Abnormal Vascular Responses to Supine Exercise in Hypertrophic Cardiomyopathy

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Background. Exercise hypotension has been documented in hypertrophic cardiomyopathy. It is not the result of an inability to augment cardiac output but instead relates to an inappropriate and exaggerated decrease in systemic vascular resistance at high work loads.

Methods and Results. To enable us to examine the behavior of the peripheral vasculature during exercise, 103 consecutive patients underwent maximal symptom-limited supine bicycle exercise with measurement of forearm blood flow. A minimum reduction of 12% from the basal value was defined as a normal response based on the study of 25 normal controls. In the patients, two patterns of forearm blood flow were observed. Sixty-four patients had an appropriate reduction in forearm blood flow of 40±16% from resting flow. In 39 patients, the forearm blood flow either failed to decrease or increased with exercise by 45±105% of the resting value. Patients with an abnormal forearm vasodilator response were younger (31±13 versus 46±14 years), and more of them had a family history of hypertrophic cardiomyopathy and sudden death than did those with a normal vasoconstrictor response (16 of 39 versus eight of 64). Left ventricular end-diastolic cavity dimensions were smaller in those with an abnormal forearm blood flow response, but other clinical, echocardiographic, and arrhythmic variables were similar. To assess the relation of abnormal peripheral vascular responses to erect exercise blood pressure response, patients underwent treadmill exercise testing with careful monitoring of systolic blood pressure response. Thirty-eight patients had significant exercise hypotension with failure of the systolic blood pressure to increase during progressive exercise (n=6) or an abrupt decrease in systolic blood pressure (20–60 mm Hg) from the peak value (n=32); 65 patients had a normal exercise blood pressure response, but 18 of these patients had an oscillation in systolic blood pressure of 10 mm Hg or more early in the recovery phase. Thirty-one of 39 patients with an abnormal forearm blood flow response demonstrated exercise hypotension during the erect exercise testing, and the remaining eight patients had a normal exercise blood pressure response; however, five of these eight had abnormal oscillations in blood pressure during recovery (r=0.61, p<0.001).

Conclusions. The relation of abnormal peripheral vascular responses to exercise hypotension confirms the observation of hemodynamic instability in patients with hypertrophic cardiomyopathy. The finding of abnormal vascular responses in patients known to be at increased risk (young age and a family history of hypertrophic cardiomyopathy and sudden death) suggests that hemodynamic mechanisms may be important in the occurrence of sudden death in hypertrophic cardiomyopathy. (Circulation 1991;84:686–696)

Sudden death is common in patients with hypertrophic cardiomyopathy (HCM).1,2 The risk of sudden death is greatest in children and young adults, but the identification of those likely to die in this age group is problematic.3,4 Conventional indexes of clinical, echocardiographic, and ambulatory electrocardiography have not proved useful in risk stratification.4–6 Exercise hypotension has been documented in one third of patients with HCM and is strongly associated with young age and a family history of sudden death. This propensity for hemodynamic collapse relates to an exaggerated decrease in systemic vascular resistance and occurs despite an appropriate increase in cardiac output.7

Similar inappropriate peripheral vascular responses to physical stress have been documented in patients with aortic stenosis and, more recently, in patients with ischemic heart disease, suggesting that

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ventricular-derived baroreflexes are important in overall circulatory adaptation to exercise.\textsuperscript{8–10} To assess peripheral vascular responses during physical stress, we performed symptom-limited supine bicycle exercise testing with measurement of forearm blood flow in a consecutive population with HCM.

**Methods**

**Clinical Characteristics of Patients**

One hundred three consecutive patients with HCM from St. George’s Hospital, London, were studied. The present group includes 61 patients who had been included in a study examining blood pressure responses in patients with HCM.\textsuperscript{7} The diagnosis was made 24±12 months before the study and was based on typical clinical, echocardiographic, and hemodynamic features.\textsuperscript{11} All patients had left ventricular hypertrophy of 1.5 cm or more demonstrated on two-dimensional echocardiography in the absence of cardiac or systemic disease that could have caused hypertrophy.\textsuperscript{1} Patients with blood pressure of more than 160/90 mm Hg were excluded. Patient age range was 8–74 years (mean age, 41 years); 41 patients were less than 35 years old, 48 patients were 35–60 years old, and 14 were more than 60 years old. Sixty-five patients were male, and 38 were female. One hundred one patients were in sinus rhythm, and two were in established atrial fibrillation. Fifty-one patients had a family history of HCM; of these, 25 also had a family history of premature (age of less than 55 years) sudden cardiac death. This relatively high proportion is accounted for by the inclusion of seven patients from two families with a malignant family history (sudden cardiac death under the age of 50 years occurring in two or more first-degree relatives). Twenty-one patients (20\%) had experienced syncope, 40 (39\%) had exertional chest pain, and 42 (41\%) had dyspnea, New York Heart Association functional class II (n=38) or III (n=4). At the time of study, 87 patients had discontinued all hemodynamically active medications for at least five half-lives. Sixteen patients were receiving low-dose amiodarone (200 mg/day or less) with a mean plasma level of 0.9±0.3 mg/l. Of these, 10 were receiving amiodarone because of nonsustained ventricular tachycardia on ambulatory electrocardiographic monitoring, one for recurrent symptomatic ventricular tachycardia, two after resuscitation from out-of-hospital ventricular fibrillation, and three for frequent and refractory episodes of paroxysmal atrial fibrillation.

On two-dimensional and M-mode echocardiography using established methods,\textsuperscript{12,13} maximum left ventricular wall thickness was 24±7 mm; left ventricular end-systolic and end-diastolic cavity dimensions were 27±6 and 45±6 mm, respectively; and left atrial dimension was 43±9 mm and more than 45 mm in 43 patients. Complete systolic anterior motion of the mitral valve with septal contact was present in 20; 19 patients had a Doppler-calculated resting left ven-

tricular outflow tract gradient of more than 30 mm Hg.\textsuperscript{14,15}

All patients underwent 48-hour electrocardiographic monitoring off all cardioactive medication at the time of diagnosis or within 6 months of the study.\textsuperscript{16} Thirty patients (29\%) had episodes of paroxysmal atrial fibrillation (n=5) or supraventricular tachycardia (n=25) defined as three or more consecutive narrow complex extrasystoles at a mean rate of more than 120 beats/min, and 23 (22\%) had nonsustained ventricular tachycardia defined as three or more consecutive ventricular extrasystoles with a mean rate of more than 120 beats/min for less than 30 seconds. Medication during follow-up included verapamil in 12, \(\beta\)-blockers in 33, and amiodarone in 18 patients.

The study group included two adolescent patients (14 and 16 years old) who had experienced sudden death; both were resuscitated from out-of-hospital ventricular fibrillation. Neither patient had supraventricular or ventricular arrhythmias during 4 and 5 days, respectively, of continuous electrocardiographic monitoring. Arrhythmias were not induced during programmed ventricular stimulation using two ventricular extrastimuli during sinus rhythm and at three drive cycles.\textsuperscript{17} Twenty-five healthy volunteers (12 males and 13 females; age range, 11–52 years; mean age, 31 years) were also studied to confirm the normal pattern of exercise forearm blood flow.\textsuperscript{18–20}

**Forearm Blood Flow**

Patients were studied in a quiet environment at a constant room temperature of 22–24°C. Forearm blood flow was measured using a Whitney-type temperature-compensated mercury-in-Silastic strain-gauge plethysmograph\textsuperscript{21} during maximal symptom-limited supine bicycle exercise. Patients were positioned in the supine position on a floor mattress. The right forearm was elevated sufficient to allow free venous drainage. A pneumatic “collecting” cuff around the upper arm was inflated to 40 mm Hg for recording of flows for 10 seconds every 15 seconds. A second cuff was placed around the wrist and inflated for the duration of recordings to suprasystolic pressure to exclude the hand circulation from the measurements. Venous occlusion interrupts venous drainage but does not affect arterial inflow until the veins become distended. The rate of increase in forearm blood volume during the first few seconds of venous occlusion is proportional to forearm blood flow. The voltage output from the strain gauge was measured using a high-gain preamplifier (Lectromed-5240, Jersey, UK) and recorded graphically against time (Lectromed Multitrace-8 5041, Jersey, UK). Forearm blood flow was determined from the rate of increase in forearm volume using a computer algorithm derived from the method described by Greenfield et al.\textsuperscript{22} The mean of five measurements was taken as the flow for each recording period.

After measurements were made at rest, patients performed symptom-limited supine bicycle exercise with increasing work loads (50–100 W). The work
loads during exercise were selected according to the patient's functional capacity, thus ensuring adequate cardiovascular stress and avoiding premature leg fatigue. Mean arterial blood pressure (2/3 diastolic blood pressure plus 1/3 systolic blood pressure) and heart rate were recorded at rest and at 1-minute intervals up to peak exercise using an automatic oscillometric blood pressure recorder and electrocardiograph oscilloscope (Datascope "Accutor 1A," Paramus, N.J.). Forearm blood flow was measured at rest at 2 minutes of exercise and at 2-minute intervals thereafter. Forearm vascular resistance (FVR) expressed in resistance units was calculated as follows:

\[
\text{Mean arterial pressure (mm Hg)} \div \text{Forearm blood flow (ml \cdot 100 ml^{-1} \cdot min^{-1})} = \text{FVR units}
\]

Based on the forearm blood flow change in controls, a minimum decrease in forearm blood flow of 12% defined a normal plethysmographic response. The percentage of maximal heart rate achieved was used to assess the degree of cardiovascular stress during exercise and was calculated from the following formulas:23

\[
220 - \text{age (yr)} = \text{maximum predicted heart rate (males)}
\]

\[
210 - \text{age (yr)} = \text{maximum predicted heart rate (females)}
\]

As part of clinical follow-up, 25 patients underwent repeat noninvasive evaluation 4–24 months after the initial study.

**Treadmill Exercise Testing**

Maximal symptom-limited exercise testing was performed using a Bruce or modified Bruce protocol with continuous measurement of oxygen consumption.24 Respiratory gases were collected using a face-mask, and analysis was performed using established methodology with a metabolic cart (SensorMedics Horizon MMC, Anaheim, Calif.). Oxygen consumption was measured with a temperature-controlled rapid polargraphic sensor linked to an on-board microprocessor. Printouts of minute ventilation, oxygen consumption, and carbon dioxide production were obtained at 15-second intervals during exercise and recovery.25 Before study, patients were practiced in the techniques of exercise and respiratory gas collection and had demonstrated a less-than-10% difference in maximal oxygen consumption on at least two consecutive tests. The age-predicted maximal oxygen consumption (\(\dot{V}O_2\)) was calculated for adults according to the following formulas:26,27

Males' maximum \(\dot{V}O_2\) (ml/kg/min) = (age \(\times 0.55\)) – 60

Females' maximum \(\dot{V}O_2\) (ml/kg/min) = (age \(\times 0.37\)) – 48

An appropriate formula for the five patients less than 18 years old was used to calculate maximal oxygen consumption.28

Systolic blood pressure was measured using a mercury sphygmomanometer and digital palpation of the brachial artery \((n=70)\) or directly by intra-arterial manometry \((n=33)\). Blood pressure recordings were made at rest, at 1-minute intervals during exercise, and at 15-second intervals during the initial 5 minutes of the postexercise recovery period.

The plethysmographic recordings and the treadmill exercise tests were performed in random order by different investigators.

**Statistical Analysis**

Data are expressed as mean±1 SD. Statistical analysis was performed by paired and unpaired t tests and \(\chi^2\) test where appropriate. A probability value of less than 0.05 was considered significant.

**Results**

**Forearm Blood Flow**

Supine exercise was completed without complication in all patients. The predominant limiting symptom was breathlessness in 42, chest pain in 37, and leg fatigue in 24. The limiting symptom in the control subjects was leg fatigue. The forearm blood flow decreased in all control subjects by a mean percentage of 34% (range, 8–62%). Patients were assigned as having normal or abnormal responses if they fell within 1 SD of the mean of the control group; thus, patients in whom forearm blood flow decreased by more than 12% were considered to have a normal response.

Two patterns of forearm blood flow response were observed in the patients (Figure 1). In 64 patients (62%), the forearm blood flow \(\text{(ml \cdot 100 ml^{-1} \cdot min^{-1})}\) decreased from 3.7±2.0 at rest to 2.1±1.1 at peak exercise, whereas in 39 patients (38%), forearm blood flow increased during exercise or decreased by less than 12% from rest to peak exercise (3.4±2.0 to 4.3±2.3, respectively). The resting forearm blood flow was similar in the 64 patients with a normal forearm blood flow response and the 39 patients with an abnormal exercise response \((3.7±2.0 \text{ versus } 3.4±2.0 \text{ ml \cdot 100 ml^{-1} \cdot min^{-1}}, p=\text{NS})\) (Figure 2). At the peak of supine exercise, forearm blood flow decreased by 40±16% in those with a normal response, whereas in those with an abnormal response, forearm blood flow increased by 45±105%. In patients with an abnormal forearm blood flow response, the range of the percentage change in blood flow varied widely, from a decrease of 11% to an increase of 397%. The FVR was similar at rest in both normal and abnormal groups \((32±15 \text{ versus } 36±23 \text{ FVR units}, p=\text{NS})\) (Figure 3); however, the percentage change in FVR at the end of exercise was significantly different in the two groups. There was an
increase in those with a normal plethysmographic response and a decrease in those with an abnormal vasodilator response (+124±94% versus -4±32%, respectively; p<0.0001) (Figure 4).

Of the 16 patients receiving amiodarone, 11 had a normal response with a decrease in flow from 3.2±1.9 at rest to 1.7±0.8 at peak exercise, and five had a vasodilator response with an increase in flow.
from 3.7±2.4 at rest to 4.5±3.1 at peak exercise. The resting and exercise blood flows were similar to those of patients not receiving amiodarone.

At peak exercise, mean arterial pressure was 116±16 mm Hg in the normal response group and 101±16 mm Hg in patients with a vasodilator response (p<0.0001). Resting and peak heart rates were similar in both groups (74±13 versus 74±9 and 114±22 versus 121±22 beats/min, respectively) (Table 1). To compare the degree of physical work achieved by both groups, the age-predicted maximal heart rates were computed, and the percentage maximal heart rates were calculated. The percentage of predicted maximal heart rate achieved during supine exercise was also similar in the two groups (66±14% versus 65±11%, p=NS).

**Erect Treadmill Exercise Blood Pressure Responses**

Symptom-limited treadmill exercise testing was completed without complication in 99 patients and was terminated by the physician in four cases because of supraventricular arrhythmia (n=1) and systolic hypotension (decrease in systolic blood pressure by more than 50% from peak value) (n=3). Three patients spontaneously volunteered symptoms of impaired consciousness as the predominant factor limiting exercise. In 65 patients, there was a normal exercise blood pressure response with a linear increase in systolic blood pressure to a maximum at peak exercise. Eighteen of these 65 patients demonstrated an abnormal pattern of oscillating systolic blood pressure in the initial 3 minutes of the recovery phase with a rapid decrease of 10 mm Hg or more and subsequent increase in systolic blood pressure of more than 10 mm Hg from the minimum recovery blood pressure.

Thirty-eight patients demonstrated exercise hypotension; in six patients, systolic blood pressure failed to increase by more than 20 mm Hg from the resting

**FIGURE 2.** Plots of resting and peak forearm blood flow responses in 25 control subjects and 103 patients with hypertrophic cardiomyopathy (HCM); 64 had a normal response and 39 had a vasodilator response to supine exercise. •, Mean±SD values.

**FIGURE 3.** Plots of resting and peak forearm vascular resistance in 25 control subjects and 103 patients with hypertrophic cardiomyopathy (HCM); 64 had a normal response and 39 had a vasodilator response to supine exercise. •, Mean±SD values.
value, and in 32 patients, there was an appropriate initial increase in systolic blood pressure to a peak value with a subsequent fall of at least 20 mm Hg from the peak blood pressure as exercise progressed (range, 20–60 mm Hg). Blood pressure at rest was similar in the hypertensive and normal response groups (126±24 versus 129±23 mm Hg, p=NS). At peak exercise, systolic blood pressure was significantly lower in those with exercise hypotension than in those with a normal blood pressure response (132±38 versus 170±42 mm Hg). In the two groups, there was no difference in the peak blood pressure achieved (165±36 versus 176±38 mm Hg, p=NS) or in the degree of cardiovascular stress achieved as judged by maximal heart rate attained and demonstration of anaerobic metabolism (Table 2). The patients with exercise hypotension were significantly younger than the patients with a normal blood pressure response (32±14 versus 47±13 years, p<0.0001). Similarly, maximal oxygen consumption was higher in those with exercise hypotension (31±11 versus 25±9 ml/kg/min); when these results were corrected for age, there was no difference in percentage of age-predicted maximal oxygen consumption achieved for the hypertensive and normal groups, respectively (78±24 versus 75±20, p=NS).

Forearm Blood Flow and Exercise Blood Pressure Responses

Of the 39 patients who demonstrated abnormal forearm blood flow responses during supine exercise, 31 demonstrated systolic hypotension on erect exercise (r=0.61, p<0.0001). Of the remaining eight patients with abnormal forearm blood flow responses, five demonstrated a normal exercise blood pressure response but had an abnormal pattern of blood pressure during recovery. Three patients with abnormal plethysmography had normal erect exercise blood pressure responses (Figure 5).

There was a weak but nonsignificant correlation between the magnitude of the increase in forearm blood flow and the magnitude of the decrease in systolic blood pressure (r=0.2, p=NS). However, five of eight patients with increases in forearm blood flow of more than 50% had decreases in systolic blood pressure of more than 35 mm Hg on erect exercise.

The percent increase in mean arterial pressure during supine exercise was less in those with erect exercise hypotension than in those with a normal upright blood pressure response (16±16% versus 25±21%, p=0.03) (Figure 6).

**Forearm Blood Flow and Clinical Associations**

The 39 patients with an inappropriate vasodilator response during supine exercise were significantly younger (31±13 versus 46±14 years, p<0.0001) than the 65 who demonstrated a normal vasoconstrictor response. An inappropriate vasodilator response was significantly associated with a family history of HCM and sudden death (16 of 39 versus nine of 64, p=0.002). Left atrial dimension was less in those with an abnormal plethysmography response than in those with an appropriate response (39±8 versus 45±8 mm, p<0.0001). Patients with a vasodilator response had smaller left ventricular end-diastolic dimensions than those with a normal response (42±5 versus 46±7, p=0.01), but left ventricular end-systolic dimensions were similar (26±5 versus 28±7, p=NS). There was no difference between the two groups in relation to frequency or severity of symptoms, the presence or magnitude of a resting left ventricular outflow tract gradient, or the incidence and frequency of arrhythmia on ambulatory electrocardiographic monitoring (Table 1).

During a mean follow-up of 18 months, 25 patients have undergone repeat forearm plethysmography. In 22 patients, the pattern of blood flow response was similar to that seen at the index study although the magnitude of the change in blood flow varied. Three patients demonstrated a different response on follow-up study; of these three, one reverted from a vasodilator response to a normal response and the other two patients, who previously had normal responses, had a vasodilator response on repeat study. Both of these patients had abnormal recovery blood pressure responses during upright exercise. Among those restudied were three patients receiving amiodarone; none of these patients showed a change in the pattern of response. Four of the 25 patients who underwent repeat study had been receiving amiodarone but had discontinued it spontaneously more than 6 months previously, and all had plasma levels of less than 0.2 mg/l. The pattern of blood flow response in these patients was the same as that in patients in the original study. Similarly, three patients had commenced amiodarone in the interval between the original study and the follow-up and demonstrated no qualitative difference in response on repeat study.
TABLE 1. | Supine Exercise Forearm Blood Flow Response in 103 Patients With Hypertrophic Cardiomyopathy

<table>
<thead>
<tr>
<th></th>
<th>Normal (n=64)</th>
<th>Vasodilator (n=39)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>44 (69)</td>
<td>22 (54)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>20 (31)</td>
<td>17 (46)</td>
<td></td>
</tr>
<tr>
<td><strong>Age (yr)</strong></td>
<td>46±14</td>
<td>31±13</td>
<td>0.0001</td>
</tr>
<tr>
<td><strong>Family history</strong></td>
<td></td>
<td></td>
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<tr>
<td>HCM</td>
<td>24 (37)</td>
<td>27 (69)</td>
<td></td>
</tr>
<tr>
<td>HCM and SD</td>
<td>9 (14)</td>
<td>16 (41)</td>
<td>0.002</td>
</tr>
<tr>
<td><strong>NYHA</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>25 (39)</td>
<td>13 (33)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>3 (5)</td>
<td>1 (2)</td>
<td></td>
</tr>
<tr>
<td>Chest pain</td>
<td>26 (41)</td>
<td>14 (35)</td>
<td></td>
</tr>
<tr>
<td>Syncope</td>
<td>11 (17)</td>
<td>10 (26)</td>
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<tr>
<td>Sinus rhythm</td>
<td>63 (98)</td>
<td>38 (97)</td>
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<tr>
<td>Established AF</td>
<td>1 (2)</td>
<td>1 (3)</td>
<td></td>
</tr>
<tr>
<td>SVT/PAF</td>
<td>18 (28)</td>
<td>12 (31)</td>
<td></td>
</tr>
<tr>
<td>VT</td>
<td>16 (25)</td>
<td>7 (18)</td>
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</tr>
<tr>
<td>SAM</td>
<td>12 (22)</td>
<td>7 (15)</td>
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</tr>
<tr>
<td>PG &gt;30 mm Hg</td>
<td>15 (23)</td>
<td>4 (10)</td>
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</tr>
<tr>
<td>LVEDD (mm)</td>
<td>46±7</td>
<td>42±5</td>
<td>0.01</td>
</tr>
<tr>
<td>LVESD (mm)</td>
<td>28±7</td>
<td>26±5</td>
<td>NS</td>
</tr>
<tr>
<td>LA (mm)</td>
<td>45±8</td>
<td>39±8</td>
<td>0.0001</td>
</tr>
<tr>
<td>Maximum LVWT (mm)</td>
<td>23±7</td>
<td>25±8</td>
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</table>

**Plethysmography**

<table>
<thead>
<tr>
<th></th>
<th>Normal (n=64)</th>
<th>Vasodilator (n=39)</th>
<th>p</th>
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</thead>
<tbody>
<tr>
<td>Resting heart rate</td>
<td>74±13</td>
<td>74±9</td>
<td></td>
</tr>
<tr>
<td>Maximum heart rate</td>
<td>113±22</td>
<td>121±22</td>
<td></td>
</tr>
<tr>
<td>Maximum predicted heart</td>
<td>66±14</td>
<td>65±11</td>
<td>NS</td>
</tr>
<tr>
<td>Peak MAP (mm Hg)</td>
<td>116±16</td>
<td>101±16</td>
<td>0.0001</td>
</tr>
<tr>
<td>Resting FBF (ml·100 ml⁻¹·min⁻¹)</td>
<td>3.7±2.0</td>
<td>3.4±2.0</td>
<td></td>
</tr>
<tr>
<td>Peak FBF (ml·100 ml⁻¹·min⁻¹)</td>
<td>2.1±1.1</td>
<td>4.3±2.3</td>
<td></td>
</tr>
<tr>
<td>Resting FVR (units)</td>
<td>32±15</td>
<td>36±23</td>
<td></td>
</tr>
<tr>
<td>Peak FVR (units)</td>
<td>67±29</td>
<td>33±26</td>
<td>0.0001</td>
</tr>
<tr>
<td>Change FBF (%)</td>
<td>−40±17</td>
<td>+45±105</td>
<td></td>
</tr>
<tr>
<td>Change FVR (%)</td>
<td>+124±94</td>
<td>−4±32</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

HCM, hypertrophic cardiomyopathy; SD, sudden death; NYHA, New York Heart Association functional class; AF, atrial fibrillation; SVT, supraventricular tachycardia; PAF, paroxysmal atrial fibrillation; VT, nonsustained ventricular tachycardia; SAM, systolic anterior motion; PG, pressure gradient; LVEDD or LVESD, left ventricular end-diastolic or end-systolic dimension; LA, left atrial; LVWT, left ventricular wall thickness; MAP, mean arterial pressure; FBF, forearm blood flow; FVR, forearm vascular resistance.

Values in parentheses indicate percentages.

**Discussion**

Exercise hypotension has been documented in patients with HCM. The potential for hemodynamic collapse was recognized by early investigators because of the association of sudden death during or soon after periods of exertion. Subsequently, a number of investigators have reported hemodynamic collapse occurring in association with rapid heart rates.

In a consecutive series of 129 patients with HCM, we documented exercise hypotension in 33%. Invasive hemodynamic exercise testing in a selected subgroup of patients with normal and abnormal blood pressure responses to exercise demonstrated that the decrease in blood pressure occurred because of an excessive decrease in total systemic vascular resistance and that this occurred despite an appropriate increase in cardiac index. These results suggested...
that abnormal hemodynamic responses are not infrequent in HCM and might be important in relation to the genesis of sudden death, particularly in younger patients.

The present study was undertaken to examine peripheral vascular responses during exercise in a consecutive, mainly prospectively recruited patient population with HCM in an effort to confirm our previous observation of exercise hypotension and determine a possible mechanism.

In this consecutive group of 103 patients with HCM, abnormal forearm blood flow responses to supine exercise were seen in 39 patients (38%). The normal response to supine exercise is vasoconstriction of nonexercising vascular beds leading to a reduction in forearm, mesenteric, and renal blood flows as blood is preferentially redistributed to the exercising lower limbs.18-20,35 The normal pattern of forearm blood flow response to supine exercise is well defined and was confirmed in our 25 normal volunteers, the minimum reduction in flow from the resting value at peak exercise in this group being 8%. To allow greater specificity for the diagnosis of abnormal responses, we chose a minimum reduction in flow of 12% based on the control data, and patients were stratified accordingly.

In the 39 patients with an abnormal response, forearm blood flow inappropriately increased or remained unchanged from the resting value. The magnitude of the increase in blood flow varied from a decrease of 11% from the resting flow to a sixfold increase in flow at peak exercise. Although there was no correlation between the magnitude of the increase in forearm blood flow and the degree of exercise hypotension, five of eight patients with marked increase in forearm flows also had significant erect exercise hypotension. This discrepancy might be explained in several ways; first, the studies were per-
formed at different times, and although the qualitative change in response is reproducible, the quantitative change in blood flow is seen to vary. Second, although forearm blood flow changes are a good reflection of the changes occurring in other vascular beds, it is unlikely that the forearm vasculature contributes to any great extent to overall systemic vascular resistance; much larger changes in flow in the renal and mesenteric vascular beds may be occurring to account for large decreases in blood pressure. Although the qualitative change in blood flow in regional beds may differ during isometric exercise, the change is similar in the forearm to that in other vascular beds during rhythmic leg exercise, albeit the magnitude of the change may be different in individual beds.66

Third, there are differences in cardiovascular hemodynamics during erect and supine exercise. During supine exercise, the effect of gravity is removed, resulting in a higher venous return and larger cardiac volumes. Similarly, stroke volume increases proportionately more during supine than during erect exercise. Therefore, the systemic vascular resistance at the start of supine exercise is lower and increases less than during erect exercise, producing a relatively smaller potential for vasodilatation.20,35 The magnitude of change in blood pressure during supine exercise will also be less because cardiac output at peak exercise is similar in the erect and supine positions. In the present study, the increase in mean arterial blood pressure during supine exercise was less in the 38 patients who demonstrated erect exercise hypotension, suggesting that the same vasodilation occurs irrespective of the position in which the exercise is performed.

The 39 patients with abnormal forearm blood flow responses were younger than those demonstrating a normal response. However, when the level of physical exertion as judged by heart rate increment was corrected for age, there was no difference between the two groups, indicating that the degree of cardiovascular stress was similar and independent of age. Abnormal coronary and forearm vascular responses to ischemia have been described in patients with HCM, and it is suggested that there is a generalized defect in autoregulation37,38; however, the reproducibility of the plethysmography response in 22 patients on repeat testing and its association with exercise hypotension suggest that the abnormal forearm blood flow response is not a spurious finding but is related to central control mechanisms of blood flow.

The study population includes 16 patients on amiodarone, and the question may arise of whether the drug influenced the forearm vascular response. Four of the 16 patients underwent repeat study, and no qualitative difference was seen in the responses. Similarly, three patients—two with an abnormal response and one with a normal response—who had commenced amiodarone in the interval between the original study and follow-up did not demonstrate a change in response, suggesting that amiodarone does not have an effect on peripheral vascular reflexes.

The mechanisms responsible for the abnormal forearm vascular reflexes are unknown but may relate to activation of ventricular mechanoreceptors.9,10,39–41 These receptors are thought to play a major role in central and peripheral hemodynamic regulation.40–42 Activation of these receptors has been implicated in patients with syncope and aortic stenosis in whom abnormalities of FVR during exercise similar to those found in patients in the present study have been described.9 More recently, Kamatsu and coworkers10 described abnormal forearm blood flow responses to exercise in patients after myocardial infarction and suggested that reflexes arising from the left ventricle are responsible. Almquist and coworkers43 documented an increased tendency to vasodepressor reflex in patients with syncope of unknown etiology and suggested that activation of cardiac receptors is responsible. Furthermore, activation of ventricular receptors clustered mainly in the inferior and posterior walls of the left ventricle occurs in the initial phase of acute inferior myocardial infarction and is related to the increased frequency of autonomic overactivity and sudden death found in this condition.44 The role of left ventricular mechanoreceptors in human cardiovascular pathophysiology is not clearly established.41,45 Detailed animal experiments suggest that these receptors are activated by distortion and stretch of ventricular myocardium providing higher centers located in the brain stem with information on the contractile state of the heart. Afferent impulses resulting from activation of these receptors are carried in the vagus nerve to nuclei in the medulla. Efferent impulses from medullary nuclei regulate sympathetic tone peripherally and vagal tone to the sinoatrial node.39–41,45 In aortic stenosis, the high wall stress developed during systole may result in activation of ventricular baroreflexes, resulting in peripheral vasodilatation and consequent syncope.4,9

Similar mechanisms may operate in patients with HCM; in areas of extensive myocyte disarray, the abnormal arrangement of muscle fibers may lead to regional increases in wall stress that, during high catecholamine drive as occurs during exercise, may be sufficient to activate the ventricular mechanoreceptor reflexes. Activation of cardiac mechanoreceptors leading to hemodynamic instability may in turn lead to regional myocardial ischemia, particularly in areas of disarray, and provide a substrate for fatal arrhythmia. Support for this conclusion in our study

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**Table 3. Association of Exercise Hypotension and Vasodilator Responses in 103 Patients With Hypertrophic Cardiomyopathy**

<table>
<thead>
<tr>
<th>Blood pressure response</th>
<th>Plethysmography response Normal (n=64)</th>
<th>Vasodilator (n=39)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal (n=65)</td>
<td>55</td>
<td>10</td>
</tr>
<tr>
<td>Exercise hypotension (n=38)</td>
<td>9</td>
<td>29</td>
</tr>
</tbody>
</table>

*p=0.0001.
comes from the finding of smaller left atrial dimensions as well as a trend toward smaller left ventricular cavity dimensions in patients with an abnormal plethysmographic response. It is precisely this small compliant ventricle in the presence of high levels of circulating catecholamines that Almquist et al. suggest is responsible for increases in ventricular wall stress and activation of ventricular receptors. Although activation of these receptors is the most likely mechanism for the abnormal plethysmographic response, other mechanisms of vasovagal syncope are recognized.

An alternate mechanism for the abnormal vascular responses to exercise may relate to increased sensitivity of arterial baro reflexes. Evidence for this comes from study of a subgroup of 43 patients in whom arterial baroreflex sensitivity was measured. In the 17 with a vasodilator response, the baroreflex sensitivity was higher than in those with a normal plethysmographic response. Our study population includes nine patients from two families with a "malignant" family history. Autopsy data from deceased relatives of these nine patients demonstrated mild hypertrophy but extensive disarray (unpublished data). None of the nine patients from these families included in our study had severe hypertrophy or a left ventricular gradient, but eight demonstrated abnormal plethysmographic responses. Similarly, the two patients evaluated after resuscitation from out-of-hospital ventricular fibrillation had abnormal vascular responses.

Although we did not measure catecholamines, the absence of any effect on heart rate in our patients may be due to the masking effect of high levels of circulating catecholamines found during exercise. The absence of an association of left ventricular outflow tract gradient with abnormal peripheral vascular responses further suggests that it is the extent of myocyte disarray that is critical in the activation of the reflex, not obstruction to outflow.

The relation of abnormal peripheral vascular responses to young age and a family history of sudden death confirms the observation of early investigators that hemodynamic instability is an important potential initiating mechanism for sudden death in HCM. The contribution of the forearm vasculature to overall peripheral resistance is small. Further studies to examine the vascular changes in other regional beds that provide a greater contribution to total peripheral resistance (e.g., mesenteric and renal vasculature) are warranted.

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