**Pathophysiology of Takotsubo Syndrome**

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**ABSTRACT**

Originally described by Japanese authors in the 1990s, Takotsubo Syndrome (TTS) generally presents as an acute myocardial infarction characterized by severe left ventricular (LV) dysfunction. TTS, however, differs from an acute coronary syndrome because patients have generally a normal coronary angiogram and LV dysfunction, which extends beyond the territory subtended by a single coronary artery and recovers within days or weeks. The prognosis was initially thought to be benign, but subsequent studies have demonstrated that both acute and long-term mortality are higher than previously recognized. Indeed, mortality reported during the acute phase in hospitalized patients is ~4-5%, a figure comparable to that of ST elevation myocardial infarction in the era of primary percutaneous coronary interventions.

Despite extensive research, the etiology and pathogenesis of TTS remain incompletely understood. The aim of the present review is to discuss the pathophysiology of TTS with particular emphasis on the role of the central and autonomic nervous systems.

Different emotional or psychological stressors have been identified to precede the onset of TTS. The anatomical structures that mediate the stress response are found both in the central and autonomic nervous systems. Acute stressors induce brain activation, increasing bioavailability of cortisol and catecholamine. Both circulating epinephrine and norepinephrine, released from adrenal medullary chromaffin cells, and norepinephrine released locally from sympathetic nerve terminals are significantly increased in the acute phase of TTS. This catecholamine surge leads, through multiple mechanisms - i.e. direct catecholamine toxicity, adrenoceptor-mediated damage, epicardial and microvascular coronary vasoconstriction and/or spasm, and increased cardiac workload - to myocardial damage whose functional counterpart is the transient apical LV ballooning. The relative preponderance among post-menopausal women suggests that estrogen deprivation may play a facilitating role probably mediated by endothelial dysfunction. Despite the substantial improvement in our understanding of the pathophysiology of TTS, a number of knowledge gaps still remain.

**Key Words:** cardiomyopathy; catecholamine; ischemic heart disease; Takotsubo syndrome.

Originally described bySato et al.1 in the 1990’s, Takotsubo Syndrome (TTS) presents as an acute coronary syndrome (ACS) characterized by severe left ventricular (LV) dysfunction that typically recovers spontaneously within days or weeks. Patients may present with abrupt onset chest pain and/or dyspnea. Several stressors have been identified to precede the onset of TTS in a substantial proportion of patients.2 Emotional or psychological stress due to the unexpected death of a relative or a friend, suppressed terror, the occurrence of natural disasters or strenuous physical stress usually precede its onset.3 About one in 5 patients, however, does not report any form of stress preceding the onset of the condition. Recently, it has been shown that TTS can also occur following a ‘positive’ life event, hence the recently proposed denomination of ‘*happy heart syndrome*’.4

Despite extensive research, the etiology and pathogenesis of TTS remain incompletely understood. The aim of the present review is to discuss the pathophysiology of TTS with particular emphasis on the role of the central and autonomic nervous systems.

*Clinical presentation*

Symptoms, clinical signs, echocardiographic and electrocardiographic findings in TTS patients are suggestive of an acute coronary syndrome.5 The most common symptoms at presentation are chest pain and dyspnea. TTS can also present as syncope and pulmonary edema. Cardiac arrest, cardiogenic shock, and serious ventricular arrhythmias occur more rarely in TTS patients. Symptoms such as generalized weakness, unexplained cough, and fever have also been reported.6

*ECG patterns*

Abnormalities on the ECG are common at the time of presentation. The most frequent finding on the admission ECG is ST-segment elevation, which most often occurs in the precordial leads.7 The magnitude of ST-segment elevation and the number of leads with this pattern is usually less in patients with TTS than in cases of ST-elevation myocardial infarction (STEMI).8 Interestingly, reciprocal ST segment changes and abnormal Q waves are often absent in TTS. Moreover, ST segment depression is less common in TTS, as compared to coronary artery disease-related ACS.9 Some TTS patients may present with diffuse T-wave inversion particularly in the anterior and lateral leads of the ECG. A prolongation in the QT interval - corrected for heart rate - has been reported in a substantial proportion of TTS patients. These ECG changes are often transient and their presence or absence depends on when the ECG is recorded after symptom onset. However, it is challenging to distinguish TTS from an ACS on the basis of the ECG alone and therefore access to emergency coronary angiography should not be delayed.5

*Biomarkers*

Typically, TTS patients manifest modest increases in creatine kinase-MB and cardiac troponin concentrations as compared to STEMI patients. Of interest, in TTS there is a disparity between the degree of biomarker elevation and extent of myocardial dysfunction observed at left ventriculography. In a minority of TTS patients, however, the elevation of biomarkers of necrosis can be substantial, probably reflecting more severe myocardial damage.5 Significantly elevated serum brain natriuretic peptide or N-terminal pro-brain natriuretic peptide can also be detected during the acute phase of TTS.10 The production and release of these peptides appears to be mainly related to ventricular stretching.11 Because in most cases TTS is characterized by LV distension and relatively mild tissue necrosis, a greater increase in plasma natriuretic peptides compared with biomarkers indicative of necrosis can be detected.10

*Coronary and LV angiography*

Diagnostic coronary angiography shows normal coronary arteries or non-obstructive coronary artery disease in the vast majority of patients.5 Yet, about 15% of patients with TTS have obstructive coronary atherosclerosis.6 In these patients, the diagnosis of TTS is suggested by the fact that the area of dysfunction detected on LV angiography extends beyond the territory subtended by a single coronary artery and by the reversibility of LV dysfunction. Hence, the mere presence of obstructive coronary atherosclerosis does not allow for excluding the diagnosis of TTS.12

*Different types of LV dysfunction*

Different patterns of LV dysfunction have been reported in TTS, including the classical apical variant, a mid-ventricular variant, a basal or inverted variant and regional variants.13 About 80% of patients exhibit the apical variant.14 As the heart is densely innervated by sympathetic nerves that follow a regional distribution, it has been hypothesized that the typical apical pattern of LV dysfunction results from this anatomical substrate,3 as well as from the regional distribution of sympathetic adrenoceptors. 15

*Clinical Outcome*

The prognosis of TTS was initially thought to be benign.16 Subsequent series, however, have demonstrated that both acute and long-term mortality are higher than previously recognized.17 Indeed, mortality reported during the acute phase in hospitalized patients is ~4-5%, a figure comparable to that of STEMI in the era of primary percutaneous coronary interventions.18 Of interest, despite the recovery of LV function and absence of significant coronary disease in most cases, mortality after hospital discharge is worse than that in an aged-matched healthy population.19 A recent meta-analysis of clinical correlates of acute mortality in TTS has reported that the average in-hospital mortality is 4.5%.20 Japanese investigators have recently pointed out that TTS is associated with an elevated in-hospital mortality due to co-existing chronic comorbidities and acute medical illnesses.21 In one of the largest published series (n=1750), Templin et al. reported a 30-day mortality of 5.9% and a long-term death rate of 5.6% per patient per year.6 Major adverse events, including cardiogenic shock, cardiac arrest and mortality, are more frequent in women than in men with TTS. There is uncertainty as to the real recurrence rate of TTS due to the paucity of data on the risk of a further episode after the index event. Available evidence points to figures ranging from 0 to 22% depending upon the size of the population investigated and the duration of follow up.5

*TTS ‘Phenocopies’*

Generally, TTS is preceded by intense emotional triggers, although in up to one third of patients no trigger can be identified. A TTS-like syndrome can be observed in several medical conditions including sepsis, neurological disorders (e.g. subarachnoid hemorrhage, seizures, stroke/transient ischemic attack, cerebral tumors, head trauma)22 and pheochromocytoma.23 Furthermore, a TTS-like syndrome can be triggered by drugs (e.g. dopamine, dobutamine, epinephrine, or norepinephrine in the setting of cardiovascular stress tests, anesthesia, etc.).24 In our view, all these conditions should be differentiated from the classic ‘phenotype’ of TTS and could be labeled as TTS ‘phenocopies’.

*Epidemiology*

About 90% of patients with TTS are post-menopausal females with a similar prevalence across ethnic groups.6 In recent years, the increasing number of patients referred to coronary angiography with suspected ACS has allowed better appreciation of the true incidence of TTS. At present, it is estimated that approximately 2% of all patients undergoing emergency coronary angiography for a suspected ACS are TTS12, and it has been calculated that the incidence of TTS is approximately 100 new cases per million population per annum.25 Indeed, the improved clinical characterization of the condition has led to a paradigm shift: from what was initially the exclusion of STEMI, to the recognition that TTS has a number of distinctive diagnostic features.

**Pathophysiology**

*Sympathetic activation in TTS and its mechanisms*

The environmental events experienced by the majority of these patients and perceived as threatening become profoundly stressful if one is not able to cope with them.26 Stress is a physiological response that mediates the action of a stressor on its target organ.27 The anatomical structures that mediate the stress response are found both in the central and autonomic nervous systems [**Figure 1**]. Acute emotional stressors have been shown to induce brain activation, increasing bioavailability of cortisol, epinephrine and norepinephrine.27 In a small series of patients in the acute phase of TTS, Suzuki et al. have measured regional cerebral blood flow, a well-established index of brain activity, and demonstrated a significant cerebral blood flow increase in the hippocampus, brainstem and basal ganglia, paralleled by a decrease in the prefrontal cortex.28  Although these changes subsided gradually, they were still present in the chronic phase of TTS even after the typical cardiac wall motion abnormalities had disappeared [**Figure 2**].

The fundamental anatomical structures involved in the stress response are the neocortex, the limbic system, the reticular formation, the brain stem and the spinal cord.29  Following the complex neocortical and limbic integrations that occur in the interpretation of a stimulus as “threatening”, 30 the neural stress response first occurs through activation of brain stem noradrenergic neurons and sympathetic adrenomedullary circuits, stimulating the secretion of catecholamine.

The principal site for the synthesis of norepinephrine in the brain is the locus coeruleus, which is located in the posterior area of the rostral pons in the lateral floor of the fourth ventricle.31 As a crucial homeostatic control center, the locus coeruleus receives afferents from the hypothalamus, the cingulate gyrus and the amygdala, allowing emotional stressors to trigger noradrenergic responses. The locus coeruleus contains the largest cluster of noradrenergic neurons in the brain and innervates large segments of the neuroaxis.31 Its activation leads to increased norepinephrine secretion, which in turn stimulates the hypothalamic-pituitary-adrenal axis.29

Adrenal medullary chromaffin cells synthesize, store, and release predominantly epinephrine and norepinephrine which constitute the hormonal output of the neuroendocrine stress-response axis.32 Activation of the latter is crucial to maintain high levels of stress arousal for prolonged periods. The hypothalamic-pituitary-adrenal axis is a complex set of direct influences andfeedback interactions among three endocrine glands: thehypothalamus, the pituitary gland, and the adrenal gland [**Figure 1**].

Apart from the locus coeruleus, the neural impulses also descend into the posterior hypothalamus, i.e. the pathway of sympathetic activation. From here, sympathetic neural pathways descend through the cranial and sacral spinal cord regions and trigger the release of norepinephrine.33 There are sympathetic preganglionic neurons that lay in the lateral grey column from T1 to L2/3 which synapse with their postganglionic neurons. Sympathetic cardiac innervation originates mainly in the right and left stellate ganglia. These fibers travel along the epicardial vascular structures of the heart into the underlying myocardium and end as sympathetic nerve terminals reaching the heart muscle and coronary circulation. The sympathetic nerve endings release norepinephrine directly into the synaptic cleft activating  and  postsynaptic adrenoceptors.34 Thus, all the epinephrine in the body and a significant amount of circulating norepinephrine derive from the adrenal medulla, and the total amount of catecholamine presented to cardiac adrenergic receptors at any given time is composed of circulating norepinephrine and epinephrine coupled with norepinephrine released locally from sympathetic nerve terminals.35 In normal humans, under resting conditions, only about 2-8% of the circulating norepinephrine is released by the adrenal medulla and the rest is released by sympathetic nerve endings.26

*Increased circulating and myocardial catecholamine levels*

Akashi and colleagues were the first to report elevated serum catecholamine levels in patients with TTS.36 Wittstein et al. subsequently showed that in the acute phase, TTS patients have increased concentrations of plasma catecholamines (i.e. epinephrine, norepinephrine, and dopamine) and stress-related circulating neuropeptides that are several times higher than those in patients with STEMI. These levels remain markedly elevated even a week after the onset of symptoms [**Figure 3**].37

A recent study in a murine model has demonstrated that the infusion of high concentrations of epinephrine can produce the characteristic reversible apical LV ballooning coupled with basal hyper-contractility observed in patients with TTS.38

Indeed in the acute phase of TTS, along with an increased concentration of circulating catecholamine, 37 there is also evidence of increased catecholamine at the myocardial level. Kume et al. have demonstrated increased norepinephrine spillover in the coronary sinus in a small series of TTS patients, suggesting increased local myocardial release of catecholamine.39 Increase in local catecholamine levels has been demonstrated also in the so-called neurogenic stunned myocardium which appears to be mediated by neuronally transmitted norepinephrine.40 The clinical presentation of this condition, which is found in patients with aneurysm-related subarachnoid hemorrhage, resembles closely that of TTS and is characterized by a fully reversible form of acute LV dysfunction.41 Accordingly, experimental work has shown that elevated activity of the sympathetic nervous system in the acute phase of subarachnoid hemorrhage induces myocardial damage and contributes to the development of cardiac dysfunction.42

The local release of catecholamine from cardiac nerve endings results in an elevated norepinephrine concentration in the synaptic cleft due to increased exocytosis of norepinephrine from presynaptic vesicles, paralleled by a decrease in terminal nerve axon norepinephrine re-uptake through the specific uptake-1 transporter [**Figure 4**].43 This process has been originally demonstrated by means of iodine-123 meta-iodo-benzyl-guanidine, i.e. a gamma-emitting norepinephrine analogue that is used to image myocardial sympathetic nerve terminals with single photon emission computed tomography. Akashi et al. examined 8 patients with TTS within 3 days of admission and at 3 month follow up after normalization of LV dysfunction.44 The acute scan showed a pattern of cardiac sympathetic hyperactivity with improvement at follow up.44 The evidence of reduced iodine-123 meta-iodo-benzyl-guanidine retention in dysfunctional segments is consistent with a regional disturbance of sympathetic neuronal activity that can persist for months.45 Recently, Christensen et al. have demonstrated myocardial sympathetic hyperactivity in the subacute phase of TTS paralleling plasma epinephrine levels, that were also elevated compared with follow-up concentrations.46

*Role of endothelial dysfunction and estrogen deficiency*

New information has shed additional light on the pathogenesis of TTS supporting the concept that the condition differs markedly from cardiomyopathies, as currently defined. Specifically, recent data show that endothelial dysfunction is common in patients with TTS, which could explain the propensity to epicardial and/or microvascular coronary artery spasm which are two likely pathogenetic mechanisms for TTS.47 Indeed, endothelial dysfunction, a pathological state of the endothelium characterized by an imbalance between vasoconstricting and vasodilating factors, may represent an important link between stress and myocardial dysfunction in TTS.47 Therefore, transient myocardial ischemia followed by stunning might be the cause underlying the typical, reversible LV dysfunction.

Endothelial dysfunction can also explain why TTS is more common in post-menopausal women, as they have been shown to have both age-related and estrogen deficiency-related coronary vasomotor abnormalities.48-50  Under physiologic circumstances estrogen beneficially affects the coronary microcirculation via endothelium-dependent and -independent mechanisms, improving coronary blood flow.50 During menopause, both increased sympathetic drive and endothelial dysfunction are a consequence of reduced estrogen levels.49  In an elegant experimental study in animals, Ueyema et al. have shown that stress-induced LV apical ballooning can be prevented by pretreatment with - and β-adrenoceptor blockers and estrogen.51 Estrogen supplementation attenuated the stress­induced hypothalamo­sympatho-adrenal outflow from the central nervous system to the target organs. In addition, estrogen treatment upregulated the cardiac levels of cardioprotective substances, such as atrial natriuretic peptide and heat shock protein 70. These data suggest that estrogen deficiency following menopause might facilitate the occurrence of TTS - particularly that linked to emotional stress - either by indirect action on the nervous system or by direct action on the heart. Moreover, impairment of endothelial function is associated with the presence of traditional risk factors and has been described in the setting of various systemic inflammatory disorders with high cardiovascular morbidity and mortality.49  Recently, data in large cohorts have shown that TTS patients have a non-negligible prevalence of cardiovascular risk factors, i.e. hypertension, hypercholesterolemia, and smoking.2,6,18 In addition, there is now evidence that most cases of TTS occur in patients with various co-morbidities, including neurologic, psychiatric, pulmonary, kidney, liver and connective tissue disease,2 that are associated with endothelial dysfunction and might therefore constitute a previously unrecognized predisposing factor for TTS.52

Based on these multiple observations, the possibility exists that endothelial dysfunction might constitute a crucial link between a sympathetic surge and myocardial ischemia in TTS.

*Mechanisms of LV dysfunction induced by sympathetic hyperactivity*

Although there is agreement that TTS is characterized by increased circulating and cardiac catecholamine levels, how this translates into the typical LV dysfunction remains incompletely understood. 53 Multiple mechanisms have been postulated to explain the cardiotoxicity of catecholamines.54 The surge in stimulation of adrenoceptors enhances heart rate and cardiac contractility with a secondary imbalance in the ratio of oxygen supply to oxygen demand thus creating areas of myocellular hypoxia.55 Myocyte hypoxia can be further aggravated by metabolic changes, 56 such as excessive deposition of lipid droplets in cardiomyocytes. These changes might result in an uncoupling of oxidative phosphorylation in mitochondria which inhibits the coupling between the electron transport and phosphorylation reactions that in turn will interfere with ATP synthesis.57 Changes in membrane permeability might also lead to electrolyte changes. These include hypokalemia, hypocalcemia and hypomagnesemia with resultant elevations in parathyroid hormone, and hypozincemia with hyposelenemia, which compromise antioxidant defenses. Altered cationic homeostasis might affect several cellular processes and contribute to myocardial toxicity.58 Norepinephrine and epinephrine are also potential sources of free radicals. These oxygen-derived free radicals may interfere with calcium and sodium transporters, which may result in additional myocyte dysfunction.3

Direct catecholamine toxicity

Some authors favor the hypothesis of direct catecholamine-induced myocardial toxicity in TTS. For instance, myocardial necrosis can occur in patients with acute neurovascular events, and this is caused by direct toxicity of endogenous catecholamine released into the heart via nerve terminals.59 Catecholamine released directly into the myocardium via sympathetic nerves has been suggested to have a greater “toxic” effect than that reaching the heart via the bloodstream.60 Indeed, norepinephrine spillover from the cardiac sympathetic nerve terminals can decrease myocyte viability through cyclic adenosine monophosphate-mediated calcium overload resulting, histologically, in contraction band necrosis which is one of the pathological hallmarks of TTS,61 along with increased production of extracellular matrix leading to a rapid increase in fibrosis and mild neutrophil infiltration. Nef et al. studied serial myocardial biopsies in 8 patients with TTS during the phase of severe LV dysfunction and found histological signs of catecholamine toxicity, i.e. focal mononuclear inflammatory cells, areas of fibrotic response, and characteristic contraction bands. They noted that TTS can be accompanied by *“severe morphological alterations potentially resulting from catecholamine excess followed by microcirculatory dysfunction and direct cardiotoxicity. However, the affected myocardium represents a high potential of structural reconstitution which correlates with the rapid functional recovery function is accompanied by an equally fast reconstitution of myocardial integrity”*. 62

Contraction band necrosis is a unique form of myocyte injury characterized by hypercontracted sarcomeres, dense eosinophilic transverse bands, and an interstitial mononuclear inflammatory response and is distinct from the polymorphonuclear inflammation seen in infarction.61 Contraction band necrosis has been found in patients with pheochromocytoma, 23 and those with subarachnoid hemorrhage40 both characterized by a catecholamine excess. It has also been observed post-mortem in people who died under terrifying circumstances such as fatal asthma and violent assault, suggesting that catecholamine excess represents an important link between emotional stress and cardiac injury.63 The lack of persistent, significant morphological changes in most cases of TTS is further demonstrated by data accrued so far with cardiac magnetic resonance (CMR). Different studies have pointed out that the acute phase of the disease is characterized only by remarkable myocardial edema with no evidence of significant late gadolinium enhancement[**Figure 5**].64 These findings are of major importance, as they exclude the possibility that TTS is mainly the consequence of a catecholamine-mediated myocarditis, which commonly occurs in pheochromocytoma.23 Although TTS and pheochromocytoma are both characterized by increased catecholamine concentrations, this causes a distinct entity in pheochromocytoma only, leading to degenerative changes in muscle fibers, foci of necrosis, acute inflammation, chronic interstitial inflammatory exudation, and reparative fibrosis.65  At CMR, these abnormalities may be observed noninvasively as myocardial necrosis (late enhancement), edema, and focal and diffuse fibrosis that may lead to short- or long-term LV dysfunction.23 A different pattern is observed in TTS patients. Testa and Feola performed serial CMR scans in patients with TTS and found no evidence of delayed enhancement either in the acute phase or at 3 months follow up, suggesting that the damage in dysfunctional myocardium was transient and did not include significant tissue fibrosis.66

In summary, it may be hypothesized that direct catecholamine toxicity plays a role both in TTS and pheochromocytoma, but with important quantitative differences. The myocardial damage in pheochromocytoma is probably more extensive because of the persistent exposition of patients to elevated catecholamine levels. In TTS, the elevation is transient and generally results in less evident damage as demonstrated by the relatively mild elevation of necrosis biomarkers, 5,6 and absence of late enhancement at CMR in most cases.66 The latter in particular might be a consequence of the limited spatial resolution of CMR, i.e. 0.6 to 1 cm3, which may not detect smaller or patchy areas of damage that are present in TTS.67

Microvascular spasm

A further “vascular” pathogenetic mechanism that could be involved in TTS is acute, transient myocardial ischemia. Since the first description of TTS, coronary vasospasm has been suggested as a plausible causative factor. In their original report, Dote et al. hypothesized that TTS was caused by multivessel coronary vasospasm, as 4 of 5 patients in their series had “spontaneous” or induced coronary vasospasm at coronary angiography.68 Sato et al. reported epicardial coronary artery spasm in 8 of 35 patients (23%) and diffuse coronary vasoconstriction in 19 (54%).1 Similarly, Tsuchihashi et al. reported epicardial coronary spasm in 10 of 48 TTS patients (21%).69 Although the causative role of coronary spasm has been questioned by many authors, in a prospective study Angelini et al. confirmed the development of coronary spasm in TTS patients who underwent acetylcholine testing.70 Indeed, severe, sub-occlusive epicardial coronary artery spasm occurred in these patients, which was associated with echocardiographic evidence of transient LV dysfunction, as classically observed in TTS. Another epicardial coronary abnormality that might cause TTS is spontaneous coronary artery dissection, which is a form of TTS triggered by an ischemic insult leading to post-ischemic myocardial stunning.71

In addition to abnormalities of the epicardial arteries, coronary microvascular dysfunction could play a pathogenetic role in TTS [**Figure 6**].72

Abnormal coronary microvascular responses have been documented in TTS using invasive and non-invasive diagnostic tools.73 Reduced TIMI (Thrombolysis in Myocardial Infarction) frame count in most patients undergoing emergency coronary angiography with spontaneous improvement of coronary flow reserve at 1-month follow-up has been reported by some authors,16 albeit this has not been a universal finding.74,75  Interestingly, using myocardial contrast echocardiography, Galiuto et al. demonstrated reversible coronary microvascular dysfunction in TTS patients.76 A clear perfusion defect was observed in the LV segments showing reduced contractility. In contrast to what is commonly observed in patients with ST elevation myocardial infarction, the perfusion defect in TTS patients transiently improved following the infusion of intracoronary adenosine and recovered permanently at 1-month of follow-up [**Figure 7**]. The close relationship between the improvement of myocardial perfusion and LV dysfunction observed in this study suggests a pathogenetic role for the coronary microvascular dysfunction in this condition.76  Several single photon emission computed tomography perfusion studies have shown a decrease in tracer uptake during the acute phase of TTS and a return to normal at follow-up, suggesting a role for coronary microvascular dysfunction as a trigger of myocardial ischemia in this condition.77-79

*Mechanisms of myocardial protection*

The severe wall motion abnormalities seen in TTS are transient in the vast majority of patients which strongly suggests that protective mechanisms are likely to operate to preserve myocardial integrity. Overactive adrenoceptor signaling, in the presence of supra-physiological catecholamine concentrations, might be the trigger of LV dysfunction.80 It is well established that catecholamine signaling through β-adrenoceptors mediates endogenous regulation of chronotropic, inotropic, and lusitropic cardiac functions. There is general consensus that this “brain-cardiac” process occurs via the β-adrenoceptor–mediated cyclic-AMP–dependent protein kinase pathway.81 Regional differences in adrenoceptor density might explain the pattern of LV dysfunction often seen in TTS. Experimental data have shown that β2-adrenoceptors are more frequently expressed in apical than in basal segments of the LV while a reverse distribution is present for norepinephrine β1-adrenoceptors and sympathetic nerve terminals of the neuro-cardiac axis, which are much more expressed at the base than at the apex of the LV.15

With this background, it might be considered that both epinephrine and norepinephrine elicit positive inotropic responses through Gs-coupling protein, but they function differently when activating the β2-adrenoceptors. Indeed, supra-physiological levels of epinephrine trigger β2-adrenoceptor to switch from Gs to Gi coupling.82 The switch to Gi, which causes a negative inotropic response thus contributing to the apical ballooning, may be a mechanism to protect myocytes from the cardiotoxic activation of β1- and β2-adrenoceptor Gs pathways, thus limiting the degree of acute myocardial injury in response to the catecholamine storm.This mechanism has been elegantly shown by Paur et al. who demonstrated that high-dose epinephrine can induce direct myocyte cardio-depression and cardio-protection in a Gi-dependent manner.39  In a rat model, these authors showed that high-dose of intravenous epinephrine given quickly as a bolus, to mimic the catecholamine surge following acute stress, produced the characteristic reversible apical depression of myocardial contraction coupled with basal hypercontractility, whereas an equivalent bolus of norepinephrine did not.39  This implies that the mechanism is epinephrine-specific and confirms the observation that dysfunction is not typically observed in the region with the highest density of norepinephrine-releasing sympathetic nerve terminals.83

Besides the inhibition of Gs protein, a major signaling pathway regulated by β2-adrenoceptors in TTS seems to be the phosphatidylinositol-3-kinase (PI3K) and protein kinase B (AKT) signaling cascade. 57 Gene expression profiling, using the microarray technique, has demonstrated that genes coding for the PI3K/AKT signaling pathway proteins are differentially expressed in TTS. Indeed, Nef et al. analyzed biopsies from 16 patients and found that increased catecholamine levels in TTS activate the PI3K/AKT signaling pathway in the acute phase of the disease, as shown by an upregulation of PI3K, an increase in AKT phosphorylation and a down-regulation of the PI3K antagonist PTEN.84 AKT is critical for postnatal cardiac growth and coronary angiogenesis. Also, its downstream targets, especially mechanistic target of rapamycin (mTOR) and glycogen synthase kinase 3 (GSK3), have been shown to play crucial roles in cell survival.85 Noteworthy, mechanisms of myocardial protection seem to act differently in different patients as a consequence of genetic variability. Over the past decade, several studies analyzing polymorphisms potentially involved in the pathogenesis of TTS have demonstrated differences in the various subtypes of adrenoceptors,86 and estrogen receptors.87 Genetic predisposition to TTS might explain why some patients may develop the disease even with no preceding stressor and are at risk of recurrence.88 Finally, since myocardial ischemia seems to play a key role in the pathophysiology of TTS - see the next section of this review - it could also be hypothesized that mechanisms triggered by transient ischemia could confer some additional myocardial protection.

**Putting it all together**

The most recent evidence supports the concept that in the acute phase of TTS there is an increased concentration of catecholamine that might induce direct myocardial injury and coronary spasm, mostly at the microvascular level, together with an increased cardiac workload that contribute to an acute situation of ‘supply-demand mismatch” followed by post-ischemic stunning. The functional counterpart at the LV level would be the typical apical ballooning that persists due to the presence of stunned myocardium, but which is followed by complete functional recovery over relatively short periods of time in most cases [**Figure 8**].

Physiologically, small coronary arteries and arterioles are the principal determinants of coronary vascular resistance. These vessels receive autonomic innervation and their diameter is modified by activation of these nerves. In normal subjects the overall response to sympathetic activation is vasodilatation mainly through activation of coronary 2-adrenoceptors. Conversely, increased cardiac sympathetic activity can induce coronary microvascular constriction in the context of endothelial dysfunction instead of the vasodilatation observed normally because -adrenergic vasoconstriction becomes unrestrained and powerful enough to reduce coronary blood flow thus contributing to myocardial ischemia.89-91 Both 1- and 2-adrenoceptors mediate coronary vasoconstriction, with 1-adrenoceptors predominant in larger vessels and 2--adrenoceptors more abundant in the microcirculation.92,93  In the context of endothelial dysfunction, both 1- and 2-adrenoceptors and microvascular constriction are augmented and can induce myocardial ischemia.94

Cardiac sympathetic hyperactivity in the acute phase of TTS is accompanied by metabolic abnormalities appearing as a flow/metabolism mismatch.95,96 Specifically, cardiac positron emission tomography with [18F]2-fluoro-deoxy-glucose has demonstrated reduced glucose metabolism in the context of normal myocardial perfusion. Similar findings have been observed using free fatty acid analogs. This pattern is known as ‘inverse metabolic perfusion mismatch’ and represents a transient metabolic abnormality despite preserved myocardial blood flow which is typically observed in stunned myocardium.97-99 Using positron emission tomography in the acute phase, Feola et al. have demonstrated impairment of tissue metabolism in the dysfunctional myocardium, mainly at the apex and progressively less in the mid-ventricular myocardium, which normalized at 3 month follow up. In the same study, hyperemic myocardial blood flow and coronary flow reserve were shown to be reduced in dysfunctional myocardium, and these abnormalities recovered at follow-up.98

There are some apparent discrepancies between the flow data obtained with echocardiography and single photon emission computed tomography on one hand and positron emission tomography on the other. Two main reasons likely explain these differences. The first is the time in the course of the disease when the studies were performed and the second is related to differences inherent to these techniques. In fact, positron emission tomography is the only technique that can provide absolute myocardial blood flow in mL/min per gram of tissue. By contrast, echocardiography and single photon emission computed tomography only provide relative regional differences in tracer concentration that, also for differences within the normal range, will appear as regional defects: e.g., if one myocardial region has an absolute resting flow of 0.7 mL/min per gram and another a flow of 0.9 mL/min per gram (both these values are within the normal baseline flow range), single photon emission computed tomography and echocardiography might show a defect in the former relative to the latter whereas positron emission tomography will show that both flows are within the normal range.

The possibility exists that ischemic stunning confers protection against subsequent episodes of ischemia and preserves energy metabolism by down-regulating contractile function and metabolism, thus facilitating recovery of LV systolic function.100  It is likely that different pathogenetic mechanisms operate in different patients presenting with TTS and thus further mechanistic research is required to appropriately unveil the different etiologies responsible for this intriguing and complex condition.

**Conclusions and perspectives**

In the past few years, several studies have clarified mechanisms responsible for TTS showing that a catecholamine surge results in direct and indirect myocardial damage. The frequent spontaneous resolution of LV dysfunction appears to be related to the activation of survival pathways like those observed in post-ischemic stunning. The high prevalence in post-menopausal women suggests that estrogen deprivation may play a facilitating role, probably mediated by endothelial dysfunction.

In spite of the substantial increment in our knowledge of TTS, a number of knowledge gaps still remain, including: 1) causes of the sympathetic surge in patients who have TTS in the absence of psychological or physical stress, of neurological disorders, or pheochromocytoma; 2) mechanisms making patients, at a certain point in time of their life, susceptible to develop TTS in the presence of a catecholamine surge; 3) reasons of the different distributions of wall motion abnormalities in different patients; 4) causes of the poor outcome observed in a sizeable proportion of these patients; 5) causes of the recurrence of TTS occasionally observed during medium-term follow-up.6  These important issues need to be carefully addressed in future studies together with work to identify targeted therapies.

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**Legends to the figures**

**Figure 1. Central and autonomic nervous system interplay**

Right: somatic nervous system (motor system and sensory systems) and environment. Left: autonomic nervous system, neuroendocrine system and body organs. In the middle, spinal cord, brain stem, hypothalamus’ limbic system and neocortex. The afferent feedback from the body is neuronal, hormonal and humoral (physicochemical; e.g., glucose concentration, osmolality) and of other types (e.g., body temperature). Solid line arrows, neuronal; dashed line arrow, hormonal; dotted, neuroendocrine system, hormonal and humoral feedback. Limbic system is anatomically descriptive and a collective term denoting brain structures common to all mammals that include hippocampus, dentate gyrus with archicortex, cingulate gyrus, septal nuclei and amygdala. These forebrain structures are functionally heterogeneous and not a unitary system (as the term ‘‘limbic system’’ may imply). They are involved in the generation of emotional and motivational aspects of behavior). Note the reciprocal communication between hypothalamus, limbic system and neocortex (symbolized by the shaded arrows) indicating that the centers of the cerebral hemispheres have powerful influence on all autonomic regulations.

 [*Reprinted with permission from Janig W. The Integrative Action of the Autonomic Nervous System. 2006; Cambridge University Press. The Edinburgh Building, Cambridge, UK. Ref. 26*].

**Figure 2. Brain activation in patients with TTS**

LV angiograms (top) and single photon computed emission tomography images of the brain in 3 patients with TTS. In patient 1, LV angiograms showed typical apical ballooning in the acute phase (day of onset; A), which disappeared in the chronic phase (29 days after onset; B). Normalization of wall motion abnormality was confirmed by echocardiography in patients 2 and 3. In all patients, brain activation was noted in the acute phase (1, 1 and 4 days after onset, respectively; C, E, G), which subsided in the chronic phase (28, 28 and 39 days after onset, respectively; D, F, H). The yellow, red, green and blue arrowheads indicate the hippocampus, brainstem, basal ganglia and prefrontal cortex, respectively.

*[Reprinted with permission from Suzuki H. Evidence for brain activation in patients with takotsubo cardiomyopathy. Circ J. 2014; 78: 256-258. Ref. 28].*

**Figure 3. Plasma catecholamine levels in patients with TTS and patients with myocardial infarction**

In the acute phase, TTS patients have increased concentrations of plasma catecholamine (i.e. epinephrine, norepinephrine, and dopamine) and stress-related circulating neuropeptides that are several times higher than those in patients with myocardial infarction and remain markedly elevated even a week after the onset of symptoms

[*Modified from Wittstein IS, et al. Neurohumoral features of myocardial stunning due to sudden emotional stress. N Engl J Med. 2005;352: 539-54*8. *Ref. 37*].

**Figure 4. Autonomic Nervous System activation and cardiovascular system**

Autonomic Nervous System (ANS) activation is mediated by release of norepinephrine and epinephrine and occurs via the following mechanisms: (1) norepinephrine is released by cardiac sympathetic nerve terminals (resulting in tachycardia and an increased force of contraction); (2) epinephrine is released into the circulation by the adrenal medulla, modulating both myocardium and peripheral vessels; and (3) local release of norepinephrine and epinephrine by various peripheral ANS’s that can synthesize and release these catecholamines in an autocrine/paracrine manner and are located in blood vessels and in cardiac myocytes themselves.

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**Figure 5. Cardiovascular magnetic resonance identification of myocardial edema in TTS**

T2-weighted images (short-axis view, top row) demonstrating normal signal intensity of the basal myocardium (left panel), but global edema of the mid and apical myocardium (middle and right panels). Computer-aided signal intensity analysis (bottom row) of the T2- weighted images with color-coded display of relative signal intensity normalized to skeletal muscle (blue indicates a signal intensity ratio of myocardium to skeletal muscle of 1.9 or higher, indicating edema; green/yellow indicates a normal signal intensity ratio of 1.9) confirm the presence of global mid and apical edema.

 [*Reprinted with permission from Eitel I et al. Clinical characteristics and cardiovascular magnetic resonance findingsin stress (Takotsubo) cardiomyopathy. JAMA. 2011; 306:277-286. Ref 64*]

**Figure 6. Mechanism of myocardial ischemia**

In addition to the ‘classic mechanisms’ (i.e. atherosclerotic disease and epicardial coronary vasospasm) that lead to myocardial ischemia, coronary microvascular dysfunction has recently emerged as a ‘third’ potential mechanism of myocardial ischaemia. As in the case of the other two mechanisms, coronary microvascular dysfunction (alone or in combination with the other two) can lead to transient myocardial ischemia as in patients with coronary artery disease (CAD) or cardiomyopathy (CMP) or to severe acute ischemia as observed in TTS.

(CFR= coronary flow reserve)

[*Reprinted with permission from Crea F, Camici PG, Bairey Merz CN. Coronary microvascular dysfunction: an update. Eur Heart J. 2014; 35:1101-1111.* *Ref 72*].

**Figure 7. Myocardial contrast echocardiography in TTS**

Under baseline condition, a clear perfusion defect is present within LV apical myocardium (panel A) while during adenosine a significant decrease in the extent of the perfusion defect is evident (panel B). Contrast score index (panels C and D; arbitrary units) and contrast defect length (panels E and F) at baseline (Bsl), at peak of 90 s adenosine infusion (Adn) and at 1-month follow-up (FUP) in patients with TTS (ABS) and patients with ST-elevation myocardial infarction (STEMI). \*P<0.001 vs. baseline.

 [*Reprinted with permission from Galiuto L et al. Reversible coronary microvascular dysfunction: a common pathogenetic mechanism in apical ballooning or Takotsubo syndrome. Eur Heart J 2010;31:1319–1327. Ref 76*]

**Figure 8. Key pathogenetic aspects in TTS**

The interplay among triggers, pathogenetic factors, mechanisms of cardiac injury and clinical consequences.

(ANS= autonomic nervous system; CNS= central nervous system; LV=left ventricular; MVO2= myocardial oxygen consumption).