Effect of the sympathetic nervous system on limb circulation and metabolism during exercise in patients with heart failure

JOHN R. WILSON, M.D., NANCY FERRARO, R.N., AND DAVID H. WIENER, M.D.

ABSTRACT During exercise in patients with heart failure, activation of sympathetic vasoconstrictor nerves may impair vasodilation in active skeletal muscle and thereby interfere with skeletal muscle blood flow. To investigate this hypothesis, we examined the effect of acute a-adrenergic blockade with systemic administration of prazosin (10 patients) or regional administration of phentolamine (eight patients) on blood flow, vascular resistance, oxygen consumption (VO₂), and lactate release in the leg during maximal bicycle exercise in patients with heart failure. During control exercise, systemic VO₂ increased to 12.6 ± 4.3 ml/min/kg (normal > 20 to 25 ml/min/kg), leg blood flow to 2.8 ± 1.8 liters/min, and leg lactate release to 362 ± 256 mg/min. Prazosin decreased systemic vascular resistance (12.5 ± 3.2 to 9.7 ± 2.5 units; p < .003) and mean arterial pressure (101 ± 20 to 87 ± 22 mm Hg; p < .002) at maximal exercise, supporting the presence of substantial sympathetic vasoconstrictor nerve activity. Prazosin also decreased leg resistance during exercise. However, the magnitude of leg blood flow, leg oxygen extraction, and leg VO₂ during exercise were unchanged, suggesting that vasodilation in the leg was produced by an autoregulatory response to the drop in blood pressure rather than by blockade of sympathetic vasoconstriction. Maximal systemic VO₂ and leg lactate release were also not improved. Regional blockade with phentolamine did not substantially drop the arterial blood pressure and had no effect on vasodilation, blood flow, VO₂, and lactate release in the leg during exercise. These data suggest that during exercise in patients with heart failure, the sympathetic nervous system helps to sustain arterial blood pressure and that this beneficial effect is not associated with adverse effects on blood flow to working skeletal muscle.

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BLOOD FLOW to working skeletal muscle is frequently reduced during exertion in patients with heart failure.¹ ¹ 3 This reduced perfusion of muscle is thought to be responsible, at least in part, for one of the major clinical symptoms experienced by such patients: exertional fatigue.¹ ¹ 4 ⁵ Therefore, to develop therapeutic strategies for alleviating exertional fatigue in patients with heart failure, it is important that the mechanism responsible for this reduced skeletal muscle blood flow be identified.

Previous observations suggest that impaired dilation of resistance vessels within working muscle may be an important contributor to this reduced muscle flow. We have noted that leg vascular resistance does not decrease normally during maximum upright bicycle exercise in patients with heart failure.¹ Zelis et al.⁶ have reported that forearm vascular resistance does not decrease normally during forearm exercise in patients with heart failure. In an experimental canine preparation of heart failure, Higgins et al.⁷ noted that iliac bed resistance did not decrease normally during exercise.

One potential mechanism responsible for impaired vasodilation in working muscle is activation of the sympathetic nervous system. In patients with heart failure, physical exertion usually produces earlier and more intense activation of the sympathetic nervous system than in normal subjects.⁸ ⁹ This activation produces vasoconstriction in inactive, nonessential vascular beds and thereby serves the useful purpose of supporting the systemic blood pressure and redistributing blood flow to vital organs. However, this activation also subjects the resistance vessels in active skeletal muscle to substantial vasoconstrictor influences. If
sufficiently intense, these influences could impair arteriolar vasodilation and thereby interfere with skeletal muscle blood flow.10,11

This study was undertaken to investigate this specific hypothesis. In previous studies we have demonstrated that patients with heart failure have higher leg vascular resistance and lower leg blood flow during maximum upright bicycle exercise than do normal subjects.4,12 These hemodynamic abnormalities are accompanied by metabolic evidence of reduced nutritive flow to working muscles, including reduced maximum systemic and leg oxygen consumption (VO2), markedly increased leg oxygen extraction, and earlier than normal onset of leg lactate release.1,12 If sympathetic nerve activation reduces muscle flow by impairing vasodilation within working muscle, we hypothesize that α-adrenergic blockade should reduce leg vascular resistance during exercise, increase leg blood flow, and improve metabolic indexes of muscle nutritive flow.

Methods

Patients. Seventeen men with chronic left ventricular dysfunction (ejection fractions 21 ± 8%) were studied. The mean age was 56 ± 10 years. All patients had exertional breathlessness and/or fatigue despite administration of digoxin and diuretics and all were classified as New York Heart Association functional class II or III. None had peripheral edema, ascites, angina pectoris, intermittent claudication, or reduced pulses in their legs at the time of study. Before enrollment in this study, optimal diuresis was achieved in all patients by increasing diuretic dosage until evidence of fluid retention was gone or until mild prerenal azotemia was noted. All patients had maximum oxygen uptakes below the normal range for their ages, the average maximum oxygen uptake being 12.6 ± 4.3 ml/min/kg.13 Left ventricular dysfunction was attributed to coronary artery disease in 11 patients and to idiopathic congestive cardiomyopathy in six patients. No patient had received any vasodilator for at least 1 week. The protocol was approved by the Committee on Studies Involving Human Subjects at the University of Pennsylvania. Written informed consent was obtained from all subjects.

Protocol. The protocol consisted of having each patient perform maximal upright bicycle exercise before and after α-adrenergic blockade. Systemic α-adrenergic blockade was accomplished with orally administered prazosin in 10 patients. In all of these patients, a control exercise test was performed first. Three or more hours later, the exercise test with prazosin was carried out. In eight patients regional α-adrenergic blockade of one leg was accomplished by injecting phentolamine into the femoral artery. In these patients the sequence of control exercise and exercise with phentolamine was alternated. In one of the four patients who performed exercise with phentolamine first, control exercise was followed by administration of prazosin and a third exercise test.

On the day before study, a trial maximal exercise test was performed to acquaint the patient with the exercise protocol. Exercise was performed on an upright, mechanically braked bicycle ergometer (Monarch), beginning at a workload of 20 W. Every 3 min the workload was increased by 20 W to symptomatic maximum. All exercise tests were performed at least 4 hr after meals.

The following morning, digoxin and diuretics were withheld. A Swan-Ganz catheter was inserted via an antecubital vein and positioned in the pulmonary artery. A No. 5F thermistor catheter was inserted percutaneously into the left femoral vein and advanced 15 to 16 cm anterograde into the iliac vein. In the patients who received phentolamine, a 12 cm polyethylene catheter was inserted into the left femoral artery. In the remaining patients a short polyethylene catheter was inserted into a radial artery.

Thirty minutes after instrumentation, hemodynamic measurements were made and blood samples were obtained from the arterial and femoral venous catheters for measurement of oxygen saturation and lactate concentration. Femoral venous blood flow was measured in triplicate. Respiratory gases were measured with a Beckman Metabolic Cart equipped with oxygen and carbon dioxide analyzers and a turbine volume transducer. Phentolamine was then administered to four of the patients; the remaining subjects received no medication. Details of phentolamine administration and exercise are mentioned below. The patients not receiving medication mounted the bicycle and were allowed to equilibrate for 5 min, after which all measurements were repeated.

The patients then commenced exercise. Respiratory gas and hemodynamic measurements were made continuously. During each 3 min exercise stage, leg blood flow was measured every 30 sec starting at 30 sec and continuing until 2.5 min (total of five measurements). The average of these five measurements was then taken as the mean flow for the exercise stage. Blood sampling was performed during the last 30 sec of the stage. Leg flow was not measured during this period.

After exercise was terminated, the patients receiving prazosin were allowed to rest for 1 hr. One milligram of prazosin was then administered orally. Forty-five minutes later hemodynamic measurements were repeated. If the upright mean arterial blood pressure had decreased by 15 mm Hg or greater and/or the patient had orthostatic symptoms, no further prazosin was administered. If the upright mean blood pressure had decreased by 10 to 15 mm Hg, an additional 1 mg of prazosin was administered. If the decrease in upright blood pressure was less than 10 mm Hg, an additional 4 mg of prazosin was administered. Seven patients received a total of 5 mg, two received 2 mg, and one received 1 mg.

Three hours after control exercise, the exercise protocol was repeated. Hemodynamic and metabolic measurements were made at identical exercise times as during control exercise. If a patient exercised longer after drug administration, measurements were also made at the new maximum exercise level.

In the patients receiving phentolamine, four received phentolamine just before the first exercise test. Control exercise was then performed 3 hr later. In the other four patients, phentolamine was administered and exercise was repeated 3 hr after the control exercise test. In all patients, 1 mg of phentolamine was initially administered into the femoral artery and arterial blood pressure was monitored for 3 min to ensure that marked hypotension did not occur. An additional 1.5 mg was then administered. Three minutes later, resting measurements were made and exercise was then performed. All patients received a total of 2.5 mg of phentolamine. The timing of phentolamine administration and exercise was rigidly adhered to so as to minimize the time between administration of the test dose of phentolamine and the end of exercise. This time was 14 min in three subjects, 17 min in three, 20 min in one, and 24 min in one.

In one patient, leg blood flow was not measured during exercise because of technical difficulties. However, femoral venous effluent was measured in this patient both at rest and during exercise. In the patients receiving prazosin, supine lactate levels were not measured in general, since it was believed that upright...
lactate levels provided adequate resting data. During the phenolamine protocol, which followed the prazosin protocol, both supine and upright lactate measurements were made to ensure that this was the case. No significant difference between supine and upright measurements was noted.

**Leg blood flow.** Leg blood flow was determined by the thermodilution method described by Jorfeldt et al. 14-16 and previously used by this laboratory. 1, 12, 17 In brief, femoral vein flow was measured with a 50 cm No. 5F thermodilution catheter with the thermistor at 2 cm and injection port 12 cm from the tip. Flow was determined by rapid injection of a 2.5 ml ice-dextrose bolus, with the aid of a commercially available thermodilution computer (Elecath). Output curves were displayed on a strip-chart recorder to ensure an exponential decay curve. Jorfeldt et al. have demonstrated that femoral venous flow measured by this technique agrees closely with leg flow determined by injection of indocyanine green into the femoral artery with sampling from the femoral vein. 14 Details of the evaluation of such flow measurements in our laboratory have been reported previously. 1, 12, 17

**Reproducibility studies.** The period between exercise tests was 3 hr. To ensure that exercise results are reproducible when repeated at this interval, reproducibility measurements were made in six patients. At peak exercise, the following key measurements were found to be reproducible: systemic VO2 (1041 ± 553 vs 1000 ± 526 ml/min, first vs second exercise), arterial lactate (35.5 ± 9.4 vs 32.3 ± 9.5 mg/dl), leg flow (3.15 ± 1.40 vs 3.21 ± 1.57 liters/min), femoral venous lactate (44.6 ± 11.5 vs 43.9 ± 16.4 mg/dl), and leg arteriovenous oxygen difference (13.23 ± 1.34 vs 12.94 ± 1.72 ml/dl).

**Measured variables.** Hemoglobin concentration was measured by Coulter counter; hemoglobin oxygen saturation was measured with a co-oximeter (Instrumentation Laboratories) calibrated with human blood. Blood oxygen content was calculated as the product of hemoglobin, 1.34 ml oxygen/g hemoglobin, and percent oxygen saturation. Oxygen extraction was calculated as the ratio of the arteriovenous oxygen difference and arterial oxygen content. Cardiac output was calculated from the Fick principle as systemic oxygen uptake/systemic arteriovenous oxygen difference. Systemic vascular resistance was calculated as mean blood pressure/cardiac output.

Leg vascular resistance was calculated as (arterial pressure – femoral venous pressure)/leg flow. Leg oxygen consumption was calculated as the product of femoral flow and the arteriovenous oxygen difference across the leg. Blood for lactate determination was deproteinized with cold perchloric acid and assayed with a spectrophotometric technique. 15 Normal resting values for this technique in our laboratory are 3 to 12 mg/dl. Leg lactate release was calculated as: leg flow times (femoral venous – arterial lactate concentration). It should be noted that leg flow, oxygen extraction, and lactate data were not obtained simultaneously. Therefore calculation of leg oxygen uptake and lactate release assumes that leg flow remained relatively constant during exercise. In support of this assumption, we have observed that flow increases abruptly with the onset of exercise and stabilizes within 30 to 45 sec.

**Statistical methods.** Values are presented as mean ± SD. Submaximal exercise variables were quantified in each patient by averaging all data obtained during submaximal exercise. Differences between measurements at rest and during exercise were compared by the paired Student t test for all variables but leg resistance. The distribution of leg resistances was nonparametric. Therefore differences in this variable were compared by the rank sum test, the nonparametric analog of the paired t test. A probability of less than .05 was considered significant.

**Results**

The effects of α-adrenergic blockade on systemic and regional parameters are summarized in tables 1 to 4 and illustrated in figures 1 and 2. Submaximal exercise data were obtained in eight of the patients who received prazosin and in five of the patients who received phenolamine. The other patients did not exercise beyond the first workload.

**Systemic α-adrenergic blockade with prazosin (tables 1 and 2).** At supine rest before the administration of prazosin, cardiac output was 4.0 ± 1.1 liters/min, pulmonary wedge pressure was 19 ± 5 mm Hg, systemic vascular resistance was 22 ± 8 units, leg flow was 0.3 ± 0.1 liter/min, and leg resistance was 266 ± 150 units.

**TABLE 1**

Effects of prazosin on systemic hemodynamic and metabolic responses to exercise

<table>
<thead>
<tr>
<th></th>
<th>HR (beats/min)</th>
<th>BP (mm Hg)</th>
<th>CO (l/min)</th>
<th>PWP (mm Hg)</th>
<th>VO2 (ml/min)</th>
<th>O2 extraction (%)</th>
<th>Lactate (mg/dl)</th>
<th>SVR (units)</th>
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<td><strong>Control</strong></td>
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<tr>
<td>Lying (n = 10)</td>
<td>87 ± 10</td>
<td>83 ± 13</td>
<td>4.0 ± 1.1</td>
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<td>224 ± 44</td>
<td>38 ± 9</td>
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<td>Bike (n = 10)</td>
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<td>24 ± 7</td>
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<td>1023 ± 330</td>
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<td>40.2 ± 10.3</td>
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<td>Lying</td>
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<td>33 ± 7c</td>
<td>18.1 ± 4.9c</td>
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<tr>
<td>Bike</td>
<td>102 ± 8</td>
<td>71 ± 13c</td>
<td>4.4 ± 1.0c</td>
<td>8 ± 4c</td>
<td>289 ± 37c</td>
<td>43 ± 8c</td>
<td>13.8 ± 6.2</td>
<td>17.0 ± 4.9c</td>
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<td>120 ± 13</td>
<td>81 ± 16b</td>
<td>8.4 ± 1.1c</td>
<td>13 ± 5b</td>
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<td>Peak exercisec</td>
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<td>9.4 ± 2.6c</td>
<td>15 ± 5c</td>
<td>1097 ± 437</td>
<td>68 ± 6b</td>
<td>37.7 ± 10.1</td>
<td>9.7 ± 2.5b</td>
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</table>

BP = blood pressure; CO = cardiac output; HR = heart rate; PWP = pulmonary wedge pressure; SVR = systemic vascular resistance.

*Values obtained at the highest identical work time achieved during both exercise tests.

*Measured at identical work times as during control exercise.

1p < .05 compared with control.

2p < .01 compared with control.
TABLE 2
Effects of prazosin on leg hemodynamic and metabolic responses to exercise

<table>
<thead>
<tr>
<th>Control</th>
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<th>Bike (n = 10)</th>
<th>Submaximal exercise (n = 8)</th>
<th>Peak exercise (n = 10)</th>
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<tbody>
<tr>
<td>Leg flow (l/min)</td>
<td>0.3±0.1</td>
<td>0.3±0.1</td>
<td>1.9±0.8</td>
<td>2.6±1.4</td>
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<td>Leg VO2 (ml/min)</td>
<td>16±5</td>
<td>24±8</td>
<td>234±108</td>
<td>327±192</td>
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<td>Leg resistance (units)</td>
<td>266±76</td>
<td>289±69</td>
<td>69±52</td>
<td>50±32</td>
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<td>Leg O2 extraction (%)</td>
<td>38±12</td>
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<td>82±6</td>
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<td>Femoral venous lactate (mg/dl)</td>
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<td>—</td>
<td>—</td>
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<tr>
<td>Venous-arterial lactate difference (mg/dl)</td>
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<tr>
<td>Leg lactate release (mg/min)</td>
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Prazosin

<table>
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<th>Bike</th>
<th>Submaximal exercise</th>
<th>Peak exercise</th>
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<tbody>
<tr>
<td>Lying</td>
<td>0.3±0.1</td>
<td>0.5±0.6</td>
<td>2.2±0.9c</td>
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<td>Bike</td>
<td>17±6</td>
<td>28±13</td>
<td>44±24</td>
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<td>Submaximal exercise</td>
<td>212±72c</td>
<td>193±115c</td>
<td>72±7c</td>
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<td>Peak exercise</td>
<td>32±8</td>
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<td>Femoral venous lactate (mg/dl)</td>
<td>51.3±9.4</td>
<td>15.7±3.7c</td>
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<td>Venous-arterial lactate difference (mg/dl)</td>
<td>13.7±7.2</td>
<td>0.9±4.4</td>
<td>6.5±3.5</td>
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<tr>
<td>Leg lactate release (mg/min)</td>
<td>389±247c</td>
<td>3±12</td>
<td>134±61</td>
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</table>

Values obtained at the highest identical work time achieved during both exercise tests.

*Measured at identical work times as during control exercise.

>p < .05 compared with control.

*p < .01 compared with control.

76 units. During maximal exercise, patients exercised to a maximal VO2 of 1033 ± 322 ml/min, invariably terminating exercise because of leg fatigue. Exercise increased the cardiac output to 8.4 ± 1.9 liters/min and the pulmonary wedge pressure to 30 ± 7 mm Hg. Leg blood flow increased from 0.3 ± 0.1 to 2.6 ± 1.4 liters/min, leg VO2 from 16 ± 5 to 327 ± 192 ml/min, leg oxygen extraction from 38 ± 12% to 82 ± 6%, and leg lactate release from 4 ± 8 to 237 ± 115 mg/min.

Administration of prazosin decreased the resting systemic vascular resistance by 18 ± 8% to 18 ± 5 units (p < .002 vs control) and resting leg vascular resistance by 18 ± 24% to 212 ± 72 units (p < .02 vs control) (figure 1). The percentage change in systemic and regional resistance were not significantly different. This vasodilation was associated with an increase in the resting cardiac output from 4.0 ± 1.1 to 4.5 ± 1.2 liters/min (p < .003) and a decrease in the pulmonary wedge pressure from 19 ± 5 to 13 ± 5 mm Hg (p < .001) but no change in leg blood flow or leg oxygen extraction.

During maximal exercise testing after administration of prazosin there was no significant change in maximal VO2 (1033 ± 322 to 1105 ± 439 ml/min; p = NS) or exercise duration. Exercise duration was identical in eight patients, increased in one, and decreased in one.

To examine the effect of prazosin on exercise data, variables were compared at the highest identical peak exercise time achieved during both tests. At this peak exercise point, prazosin decreased systemic vascular resistance by 25 ± 14% associated with a substantial decrease in mean arterial blood pressure from 101 ± 20 to 87 ± 22 mm Hg (p < .002) (figure 1). Leg vascular resistance decreased by 23 ± 20%, from 50 ± 32 to 35 ± 17 units (p < .04) (figure 1). However, there was no significant change in leg blood flow (2.6 ± 1.4 to 2.8 ± 1.6 liters/min; p = NS) or leg VO2 (327 ± 192 to 344 ± 205 ml/min; p = NS) (figure 2). Leg lactate release actually increased from 237 ± 115 to 389 ± 247 mg/min (p < .03) (figure 2).

Regional α-adrenergic blockade with phentolamine (tables 3 and 4). At supine rest before the administration of phentolamine, cardiac output was 3.3 ± 0.8 liters/min, pulmonary wedge pressure was 25 ± 5 mm Hg, systemic vascular resistance was 29 ± 8 units, leg flow was 0.4 ± 0.1 liter/min, and leg resistance was 242 ± 64 units. During maximal exercise, patients exercised to a maximal VO2 of 754 ± 354 ml/min, invariably terminating exercise because of leg fatigue. Exercise increased the cardiac output to 6.0 ± 2.8 liters/min and the pulmonary wedge pressure to 28 ± 7 mm Hg. Leg flow increased from 0.4 ± 0.1 to 2.8 ± 2.0 liters/min, leg VO2 from 26 ± 7 to 365 ± 276 ml/min, leg oxygen extraction from 45 ± 11% to 78 ± 9%, and leg lactate release from 4 ± 8 to 316 ± 212 mg/min.

Administration of phentolamine decreased the resting leg vascular resistance by 29 ± 18% (figure 1). Systemic vascular resistance decreased by 20 ± 16% (figure 1), significantly less than did leg resistance (p
Heart failure is accompanied by a reduction in blood flow to peripheral tissues both at rest and during exercise.\(^1\) This reduced flow leads to the recruitment of a number of compensatory vasoconstrictor mechanisms designed to sustain the systemic blood pressure and redistribute blood flow to vital organs. The most important of these mechanisms is activation of the sympathetic nervous system.\(^8\)

At rest, when peripheral tissue oxygen demands are low, activation of the sympathetic nervous system is usually modest and largely beneficial. During exercise, however, it remains uncertain whether these va-
TABLE 3

Effects of phentolamine on systemic hemodynamic and metabolic responses to exercise

<table>
<thead>
<tr>
<th></th>
<th>HR (beats/min)</th>
<th>BP (mm Hg)</th>
<th>CO (l/min)</th>
<th>PWP (mm Hg)</th>
<th>VO₂ (ml/min)</th>
<th>O₂ extraction (%)</th>
<th>Lactate (mg/dl)</th>
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<td>Control</td>
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<tr>
<td>Lying (n = 8)</td>
<td>87 ± 12</td>
<td>91 ± 7</td>
<td>3.3 ± 0.8</td>
<td>25 ± 5</td>
<td>241 ± 60</td>
<td>44 ± 4</td>
<td>11.2 ± 2.9</td>
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<td>97 ± 15</td>
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<td>263 ± 57</td>
<td>53 ± 9</td>
<td>12.7 ± 2.9</td>
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<td>95 ± 11</td>
<td>5.3 ± 1.9</td>
<td>25 ± 7</td>
<td>620 ± 222</td>
<td>69 ± 5</td>
<td>23.6 ± 5.2</td>
<td>20.9 ± 10.6</td>
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<tr>
<td>Maximal exercise (n = 8)</td>
<td>123 ± 19</td>
<td>95 ± 11</td>
<td>6.0 ± 2.8</td>
<td>28 ± 7</td>
<td>754 ± 354</td>
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<tr>
<td>Lying</td>
<td>88 ± 7</td>
<td>82 ± 6c</td>
<td>3.8 ± 1.1b</td>
<td>19 ± 10b</td>
<td>234 ± 54</td>
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<td>94 ± 9</td>
<td>82 ± 8c</td>
<td>3.3 ± 1.0</td>
<td>21 ± 10</td>
<td>268 ± 65</td>
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<tr>
<td>Maximal exerciseA</td>
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<td>90 ± 11b</td>
<td>6.5 ± 3.3</td>
<td>27 ± 7</td>
<td>756 ± 365</td>
<td>70 ± 7c</td>
<td>28.1 ± 12.4</td>
<td>17.5 ± 10.0c</td>
</tr>
</tbody>
</table>

Abbreviations as in table 1.

A Measured at identical work times as during control exercise.

b p < .05 compared with control.

c p < .01 compared with control.

soconstrictor mechanisms are beneficial or deleterious. In patients with heart failure, exercise activates the sympathetic nervous system much more intensively than at rest. From the standpoint of blood flow to working skeletal muscle, this activation on the one hand serves to sustain muscle perfusion pressure, a key determinant of muscle flow. However, this activation also exerts vasoconstrictor influences on arterioles in working muscle and thereby may interfere with the other key determinant of muscle flow, muscle vasodilation.

Determining which of these effects is dominant has major clinical as well as scientific importance. If activa-

TABLE 4

Effects of phentolamine on leg hemodynamic and metabolic responses to exercise

<table>
<thead>
<tr>
<th></th>
<th>Leg flow (l/min)</th>
<th>Leg VO₂ (ml/min)</th>
<th>Leg resistance (units)</th>
<th>Leg O₂ extraction (%)</th>
<th>Femoral venous lactate (mg/dl)</th>
<th>Venous-arterial lactate difference (mg/dl)</th>
<th>Leg lactate release (mg/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lying (n = 8)</td>
<td>0.4 ± 0.1</td>
<td>26 ± 7</td>
<td>242 ± 64</td>
<td>45 ± 11</td>
<td>12.1 ± 3.6</td>
<td>0.9 ± 2.2</td>
<td>4 ± 8</td>
</tr>
<tr>
<td>Bike (n = 8)</td>
<td>0.4 ± 0.1</td>
<td>32 ± 13</td>
<td>237 ± 62</td>
<td>58 ± 13</td>
<td>13.0 ± 3.0</td>
<td>0.3 ± 2.1</td>
<td>2 ± 7</td>
</tr>
<tr>
<td>Submaximal exercise (n = 5)</td>
<td>2.7 ± 1.7</td>
<td>358 ± 236</td>
<td>46 ± 25</td>
<td>78 ± 7</td>
<td>32.4 ± 5.0</td>
<td>8.9 ± 4.6</td>
<td>154 ± 158</td>
</tr>
<tr>
<td>Maximal exercise (n = 8)</td>
<td>2.8 ± 2.0</td>
<td>365 ± 276</td>
<td>37 ± 25</td>
<td>78 ± 9</td>
<td>43.9 ± 20.1</td>
<td>13.3 ± 4.4</td>
<td>316 ± 212</td>
</tr>
<tr>
<td>Phentolamine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lying</td>
<td>0.5 ± 0.2c</td>
<td>20 ± 5c</td>
<td>168 ± 55c</td>
<td>25 ± 10c</td>
<td>11.6 ± 3.1</td>
<td>1.1 ± 1.6</td>
<td>6 ± 9</td>
</tr>
<tr>
<td>Bike</td>
<td>0.5 ± 0.1b</td>
<td>35 ± 8</td>
<td>174 ± 62c</td>
<td>47 ± 12c</td>
<td>12.7 ± 4.2</td>
<td>2.1 ± 2.2</td>
<td>11 ± 14</td>
</tr>
<tr>
<td>Submaximal exerciseA</td>
<td>2.6 ± 1.4</td>
<td>347 ± 187</td>
<td>36 ± 17</td>
<td>77 ± 5</td>
<td>28.3 ± 3.1b</td>
<td>7.8 ± 1.8</td>
<td>164 ± 108</td>
</tr>
<tr>
<td>Maximal exerciseA</td>
<td>2.7 ± 1.9</td>
<td>367 ± 258</td>
<td>33 ± 18b</td>
<td>77 ± 7</td>
<td>39.9 ± 16.6</td>
<td>11.9 ± 5.4</td>
<td>327 ± 191</td>
</tr>
</tbody>
</table>

A Measured at identical work times as during control exercise.

b p < .05 compared with control.

c p < .01 compared with control.
the balance between these two competing influences is such that constrictor influences are markedly attenuated. However, abnormally high levels of vasoconstrictor activity, as occur in heart failure, may be sufficient to interfere with metabolic vasodilation and thereby impair blood flow to working skeletal muscle.

In this study we sought to investigate this possibility by examining the effect of \( \alpha \)-adrenergic blockade on vascular resistance, blood flow, and lactate release in the leg during maximal exercise in patients with heart failure. Leg resistance and blood flow were used as indexes of skeletal muscle resistance and flow, respectively; flow to nonmuscular tissue makes up only a small portion of leg blood flow during exercise. Systemic and leg oxygen uptake and leg lactate release were used as indexes of the adequacy of oxygen delivery to working muscle. To evaluate changes in these variables during exercise, the variables were compared at identical work times. Exercise level influences muscle blood flow and metabolism. Therefore, comparison of data at different work times would leave uncertain whether any change that is observed is caused by \( \alpha \)-adrenergic blockade or by differences in workload.

Two forms of \( \alpha \)-adrenergic blockade were used: prazosin and phentolamine. Prazosin in the dosages used has previously been shown to produce \( \alpha_1 \)-adrenoceptor blockade. Phentolamine produces both \( \alpha_1 \)- and \( \alpha_2 \)-adrenoceptor blockade. We chose a dose of phentolamine exceeding dosages previously shown to produce leg \( \alpha \)-adrenergic blockade; we considered it unreasonable to burden the patients with additional studies to titrate the dose in each patient. Regional phentolamine was used for several reasons. First, with this approach we sought to minimize the effect on arterial blood pressure during exercise so as to alter muscle perfusion pressure as little as possible. This goal was largely achieved, since mean blood pressure at peak exercise decreased only slightly with phentolamine from 95 \( \pm \) 11 to 90 \( \pm \) 11 mm Hg. In contrast, prazosin decreased mean blood pressure at peak exercise from 101 \( \pm \) 20 to 87 \( \pm \) 22 mm Hg. Second, we wished to block \( \alpha_2 \)-receptors because there is evidence that these receptors may also mediate vasoconstrictor influences. Third, use of phentolamine permitted us to alternate control and interventional studies so as to avoid any bias that might result from obtaining all control studies first. Prazosin was used to examine blockade of the sympathetic nervous system with presynaptic \( \alpha_2 \)-receptors intact. In addition, phentolamine is relatively transitory in its effect; after a 5 mg bolus injection of phentolamine in normal subjects, hemodynamic variables often return to baseline within 30 min. In this study, all measurements were made within 20 min of phentolamine administration in seven patients and by 24 min in the remaining patient. Nevertheless, it is possible that the degree of \( \alpha \)-adrenergic blockade had begun to wane by the end of exercise. Use of prazosin avoided any concern with dissipation of blockade.

During control exercise, all patients developed metabolic changes suggesting impaired blood flow to working skeletal muscle. Specifically, patients were limited by fatigue at reduced maximum oxygen uptakes of 12.6 \( \pm \) 4.3 ml/min/kg, the normal maximum oxygen uptake being in excess of 20 to 25 ml/min/kg. The leg oxygen extraction and leg lactate release noted at maximum exercise were markedly increased above levels observed in normal subjects at comparable workloads. The limb vascular resistance noted at maximum exercise was also higher than levels observed by us in patients with normal exercise capacity, suggesting reduced limb vasodilation.

\( \alpha \)-Adrenergic blockade with both prazosin and phentolamine reduced systemic and limb vascular resistance at rest. With phentolamine, leg vasodilation exceeded systemic vasodilation, consistent with greater regional than systemic vasodilation. These findings serve to reinforce prior observations indicating that the sympathetic nervous system is an important mechanism in heart failure for sustaining resting arterial blood pressure. \( \alpha \)-Adrenergic blockade was also accompanied by improved pump function at rest, as shown by a reduction in the pulmonary wedge pressure and an increase in the cardiac output.

Of greater interest, however, were the changes during exercise. At peak exercise, prazosin decreased systemic vascular resistance by 25 \( \pm \) 14\% accompanied by a substantial drop in mean arterial pressure. Phentolamine also decreased systemic resistance modestly. Thus the sympathetic nervous system also contributed importantly to sustaining blood pressure during exercise and therefore to optimizing muscle perfusion pressure.

Was this beneficial effect of sympathetic nerve activation offset by evidence of vasoconstriction in active muscle and consequent impaired muscle nutritive flow? Our finding that phentolamine had no effect on leg vascular resistance, leg blood flow, and leg oxygen extraction during exercise suggests that substantial \( \alpha \)-adrenergic vasoconstriction was not present in the leg. Prazosin modestly decreased leg resistance. This is not inconsistent with the findings with phentolamine. Pra-
Zosin produced a major drop in arterial blood pressure and no change in leg blood flow or leg oxygen extraction. The accompanying decrease in leg resistance therefore most likely reflected an autoregulatory compensatory response on the part of resistance vessels to keep muscle flow constant.

The metabolic changes noted with α-adrenergic blockade further support the absence of significant vasoconstriction in active muscle. If sympathetic activity did interfere with muscle flow, one would expect that α-adrenergic blockade would increase muscle oxygen uptake and reduce muscle lactate release. In fact, neither prazosin nor phentolamine augmented leg VO₂ during exercise or decreased leg lactate release. Prazosin actually increased leg lactate release at peak exercise, possibly because of adverse effect on muscle perfusion pressure caused by the substantial drop in mean arterial pressure. Maximal VO₂, another variable thought to be determined by the adequacy of muscle oxygen delivery,¹⁻⁵ was also unchanged by α-adrenergic blockade.

Therefore, the overall circulatory effect of sympathetic nerve activation during exercise in patients with heart failure is probably best viewed as beneficial. During exercise, this system helps to increase vascular resistance in nonexercising vascular beds and thereby to optimize the perfusion pressure of critical organs. In active skeletal muscle, sympathetic vasoconstrictor activity appears to be abolished by local metabolic factors.

This conclusion must be viewed within the context of several potential limitations. The use of skeletal muscle glycolysis as a marker of blood flow to working muscle is supported by prior observations that reducing muscle flow augments glycolysis.²⁴,²⁵ Nevertheless, glycolysis occurs normally in well-oxygenated working muscle and is affected by pH and substrate availability.²⁴,²⁵ We cannot totally exclude the possibility that changes in these other variables affected our results, but we doubt that such changes occurred. Second, the adequacy of α-adrenergic blockade was not directly established. To avoid marked hypotension, we chose to administer prazosin in sequential dosages depending on the blood pressure response. Hypotension would have precluded repeat exercise and, more importantly, might have offset a potentially beneficial regional effect of α-adrenergic inhibition by markedly reducing muscle perfusion pressure. It is therefore possible that α-adrenergic blockade was not complete in all patients. Nevertheless, the changes in systemic vascular resistance noted with prazosin suggest substantial blockade. Another possible criticism of our study is that we did not obtain plasma catecholamine levels. Prior studies have uniformly demonstrated higher than normal norepinephrine and epinephrine levels during exercise in similar patients with heart failure.⁸,⁹ Therefore it is likely that both sympathetic nerve activity and adrenal activation were increased in all of our patients.

A final limitation of this study is that it does not provide direct information about regional distribution of flow within skeletal muscle. Norepinephrine and sympathetic nerve activation not only produce α-adrenergically mediated vasoconstriction but also β-adrenergically mediated vasodilation after α-adrenergic blockade.³⁶,³⁷ The interaction between these two effects may play an important role in microcirculatory regulation during exercise.³⁷ For example, Nellis et al.³⁸ have demonstrated that α-adrenergic stimulation may actually enhance oxygen delivery to ischemic skeletal muscle by optimizing flow distribution. A comprehensive understanding of the impact of sympathetic activation on skeletal muscle in patients with heart failure must include attention to such issues. Other important related issues include the role of epinephrine in heart failure, a hormone with more pronounced β-adrenergic effects than norepinephrine, and the role of changes in vascular adrenergic receptors. From a clinical standpoint, it is important to address the effects of pharmacologic agents on the skeletal muscle vasculature. As an example, β-adrenergic blockade could exacerbate vasoconstriction in skeletal muscle by blocking β-adrenergically mediated vasodilation. However, these issues were beyond the scope of this study.

To our knowledge, this study represents the first to examine the effects of α-adrenergic blockade on limb flow and metabolism during maximal exercise in patients with heart failure. Nevertheless, our findings and conclusions are consistent with several prior observations. Zelis et al.⁶ examined the effect of α-adrenergic blockade on forearm blood flow and forearm VO₂ during forearm exercise in patients with heart failure. Blockade had no effect on either variable. Rubin et al.⁹ examined the effect of prazosin on systemic lactate levels during upright maximal bicycle exercise in patients with heart failure. These investigators also failed to observe any change in either lactate levels or exercise duration with prazosin. Finally, our conclusion that local metabolic factors abolished sympathetic vasoconstriction in the active muscles of our patients is supported by a number of observations in normal human subjects and experimental animals indicating that the constrictor response to sympathetic nerve activation and/or norepinephrine administration in
skeletal muscle is significantly attenuated during exercise.10, 11, 19, 20

The findings of this study have important clinical implications. The overall effect of sympathetic nerve activation during exercise in patients with heart failure appears to be beneficial when viewed from the standpoint of active skeletal muscle. This activation augments muscle perfusion pressure without affecting vasodilation in active muscle. Administration of α-adrenergic agents to such patients for the purposes of improving muscle blood flow and thereby relieving muscular fatigue is therefore not likely to be of value. This conclusion is consistent with the findings of two recent double-blind studies, which indicated that long-term prazosin therapy does not improve the maximal exercise capacity of patients with heart failure20, 21; maximal exercise capacity in such patients is thought to be determined by the adequacy of blood flow to working skeletal muscle.1, 4, 5

In summary, our results suggest that the sympathetic nervous system helps to sustain arterial blood pressure both at rest and during exercise in patients with chronic heart failure and that this beneficial effect is not associated with adverse effects on blood flow to working skeletal muscle.

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