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Chapter

Takotsubo Syndrome and Nitric Oxide Bioavailability

Michael Demosthenous, Konstantinos Triantafyllou and Nikolaos Koumallos

Abstract

Takotsubo cardiomyopathy, also known as broken heart syndrome or stress cardiomyopathy, is a form of transient left ventricular dysfunction. Severe apical and mid left ventricular hypokinesis with hypercontractility of the basal segments is observed. Numerous underlying causes and pathophysiological mechanisms have been proposed including sudden sympathetic activation and increase in the circulating levels of catecholamines resulting in multivessel coronary spasm. Another possible mechanism related to catecholamine-mediated myocardial stunning is direct myocyte injury. Increasing data show that endothelial dysfunction and depleted nitric oxide bioavailability are common in patients with Takotsubo cardiomyopathy. In this chapter we examine in depth the relation between endothelial dysfunction and Takotsubo syndrome.

Keywords: Takotsubo cardiomyopathy, broken heart syndrome, nitric oxide, endothelial dysfunction, ADMA

1. Introduction

Takotsubo cardiomyopathy (TC), also known as broken heart syndrome or stress cardiomyopathy, is a form of transient left ventricular (LV) dysfunction. Severe apical and mid left ventricular hypokinesis with hypercontractility of the basal segments is observed [1–4]. The name derives from the fact that the shape of the LV of patients with Takotsubo syndrome resembles the octopus fishing pot used in Japan where the first studied case of TC was done by Sato et al. in the early 1990s (**Figure 1(a)** and **(b)**).

The InterTAK diagnostic score is a score that predicts the probability of Takotsubo cardiomyopathy and differentiates form acute coronary syndrome. Female sex and emotional stress yield the highest score. Other predisposing factors include physical stress, psychiatric disorders, and neurological disorders.

Takotsubo cardiomyopathy usually presents with shortness of breath, hypotension, angina or syncope. Laboratory work may reveal elevated troponin levels. Electrocardiogram may show signs of ischemia, such as T wave inversion or even ST elevation [1]. Coronary angiogram typically reveals normal coronary arteries.

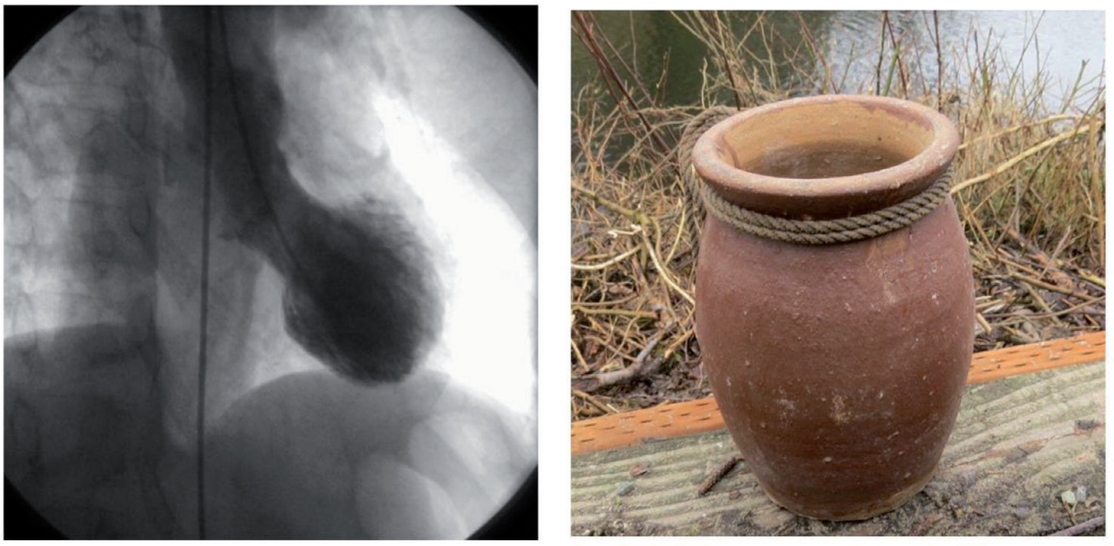

Figure 1.
(a) Angiogram of a patient with Takotsubo cardiomyopathy showing the apical balloning of the left ventricle. (b) The Takotsubo fishing pot after syndrome was named. You can appreciate the resemblance with angiographic image on the left.

2. Pathophysiology

The pathophysiology of TC is quite complex and a number of different mechanisms have been proposed, including sudden sympathetic activation and increase in the circulating levels of catecholamines resulting in multivessel coronary spasm [5–15]. Coronary vasospasm and sympathetic mediated microvascular dysfunction have been observed in patients with TC.

According to Gupta et al. [16], the pathophysiology of sympathetic mediated coronary vasospasm and microvascular dysfunction can be divided in two phases.

According to the authors, the first phase starts with cognitive centers of the brain. As a response to stress, the hypothalamic-pituitary-adrenal axis is activated and releases catecholamines. In the case of TC, catecholamine and brain natriuretic peptide (BNP) levels are elevated significantly more than in patients with decompensated heart failure after an acute coronary syndrome. Catecholamine levels then start to decline, but remain significantly higher than in patients with acute coronary syndromes even a week after the event. On the other hand, plasma BNP levels decline rapidly, compared to patients with acute coronary events, and this is in parallel with the rapid improvement of the LV systolic function in TC. During the second phase, myocardial stunning occurs as a result of increased catecholamine levels.

3. Proposed mechanisms of Takotsubo syndrome

Plasma catecholamine levels are shown to be closely correlated with TC. In a study by Wittstein et al. [8], plasma catecholamine levels in 13 patients with stress-related myocardial dysfunction were compared with those in 7 patients who presented with acute pulmonary edema after myocardial infarction (Killip class III). The study showed that plasma catecholamine levels (epinephrine, norepinephrine, and dopamine) at presentation were markedly higher among patients with stress-induced cardiomyopathy than among those with Killip class III myocardial infarction. According to the results of this study, patients with stress cardiomyopathy had

supraphysiologic levels of plasma catecholamines. Initial plasma levels were several times those of patients with myocardial infarction and remained markedly elevated even a week after the onset of symptoms [8].

The mechanism underlying the association between sympathetic activity and myocardial stunning is unknown.

Increased catecholamine levels result in either direct cardiomyocyte damage through increased calcium levels or in vascular spasm and microvascular dysfunction, which leads to ischemia [5–7]. Abnormal coronary flow in the absence of obstructive disease has recently been reported in patients with stress-related myocardial dysfunction [17]. Increased sympathetic activity and vascular spam also cause an increase in left ventricular afterload adding even more to the pathophysiology of TC [8].

Oxygen-derived free radical circulating levels can be increased by catecholamines and they can cause myocardial injury, which can be attenuated by antioxidants [18]; they can also interfere with sodium and calcium channels, increasing trans-sarcolemmal calcium influx resulting in myocyte dysfunction [19].

Oxidative stress often exaggerates myocardial stunning by affecting calcium homeostasis and causing excitation-contractive uncoupling resulting in myocardial dysfunction [6–8]. The histopathology of the myocardium in this condition differs from that found in ischemic insults and includes a neutrophil-predominant inflammation, contraction band necrosis, and fibrosis [9]. These changes probably reflect calcium cardiotoxicity rather than ischemic necrosis. The pattern of ventricular wall abnormality in TC also points toward a neurally mediated mechanism of cardiac injury [11–13].

One other possibility is ischemia resulting from epicardial coronary arterial spasm. Increased sympathetic tone from mental stress can cause vasoconstriction in patients without coronary disease [20].

A third possible mechanism of catecholamine-mediated myocardial stunning is direct myocyte injury. Elevated catecholamine levels decrease the viability of myocytes through cyclic AMP-mediated calcium overload [21].

4. Nitric oxide: endothelial dysfunction and Takotsubo cardiomyopathy

In 1980, Furchgott and Zawadzki [22] identified the "endothelium-derived relaxing factor" (later recognized as the free gas nitric oxide (NO)) as responsible for the relaxation of vascular smooth muscle cells in response to acetylcholine.

NO is synthesized by the enzyme NO synthase (NOS). This enzyme was first identified and described in the late 1980s. The enzyme NOS catalyzes the biosynthesis of NO through a reaction involving the conversion of L-arginine to L-citruline [23]. NOS is a dimer consisting of two identical monomers, which can be divided into two major domains: the C-terminal reductase and the N-terminal oxygenase domain [24]. It contains binding sites for flavin adenine nucleotide (FAD), nicotinamide adenine dinucleotide phosphate (NADPH) and flavin mononucleotide (FMN) in close relation with cytochrome P-450 reductase. The latter binds haem, tetrahydrobiopterin (BH4), and L-arginine, which acts as a substrate.

There are three different NOS isoforms, which differ between them in structure and function [25]. Endothelial NOS (eNOS) and neuronal NOS (nNOS) are Ca^{2+}-dependent enzymes (despite the fact that eNOS can be activated and in an Ca^{2+}-independent manner) [26]. Inducible NOS (iNOS) is only expressed at high levels after induction by cytokines (thus the name inducible) or other inflammatory agents. Its activity is independent of intracellular Ca^{2+} levels. The three NOS isoforms are similar in the way that they have regions of high homology

(the oxygenase and the reductase domains) while at the same time each isoform exhibits unique features, which signify their specific functions.

The main source of endothelial NO production is eNOS. Specific properties of eNOS enable the enzyme to perform its specialized functions. These are Ca^{2+} sensitivity and the post-translational modifications, which facilitate sub-cellular localization. These properties enable eNOS to respond not only to hemodynamic forces but to neurohormonal agents as well. There are several factors such as estrogens, hypoxia, and exercise that are known to modify its expression, likely having an impact on cardiovascular function.

4.1 Physiological role of NO: role of NO in vasomotion (vasorelaxation)

As mentioned above, Furchgott and Zawadzki [22] first demonstrated that endothelium reversed the intrinsic constrictive effects of acetylcholine on the vascular smooth muscle through the release of NO. Numerous experimental and clinical studies confirmed that all the arterial endothelium, and to a lesser extent vein endothelium, releases NO. When the endothelium is normal, vasoconstriction is counteracted by the potent vasorelaxing effect of NO. The importance of NO in vasodilation varies between vascular beds and among animal species. Chemical modifications of the guanidino group of L-arginine result in compounds that inhibit NO synthase. NG-nitro-L-arginine (L-NA), NG-monomethyl-L-arginine (L-NMMA), and NG-nitro-L-arginine methyl ester (L-NAME) inhibit the release of NO from endothelial cells, indicating that there is continuous release of NO, which maintains the vasodilator tone.

4.2 The role of L-arginine analogues in eNOS function

ADMA is an amino acid that circulates in plasma, is excreted in urine, and is found in tissues and cells [27–29]. ADMA synthesis involves methylation of arginine residues by protein arginine methyltransferases (PRMTs) [30]. During methylation, either one or two methyl groups are added to the guanidine nitrogens of arginine, which are incorporated into proteins. There are two types of PRMT. Type 1 catalyzes the formation of ADMA and type 2 catalyzes the formation of symmetric dimethylarginine (SDMA) through the methylation of both guanidino nitrogens. Both PRMTs can monomethylate as well. Monomethylation leads to the formation of another asymmetrical form called *NG*-monomethyl-L-arginine (L-NMMA) [31].

The asymmetrical forms (ADMA and L-NMMA) are natural inhibitors of all NOS isoforms, whereas the symmetrical form (SDMA) is not. ADMA and L-NMMA inhibit all three isoforms of NOS [32, 33]. L-NMMA may also uncouple NOS leading to the generation of free radicals and more specific of superoxide [34]. Superoxide formation by this process further results in myocardial injury seen in TC.

Increased sympathetic activity and alterations in NO synthesis attributable to accumulation of ADMA is now recognized as an important mechanism involved in cardiovascular complications [35].

ADMA plasma levels are found to be related to insulin resistance, blood pressure, carotid intima thickness, and age even in healthy individuals, free from cardiovascular disease [36, 37] suggesting that increased ADMA levels are a marker for arteriosclerotic changes.

4.3 Endothelial dysfunction and TC

Increasing data show that endothelial dysfunction is common in patients with TC, which could explain the two of the proposed mechanisms reported at the

beginning of this chapter: propensity for epicardial and/or microvascular coronary artery spasm. Indeed, endothelial dysfunction may be a crucial link between myocardial dysfunction seen in TC and stress [38]. Consequently, the reversible LV dysfunction seen in TC may be the result of myocardial stunning due to this ephemeral myocardial ischemia caused by endothelial dysfunction. This mechanism, attenuated by endothelial dysfunction, may also be the cause of high prevalence of TC in postmenopausal women due to estrogen level depletion, which is related to vasomotor abnormalities [39–41].

Under physiological circumstances, estrogens are beneficial for coronary microcirculation. Estrogens have a pivotal role in improving coronary blood flow through endothelium-dependent or independent-mechanisms [41]. Reduced estrogen levels in menopause positively affect endothelial dysfunction and sympathetic drive [40]. Through this effect, postmenopausal estrogen deficiency possibly facilitates the occurrence of TC, especially when emotional stress is in the equation.

Endothelial dysfunction is closely associated to the traditional risk factors for cardiovascular disease. On the other hand, traditional risk factors for cardiovascular disease (smoking, dyslipidemia and hypertension) are present in patients with TC in a non-negligible prevalence [42–44]. In addition, there is growing evidence that patients with TC also have various comorbidities, including neurological, pulmonary, kidney, and liver disease [42], conditions mostly associated with endothelial dysfunction and might therefore constitute a previously unrecognized predisposing factor for TC [45].

5. Conclusion

TC is now a well-recognized syndrome with a very complex pathophysiology. Increased sympathetic activity and plasma catecholamine levels have a pivotal role in the expression of TC. Recent data suggest that endothelial dysfunction and NO depletion are crucial predisposing factors for this syndrome and could be a crucial link between emotional stress and myocardial dysfunction.

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