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EDITORIAL COMMENT

Takotsubo Syndrome

Latest Addition to the Expanding Family of Immune-Mediated Diseases?*

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Takotsubo syndrome (TTS), also known as broken heart syndrome, is a severe and acute heart failure syndrome that often resolves spontaneously but can also be associated with significant mortality. TTS predominantly affects postmenopausal women and is usually triggered by identifiable physical or emotional stress. Considerable evidence suggests the precipitating factor to be the catecholamine surge from excess sympathetic activity that occurs during these events because it can be mimicked by exogenous catecholamine administration (1). TTS was first described in 1990 in Japan (2), when the shape formed by an akinetic left ventricular apex with hyperkinetic basal segments was compared to a Japanese Octopus pot, or takotsubo.

The importance of catecholamines in the induction of TTS has since been robustly demonstrated in vivo in preclinical rodent models. A number of groups have used these models to investigate the pathophysiology of TTS, including how the direct catecholaminergic myocardial stunning occurs through β-adrenergic receptors (βARs). β_1AR signals via the canonical stimulatory G-protein (Gαs) pathway, whereas β_2AR signals via Gαs or the inhibitory G-protein (Gαi). Excess adrenaline limits the inotropic and toxic effects of Gαs by a shift in coupling to Gαi in a process known as stimulus trafficking, which is enhanced by cyclic adenosine monophosphate–dependent phosphorylation of the β_2AR. The cardiodepressive effect of this shift to Gαi occurs more strongly at the apex because of the increased ratio of β_2AR to β_1AR (3).

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Although the initial cardiodepression during TTS can be explained by these pathways, the pathophysiological mechanism of longer term TTS is less understood. The study by Wilson et al. (4) presented in this issue of *JACC: Basic to Translational Science* described an inflammatory response and explored the underlying changes in neutrophil and macrophage recruitment that accompanied it. The investigators suggested that this inflammation was the basis of long-term damage and might present a therapeutic target. The study was not state-of-the-art in terms of macrophage characterization and quantitation, because multicolor flow cytometry panels are currently standard, and the human tissue samples were too small in number to make any firm conclusions. However, the study does build on several previous reports of inflammatory damage in TTS patients and also feeds into a large body of literature from animal models with similar observations.

Evidence over many years suggested the activation of inflammatory components by high catecholamine levels. In TTS patients, endomyocardial biopsies showed mononuclear infiltrate, contraction-band necrosis (5), and myocardial inflammation–mediated edema (6). In rodent models, the involvement of catecholamines in stress-induced heart injury was first described in 1959 (7). This study showed necrotic myocardial lesions induced by isoproterenol in the rat, and was followed by many subsequent studies

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that used bolus injections of high-dose adrenaline (3) or isoproterenol (8) to induce cardiac damage. Inflammatory changes, including increased numbers of CD68+ macrophages, were detected in the myocardium 24 h after isoproterenol administration (9). Due to the induction of acute myocardial lesions, the same treatment was also used to model myocardial infarction (MI). In addition to cardiac damage markers, inflammatory biomarkers including C-reactive protein, tumor necrosis factor-α and interleukin-10, are detectable in the serum of isoproterenol-treated rats (10).

Considering basic mechanisms of tissue homeostasis, an immune response initiated by necrotic cell death does not come as a surprise. Immune cell infiltration into damaged tissue to remove necrotic debris is an essential part of wound healing; it is mediated by the passive leakage of intracellular molecules that act as danger-associated molecular patterns. This process is called sterile inflammation because the immune system is activated despite the lack of a discernible infectious insult. Depending on a range of factors, including the degree of initial damage, genetic susceptibility, and additional preexisting immunological or metabolic disturbances, an acute sterile immune response may not self-resolve, but instead cause excessive inflammation. This can break immunological tolerance to self-antigens and cause antigen-dependent autoimmunity. The persistent presence of the triggering self-peptide will sustain autoreactivity and further exacerbate immune-mediated tissue damage.

The heart is particularly susceptible to such a break in immunological self-tolerance. Tolerance to most self-antigens is ensured through a T-cell maturation step in the thymus. However, the process of inducing central tolerance is missing for cardiac myosin (11). T cells with the potential to react to cardiac myosin are present in healthy individuals and easily activated if cardiac myosin is encountered under inflammatory conditions. Once an autoimmune attack is initiated, the immunological phenomenon of epitope spreading expands the repertoire of self-reactive T and B cells, and further exacerbates damage.

Although this may be a relatively new concept, supporting evidence has been available for a long time. Clinical signs of persistent adaptive immune activation post-MI have been recognized for decades and the presence of anti-heart auto-antibodies in post-MI serum is well known to cardiologists. However, except for rare cases of the clinically obvious post-MI autoimmune syndrome, a certain degree of subclinical autoreactivity is most likely always present and can cause ongoing persistent damage to previously healthy myocardial tissue (12). This may exacerbate adverse remodeling and increase susceptibility to development of heart failure.

Although an MI is an obvious trigger for cardiomyocyte necrosis, immune cell infiltration into the heart and signs of adaptive immune activation have been demonstrated to be a feature of a range of heart diseases, including nonischemic cardiomyopathies such as infectious, toxic, or hypertensive cardiomyopathies (13). Thus, it would be informative to investigate if TTS follows this common pattern of immunological activation and long-term adaptive autoreactivity after cardiomyocyte necrosis. A first step might be to test TTS patients for anti-heart reactive T and B cells and auto-antibodies. This knowledge may increase future treatment options because TTS patients may benefit from the same long-term immunomodulatory treatment as post-MI patients. A range of immunomodulatory therapies have been tested in acute MI and heart failure, with a focus on innate immunity. The most promising target to date is interleukin-1 (14). However, a clinical trial targeting B cells (RITA-MI [Rituximab in Patients With Acute ST-elevation Myocardial Infarction Study]) is currently recruiting participants. Notably, TTS, MI, and heart failure patients already receive similar pharmacotherapy, including antiplatelet therapy, β-blocker, statins, or angiotensin-converting enzyme inhibitors (15). All of these also affect the immune response, leaving room to speculate that some of their beneficial effects may be due to fortuitous immunomodulation (16).

In conclusion, it is not inconceivable for TTS to fall into an expanding category of disease, including atherosclerosis and heart failure, that are now being recognized to have a significant auto-inflammatory and/or autoimmune component. We therefore believe that there is great benefit in thorough studies of the acute and long-term immunological effects of TTS.

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