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EDITORIAL COMMENT

Takotsubo Syndrome

Stress or NO Stress?*

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Takotsubo syndrome (TTS), also known as broken heart syndrome or stress-induced cardiomyopathy, is a severe but reversible acute heart failure syndrome that predominantly affects post-menopausal women (1,2). This condition results from a surge in catecholamines (3) that typically occurs in situations of physical or emotional stress (2), or even during happy events such as weddings (4). It was first identified in Japan by Sato et al. in 1990 (5), where the pathognomonic shape of the left ventricle (LV), with an akinetic apex and hyperkinetic basal segments, was compared to a Japanese Octopus pot, or *takotsubo*. Patients with TTS closely resemble those with acute myocardial infarction, presenting most frequently with ST-segment elevation on electrocardiography and chest pain (2); however, there is an absence of culprit coronary artery disease. It is only with recently increasing interest that TTS is becoming routinely recognized. Despite the usual recovery from TTS within days to weeks of the incidence, the profound contractile deficit that defines TTS can lead to serious complications, including cardiogenic shock, thrombi formation, ventricular wall rupture, pulmonary edema, and arrhythmia. This results in a significant mortality rate of 4% to 5%, which is also comparable to the in-hospital rate of acute myocardial infarction (1,2). It has recently been recognized that despite the apparent recovery, patients with TTS develop long-term contractile dysfunction (6). Despite an increasing understanding of the disease course of TTS, there is currently no evidence-based treatment in the acute phase, or for the chronic management of these patients (1).

Although the correlation of TTS with a surge in catecholamines is well-evidenced, there is no established pathophysiologic mechanism. Several hypotheses exist, including direct catecholaminergic myocardial stunning, acute LV outflow tract obstruction, microvascular endothelial dysfunction, multivessel coronary vasospasm, and abnormal lipid metabolism.

TTS has been recapitulated in vivo in preclinical rodent models by bolus injection of high concentration epinephrine, or its analogue isoproterenol (7,8). These articles examine the involvement of the β-adrenergic receptors in the localized negative inotropic effect of catecholamines. Indeed, although the β_1AR only signals via the canonical stimulatory G-protein (G_s) pathway, the pleiotropic β_2AR can signal via G_s or the inhibitory G-protein (G_i). Physiologically, this has the consequence of limiting the toxic effects of G_s activity by shifting receptor coupling to G_i as increasing amounts of G_s signaling occurs, a process known as stimulus trafficking or biased agonism. In doing so, this also reverses the contractile effect of G_s activity, as well as having a direct cardiodepressive effect. This occurs more at the apex owing to the increased density of βAR and a greater β_2AR response (7). The switch of β_2AR to G_i is triggered by receptor phosphorylation after the large initial cyclic adenosine monophosphate response caused by both β_1AR and β_2AR activation.

Beyond the initial contractile deficit, the long-term sequelae seem to involve cardiac inflammation. Indeed, endomyocardial biopsy shows mononuclear infiltrates and contraction band necrosis (3), and slowly resolving global myocardial edema is present

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on magnetic resonance imaging (9). As this subsides, a process of global microscopic fibrosis develops in its place, which can be detected as early as 4 months (6). Therefore, it is important to understand the processes linking the acute changes in contractility with the downstream inflammatory changes that worsen long-term prognosis.

The current authors (10) have previously demonstrated the presence of altered nitric oxide signaling in patients with TTS (11), a point that is particularly interesting given that nitric oxide synthase can couple to the β_2AR (12). Their pilot immunohistologic studies of LV myocardium from patients with TTS showed evidence of nitrosative stress, with increased 3-nitrotyrosine (a marker of nitrosative stress) and potentially poly(ADP-ribose), a downstream product of poly (ADP-ribose) polymerase (PARP)-1 activation (13), which can impair cardiac energetics.

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In this issue of *JACC: Basic to Translational Science*, Surikow et al. (10) recapitulate the preclinical rodent model of TTS established by Shao et al. (8) by injection of 5 mg/kg isoproterenol intraperitoneally and observe an expected decrease in fractional shortening in the apex. Although the decrease in the ejection fraction was minor, these investigators observed concomitant decreases in apical strain and increased LV wall thickness. The authors suggest this could be due to the presence of myocardial edema, although they have not confirmed this. Twenty-four hours after injection of isoproterenol, inflammatory changes were observed within the myocardium, including increases in $CD68^+$ macrophages and levels of inflammatory markers (3-nitrotyrosine, poly[ADP-ribose], and thioredoxin-interacting protein). Indeed, thioredoxin-interacting protein also exhibited a clear difference in expression between apex and base after isoproterenol administration.

The authors hypothesized that PARP-1 might be the link from nitrosative stress to the decline in systolic function, because of its effects on myocardial energetics. Pre-treatment of the PARP-1 inhibitor 3-aminobenzamide (50 mg/kg intraperitoneal injection) administered 30 min before isoproterenol significantly limited the reduction in the apical radial strain and fractional shortening. However, there were no changes in the inflammatory markers previously measured, and poly(ADP-ribose) and thioredoxin-interacting protein were further increased in the 3-aminobenzamide pre-treated group, indicating failure to prevent inflammation, or the rebound increase in oxidative stress (14). One thing of note was that the rate of sudden arrhythmic death produced by isoproterenol was unchanged. This finding contrasts with other attempts to oppose TTS by β_2AR blockade, G_i inhibition, or p38 MAP kinase blockade, where sudden cardiac death was precipitated even when the systolic dysfunction of TTS was prevented (7,8).

In terms of advancing the understanding of TTS, the analysis here takes the story further than the initial insult and starts to address potential mechanisms for ongoing deficits in cardiac function. Inflammation is clearly key, but the persistence of this and of the possible edema will need to be explored in a more extensive time series study. In terms of potential therapeutic avenues, PARP-1 inhibition did show some benefit for systolic function, although incomplete. It will be important to know whether this is observed if the inhibitor is given after the isoproterenol, because the clinical presentation of TTS is usually some after the catecholamine surge. However, the lack of effect of PARP-1 inhibitor on the inflammatory state suggests that ongoing inflammation is a problem that may need to be addressed separately in the treatment of these patients.

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