

# Long-term injury after Takotsubo syndrome (stress cardiomyopathy)

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## KEYWORDS

Takotsubo syndrome;  
Prognosis

Takotsubo syndrome is a clinical condition characterized by transient impairment of left ventricular contractility, in association with symptoms, increase in indices of myocardial necrosis, as well as electrocardiographic changes, but without a coronary culprit lesion, and often after a significant psychological or physical stress. Albeit very similar to acute coronary syndrome (ACS) as far as presentation and clinical course, Takotsubo syndrome was considered, up until recently, a condition with very favourable long-term prognosis, in view of the frequent complete functional recovery. More recently, several retrospective observational studies as well as registers, unexpectedly called attention to a significant incidence of major adverse cardiovascular events, not limited to the recovery period but also during the long-term follow-up, in a way very similar to the outcome of patients after ACS. Several negative prognostic factors have been isolated, such as physical stress as trigger of the condition, the presence of severe left ventricular dysfunction, and the consequent cardiogenic shock during the acute phase. These factors are able to classify better the patient's prognosis, both in the short- and long-term, and identify patients requiring a more stringent clinical follow-up, considering the higher likelihood of adverse cardiovascular events.

## Introduction

Takotsubo syndrome (TTS) is a clinical condition characterized by the appearance of transient alterations of left ventricular parietal kinetics in association with symptoms, increased myocardial-cytonecrosis indices, electrocardiogram (ECG) alterations in the absence of a culprit coronary lesion, frequently secondary to significant physical or psychological stress. Even in the presence of a significant risk of in-hospital complications in the acute phase of TTS, the first studies in this regard reported a long-term complete anatomical and functional recovery in the affected patients. Subsequent observations, however, have dispelled this myth, raising worrying data on the real prognosis of this pathology both in the short- and long-term, to the point of equating it with that of acute coronary syndromes (ACS).

## Diagnostic and pathophysiological criteria

Originally described in Japan, over the last few decades, TTS has been widely recognized also in the rest of the world population, especially in the Caucasian ethnicity, representing the final diagnosis in 1-3% of all patients hospitalized for suspected ACS with ST elevation, reaching the 6% in female sex in which it shows a clear prevalence especially in post-menopausal age.<sup>1</sup>

In a recent international consensus document, the distinctive diagnostic criteria of the TTS (InterTAK Diagnostic Criteria) have been published which highlight its peculiar characteristics.<sup>2</sup> The clinical presentation in analogy with the ACS is frequently characterized by chest pain, dyspnoea, or syncope but an accidental diagnosis is not infrequent for the appearance of ECG alterations or positivity of myocardial-cytonecrosis indices especially in forms secondary to physical stress, such as ischaemic stroke.

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Electrocardiogram alterations can be varied (ST elevation, T-wave inversion, QT prolongation, anterior Q waves secondary to electrical stunning, reduced potentials related to oedema, less frequently ST depression, or left bundle branch block occurrence) or rarely missed. The movement of the myocardial-cytonecrosis indexes is generally relatively modest, especially when compared with the extent of kinetic alterations, while there is a significant increase in the atrial natriuretic peptide, result of significant left ventricular dysfunction.

From a physiopathological point of view, hyperactivation of the sympathetic system seems to play a key role in the pathogenesis of TTS.<sup>3</sup> A physical stress (ischaemic stroke, subarachnoid haemorrhage, convulsions, and pheochromocytoma) or emotional stress (generally of negative value but sometimes also positive) is in fact frequently recognized before the TTS, but this condition is not necessary to make the diagnosis.

In a recent publication, Pelliccia *et al.*<sup>4</sup> highlighted the marked differences between TTS and cardiomyopathies, on the contrary underlining the points in common with ACS both in terms of clinical presentation and prognosis, suggesting the use of the term 'Takotsubo (stress) syndrome' rather than 'stress cardiomyopathy' as previously suggested by international guidelines.

As for the ventricular kinetics, the most typical form is characterized by the appearance of dyskinesia of the mid-apical portions with preservation of the basal segments, so as to remind, in systole, the shape of the vessel used in Japan for the capture of the octopus from which the syndrome takes its name (*Figure 1*), but there may be other types of distribution of the dyskinetic areas (mid-ventricular, basal or focal, or finally of the right ventricle) generally, but not necessarily, with a distribution that extends beyond the tributary area of a single epicardial coronary artery. The alterations of mid-apical kinetics with compensatory hyperkinesia of the basal portions may not infrequently favour the development of a dynamic sub-valvular aortic gradient [left ventricular outflow tract obstruction (LVOTO), described in up to 20% of cases], especially in the presence of septal hypertrophy, sometimes associated with systolic anterior motion (SAM) of the anterior mitral leaflet resulting in significant mitral insufficiency.<sup>5</sup>

The diagnosis of TTS almost invariably passes through the execution of coronary angiography to exclude the presence of ACS, except in haemodynamically stable patients, without ECG signs of ST-segment elevation and with circular distribution of dyskinesia at echocardiogram in which it can be performed in alternative the coronary computed tomography. The finding of a coronary artery disease (CAD) especially if not territorially overlapping with the alterations of the left ventricular kinetics does not exclude the diagnosis of TTS. If myocarditis is suspected in the diagnostic work-up, cardiac magnetic resonance (MR) is also indicated for the differential diagnosis.

### In-hospital prognosis

The well-established belief of a likely benign in-hospital course of TTS has been questioned by the evidence provided by extensive observational studies.

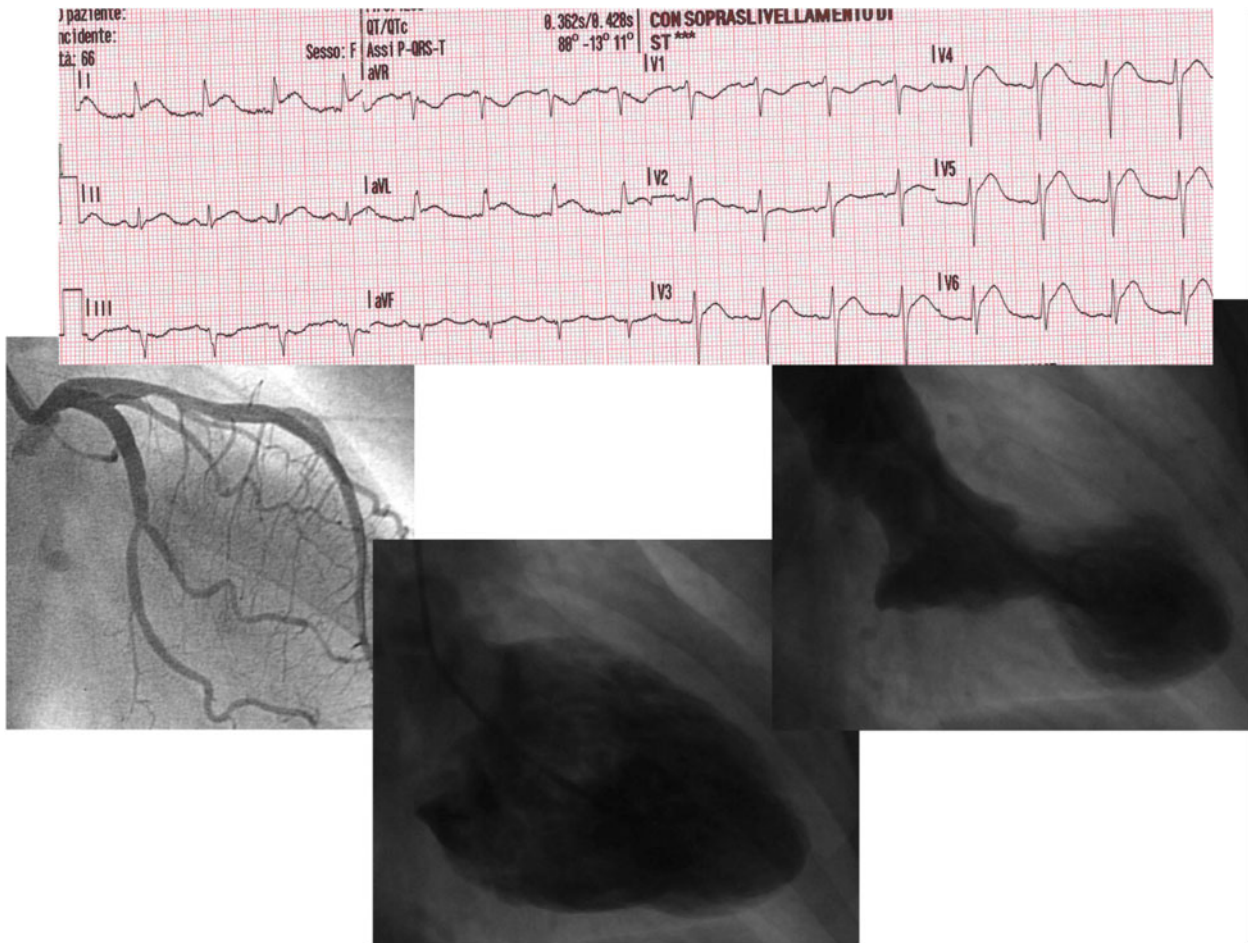
Brinjikji *et al.*<sup>6</sup> documented an incidence of in-hospital mortality of 4.2% in 24 701 patients with TTS. In this study, the male sex was correlated to a significant increase in mortality (8.4 vs. 3.6%,  $P < 0.0001$ ), partly due to a more frequent coexistence of other critical illnesses in males suffering from TTS compared to females (36.6% vs. 26.8%,  $P < 0.0001$ ). The correlation between mortality and physical stress was confirmed by Sobue *et al.*<sup>7</sup> in a subsequent study of 1800 patients with suspected ACS, 4.6% of whom with confirmed diagnosis of TTS, in which mortality was independently and statistically significant correlated with male sex and physical stress.

Templin *et al.*<sup>8</sup> published a large multicentre observational study on in-hospital events in 455 subjects diagnosed with TTS comparing them with 455 patients with similar characteristics admitted for ACS, without documenting any significant difference in terms of cardiogenic shock (12.4 vs. 10.5%,  $P = 0.39$ ) and total mortality (3.7 vs. 5.3%,  $P = 0.26$ ). In this study, the in-hospital prognosis was also analysed in a larger population of 1750 patients admitted with TTS diagnosis. In about one-fifth of patients (21.8%), there were major in-hospital clinical events (including ventricular tachycardia in 3%, left endoventricular thrombosis in 1.3%, and heart rupture in 0.2%), with higher incidence in males. Multivariate analysis allowed to identify some independent predictors of poor prognosis: severe left ventricular systolic dysfunction (left ventricular ejection fraction  $< 45\%$ ), physical stress triggers, acute neurological pathology, psychiatric pathology, and elevated troponin levels at admission ( $> 10$  times the upper limit of normal).

In a recent consensus document published by Ghadri *et al.*,<sup>9</sup> the most frequent in-hospital complications of TTS were acute heart failure (12-45%), mitral insufficiency (14-25%), LVOTO (10-25%), and cardiogenic shock (6-20%). Atrial fibrillation (5-15%), left endoventricular thrombosis (2-8%), cardiac arrest (4-6%), and atrioventricular block (5%) are also not infrequent. Finally, *torsade de point* (2-5%), ventricular tachycardia or ventricular fibrillation (3%), heart rupture ( $< 1\%$ ), and death (1-4%) are rarer but not exceptional.

The existence of prognostic differences depending on the site of kinetic alterations was analysed by Ghadri *et al.*<sup>10</sup> in another work derived from the International Takotsubo Registry which compared 1430 patients with apical dyskinesia (typical TTS form) with 320 patients with mid-ventricular, basal, or segmental dyskinesia (atypical TTS form). Despite some epidemiological differences (the atypical form was more frequent in younger subjects, with less compromised left ventricular function, lower levels of atrial natriuretic peptide, and greater prevalence of ST depression), the in-hospital mortality in the two forms was similar (typical forms 4.3% vs. atypical forms 3.1%,  $P = 0.32$ ).

Potentially fatal arrhythmias are concentrated mainly in the first days of hospitalization (2nd-4th day) in conjunction with T-wave inversion and QT elongation, an expression of marked delay and dis-homogeneity of ventricular repolarization present in the first days and corresponding to oedema on cardiac magnetic resonance imaging (MRI). The arrhythmic risk becomes particularly high when the QTc exceeds 500 ms, concurring a condition similar to an



**Figure 1** Electrocardiogram of onset, coronary angiography, and ventriculogram of a patient with typical form of Takotsubo syndrome.

'acquired' long QT syndrome with the consequent possibility of triggering malignant ventricular arrhythmias.<sup>11</sup>

Regarding therapy, Templin *et al.*<sup>8</sup> in a subsequent publication reported high in-hospital mortality in TTS patients treated with catecholaminergic inotropes especially in patients with LVOTO (odds ratio 9.66), although this finding could be burdened by selection bias, while there are other reports in favour of levosimendan, a calcium-sensitizer inotrope that appears to have beneficial effects in this condition.<sup>12</sup> Given the causal role of catecholamines, the use of beta-blockers can have beneficial effects up to the complete recovery of ventricular function, especially in the presence of LVOTO, but it is frequently to be avoided due to excessive bradycardia and lengthening of QT. Nitro-derivatives, useful in the presence of pulmonary congestion, can on the contrary aggravate a pre-existing condition of LVOTO and should be used with caution.

In conclusion, in the acute phase, the TTS is burdened by the same complications as myocardial infarction, with electrical and haemodynamic instability in about one-fifth of the patients, and therefore requires a similar period of clinical and electrocardiographic monitoring in cardiac intensive care unit especially in subjects with additional clinical risk factors.

### Short-term prognosis

Typically, a complete recovery of ventricular function is observed over a period ranging from 4 to 8 weeks.<sup>8</sup> Some cardiac segments may show an earlier recovery than others. Eitel *et al.*<sup>13</sup> in a multicentre study evaluated 158 patients with TTS subjecting them to cardiac MR both baseline and at 1 and 6 months, with evidence of complete functional recovery in all cases without significant residual fibrosis. Parallel to functional recovery, there is a regression of any sub-valvular aortic obstruction and associated mitral insufficiency. Similarly, the gradual attenuation is highlighted up to the disappearance of the repolarization alterations (negative Twaves and prolonged QT).

To assess whether a complete normalization of myocardial structure and function occurred in an apparent full functional recovery in these patients, Schwarz *et al.*<sup>14</sup> conducted an observational study comparing 52 patients with typical TTS (onset with elevated ST or malignant arrhythmias and a classic apical ballooning aspect) and 44 healthy subjects subjecting both groups to echocardiography and cardiac MRI. After a 4-month follow-up compared to a full recovery in terms of parietal kinetics, volumes and ventricular ejection fraction, patients with TTS showed a significant persistent alteration of fine echocardiographic

functional indices, such as longitudinal and radial strain, and the finding at cardiac MRI of an expansion of the extracellular volume, a consequence of a process of extensive myocardial fibrosis.

Stiermaier *et al.*<sup>15</sup> evaluated the short-term mortality in 286 patients admitted for TTS comparing them with an identical number of subjects with acute ST-elevation myocardial infarction (STEMI). At 28 days, the total mortality was comparable in the two groups (total mortality TTS 5.5% vs. STEMI 5.7%;  $P = 0.91$ ).

In the multicentre observational study by Templin *et al.*,<sup>8</sup> in the first 30 days after admission for TTS, there is a high incidence of cardiac-cerebrovascular events including death (3.5%) and transient ischaemic attack/stroke (7.1%), more frequent in male (13.7 vs. 6.3%,  $P = 0.002$ ).

A recent large observational study published by Smilowitz *et al.*<sup>16</sup> evaluated the incidence of hospitalizations within 1 month of discharge in over 61 000 patients with TTS, finding 11.9% of readmissions mainly secondary to heart failure (10.6%), with a peak in the first 2 weeks.

These studies highlight a significant incidence of cardiovascular events in the first month after admission for TTS and the need for close follow-up in the post-acute phase especially in patients with more pronounced ventricular dysfunction.

### Long-term prognosis

A first study published in 2007 by Elesber *et al.*<sup>17</sup> out of 100 patients discharged with a diagnosis of TTS and followed up with for an average of over 4 years, although they found a high incidence of chest pain (31% of patients) and TTS recurrence (11.4% over the entire period) documented an incidence of total and cardiovascular mortality comparable to that expected in the general population. Sharkey *et al.*<sup>18</sup> published an observational study involving 249 patients admitted consecutively for TTS, 19% of whom with a course complicated by electrical or haemodynamic instability. The subsequent follow-up lasting over 4 years showed an excess of mortality compared to the general US population (standardized mortality ratio 1.4;  $P = 0.005$ ) with a peak in the first year after the event (standardized mortality ratio 2.9;  $P < 0.001$ ) and a higher incidence in patients with unstable clinical presentation (26% vs. 7%;  $P < 0.001$ ). Since the increased mortality detected in the follow-up of patients with TTS was mainly secondary to non-cardiac comorbidities, such as cancer and chronic obstructive pulmonary disease, the authors conclude that in these patients TTS could represent a marker of severity of the underlying pathology responsible for excess mortality.

In the study by Templin *et al.*,<sup>8</sup> in 1750 patients with TTS followed up to 10 years, the long-term prognosis was surprisingly burdened by a significant incidence of clinical events: total mortality 5.6%/year (males 12.9%/year, females 5%/year;  $P < 0.001$ ), cardiac and cerebrovascular events greater 9.9%/year (males 16%/year, females 8.7%/year;  $P < 0.002$ ), recurrence of TTS 1.8%/year, so as to reconsider the belief of a long-term favourable prognosis in patients with TTS. In these patients, the prescription at discharge of angiotensin-converting enzyme inhibitors or

angiotensin II receptor antagonists was correlated to a better survival at 1 year ( $P = 0.001$ ), while no significant benefits were found for the use of beta-blockers ( $P = 0.72$ ).

Ghadri *et al.*<sup>10</sup> examined the effects on the prognosis of the different phenotypic variants of TTS through a multicentre study that differentiated 1750 patients between 'typical' (82%) and 'atypical' (18%) without finding differences in the incidence of cardiac major cerebrovascular events (typical TTS 10% vs. atypical TTS 9.2%,  $P = 0.42$ ) nor mortality between the two groups after appropriate adjustments at the multivariate analysis. Independent predictors of mortality remained only the reduced ventricular function (left ventricular ejection fraction  $< 45\%$ ), the presence of atrial fibrillation or neurological pathologies. The authors conclude by emphasizing the need for remote monitoring of 'atypical' forms of TTS, especially in the presence of additional risk factors.

A very recent observational study by Almendro-Delia *et al.*<sup>19</sup> on data derived from the RETAKO Registry in a population of 711 patients admitted with TTS found prevalence of cardiogenic shock of 11.4%. The variables associated with cardiogenic shock were male gender, QT prolongation, a decreased left ventricular ejection fraction at admission, a physical trigger, and a significant left intraventricular gradient. This condition was correlated not only with a higher mortality rate, as expected, but also with an increase in total mortality [hazard ratio (HR) 5.38], cardiovascular (HR 4.29) and non-cardiac (HR 3.29) in the subsequent median follow-up of 284 days. The presence of beta-blocker therapy at discharge was a protective prognostic factor in patients with TTS and cardiogenic shock (HR 0.52).

Several studies have compared the prognosis of patients admitted for TTS with that of patients admitted for ACS, finding comparable results. In the study by Stiermaier *et al.*,<sup>15</sup> long-term mortality was assessed among 286 patients with TTS and 286 with STEMI, finding a clearly worse prognosis in the first group at 3.8 years (total TTS mortality 24.7% vs. STEMI 15.1%;  $P = 0.02$ ) without significant differences in cardiovascular mortality (total TTS mortality 8.5% vs. STEMI 7.9%;  $P = 0.86$ ). The predictors of increased mortality in patients with TTS at multivariate analysis were male sex, the Killip 3-4 class and diabetes mellitus.

Tornvall *et al.*<sup>20</sup> analysing data from a Swedish registry (Swedish Angiography and Angioplasty Register) compared the prognosis in 505 patients with TTS without coronary lesions with 1010 patients with ACS (control group with CAD), 1005 patients without ACS nor coronary lesions (control group without CAD).

In the subsequent follow-up of over 4 years, the total mortality in patients with TTS was higher than in the control group without CAD ( $P < 0.01$ ) and comparable to the control group with CAD ( $P = 0.46$ ). Regarding specifically cardiovascular mortality, patients with TTS had a lower incidence than controls without CAD but greater than those with CAD.

In a recent work, Ghadri *et al.*<sup>21</sup> compared the prognosis of 1613 patients with TTS based on the causal factor, distinguishing between emotional stress (30%), physical stress (39%) (neurological pathologies or other physical stress such as physical activity, medical pathology, or procedure), and 31% of patients in whom a causal factor could not be

**Table 1** Classification of patients with TTS according to the causal factor (InterTAK Classification)<sup>21</sup>

| Causal factor |  |
|---------------|--|
| Class 1       | Emotional stress   |
| Class 2a      | Stress from physical activity, medical, or procedure related |
| Class 2b      | Stress from neurological condition                           |
| Class 3       | No identifiable factors                                      |

identified. Thirty-day mortality was significantly higher in patients with TTS secondary to neurological diseases, while in subjects with TTS secondary to emotional stress was lower. Long-term mortality (over 5 years) has also shown the same tendency according to the causal factor. Compared to patients with emotional stress, HR was 5.76 in patients with neurological diseases and 3.78 in patients with other physical stresses. The comparison with the long-term prognosis in 455 patients with ACS confirmed an overall mortality comparable to patients with TTS ( $P=0.49$ ), with a significant difference between patients with TTS due to emotional stress with a better prognosis and patients with TTS from physical stress that show a much higher mortality. On the basis of these observations, the authors proposed a classification of patients with TTS according to the causal factor (InterTAK Classification) in order to allow a better prognostic stratification (Table 1).

Scally *et al.*<sup>22</sup> investigated the persistence of subclinical symptoms and functional alterations in a case-control study in 37 patients admitted for TTS and followed for more than 1 year. After this interval, the majority of subjects with TTS showed both the persistence of symptoms compatible with heart failure and the functional limitation at the cardiorespiratory exercise test ( $VO_2$  max 24 mL/kg/min vs. 31 mL/kg/min,  $P<0.001$ ). Despite the finding of a normal left ventricular function also in patients with TTS, the persistence of altered indices of cardiac deformation was observed with respect to the control subjects (global longitudinal strain  $-17\%$  post-TTS vs.  $-20\%$  in control;  $P=0.006$ ). The authors conclude by advancing the hypothesis that TTS may lead to persistent impairment of the heart's energy state with consequent persistent functional limitations that may impact quality of life.

## Conclusions

In conclusion, the first theories of a presumed benignity of TTS have been refuted by numerous observational evidences that have assimilated the prognosis of this pathology to that of patients with ACS, both in the acute phase and in the subsequent follow-up despite the apparent full functional recovery. It is likely that within the broad clinical spectrum of TTS there are higher-risk phenotypes characterized by a worse short-term and long-term prognosis, such as those with acute cardiogenic shock. The recognition of the causal factors (triggers) seems to be useful for a short-term prognostic stratification and for the

identification of subjects requiring a closer clinical follow-up in consideration of the greater risk of long-term adverse events.

**Conflict of interest:** none declared.

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