The Sympathetic Nervous System in the Pathogenesis of Takotsubo Syndrome

Ilan S. Wittstein, MD

KEYWORDS

• Takotsubo syndrome • Stress cardiomyopathy • Sympathetic nervous system • Catecholamines • Ventricular ballooning

KEY POINTS

- Enhanced sympathetic stimulation seems to be central to the pathogenesis of takotsubo syndrome.
- Catecholamines may affect cardiac function in takotsubo syndrome through a variety of mechanisms, including epicardial spasm, microvascular dysfunction, and direct myocyte injury from adrenergic-receptor–mediated calcium overload.
- Risk factors that increase sympathetic tone and/or enhance myocyte and microvascular catecholamine sensitivity may increase individual susceptibility to takotsubo syndrome.

INTRODUCTION

There is considerable evidence supporting a strong association between acute psychological stress and cardiovascular morbidity and mortality. Case-crossover studies have demonstrated that the risk of myocardial infarction more than doubles following acute emotional triggers, such as anger and sadness[1,2]; large population-based studies have shown that emotionally charged events, such as earthquakes,[3] acts of terrorism,[4] and even sporting events,[5] are associated with an increased risk of myocardial infarction and ventricular arrhythmia. More recently, it has become increasingly clear that acute psychological stress can also have a direct effect on cardiac contractile function; during the past 15 years, a novel syndrome of acute systolic heart failure precipitated by emotional or physical stress has been reported. The clinical features of *takotsubo syndrome* (TS), also referred to as stress cardiomyopathy, left ventricular apical ballooning syndrome, and broken heart syndrome, have been well described in the medical literature[6–8] and are reviewed in subsequent articles of this issue. Despite the increased awareness of TS by clinicians worldwide, the precise pathophysiology of this unique syndrome remains elusive and poorly understood. Numerous mechanisms have been proposed, but the preponderance of evidence suggests that the contractile dysfunction characteristic of TS is likely catecholamine mediated.[9] Increased sympathetic stimulation may induce transient myocardial stunning through a variety of mechanisms that include epicardial spasm, ischemia due to microvascular dysfunction, and direct cardiomyocyte toxicity from catecholamine-mediated calcium overload. This article summarizes the evidence supporting enhanced sympathetic stimulation as central to

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Division of Cardiology, The Johns Hopkins University School of Medicine, 7125 Zayed Tower, 1800 Orleans Street, Baltimore, MD 21287, USA
E-mail address: iwittste@jhmi.edu

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the pathogenesis of TS. Further, risk factors are reviewed that may influence individual susceptibility to TS by increasing sympathetic tone and/or by augmenting myocyte and microvascular catecholamine sensitivity.

A PARADIGM FOR SYMPATHETIC STIMULATION AND TAKOTSUBO SYNDROME

Fig. 1 illustrates a proposed paradigm for how sympathetic stimulation may be implicated in the development of TS. First, an individual is exposed to an acute stressor, which may be either emotional or physical. The physiologic response that follows is activation of the sympathetic nervous system (SNS) and release of catecholamines. Depending on the specific nature of the acute trigger, the predominant sympathetic response may be either sympathoneural resulting in local myocardial norepinephrine release or adrenomedullary hormonal leading to an increase in blood born catecholamines. This catecholamine surge may then affect the heart through a variety of pathophysiologic mechanisms, including epicardial spasm, microvascular dysfunction, and direct cardiomyocyte injury. Individual susceptibility to developing clinical TS is determined in large part by a variety of factors that may amplify the sympathetic response and/or enhance myocyte and microvascular sensitivity to catecholamines. Some of these risk factors that have been suggested from clinical observations and basic research are discussed in more detail later in this article.

EVIDENCE SUPPORTING THE CENTRAL ROLE OF SYMPATHETIC NERVOUS SYSTEM ACTIVATION IN TAKOTSUBO SYNDROME

Presence of an Acute Trigger

In most patients presenting with TS, an antecedent acute emotional or physical stressor can be identified. The observation of this temporal relationship is precisely what led investigators to initially suspect a sympathetic pathogenesis and to refer to the syndrome as *stress cardiomyopathy*.[6] Early reports highlighted primarily the emotional triggers of TS, but increased recognition of the syndrome has made it clear that TS can also be precipitated by a wide variety of physical stressors.[10] Many investigators initially thought that a dramatic stressor and subsequent massive catecholamine surge were required to precipitate TS. It is now clear, however, that even minor stressors can trigger the syndrome and that roughly 30% of patients with TS have no identifiable trigger at all.[11,12] The absence of an identifiable dramatic stressor, however, does not exclude a sympathetically mediated pathogenesis. As is suggested later in this article, even a relatively mild stressor

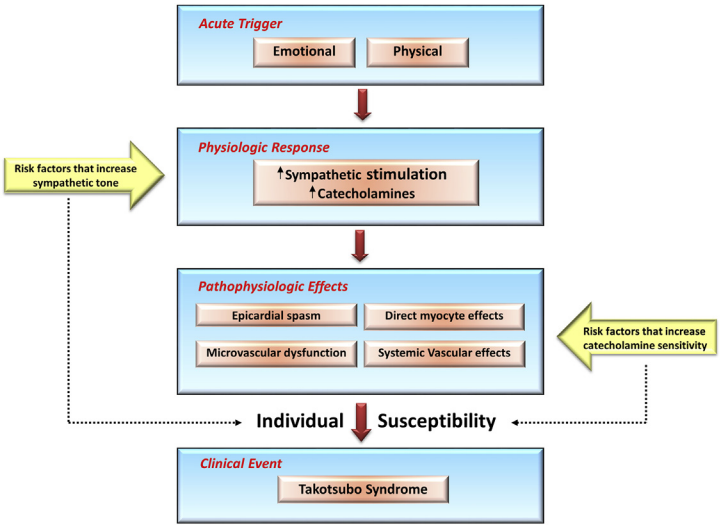

Fig. 1. A proposed paradigm illustrating the link between acute stress and the syndrome of stress cardiomyopathy. Acute emotional or physical stress results in activation of the sympathetic nervous system and an increase in local myocardial catecholamine levels. Catecholamines may mediate myocardial stunning through a variety of mechanisms that include coronary vasospasm, microvascular dysfunction, and myocyte calcium overload. Risk factors that enhance sympathetic tone and/or myocardial sensitivity to catecholamines likely increase individual susceptibility to takotsubo syndrome during periods of acute stress. (*Adapted from* Bhattacharyya MR, Steptoe A. Emotional triggers of acute coronary syndromes: strength of evidence, biological processes, and clinical implications. Prog Cardiovasc Dis 2007;49:354.)

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