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Diabetes Mellitus as a Protective Factor in Takotsubo Cardiomyopathy

LETTER TO THE EDITOR

To the Editor,

Thangjui et al[1] presented a very interesting analysis in their study about the incidence of cardioversion-associated Takotsubo cardiomyopathy (TC) in patients with atrial fibrillation undergoing electrical cardioversion. The authors evaluated a large patient population using the National Readmission Database (NRD 2018) comprising about 155 000 patients and found that this is a very rare clinical phenomenon with a reported incidence rate of 0.027% in those undergoing cardioversion. Most of the patients were women, presented with symptoms of acute heart failure, and relatively had a benign outcome as most of them demonstrated a nearly complete recovery in about 2 weeks with supportive medical therapy.[1]

After multivariate logistic regression analysis, one of the most striking findings that the authors reported was that the prevalence of diabetes mellitus (DM) in patients with TC was significantly much lower than in those without TC, and this was in fact the only variable that showed statistical significance ($P = .028$) besides female sex predominance.[1] This implies that the prevalence of DM likely offers a significant protective effect in the development of cardioversion-associated TC. The authors note in their discussion that this protective effect is unclear.

The protective effect of DM in TC has previously been well described in some studies using the data from large original studies and registries.[2-5] Our group also previously published a very comprehensive systematic review using the data from published articles between the years 1990 and 2016. We found evidence supporting a strong probability of the protective effect of DM in TC.[2]

The pathogenesis of TC is thought to involve an autonomic or catecholaminergic storm, with primarily locally released catecholamines and blood-borne systemic catecholamines.[6-8] Since cardiac autonomic innervation is extensive, the catecholamine storm toxicity may exert neurocardiac deleterious effects, leading to myocardial stunning. The most plausible explanation of the protective effect of DM is that autonomic neuropathy from DM leads to cardiac sympathetic and splanchnic autonomic dysfunction resulting in reduced local norepinephrine release and reduced systemic epinephrine release from chromaffin cells in the adrenal medulla, respectively. This autonomic neuropathy and catecholamine hyposecretion may potentially lead to significant blunting and amelioration of cardiomyocyte injury and myocardial stunning, resulting from the catecholamine surge associated with the pathogenesis of TC.[2] Diabetic neuropathy can affect up to 50% of patients with both type 1 and type 2 DM, with a reduction of counter-regulatory catecholamine secretion.[2,3] Some clinical studies have documented a reduced norepinephrine release in cardiac tissue in patients with type 2 DM, and this has also been seen in rat models. Similarly, some animal studies have shown the beneficial effects of the sympathetic blockade in the prevention of the development of TC. Thus, DM may serve as a protective factor in the development of TC due to blunting of cardiac and splanchnic autonomic nervous system effects (Figure 1).

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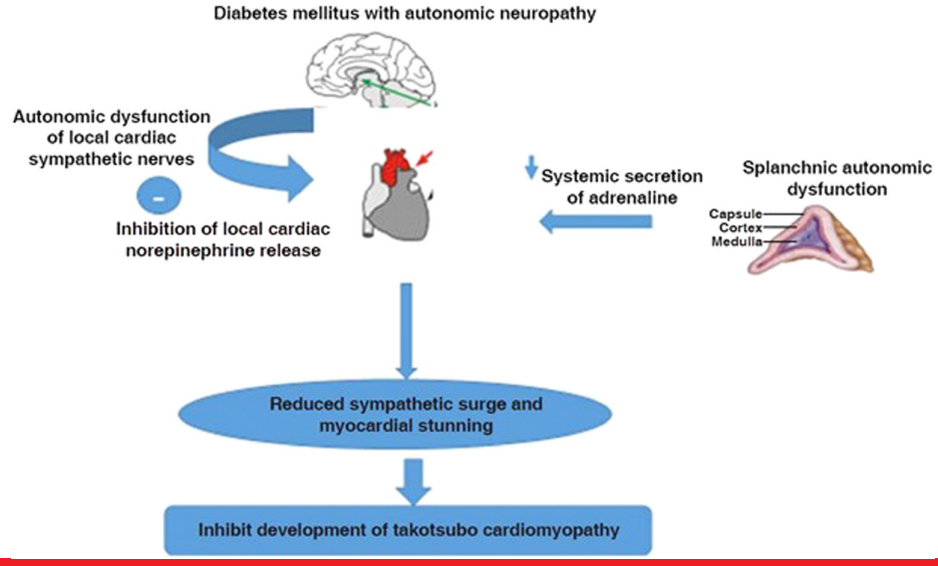

Figure 1. Schematic illustration demonstrating pathophysiologic mechanism of the protective effects of diabetes mellitus on development of takotsubo cardiomyopathy. Adapted from authors' own work from Reference 1 (Authors' copyright).

I applaud the authors and congratulate them for their interesting work which certainly further substantiates our knowledge about cardioversion-associated TC. Future data from larger registries would continue to further strengthen our understanding of this subject.

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Reply to Letter to the Editor: "Diabetes Mellitus as a Protective Factor in Takotsubo Cardiomyopathy"

LETTER TO THE EDITOR
REPLY

To the Editor,

We thank the author of the letter to the editor[1] for his/her knowledgeable comments on our study.[2] Takotsubo cardiomyopathy (TC) is a disease that needs more understanding of its natural history and pathophysiology. The main finding of our study reassured us that the incidence of TC after the cardioversion is low, and it is a relatively safe procedure if indicated. Apart from the incidence, our study adds to the current knowledge on the pathophysiology of TC by demonstrating that diabetes mellitus has a protective effect on the development of TC in a patient with physical stress. However, our study did not directly look at this association in TC as a whole disease but only in patients who developed TC after cardioversion. The protective role of DM on TC development was explained in detail by Gowdar et al[3] in their comprehensive review and summarized in figure. We agree with the author of the letter to the editor that further study on TC patients would help us understand the disease and hopefully create a strategy to prevent the disease in the future.

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THE ANATOLIAN JOURNAL OF CARDIOLOGY

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Paradoxical Role of Interleukin-1R2 in Cardiovascular Disorders

LETTER TO THE EDITOR

To the Editor,

I read the article by Chen et al[1] about the role of interleukin (IL)-1R2 in the pathogenesis of coronary artery disease (CAD). Their findings highlight the importance of IL-1R2 in CAD pathogenesis, but no mention is made regarding the underlying molecular mechanisms. As it is known, the biological effects of cytokines are mediated through interactions with receptors which exist in membrane-bound and soluble form.

The existence of cytokine receptors for a cytokine on different cell types, their functional plasticity, and their variable expression leads to complex functional networks. Cellular responsiveness to cytokines can be modified by altering the expression of receptors. Receptor density has an important influence on cellular events, including cell proliferation, apoptosis, and metabolism. Therefore, considerable attention is being devoted to understanding the role of cytokine receptors under normal and pathological conditions.

Interleukin-1R2 is a cytokine receptor that belongs to the IL-1 receptor family. It is recognized as an endogenous inhibitor of IL-1 signaling due to the absence of cytosolic Toll/interleukin-1 receptor domain (which is essential for IL-1R activities). Interleukin-1 signaling may also be inhibited by the soluble type II IL-1 receptor (sIL-1R2), which serves as a competitive inhibitor for IL-1. Experimental researches indicate that variations in the level of IL-1R2 could contribute to the pathogenesis of different diseases, including cardiovascular diseases (CVDs), although the exact mechanism remains unknown.

They may constitute a compensatory response that protects the cardiovascular system from the adverse effects of IL-1 or may play a causal role in disease pathogenesis. The first hypothesis is supported by empirical evidence including the following: (i) benefits of IL-1R2 overexpression on the rat cardiac allograft via reducing the intragraft infiltration of inflammatory cells and inhibition of pro-inflammatory cytokine production; (ii) IL-1R2 upregulation that attenuates cardiomyocyte apoptosis by downregulating the expression of proapototic molecules including Bax[2]; (iii) elevated levels of sIL-1R2 in patients with acute myocardial infarction following interventional therapy[3]; (iv) ameliorative effect of recombinant IL-1RII-Ig on experimental autoimmune myocarditis in rats.[4]

The second hypothesis is based on the functional impact of decreased IL-1R2 production in the pathogenesis of CVD. This concept is supported by empirical evidence including the following: (i) reduced IL-1R2 expression upon stimulation of monocytic cell lines with lipoproteins (a cardiovascular risk factor); (ii) reduced IL-1R2 expression in human atherosclerotic vessels and monocytes/macrophages of hyperlipidemic patients[5]; (iii) association between low circulating levels of sIL-1R2 and worse clinical outcomes in patients with acute myocardial infarction; (iv) increased infarct size and cardiomyocyte apoptosis in IL-1R2-deficient mice; and (v) an enhanced expression of IL-1R2 in PBMCs of patients with severe CAD compared with those with mild-to-moderate CAD and its positive correlation with Ox-LDL.[1] Such alterations may increase the risk of cardiovascular problems via

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several mechanisms, including the development of aberrant inflammatory responses.

Overall, IL-1 plays a critical role in the pathophysiology of heart diseases, and its activities are tightly regulated by IL-1R2. Available data suggest a key role for IL-1R2 variation in the development of different types of heart disease. Therefore, quantification of IL-1R2 has clinical significance, provides insights into pathological processes, and could be useful for diagnosis and treatment.

Editor's Note: Despite our repeated emails, we received no response from the authors.

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