Stress cardiomyopathy is a syndrome of transient cardiac dysfunction precipitated by intense emotional or physical stress. Excessive sympathetic stimulation is believed to be central to the pathogenesis of this disorder, but a causal link has not been convincingly demonstrated.

We observed 9 cases of stress cardiomyopathy precipitated immediately by the intravenous administration of epinephrine (n = 6) or dobutamine (n = 3). Patients were evaluated with coronary angiography and with serial echocardiography, electrocardiography, and cardiac enzymes.

The median age was 44 years (interquartile range [IQR]: 30 to 48 years), and 7 (78%) were woman. Troponin-I was mildly elevated (median 4.07 ng/ml, IQR: 0.47 to 5.63 ng/ml), but none of the patients undergoing angiography had obstructive coronary disease. All patients developed corrected QT interval (QTc interval) prolongation (median QTc interval 504 ms, IQR: 477 to 568 ms) within 24 h of receiving drug. All 3 previously described variants of left ventricular “ballooning” (apical, midventricular, and basal) were observed. The median ejection fraction on admission was 35% (IQR: 35% to 40%). During follow-up (median 7 days, IQR: 4 to 13 days) there was recovery of left ventricular systolic function in all patients (median ejection fraction 55%, IQR: 40% to 60%, p < 0.001 vs. admission).

Exposure to catecholamines and beta-receptor agonists used routinely during procedures and diagnostic tests can precipitate all the features of stress cardiomyopathy, including cardiac isoenzyme elevation, QTc interval prolongation, and rapidly reversible cardiac dysfunction. These observations strongly implicate excessive sympathetic stimulation as central to the pathogenesis of this unique syndrome.

Stress cardiomyopathy (SCM) is a syndrome of profound yet reversible cardiac dysfunction precipitated by acute emotional or physical stress. The cause of SCM is unknown, but its frequent association with sudden and intense stress suggests that the mechanism of transient myocardial dysfunction might be sympathetically mediated. This is supported by the observation that plasma catecholamine levels are markedly elevated in acute SCM compared with acute myocardial infarction (1). Case reports have also described the onset of SCM in patients with catecholamine-secreting tumors (2). Endomyocardial biopsy samples from patients with SCM have demonstrated contraction band necrosis, a unique form of myocyte injury observed in clinical states of catecholamine excess (1). Despite these reports, a causal link between catecholamine exposure and SCM has not been convincingly demonstrated. In this observational case series, we report the clinical characteristics of 9 patients who developed SCM immediately after the intravenous administration of catecholamines and beta-receptor agonists.

Methods

Between 2001 and 2008, 143 patients were diagnosed with SCM at our institution. Nine of these patients (6.3%) developed SCM immediately after the intravenous administration of epinephrine or dobutamine. SCM was diagnosed on the basis of characteristic patterns of left ventricular (LV) dysfunction extending beyond a single epicardial coronary artery territory (“ventricular ballooning”). Specific patterns of regional wall motion included apical and midventricular akinesis with sparing of the base (apical ballooning variant); midventricular akinesis with preserved contraction of the apex and base...
(midventricular ballooning variant); and midventricular and basal akinesis with normal apical contractility (basal ballooning variant) (1,3,4). Additional clinical evidence supporting the diagnosis of SCM included minimal elevation in cardiac isoenzymes, despite the presence of large regions of focal akinesis, the evolution of electrocardiographic (ECG) abnormalities that frequently included deep diffuse T-wave inversion and corrected QT interval (QTc interval) prolongation, the absence of obstructive coronary artery disease by angiography, and the rapid improvement in LV systolic function (1).

Patients were evaluated in the acute setting with serial ECGs, cardiac isoenzymes, and transthoracic echocardiography. Seven patients underwent coronary angiography at the discretion of the treating physician. Cardiac catheterization was deferred in 2 young patients (Patients #5 and #8), because coronary artery disease was deemed highly unlikely. All patients had follow-up echocardiography within 2 weeks.

Continuous variables are presented as median and interquartile range (IQR). Wilcoxon signed rank test was used to compare ejection fractions at various time intervals after onset of SCM. A 2-tailed p < 0.05 was considered statistically significant. The study was approved by the institutional review board of Johns Hopkins University School of Medicine.

**Results**

The median age of the patients was 44 years (IQR: 30 to 48 years), and 7 patients (78%) were women (Table 1). Three patients were Caucasian, 4 were African American, 1 was Vietnamese, and 1 was from Bermuda. Six patients had no coronary risk factors, 2 patients had a history of tobacco use, and 1 patient had hypertension and diabetes mellitus.

Patients #1, #2, and #3 experienced the onset of symptoms while receiving standard doses of intravenous dobutamine (30 to 40 µg/kg/min) during stress echocardiography (Table 2, Fig. 1). Patient #4 was a health care provider who attempted suicide by intravenously injecting multiple vials of epinephrine (estimated dose 40 mg). Patient #5 inadvertently received 1 mg of intravenous epinephrine during

### Table 1 Clinical Features on Admission of Patients With Stress Cardiomyopathy

<table>
<thead>
<tr>
<th>Patient #</th>
<th>Age (yrs)</th>
<th>Sex</th>
<th>Drug</th>
<th>Event</th>
<th>HR (beats/min)</th>
<th>MAP (mm Hg)</th>
<th>Killip Class</th>
<th>Peak Tn-I (ng/ml)</th>
<th>Max QTc (ms)</th>
<th>Hemodynamic Support</th>
<th>Ballooning Pattern</th>
<th>EF (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>46 M</td>
<td>Dobutamine</td>
<td>Dobutamine echo</td>
<td>Dobutamine echo</td>
<td>92</td>
<td>55</td>
<td>1</td>
<td>0.17</td>
<td>475</td>
<td>None</td>
<td>Apical</td>
<td>35</td>
</tr>
<tr>
<td>2</td>
<td>51 F</td>
<td>Dobutamine</td>
<td>Dobutamine echo</td>
<td>Dobutamine echo</td>
<td>59</td>
<td>60</td>
<td>2</td>
<td>0.46</td>
<td>652</td>
<td>IABP</td>
<td>Midventricular</td>
<td>35</td>
</tr>
<tr>
<td>3</td>
<td>41 F</td>
<td>Dobutamine</td>
<td>Dobutamine echo</td>
<td>Dobutamine echo</td>
<td>63</td>
<td>77</td>
<td>1</td>
<td>4.1</td>
<td>477</td>
<td>None</td>
<td>Midventricular</td>
<td>35</td>
</tr>
<tr>
<td>4</td>
<td>30 F</td>
<td>Epinephrine</td>
<td>Suicide attempt</td>
<td>Dobutamine echo</td>
<td>88</td>
<td>55</td>
<td>4</td>
<td>0.47</td>
<td>499</td>
<td>Dopamine</td>
<td>Apical</td>
<td>15</td>
</tr>
<tr>
<td>5</td>
<td>24 F</td>
<td>Epinephrine</td>
<td>Liposuction</td>
<td>Dobutamine echo</td>
<td>100</td>
<td>55</td>
<td>3</td>
<td>3.2</td>
<td>540</td>
<td>Dopamine</td>
<td>Apical</td>
<td>15</td>
</tr>
<tr>
<td>6</td>
<td>48 F</td>
<td>Epinephrine</td>
<td>Face lift</td>
<td>Dobutamine echo</td>
<td>85</td>
<td>69</td>
<td>3</td>
<td>5.6</td>
<td>568</td>
<td>None</td>
<td>Basal</td>
<td>35</td>
</tr>
<tr>
<td>7</td>
<td>44 F</td>
<td>Epinephrine</td>
<td>Keloid repair</td>
<td>Dobutamine echo</td>
<td>136</td>
<td>67</td>
<td>3</td>
<td>12</td>
<td>471</td>
<td>Norepinephrine</td>
<td>Basal</td>
<td>40</td>
</tr>
<tr>
<td>8</td>
<td>20 F</td>
<td>Epinephrine</td>
<td>Colonoscopy</td>
<td>Dobutamine echo</td>
<td>100</td>
<td>57</td>
<td>3</td>
<td>7.4</td>
<td>607</td>
<td>None</td>
<td>Basal</td>
<td>40</td>
</tr>
<tr>
<td>9</td>
<td>54 F</td>
<td>Epinephrine</td>
<td>Vasovagal syncope</td>
<td>Dobutamine echo</td>
<td>100</td>
<td>121</td>
<td>1</td>
<td>4.4</td>
<td>504</td>
<td>None</td>
<td>Basal</td>
<td>40</td>
</tr>
</tbody>
</table>

EF = ejection fraction by echocardiography; HR = heart rate; IABP = intra-aortic balloon pump; MAP = mean arterial pressure; Max QTc = maximum corrected QT interval; Tn-I = troponin-I.

### Table 2 Clinical Characteristics of Patients Developing Stress Cardiomyopathy During Dobutamine Stress Echocardiography

<table>
<thead>
<tr>
<th>Patient #</th>
<th>Indication</th>
<th>Dobutamine (µg/kg/min)</th>
<th>HR (beats/min)</th>
<th>BP (mm Hg)</th>
<th>ECG Findings</th>
<th>Echocardiographic Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pre-operative evaluation</td>
<td>40</td>
<td>83</td>
<td>146</td>
<td>86/54</td>
<td>148/90</td>
</tr>
<tr>
<td>2</td>
<td>Atypical chest pain</td>
<td>40</td>
<td>59</td>
<td>125</td>
<td>136/72</td>
<td>194/100</td>
</tr>
<tr>
<td>3</td>
<td>Atypical chest pain</td>
<td>30</td>
<td>59</td>
<td>126</td>
<td>112/72</td>
<td>173/97</td>
</tr>
</tbody>
</table>

AK = akinesis; BP = blood pressure; ECG = electrocardiogram; EF = ejection fraction; HK = hypokinesis; HR = heart rate; LBBB = left bundle branch block; STD = ST-segment depression; STE = ST-segment elevation; WMA = wall motion abnormality.
outpatient liposuction, and Patient #6 was given 1 mg of intravenous epinephrine during cosmetic facial surgery. Patient #7 was administered an unknown dose of epinephrine directly into a superficial vein during repair of a keloid scar. Patient #8 was mistakenly treated with undiluted epinephrine (1:1,000 dilution) injected into a bleeding rectal vein during colonoscopy (estimated dose approximately 5 mg). Patient #9 was an inpatient who was incorrectly given 1 mg of intravenous epinephrine after an episode of vasovagal syncope.

All patients developed chest pain after drug administration, and 6 patients (67%) developed symptomatic heart failure with a median Killip class of 3 (IQR: 1 to 3). One patient was intubated for pulmonary edema, 1 patient required an intra-aortic balloon pump, and 3 patients required vasopressor support (Table 1). There were no sustained arrhythmias or in-hospital deaths.

The presenting ECG showed ST-segment depression in 2 patients, 1 in inferior and lateral leads and the other diffusely. One patient had diffuse precordial ST-segment elevation at the time of admission. T-wave inversions were present on admission in 3 patients. One patient had Q waves in leads V1 to V3 on presentation that resolved during recovery. Within 24 h of receiving drug, all 9 patients developed prolongation of the QTc interval (median QTc interval 504 ms, IQR: 477 to 568 ms), and 7 of the 9 patients developed diffuse T-wave abnormalities. Deep inverted T waves evolved in patients with apical ballooning, whereas broad upright T waves were observed in patients with the basal ballooning variant. Patients with midventricular ballooning were more likely to have nonspecific T-wave abnormalities (Fig. 2).

Despite severe LV dysfunction at the time of admission, cardiac enzymes were only mildly elevated with a peak creatinine phosphokinase of 319 IU/l (IQR: 175 to 417 IU/l) and a peak MB of 24 ng/ml (IQR: 17 to 33 ng/ml). Peak troponin I was 4.2 ng/ml (IQR: 0.47 to 6.5 ng/ml) (Table 1).

All 7 patients undergoing coronary angiography had normal coronary arteries. The median interval between drug administration and left heart catheterization was 1 day (IQR: 1 to 2 days). Left ventriculography was performed in 5 patients with a median ejection fraction of 35% (IQR: 20% to 35%) and median LV end-diastolic pressure of 24 mm Hg (IQR: 18 to 25 mm Hg).

All patients underwent echocardiography at the time of admission, and all 3 LV ballooning variants of SCM were observed (Fig. 3). Apical ballooning was observed in 3 patients (33%), midventricular ballooning occurred after dobutamine administration in 2 patients (22%), and 4 patients (44%) developed basal ballooning after receiving epinephrine. The median ejection fraction at the time of admission was 35% (IQR: 35% to 40%). Right ventricular function was normal in all patients except Patient #4, who had moderate global right ventricular dysfunction. Repeat echocardiography performed during follow-up (median 7 days, IQR: 4 to 13 days) demonstrated near complete recovery of LV systolic function in all patients, with a
median ejection fraction of 55% (IQR: 40% to 60%, p < 0.001 vs. admission).

**Discussion**

The current report highlights several important observations. First, all of the characteristic clinical features of SCM were precipitated acutely by the direct infusion of intravenous catecholamines. These features included mild cardiac enzyme elevation in the absence of obstructive coronary disease, a prolonged QTc interval and diffuse T-wave abnormalities on ECG, ventricular ballooning, and rapid recovery of LV systolic function. Second, SCM occurred after routine diagnostic tests and outpatient procedures and was precipitated not only by supratherapeutic doses of epinephrine but also by standard doses of dobutamine typically used in clinical practice. Finally, the administration of intravenous catecholamines and beta-receptor agonists resulted in all 3 ventricular ballooning patterns associated with SCM.

Considerable evidence suggests that enhanced sympathetic activity might play a pathogenic role in the transient myocardial dysfunction seen with SCM. Plasma catecholamine and neuropeptide levels in patients with SCM induced by acute emotional stress are markedly elevated compared with patients with myocardial infarction (1). 123I-metaiodobenzyl-guanidine imaging in patients with apical ballooning reveals impaired sympathetic innervation in the dysfunctional apex, despite normal perfusion (5). Case reports of SCM due to catecholamine-secreting tumors (2) and acute brain injury (6) further support the notion of sympathetically mediated myocardial stunning. The current report further implicates enhanced sympathetic stimulation in the pathogenesis of this syndrome by demonstrating a causal link between beta-adrenergic stimulation and the development of SCM.

The precise mechanism of catecholamine-mediated myocardial stunning in SCM remains unknown. Ischemia due to epicardial spasm seems unlikely and would...
not readily explain the various ballooning patterns seen with this syndrome. Decreased coronary flow velocity and higher thrombolysis in myocardial infarction frame counts in patients with SCM suggest the possibility of catecholamine-mediated microvascular dysfunction (7), but these findings could be secondary effects of myocardial stunning rather than the primary cause. An alternative explanation is a direct toxic effect of catecholamines on cardiac myocytes. Catecholamines decrease myocyte viability through cyclic adenosine monophosphate-mediated calcium overload, resulting in contraction band necrosis, a histologic pattern of myocyte injury observed in SCM (1) and other hyperadrenergic disease states (8). In an experimental animal model, acute catecholamine overload resulted in myocyte apoptosis and necrosis mediated by hyperphosphorylation of the ryanodine receptor-2 (9). In rodent models of SCM, myocardial injury was prevented by treatment with alpha and beta-adrenergic receptor antagonists (10). The mechanism and determinants of the various ventricular ballooning patterns observed in SCM are also unknown. In the canine heart, the apical myocardium has a greater density of beta-adrenergic receptors and an increased response to sympathetic stimulation compared with the base (11). This observation has been used to explain the apical ballooning pattern, although a similar gradient in receptor density has not been demonstrated in humans. In fact, the basal portion of the human LV possesses the highest concentration of sympathetic nerve endings (12). Whereas neural control of the human heart remains incompletely characterized, it is likely that the different ballooning patterns seen with SCM result from the complex interplay between sympathetic innervation, beta-receptor density and function, and catecholamine sensitivity.

Whereas 2 patients in this series (Patients #4 and #8) clearly received an overdose of epinephrine, the majority of patients developed SCM after exposure to drug doses routinely used in clinical practice. This suggests there might be individual susceptibility to catecholamine-mediated myocardial dysfunction. The strong female preponderance in this series and in other published reports of SCM (1,13) highlights the potentially important influence that sex hormones might have on the cardiac response to emotional and physiologic stressors (14). Genetic variability in myocardial adrenergic signaling or other signal transduction pathways might also influence susceptibility to SCM. Troponin elevation and myocardial dysfunction after subarachnoid hemorrhage have been associated with certain alpha and beta-adrenergic receptor polymorphisms (15). Similar genetic factors might play an important pathogenic role in
the development of SCM after emotional triggers or direct catecholamine infusion.

In summary, this observational series provides compelling evidence that exaggerated sympathetic stimulation is sufficient to precipitate the syndrome of SCM in susceptible individuals. Although many questions regarding SCM remain unanswered, this report offers unique insight into the pathogenesis of this increasingly recognized clinical syndrome.

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REFERENCES


Key Words: beta-receptor agonists • catecholamines • stress cardiomyopathy • ventricular ballooning.

APPENDIX

For supplementary videos and their legends, please see the online version of this article.