Relation Between Central and Peripheral Hemodynamics During Exercise in Patients With Chronic Heart Failure

Muscle Blood Flow Is Reduced With Maintenance of Arterial Perfusion Pressure

Martin J. Sullivan, MD, J. David Knight, PhD, Michael B. Higginbotham, MB, and Frederick R. Cobb, MD

We studied the central hemodynamic, leg blood flow, and metabolic responses to maximal upright bicycle exercise in 30 patients with chronic heart failure attributable to severe left ventricular dysfunction (ejection fraction, 24±8%) and in 12 normal subjects. At peak exercise, patients demonstrated reduced oxygen consumption (15.1±4.8 vs. 32.1±9.9 ml/kg/min, p<0.001), cardiac output (8.7±3.2 vs. 18.6±4.4 l/min, p<0.001), and mean systemic arterial blood pressure (116±15 vs. 135±13 mm Hg, p<0.01) compared with normal subjects. Leg blood flow was decreased in patients versus normal subjects at rest and matched submaximal work rates and maximal exercise (2.1±1.9 vs. 6.4±1.4 l/min, all p<0.01). Mean systemic arterial blood pressure was no different in the two groups at rest or at matched submaximal work rates, whereas leg vascular resistance was higher in patients compared with normal subjects at rest, submaximal, and maximal exercise (all p<0.01). Although nonleg blood flow was decreased at rest in patients, it did not decrease significantly during exercise in either group. Peak exercise leg blood flow was related to peak exercise cardiac output in patients (r=0.66, p<0.01) and normal subjects (r=0.67, p<0.01). In patients, leg vascular resistance was not related to mean arterial blood pressure, pulmonary capillary wedge pressure, arterial catecholamines, arterial lactate, or femoral venous pH at rest or during exercise. Compared with normal subjects during submaximal exercise, patients demonstrated increased leg oxygen extraction and lactate production accompanied by decreased leg oxygen consumption. Thus, in patients with chronic heart failure compared with normal subjects, skeletal muscle perfusion is decreased at rest and during submaximal and maximal exercise, and local vascular resistance is increased. Our data indicate that nonleg blood flow and arterial blood pressure were preferentially maintained during exercise at the expense of leg hypoperfusion in our patients. This was associated with decreased leg oxygen utilization and increased leg oxygen extraction when compared to normal subjects, providing further evidence that reduced perfusion of skeletal muscle is important in causing early anaerobic skeletal muscle metabolism during exercise in subjects with this disorder. Although these results do not define the mechanisms responsible for increased leg vascular resistance during exercise in subjects with chronic heart failure, our finding that arterial blood pressure in patients was closely regulated suggests a role for reflex-mediated peripheral vasoconstriction in linking the cardiac output and skeletal muscle blood flow responses to exercise in subjects with this disorder. (Circulation 1989;80:769–781)

Exercise intolerance is a major cause of morbidity in patients with chronic heart failure. Recent studies indicate that early skeletal muscle anaerobic metabolism,1–4 not increased pulmonary capillary wedge pressure, is the primary factor limiting exercise performance in stable ambu-

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latory patients with this disorder. Decreased perfu-
sion of skeletal muscle during exercise is known to
be a powerful stimulus for early anaerobic
metabolism5–7 and has been demonstrated by numer-
ous investigators over the past two decades in
patients with chronic heart failure.8–14 However,
the pathophysiologic basis of decreased muscle
blood flow during isotonic exercise in subjects with
this disorder has not been clearly defined. Wilson et
al15 have suggested that relative arterial hypoten-
sion may be an important factor in reducing periph-
eral blood flow in patients with this disorder, and
studies have demonstrated that hypotension is an
important factor reducing muscle blood flow in
animal models of heart failure.16,17 In contrast,
studies by Zelis et al18 have demonstrated that the
vasodilator response to a number of stimuli is
reduced in patients with heart failure, suggesting
that intrinsic abnormalities in limb vasodilator capa-
city are responsible for peripheral blood flow abnor-
malities. Thus, the relative roles of increased vas-
cular resistance and arterial hypotension in causing
skeletal muscle hypoperfusion during isotonic exer-
cise involving large muscle groups in patients with
chronic heart failure have not been clearly defined.
This distinction may have important therapeutic
implications because vasodilator therapy may cause
a worsening of hypotension and, therefore, may
actually decrease peripheral blood flow during exer-
cise in some patients with chronic heart failure,
which may influence the variable clinical response
to vasodilator therapy in this disorder.13 However,
several studies suggest that improvements in periph-
eral vascular conductance, not changes in arterial
blood pressure, are important in determining the
long-term response to vasodilators19 or exercise training20 in subjects with this disorder.

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The present study was designed to determine the central hemodynamic, metabolic, neuro-
humoral, and leg blood flow (LBF) responses to
maximal upright bicycle exercise in patients with
chronic heart failure and to compare these results
with data obtained from identical testing in a group
of normal volunteers. The study was designed to
determine the relative roles of arterial hypotension
and increased leg vascular resistance in determin-
ing LBF abnormalities, and to examine the distribu-
tion of cardiac output during exercise in patients
with this disorder.

Methods

Patient Group

Thirty-two men and one woman with New York
Heart Association functional Classes I–IV conges-
tive heart failure participated in the study. Due to
technical difficulties, three male patients did not
have LBF measurements and were excluded from
analysis. Of the 30 patients studied, three had New
York Heart Association functional Class I, 12 had
functional Class II, 11 had functional Class III, and
four patients had functional Class IV heart failure.
All subjects had heart failure on the basis of severe
left ventricular dysfunction (ejection fraction,
24±8%; range, 8–36%); 22 had coronary artery
disease and eight had idiopathic dilated cardiomy-
opathy. All subjects were limited by dyspnea or
fatigue during maximal exercise testing, and no
patient had pulmonary rales, claudication, or perip-
eral bruits; 10 patients had mild pedal edema.
Twenty-four of the patients had stable symptoms
for 2 months before study; six patients had increas-
ing symptoms over the previous 2 months but were
stabilized for 72 hours prior to study. Twenty-eight
patients were taking digoxin, and 29 were taking
diuretics. Five patients with severe symptoms (four
Class IV and one Class III) were unable to be
withdrawn from chronic vasodilator therapy (cap-
topril, n=3; nitrates, n=2) prior to study. Four
patients were engaged in regular aerobic exercise
prior to study.

Normal Subjects

Twelve men with normal medical histories and
physical examinations who were on no medications
volunteered to serve as control subjects. All had a
normal electrocardiographic response to a screen-
ing maximal bicycle exercise test. Three subjects
were engaged in regular aerobic exercise.

Study Protocol

All studies were performed under a research
protocol approved by the Institutional Review
Boards at both the Duke University and Durham
Veterans Administration Medical Centers. Twenty-
eight patients and all normal subjects underwent a
familiarization maximal bicycle exercise test with
expired gas analysis 2–14 days prior to the study;
two patients did not. Patients were given their usual
cardiac medications 3 hours before testing, which
was usually at 11:00 A.M. Exercise studies were
performed using an isokinetic bicycle at least 2 hours
after subjects had eaten. All subjects performed
graded exercise with the work rate beginning at 150
kilopond meters (kpm)/min and advancing in 3-
millie of 150 kpm/min to a symptom-limited
maximum. Heart rate was monitored by electrocar-
diography, and arterial blood pressure was measured
by a sphygmomanometer during the familiarization
study and by direct intra-arterial pressure recording
in all subjects during the hemodynamic study. Expired
gases were continuously analyzed in our laboratory
using a Sensormedics (Anaheim, California) 4400
breath-by-breath unit as previously described.20,21

Central Hemodynamics

Twenty-five patients and 10 normal subjects had
a 7F Swan-Ganz catheter positioned in the right
pulmonary artery via an antecubital vein, and all
subjects had a femoral venous catheter and a bra-
chal artery cannula inserted 1 hour before exercise.
Pulmonary and systemic arterial pressures were
recorded continuously, and pulmonary capillary wedge pressure was recorded intermittently at rest and at each workload using Hewlett-Packard transducers, amplifiers, and recorders (Andover, Massachusetts) as previously described.\textsuperscript{20,21} At rest and in the third minute of each workload, blood samples were taken and were immediately chilled in an ice bath. Oxygen content and saturation of arterial, femoral venous, and mixed venous blood samples were measured on a calibrated Instruments Laboratory 282 cooximeter. Arterial and femoral venous blood lactate concentrations were determined with a Calbiochem-Behring rapid lactate kit (San Diego, California). Blood catecholamine levels were determined at rest, submaximal (300 kpm/min), and maximal exercise in arterial samples of 12 patients using high-pressure liquid chromatography.\textsuperscript{22} From 12 normal subjects and 18 patients, arterial and femoral venous blood was drawn for measurement of pH (Instruments Laboratory, model 1303, Lexington, Massachusetts).

**Leg Blood Flow**

In all subjects, LBF was measured with a thermodilution catheter (model 93 A-105-5F, Edwards Laboratory, Santa Ana, California) inserted in the femoral vein 2 cm below the inguinal ligament with the distal thermistor tip positioned 10–12 cm above the inguinal ligament under fluoroscopic guidance as previously described.\textsuperscript{20} The catheter was interfaced with a Gould Statham SP 1435 cardiac output computer (Oxnard, California), and bolus injections of 1–6 ml iced or room temperature saline were used to obtain 2–4 blood flow measurements at rest and in the last 90 seconds of each work rate (which were then averaged). Thermolodulation curves were displayed on the Gould recorder to assure a monophasic curve morphology with exponential decay. Previous studies by Sullivan et al.\textsuperscript{23} have shown a close relation near the line of identity between thermodilution flow measured with this catheter system and the simultaneous paired electromagnetic flow probe measurement in a perfused canine preparation ($r=0.98$, $p<0.001$). Regression of paired averaged determinations from duplicate submaximal exercise studies of six subjects in our laboratory demonstrated an excellent correlation ($r=0.96$, $p<0.001$) with an SEE of 0.44 l/min.\textsuperscript{20}

**Derived Variables**

Cardiac output was determined by the direct Fick technique. Stroke volume was determined by dividing cardiac output by heart rate. Systemic vascular resistance and pulmonary vascular resistance were calculated using standard formulae and are expressed (mm Hg/l/min). Leg vascular resistance (LVR) was calculated as: (mean arterial pressure—right atrial pressure)/LBF and was expressed (mm Hg/l/min). Leg oxygen consumption and lactate production were calculated using the Fick principle. To describe cardiac output distribution during exercise, nonleg blood flow (NLF) was calculated for each individual as: cardiac output—(LBF×2). The percentage of cardiac output distributed to the two legs (%LBF) was determined as: (LBF×2)/cardiac output.

**Statistical Analysis**

Intergroup comparisons of variables were made at rest, 150 kpm/min, 300 kpm/min, and maximal exercise using the Wilcoxon rank sum test. To determine the relation of rest and exercise variables, linear regression analysis was performed using the least-squares method. To determine the rate of change with respect to exercise work rate for selected variables, individual regression equations were derived and the group mean values for slopes and intercepts were compared using the Wilcoxon rank sum test, with $p<0.05$ considered as statistically significant. Group data are expressed as mean±SD.

**Results**

Patients were older than normal subjects (55±10 vs. 45±13 years, $p<0.01$), although the age ranges were similar (patients, 31–76 years; normal subjects, 27–70 years). To examine the effects of this modest age difference, we determined the relation of age and the major physiologic variables at maximal and submaximal exercise (300 · kpm/min) in the two groups. Oxygen consumption ($V_{O_2}$), LBF, and LVR were not closely related to age in patients or in our 12 normal subjects (all $r^2<0.25$, all $p>0.10$) at maximal or submaximal exercise. There were no significant differences in the averaged body weight (71±13 vs. 76±6 kg, $p=NS$) or surface area of the two groups (1.82±0.17 vs. 1.90±0.09 m$^2$, $p=NS$).

**Ventilatory Exercise Response**

The peak exercise work rate was reduced in patients compared to normal subjects (451±136 vs. 887±162 kpm/min, $p<0.001$). All 30 patients completed the 150 kpm/min work rate and 28 completed at least the 300 kpm/min work rate. Peak $V_{O_2}$ (Figure 1, A) was decreased in patients (1.06±0.36 l/min or 15.1±4.8 ml/kg/min) compared to normal subjects (2.42±0.61 l/min or 32.1±9.9 ml/kg/min, both $p<0.001$). Rest $V_{O_2}$ was slightly decreased in patients, and the slope of $V_{O_2}$ versus work rate was decreased in patients compared to normal subjects (the slopes and intercepts of the derived regression equations of variables versus work rate are shown in Table 1). By pairwise comparison, $V_{O_2}$ at submaximal exercise was slightly decreased in patients, although this did not reach statistical significance at 150 kpm/min. Carbon dioxide production ($V_{CO_2}$), respiratory exchange ratio, and ventilation (Figure 1, Panels B–D) in patients all increased at a faster rate during exercise. Maximal values for $V_{CO_2}$ and ventilation were reduced in the patient group, reflecting the attainment of a lower work rate. However, the peak exercise respiratory exchange ratio was 1.36±0.16 in patients and 1.31±0.10 in...
normal subjects (p=0.6), indicating the attainment of maximal or near maximal exercise in both groups.

Central Hemodynamic Exercise Response

Heart rate (Figure 2, Panel A) was increased in patients at rest compared to normal subjects and reached a lower value at maximal exercise, although the slope of the increase was not different in the two groups. Cardiac output (Figure 2, Panel B) was decreased in the patient group at rest, submaximal, and maximal exercise; the slope of the increase in cardiac output with exercise was also markedly decreased in patients. Maximal cardiac output was 18.7±6.4 l/min in normal subjects compared with 8.9±1.7 l/min in patients (p<0.001). Stroke volume (Figure 2, Panel C) was significantly lower in patients compared with normal subjects at rest and at all exercise work rates, although the slope of the increase in stroke volume during exercise was not different in the two groups. Central arteriovenous

<table>
<thead>
<tr>
<th>Variable</th>
<th>Intercept</th>
<th>Slope</th>
</tr>
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<tbody>
<tr>
<td><strong>Central hemodynamics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VO₂ (ml/min)</td>
<td>270±45</td>
<td>261±60</td>
</tr>
<tr>
<td>VCO₂ (ml/min)</td>
<td>208±60</td>
<td>196±64</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>75±12</td>
<td>86±17</td>
</tr>
<tr>
<td>Cardiac output (l/min)</td>
<td>5.4±1.2</td>
<td>4.0±1.2</td>
</tr>
<tr>
<td>Stroke volume (ml)</td>
<td>75±12</td>
<td>49±15</td>
</tr>
<tr>
<td>Central AVo₂ difference (ml/dl)</td>
<td>5.6±1.0</td>
<td>7.3±1.8</td>
</tr>
<tr>
<td>mSAP (mm Hg)</td>
<td>98±10</td>
<td>93±11</td>
</tr>
<tr>
<td><strong>Leg hemodynamics and metabolism</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leg blood flow (l/min)</td>
<td>0.37±0.22</td>
<td>0.31±0.21</td>
</tr>
<tr>
<td>Leg AVo₂ difference (ml/dl)</td>
<td>8.3±2.3</td>
<td>11.1±2.8</td>
</tr>
<tr>
<td>Leg VO₂ (ml/min)</td>
<td>13±19</td>
<td>34±31</td>
</tr>
<tr>
<td>NLF (l/min)</td>
<td>4.7±1.1</td>
<td>3.5±1.1</td>
</tr>
</tbody>
</table>

VO₂, oxygen consumption; VCO₂, carbon dioxide production; AVo₂, central arteriovenous oxygen; mSAP, mean systemic arterial pressure; NLF, nonleg blood flow. Intergroup comparisons were performed using the Wilcoxon rank sum test.

*Slopes are expressed as change per exercise stage (150 kpm/min).
oxygen (AVO₂) difference (Figure 2, Panel D) was increased in patients at rest and during submaximal exercise; at maximal exercise, central AVO₂ difference was not different in the two groups. The rate of change of central AVO₂ difference during exercise was higher in patients. Mean systemic arterial blood pressure (mSAP) (Figure 3, Panel A) was no different at rest or submaximal exercise but was significantly lower in patients compared with normal subjects at peak exercise. However, mSAP in patients at maximal exercise (451±136 kpm/min) was no different from the mSAP in normal subjects at the 450 kpm/min work rate, and the slope of mSAP versus work rate was higher in patients (p<0.05). Right atrial pressure was increased in certain patients, but the group means were no different at rest (4±7 vs. 1±1 mm Hg, p=0.3) or at peak exercise (7±4 vs. 4±1 mm Hg, p=0.2). Mean pulmonary artery and pulmonary capillary wedge pressures (Figure 3, Panel B) were increased in patients compared with normal subjects at rest and during exercise. Systemic vascular resistance and pulmonary vascular resistance were higher in patients than normal subjects at rest and during exercise (Figure 3, Panels C and D).

Leg Hemodynamics

Single LBF (Figure 4, Panel A), which is closely related to skeletal muscle blood flow especially during exercise,24 was reduced in patients compared with normal subjects at rest, submaximal, and maximal exercise. With exercise, the rate of increase in LBF was also markedly decreased in patients. LVR (Figure 4, Panel B) was elevated at rest and during exercise in patients compared to normal subjects. Femoral AVO₂ difference (Figure 4, Panel C) was increased at rest and during submaximal exercise but was normal at peak exercise in patients. The slope of the increase in femoral AVO₂ difference versus work rate was not different in the two groups. Single leg VO₂ (Figure 4, Panel D) was no different in the two groups at rest but was decreased at submaximal and maximal exercise in patients compared with normal subjects. The slope of the increase in leg VO₂ versus work rate was also decreased in patients compared to normal subjects. Femoral venous oxygen content and femoral venous oxygen saturation were decreased at rest and during submaximal exercise in patients but were not different from those of normal subjects at maximal exercise (Figure 4, Panels E and F).

Metabolic Response to Exercise

Table 2 illustrates arterial catecholamines in patients and arterial and femoral venous pH in patients and normal subjects. Arterial norepinephrine was increased in patients at rest compared with normal upright values and further increased during exercise. Arterial pH in patients versus normal subjects was increased at rest and during exercise. Femoral venous pH was similar in the two groups at rest but was decreased in patients compared to normal subjects at 300 kpm/min. Despite no difference in peak respiratory exchange ratios in the two groups, peak femoral venous pH was higher and peak arterial and femoral venous lactates (Figure 5, Panels A and B) were lower in patients than in normal subjects. There were no differences between
FIGURE 3. Resting and exercise mean arterial blood pressure in 30 patients and 12 normal subjects, and resting and exercise mean pulmonary capillary wedge pressure, systemic and pulmonary vascular resistances in patients with chronic heart failure (n=25) (■) and normal subjects (n=10) (●); *p<0.05, †p<0.01 patients versus normal subjects. Dashed lines indicate intergroup comparisons of maximal data.

FIGURE 4. Resting and exercise single leg blood flow, leg vascular resistance, leg arteriovenous oxygen difference, single leg $V_O$, femoral venous $O_2$ content, and femoral venous $O_2$ saturation in patients with chronic heart failure (n=30) (□) and normal subjects (n=12) (●); *p<0.05, †p<0.01 patients versus normal subjects. Dashed lines indicate intergroup comparisons of maximal data.
TABLE 2. Arterial Catecholamine Concentrations in Patients \((n=12)\) and Arterial and Femoral Venous pH in Patients \((n=18)\) and Normal Subjects \((n=12)\) at Rest, Submaximal \((300 \text{ kpm/min})\), and Maximal Exercise

<table>
<thead>
<tr>
<th></th>
<th>Rest Patients</th>
<th>Rest Normal subjects</th>
<th>Submaximal exercise ((300 \text{ kpm/min})) Patients</th>
<th>Submaximal exercise ((300 \text{ kpm/min})) Normal subjects</th>
<th>Maximal exercise Patients</th>
<th>Maximal exercise Normal subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norepinephrine ((\text{pg/dl}))</td>
<td>508±279</td>
<td>—</td>
<td>734±253§</td>
<td>—</td>
<td>1646±576§</td>
<td>—</td>
</tr>
<tr>
<td>Epinephrine ((\text{pg/dl}))</td>
<td>98±86</td>
<td>—</td>
<td>132±132</td>
<td>—</td>
<td>205±130§</td>
<td>—</td>
</tr>
<tr>
<td>Arterial pH</td>
<td>7.42±0.03*</td>
<td>7.38±0.03</td>
<td>7.40±0.02*</td>
<td>7.36±0.04‡</td>
<td>7.38±0.03†‡</td>
<td>7.32±0.06§</td>
</tr>
<tr>
<td>Femoral venous pH</td>
<td>7.35±0.05</td>
<td>7.34±0.03</td>
<td>7.25±0.05†§</td>
<td>7.31±0.03§</td>
<td>7.22±0.09*§</td>
<td>7.15±0.07§</td>
</tr>
</tbody>
</table>

Catecholamine levels were not obtained in normal subjects.

*\(p<0.05\), ‡\(p<0.01\) patients vs. normal subjects by the Wilcoxon rank sum test; †\(p<0.05\), §\(p<0.01\) vs. resting value by the Wilcoxon signed rank test.

the two groups in resting arterial lactate, femoral venous lactate, femoral arteriovenous lactate difference, or leg lactate production (Figure 5, Panels A–D). During exercise, each of these variables increased at an accelerated rate in patients compared to normal subjects. The femoral arteriovenous lactate difference during exercise was increased in patients compared with normal subjects. Because of the higher arteriovenous lactate difference in patients, peak-exercise leg lactate production in the two groups was not different.

Distribution of Cardiac Output

NLF (Figure 6, Panel A) was decreased in patients at rest and tended to be lower during exercise, but this difference was not statistically significant (all \(p>0.15\)). The slope of NLF versus work rate was not different in the two groups. The percentage of cardiac output distributed to both legs (Figure 6, Panel B) was no different at rest than during matched submaximal work rates. This value was higher in normal subjects (76±12%) compared with patients (51±17%, \(p<0.01\)) at maximal exercise because the increase in LBF with exercise was attenuated in patients, whereas NLF did not change significantly in either group. To characterize further the distribution of cardiac output, individual regression equations were determined for the increase in single LBF versus the increase in cardiac output during exercise. The slope of this relation represents the ratio of the change in single LBF to the change in cardiac output during exercise. Figure 7 illustrates individual plots of single LBF versus work rate (Panels A and C) and single LBF versus cardiac output (Panels B and D) in patients and in normal subjects. There was no difference in the slope of LBF versus cardiac output between patients (0.47±0.32) and normal subjects (0.52±0.09,

**FIGURE 5.** Resting and exercise arterial lactate, femoral venous lactate, femoral arteriovenous lactate difference, and single leg lactate production in patients with chronic heart failure \((n=30)\) (○) and normal subjects \((n=12)\) (■); *\(p<0.05\), †\(p<0.01\) patients versus normal subjects. Dashed lines indicate intergroup comparisons of maximal data.
distribution of cardiac output in the two groups during exercise.

Due to the severity of symptoms, five patients could not be withdrawn from vasodilator therapy prior to study. Peak exercise hemodynamics were reduced in the five patients taking vasodilators compared with the 25 patients not taking vasodilators, as indicated by lower values for peak \( \text{VO}_2 \) (740±298 vs. 1,099±348 ml/min, \( p<0.05 \)), peak \( \text{LBF} \) (1.1±0.6 vs. 2.2±0.9 l/min, \( p<0.02 \)), and peak cardiac output (5.9±3.0 vs. 9.0±3.2 l/min, \( p=0.09 \)).

To examine the effects of vasodilator therapy on the relative distribution of cardiac output, we compared the hemodynamic responses of the five patients taking vasodilators to the six patients with the most severe symptoms selected from those patients taking digoxin and diuretics who were matched for reduced peak \( \text{VO}_2 \) (Table 3). There was no difference in mSAP or \%LBF \( \text{at rest or during submaximal exercise in the two groups, although peak mSAP was reduced in patients on vasodilators. The slope of LBF/cardiac output was no different in}

![Figure 6](http://circ.ahajournals.org/)

**Figure 6.** Resting and exercise nonleg blood flow (cardiac output−(2×leg blood flow) and fraction of cardiac output directed to both legs (%leg blood flow, calculated as \( \text{LBF} \times 2/\text{cardiac output} \)) in patients with chronic heart failure (n=25) (■) and normal subjects (n=10) (▲); \( p<0.01 \) patients versus normal subjects. Dashed lines indicate intergroup comparisons of maximal data.

![Figure 7](http://circ.ahajournals.org/)

**Figure 7.** Individual plots of the relation of leg blood flow to work rate in normal subjects (n=12) (Panel A) and patients (n=30) (Panel C), and the relation of leg blood flow to cardiac output in normal subjects (n=10) (Panel B) and patients (n=25) (Panel D).
TABLE 3. Summary of Rest and Exercise Hemodynamics in the Five Patients Taking Vasodilators and Six Patients Not Taking Vasodilators (Controls) but Matched for Severely Reduced Peak \( \text{VO}_2 \)

<table>
<thead>
<tr>
<th></th>
<th>Vasodilators</th>
<th>Controls</th>
<th>Vasodilators</th>
<th>Controls</th>
<th>Vasodilators</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \text{VO}_2 ) (ml/min)</td>
<td>299±76</td>
<td>228±37</td>
<td>454±144</td>
<td>461±67</td>
<td>740±298</td>
<td>664±101</td>
</tr>
<tr>
<td>Cardiac output (l/min)</td>
<td>3.4±1.0</td>
<td>3.3±1.2</td>
<td>4.4±2.1</td>
<td>5.1±1.8</td>
<td>5.9±3.0</td>
<td>5.6±1.4</td>
</tr>
<tr>
<td>Leg blood flow (l/min)</td>
<td>0.2±0.04</td>
<td>0.25±0.11</td>
<td>0.69±0.29</td>
<td>0.84±0.30</td>
<td>1.10±0.62</td>
<td>1.25±0.35</td>
</tr>
<tr>
<td>mSAP (mm Hg)</td>
<td>97±8</td>
<td>100±9</td>
<td>103±14</td>
<td>113±11</td>
<td>101±11</td>
<td>125±17</td>
</tr>
<tr>
<td>%LBF</td>
<td>11±4%</td>
<td>13±5%</td>
<td>30±13%</td>
<td>29±9%</td>
<td>45±33%</td>
<td>41±7%</td>
</tr>
</tbody>
</table>

* \( p<0.05 \) patients taking vasodilators vs. patients not taking vasodilators by the Wilcoxon rank sum test.

\( \text{VO}_2 \), oxygen consumption; mSAP, mean systemic arterial pressure; %LBF, percent leg blood flow.

The slope of LBF/cardiac output was no different in patients taking vasodilators (0.50±0.37) versus those not taking vasodilators (0.34±0.13, \( p=0.44 \)). Inclusion of patients on vasodilator therapy may have improved both the cardiac output and LBF response to exercise in the patient group.\(^{19}\) Thus, inclusion of these data may have decreased the hemodynamic differences between patients and normal subjects. However, administration of vasodilators did not appear to alter the relation of LBF to cardiac output during exercise.

Ten patients had mild peripheral edema that may have influenced leg vasodilator responses due to increased vascular stiffness.\(^{14}\) To examine the effects of edema on the relative distribution of cardiac output, patients were subgrouped into those with clinical peripheral edema (\( n=10 \)) and those free of edema (\( n=20 \)). Table 4 illustrates the exercise responses in these two groups. Patients with edema had more severe heart failure and reached a lower maximal exercise work rate (405±142 vs. 480±125 kpm/min, \( p=0.14 \)) and peak \( \text{VO}_2 \) than patients without edema. Both cardiac output and LBF were decreased at submaximal and maximal exercise in patients with edema. There was no difference in mSAP in the two groups at rest or during submaximal exercise, whereas mSAP was higher at maximal exercise in patients without edema, reflecting the attainment of a higher workload. Although rest and exercise LVR tended to be higher in patients with edema, intergroup differences in LVR did not reach statistical significance (all \( p>0.16 \)). The slope of the relation of the change in single LBF versus the change in cardiac output was not different in patients with edema (0.49±0.27) versus patients without edema (0.46±0.34, \( p=0.36 \)). Thus, although peripheral edema was associated with reduced peak aerobic performance and lower values for both LBF and cardiac output during exercise, it did not appear to alter the relative distribution of cardiac output to working skeletal muscle.

**Relation of LBF to the Central Hemodynamic and Metabolic Exercise Response**

Peak \( \text{VO}_2 \) was closely related to peak LBF in patients (\( r=0.81, \ p<0.01 \)) and in normal subjects (\( r=0.82, \ p<0.01 \) (Figure 8, Panel A), as was peak cardiac output in both patients (\( r=0.88, \ p<0.001 \)) and normal subjects (\( r=0.82, \ p<0.001 \) (Figure 8, Panel B). In patients, peak LBF was related to peak cardiac output (\( r=0.66, \ p<0.001 \), and peak LVR was inversely related to both peak cardiac output (\( r=-0.53, \ p<0.01 \)) and peak \( \text{VO}_2 \) (\( r=-0.60, \ p<0.01 \). In normal subjects, peak LBF was related to peak cardiac output (\( r=0.67, \ p<0.01 \), and peak LVR was related to peak \( \text{VO}_2 \) (\( r=-0.78, \ p<0.001 \) and peak cardiac output (\( r=-0.76, \ p<0.001 \). In both patients and normal subjects, LBF and LVR at rest, submaximal (300 kpm/min), and maximal exercise were not closely related (all \( r<0.2, \ p>0.03 \) to the corresponding values for arterial lactate, arterial norepinephrine or epinephrine, pulmonary capillary wedge pressure, or mSAP. Femoral venous pH was unrelated to LBF in patients at rest or during exercise.

**TABLE 4. Summary of Rest and Exercise Hemodynamics in Patients With Peripheral Edema \( (n=10) \) and Patients Without Peripheral Edema \( (n=20) \)**

<table>
<thead>
<tr>
<th></th>
<th>Edema</th>
<th>No edema</th>
<th>Edema</th>
<th>No edema</th>
<th>Edema</th>
<th>No edema</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \text{VO}_2 ) (ml/min)</td>
<td>274±61</td>
<td>259±46</td>
<td>465±107</td>
<td>528±109</td>
<td>866±328</td>
<td>1,126±354†</td>
</tr>
<tr>
<td>Cardiac output (l/min)</td>
<td>3.6±0.8</td>
<td>3.9±1.2</td>
<td>4.8±1.6</td>
<td>6.2±1.6†</td>
<td>6.8±2.4</td>
<td>9.4±3.4†</td>
</tr>
<tr>
<td>Leg blood flow (l/min)</td>
<td>0.20±0.03</td>
<td>0.27±0.14</td>
<td>0.77±0.31</td>
<td>1.11±0.46*</td>
<td>1.5±0.7</td>
<td>2.3±1.0*</td>
</tr>
<tr>
<td>mSAP (mm Hg)</td>
<td>93±9</td>
<td>94±12</td>
<td>100±14</td>
<td>102±13</td>
<td>107±11</td>
<td>119±13*</td>
</tr>
<tr>
<td>LVR (mm Hg/l/min)</td>
<td>466±112</td>
<td>416±131</td>
<td>141±46</td>
<td>107±53</td>
<td>75±27</td>
<td>63±49</td>
</tr>
<tr>
<td>Fem lactate (mM/l)</td>
<td>1.4±0.5</td>
<td>1.0±0.6†</td>
<td>2.5±1.0</td>
<td>1.9±0.9</td>
<td>7.7±3.5</td>
<td>8.7±3.1</td>
</tr>
<tr>
<td>Leg AV lactate (mM/l)</td>
<td>0.3±0.3</td>
<td>0.1±0.3</td>
<td>1.0±0.6</td>
<td>0.6±0.6</td>
<td>3.1±1.1</td>
<td>2.9±1.9</td>
</tr>
</tbody>
</table>

LVR, Leg vascular resistance; Fem lactate, femoral venous lactate; Leg AV lactate, Femoral venoarterial lactate difference.

* \( p<0.05 \), † \( p<0.09 \), patients without edema vs. patients with edema by the Wilcoxon rank sum test.
submaximal exercise, but was related to peak LBF in normal subjects \((r=-0.74, p<0.01)\).

**Discussion**

The present study demonstrates that in patients with chronic heart failure, LBF was reduced and LVR was increased at rest and during exercise compared to normal subjects. Our results are consistent with previous studies of patients with this disorder,\(^5\,^9\,^{13}\) demonstrating that skeletal muscle perfusion was reduced compared to normal subjects during isotonic exercise involving large muscle groups. We extend these observations by demonstrating that arterial hypotension is not the primary mechanism causing peripheral blood flow abnormalities in stable patients with chronic heart failure. Although previous studies have defined abnormalities in the baroreceptor response to a number of stimuli in the heart failure state,\(^{25,26}\) our patients demonstrated a normal blood pressure response to the complex physiologic challenge of upright isotonic exercise. Although the results of the present study do not define the specific mechanisms responsible for reduced LBF in subjects with this disorder, our data suggest that stable patients with chronic heart failure preferentially maintain arterial perfusion pressure and blood flow to nonexercising regions at the expense of leg hypoperfusion during exercise.

Previous studies by Leithe et al\(^{27}\) and Zelis et al\(^{14,18}\) also have demonstrated an abnormally low limb blood flow at rest in patients with chronic heart failure, and several investigators have demonstrated that limb blood flow is reduced during maximal exercise in subjects with this disorder.\(^8\,^{10,11,13}\) In contrast, Wiener et al\(^{28}\) and Massie et al\(^{29}\) have demonstrated that exercise forearm blood flow is not decreased in patients with chronic heart failure. It is possible that this difference may be related, in part, to the smaller muscle mass used in forearm exercise, which may have represented less of a challenge to cardiovascular reserve and therefore less of a stimulus for muscle vasoconstriction. Our results indicate that during exercise involving a large muscle mass, skeletal muscle perfusion is reduced in patients at rest and at all exercise work rates. This may have important implications because even low-level exercise was accompanied by skeletal muscle hypoperfusion in our patients. In addition to the importance of decreased skeletal muscle blood flow in causing early skeletal muscle anaerobic metabolism,\(^5,7,8\) it is possible that chronic exposure to hypoperfusion may cause vascular and metabolic changes in skeletal muscle, which may further accelerate anaerobic metabolism during exercise in patients with chronic heart failure.\(^{26,29}\)

At present, the physiologic mechanisms that control skeletal muscle blood flow during exercise in normal humans are not well understood. During exercise in normal subjects, skeletal muscle oxygen delivery is precisely coupled to the work rate even in the presence of altered temperature.\(^{30}\) or hypoxia.\(^{31}\) Recent studies by Saltin et al\(^{30–32}\) demonstrated very high perfusion rates in skeletal muscle during one-legged knee extensor exercise by normal subjects. These data indicate that skeletal muscle vascular conductance may be limited by the exercise cardiac output and not by local constraints on vasodilator capacity, and suggest that the peripheral circulation is under the control of tonic vasoconstrictor mechanisms that are further released during exercise not challenging maximal central hemodynamic reserve. This is consistent with studies by Strandell and Shepherd\(^{33}\) and Mack et al\(^{34}\) demonstrating that normal subjects actively regulate mean arterial blood pressure during exercise by increasing skeletal muscle vascular tone when cardiac output is decreased by lower-body negative pressure. Thus, maximal muscle conductance in normal subjects appears to be, in part, determined by a functional interaction of muscle metabolism, cardiac output, and arterial blood pressure through mechanisms that are currently not well understood.\(^{32}\)

Previous studies also have not completely defined the relative roles of intrinsic abnormalities in limb vasodilator capacity and activation of adrenergic vasoconstrictor reflexes in limiting skeletal muscle blood flow during exercise in patients with chronic heart failure.\(^{13,14,18,35}\) Our finding that patients without edema had marked abnormalities in leg hemodynamics during exercise is consistent with the recent study by Sinoway et al\(^{36}\) demonstrating that treatment of edema did not entirely reverse limb vasodilator abnormalities in patients with chronic heart failure. Although our results do not quantify
the importance of intrinsic vasodilator abnormalities in increasing leg vascular resistance in subjects with this disorder, our finding that arterial blood pressure was closely regulated in patients suggests that LVR is determined, in part, by dynamic alterations in leg vasomotor tone during exercise.

The present study is one of the first to measure cardiac output and LBF during maximal graded exercise in normal subjects. Our finding that the slope of the increase in single LBF versus cardiac output was 0.52±0.08 in normal subjects is consistent with the concept, derived mainly from animal studies, that increments in cardiac output during exercise are directed primarily to working skeletal muscle in man. As described in previous studies, LBF increased linearly in relation to work rate in our normal subjects and did not plateau during submaximal exercise. At the onset of exercise, LVR decreased markedly in both patients and normal subjects and then decreased more gradually as the exercise intensity increased. Thus, increases in LBF were dependent on increases in mSAP during moderate and severe exercise by both groups. Although patients in the present study did not demonstrate arterial hypotension during exercise, our results do not exclude the possibility that arterial hypotension may play a role in reducing skeletal muscle blood flow during exercise in unstable patients with more severe heart failure or in patients who develop hypotension while initiating vasodilator therapy.

NLF calculated as: cardiac output—(LBF×2), represents flow to both nonexercising regions (visceral organs, brain) and exercising regions (trunk and respiratory muscles, heart). Therefore, changes in this variable during exercise likely represent increases in flow to exercising regions and decreases in flow to splanchnic and renal beds, with variable changes in skin blood flow. Although the distribution of cardiac output to individual organs during exercise was not determined in the present study, our finding that NLF was maintained in patients during exercise is consistent with the concept of Zelis et al.14 that intense skeletal muscle vasconstriction during exercise in patients with chronic heart failure may prevent hypoperfusion and, possibly, ischemia in vital nonexercising regions.

Zelis et al.10,11 have previously reported an attenuation in oxygen uptake during forearm exercise in patients with chronic heart failure. Our findings demonstrate a similarly reduced limb VO₂ in patients compared to normal subjects, during both submaximal and maximal leg exercise, and indicate that this occurred despite an increase in oxygen extraction during submaximal exercise. Although previous studies have suggested that skeletal muscle metabolic abnormalities are present in patients with chronic heart failure, our data indicate that peripheral oxygen utilization in subjects with this disorder is limited partly by hypoperfusion. However, our patients did not demonstrate maximal leg AVO₂ differences that were higher than those seen in normal subjects. In contrast, an increase in leg oxygen extraction at peak exercise has previously been demonstrated in patients with leg hypoperfusion due to claudication.

Hansen et al.43 and Koike et al.44 have demonstrated that patients with cardiac dysfunction have a reduced systemic VO₂ to work rate relation compared to normal subjects. The present study has demonstrated a similar reduction in the systemic VO₂ to work rate relation in patients with chronic heart failure. Our finding that leg VO₂ during exercise was also decreased in patients compared to normal subjects suggests that the reduced systemic VO₂ to work rate relation was directly attributable to decreased oxygen delivery to working skeletal muscle.

Our patients demonstrated an accelerated rise in blood lactate levels during exercise, which has previously been described by Weber et al.45 and Wilson et al.24 for similar patient groups. The present study extends these observations by demonstrating that increased blood lactate levels in patients were associated with markedly increased skeletal muscle lactate production. This finding suggests that reduced lactate clearance is not the primary mechanism responsible for increased blood lactate concentrations in patients, and is consistent both with 31P-NMR studies demonstrating accelerated intramuscular acidosis30,29 and with exercise-skeletal-muscle biopsy studies in our laboratory46 demonstrating increased intramuscular lactate content during submaximal exercise in patients with this disorder. Although intrinsic abnormalities in skeletal muscle histology and biochemistry40–42 and heightened adrenergic stimulation may play an important role in determining the metabolic response to exercise in subjects with this disorder, our finding that leg VO₂ was decreased and leg lactate production was increased supports the concept that skeletal muscle hypoperfusion during exercise contributes to early anaerobic metabolism in subjects with this disorder.2,3,8

Previous studies have demonstrated that left ventricular ejection fraction is not related to maximal aerobic exercise capacity in patients with chronic heart failure.47,48 This has often been interpreted to indicate that aerobic performance is unrelated to the cardiac output response to exercise and is determined primarily by peripheral factors in subjects with this disorder. The results of the present study and those of Wilson et al.4 indicate that peak LBF is closely related to peak VO₂ in patients. In our patients, peak cardiac output was related to both peak VO₂ and peak LBF. Thus, although left ventricular ejection fraction is not related to peak VO₂ in patients with heart failure, our data suggest that the exercise cardiac output response, which is not determined solely by the left ventricular ejection fraction, is an important determinant of the LBF response and, therefore, of peak aerobic per-
formance in this disorder. This is consistent with the results of previous studies,47 that have shown peak cardiac output related to peak VO₂ and that, as the severity of heart failure worsens, the slope of the cardiac output response in relation to VO₂ decreases.45 Our finding that LBF was closely related to peak VO₂ underscores the ultimate importance of skeletal muscle perfusion in determining peak exercise performance in both patients and normal subjects.

The present study has demonstrated that, in patients with chronic heart failure compared to normal subjects, LBF is reduced at rest and during submaximal and maximal exercise and is accompanied by an increase in LVR. Despite a reduced cardiac output response, our patients maintained a normal mean arterial blood pressure response to submaximal exercise and did not decrease NLF during exercise. In patients compared to normal subjects, LBF abnormalities during submaximal exercise were associated with early lactate production and reduced skeletal muscle oxygen consumption, despite heightened oxygen extraction, suggesting that skeletal muscle hypoperfusion played a role in the metabolic acidosis in subjects with this disorder in response to exercise. Our data suggest that in patients with chronic heart failure, increased skeletal muscle vascular resistance and reduced LBF during exercise function to maintain arterial blood pressure and, thereby, maintain perfusion of important nonexercising regions in the setting of an inadequate cardiac output response.

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