Altered Skeletal Muscle Metabolic Response to Exercise in Chronic Heart Failure

Relation to Skeletal Muscle Aerobic Enzyme Activity

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Background. Exertional fatigue, which frequently limits exercise in patients with chronic heart failure, is associated with early anaerobic metabolism in skeletal muscle. The present study was designed to examine the skeletal muscle metabolic response to exercise in this disorder and determine the relation of reduced muscle blood flow and skeletal muscle biochemistry and histology to the early onset of anaerobic metabolism in patients.

Methods and Results. We evaluated leg blood flow, blood lactate, and skeletal muscle metabolic responses (by vastus lateralis biopsies) during upright bicycle exercise in 11 patients with chronic heart failure (ejection fraction 21±8%) and nine normal subjects. In patients compared to normal subjects, peak exercise oxygen consumption was decreased (13.0±3.3 ml/kg/min versus 30.2±8.6 ml/kg/min, p<0.01), whereas peak respiratory exchange ratio and femoral venous oxygen content were not different (both p>0.25), indicating comparable exercise end points. At rest in patients versus normals, there was a reduction in the activity of hexokinase (p=0.08), citrate synthetase (p<0.02), succinate dehydrogenase (p=0.0007), and 3-hydroxyacyl CoA dehydrogenase (p=0.04). In patients, leg blood flow was decreased at rest, submaximal, and maximal exercise when compared to normal subjects (all p<0.05), and blood lactate accumulation was accelerated. In patients, during submaximal exercise blood lactate levels were not closely related to leg blood flow but were inversely related to rest citrate synthetase activity in skeletal muscle (r=-0.74, p<0.05). At peak exercise there were no intergroup differences in skeletal muscle glycolytic intermediates, adenosine nucleotides, or glycogen, whereas in patients compared to normal subjects less lactate accumulation and phosphocreatine depletion were noted (both p<0.05), suggesting that factors other than the magnitude of phosphocreatine depletion or lactate accumulation may influence skeletal muscle fatigue in this disorder.

Conclusions. The results of the present study suggest that in patients with chronic heart failure reduced aerobic activity in skeletal muscle plays an important role in mediating the early onset of anaerobic metabolism during exercise. Our findings are consistent with the concept that reduced aerobic enzyme activity in skeletal muscle is, in part, responsible for determining exercise tolerance and possibly the response to chronic interventions in patients with chronic heart failure. (Circulation 1991;84:1597–1607)

Recent studies indicate that skeletal muscle fatigue associated with early anaerobic metabolism is the primary factor limiting exercise tolerance in patients with chronic heart failure.\(^1\)\(^–\)\(^4\) Although skeletal muscle hyperperfusion likely plays an important role in early lactate production,\(^2\)\(^–\)\(^6\) recent studies in our laboratory\(^7\) and others\(^8\)\(^–\)\(^9\) have identified reduced aerobic enzyme activity and an increased percentage of fast-twitch type IIb fibers in skeletal muscle in patients with chronic heart failure. These alterations have previously been shown to be a potent stimulus for early anaerobic

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metabolism during exercise in animals\textsuperscript{10,11} and in normal humans\textsuperscript{12,13} and may also play a role in mediating early lactate production in this disorder. This concept is supported by the findings of \textsuperscript{31}P-nuclear magnetic resonance (\textsuperscript{31}P-NMR) studies by Weiner et al\textsuperscript{14} and Massie et al,\textsuperscript{15,16} which have demonstrated an abnormal metabolic response to arm exercise in this disorder that appears to be independent of hemodynamic abnormalities. Although intrinsic skeletal muscle biochemical and histological changes that may lead to early anaerobic metabolism have been demonstrated in patients, the relation between these changes and the metabolic response to exercise in this disorder has not been clearly defined.

The present study was designed to examine the skeletal muscle metabolic response to maximal upright bicycle exercise in patients with chronic heart failure and in normal subjects using direct biochemical analysis of rest and exercise biopsy samples of the vastus lateralis muscle. We have previously reported the rest skeletal muscle biochemical and histological characteristics, demographies, peak exercise oxygen consumption (VO\textsubscript{2}), and femoral venous blood lactate and oxygen saturation response to exercise in the 11 patients and nine normal subjects who form the study groups in this report.\textsuperscript{7} This previous study demonstrated that in patients compared to normal subjects, skeletal muscle aerobic enzyme content and percent composition of type I fibers were reduced, whereas glycolytic enzyme content was not changed. Although these skeletal muscle alterations in patients may be largely due to chronic exercise deconditioning, it is possible that the heart failure state itself may also contribute. The present study combines leg blood flow and blood lactate measurements during exercise and vastus lateralis biopsies at rest and during exercise to examine the relation between hemodynamic and intrinsic skeletal muscle alterations in determining the metabolic response to exercise in this disorder. An important aim of the study was to evaluate muscle phosphagen, substrate stores, and lactate content at peak exercise in patients and normal subjects. This study also examines the relation of blood lactate levels to intramuscular lactate and phosphocreatine (PCr) in patients and in normal subjects.

**Methods**

Eleven men with chronic heart failure due to left ventricular systolic dysfunction (left ventricular ejection fraction, $21\pm8\%$) participated in the study. All subjects were taking stable dosages of digoxin and diuretics, and all were free of rales or peripheral bruits. Three subjects were chronically taking vasodilators (captopril, $n=2$; nitrates, $n=1$), and one was taking an oral phosphodiesterase inhibitor (enoxime). Patients were included only if limited primarily by general and/or leg fatigue during bicycle ergometry. The New York Heart Association functional classification of the patients was as follows: one was class I, three were class II, six were class III, and one was class IV. Nine healthy men volunteered to participate in the protocol. All had normal physical examinations and electrocardiographic responses to a screening bicycle exercise study, and none was taking medications. All studies were performed under a research protocol approved by the Institutional Review Boards at Duke University Medical Center and Durham Veterans Administration Medical Center.

**Study Protocol**

All subjects underwent three maximal exercise tests on a Fitron isokinetic bicycle in the upright position with the exercise work rate beginning at 150 kilopond (kpm) per minute and increasing in 3-minute stages of 150 kpm/min. During the first two exercise studies, expired gases were measured continuously in all subjects at rest and during exercise using a Sensormedics 4400 unit (Anaheim, Calif.).\textsuperscript{4,17} Two to 14 days after a familiarization test, subjects underwent two identical exercise tests within a 10-day period. All vasodilators and phosphodiesterase inhibitors were discontinued 48 hours prior to the second and third exercise tests. During the second study, hemodynamic measurements and blood lactate levels were obtained, and during the third study rest and exercise biopsies were obtained from the vastus lateralis muscle. During the second exercise session, all normal subjects and 9 patients had a brachial artery cannula and a femoral venous catheter (model 93a-105-5F, Edwards Laboratory, Santa Ana, Calif.) inserted under local anesthesia 1 hour prior to exercise. Leg blood flow was measured at upright rest and two to four times during each work rate, using a bolus thermodilution technique as previously described in our laboratory.\textsuperscript{5,17} At upright rest and in the last minute of each work rate, arterial and femoral venous blood samples were taken and immediately chilled in an ice bath. Oxygen content and saturation were measured using a calibrated Instruments Laboratory 282 CO-Oximeter (Lexington, Mass.), and lactate concentration was analyzed using a Calbiochem Behring rapid lactate kit (San Diego, Calif.). In all normal subjects and five patients, femoral venous blood was also analyzed for pH and PCO\textsubscript{2} (Instruments Laboratory, Lexington, Mass.).

During the second exercise session, subjects performed an identical exercise protocol and reached at least the same peak work rate achieved during the hemodynamic exercise study. Before this exercise, biopsy sites on the anterior thigh were anesthetized with 2\% xylocaine, and 0.5-cm incisions were made through the skin and fascia lata. Biopsies of the vastus lateralis muscle were obtained using the modified Bergstrom technique\textsuperscript{18} at rest, $3-8$ seconds after an interruption of exercise at a work rate representing $55\pm13\%$ of the peak work rate, and $3-8$ seconds after peak exercise. Biopsy samples were immediately placed in liquid nitrogen and transferred to a freezer at $-70\^\circ$C. It was not technically possible to obtain both submaximal and maximal exercise biop-
bies during this continuous exercise protocol in all subjects. Submaximal exercise biopsies were not obtained in two normal subjects and in four patients, and maximal exercise biopsies were not obtained in two patients. Biopsy samples were weighed, freeze-dried, and extracted according to the method of Harris et al.\textsuperscript{19} Creatine, PCr, inorganic phosphate, glycogen, glucose, glucose-1-phosphate, glucose-6-phosphate, fructose-6-phosphate, and lactate were analyzed fluorometrically using methods as previously described.\textsuperscript{7,20} Adenosine triphosphate (ATP) and adenosine diphosphate (ADP) were determined using high-pressure liquid chromatography.\textsuperscript{7,20}

In a preliminary study, we examined the effects of the time duration between obtaining the skeletal muscle biopsy and the freezing of samples on biochemical determinations of muscle metabolism. We obtained biopsies of the vastus lateralis at rest, at submaximal, and at maximal bicycle exercise in two normal subjects; the biopsies were then divided and placed in liquid nitrogen after delaying freezing by 0–70 seconds. Figure 1 illustrates the stability of measurements of water content, ATP, PCr, and lactate with variations in time to freezing. Our results are consistent with previous studies by Soderlund and Hultman\textsuperscript{21} in demonstrating that determination of skeletal muscle metabolism by biopsy and direct biochemical analysis is not significantly influenced by short delays in freezing specimens. To examine the day-to-day reproducibility of rest and exercise skeletal muscle biochemical analysis from biopsies in our laboratory, three normal subjects underwent identical exercise studies on two separate days with biopsies obtained at rest, at identical submaximal work rates, and at maximal exercise. Regression of paired rest and exercise measurements of PCr, lactate, ATP, and glycogen demonstrated good day-to-day reproducibility (all $r>0.75$, $p<0.01$), with the slope of the derived regression equations not different from the line of identity (Figure 2).

**Statistical Analysis**

Intergroup and intragroup comparisons were performed using unpaired and paired Student’s $t$ tests where appropriate. To determine the relation of variables, linear regression analysis was performed using the least squares method. Probability values less than 0.05 were considered statistically significant. All data are presented as mean±SD.

**Results**

Although in patients (PT) versus normals (NL) there were minor differences in age (PT, 59±13 versus NL, 49±12 years; $p=0.10$), weight (PT, 69±12 kg versus NL, 77±6 kg, $p=0.10$), and surface area (PT, 1.79±0.16 m$^2$ versus NL, 1.90±0.10 m$^2$; $p=0.08$), these differences did not reach statistical signifi-
cance. Table 1 summarizes the hemodynamic and metabolic response to exercise in patients and normals. There was no difference in blood hemoglobin at rest in patients when compared with normal subjects (PT, 14.6±2.4 versus NL, 15.3±0.8 g/dL; p=0.54). At peak exercise in patients compared with normals, VO₂ was decreased (PT, 13.0±3.3 versus NL, 30.2±8.6 ml/kg/min; p<0.001). There were no intergroup differences in peak respiratory exchange ratios (PT, 1.37±0.14 versus NL, 1.31±0.09, p=0.25) or femoral venous oxygen saturation (PT, 21±9% versus NL, 27±6%; p=0.20). It is important to note that both patients and normals were coached to exercise until general exhaustion or leg fatigue limited work output and that the peak respiratory exchange ratios reported indicate a comparable maximal or near-maximal exercise effort in both groups. In patients, leg blood flow was reduced at rest and during exercise and was accompanied by reduced femoral venous oxygen content and saturation at rest and during submaximal exercise. Arterial lactate, femoral venous lactate, and the femoral venoarterial lactate difference were comparable in the groups at rest, but all were increased in patients versus normals at 300 kpm/min. At peak exercise both femoral venous and arterial lactate levels were lower in patients versus normals. Leg production of lactate was no different at rest or at maximal exercise but tended to be higher in patients at 300 kpm/min (p<0.07). There were no intergroup differences in femoral venous pH and PCO₂ at rest; however, femoral venous pH was decreased at 300 kpm/min in patients but was higher than normals at peak exercise. It should be noted that of the five patients who had femoral venous blood gas measurements, four completed only the 300 kpm/min work rate. Femoral venous PCO₂ was higher in patients at 300 kpm/min but was not different from normals at peak exercise.

Skeletal Muscle Metabolic Response

Table 2 and Figure 3 summarize muscle biochemical analyses at rest and during exercise in patients and normals. Submaximal biopsies were obtained at 300±87 kpm/min in seven patients and at 471±57 kpm/min in seven normal subjects (p<0.01). Although in patients versus normals this represented a similar percent of the peak exercise work rate (PT, 57±14% versus NL, 53±14%, p=0.51), the percent of peak VO₂ was different (PT, 76±9% versus NL, 60±12%; p<0.05). At rest, glycogen content tended to be slightly lower in patients (p=0.08). At submaximal exercise, PCr, inorganic phosphate, ATP, and ADP were not different in the two groups. At submaximal exercise glycogen tended to be slightly lower in patients, but this difference did not reach statistical significance (p=0.11), and glucose and glucose-6-phosphate were increased in patients compared to normals. Although these submaximal measures were performed at different relative percentages of peak VO₂ in the two groups, the results indicate that accumulation of glucose and glucose-6-phosphate occurred in patients at levels of exercise that would be encountered during routine daily activities in normal subjects.

To compare the rate of change of skeletal muscle metabolism in relation to absolute work rate, maximal data from patients were compared to the submaximal data from normals. The maximal work rate of patients (500±150 kpm/min) was similar to the submaximal work rate at which biopsies were obtained in normal subjects (471±57 kpm/min, p=0.61). Although phosphagens and adenosine nucleotides were not different in the two groups, in patients versus normals, glycogen was decreased whereas glycolytic intermediates and lactate were increased (see Figure 3). Thus, glycolysis and glyco-genolysis were accelerated in relation to absolute work rate in patients.

Table 1. Rest and Exercise Hemodynamic and Metabolic Parameters in Patients and Normal Subjects

<table>
<thead>
<tr>
<th>Variable</th>
<th>Upright rest</th>
<th>300 kpm/min</th>
<th>Peak exercise</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients</td>
<td>Subjects</td>
<td>Patients</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>84±17</td>
<td>75±10</td>
<td>109±20</td>
</tr>
<tr>
<td>RER</td>
<td>0.91±0.08</td>
<td>0.89±0.07</td>
<td>1.22±0.11†</td>
</tr>
<tr>
<td>LBF (l/min)</td>
<td>0.3±0.1*</td>
<td>0.4±0.2</td>
<td>1.4±0.5†</td>
</tr>
<tr>
<td>FVo₂ST (%)</td>
<td>38±16*</td>
<td>55±12</td>
<td>24±9%</td>
</tr>
<tr>
<td>FVo₂CT (ml/dl)</td>
<td>8.0±3.8*</td>
<td>11.8±2.4</td>
<td>4.7±2.6*</td>
</tr>
<tr>
<td>FLAC (mM/l)</td>
<td>1.1±0.7</td>
<td>0.9±0.5</td>
<td>4.2±1.5†</td>
</tr>
<tr>
<td>ARTLAC (mM/l)</td>
<td>0.8±0.7</td>
<td>0.8±0.5</td>
<td>2.9±1.0†</td>
</tr>
<tr>
<td>LAVL (mM/l)</td>
<td>0.2±0.3</td>
<td>0.2±0.2</td>
<td>1.3±1.0*</td>
</tr>
<tr>
<td>PLLA (mM/min)</td>
<td>0.1±0.1</td>
<td>0.1±0.1</td>
<td>1.9±1.5</td>
</tr>
<tr>
<td>FVPpH</td>
<td>7.36±0.01</td>
<td>7.35±0.03</td>
<td>7.25±0.05*</td>
</tr>
<tr>
<td>FVPpCO₂ (mm/Hg)</td>
<td>45±4</td>
<td>43±3</td>
<td>52±4*</td>
</tr>
</tbody>
</table>

HR, heart rate; RER, respiratory exchange ratio; LBF, single leg blood flow; FVo₂ST, femoral venous oxygen saturation; FVo₂CT, femoral venous oxygen content; FLAC, femoral venous lactate concentration; ARTLAC, arterial lactate; LAVL, femoral venous arterial lactate difference; PLLA, leg production of lactate; FVPpH, femoral venous pH; FVPpCO₂, femoral venous PCO₂.

*p<0.05, †p<0.001, ‡p<0.01 patients vs. normals.
TABLE 2. Summary of Rest and Exercise Skeletal Muscle Metabolism in Patients and Normal Subjects

<table>
<thead>
<tr>
<th></th>
<th>Rest (n=11)</th>
<th>Subjects (n=9)</th>
<th>Submaximal exercise (n=7)</th>
<th>Subjects (n=7)</th>
<th>Peak exercise (n=9)</th>
<th>Subjects (n=9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VO₂ (ml/min)</td>
<td>233±36*</td>
<td>290±16</td>
<td>759±199*†</td>
<td>1233±178†</td>
<td>875±307A*†§</td>
<td>2309±640§</td>
</tr>
<tr>
<td>Work rate (kpm/min)</td>
<td>0</td>
<td>0</td>
<td>300±87*†</td>
<td>471±57†</td>
<td>500±150*†§</td>
<td>983±200§</td>
</tr>
<tr>
<td>Total creatine</td>
<td>114±13</td>
<td>114±11</td>
<td>111±14</td>
<td>116±14</td>
<td>108±24</td>
<td>112±12</td>
</tr>
<tr>
<td>PCr</td>
<td>556±160</td>
<td>556±99</td>
<td>467±64</td>
<td>486±102</td>
<td>412±123*</td>
<td>244±184†</td>
</tr>
<tr>
<td>Pi</td>
<td>336±95</td>
<td>313±56</td>
<td>392±85</td>
<td>421±81†</td>
<td>442±59†</td>
<td>596±231†</td>
</tr>
<tr>
<td>ATP</td>
<td>188±18</td>
<td>190±23</td>
<td>183±21</td>
<td>188±22</td>
<td>181±20</td>
<td>163±26</td>
</tr>
<tr>
<td>ADP</td>
<td>38.3±7.3</td>
<td>35.5±5.4</td>
<td>36.5±9.2</td>
<td>34.8±7.5</td>
<td>39.4±9.1</td>
<td>37.5±8.5</td>
</tr>
<tr>
<td>Glycogen</td>
<td>2320±380</td>
<td>2630±390</td>
<td>2200±220</td>
<td>2480±370</td>
<td>1940±300†§</td>
<td>1980±740§</td>
</tr>
<tr>
<td>Glucose</td>
<td>44.0±30.3</td>
<td>31.4±21.2</td>
<td>74.4±43.3*</td>
<td>31.9±14.4</td>
<td>69.0±34.5</td>
<td>84.8±38.1†</td>
</tr>
<tr>
<td>Glucose-6-PO₄</td>
<td>35.3±35.2</td>
<td>42.4±39.3</td>
<td>58.8±32.4*</td>
<td>24.0±5.2</td>
<td>77.9±33.7†</td>
<td>69.7±22.4§</td>
</tr>
<tr>
<td>Glucose-1-PO₄</td>
<td>3.41±2.67</td>
<td>4.05±2.08</td>
<td>3.23±2.29</td>
<td>3.20±2.32</td>
<td>5.93±3.31**</td>
<td>5.06±3.13*</td>
</tr>
<tr>
<td>Fructose-6-PO₄</td>
<td>5.09±5.51</td>
<td>4.85±3.93</td>
<td>7.40±3.81</td>
<td>7.12±8.96</td>
<td>9.5±5.7</td>
<td>17.2±25.9</td>
</tr>
<tr>
<td>Lactate</td>
<td>106±121</td>
<td>58±49</td>
<td>184±96</td>
<td>146±59‡</td>
<td>363±180*§</td>
<td>669±327§</td>
</tr>
</tbody>
</table>

Total creatine is expressed in mM/kg dry wt; all other biochemical variables in mM/mM total creatine×10³. VO₂, oxygen consumption; PCr, creatine phosphate; Pi, inorganic phosphate; ATP, adenosine triphosphate; ADP, adenosine diphosphate.

*p<0.05 patients vs. normal subjects; †p<0.01, ‡p<0.05 vs. rest; §p<0.01, ||p<0.05 peak vs. submaximal exercise.

At peak exercise, glycogen and glycolytic intermediates were not different in the two groups, but skeletal muscle lactate accumulation and PCr depletion were less in patients versus normals. This was accompanied by a tendency for patients to demonstrate lower values for peak inorganic phosphate (p=0.08) and higher values for ATP (p=0.12) when compared to normals, although these differences did not reach statistical significance. In both groups PCr and glycogen decreased from rest to peak exercise (all p<0.05), and ATP decreased from rest to peak exercise in normals (p<0.05) but not in patients.

Determinants of the Metabolic Exercise Response

To assess the relations of hemodynamics and skeletal muscle factors in determining the onset of anaerobic metabolism, we performed linear regression analysis of femoral venous lactate at submaximal
exercise with rest skeletal muscle biochemistry and histology and hemodynamic data at the corresponding work rate. Exercise work rates of 300 kpm/min were chosen in patients and 600 kpm/min in normal subjects, although similar results were obtained at 150 kpm/min and 450 kpm/min in the two groups, respectively. In patients, femoral venous lactate levels at 300 kpm/min were significantly inversely correlated with citrate synthetase \( (r = -0.74, p < 0.05) \) (Figure 4) and succinate dehydrogenase activity \( (r = -0.67, p < 0.05) \) but were not significantly correlated with leg blood flow or femoral venous oxygen saturation.

**Figure 4.** Relations of leg blood flow, femoral venous oxygen saturation, skeletal muscle capillary density, and citrate synthetase to femoral venous blood lactate at 300 kpm/min in patients with chronic heart failure. \( r = \) correlation coefficient.

**Figure 5.** Lactate content in arterial and femoral blood, skeletal muscle, and the calculated skeletal muscle-to-arterial blood lactate gradient at rest and during submaximal and maximal exercise in patients and normal subjects. Lactate in skeletal muscle is expressed in mM/kg wet weight. *p < 0.05 patients vs. normal subjects; **p < 0.01 patients vs. normal subjects; †p < 0.05 vs. rest; ††p < 0.01 vs. rest.
saturation, fiber typing, rest glycogen content, glycolytic enzyme activity, capillary density, or hexokinase activity. In normal subjects, femoral venous lactate levels at 600 kpm/min were significantly inversely correlated with the corresponding leg blood flow \((r = -0.76, p < 0.05)\), succinate dehydrogenase \((r = -0.76, p < 0.05)\) and citrate synthetase activity \((r = -0.61, p = 0.08)\), and rest glycogen content \((r = -0.64, p = 0.06)\) but were not significantly correlated with femoral venous oxygen saturation, glycolytic enzyme activity, or capillary density. In patients, peak \(\text{Vo}_2\) was significantly correlated with succinate dehydrogenase activity \((r = 0.68, p < 0.05)\), citrate synthetase activity \((r = 0.54, p = 0.08)\), and average fiber size \((r = 0.77, p < 0.01)\) but was unrelated to relative fiber typing, glycogen content, glycolytic enzyme activity, or capillary density. Peak leg blood flow was significantly correlated with citrate synthetase activity in both groups (both \(r > 0.77, p < 0.05\)). In normal subjects, peak \(\text{Vo}_2\) was related to citrate synthetase activity \((r = 0.81, p < 0.01)\) but was unrelated to glycolytic enzyme activity, glycogen content, fiber size, relative fiber composition, or capillary density.

**Relation of Blood to Muscle Lactate in Patients and Normal Subjects**

Figure 5 illustrates blood and muscle lactate data at rest and during exercise in the two groups. Lactate tended to be higher in skeletal muscle when compared to femoral venous or arterial blood in both groups at maximal exercise (both \(p < 0.08\)), although these differences did not reach statistical significance. There were no differences in the calculated gradients of skeletal muscle to femoral venous or arterial blood lactate in the two groups at rest, submaximal, or maximal exercise. Figure 6 demonstrates the relation of arterial lactate to skeletal muscle lactate at rest and during exercise in patients and normal subjects. In both groups, the predicted slope is less than unity, indicating that as arterial lactate levels increase so does the muscle-to-arterial blood lactate gradient. Figure 7 illustrates the relation of arterial lactate to skeletal muscle lactate and PCr in patients and normals. Arterial lactate and skeletal muscle lactate were inversely significantly correlated with skeletal muscle PCr in both groups. Although the derived intercept was higher and the slope steeper in normals, similar relations of these two variables with PCr were noted in the range of PCr and lactate seen in patients, suggesting similar muscle buffer capacity for lactate in skeletal muscle in the two groups.

**Discussion**

The present study demonstrates important differences in the skeletal muscle metabolic response to submaximal and maximal upright exercise in patients with chronic heart failure compared to normal subjects. Our finding that glycolysis and glycogenolysis were accelerated in relation to absolute work rate in patients is consistent with previous studies evaluating the blood lactate\(^1\),\(^2\),\(^5\) and the \(^{31}\)P-NMR response\(^6\),\(^15\),\(^16\) to exercise in this disorder. Our results extend these observations by demonstrating that oxidative enzyme activity in skeletal muscle was inversely related to blood lactate accumulation during submaximal exercise in patients and support the concept that reduced skeletal muscle aerobic enzyme activity plays a role in determining the metabolic response to exercise in patients with chronic heart failure. In addition to examining the determinants of the skeletal muscle metabolic response to exercise, the present study demonstrates that during peak bicycle exercise, skeletal muscle PCr depletion and lactate accumulation were less in patients versus normals despite attaining comparable respiratory exchange ratios and near complete oxygen extraction in working skeletal muscle. Although these data do not delineate the mechanisms responsible for fatigue in patients, our results suggest that the magnitude of PCr depletion or lactic acidosis in skeletal muscle may not be the primary factors underlying early muscle fatigue in patients with chronic heart failure.

Our finding that blood lactate accumulation at a given work rate was inversely related to aerobic enzyme activity is consistent with previous studies that have suggested that aerobic enzyme content is an important determinant of lactate production during exercise in humans\(^11\),\(^12\),\(^22\) and animals.\(^10\),\(^11\) Although Mancini et al\(^8\) did not demonstrate a relation between skeletal muscle biochemical alterations and exercise metabolism in this disorder, our data are consistent with previous studies by Drexler et al\(^23\) that have demonstrated a relation between ultrastructural alterations in skeletal muscle and peak \(\text{Vo}_2\) in patients with chronic heart failure. Several lines of evidence are consistent with this concept that intrinsic skeletal muscle alterations play a role in determining exercise tolerance in this disorder. A number of studies\(^24\)–\(^26\) have consistently demonstrated no relation between peak \(\text{Vo}_2\) and resting left ventricular ejection fraction in patients. Acute administration of vasodilators or inotropic agents do not increase peak \(\text{Vo}_2\) despite immediate improvements in central hemodynamics\(^24\) and leg blood flow.\(^28\),\(^29\) However, chronic vasodilator therapy with nitrates or angiotensin converting enzyme inhibitors may improve peak \(\text{Vo}_2\) after a period of weeks or months, suggesting that peripheral training-like effects may play a role in this response.\(^24\) A recent study by Drexler et al\(^29\) has demonstrated that chronic therapy with an angiotensin converting enzyme inhibitor improves peak \(\text{Vo}_2\) and is accompanied by increased femoral venous oxygen extraction during peak exercise. Previous studies in our laboratory\(^17\) have demonstrated that exercise training in this disorder decreases blood lactate levels during submaximal exercise and improves endurance exercise without altering submaximal exercise cardiac output or leg blood flow. Our findings after exercise training\(^17\) and those of Drexler et al\(^29\) after chronic vasodilator therapy suggest that increases in aerobic enzyme activity in skeletal mus-
FIGURE 6. Relations of arterial blood lactate to skeletal muscle lactate in patients and normal subjects. r = correlation coefficient.

Lactate may play an important role in improving exercise tolerance after long-term interventions in this disorder. It is important to note that our finding that submaximal leg blood flow was not significantly correlated with submaximal blood lactate in patients does not necessarily indicate that skeletal muscle hypoperfusion does not contribute to early anaerobic metabolism in this disorder.

The changes in PCr, ATP, lactate, and glycogen noted in our normal subjects are consistent with previous studies examining short-term isotonic exercise in normal men. At peak exercise in normal subjects, PCr was reduced to 40% of resting values, lactate increased 10-fold, and ATP was reduced by 14%, indicating a maximal exercise effort. Although the precise factors mediating fatigue in skeletal muscle in normal subjects have not been clearly defined, previous studies have suggested that biochemical events including monobasic phosphate accumulation, high energy phosphate accumulation, or lactic acidosis play an important role in limiting exercise during short-term isotonic exercise in normal subjects.

Although increased intrapulmonary pressures may be important in producing dyspnea in acute heart failure, recent evidence suggests that skeletal muscle fatigue is the primary factor limiting exercise in stable ambulatory patients with chronic heart failure. Previous studies in these patients have demonstrated that during short-term maximal exercise 1) most are limited by leg fatigue, 2) pulmonary wedge pressures are not higher in patients limited by dyspnea versus those limited by fatigue, 3) pulmonary dead space and ventilation are related to decreased cardiac output and not to increased pulmonary wedge pressures, and 4) peak VO₂ is not related to peak pulmonary wedge pressures.

Although our patients attained a maximal or near-maximal exercise effort, as indicated by severe subjective leg fatigue, near-complete femoral venous oxygen extraction, high femoral venous PCO₂ levels, marked increases in glycolytic intermediates, and a high respiratory exchange ratio (1.37±0.14), they demonstrated less PCr depletion and lactate accumulation in skeletal muscle at peak exercise as compared with normal subjects. These data suggest that factors other than the magnitude of depletion of high-energy phosphates or intramuscular lactate accumulation are important in the pathophysiology of skeletal muscle fatigue during exercise using large muscle groups in patients with chronic heart failure. Wilson et al have recently demonstrated that reducing blood lactate accumulation by administering dichloroacetate does not improve exercise tolerance in patients with chronic heart failure, suggesting that lactic acidosis is not the sole mediator of muscle fatigue in this disorder. Studies by Eiken et al and Green et al in normal subjects have demonstrated that skeletal muscle hypoperfusion and/or hypoxia during exercise leads to reduced lactate accumulation and PCr depletion during peak exercise. Eiken et al demonstrated in normal subjects that blood lactate levels at peak exercise were markedly reduced after external compression of the legs to limit muscle blood flow, suggesting that although early anaerobic metabolism was present, it was not primarily responsible for limiting exercise tolerance during hypoperfusion. Green et al examined peak exercise vastus lateralis biopsy specimens obtained in normal subjects at sea level and during chronic exposure to hypoxia in a hypobaric chamber. After exposure to chronic hypoxia, highly motivated normal subjects demonstrated markedly reduced exercise tolerance. Despite similar high levels of subjective fatigue at peak exercise, the normal subjects also demonstrated less PCr depletion and lactate accumulation in skeletal muscle at simulated altitude when compared to sea level. The higher PCr levels and lower lactate levels in peak exercise biopsies in our patients are similar to these results by Green et al in normal subjects after exposure to hypobaric hypoxia and suggest that the physiological basis for skeletal muscle fatigue was altered in our patients. Several neuromuscular and biochemical mechanisms have been identified that may cause muscle fatigue independent of acidosis, phosphagen depletion, or monobasic phosphate accumulation, including failure of neuromuscular transmission, impaired calcium release by the sarcoplasmic reticulum, or alterations in contractile protein binding. It has been suggested that in
normal subjects during hypoxia or hypoperfusion that central nervous system inhibition of skeletal muscle afferents may limit exercise tolerance.7,9,37–39 This has been termed metabolic arrest7 or central fatigue38,39 and may act as a protective mechanism that prevents hypoxic damage to vital organs under severe stress. Although our data do not define the physiological significance of the altered peak exercise metabolic end point seen in our patients, it is possible that central fatigue mechanisms may have contributed to exercise limitation in our patients.

Our findings in patients at peak exercise are in contrast to previous studies using 31P-NMR that have demonstrated advanced acidosis and markedly decreased PCr/inorganic phosphate ratios in this disorder.8,14–16,40 Although several mechanisms could account for these differences, the physiological basis for the skeletal muscle metabolic results at peak exercise in our patients are not clearly defined. Indexes of exercise effort at peak exercise, including blood lactate, respiratory exchange ratio, femoral venous oxygen extraction, and the skeletal muscle content of glycolytic intermediates, indicate that our patients achieved a maximal exercise effort as compared to comparable end points reported in previous exercise studies in this disorder.1–3,24–29 Although the absolute peak lactate levels were less in patients compared with normals, it is possible that an accelerated rate of accumulation of lactate, glucose-1-PO4, or glucose-6-PO4 may have contributed to fatigue in our patients. Previous 31P-NMR studies have generally employed exercise involving smaller muscle groups that do not challenge maximal cardiac output or muscle blood flow capacity. In the present study, bicycle exercise was used that activates gluteal, thigh, and calf muscles and results in significant hypoperfusion of skeletal muscle with near-maximal femoral and central venous oxygen extraction.5 It is possible that in patients fatigue is mediated more by neuromuscular factors during maximal isotonic exercise, eliciting peak VO2 and more by skeletal muscle acidosis and PCr depletion during exercise involving small muscle groups. Thus, central fatigue mechanisms may be activated during large muscle exercise because of hypoperfusion of nonexercising organs or exercising skeletal muscle that are not activated during small muscle exercise that does not represent a challenge to maximal cardiac output.

Studies have consistently identified a gradient of lactate from skeletal muscle to arterial blood during intense exercise in normal subjects.41,42 Jorfeldt et al42 have suggested that during exercise the mechanisms that mediate lactate removal from muscle to blood are overwhelmed, causing accumulation of muscle lactate faster than blood lactate. Although previous studies by Bjarke et al43 have demonstrated an increase in this gradient during exercise in children with heart failure due to tetralogy of Fallot, the results of the present study demonstrate that the skeletal-muscle-to-blood lactate gradient is not altered in the presence of chronic heart failure because of systolic left ventricular dysfunction. Our data indicate that lower peak exercise arterial lactate levels in patients with chronic heart failure reflect less advanced skeletal muscle lactate accumulation and PCr depletion and are not due to alterations in the skeletal-muscle-to-blood lactate gradient.

In summary, the present study demonstrates that the skeletal muscle metabolic response to exercise is altered in patients with chronic heart failure. Consistent with the results of previous studies, demonstrating early blood lactate accumulation during exercise in this disorder,5,6 our patients demonstrated accelerated glycolysis and glycogenolysis in relation to absolute work rate when compared to normal subjects. In our patients, anaerobic metabolism, assessed by blood lactate accumulation during submaximal exercise, was inversely related to rest aerobic enzyme activity in skeletal muscle. Fatigue at peak exercise in patients was associated with less PCr depletion and lactate accumulation in skeletal muscle as compared to normal subjects, suggesting that factors other than the magnitude of lactic acidosis or high-energy phosphate depletion are important in mediating fatigue in this disorder. The results of the present study support the concept that reduced aerobic enzyme activity in
skeletal muscle plays an important role in determining the metabolic response to exercise in patients with chronic heart failure and suggest that long-term interventions that improve exercise tolerance may act, in part, through effects on skeletal muscle.

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