Mechanism of Exercise Hypotension in Patients With Ischemic Heart Disease
Role of Neurocardiogenically Mediated Vasodilation

Suhas S. Lele, MD; Greg Scalia, MBBS; Helen Thomson, MBBS; David Macfarlane, MBBS; Darren Wilkinson, BSc(Hons); Wayne Stafford, FRACP; Fred Khafagi, FRACP; Michael Frenneaux, MD, FRACP

Background Exercise-induced hypotension in patients with coronary artery disease (CAD) has been considered to be due to an inability to achieve an adequate increase in cardiac output to match the demands of exercise. We investigated 10 consecutive patients (9 men and 1 woman; age, 38 to 71 years; mean, 52 years) with angiographically documented CAD and exercise-induced hypotension (EIH) (BPrest <BPpeak). Ten approximately age- and sex-matched patients with documented CAD and normal exercise blood pressure response (NBP) served as control subjects.

Methods and Results Nine patients with EIH and all 10 control subjects underwent forearm plethysmography and radionuclide ventriculography (RNV) during semierect cycle exercise. Forearm vascular resistance (FVR) fell by 35±21% in exercise-induced hypotension patients versus an increase of 78±65% in patients with an NBP response (P<.0001). Left ventricular ejection fraction increased by 5.1±7.5% in the group with EIH versus a fall of 4.1±6.2% in the control group (P=.004). Cardiac output at peak exercise (RNV) increased by 2.2±0.89-fold in the group with EIH versus 1.49±0.47-fold in the control group (P=.04). The tenth patient in the group with EIH underwent invasive hemodynamic evaluation during erect exercise. Systolic blood pressure fell (136/80rest to 50/ 40peak) and cardiac output (Fick) tripled, whereas calculated systemic vascular resistance decreased by a factor of 10. Successful angioplasty to an isolated circumflex lesion resulted in resolution of symptoms and abnormal hemodynamic responses during exercise.

Conclusions Abnormal vasodilation associated with a normal or even increased rather than decreased cardiac output response appears to be an important mechanism underlying EIH in some patients with CAD. In the present study, this appears to have been the dominant mechanism in 8 and contributory in 2 of the consecutive patients studied. (Circulation. 1994;90:2701-2709.)

Key Words • exercise • hypotension • vasodilation • baroreceptors

Exercise-induced hypotension (defined as a systolic blood pressure at peak exercise less than at rest) has been reported in 8% of patients with recent myocardial infarction and 9.5% of patients with old myocardial infarction and is associated with a poor prognosis.3,4 This has been associated with severe proximal three-vessel disease, disease of the left main coronary artery, and/or left ventricular systolic dysfunction.4 It has been assumed that the abnormal response during exercise is due to profound left ventricular systolic dysfunction with a consequent failure of cardiac output to rise.5,6 However, a recent study has reported similar resting ejection fractions and extent of coronary artery disease in patients with both hypotensive and normal exercise blood pressure responses. This led the authors to question whether fixed or ischemia-mediated left ventricular systolic dysfunction was the sole cause of exercise-induced hypotension in such patients.7

We have previously demonstrated that exercise-induced hypotension in patients with hypertrophic cardiomyopathy is due to an abnormal vasodilator response in nonexercising vascular beds rather than an impaired cardiac output response.8,9 Another group has recently demonstrated attenuated forearm vasoconstrictor responses at low (submaximal) levels of supine exercise in patients with coronary artery disease and exercise hypotension.10 We hypothesized that abnormal vasodilation occurring during maximal exercise may result in hypotension in some patients with coronary artery disease. We therefore studied the responses to exercise in a consecutive series of 10 patients with ischemic heart disease and exercise-induced hypotension to assess the relative importance of abnormal vasodilation and systolic dysfunction.

Methods

Patients
The study population was selected from 375 consecutive patients who underwent diagnostic exercise testing in the Royal Brisbane Hospital between June 1992 and January 1993. The clinical diagnosis was coronary artery disease in 177, atypical chest pain without objective evidence of ischemia in 188, and hypertrophic cardiomyopathy in 10. Exercise-induced hypotension (systolic blood pressure at peak exercise less than rest) was observed in 17 of the 375 patients; none exhibited an initial rise in systolic blood pressure early in exercise and a subsequent fall of ≥20 mm Hg (but still above baseline) by peak exercise. Four of the patients with exercise hypotension

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From the Departments of Cardiology (S.S.L., G.S., H.T., D.W., W.S., M.F.) and Nuclear Medicine (D.M., F.K.), Royal Brisbane Hospital and Department of Medicine, University of Queensland, Herston, Brisbane, Australia.
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Correspondence to Dr Michael Frenneaux, Department of Cardiology, Royal Brisbane Hospital, Herston Rd, Brisbane, Australia 4029.
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TABLE 1. Serial Changes in Forearm Vascular Resistance and Relative Cardiac Outputs During Progressive Semierect Cycle Exercise in 9 Patients With Exercise-Induced Hypotension

<table>
<thead>
<tr>
<th>Patient</th>
<th>Systolic Blood Pressure, mm Hg</th>
<th>FVR, Units</th>
<th>Cardiac Outputs Relative to Rest (RNV)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rest</td>
<td>Stage 1</td>
<td>Stage 2</td>
</tr>
<tr>
<td>1</td>
<td>116</td>
<td>118</td>
<td>118</td>
</tr>
<tr>
<td>2</td>
<td>120</td>
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<td>120</td>
</tr>
<tr>
<td>3</td>
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<td>128</td>
</tr>
<tr>
<td>9</td>
<td>104</td>
<td>108</td>
<td>112</td>
</tr>
</tbody>
</table>

FVR indicates forearm vascular resistance; RNV, radionuclide ventriculography.

had hypertrophic cardiomyopathy and 2 had a history of neurally mediated syncope and a positive tilt test. Angiographically proven coronary artery disease and objective evidence of ischemia was present in 11 patients. Nine of the 11 patients had diagnostic changes of ischemia on exercise electrocardiography (≥2 mm ST depression 80 milliseconds after the J point). Two of these 9 patients also underwent exercise thallium scintigraphy and both exhibited reversible defects. One of the remaining 2 patients had a resting left bundle branch block but a reversible exercise thallium defect and the other patient developed chest tightness during exercise testing without diagnostic ECG changes but had a reversible thallium defect. One of these 11 patients developed hypertensive collapse on the treadmill (systolic blood pressure of 40 mm Hg) and then ventricular tachycardia; it was believed to be inappropriate to perform further stress tests in this patient to elucidate the mechanism of the hypotension, and he was therefore excluded from the study.

The remaining 10 patients comprised the study group and gave written informed consent to undergo further investigation to assess the cause of their hypotension. Eight of these had suffered previous myocardial infarction and 3 had exertional angina. Ten age- and sex-matched patients with angiographically proven significant coronary artery disease and objective evidence of ischemia (on exercise ECG or thallium scintigraphy as outlined above) but with a normal blood pressure response during exercise gave written informed consent to serve as control subjects.

**Study Protocols**

Patients were studied in the fasting state, having not taken any cardioactive medications for at least 5 half-lives. The study protocol was approved by the Royal Brisbane Hospital Ethics Committee. Patients 1 through 9 (Table 1) and all 10 control patients underwent exercise radionuclide ventriculography and exercise plethysmography. Patient 1 also underwent invasive hemodynamic studies during exercise. Patient 10 underwent only invasive hemodynamic studies during exercise.

**Exercise Radionuclide Ventriculography**

Left ventricular function was evaluated by equilibrium R-wave gated blood pool scintigraphy at rest and during graded semirecumbent exercise on a cycle ergometer. Ten minutes after the intravenous injection of approximately 1.7 mg of stannous pyrophosphate, 5 mL of blood was drawn into a heparinized syringe and incubated for 20 minutes with 925 MBq (25 mCi) of Tc-99m pertechnetate before reinjection. Studies were acquired on a small field-of-view gamma camera (GE300A, GE Medical Systems) fitted with a low-energy, general-purpose, parallel-hole collimator and interfaced to a dedicated minicomputer (MaxDelta, Siemens). With the patient on the cycle ergometer, the detector was adjusted for the left anterior oblique view with the best ventricular separation and 10° to 15° of caudal tilt. A 15° tolerance window was set about the patient's heart rate, and each RR interval was divided into 28 equal frames. Data from each beat were acquired in a memory buffer in a 64×64 “word” matrix and if accepted were reformatted using ⅔ forward, ⅑ backward gating.

Four minutes of data was acquired at rest and at each incremental level of exercise after a 30-second period for stabilization of heart rate at the commencement of each stage. The initial workload was set at 25 W, increasing by 12.5-W increments. Exercise was terminated due to patient fatigue, breathlessness, progressive chest pain, arrhythmia, heart rate >200 beats per minute, or hypotension (systolic blood pressure lower than baseline).

Rest and exercise radionuclide ventriculograms were analyzed by a single operator unaware of the patient's history or exercise performance. The composite cycle derived from each stage was spatially and temporally filtered. Left ventricular counts in each frame were determined by a semiautomated edge-detection algorithm. Left ventricular ejection fraction was calculated from the background-corrected left ventricular activity-time curve. Stroke counts were calculated as an index of stroke volume from the product of the background-corrected end-diastolic counts and the left ventricular ejection fraction. The product of stroke counts and heart rate was used as a measure of cardiac output (no patient had evidence of mitral or aortic regurgitation).

**Exercise Forearm Plethysmography**

Patients were studied in a quiet environment at a constant room temperature of between 22° and 24°C. Forearm blood flow was measured using a mercury-in-Silastic strain gauge plethysmography technique (Hokanson). Measurements were made at rest and during maximum symptom-limited semirecumbent cycle exercise. Patients were positioned semirecumbent on a cycle ergometer. The right forearm was elevated to allow free venous drainage. A pneumatic collecting cuff was placed around the upper arm and a second cuff was placed around the wrist and inflated for the duration of the recordings to suprasystolic pressure to exclude the hand circulation from the measurements. Measurements of forearm blood flow were obtained by inflating the collecting cuff to 40 mm Hg to prevent venous return. The rate of increase of forearm girth is
then proportional to forearm blood flow. The cuff was inflated to 40 mm Hg for 10 seconds and deflated for 10 seconds. This was repeated three times and the forearm flow calculated from the mean of the three slopes. The volume variations of the limb segment were measured by means of the electrical resistance variations of the mercury-filled strain gauge. The voltage output from the strain gauge was measured using a high-sensitivity preamplifier and recorded using an Apple McIntosh IIG computer and an Acq Knowledge multichannel data acquisition system (Biopac Systems). Blood pressure was measured in the index finger of the opposite upper limb using a Finapress finger plethysmograph recorder (Omeda 2300), and these data, together with standard surface ECG recordings, were also fed to the multichannel recording system on the computer. After measurements were made at rest, patients performed symptom-limited semirecumbent cycle exercise commencing at 25 W and increasing by 12.5 W every 3 minutes. Forearm blood flow was measured at the end of each 3-minute stage and at peak exercise. Forearm vascular resistance (FVR), expressed in resistance units, was calculated as the quotient of the mean arterial pressure (mm Hg) and forearm blood flow (mL/100 mL per minute):

\[
\text{FVR (Units)} = \frac{\text{Mean arterial pressure (mm Hg)}}{\text{Forearm blood flow (mL/100 mL/min)}}
\]

**Invasive Studies**

A Swan-Ganz catheter was inserted into a central vein under local anesthesia and advanced into the pulmonary artery. A 20-gauge cannula was inserted into the brachial artery of the nondominant arm. Pressures were recorded using Gould-Statham transducers referenced to atmosphere at midchest level and recorded using a Mingograf 7 multichannel recorder. Respiratory gas analysis was performed using an Airspec 200 MGA mass spectrometer linked by an analog-to-digital converter to a BBC microcomputer that gave 10-second printouts of oxygen consumption, carbon dioxide production, respiratory quotient, and minute ventilation. Mixed venous (pulmonary artery) and arterial blood samples were taken at rest, after each 3 minutes of exercise, and at peak exercise to enable calculation of cardiac output at each of these stages by the direct Fick method. Systemic vascular resistance was calculated by the following formula:

\[
\text{SVR (absolute resistance units)} = \frac{(\text{Mean arterial} - \text{mean right atrial pressure}) \times 80}{\text{Cardiac output (L/min)}}
\]

**Statistical Analysis**

Results are expressed as mean±1 SD. The Student’s t test for paired and unpaired data was used for normally distributed variables and Wilcoxon’s test for nonparametric data. A value of \(P<.05\) was considered significant.

**Results**

In the study group of 11 patients, the systolic blood pressure was 138±12 mm Hg at rest and 122±18 mm Hg at peak exercise; in the remaining 358 patients with a normal exercise response, systolic blood pressure rose from 128±18 mm Hg at rest to 172±16 mm Hg at peak exercise. In the control group of 10 patients with a normal blood pressure response, the systolic blood pressure was 128±18 mm Hg at rest and 170±18 mm Hg at peak exercise. Objective ECG evidence of ischemia preceded the development of hypotension in 9 of the 11 patients studied. In the 2 patients who had only thallium evidence of ischemia it was not possible to evaluate if the ischemia preceded the development of

![Figure 1](http://circ.ahajournals.org/)

**Figure 1.** Plot shows changes in forearm vascular resistance (FVR) during semirecumbent exercise in 9 patients with ischemic heart disease and exercise-induced hypotension and 10 with a normal blood pressure response.
control patients (79±20 versus 71±14 and 118±20 versus 116±17 beats per minute, respectively). Resting systolic blood pressure was also similar (118±10 versus 116±17 mm Hg), but at peak exercise, systolic blood pressure was lower in the study group (116±16 versus 165±18 mm Hg; <.0001). Forearm flow rates were similar at rest in the two groups (2.0±1.4 versus 1.9±0.5 mL/100 mL per minute), but at peak exercise, the flow rates were higher in the hypertensive group (3.5±1.9 versus 1.5±0.4 mL/100 mL per minute; <.0001). Forearm vascular resistance fell by 35±25% in the study group versus an increase of 78±65% in the control group (<.0001). The change in forearm vascular resistance in the control patients was similar to that in 25 normal healthy control subjects in whom forearm vascular resistance increased by 99±56%. The serial changes in forearm vascular resistance at each stage of exercise in the 9 hypertensive responders studied are presented in Table 1. Forearm vascular resistance decreased progressively in 8 of the 9 patients studied but remained virtually unchanged in 1 patient.

### Radionuclide Ventriculography

The results of exercise radionuclide ventriculography in the 9 patients with ischemic heart disease and exercise-induced hypotension and those with normal blood pressure responses are shown in Figs 2 through 4 and are summarized in Tables 1 and 4. Resting and peak heart rates were similar in the two groups (77±20 versus 73±14 and 128±20 versus 125±30 beats per minute, respectively). Resting systolic blood pressure was also similar in the two groups (120.0±9.0 versus 120.0±7.8 mm Hg), but at peak exercise, systolic blood pressure was lower in the study group (119.0±7.6 versus 179.0±16.0 mm Hg; <.0001). Resting ejection fraction was similar in both groups (42±17% versus 47±12.8%).

During exercise, ejection fraction increased 5.1±7.5% in the study group but decreased by 4.1±6.2% in the control group (<.0001). Resting stroke counts were similar in the two groups (410±152 versus 540±344). During exercise, stroke counts increased by 115±179 in the study group versus a decrease of 66.9±147.0 counts

### Table 3. Hemodynamic and Forearm Vascular Changes During Semierect Cycle Exercise

<table>
<thead>
<tr>
<th>Study Group</th>
<th>Control Group</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR rest, bpm</td>
<td>79±20</td>
<td>71±14</td>
</tr>
<tr>
<td>HR exercise</td>
<td>118±20</td>
<td>122±30</td>
</tr>
<tr>
<td>SBP rest, mm Hg</td>
<td>116±10</td>
<td>116±17</td>
</tr>
<tr>
<td>SBP exercise</td>
<td>118±16</td>
<td>165±18</td>
</tr>
<tr>
<td>FFR rest, mL/100 mL per minute</td>
<td>2±1.4</td>
<td>1.9±5</td>
</tr>
<tr>
<td>FFR exercise</td>
<td>3.5±1.9</td>
<td>1.5±4</td>
</tr>
<tr>
<td>FVR rest, U</td>
<td>57.9±41</td>
<td>44.7±11</td>
</tr>
<tr>
<td>FVR exercise</td>
<td>35±25</td>
<td>74±18</td>
</tr>
<tr>
<td>Change in FVR on exercise, %</td>
<td>-35±21%</td>
<td>78±65%</td>
</tr>
</tbody>
</table>

HR indicates heart rate; bpm, beats per minute; MBP, mean blood pressure; FFR, forearm flow rates; and FVR, forearm vascular resistance.

### Table 4. Hemodynamic Changes Assessed by Radionuclide Ventriculography During Semierect Cycle Exercise

<table>
<thead>
<tr>
<th>Study Group</th>
<th>Control Group</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR rest, bpm</td>
<td>77±20</td>
<td>73±14</td>
</tr>
<tr>
<td>HR peak exercise</td>
<td>128±20</td>
<td>125±30</td>
</tr>
<tr>
<td>SBP rest, mm Hg</td>
<td>120±9</td>
<td>120±7.8</td>
</tr>
<tr>
<td>SBP peak exercise</td>
<td>119±7.6</td>
<td>179±16</td>
</tr>
<tr>
<td>EF rest, %</td>
<td>42±17</td>
<td>47±12.8</td>
</tr>
<tr>
<td>EF peak exercise</td>
<td>47±17</td>
<td>42±12</td>
</tr>
<tr>
<td>Change EF, %</td>
<td>+5.1±7.5</td>
<td>-4.1±6.2</td>
</tr>
<tr>
<td>SC rest, counts</td>
<td>410±152</td>
<td>540±344</td>
</tr>
<tr>
<td>SC peak exercise</td>
<td>526±266</td>
<td>347±111</td>
</tr>
<tr>
<td>EDC peak exercise</td>
<td>104±18</td>
<td>86±25</td>
</tr>
<tr>
<td>Change SC</td>
<td>+115±179</td>
<td>-66.9±147</td>
</tr>
<tr>
<td>CO peak/CO rest</td>
<td>2.2±.9</td>
<td>1.5±.47</td>
</tr>
</tbody>
</table>

HR indicates heart rate; bpm, beats per minute; SBP, systolic blood pressure; EF, ejection fraction; SC, stroke counts; EDC, end-diastolic counts; and CO, cardiac output (radionuclide ventriculography).
per beat in the control group ($P=.01$). Noninvasively measured cardiac output increased by 2.2±0.9-fold in the study group versus 1.5±0.5-fold in the control group ($P=.04$). The serial changes in relative cardiac output at each stage of exercise in the 9 hypotensive patients studied are presented in Table 1. Cardiac output increased at each stage of exercise in all the study patients.

**Invasive Studies**

The hemodynamic changes during exercise in the 2 patients studied invasively are shown in Fig 5. Hypotension developed during exercise in both patients; however, cardiac output increased by 3.0-fold and 3.7-fold, and calculated systemic vascular resistance fell by 10.0-fold and 5.4-fold.

**Discussion**

During erect symptom-limited dynamic exercise in untrained normal subjects, cardiac output increases by approximately threefold due to an increase in both heart rate and stroke volume. Systemic vascular resistance decreases by approximately twofold with vasodilation in the exercising vascular beds (legs) and vasoconstriction in the nonexercising vascular beds (including the forearm).13,14 As a result, mean arterial pressure increases by approximately 40%, with a marked increase in systolic blood pressure and little change in diastolic pressure. In a minority of patients with ischemic heart disease, blood pressure falls during exercise. It is generally believed that this is caused by exercise-induced left ventricular systolic dysfunction with an inadequate rise in left ventricular ejection fraction and cardiac output.

In the literature, exercise hypotension is reported in 5% to 8% of all exercise tests,1 and the incidence of hypotension in our series is 4.5%. Three patterns of exercise hypotension are commonly described. In the first, there is a failure of systolic blood pressure to increase during exercise; in the second, systolic blood pressure initially rises during exercise but then falls by at least 20 mm Hg; in the third, systolic blood pressure at peak exercise is less than at rest. In our previous large series of patients with hypertrophic cardiomyopathy we used all three definitions of exercise hypotension, but in that study all exercise tests were performed by one observer. This study reflects the experience of a hospital rather than a research exercise laboratory, with several observers measuring blood pressures during the 375 consecutive routine exercise tests. In this context, we believed that the final definition (systolic blood pressure at peak exercise lower than at rest) was the most clear cut, with little room for interobserver variability, and this definition was therefore used exclusively.

In the present study, we documented that the cause of exercise-induced hypotension in our patients with ischemic heart disease was not an inadequate increase in cardiac output but that there was an inappropriate decrease in systemic vascular resistance. In fact, cardiac output increased to a greater extent in this group as compared with the control group. This series, although small, represents an unselected, consecutive group of patients exhibiting hypotension during treadmill exercise testing in whom reversible myocardial ischemia was demonstrated.

The two patients who underwent invasive hemodynamic studies both had a normal increase in cardiac output but a very exaggerated decrease in systemic vascular resistance. Patient 1 is of particular interest because he has severe proximal three-vessel coronary artery disease and moderate to severe resting left ventricular systolic dysfunction (ejection fraction, 28%). Exercise-induced hypotension in this patient might have been presumed to be due to a failure to increase cardiac output during exercise. However, during semierect cycle exercise, his ejection fraction increased to 37% and his cardiac output increased by 3.7-fold. While one can argue that the cardiac output response was inadequate for the fall in systemic vascular resistance, the main cause of the hypotension was clearly profound vasodi-
lation. By contrast, patient 10 had normal resting left ventricular systolic function and an isolated lesion in a nondominant circumflex lesion. The observation of a normal rise in cardiac output during exercise in association with a profoundly exaggerated fall in systemic vascular resistance was believed by the clinician to be so conclusive of vasodilation rather than systolic dysfunction as the cause of his exercise hypotension that exercise plethysmography and exercise radionuclide ventriculography were deemed unnecessary. Subsequently, this patient underwent successful angioplasty to the lesion, with resolution of his angina and exercise presyncope and the development of a normal exercise blood pressure response. It is interesting to note that in the second patient, systemic vascular resistance decreased progressively throughout exercise, yet systolic blood pressure only decreased during the latter part of exercise (Fig 5). This pattern is similar to that seen in the majority of patients we studied with hypertrophic cardiomyopathy who exhibit exercise hypotension.5,15 Whereas patients with hypertrophic cardiomyopathy and a normal exercise blood pressure response had a rapid decline in systemic vascular resistance in the first 2 to 3 minutes of exercise and a minimal decline during the remainder of exercise, the decrease in the later stages of exercise was more brisk in the patients with hypotension. We assume that during the early stages of exercise, the rapid increment in cardiac output results in an increase in blood pressure, but as the systemic vascular resistance continues to fall later in exercise and the cardiac output starts to plateau, blood pressure falls.

Changes in Forearm Vascular Resistance
As a group, the patients with exercise-induced hypotension had markedly abnormal forearm vascular responses during semierect cycle exercise compared with the control patients with coronary artery disease who had a normal exercise blood pressure response. The response of the control patients was similar to what we have previously reported in normal subjects.9 In 8 of the 9 study patients, the forearm vascular response on exercise was vasodilation. In the ninth patient, there was no net change in forearm vascular resistance during exercise. This response is nevertheless abnormal and if reflected in other non-exercising vascular beds, when combined with the profound vasodilation known to occur in exercising vascular beds, would result in an exaggerated fall in systemic vascular resistance on exercise. As a group, the ischemic control patients exhibited a slightly lesser forearm vasoconstrictor response than normal subjects; indeed, 1 patient exhibited a vasodilator response, but the difference in this small series was not statistically significant.

Changes in Left Ventricular Function
As a group, patients with exercise-induced hypotension who underwent exercise radionuclide ventriculography had different responses compared with those patients with normal blood pressure responses. Ejection fraction and stroke counts (a measure of stroke volume) increased in patients with exercise-induced hypotension but fell in those with a normal blood pressure response. End-diastolic counts (a measure of end-diastolic volume) decreased during exercise in patients with exercise hypotension but did not change significantly in those with a normal blood pressure response. Although absolute cardiac outputs were not measured, the patients with exercise-induced hypotension exhibited a greater relative increase in cardiac output than those with a normal blood pressure response. Our calculations of change in cardiac output on exercise are based on stroke counts and heart rate and therefore do not account for any valvular regurgitation. However, none of the patients had significant resting mitral or aortic regurgitation. Furthermore, given the profound afterload reduction and reduction in cardiac size during exercise in
patients with exercise-induced hypotension compared with those without hypotension, we believe that valvular regurgitation is unlikely to have contributed importantly to our results.

Our observations are in contrast to those of a previous study in which left ventricular ejection fraction fell slightly during exercise in a series of patients with coronary artery disease and exercise-induced hypotension but did not change in a group with a normal response. However, they are consistent with another study in which patients with ischemic heart disease and exercise-induced hypotension had similar resting ejection fractions and extent of coronary disease to those with a normal blood pressure response, leading the authors to question the role of fixed or ischemia-mediated left ventricular systolic dysfunction in the pathophysiology of the hypotension. It may well be that systolic dysfunction may be an important mechanism of hypotension in some patients; however, our data from this small consecutive series suggest that a more important mechanism of exercise-induced hypotension may be a fall in systemic vascular resistance caused by an abnormal vasodilator response in nonexercising vascular beds. In 8 of our 10 patients, this appears to have been the dominant mechanism, whereas in 2 patients it seems likely that abnormal vasodilation and left ventricular systolic dysfunction both played significant roles (Table 5).

### Mechanism of Abnormal Vasodilation

The mechanism of the abnormal vasodilator response has not been fully clarified. Vasodilation in vascular beds of exercising limbs occurs as a result of the local effect of metabolic products of exercise. The response of nonexercising vascular beds is largely determined by three factors. First, cortical influences (central command reflex) result in vasoconstriction in nonexercising beds. Second, activation of metaboreceptors in skeletal muscle during exercise results in reflex vasoconstriction in nonexercising vascular beds. Third, venous baroreceptor activity is increased during interventions similar to exercise in animals (pressure overload or inotropic drug stimulation), and it seems likely that ventricular baroreceptor activation occurs during exercise leading to vasodilation. This will tend to attenuate the vasoconstrictor effects of the central command and skeletal muscle metaboreceptor reflexes. It is possible that the abnormal vasodilator response in these patients is due to a profound ventricular baroreceptor activation that overwhelms the central command and skeletal muscle metaboreceptor reflexes. Activation of ventricular baroreceptors is presumably a consequence of ischemia. Objective evidence of ischemia preceded the development of hypotension in 9 of the patients with ischemic heart disease and exercise-induced hypotension. Ventricular baroreceptors are most prominent in the anterior and posterior left ventricular walls. In some of the patients, ischemia may have involved these segments, in which case, abnormal regional wall stresses in these segments might stimulate mechanoreceptors. In those in whom the inferior and posterior walls were not ischemic, hypotension could have either been a consequence of stimulation of mechanoreceptors in the anterior wall of the left ventricle, or alternatively, anterior ischemia or infarction may have resulted in abnormal regional wall stresses on the inferior and posterior left ventricular walls. Venous baroreceptors sensitive to chemical stimuli also exist, and it is possible that in the context of myocardial ischemia, activation of these receptors may play a role. Mark et al. demonstrated abnormal forearm vasodilator responses during exercise in patients with critical aortic stenosis, a response that was reversed after successful aortic valve replacement. We have observed similar abnormal vasodilator responses during exercise in association with exercise hypotension in approximately one third of a large series of patients with hypertrophic cardiomyopathy. In hypertrophic cardiomyopathy, this abnormal vasodilator response is associated with markers of adverse prognosis. In normal subjects, postexercise hypotension is well documented and is thought to reflect a sudden fall in cardiac output associated with low systemic vascular resistance immediately after exercise. Hypotension during exercise rather than immediately after exercise is rare in normal subjects. We recently observed a small series of subjects who exhibited symptomatic hypoten-

### Table 5. Suggested Mechanism of Exercise-Induced Hypotension in Patients Studied

<table>
<thead>
<tr>
<th>Patient</th>
<th>ΔEF, u</th>
<th>ΔSC, Counts</th>
<th>ΔFVR, %</th>
<th>CO Peak/CO Rest</th>
<th>Dominant Mechanism of Hypotension</th>
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<tbody>
<tr>
<td>1</td>
<td>+9</td>
<td>+30</td>
<td>-16.7</td>
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<td>Dilatation</td>
</tr>
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<td>2</td>
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<td>+544</td>
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<td>3</td>
<td>+9</td>
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<td>1.8</td>
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<td>-58</td>
<td>-43.6</td>
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<tr>
<td>5</td>
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<td>6</td>
<td>+8</td>
<td>+202</td>
<td>-35.4</td>
<td>1.7</td>
<td>Dilatation</td>
</tr>
<tr>
<td>7</td>
<td>+15</td>
<td>+102</td>
<td>-41.5</td>
<td>1.7</td>
<td>Dilatation</td>
</tr>
<tr>
<td>8</td>
<td>-1</td>
<td>+10</td>
<td>+0.2</td>
<td>1.7</td>
<td>Abnormal vascular response+systolic dysfunction</td>
</tr>
<tr>
<td>9</td>
<td>+3</td>
<td>+28</td>
<td>-69.5</td>
<td>1.8</td>
<td>Dilatation</td>
</tr>
</tbody>
</table>

ΔEF indicates change in ejection fraction with exercise; ΔSC, change in stroke counts with exercise; ΔFVR, change in forearm vascular resistance with exercise; and CO, cardiac output.

Patient 10 underwent only invasive hemodynamic studies. Cardiac output rose 3-fold and systemic vascular resistance fell 10-fold during exercise, suggesting vasodilation as the mechanism.
sion during exercise and who had normal hearts. All of them had positive tilt table test and abnormal forearm vasodilator responses during exercise. 23 Another study recently reported a high incidence of positive tilt tests in a group of healthy athletes with normal hearts who had exercise syncope due to hypotension. 24 This suggests that neurogenically mediated exercise hypotension may rarely occur in otherwise healthy individuals as well as in patients with aortic stenosis, hypertrophic cardiomyopathy, and ischemic heart disease. Subsequent to these studies, 1 of the 10 patients has undergone coronary artery bypass grafting and another successful percutaneous transluminal coronary angioplasty of an isolated circumflex lesion. Both patients had a normal blood pressure response during repeat exercise testing. In 7 of the remaining patients, exercise tests were performed while on β-blocker therapy. These patients achieved a higher workload before the development of hypotension, implying some attenuation of the process.

Study Limitations

Forearm plethysmography is technically difficult to perform during exercise. However, we have used this technique extensively, particularly in the investigation of exercise vascular responses in patients with hypertrophic cardiomyopathy. 8 We restudied 25 patients with hypertrophic cardiomyopathy at a mean follow-up of 18 months, and in 23 the pattern of the forearm vascular response was identical to that observed in the first study. 15 We are therefore confident of the validity of the technique in our laboratory.

Forearm vascular responses during exercise may not necessarily mirror changes in the quantitatively more important splanchnic vascular bed, although the literature suggests that changes in both vascular beds during exercise are usually similar. In the one patient studied both invasively and by exercise forearm plethysmography, the forearm vascular response and the abnormal fall in systemic vascular resistance were in agreement. Notwithstanding the above caveat, the forearm vascular responses of patients with exercise-induced hypotension were clearly abnormal. Abnormal vascular responses during exercise may well be relatively common in patients with ischemic heart disease, and the exercise blood pressure response during exercise will thus be determined by the degree of the abnormality of the vascular response and by the ability of the heart to increase cardiac output.

The exercise forearm vascular studies and radionuclide studies were performed during semierect cycle exercise rather than during erect treadmill exercise. It is noteworthy that while by definition all 10 patients exhibited hypotension on erect treadmill exercise testing, 4 of the 10 patients did not exhibit hypotension during semierect cycle exercise testing although the blood pressure response was very flat. We observed similar discrepancies in blood pressure response comparing erect versus supine exercise testing in our large series of patients with hypertrophic cardiomyopathy. 8, 9 Several mechanisms may be responsible. Higher filling pressures in the supine or semierect positions may result in a higher cardiac output. Local left ventricular wall stresses may be different in the semierect versus the erect position, and this may influence activity of the left ventricular mechanoreceptors putatively involved in this abnormal response. Neither forearm plethysmography nor gated heart pool scanning are technically feasible during erect exercise testing, and semierect cycle testing is therefore a compromise.

This study suggests that abnormal vasodilation may be an important mechanism of exercise hypotension in patients with ischemic heart disease. While the series represents a consecutive, unselected series of such patients, it is of course rather small and it is possible (indeed likely) that in some patients with severe extensive coronary artery disease, the mechanism of hypotension may be a poor cardiac output due to ischemia-mediated left ventricular dysfunction. In particular, none of the patients had left main stem disease. This is a reflection of sample size rather than a selection bias. Recent literature reports that between 10% and 15% of patients with exercise hypotension have left main stem disease, and the absence of such patients in a series of only 11 is therefore not surprising. It is noteworthy, however, that patient 1 had severe three-vessel coronary artery disease and severe resting left ventricular systolic dysfunction, yet the mechanism of hypotension was clearly an abnormal vasodilator response rather than an inadequate cardiac output response.

Conclusions

We have demonstrated that an abnormal vasodilator response may be the cause of exercise-induced hypotension in some patients with ischemic heart disease. The true incidence of such a vasodilator response compared with systolic dysfunction as a cause of exercise-induced hypotension will require clarification in a larger consecutive series. The pathophysiological importance of this observation is underscored by the known association between exercise hypotension in ischemic heart disease and a poor prognosis.

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Mechanism of exercise hypotension in patients with ischemic heart disease. Role of neurocardiogenically mediated vasodilation.

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