Stress cardiomyopathy associated with vasodilator stress testing

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Stress cardiomyopathy, also known as takotsubo cardiomyopathy, is a clinical syndrome that has been increasingly recognized over the past 30 years, and is manifested by temporary left ventricular (LV) systolic dysfunction that is not caused by an acute coronary syndrome.¹ The classic description is hypokinesis of the LV apex with hyperkinesis of the base, also known as the “apical ballooning” pattern. This classical pattern is what lends the name takotsubo (Japanese term referring to an octopus trap which has a wide and rounded bottom with a narrow neck, thus resembling the LV shape on ventriculography in these patients) to the disease. Nevertheless, this pattern is not required for diagnosis and up to 25% of patients have other variants including mid-ventricular hypokinesis, and the less common inverted form with basal hypokinesis.² Awareness of these variants is important to accurately suspect and diagnose stress cardiomyopathy that may present atypically. Patients with stress cardiomyopathy are classically postmenopausal women, and frequently present with a clinical picture that is similar to an acute coronary syndrome including signs and symptoms such as substernal chest pain, dyspnea, ECG changes (ST elevation, T wave inversion, and prolonged QT interval), cardiac arrhythmias and positive cardiac biomarkers.³ The condition has been referred to as the “broken heart syndrome” as it is often, but not always, preceded by an

intense emotional or physical stress. Nevertheless, nearly a third of patients with stress cardiomyopathy may not have a clearly identifiable stressor.³ The Mayo Clinic diagnostic criteria require transient LV systolic dysfunction extending beyond a single coronary artery distribution, absence of obstructive coronary disease or angiographic evidence of acute plaque rupture, presence of new ECG abnormalities or cardiac biomarker elevation, and absence of pheochromocytoma or myocarditis.^{1,4}

Traditionally, stress cardiomyopathy is considered a transient and reversible disease with an ultimate recovery of LV systolic function which could occur quickly or could take weeks. In opposition to this benign outlook, it is now recognized that this entity is associated with a significant burden of complications including arrhythmia, cardiogenic shock, and death. Furthermore, the high recurrence rate (up to 20% at 10 years in some studies) suggests that the underlying dysfunction is not completely reversible.² Consistent with this observation, Scally et al. recently reported persistence of heart failure symptoms, functional limitations and subclinical cardiac dysfunction by strain analysis at a median of 20 months after the index event despite normalization of LV ejection fraction.⁵

Imaging modalities most often used to assess for LV regional wall motion abnormalities associated with stress cardiomyopathy include echocardiography and invasive ventriculography that is obtained at the time of coronary artery evaluation. Alternatively, cardiac magnetic resonance imaging (CMR) can be used to further assess LV and right ventricular function. CMR can be helpful in differentiating stress cardiomyopathy from other diagnoses such as myocardial infarction or myocarditis by assessing for fibrosis, necrosis, and inflammation or edema.^{6,7} On CMR, late gadolinium enhancement (LGE) can sometimes be detected at a low threshold in stress cardiomyopathy, but is

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distinguishable from myocardial infarction which usually has intense LGE (> 5 standard deviations above the mean of remote myocardium) and myocarditis which has patchy LGE.⁶ Furthermore, the location of LGE can assist in the differential diagnosis as myocardial infarction often manifests with LGE that is either transmural or sub-endocardial, while in myocarditis the LGE is typically mid-wall or sub-epicardial.⁷ Finally, gated single photon emission computed tomography has also been used to identify patients with stress cardiomyopathy.^{8–10} This is clinically relevant since, as discussed above, many of these patients present with signs and symptoms that could be attributed to coronary artery disease and may, therefore, undergo non-invasive assessment of myocardial perfusion. It is, therefore, important for the imager to comment on regional wall motion abnormality and raise the suspicion for this clinical diagnosis in the appropriate setting so that further assessment can be performed.

The aetiology of stress cardiomyopathy is not well understood. Several mechanisms have been proposed including excessive sympathetic stimulation, microvascular dysfunction, metabolic dysfunction and hormonal effects (which may help explain the preponderance of this entity in postmenopausal women). It is postulated that catecholamines play a significant role in inducing stress cardiomyopathy either by microvascular spasm¹¹ or direct cardiotoxicity.¹² This mechanism is supported by imaging studies using ¹²³I-metaiodobenzylguanidine (MIBG), a norepinephrine analogue, which demonstrate a decreased heart-to-mediastinal ratio and increased washout rate in these patients.¹³ Importantly, this sympathetic disruption persists for several months after the acute event. The presence of excess catecholamines can occur due to an extreme stressor leading to physiologic release of endogenous catecholamines, or can be iatrogenic in some cases. For example, some cases have been reported following the administration of intravenous epinephrine and dobutamine.¹⁴ The mechanism predisposing some individuals to develop cardiomyopathy in response to a stressor while others are unaffected by the same stressor is not entirely understood.

An interesting case report of stress cardiomyopathy induced by exercise treadmill testing demonstrated normal myocardial perfusion on imaging at the onset of the trigger for the syndrome.⁸ This report makes a strong argument for metabolic rather than vascular abnormality as the cause of contractile dysfunction. Positron emission tomography studies using F-18 labelled Fludeoxyglucose have demonstrated a metabolic abnormality in the affected area in the presence of normal or nearly normal perfusion—an imaging pattern that has been labelled as inverse perfusion/metabolism

mismatch to contrast this with the imaging pattern seen in hibernating myocardium.^{15,16}

In this issue of the Journal, Koester et al. report on a case of 72-year-old woman with known asthma who experienced stress cardiomyopathy following administration of adenosine and subsequent development of bronchospasm during cardiac stress testing.¹⁷ Unfortunately, myocardial perfusion imaging could not be performed in this patient since she underwent emergent cardiac catheterization. Adenosine is known to cause bronchospasm during stress testing and bronchospasm is one of the indications for reversal of vasodilator stress using intravenous aminophylline or other agents.^{18,19} This patient was appropriately treated with bronchodilators, oxygen, intravenous aminophylline, and intramuscular epinephrine. As the authors point out in the case study, there were multiple potential triggers of stress cardiomyopathy in this case including adenosine-induced bronchospasm, the administration of high doses of inhaled bronchodilators and intramuscular epinephrine. There have been several other case reports of stress cardiomyopathy attributed to bronchospasm in the context of pulmonary disease.^{20,21} One case series described five patients that each presented with an acute COPD exacerbation, and were subsequently diagnosed with stress cardiomyopathy.²¹ The authors of the case series describe the novel term “bronchogenic stress cardiomyopathy,” and postulate that the cardiomyopathy could be due to the bronchospasm itself, or the high doses of inhaled bronchodilators (beta agonists and muscarinic antagonists) that the patients received. All five of the patients also received oral corticosteroids as a part of their treatment which provides yet another potential contributing factor to their development of stress cardiomyopathy.

It is important to note that activation of adenosine receptors, with adenosine or other agents such as regadenoson and dipyridamole, induces a sympathetic surge in the heart that is most manifested by an increase in the heart rate following the administration of these agents.^{22–24} This is yet another mechanism for a possible trigger of stress cardiomyopathy in this patient and simultaneously provides supportive evidence of sympathetic stimulation as a root cause of the syndrome as discussed above. Indeed, there are other reported cases of stress cardiomyopathy associated with vasodilator stress tests in the absence of bronchospasm.^{25,26}

Stress laboratories should be cognizant of potential complications of stress testing including the rare occurrence of stress cardiomyopathy that has been described with both exercise and vasodilator stress.

Disclosure

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