Systolic and Diastolic Mechanics in Stress Cardiomyopathy

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Background—Stress cardiomyopathy (SCM) is a peculiar form of reversible left ventricular dysfunction seen predominantly in women and occurs in response to emotional or physical stress. Because dysfunction in SCM is reversible and that of acute myocardial infarction (MI) is not, we hypothesized that these fundamental mechanistic differences between SCM and MI would be associated with different systolic and diastolic properties.

Methods and Results—We examined 3 groups, all women: patients with SCM (n=24; mean age, 63±12 years), those with left anterior (LAD) ST-segment–elevation MI (n=36; mean age, 63±10 years), and referent control subjects (n=30; mean age, 62±8 years). All underwent angiography, ventriculography, and pressure measurements within 48 hours of presentation. Left ventricular volumes, diastolic pressures, and diastolic stiffness were higher in SCM and LAD MI patients than in control subjects but no different from each other. Similarly, left ventricular diastolic pressures and diastolic stiffness were elevated in the SCM and LAD MI groups compared with the control group. Left ventricular ejection fraction in SCM and LAD MI were 40.8±12.3% and 49.6±5.6%, respectively, versus 70.4±9.4% in control subjects (P<0.001), and stroke work less than half the value of control subjects. Indexes of contractility and ventricular-arterial coupling were similarly abnormal in SCM and LAD MI.

Conclusions—SCM and LAD MI show severe diastolic dysfunction. At similar left ventricular volumes, their diastolic pressures are more than twice as high as in control subjects, and systolic dysfunction is equally reduced in SCM and LAD MI. Despite a completely different pathophysiology in terms of systolic and diastolic function, SCM is indistinguishable from acute LAD-territory MI. (Circulation. 2014;129:1659-1667.)

Key Words: cardiomyopathies ■ diastole ■ echocardiography ■ heart failure ■ myocardial infarction

We and others have called attention to a peculiar form of reversible cardiomyopathy, which usually occurs in the setting of emotional or physical stress. This syndrome of stress-related cardiomyopathy (SCM) has been given various names, in part depending on the geometric pattern of systolic dysfunction. Although there have been many reports on this subject in the past decade, since the signal case series of Tsuchihashi and coworkers was published, most of these studies have been descriptive in nature, with little attention devoted to the mechanism underlying the systolic dysfunction and virtually no investigation of the systolic or diastolic properties of the left ventricle (LV) of patients with this syndrome.

Clinical Perspective on p 1667

Accordingly, to better understand the systolic and diastolic function of patients with acute SCM, we decided to review diastolic pressure-volume relations in a consecutive series of women undergoing echocardiography and contemporaneous left heart catheterization who fulfilled diagnostic criteria for SCM. We chose as 2 comparison groups women undergoing left heart catheterization for the diagnosis of acute left anterior descending coronary artery (LAD) territory myocardial infarction (LAD MI) and women undergoing catheterization for the diagnosis of chest pain who did not have obstructive coronary artery disease in the same time period (referent control subjects). We restricted our analysis to women because they make up at least 90% of patients with SCM and would allow us to reduce the impact of confounding variables.

It is now accepted that SCM is caused by a primary activation of the sympathetic nervous system and LAD MI is caused by a primary ischemic event, that SCM causes a global injury and LAD-territory MI causes a regional injury, and that SCM is reversible and changes related to LAD MI are not. We hypothesized that in view of these significant pathophysiological differences, the systolic and diastolic properties of SCM patients would be easy to differentiate from those of patients with acute LAD MI.

Methods

Patient Population

We retrospectively examined 3 patient groups: SCM patients, patients with acute LAD-territory MI, and patients undergoing left heart
catheterization for chest pain who were found to have no obstructive coronary artery disease (see Figure 1 and Table 1). Patients were identified by a systematic search of the computerized database of the echocardiography and cardiac catheterization laboratories of UMass Memorial Healthcare of patients underwent study during the calendar years 2007 through 2011; the study was approved by the UMass Memorial Human Subjects Committee. All patients chosen were women who underwent diagnostic cardiac catheterization, coronary arteriography, left ventriculography, and catheter-based hemodynamic studies. In addition, each patient underwent a (baseline) echocardiogram within 24 hours of the catheterization. All SCM patients were required to fit the definition of the syndrome as described by Tsushimaishi et al: “A heart syndrome exhibiting acute onset, transient (reversible) LV apical wall motion abnormalities with chest symptoms, electrocardiographic (ECG) changes, (ST elevation or depression, abnormal Q-wave) and minimal myocardial enzymatic release mimicking acute MI...in patients without angiographic stenosis on coronary angiogram....” Figure 1 shows a flow diagram that summarizes patient selection for this retrospective study.

As is shown in Table 1, the SCM group comprised women with a mean age of 63±12 years. The LAD MI group comprised 36 women 63±10 years old who were treated for a LAD ST-segment–elevation MI; for these patients, the average time between arrival at the hospital and the catheterization procedure was 97.3 minutes. We also studied as a referent control group 30 women 62±8 years of age who underwent cardiac catheterization for chest pain who were found to have no obstructive coronary artery disease, MI, heart failure, or heart valve disease; these patients were ultimately deemed to have noncardiovascular causes of chest pain. In addition, all referent control patients were required to have a normal (<16 mm Hg) LV end-diastolic pressure (EDP). During the time period when the SCM and LAD MI patients were recruited to this study (2007–2011), 30 consecutive female patients >50 years of age who fit the entrance criteria stated above for control subjects were enrolled in this study. Biomarker and selected laboratory data obtained in all 3 groups at the time of presentation are shown in Table 2.

**Measurements and Calculations: Echocardiography, Cardiac Catheterization, and Analysis**

**Doppler Echocardiography**

Echocardiography was performed in all patients within 24 hours of heart catheterization. Follow-up echocardiographic data were also obtained in all of the SCM patients and in 22 of 36 LAD MI patients. Echocardiography was performed with standard techniques. LV dimensions, wall thickness, and LV mass were measured according to the recommendations of the American Society of Echocardiography, and LV mass was indexed to body surface area. Standard Doppler assessment of diastolic function was performed according to American Society of Echocardiography guidelines.

**Cardiac Catheterization**

Cardiac catheterizations were performed with standard techniques. A fluid-filled catheter was placed into the LV, and LV pressures were recorded, as were aortic systolic and diastolic pressures. Left ventriculography was performed in all patients with the use of a pigtail catheter. Heart rate, height, weight, and body surface area were recorded. Angiographic LV volumes were computed with standard methods. LV end-diastolic volume (EDV), LV end-systolic volume (ESV), and stroke volume (SV) were measured. In addition, LV pre-A-wave volume was calculated with a combination of ventriculography and echocardiography based on the method described below.

**Doppler Echocardiography and Estimation of Pre-A-Wave Volume**

LV pre-A-wave volume was calculated as the sum of the SV during early rapid filling and the ESV:

- **Step 1:** the fraction of the SV that occurred during early rapid filling (during E wave) was calculated through the use of Doppler echocardiographic techniques. The velocity-time integral of the E wave (ETVI) was divided by the total velocity-time integral of both the E and A waves (TTVI).
- **Step 2:** this fraction (ETVI/TTVI) was multiplied by the angiographic SV to derive the fraction of the SV that occurred during early rapid filling.
- **Step 3:** this product, (ETVI/TTVI) x SV, was added to the ESV to derive the pre-A-wave volume.

**LV and Aortic Pressure Data**

Analyses of LV and aortic pressure data were performed in the hemodynamic core laboratory at the Medical University of South Carolina by an author (C.E.B.) who was blinded to patient identification. The following hemodynamic data were measured: LV minimum diastolic pressure (Min DP), LV pre-A-wave diastolic pressure, LV EDP, aortic peak systolic pressure, aortic diastolic pressure, and aortic diastolic notch pressure. In addition, all of the indexes of systolic and diastolic properties were calculated at the Medical University of South Carolina core laboratory.

**Figure 1.** Flow diagram illustrating patient selection for this study. Only women were chosen for the study. Patients with stress cardiomyopathy (SCM) and those with a left anterior descending coronary artery myocardial infarction (LAD-MI) were culled from the catheterization laboratory database on the basis of their clinical history, catheterization findings, and availability of a contemporary echocardiogram. SCM patients were required to have a follow-up study, performed in our laboratory, documenting recovery of systolic function. ACS/STEMI indicates acute coronary syndrome/ST-segment–elevation myocardial infarction; and CAD, coronary artery disease.
LV Systolic Performance
Stroke work (SW) was calculated as SW=SV×(MAP−min DP/2−EDP/2)×0.00133 (in kg force·cm), where MAP=(SBP+2×DBP)/3 is the aortic mean systolic pressure, SBP is systolic blood pressure, and DBP is diastolic blood pressure. LV cardiac output was calculated as the product of SV and heart rate (HR): SV × HR/1000.

LV Systolic Function
Ejection fraction (EF) was calculated by standard formula: EF (%)=SV/EDV×100. The SW/EDV ratio was determined for all 3 groups of patients.

LV Contractility
LV end-systolic elastance (Ees) was calculated as the ratio of aortic mean systolic pressure versus end-systolic volume: Ees=MAP/ESV.16

Vascular Properties
Effective arterial elastance (Ea) was calculated as the ratio of aortic mean systolic pressure versus SV: Ea=MAP/SV. Ea was used in the calculation of the arterial-ventricular coupling index, CLV/A = Ea/Ees.17

LV Stiffness
LV stiffness represents the slope of the diastolic pressure-volume curve and was evaluated in 3 different ways:
- Method 1: LV stiffness 1 was approximated as dP/dV=(EDP−Min DP)/(EDV−ESV).
- Method 2: LV stiffness 2 was approximated as the end-diastolic pressure-volume ratio: EDP/EDV.
- Method 3: LV stiffness 3 was defined as the exponential coefficient β that was solved for by the exponential diastolic pressure-volume relationship P=P0e^{βV}, which has been curve fitted through 3 pressure-volume data: (min DP, ESV), (pre-A pressure, pre-A volume), and (EDV, EDV).

Statistical Analysis
For Tables 1–6, continuous data were presented as mean±SD. Differences between the 3 groups of patients in continuous variables were tested with a 1-way ANOVA with significant differences evaluated at \( P < 0.05 \), followed by a Bonferroni post hoc test for between-group pairwise comparisons with significant differences evaluated at \( P < 0.01 \). Categorical data were presented as percent, and differences between groups were determined using a \( \chi^2 \) test with significant differences evaluated at \( P < 0.05 \) (SigmaStat 3.5, Systat Software, Inc, San Jose, CA).

Mathematical modeling was used to analyze the data presented in Figures 2 and 3. In Figure 3, data examining the relationship between LV EDP versus E/E' and LV minimum pressure versus E' were analyzed with a linear least-squares best-fit regression analysis. In Figure 2, data examining the relationship between LV diastolic pressure and LV diastolic volume were analyzed by fitting 3 different curves to the data.

Table 1.  Clinical and Demographic Data

|                         | SCM (n=24) | LAD MI (n=36) | Control Group (n=30) | P Value  
|-------------------------|------------|--------------|----------------------|---------
| Demographics            |            |              |                      | ANOVA   |
| Age, y                  | 63.3±12.0  | 62.8±10.2    | 61.6±8.4             | 0.814   |
| Female, %               | 100        | 100          | 100                  | 1.000   |
| Height, cm              | 160.7±6.7  | 161.3±5.8    | 161.6±9.7            | 0.908   |
| Weight, kg              | 68.6±21.6  | 69.8±15.8    | 72.8±21.2            | 0.694   |
| BSA, m^2                | 1.7±0.25   | 1.7±0.20     | 1.8±0.25             | 0.160   |
| Chest pain, %           | 89         | 100          | 77                   | 0.170   |
| Dyspnea, %              | 52         | 22.4         | 21                   | 0.030   |
| Diabetes mellitus, %    | 32         | 22           | 21                   | 0.700   |
| Hypertension, %         | 76         | 69           | 72                   | 0.912   |
| Hyperlipidemia, %       | 52         | 61           | 54                   | 0.850   |
| Smoking, %              | 16         | 44           | 18                   | 0.010   |
| Psychiatric history, %  | 68         | 22           | 30                   | 0.001   |

Data shown are mean±SD for continuous variables and percent for categorical values. Statistical differences between continuous variables were determined by 1-way ANOVA followed by Bonferroni post hoc test for multiple comparisons. Statistical differences between categorical data were determined with the \( \chi^2 \) test. BSA indicates body surface area; LAD MI, left anterior descending coronary artery myocardial infarction; and SCM, stress cardiomyopathy.

Table 2.  Laboratory Data at Presentation

<table>
<thead>
<tr>
<th></th>
<th>SCM (n=24)</th>
<th>LAD MI (n=36)</th>
<th>Control Group (n=30)</th>
<th>P Value, ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Troponin I, ng/mL</td>
<td>5.6±5.6</td>
<td>77.3±63.1†</td>
<td>0.38±1.03</td>
<td>&lt;0.03</td>
</tr>
<tr>
<td>CPK, IU/L</td>
<td>406.5±586.7</td>
<td>2275.8±1732.4†</td>
<td>143±37</td>
<td>&lt;0.03</td>
</tr>
<tr>
<td>BNP, pg/dL</td>
<td>831.8±956.3‡</td>
<td>865.4±618.3‡</td>
<td>226.0±188.8</td>
<td>&lt;0.03</td>
</tr>
<tr>
<td>BUN, mg/dL</td>
<td>15.2±5.7</td>
<td>12.1±4.8</td>
<td>13.7±4.8</td>
<td>0.420</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>0.74±0.1</td>
<td>0.81±0.1</td>
<td>0.80±0.3</td>
<td>0.354</td>
</tr>
</tbody>
</table>

Data shown are mean±SD. Statistical differences were determined by 1-way ANOVA followed by Bonferroni post hoc test for multiple comparisons. BNP indicates brain natriuretic peptide; BUN, blood urea nitrogen; CPK, creatine phosphokinase; LAD MI, left anterior descending coronary artery myocardial infarction; and SCM, stress cardiomyopathy.

*P<0.01 between SCM and LAD MI.
†P<0.01 between LAD MI and the control group.
‡P<0.01 between SCM and the control group.
Clinical Characteristics
SCM patients fit the typical clinical profile of this syndrome: middle-aged (63±12 years old) women with a background history of risk factors for coronary artery disease, including hypertension, diabetes mellitus, and smoking (Tables 1 and 2). There was a high prevalence of psychiatric diagnoses (eg, depression) among these patients, as has been observed previously. As is typical for patients with SCM, most individuals presented with either chest pain or shortness of breath. Laboratory data also confirmed what has been well established in prior reports on this syndrome: The total creatine phosphokinase was mildly elevated, and there was at most a mild elevation in troponin I; neither was statistically different from the referent control group. The LAD MI group was also characterized by risk factors for coronary artery disease and had a higher prevalence of current smoking than either the SCM group or the referent control group. These patients had clinical features of acute MI with statistically significant elevation of creatine phosphokinase and troponin I levels compared with the referent control group.

The referent control group most commonly had symptoms of chest pain; dyspnea was also a common complaint. These patients had only minor elevations in brain natriuretic peptide level, as expected. The mean brain natriuretic peptide levels were higher in the SCM and LAD MI groups than in the referent control group, but likely as a result of high standard errors associated with these data, the differences were not statistically significant. There were no differences in indexes of renal function among the groups.

Echocardiographic Data
LV end-diastolic dimension, LV wall thickness, and LV mass index in the SCM and LAD MI group were similar to those in the referent control group (Table 3). LV end-systolic dimension was increased in both the SCM and LAD MI groups compared with the control group. As far as diastolic function was concerned, E’ was lower and the E/E’ ratio was higher in the SCM and LAD MI groups compared with the control group, but they were not different from each other.

Invasive Hemodynamic Assessment
LV volume, Pressure, and Systolic Function
LV diastolic volumes were 10% to 15% greater in the SCM and LAD MI groups than in the referent control group (but this difference was not statistically significant), whereas systolic volumes were approximately twice those in the control group (P<0.001; Table 4). Both SCM and LAD MI patients had significant reductions in EF. This paralleled a lower cardiac output and cardiac index in SCM and LAD MI. All invasive LV diastolic pressures were equally abnormal in the SCM and LAD MI groups (Table 5) and were significantly higher than in the referent control group.

There was a significant elevation in the Min DP in SCM (14.7 mm Hg), approximately equivalent to what was observed in acute LAD MI. This value was 3 times what was seen in the referent control subjects. LV EDPs were equivalently abnormal in the SCM and LAD MI group, roughly double what was observed in the referent control group. Min DP was increased in SCM and LAD MI, usually because of incomplete LV relaxation. In addition, LV diastolic stiffness values, using methods 1 and 2, were abnormal but equally so in SCM and LAD MI and approximately twice what was found in referent control subjects.

LV Diastolic Pressure-Volume Relationship
The diastolic pressure-volume relations were remarkably similar between the 2 patient groups, and both curves were shifted upward and were steeper than that of the control group (Figure 2). Thus, for both SCM and LAD MI patients, at any given diastolic volume, diastolic pressure was higher than that seen in control subjects. LV filling pressure was no longer different between the patient groups and the control group. There was a similar increase in LV diastolic pressure from LV pre-A to LV EDP (of 5 mm Hg) in all 3 groups. However, the associated increase in volume was smaller in the SCM and LAD MI groups than in the control group.

LV Systolic Performance, Contractility, and Coupling
LV systolic performance was severely deranged in both study groups, with stroke work (using developed pressure) less than half the value of the referent control patients. This was related to both
a reduction in LV contractility and an increase in arterial stiffness. Consequently, LV-arterial coupling was significantly different in the patient groups compared with the control group (Table 6).

**Correlation Between Invasive and Noninvasive Assessment of Diastolic Function**

We examined the relationship between invasive and noninvasive measures of diastolic function in the entire study population. As shown in Figure 3, significant correlations existed between E/E′ and LV EDP and between LV minimum pressure and E′ in the study population as a whole. The latter inverse correlation reflects the fact that E′ and the invasive parameters have a common determinant, the rate of diastolic relaxation. Consequently, as relaxation improves, E′ increases and LV minimum pressure decreases.

**Follow-Up Data**

As expected, in the SCM group, EF improved from presentation to follow-up from 34.7±10.5% to 60.7±7.4%, and the E/E′ ratio fell (14.7±5.2 to 11.0±3.6; *P*<0.01). In contrast, in the LAD MI group, there were no significant changes in either EF (45.2±12.9% at baseline versus 42.0±15.9% at follow-up) or E/E′ ratio (10.8±3.4 at baseline versus 11.3±3.6 at follow-up).

**Discussion**

We undertook this study of invasive hemodynamics and cardiac mechanics in a group of patients with SCM to determine whether the underlying differences in pathophysiology and origin of SCM compared with acute LAD-territory MI would be associated with differences in systolic and diastolic properties. Our data show that at 24 to 48 hours after presentation, SCM

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**Table 3. Echocardiographic Data (Presentation)**

<table>
<thead>
<tr>
<th></th>
<th>SCM (n=24)</th>
<th>LAD MI (n=36)</th>
<th>Control Group (n=30)</th>
<th><em>P</em> Value, ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVIDd, mm</td>
<td>45.6±6.9</td>
<td>45.0±6.1</td>
<td>44.8±5.3</td>
<td>0.885</td>
</tr>
<tr>
<td>LVIDs, mm</td>
<td>31.9±8.0</td>
<td>30.2±6.8</td>
<td>27.1±5.0</td>
<td>&lt;0.03</td>
</tr>
<tr>
<td>PWTd, mm</td>
<td>9.7±1.6</td>
<td>10.2±1.6</td>
<td>9.5±2.1</td>
<td>0.264</td>
</tr>
<tr>
<td>IVSTd, mm</td>
<td>9.6±1.8</td>
<td>10.7±2.1</td>
<td>9.8±1.9</td>
<td>0.065</td>
</tr>
<tr>
<td>LV mass, g</td>
<td>153.7±51.4</td>
<td>166.9±53.5</td>
<td>149.9±53.1</td>
<td>0.394</td>
</tr>
<tr>
<td>LVMI, g/m²</td>
<td>89.1±25.8</td>
<td>97.3±30.3</td>
<td>82.6±25.3</td>
<td>0.101</td>
</tr>
<tr>
<td>E, m/s</td>
<td>0.88±0.2*</td>
<td>0.72±0.1</td>
<td>0.77±0.1</td>
<td>&lt;0.03</td>
</tr>
<tr>
<td>A, m/s</td>
<td>0.79±0.3</td>
<td>0.76±0.2</td>
<td>0.77±0.2</td>
<td>0.911</td>
</tr>
<tr>
<td>E/A</td>
<td>1.72±2.9</td>
<td>0.99±0.3</td>
<td>1.06±0.3</td>
<td>0.157</td>
</tr>
<tr>
<td>E′, m/s</td>
<td>0.06±0.03</td>
<td>0.06±0.02</td>
<td>0.10±0.09</td>
<td>&lt;0.03</td>
</tr>
<tr>
<td>E/E′</td>
<td>14.7±5.2*†</td>
<td>10.8±3.4‡</td>
<td>7.8±2.3</td>
<td>&lt;0.03</td>
</tr>
</tbody>
</table>

Data shown are mean±SD. Statistical differences were determined by 1-way ANOVA followed by Bonferroni post hoc test for multiple comparisons. IVSTd indicates interventricular septal thickness, diastole; LAD MI, left anterior descending coronary artery myocardial infarction; LV, left ventricular; LVIDd, left ventricular internal dimension, diastole; LVIDs, left ventricular internal dimension, systole; LVMI, left ventricular mass index; and SCM, stress cardiomyopathy. *P*<0.01 between SCM and LAD MI. †*P*<0.01 between SCM and the control group. ‡*P*<0.01 between LAD MI and the control group.
patients show evidence of severe diastolic dysfunction: At only slightly (nonsignificantly) higher diastolic volumes than control subjects, SCM patients have diastolic pressures that are as abnormal as those in a group of age-matched women suffering an acute LAD-territory MI. In fact, the LV diastolic stiffness and the diastolic pressure-volume relationship are indistinguishable between the 2 patient groups. In addition, systolic mechanics are significantly impaired in SCM. Function (EF), performance (stroke work), ventricular-arterial coupling, and contractility (Ees) are abnormal in a manner similar to what is observed in acute LAD MI. All of these systolic and diastolic abnormalities are significantly different from those observed in a referent control group of women undergoing heart catheterization for chest pain or shortness of breath.

Study Rationale
SCM is a fascinating and increasingly recognized syndrome with a distinctive phenotype: a woman in her seventh decade who presents with chest symptoms in close temporal association with physical or emotional stress. Although there have been many descriptive studies of SCM, very little is known about ventricular properties in this disorder. Studies of SCM have for the most part focused on systolic function and clinical features. To the best of our knowledge, the diastolic properties have not been well defined. Anecdotally, we have been struck by the lack of respiratory compromise or frank pulmonary edema in many of the patients we have seen with this syndrome despite biomarker and imaging evidence of severe systolic dysfunction. In part, it was this dissociation that motivated us to try to better understand the diastolic properties of this syndrome.

Our study population comprised only adult women, given that women are most frequently affected by this disorder and to facilitate comparison with women with acute MI by avoiding whatever confounding effects that sex might introduce. We believe that the population studied was indeed representative of what has been reported elsewhere in their mean age (63±12 years), mode of presentation (52% with dyspnea, 89% with chest pain),1–10,19 and presence of a physical or emotional trigger. In addition, the pattern of biomarker release was similar to what has been previously reported and reflects the relatively small amount of troponin release,1–10,19 despite an impairment of systolic and diastolic function that was similar to that seen in women suffering an acute MI whose mean peak troponin I was 77 ng/mL.

Table 5. Pressures and Diastolic Function

<table>
<thead>
<tr>
<th></th>
<th>SCM (n=24)</th>
<th>LAD MI (n=36)</th>
<th>Control Group (n=30)</th>
<th>P Value, ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aortic peak systolic pressure, mm Hg</td>
<td>123.7±25.4</td>
<td>121.6±25.6</td>
<td>137.7±22.3</td>
<td>&lt;0.03</td>
</tr>
<tr>
<td>Aortic diastolic pressure, mm Hg</td>
<td>70.2±14.8</td>
<td>68.3±13.2</td>
<td>66.2±14.3</td>
<td>0.583</td>
</tr>
<tr>
<td>Aortic mean pressure (mmHg)</td>
<td>88±15.7</td>
<td>86.1±15.2</td>
<td>92.0±18.6</td>
<td>0.349</td>
</tr>
<tr>
<td>Dicrotic notch pressure, mm Hg</td>
<td>94.3±18.2</td>
<td>95.5±17.1</td>
<td>102.7±16.5</td>
<td>0.139</td>
</tr>
<tr>
<td>LV minimum diastolic pressure, mm Hg</td>
<td>14±7.2*</td>
<td>14.7±5.1†</td>
<td>5.2±4.5</td>
<td>&lt;0.03</td>
</tr>
<tr>
<td>Pre-A LV diastolic pressure, mm Hg</td>
<td>23.9±4.4*</td>
<td>23.4±7.1†</td>
<td>10.0±5.7</td>
<td>&lt;0.03</td>
</tr>
<tr>
<td>LV end-diastolic pressure, mm Hg</td>
<td>25.3±6.4*</td>
<td>26.2±7.2†</td>
<td>13.2±6.0</td>
<td>&lt;0.03</td>
</tr>
<tr>
<td>Stiffness 1, dP/dV, mm Hg/mL</td>
<td>0.214±0.119*</td>
<td>0.206±0.17†</td>
<td>0.093±0.57</td>
<td>&lt;0.03</td>
</tr>
<tr>
<td>Stiffness 2, mm Hg/mL</td>
<td>0.183±0.057*</td>
<td>0.193±0.057†</td>
<td>0.107±0.057</td>
<td>&lt;0.03</td>
</tr>
</tbody>
</table>

Data shown are mean±SD. Statistical differences were determined by 1-way ANOVA followed by Bonferroni post hoc test for multiple comparisons. LAD MI indicates left anterior descending coronary artery myocardial infarction; LV, left ventricular; and SCM, stress cardiomyopathy.

*P<0.01 between SCM and the control group.
†P<0.01 between LAD MI and the control group.
Merli and coworkers have shown that there is postsystolic LV dysfunction. Our analysis, in contrast, used noninvasive characterization by high wall stress, which helps perpetuate the LV into 2 chambers, with the dysfunctional apical segment hypothesized that this midventricular obstruction divides the acutely ischemic myocardium. In their series, midventricular obstruction was present in all patients, and the authors allowed us to conclude that for an equivalent (or even slightly better, the extent of systolic dysfunction. This would, in turn, enable us to better understand how SCM affects the diastolic properties of the LV. Indeed, the 2 systolic dysfunction patient groups were reasonably well matched for many demographic features, as well as heart size and diastolic pressure. We believe that these data allowed us to conclude that for an equivalent (or even slightly greater) degree of acute impairment of systolic function, there was a remarkable similarity in systolic and diastolic mechanics between 2 disorders with different pathophysiology and outcome.

### Comparator Groups

We chose 2 comparator groups for our study. The first was a series of age-matched women with an acute LAD-territory MI. We reasoned that this group would serve to control for, as much as possible, the extent of systolic dysfunction. This would, in turn, enable us to better understand how SCM affects the diastolic properties of the LV. Indeed, the 2 systolic dysfunction patient groups were reasonably well matched for many demographic features, as well as heart size and diastolic pressure. We believe that these data allowed us to conclude that for an equivalent (or even slightly greater) degree of acute impairment of systolic function, there was a remarkable similarity in systolic and diastolic mechanics between 2 disorders with different pathophysiology and outcome.

### Systolic Function/Performance

Previous studies on diastolic dysfunction in SCM have focused mostly on echocardiographic and Doppler assessments. However, some authors have applied systolic strain analysis to the study of ventricular dysfunction in these patients. Merli and coworkers have shown that there is post-systolic shortening in the dysfunctional apical segment in patients with the apical form of SCM, in a pattern similar to what is seen in acutely ischemic myocardium. In their series, midventricular obstruction was present in all patients, and the authors hypothesized that this midventricular obstruction divides the LV into 2 chambers, with the dysfunctional apical segment characterized by high wall stress, which helps perpetuate the LV dysfunction. Our analysis, in contrast, used noninvasive imaging to initially characterize patients and LAD MI control subjects and to document recovery in SCM patients, but it focused on the invasive assessment of LV volumes, systolic function, performance, and ventricular-arterial coupling.

On the basis of the data provided, we conclude that LV dysfunction in SCM is principally the result of an acute impairment of LV contractility; the small increase in LV EDV is obligatory to maintain as high a SV as possible given the acute loss of contractile function. However in the acute phase, the LV diastolic volume is greater than that seen in control patients by only 10% to 15%. Consequently, systolic function and performance are reduced. Thus, acutely, the reduction in contractility resulting from the impairment of contractile elements, presumably caused by direct injury mediated by catecholamine tone or endothelial dysfunction, cannot be offset by chamber dilation.

### Diastolic Function

We believe that the principal new finding of our study is the significant diastolic dysfunction seen in patients with SCM, similar in magnitude to that observed in acute LAD MI. Hearts of SCM patients are characterized by increased stiffness and the inability to fill adequately at normal pressure, a working definition of diastolic dysfunction that we have found useful. The curves shown in Figure 2 illustrate that this inability to fill at normal pressure is not simply strain dependent: The diastolic volume and volume index of SCM patients are only 10% higher than those of control subjects at a time when the LV EDP is roughly double that seen in control subjects. This higher LV EDP is associated with an upward shift in the diastolic pressure-volume relation. In addition, the late diastolic properties of the LV of SCM patients bespeak a marked increase in stiffness compared with control subjects. For every 1-mm Hg increase in diastolic pressure associated with atrial systole, the diastolic volume of the SCM patients increases 8.5 mL; in contrast, in the control group, that proportion is less than half, that is, 3.9 mL per 1-mm Hg increase in diastolic pressure. For reference, in the LAD MI group, the corresponding proportion is 4.7. Looked at differently, atrial systole in both SCM and LAD MI was associated with a much smaller increment in LV volume than is seen in referent control subjects. For every 1-mL change in LV diastolic volume associated with atrial systole in referent control subjects, the LV pressure rose 0.17 mm Hg; the corresponding change in LV diastolic pressure for each 1-mL in SCM and LAD MI was 0.35 mm Hg, reflecting differences in diastolic stiffness between the 2 patient groups and the referent control group.

As has stated above, compared with the number of descriptive reports of SCM, there are very few data compiled to date on diastolic function in SCM. We were able to find only a handful of other reports of invasive diastolic properties in SCM.
(see Table 7), and our data are in line with what these authors have presented. In the signal report of Tsuchihashi and coworkers\textsuperscript{1} in which 22% of patients were described as having pulmonary edema, the mean LV EDP was 17 mm Hg. These hemodynamic data were compiled at a mean of 8 hours after presentation. At that time, as shown in Table 7, the mean ESV and EDV was 80 mL/m\textsuperscript{2} compared with our value of 82 mL/m\textsuperscript{2}. We interpret these data as illustrating that the hearts of SCM patients, as a result of acutely increased LV diastolic stiffness, must operate at higher than normal pressures to provide adequate preload.

In the series of Wittstein et al\textsuperscript{4}, patients undergoing heart catheterization on day 1 had “a median left ventricular end-diastolic pressure of 30 mm Hg.” The only other data concerning filling pressures and heart failure are to be found in a research letter by Madhavan et al.\textsuperscript{25} Of the 118 patients described in their report, 45% had evidence of heart failure. In the group as a whole, the mean LV EDP was 25 mm Hg; patients with evidence of heart failure on average had higher LV EDP (mean difference, 5 mm Hg; \(P < 0.01\)). Interestingly, the data of Madhavan et al illustrate that there may not be a strong relationship between the magnitude of LV EDP elevation and the syndrome of acute pulmonary edema. In addition, we have shown that noninvasive markers of diastolic function (\(E'/E\)) and filling pressure (\(E/E'\)) correlate with the invasive data, namely LV EDP and LV minimum pressure. This suggests to us that these noninvasive parameters can be used not only for diagnostic purposes but possibly for following up SCM patients as they recover. To the best of our knowledge, such correlation between these 2 types of variables is unique in the SCM literature.

### Limitations

Some limitations should be noted. The study was retrospective, and the number of patients included in the study was a fraction of all patients undergoing catheterization for suspected acute MI or acute coronary syndrome in the time period in question. An important exclusion was the lack of availability of follow-up echocardiographic data in many of the LAD MI patients. Because our institution serves as a referral center for patients in central New England, some of the follow-up echocardiograms in the LAD MI group were performed elsewhere in our network. Other patients did not undergo echocardiography or ventriculography at all and thus were excluded from the study. It is difficult to know whether these exclusions introduced bias into the study.

It can be argued that the use of standard fluid-filled catheters for the hemodynamic assessment is a limitation. However, given that we included 2 control groups, we do not see any reason to believe that any inaccuracies created by these catheters would apply preferentially to one group or another. It is also an acknowledged limitation that we used single-beat methods for evaluating \(E_{es}\) and the stiffness parameters. However, each of these methods has been validated, and those measures that have limitations based on the single-beat method are concordant with those that are not; thus, all measures of function were changed by SCM and LAD MI in a similar fashion. In addition, the clinical and retrospective nature of this study limited the choices we had with respect to methodology.

### Conclusions

We believe that this study contributes the following observations to the literature on SCM. We have found that patients with SCM have profound diastolic dysfunction with elevations in LV EDP and abnormalities in stiffness. LV EDV is only mildly elevated in SCM at a time when LV EDP is markedly elevated. This suggests that the increased LV EDP is not a strain-dependent increase in LV stiffness but rather that the stiffness of the LV is altered; the reduced proportion of EDV that was contributed by atrial systole supports this conclusion. Furthermore, systolic properties in SCM are altered, and abnormalities in \(E_{es}\) and stroke work appear to be the result of abnormalities in contractility and ventricular-arterial coupling. Thus, there are profound, parallel derangements in systolic and diastolic function in this syndrome, and these derangements are remarkably similar in nature and magnitude to a disorder with a completely different pathogenesis: acute coronary occlusion. Follow-up prospective studies are in progress to track the resolution of the diastolic function abnormalities in these patients.

The similarity in systolic and diastolic dysfunction we have observed will likely be interpreted as showing that SCM behaves much like an acute anterior infarction in terms of systolic and diastolic function. However, we believe that the converse is also true, that acute ischemic injury, to the extent that it involves myocardial stunning, would likely feature some LV dilation/shape distortion that is reversible. In fact, serial noninvasive imaging studies such as those performed by Kramer et al\textsuperscript{26} using magnetic resonance imaging demonstrate that, compared with their acute MI study, a certain percentage of patients will have a reduction in EDV index at follow-up performed 1 year later. One interpretation of these data is that the mechanisms that contribute to acute, reversible LV dilation and dysfunction in SCM may also be operative in some patients with acute ischemic injury.

### Disclosures

None.

### References


### Table 7. Data on Structure and Function in Stress Cardiomyopathy: Prior Studies

<table>
<thead>
<tr>
<th>Author</th>
<th>n</th>
<th>EF, %</th>
<th>LV EDVI, mL/m\textsuperscript{2}</th>
<th>LV EDP, mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tsuchihashi et al\textsuperscript{1}</td>
<td>88</td>
<td>41±11</td>
<td>80±18</td>
<td>17±6</td>
</tr>
<tr>
<td>Wittstein et al\textsuperscript{4}</td>
<td>19</td>
<td>20 (15–30)</td>
<td>NA</td>
<td>30 (IQR, 25–31)</td>
</tr>
<tr>
<td>Madhavan et al\textsuperscript{25}</td>
<td>53</td>
<td>41±13</td>
<td>NA</td>
<td>25±7</td>
</tr>
</tbody>
</table>

EDP indicates end-diastolic pressure; EDVI, end-diastolic volume index; EF, ejection fraction; LV, left ventricular; and IQR, interquartile range.
Ventricular dysfunction in patients with acute ischemic injury (LAD MI) may be due to catecholamine injury. The prospects for reversibility. The similarity of these phenotypes suggests to us the controversial hypothesis that some of the left ventricular diastolic pressures and diastolic stiffness were similarly abnormal in SCM and LAD MI. Functionally, in the initial hours to days after presentation, SCM is strikingly higher than in control subjects but no different from each other; and (3) indexes of contractility and ventricular-arterial coupling were similarly abnormal in SCM and LAD MI. We therefore examined 3 groups, all women: an SCM group (n=24; mean age, 63±12 years), a left anterior (LAD) ST-segment–elevation MI group (n=36; mean age, 63±10 years), and a referent control group (n=30; mean age, 62±8 years).


**CLINICAL PERSPECTIVE**

Stress cardiomyopathy (SCM) is an increasingly recognized syndrome seen predominantly in women and occurs in response to emotional or physical stress. SCM is thought to be related to acute catecholamine myocardial injury and is reversible, whereas the ischemic injury underlying acute myocardial infarction (MI) is not. We hypothesized that these fundamental mechanistic differences between SCM and acute MI would be associated with different profiles of systolic and diastolic function. We therefore examined 3 groups, all women: an SCM group (n=24; mean age, 63±12 years), a left anterior (LAD) ST-segment–elevation MI group (n=36; mean age, 63±10 years), and a referent control group (n=30; mean age, 62±8 years). All underwent angiography, ventriculography, and pressure measurements within 48 hours of presentation. Echocardiography documented return to normal systolic function in all SCM patients, per inclusion criteria. Our principal findings were the following: Left ventricular diastolic pressures and diastolic stiffness were similarly elevated in the SCM and LAD MI groups compared with the control group; left ventricular end-systolic and end-diastolic volumes in the 2 disorders were correspondingly higher than in control subjects but no different from each other; and (3) indexes of contractility and ventricular-arterial coupling were similarly abnormal in SCM and LAD MI. Functionally, in the initial hours to days after presentation, SCM is indistinguishable from acute LAD-territory MI. This is surprising in view of the completely different pathophysiology and prospects for reversibility. The similarity of these phenotypes suggests to us the controversial hypothesis that some of the left ventricular dysfunction in patients with acute ischemic injury (LAD MI) may be due to catecholamine injury.
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