

EDITORIAL POINT OF VIEW

Novel Hypothesis for Takotsubo Syndrome

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Abstract

In this issue, Hirano et al. addressed a novel hypothesis for the onset of takotsubo syndrome. The authors presented the two-step energy failure hypothesis. The first step is sudden stress increase in cardiac energy demands, following the additional supply from stored triglycerides. The second step is the prolonged stunning of the ventricle due to impaired uptake of energy substrates in the myocardium. They insisted that these steps might be one of the underlying mechanisms to develop this syndrome. To understand this mechanism would be helpful as a future option for the treatment and prevention of takotsubo syndrome.

Keywords: Catecholamine, MicroRNA, Stress, Takotsubo, Triglyceride

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The pathophysiology of takotsubo syndrome is complicated because of the association with both neuroendocrine physiology and cardiovascular responses to the sudden sympathetic activation. Biopsies during acute takotsubo syndrome are characterized by multiple morphological changes that are similar to those after catecholamine cardiotoxic effects supporting a direct effect in addition to the vascular influences. The former researchers insisted that the stimulation of β -adrenoceptors by the supraphysiological levels of catecholamines would lead to the alteration of calcium-regulated proteins in takotsubo syndrome (1). In this issue of Annals of Nuclear Cardiology, Hirano et al. addressed a novel hypothesis concerning the onset of takotsubo syndrome (2); that is, “two-step energy failure”. Initial energy failure is due to severe imbalance between energy demand and supply. According to the results from the earlier reports, the authors insisted that sympathetic stimulation induced lipolysis in the adipose tissue (3). However, adipocytes generate less lipolysis and are resistant to sympathetic stimuli in the aged women (4). This is one of the reasons that the postmenopausal women with low-fat tend to suffer from this syndrome. The authors speculated that remarkable decrease in epicardial adipose tissue (EAT) might affect low energy supply when

needed. EAT can be evaluated by computed tomography and magnetic resonance imaging; the distribution of EAT influencing various wall motion abnormalities should be proven. Further accumulation of imaging data is necessary to clarify the first step of their hypothesis.

The authors hypothesized from the experimental results that the second energy failure, which led to prolonged stunning, was due to impaired recruitment of receptors for energy substrates. CD36 receptor imaging using Iodine-123 labeled 15-(4-iodophenyl)-3-(R, S)-methyl-iodophenyl pentadecanoic acid (^{123}I -BMIPP) would be useful to acquire this phenomenon in the myocardium as an imaging technique (5). Injected ^{123}I -BMIPP is usually taken up into the cardiomyocytes from blood by passive diffusion due to concentration gradient and CD36 transported to the myocardial cell membrane. Most of ^{123}I -BMIPP is stored in a lipid pool, such as triglyceride, an image is acquired as a descriptive for fatty acid metabolism. This image is quite useful to distinguish takotsubo syndrome from acute anterior myocardial infarction in the subacute clinical settings (6). Not only apical ballooning but also mid-ventricular ballooning, ^{123}I -BMIPP imaging depicts a wall motion abnormality as a defect (7). Since the hypothesis of the present study was based on the experimental models, further investigations are required to support their hypothesis as the authors described in the perspective. It remains unclear

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whether this disease is actually derived from the heart or the brain. We have previously reported the first pathophysiology of takotsubo syndrome developing in the cognitive centers of the brain and hypothalamic-pituitary-adrenal (HPA) axis and adrenaline and noradrenaline release in response to stressful events. A significantly elevated serum catecholamine level can be observed in a patient with takotsubo syndrome on admission compared to that at rest in the same patient and that in a comparable patient with acute heart failure secondary to acute myocardial infarction. This fact suggests excessive HPA gain and epinephrine in susceptible individuals (8). The second pathophysiology is a cardiovascular response to the sudden sympathetic activation and surge in circulating catecholamines. The preclinical models and the biopsy specimens in the acute phase support this pathophysiology. Concomitant vasospasm caused by high norepinephrine and epinephrine levels via α -adrenoceptors in the vasculature and myocardial stunning via β -adrenoceptor signaling are considered to trigger the systemic activation and surge in catecholamines.

One study investigating the circulating microRNA profile in the patients with takotsubo syndrome presented the striking difference compared to those with ST-segment elevation acute myocardial infarction (9). A recent study demonstrated that the presence of a g2252c polymorphism in the Gcl2-associated athanogene 3 (BAG3) 3' untranslated region (3'-UTR) determined the loss of miR-371a-5p binding, resulting in an altered response to epinephrine, potentially representing a new molecular mechanism which contributes to pathogenesis of takotsubo syndrome (10). Gene investigation would be a novel approach to clarify the pathogenesis of this syndrome. Although there are a lot of hypotheses concerning takotsubo syndrome, we should provide the most appropriate treatment to the patients with this syndrome individually with great interests of underlying mechanisms.

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Conflicts of interest

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