Chapter 6

Abnormal Skeletal Muscle Metabolism in Patients with Chronic Heart Failure as a Major Determinant of Exercise Capacity

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Introduction

Exercise tolerance is impaired in patients with chronic heart failure (CHF). Traditionally, exercise intolerance was thought to be related to central hemodynamic disturbance in patients with CHF; however, recent studies have reported that skeletal muscle abnormalities are important contributors to exercise intolerance[1)-14)]. This chapter will present our four studies concerning skeletal muscle metabolism in patients with CHF.

1. Skeletal muscle metabolism during localized exercise in patients with CHF

In the last decade, several studies have shown that skeletal muscle abnormalities, such as reductions in skeletal muscle mass, aerobic enzyme activity and mitochondrial volume, and an increased percentage of fast-twitch (IIb) fibers were seen in the skeletal muscle of patients with CHF. These abnormalities can induce early anaerobic metabolism during exercise and may limit exercise capacity[1), 5)-9), 11)]. These findings have been confirmed in localized muscle exercise of the forearm or calf by studies using 31P-magnetic resonance spectroscopy (^{31}P-MRS)[2)-4), 7), 10)]. We discuss here the study of muscle metabolism during localized muscle exercise. In this study, we measured muscle metabolism of both the forearm and the calf in each patient and control.

Methods

We studied 13 patients with CHF and 11 age- and size-matched normal subjects (Table 1). Before participation in the study, subjects underwent examinations to detect peripheral vascular diseases including palpation of peripheral pulses. Informed consent was obtained from all subjects.

^{31}P-MRS was performed using an 80-mm surface coil in a 55-cm bore and a 1.5-tesla superconducting magnet (Magnetom H15, Siemens Medical Systems, Germany). Shimming was adjusted by using the proton signal from water. Spectra were obtained with a pulse width of 500 ms, a transmitter voltage of 20.0 V, and a repetition time of 2000 ms. Each spectrum represented the average of 16 scans. One measurement required about 40 s. Since only the relative changes in high-energy phosphates were evaluated, we did not correct values for saturation. Phosphocreatine (PCr) was standardized as follows: $[PCr]/([PCr]+[Pi])$, where Pi is inorganic phosphate. The muscle pH was calculated from changes in the

Table 1 Baseline Characteristics of Normal Controls and Patients With Chronic Heart Failure (study 1)

	Normal controls	Patients with CHF
Subject (n)	11	13
Male (n)	6	7
Female (n)	5	6
Age (yr)	49±6	52±12
Height (cm)	158±7	161±8
Weight (kg)	54±6	59±8
NYHA functional class (n)		
II		7
III		6
Peak Vo_2 (mL/min/kg)	30.9±6.5	18.9±4.4*
AT (mL/min/kg)	21.5±4.3	13.9±2.9*

NYHA, New York Heart Association; BMI, body mass index. All values are the mean±SD. *p< 0.0001, vs. controls.

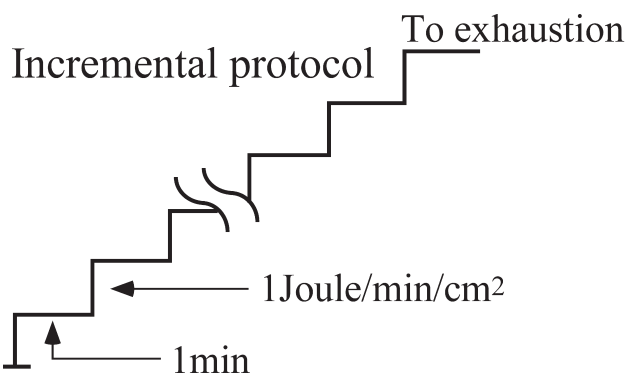

Fig. 1 Protocol for localized muscle exercise.

chemical shifts of Pi relative to PCr (pH=6.75+log [(s-3.27)/(5.69-s)] : s(ppm)= Pi-PCr)[14)-17)].

In order to load a subject, we set a pulley system to the whole-body magnetic resonance system. The supine unilateral plantar flexion or forearm flexion was performed with a multistage incremental protocol (Fig. 1). Protocols for the forearm and the calf were the same[14), 15)]. 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[18)]. 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 is equal to 1 J/min/cm². During exercise, the subject's muscle metabolism was measured by ^{31}P-MRS every minute. To evaluate the metabolic capacity

during calf plantar flexion and forearm wrist flexion, we calculated the slope of the PCr decrease in relation to increases in the workload by linear regression (PC-slope). Since PCr decreases linearly in response to a progressively increasing workload, the PC-slope is a simple indicator of the rate of PCr breakdown against the workload, which may mainly reflect the oxidative capacity of skeletal muscle. We used the muscle pH at the submaximal workload to evaluate muscle acidification. In this study, submaximal was determined to be 70% of the maximal work rate. Systemic exercise capacity was derived with an upright bicycle ergometer (Corival 400, Lode, Holland) using a ramp protocol. Respiratory gas analysis was performed using a breath-by-breath apparatus (Aeromonitor AE-280, Minato Medical Science, Osaka, Japan). The gas exchange anaerobic threshold was determined by the V-slope method, as described by Wasserman et al[19].

Results

There were no statistical differences in forearm and calf sizes between patients and controls (Table 2). However, there is a significant difference in the proportion of forearm to calf size. This would mean that the calf muscle was relatively atrophied compared with the forearm in patients with CHF. In both muscles, there was no statistically significant difference in the maximal work rate normalized by muscle mass between patients and controls.

Fig. 2 shows the time course of changes in PCr and muscle pH during calf plantar flexion. The PCr and muscle pH decreased more rapidly as the workload increased in patients than in controls. Patients with CHF performed at a nearly normal maximal work rate accompanied by an enhanced anaerobic metabolism.

The calculated PC-slope is steeper in patients than in controls in both muscles (Table 2), but a significant difference is seen only in the calf. There was a significant correlation between metabolic capacity evaluated as PC-slope and peak oxygen uptake in each muscle (Fig. 3). There was also a significant correlation between PC-slope and gas exchange anaerobic threshold in the calf muscle ($r=0.80$,

Table 2 Results from localized muscle exercise (study 1)

	Normal controls	patients with CHF	significance
Forearm MCA (cm^2)	13.0±3.8	15.8±3.1	ns
Calf MCA (cm^2)	41.5±8.6	38.6±4.8	ns
Ratio of forearm to calf	0.31±0.04	0.42±0.11	$p<0.01$
Maximal forearm work rate (joule)	6.6±1.3	5.8±1.0	ns
Maximal calf work rate (joule)	7.3±0.8	6.6±1.0	ns
PCr-slope of forearm	−0.060±0.025	−0.074±0.030	ns
PCr-slope of calf	−0.064±0.016	−0.082±0.019	$p<0.05$
Forearm muscle pH at the submaximal work rate	6.78±0.19	6.70±0.27	ns
Calf muscle pH at the submaximal work rate	7.04±0.05	6.89±0.06	$p<0.0001$

MCA, maximal cross-sectional area.

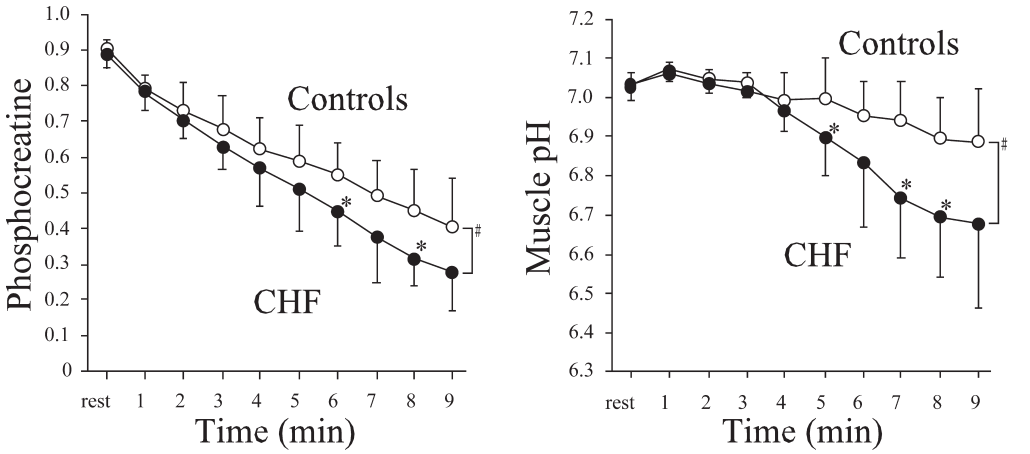

Fig. 2 Time course of changes in PCr and muscle pH during calf plantar flexion with the incremental protocol. The PCr and pH decreased more rapidly versus work rate in patients than in controls. *p<0.05 by student *t* test, ♯p<0.05 by ANOVA vs. controls.

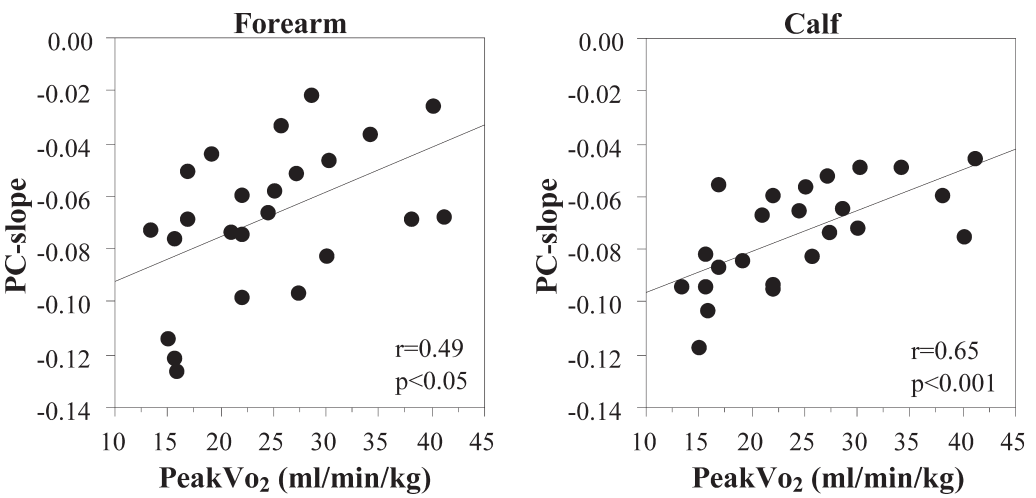

Fig. 3 The relationship between metabolic capacity evaluated as PC-slope and peak oxygen uptake (peak Vo_2) in the forearm and calf.

p<0.0001) but not in the forearm muscle (r=0.42, p=0.06).

There was a significant difference in muscle pH at the submaximal work rate (70% of 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. There was a significant correlation between muscle pH at the submaximal work rate and peak oxygen uptake in the calf (r=0.78, p<0.0001) but not in the forearm (r=0.31, p=0.14). There was also a significant correlation between muscle pH at the submaximal work rate and gas exchange anaerobic threshold in the calf muscle but not in the forearm (Fig. 4).

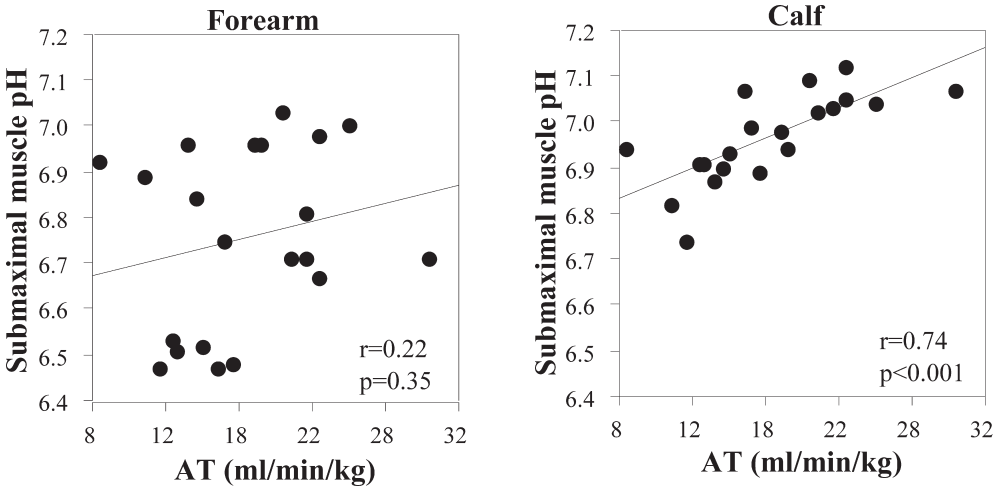

Fig. 4 The relationship between muscle acidification evaluated as the muscle pH at the submaximal work rate and gas exchange anaerobic threshold (AT) in the forearm and calf.

Conclusions

Impaired skeletal muscle metabolism during exercise is seen in both the lower and upper limbs in patients with CHF, with muscle metabolic abnormalities being more prominent in the lower limbs than in the upper limbs in these patients. Muscle abnormalities, especially in the lower limbs, are related to systemic exercise tolerance. The first possible reason for the different results between the forearm and calf is the difference in muscle mass between them. The larger the muscle mass, the more muscle metabolism is governed by muscle blood flow. The second reason for the difference is the difference in fiber type distribution between the forearm and calf. Forearm muscles might be composed of a large individual variety of fiber types, which might make the difference in muscle metabolism between controls and patients undetectable. The third reason for the different results is that muscle deconditioning might be greater in the lower limbs than in the upper limbs. The fourth reason is that systemic exercise capacity is measured during lower limb exercise. If the peak oxygen uptake and anaerobic threshold were measured with an arm ergometer, a different picture might emerge.

2. Dissociation between muscle metabolism and oxygen kinetics during recovery from exercise in patients with CHF

Recent studies using near-infrared spectroscopy (NIRS) to evaluate skeletal muscle oxygen kinetics have shown that peripheral muscle oxygenation is impaired during systemic exercise in patients with chronic heart failure[20), 21)]. Both muscle metabolism and muscle oxygen kinetics are important determinants of exercise capacity and these factors have been separately evaluated in patients with chronic heart failure. In normal subjects, only a few studies have assessed both muscle

metabolism and oxygen kinetics. McCully et al. suggested that oxy-Hb recovery is rate limiting for ATP synthesis, evaluated as the rate of PCr recovery after submaximal exercise[23]. In patients with chronic heart failure, both skeletal muscle metabolism and oxygen delivery are impaired and these abnormalities are potential contributors to exercise intolerance. Therefore the combination of ^{31}P-MRS and NIRS would appear to be useful for assessing exercise intolerance. To elucidate the relation between muscle metabolism and oxygen kinetics, we measured PCr and oxy-Hb during recovery from submaximal constant load exercise in patients with chronic heart failure and in normal subjects.

Methods

We studied 15 patients with chronic heart failure, mean age 58±8 years, and 16 age matched normal subjects. The mean ejection fraction of the patients was 29 (13)%. Eight had symptoms consistent with NYHA class II and seven with class III. Before the study, muscle strength was measured in all subjects by the one repetition maximum (1 RM) method, which measures the maximum weight that can be lifted only once. The workload was adjusted to 50% of 1 RM. Plantar flexion was performed once every 1.5 seconds for six minutes against a pedal. Measurements were obtained from the one minute rest period before exercise through the six minute recovery period after exercise. We obtained ^{31}P-MRS data of calf muscle using the same methods described in prior paragraph. PCr recovery after exercise was fitted to a single exponential curve obtained by least squares regression, and the time constant for PCr recovery (τPCr) was calculated as follows: $[PCr] = C1 + C2\ (1\text{-}e^{-kt})$, where [PCr] is the PCr concentration, C1 is the initial [PCr], C2 is the difference between the final and initial [PCr], t is time, and k is the rate constant ($1/k = \tau$). NIRS was performed with a dual wave spectrometer (HEO100, Omron, Tokyo, Japan), a tissue oximeter that uses a two wavelength light emitting diode (LED), with wavelengths of 760 and 840 nm, as a light source. As in previous studies discussing recovery rate of oxy-Hb,[22), 23)] we evaluated the recovery kinetics of calf muscle by means of time constants. The oxy-Hb recovery was fitted to a single exponential curve and the time constant for oxy-Hb recovery (τoxy-Hb) was calculated as the τPCr. Measurements by ^{31}P-MRS and NIRS were obtained with the same protocol on alternate days within a week.

Results

Representative data of ^{31}P-MRS and NIRS spectra after exercise in a patient and a normal subject are shown in Fig. 5. Both the rate of oxy-Hb recovery evaluated as the τoxy-Hb and the rate of PCr recovery evaluated as the τPCr were significantly greater in patients with chronic heart failure than in normal subjects (τPCr: 76.3±30.2 sec vs. 36.5±5.8 sec; τoxy-Hb: 48.3±7.3 sec vs. 30.1±7.7 sec; $p < 0.01$), indicating that PCr and oxygen recovery was impaired in patients with chronic heart failure.

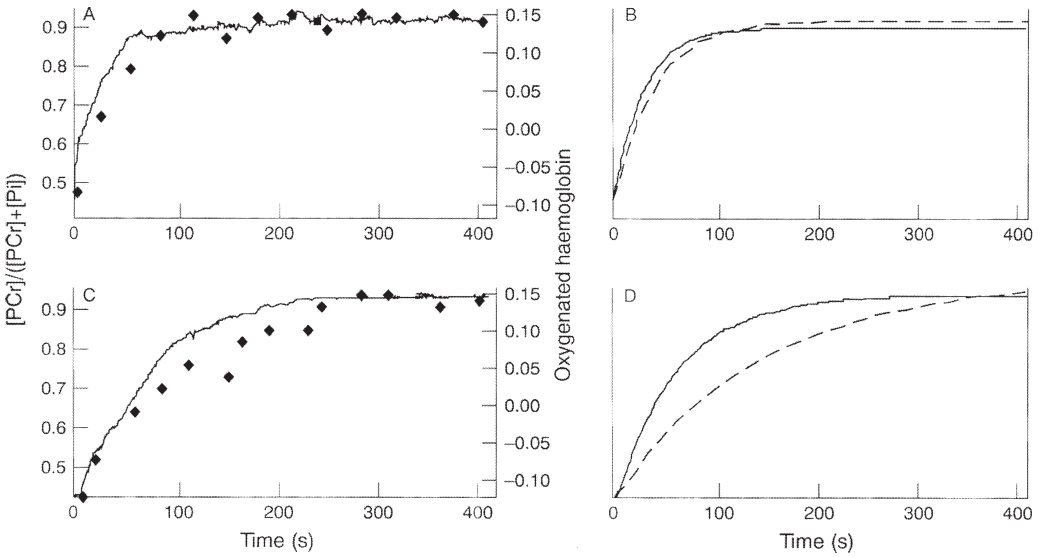

Fig. 5 Representative spectra showing recovery of phosphocreatine (PCr, filled symbols) and oxygenated haemoglobin (oxy-Hb, solid line) in normal subjects (A) and patients with chronic heart failure (C). Each dataset is fitted with a single exponential curve (B and D). A dotted line indicates the fitting curve of PCr and a solid line shows that of oxy-Hb. The time constants are as follows: B (normal subject): τoxy-Hb=28 sec; τPCr=33 sec. D (patient with chronic heart failure): τoxy-Hb=53 sec; τPCr=110 sec. τoxy-Hb, time constant for oxy-Hb resaturation; τPCr, time constant for PCr resynthesis. (Data from reference 13)

The τPCr and theτoxy-Hb was similar in normal subjects. In patients with chronic heart failure, however, the τPCr was significantly greater than the τoxy-Hb. Moreover, the difference in the τPCr between the two groups was remarkably greater than the difference in the τoxy-Hb. The τPCr in patients with chronic heart failure showed a wide variance. These results are shown in Fig. 6.

Conclusions

The slower recovery of PCr compared with oxy-Hb in patients with chronic heart failure indicates that haemoglobin resaturation is not a major rate limiting factor of PCr resynthesis. It is suggested that muscle metabolic recovery may depend more on oxygen utilisation than on haemoglobin resaturation or oxygen delivery in patients with chronic heart failure.

3. Skeletal muscle metabolism during systemic exercise.

Does skeletal muscle metabolism contribute to systemic exercise capacity? Results from ^{31}P-MRS studies were based on local exercises involving only a small muscle mass (the unilateral forearm or calf)[2)-4), 7), 10)]. Whether or not the metabolic abnormalities observed with such a local exercise are also associated with systemic exercise and whether the muscle metabolism affects systemic exercise capacity

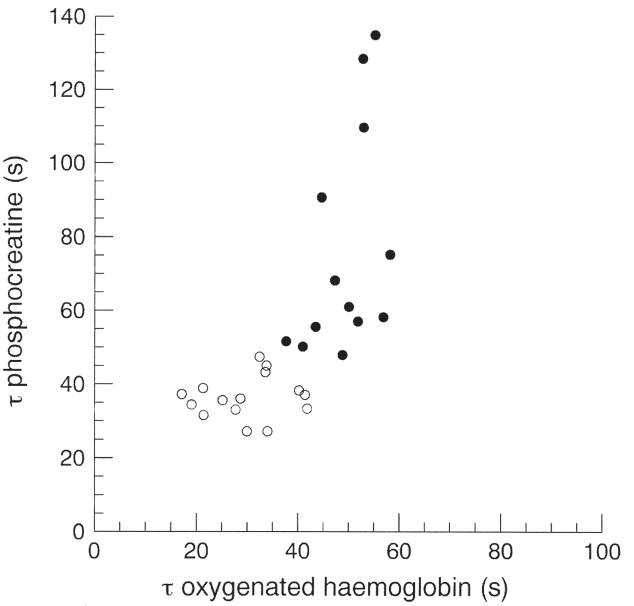

Fig. 6 The relation between τPCr and τoxy-Hb presented by two dimensional plotting. Empty circles indicate normal subjects and filled circles indicate patients with chronic heart failure. (Data from reference 13)

have not been clarified. Thus, we attempted to measure skeletal muscle metabolism during systemic exercise and to investigate the effect of muscle metabolism on exercise tolerance. There are technical difficulties in performing ^{31}P-MRS during systemic exercise, such as an upright bicycle, mainly because of the small MR bore size. Therefore, we chose the metabolic freeze method to stop the metabolism[24), 25)]. This method was first described by Harris in 1976[24)]. When the circulation to the working muscle is suddenly stopped by a cuff simultaneously with the cessation of exercise, the metabolism is 'frozen' for at least several minutes and is preserved as it was during exercise. Only after the circulation is restored does metabolic recovery occur. We have confirmed the validity of the metabolic freeze method in a previous study[12)]

Methods

We studied 12 Japanese male patients with CHF and 7 age- and size-matched normal male subjects (Table 3). None of the patients had peripheral vascular disease. Informed consent was obtained from all subjects.

First, we placed a cuff around the thigh of each subject and performed a resting measurement. Next, the subject performed maximal upright bicycle exercise outside of the MRI apparatus. As soon as the subject indicated that he could not continue, he was asked to stop pedaling suddenly and the cuff was simultaneously

Table 3 Baseline Characteristics of Normal Controls and Patients With Chronic Heart Failure (study 2)

	Normal controls	Patients with CHF
Subject (n)	7	12
Age (yr)	50±7	57±8
Height (cm)	168±6	167±2
Weight (kg)	64±3	65±6
NYHA functional class		
II		7
III		5
Dilated cardiomyopathy		10
Ischemic heart disease		2
Atrial fibrillation		4
Peak Vo_2 (mL/min/kg)	31.8±3.7	20.2±3.0*
AT (mL/min/kg)	22.3±2.5	14.3±2.4*
LVEF (%)		0.23±0.10
Beta-blockers		4

NYHA, New York Heart Association. All values are the mean±SD.
*$p<0.0001$, vs. controls.

inflated to a supra-systolic pressure. The subject was then transferred to the MRI apparatus and ^{31}P-MRS was started immediately. The interval between the cessation of exercise and the start of measurement was usually 1 to 2 minutes.

To document the time course of the PCr and muscle pH changes in response to the increased workload with this method, the metabolic freeze was employed at various workloads during bicycle exercise in two patients and two controls. The PCr decreased linearly with increasing workloads (Fig. 7). Thus, we calculated the slope of the relation between the power output and the PCr decrease (Sys-slope) to evaluate metabolic capacity.

We also evaluated metabolic capacity during plantar flexion in each subject using the same method of the former study. The capacity was described as the Loc-slope (the slope of the PCr decrease in relation to increases in the workload during plantar flexion).

Results

Fig. 8 shows muscle metabolism during the peak exercise in both groups. The PCr was nearly depleted at this point in both groups. Muscle pH was more severely decreased in the patients than in the controls. These findings suggested that metabolic limitation coincides with the end of exercise. Metabolic limitation occurred at a significantly lower peak workload and oxygen uptake in patients than in controls. Muscle metabolic capacity evaluated as the Sys-slope was significantly correlated with the peak oxygen uptake and the anaerobic threshold (Fig. 9).

The Loc-slope derived from localized muscle exercise was significantly correlat-

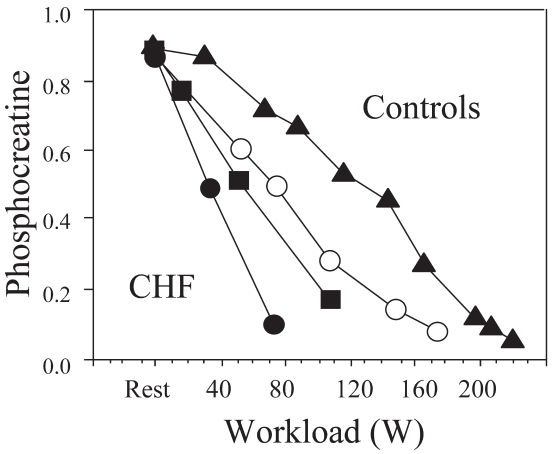

Fig. 7 Time course of PCr change in response to increased workload during upright bicycle exercise in two patients (solid circles and squares) and controls (open circles and solid triangles).

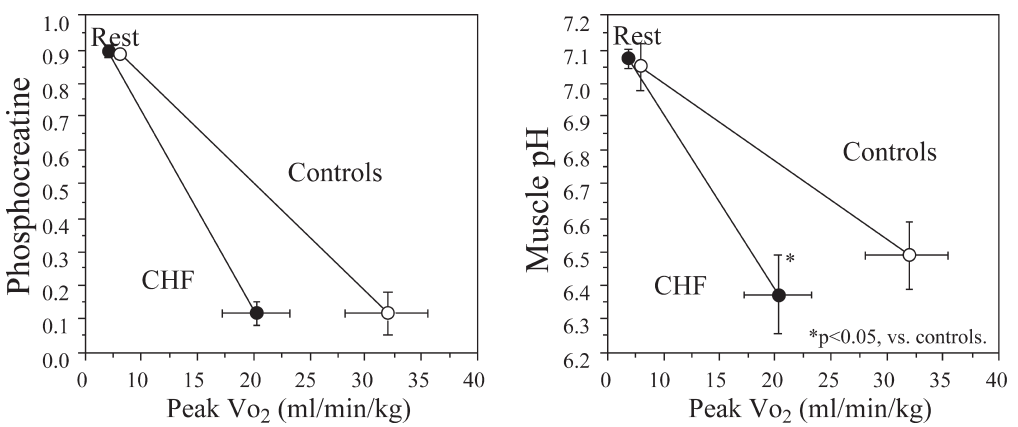

Fig. 8 The PCr and muscle pH decrease during maximal bicycle exercise in patients with CHF and controls.

ed with the Sys-slope, the peak oxygen uptake, and the anaerobic threshold in patients with CHF (Fig. 10).

Conclusions

These results suggest that impaired muscle metabolism associated with early metabolic limitation determines exercise capacity during maximal systemic exercise in patients with CHF. The intrinsic metabolic capacity during local exercise was significantly correlated with the metabolic capacity during systemic exercise and with the exercise capacity. The present studies suggest that exercise tolerance is governed largely by peripheral muscles. Factors affecting muscle metabolism,

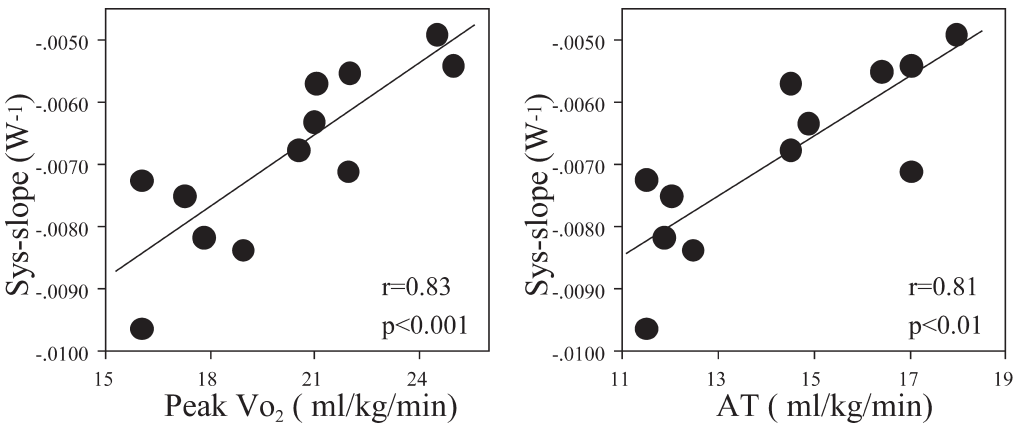

Fig. 9 Significant correlations between muscle metabolic capacity evaluated as Sys-slope (PCr decrease to power output at the end of exercise) and the peak oxygen uptake (peak Vo_2) and the anaerobic threshold (AT). (Data from reference 12)

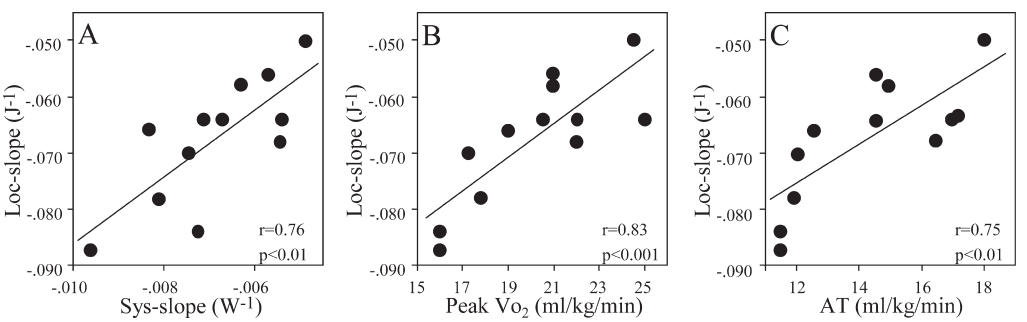

Fig. 10 A, relationship between the metabolic capacity during maximal systemic (Sys-slope) and local exercise (Loc-slope; the slope of the PCr decrease in relation to increases in the workload) in patients with CHF. B, relationship between the peak Vo_2 and the Loc-slope in patients with CHF. C, relationship between the AT and the Loc-slope in patients with CHF. (Data from reference 12)

such as muscle intrinsic abnormalities, muscle mass, and muscle perfusion, may determine the 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[26]. 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 to the central hemodynamic function[27), 28]. We suggest that in most patients with CHF, skeletal muscle dysfunction may predominate over circulatory dysfunction. Thus, skeletal muscle training may improve exercise tolerance to the level that matches the circulatory capacity. And, if circulatory dysfunction is predominant, circulatory improvement may immediately improve exercise capacity by improving muscle

perfusion.

4. Localized skeletal muscle training

Can impaired skeletal muscle metabolism be improved by training without an improvement in cardiovascular performance? To determine an answer, we performed localized skeletal muscle training in patients with CHF.

Methods

Seven patients with CHF caused by idiopathic dilated cardiomyopathy were recruited into our training program[29]. The patients' mean age was 57 years, mean height was 167 cm, and mean weight was 69 kg. Six were in class II of the New York Heart Association rankings for CHF, and the other patient was in class III. All patients were taking digitalis, five were on angiotensin-converting enzyme inhibitors, and four were on beta-blockers. Pharmacological treatment was not altered for three months before and during the duration of the study. We contrived the training equipment for the right calf. The training protocol consisted of 1 set of right calf plantar flexion for 6 minutes. The workload was first set at 5 kg and was gradually increased up to 30 kg according to the subject's performance. Each patient did 4 sets of training a day, 5-7 days a week. Training was continued for 8 weeks. We evaluated the effects of training on muscle metabolism by having subjects do 6 minutes of plantar flexion at the submaximal workload (70% of the maximal work rate). The workload was determined according to the plantar flexion work capacity of first incremental plantar flexion exercise test of each patient. We also measured muscle blood flow during plantar flexion by impedance plethysmography, and we evaluated systemic exercise tolerance with an upright bicycle ergometer. Comparisons were performed between post-training and 8 weeks of detraining.

Results

Fig. 11 shows the general effects of the plantar flexion training. Exertional fatigue was lessened with the training, and the maximal cross-sectional area of the calf and the maximal voluntary contraction increased. Fig. 12 shows the effect of training on muscle metabolism during exercise. There was a significant improvement in muscle metabolism during the training phase compared with the detraining phase. During 6 min of plantar flexion at the matched workload, both PCr and muscle pH were less decreased during the training phase than during the detraining phase. There was no significant change in calf blood flow between the training and detraining phases (rest, 2.5 ± 0.4 vs. 2.7 ± 0.4, ns; exercise, 27.6 ± 2.4 vs. 29.8 ± 2.7 ml/100ml/min, ns, training, detraining, respectively)[25]. Systemic exercise performance (peak oxygen uptake) was not changed significantly by this training (23.4 ± 2.2 vs. 22.1 ± 1.7 ml/min/kg, ns, training, detraining, respectively).

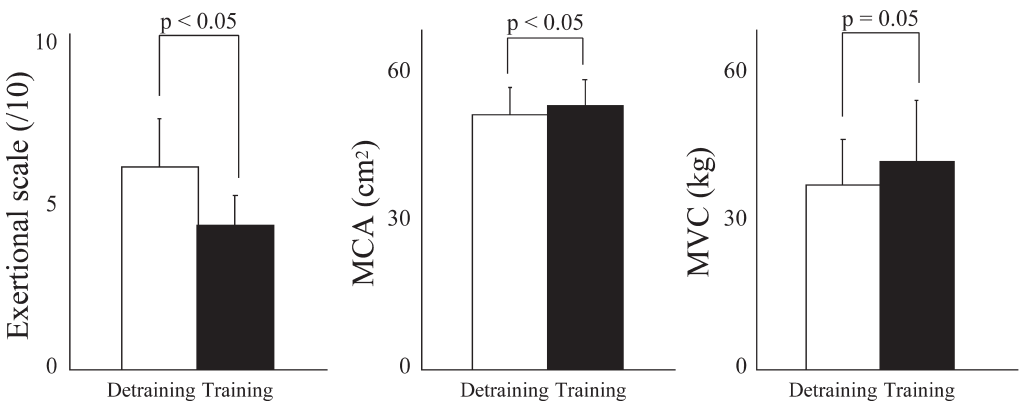

Fig. 11 General effects of the exercise training of this study. Exertional scale (10 point scale of Borg), MCA, maximal cross-sectional area. MVC, maximal voluntary contraction. Open column; Detraining phase, solid column; training phase.

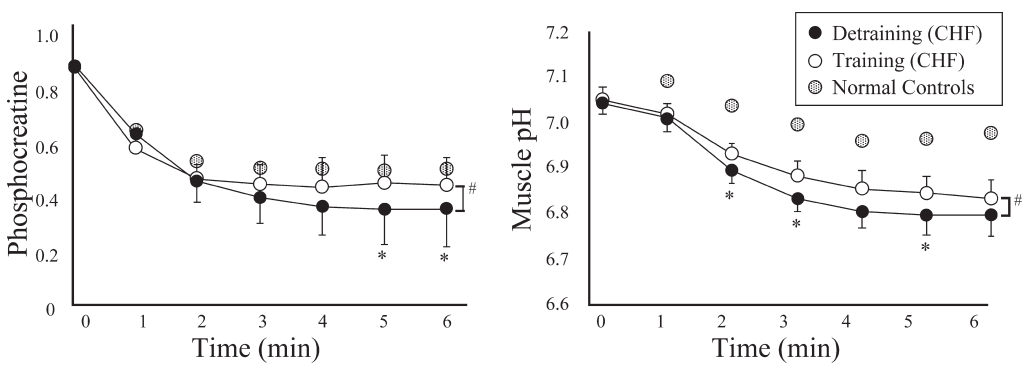

Fig. 12 Significant training effect on muscle PCr depletion and muscle pH decrease during 6 min of plantar flexion at a constant workload. *$p<0.05$, #$p<0.05$ by ANOVA, vs. training phase.(Data from reference 29)

Conclusions

Impaired skeletal muscle metabolism during exercise was partly improved by the training, which might not have had any effect on cardiovascular capacity. The exertional symptoms that normally occur during exercise may also be improved by this training. There may be a specific muscle abnormality that is not related to muscle perfusion in patients with CHF. This type of training puts little stress on the cardiovascular system and can be performed safely. However, some problems remain. Although the training was continued for 8 weeks, muscle metabolism was not improved to a normal level. It is unknown if this type of training can improve a patient's prognosis as well as quality of life.

Summary

In the four studies reported here, we emphasize the important role of skeletal muscle metabolism during exercise in patients with CHF. Possible mechanisms for

impaired muscle metabolism may be muscle atrophy, decreased aerobic enzyme activity, reduced mitochondrial volume, and fiber type alteration. Moreover, beyond the muscle, peripheral endothelial function, increased sympathetic nerve activity, and cardiac function might also be potential contributors. Since impaired muscle metabolism is observed during low levels of small muscle exercise, cardiac performance may not be a major reason for the impairment. One of the main mechanisms may be muscle deconditioning due to impaired cardiac performance. However, other researchers and we could not normalize the muscle metabolism even during localized muscle exercise by exercise training. This indicates that the important systemic factors may significantly affect the muscle metabolism.

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