailored to individual patient profiles is essential, especially in managing severe complications such as cardiogenic shock. This approach enables precise interventions through multidimensional assessment, integrating clinical, imaging and biomarker data. Biomarker-guided strategies integrating miRNA expression patterns, circulating

Table II. Management for arrhythmias in Takotsubo syndrome.

Authors, year	Phase	Clinical scenario	Recommended management	Cautions/Contraindications	(Refs.)
	Acute phase (0-72 h)	Ventricular arrhythmias			
Gili *et al*, 2019; Stanaitiene *et al*, 2008		VF/pulseless VT	Immediate non-synchronized defibrillation	Avoid delay; correct electrolyte abnormalities	(106,145)
La Vecchia *et al*, 2024; Stanaitiene *et al*, 2008		Hemodynamically stable sustained VT	Synchronized cardioversion	If recurrent, consider IV amiodarone (caution with QT prolongation)	(67,145)
La Vecchia *et al*, 2024; Medina de Chazal *et al*, 2018		TdP	V magnesium + electrolyte repletion; temporary pacing (for bradycardia-dependent TdP)	Avoid QT-prolonging drugs (for example, sotalol, ibutilide)	(67,109)
		Atrial arrhythmias			
La Vecchia *et al*, 2024; Kukendrarajah *et al*, 2024; Sarkozy *et al*, 2003		AF/AFL with rapid ventricular response	Rate control: beta-blockers or digoxin; rhythm control: amiodarone	Avoid flecainide, propafenone (contraindicated in structural heart disease)	(67,142,143)
Del Buono *et al*, 2026; Stanaitiene *et al*, 2008		Hemodynamic instability	Synchronized cardioversion	Anticoagulation decision must be individualized	(120,145)
		Bradyarrhythmias			
El-Battrawy *et al*, 2020; Stiermaier *et al*, 2016		Sinus bradycardia/ sinus arrest	Asymptomatic: observe; symptomatic: temporary pacing	Isoproterenol contraindicated in LVOTO	(121,122)
Stiermaier *et al*, 2016; Hussein *et al*, 2026		High-degree AV block	Temporary pacing; if persistent beyond acute phase, consider permanent pacemaker	Atropine may be ineffective in high-degree AV block	(122,147)
		Special considerations			
Medina de Chazal *et al*, 2018; Hanmandlu *et al*, 2025		LVOTO	Volume loading; pure alpha-agonist (phenylephrine); short-acting beta-blockers (esmolol, landiolol)	Contraindicated: catecholamines, inotropes, nitrates, afterload-reducing agents	(109,144)
La Vecchia *et al*, 2024; Hanmandlu *et al*, 2025		QT prolongation	Avoid Group III antiarrhythmics (sotalol, ibutilide); correct hypokalemia and hypomagnesemia	Continuous ECG monitoring if QTc >500 ms	(67,144)
Gili *et al*, 2019	Subacute phase (3-30 days)	Ventricular arrhythmias	Continuous or wearable ECG monitoring (high-risk: QTc >500 ms, LVEF <40%, early VA)	If recurrent, evaluate reversible triggers; consider EPS/ablation (see recovery phase)	(106)

Table II. Continued.

Authors, year	Phase	Clinical scenario	Recommended management	Cautions/Contraindications	(Refs.)
Santoro *et al*, 2017; Del Buono *et al*, 2026		Atrial arrhythmias	Continue anticoagulation if LV thrombus present; reassess after thrombus resolution	Recheck LVEF and left atrial size	(118,120)
Stiermaier *et al*, 2016		Bradyarrhythmias	If pacing dependence persists, evaluate indication for permanent pacemaker	Conduction disturbances may persist after LV function recovery	(122)
	Recovery phase (>1 month)	Ventricular arrhythmias			
Yalta *et al*, 2024		No recurrence, LVEF recovered	ICD not recommended	ICD generally discouraged	(151)
Jesel *et al*, 2018; Yalta *et al*, 2024		Persistent LVEF <35% (>3-6 months) or recurrent monomorphic VT	Individualized consideration of ICD	Exclude reversible causes; assess LGE and EPS	(111,151)
Desai *et al*, 2024		Drug-refractory VT/VF	Consider EPS + catheter ablation	Ablation itself can trigger TTS; monitor for at least 1 week	(146)
		Atrial arrhythmias			
Desai *et al*, 2024		Pre-existing or recurrent AF, LV function recovered Bradyarrhythmias	Consider catheter ablation according to standard AF indications	Requires resolution of inflammation and LV functional recovery	(146)
Stiermaier *et al*, 2016; Hussein *et al*, 2026		Persistent high-degree AV block or symptomatic sinus node dysfunction	Permanent pacemaker implantation	EPS may help determine the level of block	(122,147)
Li *et al*, 2022; Raposeiras-Roubin *et al*, 2025; Templin *et al*, 2015		Long-term pharmacotherapy	Beta-blockers (carvedilol preferred; bisoprolol if LVOTO); ACEi/ARB; diuretics as needed	Maintain for at least 3 months or until LV function recovery	(148-150)

AF, atrial fibrillation; AFL, atrial flutter; AV, atrioventricular; ECG, electrocardiogram; EPS, electrophysiology study; ICD, implantable cardioverter-defibrillator; LGE, late gadolinium enhancement; LV, left ventricle; LVEF, left ventricular ejection fraction; LVOTO, left ventricular outflow tract obstruction; TdP, torsades de pointes; VF, ventricular fibrillation; VT, ventricular tachycardia.

catecholamine levels, or specific inflammatory signatures can help identify high-risk patients and optimize drug selection and dosing regimens.

Digital health and novel therapeutics. The integration of digital health technologies facilitates real-time monitoring and dynamic management. Wearable devices combined with artificial intelligence algorithms allow continuous tracking of QT intervals and heart rate variability, enabling timely detection of arrhythmia events and early intervention.

Beyond conventional β-blockers, novel therapeutic avenues are emerging. Recent studies indicate that in specific TTS subpopulations, calcium channel sensitizers, rather than inhibitors, may offer superior therapeutic benefits by improving myocardial contractility without exacerbating calcium overload. For instance, Levosimendan counteracts TTS-induced cardiac depression via cAMP-independent Ca^{2+} sensitization of troponin C, restoring contractility without exacerbating β_2AR/Gi-mediated arrhythmogenesis (24,156).

Furthermore, gene therapy presents a transformative potential for precision medicine in TTS. Concurrently, device-based therapy is evolving. Cardiac resynchronization therapy (CRT) has been described in a case report of patients with TTS with concomitant persistent high-grade AV block and severe LV dysfunction. However, current evidence is limited to case reports, and CRT should be reserved for patients with established indications independent of TTS, such as persistent high-grade AV block with reduced ejection fraction (157).

Long-term outcomes. The long-term outcomes of patients with TTS with arrhythmias are critically influenced by the effectiveness of risk stratification in predicting mortality and morbidity. Risk assessment based on initial ECG findings, troponin levels and LV function successfully identifies high-risk individuals, with those exhibiting complex ventricular arrhythmias facing substantially increased long-term adverse event risks (158,159).

However, current risk stratification for TTS-related arrhythmias faces several challenges: The lack of a unified prognostic scoring model, undefined thresholds and weighting for key indicators, and insufficient long-term follow-up data. Future approaches could integrate multimodal data to develop artificial intelligence-driven predictive models, shifting from 'event-driven' to 'mechanism-driven' risk assessment.

8. Conclusion

Arrhythmias represent a critical determinant of acute-phase risk and long-term outcomes in TTS. The present review consolidates the evidence that the electrophysiological substrate for these arrhythmias arises from a complex interplay of multiple pathophysiological mechanisms. These mechanisms are best understood as a single, stage-dependent framework rather than as independent pathways, an organization that also clarifies why arrhythmic risk evolves over time and why interventions directed at the upstream trigger or at the shared molecular core are more likely to succeed than those targeting individual ion channels.

The clinical implications of these electrical disturbances are profound, necessitating a high index of suspicion and prompt intervention. Early recognition of TTS and its associated arrhythmias, achievable through vigilant electrocardiographic monitoring and advanced imaging studies, is paramount. Appropriate management, encompassing both pharmacotherapy and non-pharmacological interventions, plays a vital role in controlling arrhythmic events and improving clinical outcomes. In the long term, a tailored approach that addresses the multifaceted nature of TTS is essential for mitigating recurrence and preventing SCD.

Nevertheless, the electrophysiological mechanisms of TTS remain incompletely elucidated, and both diagnostic criteria and therapeutic strategies require further refinement. The existing knowledge gaps underscore the necessity for sustained and focused research efforts.

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Availability of data and materials

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Authors' contributions

DX, XC, MH, XZ, QX and HL contributed to the conception and design of the review. The DX, XC, MH, BZ, QQX and WH wrote the first draft. XZ, QX and HL revised the manuscript. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

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Not applicable.

Competing interests

The authors declare that they have no competing interests.

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