Skeletal Muscle Metabolism Limits Exercise Capacity in Patients With Chronic Heart Failure

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Background—Several studies have indicated that skeletal muscle is important in determining the exercise capacity of patients with chronic heart failure (CHF). However, this theory has been investigated only in experiments based on local exercise involving a small muscle mass. We investigated skeletal muscle metabolism during maximal systemic exercise to determine whether muscle metabolism limits exercise capacity in patients with CHF. We also studied the relationship between muscle metabolic abnormalities during local and systemic exercise.

Methods and Results—Skeletal muscle metabolism was measured during maximal systemic exercise on a bicycle ergometer by a combination of the metabolic freeze method and $^{31}$P magnetic resonance spectroscopy in 12 patients with CHF and 7 age- and size-matched normal subjects. We also evaluated skeletal muscle metabolism during local exercise while subjects performed unilateral plantar flexion. Muscle phosphocreatine (PCr) was nearly depleted during maximal systemic exercise in patients with CHF and normal subjects (12.5±0.04% and 12.3±0.07%, respectively, of initial level). PCr depletion occurred at a significantly lower peak oxygen uptake (peak $\dot{V}O_2$) in patients with CHF than in normal subjects (CHF, 20.2±3.0 versus normal, 31.8±3.7 mL · min⁻¹ · kg⁻¹, $P<0.0001$). Muscle metabolic capacity, evaluated as the slope of PCr decrease in relation to increasing workload, was correlated with peak $\dot{V}O_2$ during maximal systemic exercise in patients with CHF ($r=0.83$, $P<0.001$). Muscle metabolic capacity during local exercise was impaired in patients with CHF and was correlated with capacity during systemic exercise ($r=0.76$, $P<0.01$) and with peak $\dot{V}O_2$ ($r=0.83$, $P<0.001$).

Conclusions—These results suggest that impaired muscle metabolism associated with early metabolic limitation determines exercise capacity during maximal systemic exercise in patients with CHF. There was a significant correlation between muscle metabolic capacity during systemic and local exercise in patients with CHF. (Circulation. 1998;98:1886-1891.)

Key Words: heart failure ▪ exercise ▪ muscles

Exercise tolerance is impaired in patients with chronic heart failure (CHF). Recent studies have shown that reductions in skeletal muscle blood flow, skeletal muscle mass, and aerobic enzyme activity and an increased percentage of fast-twitch–type (IIb) fibers in skeletal muscle can induce early anaerobic metabolism during exercise and may limit exercise in patients with CHF.¹ These findings have been confirmed by studies using $^{31}$P magnetic resonance spectroscopy ($^{31}$P MRS), which revealed intrinsic intracellular abnormalities of skeletal muscle metabolism manifested by a greater magnitude (and increased rate) of phosphocreatine (PCr) depletion and a decreased pH in patients with CHF.¹,³ However, $^{31}$P MRS results were based on local exercises involving only a small muscle mass (unilateral forearm or calf). Whether the metabolic abnormalities observed with such a local exercise are also associated with systemic exercise and whether muscle metabolism affects systemic exercise capacity and peak oxygen uptake (peak $\dot{V}O_2$) have not been clarified.

Studies in which subjects performed systemic exercises involving a large muscle mass using an upright bicycle or a treadmill have shown that PCr depletion and lactate accumulation in blood samples and muscle biopsy samples at maximal exercise are smaller in patients with CHF than in normal subjects.⁴–⁶ These studies have suggested that factors other than the magnitude of PCr depletion and lactate accumulation may influence skeletal muscle fatigue and exercise tolerance during maximal systemic exercise in patients with CHF. The results of studies based on blood sampling and muscle biopsy that used systemic exercises are not consistent with the results of $^{31}$P MRS studies.

In the present study, we measured skeletal muscle metabolism by $^{31}$P MRS during maximal bicycle exercise using the metabolic freeze method⁷ and investigated the effect of muscle metabolism on exercise tolerance and the relationship between metabolic abnormalities in local and systemic exercise.
TABLE 1. Baseline Characteristics of Normal Subjects and Patients With CHF

<table>
<thead>
<tr>
<th></th>
<th>Normal Subjects</th>
<th>Patients With CHF</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n=7)</td>
<td>(n=12)</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>50±7</td>
<td>57±8</td>
</tr>
<tr>
<td>Height, cm</td>
<td>167.6±5.8</td>
<td>167.3±2.2</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>63.6±2.6</td>
<td>64.8±6.1</td>
</tr>
</tbody>
</table>
| NYHA functional class, n | NA            | 5
| II                   | 7               |                 |
| III                  | 5               |                 |
| Dilated cardiomyopathy, n | NA        | 10              |
| Ischemic heart disease, n | NA      | 2               |
| Atrial fibrillation, n | NA            | 4               |
| LVEF, %              | NA              | 23±10            |
| β-Blockers, n        | NA              | 4               |

NYHA indicates New York Heart Association; NA, not applicable, and LVEF, left ventricular ejection fraction.

Methods

Subjects
We studied 12 Japanese male patients with CHF (Table 1). Medications included diuretics and vasodilators in 12 patients, digoxin in 4, and β-blockers (metoprolol, a β1-selective antagonist) in 4. Patients with peripheral vascular disease were excluded. We also studied 7 age- and size-matched normal male subjects. Written informed consent was obtained from all subjects.

Systemic Exercise Protocol
Subjects exercised on an upright electromechanical bicycle ergometer using a ramp protocol (15 W/min for CHF patients, 25 W/min for control subjects after a 3-minute warm-up). Respiratory gas analysis was performed with a breath-by-breath apparatus (Aeromonitor AE-280, Minato Medical Science). The severity of exertional dyspnea and leg fatigue was evaluated on a 10-point scale (new Borg scale). Blood samples were obtained from the opisthenar vein for measurements of lactate. The forearm and hand were warmed by hot water.

Magnetic Resonance Spectroscopy
31P MRS was performed with an 80-mm surface coil in a 55-cm bore, 1.5-T superconducting magnet (Magnetom H15, Siemens). One measurement required ~40 seconds. Standardized PCr ([PCr]/([PCr]+[Pi])) and muscle pH were calculated.

To evaluate metabolic capacity during local and systemic exercise, we calculated the slope of the relation between the power output (workload) and the PCr decrease (for systemic exercise, Sys-slope was calculated as the ratio of the PCr decrease to the peak workload, and for local exercise, Loc-slope was calculated by linear regression). We calculated the slope because PCr decreased linearly in response to a progressive workload.

Systemic Exercise With Metabolic Freeze
First, a cuff was placed around the thigh. Resting 31P MRS was performed with the surface coil placed on the thigh. Next, the subject performed maximal upright bicycle exercise outside of the magnet. As soon as the subject indicated that he could not continue, he was asked to stop pedaling suddenly, and the cuff was simultaneously inflated to a suprasystolic pressure. The load was then transferred to the magnet, and 31P MRS was started immediately. The interval between the cessation of exercise and the start of 31P MRS was usually 1 to 2 minutes. Details have been described in a previous study.

Local Exercise Protocol
Supine unilateral plantar flexion consisted of multistage incremental exercise. The load was lifted 5 cm each time the subject pedaled via a pulley system. Plantar flexion was repeated 40 times per minute, and 31P MRS was performed every minute. The load was initially set at 0.05 kg/cm² of the maximal calf flexor muscle cross-sectional area (MCA) and was increased by 0.05 kg/cm² of the MCA every minute (1 J · min⁻¹ · cm⁻²).

Metabolic Freeze Method
Harris et al previously demonstrated that arterial occlusion abolished the resynthesis of PCr and the pH change during 6 minutes of occlusion. We confirmed the validity of this method during local and systemic exercise in a previous study.

Metabolic Recovery Without Metabolic Freeze
To validate the necessity of the metabolic freeze method, we measured metabolic recovery without circulatory occlusion. Subjects performed plantar flexion at a constant workload of 50% of maximal voluntary contraction for 6 minutes. MR spectra were obtained with a repetition time of 1000 ms and an acquisition of 2 scans. PCr recovered rapidly; 19±8% of recovery occurred within the first 7 seconds after exercise and 37±13% occurred after 22 seconds (Figure 1). Other studies have shown similar results.

Statistical Analysis
Results are shown as mean±SD. Intergroup comparisons of single measurements were performed with the Student unpaired t test. Whenever serial measurements of the same metabolite were performed during exercise, ANOVA was used. The relationship between variables was examined by linear regression analysis. A level of P<0.05 was accepted as statistically significant.

Results
Physiological Responses to Maximal Systemic Exercise
Peak respiratory ratio and severity of exertional leg fatigue and dyspnea were similar in patients with CHF and normal subjects (Table 2). Blood lactate concentration at rest was slightly greater in patients with CHF than in normal subjects, but the difference was not significant. Blood lactate concentration at peak exercise was significantly lower in patients with CHF than in normal subjects.
Skeletal Muscle Metabolism During Maximal Systemic Exercise

Representative MR spectra are shown in Figure 2. PCr was nearly depleted at peak exercise in both groups (Table 2). The decrease in muscle pH was significantly greater in patients with CHF. Muscle pH was not consistent with blood lactate level at rest or at peak exercise in patients with CHF or in normal subjects. Muscle metabolic capacity evaluated as the Sys-slope was significantly correlated with peak VO$_2$ and the anaerobic threshold (AT) (Figure 3).

Skeletal Muscle Metabolism During Local Exercise

Muscle metabolic capacity evaluated as the Loc-slope was significantly steeper in patients with CHF than in normal subjects (Table 3), indicating that PCr depletion occurred more rapidly at equivalent workloads in patients with CHF. The Loc-slope was significantly correlated with the Sys-slope, peak VO$_2$, and AT (Figure 4). These findings were independent of muscle mass, because the workload was imposed per MCA.

Discussion

Major Findings

In this study, PCr was nearly depleted during maximal systemic exercise in patients with CHF and in normal subjects, indicating that the skeletal muscle metabolic limitation coincided with the end of exercise. PCr depletion occurred at a significantly lower peak workload and peak VO$_2$ in patients with CHF than in normal subjects, and the decrease in muscle pH was also greater in patients with CHF than in normal subjects. Impaired muscle metabolic capacity (Sys-slope) was closely correlated with exercise capacity, peak VO$_2$, and AT. Thus, skeletal muscle metabolism was a primary limiting factor even during maximal systemic exercise and was an important determinant of exercise capacity in patients with CHF.

In the present study, patients with CHF also showed an impaired metabolic capacity during local exercise. Moreover, metabolic capacity during local exercise (Loc-slope) was correlated with metabolic capacity during systemic exercise (Sys-slope) in patients with CHF.

Skeletal Muscle Metabolism During Maximal Systemic Exercise

At peak exercise, PCr was severely depleted in the quadriceps in patients with CHF and in normal subjects. This depletion indicated that there was no or little energy reserve in the quadriceps, which probably made it difficult to continue the exercise.$^{11}$ That is, all the available muscle fibers, including slow- and fast-twitch fibers, had been recruited and exhausted. Muscle pH was also markedly decreased in both groups, especially in patients with CHF, indicating that anaerobic metabolism and muscle acidosis were more accelerated in patients with CHF than in normal subjects.

Only a few studies have examined skeletal muscle energy metabolism during incremental maximal systemic exercise in patients with CHF. Sullivan et al$^4$ reported that at maximal bicycle exercise, PCr depletion and lactate accumulation in
muscle biopsy samples were significantly less in patients with CHF than in normal subjects. Schaufelberger et al. found similar results. However, Náveri et al. reported that PCr depletion and lactate accumulation during maximal bicycle exercise were similar in patients with CHF and normal subjects as determined by examination of muscle biopsy samples. In those studies, a significant amount of PCr remained after exercise in both groups.

The discrepancy between the present results and previous studies may be related to differences in methodology. The first possible factor is the time lag from the end of the exercise to completion of the muscle biopsy procedure in previous studies. The muscle biopsy is completed at least several seconds after exercise is stopped, and PCr recovers rapidly after exercise (Figure 1). Thus, the PCr level may change significantly by the time the biopsy sample is obtained. Moreover, PCr level may recover even when exercise intensity is reduced without termination of exercise. In the present study, we used the metabolic freeze method to avoid recovery of PCr and muscle pH. Differences in the sample volumes may also have contributed to the differences in results. Biopsy samples are generally obtained with a needle at a depth of 10 to 40 mm, whereas we used a surface coil with a diameter of 80 mm. The variability of the fiber-type distribution within muscles may also have been a contributing factor. Another possibility is that 31P MRS measures only soluble PCr, whereas the biochemical assay of muscle samples measures both soluble and insoluble PCr.

**Intramuscular pH and Blood Lactate**

Blood lactate concentration during maximal systemic exercise was lower in patients with CHF than in normal subjects in the present study, which is consistent with the results of

![Figure 2. MR spectra in a representative normal subject (left) and a patient with CHF (right). The PCr signal almost disappeared in both cases, and the pH decreased more severely in a patient with CHF.](image)

![Figure 3. Left, Relationship between peak VO2 and metabolic capacity during maximal systemic exercise (Sys-slope) in patients with CHF. Right, Relationship between AT and Sys-slope in patients with CHF.](image)
previous studies. However, there was a discrepancy between blood lactate concentration and muscle pH measured by 31P MRS. Muscle pH at peak exercise was significantly lower in patients with CHF than in normal subjects. One possible explanation for the discrepancy is that lactate production is not the major source of H⁺ in exercising skeletal muscle. During progressive exercise or heavy exercise, progressive acidosis is more likely to be caused by acceleration of CO₂ and H⁺ production from CHO metabolism than by lactate accumulation. It is also possible that there was a blood/muscle lactate gradient in patients with CHF in the present study.

Study Limitations

Peak VO₂ was higher in patients with CHF in the present study than in previous reports because our patients were not obese (body mass index, 23.1 ± 1.9).

We measured lactate by the arterialized venous sampling technique. Ideally, we should have measured femoral venous lactate concentration. However, it has been demonstrated that the lactate concentration in arterialized venous blood obtained after the sample site has been warmed is similar to the arterial lactate concentration and that the arterial and femoral venous lactate concentrations show similar kinetics.

### TABLE 3. Results From Maximal Local Exercise (Plantar Flexion)

<table>
<thead>
<tr>
<th></th>
<th>Normal Subjects (n=7)</th>
<th>Patients With CHF (n=12)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximal cross-sectional area, cm²</td>
<td>57.8±4.2</td>
<td>51.1±7.3</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Peak workload, kg</td>
<td>31.3±8.0</td>
<td>23.4±6.6</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Peak J, min⁻¹ · cm⁻²</td>
<td>11.1±2.2</td>
<td>9.9±1.9</td>
<td>0.21, NS</td>
</tr>
<tr>
<td>Standardized PCr</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td>0.90±0.04</td>
<td>0.91±0.03</td>
<td>NS</td>
</tr>
<tr>
<td>Peak</td>
<td>0.36±0.24</td>
<td>0.24±0.14</td>
<td>0.07, NS</td>
</tr>
<tr>
<td>Muscle pH</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td>7.07±0.04</td>
<td>7.01±0.06</td>
<td>NS</td>
</tr>
<tr>
<td>Peak</td>
<td>6.76±0.20</td>
<td>6.57±0.22</td>
<td>0.06, NS</td>
</tr>
<tr>
<td>Loc-slope, J⁻¹</td>
<td>−0.051±0.005</td>
<td>−0.067±0.011</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

### Figure 4

A. Relationship between metabolic capacity during maximal systemic (Sys-slope) and local exercise (Loc-slope) in patients with CHF. B. Relationship between peak VO₂ and Loc-slope in patients with CHF. C. Relationship between AT and Loc-slope in patients with CHF.
Conclusions
We demonstrated that muscle metabolic capacity was closely related to exercise capacity during maximal systemic exercise. The intrinsic metabolic capacity during local exercise was significantly correlated with the metabolic capacity during systemic exercise and with exercise capacity. Thus, the present study suggests that exercise tolerance is governed largely by peripheral muscle. Factors affecting muscle metabolism, such as muscle intrinsic abnormalities, muscle mass, and muscle perfusion, may determine exercise capacity in patients with CHF.

Previous studies have shown that an acute improvement in hemodynamics does not lead to an acute improvement in exercise tolerance in patients with CHF.\(^1,14\) The explanation for this observation may be that an improvement in exercise tolerance requires an improvement in skeletal muscle metabolism. In fact, recent studies have demonstrated that exercise training can improve exercise tolerance, largely via peripheral adaptations in the absence of improvements in central hemodynamic function.\(^15,16\) We suggest that skeletal muscle dysfunction may predominate over circulatory dysfunction in many patients with CHF. Thus, skeletal muscle training through exercise may improve exercise tolerance to a level that matches the circulatory capacity. In contrast, if circulatory dysfunction is predominant, circulatory improvement may immediately improve exercise capacity by improving muscle perfusion.

The present study emphasizes the central role of skeletal muscle in determining exercise capacity in patients with CHF.

References
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