Exercise intolerance in patients with chronic heart failure: role of impaired nutritive flow to skeletal muscle

JOHN R. WILSON, M.D., JACK L. MARTIN, M.D., DAVID SCHWARTZ, M.D., AND NANCY FERRARO, R.N.

ABSTRACT  The maximal exercise capacity of patients with chronic heart failure is frequently reduced. It has recently been suggested that this exercise intolerance is primarily caused by inadequate nutritive flow to working skeletal muscle, since patients with heart failure have reduced cardiac outputs, early increases in lactate concentration, and augmented limb O_2 extraction during exercise. However, it has yet to be directly demonstrated that perfusion of working skeletal muscle is impaired during upright maximal exercise in such patients.

Accordingly, this study was undertaken to determine whether blood flow in skeletal muscle is reduced during maximal exercise in patients with chronic heart failure and to investigate whether maximal exercise capacity in such patients correlates with the adequacy of flow to skeletal muscle.

Methods

Patients.  Twenty-three sedentary men with a mean age of 50 years (range 26 to 69) were studied. These patients were divided into three groups according to the maximum O_2 uptake (VO_2max) achieved during upright bicycle exercise: group A, >20 ml/min/kg (seven patients); group B, 15 to 18 ml/min/kg (eight patients); and group C, <14 ml/min/kg (eight patients). Patients in group A were considered to have exercise capacity within the normal range for sedentary individuals, while those in groups B and C were considered to have moderate and severe exercise impairment, respectively. Group A consisted of one normal subject, two patients with mild mitral stenosis, one patient with mitral regurgitation, and three patients with left ventricular dysfunction caused by idiopathic cardiomyopathy.

All group B and C patients had left ventricular dysfunction caused by idiopathic cardiomyopathy (n = 6) or by coronary artery disease (n = 10). All patients with left ventricular dysfunction, including those in group A, had documented histories of heart failure, left ventricular ejection fractions ≤35%, and were taking digoxin and diuretics. None of the patients in the study had peripheral edema, pulmonary rales, ascites, anginal symptoms, chronic lung disease, intermittent claudication, or reduced pulses in the legs. All patients had comparable ages.
weights, and body surface areas (table 1). The protocol was approved by the Human Investigation Review Committee of our institution. All patients gave written informed consent to the study. Data from seven of the patients have been reported in a previous study in which the effects of hydralazine on leg flow and metabolism were examined.7

Protocol. 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 bicycle ergometer (Monarch), beginning at a workload of 20 W. Every 3 min the workload was increased by 20 W to symtomatic maximum. All exercise tests were performed at least 4 hr after meals.

The following morning a Swan-Ganz catheter was inserted via an antecubital vein and positioned in the pulmonary artery. A short polyethylene catheter was inserted into a radial artery. A No. 5F thermodilution catheter was inserted percutaneously into the left femoral vein and advanced 15 to 16 cm anterograde into the iliac vein.

Thirty minutes after instrumentation, hemodynamic measurements were made and blood samples were obtained from the radial artery and femoral vein for determination of O2 saturation and lactate concentration and from the pulmonary artery for determination of O2 saturation. Femoral venous blood flow was measured in triplicate. Respiratory gases were measured with a Beckman Metabolic Cart equipped with O2 and CO2 analyzers and a turbine volume transducer. The patient then mounted the bicycle and was allowed to equilibrate for 5 min, after which all measurements were repeated.

Respiratory gas measurements were made continuously while the patient exercised. Blood sampling and hemodynamic measurements were repeated at the end of each exercise stage and at peak exercise. In one patient blood sampling from the femoral vein during exercise was not performed because of technical problems.

Leg blood flow. Leg blood flow was determined as previously described.7 In brief, femoral venous flow was measured with a 50 cm No. 5F thermodilution catheter with the thermistor at 2 cm and injection port at 12 cm. Flow was determined by rapid injection of a 2.5 ml iced dextrose bolus injected into a commercially available thermodilution catheter (Elecath). Output curves were displayed on a strip-chart recorder to ensure an exponential decay curve. Flow determined by this system correlated closely with known flow rates (0.2 to 6.0 liters/min) (r = .99) when evaluated in a closed-loop system in which 37°C water was continuously circulated by a roller pump through 7 mm polyethylene tubing.

The coefficient of variation of duplicate flow measurements made sequentially in patients during the same exercise test was 9 ± 10% at rest and 16 ± 12% during exercise (± SD). This variation was in part caused by normal phasic alterations in flow. Therefore flow measurements were routinely made every 30 sec after the first 30 sec of an exercise stage. Measurements at any given stage were then averaged. In four patients, two exercise tests were performed 2½ hr apart to evaluate the reproducibility of such averaged flow measurements. The coefficient of variation of repeated flow measurements was 16 ± 10% (n = 14). Averaged group flow measurements made during the first and second exercise periods were reproducible: resting (0.35 ± 0.05 vs 0.34 ± 0.03 liter/min), submaximal exercise (2.64 ± 1.40 vs 2.52 ± 1.06 liters/min), and maximal exercise (3.05 ± 1.00 vs 3.00 ± 1.24 liters/min).

We have previously demonstrated a close correlation between leg blood flow measured by this technique and systemic VO2.7 The measured leg blood flow levels observed in this study are comparable to those reported for other methods.6-12 The validity of using the thermodilution technique to measure leg blood flow during upright bicycle exercise has also been confirmed by other investigators.10

Measured variables. Hemoglobin concentration was measured by Coulter counter; hemoglobin O2 saturation was measured with a co-oximeter (Instrumentation Laboratories) precalibrated with human blood. Blood O2 content was calculated as the product of hemoglobin, 1.34 ml O2/g of hemoglobin, and percent O2 saturation. Oxygen extraction was calculated as the ratio of the arteriovenous O2 difference and arterial O2 content. Cardiac output was calculated from the Fick principle as VO2/arteriovenous O2 difference. Blood for lactate determination was deproteinized with cold perchloric acid and assayed with a spectrophotometric technique.13 Normal resting values for this technique in our laboratory are 3 to 12 mg/dl. Leg vascular resistance was calculated as (mean arterial pressure − femoral venous pressure)/leg blood flow. Leg O2 consumption was calculated as the product of femoral flow and the arteriovenous O2 difference across the leg. Systemic vascular resistance was calculated as (mean blood pressure − right atrial pressure)/cardiac output. During exercise, the right atrial pressure was assumed to remain the same as at rest.

Statistical analysis. All values are expressed as mean ± SEM. Intergroup differences between measurements at rest and at peak exercise were analyzed by one-factor analysis of variance and the modified t test.14 For each group, linear regression analysis was used to determine the relation between each variable and workload. To determine significant intergroup differences between these responses, comparisons of regression line slopes and intercepts were performed.15 Comparison of resistance and O2 extraction data was performed only on data obtained during exercise. The square of the correlation coefficient from all curves exceeded 0.7, supporting the linearity of these curves. Minimal acceptable significance for all comparisons was determined by the Bonferroni method.14

Results

Results are summarized in tables 2 to 4 and figures 1 to 4. In the figures, values are given as mean ± SEM at each workload and are then connected. The resultant

<table>
<thead>
<tr>
<th>TABLE 1</th>
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<tbody>
<tr>
<td>Clinical characteristics of the patients</td>
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<tr>
<td><strong>Age</strong> (yr)</td>
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<tr>
<td>Group A (n = 7)</td>
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<td>Group B (n = 8)</td>
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<td>Group C (n = 8)</td>
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</table>

Ao Hb = aortic hemoglobin.

Statistical comparisons: *p < .025 vs A; **p < .025 vs B.
TABLE 2
Comparison of systemic hemodynamic and metabolic responses to exercise in groups A, B, and C

<table>
<thead>
<tr>
<th>Group</th>
<th>HR (beats/min)</th>
<th>BP (mm Hg)</th>
<th>PWP (mm Hg)</th>
<th>Cardiac output (liters/min)</th>
<th>SVR (units)</th>
<th>O₂ extraction (%)</th>
<th>Arterial lactate (mg/dl)</th>
<th>VO₂ (ml/min)</th>
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<tbody>
<tr>
<td>Group A</td>
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<tr>
<td>Supine</td>
<td>79 ± 7</td>
<td>89 ± 4</td>
<td>11 ± 2</td>
<td>4.9 ± 0.2</td>
<td>18.2 ± 0.7</td>
<td>28 ± 1</td>
<td>—</td>
<td>245 ± 8</td>
</tr>
<tr>
<td>Bike</td>
<td>87 ± 6</td>
<td>90 ± 5</td>
<td>10 ± 2</td>
<td>4.3 ± 0.2</td>
<td>22.9 ± 1.7</td>
<td>37 ± 2</td>
<td>10 ± 1</td>
<td>271 ± 11</td>
</tr>
<tr>
<td>Max Ex</td>
<td>155 ± 7</td>
<td>121 ± 5</td>
<td>29 ± 7</td>
<td>12.4 ± 1.0</td>
<td>10.1 ± 0.4</td>
<td>74 ± 2</td>
<td>57 ± 6</td>
<td>1685 ± 141</td>
</tr>
<tr>
<td>Group B</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Supine</td>
<td>83 ± 4</td>
<td>86 ± 4</td>
<td>22 ± 3³</td>
<td>3.9 ± 0.4</td>
<td>22.3 ± 2.3</td>
<td>40 ± 4</td>
<td>—</td>
<td>256 ± 7</td>
</tr>
<tr>
<td>Bike</td>
<td>86 ± 5</td>
<td>86 ± 5</td>
<td>16 ± 3</td>
<td>3.5 ± 0.3</td>
<td>25.8 ± 3.0</td>
<td>48 ± 4</td>
<td>11 ± 1</td>
<td>286 ± 6</td>
</tr>
<tr>
<td>Max Ex</td>
<td>124 ± 9²</td>
<td>103 ± 7</td>
<td>35 ± 4</td>
<td>8.7 ± 0.9²</td>
<td>12.7 ± 1.4</td>
<td>80 ± 2</td>
<td>45 ± 5</td>
<td>1190 ± 61²</td>
</tr>
<tr>
<td>Group C</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Supine</td>
<td>88 ± 4</td>
<td>87 ± 2</td>
<td>25 ± 3³</td>
<td>3.2 ± 0.3³</td>
<td>27.7 ± 3.6</td>
<td>47 ± 4³</td>
<td>—</td>
<td>241 ± 13</td>
</tr>
<tr>
<td>Bike</td>
<td>97 ± 6</td>
<td>85 ± 3</td>
<td>20 ± 4</td>
<td>3.0 ± 0.3³</td>
<td>31.0 ± 4.5</td>
<td>57 ± 3³</td>
<td>14 ± 2</td>
<td>274 ± 20</td>
</tr>
<tr>
<td>Max Ex</td>
<td>124 ± 8³</td>
<td>99 ± 4³</td>
<td>34 ± 3</td>
<td>5.5 ± 0.7³,²</td>
<td>21.2 ± 3.7³</td>
<td>83 ± 2³</td>
<td>34 ± 4³</td>
<td>751 ± 85³,²</td>
</tr>
</tbody>
</table>

Max Ex = maximum exercise.
Statistical comparisons: ³p < .025 vs A; ²p < .025 vs B.

Curves illustrate trends in the raw data, not the actual lines used in intergroup comparisons. Patients in each group achieved different maximal exercise loads. Mean values shown at the highest workload in each group therefore do not include data from all patients.

All patients terminated exercise primarily because of severe leg fatigue. Dyspnea was also present in some of the patients but was not reported by these patients to be a limiting factor.

**Systemic hemodynamic and metabolic responses to exercise.** Upright on the bicycle before exercise, patients in all three groups had similar systemic VO₂ values (A, 271 ± 11; B, 286 ± 6; C, 274 ± 20 ml/min) and arterial lactate concentrations (A, 10 ± 1; B, 11 ± 1; C, 14 ± 2 mg/dl). With exercise, VO₂ rose linearly with increasing work in all three groups, with the VO₂ attained at any given workload being similar in all groups (figure 1). However, as the severity of exercise intolerance increased from group A to C, there was a progressive decrease in cardiac output and increase in systemic O₂ extraction and arterial lactate concentration at any given workload (figures 1 and 2) as well as a progressive decrease in maximal VO₂ (A, 1685 ± 141 ml/min; B, 1190 ± 61; C, 751 ± 85 ml/min) and maximal cardiac output (A, 12.4 ± 1.0; B, 8.7 ± 0.9; C, 5.5 ± 0.7 liters/min) (figure 3).

The mean blood pressure during exercise was reduced in patients in groups B and C compared with that in patients in group A (figure 2). In group B patients this reduction was associated with a decrease in systemic vascular resistance similar to that noted in group A patients (figure 2). In contrast, group C patients had a smaller decrease in vascular resistance at any given workload compared with the other two groups (figure 2).

**Leg hemodynamic and metabolic responses to exercise.** At supine and upright rest, blood flow, resistance, O₂ extraction, and VO₂ in the leg were similar in all three groups (table 3). However, femoral lactate concentration was significantly higher in patients in group C (17 ± 2 mg/dl) than that in patients in the other two groups (A, 11 ± 1; B, 11 ± 1 [both p < .025 vs group C]).

With exercise, leg VO₂ rose linearly with increasing workload in all three groups, with the VO₂ attained at any given workload being similar in all groups (figure 4). Leg blood flow also increased linearly with increasing workload in all groups (figure 5). However, as the severity of exercise intolerance increased from group A to C, there was a progressive decrease in leg blood flow. In group A the relation between flow and workload (flow = 0.039 W + 0.79 liter/min) was comparable to the relation previously noted in normal subjects by Wahren, Pernow, and co-workers¹¹,¹² (flow = 0.0375 watts + 0.89 liter/min). Leg blood flow was significantly lower in group B and C patients at any given workload, with group B patients having average flow reductions of 20% and group C patients having reductions averaging 40%. Maximal leg blood flow also decreased progressively with increasing exercise intolerance (figure 3).

This progressive reduction in leg blood flow was associated with progressive reductions in maximal leg VO₂ (A, 564 ± 49; B, 403 ± 41; C, 213 ± 35 ml/min) (figure 3) and earlier increases in femoral venous lactate concentration (figure 4). In addition, increasing exercise intolerance was associated with heightened...
leg O₂ extraction. In all three groups leg O₂ extraction increased most markedly with the onset of exercise; thereafter it tended to plateau at approximately 70% in group A compared with 80% in group B and 85% in group C (both p < .01 vs group A). Group C also tended to have higher leg O₂ extraction than group B (p < .04), although this difference did not reach statistical significance with the Bonferroni statistic.

In all three groups exercise produced a marked reduction in leg vascular resistance (figure 5). However, leg vascular resistance was higher in group C patients than in the other two groups. Moreover, the minimal leg resistance achieved was higher in group C patients (62 ± 8 units) than in the other two groups (A, 28 ± 1; B, 37 ± 6 units [both p < .025 vs group C]).

**Relation of termination of exercise to metabolic changes.** Exercise was terminated in all patients by severe leg fatigue. At exhaustion, patients in all three groups had similarly elevated femoral-arterial lactate gradients (A, 15.4 ± 2.6; B, 18.3 ± 3.5; C, 19.2 ± 3.6 mg/dl). Leg O₂ extraction was also markedly elevated in all groups, although to a greater extent in group C (89 ± 1%) than in groups A or B (A, 80 ± 2%; B, 83 ± 3%) (p < .025). Femoral venous lactate concentrations tended to be higher in group A, but not significantly (A, 73 ± 7; B, 64 ± 7; C, 52 ± 3 mg/dl).

At any given workload, patients who terminated exercise exhibited significantly higher levels of leg O₂ extraction and femoral venous lactate concentrations than patients who were able to continue exercising (table 4). Moreover, 13 of the 15 group B and C patients had both higher leg O₂ extraction and femoral venous lactate concentration at termination of exercise than did nonfatigued patients exercising at the same workload.

**Discussion**

Patients with congestive heart failure frequently have limited exercise capacity, even when they are asymptomatic at rest. It is becoming an increasingly common practice to quantify this exercise intolerance by maximal exercise testing. Investigators are also widely using maximal exercise testing to evaluate serially the effects of drugs on exercise capacity in patients with heart failure. Therefore it is of major interest to determine the factor or factors responsible for the reduced maximal exercise capacity of such patients.

In this study we investigated the hypothesis that this reduced exercise capacity is primarily caused by inadequate perfusion of skeletal muscle and resultant muscular fatigue. Leg blood flow and O₂ extraction were used as indexes of skeletal muscle perfusion, since flow to nonmuscular tissue makes up only a very small portion of leg blood flow during exercise. Femoral venous lactate concentration was used to assess nutritional flow to working muscle. Prior studies have demonstrated that a reduction in nutritional flow to working muscle causes increased lactate production. Our results strongly suggest that nutritive flow to skeletal muscle is impaired in patients with chronic heart failure and reduced maximal exercise capacity. In addition, our results suggest that the level of exercise intolerance is a direct function of the degree of impairment of nutrient flow. In group A patients, all of whom had VO₂ max in the normal range for sedentary individuals, exercise was associated with changes in cardiac output, leg blood flow, leg O₂ extraction, and femoral venous lactate concentration comparable to
those reported previously for normal sedentary subjects. In contrast, group B patients, who had moderately reduced \( \text{VO}_2\text{max} \), were limited by leg fatigue and exhibited reductions in cardiac output and leg blood flow, suggesting reduced perfusion of skeletal muscle. These flow abnormalities were accompanied by heightened leg \( \text{O}_2 \) extraction and early leg lactate release, consistent with inadequate nutritive flow to skeletal muscle and increased dependence on anaerobic metabolic processes for energy production. Group C patients, who had more severe exercise intolerance, were also limited by leg fatigue and exhibited similar but more severe flow and metabolic abnormalities than those in group B patients.

The association noted between termination of exercise and leg metabolism further supports a close relationship between exercise capacity and the adequacy of nutritive flow to skeletal muscle. Specifically, in all three groups, termination of exercise was invariably caused by severe leg fatigue and appeared to be associated with achievement of a critical level of marked leg \( \text{O}_2 \) extraction and leg lactate release. Moreover, exhaustion in group B and C patients was characteristically associated with higher leg \( \text{O}_2 \) extractions and higher femoral venous lactate concentrations when compared with nonfatigued patients exercising at the same workloads. Leg \( \text{O}_2 \) extraction at a certain work intensity is determined by the balance between muscle \( \text{O}_2 \) delivery and muscle \( \text{O}_2 \) consumption. Systemic, leg, and presumably muscle \( \text{O}_2 \) consumption at any

**FIGURE 2.** Cardiac output, mean arterial blood pressure, systemic \( \text{O}_2 \) extraction, and systemic vascular resistance (SVR) in patients in groups A, B, and C. Mean ± SEM at each workload is given and then connected to illustrate trends in mean data. The statistical results of intergroup comparisons are shown on each panel.

**FIGURE 3.** Relationships among systemic \( \text{VO}_2\), cardiac output, leg blood flow, and leg \( \text{VO}_2 \) at maximal exercise and the maximal workload achieved. Individual data points are given for each patient but with different symbols for groups A, B, and C.
given workload was similar in all three groups of patients. Therefore the higher leg \( \text{O}_2 \) extraction noted in exhausted patients suggests that exhaustion was associated with more severe muscle underperfusion than in nonexhausted patients. The higher femoral venous lactate concentrations noted in the exhausted patients further support this conclusion.

These findings provide the first direct evidence that patients with chronic heart failure are limited during maximal exercise primarily by inadequate nutritive flow to skeletal muscle. However, our findings are consistent with a number of prior observations. Weber et al.\(^3\) recently reported a direct relationship in patients with chronic heart failure between maximal exercise capacity and their cardiac output and mixed venous lactate responses to exercise; they proposed that exercise intolerance was therefore caused by inadequate muscle perfusion. Donald et al.\(^5\) and others\(^24\) have noted heightened leg \( \text{O}_2 \) extraction and femoral venous lactate concentrations during supine moderate exercise in patients with heart failure, and suggested that skeletal muscle perfusion was reduced. Zelis et al.\(^25,26\) have demonstrated that forearm blood flow is reduced during forearm exercise in patients with heart failure.

TABLE 3
Comparison of leg hemodynamic and metabolic responses to exercise in groups A, B, and C

<table>
<thead>
<tr>
<th></th>
<th>Leg flow (liters/min)</th>
<th>Leg resistance (units)</th>
<th>Leg ( \text{O}_2 ) extraction (%)</th>
<th>Arteriovenous ( \text{O}_2 ) difference (ml/dl)</th>
<th>Leg ( \text{VO}_2 ) (ml/min)</th>
<th>Femoral venous lactate (mg/dl)</th>
<th>Femoral-arterial lactate (mg/dl)</th>
</tr>
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<tbody>
<tr>
<td>Group A</td>
<td></td>
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<tr>
<td>Supine</td>
<td>0.28 ± 0.02</td>
<td>298 ± 39</td>
<td>32 ± 2</td>
<td>5.50 ± 0.37</td>
<td>16 ± 1</td>
<td></td>
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</tr>
<tr>
<td>Bike</td>
<td>0.26 ± 0.03</td>
<td>348 ± 34</td>
<td>59 ± 3</td>
<td>10.40 ± 0.47</td>
<td>27 ± 2</td>
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</tr>
<tr>
<td>Max Ex</td>
<td>4.00 ± 0.30</td>
<td>28 ± 1</td>
<td>80 ± 2</td>
<td>14.07 ± 0.51</td>
<td>564 ± 49</td>
<td>73 ± 7</td>
<td>15.4 ± 2.6</td>
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<tr>
<td>Group B</td>
<td></td>
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</tr>
<tr>
<td>Supine</td>
<td>0.21 ± 0.02</td>
<td>338 ± 13</td>
<td>37 ± 4</td>
<td>6.72 ± 0.76</td>
<td>14 ± 2</td>
<td></td>
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</tr>
<tr>
<td>Bike</td>
<td>0.24 ± 0.03</td>
<td>353 ± 29</td>
<td>55 ± 6</td>
<td>9.96 ± 1.37</td>
<td>21 ± 3</td>
<td>11 ± 1</td>
<td>0.4 ± 1.0</td>
</tr>
<tr>
<td>Max Ex</td>
<td>2.60 ± 0.40(^\text{A})</td>
<td>37 ± 6</td>
<td>83 ± 3</td>
<td>15.07 ± 1.07</td>
<td>403 ± 41(^\text{A})</td>
<td>64 ± 7</td>
<td>18.3 ± 3.5</td>
</tr>
<tr>
<td>Group C</td>
<td></td>
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</tr>
<tr>
<td>Supine</td>
<td>0.27 ± 0.02</td>
<td>266 ± 17</td>
<td>45 ± 6</td>
<td>7.43 ± 0.81</td>
<td>20 ± 3</td>
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</tr>
<tr>
<td>Bike</td>
<td>0.28 ± 0.03</td>
<td>273 ± 20</td>
<td>63 ± 5</td>
<td>10.32 ± 0.69</td>
<td>29 ± 5</td>
<td>17 ± 2(^\text{B})</td>
<td>2.6 ± 0.6</td>
</tr>
<tr>
<td>Max Ex</td>
<td>1.40 ± 0.20(^\text{A},\text{B})</td>
<td>62 ± 8(^\text{A})</td>
<td>89 ± 1(^\text{A})</td>
<td>14.90 ± 0.68</td>
<td>213 ± 35(^\text{A},\text{B})</td>
<td>52 ± 3</td>
<td>19.2 ± 3.6</td>
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<table>
<thead>
<tr>
<th></th>
<th>Femoral venous lactate (mg/dl)</th>
<th>Femoral-arterial lactate (mg/dl)</th>
</tr>
</thead>
</table>

Max Ex = maximum exercise.
Statistical comparisons: \(^*p < .025\) vs A; \(^*p < .025\) vs B.

FIGURE 4. Leg \( \text{VO}_2 \), femoral venous lactate concentration, leg \( \text{O}_2 \) extraction, and femoral-arterial lactate gradients in patients in groups A, B, and C. Mean ± SEM at each workload is given and then connected to illustrate trends in mean data. The statistical results of intergroup comparisons are shown on each panel.
function and vasoconstriction in nonexercising tissues, and vasodilation in working skeletal muscle.\textsuperscript{16} In patients in groups B and C we observed a reduced mean blood pressure during exercise. Since peripheral vasoconstriction during exercise is heightened in patients with heart failure,\textsuperscript{29} this reduction in muscle perfusion pressure was most likely caused by pump dysfunction. Therefore impaired skeletal muscle blood flow in patients with heart failure may be caused in part by cardiac pump dysfunction.

However, we also observed that the decrease in leg vascular resistance in group C patients during exercise was not as great as that in group A and B patients. This finding suggests that the impaired nutritive flow to skeletal muscle in patients with severe exercise intolerance may also be caused in part by impaired vasodilation in working muscle. Previous investigators have also reported impaired vasodilation in working skeletal muscle both in patients with severe heart failure performing forearm exercise\textsuperscript{25} and in dogs with experimentally produced heart failure performing treadmill exercise.\textsuperscript{37}

Other factors that potentially could contribute to the exercise intolerance and metabolic abnormalities noted in the group B and C patients include deconditioning and/or changes in skeletal muscle that increase cellular glycolysis. Marked deconditioning, for example, produces a modest fall in maximal $\mathrm{VO}_2$, mean blood pressure, and cardiac output during exercise.\textsuperscript{29} Factors such as muscle enzymatic activity and substrate availability can definitely alter lactate production in the absence of changes in nutritive flow.\textsuperscript{30, 31} It is possible that deconditioning contributed in part to the exercise tolerance in the group B and C patients. In contrast, enzymatic changes probably did not contribute. If any enzymatic change occurs in skeletal muscle in patients with heart failure, it is likely to involve an increase in oxidative capacity. In patients with peripheral vascular disease, leg blood flow during exercise has been shown to be depressed to a degree similar to that observed in the group B and C patients.\textsuperscript{11} This flow impairment results in increased activity of oxidative enzymes in skeletal muscle, not of glycolytic enzymes.\textsuperscript{32, 33}

Nevertheless, it is important to realize that use of femoral venous lactate concentration as a marker of muscle nutritive flow has limitations, since glycolysis in muscle is influenced not only by changes in nutritive flow but also by other factors such as the relative quantity of red and white fibers and substrate availability.\textsuperscript{30, 31} Blood lactate levels also may not reflect tissue lactate levels, particularly at high tissue levels, be-

![FIGURE 5. Leg blood flow and leg vascular resistance in patients in groups A, B, and C. Mean ± SEM at each workload is given and then connected to illustrate trends in mean data. The statistical results of intergroup comparisons are shown on each panel.](http://circ.ahajournals.org/doi/figure/10.1161/01.HYP.69.3.1085)
cause of impaired translocation of lactate from tissue to blood. Nevertheless, previous studies support the use of lactate levels as a marker of muscle nutritive flow. Moreover, our observation that high femoral venous lactate concentration correlates with low cardiac outputs and high leg VO₂ extraction suggests a direct inverse relation between femoral venous lactate and nutritive flows to muscle.

Another potential limitation of this study is the inclusion of patients with cardiac abnormalities in group A. However, this is unlikely to have influenced our results, since the metabolic responses in this group were within the normal range. Moreover, if only normals had been included in group A, even more dramatic differences between this group and groups B and C might be expected.

One last potential concern relates to the patterns of systemic and leg VO₂ observed at maximal exercise. During maximal exercise in normal, active, and highly motivated subjects, VO₂ reaches a definite plateau beyond which further increments in workload produce no further increments in VO₂. Classically, detection of such a plateau has been used as evidence that nutritive flow reserve in skeletal muscle and the capacity of muscle to extract O₂ are both exhausted. Few of our patients reached a definite plateau in systemic VO₂. This has also been the experience of other investigators. Nevertheless, it is likely that our patients were at the point of reaching a plateau given the regional and systemic metabolic parameters noted at the end of exercise. Furthermore, in those of our patients who continued exercising to higher workloads after the onset of severe leg fatigue, a definite VO₂ plateau has been observed. It is possible that leg VO₂ actually plateaued in our patients but that this plateau was not detected. We have previously noted that leg VO₂ is subject to modest quantitative errors.

Our results therefore indicate that impaired nutritive flow to skeletal muscle is most likely the principal factor responsible for the reduced maximal exercise capacity of patients with heart failure. This conclusion suggests that maximal exercise testing provides an objective method of assessing the capacity of a patient’s circulatory system to perfuse skeletal muscle during exercise. This conclusion also suggests that altered nutritive flow to skeletal muscle may play a role in limiting the exercise capacity of patients during daily activities, at least during strenuous exertion. Therefore investigation of the mechanisms responsible for this impaired nutritive flow are clearly needed to identify methods for treating this abnormality.

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