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Review

Stress cardiomyopathy: Is it limited to Takotsubo syndrome? Problems of definition

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ABSTRACT

In 2006, Takotsubo syndrome (TTC) was described as a distinct type of stress-induced cardiomyopathy (stress cardiomyopathy). However, when thinking about Takotsubo cardiomyopathy from the viewpoints of the AHA and ESC classifications, 2 possible problems may arise.

The first potential problem is that a forecast of disease outcome is lacking in the ESC classification, whereas the AHA only states that 'outcome is favorable with appropriate medical therapy'. However, based on the literature data, one can make a general conclusion that occurrence of myocardial lesions in TTC (i.e., myocardial fibrosis and contraction-band necrosis) causes the same effects as in other diseases with similar levels of myocardial damage and should not be considered to have a lesser impact on mortality. To summarise, TTC can cause not only severe complications such as pulmonary oedema, cardiogenic shock, and dangerous ventricular arrhythmias, but also damage to the myocardium, which can result in the development of potentially fatal conditions even after the disappearance of LV apical ballooning.

The second potential problem arises from the definition of TTC as a stress cardiomyopathy in the AHA classification. In fact, the main factors leading to TTC are stress and microvascular anginas, since, as has been already discussed, coronary spasm can cause myocardium stunning, resulting in persistent apical ballooning.

Thus, based on this review, 3 distinct types of stress cardiomyopathies exist (variant angina, microvascular angina, and TTC), with poor prognosis. Adding these diseases to the classification of cardiomyopathies will facilitate diagnosis and preventive prolonged treatment, which should include intensive anti-stress therapy.

1. Introduction

H. Sato first proposed the term 'Takotsubo', in a book edited by K. Kodama, to indicate left ventricular (LV) dysfunction after a multi-vessel coronary spasm [1].

The original name (Takotsubo) reflects the changes in the geometry of the heart, which resembles a traditional Japanese octopus trap with a circular base and a narrow neck. A number of other names for Takotsubo syndrome appeared thereafter, including 'ampulla cardiomyopathy' [2] and apical ballooning syndrome [3].

However, Takotsubo syndrome received recognition only after publication of the article by K. Dote et al., describing 5 patients with suspected acute myocardial infarction (MI). The patients had chest pain and electrocardiographic abnormalities matching the symptoms of acute MI [4]. Left ventriculography revealed akinesis in the apical, diaphragmatic, and/or anterolateral segments, but hyperkinesis in the basal segments, which were transient and resolved within 7 days. Despite the fact that ST elevation was observed in 4 patients, R waves decreased transiently in 1, and Q waves developed in 1 patient, no coronary artery stenosis was detected by angiography; instead, diffuse multi-vessel spasms were revealed in 2 patients and were observed in additional 2 patients after ergonovine administration [4].

The next step in the study on Takotsubo syndrome was made by K. Tsuchihashi et al., who performed a multi-centre, retrospective, enrolment study on 88 patients (12 men and 76 women). The significance of this study was in the identification of higher prevalence of this syndrome in women than in men [3].

Further research, conducted using magnetic resonance imaging in 239 patients, identified 4 different types of 'ampulla cardiomyopathy': apical (82%), biventricular (34%), midventricular (17%), and basal (1%) [5].

In 2006, Takotsubo syndrome was described by the American Heart Association as a distinct type of stress-induced cardiomyopathy (stress cardiomyopathy) [6].

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2. Prevalence of Takotsubo cardiomyopathy

The prevalence of Takotsubo cardiomyopathy (TTC) among patients with suspected acute coronary syndrome (ACS) ranges from 0.7% to 2.5% [4,7], and 5% of patients do not have significant coronary lesions [8].

Moreover, for the total prevalence of TTC of about 2.5% among patients with suspected ACSs, the prevalence of TTC in women is 8.2% versus 0.2% in men, and the annual incidences of TTC were estimated to be 29.8 per 1,000,000 people, 48.2 per 1,000,000 women, and 187.4 per 1,000,000 women over the age of 60 years [9].

3. Aetiology of TTC

The aetiology of TTC has not been clearly established, but exaggerated sympathetic stimulation [7] due to emotional stress is thought to be central to this syndrome [10–12].

In addition, not only acute but also chronic stress may cause the development of TTC. Thus, the incidence of anxiety and depression in patients with TTC ranges from 21% [13] to 40% [14,15], making stress a more common risk factor than the traditional risk factors of coronary diseases, such as smoking and diabetes. Furthermore, as correctly noticed by J. Hefner et al., not only acute and chronic stress but also acute and chronic distress can trigger TTC [12]. Indeed, electrocardiographic and ventriculographic abnormalities similar to those that are characteristic of TCC are observed in rats after immobilisation stress but not after combined blockade of alpha- and beta-adrenergic receptors (ARs) [16].

The ratio between emotional and physical types of stress, both of which can play a key role in TTC development [3,17], significantly varied in different studies. According to K. Tsuchihashi et al., emotional stress was revealed in 27% of patients and physical stress in 43% of patients [3]. In contrast, in the work of S.W. Sharkey et al., the ratio between emotional and physical stress was about 1 (50.4% vs. 49.6%) [18]. The frequency of a proven stress event prior to the occurrence of TTC, according to various authors, ranged from 71% [5] to 94% [19]. Moreover, based on a study according to which only 50% of patients had a stressor identified before confirmation of the diagnosis, E.N. Quattromani et al. concluded that the causative nature of stress in the development of TTC could not be firmly established from any existing data [20]. It is possible that the abovementioned discrepancies are caused by the fact that most researchers only took into account acute stress and did not consider the possibility of chronic distress.

4. Pathophysiological mechanisms

Debates are currently ongoing among the researchers about the pathogenetic mechanisms and triggering events of TTC [10,21–23]. While some researchers have focused on several exact mechanisms, others have suggested different sets or combinations of pathogenetic mechanisms [10,21–23].

According to J.P. Bounhoure, the pathogenetic mechanisms of TTC involve direct catecholamine toxicity, microvascular spasm, and myocardial sudden stunning, with the catecholamine surge playing the pivotal role [10]. In contrast, according to J.E. Dimsdale, myocardial stunning resulting from coronary spasm induced by psychological stress is the most plausible cause of TTC [23]. Catecholamine toxicity and neurogenic stunned myocardium were considered the main pathogenetic mechanisms of TTC by Y.J. Akashi et al. [22]. Increased levels of catecholamines, multi-vessel epicardial coronary artery spasm, or diffuse capillary spasm were mentioned as the causes of TTC development in the work of E. Merli et al., with the conclusion that the pathophysiology of TTC remains to be fully elucidated [23].

The main reason for the existence of such different ideas about the catecholamine action is the fact that most researchers studied each potential mechanism of catecholamine action separately, whereas actual consequences of catecholamine overload are multifactorial and may include both changes in peripheral vascular permeability and changes in central haemodynamics [24].

4.1. Coronary artery spasms

Myocardial ischaemia due to epicardial coronary artery spasm, without signs of significant coronary sclerosis, is called Prinzmetal's angina, variant angina, Prinzmetal's variant angina, or angina inversa. According to the literature, spontaneous coronary artery spasm was detected in 7% [25] to 40% [4] of patients with TTC, whereas provoked coronary spasm occurred in 14–21% [3,19], in up to 40% [4], and even in 71–75% [25,26] of patients.

The work of P. Angelini on patients who were prospectively subjected to acetylcholine (ACH) testing during the early recovery period after they had presented with TTC is of great interest in this regard. The provocative ACH test caused sustained coronary spasm, which was accompanied by the appearance of symptoms identical to original spontaneous TTC symptoms, with the recurrence of apical bladder syndrome [27]. However, there is currently no common opinion about the mechanisms underlying the development of local coronary spasm in intact vessels. For instance, in 1 study the measured flow-mediated dilation of the brachial artery in 30 patients with vasospastic angina (VSA) with positive results of spasm provocation test and without evidence of significant coronary stenosis (VSA group, $4.8 \pm 0.5\%$) was lower than that in 30 patients with negative results of spasm provocation test and without evidence of significant coronary stenosis (control group, $9.4 \pm 0.7\%$, $p < 0.0001$), which allowed the researchers to conclude that endothelial dysfunction might be an independent factor responsible for the development of VSA [28].

In contrast, according to the results obtained by K. Egashira et al., endothelium-dependent vasodilation evoked with substance P caused dose-dependent and comparable increases in the coronary diameter at the spastic and control sites, whereas ACH at a high dose (100 μg/min) provoked coronary vasospasm associated with anginal attack in all patients [29]. Those results, according to the authors, indicated that the ACH-induced coronary vasospasm in the patients with variant angina resulted from hyper-reactivity of the vascular smooth muscle to ACH but not from endothelial dysfunction [29].

In the work of K. Kandabashi et al., up-regulation of Rho-kinase and significantly greater extent of phosphorylation of the myosin-binding subunit of myosin phosphatase (MBS), a major substrate of Rho-kinase, at the spastic site were demonstrated, and a highly significant correlation between the extent of MBS phosphorylation and that of contractions was obtained [30]. Therefore, according to K.G. Lamping, one of the mechanisms underlying coronary spasm might be the increased activity of Rho-kinase, which causes hyper-contraction of vascular smooth muscle [31]. The abovementioned results were confirmed in the clinical study by A. Masumoto et al., which showed that intracoronary infusion of fasudil, a selective Rho-kinase inhibitor, markedly attenuated the coronary constriction induced by ACH ($p < 0.001$) and prevented the occurrence of chest pain and ischaemic electrocardiographic (ECG) changes in all treated patients ($p < 0.01$ versus saline in both cases) [32]. Later, it was shown that inflammatory stimuli, such as angiotensin II and interleukin (IL)-1beta, up-regulate Rho-kinase expression and activity in human coronary vascular smooth muscle cells via intracellular signal transduction mediated by protein kinase C and nuclear factor-kappaB [33].

The stress-induced rise of interleukins levels, undoubtedly, plays a special role in the occurrence of coronary artery spasm. Immobilisation stress was shown to increase the level of biologically active IL-1 in the hypothalamus, with the effects occurring within 5 min and peaking at 60 min after stress initiation. Since, according to F. Shintani et al., an interval of 5 min is too short for immobilisation stress to induce production of IL-1, stress might augment the effects of IL-1 pre-existing in the hypothalamus [34]. Moreover, it was shown that pre-treatment with an IL-1 receptor antagonist (IL-1Ra) inhibited immobilisation stress induced elevations of levels of hypothalamic norepinephrine, dopamine,