Randomized trial of progressive resistance training to counteract the myopathy of chronic heart failure

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Pu, Charles T., Meredith T. Johnson, Daniel E. Forman, Jeffrey M. Hausdorff, Ronenn Roubenoff, Mona Foldvari, Roger A. Fielding, and Maria A. Fiatarone Singh. Randomized trial of progressive resistance training to counteract the myopathy of chronic heart failure. J Appl Physiol 90: 2341–2350, 2001.—Chronic heart failure (CHF) is characterized by a skeletal muscle myopathy not optimally addressed by current treatment paradigms or aerobic exercise. Sixteen older women with CHF were compared with 80 age-matched peers without CHF and randomized to progressive resistance training or control stretching exercises for 10 wk. Women with CHF had significantly lower muscle strength (P < 0.0001) but comparable aerobic capacity to women without CHF. Exercise training was well tolerated and resulted in no changes in resting cardiac indexes in CHF patients. Strength improved by an average of 43.4 ± 8.8% in resistance trainers vs. −1.7 ± 2.8% in controls (P = 0.001), muscle endurance by 299 ± 66% vs. 1 ± 3% (P = 0.001), and 6-min walk distance by 49 ± 14 m (13%) vs. −3 ± 19 m (−3%) (P = 0.03). Increases in type I fiber area (9.5 ± 16%) and citrate synthase activity (35 ± 21%) in skeletal muscle were independently predictive of improved 6-min walk distance (r² = 0.78; P = 0.0024). High-intensity progressive resistance training improves impaired skeletal muscle characteristics and overall exercise performance in older women with CHF. These gains are largely explained by skeletal muscle and not resting cardiac adaptations.

exercise; aging; type I fibers

CHRONIC SYSTOLIC HEART FAILURE (CHF) is the only cardiac diagnosis that is continuing to increase in prevalence in the United States due to the prolonged survival of those with hypertension and ischemic heart disease, as well as improved average life span of the population (35, 42). The clinical hallmark of the disease is exercise intolerance, manifested as fatigue and dyspnea during increasingly minimal activities (21).

Mounting evidence suggests that peripheral skeletal muscle abnormalities figure prominently in the exercise intolerance associated with CHF (15–17, 26, 40, 53, 54), whereas central hemodynamic parameters, such as ejection fraction, are far less predictive of clinical symptoms or mortality (34). These peripheral abnormalities include a skeletal muscle myopathy characterized by preferential loss and atrophy of type I (slow, oxidative) fibers, decreased oxidative enzyme capacity and mitochondrial volume density, early activation of glycolytic pathways of ATP generation during work, and reduced muscle endurance, strength, power, and overall exercise tolerance compared with healthy, age-matched individuals (39). The selective loss of oxidative fibers distinguishes this condition from type II fiber selectivity of muscle atrophy common to aging and disuse syndromes (29, 47, 66) and suggests that a different pathogenic mechanism may be operative.

The degree of exercise intolerance in CHF correlates strongly with both mortality and quality of life (69, 70); yet current medical therapies often fail to specifically address many of the potential mechanisms that underlie these symptoms (25). Aerobic exercise interventions have been shown to be tolerable in middle-aged and young-old patients with stable CHF and result in improved aerobic capacity without improving central hemodynamic features (contractility, stroke volume, ejection fraction, chamber diameter, filling times) of the disease (1, 18–20, 24, 62), as well as improved survival, quality of life, and reduced rate of hospitalizations (5, 27). However, the limited experience reported from the...

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European Heart Failure Training Group in women (n = 9) and patients over 70 yr (n = 14) suggests that the improvements in exercise capacity seen in younger men after aerobic training may not extend to older individuals (27).

Therefore, we first conducted a cross-sectional comparison of older patients with CHF and subjects with chronic illnesses but no CHF to test our hypothesis that muscle function would be more specifically impaired than aerobic capacity in elderly patients with CHF. Next, we conducted a randomized controlled clinical trial to determine the efficacy of high-intensity progressive resistance training (PRT) in older patients with CHF. We hypothesized that strength training in these patients would be well tolerated and result in improved overall exercise performance without changes in central cardiac function. Moreover, we hypothesized that the adaptations in skeletal muscle following strength training would explain much of the improvement in overall functional capacity.

METHODS

Study Design

Patients with CHF were compared with older women with other chronic diseases selected for functional impairment but without a clinical diagnosis or physical signs of CHF (31). A 10-wk, randomized, placebo-controlled trial was conducted, in which subjects with CHF received either the experimental intervention of high-intensity PRT or a placebo control stretching program. The protocol was approved by the Human Investigation Review Committees at Tufts University New England Medical Center and the Hebrew Rehabilitation Center for Aged. Written, informed consent was obtained from each subject.

Subject Recruitment and Eligibility

Subjects were recruited via advertisement at a local senior apartment complex for measurements of exercise capacity and later enrollment into an exercise program and via volunteer databases. Inclusion criteria for CHF subjects were community-dwelling women, 65 yr or older with mild to moderate, stable systolic heart failure defined by New York Heart Association (NYHA) class I to III (12) and a resting left ventricular ejection fraction <45%. Inclusion criteria for the controls were community-dwelling women at least 70 yr of age, with one or more impairments on the Physical Function Subscale of the Medical Outcomes Survey (SF-36) (67). Exclusion criteria for the CHF patients were NYHA class IV heart failure, myocardial infarction within 6 mo of randomization, hospitalization for CHF within 2 mo, change of CHF therapy within 1 mo, unstable angina pectoris, fixed ventricular rate pacemaker, abdominal aortic aneurysm >4 cm, major limb amputation, symptomatic abdominal oringuinal hernias, Folstein mini-mental state examination score <23 (32), significant abnormalities on maximal treadmill testing or screening strength testing (>3 mm ST-segment depression, ventricular tachycardia, new atrial fibrillation, heart block or any hemodynamically significant arrhythmia), or any unstable medical condition. Similar exclusions applied to controls who, in addition, had no history or clinical evidence of CHF, although other chronic diseases were acceptable.

Intervention Protocols

PRT group. Subjects in the experimental group participated in high-intensity PRT 3 days/wk for 10 wk under the supervision of a research assistant. High-intensity PRT was defined as training with 80% of the maximal weight that could be lifted in good form [the one repetition maximum (1 RM)]. Strength was retested every tenth session to establish a new 1 RM. Dynamic contractions of the large upper and lower body muscle groups (seated leg press, chest press, knee extension, triceps and knee flexion) were performed on pneumatic-resistance training equipment (Keiser Sports Health Equipment, Fresno, CA). Training sessions averaged 60 min and were preceded by 2 min of walking or cycling for warm-up and ended with 5 min of stretching. Subjects performed three sets of eight repetitions on each machine before moving on to the next. Each repetition lasted 6–9 s with a 2- to 3-s rest between repetitions and a 60- to 90-s rest between sets. As needed, rest periods of 1–3 min were inserted between machines.

Placebo control group. Subjects in the placebo control group participated 2 days/week in supervised, low-intensity stretching exercises, without resistance other than that imposed by gravity, that were designed as a “sham exercise” condition. Exercise sessions lasted 1 h and included stretching exercises of the neck, trunk, and extremities.

Exercisers in both groups were supervised by the same trainer, with one to three subjects per session. All subjects were instructed not to begin any new exercise regimen during the course of the study. Health status was monitored at each training session by the trainer and weekly by the principal investigator.

Outcome Measures

Our primary outcomes were overall exercise capacity (6-min walk distance) and muscle function. Our secondary outcomes were muscle metabolism and histology, body composition, maximal oxygen consumption, and cardiac function. All outcome measures were performed by the same assessor the week before and after the 10-wk training protocol. All measures were double-blinded except for musculoskeletal and overall exercise performance outcomes, which were single-blinded. Clinical status was determined by history and physical examination, and review of medical records was done by the principal investigator.

Overall functional performance. The 6-min walk, as described by Guyatt et al. (36), was used to measure overall functional exercise performance. The distance walked was recorded to the nearest foot by a rolling measuring wheel (RediMeasure, Redington, Windsor, CT). The self-perceived exertion scale defined by Borg and Linderholm (9) was obtained from the subject on completion of each test.

Aerobic capacity. Peak aerobic capacity (\(\text{VO}_2\)) and time to exhaustion were measured on a motorized treadmill (Woodway, Waukesha, WI) by a symptom-limited, graded test to exhaustion. Treadmill speed was held constant at 80% of the subject’s habitual gait speed, as determined by an ultrasonic gait monitor (Ultratimer, DCPB Electronics, Glasgow, Scotland), a device that measures speed (m/s) via an ultrasonic transmitter. Beginning at 0% grade for the first 2 min, the grade was then increased 2% every minute until subject exhaustion was reached. The subject’s expired gases were obtained through a Hans Rudolph face mask (series 8930 no. 5, Hans Rudolph, Kansas City, MO) custom-fitted with a thin compliant sealant (Elastogel) around the mask to prevent air leakage, a method validated in older populations (52). Expired gases were continuously analyzed by a Beckman LB-2.
CO₂ analyzer and an Applied Electrochemistry S-3A O₂ analyzer using standard procedures (31). The higher of the two values for peak VO₂ obtained during screening and baseline testing was used in the analyses.

Musculoskeletal performance indexes: strength and endurance. Dynamic concentric muscle strength was determined using the same type of pneumatic resistance equipment as that used in the training intervention by the 1-RM method and expressed in newtons (N). To minimize improvement related to repeated testing, the best of two measurements taken 1 wk apart was used as the baseline value. 1-RM measurements were reliable with test; retest differences ranged from 5.0 ± 2.2% (leg press) to 9.1 ± 3.2% (chest press).

On a separate day, muscle endurance, a test of submaximal muscle performance, was determined by the number of dynamic repetitions that could be correctly completed at a fixed load (90% of baseline 1 RM) at the subject’s self-determined but continuous pace (31).

Skeletal muscle biopsy procedures. Percutaneous needle biopsies of the nondominant vastus lateralis (knee extensor) muscle were obtained under local anesthetic (1% Xylocaine hydrogen chloride) using the method described by Evans et al. (28). To determine citrate synthase activity (CSA), biopsies were quick-frozen in liquid nitrogen, homogenized, and assayed spectrophotometrically using the method described by Srere (64), and values were normalized to the total protein content of each muscle homogenate obtained using the Bradford colorimetric assay (Bio-Rad, Sunnyvale, CA) (10). The mean of duplicate values was used for analyses.

For histochemistry, muscle samples were mounted in embedding medium (OCT, Miles Laboratories, Naperville, IL), frozen, sectioned, and stained for myosin ATPase activity using the method described by Padykula and Herman (59). Fiber-type distribution and fiber cross-sectional areas were determined using manual planimetry. The coefficients of variation (CV) for type I and II fiber area measurements in our laboratory are 7.5 and 4.0% for type I and II fiber distribution and 6.3 and 5.5% for type I and II fiber areas.

Total body muscle mass. Total body skeletal muscle mass was estimated from a 24-h urine creatinine collection obtained in an outpatient setting as described by Heymsfield et al. (41). Urine collections were obtained following a 3-day meat-free diet that was continued throughout the urine collection. Creatinine was measured by the Jaffe kinetic reaction on a clinical chemistry analyzer (Roche Diagnostic Systems, Montclair, NJ), according to the procedures of Jaffe (43) as modified by Roche Diagnostic Systems. CV of this assay in our laboratory is 4.0%. Urinary 3-methylhistidine excretion was measured from the same urine samples used for creatinine analyses as an index of myofibrillar protein breakdown, according to the method of Wassner et al. (68). The mean of two 24-h urine collections was used in analyses.

Cardiac function. Resting cardiac function was determined in the left lateral supine position by transthoracic M-mode and two-dimensional Doppler echocardiography (Sonos 2500, Hewlett-Packard, Palo Alto, CA). Left ventricular (LV) function was assessed using ejection fraction measured from the apical images. LV diastolic function was determined by mitral valve inflow from the apical four-chamber image in all patients who were not in atrial fibrillation. LV morphology was measured using M-mode measurements of the LV posterior wall, anterior wall, and the intraventricular diameter in the parasternal long view. All echo images were analyzed blindly by a cardiologist on an off-line workstation (Tomtec, CA).

Statistical Analysis

All data were analyzed with Statview or SuperANOVA software (Abacus, Berkeley, CA). Intention-to-treat analyses were used for all outcomes. Data were inspected visually and statistically for normality and then expressed as means ± SE unless otherwise indicated. Comparisons between groups were analyzed by unpaired t-tests or analysis of covariance (ANCOVA) models for continuous variables and Fisher’s exact test for categorical data. Repeated-measures ANOVA and ANCOVA models were constructed to analyze the effect of time, treatment, and time-by-treatment interactions for all primary outcome variables, with adjustment for baseline values as appropriate. Post hoc t-tests were used to compare means when a significant F ratio was noted in ANOVA models of main effects. Relationships between variables of interest were analyzed by simple and forward stepwise multiple regression models, as appropriate. Two-sided P values ≤0.05 were considered significant.

RESULTS

Subject Characteristics

Eighty community-dwelling women with functional impairment and other chronic diseases were enrolled as controls for baseline comparisons with the CHF patients. Sixteen community-dwelling women with a history of compensated heart failure due to impaired systolic function were enrolled. Baseline comparisons of controls and CHF patients are shown in Table 1. The non-CHF group had fewer chronic diseases than CHF patients. The major chronic diseases in both groups were arthritis, hypertension, coronary artery disease, diabetes, and osteoporosis. CHF patients, randomized into placebo and experimental exercise regimens, were well-matched at baseline as summarized in Table 2.

Compliance, Safety, and Health Status

All subjects completed the 10-wk intervention. There were no hospitalizations or deaths. Attendance at exercise sessions for both groups averaged 98%. The mean training load in the resistance trainers was 82 ± 1% of the most recent 1 RM. Minimal changes in medications occurred among patients in either group.

Table 1. Comparison of CHF patients and non-CHF controls

<table>
<thead>
<tr>
<th>Variable</th>
<th>Women with CHF (n = 16)</th>
<th>Controls (n = 80)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>77 ± 6</td>
<td>75 ± 5</td>
<td>0.215</td>
</tr>
<tr>
<td>Chronic diseases, number</td>
<td>7.1 ± 2.3</td>
<td>3.2 ± 0.2</td>
<td>0.017</td>
</tr>
<tr>
<td>Aerobic capacity, ml-kg⁻¹-min⁻¹</td>
<td>15.0 ± 3.7</td>
<td>17.3 ± 3.3</td>
<td>0.155</td>
</tr>
<tr>
<td>Muscle strength, N</td>
<td>1,292 ± 344</td>
<td>1,994 ± 43</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Values are means ± SE; n = no. of subjects. Aerobic capacity was measured as peak oxygen consumption during the best of 2 baseline graded treadmill tests to exhaustion. Muscle strength was measured as the best of 2 baseline 1-repetition maximum tests on the bilateral leg press machine. CHF, chronic heart failure. P values derived from t-tests between groups (age, disease) and analysis of covariance models adjusted for age and diseases (strength, aerobic capacity).
Habitual gait speed (1.5, 1.0) significantly lower leg muscle strength than non-CHF controls. Increasing severity of CHF was also related to slower fiber area was unrelated to clinical disease severity.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Resistance Training Group (n = 9)</th>
<th>Placebo Control Group (n = 7)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>76.6 ± 2.0</td>
<td>76.6 ± 2.4</td>
<td>0.99</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>24.7 ± 1.2</td>
<td>28.0 ± 1.9</td>
<td>0.15</td>
</tr>
<tr>
<td>Left ventricular ejection fraction, %</td>
<td>36.3 ± 2.7</td>
<td>36.0 ± 2.9</td>
<td>0.93</td>
</tr>
<tr>
<td>CHF duration, mo</td>
<td>29.2 ± 5.8</td>
<td>25.7 ± 5.0</td>
<td>0.67</td>
</tr>
<tr>
<td>New York Heart Association class (I–IV)</td>
<td>2.2 ± 1.0(1/6/2)</td>
<td>2.3 ± 0.2(5/6/5)</td>
<td>0.78</td>
</tr>
<tr>
<td>Etiology, no. of women (%)</td>
<td>Ischemic heart disease</td>
<td>6(67%)</td>
<td>0.59</td>
</tr>
<tr>
<td></td>
<td>Idiopathic</td>
<td>2(22%)</td>
<td>0.99</td>
</tr>
<tr>
<td></td>
<td>Valvular</td>
<td>1(11%)</td>
<td>0.99</td>
</tr>
<tr>
<td></td>
<td>Medical</td>
<td>7.3 ± 0.9</td>
<td>0.61</td>
</tr>
<tr>
<td></td>
<td>Regular medications, no./day</td>
<td>8.2 ± 1.4</td>
<td>0.83</td>
</tr>
</tbody>
</table>

Values are means ± SE.

After a baseline 1 RM determination was made, one control subject developed an exacerbation of underlying trochanteric bursitis that resolved with rest. One control subject developed exertional angina with ischemic electrocardiogram (ECG) changes during the screening exercise treadmill test but not during 1 RM testing or control exercise sessions. No potential subjects were excluded for ECG abnormalities during monitored screening weight lifting tests. Four experimental subjects required minor modifications in the resistance training regimen due to intermittent mild musculoskeletal symptoms. Overall, 48 peak exercise treadmill tests, 91 maximal strength tests, and 410 exercise training sessions (experimental and control) were completed without cardiovascular complications.

**Exercise Capacity in Normal Controls and CHF Patients**

As shown in Table 1, women with CHF had significantly lower leg muscle strength than non-CHF controls, after adjusting for age and number of chronic illnesses (P < 0.0001). By contrast, peak aerobic capacity was only slightly and not significantly lower in women with CHF than in controls.

Clinical status of heart failure patients, categorized by NYHA class, was related to several musculoskeletal indexes and performance measures. Patients with increasingly severe CHF had smaller mean type I muscle fiber area (P = 0.028) and lower urinary 3-methylhistidine excretion (187.9, 112.0 ± 12.1, and 70.1 ± 7.8 μmol/g creatinine for class I, II, and III, respectively; P = 0.028; see Fig. 1). By contrast, mean type II muscle fiber area was unrelated to clinical disease severity. Increasing severity of CHF was also related to slower habitual gait speed (1.5, 1.0 ± 0.1, 0.6 ± 0.0 m/s for class I, II, and III, respectively; P = 0.003), lower peak aerobic capacity (18.5, 16.1 ± 0.9, and 11.0 ± 1.0 ml·kg⁻¹·m⁻¹ for class I, II, and III, respectively; P = 0.02), and poorer performance on the 6-min walk (341, 426 ± 24, and 219 ± 41 m for class I, II, and III, respectively; P = 0.003). Ejection fraction and other cardiac indexes were unrelated to NYHA class.

**Intervention Outcomes**

**Overall exercise performance.** There were no baseline differences in peak exercise measurements between groups. Baseline 6-min walk distance was significantly correlated with both knee extensor strength (r = 0.559; P = 0.02) and peak VO₂ (r = 0.768; P = 0.0005). The results of strength training on overall exercise performance are summarized in Table 3.

Six-minute walk distance increased significantly by 49 ± 14 m (13 ± 4%) in the resistance-trained group vs. −3 ± 19 m (−3 ± 7%) in the controls (P < 0.03). Improvements in the 6-min walk were significantly associated with the proportion of type I fibers at baseline and positive changes in knee extensor strength and endurance, type I fiber area, type I fiber type proportion, and oxidative enzyme capacity, as summarized in Table 4. Changes in type I fiber area and oxidative enzyme capacity remained independently predictive of changes in 6-min walk distance when analyzed in a forward stepwise multiple regression model of all these variables with univariate associations (r² = 0.78; P = 0.0024) (see Fig. 2).

Treadmill exercise time to exhaustion increased by 47 ± 34 s in the experimental group, whereas it decreased by 41 ± 20 s in the controls (P = 0.06). There were no significant changes in peak VO₂, ventilation, heart rate, or respiratory exchange ratio.

**Changes in musculoskeletal performance.** Musculoskeletal performance between treatment groups was comparable at baseline (see Table 5). Significant strength and endurance gains were achieved for all resistance-trained subjects in every muscle group tested, whereas no significant changes were seen in the controls. Gains in muscle strength ranged from 33.5 ± 0.026 to 426 ± 0.003; see Fig. 1). By contrast, mean type II muscle fiber area was unrelated to clinical disease severity. Increasing severity of CHF was also related to slower habitual gait speed (1.5, 1.0 ± 0.1, 0.6 ± 0.0 m/s for class I, II, and III, respectively; P = 0.003), lower peak aerobic capacity (18.5, 16.1 ± 0.9, and 11.0 ± 1.0 ml·kg⁻¹·m⁻¹ for class I, II, and III, respectively; P = 0.02), and poorer performance on the 6-min walk (341, 426 ± 24, and 219 ± 41 m for class I, II, and III, respectively; P = 0.003). Ejection fraction and other cardiac indexes were unrelated to NYHA class.

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7.3% (leg press) to 68.0 ± 13.2% (knee extension) for a mean gain of 43.4 ± 8.8% compared with 2.8 ± 2.8% in the controls (P < 0.001). Submaximal muscle endurance increased 299 ± 66% in the resistance trained group compared with 163% in the controls (P < 0.001) (see Fig. 3).

Skeletal muscle adaptations. Metabolic and morphological musculoskeletal adaptations are summarized in Table 6.

**Muscle Mass**

There was no significant change in total body muscle mass after the intervention: 1.81 ± 1.07 kg increase in the resistance trained group vs. −0.18 ± 1.6 kg in the controls (P = 0.30)

**Oxidative Capacity**

Oxidative capacity in skeletal muscle increased substantially by 20.2 ± 11.8 μmol·g−1·min−1 (35.2 ± 20.5%) in the resistance trained group, whereas it changed minimally (2.9 ± 4.2 μmol·g−1·min−1; 5.1 ± 9.0%) in the controls, although these results did not reach statistical significance (P = 0.19).

**Mean Fiber Area and Fiber-type Distribution**

Skeletal muscle histology at baseline in both groups was similar and characterized by a predominance of type II fibers. There were no significant changes in fiber-type distribution following the intervention period. The relative increase in type I fiber area approached significance after resistance training [9.5 ± 15.6% vs. −6 ± 8.9% in controls; P = 0.079, ANCOVA model adjusted for age and body mass index (BMI)]. Type II fiber area exhibited similar but nonsignificant increases after resistance training (13.6 ± 10.3% vs. 0.3 ± 10.6% in controls; P = 0.810, ANCOVA model adjusted for age and BMI).

Relationships between musculoskeletal performance and other muscle characteristics. Baseline knee extensor strength was significantly related to baseline muscle mass (r = 0.644; P = 0.007), and similar trends were observed with other muscle groups (data not shown). Changes in knee extensor strength after training were directly associated with changes in muscle

Table 3. Effects of intervention on resting cardiac function

<table>
<thead>
<tr>
<th>Cardiac Parameter</th>
<th>Progressive Resistance Training Group (n = 9)</th>
<th>Placebo Control Group (n = 7)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre</td>
<td>Post</td>
<td>Pre</td>
</tr>
<tr>
<td>Left ventricular ejection fraction, %</td>
<td>36.3</td>
<td>37.8</td>
<td>36.0</td>
</tr>
<tr>
<td>E:A ratio</td>
<td>0.95</td>
<td>0.94</td>
<td>0.64</td>
</tr>
<tr>
<td>Left ventricular diameter, cm</td>
<td>5.2</td>
<td>5.2</td>
<td>5.5</td>
</tr>
</tbody>
</table>

Values are means ± SE. E:A ratio was measured in 9 subjects not in atrial fibrillation. E:A ratio, ratio of early to atrial filling during diastole, measured by echocardiography at rest (see METHODS).

Fig. 2. Musculoskeletal indexes that independently predict functional performance measured by 6-min walk in stepwise multiple regression analysis. A: change in 6-min walk as a function of change in type I muscle fiber area. B: change in 6-min walk as a function of change in muscle oxidative capacity.
Table 5. Effect of intervention on overall exercise tolerance

<table>
<thead>
<tr>
<th>Overall Exercise Tolerance Measure</th>
<th>Resistance Training Group (n = 9)</th>
<th>Placebo Control Group (n = 7)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre Post</td>
<td>Pre Post</td>
<td>Time Group × time</td>
</tr>
<tr>
<td>Aerobic exercise capacity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak (\text{Vo}_{2}), ml·kg(^{-1})·min(^{-1})</td>
<td>15.46 ± 1.04 15.08 ± 1.62</td>
<td>14.40 ± 1.13 14.75 ± 0.94</td>
<td>0.88 0.41</td>
</tr>
<tr>
<td>Peak (\text{Ve})</td>
<td>28.9 ± 2.4 28.2 ± 2.9</td>
<td>32.1 ± 2.9 29.7 ± 2.4</td>
<td>0.38 0.64</td>
</tr>
<tr>
<td>Peak RER</td>
<td>0.99 ± 0.04 0.92 ± 0.04</td>
<td>0.91 ± 0.03 0.89 ± 0.03</td>
<td>0.07 0.44</td>
</tr>
<tr>
<td>Peak HR, beats/min</td>
<td>120 ± 7 111 ± 9</td>
<td>128 ± 12 128 ± 12</td>
<td>0.17 0.24</td>
</tr>
<tr>
<td>Treadmill time to exhaustion, s</td>
<td>438 ± 68 485 ± 57</td>
<td>423 ± 36 392 ± 26</td>
<td>0.69 0.06</td>
</tr>
<tr>
<td>Functional performance</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6-min walk, m</td>
<td>372 ± 42 421 ± 50</td>
<td>365 ± 42 362 ± 31</td>
<td>0.91 0.036</td>
</tr>
</tbody>
</table>

Values are means ± SE. \(\text{Vo}_{2}\), aerobic capacity; \(\text{Ve}\), exhalation flow rate; RER, respiratory exchange ratio; HR, heart rate.

mass \((r = 0.489; P = 0.056)\) but not with changes in oxidative enzyme capacity (Fig. 4A). Changes in knee extensor muscle endurance were, by contrast, significantly correlated with changes in oxidative capacity in that muscle group \((r = 0.693; P = 0.012)\) (see Fig. 4B).

**Cardiac function.** Systolic ejection fraction was not related to baseline exercise capacity, NYHA class, Minnesota Living with Heart Failure Scale score, or muscular skeletal morphology or function. Neither resting indexes of systolic nor diastolic function changed during the study in either group, as summarized in Table 7. Moreover, there were no associations between changes in any measure of resting cardiac function and muscle performance or overall exercise capacity.

**DISCUSSION**

This is the first randomized controlled trial of whole body, high-intensity PRT in elderly women with CHF. We studied PRT based on the theoretical advantages of this exercise modality for the skeletal muscle derangements associated with this condition, as well as the lack of clear efficacy of aerobic exercise in this subpopulation of CHF patients.

There were four major findings in this study. First, at baseline, muscle dysfunction was evident from both the cross-sectional study comparing controls without CHF to CHF patients, as well as from the relationships between disease severity and muscle parameters. Women with CHF had ~60% of the muscle strength of women with functional impairment and other chronic diseases but comparable aerobic capacity. Previous cross-sectional studies have generally compared healthy age-matched individuals to patients with CHF rather than to other populations with chronic diseases, perhaps explaining the deficits found in both strength and aerobic capacity (39). As disease severity increased within our CHF cohort, the women were characterized by increased type I fiber skeletal muscle atrophy and lower 3-methylhistidine excretion, an index of myofibrillar protein breakdown, as well as lower aerobic capacity. Compared with cross-sectional fiber areas in elderly nursing home residents of 87 ± 1 yr that we have previously reported (29), the patients with CHF in this study had larger type II fiber areas \((2,456 ± 178 \mu m^3\) in CHF vs. \(2,229 ± 146 \mu m^3\)) but smaller type I fiber areas \((3,268 ± 192 \mu m^3\) in CHF vs. \(3,603 ± 244 \mu m^3\)). This decreasing myofibrillar protein degradation with increasing severity of heart failure has not been previously reported. Because our 3-methylhistidine values are normalized to muscle mass estimated from creatinine excretion, they do not simply reflect lower muscle mass but suggest other changes in muscle metabolism related to the progressive myopathy of CHF in these women.

Second, resistance training improved both peripheral muscular skeletal as well as overall exercise performance. Third, the improvements in muscular skeletal performance were closely related to the improved overall exercise tolerance after training. Fourth, our data suggest that the improvements in muscular skeletal function and overall exercise performance were mediated through beneficial adaptations in peripheral muscle without improving or adversely affecting central resting cardiac function.

Collectively, the above four findings extend the previous literature, attesting to the central role of peripheral skeletal muscle pathology in the exercise intolerance of CHF, highlight the oxidative, slow-twitch fiber specificity of this myopathy (16), and identify a potential treatment for the pathophysiology demonstrated.

The observed changes in submaximal muscle endurance may be more important from the patient’s perspective than maximal force production since most...
daily activities are done at submaximal force levels. This result is parallel to many aerobic training interventions in CHF, which have shown more significant improvements in submaximal aerobic capacity or anaerobic threshold than in peak \( \dot{V}_O_2 \) or maximal work load achievable (14). The adaptations leading to such improvements in both aerobic and anaerobic work capacity are clearly inducible with targeted training stimuli despite the central and peripheral pathology of CHF.

As hypothesized, these improvements in skeletal muscle metabolism and function following strength training were accompanied by clinically significant improvements in overall functional performance measured by the 6-min walk, a test widely used to assess the effectiveness of treatment regimens in CHF and other chronic diseases. Strength-trained subjects increased their walking distance by nearly 50 m compared with controls participating in low-intensity exercise. This relative gain of 13% is somewhat less than the gains reported after intensive aerobic training protocols (19, 44, 46) but comparable to lower-intensity aerobic protocols (6, 45), as well as pharmacological management of CHF (4, 33, 71), and virtually identical to benefits reported in a recent meta-analysis of 18 controlled trials of aerobic training programs in chronic airways disease (49 m).

Previous reviews of the benefits of aerobic exercise in CHF indicate that patients over 70 had little or no improvement in exercise tolerance compared with younger patients [e.g., increases in treadmill duration of 0.8 ± 1.2 m (older) vs. 1.8 ± 3.2 m (younger); and increases in peak \( \dot{V}_O_2 \) of 0.2 ± 1.8 ml·kg\(^{-1}\)·m\(^{-1}\) (older) vs. 1.7 ± 1.8 ml·kg\(^{-1}\)·m\(^{-1}\) (younger)] (54). Also, patients who had a baseline maximal exercise test duration of >7 min did not respond to aerobic training. By contrast, our CHF patients responded to resistance training despite the fact that they ranged in age from 67 to 85 yr, and 50% of them had a baseline maximal exercise test of >7-min duration. This suggests that resistance training may be applicable in CHF subpopulations in whom the efficacy of aerobic exercise has not been adequately demonstrated.

Importantly, the improvement in overall functional performance in this study was related to a number of peripheral factors, including muscle strength, endurance, type I fiber area, and oxidative enzyme capacity but not to changes in any resting central hemodynamic factors or changes in peak \( \dot{V}_O_2 \). Seventy-eight percent of the variance in improved exercise capacity was explained by adaptations within slow-twitch fibers (increase in type I fiber area and oxidative enzyme capacity). These findings suggest a mechanism by which resistance training may be providing benefit in CHF and document the metabolic and morphological adap-

<table>
<thead>
<tr>
<th>Muscle Performance Measure</th>
<th>Progressive Resistance Training Group (n = 9)</th>
<th>Placebo Control Group (n = 7)</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre Post</td>
<td>Pre Post</td>
<td>Time</td>
</tr>
<tr>
<td>Leg press</td>
<td>1,275 ± 121 1,630 ± 172</td>
<td>1,314 ± 131 1,292 ± 133</td>
<td>0.003 0.003</td>
</tr>
<tr>
<td>Leg extension</td>
<td>152 ± 20 248 ± 30</td>
<td>145 ± 17 131 ± 18</td>
<td>0.0005 0.0001</td>
</tr>
<tr>
<td>Leg curl</td>
<td>228 ± 17 304 ± 18</td>
<td>257 ± 32 247 ± 30</td>
<td>0.016 0.028</td>
</tr>
<tr>
<td>Chest press</td>
<td>91 ± 9 123 ± 11</td>
<td>89 ± 13 88 ± 11</td>
<td>0.0005 0.0005</td>
</tr>
<tr>
<td>Triceps</td>
<td>59 ± 7 82 ± 8</td>
<td>52 ± 10 51 ± 8</td>
<td>0.0005 0.001</td>
</tr>
</tbody>
</table>

Values are means ± SE. Twelve subjects (7 exercise and 5 control) were tested in the leg curl exercises due to equipment changes. Fifteen subjects (7 exercise and 6 control) were tested in the triceps exercises due to equipment failure at time of testing.

Fig. 4. Relationship between changes in musculoskeletal performance and skeletal muscle adaptations following 10 wk of PRT. A: changes in knee extensor (KE) strength are significantly correlated to changes in muscle mass measured by 24 h urine creatinine. B: changes in KE endurance are related to changes in muscle oxidative capacity measured by citrate synthase activity in the vastus lateralis muscle.
mal changes in strength, as might be expected from the endurance (18–25%), and NYHA classification but minimis in cardiopulmonary indexes, muscle enlent to moderate intensity (60–80% of the 10 RM; equiva-
taining of upper leg, shoulders and abdomen was low aged (41–68 yr) patients (3 women) with CHF. Strength results of an uncontrolled study over 6 mo of hospital-
type capacity improved after endurance training, whereas capillary density and oxidative adaptations were specific to the mode of training. 
forms of exercise improved work capacity, although the tations still possible within these affected fibers with targeted training regimens. It is also possible that the resistive exercise was associated with alterations in habitual activity patterns and/or status of chronic diseases, such as arthritis, which indirectly could have improved exercise performance in these subjects. Future studies should include detailed assessments of these possible mechanistic factors and the physiological factors evaluated in this study.

Despite the wealth of evidence that skeletal muscle abnormalities contribute to symptoms in CHF (2, 16, 17, 40, 60), previous interventions generally have not been designed with anabolism in mind and thus the full potential of exercise in this condition has likely not yet been defined. Peripheral muscle adaptations in CHF patients have been demonstrated following nonaerobic exercise interventions in three previous uncontrolled or nonrandomized studies. Minotti and colleagues (55) reported increases in localized muscle endurance of 260% following a 4-wk, single-arm, iso-
tonic handgrip training program. This improvement was associated with improved muscle energetics at submaximal work loads without changes in cardiac hemodynamics. Magnussen et al. (48) compared aero-
bic vs. strengthening exercises for the quadriceps mus-
cle in an uncontrolled study of 11 CHF patients. Both forms of exercise improved work capacity, although the adaptations were specific to the mode of training. Strength and muscle area improved after the resistance training, whereas capillary density and oxidative enzyme capacity improved after endurance training only. Recently, Delagardelle et al. (23) reported the results of an uncontrolled study over 6 mo of hospital-based aerobic and strengthening exercise in 14 middle-aged (41–68 yr) patients (3 women) with CHF. Strength training of upper leg, shoulders and abdomen was low to moderate intensity (60–80% of the 10 RM; equiva-
ent to ~48–64% of the 1 RM). There were significant improvements in cardiopulmonary indexes, muscle en-
durance (18–25%), and NYHA classification but min-
imal changes in strength, as might be expected from the relatively low intensity of the strengthening compo-
ment. Overall, the design limitations inherent in these uncontrolled studies do not allow definitive conclusions to be drawn about the significance of their findings.

In conclusion, the morbidity, mortality, and societal costs of CHF in the elderly are substantial, and our current treatment paradigms do not optimally address what appears to be a primary derangement in muscle morphology, metabolism, and function. We have reported, for the first time in this trial, the safety of isolated high-intensity PRT in frail, older women with CHF, including the absence of symptomatic ischemia, arrhythmias, hemodynamic compromise, and unal-
tered resting cardiac function after 10 wk of exercise. These findings extend the previous literature on the lack of acute adverse hemodynamic consequences during single exposures to weight-lifting exercise in patients with CHF (50, 51) as well as other conditions (49). The plasticity of the musculoskeletal system, previously demonstrated even in the face of severe frailty and advanced age (29), now has been shown to extend to the skeletal myopathy accompanying CHF in the elderly. Ongoing research will further target the type I specificity of this myopathy, define the mechanistic features most amenable to intervention, and monitor the long-term adaptations in other subpopulations with CHF.

We wish to express our deep appreciation to Evelyn O’Neill for assistance with training of the experimental group, Lori Laviolette for design of the control group activity and help with training of this group, the Fit For Your Life Exercise Program of the Hebrew Rehabili-
tion Center for Aged for use of the exercise space, Suneetha Kedahila for assistance with data entry, Gerald Dallal for assistance with data analysis, the Metabolic Research Unit and Nutrition Evaluation Laboratory at the Human Nutrition Research Center (HNRC) for their technical support, the Harvard Cooperative Program on Aging and the Recruiting Department of the HNRC for help with patient recruitment, Dennis Keiser and Keiser Sports Health Equipment for their donation of resistance training equipment, and the Woodway for donation of the treadmill. Finally, we wish to thank each of the volunteers whose enthusiasm and dedication made this study possible.

<table>
<thead>
<tr>
<th>Muscle Parameter</th>
<th>Resistance Training Group (n = 7)</th>
<th>Placebo Control Group (n = 7)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre</td>
<td>Post</td>
<td>Pre</td>
</tr>
<tr>
<td>Total body muscle mass, kg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n = 7</td>
<td>11.74 ± 1.07</td>
<td>13.55 ± 1.14</td>
<td>13.66 ± 1.89</td>
</tr>
<tr>
<td>Muscle fiber cross-sectional area,  ( \mu m \times 10^{-3} ) (%change)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type I</td>
<td>3,340 ± 353</td>
<td>3,649 ± 637</td>
<td>(9.5 ± 15.6%)</td>
</tr>
<tr>
<td>Type II</td>
<td>2,131 ± 271</td>
<td>2,419 ± 225</td>
<td>(15.6 ± 10.3%)</td>
</tr>
<tr>
<td>Fiber-type distribution, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type I</td>
<td>45.1 ± 9.0</td>
<td>34.9 ± 3.5</td>
<td>27.2 ± 4.7</td>
</tr>
<tr>
<td>Type II</td>
<td>54.9 ± 9.0</td>
<td>65.1 ± 3.5</td>
<td>72.8 ± 4.7</td>
</tr>
<tr>
<td>Citrate synthase activity, ( \mu mol/g \times min )</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>62.19 ± 7.14</td>
<td>82.38 ± 12.36</td>
<td>54.77 ± 6.12</td>
</tr>
</tbody>
</table>

Values are means ± SE. An average of 48 ± 8 fibers were counted per subject. Fourteen subjects (7 exercise and 7 controls) were tested in the citrate synthase activity experiments due to refusal for biopsy in 1 subject and warfarin therapy in another. Muscle fiber cross-sectional area and fiber-type distribution experiments included only thirteen subjects (6 exercise and 7 controls) due to insufficient tissue sample in 1 other subject.
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R. A. Fielding is a Brookdale National Fellow at Boston University.

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Any opinions, findings, conclusions, or recommendations expressed in this publication are those of the authors and do not reflect the view of the U.S. Department of Agriculture.

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