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Endothelial dysfunction: Can it differentiate Takotsubo syndrome from spontaneous coronary artery dissection?

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It was with interest that the present authors read an article by Victoria L. Cammann et al., who compared clinical features and outcomes in patients with Takotsubo syndrome (TTS) and spontaneous coronary artery dissection (SCAD) [1]. The study compared the clinical characteristics and outcomes of 2098 TTS patients from the International Takotsubo Registry to 750 SCAD patients from the Canadian Spontaneous Coronary Artery Dissection Cohort Study. Both TTS and SCAD are increasingly recognized as non-atherosclerotic causes of myocardial infarction (MI) and have a predilection for the female gender. The authors found that TTS patients were significantly older (66.9 ± 12.8 years vs. 51.8 ± 10.2 years; $p < 0.001$),

had more major cardiovascular risk factors, and had a more impaired left ventricular ejection fraction than SCAD patients. On admission, TTS patients more often had dyspnoea (46.8% vs. 0.9%; $p < 0.001$), but less frequently presented with chest pain (74.4% vs. 91.5%; $p < 0.001$). Thirty-day mortality was significantly higher in the TTS group (4.4% vs. 0.1%; $p < 0.001$). This study gave noteworthy findings about the unique populations of patients with TTS and SCAD. SCAD relates to the spontaneous formation of intra-mural hematoma within the tunica media of a coronary artery. Two pathophysiological theories have been described: the “inside-out” proposes that primarily a disruption in the vessel wall develops and allows blood to enter and generate a false lumen and in the “outside-in” the hematoma arises de novo from the vasa vasorum [2]. As the exact pathophysiology of both conditions remains unclear, here we review the literature in search of the role of endothelial dysfunction in the pathogenesis of TTS, including (i) catecholamine-induced myocardial injury, (ii) failure of coronary vasomotor function, (iii) role of estrogens in TTS pathophysiology, (iv) role of oxidative stress in TTS pathophysiology (Fig. 1).

Catecholamine-induced myocardial injury is the most established theory of TTS pathogenesis, but it does not explain all aspects of the clinical presentations of this condition. Catecholamines seem to play a central role in the pathophysiology of TTS, as acute episodes are often caused by sudden stress, intuitively associated with an endogenous adrenergic surge. Therefore, TTS is also known as stress cardiomyopathy or broken heart syndrome. Interestingly, in Cammann et al. study, physical triggers were more common in TTS patients (36.1% vs. 28.8%; $p < 0.001$), while emotional triggers (50.3% vs. 29.6%; $p < 0.001$) and anxiety disorders (19.7% vs. 6.7%; $p < 0.001$) were more common in SCAD patients. There are three main aspects of catecholamine-induced myocardial injury: (i) the release of catecholamines, (ii) the cardiac response, and (iii) results in the left ventricular dysfunction. The levels of plasma catecholamine were even three times higher in patients with TTS than in patients with acute MI [3]. Mild to moderate elevations of noradrenaline and normetanephrine concentrations were found in 48% and 35% of TTS patients, respectively [4]. TTS is presumably caused by a catecholaminergic wave, leading to myocardial stunning through an action on β2-receptors, which hyperactivity negatively influences endothelial function. It can be detected based on decreased brachial flow mediated dilation.

Failure of coronary vasomotor function is proposed to be another explanation of TTS, including (i) microvascular spasm and (ii) epicardial spasm. Endothelin-1 represents one of the most potent vasoconstrictors and mediators of microvascular spasm in TTS. A significant

increase of endothelin-1 was observed in patients with TTS [5]. In addition, women with a history of TTS showed an impaired endothelium-dependent vasodilation and excessive vasoconstriction, compared to patients with MI [6]. In the Kurisu et al. study, epicardial coronary spasm by acetylcholine infusion was induced in 23% of TTS patients. Several studies confirmed abnormal coronary vasomotor responses to acetylcholine in TTS patients.

Takotsubo syndrome mostly develops in postmenopausal women, who have a reduced level of estrogen. The effect of estrogen supplementation upregulates cardioprotective substrates such as atrial natriuretic peptide and heat shock protein 70. Furthermore, estrogen inhibits sympathetic nervous system activity and induces endothelial nitric oxide (NO) production [7]. Increased sympathetic vasoconstriction and impaired vasodilation affect the inadequate response to increased levels of psychological stress, and are also associated with reduced estrogen levels [8]. This may also be related to the role of estrogen as a factor in increasing the sensitivity of α-receptors to catecholamines, and thus promoting vasodilation. In postmenopausal women, the sensitivity of β-receptors to catecholamines is reduced, while sensitivity of α-receptors remains unchanged, resulting in a predominance of vasoconstriction over vasodilation [8].

Nitric oxide-related oxidative stress is another factor associated with the development of TTS. Several studies investigated the levels of homoarginine, a substrate for NO synthase, which is an important marker in cardiovascular disease. Homoarginine levels were significantly lower in patients with TTS compared to healthy controls (median 1403 nmol/L vs. 1634 nmol/L; $p = 0.031$). In contrast, 3-nitrotyrosine plasma concentrations, a biomarker of NO-dependent oxidative stress, showed no significant differences between groups (median 1915 pmol/L vs. 2170 pmol/L; $p = 0.4726$) [9]. Kayacelebi et al. [9] confirmed the results of previous studies showing that homoarginine is a marker of cardiovascular disease and that oxidative stress has an influence on the pathomechanism of TTS.

Considering L-arginine, another substrate for NO synthase, a shift toward a competitive metabolic pathway involving arginase correlated with the occurrence of thin-cap fibroatheroma, that is a feature of acute coronary syndrome, and with thickening of the intima-media in the chronic phase [10].

Understanding the underlying etiology of TTS seems critical from a clinical point of view to develop appropriate treatments for both the acute phase and the prevention of long-term recurrent events. It may also bring us closer to discovering biomarkers for diagnosis and risk prediction. Endothelial dysfunction appears to play an important role in the pathogenesis of TTS. As Cammann et al. [1] showed, differences exist between the populations of patients

with TTS and SCAD. However, this study did not evaluate the potential differences in endothelial dysfunction in both diseases. Hence, it would be interesting to investigate the role of endothelial dysfunction both in patients with TTS and SCAD, with the goal of comparing the pathogenesis of these two diseases.

Conflict of interest: None declared

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Figure 1. Role of endothelial dysfunction in the pathogenesis of Takotsubo syndrome; NO — nitric oxide.