Metabolic abnormality of calf skeletal muscle is improved by localised muscle training without changes in blood flow in chronic heart failure

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Abstract

Objective—To investigate whether localised skeletal muscle training, which does not have a great influence on the heart, improves abnormalities of calf muscle metabolism in patients with chronic heart failure.

Methods—Seven cardiac patients in New York Heart Association class II and III undertook a random order crossover trial. Training consisted of unilateral calf plantar flexion exercise. Before and after training, the patients’ metabolic responses were examined during the calf exercise test with phosphorus-31 nuclear magnetic resonance spectroscopy ("P-MRS) and calf blood flow with plethysmography. The new Borg scale was employed as a subjective fatigue scale.

Results—In a constant load exercise test (70% of maximum load achieved during the incremental exercise), standardised phosphocreatine and intracellular pH decreased less after training (p < 0.05). Blood flow did not change significantly in either test.

Conclusions—In patients with chronic heart failure, localised calf skeletal muscle training improved oxidative capacity without changes in calf blood flow. This training also improved the subjective fatigue scale. This training method may therefore alleviate leg fatigue experienced in daily activities.

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Keywords: heart failure; magnetic resonance spectroscopy; skeletal muscle; localised training

In patients with chronic heart failure, central haemodynamics improve with vasodilator treatment within the short term, but increases in exercise capacity are delayed for weeks or months.1 This suggests that cardiac function is not the sole factor determining exercise capacity. Using phosphorus-31 nuclear magnetic resonance spectroscopy ("P-MRS), many investigators have reported that patients with chronic heart failure have abnormal forearm skeletal muscle metabolism,2,3 and Mancini et al4 reported abnormal metabolism in the calf muscle. Sullivan et al5 speculated that peripheral factors play an important role in exercise capacity in chronic heart failure.

In recent years, investigations into cardiac rehabilitation have suggested that exercise training increases peak oxygen uptake (VO2) of patients with chronic heart failure.6–8 Most previous training studies employed large muscle group training such as bicycle exercise. However, some patients may not be able to perform such exercise because of poor cardiac function. Therefore, if patients were able to achieve metabolic improvement in their muscles by localised small muscle group training, which does not have a large influence on haemodynamics, this would be advantageous for them. Though few investigations on localised training have been reported, Minotti et al9 and Stratton et al10 using "P-MRS, conducted controlled trials of single forearm training and found that the abnormal forearm muscle metabolism could be improved by localised training without affecting cardiac function.

In daily life, the activity of cardiac patients is frequently limited because of leg fatigue. Lower extremities are closely related to fundamental daily actions such as walking, sustaining posture, and so on. It is reported that muscle composition11–13 and metabolism during exercise14–16 are different in the upper and lower extremities. However, in spite of these differences, there have been few training studies focused on the lower extremities. Magnnsson et al17 studied localised training in the quadriceps femoris muscle in patients with chronic heart failure and reported that the work capacity of trained muscles increased. Employing a muscle biopsy technique, they also found histochernical changes. This training resulted in some systemic effect, probably because the quadriceps femoris is a relatively large muscle group. Using "P-MRS, Adamopoulos et al18 suggested that exercise training with a bicycle ergometer improved calf muscle metabolism during plantar flexion exercise, but this result was derived from large muscle group training. It remain unclear whether localised calf muscle training, as a model for small muscle training, can improve abnormal muscle metabolism in patients with chronic heart failure. Also, there has been no localised training study of leg muscles using "P-MRS. In the present cross-over study, we designed a localised training method in which the ankle joint motion was similar to that in walking, because walking is the most basic action in daily life.
Using $^{31}$P-MRS, we examined the hypothesis that isotonic localised training of the calf muscles improves their metabolism, and whether this training decreased the patients' fatigue scores. If our hypothesis proved correct, then localised calf muscle training may be safely used for cardiac rehabilitation to improve patients' quality of life.

**Methods**

**STUDY POPULATION**

We studied seven stable patients with chronic heart failure caused by idiopathic dilated cardiomyopathy (six men and one woman). The mean (SD) age of patients was 56.9 (5.6) years (range 52 to 66 years), height 166.6 (3.3) cm, and weight 69.4 (8.0) kg. Six were in New York Heart Association functional class II and the other was in class III. We explained the details of this study to the patients and informed consent was obtained. The institutional committee on human research approved the study protocol.

All patients were taking diuretics, four were on angiotensin converting enzyme inhibitors, and four were on β blockers. Pharmacological treatment was not altered for three months before and during the duration of the study in any subject.

The mean (SD) radionuclide left ventricular ejection fraction was 32.0 (10.4)%. Cardiac echocardiography showed that left ventricular fractional shortening was 23.1 (2.9)%, and the left ventricular end diastolic dimension, 60.6 (4.9) mm.

The study was designed as a random order crossover comparison of eight weeks of localised training (training phase) and eight weeks of restricted activity (detraining phase). As a prestudy assessment before this crossover study, our patients underwent a cardiopulmonary exercise test with an upright electrical ergometer. The study protocol was approved by the ethics committee on human research, and informed consent was obtained. The institutional committee on human research also approved the study protocol.

**TRAINING PROTOCOL**

The training protocol consisted of repetitive isotonic right foot plantar flexion exercise at a rate of 40 per minute. Patients performed six minutes of plantar flexion as one set. The training routine consisted of four sets per day, five to seven days per week. For this study, we designed an original plantar flexion training apparatus in which loads could be changed in 5 kg increments, from 5 to 30 kg, by adjusting springs.

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**EXERCISE TESTING PROTOCOLS FOR $^{31}$P-MRS STUDIES**

First, using magnetic resonance imaging (MRI), the maximum calf flexor muscle cross sectional area was determined. The patients then performed right foot plantar flexion exercise 40 times per minute, and muscle energy metabolism was studied with $^{31}$P-MRS. Thereafter, they were enrolled either in the training phase or detraining phase. Four patients were in the training first group, and the other three were in the detraining first group.

Seven normal control subjects also underwent both tests done in the prestudy assessment. The mean (SD) age of normal subjects was 54.1 (6.0) years (range 48 to 64 years) and was not significantly different from the patients' mean age. Three of them were male and four were female. Their mean height was 156.6 (7.2) cm and body weight 52.8 (12.4) kg. They were all healthy and did not take any medication. They did not habitually participate in sports.

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prestudy assessment—70% of maximum load achieved during the incremental exercise—was employed in both phases. Patients performed the constant load test for six minutes. The fatigue score at the end of plantar flexion exercise was evaluated using the new Borg scale. 

Calf blood flow

Within five days after the \(^{31}\)P-MRS test, strain gauge plethysmography was performed during the two exercise protocols, that is, the incremental exercise test and the constant load exercise test. We used two inflation cuffs, with the upper cuff secured around the thigh and the lower cuff secured around the ankle. When the upper cuff was inflated to 40 mm Hg, venous outflow was obstructed; when the lower cuff was inflated to 200 mm Hg, arterial inflow to the foot was obstructed. At the end of each stage in the incremental exercise test and every minute in the constant load exercise test, calf blood flow was measured while interrupting plantar flexion exercise for five seconds. Calf blood flow was determined from the rate of change in calf circumference and was expressed as ml/100 ml/min.

Maximum voluntary calf contraction

The force of maximum voluntary contraction of the calf (kg) was determined using a load cell (LC 1205-K 200, A&D Co, Tokyo, Japan). Measurement was performed with the pulley system used to evaluate calf muscle metabolism (described above).

Cardiopulmonary exercise test

Peak VO\(_2\) and ventilatory anaerobic threshold were measured on an upright electrical ergometer (Cronval 400 Lobe bv, Groningen, The Netherlands) using a breath by breath respiratory gas analyser AE-280 (Minato Medical Science Co, Osaka, Japan). Patients underwent cardiopulmonary tests during the prestudy assessment, the training phase, and the detraining phase. Resting heart rate, resting blood pressure, peak work load, peak heart rate, and peak blood pressure were also measured. Exercise was performed employing a 15 W/min ramp protocol after three minutes of warm up exercise at 0 W. Ventilatory anaerobic threshold was determined using the V-slope method.

Hormonal factors

Before the cardiopulmonary test, after at least 30 minutes of rest, plasma noradrenaline, adrenaline, plasma renin activity (PRA), aldosterone, and atrial natriuretic factor (ANF) concentrations were measured in the training phase and the detraining phase.

Statistical methods

All data were analysed with a commercial statistical package (StatView—J 4.11, Abacus Concepts), and we compared the training phase and the detraining phase. Repeated measures analysis of variance (ANOVA) was used to compare changes of standardised phosphocreatine, intracellular pH, and blood flow during calf plantar flexion exercise in the training and detraining phases. Concerning the incremental exercise test, data for 0 to 6 J/min/cm\(^2\) were used because all patients could complete at least 6 J/min/cm\(^2\). The paired \(t\) test was also used to compare changes of other factors between the training phase and the detraining phase. In prestudy assessment, comparison between cardiac patients and normal subjects was made with an unpaired \(t\) test. Statistical significance was assumed for \(P\) values < 0.05. Data are expressed as mean (SEM).

Results

Prestudy assessment

Our patients showed a significantly lower peak VO\(_2\) and ventilatory threshold than normal control subjects (peak VO\(_2\), 24.1 (1.6) vs 32.0 (2.6) ml/kg/min, \(p < 0.01\); ventilatory threshold, 16.4 (1.3) vs 22.6 (2.1) ml/kg/min, \(p < 0.05\)). During the plantar flexion exercise, the metabolic responses were significantly different between normal subjects and patients, during both incremental exercise (fig 1) and constant load exercise (fig 2).

Figure 1 Comparison of standardised phosphocreatine (PCr) utilisation (A) and intracellular pH (B) in incremental exercise between patients with chronic heart failure and normal control subjects. There was no significant difference between the two groups in either standardised PCr or intracellular pH by repeated measures analysis of variance (ANOVA). Data on exercise ranging from 0 to 9 J/min/cm\(^2\) are presented. Since all patients could complete at least 6 J/min/cm\(^2\), data for 0 to 6 J/min/cm\(^2\) were used to compare the two groups by repeated measures ANOVA. When matched points were compared, both standardised PCr values and intracellular pH were significantly different at 5 to 9 J/min/cm\(^2\). *\(p < 0.05\), ††\(p < 0.01\), compared by unpaired \(t\) test. Empty squares, normal control subjects; filled squares, patients with chronic heart failure.
The skeletal muscle metabolic responses of the training phase and the detraining phase were compared.

Incremental exercise test
There was a tendency towards higher pH after training (p < 0.10 by repeated measures ANOVA). Comparing matched work loads, intracellular pH was higher mainly for low intensity work loads after training versus detraining (p<0.05 at 2 and 3 J/min/cm²).

Constant load exercise test
The decrease in standardised phosphocreatine during the plantar flexion exercise (fig 3A) was significantly smaller after training (p < 0.05 by repeated measures ANOVA). When matched points were compared, there were significant differences at 5 and 6 minutes (p < 0.01). After training, intracellular pH also showed a blunted decrease during exercise (fig 3B; p<0.05 by repeated measures ANOVA). Comparing matched points, there were significant differences between the training phase and the detraining phase at 2, 3, and 5 minutes.

Figure 2 Comparison of standardised phosphocreatine (PCr) utilisation (A) and intracellular pH (B) in constant load exercise test between patients with chronic heart failure and normal control subjects. Patients showed more depletion than normal control subjects by repeated measures analysis of variance (ANOVA). Comparing matched points, standardised PCr values were significantly different at 2 to 6 minutes, and intracellular pH at 1 to 6 minutes.

Figure 3 Effects of localised training on standardised phosphocreatine (PCr) utilisation (A) and intracellular pH (B) in constant load exercise test. There was less standardised PCr depletion as well as less intracellular pH reduction after training. ‡ p<0.05, compared by repeated measures analysis of variance. * p<0.05, † p<0.01, comparing matched points by paired t tests. Empty circles, training phase; filled circles, detraining phase.

(p < 0.05) and at 6 minutes (p < 0.06). Even when the standardised phosphocreatine at 6 minutes (steady state value) was adjusted by the individual ratio of training/detraining maximum calf area ([training phase PCr value] × [detraining phase PCr value] × the ratio of training/detraining MCA), there was a significant difference between the training phase and the detraining phase in the constant load exercise test (0.44 (0.04) v 0.39 (0.05), p<0.05).

LOCALISED TRAINING EFFECTS ON BLOOD FLOW, NEW BORG SCALE, AND OTHER FACTORS
Data for these are shown in table 1.

Incremental exercise test
There was no significant difference in calf blood flow change between the training phase and the detraining phase by repeated measures ANOVA, and when matched work loads were compared by paired t test there was no difference between the two phases either. The new Borg scale did not change significantly. When work loads were expressed per unit of calf cross sectional area, the peak work load (J/min/cm²) did not change significantly. However, the absolute peak work load (J/min) was higher after training (p < 0.05).

Constant load exercise test
Blood flow in the training phase and the detraining phase did not differ (fig 4; p = NS by repeated measures ANOVA), and when matched
Table 1  Data for right calf between the training phase and the detraining phase

<table>
<thead>
<tr>
<th>Blood flow (ml/100 ml/min)</th>
<th>Training phase</th>
<th>Detraining phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Incremental)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td>2.5 (0.4)</td>
<td>2.7 (0.4)</td>
</tr>
<tr>
<td>6 J/min/cm² (Constant)</td>
<td>26.1 (3.0)</td>
<td>30.2 (4.6)</td>
</tr>
<tr>
<td>Rest</td>
<td>2.5 (0.4)</td>
<td>2.7 (0.4)</td>
</tr>
<tr>
<td>6 min</td>
<td>27.6 (2.4)</td>
<td>29.8 (2.7)</td>
</tr>
<tr>
<td>MCA (cm²)</td>
<td>55.6 (2.4)*</td>
<td>53.8 (2.6)</td>
</tr>
<tr>
<td>MVC (kg)</td>
<td>44.6 (5.2)</td>
<td>39.5 (4.0)</td>
</tr>
<tr>
<td>Peak work load in incremental exercise (J/min/cm²)</td>
<td>9.7 (0.8)</td>
<td>8.9 (0.8)</td>
</tr>
<tr>
<td>Absolute peak work load in incremental exercise (J/min)</td>
<td>539.8 (49.2)*</td>
<td>476.8 (44.7)</td>
</tr>
<tr>
<td>New Borg scale (/10)</td>
<td>7.6 (0.3)</td>
<td>8.6 (0.2)</td>
</tr>
<tr>
<td>Incremental</td>
<td>3.9 (0.3)*</td>
<td>5.7 (0.6)</td>
</tr>
</tbody>
</table>

* p < 0.05 v the detraining phase. Data are mean values (SEM). Blood flow in incremental test was compared between data at rest and at 6 J/min/cm², because all patients could complete at least 6 J/min/cm². MCA, maximum cross sectional area; MVC, maximum voluntary contraction.

Table 2  Haemodynamic data

<table>
<thead>
<tr>
<th>Training phase</th>
<th>Detraining phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak VO₂ (ml/kg/min)</td>
<td>23.4 (2.2)</td>
</tr>
<tr>
<td>VT (ml/kg/min)</td>
<td>15.7 (1.1)</td>
</tr>
<tr>
<td>Peak work load (watt)</td>
<td>131.7 (15.2)</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>76.7 (3.9)</td>
</tr>
<tr>
<td>Blood pressure (mm Hg)</td>
<td>Rest</td>
</tr>
<tr>
<td></td>
<td>Peak</td>
</tr>
</tbody>
</table>

Data are mean values (SEM). There was no significant change between the training phase and the detraining phase. All data were measured during upright ergometer exercise test. Peak VO₂, peak oxygen uptake; VT, ventilatory anaerobic threshold.

Discussion

Training for patients with chronic heart failure has been investigated for several years. Initially, large muscle group training such as bicycle ergometer exercise was investigated. The results showed increasing systemic exercise time and peak VO₂ without improvement in cardiac function. Sullivan et al.16 speculated that peripheral factors played an important role in improving exercise capacity. Thereafter peripheral factors—such as muscle metabolism, vascular resistance, and so on—have attracted more attention and localised skeletal muscle training has been examined. However, to our knowledge, there has been only one localised training study on the lower extremities, by Magnusson et al.,17 who reported that single thigh training in chronic heart failure improved exercise capacity. Employing a muscle biopsy technique, they also showed that there were histochemical changes in thigh muscle after training. Since the calf muscle group has a naturally greater proportion of oxidative fibres11–13 and its metabolic responses during exercise are different from those of upper extremities,14–16 we speculated that the training effect on this muscle group might be different from that of the forearm.

Our study showed that the decrease in intracellular pH diminished. Several effects of training have been reported, including reductions in lactate production,17–19 increases in the lactate clearance rate,20–22 and improvement of acid buffering capacity.23 These mechanisms may have contributed to the improvement in intracellular pH observed in our study.

Figure 4  Effects of localised training on calf blood flow in constant load exercise test. There was no difference between the training phase and the detraining phase by repeated measures analysis of variance (p = NS). Comparing matched points, there were no significant changes. Empty circles, training phase; filled circles, detraining phase.

MCA, maximum cross sectional area; MVC, maximum voluntary contraction.

Thermic effect of food was measured for the first time during a period of starvation, and the results were published in 1910. The thermic effect of food was subsequently studied extensively, and it was found that the energy expenditure associated with the digestion and absorption of food was a significant fraction of the total energy intake. This finding was important because it suggested that a decrease in food intake could have a greater impact on weight loss than previously thought.

In the late 19th century, it was recognized that the thermic effect of food could be used to estimate the basal metabolic rate (BMR). The BMR is the energy expenditure of the body at rest, and it is used to calculate the energy requirements of individuals. The thermic effect of food was shown to be a reliable method for estimating the BMR, and it is still used today for this purpose.

One of the earliest studies of the thermic effect of food was conducted by Faye and Benedict in 1905. They measured the energy expenditure of a group of subjects before and after the consumption of a meal and found that the energy expenditure increased significantly. This study was important because it demonstrated that the thermic effect of food could be used to estimate the BMR.

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decrease in standardised phosphocreatine was also smaller after training. This suggested that there was improvement of oxidative capacity in our study.18

To evaluate the metabolic response to localised exercise, with 31P-MRS, we have advocated the usefulness of combining two exercise protocols, an incremental exercise protocol and a 70% maximum, constant load exercise protocol. Our previous data suggested that during calf plantar flexion exercise, 70% of the maximum work load was a suitable value for comparing metabolic differences between cardiac patients and normal subjects.27 In the present study, the 70% maximum constant load exercise resulted in more definite metabolic improvements than incremental exercise. We suggest that the combination of these two exercise protocols is also useful for studying training effectiveness in patients with chronic heart failure.

Nishida et al28 proposed that if the same absolute load was imposed on all subjects regardless of muscle cross sectional area, the load per unit of muscle fibre would be less in subjects with a greater muscle cross sectional area. As far as we know, there has been no localised training study adjusting for muscle cross sectional area. Though our incremental exercise test imposed a work load adjusted in this way, there was still a tendency towards higher pH after training. In the constant load exercise test, we did not adjust for muscle cross sectional area in order to compare the metabolic responses to the same absolute work load of the training phase and the detraining phase. However, after applying this adjustment, a significant difference in standardised phosphocreatine remained. Thus the training effect on muscle metabolism could not be explained by the changes of muscle cross sectional area alone.

Our study showed that calf blood flow did not change in spite of an improvement in muscle metabolism. Minotti et al9 also reported that there was no significant change in blood flow after localised forearm training. On the other hand, Sullivan et al26 reported that leg blood flow increased after training with a bicycle ergometer. Both we and Minotti et al9 trained a relatively small muscle group and evaluated blood flow with strain gauge plethysmography, whereas Sullivan et al26 trained a large muscle group with an ergometer and measured blood flow with a thermiloduction catheter. We believe that blood supply to small working muscle groups, such as those of the forearm or calf, is sufficient even in cardiac patients during localised exercise.

In incremental exercise, because of the symptom limited protocol, the score of the new Borg scale at peak exercise did not change between the training phase and the detraining phase. On the other hand, in constant load exercise, the score improved significantly. Thus, patients were able to perform plantar flexion exercise with less effort after training. In previous localised training studies3 10 fatigue scores were not evaluated.

CONCLUSIONS

In patients with chronic heart failure, localised calf skeletal muscle training improved muscle oxidative capacity without changes in calf blood flow. The calf fatigue scale also improved significantly after training. Since cardiac patients are often limited by leg fatigue, this training method may improve muscle fatigue symptoms occurring in the course of daily activities. Patients whose cardiac function is impaired may be provided with additional safety benefits by localised training, since it does not have an important influence on the heart.
We thank the Mutou Corporation for technical advice and support.


