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Pathophysiology of Takotsubo Syndrome

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ABSTRACT

Takotsubo syndrome (TTS) has been a recognized clinical entity for 31 years, since its first description in 1990. TTS is now routinely diagnosed in patients who present with acute chest pain, electrocardiographic changes, troponin elevation, unobstructed coronary arteries, and a typical pattern of circumferential left ventricular wall motion abnormalities that usually involve the apical and midventricular myocardium. Increasing understanding of this intriguing syndrome stems from wider recognition, possible increasing frequency, and a rising number of publications focused on the pathophysiology in clinical and laboratory studies. A comprehensive understanding of TTS pathophysiology and evidence-based treatments are lacking, and specific and effective treatments are urgently required. This paper reviews the pathophysiology of this fascinating syndrome; what is known from both clinical and preclinical studies, including review of the evidence for microvascular dysfunction, myocardial beta-adrenergic signaling, inflammation, and electrophysiology; and where focused research needs to fill gaps in understanding TTS. (J Am Coll Cardiol 2021;77:902–21) © 2021 Published by Elsevier on behalf of the American College of Cardiology Foundation.

Takotsubo syndrome (TTS) is an acute cardiac syndrome characterized by typical regional wall motion abnormalities that reflect impairment of myocardial contractility that leads to acute heart failure in the absence of culprit epicardial coronary artery disease (1). Patients with TTS can present with a variety of different clinical patterns; the syndrome is precipitated frequently by significant emotional stress or serious physical illness accompanied by activation of the sympathetic nervous system (2,3) (**Figure 1**). Over the last 31 years, there has been an increased awareness of this clinical syndrome, with patients presenting with acute cardiac chest pain to urgent coronary angiography, in which culprit coronary disease is excluded. TTS can be diagnosed promptly with access to modern cardiac imaging. TTS is most frequently seen in postmenopausal women, and the clinical presentation is usually similar to acute myocardial infarction, with chest pain and/or dyspnea, ST-segment elevation or depression and/or T-wave inversion on the resting electrocardiogram (ECG), and elevation of serum cardiac troponin (1,2,5). However, there are substantial differences between cases with TTS and acute myocardial infarction, and TTS is now recognized as a separate clinical entity. Acute complications can be severe, including a 4% to 5% in-hospital mortality related to cardiogenic shock and cardiac arrest (6,7). There is a growing recognition that survivors of TTS may experience long-term cardiac and noncardiac

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HIGHLIGHTS

- The pathophysiology of the Takotsubo form of acute heart failure is incompletely understood.
- Excessive release of cardiac neuronal and systemic catecholamines contributes to acute myocardial dysfunction in patients with Takotsubo syndrome, but impaired microvascular perfusion, myocardial inflammation, and electrophysiological derangements contribute to its clinical manifestations.
- Takotsubo stunning, which involves both catecholaminergic and ischemic mechanisms, is the pathophysiological framework underlying this syndrome, which is critical to the development of effective diagnostic and therapeutic strategies.

health problems, and increased long-term mortality (8,9). Therefore, TTS is not the benign condition it was previously considered to be, and in the absence of evidence-based treatments, patients with TTS continue to have an increased risk of complications, morbidity, and mortality (1,6,7,10). TTS is classified as a myocardial injury, but not infarction, in the recent Fourth Universal Definition of Myocardial Infarction (11).

In this review, we discuss the pathophysiology of this fascinating syndrome, areas of controversy, and where we need to focus research to fill gaps in our understanding.

PATHOPHYSIOLOGY OF TTS

The exact pathophysiology of TTS is not known. However, significant progress has been made over the last decade in our understanding of this syndrome (12–16). This progress is evident from the increasing number of publications of laboratory and clinical studies on the pathophysiology of TTS. Several hypotheses have been proposed but none offer a comprehensive explanation (12).

Various elements need to be considered to explain the pathophysiology of TTS, including answers to the following questions:

1. What is the cause of severe mechanical dysfunction (akinesia) and for the characteristic distribution of akinesia in the left and right ventricles (apical, midventricular, basal, biventricular)?
2. Why do some individuals develop TTS, whereas others do not (ceteris paribus—all other things being equal—when exposed to the same stressor event)?
3. Why do some patients with TTS tolerate such extensive left ventricular (LV) dysfunction compared with patients with acute myocardial infarction when acute myocardial infarction involving a similarly sized portion of the LV would usually lead to death?
4. Why is there such a strong preponderance of postmenopausal women affected by TTS?
5. What are the mechanisms behind the recovery of LV function that typically occur within a few days?
6. Why are some TTS survivors left with significant cardiac abnormalities (e.g., arrhythmias, chest pain, exertional limitation) and others are not?

In addition to the preceding questions, it has been debated whether TTS is a primarily maladaptive or protective cardiocirculatory response. Therefore, in the opinion of the authors, it is likely that several different pathophysiological pathways may act, individually or synergistically, to cumulatively lead to TTS.

INTENSE SYMPATHETIC ACTIVATION AND ELEVATED CIRCULATING CATECHOLAMINE LEVELS

Catecholamines appear to have a central role in the pathophysiology of TTS because acute episodes are frequently triggered by sudden, unexpected stress (primary TTS) or major physical illness or trauma (secondary TTS) (1,2) (**Figure 1**). In most patients, the clinical signs of intense sympathetic activation are present at the onset of TTS, and many patients with TTS describe the feeling of an intense adrenaline rush with the triggering stress at the onset of the acute episode.

There are 2 initial elements of physiology to consider. The first is the cognitive centers of the brain and hypothalamic-pituitary-adrenal axis, the perception of stress, and how much epinephrine and norepinephrine are released in response to a given stress (i.e., the gain of the hypothalamic-pituitary-adrenal axis). The second is the response of the cardiovascular system (including the myocardium, coronary arteries, and peripheral vasculature) and the sympathetic nervous system to the sudden sympathetic activation and a surge in circulating catecholamines.

Several pieces of evidence support the hypothesis that catecholamines have a central role in the

ABBREVIATIONS AND ACRONYMS

ANS = autonomic nervous system

APD = action potential duration

ATP = adenosine triphosphate

βAR = β-adrenoreceptor

cAMP = cyclic adenosine monophosphate

ECG = electrocardiography

iPSC-CMs = inducible pluripotent stem cell-derived cardiomyocytes

LV = left ventricle

MIBG = 123I-metaiodobenzylguanidine

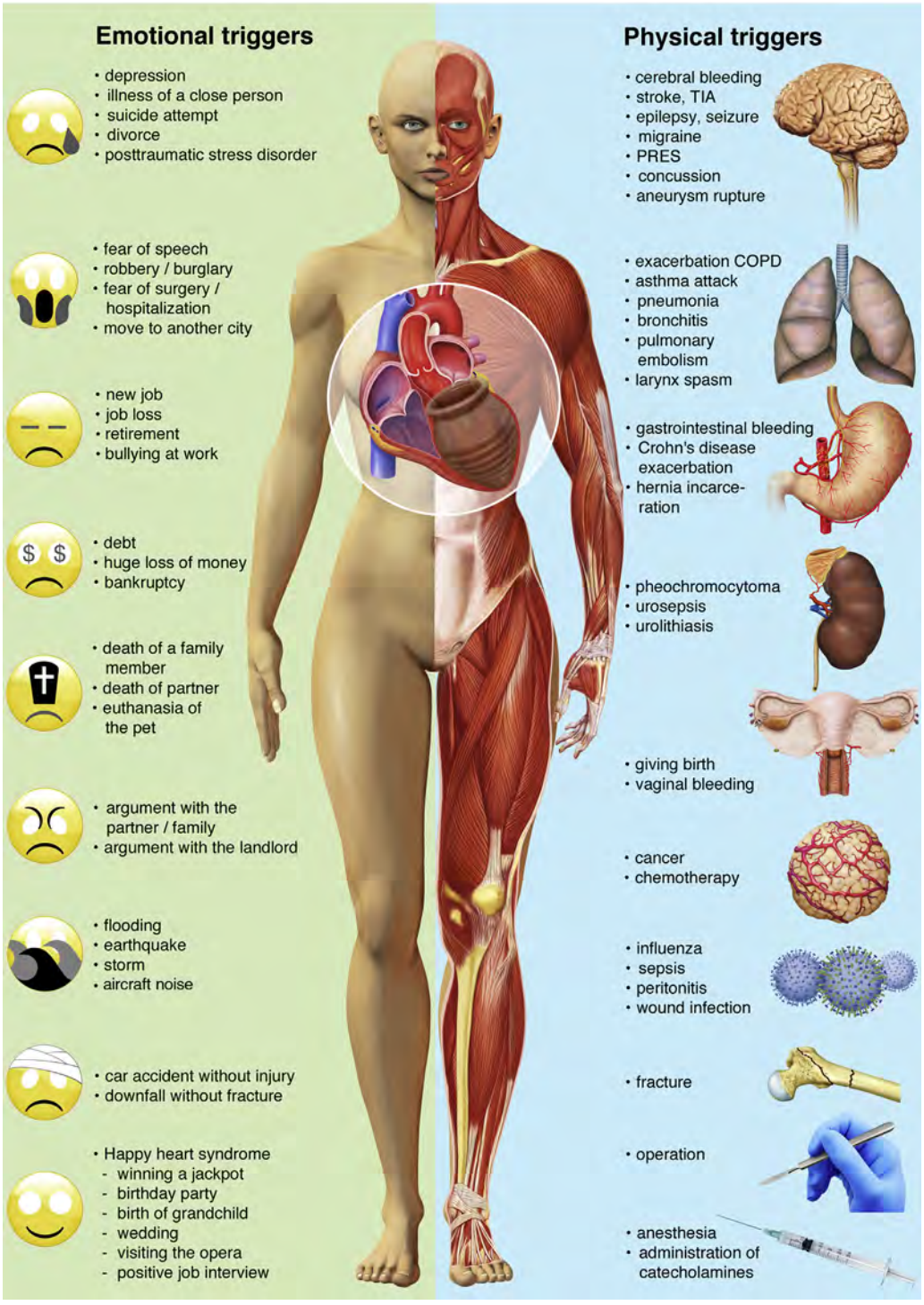
NO = nitric oxide

PCr = phosphocreatine

SERCA2a = sarcoplasmic reticulum (SR) Ca^{2+}-adenosine-triphosphatase 2a

TTS = Takotsubo syndrome

FIGURE 1 Examples of Primary (Emotional) and Secondary (Medical) Causes of Takotsubo Syndrome



There are many potential triggers of Takotsubo syndrome including emotional events **(left panel)** and physical and acute medical or surgical triggers **(right panel).** COPD = chronic obstructive pulmonary disease; PRES = posterior reversible encephalopathy syndrome; TIA = transient ischemic attack. Reprinted with permission from Schlossbauer et al. (4).

pathophysiology of TTS (**Figure 2**). First, the levels of plasma catecholamine are substantially elevated in patients with TTS, up to 3 times higher than those in patients presenting with acute myocardial infarction and post-infarction heart failure (19). Second, TTS has been reported in many patients as a cardiac complication of pheochromocytoma (20). Third, iatrogenously administered catecholamines (epinephrine, dobutamine) and β-adrenoreceptor (βAR) agonists (salbutamol) have been documented to directly trigger episodes of TTS (21,22). Fourth, the sympathetic storm associated with subarachnoid hemorrhage, particularly when affecting the posterior circulation and hypothalamus, is a recognized cause of TTS. Fifth, iodine-123 meta-iodo-benzyl-guanidine myocardial scintigraphy studies have shown an acute reduction in cardiac sympathetic neuronal uptake in the affected segments. This is consistent with acute dysregulation of localized myocardial sympathetic physiology that contributes to higher local myocardial catecholamine levels as clearance kinetics are reduced. Sixth, the histopathological findings from hearts of patients with TTS, either postmortem or via endomyocardial biopsy, are similar to those from patients who died in the context of catecholamine excess (e.g., pheochromocytoma and subarachnoid hemorrhage), with features typical of excessive catecholamine activation, including contraction band necrosis (23), increased cardiomyocyte lipid droplet accumulation (24), and increased nitrosative stress (25). Finally, the administration of high catecholamine doses in preclinical models can recapitulate TTS features with reversible apical and midventricular hypokinesis, and in some experiments, the basal or inverted variant can be induced (24,26–29).

In support of excessive cardiac and systemic sympathetic stimulation, elevated norepinephrine levels in the coronary sinus have been found in patients with TTS, which suggests an increase in the local release of myocardial catecholamines (30). Heart rate variability analyses in patients with TTS have also demonstrated a sympathetic predominance and marked depression of parasympathetic activity during the acute phase (31). Micro-neurographic studies of peripheral sympathetic nervous system activity have shown conflicting results. Although some studies have reported increased activity (32), others have shown paradoxically reduced peripheral sympathetic nerve activity (33). This discrepancy may depend on the timing of measurements concerning the onset of TTS and on different patient populations included in studies regarding age, sex, and the presence of traditional cardiovascular risk factors (e.g., hypertension and smoking habits). Micro-neurographic studies have shown decreased spontaneous baroreflex control of sympathetic tone in some patients with TTS. During the acute phase, there is reduced cardiac sympathetic neuronal function, which is measured using 123I-meta-iodobenzylguanidine myocardial scintigraphy in the aftermath of the sympathetic storm (34) (**Figure 2**).

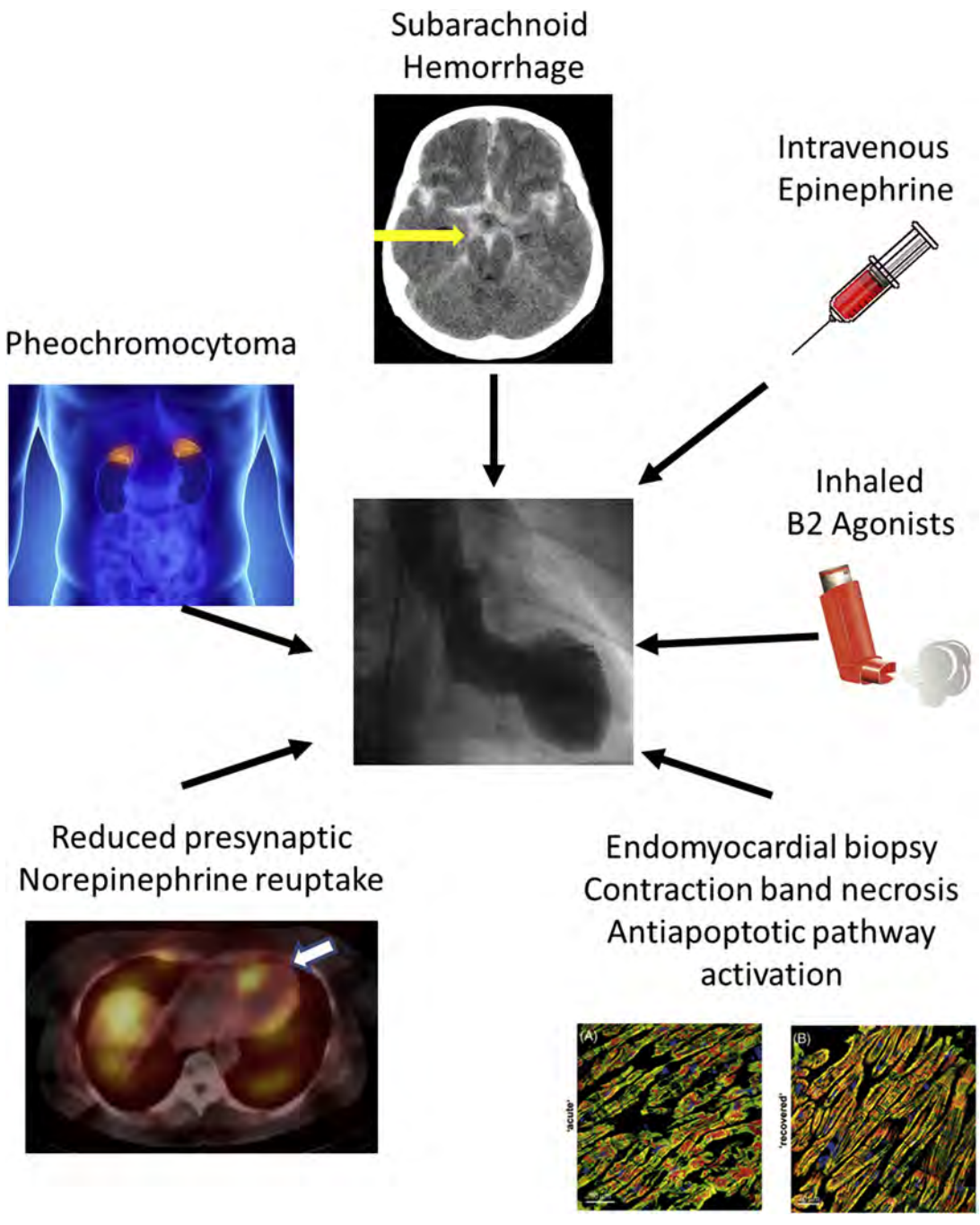
Overactivation of myocardial sympathetic function is associated with an interstitial mononuclear inflammatory response and contraction band necrosis (a hallmark of catecholamine toxicity) (19). The central role of βAR stimulation in TTS has been demonstrated in several animal models (26,35,36). Apical ballooning can be provoked in rats by immobilization stress and attenuated by α- and βAR blockade (37).

However, up to 25% of cases have no identifiable stressful trigger. In these cases, either a spontaneous internal trigger must occur (e.g., inflammation-induced catecholamine release) or cumulative effects of previous stresses may be responsible in the absence of a stressful event on the day of presentation.

SEX DISPARITY IN INCIDENCE OF TTS

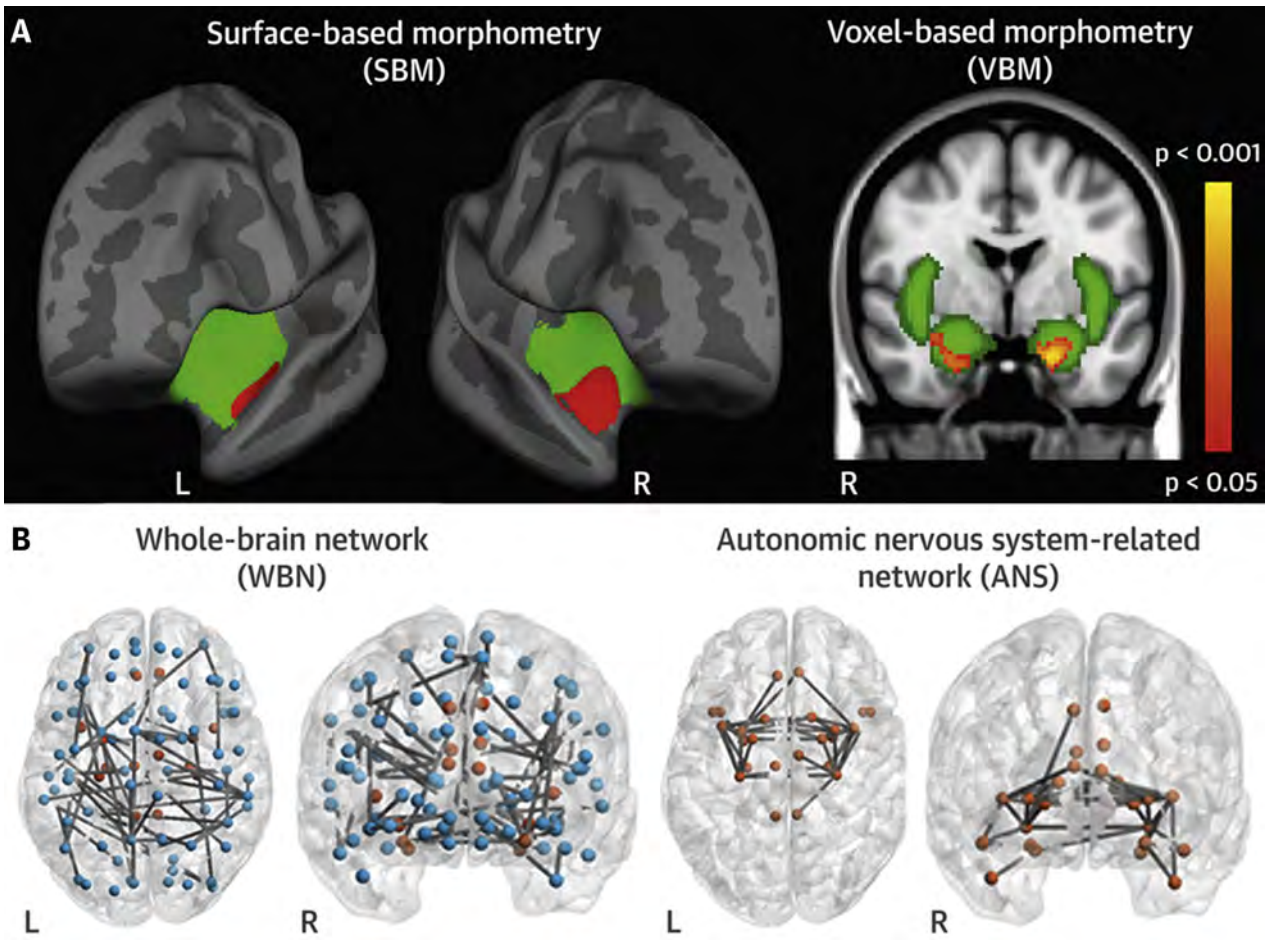
Most patients with TTS are postmenopausal women. The reason for the large sex disparity in the incidence of TTS is not well understood. Several hypotheses centered on estrogen deprivation have been proposed. Under physiological circumstances, estrogen plays a permissive role in adrenergic receptor signaling, such that estrogen (via receptor crosstalk) inhibits signal transduction through βARs (38). Estrogen has a sympatholytic effect and decreases the number of βARs receptors in cardiac cells. Reduced estrogen levels during menopause increase sympathetic drive and endothelial dysfunction. In an experimental study, Ueyama et al. (37) showed that stress-induced LV apical ballooning in rats could be prevented by pre-treatment with estrogen. Estrogen supplementation attenuated the stress-induced hypothalamo-sympatho-adrenal outflow from the central nervous system to the target organs (37). Postmenopausal women have increased sympathetic and decreased parasympathetic tone compared with women with a menstrual cycle (39). The alteration in the autonomic nervous system during menopause could facilitate TTS development in susceptible subjects upon exposure to emotional and physical stress triggers. The sex disparity in TTS could be the consequence of different coping strategies for stress in men and women. Although men use problem-focused methods of handling stressful experiences,

FIGURE 2 Potential Causes of High Catecholamines Levels and Sympathetic Activation in Takotsubo Syndrome



(Top panel) A contrast computed tomogram of brain subarachnoid hemorrhage **(yellow arrow)**. **(Middle panels)** Causes, including pheochromocytoma **(left)**, intravenous epinephrine **(middle upper right)**, and inhaled beta agonists **(middle lower right)**. **(Bottom panels)** Changes in the myocardial sympathetic neuronal update of 123I-metaiodo-benzylguanidine reduced in the affected apical segments (**lower left; white arrow** indicates apical segments) (reprinted with permission from Cimarelli et al. [17]) and the histological changes during the acute phase following catecholamine excess with contraction band necrosis during the acute phase, which resolved at follow-up biopsy **(lower right)**. Reprinted with permission from Nef et al. (18).

FIGURE 3 Brain Structural and Functional Changes in Patients With TTS



(A) Reduced anteroventral insular cortical thickness (surface-based morphometry [SBM], **red clusters**, cluster-wise $p < 0.05$ corrected; insula in **green**), reduced amygdalar gray matter volume (voxel-based morphometry [VBM], **red-yellow clusters**, voxel-wise $p < 0.05$ corrected; insula and amygdala in **green**), and **(B)** reduced structural connectivity among limbic brain regions (whole-brain network [WBN] and autonomic nervous system [ANS]; ANS nodes in **orange**, all other nodes in **blue**) in patients with Takotsubo syndrome (TTS) compared with control subjects. Reprinted with permission from Hiestand et al. (42).

women tend to use coping strategies that are aimed at changing their emotional responses to a stressful situation (40). Sex differences in coping strategies could explain both why women report more psychological distress than men and why women are more prone to develop TTS.

ABNORMALITIES OF CENTRAL AUTONOMIC NERVOUS SYSTEM IN TTS

Recent studies reported abnormalities in both the functional structure and activity in the areas of the brain related to both emotions and the sympathetic nervous system. The first report in 2014 measured regional blood flow in the brains of 3 patients with TTS during the acute phase and at follow-up after TTS and showed significant changes with increased flow in the basal ganglia, hippocampus, and brain stem (41). Using brain functional magnetic resonance imaging, Hiestand et al (42) studied the structure and resting state functional connectivity of the brain's sympathetic and parasympathetic networks in TTS survivors. The functional magnetic resonance imaging brain scans showed reduced anteroventral cortical thickness of the insular gyrus and reduced amygdala gray matter volume (**Figure 3A**) (42). Both parasympathetic- and sympathetic-associated networks showed reduced resting state functional connectivity in patients with TTS compared with control subjects (43). Function brain networks included the

amygdala, hippocampus, and insula where the structural changes were observed (**Figure 3B**), which supported the evidence of limbic system dysfunction in patients with TTS after an acute episode. A key question is whether these changes were pre-existing and contributed to vulnerability to TTS or were acquired as a result of a major catecholamine storm and TTS episode.

Patients with TTS have altered autonomic nervous system (ANS) function long after index hospitalization and full recovery. Studies about heart rate variability—a marker of sympathetic activity and sympathovagal balance—showed that heart rate variability was altered not only during the acute phase but also several months after the index hospitalization (44). Myocardial scintigraphy with 123I-metaiodo-benzylguanidine (MIBG)—a norepinephrine analogue—was used for imaging in the detection of cardiac autonomic sympathetic denervation. MIBG studies in patients with TTS showed that regional myocardial uptake of MIBG was markedly decreased in the apical akinetic regions of the LV, which suggested disturbances in pre-synaptic norepinephrine uptake and an increased pre-synaptic catecholamine discharge. These abnormalities may persist even 12 months after recovery of contractile function (45).

CONSEQUENCES OF HIGH-CIRCULATING CATECHOLAMINE LEVELS AND ENHANCED SYMPATHETIC STIMULATION

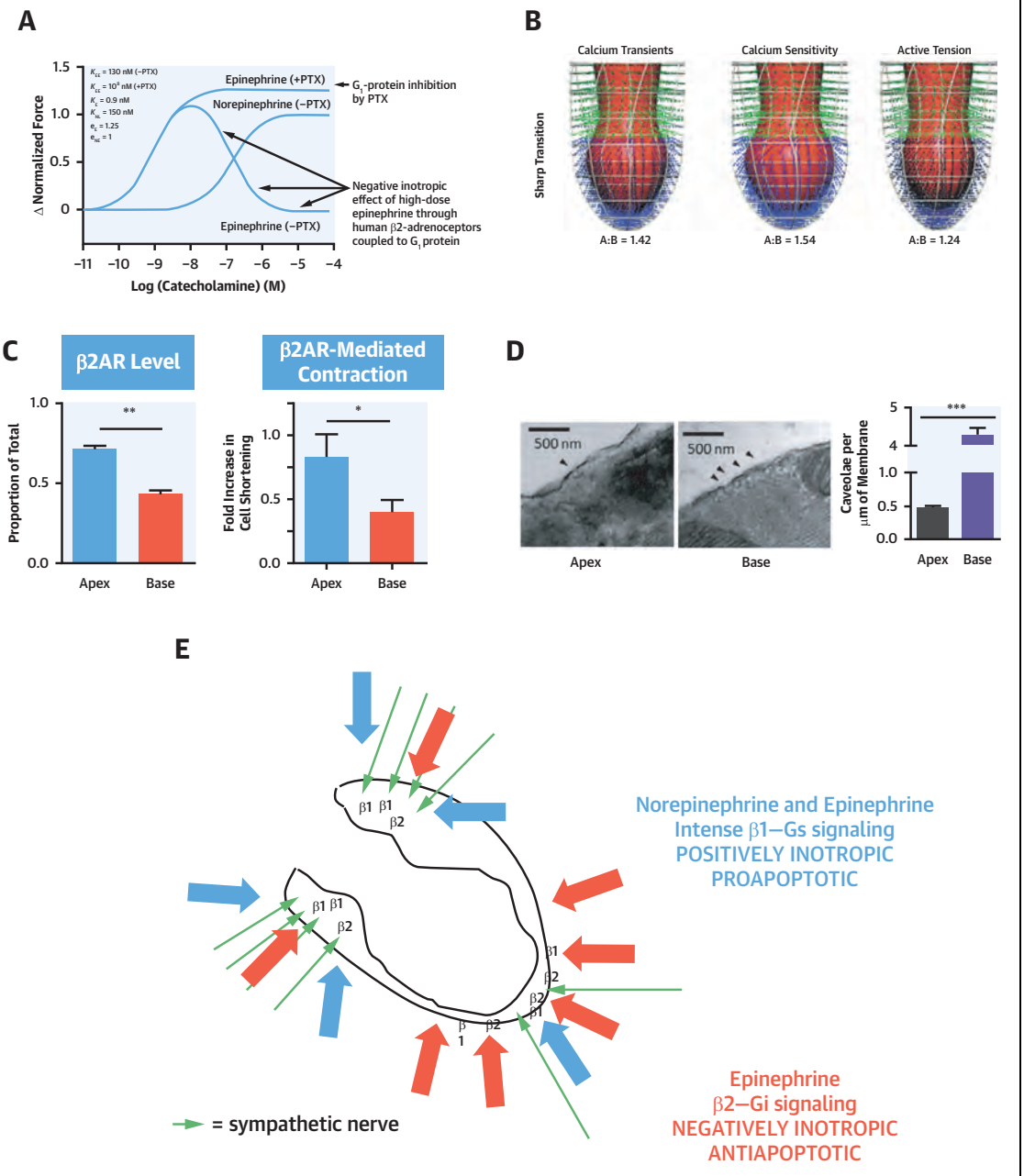
The mechanism by which catecholamine excess precipitates myocardial stunning in the variety of regional ballooning patterns that characterize this syndrome is unknown. Several hypotheses have been proposed as follows.

DYSFUNCTION OF CORONARY MACRO-CIRCULATION AND MICRO-CIRCULATION. Sato et al. (46), who first described a case of TTS in 1990, proposed that microvascular dysfunction and coronary artery spasm caused TTS. This hypothesis was supported by a few case series (47). In addition, reversible perfusion defects in the apical segment of the LV was documented in some patients with TTS. However, these defects in myocardial perfusion were detected at the later stage after the development of cardiac dysfunction (48,49). Therefore, these observations could not be taken as evidence that disturbed myocardial perfusion was the cause of contractile dysfunction in TTS, because coronary perfusion is dependent upon myocardial relaxation (50). Myocardial energy demand, measured by fluorodeoxyglucose–positron emission tomography, is significantly decreased in the akinetic areas in TTS (51). Myocardial fatty acid metabolism is reduced in the akinetic segments of the heart in TTS (49). Autoregulatory mechanisms ensure close correlation between myocardial energy requirements and regional perfusion; therefore, decreased perfusion in these regions is an expected consequence of an episode of TTS if diastolic dysfunction and the metabolic disturbance precede changes in coronary flow (52). Other studies demonstrated normal myocardial perfusion in patients with TTS during the acute phase; perfusion was similar in akinetic apical and hyperkinetic basal LV segments (53). Experimental evidence suggested that catecholamine-induced, TTS-like cardiac dysfunction could occur in the absence of severely disturbed myocardial perfusion. There were no detectable regional perfusion defects preceding or during the development of TTS-like cardiac dysfunction in a pre-clinical rat TTS model (54).

Aborted myocardial infarction was originally proposed by some investigators, but studies using coronary intravascular ultrasound reported no evidence of plaque, dissection, or thrombus in a series of patients with TTS (55).

Epicardial coronary vasospasm was reported during diagnostic angiography in several patients with TTS, and anecdotally, some patients with TTS had a history of Raynaud phenomenon, which suggested they were susceptible to vasospasm. However, vasospasm could be an epiphenomenon following systemic exposure to high epinephrine and norepinephrine levels because TTS can occur in the absences of a perfusion defect. Also, conceptually, vasospasm would have to occur in the mid and distal segments of all major coronary arteries simultaneously to cause typical TTS. This would also have to occur in the basal side branches, but not the main epicardial vessels, to explain the basal and mid-ventricular variants, which appears unlikely in the absence of other factors. The degree of troponin elevation in patients with TTS is relatively modest and disproportionately low compared with the territory of dysfunctional myocardium, suggesting that mechanisms other than ischemic myocyte necrosis are involved in the troponin leak. The lack of substantial necrosis is consistent with low troponin levels and the absence of late gadolinium enhancement in most cases during both the acute phase and at follow-up (19,50). In our opinion, epicardial coronary vasoconstriction could contribute to the pathophysiology in a subset of patients with TTS (56), with the double hit of vasospastic ischemia superimposed on the LV myocardium exposed to high catecholaminergic stimulation (i.e., combined ischemic and

FIGURE 4 Myocardial Responses to High Epinephrine Levels and Activation of β2AR-Gi Signaling With Negatively Inotropic and Anti-Apoptotic Signaling



(A) Contraction dose–response curves for right ventricular myocardial strips from a transgenic mouse overexpressing the human beta 2 adrenergic receptor (β2AR) in response to norepinephrine, epinephrine, and epinephrine following pre-treatment with the G_i inhibitor pertussis toxin (reprinted with permission from Heubach et al. [65]). **(B)** Computer modeling demonstrating the impact of apical-basal βAR gradients on myocardial calcium transients, myofilament calcium sensitivity, and active tension in an in silico model of the left ventricle model with the generation of apical dysfunction with sharp transition of the apical-basal βAR gradients (reprinted with permission from Land et al. [66]). **(C)** Increased β2AR level and responses in apical ventricular cardiomyocytes versus basal ventricular cardiomyocytes (reprinted with permission from Paur et al. [26]). *$p < 0.05$, **$p < 0.01$. **(D)** Increased caveolae in the sarcolemmal membrane of basal ventricular cardiomyocytes compared with the apical ventricular cardiomyocytes that sequester βAR (reprinted with permission from Wright et al. [67]). ***$p < 0.001$. **(E)** Schematic of the opposing sympathetic innervation and βAR gradients in the left ventricle with differential responses to epinephrine and norepinephrine (adapted with permission from Lyon et al. [62]). PTX = pertussis toxin.

neurogenic stunning). However, most patients with TTS do not show any evidence of epicardial spasm, even with the use of provocative agents.

Reduced microvascular blood flow and coronary flow reserve were reported in the acute phase of TTS by some investigators (52-54), and intravenous administration of adenosine was shown to transiently improve myocardial perfusion, wall motion score index, and LV ejection fraction in some, but not all, patients with TTS (55). Administration of the coronary vasoconstrictor acetylcholine in patients with TTS during the convalescence phase was shown to blunt vasomotor responses in a subgroup of patients (56). It should be recognized that adenosine (acting through purinergic receptors) also has potent anti-cathecholaminergic effects mediated by a decreased release of norepinephrine from neuromuscular synapses and by inhibition of signal transduction through adrenergic receptors. Adenosine also has direct effects upon cardiomyocyte function, and therefore, observed effects may not purely be due to a microvascular effect (24,57-60).

There is also clinical and experimental evidence against the "microcirculatory hypothesis." In the largest positron-emission tomography perfusion study to date, Christensen et al. (61) reported that the primary abnormality in TTS is hyperperfusion in basal segments and normal perfusion in apical akinetic segments. Using contrast echocardiography in the experimental model of TTS in rats (with a time resolution of 5 min until the development of isoprenaline-induced apical akinesia), Redfors et al. (29) demonstrated that contractile dysfunction was not preceded by any alteration in myocardial perfusion.

Another proposed hypothesis involves the hormone endothelin-1. Patients with TTS have decreased microRNA 125a-5p and increased plasma levels of its target endothelin-1, which is a potent arteriole vasoconstrictor (57). Endomyocardial biopsies from patients with TTS have shown apoptosis of microvascular endothelial cells (58). In some patients, a cold pressor test 1 to 3 years after the acute episode results in an elevation of catecholamines and transient apical and mid-LV wall motion abnormalities (59).

There is growing evidence of both acute edema and persistent chronic inflammation in the affected LV segments in TTS (see the the section on Inflammation in TTS). Myocardial edema and inflammation could also involve the coronary microvasculature and also lead to acquired microvascular dysfunction. These results were observed in intracoronary provocation and vasodilator pharmacological studies.

In summary, macrovascular and microvascular dysfunction with abnormal vasomotor reactivity are common findings in patients with TTS, but it is not clear if these are the specific cause or a result of the acute TTS episode. Microcirculatory dysfunction, when present in the acute phase of TTS, is transient, and its recovery correlates with improved myocardial function. This suggests that alterations in coronary microcirculation (with previously described associated manifestations) are probably an integral part of the progression of TTS.

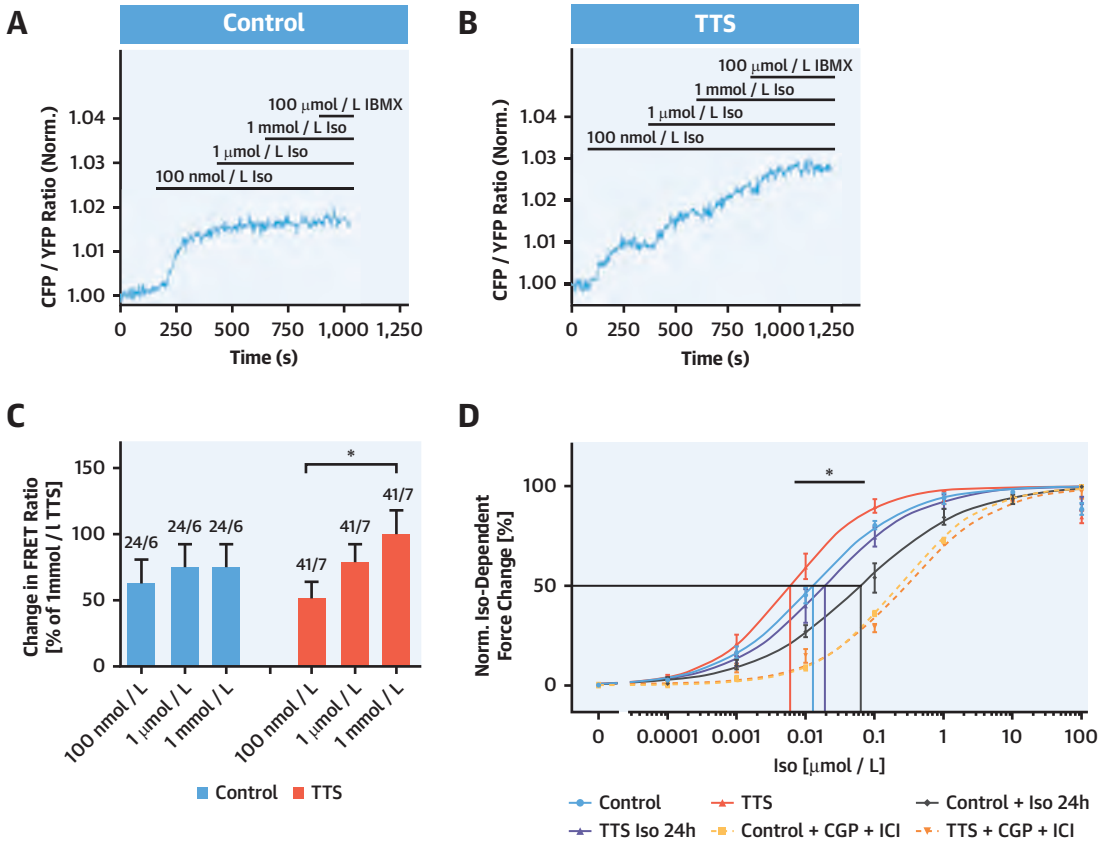
DIRECT EFFECTS OF HIGH CATECHOLAMINES LEVELS ON CARDIOMYOCYTE FUNCTION

Because of the evidence for supraphysiological levels of circulating catecholamines in the serum of patients with TTS (19), several pharmacological studies in preclinical models suggested the myocardial adrenergic receptor pathways are important in the pathophysiology of TTS in response to the supraphysiological catecholamine levels.

There is clinical and preclinical evidence that transient LV dysfunction in TTS may result from the direct effects of catecholamines on the ventricular myocardium, which are known as neurogenic or catecholaminergic stunning. Catecholamines can induce cardiomyocyte dysfunction, arrhythmias and irreversible cellular injury via calcium overload, reactive oxidative species production, and mitochondrial dysfunction following intense activation of the βARs coupled to the stimulatory G_s protein-adenylyl cyclase-cyclic adenosine monophosphate (cAMP)–protein kinase A secondary messenger pathway.

In the healthy mammalian LV from all the species studied, the β1AR and β2AR density is highest in the apex. At the same time, sympathetic innervation is highest in the basal LV myocardium and lowest in the apical myocardium (60,62-64), which suggests that the apical myocardium may be more sensitive to high levels of catecholamines released by the adrenal glands (predominantly epinephrine). Although the receptor density is unknown in human hearts, the apical-basal gradient of sympathetic nerve density is the same as other mammals, with the lowest sympathetic nerve terminal density in the LV apical myocardium and the highest sympathetic nerve terminal density in the LV basal myocardium (60). It is now recognized that although epinephrine is a positive inotrope at low and modest levels via the classical β1AR-G_s and β2AR-G_s pathways, paradoxically, at high levels, epinephrine exerts a negative inotropic effect (26). This negative inotropic effect is due to a

FIGURE 5 Increased Catecholamine-Induced βAR Signaling and Contractile Responses in iPSC-CM From Patients With TTS Compared With Control Subjects Without TTS (71)



(A and B) Representative cyclic adenosine monophosphate (cAMP)-FRET traces from the Epac1-cAMP-FRET sensor in adenovirally transduced inducible pluripotent stem cell-derived cardiomyocytes (iPSC-CMs) from patients with TTS and control subjects stimulated with increasing βAR agonist concentrations (100 to 1 mmol/l Iso). **(C)** Quantification of the FRET experiments. βAR stimulations led to stronger FRET responses in the cytosol in TTS-iPSC-CMs compared with control subjects at higher Iso concentrations of 1 mmol/l. Electrical disturbances in iPSC-CMs of patients with TTS after catecholamine treatment. **(D)** Normalized inotropic dose–response curves of engineered heart tissue synthesized from control subjects **(blue)** and patients with TTS **(orange)**–derived iPSC-CMs in the presence **(dashed lines)** or absence **(solid lines)** of β1AR blockade (CGP) and β2AR blockade (ICI) showing relatively more sensitive responses to low dose isoproterenol stimulation via β1ARs and β2Ars. *P < 0.05. CFP = cyan fluorescent protein; CGP = CGP20712A; FRET = fourier resonance energy transfer; ICI = 118,551; ISO = isoproterenol; YFP = yellow fluorescent protein; other abbreviations as in Figures 3 and 4. Adapted with permission from Borchert et al. (71).

molecular switch of the β2AR from the positive inotropic G_s to the negatively inotropic G_i pathway. It is specific to epinephrine, which is known as stimulus trafficking (Figure 4) (68,69). Although this can reproduce the TTS phenotype, others have demonstrated that β2AR alone is not necessarily the cause for TTS-like dysfunction, at least under the experimental settings (12,35). This suggests that the intense activation of the more prevalent β1AR-Gs may be the initiating step, and the resulting β2AR-phosphorylation and stimulus trafficking to G_i then leads to the negative inotropic response with subsequent epinephrine-mediated β2AR activation. A phosphodiesterase (PDE) inhibitor (e.g., milrinone), by increasing cAMP levels and protein kinase A activation, could also reproduce the same phenomenon (35).

A clinical observation showed that a different regional type of akinesia was reported in 20% of cases of recurrent TTS (70). Although this appeared to conflict with the increased apical distribution of β1AR and β2ARs and the G_s-G_i switch hypothesis, βAR expression was downregulated after sympathetic stimulation. This might lead to different regional β1AR distribution following a TTS episode, and

therefore, change the anatomical TTS variant for some patients during a subsequent episode.

Several studies reported increased βAR density in apical cardiomyocytes compared with basal ventricular cardiomyocytes from the same heart. This supported the observations of many differences in apical and basal responsiveness to catecholamines, with apical cells showing increased sensitivity and inotropic responses to normal physiological levels of catecholamines (26). Recently, more studies showed ultrastructural differences between apical and basal ventricular cardiomyocytes isolated from the same rodent hearts which might explain the apical–basal differences (67). Basal ventricular cardiomyocytes have almost a 10-fold higher density of caveolae on the sarcolemmal membrane compared with apical ventricular cardiomyocytes from the same heart (67) (**Figure 4**). β2ARs are known to be sequestered in caveolae. This restricts access to catecholamine ligands in the extracellular space and uncouples β2ARs from the G-protein secondary messenger pathways, so ligand activation does not result in cAMP production. Pharmacological disruption of caveolae in cellular studies converted basal ventricular cardiomyocytes to a more apical phenotype with increased catecholamine sensitivity (67). Furthermore, in silico modeling studies showed that increased βAR density at the apex versus the basal LV myocardium resulted in apical ballooning with intense activation (66) (**Figure 4**).

The central role of βARs was recently highlighted in studies of inducible pluripotent stem cell–derived cardiomyocytes (iPSC-CMs) and engineered heart tissue generated from patients with TTS and compared with iPSC-CMs from female control subjects without TTS. (**Figure 5**) (71). Increased β1AR-cAMP responses were identified, as well as greater sensitivity to catecholamine-induced electrical quiescence at higher doses (**Figure 5**) (71). These responses suggested higher catecholamine sensitivity in ventricular cardiomyocytes from patients with TTS compared with sex-matched control subjects. The same study also engineered heart tissue from iPSC-CMs derived from patients with TTS and showed reduced basal contractile function and increased catecholamine responses. The investigators also reported abnormal lipid metabolism and identified potential differences in cardiomyocyte lipid transporters between patients with TTS and control subjects (71). These insights from iPSC-CM TTS models are interesting, and further studies with cells from age-matched women who have been exposed to similar stresses but were resistant to developing TTS are needed (72).

The β2AR is linked via G_i activation to stimulation of endothelial nitric oxide (NO) synthase, which increases production of NO. NO can react with hydrogen peroxide generated during intense β1AR activation, which generates the toxic-free radical peroxynitrite. It is possible that peroxynitrite-mediated nitrosative stress contributes to the decreased contractility and inflammation in TTS. It has been reported that patients with TTS have increased markers of NO signaling (73) and nitrosative stress (25). Peroxynitrite release results in activation of poly(adenosine diphosphate–ribose)–transferase-1, which might cause impairment in production, transportation, and use of high-energy phoshophometabolites (phosphocreatine [PCr] and adenosine triphosphate [ATP]). Severely decreased PCr/ATP ratio has been reported in patients with TTS (74), although it is yet unknown whether alterations in myocardial energy metabolism is a cause or an adaptive or maladaptive consequence of TTS.

Several alterations in genes regulating intracellular calcium metabolism have been reported in heart biopsies from patients with TTS during the acute phase. Sarcoplasmic reticulum (SR) Ca^{2+}-adenosine-triphosphatase 2a (SERCA2a) gene expression is downregulated, whereas that of sarcolipin is upregulated, and phospholamban is dephosphorylated in endomyocardial biopsies from patients TTS during the acute phase (75). These molecular changes all cumulate in reduced SERCA2a activity that leads to decreased sarcoplasmic reticulum calcium reuptake and sarcoplasmic reticulum calcium stores, which results from the increased phospholamban/SERCA2a ratio and contributes to both systolic and diastolic dysfunction in affected segments. In healthy rodents, the administration of the selective β1AR and β2AR agonist isoproterenol causes myocardial fibrosis selectively in the apical segments (76), with associated contractile dysfunction and disturbed myocardial metabolism (77). These features have been reported in apical segments during the acute phase in patients with TTS using fluorodeoxyglucose-positron emission tomography (61). At the cellular level, in the apical myocardium from both animal models of TTS following isoproterenol injection and endomyocardial biopsies of patients with TTS during the acute phase, there is significant intracellular accumulation of lipid droplets in cardiomyocytes but not after recovery (24,64). This is consistent with a shutdown of mitochondrial metabolism in hypokinetic or akinetic apical segments, reduction of free fatty acid consumption, and accumulation of lipid droplets in the cytoplasm.

Endomyocardial biopsies from patients with TTS also revealed contraction band necrosis, which has also been observed in endomyocardial biopsies from patients with pheochromocytoma or subarachnoid hemorrhage. Intense activation of myocardial βARs by catecholamines during sympathetic storms leads to cytosolic calcium overload (75,78).

Various genetic studies in small TS cohorts failed to identify a consistent genetic abnormality that reflects heterogeneity of populations and small sample sizes (79,80). One study reported that a polymorphism of the G-protein receptor kinase 5 gene L41Q that activates β_2-G_i trafficking was more common in patients with TTS than that of a matched control population (81). However, this finding was not confirmed in 2 subsequent studies (79,80). Another study reported a higher prevalence of specific polymorphisms of the anti-apoptotic protein BAG3 were enriched in a TTS population compared with control subjects (82), but again this was not reproducible in another population (80). Larger, appropriately powered genetic studies are required to determine if there is a contributory genetic susceptibility to TTS.

Recent experimental evidence showed that TTS-like apical ballooning in the rat model could be induced by inhibition of intracellular phosphodiesterase with milrinone. This would increase cAMP levels, which is a mechanism downstream of adrenergic receptors that highlights the relevance of the βAR-Gs- adenylyl cyclase (AC)-cAMP-protein kinase A pathway (83). It is possible that autoactivation of this pathway in the absence of catecholamine ligand binding and βAR activation, while adding to the complexity of TTS pathophysiology, may also explain why not all patients who develop TTS have increased levels of circulating catecholamines or a stressful trigger (spontaneous cases). This has important implications for treatment choices in the management of patients with cardiogenic shock. In our opinion, both catecholamine inotropes (epinephrine, norepinephrine, dobutamine) and phosphodiesterase inhibitors that increase cAMP (milrinone, enoximone) should be avoided.

In support of excessive cardiac and systemic sympathetic stimulation, elevated norepinephrine levels in the coronary sinus have been found in patients with TTS, which suggests an increase in the local release of myocardial catecholamines (30). Heart rate variability analyses in patients with TTS also demonstrate a sympathetic predominance and marked depression of parasympathetic activity during the acute phase (31). Micro-neurographic studies of peripheral sympathetic NS activity have shown conflicting results. Although some studies have reported increased (32) activity, others have shown paradoxically reduced peripheral sympathetic nerve activity (33). This discrepancy may depend on the timing of measurements in relation to the onset of TTS and on different patient populations that were included in the studies in regard to age, sex, and the presence of traditional cardiovascular risk factors (e.g., hypertension and smoking habits). Micro-neurographic studies have shown decreased spontaneous baroreflex control of sympathetic tone in some patients with TTS. During the acute phase, there is reduced cardiac sympathetic neuronal function measured using 123I-meta-iodobenzylguanidine myocardial scintigraphy in the aftermath of the sympathetic storm (34) (**Figure 2**).

Altered myocardial sympathetic function is associated with an interstitial mononuclear inflammatory response and with contraction band necrosis (a hallmark of catecholamine toxicity) (19). The central role of βAR stimulation in TTS has been demonstrated in several animal models (26,36,64). Apical ballooning can be provoked in rats by immobilization stress and attenuated by α- and βAR blockade (37).

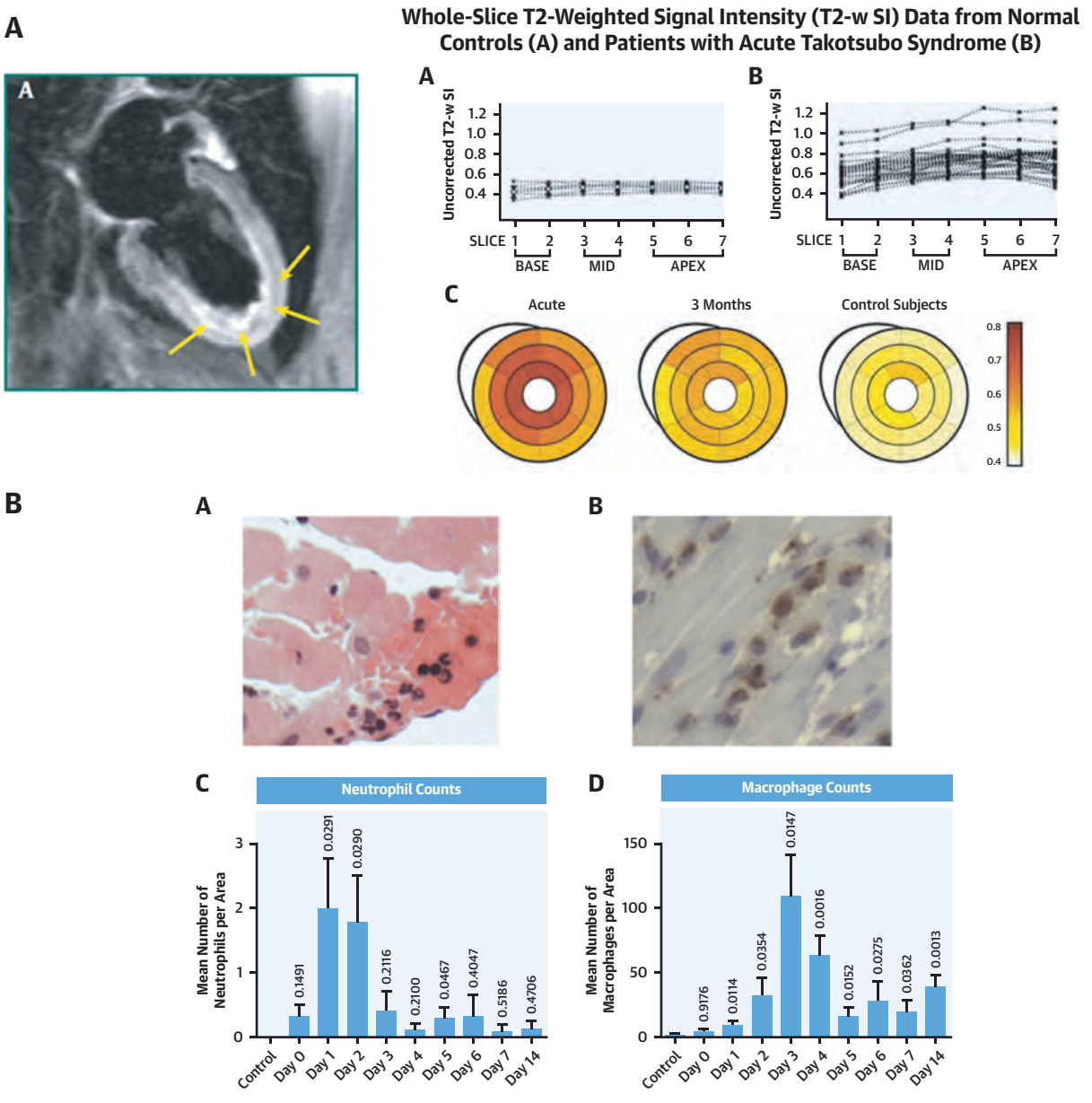
ABNORMAL MYOCARDIAL METABOLISM IN TTS

Abnormal myocardial metabolism was reported in apical segments during the acute phase in patients with TTS using fluorodeoxyglucose-positron emission tomography (84). Regional free fatty acid use and extracellular glucose transport were acutely reduced in the affected apical myocardial segments, but not the basal segments, during the acute phase (85). At the cellular level in the apical myocardium from both animal models of TTS following isoproterenol injection and endomyocardial biopsies of patients with TTS during the acute phase, there was significant intracellular accumulation of lipid droplets in cardiomyocytes but not after recovery (24,35). This was consistent with a shutdown of mitochondrial metabolism in the hypokinetic or akinetic apical segments, reduction of free fatty acid consumption, accumulation of lipid droplets in the cytoplasm, and might be a form of catecholamine or combined catecholamine- and ischemia-induced acute metabolic stunning (86).

INFLAMMATION IN TTS

There is a growing body of evidence that myocardial inflammation occurs during the acute phase, and

FIGURE 6 **Acute Inflammation in TTS and Potential Mechanisms of Catecholaminergic Myocarditis**



(A) Increased T2STIR in the affected apical segments on CMR from cases with Takotsubo syndrome acutely (typical example in **left panel** of a CMR with **yellow arrows** highlighting apical segments with increased T2STIR) and persisting at 3 months (from Neil et al. [86] with permission). **(B)** Acute infiltration of neutrophils **(A)** and macrophages **(B)** into the ventricular myocardium in a rat model of Takotsubo syndrome induced by high dose isoproterenol injection with time dependent changes in myocardial neutrophils **(C)** and macrophages **(D)** over 14 days following high dose isoproterenol injection (from Wilson et al. [87] with permission). Abbreviation as in Figure 3.

inflammation may be important if it persists in the subacute and chronic phases in contributing to long-term cardiac dysfunction and symptoms (Figure 6). Cardiac magnetic resonance imaging studies reported the presence of an increased T2STIR signal, which probably reflected acute myocardial edema, in the affected, but not unaffected, segments in patients with TTS during the acute phase and in tracking the specific anatomical variant (84,85). Neil et al. (86) first reported the presence of persistent edema in the affected segments 3 to 4 months after the acute episode, and recently, Scally et al. (74)

demonstrated abnormalities, including low-grade inflammation ≥12 months after the acute TTS episode in some patients.

The same investigators also studied the impact of high-dose catecholamines on myocardial inflammation in a preclinical rat model. They reported the time course for infiltration of neutrophils in the first 72 h, followed by type 1 macrophages over 3 to 5 days, with associated inflammation, followed by resolution and recovery of contractile dysfunction (87). Increased macrophages were also present in post-mortem heart samples from patients with TTS (87) and in other studies that showed increased oxidative stress (25).

There are examples of TTS cases triggered by the influenza vaccination and also by immune checkpoint inhibitors for cancer (which activate T lymphocytes), which suggest it is possible to trigger TTS via immune activation and inflammation. More research is required to understand the specific immunological mechanisms that drive inflammation during the acute phase in TTS, what determines effectively switching off the immune response versus those patients who have chronic myocardial inflammation, and whether targeting the inflammatory response therapeutically might be a treatment option.

PRO-ARRHYTHMIC ELECTROPHYSIOLOGICAL CHANGES IN TTS

Recent studies shed light on the prognostic implications of supraventricular and ventricular arrhythmias in TTS by emphasizing a substantial risk of severe complications and considerable short- and long-term mortality rates (88–90). Various mechanisms involving electrophysiological substrate modification, re-entry, triggered activity, and abnormal automaticity were proposed to contribute to electrical instability in TTS syndrome.

ATRIAL ARRHYTHMIAS. Acute atrial stretch and inflammation could occur either as an indirect consequence of an increase in left filling pressure or as a direct consequence of high catecholamines at the atrial myocardium. Left atrial emptying function was correlated with LV ejection fraction and was found to recover at follow-up (91). Inflammation is believed to contribute to the initiation and perpetuation of atrial arrhythmias consistent with the description of elevated circulating levels of inflammatory markers and myocardial infiltration by inflammatory cells in patients with TTS. A recent study associated systemic inflammatory markers with atrial arrhythmias and prognosis in patients with TTS (88).

VENTRICULAR ARRHYTHMIAS. Numerous investigations previously demonstrated that infusion of low-dose catecholamines or mental stress was associated with QT shortening (92). In contrast, patients with TTS frequently have QT prolongation during the acute phase, with an acquired long QT syndrome and T-wave inversion (Wellen's sign) pattern that has also been also reported in patients with pheochromocytoma (93,94). In TTS, QT prolongation and maximal T-wave depth were evidenced 3 to 4 days after TTS onset and returned to baseline values after 3 months (93). Epinephrine release, inflammation, myocardial edema, ischemia, oxidative stress, and low estrogen hormones levels were proposed as important mechanisms involved in QT prolongation and T-wave inversion in TTS. By analogy to the congenital long QT syndrome, the slowing of repolarization rate and the prolongation of action potential duration (APD) is likely to involve the upregulation of inward currents including I_{Ca} and I_{Na} and the downregulation of outward currents such as I_{to} or potassium channels. In the setting of prolonged APD and QT, the triggered beats might cause Torsade de pointes or polymorphic ventricular arrhythmias. Using human iPSC-CMs, a recent experimental study depicted the electrophysiological mechanism by which catecholamines could induce APD and QT prolongation (95). In this model, isoprenaline at toxic concentration increased reactive oxidative species production and prolonged APD due to the increase in late I_{Na} and decreased $I_{to.}$ β-estradiol reduced the expression of βARs, including β2AR, blunted reactive oxidative species production induced by adrenoreceptor overstimulation, and prevented the effects of isoproterenol on human iPSC-CMs electrophysiological characteristics. These findings suggested that reduction in estrogen levels might lead to higher expression of βARs and lent support for the higher susceptibility of TTS in postmenopausal women (95).

In experimental studies, various pro-inflammatory cytokines such as tumor-necrosis factor-α and interleukin-6 were demonstrated to induce APD and QT prolongation by decreasing the transient outward current I_{to} or by enhancing the L-type calcium current (96,97). Myocardial edema might also contribute to QT prolongation and T-wave dispersion. A transmural myocardial edema with an apical-basal gradient was reported in the acute phase using cardiac magnetic resonance (93). Correlations between myocardial edema and electrocardiographic repolarization indexes were demonstrated. In addition, a parallel time course of development and resolution of ventricular repolarization abnormalities and LV myocardial edema were evidenced, which suggested a causal

association (93). Increased automaticity, APD, QT interval and dispersion, induction of early and delayed after depolarization, and increased transmural dispersion of repolarization might lead to cardiac reentry and the onset of ventricular arrhythmia. Other reports emphasized that edema could also contribute to conduction disturbances observed in TTS, including complete atrioventricular block, sinoatrial block, or transient pacing failure (98). Although the ventricular arrhythmic risk is mainly viewed as transient, the persistence of conduction disturbances, together with the high rate of ventricular pacing in patients with TTS who require pacemaker implantation, points to a particular sensitivity of conduction fibers to edema, inflammation, ischemia, or catecholamine surge (89).

TTS AS PROTECTIVE CARDIAC RESPONSE TO STRESS

The severe wall motion abnormalities seen in TTS are transient, which suggests that protective mechanisms may operate to preserve myocardial integrity. At least 2 known different mechanisms may elicit myocardial protection. The first one is represented by βAR-related protective mechanisms. As discussed previously, supra-physiological levels of epinephrine triggers β2AR to switch from G_s to G_i coupling, thus causing a negative inotropic response but also activates protective anti-apoptotic pathways (26,62). One important cell survival pathway activated by β2AR-Gi pathway is the phosphoinositide 3-kinase/protein kinase B survival pathway, which is activated during the acute phase of TTS in patient endomyocardial biopsies (**Figure 5**) (23). Protein kinase B is critical for postnatal cardiac growth and coronary angiogenesis. Also, protein kinase B downstream targets, especially the mechanistic targets of rapamycin and glycogen synthase kinase 3, which are well-established regulators of metabolism, proliferation, and cell survival. Cell survival is achieved through various mechanisms: 1) direct inhibition of apoptosis; 2) inhibition of pro-apoptotic transcriptional factors; 3) enhancement of anti-apoptotic transcriptional factors; and 4) enhancement of cell metabolism by inhibition of glycogen synthase kinase 3. The demonstration that downregulation of myocardial function is a protective mechanism caused by a severe reduction of perfusion has bee confirmed by several clinical studies that showed an inverse perfusion-metabolism mismatch, which is typically observed during myocardial stunning (53).

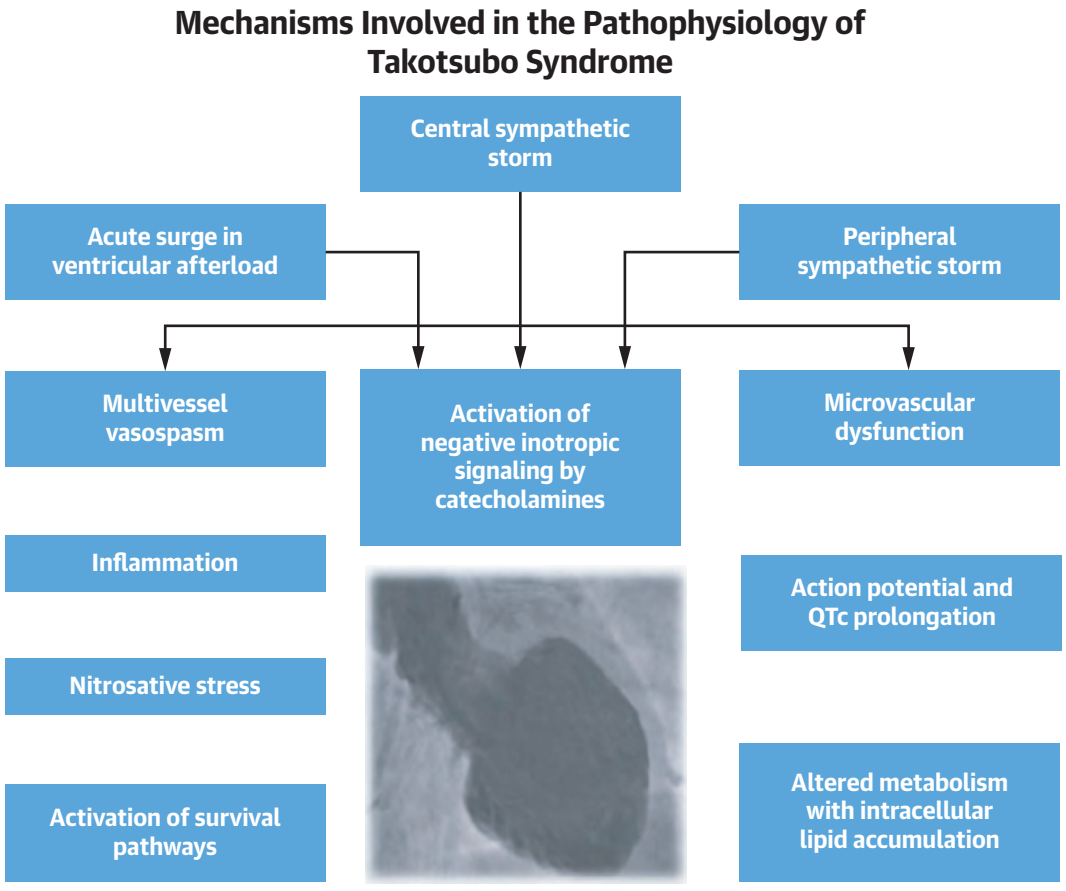
TTS AS A CARDIOCIRCULATORY SYNDROME

Beyond the direct effects of stress upon the myocardium and coronary vasculature, the effects of high catecholamines systemically, and particularly upon peripheral vasculature, should also be considered. Administration of different catecholamines cause the various ventricular TTS variants, with an afterload-dependent mechanism contributing to the development of TTS (12). Based on these experimental observations, Redfors et al. (28) proposed that TTS might be a unique form of myocardial stunning (Takotsubo stunning). In TTS, the basis for this stunning might be an excessive oxygen demand from the excessive catecholamine-mediated β1AR and β2AR activation rather than a shortage of oxygen supply during ischemic stunning. Because the oxygen supply remains adequate for the maintenance of basal cellular functions, self-initiated severe downregulation of contractile activities effectively corrects the supply–demand mismatch in TTS. This model showed that strong vasodilator and inotropic stimuli override autonomic reflex arcs. Thus, increased contractility and reduced afterload cause the ejection fraction to increase, with near obliteration of the LV lumen during systole during the first few seconds after the catecholamine surge (immediate phase). Apical akinesia develops over the subsequent minutes. In this preclinical model, apical ballooning may switch to basal ballooning simply by manipulation of peripheral vascular resistance (12). Apical ballooning may develop in the setting of low afterload, whereas basal ballooning develops in high afterload.

TAKOTSUBO STUNNING—CATECHOLAMINERGIC OR COMBINED CATECHOLAMINERGIC AND ISCHEMIC STUNNING—A SEPARATE PATHOPHYSIOLOGICAL ENTITY. In summary, there is growing evidence from experimental and clinical studies that intense βAR activation, perhaps initially dominated by β1AR, activates G_s, which leads to increased oxidative stress and transient hypercontractility during the initial seconds. Then there is activation of the cardioprotective β2AR-G_i pathway, particularly at higher levels of epinephrine with differential responses between the apical and basal ventricular myocardium. The β2AR-G_i pathway then activates the anti-apoptotic and cardioprotective phosphoinositide 3-kinase/protein kinase B pathway, which limits myocyte necrosis and allows myocardial recovery.

An integrated hypothesis to explain all the observations could center around simultaneous and

CENTRAL ILLUSTRATION **Schematic Summarizing the Contributing Mechanisms of Myocardial Dysfunction and Takotsubo Stunning in Takotsubo Syndrome**



Lyon, A.R. et al. J Am Coll Cardiol. 2021;77(7):902–21.

The initial intense activation of the sympathetic nervous system activates central neural activation and stimulates epinephrine release from the adrenal glands. The result is a surge in ventricular afterload, coronary vasospasm, and microvascular dysfunction, and direct catecholaminergic stunning via altered β-adrenergic receptor signaling. These changes result in acute myocardial dysfunction, typically in the apical and midventricular segments, as shown in this example of cardiac magnetic resonance in end-systole in the **central image**, and are associated with altered cardiac electrophysiology, including significant QTc prolongation and risk of ventricular arrhythmias. Within the affected myocardial segments, there is activation of inflammation with macrophage and lymphocytic infiltration, increased nitrosative stress, activation of anti-apoptotic survival pathways, and altered metabolism that lead to the accumulation of lipid droplets in the cytoplasm of cardiomyocytes.

superimposed myocardial ischemia that occurs secondary to epicardial vasospasm and/or microvascular dysfunction. This perhaps results in epinephrine- and norepinephrine-mediated αAR-dependent vasoconstriction, increased reactive species generation, impaired mitochondrial function with lipid droplet accumulation, and higher NO levels produced by intense β2AR-G_i activation. which causes peroxynitrite generation. All these factors lead to contractile dysfunction and inflammation. The interaction between the ventricle and vascular afterload (ventricular-arterial coupling) and inducible LV outflow tract obstruction will influence LV intracavity pressure gradients and dynamics, and together with the distribution of sympathetic nerve endings and β1ARs and β2ARs, will determine whether an apical, mid-LV, or basal variant develops. The role of the endocardium, which will be exposed to high transient shear stress and endocardial NO supply to the adjacent myocardium in effected segments, remains to be determined (99).

This model can be considered either isolated catecholaminergic stunning or combined catecholaminergic and ischemic stunning and could be considered as Takotsubo stunning. We hypothesize that cases with isolated catecholaminergic stunning will generally make a complete recovery with minimal residual inflammation or clinical complications. In contrast, the cases with combined catecholaminergic and ischemic stunning have a higher degree of acute inflammation, greater myocardial injury, and a higher risk of acute complications. Survivors will be more likely to develop longer term cardiac problems due to persistent inflammation (**Central Illustration**).

IMPLICATIONS FOR CLINICAL MANAGEMENT

There are no randomized clinical trials to support specific treatment recommendations for Takotsubo syndrome. All published documents about the treatment recommendations are based on expert opinion and require validation in randomized trials (1,10). Because the key feature of TTS is rapid recovery of normal cardiac function in most cases, the most important doctrine that should guide decision-making is the fundamental ethical principle in medicine: primum non nocere (first, do no harm). The major objective of in-hospital treatment should be supportive care to sustain life and to minimize complications during recovery. In mild cases, no treatment or a short course of limited medical therapy may be sufficient. In severe cases complicated by progressive circulatory failure and cardiogenic shock, early mechanical support should be considered as a bridge-to-recovery. Patients with TTS who have significant LV systolic dysfunction (LV ejection fraction <40%) should be treated with angiotensin-converting enzyme inhibitors and beta-blockers licensed for heart failure. We recommend carvedilol as the preferred beta-blocker, unless clinically significant LV outflow tract obstruction is present. If LV outflow tract obstruction is present, then a β1-selective beta-blocker is preferred (e.g., bisoprolol). Both the angiotensin-converting enzyme inhibitors and beta-blocker can be weaned once LV function has recovered and providing there are no other indications (e.g., tachyarrhythmias, hypertension).

CONCLUSIONS

TTS is a complex clinical condition in which emotional or physical stressors trigger an episode. The recognition of this acute heart failure syndrome has progressively accelerated in recent years, with the understanding that it is not a benign condition because of mortality during the acute phase, long-term mortality, persistent cardiovascular abnormalities, and risk of recurrence. Each of the discussed pathophysiological hypotheses is an important contribution, but in isolation, none fully explains all the mechanisms that lead to TTS stunning. There are still many aspects of TTS that we still do not fully understand. Further research efforts are necessary to corroborate, refute, refine, and/or unify these hypotheses. Clinical trials are needed to evaluate new treatment strategies during the acute phase, to assess treatments to reduce the risk of residual cardiovascular problems in TTS survivors, and to prevent recurrence in high-risk cases. Future research should focus upon myocardial specific mechanisms that underlie the abnormalities of βAR signaling and downstream pathways, inflammation, metabolism, genetic and epigenetic risk factors, and microvascular dysfunction to identify targets for treatment. Sex differences in all these mechanisms remain to be explored. Hopefully, a new clinical evidence base will be developed in the future to guide clinical decision-making and improve the quality of life and outcomes for patients with TTS.

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