Abnormal skeletal muscle bioenergetics during exercise in patients with heart failure: role of reduced muscle blood flow

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ABSTRACT Using phosphorous nuclear magnetic resonance, we have previously demonstrated that patients with heart failure often exhibit abnormal forearm muscle metabolism during forearm exercise. To determine if this altered metabolism is due to reduced muscle flow, we measured forearm blood flow with phlethysmography and forearm muscle inorganic phosphate (Pi), phosphocreatine (PCr), and pH with 31P nuclear magnetic resonance spectroscopy at rest and during mild forearm exercise (0.2, 0.4, and 0.6 W) in 21 men with heart failure and in 12 aged-matched normal male subjects. The Pi/PCr ratio was correlated with power output and the slope of this relationship was used as an index of forearm metabolism. At rest, both groups had similar Pi/PCr ratios (normal subjects 0.11 ± 0.05; patients with heart failure 0.11 ± 0.03; p = NS) and forearm blood flows (normal subjects 2.9 ± 1.4 ml/min/100 ml; patients with heart failure 2.0 ± 1.2 ml/min/100 ml; p = NS). In both groups, exercise resulted in a progressive increase in both P/PCr and forearm blood flow as power output increased. However, the patients exhibited a steeper slope of the Pi/PCr-to-power output relationship than the normal subjects (normal subjects 1.4 ± 0.6 P/PCr U/W; patients with heart failure 3.0 ± 2.4 P/PCr U/W; p < .03). In contrast, forearm blood flow was similar in both groups during exercise (at 0.2 W, 6.3 ± 3.3 and 6.8 ± 3.2 ml/min/100 ml in normal subjects and patients with heart failure, respectively; at 0.4 W, 8.7 ± 6.5 and 8.3 ± 3.3; at 0.6 W, 12.8 ± 7.9 and 12.0 ± 4.6; all p = NS). Nine of the 21 patients with heart failure had slopes of the Pi/PCr-to-power output relationship above the normal range. These nine patients also had forearm blood flows comparable to flows observed in the normal subjects. These data indicate that forearm muscle metabolism during forearm exercise is altered in a subpopulation of patients with heart failure. This metabolic alteration does not appear to be due to decreased muscle blood flow, suggesting that other mechanisms, such as alterations in mitochondrial population or substrate utilization, may be responsible.

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PATIENTS with chronic heart failure are frequently limited by exertional fatigue.1,2 This fatigue is typically associated with abnormally elevated blood lactate levels, suggesting that altered muscle metabolism may be responsible.1,2 Therefore, we recently sought to investigate muscle metabolism in patients with heart failure using phosphorous nuclear magnetic resonance (NMR).3 This technique permits continuous and non-invasive monitoring of inorganic phosphate (Pi), phosphocreatine (PCr), and intracellular pH.4,7 These variables in turn permit assessment of muscle oxidative regulation and intramuscular glycolytic activity.

Mitochondrial oxidative metabolism and, to a lesser extent, cellular glycolysis are regulated by the relative concentrations of ADP and P.8,9 As work output increases, ADP and P are released from the breakdown of ATP and PCr. These changes stimulate mitochondrial respiration and glycolysis, ensuring close coupling between ATP utilization and ATP resynthesis. The P/PCr ratio measured with 31P NMR is directly related to the ADP level and correlates linearly with the velocity of mitochondrial oxidative respiration.10 Therefore, evaluation of the relationship of work to the P/PCr ratio provides an index of mitochondrial oxidative regulation and, to a lesser extent, of glycolytic regulation. Evaluation of the relationship of work versus pH provides an index of glycolytic activity.
In our prior study, we used this conceptual approach to determine if forearm muscle mitochondrial oxidative regulation and intramuscular glycolysis are altered in patients with heart failure. We observed that, during forearm exercise, such patients frequently exhibit a greater than normal increase in the P/PCr ratio and a greater than normal decrease in muscle pH relative to power output. This led us to conclude that muscle metabolic activity is altered in some patients with heart failure. However, this prior study provided no information about the mechanism responsible for this altered metabolism. A number of factors influence mitochondrial oxidative metabolism, including O₂ delivery, the mitochondrial population, the efficiency of oxidative metabolism, and substrate availability. Based on prior reports that skeletal muscle flow is decreased during forearm exercise in patients with heart failure, we speculated that reduced muscle O₂ delivery may be important. However, we obtained no data to support or refute this hypothesis.

Therefore, in the present study we sought to investigate whether reduced muscle flow is responsible for altered forearm metabolism in patients with heart failure.

**Methods**

**Subjects.** Twenty-one male patients with chronic congestive heart failure and an average age of 59 ± 9 years (SD; range 39 to 68 years) were studied. All patients were in New York Heart Association functional class II or III and were taking digoxin and diuretics. None had diabetes, peripheral edema, jugular venous pressure greater than 5 cm of water, ascites, angina pectoris, valvular heart disease, or intermittent claudication at the time of study. All patients had diffuse left ventricular dysfunction (ejection fraction of 24 ± 9%) and reduced maximal exercise capacity (peak VO₂ 14.5 ± 3.8 ml/min/kg; normal 20 ml/min/kg or greater). Cardiac dysfunction was attributed to idiopathic cardiomyopathy in 14 patients and to coronary artery disease in seven. Vasodilator therapy was withheld for 24 hr before the study. For comparison, 12 age-matched (55 ± 8 years, range 42 to 71 years) sedentary male control subjects were studied. These subjects had no history of heart disease and no cardiac abnormalities on physical exam.

The protocol was approved by the Committee on Studies Involving Human Subjects at the University of Pennsylvania. Written informed consent was obtained from all subjects.

**NMR protocol.** The muscle exercise protocol follows that used in previous studies. In these prior studies, forearm tensor/flexor exercise was performed within the magnet, thereby enabling metabolic change within the forearm to be measured continuously during exercise. All studies were performed at least 2 hr after a meal.

The seated subject placed his forearm in a 1.9 tesla, 29.2 cm bore superconducting magnet interfaced with a TMR 32 Oxford Research Systems spectrometer operating at 32.5 MHz for phosphorous. The flexor compartment of the forearm was positioned over a 4.5 cm diameter surface coil that allows examination of approximately 25 ml of tissue. Data acquisition was accomplished with the application of radio frequency pulses (pulse width empirically optimized at 25 to 35 msec) applied every 5 sec.

After positioning of the subject’s forearm within the magnet and optimization of field homogeneity, a 5 min resting 31P NMR spectrum was obtained. The subject then performed wrist flexion every 5 sec for 7 min at a workload of 1 J (average power output 0.2 W). Exercise consisted of depressing a handle that elevated a bar. The workload was varied by hanging different weights from the end of this bar. The workload was determined with the use of standard formulas from the weight lifted and the distance moved by the weight.

As in previous protocols, the steady state of arm exercise was established during an initial period of 1 min in which NMR spectra were not recorded. Data were then accumulated during the following 6 min in three 2 min intervals. After completion of exercise the subject was allowed to remove his arm from the magnet and rest for 15 min. At the end of this rest period, a repeat 2 min resting scan was obtained to ensure full recovery to baseline. Full recovery was always noted before the start of exercise at the next workload. The subject then repeated the protocol at 2 J (0.4 W) and 3 J (0.6 W).

**Spectral analysis.** Quantitation of metabolic components was obtained from the Fourier-transformed NMR spectra by signal-amplitude analysis. An exponential multiplication equivalent to a line broadening of 15 Hz was used, yielding a width at half height for PCr of less than 1 ppm. P_i and PCr peaks were measured and used to calculate the ratio P_i/PCr. Changes in PCr and P_i could be expressed as a ratio since these compounds are in a relatively fixed pool. Intracellular pH was measured as the chemical shift difference of P_i from PCr (pKₐ 4.6). Prior studies, as well as observations during this study, indicate that the P_i/PCr ratio is stable after 3 min of exercise. Therefore, the data accumulated during the last 4 min of exercise were used to calculate the P_i/PCr ratio. In contrast, pH was observed to decrease over time in some subjects so that the chemical shift during the last 2 min of exercise was used to calculate intracellular pH. Chance et al. have shown that the relationship between P_i/PCr and power output is linear at P_i/PCr values below 1.0. We have previously demonstrated the linearity of this relationship in patients with heart failure and in normal subjects. The slope of this relationship was therefore calculated for each subject based on the P_i/PCr values obtained that were 1.0 or less. The P_i/PCr ratio exceeded 1.0 at all three workloads in five of the patients with heart failure. In these patients, a slope was calculated based on the P_i/PCr at rest and at the lowest workload.

**Forearm blood flow.** Forearm blood flow measurements were made by plethysmography at least 2 hr before and after NMR spectroscopy. The same arm and the identical exercise protocol were used. The study was performed with the subject seated in a quiet room with the arm at the same height as the shoulder to ensure that there was no obstruction to venous return. A mercury-in-silicone rubber strain gauge was placed approximately 5 cm below the antecubital crease. Flow was determined by rapidly inflating a cuff around the upper arm to 40 mm Hg with a pneumatically powered Rapid Cuff Inflator (D.E. Hokanson, Inc., Issaquah, WA). Forearm blood flow was calculated from the rate of increase in forearm circumference during venous occlusion measured on a plethysmograph (Parks Electronics Laboratory, Beaverton, OR), and expressed in milliliters per minute per 100 milliliters forearm volume. The blood pressure was measured in the other arm with a sphygmomanometer. Circulation to the hand was arrested by inflating a cuff around the wrist to suprasystolic pressure at least 1 min before determination of forearm blood flow. During exercise, the wrist cuff was inflated continuously.

Four to five forearm flow measurements were made in sub-
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jcts at rest. Exercise was then initiated at 0.2 W. Flow was determined after each minute of exercise by rapidly inflating the venous occlusion cuff while the subject paused for 10 sec. Data for the last 4 min of exercise were averaged to calculate the mean forearm blood flow at each workload. The subject then rested for 10 min. Flow was remeasured at the end of the rest period to ensure full recovery to baseline and return to previous resting flow values was always noted before the next exercise level began. The exercise protocol was repeated at 0.4 and 0.6 W.

To ensure that flow during exercise was stable over the last 4 min of exercise, flows at each of the last 4 min of each workload were compared in six of the normal subjects and six of the patients with heart failure. Flows did not significantly change over the 4 min (table 1).

Forearm blood flow was not measured in three of the normal subjects and three of the patients with heart failure due to technical difficulties.

Reproducibility studies. To investigate the reproducibility of NMR and forearm blood flow data, three normal subjects and three patients with heart failure underwent duplicate NMR and flow studies on the same day. Each subject exercised at three loads for each test. Therefore, nine duplicate exercise measurements were obtained in the normal subjects. A comparable number was obtained in the patients with heart failure.

In the normal subjects, the P/PCr ratios measured in the two studies varied by 15 ± 12%, pH varied by 1.3 ± 1.5%, and forearm blood flow measurements varied by 9.2 ± 7.2% (all n = 9). In the patients with heart failure, P/PCr ratios varied by 50 ± 42%, pH by 3.4 ± 1.1%, and forearm blood flows by 19 ± 11%. The substantial variability in the P/PCr ratio in the three patients with heart failure was primarily due to the variability in the ratio when it exceeded 2. Variability of the P/PCr ratio when it was less than 2 was 30 ± 23%. This variability of metabolic measurements at high P/PCr ratios is consistent with functioning of mitochondrial oxidation in an unstable metabolic state. Chance et al.4-6 have suggested that such a state is present when the P/PCr ratio exceeds approximately 1 to 2.

Statistical analysis. Data from patients with heart failure and normal subjects at rest and during exercise were compared with Student’s nonpaired t test. The relationships between variables were examined by linear regression analysis. A p value < .05 was considered indicative of a significant difference. All data are expressed as mean ± SD.

Results

Results are summarized in table 2 and figures 1 to 4. The weight of the patients with heart failure was less than that of the normal subjects (72 ± 11 vs 80 ± 8 kg; p < .05). However, the groups had similar body surface areas (1.8 ± 0.2 vs 1.9 ± 0.1 m²) and forearm circumferences (24.7 ± 1.6 vs 25.4 ± 1.9 cm; both p = NS).

Hemodynamic and metabolic responses to exercise. At rest, normal subjects and patients with heart failure had similar P/PCr ratios, pH, and forearm blood flows (table 2). In both groups, exercise resulted in a progressive increase in P/PCr and forearm blood flow and a decrease in pH as power output increased (figures 1 to 3). However, the patients with heart failure exhibited higher P/PCr ratios at 0.4 and 0.6 W (figure 3 and table 2) and a steeper slope of the P/PCr-to–power output relationship than the normal subjects (normal subjects 1.4 ± 0.6 P/PCr U/W; patients with heart failure 3.0 ± 2.4 P/PCr U/W; p < .03; figure 4). In contrast, forearm blood flow was similar in the two groups at all three workloads (figure 3 and table 2).

Nine of the 21 patients with heart failure had P/PCr-to–power output slopes above the normal range and a greater than normal decrease in pH (figure 4 and table 2). These nine patients also had forearm blood flows within the normal range at rest and during exercise (table 2). ³¹P NMR spectra obtained in one of these patients are contrasted with spectra obtained in one of the normal subjects in figures 1 and 2.

Relationship of P/PCr to clinical variables. In the patients with heart failure, no linear relationship was found between the slope of the P/PCr-to–power output relationship and either age (r = .01) or peak exercise oxygen uptake (r = .14). In addition, when patients with normal P/PCr-to–power output slopes were compared with patients with greater than normal slopes, they were of comparable ages (59.4 ± 9.2 vs 58.4 ± 8.4 years) and had similar peak VO₂ levels (13.8 ± 3.9 vs 15.9 ± 3.8 ml/min/kg), left ventricular ejection fractions (22.7 ± 8.8 vs 23.6 ± 9.8%),

| TABLE 1 |
| Forearm blood flow over the last 4 min of exercise a |

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aFlows at 1 to 4 min were not significantly different by analysis of variance.
and arm circumferences (25.0 ± 1.8 vs 24.2 ± 1.3 cm; all p = NS).

**Discussion**

In a previous study, we demonstrated with 31P NMR that patients with chronic heart failure frequently exhibit markedly abnormal metabolic changes in exercising forearm muscle. In that study, we hypothesized that these metabolic abnormalities were due to reduced skeletal muscle blood flow. In the present study, we sought to test this hypothesis by examining the relationship between muscle metabolism and flow in the exercising forearm.

To assess forearm muscle metabolism, we monitored muscle P1, PCR, and intracellular pH at three different power outputs. We then examined the relationship between power output and the P1/PCr ratio and pH. Examination of the relationship between power output and pH provides an index of glycolytic activity during exercise. Examination of the relationship between power output and the P1/PCr ratio provides an index of cellular energy regulation. During exercise, mitochondrial respiration and, to a lesser extent, cellular glycolysis is regulated by the relative concentrations of ADP and P1. As power output increases, ADP and P1 are released from the breakdown of ATP and PCR, thereby stimulating mitochondrial respiration and glycolysis and ensuring close coupling between ATP utilization and ATP resynthesis. The P1/PCr ratio measured with 31P NMR is directly related to the ADP level. Therefore, by plotting power output, a measure of ATP utilization, versus P1/PCr, an indirect measure of ADP, one can assess how cellular metabolism is responding to increasing ATP utilization. Any factor that influences ATP resynthesis, such as mitochondrial population, O2 delivery, the efficiency of oxidative metabolism, and substrate availability, should alter this relationship.

To assess forearm muscle flow, we measured forearm blood flow by plethysmography. Since posture influences flow, we performed flow measurements with the subjects upright, as in the NMR experiment. Care was taken to ensure that the arm had adequate venous drainage. Total forearm flow was taken as an index of muscle flow since most of the forearm is made up of muscle. Nevertheless, it should be recognized that the forearm also includes nonmuscular tissue and inactive muscles, making our flow values only an approximation of flow to working muscle.

**Forearm metabolism and flow in normal subjects and patients with heart failure.** In the normal subjects, resting forearm muscle flows and 31P NMR spectra were similar to those reported previously by us and others. Forearm flow tended to be lower, however, than that observed in supine subjects. This is to be expected since it is known that forearm muscle flow decreases when a subject assumes the upright posture. Exercise produced a progressive rise in the
FIGURE 1. $^{31}$P NMR spectra and plethysmographic data obtained at rest and with exercise in a normal subject.
FIGURE 2. $^{31}$P NMR spectra and plethysmographic data obtained at rest and with exercise in a patient with heart failure. The scale on the plethysmographic curves is different than than in figure 1.
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P/PCr ratio and a drop in muscle pH, consistent with stimulation of both mitochondrial oxidative metabolism and glycolysis. The slope of the P/PCr ratio, 1.4 ± 0.6 P/PCr U/W, was in the same range as observed previously by us and by Chance et al.3-6 Forearm blood flow increased in the same general range as observed by other investigators using mild forearm exercise protocols.16, 17

In the patients with heart failure, the resting P/PCr ratios were not significantly different from normal, as noted in our previous study.3 With exercise, the patients exhibited a progressive increase in the P/PCr ratio and forearm flow and a decrease in pH, as in the normal subjects. However, the P/PCr ratio increased to a greater extent than in the normal subjects at 0.4 and 0.6 W, and the slope of the power output-to-P/PCr relationship was steeper than normal. This pattern was also identical to that previously noted by us in a smaller group of patients.3 Of particular interest was that patients exhibited a wide range of metabolic responses to exercise. Nine of the 21 patients had slopes of the power output-to-P/PCr relationship above the normal range. A similar heterogeneity of responses was noted in our previous study, with only six of nine patients exhibiting slopes outside the normal range.

Despite the presence of abnormal metabolic patterns in many of the patients, we found no evidence of concurrent reduced muscle flow. Resting forearm blood flow was in the normal range. With exercise, forearm blood flow increased progressively and normally both in the entire heart failure population and in the subgroup with distinctly abnormal metabolic patterns.

A number of prior investigators have reported that plethysmographic forearm blood flow is reduced at rest in supine patients with heart failure.16, 17, 22-24 Zelis and his colleagues16, 17 have also previously reported that forearm blood flow is lower than normal during progressive dynamic and during sustained isometric exercise in supine patients. There are several possible reasons why our findings differ from these prior observations. First, patients were studied while upright in the present study but were supine in prior studies. With the assumption of the upright posture forearm blood flow decreases in normal subjects but not in patients with heart failure.21, 22 Therefore, one would anticipate that differences between resting forearm blood flows in normal subjects and patients with heart failure would be less marked and possibly totally absent in the upright position. This same phenomenon may also have contributed to our finding of normal flow during exercise in our patients. Second, we may have studied

patients with less severe circulatory dysfunction than did previous investigators; Leithe et al.\textsuperscript{23} have shown that resting forearm blood flow is directly related to the level of circulatory dysfunction. This factor may be particularly important in explaining why our observations concerning exercise flows differ from those of Zelis et al.\textsuperscript{2, 16, 17} We studied ambulatory, optimally diur- esed patients, whereas Zelis et al. primarily studied edematous patients with more severe circulatory impairment. Forearm exercise may have taxed circulatory reserve more severely in the patients of Zelis et al. than it did in our patients. An adverse effect of edema on forearm vasodilation may also have contributed to the reduced forearm blood flow observed by Zelis and Flaim.\textsuperscript{25} Nevertheless, it should be pointed out that the range of peak VO\textsubscript{2} levels noted in our patients is consistent with moderate-to-severe exercise intolerance and circulatory dysfunction.\textsuperscript{2}

A third factor that may have contributed to differences between our results and those of prior investiga- tors is differences in the age and sex of populations. We studied age-matched male subjects whereas most other investigators have not matched normal and heart failure populations for sex and have usually compared younger normal subjects with older patients with heart failure.\textsuperscript{16, 17, 22, 24} Hellon and Clark\textsuperscript{26} observed that forearm blood flow decreased with age in 32 men but increased with age in 48 women. The fact that prior investigators often studied younger normal populations could therefore have produced an apparent but not real effect of heart failure on forearm flow.

**Potential limitations.** There are three important potential limitations of the present study. First, measurement of plethysmographic forearm blood flow has methodologic limitations. Forearm blood flow does not exclusively measure flow to working skeletal muscle. Flow to skin, nonmuscular tissues, and inactive muscle is included in forearm blood flow. Moreover, measurement by plethysmography of forearm blood flow during exercise may under- or overestimate forearm flow in some patients.\textsuperscript{27}

The second potential limitation of the present study relates to evaluation of forearm muscle metabolism with \textsuperscript{31}P NMR. This evaluation involves positioning the forearm over a surface coil, which allows examination of approximately 25 ml of tissue. The wrist flexion exercise protocol used in the present study does not work all forearm flexor muscles to the same extent. Every attempt was made to ensure that the surface coil was positioned over the same muscle group in all sub-

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**FIGURE 4.** Comparison of the slopes of the P/PCr-to-power output relationship in normal subjects and patients with heart failure.
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jects and that the orientation of the arm was similar. Nevertheless, there undoubtedly were some differences in the relationship of the surface coil to active muscle. This technical problem may have contributed to the variability in metabolic responses observed in the normal subjects and patients with heart failure. Specifically, subjects in whom the coil was over more intensively activated muscle would show a greater increase in P/PCr than subjects in whom the coil was located over less active muscle. However, these problems should have occurred equally in both normal and heart failure groups so that group comparisons of muscle metabolism are probably valid.

A third potential limitation of this study related to the exercise ergometer used. For purposes of simplicity, exercise consisted of lifting a weight every 5 sec via wrist flexion. Depending on the orientation of the arm in the magnet, different muscle groups potentially could be used for this form of exercise. The arm was strapped in place to minimize this problem. However, there still undoubtedly were differences in muscle recruitment patterns. An additional problem with the ergometer was that the duration of exercise and the velocity of contraction were not precisely controlled. We attempted to ensure a 1 sec contraction period and to discourage marked early increases in velocity by monitoring contraction patterns during plethysmography with the strain gauge and then instructing subjects to change their contraction pattern if necessary. Nevertheless, some differences in work undoubtedly existed between subjects. This problem probably did not influence the overall results, but is one that we are currently trying to circumvent by modifying the ergometer.

Clinical implications. The presence of normal forearm flow in patients regardless of forearm metabolic patterns strongly suggests that altered forearm muscle metabolism in heart failure is not due simply to reduced skeletal muscle flow. Therefore, it is likely that some other factor is operative. One possibility is that skeletal muscle cannot efficiently utilize delivered flow, for example, due to maldistribution of the flow or impaired diffusion of O₂. Longhurst et al.⁰ have in fact reported increased skeletal muscle capillary membrane thickness in patients with heart failure. Alternatively, skeletal muscle itself may be altered; a reduction in the muscle mitochondrial population or the efficiency of muscle oxidative metabolism could produce metabolic abnormalities similar to those observed in our patients. One potential mechanism that could produce such intrinsic muscle changes is deconditioning due to inactivity, an intervention known to reduce muscle oxidative capacity.²⁹ However, the lack of a correlation between muscle metabolism and peak exercise VO₂ is evidence against this hypothesis; one might expect that patients with the lowest VO₂ would be the most inactive and deconditioned.

In any event, our finding that skeletal muscle metabolism during mild exercise is altered in some patients but not others suggests that the impact of heart failure on skeletal muscle behavior is variable. Specifically, a subpopulation of patients appear to have intrinsic skeletal changes that cause increased ADP and Pₐ, levels at any given workload. These metabolic changes in turn augment cellular glycolysis, an effect that may precipitate or contribute to muscle fatigue.⁰⁻²² Further studies are needed to determine the mechanism responsible for this abnormal metabolic behavior.

References

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