Comparisons of the Skeletal Muscle Metabolic Abnormalities in the Arm and Leg Muscles of Patients With Chronic Heart Failure

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Background It has been suspected for some time that patients with chronic heart failure (CHF) have abnormal muscle metabolism, so in the present study the muscle metabolism of the arm and leg were compared by \(^{31}\text{P}\)-magnetic resonance spectroscopy (\(^{31}\text{P}\)-MRS) to examine the relationship to exercise tolerance.

Methods and Results The study group comprised 13 patients and 11 normal controls. Calf-plantar and forearm-wrist flexion were performed to evaluate the metabolic capacity assessed as the phosphocreatine breakdown rate (PCr-slope) and muscle pH at a submaximal (70% peak) work rate (submax-pH). Exercise of both the arm and leg resulted in an earlier decrease in PCr and muscle pH in patients with CHF compared with controls. There were significant correlations between peak oxygen uptake (peak VO\(_2\)) and the PCr-slope in both limbs in patients with CHF (forearm: r=0.63, p<0.05; calf: r=0.60, p<0.05), but no correlations in normal controls. There was a close correlation between the ventilatory anaerobic threshold (AT) and the PCr-slope in the calf (r=0.85, p<0.01), but not in the forearm in patients with CHF. Submax-pH in both upper and lower limbs was not significantly correlated to peak VO\(_2\) or AT in either patients with CHF or controls.

Conclusions Although metabolic abnormalities during exercise are seen in both arms and legs, leg muscle abnormalities, in particular, are closely related to systemic exercise intolerance in patients with CHF. (Circ J 2004; 68: 573–579)

Key Words: Exercise tolerance; Heart failure; \(^{31}\text{P}\)-magnetic resonance spectroscopy; Skeletal muscle metabolism

I t has been repeatedly demonstrated that there is a weak or no relation between indices of central hemodynamic function and exercise capacity in patients with chronic heart failure (CHF).1,2 Moreover, if central hemodynamic variables are improved quickly with vasodilators,3 inotropic support,4 or even cardiac transplantation,5 there is no immediate improvement in exercise tolerance but rather a gradual change over weeks and sometimes months. Therefore, abnormal muscle metabolism has been suspected for more than a decade in patients with CHF.

Studies have demonstrated remarkable early anaerobic metabolism in patients with CHF, which may be related to reductions in the skeletal muscle blood flow, skeletal muscle mass, aerobic enzyme activity, and an increased percentage of fast-twitch type (IIb) fibers in skeletal muscle.6–21 However, these studies have not, in fact, reported consistent patterns of abnormalities and some studies reported correlations between muscle abnormalities and exercise tolerance whereas other studies reported that there was no relationship between them.6,8,9,11–17,19 The different findings among the studies might be partly related to the different exercise protocols used. Some investigators studied the upper limbs7,12 and others the lower limbs8,10–19 Although upper and lower limbs have been similarly used as examples of peripheral muscles and have been exercised using small muscle-mass exercises, the functional and morphologic concordance and/or differences between them in the same individuals have never been elucidated.

The aim of this study was to compare the muscle abnormalities of the upper and lower limbs and examine their relationship to systemic exercise intolerance in patients with CHF.

| Table 1 Baseline Characteristics of Normal Controls and Patients With Chronic Heart Failure |
|------------------------------------------|-------------------------|-------------------------|
| Subjects (n)                             | 11                      | 13                      |
| Male (n)                                 | 6                       | 7                       |
| Female (n)                               | 5                       | 6                       |
| Age (years)                              | 49±6                    | 52±12                   |
| Height (cm)                              | 158±8                   | 161±8                   |
| Weight (kg)                              | 54±6                    | 59±8                    |
| NYHA functional class (n)                |                          |                         |
| II                                       | 7                       |                         |
| III                                      | 6                       |                         |
| Peak work rate (W)                       | 153±541                 | 101±28*                 |
| Peak VO\(_2\) (mL/min per kg)            | 30.9±6.5                | 18.9±4.4*               |
| AT (mL/min per kg)                       | 21.5±4.3                | 13.8±2.5*               |

AT, anaerobic threshold; CHF, chronic heart failure; NYHA, New York Heart Association. All values are mean±SD. *p<0.005, vs controls.
Methods

Subjects

We studied 13 patients with CHF and 11 age- and size-matched normal controls (Table 1). The etiologies of CHF were dilated cardiomyopathy (3 patients), ischemic cardiomyopathy (1 patient), old myocardial infarction (2 patients), valvular heart disease (6 patients), and hypertensive heart disease (1 patient). Patients were administer the following medicines: diuretics (65%), digitalis (29%), ß-blockers (42%) and vasodilators (76%). The ejection fraction of the left ventricle (mean ± SD) was 23±10% (42%) and vasodilators (76%). The ejection fraction of the left ventricle (mean ± SD) was 23±10% (42%). All patients except for those with valvular disease was 23±10% (mean±SD). Before participation in the study, subjects underwent examinations to detect peripheral vascular diseases including palpation of peripheral pulses. Written informed consent approved by the hospital’s ethical committee was obtained from all subjects.

Systemic Exercise Capacity

Subjects exercised on an upright electromechanical bicycle ergometer (Corival 400, Lode, Holland) using a RAMP protocol (15 W/min for CHF patients, 25 W/min for controls after a 3-min warm-up). Subjects were asked to exercise up to the symptom-limited maximal point. Electrocardiograms were monitored during exercise. Respiratory gas analysis was performed using a breath-by-breath ventilatory anaerobic threshold (AT) apparatus (Aeromonitor AE-280, Minato Medical Science, Osaka, Japan). The ventilatory anaerobic threshold (AT) was determined by the V-slope method, as described by Osaka, Japan). The ventilatory anaerobic threshold (AT) was determined by the V-slope method, as described by Wasserman et al.

Magnetic Resonance Spectroscopy

31P magnetic resonance spectroscopy (31P-MRS) was performed using an 80-mm surface coil in a 55-cm bore, with a 1.5-tesla superconducting magnet (Magnetom H15, Siemens Medical Systems, Germany). Shimming was adjusted by using the proton signals from water. Spectra were obtained with a pulse width of 500 μs, a transmitter voltage of 20.0 V, and a repetition time of 2,000 ms. Each spectrum represented the average of 16 scans. One measurement required approximately 40 s. Because only the relative changes in high-energy phosphates were evaluated, we did not correct values for saturation. Phosphocreatine (PCr) was standardized as follows: standardized PCr = [PCr]/([PCr] + [Pi]), where Pi is inorganic phosphate. The muscle pH was calculated from changes in the chemical shifts of Pi relative to PCr:

\[
\text{pH} = 6.75 + \log\left(\frac{s - 3.27}{5.67 - s}\right) \text{ ppm} = \text{Pi-PCr}
\]

Forearm and Calf Exercise

In order to load a subject, we devised a pulley system for the whole-body magnetic resonance system. Supine unilateral plantar flexion or forearm flexion was performed with a multistage incremental symptom-limited protocol that was the same for the forearm and the calf.19,25 We normalized the workload to adjust for differences in muscle mass. First, we measured the maximal cross-sectional area (MCA) of the flexor muscles in each subject using magnetic resonance imaging (MRI). Recruited muscles in the exercise protocol were determined by T2-weighted MRI in another experiment.26 The subject’s right arm or calf was placed on a pedal attached via a pulley system to loads. The load was initially set at 0.05 kg/cm² of the MCA and was increased by 0.05 kg/cm² every minute. The load was lifted 5 cm each time and the lifting was repeated 40 times/min. Thus, the workload was equal to 1 J/min per cm². During exercise, the subject’s muscle metabolism was measured by 31P-MRS every minute with a surface coil placed under the muscles.

To evaluate the metabolic capacity of skeletal muscle during calf plantar flexion and forearm wrist flexion exercise, we calculated the slope of the standardized PCr decrease in relation to increases in the work rate by linear regression. The calf-slope was determined for calf plantar flexion and the arm-slope for forearm flexion. Because standardized PCr decreases linearly in response to a progressively increasing work rate,5,27,28 the PCr slope is a simple indicator of the rate of PCr breakdown against the work rate, which may mainly reflect the oxidative capacity of skeletal muscle. We used the muscle pH at the submaximal work rate to evaluate muscle acidification. In this study the submaximal work rate was determined to be 70% of the maximal work rate.

Statistical Analysis

Results are the mean value ± SD. Intergroup comparisons of single measurements were performed using the Student’s unpaired t-test. Differences in the values of localized muscle exercise between the forearm and calf were evaluated by using Student’s paired t-test in each group. The relationship between variables was examined by linear regression analysis. Repeated measures analysis of variance (ANOVA) were used to compare changes in the standardized PCr, muscle pH during forearm wrist and calf plantar flexion exercise in normal controls and in patients with CHF. A p-value <0.05 was accepted as statistically significant.
Results

Systemic Exercise Capacity
The peak work rate, the AT and the peak oxygen uptake (peak $\dot{V}_{\text{O}_2}$) were significantly greater in normal controls than in patients with CHF (Table 1). In this study we could not determine AT in 3 patients with CHF.

Forearm and Calf Size
There were no significant differences in forearm and calf sizes between patients and controls (Table 2), but there was a significant difference in the proportion of forearm to calf size, which suggests that the calf muscle was relatively atrophied compared with the forearm in patients with CHF. Both the forearm and calf MCAs in normal controls, but not in patients with CHF, significantly correlated with peak $\dot{V}_{\text{O}_2}$ and AT (Fig 1). There was a very close correlation between forearm MCA and calf MCA in normal controls ($r=0.73, p=0.01$ for controls and $r=0.34, p=0.33$ for CHF patients), but no correlation in patients with CHF.

Forearm and Calf Exercise
Both wrist and plantar flexion against an incremental work rate resulted in a progressive decrease in standardized PCr in the patients with CHF and the normal controls. Fig 2 shows the time course of the changes in standardized PCr and muscle pH during forearm wrist flexion and calf plantar flexion. In the forearm muscle, the time course of changes in standardized PCr did not differ significantly by ANOVA between normal controls and patients with CHF, but differed significantly in muscle pH. In the calf muscle, there were significant steeper decreases in both standardized PCr and muscle pH in the patients with CHF than in normal controls. The standardized PCr and muscle pH decreased more rapidly as the work rate increased in patients than in controls, indicating that PCr depletion occurred more rapidly at equivalent work rate in patients with CHF.

The standardized PCr depletion and the pH decrease at the maximal work rate tended to be greater in patients with CHF than in normal controls. For both forearm and calf muscles, there was no statistically significant difference in the maximal work rate normalized by muscle mass between patients and controls (Table 2). Patients with CHF performed at a nearly normal maximal work rate accompanied by an enhanced anaerobic metabolism.

Muscle metabolic capacity evaluated as the PCr-slope was steeper in patients than in controls for both the arm and
Fig 2. Time course of changes in standardized phosphocreatine (PCr) and muscle pH during forearm wrist and calf plantar flexion with the incremental protocol. The standardized PCr and pH decreased more rapidly versus work rate in patients than in controls. *p<0.05 by Student’s t-test, #p<0.05 by ANOVA vs controls.

Fig 3. Relationship between metabolic capacity, evaluated as phosphocreatine breakdown rate (PCr-slope), and peak oxygen uptake (peak \( \dot{V}O_2 \)) in the forearm and calf.
leg muscles (Table 2), but a significant difference was seen only in the calf. In patients with CHF, there was a significant correlation between the PCr-slope and peak \( \dot{V}O_2 \) in each limb (Fig 3). There was also a significant correlation between the PCr-slope and AT in the calf muscle \((r=0.85, p=0.002)\), but not in the forearm muscle. In normal controls, there was no correlation between the PCr-slope and peak \( \dot{V}O_2 \) in either limb (Fig 3). There was a significant correlation between the PCr-slope and AT only in the calf muscle in normal controls \((r=0.85, p=0.003)\).

Fig 4 shows that there was a significant correlation between the PCr-slope of the forearm and calf in patients with CHF, but not in controls, which suggested that those muscle abnormalities were intrinsic and associated with pathophysiology in this disorder. There was a significant difference in muscle pH at the submaximal work rate (70% of the maximal work rate) in the calf between patients and controls, but not in the forearm (Table 2). A lower muscle pH at the submaximal work rate indicates an earlier onset of anaerobic metabolism.

Muscle pH at the submaximal work rate did not correlate with peak \( \dot{V}O_2 \) or AT in either limb of both normal controls and patients with CHF (CHF: to peak \( \dot{V}O_2 \): in forearm \( r=0.38, p=0.30 \), in calf \( r=0.46, p=0.11 \); to AT: in forearm \( r=0.04, p=0.92 \), in calf \( r=0.34, p=0.33 \); normal controls: to peak \( \dot{V}O_2 \): in forearm \( r=0.23, p=0.50 \), in calf \( r=0.47, p=0.15 \); to AT: in forearm \( r=0.35, p=0.29 \), in calf \( r=0.49, p=0.13 \) ) However, in patients with CHF whose peak \( \dot{V}O_2 \) was lower than in normal controls, muscle pH at the submaximal work rate in the calf muscle was also lower than in normal controls. On the other hand, in the forearm muscle there was no significant difference in muscle pH at the submaximal work rate between patients with CHF and normal controls (Fig 5).

In both the controls and patients with CHF, we observed a lower muscle pH at the submaximal work rate in the forearm muscle than in the calf muscle (Table 2).

**Discussion**

Previous investigators of the metabolic abnormalities in patients with CHF have studied either upper limbs or lower limbs, so they have not reported consistent patterns of the metabolic abnormalities of both or the relationships between such abnormalities and exercise tolerance. The present study evaluated the muscle metabolisms of both lower and upper limbs in individual patients with CHF.

We normalized the work rate by the MCA obtained with MRI to adjust for differences in muscle mass because such adjustments for muscle mass differences have not been done in previous studies. The present findings showed that impaired muscle metabolic capacity during local exercise was independent of muscle mass.

We could not directly demonstrate that there were metabolic abnormalities in upper limbs in patients with CHF evaluated by the PCr-slope or muscle pH at the submaximal work rate. However, we were able to show that muscle pH decreased more rapidly as the work rate increased in patients compared with controls (Fig 2) and that there was a correlation between upper limb PCr-slope and lower limb PCr-slope (Fig 4). Therefore, we considered that the skeletal
tal muscle metabolism was impaired during exercise in both upper and lower limbs in patients with CHF.

We previously demonstrated that there was no difference in blood flow volume in local muscles between normal controls and patients with CHF during peripheral skeletal muscle exercise. Thus the finding of skeletal muscle metabolic abnormalities in the patients with CHF in the present study would not be related to blood flow, but rather to intrinsic changes associated with CHF.

**PCr-Slope and MCA**

We measured systemic exercise capacity by using a bicycle ergometer during lower limb exercise. Thus, the measured values of peak VO2 and AT were more influenced by the metabolic capacity of the lower limbs than that of the upper limbs. We considered that the AT values were influenced prominently by the metabolic capacity of the lower limbs in both normal controls and patients with CHF because of the significant correlations between AT and the lower limb PCr-slope, which should mainly reflect the oxidative capacity of skeletal muscle.

However, considering peak VO2, in normal controls there was no correlation with PCr-slope in either limb, but rather a significant correlation between peak VO2 and MCA. In patients with CHF, peak VO2 correlated with PCr-slope, but not with the MCA, of both limbs (Figs 1,3). These findings suggest that in normal controls who had normal metabolic capacity of skeletal muscles, the peak VO2 of systemic exercise capacity was mainly determined by MCA and that in patients with CHF who had impaired skeletal muscle metabolism, the peak VO2 of systemic exercise capacity was more prominently regulated by the metabolic capacity of skeletal muscle than by MCA.

**Muscle pH at the Submaximal Work Rate**

Systemic exercise capacity (peak VO2 and AT) did not correlate with muscle pH at the submaximal work rate in either the upper or lower limb of any subject. On the other hand, the maximal work rate of peripheral exercise in both limbs did not differ between normal controls and patients with CHF although muscle pH was lower in patients with CHF than in normal controls (Table 2). Thus, we consider that exercise capacity is not directly regulated by muscle pH. However, because patients with CHF accompanied by a decreased peak VO2 had a decreased muscle pH in the lower limbs at the submaximal work rate (Fig 5, Right), we hypothesize that decreased muscle pH in the lower limbs essentially contributes to the impaired exercise capacity.

In both the controls and patients with CHF, we observed a lower muscle pH at the submaximal work rate in the forearm muscle than in the calf muscle (Table 2) and we consider that there were differences not caused by the condition of CHF but by the characteristics of skeletal muscle. It is necessary to consider this when interpreting the results.

**Comparison of the Impaired Muscle Metabolism in the Lower and Upper Limbs**

In patients with CHF, muscle metabolism evaluated as PCr-slope and muscle pH at the submaximal work rate was impaired only in the lower limbs, for the following possible reasons.

First, muscle deconditioning would be more likely in lower limbs than in upper limbs. Second, there is a difference in the distribution of the fiber types between the lower and the upper limbs. The upper limbs might have a large individual variety of fiber types which might cause the difference in muscle metabolism between controls and CHF to be undetectable.

**Muscle Atrophy**

It has been clinically recognized that patients with severe CHF show muscle wasting, known as cardiac cachexia (ie, cell damage caused by neurohormonal effects), which is thought to be one of the factors in the impaired muscle metabolism, in addition to deconditioning. Mancini et al reported that skeletal muscle atrophy was seen even in mild CHF and contributed to exercise intolerance. Although we did not find significant muscle atrophy in patients with mild to moderate CHF, we did find that the leg muscle, but not the arm muscle, tended to be smaller in patients with mild to moderate CHF than in controls, which means that the muscle atrophy might be caused by deconditioning rather than cardiac cachexia in the present cases.

**Explanation of the Changes in Muscle Metabolism in Patients With CHF**

Previous studies using 31P-MRS have shown that both exercise performance and muscle metabolism in the lower and upper limbs are impaired in patients with CHF. However, the present study demonstrated that, adjusted for muscle MCA, both the forearm and calf achieved near normal peak work rate in patients with CHF. We think that the performance of short periods of exercise is compensated for by an alternative anaerobic metabolism in the peripheral muscles, even in patients with CHF who have a damaged oxidative metabolic pathway.

In patients with CHF, skeletal muscle metabolism shifted from aerobic to anaerobic, which is deleterious from the aspect of energy efficiency, but can be thought of as an adaptation to allow activities related to daily life, independent of O2 delivery.

**Study Limitations**

We interpreted the 31P-MRS data based on the hypothesis that the ATP cost per muscle fiber for a matched work rate was similar in normal controls and patients with CHF. The differences in mechanical efficiency and metabolic efficiency could be potential confounding factors.

**Conclusion**

The present study evaluated the muscle metabolism of both lower and upper limbs in individual CHF patients. We consider that the impaired oxidative capacity of both limbs was affected intrinsically by the conditions related to CHF on the basis of the correlation of the PCr-slope of the upper and lower limbs. The muscle metabolic abnormalities were more prominent in the lower limbs than in the upper limbs in patients with CHF. Variables of the leg muscles are more closely related to exercise tolerance than those of the arm muscles in patients with CHF, so we recommend that researchers who are using 31P-MRS to investigate muscle metabolism should study the leg muscles.

Impaired skeletal muscle metabolism during exercise is seen in both the lower and upper limbs of patients with CHF, but the metabolic abnormalities are more prominent in the lower limbs and are related to systemic exercise tolerance.
References


