Skeletal muscle metabolism in patients with congestive heart failure: relation to clinical severity and blood flow


ABSTRACT We and others have previously demonstrated excessive phosphocreatine (PCr) depletion and acidosis in skeletal muscle during exercise in patients with congestive heart failure (CHF). In the present study, we performed serial measurements of PCr and pH during gradually incremental flexor digitorum superficialis exercise in 22 patients with CHF and 11 age-matched controls to determine: (1) whether abnormalities were present at the same relative workloads (a comparison that would at least partially compensate for differences in muscle mass), (2) the temporal course of the metabolic changes, (3) the relationship of the metabolic findings to clinical variables, and (4) the relationship of the metabolic abnormalities to forearm blood flow. The patients with CHF had significantly lower [PCr] and pH at all submaximal levels of exercise, and these abnormalities were apparent from the onset of low-level exercise. There was considerable heterogeneity among the patients with CHF with respect to the metabolic findings, with 14 of 22 exhibiting either PCr or pH values more than 2 SDs below normal. Patients whose capacity was more limited during the protocol had lower [PCr], and especially pH, at low loads than did other patients with CHF or the control subjects. The more symptomatic patients and those with more limited bicycle exercise tolerance also had lower pH values. In contrast, there were no significant differences in forearm blood flow between the patients and controls and no relationship between forearm blood and either clinical variables or the metabolic findings. These results indicate that skeletal muscle metabolic abnormalities are present in many patients with CHF and that they are not primarily due to either muscle atrophy or impaired blood flow. These changes may explain in part the marked heterogeneity of symptom status and exercise capacity of patients with similar degrees of cardiac dysfunction.


BECAUSE a number of studies have found poor correlations between exercise tolerance and measurements of cardiac function in patients with congestive heart failure,1, 2 considerable attention has focused on the role of peripheral factors as determinants of exercise limitation. Abnormalities of the peripheral circulation have been frequently described in the past,3, 4 and muscle atrophy may play an important role in chronically incapacitated subjects.5 We have shown, by 31P nuclear magnetic resonance (NMR) during fatigue-limited exercise, that patients with chronic congestive heart failure exhibit excessive phosphocreatine (PCr) depletion and increased glycolytic metabolism.6 Similar findings have been reported by Wilson et al.7 during less strenuous steady-state exercise. Previous studies have not detected a relationship between these metabolic changes and the severity of congestive heart failure; however, these have been limited by small numbers of subjects or have concentrated on steady-state measurements of high-energy phosphates. Several investigators have suggested that pH may be a more important determinant of fatigue.8-10

Despite the extensive literature demonstrating abnormalities of peripheral blood flow in congestive heart failure,3, 4 a recent study found no relationship...
between plethysmographic measurements of forearm blood flow and muscle metabolism during exercise, and surprisingly, the former values were similar to those in normal control subjects. In that study, however, comparisons between patients and control subjects were made at the same workloads, without correcting for the probably smaller muscle mass and lower work capacity of the patients. Furthermore, blood flow measurements were recorded only under steady-state exercise conditions, thus not permitting the detection of earlier flow reductions that could have resulted in an initial period of excessive glycolytic metabolism.

The present study was conducted to examine skeletal muscle metabolism in patients with heart failure and control subjects over a wide range of exercise loads with the use of a protocol that provides data from what approximates steady-state conditions in a single test and facilitates comparisons between patients and control subjects at comparable relative loads. Forearm blood flow was also examined during the same protocol in a subset of subjects, and comparisons were made in the “warm up” phase as well as at comparable absolute and relative loads. Finally, the metabolic findings were related to clinical variables and measurements of exercise tolerance to determine whether they could, at least in part, explain the marked variability in symptoms among patients with similar degrees of cardiac dysfunction.

Methods

Study population. Twenty-two men with stable congestive heart failure of 1 to 72 months’ duration were studied. Their mean age was 58 ± 8 years (mean ± 1 SD). The cause of heart failure was ischemic cardiomyopathy and primary cardiomyopathy in 12 and 10 subjects, respectively, and one, 13, six, and two were in New York Heart Association functional classes I, II, III, and IV, respectively. Their mean left ventricular ejection fraction by either radionuclide angiography or two-dimensional echocardiography was 23 ± 7% (range 13% to 40%).

A control group of 11 size- and age-matched untrained volunteers was studied by the same NMR protocol. All subjects gave informed consent according to a protocol approved by the local ethics committee.

NMR techniques. NMR spectroscopy was performed with a 1.89 tesla, 20 cm bore superconducting magnet (Oxford Instruments, Oxford, U.K.) interfaced with a Fourier transform spectrometer (TMR 32, Oxford Research System, Oxford, U.K.), operating at frequencies of 32.5 and 80.285 MHz for 31P and 1H, respectively. The spectroscopy procedures have been described previously. In brief, subjects sat beside the magnet positioned so that the flexor digitorum superficialis muscle of the dominant arm rested on a 2.5 cm diameter surface coil. The magnetic field was adjusted for homogeneity during repetitive pulsing at the 1H frequency, so that the line width at half maximum for water protons was below 40 Hz. 31P spectra were obtained with use of a 70 degree excitation pulse with a 1 sec repetition rate. An initial 256 pulse resting spectrum was obtained; thereafter, time-averaged 64 transient spectra were obtained at rest, during exercise, and during late recovery. Six 32 scan spectra were obtained during the initial minutes of recovery to assess the rapid metabolic changes during this period.

Spectral analysis. The time-averaged free induction decays were baseline corrected, apodized, subjected to an exponential multiplication yielding a line broadening of 6 Hz, and Fourier transformed. Quantitative analysis was conducted by previously described methods. The relative concentrations of intracellular PCr, inorganic phosphate (Pi), and the β-phosphate of ATP were determined by triangulation of their respective peaks, with correction for differential saturation due to the relatively short interpulse delay. The effects of partial saturation were examined by comparing fully relaxed spectra to 1 sec spectra in four patients and four control subjects and were found to be comparable in the two groups.

Changes in [PCr] were followed as a normalized PCr ratio, [PCr]/([PCr] + [Pi]), to minimize the effect of fluctuations in total signal intensity due to arm movement. During recovery, there was often some loss in total signal compared with the preexercise spectra, so that an assumption that PCr recovered fully after 12 min was used to back-correct the [PCr] during early recovery. Intracellular pH was calculated from the chemical shift of Pi.

Exercise protocol. The exercise routine consisted of repetitive finger flexion pulling a lever with the two distal phalanges at a rate of 40/min. The lever was attached via a two-pulley system to a bucket that was lifted a fixed distance of 5 cm with each repetition. Exercise was commenced with an initial weight of 0.75 kg, which was maintained for 4.8 min (four spectra, including dead time for storage) and then increased at a constant rate of 0.25 kg/min by the addition of water with a peristaltic pump. Exercise was continued until the point of fatigue. Spectra were obtained at 1.2 min intervals. This protocol has been shown to yield concentrations of PCr and Pi at any given load (weight) essentially identical to those obtained during steady-state exercise runs at the same weight for loads ranging from 20% to 70% of maximum in five normal subjects and three patients with congestive heart failure.

Plethysmography. Plethysmography was performed within 24 hr of NMR spectroscopy, with the two procedures being conducted in random order. Each patient was studied in a quiet, temperature-controlled room while sitting with his arm resting comfortably on a support apparatus built so that the elbow was at the level of the sternal notch and the forearm was elevated at a 30 degree angle. Patients with jugular venous pressures exceeding 8 cm of water whose forearm veins in this position were either distended at rest or did not empty rapidly after release of occlusion did not continue in this protocol. A mercury-in-silicone rubber strain gauge was placed around the forearm 4 to 6 cm below the antecubital crease. A pediatric cuff was placed around the wrist and an appropriately sized cuff was placed around the upper arm. Cuff inflation was accomplished with a specially built system that raised the wrist cuff pressure to 250 mm Hg and the arm cuff to 50 mm Hg within 1 sec and accomplished complete deflation within 3 sec. The hand was excluded by inflation of the wrist cuff 10 sec before each measurement. Forearm blood flow was determined from the rate of change in forearm circumference in the 3 to 10 sec period after venous occlusion and expressed in milliliters per minute per 100 ml forearm volume. Systemic blood pressure was measured simultaneously by an automated oscillimetric device placed on the opposite arm.

Eight control subjects and 13 patients underwent plethysmographic measurements. A minimum of five measurements at 1 min intervals were obtained at rest. Subjects then performed exercise according to the identical protocol and with the use of
a facsimile of the device used during the NMR studies. In the middle of each 1.2 min period (equal to the time for collection and storage of each 64 scan spectrum during the NMR study), exercise was discontinued for 6 to 12 sec and forearm blood flow was measured. Exercise was continued to an end point of fatigue. Immediately after cessation, four consecutive forearm blood flow determinations were made, with the highest value being taken as the peak postexercise flow. After a 10 min recovery period, an additional upper arm cuff was inflated to 100 mm Hg above systolic blood pressure for 5 min. Immediately before deflation, the wrist cuff was inflated, and then four consecutive forearm blood flow measurements were made to determine peak reactive hyperemic flow.

**Data analysis.** Measurements of intracellular pH and the normalized PCr ratio in the control subjects and patients at rest were compared by use of Student's unpaired t test and minute by minute during exercise by analysis of variance. Since the maximum weight pulled by the patients was lower than that of the controls, the weight at each minute was expressed as percent of the maximal weight (normalized load) and additional comparisons were made at 30%, 50%, and 70% of the maximal load. The significance of differences between groups was assessed by analyses of variance.

To determine the relationship between work output and PCr, plots of the normalized PCr ratio and of [Pi]/[PCr] vs normalized load (weight divided by maximal weight) were assessed for linearity. Those with an R² value greater than .75 by linear regression analysis for normalized loads between 0 and 70% were considered linear; the slopes of these fitted lines for the control subjects and patients were compared by Student's unpaired t test. Comparisons of NMR measurements between patient subgroups based on clinical variables such as age, clinical class, ejection fraction, and exercise capacity were also accomplished by Student's unpaired t tests.

Comparisons between control patients' and patients' resting, exercise, peak postexercise, and maximal postschemia forearm blood flow and vascular resistance were also made by unpaired t tests. Comparisons of flow and resistance measurements on a minute-by-minute or normalized load basis and at comparable normalized loads were made by analysis of variance.

**Results**

**Metabolic changes during exercise.** Figure 1 illustrates representative spectra at rest and during the same level of exercise in a patient and a control subject. While the differences at rest are minor, during exercise the patient exhibited a marked reduction in pH and [PCr] compared with the control subject. Table 1 presents the metabolic findings in relation to the time of exercise and exercise load, with each spectrum requiring 72 sec for accumulation and storage. At rest, the control group and patients exhibited similar findings, although the normalized PCr ratio was somewhat lower in the latter group due to a slightly higher initial [Pi]. There was little change in either pH or [PCr] over the initial six to eight spectra in the control group, whereas both pH and the normalized PCr ratio fell significantly beginning at the initial workload in the patients. pH and the normalized PCr ratio remained significantly lower in the patients throughout the protocol. There were no significant changes in the area of the β-ATP peak between the baseline spectra and the recovery spectra in either group, indicating that there was no loss of ATP.

![FIGURE 1. Spectra from a normal subject (left) and a patient with heart failure (right). The top spectra were obtained at rest and the lower ones, during exercise. The peaks are identified, and the derivation of the pH from the chemical shift of the Pi peak relation to the PCr peak is illustrated.](image)
Even though the groups were of comparable age and body size, the maximal load completed was significantly greater in the control subjects than in the patients (3.1 ± 0.6 vs 2.3 ± 0.5 kg). Exercise was limited by fatigue or muscle cramping in all patients, but there was a wide range of exercise tolerance. To determine whether the exercise endpoint was related to metabolic changes, the normalized PCr ratio and pH at 0.75 and 1.5 kg workloads (the initial load and the highest load completed by all subjects, respectively) for patients exercising 10 min or less and those completing more than 10 min were compared (figure 2). Patients with less exercise tolerance had lower pH measurements at the 0.75 and 1.5 kg loads than either the control subjects or patients with more preserved exercise tolerance, while the latter group did not significantly differ from the control subjects. Both groups of patients had lower normalized PCr ratios than the control subjects, but the intergroup differences, although significant, were not as large.

**Results of load normalization.** Because of the lower exercise tolerance in the patients than in the control subjects, comparisons based on exercise time entail comparisons at markedly different loads relative to the subjects’ maximum capacities in this protocol. Figure 3 presents the pH and normalized PCr ratio findings in relation to normalized load, expressed as a percent of each subject’s maximal load. At low loads (below 50% of maximal), the control subjects showed relatively little change in pH or in [PCr]. Even after this normalization, the patients exhibited lower pH values and normalized PCr ratios at submaximal levels of exercise.

Of note is that at the end of exercise, when limiting fatigue occurred, the two groups exhibited similar measurements, although this represented a much greater load in the control group.

The relationship between [PCr] and load was further investigated by examining plots of the normalized PCr ratio vs normalized load and of [Pi]/[PCr] vs normalized load in each subject. This latter relationship was examined because Chance et al. found it to be linearly related to power output and to reflect the status of oxidative metabolism. These plots were fit by least squares linear regression analysis and proved, except in one patient, to be linear (R² > .75) over the range of 0 (rest) to 70% of each subject’s maximal load, which encompassed 5 to 9 points, depending on the duration of exercise. Figure 4 exhibits these plots for a representative control subject and patient. Of note is the markedly steeper decline of the normalized PCr ratio and increase in [Pi]/[PCr] in the patient, reflecting the more rapid hydrolysis of PCr in relation to work output. The relationship between exercise load and pH was not linear, as can be seen in figure 4, right. Therefore, intergroup and interindividual comparisons were made at characteristic normalized loads—usually 50%.

Figure 5 illustrates the normalized PCr and [Pi]/[PCr] vs normalized load slopes for the two groups. The values for the control subjects were relatively homogeneous, while those for the patients were highly variable. Thirteen of the 21 patients whose plots were linear had steeper normalized PCr slopes than the mean ± 2 SD of the control slope, and the difference in group means was highly significant (− 0.30 ± 0.09

### Table 1

**Metabolic changes during continuous incremental exercise**

<table>
<thead>
<tr>
<th>Spectrum</th>
<th>Weight (kg)</th>
<th>% maximum weight</th>
<th>n</th>
<th>pH</th>
<th>[PCr]</th>
<th>[PCr] + [Pi]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rest 0</td>
<td>0</td>
<td>0</td>
<td>11</td>
<td>22</td>
<td>7.02 ± 0.03</td>
<td>7.02 ± 0.03</td>
</tr>
<tr>
<td>1</td>
<td>0.75</td>
<td>26</td>
<td>11</td>
<td>22</td>
<td>7.03 ± 0.05</td>
<td>7.00 ± 0.05</td>
</tr>
<tr>
<td>2</td>
<td>0.75</td>
<td>26</td>
<td>11</td>
<td>22</td>
<td>7.00 ± 0.03</td>
<td>6.94 ± 0.13</td>
</tr>
<tr>
<td>3</td>
<td>0.75</td>
<td>26</td>
<td>11</td>
<td>22</td>
<td>7.01 ± 0.04</td>
<td>6.91 ± 0.16</td>
</tr>
<tr>
<td>4</td>
<td>0.75</td>
<td>26</td>
<td>11</td>
<td>22</td>
<td>7.00 ± 0.04</td>
<td>6.89 ± 0.18</td>
</tr>
<tr>
<td>5</td>
<td>0.88</td>
<td>31</td>
<td>11</td>
<td>22</td>
<td>7.00 ± 0.05</td>
<td>6.87 ± 0.21</td>
</tr>
<tr>
<td>6</td>
<td>1.15</td>
<td>39</td>
<td>11</td>
<td>22</td>
<td>6.99 ± 0.03</td>
<td>6.81 ± 0.24</td>
</tr>
<tr>
<td>7</td>
<td>1.42</td>
<td>49</td>
<td>11</td>
<td>21</td>
<td>6.96 ± 0.08</td>
<td>6.76 ± 0.28</td>
</tr>
<tr>
<td>8</td>
<td>1.68</td>
<td>57</td>
<td>10</td>
<td>21</td>
<td>6.95 ± 0.10</td>
<td>6.67 ± 0.29</td>
</tr>
<tr>
<td>9</td>
<td>2.00</td>
<td>66</td>
<td>10</td>
<td>15</td>
<td>6.87 ± 0.13</td>
<td>6.64 ± 0.26</td>
</tr>
<tr>
<td>10</td>
<td>2.22</td>
<td>75</td>
<td>10</td>
<td>14</td>
<td>6.84 ± 0.16</td>
<td>6.54 ± 0.30</td>
</tr>
<tr>
<td>11</td>
<td>2.49</td>
<td>84</td>
<td>10</td>
<td>11</td>
<td>6.67 ± 0.27</td>
<td>6.41 ± 0.31</td>
</tr>
<tr>
<td>12</td>
<td>2.75</td>
<td>85</td>
<td>7</td>
<td>6</td>
<td>6.59 ± 0.25</td>
<td>6.16 ± 0.31</td>
</tr>
</tbody>
</table>

**CHF** = patients with congestive heart failure.

* p < .05; **p < .01; *p < .001, controls vs patients with CHF.

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**Massie et al.**

**Circulation**
FIGURE 2. The changes in the normalized PCr ratio (left) and pH (right) at low levels of exercise. The patients with congestive heart failure (CHF) are subdivided into group 1, which exercised over 10 min, and group 2, which had lower exercise tolerance. Both groups had lower PCr ratios at these loads, but only the more severely limited group displayed a marked fall in pH.

By the alternative method of analysis, 13 of 21 patients also had steeper [Pi]/[PCr] vs load slopes than the mean + 2 SD of the controls, $(0.51 \pm 0.21 \times 10^2 \text{ vs } 1.45 \pm 1.11 \times 10^2, p < .001)$. These analyses confirm that PCr was depleted at a significantly faster rate in relation to the work output. The pH measurement at 50% of maximal load was used to illustrate the values for individual subjects, and this is shown in figure 5, right. As with the other metabolic measurements, it can be seen that some (10 of the 22) patients had normal values (pH > 6.90, the mean - 2 SD for the control subjects), but the remaining 12 subjects had a lower pH.

The postexercise recovery phase was examined by determining the half-time (t½) of PCr recovery. For the control group, the t½ was $42 \pm 18$ sec. While the t½ in 13 of 18 patients with heart failure in whom it could be measured was similar to that in the controls, it was prolonged to at least 140 sec in four, resulting in a significantly higher group mean $(75 \pm 52$ sec, $p < .025$ vs control).

Relation of metabolic findings to clinical variability. From these data, it is apparent that while as a group patients with heart failure display abnormal skeletal muscle metabolism, there is considerable interindividual heterogeneity. The relationship of the metabolic
findings to several potentially relevant clinical variables was examined. These findings are shown in table 2. There were no differences in either the normalized PCr ratio or [Pi]/[PCr] vs normalized load slopes or the pH value at 50% of maximal load in groups of patients subdivided by age (above or below 60 years), cause of heart failure (coronary disease or primary cardiomyopathy), duration of heart failure (greater or less than 6 months), or ejection fraction (greater or less than 20%). Of note is that although the PCr related slopes were comparable in patients with New York Heart Association class I and II vs III and IV symptoms and in those with exercise capacities less than 100 W and in those who achieved loads equal or greater than 100 W, the pH at 50% maximal load differed (figure 6). This pH was 6.90 ± 0.16 in class I and II patients, a value not significantly lower than that in the control subjects (6.98 ± 0.04), vs 6.67 ± 0.22 in those in class III and IV (p < .02). Similarly, the patients with lower exercise capacities measured by bicycle ergometry had a mean pH at 50% of maximal load of 6.63 ± 0.16 vs 6.85 ± 0.21 in those with better exercise performance (p < .05).

Reproducibility of metabolic measurements. The repro-

| TABLE 2 | Relationship of metabolic findings to clinical variables |
|-----------------|-----------------|-----------------|-----------------|-----------------|
| | Patients with CHF | | | |
| | Controls (n = 11) | Age | Cause | Duration |
| | <60 yr (n = 12) | ≥60 yr (n = 10) | CAD (n = 12) | PCM (n = 10) | <6 mo (n = 9) | ≥6 mo (n = 13) |
| PCr ratio vs normalized load | | | | | |
| slope (× 10²) | -0.30±0.09 | -0.48±0.18 | -0.53±0.18 | -0.55±0.15 | -0.43±0.20 | -0.48±0.15 | -0.52±0.21 |
| [Pi]/[PCr] vs normalized load | | | | | |
| slope (× 10²) | 0.51±0.2 | 1.2±0.8 | 1.6±0.9 | 1.4±0.8 | 1.3±1.0 | 1.1±0.7 | 1.5±0.7 |
| pH at 50% maximal load | 6.98±0.04 | 6.78±0.24 | 6.81±0.23 | 6.77±0.24 | 6.81±0.23 | 6.83±0.22 | 6.77±0.24 |

CAD = coronary artery disease; CHF = congestive heart failure; EF = ejection fraction; PCM = primary cardiomyopathy.

* p < .05, difference between subgroups.

FIGURE 4. Plots of the normalized PCr ratio and of [Pi]/[PCr] vs normalized load for a normal subject and a patient. These were generally linear between 0 and 70% of maximal load, and were fit by linear regression to provide a slope that characterized the relationship between high-energy phosphate metabolism and work output. These slopes were steeper in the patients. The changes in pH were not linear. These subjects each underwent repeat studies within 1 week, and the results of both tests are shown as an indication of the reproducibility of the measurements.
ducibility of the NMR measurements was assessed in nine patients examined twice within 1 month while clinically stable (six within 1 week) and in three control subjects restudied within 2 months. Figure 4 shows the high degree of reproducibility that was present in many of the subjects, especially in the PCr measurements. Figure 7 presents findings on the PCr ratio vs normalized load slope and the pH at 50% maximal load from serial studies in the individual subjects. The slopes were quite reproducible and no patient went from a normal value (−0.48 × 10² or less steep) to an abnormal slope. There was somewhat more variability in the pH findings, with one patient exhibiting pronounced interstudy differences.

**Forearm blood flow.** Figure 8 presents the forearm blood flow measurements during exercise. When examined at identical times and loads, the patients and control subjects had similar mean values for forearm blood flow and (not shown) for forearm vascular resistance. The maximal exercise and posthyperemic blood flow measurements in the two groups were also compared (figure 9). These were lower in the patients, but the intergroup differences were either insignificant or of only borderline statistical significance. Furthermore, it should be remembered that the maximal exercise and postexercise measurements were recorded after the completion of substantially higher workloads in the normal subjects. Similar results were obtained when calculated forearm vascular resistances in the patients and control subjects were compared at peak exercise (12.6 ± 5.5 vs 10.3 ± 4.8 mm Hg/ml/min/100ml, p = NS) and during peak hyperemia (5.2 ± 1.9 vs 4.4

![FIGURE 5. The slopes of the PCr ratio and [Pi]/[PCr] vs normalized load. While there was considerable overlap between the control subjects and patients with CHF slightly more than half of the patients had values that were outside of the mean ± 2 SDs of control. A similar pattern was seen for pH at submaximal levels.](image-url)
by guest on July 25, 2017 http://circ.ahajournals.org/ Downloaded from

± 1.5 mm Hg/ml/min/100ml, p =NS). Of note is the considerable heterogeneity in all of these measurements among the control subjects and patients.

Relation of forearm blood flow to metabolic findings and clinical findings. As noted above, the blood flow measurements, like the metabolic findings, were extremely heterogeneous in the patients with heart failure. To determine whether differences in blood flow could explain the metabolic differences, forearm blood flow and vascular resistance measurements at rest; at the initial 0.75 kg load; at 30%, 50%, and 100% of maximal load; and during postischemic hyperemia were compared in groups of patients with normal (mean ± 2 SD of control) and those with abnormal metabolic findings. In addition, the increase in flow over time was linear during the period of increasing load, so the average rate of flow increase in each subject was determined from the slope of a line fit to these points. Representative values are listed in table 3. The only statistically significant findings concerned the difference in the groups with lower pH values at submaximal exercise. Perhaps surprisingly, the patients with a lower pH at 50% maximal load had slightly higher forearm blood flows at 70% of maximal load and at maximal load, as well as lower vascular resistance values. In addition, although there was no significant relationship between either the normalized PCr ratio or the [Pi]/[PCr] ratio and the rate of increase in forearm blood flow or rate of decline in forearm vascular resistance over time, forearm blood flow rose faster in those with lower pH values at submaximal exercise.

Discussion

The results of the present study indicate once again that skeletal muscle metabolism during exercise, as assessed by 31P NMR, is abnormal in patients with chronic congestive heart failure. This technique permits serial measurements of [PCr], [Pi], and intracellular pH. These were performed at 1.2 min intervals during an exercise protocol in which a low workload was maintained for 4.8 min and was then increased in a manner gradual enough to provide data comparable to steady-state measurements recorded at the same load. [PCr] and intracellular pH both fell faster in relation to work output in the heart failure group. We have shown this previously with a more strenuous, partially isometric exercise protocol, 6 and workers at the University of Pennsylvania have reported similar results during steady-state exercise at several power outputs. 7 In addition, as we noted in our earlier study, postexercise metabolic recovery is delayed in a minority of patients.

Previous studies, however, have not fully evaluated
several potentially important issues. Most patients with chronic heart failure have impaired exercise tolerance and are deconditioned. Lipkin et al.\(^5\) have shown that they have reduced strength and fiber atrophy. Since NMR samples a fixed volume of muscle, patients with a reduced muscle mass performing the same amount of external work would have greater energy requirements per gram of muscle examined. While we were unable to measure muscle mass directly, we found that the heart failure group had 10% lower lean body masses and 5% smaller forearm cross-sectional areas in the region in which the surface coil was placed. They also discontinued exercise at a 26% lower maximal load than the age- and size-matched control group. Since this latter difference between the two groups was quantitatively the largest, the metabolic findings were reexamined at comparable normalized loads. The intergroup differences in [PCr], [Pi], and pH at submaximal loads remained highly significant after this normalization, although as might be expected, at maximal workloads the control subjects and patients were more similar. Thus, the differences in skeletal muscle metabolism probably cannot be explained by reduced muscle mass.

Our protocol also included measurements in the initial minutes of very low-level exercise (approximately 30% of maximal load), thus permitting assessment of the temporal course of metabolic abnormalities. Our previous study used a more strenuous initial exercise phase\(^6\) and Wilson et al.\(^7\) only reported on steady-state measurements in the fourth through seventh minute of exercise. Importantly, our findings indicate that skeletal muscle bioenergetics are abnormal from the onset of exercise, and that there is not an early phase of normal or "compensated" metabolism that cannot be maintained. In fact, the subgroup of patients whose exercise was more limited because of early fatigue displayed lower pH values and normalized PCr ratios in relation to the absolute load than patients who exercised longer, suggesting that the metabolic changes may be at least partly responsible for their limited exercise tolerance.

A related observation of great interest is the finding

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

**FIGURE 9.** The blood flow measurements at peak exercise and during postischemic hyperemia. Peak blood flow after 5 min of ischemia tended to be higher in the control subjects, but the differences were not large.

### TABLE 3

<table>
<thead>
<tr>
<th>Relationship of metabolic results to forearm blood flow</th>
<th>PCr ratio slope</th>
<th>[Pi]/[PCr] slope</th>
<th>pH at 50% load</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal ((&lt; -0.48; ) n = 6)</td>
<td>Abnormal ((&gt; -0.48; ) n = 6)</td>
<td>Normal ((&lt; -0.9; ) n = 5)</td>
</tr>
<tr>
<td>Forearm blood flow (ml/min/100 ml)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td>1.2 ± 0.2</td>
<td>1.5 ± 0.6</td>
<td>1.2 ± 0.2</td>
</tr>
<tr>
<td>0.75 kg</td>
<td>3.3 ± 0.5</td>
<td>3.6 ± 1.5</td>
<td>3.3 ± 0.5</td>
</tr>
<tr>
<td>50% load</td>
<td>4.1 ± 2.0</td>
<td>4.5 ± 1.3</td>
<td>3.8 ± 2.1</td>
</tr>
<tr>
<td>Maximal load</td>
<td>10.2 ± 3.4</td>
<td>8.4 ± 2.4</td>
<td>10.2 ± 3.1</td>
</tr>
<tr>
<td>Postischemia</td>
<td>21.4 ± 3.9</td>
<td>18.5 ± 5.7</td>
<td>21.3 ± 3.6</td>
</tr>
<tr>
<td>Slope of increase (ml/min/100 ml of ex.)</td>
<td>3.6 ± 1.8</td>
<td>3.3 ± 1.3</td>
<td>3.5 ± 1.6</td>
</tr>
<tr>
<td>Forearm vascular resistance (mm Hg/ml/min/100 ml)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td>71 ± 15</td>
<td>69 ± 44</td>
<td>74 ± 16</td>
</tr>
<tr>
<td>0.75 kg</td>
<td>27 ± 11</td>
<td>27 ± 5</td>
<td>28 ± 5</td>
</tr>
<tr>
<td>50% load</td>
<td>21 ± 8</td>
<td>23 ± 9</td>
<td>22 ± 8</td>
</tr>
<tr>
<td>Maximal load</td>
<td>13 ± 5</td>
<td>11 ± 6</td>
<td>14 ± 5</td>
</tr>
<tr>
<td>Postischemia</td>
<td>5 ± 2</td>
<td>4 ± 1</td>
<td>5 ± 2</td>
</tr>
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\(^{A}p < .10; {^B}p < .05; {^C}p < .01\), normal group vs abnormal group.
of lower pH values at submaximal exercise in the more symptomatic patients. Such a relation between muscle metabolism and clinical symptoms in heart failure patients has not been previously described and may be of great importance in understanding the marked heterogeneity of symptoms in patients with similar degrees of cardiac dysfunction. Wilson and Wiener and their associates \(^7\), \(^11\) found no relationship between clinical indexes and their metabolic findings, but they did not examine pH. Several groups of investigators, using both \(^3\)P NMR and other techniques, have found that intracellular pH may be a major determinant of fatigue.\(^8\)\textsuperscript{--}\(^10\)

The most obvious explanation for the differences in muscle metabolism in normal subjects and patients with heart failure is reduced blood flow. Zelis et al.\(^3\), \(^17\)\textsuperscript{--}\(^20\) have demonstrated impaired forearm postischemic and postexercise hyperemia by strain-gauge plethysmography in patients with congestive heart failure and have provided several potential explanations for the reduced vasodilating reserve. Others using a variety of techniques have also reported reduced peripheral blood flow during exercise.\(^4\), \(^21\), \(^22\) This has been associated with excessive lactate release, indicative of inadequate oxygen delivery.\(^23\) Indeed, the rapid decline in intracellular pH, which is the most dramatic abnormality in many patients with heart failure, is often disproportionate to both work output and the decline in [PCr], indicating excessive glycolysis.\(^6\)

Thus, the clearcut lack of relationship between the degree of excessive PCr depletion and measurements of forearm blood flow in our study is somewhat surprising, although similar findings have been reported recently by Wiener et al.\(^11\) As with their NMR assessments, these workers did not report blood flow measurements in the first 3 min of exercise, thus leaving open the possibility that an initial failure to increase flow may have resulted in an anaerobic deficit that affected subsequent measurements. Our results do not support this hypothesis either, since the control subjects and patients exhibited very similar flow measurements from the onset of the exercise protocol. In fact, when the patients are subgrouped by whether or not their metabolic findings were abnormal, the only differences were higher forearm blood flows in those with lower pH measurements at submaximal exercise. This suggests that instead of impaired blood flow causing the metabolic differences, blood flow may be stimulated by the excessive acidosis in some patients. Wiener et al.\(^11\) did not relate blood flow and pH measurements, so it is not possible to determine whether this interesting finding was present in their study.

Several issues related to the forearm blood flow measurements warrant further discussion. First, our results differ from those of Zelis et al.,\(^3\), \(^17\)\textsuperscript{--}\(^20\) who showed large differences between patients with heart failure and control subjects. We found no reduction in flow at submaximal exercise and differences in maximal postexercise or postischemia hyperemia flow that were borderline and highly variable among individual subjects. These different results are probably explained by differences in the exercise protocols and in patients. We studied our patients in the sitting position, so that obstruction to venous return by elevated central venous pressures was not a factor, and we employed isotonic exercise. We also specifically excluded patients with more than mildly elevated venous pressures and did not include patients with significant edema. Zelis and Flaim\(^20\) have shown that excessive edema may impair arteriolar dilatation. Of note is that many of their patients had valvular heart disease, including mitral stenosis, while our subjects had dilated cardiomyopathies and were functionally less limited. Finally, our control subjects were substantially older than those enrolled in the study of Zelis and Flaim and they were therefore more comparable to the patient group. Since forearm blood flow may decrease with age,\(^24\) this could eliminate apparent differences. Wilson et al.\(^25\) have recently also failed to show marked abnormalities in forearm blood flow or vascular resistance in nonedematous patients exercising upright.

It should also be noted that strain-gauge plethysmography is not ideally suited for measurements during brief interruptions of exercise; movement artifacts may occur and only single measurements are possible. Longhurst et al.\(^26\) have shown that this technique may be inaccurate in some subjects. More importantly, this technique measures total flow and does not distinguish flow to exercising muscle from that to skin, nonworking muscle, or other tissues. Nonetheless, given our findings, it seems unlikely that differences in muscle flow alone could explain the metabolic differences between the control subjects and patients or among the patients themselves. Our preliminary finding of marked metabolic differences between control subjects and patients with heart failure during ischemic exercise\(^27\) supports this conclusion. In addition, unlike the pH findings, no relationship between the severity of heart failure or exercise impairment and the blood flow measurements was detected.

Since our metabolic results cannot be explained by impaired blood flow or muscle atrophy, they strongly suggest an intrinsic muscle abnormality. This could
result from an impairment of oxygen delivery caused either by shunting around capillary beds or by a block to diffusion. Perhaps more likely is an abnormality of energy production, such as reduced mitochondrial oxidative capacity or altered metabolic control, with a shift toward dependence on glycolysis. This could reflect a change in fiber type predominance or the pattern of fiber recruitment. Finally, a reduced efficiency of contraction could necessitate increased ATP hydrolysis in relation to the external work output. This kind of change could result from alterations in the handling of intracellular calcium ions or changes in regulatory proteins.

Whatever the mechanism, or more likely combination of mechanisms, responsible for the abnormalities of skeletal muscle metabolism, their severity clearly varies from individual to individual. Many of the clinical factors examined and the severity of cardiac dysfunction did not correlate with the metabolic findings. However, the pH values at submaximal load were significantly lower in the more symptomatic patients and were also lower in those with reduced exercise tolerance as measured by bicycle ergometry. These findings suggest that alterations in muscle metabolism may represent one of many factors that explain the marked heterogeneity of symptom status and exercise capacity of patients with similar degrees of left ventricular dysfunction. Further studies will be required to determine whether these observations in a small, non-weight-bearing muscle with limited blood flow requirements will also apply to the larger muscle groups that are responsible for symptomatic muscle fatigue during ordinary activity.

References

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