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 ($^{31}$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, repeated measures analysis of variance). The new Borg scale improved significantly 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.

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. This suggests that cardiac function is not the sole factor determining exercise capacity. Using phosphorus-31 nuclear magnetic resonance spectroscopy ($^{31}$P-MRS), many investigators have reported that patients with chronic heart failure have abnormal forearm skeletal muscle metabolism, and Mancini et al$^5$ reported abnormal metabolism in the calf muscle. Sullivan et al$^7$ 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 ($\dot{V}O_2$) of patients with chronic heart failure.$^6$ 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 al$^9$ and Stratton et al$^{10}$, using $^{31}$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 composition and metabolism during exercise 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. Magnusson et al$^{17}$ 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 histochecimical changes. This training resulted in some systemic effect, probably because the quadriceps femoris is a relatively large muscle group. Using $^{31}$P-MRS, Adamopoulos et al$^{18}$ 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 remains 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 $^{31}$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 and a plantar flexion exercise test 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.

**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. Patients began localised training with loads of 5, 10, or 15 kg and they were instructed to gradually increase the load as much as they could during the training phase.

The initial load of the training apparatus was set at a moderate level so that patients could perform easily. Patients were instructed to increase the load of the apparatus as much as they could. We lent this apparatus and a metronome to the patients so they could train at home. To ensure that training proceeded as planned, we maintained contact with patients by phone once or twice a week and also asked the patients to keep diaries.

**PHOSPHORUS–$^{31}$ NUCLEAR MAGNETIC RESONANCE SPECTROSCOPY**

$^{31}$P-MRS was performed by using an 80 mm surface coil in a 55 cm bore, 1.5 Tesla superconducting magnet (Siemens Magnetom 1.5 T). Shimming was adjusted by using $^1$H (proton). Spectra were obtained with a pulse width of 500 µs, a transmitter voltage of 20.0 V, and a repetition time of 2000 ms. Each spectrum consisted of an average of 16 scans. One measurement required about 40 seconds. Since only the relative changes of the high energy phosphates were evaluated, correction for saturation was not performed. Phospho-creatine (PCr) is expressed as standardised PCr, $[\text{PCr}] / ([\text{PCr}]+[\text{Pi}])$, where Pi is inorganic phosphate. The muscle pH was calculated from the changes in the chemical shifts of Pi relative to PCr ($\text{pH} = 6.75 + \log \left[\frac{(\sigma - 3.27)}{(5.69 - \sigma)}\right]$), where $\sigma$(ppm) is the chemical shift from Pi to PCr.

**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, a surface coil being placed under the right calf. The patient’s right foot was placed on a pedal attached by a pulley system to the load. During each plantar flexion, the load was lifted 5 cm. The patients were secured by belts during the test to immobilise the trunk. The supine plantar flexion test consisted of two exercises: (1) a multistage incremental exercise test; (2) a constant load exercise test. After the first incremental exercise test, patients rested for at least 30 minutes before the constant load exercise test. The incremental exercise was performed according to a symptom limited protocol. The load varied according to maximum calf area. The initial load was set at 0.05 kg/cm² calf area. It was then increased every minute by 0.05 kg/cm² calf area (1 J/min/cm²). Thus, between the training phase and the detraining phase, the absolute load increment per minute changed if maximum calf area changed, but the incremental load per unit of area stayed the same for all patients. In relation to the constant load exercise test, regardless of changes in maximum calf area between the training and detraining phases, the load determined by
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.\textsuperscript{19}

Calf blood flow
Within five days after the \textsuperscript{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\textsubscript{2} and ventilatory anaerobic threshold were measured on an upright electrical ergometer (Corival 400 Lobe by, 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.\textsuperscript{20}

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\textsuperscript{2} were used because all patients could complete at least 6 J/min/cm\textsuperscript{2}. The paired \textit{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 \textit{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\textsubscript{2} and ventilatory threshold than normal control subjects (peak VO\textsubscript{2} 24.1 (1.6) v 32.0 (2.6) ml/kg/min, p < 0.01; ventilatory threshold 16.4 (1.3) v 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).
METABOLIC CHANGES EVALUATED WITH 31P-MRS

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).

Standardised phosphocreatine did not change significantly during plantar flexion exercise from the training phase to the detraining phase (p = NS by repeated measures ANOVA).

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

Constant load 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).

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></th>
<th>Training phase</th>
<th>Detraining phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood flow (ml/100 ml/min)</td>
<td>2.5 (0.4)</td>
<td>2.7 (0.4)</td>
</tr>
<tr>
<td>(Incremental)</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 J/min/cm²</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</td>
<td>9.7 (0.8)</td>
<td>8.9 (0.8)</td>
</tr>
<tr>
<td>in incremental exercise</td>
<td>539.8 (49.2)*</td>
<td>476.8 (44.7)</td>
</tr>
<tr>
<td>Absolute peak work load</td>
<td>6min 3.9 (0.3)*</td>
<td>5.7 (0.6)</td>
</tr>
<tr>
<td>in incremental exercise</td>
<td>7.6 (0.3)</td>
<td>8.6 (0.2)</td>
</tr>
<tr>
<td>New Borg scale (10)</td>
<td>Incremental</td>
<td>7.6 (0.3)</td>
</tr>
<tr>
<td></td>
<td>Constant</td>
<td>3.9 (0.3)</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.

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.

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. 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., who reported that single leg 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 fibres and its metabolic responses during exercise are different from those of upper extremities, 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, increases in the lactate clearance rate, and improvement of acid buffering capacity. These mechanisms may have contributed to the improvement in intracellular pH observed in our study. The
increase in standardised phosphocreatine was also smaller after training. This suggested that there was improvement of oxidative capacity in our study.

To evaluate the metabolic response to localised exercise, with 31P-MRS, we 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. 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 al. 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 al. also reported that there was no significant change in blood flow after localised forearm training. On the other hand, Sullivan et al. reported that leg blood flow increased after training with a bicycle ergometer. Both we and Minotti et al. trained a relatively small muscle group and evaluated blood flow with strain gauge plethysmography, whereas Sullivan et al. trained a large muscle group with an ergometer and measured blood flow with a thermilodution 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 studies, fatigue scores were not evaluated.

Using 31P-MRS, Minotti et al. and Stratton et al. investigated localised forearm training. Both groups found that training improved the forearm metabolic response during exercise. Adamopoulos et al. used 31P-MRS to examine large muscle group training in patients with chronic heart failure. They suggested that there was significant muscle improvement during calf plantar flexion exercise after training. They used a bicycle ergometer for training, whereas plantar flexion exercise was used to assess muscle metabolism. We employed the same exercise mode in training and metabolic evaluation, and we found improvement in muscle metabolism after training. Regarding the training method, our localised training programme induced only slight cardiac stress when compared with large muscle group training, such as bicycle ergometer exercise. It therefore appears that our training programme could be advantageous for patients with chronic heart failure who cannot perform high intensity exercise training because of their poor cardiac reserve.

STUDY LIMITATIONS
The patient population was relatively small, as only a small number of patients agreed to follow the long strict study protocol. We therefore employed a crossover design for the study because it required fewer subjects.

Our patients with chronic heart failure showed a relatively high mean value for peak VO2. In relation to neurohormonal factors, the value of ANF was within the normal range, suggesting that our chronic heart failure patients were well controlled. However, as we showed in the prestudy assessment, their left ventricular ejection fraction was clearly decreased, and their skeletal muscle metabolic response during plantar flexion exercise showed a significant decrease in standardised phosphocreatine and intracellular pH compared with age matched normal subjects, thus indicating that they were suitable for training intervention.

We did not use the non-trained leg as a control. Minotti et al. and Stratton et al. reported in their localised forearm training in patients with chronic heart failure that there was no significant metabolic change in the non-trained arm. On the other hand, Ploutz et al. suggested that localised resistance training in normal subjects improved non-trained distant muscle groups. The proposed mechanism was neural. In view of these uncertainties we did not employ the non-trained leg as control.

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.


