Takotsubo Cardiomyopathy Induced by Treadmill Exercise Testing
An Insight Into the Pathophysiology of Transient Left Ventricular Apical (or Midventricular) Ballooning in the Absence of Obstructive Coronary Artery Disease

To the Editor: Although the pathogenesis of Takotsubo cardiomyopathy (TC) remains unclear, physical or emotional stress is common in the majority of reported cases (1–3). The central role for sympathetic stimulation in TC is suggested by elevations in plasma catecholamines (1–3), neuronal imaging (2,4), and animal studies (1,3). Takotsubo cardiomyopathy in rats as a result of sympathetic stimulation was not reproducible following pretreatment with beta-adrenergic blockade (1,3).

We present a patient with TC following exercise treadmill testing, a situation known to have sympathetic overdrive. To our knowledge, this is the first report during exercise and the only one with perfusion imaging at the onset of the event. The perfusion data are helpful to the understanding of the pathophysiology of TC, and the presence of normal perfusion despite characteristic wall motion abnormalities makes a strong point to the primary role of metabolic changes rather than vascular abnormalities.

A 71-year-old Caucasian woman underwent exercise sestamibi imaging for evaluation of chest pain (CP). The physical examination and electrocardiogram were normal (Fig. 1). The patient achieved target heart rate, and Tc-99m sestamibi was injected at 5 min when the patient began experiencing substernal CP with ST-segment depression (Fig. 1). She was given 1 spray of nitroglycerin, and the ST-segment changes resolved completely. Gated single-photon emission computed tomography images obtained 1 h later were normal (Fig. 1C), but there was dyskinesia of the apex (Fig. 1); the left ventricular ejection fraction (LVEF) was 51%.

The patient’s CP subsided but did not disappear completely. Coronary angiography was performed 3 h later and revealed no obstructive coronary artery disease. The left ventriculogram was abnormal (Fig. 2), and the LVEF was 55%. She did well at follow-up 1 month later, and a 2-dimensional echocardiography revealed normal LVEF with no regional wall motion abnormality.

The unique features in this patient are the temporal relationship between TC and exercise and the normal perfusion pattern at the onset of her event.

Perhaps TC results from stunning of the myocardium in the setting of excess catecholamines, but whether this stunning is due to ischemia and decreased perfusion on the basis of microvascular vasoconstriction or due to a primary metabolic abnormality is unknown (1–4). One report showed a flow-metabolism mismatch pattern; however, unlike that in coronary artery disease, the pattern seen in TC showed relatively preserved flow but reduced glucose uptake (1). The perfusion defects could be explained by a partial volume effect attributable to stunning. Furthermore, this study could be faulted by the fact that the imaging was obtained ~3 days after the initial event, but our patient showed normal perfusion even when the tracer was injected at time zero.

A reduction in glucose uptake with normal perfusion has been shown in humans and animals to be a feature of repetitive stunning (1,4). Possible mechanisms include a decrease in the activity of key enzymes of the glycolytic pathway or reduced sensitivity to calcium in stunned myocardium with inhibition of translocation of glucose transporter-4 from the intracellular pool to the sarcolemma, thus reducing glucose uptake. Also, excess catecholamines could lead to insulin resistance, which may lead to impaired glucose uptake (1).

Other studies have shown a greater impairment in fatty acid metabolism than perfusion in the mid and apical LV regions in TC (4,5). The myocardium depends on a significant amount (70% to 80%) of energy from fatty acid oxidation during aerobic conditions, and there is a marked reduction in beta-oxidation of fatty acids in the post–ischemic myocardium (5).

It seems that large-vessel spasm is an unlikely explanation of TC in the vast majority of patients (1), and provocative coronary vasospasm was induced in only 1 of 7 patients (6). Abnormal Thrombolysis In Myocardial Infarction (TIMI) frame counts have been described in all 3 major coronary arteries in patients with TC, consistent with microvascular rather than macrovascular impairment (3,5). Decreased coronary flow velocity reserve and a reduction in deceleration time of diastolic velocity of all 3 coronary arteries were demonstrated in patients within 24 h of presentation. At 3-week follow-up, these measurements improved, providing further evidence that reversible microvascular dysfunction contributes to transient LV dysfunction (3).

Other perfusion studies have shown moderate to severe reductions in tracer uptake in affected LV segments in the presence of normal angiographic coronary arteries (1,4–6). Thus, while myocardial stunning is seen in TC, it remains poorly understood whether the catecholamine excess leads to microvascular spasm, direct myocyte toxicity secondary to cyclic adenosine monophosphate–mediated calcium overload, or a primary metabolic abnormality (1,2).

Perhaps the most enigmatic finding in patients with TC is the predilection for dysfunction in the mid and apical segments...
of the LV with basal sparing (1,2). This characteristic finding is likely due to basal-to-apical gradients in both perfusion and sympathetic distribution (1–3). Sympathetic nerves and the density of receptors are not uniformly distributed in the LV myocardium of dogs and cats (3).

Finally, the most puzzling part of this syndrome is the very high predilection in women and the rarity of recurrences, despite the fact that stresses in life are rarely isolated. The role of hormones and the possibility of misdiagnosis or inappropriate diagnosis must be considered in future research projects. Although metabolic changes or vascular abnormalities appear to be the central causes of TC, the precise pathophysiology remains uncertain.

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Letters to the Editor

Cardiovascular Mortality in High-Risk Patients and T-786C Polymorphism in Promoter Region of the Endothelial Nitric Oxide Synthase Gene

Rossi et al. (1) reported very interesting and intriguing results of the first prospective study examining the possible effects of 2 single nucleotide polymorphisms (SNP) in the endothelial nitric oxide synthase (eNOS) gene (the T-786C SNP in the promoter region, and the G894T SNP in exon 7) on cardiovascular mortality among high-risk patients. Although no significant effects were found for the G894T SNP, more cardiovascular deaths were found when individuals with TT genotype for the T-786C SNP were compared with CC + CT individuals (1). The significant effect of T-786C SNP on cardiovascular mortality persisted even after many confounding factors were taken into consideration. However, a significant number of individuals (32%) were on lipid-lowering therapy at recruitment (1), and it is probable that an increased proportion of these subjects may have received statins thereafter.

Interestingly, although the T-786C SNP apparently does not significantly affect nitric oxide (NO) availability (2,3), it may modulate the responses to statins. In this regard, we have recently reported that treatment with atorvastatin significantly increased NO availability (measured as whole blood nitrite) in CC individuals, but not in TT individuals (4), thus confirming previous findings suggesting that statins may produce stronger effects on NO availability in CC individuals compared with TT individuals (5). In addition, atorvastatin significantly reduced the concentrations of inflammatory markers in subjects with CC (but not TT) genotype (6). Although these findings derive from studies that included healthy individuals, they suggest that statins may significantly modify the cardiovascular risk associated with the T-786C SNP. Indeed, it is possible that treatment with statins counteracts the effects associated with the T-786C SNP (4), thus leading to apparently paradoxical results such as those reported by Rossi et al. (1).