Takotsubo syndrome (TTS), also known as takotsubo cardiomyopathy, is an acute heart failure syndrome that typically occurs after a period of great emotional stress. The archetypal patient is a postmenopausal woman who presents with chest pain, ST-segment elevation and acute hypokinesia of the apical and middle segment of the left ventricle that extends beyond the territory of a single coronary artery, coupled with hyperkinesia of the basal myocardium. Recent preclinical and clinical studies have shown the importance of high catecholamine levels in precipitating TTS. We propose that this is caused by activation of β-adrenoceptors and the subsequent activation of a negatively-inotropic pathway, perhaps to protect the heart from catecholamine overload. We explore the pathophysiology of TTS according to its “phases”, both preclinically and clinically. This will show that the condition is not one of static apical hypokinesia that simply improves, but rather a dynamic condition that changes as the disease progresses. We hope that further exploration of TTS using its “phases” will aid in its characterization, diagnosis and treatment. (Circ J 2014; 78: 1550–1558)

Key Words: Apical ballooning; Cardiomyopathy; Pathophysiology; Phases; Takotsubo

I Wasted Time, and Now Doth Time Waste Me
– William Shakespeare –

Takotsubo syndrome (TTS), also known as takotsubo cardiomyopathy, stress cardiomyopathy and apical ballooning syndrome, is an acute, reversible heart failure (HF) syndrome that has increasingly come to medical attention over the past 24 years with wider access to early diagnostic coronary angiography for patients with acute chest pain and ECG abnormalities. The typical case is a postmenopausal woman with an extremely stressful emotional or physical trigger, who presents with chest pain and breathlessness, ECG changes and acute hypokinesia of the apical and middle segments of the left ventricle (LV) in a circumferential pattern extending beyond a single coronary territory, and in the absence of culprit obstruction of the coronary artery disease (CAD). Providing the patient survives the acute event, the dysfunctional segments recover, at least macroscopically, within days to weeks. Many other variations on this “typical case” exist, including different demographics (men, younger women), different anatomical variants (basal/inverted, mid-LV, biventricular), spontaneous cases without a triggering stressor, cases triggered by other medical, surgical or psychiatric emergencies and permanent cardiac abnormalities (permanent “new” left bundle branch block, apical transmural necrosis).

One common feature appears to be an extreme surge in catecholamines in response to the triggering stress or coexisting medical condition (eg, subarachnoid hemorrhage, pheochromocytoma, and thyrotoxicosis). Animal models can replicate the features of this HF syndrome in order to dissect its mechanisms. In contrast to the reductionist approach in most modern pathophysiological research, the more that is understood about TTS, the more it is apparent that a number of processes may result in the final common pathway of acute apical dysfunction. There are a number of mediators that may modify the severity and course of a particular episode. Defining the precise pathophysiology is challenging, and we suggest that an integrated approach to studying the cardiovascular responses to extreme surges in catecholamines is appropriate.

Here we use a novel approach to reviewing the pathophysiology of TTS. Animal and clinical studies have reported findings at different phases through the development of this condition, and it is intuitive that the observed integrated cardiovascular responses to surges in serum catecholamines and sympathetic neural outflow would change over time. We discuss the pathophysiology in a sequential fashion describing effects as they occur at different time-points, integrating the observations and explaining the negative inotropic response and potential activation of cardioprotective mechanisms.

Before discussing the temporal sequence of events, it is important to note a growing body of evidence that TTS is not a form of acute myocardial infarction (MI). Firstly, the epide-
Pathophysiology of Takotsubo Syndrome

Background to Pathophysiology of TTS

Currently, the molecular mechanisms underlying TTS are incompletely understood, but the common feature of primary and secondary TTS cases is the surge of catecholamines and enhanced sympathetic activity. The role of catecholamines appears central to the pathophysiology of TTS; this has been uncontroversial for many years and has lead to some investigators renaming TTS “stress cardiomyopathy”, underpinned by converging evidence from clinical cohorts and animal models. Specifically, clinical studies have demonstrated extremely high levels of catecholamines in TTS patients, frequent identification of an emotionally stressful event as being causative, reports of iatrogenic TTS caused by epinephrine injection, disturbances in brain activation during TTS, and the administration of other sympathomimetics, as well as the successful production of animal models of TTS using emotional stress or infusion of catecholamines in order to bring about cardiogenic shock of the type observed in sufferers of TTS.

Both arms of the autonomic nervous system are tonically active at rest, and epinephrine and norepinephrine are basally secreted in low amounts. At rest, epinephrine and norepinephrine are present in the plasma in the orders of magnitude of tens and hundreds of picograms, respectively. However, in TTS patients the serum epinephrine and norepinephrine concentrations are significantly higher even than those seen in patients with a severe MI (Figure 1). Furthermore, they remain significantly elevated. The serum half-life of epinephrine is approximately 3 min; if TTS was caused by a stressor that triggered a large, but short, catecholamine secretion, 24 h later the plasma epinephrine concentration should be 480 half-lives lower (3.2×10⁻¹⁴ fold lower): tiny concentrations of epinephrine would remain regardless of the amount initially secreted. However, the clinical observations support a more prolonged activation of the sympathetic nervous system, combined with molecular and physiological “memory” of the peak of the

Figure 1. Graph of catecholamine levels in the plasma of patients with either takotsubo cardiomyopathy (TCM) or myocardial infarction (MI). (Data with permission from Wittstein IS, et al.)

Figure 2. Schematic of the sympathetic innervation of the myocardial regions. (Adapted with permission from Lyon AR, et al.)
catecholamine storm.

We considered how the human heart might respond to such extreme surges in catecholamines and how it could result in the phenotype observed in TTS patients. We reviewed the literature regarding the distribution of sympathetic nerve terminals and β-adrenoceptors (βARs) in the mammalian heart.\(^3\) Contrary to the established view that sympathetic neural release of norepinephrine may underlie TTS, we found a consistent finding of a higher nerve density in the basal myocardium compared with the apex (Figure 2).\(^3\) Although this may explain the inverted or basal cases, it does not explain the majority of “typical” TTS cases with apical hypokinesia. Conversely, there is an apical-basal gradient of βARs, with the apical myocardium having the highest density, and greatest responses to exogenous catecholamine administration.\(^8,20\) This would allow balanced myocardial responses to sympathetic activation under low and medium levels, but at the highest levels epinephrine release from the adrenal glands would perfuse the heart via the circulation, and the receptor gradient would determine the response (Figure 2). We combined this observation of apical-basal βAR and basal-apical neural gradients with a second interesting pharmacological observation. Epinephrine at low and medium doses is a positive inotrope, but at the highest doses it becomes a negative inotrope via the β2AR, by activating a switch from the stimulatory Gs to the cardioinhibitory Gi pathway in a process known as stimulus trafficking (Figure 3),\(^21,22\) which could explain the negative inotropy observed in the apical myocardium after exposure to very high levels of circulating epinephrine. We developed a rat TTS model and demonstrated that an intravenous bolus of high-dose epinephrine triggered acute apical hypokinesia, with preserved basal contractility, recapitulating the clinical features of TTS.\(^8\) This could not be replicated by a norepinephrine bolus, but could be prevented by prior treatment with pertussis toxin, which inactivates Gi signaling.

Although we believe there are several lines of laboratory and clinical evidence to support our hypothesis, we acknowledge that it may not explain all cases, and integrating all the observations may form part of the systemic phenotype culminating in the clinical syndrome observed. However, it has also led us to consider TTS and the cardiovascular responses to stress and catecholamine surges in different timeframes, and understanding the results reported in the context of “time since catecholamine surge”, or in common terminology “time since adrenaline rush”.

Here we review the published literature in the context of different temporal phases following a stressful trigger. As we explore what is known about acute TTS in the human patient we are limited to observations after in-hospital precipitation. Overall, we are often limited to samples and physiological data obtained many hours or days after the initial stressful precipitant and clinical intervention. Most of the detailed mechanistic observations regarding the possible pathophysiology underpinning TTS in the initial seconds and minutes following the stress have been obtained from animal studies (Table), which allow the researcher to explore the mechanisms during the

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**Figure 3.** Effects of epinephrine and norepinephrine on ventricular myocardium from mice overexpressing the human β2 receptor from (A) experimental results and (B) whole-ventricle simulation. PTX, pertussis toxin. (Data with permission from Heubach JF et al.\(^{22}\))
Pathophysiology of Takotsubo Syndrome

Table. Major Features of Each Study of Takotsubo Syndrome Using Extant Animal Models

<table>
<thead>
<tr>
<th>Study</th>
<th>Species</th>
<th>Sex</th>
<th>Pharmacologic or psychogenic</th>
<th>Agent</th>
<th>Dose</th>
<th>Study time frame</th>
<th>Reversal</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ueyama et al, 2002¹⁰</td>
<td>Rat</td>
<td>F</td>
<td>Psychogenic</td>
<td>IMO</td>
<td>&lt;30 min</td>
<td>30 min</td>
<td></td>
<td>Amosulalol</td>
</tr>
<tr>
<td>Ueyama et al, 2003²⁷</td>
<td>Rat</td>
<td>F</td>
<td>Psychogenic</td>
<td>IMO</td>
<td>&lt;20 min</td>
<td>20 min</td>
<td></td>
<td>Estrogen (E2)</td>
</tr>
<tr>
<td>Izumi et al, 2009¹¹</td>
<td>Monkey</td>
<td>M</td>
<td>Pharmacologic</td>
<td>Epinephrine</td>
<td>2x10μg·kg⁻¹·min⁻¹</td>
<td>Max. 180 min</td>
<td>Metoprolol</td>
<td></td>
</tr>
<tr>
<td>Ueyama et al, 2011²⁸</td>
<td>Rat</td>
<td>M</td>
<td>Psychogenic</td>
<td>IMO</td>
<td>180 min</td>
<td>180 min</td>
<td>Prazosin, metoprolol and prazosin + metoprolol</td>
<td></td>
</tr>
<tr>
<td>Paur et al, 2012²⁵</td>
<td>Rat</td>
<td>M</td>
<td>Pharmacologic</td>
<td>Epinephrine</td>
<td>78.4 μg/kg</td>
<td>60 min</td>
<td></td>
<td>Levosimendan</td>
</tr>
<tr>
<td>Shao et al, 2013²⁶</td>
<td>Rat</td>
<td>?</td>
<td>Pharmacologic</td>
<td>Isoproterenol</td>
<td>50–450 mg/kg</td>
<td>120 min + 10 days</td>
<td>√</td>
<td></td>
</tr>
<tr>
<td>Shao et al, 2013²⁶</td>
<td>Mouse</td>
<td>?</td>
<td>Pharmacologic</td>
<td>Isoproterenol</td>
<td>400 mg/kg</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Shao et al, 2013²⁶</td>
<td>Mouse</td>
<td>?</td>
<td>Pharmacologic</td>
<td>Isoproterenol</td>
<td>400 mg/kg</td>
<td>120 min + 10 days</td>
<td>√</td>
<td>Adenosine</td>
</tr>
<tr>
<td>Redfors et al, 2014²⁵</td>
<td>Rat</td>
<td>M</td>
<td>Pharmacologic</td>
<td>Isoproterenol</td>
<td>50 mg/kg</td>
<td>90 min</td>
<td></td>
<td>Phenylephrine</td>
</tr>
<tr>
<td>Redfors et al, 2014²⁵</td>
<td>Rat</td>
<td>M</td>
<td>Pharmacologic</td>
<td>Dopamine</td>
<td>25 mg/kg</td>
<td>90 min</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Redfors et al, 2014²⁵</td>
<td>Rat</td>
<td>M</td>
<td>Pharmacologic</td>
<td>Phenylephrine</td>
<td>1 mg/kg</td>
<td>90 min</td>
<td></td>
<td>Hydralazine</td>
</tr>
<tr>
<td>Redfors et al, 2014²⁵</td>
<td>Rat</td>
<td>M</td>
<td>Pharmacologic</td>
<td>Epinephrine</td>
<td>1 mg/kg</td>
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<td>Redfors et al, 2014²⁵</td>
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<td></td>
<td>Hydralazine</td>
</tr>
</tbody>
</table>

F, female; IMO, immobilization stress; M, male.

acute phases, because TTS can be provoked and samples and physiological data can be rapidly acquired. We define time zero as the point at which the patient initially suffers the causative stressor, the administration of exogenous catecholamine, or the initiation of the stressor in animal models. The factors preceding this trigger are outside the scope of this review.

**Time Course**

0-60 Seconds

Plasma levels of catecholamines, and in some cases sympathetic neural activity, should be elevated rapidly to peak levels within seconds of a stressful trigger or exogenous bolus of intravenous catecholamines. Catecholamines will begin to bind both α- (αAR) and β-adrenergic (βAR) receptors of all subtypes. The particular organs and cells of interest are the endothelium and smooth muscle of the vasculature, both coronary and peripheral, and the cardiomyocytes of myocardium. Both αARs and βARs are G-protein coupled receptors (GPCRs), which can rapidly activate secondary messenger pathways. Because of advances in molecular biology, extremely rapid imaging of GPCR function is now relatively straightforward using Förster resonance energy transfer (FRET) microscopy, which has yielded interesting insights into the kinetics of βAR activation. In isolated cardiomyocytes, cAMP is rapidly generated in the cytoplasm following application of exogenous catecholamines, reaching a maximum at ~60 s for both the β1AR and β2AR in adult rodent cardiomyocytes.²³

In our rat TTS model,¹⁰ which involves administering a high-dose intravenous epinephrine bolus, we observe a rapid and extreme elevation in aortic blood pressure within seconds of injection, analogous to the symptoms of sympathetic drive felt by patients within seconds of the stressful trigger. This is initially a positive inotropic response throughout the LV myocardium, and peripheral vasoconstriction with rapid elevation of both systolic and diastolic aortic pressures (Figure 4). This hypertensive surge activates an initial reflex bradycardia, demonstrating the importance of observing all elements of the cardio-circulatory response, as proposed by Redfors et al.²⁴ They recently reported that multiple catecholamines (epinephrine, norepinephrine, dopamine and phenylalanine) with αAR activity/efficacy, injected intraperitoneally, are able to induce TTS-like dysfunction in rats (albeit of the inverted type) and show initial elevations in central blood pressure.²⁵ This is an intriguing finding, because isoproterenol, which robustly induces classical apical ballooning when administered to rats or mice intraperitoneally,⁹,²⁶ initially causes acute hypotension. This suggests that acute changes in systemic vascular resistance and aortic pressure may have some effect on which myocardial region is dysfunctional, and show the importance of ventriculo-arterial coupling in understanding the responses to catecholamine surges. However, as few publications have reported parameters from this phase, it is difficult to draw comparisons.

1-10 Minutes

The hypertensive phase persists in animals treated with IV epinephrine or norepinephrine, and after Gi ablation by pertussis toxin and subsequent epinephrine treatment.⁸ When injected intraperitoneally, epinephrine, norepinephrine and dopamine induce their maximal effects on pressure at diastole and systole at approximately 5 min.²⁸ There is a disconnect between models, because when injected intravenously, epinephrine induces its effects on pressure almost instantly and this is achieved with a dose many orders of magnitude lower than that supplied intraperitoneally. The data from the respective
models should be compared with caution, because pharmacokinetic factors may account for these differences. Isolated cardiomyocyte studies performed by our group exploring the effects of $\beta_1$AR or $\beta_2$AR demonstrated that stimulation of $\beta_1$AR by isoproterenol (selectively blocking $\beta_2$AR) results in rapid positive inotropy (<1 min). In contrast any inotropy caused by $\beta_2$AR stimulation only occurs in apical cells, and occurs only after 5 minutes. This may not truly correlate with activity in vivo, but one may hypothesize that at this time-point the $\beta_1$AR are beginning to exert positively inotropic effects via PKA-mediated phosphorylation of downstream effectors. We can surmise that the cardiotoxic effects of cAMP/PKA may begin at this stage. The presence of hypertension caused by both norepinephrine and epinephrine in our model suggests that within the vasculature the vasoconstrictive effects of $\alpha$AR are overwhelming the vasodilatory effects of $\beta$AR in the peripheral vasculature. The acute effects upon the coronary vasculature remain to be determined, although both preclinical and clinical studies have failed to show apical perfusion abnormalities during the acute phase.

Figure 4. Graphs of the acute effects of epinephrine, norepinephrine and epinephrine with G-protein ablated (reproduced with permission from Paur H, et al). (A) Effect of epinephrine on pressure for the first 7 min following intravenous infusion. (B) An expanded view showing the pressures in the first 40 s. (C) Comparison of the different agents' effects on peak systolic blood pressure. (D) Comparison of the effects on peak systolic blood pressure. (E) Chart presenting the lowest heart rates (HR) caused by the agents in the vagal phase.
Ultra-Acute Clinical Phase (0-1 Hour)
The delay between the onset of the patient’s symptoms and the first clinical assessment means it is rare to observe the very earliest clinical phenotype directly, though many researchers are beginning to report cardiovascular parameters from animal models at this time-point; for instance, the apical depression induced by psychogenic models of emotional stress results at approximately 20 min following this time-point. Izumi et al reported the effects of epinephrine infusion in cynomolgus monkeys as large increases in their systolic and diastolic blood pressures (~50 mmHg to 150 mmHg and ~20 mmHg to 90 mmHg, respectively). The rat data confirms that systemic hypertension is present continuously for 10 min, though epinephrine treatment did not cause any significant apical depression in relation to the base at this time-point in the rat whereas norepinephrine increased contractility. This also seems to be the case after intraperitoneal isoproterenol treatment. Clearly, there must be pharmacodynamic differences following intraperitoneal delivery, which prevents accurate temporal comparison between these models. Izumi et al report a profound depression of ejection fraction at this time-point that was only slightly ameliorated by metoprolol. Wittstein et al report that on day 1 of TTS, patients may have plasma concentrations of ≈1.2 ng/ml, when taken hours (many plasma half-lives) following the onset of symptoms.

There have been many cases of secondary TTS associated with medical, surgical or psychiatric emergencies when these have occurred in situations where medical monitoring has been present, such as during surgery, anesthesia induction and cardiac investigation. There is a broad spectrum of secondary causes with a common theme of high catecholamine levels. Indeed, interesting observations have been reported by the psychiatry community regarding the prevalence of anxiodepressive symptoms among those afflicted by TTS.

It is rare to directly observe the acute effects, and only occurs when medical monitoring is already present. Considering 2 cases of TTS with different etiologies (epinephrine and cocaine (Moffett’s solution) application to the nasopharynx and anesthesia induction with subsequent intubation), sinus tachycardia, hypertension with a pronounced pulse pressure (as high as 227/121 mmHg) and ST-segment elevation were present in both. It is known that tracheal intubation can cause hemo-
dynamic disturbances that are linked to a hyperadrenergic state, and recreational cocaine use is associated with TTS because it is a sympathomimetic.

Patients report symptoms in the seconds following their stressful trigger (in this clinical ultra-acute phase), consistent with an “adrenaline rush” or panic attack. In conscious patients, this could lead to a vicious cycle increasing the individual's adrenergic state and prolonging epinephrine release, although perhaps not to the same extent in the anesthetized individual, because the conscious fear would be removed. However, in the anesthetized patient the potential presence of antimuscarinic drugs may also limit the vagal response to hypertension, and therefore, in both the conscious and unconscious state, the initial sympathetic response may not be corrected as it should be through the usual baroreceptor negative feedback.

ST-segment elevation is a commonly reported ECG finding in TTS patients, which appears to precede the clinical apical dysfunction and cardiogenic shock. Whether the ST-segment is epiphenomenal (ie, a separate effect of increased circulating catecholamines) or is part of the disease pathophysiology is yet to be ascertained.

Another feature of this ultra-acute phase in some patients is the development of acute LV outflow tract obstruction (LVOTO). In 1 cohort, an LVOT pressure gradient was present in 4 TTS patients, with TTS recapitulated throughout this pressure gradient during dobutamine stress echocardiography, and overall ~10-15% of TTS patients have a hemodynamically significant LVOTO during the acute phase. This pressure gradient, and subsequent evolution into a mid-cavity LV obstruction, could exacerbate the apical dysfunction, because it would expose the apex to higher wall stress compared with the basal myocardium. This high apical wall stress could cause apical ischemia superimposed on the catecholaminergic stunning. This has recently been shown in an animal model of TTS, where low afterload and isoproterenol (a positive inotrope with hypertensive effects) caused an increase in wall stress in the apical myocardium because of LV lumen obliteration. However, the relevance of LVOTO in the majority of TTS patients is perhaps limited, because only 10-15% show it. Nonetheless, a subclinical LVOTO may still contribute to apical dysfunction induction.

1-12 Hours

Although the clinical presentation of a TTS is heterogeneous and may present many hours or days after the initial triggering stress and peak catecholamine surge, the textbook TTS patient presents with chest pain, dyspnea and ST-segment elevation, mimicking acute MI. At angiographic examination the coronary vessels appear unobstructed (although bystander CAD may exist) and the eponymous “octopus-pot” shape of the LV is observed during left ventriculography. At the time of clinical presentation, plasma catecholamines are still markedly raised, even above that of a severe (Killip class III) MI.

The 60-min time-point is interesting when observed in animal models. The intravenous epinephrine model of apical hypocontractility induced in rats has largely reversed by the 60-min time-point, whereas models of TTS based on intraperitoneal doses of isoproterenol do not reach complete apical ballooning until approximately 70 min. Psychogenic models of TTS do not report any physiological data following 20-30 min, but report the induction of many genes relating to HF and calcium handling. Monkeys still suffer a similar degree of LV dysfunction to that they were undergoing at 10 min. At this time-point, myocytolysis and the induction of HF-related genes are observed in these primates. Isoproterenol infusion begins to induce lipid peroxidation and accumulation at approximately 2 h. The study by Redfors et al showed that all catecholamines administered were able to induce either inverted or classical TTS by the 90-min time-point.

24-72 Hours

During this period, there are a series of molecular, structural and clinical changes that may offer clues to the underlying disease process. In a study of endomyocardial biopsies taken from TTS patients within 12 h of admission, researchers found increases in superoxide production compared with control samples and paired samples taken 21 days later when cardiac contractility had increased; this was associated with an increase in Nrf2-induced gene transcription. Furthermore, decreases in transcript number were seen for glucose and glycogen metabolism proteins, indicating a shift to lipid metabolism. In decompensated HF, glucose metabolism increases while free fatty acid decreases; perhaps in TTS the inhibition of this metabolism switch is a further attempt to protect the heart.

AKT-1 phosphorylation is increased in the acute phase (within 12 h of admission) in endomyocardial samples, and this returns to baseline after functional recovery at follow-up weeks. Cardioprotective AKT-1 activation is associated with physiological hypertrophy, whereas a reduction in the AKT/mTOR pathway is associated with pathological hypertrophy. Interestingly, it has been reported that β2AR–Gi signaling can modulate the cellular PI3K/AKT pathways, indicating a mechanistic link between catecholamine stress and metabolic defects in TTS.

This provides some clinical evidence to support the hypothesis that TTS may be cardioprotective against the toxic storm of catecholamines; the medium term prognosis of TTS is reasonable (subject to surviving the acute phase without serious complications), despite the propensity for cardiogenic shock and other acute complications, suggesting potential protection mechanisms being activated in the heart. The Gi activation in the first 30 min could lead to AKT activation.

On admission, the ejection fraction is lower than the normal range and remains depressed at 24 h after initiation. Two patterns of surface ECG exist in TTS patients: the initial ST-segment elevation is observed in the first 24 h after TTS initiation, with J waves and fragmented QRS complexes also present in a subset of TTS patients. The most striking observation is the evolution in the 24–72 h period of widespread, deep T-wave inversion and significant QT prolongation when compared with the ambulatory or admission ECG. T-wave inversion could help differentiate acute coronary syndrome (ACS) and TTS. Recent studies have shown that T-wave inversion in aVR (ie, a positive T-wave) has a high predictive accuracy; there is a low proportion of ACS patients with this ECG finding. The QTc interval then progressively prolongs in this phase. Collectively, this could be described as the second electrocardiographic TTS phase, where the initial has ST-segment elevation. The mechanisms are incompletely understood, with 1 group proposing the ECG changes may reflect preferential KATP activation of epicardial cardiomyocytes.

There is also a distinct pattern of circulating biomarkers, compared with ACS. Compared with both ST-segment elevation MI (STEMI) and non-STEMI (NSTEMI), at 24 h the plasma NT-proBNP is raised, whereas troponin T is only mildly increased relative to the extent of myocardial dysfunction. Indeed, it is rare to have a normal BNP or NT-proBNP levels during the acute phase, suggesting natriuretic peptides could form part of future diagnostic criteria.
3–7 Days
In most patients cardiac function will be improving by 3 or 4 days after the start of TTS. A study using serial echocardiography in TTS patients showed that LV systolic function measured between days 3 and 7 after admission had significantly improved compared with LV function at the time of admission, even though plasma catecholamines were still significantly raised.9 This was confirmed in a later study that showed 94 of 126 patients had normalized LV function at their first follow-up (3.3±3.4 days).4 However a significant minority of patients have less favorable outcomes, with in-hospital mortality of approximately 0.5–1% from cardiogenic shock and multi-organ failure.5

Conclusions
We are beginning to understand that TTS is a disorder that can be sparked by a multitude of stressors. The central role of catecholamines and their defined cardiotoxic mechanisms mean that there are likely to be a small number of pathophysiological mechanisms. Analogous to MI following coronary atherosclerotic plaque rupture, the pathophysiology can be considered in distinctive temporal phases, with the specific phenotype and development dependent upon the degree of severity and the context of stressors (Figure 5). Catecholamines activate GPCRs within seconds, and the acute systemic effects following intravenous epinephrine administration support this immediate positive inotropic and vasoconstrictor effect. Acute apical depression can be evoked within 20–40 min of catecholamine administration in animal models, suggesting that the mechanisms involve acutely modifying the contraction of individual cardiomyocytes, together with systemic ventriculo-arterial coupling, with these combining to define the final phenotype. As there does not appear to be an ischemic or vascular effect in most clinical cases and animal models of TTS, we hypothesize that loss of contractility is an active process rather than myocyte loss as is observed in acute MI. The observation from 2 separate groups8,9 that interfering with the signaling of β1AR, and specifically β2AR-Gi signaling, ameliorates TTS-like symptoms in rodents may suggest a central role for this process. The reversibility of TTS-like symptoms in these models further reinforces their usefulness. Metoprolol, which stimulates further enforces their usefulness. Metoprolol, which β2AR, and specifically β2AR affinity ratio ~2.3:1, slightly reverses the symptoms of TTS but not acutely and not dramatically over the days that apical depression exists.11 Two studies show that β2AR activity, protein and mRNA are higher in the apical myocardium, suggesting a regional difference in receptor expression,8,11 which may be being subverted in TTS.

A number of other observations must be integrated into the development of an advanced pathophysiological model, including the changes in endothelial and neural physiology following the acute catecholamine storm. The findings relating to lipid accumulation and effects on the induction of genes relating to calcium handling and cell survival are important,54 although perhaps reflect a later phase of the pathophysiology.

It is also appropriate to highlight that it is not known whether the apical dysfunction observed in TTS elicits before or is concomitant with the production of symptoms in TTS patients. We would encourage greater cross-collaboration with colleagues in a variety of medical disciplines to investigate this truly fascinating syndrome.

Disclosures
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