Angiology
2018, Vol. 69(2) 100-102

DOI: 10.1177/0003319717726938
journals.sagepub.com/home/ang
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Takotsubo Cardiomyopathy: A Benign Condition or a Bad Omen?

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Keywords
Takotsubo cardiomyopathy, pathogenesis, comorbidity, prognosis

Takotsubo cardiomyopathy (TC), also known as "stress cardiomyopathy" or "broken heart syndrome," is a transient disorder, typically following an acute emotional or physical stress, mimicking an acute coronary syndrome (ACS). Patients with TC complain of chest pain and show electrocardiogram dynamic changes such as ST-segment elevation or negative T waves with a mild increase in cardiac biomarkers and absence of significant coronary artery involvement. Left ventricular (LV) wall motion abnormalities in TC are typically akinesia or hypokinesia of apical segments (apical balloon-like dilation pattern) associated with hyperkinesia of the basal segments.[1-3] Echocardiography plays a key role in the diagnosis, allowing direct visualization of the typical apical ballooning pattern, and it is considered specific. New technologies, such as speckle tracking echocardiography, are useful.[4-7] Despite the fact that these findings are unlikely in ACS, coronary angiography is needed to rule out myocardial infarction.[1-3]

Do We Know the Exact Pathogenesis of TC?

Several pathophysiological mechanisms have been proposed: (1) artery vasospasm and microvascular dysfunction may to lead to the typical apical ballooning pattern, which can cause acute heart failure and (2) abnormal response to catecholamines; this seems to be the most accredited hypothesis. Activation of α- and β-adrenoceptors is widely recognized as a key element in TC abnormalities; Wittstein et al[8] found 2- to 3-fold higher concentrations of the serum catecholamine in patients with TC compared with myocardial infarction. They have suggested that serious emotional stress could play a role as precipitating factor. This hypothesis is supported by the demonstration that pheochromocytoma and catecholamines administration can cause the typical pattern.[9,10] Interestingly, stressful conditions may cause intracellular calcium overload and subsequent cardiac dysfunction through the β_1-adrenoceptor signal transduction pathway.[11] Lyon et al[12] theorized a mechanism, the so-called "stimulus trafficking," to explain the decline in myocyte contractile capability in TC. Raised levels of catecholamines that induce β_2-coupling from Gs to Gi causes a negative inotropic effect, particularly on the apical myocardium where β-adrenoceptors density is highest. The rationale of "stimulus trafficking" is that a switch to Gi plays a protective activity on the myocytes against stimulation of Gs, which causes the apoptosis. Slow but significant increases in serum troponin level may explain early minimal necrosis of myocardial tissue. Mori et al noticed an increased β_2-adrenoreceptors concentration gradient from apex to base commonly found in TC.[13] All these results validated that physical and emotional stressors by inducing the release of large amounts of epinephrine could be effective in determining the local apical response of myocardial tissue that is closely related to different distribution of β_2-receptors.[14] In this context, myocardial biopsy showed regions characterized by contraction band necrosis, inflammatory cells with macrophage infiltration, and localized fibrosis.[15] All these changes were caused by direct catecholamine toxicity on myocytes[16] and oxidative stress, leading to necrosis and wall motion abnormalities. The univalent reduction of oxygen generates reactive intermediates, also known as reactive oxygen species (ROS), responsible for oxygen-mediated toxicity. There is evidence that ROS affect the function of calcium channels.[17-19] The cardioprotective properties of estrogen are known and this mechanism has been related to the high morbidity associated with TC in postmenopausal women; about 90% of patients presenting with TC are postmenopausal women.[20,21] The authors noted a correlation between Myocardial Infarction and genetic variants of estrogen receptors ESR1 and ESR2, questioning a genetic substrate for ACS in women with specific polymorphisms.[22,23] Estrogens play a relevant role in reducing the release of epinephrine in the presynaptic cardiac sympathetic nerve fibers and in calcium-dependent myocardial contraction, and based on the prevalence of TC in postmenopausal women, we can assume a

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role played by estrogens in this nonischemic disease. In this context, ovariectomized rats exposed to stress, without estradiol supplementation, showed significantly greater increases in the heart rate and LV dysfunction compared with rats on estradiol supplementation.[24] This strengthens the idea that postmenopausal women have a lack in protective effect of estrogens, resulting in a dangerous response to serum catecholamines.

Comorbidity and Prognosis

Patients with TC frequently have a good prognosis. The consequences of TC are potentially reversible with a benign prognosis. However, concomitant acute hemodynamic decompensation and comorbidities are associated with worse prognosis.[25,26] El-Battrawy et al demonstrated that different variants of TC are closely related to different clinical presentations, complications, and prognoses. Patients with the apical form of TC show a trend for consequences and are older but less likely to smoke; patients with hypertension had a higher predilection to present with the apical form.[27] Furthermore, in a 2-year follow-up, concomitant coronary artery disease (CAD) complicated their outcome leading to raised mortality compared with TC without CAD.[28] In a recent study, El-Battrawy et al showed higher rates of in-hospital events and mortality in the patients with TC having atrial fibrillation (AF) compared with patients with TC without AF.[29] Bill et al,[30] in this issue of *Angiology*, observed that patients with TC and kidney failure (KF), compared with patients with TC without KF, have a worse prognosis. Patients ($n = 108$) with TC were divided in 2 groups, depending on the absence ($n = 76$) or presence ($n = 32$) of KF. No differences were found for gender distribution, age, cardiovascular risk factors, and clinical presentation between the 2 groups. The mean follow-up was 5 years. The authors observed that KF may affect the outcome in patients with TC due to high serum catecholamine levels. In turn, these increased levels of catecholamines may originate from lower serum renalase (which degrades catecholamines) activity, potentially leading to a worse outcome when both TC and KF coexist.[31,32] The study by Bill et al did not show differences in major adverse events during hospital stay; inhospital all-cause mortality rate was higher in patients with KF, but did not reach significance (5.2% vs 15.6%, $P = .12$), but event-free survival after a follow-up of 5 years was lower in patients with KF ($P < .01$) at any time after discharge. Although this is a single-center study with a small number of patients, the results are interesting and could encourage planning larger multicenter studies.

This interesting field is constantly in evolution and establishing the role of KF will clarify its relation with TC. The medical community should consider these findings as suggestive of a potentially worse outcome in patients with TC affected by certain comorbidities. The picture of TC, as a benign condition, could change substantially in different scenarios.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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