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Ventricular arrhythmias in patients with Takotsubo syndrome

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Abstract

Takotsubo syndrome (TTS) is a unique nonischemic cardiac disease characterized by acute myocardial dysfunction of the left and/or right ventricle. Patients are predominantly postmenopausal women and usually present with symptoms indistinguishable from acute coronary syndrome. Although the exact pathomechanisms of TTS remain elusive, increasing evidence suggests that sympathetic overdrive and catecholamine excess might play a central role. Despite the complete recovery of ventricular dysfunction within several days to weeks, patients with TTS exhibit considerable short- and long-term mortality rates and ventricular arrhythmias have been identified as key contributor to morbidity and mortality. This article summarizes the prevalence, underlying mechanisms, therapeutic strategies, and prognostic implications of ventricular arrhythmias in TTS. Furthermore, the need for implantable cardioverter-defibrillators is discussed in view of the transient character of the disease.

KEYWORDS
implantable cardioverter-defibrillator, Takotsubo syndrome, ventricular arrhythmias

1 | INTRODUCTION

Takotsubo syndrome (TTS) is a unique nonischemic cardiac disease characterized by transient left ventricular dysfunction with acute onset.[1–3] It is found predominantly in postmenopausal women and frequently triggered by physical or emotional stress.[1–3] The initial clinical presentation mimics acute coronary syndrome, with the leading symptoms of chest pain and dyspnea. Likewise, electrocardiography (ECG) and laboratory findings do not allow for the reliable discrimination of these entities. Therefore, the final diagnosis is based on several criteria[2,3] (Table 1) and requires a multimodality imaging approach including echocardiography, coronary angiography/left ventriculography, and cardiac magnetic resonance (CMR) imaging.[1,4] One major criterion used to differentiate TTS from acute myocardial infarction is the absence of significant obstructive coronary artery disease contributing to the extent of contraction abnormalities.[2,3] The distinct distribution of regional hypokinesis, akinesis, or dyskinesis of the left ventricle causes characteristic contraction patterns ("ballooning"). Following localization of the affected myocardial areas, TTS is characterized by apical, midventricular, and basal ballooning (Figure 1).[1,5] The left ventricular shape of the most common apical ballooning type reminded Sato et al,[6] who first described this syndrome in 1990, of a Japanese octopus trap called a "takotsubo," which became eponymous for the disease. Approximately, one-third of patients with TTS exhibit concomitant wall motion abnormalities of the right ventricle, and isolated right ventricular forms of TTS have also been described.[1,7] However, the contraction abnormalities are completely reversible within several days to weeks, which is also a central diagnostic feature of TTS.[2,3] Despite extensive research efforts, the exact pathomechanisms of TTS remain elusive. Generally, there is broad consensus that an activation of the sympathetic nervous system subsequent to stressful events and the effects of catecholamine excess play a central role in the development of TTS.[8–10] One possible mechanism of catecholamine effect

TABLE 1 European Society of Cardiology Heart Failure Association diagnostic criteria for Takotsubo syndrome (adapted from ref. 2)

1. Transient regional wall motion abnormalities of the left or right ventricular myocardium that are frequently, but not always, preceded by a stressful trigger (emotional or physical)
2. The regional wall motion abnormalities usually extend beyond a single epicardial vascular distribution and often result in circumferential dysfunction of the ventricular segments involved
3. The absence of culprit atherosclerotic coronary artery disease including acute plaque rupture, thrombus formation, and coronary dissection or other pathological conditions to explain the observed pattern of temporary left ventricular dysfunction (eg, myocarditis, hypertrophic cardiomyopathy)
4. New and reversible ECG abnormalities (ST-segment elevation, ST depression, left bundle branch block, T-wave inversion, and/or QT prolongation) during the acute phase (3 months)
5. Significantly elevated serum natriuretic peptide (BNP or NT-proBNP) during the acute phase
6. Usually positive but relatively small elevation in cardiac troponin measured with a conventional assay (ie, disparity between the troponin level and the amount of dysfunctional myocardium present)
7. Recovery of ventricular systolic function on cardiac imaging at follow-up (3-6 months)

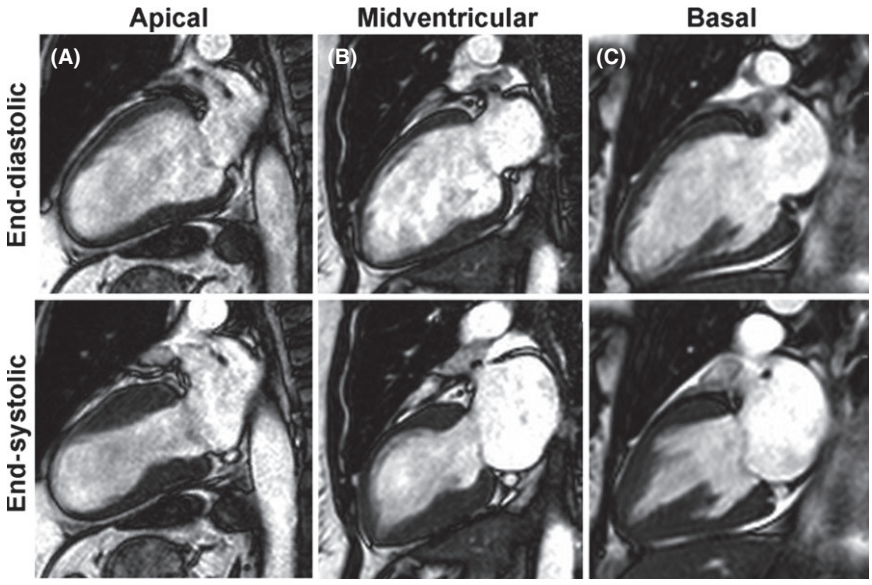

FIGURE 1 Ballooning patterns in patients with Takotsubo syndrome. End-diastolic (top) and end-systolic (bottom) images from steady-state free precession cardiac magnetic resonance (CMR) images in 2-chamber view of a patient with Takotsubo syndrome (TTS) with apical (A), midventricular (B), and basal ballooning (C)

mediation might be microvascular dysfunction with subsequent myocardial stunning.[11–13] However, the concept is not entirely conclusive as stressful triggers are not always present, and microcirculatory dysfunction might also occur secondarily due to impaired left ventricular function.[14] The natural course of TTS with complete recovery of ventricular function initially led to the assumption of a favorable prognosis. In the meantime, it has been shown convincingly that the prognosis of TTS is much worse than expected. Current data indicate that the short- and long-term mortality of patients with TTS is similar or even higher than that in patients with myocardial infarction.[15–17] Both cardiovascular and noncardiovascular causes contribute to the detrimental prognosis of patients with TTS.[16] While long-term mortality seems to be driven by noncardiovascular deaths (eg, due to malignancies), short-term mortality results predominantly from cardiovascular deaths.[18,19] During the acute phase, patients with TTS are prone to severe complications including cardiac decompensation with pulmonary edema, cardiogenic shock, dynamic obstruction of the left ventricular outflow tract, left ventricular thrombus formation, or life-threatening arrhythmias.[20–22] Ventricular arrhythmias (VA) specifically represent an important factor for morbidity and mortality in patients with TTS and are both a therapeutic challenge and a target.[22,23] This article reviews the prevalence, underlying mechanisms, prognostic implications, and management strategies of VA in patients with TTS.

2 | PREVALENCE AND PROGNOSTIC RELEVANCE OF ARRHYTHMIAS IN TAKOTSUBO SYNDROME

Arrhythmic events in patients with TTS have been recognized for many years and include asystole, pulseless electrical activity, complete sinoatrial and atrioventricular block, ventricular tachycardia (VT), and ventricular fibrillation (VF).[17,20,22–32] However, initial data were mostly limited to single case reports or small retrospective evaluations, which impeded valid estimates of the exact prevalence. A large prospective evaluation reported life-threatening arrhythmias (asystole, complete atrioventricular block, VT, VF) in 13.5% of TTS cases, whereby VA accounted for about 10% of all cases.[22] Therefore, the true burden of VA in TTS has largely been underestimated for many years, which is illustrated in a review of literature showing prevalence rates as low as 2% (Table 2). Frequency data of arrhythmias in our large, multicenter TTS registry, particularly regarding VA, are provided in Figure 2 and prove that rates are at

TABLE 2 Prevalence of ventricular arrhythmias[a] in Takotsubo syndrome—review of literature

Reference	Number of patients	Study design	Prevalence (%)
Tsuchihashi et al[24]	88	Retrospective	8
Kurisu et al[25]	30	Retrospective	3
Elesber et al[26]	100	Retrospective	2
Syed et al[27]	816	Literature review	3
Madias et al[28]	93	Retrospective	9
Pant et al[29]	16 450	NIS-analysis	4
Migliore et al[30]	61	Prospective	5
Murakami et al[31]	107	Retrospective	3
Schneider et al[20]	209	Retrospective	8
Templin et al[17]	1750	Retrospective	3[b]
Sharkey et al[32]	249	Retrospective	2[c]
Stiermaier et al[22]	178	Prospective	10
Stiermaier et al[23]	286	Retrospective	8

NIS, Nationwide inpatient sample.
[a]Ventricular arrhythmias include VT and VF.
[b]Only data concerning VT provided.
[c]Only data concerning VF provided.

the upper end of the reported prevalence.[23] VF comprises about one-third of VA and is frequently the first documented heart rhythm in patients with TTS requiring cardiopulmonary resuscitation. The majority of ventricular events in TTS are sustained and nonsustained VT.[22] In particular, polymorphic VT in the setting of QT prolongation (torsade de pointes) has been documented repeatedly.[30] However, a considerable number of monomorphic VT in patients with normal QT duration has been reported as well.[22] The presence of a J wave was identified as an indicator for the occurrence of VT in TTS and might help to identify patients with increased risk for arrhythmias.[33]

The occurrence of VF or VT has been clearly linked to worsened survival in patients with TTS, not only during acute stages of the disease, but also in the convalescent phase.[22] Among the different types of VT, persistence of arrhythmia is obviously a crucial factor given the higher mortality in sustained compared with nonsustained VT. Furthermore, monomorphic rather than polymorphic VT seems to contribute notably to increased mortality.[22]

3 | MECHANISMS OF VENTRICULAR ARRHYTHMIAS IN TAKOTSUBO SYNDROME

The predominant mechanisms underlying most VA are reentry, triggered activity, and abnormal automaticity.[34] Potential substrates and explanatory approaches for these mechanisms in patients with TTS are now discussed.

3.1 | Reentry

Reentry is the most prevailing mechanism of VA, particularly monomorphic VT, in the context of structural heart disease.[34] Patients with certain cardiomyopathies (eg, ischemic, hypertrophic, or infiltrative) or myocarditis exhibit myocardial damage with fibrosis and scar formation. The myocardium surrounding scars and fibrotic areas is characterized by relatively slow and discontinuous electrical conduction creating an electrophysiological and anatomical substrate for reentrant arrhythmias.[34] However, TTS is a nonischemic disease and CMR imaging studies demonstrated the absence of significant late gadolinium enhancement, the noninvasive reference standard for visualization of scarring/fibrosis.[1] Therefore, an anatomical substrate for reentry in TTS is not directly evident. A closer look, however, shows that patchy late gadolinium enhancement can be found in about 9% of patients with TTS when the commonly used threshold of signal intensity is slightly lowered.[1] Another study confirmed late enhancement in some patients with TTS and found a disproportionate increase in extracellular matrix (collagen-1) as a possible correlate in endomyocardial biopsies.[35] Although both studies reported the lack of late gadolinium enhancement on follow-up CMR imaging,[1,35] it might represent an arrhythmic substrate during the acute/subacute phase of TTS. Furthermore, electrophysiological heterogeneities causing functional reentry without a classic anatomical substrate must be considered as well. Extensive myocardial edema throughout the entire myocardium affected by contraction abnormalities is a typical finding in the

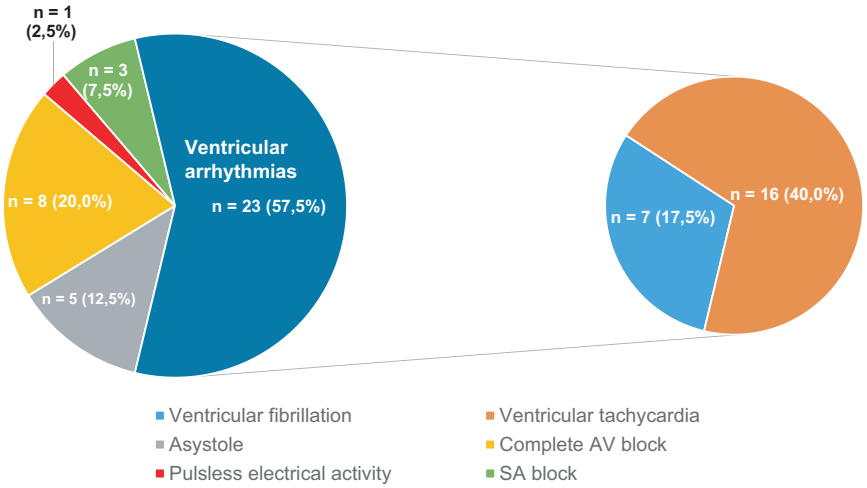

FIGURE 2 Prevalence of arrhythmias in Takotsubo syndrome. Frequency of arrhythmias in a large multicenter Takotsubo syndrome (TTS) population. Among the investigated 286 patients with TTS, 35 individuals experienced arrhythmias, with multiple arrhythmias occurring in 5 patients. VT and VF accounted for about two-thirds of the arrhythmic events. AV, atrioventricular; SA, sinoatrial

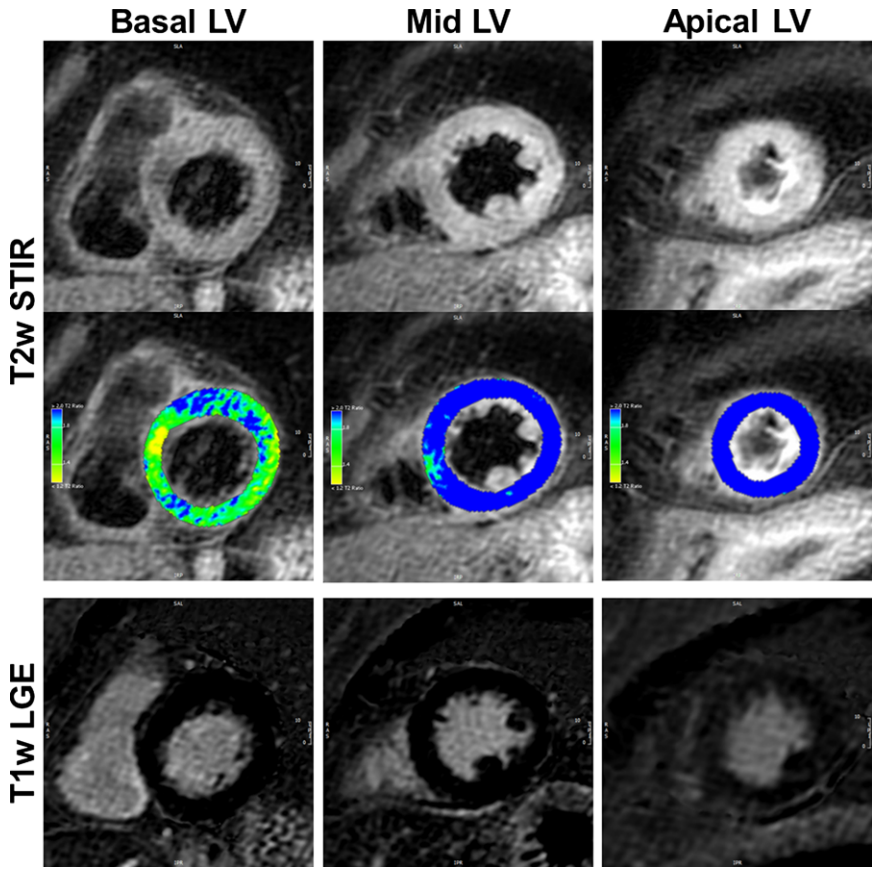

FIGURE 3 Cardiac magnetic resonance tissue characteristics in Takotsubo syndrome. Cardiac magnetic resonance (CMR) imaging in a patient with typical apical Takotsubo syndrome (TTS). T2-weighted short tau inversion recovery images (top row) demonstrating normal signal intensity of the basal myocardium but global edema of the mid and apical segments with impaired systolic function. Computer-aided signal intensity analysis of the edema images (middle row; blue indicates a signal intensity ratio of myocardium to skeletal muscle ≥1.9 equivalent to edema; green/yellow indicates a normal signal intensity ratio < 1.9). T1-weighted late gadolinium enhancement images (bottom row) demonstrating an absence of significant scarring/fibrosis. LV, left ventricle; T1w LGE, T1-weighted late gadolinium enhancement; T2w STIR, T2-weighted short tau inversion recovery

majority of patients with TTS (Figure 3).[1] These edematous areas could induce electrical alterations similar to those previously described in acute myocarditis and myocardial infarction.[36–38] Consequently, the coexistence of myocardial areas with different electrical conductivities might predispose to VA due to functional reentry.

3.2 | Triggered activity

Electrical inhomogeneity is also reflected in the multifaceted and dynamic ECG abnormalities in patients with TTS. A characteristic pattern of repolarization changes has been described,[39] although not all phases are documented in every patient with TTS depending on the time of ECG recording after symptom onset. Accordingly, the initial phase is characterized by ST-segment elevations, followed by giant T-wave inversions that persist for several weeks until recovery (Figure 4).[39] Analogously to the left ventricular contraction abnormalities, the ECG findings cannot be assigned to the supply area of a single coronary artery in patients with TTS. A strong correlation between myocardial edema and the extent of repolarization abnormalities has been reported, which suggests a causal

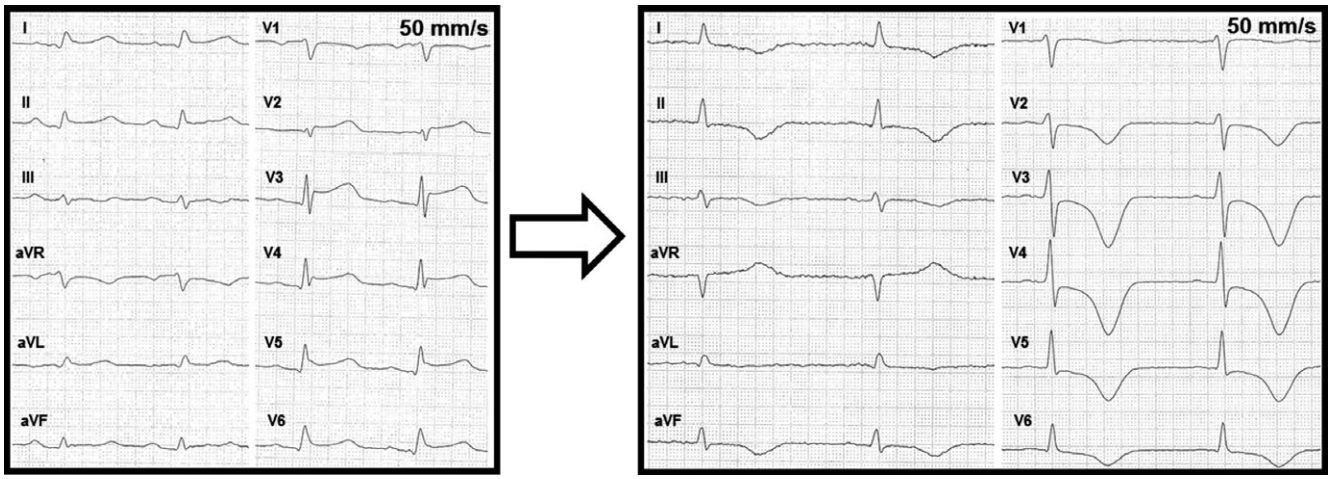

FIGURE 4 Dynamic repolarization changes during acute Takotsubo syndrome. A 75-year-old female patient with Takotsubo syndrome (TTS) presented with ST-segment elevations that converted to giant T-wave inversions 2 days after admission

association.[38,40,41] Furthermore, microcirculatory dysfunction might contribute, to some extent, to repolarization changes. Importantly, the deep T-wave inversions are often accompanied by substantial QT interval prolongation (Wellens' sign).[38] The amplitude of the negative T-wave has been directly correlated with the duration of the QT interval in TTS, both of which peaked on day 3 after admission in a small single-center evaluation. Sympathetic activity and catecholamines, which are presumably major factors in TTS, further impact QT duration.[34] QT interval prolongation has been reported in a considerable number of patients with TTS in various cohorts, which led to the disease being considered a form of acquired long-QT-syndrome.[25,30,39] Consequently, early afterdepolarization-induced triggered activity in the setting of prolonged action potentials is a conceivable mechanism of arrhythmias in TTS, particularly polymorphic VT/torsade de pointes. Moreover, catecholamine excess can promote delayed afterdepolarization-induced triggered activity by causing intracellular calcium overload.[34]

3.3 | Abnormal automaticity

Nonpacemaker myocardial cells usually do not show spontaneous activity, but can exhibit abnormal automaticity under certain conditions. This mechanism is thought to play a role in catecholamine-induced arrhythmias and therefore might also cause VA in patients with TTS.[34]

3.4 | Final considerations

All of the abovementioned mechanisms are conceivable contributors to the occurrence of VA in TTS, although the impact is likely to vary over the clinical course of the disease. In view of the presumed causal association with the onset of TTS, catecholamines and sympathetic activity seem to be particularly important factors in very early arrhythmic events. In contrast, structural myocardial alterations and repolarization disturbances evolve over several hours/days and seem to play a major role during this period. As complete recovery of myocardial edema and QT interval normalization occurs over several weeks, ongoing increased risk of VA must be assumed until complete recovery of all alterations. However, one should not forget the possibility that TTS might have emerged secondarily due to heart rhythm disease in patients with preexisting disorders (eg, long-QT-syndrome, catecholaminergic polymorphic VT, or arrhythmogenic right ventricular cardiomyopathy).

4 | CLINICAL MANAGEMENT AND THERAPEUTIC STRATEGIES

4.1 | ECG monitoring and electrolyte balance

As VA contribute considerably to morbidity and mortality in patients with TTS,[22] awareness of this potential complication is critical for early detection and the immediate initiation of appropriate treatment strategies. Indeed, a recently published position statement recommends continuous ECG monitoring at coronary care units for at least 24 hours in all patients with suspected TTS.[2] Furthermore, 12-lead ECG recording should be regularly performed to document the dynamic repolarization changes associated with TTS and to assess QT interval duration. In the case of additional risk factors for arrhythmias (eg, preceding syncope, ongoing severe impairment of left ventricular function, or QT prolongation), monitoring should be extended individually.[2]

Electrolyte imbalances can trigger the occurrence of arrhythmic events. Hence, electrolyte levels (especially potassium) should be routinely checked in patients with TTS and corrected to normal values if necessary.

4.2 | Pharmacotherapy

The current literature does not provide much evidence-based data on drug therapy in TTS or the best strategy to treat or prevent arrhythmias.[42] In the absence of concrete recommendations, patients with TTS usually receive standard heart failure treatment. Beta-blockers are used frequently based on the assumption of enhanced sympathetic activity in these patients. Presumably, beta-blockers are also effective for the primary and secondary prevention of VA. Nevertheless, the risk of conduction disorders resulting in relevant bradyarrhythmias as well as bradycardia-induced VT should be considered. Likewise, the use of other antiarrhythmic drugs is not generally recommended and must always be weighed individually against potential side effects. In particular, QT interval prolonging drugs should be avoided given the high prevalence of QT interval prolongation in TTS.

Acceleration of recovery in patients with TTS and with severely reduced left ventricular function might also be a potential strategy to prevent arrhythmias. However, randomized data that would justify general recommendations regarding the use of positive inotropic agents, for example, are missing. Small preliminary studies suggest a potential benefit of the calcium sensitizer levosimendan and the phosphodiesterase-3-inhibitor milrinone in patients with TTS with cardiogenic shock, but this requires validation in future studies.[43,44] Of note, the use of catecholamines (eg, dobutamine or epinephrine) should be avoided whenever possible as they might worsen the clinical course owing to their potential proarrhythmic effects and the presumed causal association of catecholamines with the occurrence of TTS.

4.3 | Permanent device implantation

The need for implantable cardioverter-defibrillators (ICD) in TTS patients with VA is discussed controversially in view of the natural course of the disease with complete recovery of left ventricular function during follow-up. Similarly, repolarization changes and QT interval prolongation have been shown to resolve completely.[39] The arrhythmic risk has also been considered transient as VA occur almost exclusively during the acute and subacute phase.[22] Accordingly, a single-center study reported that 2 patients with TTS who

received an ICD did not require device interventions during long-term follow-up.[30] These data suggest that the risk of complications (eg, bleeding, pneumothorax, device infections, or inappropriate shocks) might outweigh the potential benefits of cardioverter-defibrillator implantation and support a conservative approach.[23] On the other hand, a considerable number of patients with TTS die during follow-up with the circumstances of death remaining unclear.[16] Delayed arrhythmic events cannot be excluded in these patients. Furthermore, monomorphic VT represents a considerable portion of VA in TTS and has been linked to increased mortality.[22] While polymorphic VT could be interpreted in the context of transient QT interval prolongation, the underlying mechanisms of monomorphic VT are less obvious and cannot be clearly attributed to transient factors. More data regarding recurrence of VA in TTS are needed to identify patients who might benefit from ICD implantation. Currently, individualized appraisal is required with consideration of patient characteristics (eg, age, comorbidities), the type of VA, and recovery of left ventricular function and QT interval prolongation. Transient treatment approaches such as wearable cardioverter-defibrillators or transient right ventricular pacing in the case of bradycardia-induced VA could be used to bridge the gap to recovery from TTS and postpone the final decision regarding a permanent ICD to avoid unnecessary device implantation. In this context, it should also be mentioned that the situation appears differently in cases of complete atrioventricular block in patients with TTS. Although some data have suggested the restoration of atrioventricular conduction,[30] in another study, regular device check-ups revealed an ongoing need for ventricular pacing even years after recovery from TTS.[23] These data favor permanent pacemaker implantation, especially in cases of early and persisting high-degree block, and underscore the possibility of TTS occurring secondarily due to heart rhythm disease, which should be included in the therapeutic considerations.

5 | CONCLUSIONS

Ventricular arrhythmic events are frequent and a major determinant of morbidity and mortality in patients with TTS. Awareness of this fact must be increased among treating physicians to ensure appropriate management with continuous ECG monitoring during the acute phase. The underlying mechanisms of VA in TTS seem to involve multiple factors including extensive myocardial edema, repolarization disturbances, catecholamines, and sympathetic overdrive. Evidence-based therapeutic strategies are lacking, and the need for permanent ICDs is a matter of debate in view of the transient nature of the disease. Therefore, comprehensive case-by-case determinations are required until further studies provide a basis for general treatment recommendations.

CONFLICT OF INTEREST

Authors declare no Conflict of Interests for this article.

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