Systole-diastole mismatch in hypertrophic cardiomyopathy is caused by stress induced left ventricular outflow tract obstruction

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Background  Pharmacological stress is used to assess the degree of left ventricular (LV) subvalvular gradient in patients with hypertrophic cardiomyopathy (HCM), but there is little information about associated physiological changes.

Methods  Echocardiography-Doppler ultrasound scanning measurements in 23 patients with HCM and 23 control subjects of similar age were studied at rest and at the end point of dobutamine stress.

Results  In patients, the systolic time was normal at rest, but increased abnormally with stress. In patients, the total isovolumic contraction time failed to shorten, and the total ejection time increased abnormally. Changes in total ejection time correlated with an increase in peak subvalvular gradient in control subjects and patients (r = 0.52 and r = 0.66, respectively; P < .01 for both). In patients, the diastolic time was normal at rest, but shortened abnormally with stress. In patients, the isovolumic relaxation time fell abnormally, as did the filling time. Mitral E wave acceleration and left atrium size were unchanged with stress in control subjects, but consistently increased in patients with HCM, which indicates an increased early diastolic atrioventricular pressure gradient.

Conclusion  In HCM, systolic period increases abnormally with stress. This is not because of a loss of inotropy, but is directly related to the degree of LV outflow tract obstruction. As a result, the diastolic period fails to increase, reducing the time available for coronary flow, the LV filling pattern is modified, and the diastolic atrioventricular pressure gradient increases. These changes may contribute to symptom development and suggest why reducing LV outflow tract obstruction per se may be therapeutically useful in HCM. (Am Heart J 2004;148:903–9.)
stopped medication at least 24 hours before the stress echocardiogram. The results were compared with 23 healthy subjects of similar age (Table II).

Dobutamine infusion protocol

Patients and control subjects were studied at rest and during dobutamine stress. Dobutamine was administered via an infusion pump (IVAC 770 syringe driver), starting at a dose of 5 μg/kg/min and increasing every 3 minutes by a similar amount to a maximum dose of 40 μg/kg/min. Systolic and diastolic blood pressure was measured automatically at each stage with a Critikon Dinamap monitor (Critikon, Tampa, Fla). Pre-determined stress end points for healthy subjects were reaching 85% predicted target heart rate (beats/min, 220 minus age in years) or the maximum dobutamine dose (corresponding to stage 8 of the dobutamine protocol). In the patients, development of chest pain or breathlessness, 2 mm ST segment shift (elevation or depression), or a 20 mm drop in systolic blood pressure from baseline were predefined as end points.

Electrocardiogram

A standard 12-lead electrocardiogram (ECG) was recorded at rest and during dobutamine stress with a Hewlett-Packard Pagewriter Xli, with a built in analysis package (Andover, Mass). ECG intervals were measured automatically and registered on a printed chart at a speed of 25 mm/sec. The frequency response of the machine was 0.05 to 150 Hz with the baseline filter (0.4 Hz) inactivated.

Echocardiography Doppler ultrasound scanning

Transthoracic echocardiography was performed with the subject lying in the semilateral supine position using a Hewlett Packard Sonos 5500 echocardiograph with a 2.5-MHz transducer. Two-dimensional guided M mode echograms of the left ventricle (LV), the left atrium, and the aortic root were recorded in the minor axis view at rest according to the guidelines of the American Society of Echocardiography.10 Continuous wave Doppler ultrasound scanning was used to record subvalvular velocities from the apical 5-chamber view, whereas pulse wave Doppler ultrasound scanning was used to record diastolic flow velocities across the mitral valve from the apical 4-chamber view, both at rest and at peak stress. Color-flow Doppler ultrasound scanning was used to assess the severity of mitral regurgitation. All measurements were recorded on paper at a speed of 100 mm/sec, with a superimposed ECG (lead II) and a phonocardiogram.

Measurements

ECG. Heart rate and QRS duration were measured at rest and at peak stress with in-built software. The ST segment shift was measured manually 80 ms after the J point in the lead showing the most change.

Echocardiogram. Left ventricular (LV) dimensions, septal and posterior wall thickness, and left atrium dimensions were measured according to the guidelines of the American Society of Echocardiography. Peak systolic velocities in the outflow tract were taken as those registered in mid- rather than late-systole. Isovolumic contraction time was measured as the interval from the mitral closure artefact at the end of the mitral A wave to the onset of forward flow across the outflow tract. Ejection time was measured from the onset of the forward flow across the outflow tract to that of the first high frequency vibration of aortic component of second heart sound on the phonocardiogram (A2). LV isovolumic relaxation time was taken as the interval from A2 to the onset of mitral flow on transmitral pulsed Doppler ultrasound scanning. Filling time was measured from the onset of the mitral E wave to the end of the A wave. Summation filling was diagnosed when mitral E and A waves were superimposed; filling time was then measured as the total duration of the transmitral flow pulse. Total cardiac times were derived as the product of the corresponding interval and heart rate and expressed in seconds per minute. Systole was taken as the sum of the total ejection time and isovolumic contraction time, and diastole was taken as the sum of the total isovolumic relaxation time and total filling time. Mitral E wave acceleration was calculated as the peak mitral E wave or summation velocity divided by the time interval from the onset of flow. The aortic component (A2) and pulmonary component (P2) of second heart sound were identified from the closure artefacts on the aortic and pulmonary Doppler ultrasound scanning recordings, respectively, and intervals from the q wave of ECG to A2 and P2 were determined.

Statistical analysis

All data are expressed as the mean plus or minus SD. Resting and stress values were compared between control subjects and patients with unpaired Student t tests. Resting val-

### Table I. Clinical details

<table>
<thead>
<tr>
<th>Variables</th>
<th>Control (n = 23)</th>
<th>Hypertrophic cardiomyopathy (n = 23)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (SD)</td>
<td>58 ± 11</td>
<td>54 ± 15</td>
</tr>
<tr>
<td>Male/female ratio</td>
<td>8:15</td>
<td>13:10</td>
</tr>
<tr>
<td>EDD (cm)</td>
<td>4.9 ± 0.4</td>
<td>4.2 ± 0.7</td>
</tr>
<tr>
<td>ESD (cm)</td>
<td>3.2 ± 0.5</td>
<td>2.6 ± 0.7</td>
</tr>
<tr>
<td>FS (%)</td>
<td>34 ± 6</td>
<td>38 ± 13</td>
</tr>
<tr>
<td>IVS ED (cm)</td>
<td>0.9 ± 0.1</td>
<td>2.3 ± 0.8</td>
</tr>
<tr>
<td>PWED (cm)</td>
<td>0.7 ± 0.1</td>
<td>1.2 ± 0.3</td>
</tr>
<tr>
<td>Clinical details</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Effort induced shortness of breath</td>
<td>-</td>
<td>16</td>
</tr>
<tr>
<td>Effort induced angina</td>
<td>-</td>
<td>10</td>
</tr>
<tr>
<td>Palpitations</td>
<td>-</td>
<td>4</td>
</tr>
<tr>
<td>NYHA class II</td>
<td>-</td>
<td>15</td>
</tr>
<tr>
<td>NYHA class III</td>
<td>-</td>
<td>8</td>
</tr>
<tr>
<td>Medication</td>
<td></td>
<td></td>
</tr>
<tr>
<td>β-Blocker</td>
<td>-</td>
<td>12</td>
</tr>
<tr>
<td>Calcium-channel antagonist</td>
<td>-</td>
<td>3</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>-</td>
<td>8</td>
</tr>
<tr>
<td>ECG changes during stress</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>ST ↑ (&gt;2 mm)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>ST ↓ (&gt;2 mm)</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Values are mean ± SD. EDD, End-diastolic dimension; ESD, end-systolic dimension; FS, fractional shortening; IVS ED, interventricular septum end-diastolic thickness; PWED, posterior wall end-diastolic thickness.

10. American Heart Journal November 2004
ues were compared with stress values within the control and patient groups with paired t tests. Correlations were calculated with the Pearson product-moment method. Differences in incidence were calculated with the χ² test. A Bonferroni correction was applied for multiple comparisons, and a significant difference was thus taken as a P value <.01.

Ethical approval

The Royal Brompton and Harefield Ethics Committee approved the protocol of the study. All subjects gave informed consent. There were no adverse effects of the investigation.

Results

Patients had smaller LV end diastolic and end systolic dimensions at rest than control subjects (P <.001 and P <.01, respectively). All healthy subjects reached the end of the dobutamine protocol (40 µg/kg/min dobutamine infusion rate), and no symptoms or ischemic ECG changes developed. In patients with hypertrophic cardiomyopathy, shortness of breath developed in 16 (of 23), chest pain developed in 4, and the systolic blood pressure fell in 3; the peak dobutamine infusion rate was 23 ± 8 µg/kg/min.

Heart rate, arterial blood pressure, and QRS duration

Resting heart rates were similar in control subjects and patients. The heart rate increased by 41 ± 12 beats/min (56%) in control subjects, compared with 29 ± 16 beats/min (41%) in patients (P <.001). The mean resting arterial blood pressure was higher in control subjects than in patients, but it remained unchanged with stress in the 2 groups. The QRS duration was 90 ± 8 ms in control subjects and 97 ± 12 ms in patients at rest. The QRS duration consistently fell by 4 ± 3 ms in control subjects, compared with patients, in whom it increased by 3 ± 4 ms at peak stress (P <.001 for the difference between effect in control subjects and patients).

Systolic time

In control subjects, the total systolic time decreased from 26 ± 2 to 24 ± 2 s/m (P <.001). In patients, a different pattern emerged, as the total systolic time increased from 25 ± 5 to 29 ± 3 s/m (P <.001).

LV ejection time

In control subjects, the total LV ejection time increased from 20 ± 2 to 22 ± 2 s/m (P <.01). Changes in total LV ejection time correlated with increase in subvalvular gradient (r = 0.52, P <.01). The resting subvalvular gradient was not predictive of stress value (r = 0.34, P = not significant [NS]).

In patients, total LV ejection time increased from 20 ± 3 to 25 ± 4 s/m (P <.001). The increment in total LV ejection time was more than in control subjects (5 ± 5 s/m vs 1 ± 2 s/m, P <.01; Figure 1). Changes in total ejection time with stress correlated with an increase in the peak subvalvular gradient (r = 0.66, P <.001; Figure 2). The resting subvalvular gradient was modestly predictive of stress value (r = 0.57, P <.01).

Ejection time per beat actually became longer in 8 patients, although the RR interval fell in all patients. In 7 of these 8 patients (87%), the subvalvular gradient increased by >36 mm Hg. Conversely, of the remain-

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Table II. Physiological response to dobutamine stress

<table>
<thead>
<tr>
<th>Variables</th>
<th>Controls</th>
<th>Stress</th>
<th>HCM</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rest</td>
<td>Stress</td>
<td>Rest</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>73 ± 12</td>
<td>115 ± 12**</td>
<td>70 ± 11</td>
</tr>
<tr>
<td>Mean BP (mm Hg)</td>
<td>96 ± 12</td>
<td>96 ± 12</td>
<td>99 ± 15</td>
</tr>
<tr>
<td>QRS duration (ms)</td>
<td>90 ± 8</td>
<td>86 ± 7**</td>
<td>97 ± 12</td>
</tr>
<tr>
<td>Systole (s/m)</td>
<td>26 ± 2</td>
<td>24 ± 2**</td>
<td>25 ± 5</td>
</tr>
<tr>
<td>LVET (s/m)</td>
<td>20 ± 2</td>
<td>22 ± 2*</td>
<td>20 ± 3</td>
</tr>
<tr>
<td>Subvalvular gradient (mm Hg)</td>
<td>4 ± 1</td>
<td>15 ± 5**</td>
<td>29 ± 21††</td>
</tr>
<tr>
<td>LVIVC (s/m)</td>
<td>5 ± 2</td>
<td>1 ± 1**</td>
<td>5 ± 3</td>
</tr>
<tr>
<td>Diastole</td>
<td>33 ± 2</td>
<td>35 ± 3*</td>
<td>34 ± 5</td>
</tr>
<tr>
<td>LVIVRT (s/m)</td>
<td>5 ± 1</td>
<td>5 ± 1</td>
<td>6 ± 2††</td>
</tr>
<tr>
<td>LVFT (s/m)</td>
<td>28 ± 3</td>
<td>30 ± 2*</td>
<td>27 ± 4</td>
</tr>
<tr>
<td>Mitral E acceleration (g)</td>
<td>1.24 ± 0.41</td>
<td>1.19 ± 0.36</td>
<td>1.13 ± 0.46</td>
</tr>
<tr>
<td>Left atrium (cm)</td>
<td>3.6 ± 0.6</td>
<td>3.7 ± 0.1</td>
<td>4.1 ± 0.6</td>
</tr>
<tr>
<td>q to P2 - q to A2 (ms)</td>
<td>26 ± 28</td>
<td>19 ± 10</td>
<td>19 ± 34</td>
</tr>
</tbody>
</table>

A2, Closure of aortic valve; BP, blood pressure; beats/min, beats per minute; HR, heart rate; LVET, left ventricular ejection time; LVFT, left ventricular filling time; LVIVC, left ventricular isovolumic contraction time; LVIVRT, left ventricular isovolumic relaxation time; P2, closure of pulmonary valve; q, start of QRS complex.

P < .001. **P < .001, comparing stress versus rest within group (paired t test).

††P < .01. †‡P < .001, resting values in patients versus resting values in controls (unpaired t test).

‡P < .01. ***P < .001, delta in patients versus delta in controls (unpaired t test).


Patients with hypertrophic cardiomyopathy (B) showed a subvalvular gradient in 13 (86%) of 15 patients, whose ejection time per beat shortened on stress, 13 (86%) showed a subvalvular gradient <36 mm Hg. This dependence of ejection time on increment in subvalvular gradient was highly significant ($\chi^2 = 15.7, P < .001$).

**Isovolumic contraction time**

The resting LV isovolumic contraction time was similar in control subjects and patients. It fell by 3 ± 2 s/m in control subjects ($P < .001$) and by 1 ± 3 s/m in patients ($P = NS$). The change in isovolumic contraction time did not correlate with that in arterial blood pressure, QRS duration, or subvalvular gradient in control subjects or patients.

**Diastolic time**

In the control subjects, the total diastolic time increased from 33 ± 2 s/m to 35 ± 3 s/m ($P < .01$). The patients showed the reverse trend, as the total diastolic time decreased from 34 ± 5 to 30 ± 3 s/m ($P < .001$).

**Isovolumic relaxation time**

The isovolumic relaxation period was shorter in control subjects than in patients (5 ± 1 s/m vs 6 ± 2 s/m, $P < .01$) at rest. It did not change in control subjects (Δ 0.01 ± 2.00 s/m), but it fell by 2 ± 2 s/m in patients ($P < .01$ for the difference between effect in control subjects and patients). In neither control subjects nor in patients was the isovolumic relaxation time related to heart rate, arterial blood pressure, QRS duration, or subvalvular gradient.

**LV filling time**

In control subjects, the total LV filling time increased from 28 ± 3 s/m to 30 ± 2 s/m ($P < .01$). In patients, the total LV filling time fell from 27 ± 4 s/m to 25 ± 3 s/m. The decrement in total filling time in patients was in contrast to the increment in control subjects (1 ± 2 s/m vs –1 ± 4 s/m, $P < .01$).

In control subjects, the total LV filling time remained >24 s/m. In 9 (of 23) patients, the total LV filling time dropped to <24 s/m. This incidence was significantly higher than normal ($\chi^2 = 12.3, P < .003$).

In control subjects, the peak mitral E wave velocity was unchanged with stress, whereas the A wave velocity increased from 0.6 ± 0.1 m/s to 0.8 ± 0.1 m/s ($P < .001$), so that the E/A ratio fell from 1.1 ± 0.3 to 0.8 ± 0.3 ($P < .001$). In 18 (of 23) patients, the peak mitral E wave velocity increased from 0.7 ± 0.2 m/s to 0.8 ± 0.3 m/s ($P < .01$), and the A wave velocity increased from 0.8 ± 0.2 m/s to 1.0 ± 0.2 m/s ($P < .001$), so that E/A ratio remained unchanged. In the other 5 patients, the E and A wave became superimposed during stress (summation filling). In all these 5 patients, the total LV filling time was <24 s/m.

In control subjects, neither the mitral E wave acceleration nor the left atrium size changed during stress. In contrast, in patients with hypertrophic cardiomyopathy, the mitral E wave acceleration increased by 0.99 ± 0.82 g and the left atrium size increased by 0.2 ± 0.2 cm ($P < .001$ for both changes). In 7 of 23 patients, mild mitral regurgitation (color flow area <35% of left atrium) was present at rest. In none of these 7 patients did it worsen during stress, and mitral regurgitation did not develop in the remaining 18 patients.

**Total duration of LV and right ventricular systole**

In control subjects, the total duration of right ventricular systole (q-P2) was slightly longer than that of LV systole (q-A2) by approximately 26 ± 28 ms at rest. Stress had no significant effect on this A2-P2 time (change, –8 ± 35 ms; $P = NS$), so that splitting of the second heart sound remained normal. In patients, resting values were indistinguishable from control subjects, but on stress, LV systole was prolonged by 39 ± 36 ms more than right ventricular systole ($P < .001$).
The result was that on stress, reversed splitting of second heart sound developed in 21 of the 23 patients, in comparison with 0 of the of 23 control subjects ($\chi^2 = 41.37, P < .001$, Figure 3).

**Discussion**

A series of abnormal physiological changes occurred throughout the cardiac cycle when LV outflow tract obstruction was induced pharmacologically in patients with hypertrophic cardiomyopathy.

The total systolic time decreased in control subjects with stress, in contrast to patients, in whom it increased, so that at the end point total systolic period was 5 s/m longer than in control subjects.

The isovolumic contraction time shortened by 3.3 s/m in control subjects. The change was independent of arterial blood pressure, QRS duration, and subvalvular gradient and thus is likely to have reflected the positive inotropic action of the drug. The shortening of isovolumic contraction in patients was smaller (4.1 ± 3 s/m), but still independent of arterial blood pressure, QRS duration, and subvalvular gradient. This difference from control subjects is in line with the lower rate of dobutamine infusion achieved.

Ejection time increased marginally in control subjects in contrast to patients, in whom it increased significantly with stress. This effect was confined to the left side of heart, so that splitting of the second heart sound commonly reversed with stress in patients, but never reversed in control subjects. In the hypertrophic cardiomyopathy group as a whole, changes in total LV ejection time correlated positively with changes in the subvalvular gradient. In 7 of 8 patients in whom the ejection time per beat was prolonged, subvalvular gradient increased by >36 mm Hg.

The total diastolic time increased with stress in control subjects in contrast to patients, in whom it decreased with stress, so that at the end point, the total diastolic period was 5 s/m shorter than in control subjects.

The isovolumic relaxation time did not change in control subjects, in contrast to patients, in whom it shortened by an abnormal amount.

Finally, the filling time in control subjects increased with stress and was consistently $>24$ s/m. In contrast, the filling time was not preserved in patients with hypertrophic cardiomyopathy at peak stress and frequently fell to $\leq 24$ s/m.

**Mechanism**

These results shed light on the normal and abnormal responses to dobutamine stress. Ventricular filling and distal coronary artery flow both occur during diastole. In healthy subjects, the diastolic period is preserved and held at approximately 27 s/m (the lower 95% CI) of the cardiac cycle as heart rate increases, by the shortening of systole. In this way, both stroke volume and coronary flow time are preserved, so tachycardia can be translated into increased cardiac output. In patients with hypertrophic cardiomyopathy, this favorable state of affairs does not apply; the mean value was below the 95% lower CI of normal, and in 9 of 23 patients, the filling time fell to $< 24$ s/m. With the well-documented reduced coronary flow reserve in hypertrophic cardiomyopathy as demonstrated with fixed or reversible exercise thallium perfusion defects,10–13 myocardial lactate production during atrial pacing14 and positron emission tomography,15,16 myocardial perfusion is likely to have been compromised, contributing to the angina that is frequently experienced in these patients with stress. Simultaneously, the combination of diastolic disease17–20 and an abnormally short LV filling period can limit stroke volume.

In the presence of ventricular disease, compensatory mechanisms are likely to come into play during stress. Ventricular filling time would have been even more compromised in patients with hypertrophic cardiomyopathy had there not been an abnormal shortening of the isovolumic relaxation time. A fall in isovolumic relaxation time is likely to reflect a rise in left atrial pressure, rather than any “improvement” in the process of relaxation itself.21,22 The abnormal increase in early diastolic F wave acceleration, indicating a corresponding increase in the atrioventricular pressure gradient, confirms that this was the case in our patients.

![Figure 3](image-url)

*Figure 3*  
Effect of stress on relative timing of A2 and P2 in control subjects (A) and patients with hypertrophic cardiomyopathy (B). In control subjects, stress had no significant effect on this relationship, but in patients, stress induced a relative delay of A2 with respect to P2 of 39 ± 36 ms. During stress, no control subject had reversed splitting of second heart sound, whereas only 2 of 23 patients had normal splitting.
whereas the increase in the left atrium size suggests that this was the direct response of a corresponding increase in left atrial pressure rather than accentuated early diastolic ventricular suction. The filling time is thus maintained at the expense of potential pulmonary congestion.

Limitations
We studied a selected group of patients; all our patients had symptoms and had been referred for detailed assessment of cardiac function, and all had an inducible subvalvular gradient. Cardioactive drugs were stopped at least 24 hours before the procedure, so the effect of β-blockers or calcium channel antagonists would not have been significant. The effect of amiodarone probably persisted, but its documented lack of effect on LV function makes it unlikely to have significantly affected the result. The development of symptoms meant that the clinical end point of the dobutamine infusion was achieved with a lower dobutamine infusion rate in patients than in control subjects. However, differences in the duration of the intervals of the cardiac cycle persisted when normalized to a constant change in heart rate. In addition, the prolongation of ejection time, both in absolute terms and for the right ventricle, and the excessive shortening of isovolumic relaxation time seen in patients could not be explained on the basis of any difference in dose, but represented qualitative differences in behavior from that in healthy subjects. The time available for the study at the time of peak stress, when patients by definition had symptoms, was necessarily limited, so we confined ourselves to measurements made from the parasternal and apical windows, with particular reference to determining the intervals of the cardiac cycle and flow velocities. Although it is tempting to assume that dobutamine stress acts as surrogate for the effects of exercise, there are fundamental differences in the two.

Conclusion
Major disturbances of cardiac function occur when dobutamine stress causes LV outflow tract obstruction in hypertrophic cardiomyopathy. An increase in ejection time was not caused by any loss of sensitivity to the inotropic effect of dobutamine, but was determined to a major extent by the emergence of LV outflow tract obstruction. The resulting abbreviation of diastole, with a compensatory increase in left atrial pressure restricting ventricular filling and coronary flow, seems to explain many of the clinical features of the end point of the test. Our results thus suggest how abolishing the outflow tract obstruction might per se give symptomatic relief by reducing both components of the time integral of systolic myocardial stress and by liberating a further segment of the RR interval for diastole.

References