Female-related skeletal muscle phenotype in patients with moderate chronic heart failure before and after dynamic exercise training

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Abstract

This study hypothesized that female patients with chronic heart failure (CHF), similarly as previously reported for male patients, have a decreased proportion of type I (slow twitch) muscle fibers combined with fiber atrophy, and respond to exercise training with an increased muscular fiber area and performance, and with an unaltered fiber type distribution. Methods: Sixteen women [age 62±10 years (mean±SD)] with stable, moderate CHF (left ventricular ejection fraction 28±8%) underwent percutaneous needle biopsies of the lateral vastus muscle, and assessments of isokinetic muscle strength and exercise tests with respiratory gas and blood lactate analyses, before and after 8 weeks of intensive knee extensor endurance training. Results: When compared to healthy age-matched women, the women with CHF unexpectedly had a normal proportion of type I fibers (51±15%), but a decreased cross-sectional area in both type I and II fibers. Exercise training increased the cross-sectional area of muscle fibers up to the reference range (21%, p=0.04), while the relative number of type I fibers decreased (12%, p<0.03). Training also increased muscle strength (16%, p<0.0001) and peak oxygen uptake (20%, p<0.0001). The increase in peak oxygen uptake was directly related to the training-induced increase in fiber areas (r=0.63; p<0.03), and decrease in lactate accumulation was inversely related to the training-induced decrease in the relative number of type I fibers (r=−0.62; p<0.02). Conclusions: As for men with CHF, a skeletal muscle atrophy was found in women, but contrary to the hypothesis, the proportion of type I muscle fibers was normal. Exercise training counteracted the atrophy suggesting skeletal muscle trainability in female CHF patients.

Keywords: Chronic heart failure; Women; Skeletal muscle fiber; Exercise training

1. Introduction

Skeletal muscle dysfunction has been suggested to be partly responsible for exercise intolerance in patients with chronic heart failure (CHF) [1–4]. Abnormalities of skeletal muscle fiber characteristics have been investigated in several studies of male patients, while data from muscle fibers in women with CHF are lacking. A decreased relative number of type I muscle fibers (type I %) [3–8] and an increased number of type IIb fibers (type IIb %) [3,5,8] have been demonstrated. Type II fiber [4,5,8] and a combined type I and II fiber atrophy [7] and decreased muscular performance [9,10] have been reported. Exercise training has been suggested to increase muscular fiber area [7,11], and muscular performance [11,12], but not to change fiber type distribution in men with CHF [7,11].

Previously we have reported that women with CHF following physical training improve exercise capacity and quality of life [3]. This study, based on the muscle biopsies in the same women, hypothesized that, similarly to men,
women with CHF (1) have a decreased type I percentage and an atrophy of muscle fibers, and (2) respond to exercise training with an increase in muscular cross-sectional fiber area and muscular performance with an unaltered fiber type distribution.

2. Methods

2.1. Patients

Sixteen consecutive female patients (age 41 to 72 years) with a history of stable, chronic congestive heart failure in New York Heart Association functional classes II and III (Table 1), gave their informed consent to participate in this study, which was approved by the local Ethics Committee. The diagnosis of chronic heart failure was based on symptoms of dyspnea, general fatigue, and congestion; medication with diuretics, angiotensin-converting enzyme inhibitors, and digoxin; and an echocardiographically determined ejection fraction at rest of $<40\%$. Patients with angina pectoris, valvular heart disease determined by Doppler echocardiography, intermittent claudication, Diabetes mellitus, chronic obstructive pulmonary disease, or any other disorder limiting physical performance other than heart failure, were excluded. The patients had been clinically stable for at least 3 months without any signs of fluid retention.

2.2. Skeletal muscle biopsy

Tissue samples were obtained at rest from the lateral vastus muscle using the percutaneous needle biopsy technique [14]. The samples were frozen in isopentane, pre-cooled in liquid nitrogen, and stored at $-80^\circ C$ until analysis. Serial transverse sections (10-μm thick) were cut. The sections were stained for myofibrillar ATPase after incubation at pH 4.3, 4.6, and 10.3 [15] and for NADH-dehydrogenase [16]. Fiber types were classified from ATPase stains as I, IIa, and IIb. The fiber type distribution was based on a minimum of 200 fibers. Consequently, biopsy specimens from two of the patients were excluded from the analyses because they were smaller than required.

The cross-sectional areas of each fiber type were measured planimetrically from NADH-dehydrogenase stains comprising a minimum of 20 fibers of each type in general. Biopsy specimens for fiber area studies were not adequate for analysis in two additional subjects, due to freezing artifacts.

Data from lateral vastus muscle biopsy specimens obtained and analyzed by the same methods as in the present study in a group of healthy women ($n=22$) from the same region as the investigated patients with a corresponding age range (40–70 years) and body mass index ($26\pm5$) [17], were used as reference values for fiber type distribution and fiber area data.

2.3. Isokinetic muscle strength

The peak torques (Nm) of concentric knee extensions were measured with a Cybex isokinetic dynamometer (Lumex, Bay Shore, NY, USA) [18] in both legs, one leg at a time. After calibration of the dynamometer, subjects were seated in the dynamometer chair and the thigh, pelvis, and chest were stabilized with straps. The input axis of the dynamometer was aligned with the rotation axis of the knee joint (the lateral femoral epicondylic) and the ankle was attached to the lever arm by a cuff proximal to the lateral malleolus. The alignment was duplicated in repeated tests by recording the length of the lever arm, elevation of the dynamometer head, and table and seat positions for each subject. Four maximal voluntary extensions were carried out at velocities of 90°/s and 180°/s. The average of the highest peak torques for both legs at each velocity are given.

2.4. Exercise test

As previously described [13], peak work rate and oxygen uptake were determined in peak exercise test on the knee extensor ergometer with continuous respiratory gas analysis. For lactate analysis blood samples were taken from an antecubital vein before, during and after the submaximal exercise test of 15 min, at a work rate of 65% of the absolute baseline peak work rate [13].

2.5. Training protocol

During the 8-week hospital-based training period, patients performed intensive bilateral dynamic knee exten-
Table 2
Muscle fiber type distribution and muscle fiber area

<table>
<thead>
<tr>
<th></th>
<th>Normals</th>
<th>Baseline</th>
<th>CHF patients After training</th>
<th>Difference (%)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Relative number (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type I</td>
<td>50±13</td>
<td>51±15NS</td>
<td>45±14NS</td>
<td>-12</td>
<td>0.03</td>
</tr>
<tr>
<td>IIa</td>
<td>34±10</td>
<td>28±70.02</td>
<td>33±9NS</td>
<td>+18</td>
<td>NS</td>
</tr>
<tr>
<td>IIb</td>
<td>15±9</td>
<td>21±130.06</td>
<td>22±120.01</td>
<td>+5</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Fiber area (μm²×10⁻²)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type I</td>
<td>3.6±0.7</td>
<td>2.7±06.0001</td>
<td>3.4±1.0NS</td>
<td>+25</td>
<td>0.002</td>
</tr>
<tr>
<td>IIa</td>
<td>3.1±0.6</td>
<td>2.6±10.85</td>
<td>3.1±1.6NS</td>
<td>+16</td>
<td>0.04</td>
</tr>
<tr>
<td>IIb</td>
<td>2.3±0.7</td>
<td>1.9±1.0NS</td>
<td>2.3±1.4NS</td>
<td>+23</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Values are expressed as mean±SD. Indexed p values indicate difference compared to normals. P values in last column indicates differences between baseline and after-training values. NS=nonsignificant.

2.6. Statistical analyses

Unless otherwise stated, data are presented as the mean±standard deviation (mean±SD). A two-tailed, paired Student’s t test was used to evaluate change between baseline and after training values in general, while change in blood lactate contents was evaluated by two-factor analysis of variance for repeated measures. The relationship between variables was examined by linear regression analysis. Statistical significance was defined as p<0.05.

2.7. Results

The average proportion of type I (slow twitch) fibers in the women studied did not differ from the type I fiber distribution in the healthy, gender- and age-matched reference population (Table 2). Nine of the patients studied had a type I fiber proportion above 50% and only three below 40%. The proportion of fast twitch, type IIa fibers was decreased and type IIb fibers was increased (Table 2). Skeletal muscle exercise training induced a shift from type I to type II fibers (Table 2).

Cross-sectional areas of muscle fibers were decreased in the women with CHF compared to the healthy reference population (Table 2). Training increased the cross-sectional areas in all fiber types and the after-training areas did not differ from those reported for the reference population (Table 2). Training also increased muscle strength (Table 3).

Increased peak oxygen uptake and work rate in the knee extension exercise (Table 3) and decreased blood lactate levels (20%, p<0.001) during and after submaximal exercise as reported in detail previously [13] were found. The training-induced change in the total muscle fiber area correlated with the training-induced change in knee extension peak oxygen uptake (r=0.63; p<0.03). The training-induced change in the relative number of type I fibers was inversely related to the training-induced change in blood lactate level during submaximal exercise and during the recovery phase after exercising (Fig. 1) and showed a trend toward a correlation with age (r=0.48; p<0.06).

3. Discussion

Even though the female skeletal muscle phenotype in moderate chronic heart failure showed a combined atrophy of both type I and type II muscle fibers, as previously reported in men [7], the relative mean number of type I (slow twitch) muscle fibers was unexpectedly within reference limits [17,19,20]. Previous studies based purely [4–6] or predominantly [3,7] on male populations have reported, in addition to muscle fiber atrophy, a reduced
stimulus to fiber type I maintenance. Skeletal muscle action involves selective recruitment of type I and type II fibers, depending on the requirements of the activity being performed. This selective recruitment is determined by the level of force demand on the muscle. During low-intensity exercise, such as walking, most of the muscle force is generated by type I fibers, while as the muscle tension requirements increase at higher exercise intensities, type IIa fibers are added to the work force. Finally, in events where maximal strength is needed, or type I and type IIa fibers have become exhausted, the type IIb fibers are also activated [23]. On the other hand, three of the women in the present study had a type I fiber proportion below 40%, indicating that the CHF muscle phenotype previously described mainly in men indeed can occur also in women with moderate CHF.

Intensive skeletal muscle training decreased the relative number of type I fibers with a shift to type II fibers in the female patients studied. Such a training response has previously been reported for healthy elderly men [24]. Some previous studies mainly in men with CHF [7,12], have reported unaltered fiber type distribution after training, while a reshift from type II to type I fibers was recently reported [25]. The training-induced decrease in type I% in this study was inversely related to the decrease in blood lactate level during and after submaximal exercise, signifying that the patients who showed the smallest decrease in the blood lactate level after training also showed the largest increase in the relative number of type II fibers. Thus the patients, who had a less pronounced training effect based on blood lactate response, also showed the largest increase in type II% and a trend towards direct relation with age. Compared with the previous studies of men with CHF [7,11,25], the average age of the women studied was ten years higher.

Training increased fiber area in all fiber types up to the percentage of type I muscle fibers in patients with CHF. Those findings have led to the view that a seminal feature of skeletal muscle phenotype in chronic heart failure is a skeletal muscle atrophy with a shift to type II fibers, which have a more anaerobic profile. Such an inactivity muscle phenotype has also been described in healthy populations subjected to inactivity [21] as well as in patients with muscle wasting due to, for example, chronic obstructive pulmonary disease [22].

None of our 16 studied female patients with moderate CHF had previously been subjected to exercise-based cardiac rehabilitation. As nine of these women indeed had a fiber type fraction above 50% and only three below 40%, a depressed type I fiber proportion is not an obligatory muscle characteristic that goes with the combined atrophy associated to the CHF, at least in women. These results should, however, be interpreted with caution. One reason could be gender-related life style differences, since women may, by virtue of habitual housekeeping activities, get a low-grade type of regular physical exercise, and thereby a

![Diagram](https://academic.oup.com/cardiovascres/article-abstract/42/1/99/325925)

Fig. 1. Relationship between the training-induced changes in the relative number of type I muscle fibers and in blood lactate concentrations during submaximal exercise for 10 min and during the recovery phase 5 min after exercise (bottom). The regression line (solid line) and the patients <65 years of age (open circles) and the patients ≥65 years of age (solid circles) are depicted.

Acknowledgements

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Skeletal muscle endurance training improves peripheral oxidative capacity, exercise tolerance, and health-related quality of life in women with chronic congestive heart failure secondary to either ischemic cardiomyopathy or idiopathic dilated cardiomyopathy. Am J Cardiol 1997;80:1025–1029.


