

Pathogenesis of Takotsubo syndrome

Daniele Masarone,¹ Valeria Maddaloni,² Marta Rubino,¹ Fiorella Fratta,¹ Anna Paola Cirillo,¹ Ludovica Spinelli Barrile,¹ Roberta Pacileo,¹ Adelaide Fusco,¹ Guido Coppola,¹ Francesca Pisacane,¹ Paolo Calabrò,¹ Raffaele Calabrò,¹ Eduardo Bossone,³⁻⁵ Maria Giovanna Russo,¹ Giuseppe Pacileo¹

¹Department of Cardiology, Monaldi Hospital, Second University of Naples;

²Genomic and Cellular Lab, Monaldi Hospital, Second University of Naples;

³Heart Department, San Giovanni di Dio e Ruggi d'Aragona University-Hospital, Salerno; ⁴Cardiology Division, Cava de' Tirreni and Amalfi Coast Hospital, Heart Department, University of Salerno, Cava de' Tirreni (SA); ⁵Cardiac Surgery Department, IRCCS Policlinico San Donato, San Donato Milanese (MI), Italy

Abstract

Takotsubo syndrome (TTS) is an enigmatic disease with a multifactorial and still unresolved pathogenesis. Postulated mechanisms include catecholamine excess, coronary artery spasm, and microvascular dysfunction, however catecholamines seem to play a central role in the pathophysiology of TTS. In fact catecholamines have relevant effects on the vasculature and myocardium. Toxic direct effects of catecholamine on myocardium are mediated by multiple pathway including functional hypoxia, metabolic changes and changes in membrane permeability leading to various electrolytic imbalances. Recently report of familial cases has suggested a genetic component. Further research is required to help clarify the proposed hypotheses and to increase our understanding of the cardiovascular responses to acute stress and the pathophysiology underpinning TTS.

There are more things in heaven and earth... than are dreamt of in your philosophy
Modified from: *Hamlet (1.5.167-8)*, *Hamlet*
to Horatio
William Shakespeare

During the past two decades, a novel cardiac syndrome with transient left ventricular systolic dysfunction has been reported.¹⁻²

Often referred to as Takotsubo syndrome

(TTS), owing to the shape and appearance of the left ventricle at end systole resembling a Japanese octopus fishing pot during the acute phase, this disorder is also termed stress cardiomyopathy, apical ballooning, and broken heart syndrome.³

TTS syndrome is classified as both a primary and an acquired cardiomyopathy by the American Heart Association (AHA),³ and as an unclassified cardiomyopathy by the European Society of Cardiology (ESC).^{4,5} Whether this disorder represents a true cardiomyopathy remains to be determined.

In the meantime, according to recent position paper of Heart Failure Association (HFA),⁶ this entity should be clinically labeled as an acute, reversible, heart failure syndrome.

The etiology of TTS remains a subject of investigation.

Observational data in patients with subarachnoid hemorrhage,⁷ reports of its occurrence in patients with pheochromocytoma, and its reproduction by infusion of epinephrine in primates⁸ strongly support the hypothesis that it is caused by excessive adrenergic/catecholamine stimulation.⁹ Alternative hypotheses include myocardial ischemia from multi-vessel coronary spasm,¹⁰ transient atherosclerotic plaque rupture¹¹ and transient left ventricular outflow tract obstruction.^{12,13}

Moreover, recent report of familial cases has suggested a genetic component.¹⁴

In this review, we discuss the pathophysiological concepts at the basis of this novel acute heart failure syndrome.

Definition

Diagnostic criteria for TTS have been proposed from several centers, using various diagnostic definition.^{6,15,16}

A detailed description of the diverse definition is behind the scope of this review; however in Table 1^{6,15,16} we summarized the diagnostic criteria more frequently used in clinical practice.

Pathophysiology

The pathophysiology of TTS is complex and reflects the integrated and systemic physiological responses to stress and the cardiovascular responses to sudden surges of catecholamines.¹⁷

The role of catecholamines seems to be central to the pathophysiology of TTS, and leads to multiple potentially relevant direct and indirect effects on the systemic vasculature, coronary vasculature, and myocardium.¹⁸

The pathophysiology of TTS can be divided

Correspondence: Daniele Masarone, Department of Cardiology, Monaldi Hospital, AORN dei Colli, Second University of Naples, via L. Bianchi, Naples 80100, Italy.
E-mail: danielemasarone@libero.it

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in two phases (Figure 1).

The first starts with increased release of catecholamines, initiated by the activation of the hypothalamic-pituitary-adrenal axis in response to a physical and emotional stress (flight to fight response).¹⁹

The second phase is the cardiovascular response to surge in circulating catecholamines.

Several hypotheses have been proposed to explain the unique cardiac appearance in TTS and the cardiac response to severe stress.²⁰

Many of these hypotheses are still being investigated, as there is no current proven pathophysiological mechanism to explain TTS (Table 2).

Catecholamine-mediated myocardial stunning

Several features of TTS, including its association with physical or emotional stress, suggest that this disorder may be caused by diffuse catecholamine-induced myocardial stunning. Support for a possible pathogenic role for catecholamines comes from studies in which plasma catecholamines were measured at presentation.

Wittstein et al found that the serum catecholamine concentration was two to three times greater in patients with TTS than that in patients with acute coronary syndrome.²¹

It has been reported that exogenously administered catecholamines,²² pheochromocytoma²³ and acute brain injury²⁴ cause similar reversible myocardial dysfunction.

In addition, myocardial biopsies of patients with TTS demonstrate typical features of catecholamine toxicity (accumulation of glycogen

in cytoplasm of myocytes, disorganization of contractile and cytoskeletal proteins, and an increased extracellular matrix) which nearly complete reversibility at 2 weeks;²⁵ and the peculiar distribution of the condition may be explained by the greater adrenergic receptor subtype density at the apex of the heart in comparison with the basal myocardium.²⁶⁻²⁹

Multiple mechanisms have been postulated to explain the cardiotoxicity of catecholamines³⁰ (Table 3).

The overstimulation of catecholamine receptors enhances cardiac contractility and heart rate, with secondary increase in myocardial oxygen demand that may outweigh oxygen delivery, creating areas of functional hypoxia

which can be exacerbated by vasoconstriction in the coronary macro- and micro-circulation and which reduce the supply of high energy phosphates.³¹

The later can be further aggravated by metabolic changes, such as the stimulation of lipolysis with deposition of neutral lipid droplets in cardiomyocytes resulting in an uncoupling of oxidative phosphorylation.³²

Changes in membrane permeability leading to various electrolytic imbalances, disturb multiple cellular homeostatic processes fostering additional myocardial toxicity.³³

Finally, Martin and coll. showed decreased reactive hyperemia in response to mental stress in patients with prior TTS;³⁴ these find-

ing suggest that vasomotor dysfunction is involved in the pathogenesis of this unique syndrome.

Coronary artery and microvascular spasm

Coronary artery spasm, including epicardial coronary spasm, microvascular spasm, or direct coronary injury, has been suggested as one of the triggering mechanisms of TTS.^{35,36}

Ibanez and colleagues suggested a common etiology in TTS syndrome and acute myocar-

Table 1. Diagnostic criteria for Takotsubo syndrome.

Mayo Clinic modified criteria (Prasad, 2008)¹⁵

Transient hypokinesis, dyskinesis, or akinesis of the left ventricular mid segments, with or without apical involvement; the regional wall-motion abnormalities extend beyond a single epicardial vascular distribution, and a stressful trigger is often, but not always, present

New electrocardiographic abnormalities (either ST-segment elevation and/or T-wave inversion) or modest elevation in cardiac troponin level

Absence of obstructive coronary disease or angiographic evidence of acute plaque rupture

Absence of pheochromocytoma or myocarditis

Italian Network criteria (Parodi, 2014)¹⁶

Typical transient LV wall motion abnormalities extending beyond a single epicardial vascular distribution with complete functional normalization within 6 weeks

Absence of potentially culprit coronary stenosis, or angiographic evidence of acute plaque rupture, dissection, thrombosis or spasm

New and dynamic ST-segment abnormalities or T-wave inversion as well as new onset of transient or permanent left bundle branch block

Mild increase in myocardial injury markers (creatine kinase-MB value <50 U/L)

Clinical and/or instrumental exclusion of myocarditis

Post-menopausal woman (optional)

Antecedent stressful event (optional)

Heart Failure Association criteria (Lyon, 2016)⁶

Transient regional wall motion abnormalities of left ventricle or right ventricle, which are frequently, but not always, preceded by a stressful trigger (emotional or physical)

The regional wall motion abnormalities usually extend beyond a single epicardial vascular distribution, and often result in circumferential dysfunction of the ventricular segments involved

The absence of culprit atherosclerotic coronary artery disease including acute plaque rupture, thrombus formation, and coronary dissection or other pathological conditions to explain the pattern of temporary left ventricle dysfunction observed (*e.g.*, hypertrophic cardiomyopathy, viral myocarditis)

New and reversible electrocardiography abnormalities (ST-segment elevation, ST depression, left bundle branch block, T-wave inversion, and/or QTc prolongation) during the acute phase (3 months)

Significantly elevated serum natriuretic peptide (BNP or NT-proBNP) during the acute phase

Positive but relatively small elevation in cardiac troponin measured with a conventional assay (*i.e.*, disparity between the troponin level and the amount of dy functional myocardium present)

Recovery of ventricular systolic function on cardiac imaging at follow-up (3-6 months)

Table 2. Summary of proposed pathophysiological hypothesis and of predisposing factor for Takotsubo syndrome.

Pathophysiological hypothesis	Catecholamine-mediated myocardial stunning Multivessel epicardial coronary artery spasm Coronary microvascular dysfunction Left ventricular (LV) outflow tract obstruction and abnormal LV-arterial coupling Acute atherosclerotic plaque rupture in the left anterior descending coronary artery
Predisposing factor	Postmenopausal hormonal status Thrombophilic status Genetic polymorphism

dial infarction secondary to left anterior descending artery occlusion, because cardiac ventriculography findings are identical.³⁷

The same investigators also documented the presence of plaque rupture on intravascular ultrasonography of the left anterior descending coronary artery of patients with angiographically non obstructive coronary artery disease and a diagnosis of TTS.³⁸

However, this mechanism does not entirely explain the extent of regional wall-motion abnormality seen in those without a wrap-around left anterior descending coronary artery, the presence of right ventricular dysfunction, and the preservation of apical function that occurs in some patients.

It is therefore unlikely that vasospasm and atherothrombosis of a single artery underlie TTS in most patients.

The possibility of myocardial injury attributable to microvascular spasm has also been suggested.³⁹

The characteristics of microvasculature dysfunction after acute psychological stress in patients with TTS include abnormality of endothelium-dependent vasodilation, excessive vasoconstriction, and impairment of myocardial perfusion.⁴⁰⁻⁴²

According to some reports, increased susceptibility to ergonovine or acetylcholine followed by large vessel spasm, similar to vasospastic angina, may contribute to transient left ventricular (LV) dysfunction.⁴³ In addition, using an intracoronary Doppler wire technique, Ako and colleagues demonstrated microcirculatory impairment during transient left ventricular dysfunction.⁴⁴

Transient and reversible coronary microcirculation dysfunction has been also demonstrated using noninvasive transthoracic Doppler echocardiography.⁴⁵

However, because only 30% of patients showed the characteristics of vasospasm in a challenge test and the histopathological features of endomyocardial biopsy samples taken from patients with TTS show patterns of myocardial abnormalities not associated with infarcted, stunned, or hibernating myocardium, a primary vascular cause for TTS, seems unlikely.

Left ventricular outflow tract obstruction

Obstruction of the left ventricular outflow tract (LVOT) has been reported in about 10-15% of patients with TTS (particularly elderly women), associated with increased midseptal thickness, systolic anterior motion of the mitral valve, and mitral regurgitation.⁴⁶

In the presence of increased catecholaminergic tone, this feature could lead to the devel-

opment of severe, transient LV midcavity obstruction, mimicking hypertrophic obstructive cardiomyopathy.⁴⁷ However, it is likely that LVOT obstruction is a consequence rather than a cause of stress cardiomyopathy, as anteroapical ballooning is extremely rare in other situations where LVOT obstruction is common.

cardioprotective substances such as atrial natriuretic peptide and heat-shock protein 70, with prevention of stress and catecholamine-induced LV dysfunction.⁴⁸

Kuo and colleagues proposed that lack of estrogen replacement in the postmenopausal state may predispose women to TTS.⁴⁹

Postmenopausal hormonal status

The female predominance of TTS has raised the possibility that estrogen may have a role in the pathogenesis of this syndrome.

In a rat model of TTS, Ueyama demonstrated that chronic estrogen supplementation blunted the stress-induced sympathoadrenal outflow from the brain to the heart and upregulated

Thrombophilic status

A whole proteome analysis performed on serum samples was performed on 9 TTS patients, in a comparison with 12 patients with acute coronary syndrome and 13 control patients. Proteomic evaluation revealed differences in fibrinogen g-chain isoforms and fibrin b chains, whose level was increased in TTS

Table 3. Mechanism of catecholamines induced cardiotoxicity.

Action	Effects
Coronary vasoconstriction	Reduced O ₂ delivery
Microvascular spasm	Reduced O ₂ delivery
Increased heart rate	Increased O ₂ demand
Increased contractility	Increased O ₂ demand
Metabolic changes	Reduced ATP production
Change membrane permeability	Induction apoptotic pathway

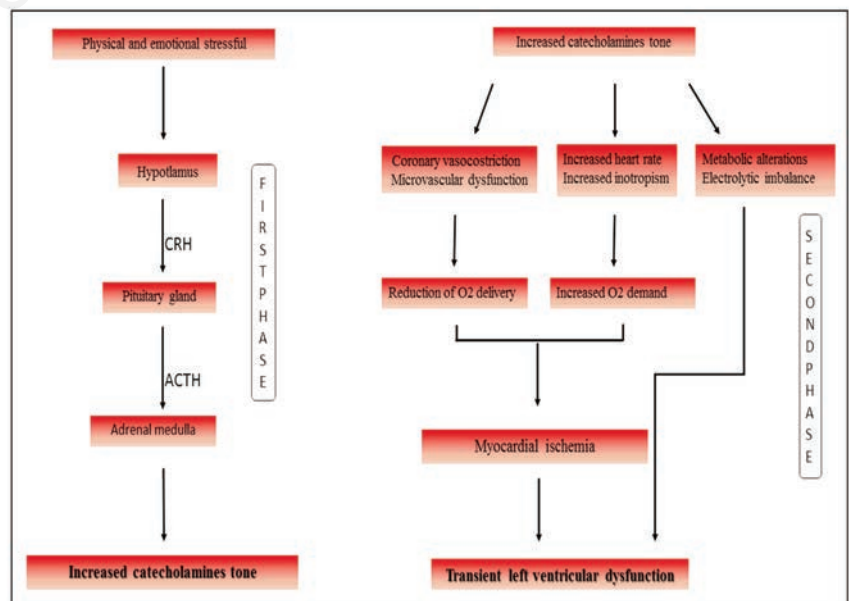


Figure 1. Pathophysiology of Takotsubo syndrome. CRH, corticotropin releasing hormone; ACTH, adreno corticotropic hormone.

patients compared with acute coronary syndrome patients and controls. Fibrinogen has a key role in fibrin formation and its action is influenced by thrombin, leading to plasma coagulation and platelet aggregation through glycoprotein IIb/IIIa receptors.

The biological activity of fibrinogen isoforms in TTS patients might reflect an activation of the intrinsic clotting cascade.⁵⁰

However, in the recent published TROTA study (Thrombophilia in Takotsubo cardiomyopathy)⁵¹ Cecchi *et al.* documented that prevalence of thrombophilic disorders in patients with TTS was similar to controls, therefore the role of thrombophilic disorder as predisposing factor of this syndrome seems unlikely.⁵²

Genetic susceptibility

The stressful trigger implies that the pathophysiology of TTS has a strong environmental component. However, it is conceivable that some people have a genetic predisposition to stress-induced TTS. Although the syndrome is not considered a primary genetic cardiomyopathy, a number of studies have explored the possibility of genetic risk factors.

A genetic predisposition has been suggested based on the few familial TTS cases described.^{53,54}

The genetics of TTS is still vastly unknown, and possible polygenic mechanisms and the strong environmental component make difficult a rapid framing.

In fact, many of the genetic studies conducted so far, but targeted to individual genes, lead to discordant results⁵⁵ and this can be probably because the genetic network of the adrenergic signaling is extremely large.

In 2011 Vriza *et al.* analyzed the larger population of TTS patients described so far. By analyzing 61 patients and 109 control subjects they found for the first time a strong association between the presence of the malignant homozygous Arg389 polymorphism in the adrenoceptor 1 and Takotsubo phenotype.⁵⁶

Another polymorphism that has been associated to TTS is L41Q polymorphism of the G protein coupled receptor kinase 5, in fact Spinelli *et al.* found in a cohort of 22 patients with TTS a higher prevalence of the leucine over the glutamine variant at amino acid 41 of GRK5 non catalytic regulatory domain.⁵⁷

Other authors focused their attention on a peculiar aspect of the Takotsubo phenotype. In 2013 Citro *et al.* focused on impaired endothelium-dependent vasodilation, excessive vasoconstriction and increased sympathetic activation after acute mental stress observed in TTS

patients. They analyzed a population of 29 patients and more than 1000 healthy controls for the presence of mutations in the protein Bcl2-associated athanogene 3 (BAG3).

This protein is expressed in only a few cell types, including cardiomyocytes: among its functions, it mediates the cellular response to stress. Sanger sequencing analysis found the presence of R71Q variation in two patients, one male and one female, and its total absence in large control population. Another variant, P407L, was present in two female patients. The two variants they found may have a role in triggering apoptosis in endothelial cells of coronary vessels and thus in the pathology of TTS.⁵⁸

The first study, not without limitations, that performed a whole-exome sequencing for genes related to catecholamines and adrenergic signaling was carried out on 28 TTS patients including a mother-daughter pair and five recurrent cases.⁵⁹

Authors identified malignant variants in 55 candidate genes, no homozygous or compound heterozygous and therefore excluded a recessive transmissibility in these patients; among these, 7 genes were common variants in more than one patient in the population analyzed.

About 93% of the patients had at least a malignant variant, and the finding of the same variants in the control population could be readily accepted by having the basic information of how the environmental influence is decisive in the development of this phenotype.⁶⁰

Given the extremely low power for studies of this size in detecting an effect of a common polymorphism, further studies with high-quality phenotyping, and sharing high-number/high-quality data in a TTS network will be necessary to estimate the potential role of the genetics as predisposing factor in TTS.^{61,62}

Conclusions

TTS is an enigmatic disease with a multifactorial and a still unresolved pathogenesis.

To explain transient myocardial damage many mechanisms have been proposed, including myocardial dysfunction mediated through catecholamine induced damage, coronary artery spasm or dysfunction, and transient left ventricular outflow tract obstruction.⁶³ Therefore, it remains much to learn regarding the underlying pathophysiology of this condition in order to improve diagnostic and treatment pathways. Further research is required to help clarify the hypotheses discussed and to increase our understanding of the cardiovascular responses to acute stress and the pathophysiology underpinning TTS.

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