Differential effects of exercise training in men and women with chronic heart failure

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Background Abnormalities of myosin heavy chain (MHC) isoforms, enzyme activity, and capillarity contribute to the exercise intolerance that is characteristic of patients with heart failure. To what extent these changes can be reversed with exercise training and whether differences exist in the responses of men and women remains uncertain. We described and compared the effects of exercise training on exercise capacity and skeletal muscle histochemistry in men and women with chronic heart failure.

Methods Fifteen patients (10 male) undergoing standard medical therapy completed a 14- to 24-week exercise training program. Peak oxygen consumption, MHC isoforms, capillary density, and selected metabolic enzymes were assessed before and after training.

Results Peak oxygen consumption was improved 14% (\( P < .05 \)); however, this increase was mostly because of the improvement observed in men versus women (20% versus 2%, respectively, \( P < .01 \)). At baseline, MHC I content was lower in men than in women (33% ± 3% vs 49.6% ± 5.5%, \( P < .05 \)). MHC I improved with training in men, to 45.6% ± 4.5% (+38%, \( P < .05 \)), versus women (−3%, \( P = .82 \)), and the increase in men tended (\( P = .12 \)) to be significant when compared with that in women. There were no significant changes in capillary density or muscle enzyme activity with training in the group as a whole or in men and women separately.

Conclusion Among patients with chronic heart failure, improvements in peak exercise capacity may be more pronounced in men than in women. This difference in response of functional capacity to training paralleled differences observed between men and women for changes in MHC I isoforms. (Am Heart J 2003;145:912-8.)
little mechanistic physiologic or biochemical information on women, either for baseline differences when compared with men or in response to exercise training.

This paper describes the effects of a 14- to 24-week exercise training program on skeletal muscle histology in patients with chronic heart failure. Also, because differences in skeletal muscle response to a decrease in peak oxygen consumption (VO2) do exist between men and women with heart failure, comparisons are made within our data about differences in the exercise-training response between men and women.

Methods

Patients

Ten men (6 from Henry Ford Hospital and 4 from Duke University Medical Center) and 5 women (from Duke University Medical Center) with chronic heart failure caused by left ventricular systolic dysfunction participated in this study. Patients were recruited from outpatient heart failure clinics or from the office of a cardiologist practicing in the Detroit community. The institutional review board at each hospital approved the study, and all patients provided written informed consent. Inclusion criteria were New York Heart Association class II or III, a resting ejection fraction of ≤35% as measured by echocardiography or gated equilibrium radionuclide angiography, and no change in medical therapy for 30 days before baseline testing. Exclusion criteria were atrial fibrillation, acute myocardial infarction within the past 3 months, angina at rest or induced by exercise, and current participation in a regular exercise program ≥2 times each week. Twelve patients were taking digoxin, 5 patients were taking a β-adrenergic blocking agent (3 men and 2 women), 14 patients were taking an angiotensin II converting enzyme (ACE) inhibitor or a vasodilator, and 13 patients were taking a diuretic.

Study design

Exercise tests and skeletal muscle biopsies were completed before and after a 14- to 24-week exercise training program. Each patient’s physician was asked not to change a subject’s drug regimen during the study period, when possible.

Exercise testing

All subjects underwent graded upright cycle ergometry (Fitron, Lumex, Ronkonkoma, NY, or Monark, Vargerb, Sweden) to symptom-limited maximum, starting at a power output of 25 watts (W) and increasing by 25 W every 3 minutes. Tests were discontinued when dyspnea occurs, calf, thigh, or generalized fatigue developed. A 12-lead electrocardiogram (ECG) and blood pressure were assessed periodically at rest, during exercise, and throughout recovery. Air expired during exercise testing was analyzed by use of a SensorMedics 4400 or Horizon II Metabolic System (Yorba Linda, Calif). All subjects achieved a respiratory exchange ratio >1.08, indicating that they provided a good voluntary effort.

Muscle biopsies

Biopsy samples were obtained from the vastus lateralis muscle by use of a modified Bergstrom needle technique.36 Biopsy sites were first anesthetized with a 2% lidocaine solution, then a 0.5-cm incision was made through the skin and fascia lata. All samples were snap frozen at −80°C. Histology samples were mounted, in cross section, in an optimal temperature compound (Miles Pharmaceutical, West Haven Conn) immediately before being frozen in isopentane cooled by liquid nitrogen.

Histological and biochemical analysis

Vascular density was determined by examining the total number of endothelial cells relative to the total number of muscle fibers. Endothelial cells were identified by use of immunohistological techniques with an established endothelial cell-specific monoclonal antibody, as previously described.12 Relative myosin heavy chain (MHC) isoforms I, IIa, and IIx were identified in accordance with methods previously reported.12 Biochemical analysis of enzymes were performed fluorimetrically by use of an end point assay.37,38

Exercise training

Each training session lasted a minimum of 40 minutes, which included 5 minutes each for warm-up and cool-down activities. The aerobic phase of training was performed by use of motor-driven treadmills, stationary cycles, rowing machines, and arm ergometers. To ensure that the vastus lateralis muscle was involved with training, a minimum of 15 minutes per session was allocated to treadmill walking or cycling.

Patients attended the exercise program 3 times per week. By use of the heart rate reserve method, exercise intensity was set at 60% for the first 2 weeks and then increased, as tolerated, to 80%. A rating of perceived exertion of 11 to 14 was also used to guide exercise intensity.

Statistical analysis

A paired t test was used to assess a change in variables of interest after training. A 2-sample Student t test was used to compare men and women at baseline and changes with time. Pearson correlation coefficients were used to describe associations between continuous variables such as skeletal muscle characteristics or peak heart rate and change in peak VO2 with training. A P value ≤ .05 was considered to be statistically significant.

Results

Demographic and clinical characteristics at baseline for both men and women are shown in Table I. There were no significant differences in age, body mass index, or exercise tolerance as measured by peak VO2. Ejection fraction, although still reduced, was higher (P < .05) in women. All patients tolerated the exercise training well, and no important clinical complications were observed. Minor changes in medication were made. Specifically, in 2 patients the dose of ACE inhibitor or vasodilator was increased, in 1 patient digoxin
therapy was discontinued, in 1 patient the dose of diuretic was increased, and in 1 patient the dose of diuretic was decreased.

**Exercise tolerance**

Absolute \((P < .05)\) and relative \((P < .01)\) peak VO\(_2\) volumes were both increased after training (Table II). These increases were almost fully attributable to the significantly greater \((P < .01)\) increase observed in men (+20%) versus women (+2%). Among men, peak VO\(_2\) increased by >13% in 8 patients, was unchanged in 1 patient, and decreased by 8% in 1 patient. In contrast, peak VO\(_2\) was essentially unchanged in all 5 women (Figure 1).

Consistent with the aforementioned, the change in peak heart rate after training was significantly different \((P < .01)\) between men and women as well (Table II). Specifically, the mean peak heart rate increased 11 + 4 min\(^{-1}\) in men with training, and decreased in women \((-14 + 8\) min\(^{-1}\)). The correlation between change in peak heart rate and change in peak VO\(_2\) was \(r = 0.56\) in men \((P = .11)\) and \(r = 0.23\) in women \((P = .77)\).

Tables III and IV describe baseline measures and training-related changes for relative content of MHC isoforms, enzyme activity, and capillary density in all subjects and for men and women separately. At baseline, MHC I content was significantly higher in women, whereas MHC IIX content was higher in men. With training, the relative content of MHC I tended to increase with training \((P < .08)\) for the entire group. This increase was mostly attributable to the 38% increase observed in men \((P < .05)\). However, this increase was not significantly different from the change observed in women \((P = .12\), change in men vs change in women). In men, the content of MHC IIX tended to decrease \((-27\%, P = .07)\).

Capillary density at baseline was significantly greater \((P < .01)\) in men \((1.42 \pm 0.08\) endothelial cells \(\times\) fiber\(^{-1}\)) than in women \((1.12 \pm 0.03\) endothelial cells \(\times\) fiber\(^{-1}\)), and neither group showed a significant change with training. When comparing men with women, there were no significant differences for muscle enzyme activity at baseline or in response to training. Finally, no significant correlations were identified between change in peak VO\(_2\) and any change in skeletal muscle characteristics, for the entire group or for men or women separately.

**Discussion**

The major finding of this study is that although we observed a significant improvement (+14%) in peak VO\(_2\) after 14 to 24 weeks of exercise training, skeletal muscle abnormalities did not improve in a group of male and female patients with stable heart failure when both sexes are considered together. The absence of any change in relative MHC content is consistent with the exercise training response that often occurs in healthy subjects, and the work of other authors who showed a decrease\(^{34}\) or no change in the relative type I fibers in patients with heart failure.\(^{33}\) Conversely, Hambrecht et al\(^{41}\) showed a small increase in the percentage of type I fibers in men after 6 months of aerobic training (from 48%-52%). Pu et al\(^{40}\) showed a 10% increase in type I fibers in women undergoing 10 weeks of progressive resistance training. Our observation of an increase in MHC I content in men but not women, as a possible indication of an apparent sex-specific response, is discussed below.

We did not observe any training-related changes in oxidative enzyme activity or muscle capillary density in our subjects. This too is consistent with the observations of Kiliovouri et al,\(^{53}\) who examined 12 patients before and after 3 months of aerobic exercise training with a cycle ergometer. However, the absence of any changes in aerobic enzyme activity (eg, citrate synthase) in our study group differs from other authors who showed improvement with endurance training\(^{28,31}\) and resistance training.\(^{40}\)

The 14% improvement in peak VO\(_2\) in our group was almost fully attributable to the 20% increase observed in men. There was no increase in the peak VO\(_2\) in the women in this study (Figure 1), which differs from several exercise trials that showed improvement in peak VO\(_2\)^{29,54} or 6-minute-walk performance\(^{30,40}\) in women with heart failure. Although it is possible that women in this study had a higher relative peak VO\(_2\) than men, when expressed as a percent of predicted peak, this does not negate that the training regimen we used is adequate to induce an increase in peak VO\(_2\) in healthy women\(^{39}\) and patients with chronic disease.\(^{41}\) There is no physiologic rationale to lead us to believe that our training stimulus was inadequate for women with a peak VO\(_2\) of 15 mL \(\times\) kg\(^{-1}\) \(\times\) min\(^{-1}\).

It was only among our male subjects that there was a significant shift in the relative content of MHC I isoforms, from 33% before training to 46% after training.
Figure 1

Individual changes in peak VO\(_2\) volume for both men and women before and after exercise training. Mean peak VO\(_2\) was significantly increased in men \((P < .01)\), but not in women \((P = .45)\) (see also Table II).

### Table II. Response of peak VO\(_2\) and peak heart rate to 14 to 24 weeks of exercise training

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>Men (n = 10)</th>
<th>Women (n = 5)</th>
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<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Change</td>
<td>Baseline</td>
</tr>
<tr>
<td>Peak VO(_2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(\text{mL} \cdot \text{min}^{-1})</td>
<td>1448 ± 132</td>
<td>193 ± 74*</td>
<td>1635 ± 164</td>
</tr>
<tr>
<td>(\text{mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1})</td>
<td>16.3 ± 0.8</td>
<td>2.3 ± 0.7*</td>
<td>16.9 ± 1.1</td>
</tr>
<tr>
<td>Peak HR (min(^{-1}))</td>
<td>140 ± 7</td>
<td>4 ± 5</td>
<td>134 ± 8</td>
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</table>

Values presented as mean ± SE.
*\(P < .05\), change compared to baseline.
†\(P < .05\), change in men versus change in women.

### Table III. Response of relative myosin heavy chain content to 14 to 24 weeks of exercise training

<table>
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<tr>
<th></th>
<th>All</th>
<th>Men (n = 10)</th>
<th>Women (n = 5)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Change</td>
<td>Baseline</td>
</tr>
<tr>
<td>MHC-I (%)</td>
<td>38.5 ± 3.3</td>
<td>8.0 ± 4.2</td>
<td>33.0 ± 3.0*</td>
</tr>
<tr>
<td>MHC-IIa (%)</td>
<td>35.8 ± 2.2</td>
<td>-6.1 ± 3.5</td>
<td>36.6 ± 3.2</td>
</tr>
<tr>
<td>MHC-IIx (%)</td>
<td>25.1 ± 3.4</td>
<td>-1.3 ± 3.5</td>
<td>29.6 ± 3.6*</td>
</tr>
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</table>

Values presented as mean ± SE; MHC, Myosin heavy chain.
*\(P < .05\), men versus women at baseline.
†\(P < .05\), change compared to baseline.

(Table III). This was the first indication of a potential difference in the skeletal muscle response of men versus women to an exercise-training stimulus. Because of the possibility of sex-specific responses, it is not surprising that when the data from men and women are combined, the responses do not reach statistical significance. These data are intriguing and, when coupled with our previous findings that skeletal muscle abnormalities that are not attributable to deconditioning develop in men with heart failure and abnormalities of the same magnitude do not develop in women,\(^{17,55}\) should prompt investigators to look more closely at sex-specific responses to exercise training in health and disease.
In other trials involving women, the number of women participating was higher than in our study, and the training regimens focused more on lower-extremity skeletal muscle training (2-legged extension model or resistance training). Because the training method and modality are known to influence the outcome, it is possible that a combination of training parameters may be needed to best elicit improvement in both exercise tolerance and skeletal muscle properties.

During each training session in our study, relative exercise intensity was maintained at similar levels for men and women with the percent heart rate reserve method. Also, compliance to the prescribed training regimen was similar in both groups (ie, >70%). This may mean that a longer or more frequent training stimulus is required in women to elicit a training effect. Alternately, women may simply respond differently to a training regimen than men. Because peak VO₂ was not different between men and women at baseline, and because all exercise tests were limited by fatigue, it may be that the significantly higher MHC I content at baseline in women (Table III) simply offered less of a potential for training-induced changes in this skeletal muscle parameter. Other possible mechanisms explaining why peak VO₂ increased in men might be improved peripheral blood flow caused by endothelial function, improved central transport, or both.

There are several limitations in this study. First, the absence of a control group limits the implications of the training-induced changes that we observed in this study. However, on the basis of other controlled trials, there is no reason to believe that spontaneous improvement would have occurred in our subjects. Additionally, the absence of a nonexercising control group does not preclude us from identifying significant differences in training responses between men and women with heart failure. The absence of changes in women, and for some of the variables in men, may be caused by limited power. It does not mean that training-induced changes do not exist. However, the lack of change in VO₂ in women was very consistent. Again, we feel the stimulus was sufficient to increase VO₂ in women with such a low absolute value at baseline, making our findings unique. Previous trials assessing changes in peak VO₂ in women with heart failure used 2-legged extension exercise or resistance training.

Second, and as aforementioned, differences in training methods may account for differences between what we observed and the results reported by other authors. Specifically, a 14- to 24-week aerobic training model that provided 45 to 90 minutes per week of stimulus to the vastus lateralis may have been an insufficient means of effecting adaptations in skeletal muscle. However, the methods used were sufficient to induce some adaptation in men (+38% increase in MHC I content). This may be a sex-specific issue, and at the very least, our information may help others as they develop other training models. Conversely, this training stimulus has been shown to be adequate to significantly improve peak VO₂ in healthy subjects and patients with a broad range of diseases. Therefore, the failure to demonstrate a significant improvement in peak VO₂ in the 5 women in our study is important and worthy of further study.

Third, a more severe limitation of left ventricular function may be required in patients with heart failure before changes in skeletal muscle develop and, therefore, are present to respond to some type of training. For example, ejection fraction was significantly higher at baseline in women than in men (35% vs 22%). Further studies addressing this issue, and that also measure central and regional blood flow, would be helpful.

In conclusion, in this study of the effects of aerobic exercise training in men and women with congestive heart failure, we observed sex-specific differences in the response of peak VO₂ and skeletal muscle MHC I.

**Table IV.** Response of select skeletal muscle enzyme activity and capillary density to 14 to 24 weeks of exercise training

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capillary density (endothelial cells · muscle fiber⁻¹)</td>
<td>Baseline</td>
<td>Change</td>
<td>Baseline</td>
</tr>
<tr>
<td></td>
<td>1.33 ± 0.07</td>
<td>0.26 ± 0.21</td>
<td>1.42 ± 0.08</td>
</tr>
<tr>
<td>Citrate synthase (mol · kg protein⁻¹ · h⁻¹)</td>
<td>3.93 ± 0.27</td>
<td>0.00 ± 0.26</td>
<td>3.80 ± 0.39</td>
</tr>
<tr>
<td>Cyto C oxidase (mol · kg protein⁻¹ · h⁻¹)</td>
<td>60.33 ± 9.10</td>
<td>11.31 ± 7.43</td>
<td>67.07 ± 15.34</td>
</tr>
<tr>
<td>HAD (mol · kg protein⁻¹ · h⁻¹)</td>
<td>3.37 ± 0.34</td>
<td>-0.14 ± 0.52</td>
<td>3.41 ± 0.55</td>
</tr>
</tbody>
</table>

Values presented as mean ± SE. HAD, 3-Hydroxylacyl-CoA dehydrogenase; Cyto, cytochrome.
content. However, more trials involving larger groups of patients, with particular attention to sex-specific responses in mechanistic biochemical and physiological parameters, are warranted.

References


Antibiotics in primary prevention of myocardial infarction among elderly patients with hypertension

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Background Given the premise that certain bacteria (such as Chlamydia pneumoniae) may play a role in the etiology of atherosclerosis, subjects treated with antibiotics that have antibacterial activity against C pneumoniae may be at lower risk for the development of an acute myocardial infarction (MI) than untreated subjects.

Methods A case-control design, nested within a cohort of 29,937 elderly subjects in whom antihypertensive therapy was initiated (1982-1995) was used, in which each subject who was hospitalized with a primary discharge diagnosis of MI between 1987 and 1995 (n = 1,047) was matched on calendar time to 5 randomly selected control subjects for exposure contrasts. Conditional logistic regression analyses were conducted to adjust for predisposing factors for MI.

Results Although no clear consistent effect of antibiotics use was found in relation to MI, a trend was observed for a decreased risk of acute MI in patients receiving a prescription for antichlamydial antibiotics in the preceding 3 months (odds ratio 0.68, 95% CI 0.46-1.00). Antibiotics without antichlamydial activity showed no benefit in MI risk.

Conclusion The beneficial effect of certain antichlamydial antibiotics in reducing the risk of MI cannot be excluded on the basis of this representative cohort of elderly patients in a routine clinical care setting. Larger prospective studies are required to confirm the usefulness of antibiotics in the primary prevention of MI. (Am Heart J 2003;145:e25.)