Improved Exercise Tolerance After Losartan and Enalapril in Heart Failure
Correlation With Changes in Skeletal Muscle Myosin Heavy Chain Composition

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Background—In congestive heart failure, fatigue-resistant, oxidative, slow type I fibers are decreased in leg skeletal muscle, contributing to exercise capacity (EC) limitation. The mechanisms by which ACE inhibitors and AII antagonists improve EC is still unclear. We tested the hypothesis that improvement in EC is related to changes in skeletal muscle composition toward type I fibers.

Methods and Results—Eight patients with congestive heart failure, NYHA classes I through IV, were treated for 6 months with enalapril (E) 20 mg/d, and another 8 with losartan (L) 50 mg/d. EC was assessed with maximal cardiopulmonary exercise testing at baseline and after treatment. Myosin heavy chain (MHC) composition of the gastrocnemius was studied after electrophoretic separation of slow MHC1, fast oxidative MHC2a, and fast glycolytic MHC2b isoforms from needle microbiopsies obtained at baseline and after 6 months. EC improved in both groups. Peak \( \dot{V}O_2 \) increased from 21.0±4.7 to 27.6±4.3 mL · kg⁻¹ · min⁻¹ \( (P=0.011) \) in the L group and from 17.5±5.0 to 25.0±5.5 mL · kg⁻¹ · min⁻¹ \( (P=0.014) \) in the E group. Similarly, ventilatory threshold changed from 15.0±4.0 to 19.9±4.9 mL \( (P=0.049) \) with L and from 12.0±1.9 to 15.4±3.5 mL \( (P=0.039) \) with E. MCH1 increased from 61.2±11.2% to 75.4±7.6% \( (P=0.012) \) and from 60.6±13.1% to 80.1±10.9% \( (P=0.006) \) with E. Similarly, MHC2a decreased from 21.20±5.5% to 12.9±4.4% \( (P=0.05) \) with L and from 19.9±7.8% to 11.8±7.9% \( (P=0.06) \) with E. MHC2b changed from 17.5±6.5% to 11.7±5.2% \( (P=0.07) \) with L and from 19.5±6.4% to 8.1±4.6% \( (P=0.0015) \) with E. There was a significant correlation between net changes in MHC1 and absolute changes in peak \( \dot{V}O_2 \left( r^2=0.29, P=0.029 \right) \) and a trend to significance for MHC2a and 2b.

Conclusions—Six months’ treatment with L and with E produces an improvement in EC of similar magnitude. These changes are accompanied by a reshift of MHCs of leg skeletal muscle toward the slow, more fatigue-resistant isoforms. Magnitude of MHC1 changes correlates with the net peak \( \dot{V}O_2 \) gain, which suggests that improved EC may be caused by favorable biochemical changes occurring in the skeletal muscle. (Circulation. 1998;98:1742-1749.)

Key Words: heart failure ▪ muscles ▪ myosin ▪ exercise

Heart failure is characterized by decreased exercise capacity (EC) because of the early appearance of symptoms such as fatigue and dyspnea. The origin of these symptoms is not clear, although it has been suggested that they may depend on intrinsic skeletal muscle abnormalities.1–8 A shift from the slow type I fibers toward the more fatigue-resistant fast type II fibers has been described.9–11 We have observed a correlation between the percent distribution of the 3 myosin heavy chains (MHC[s]), MHC isoforms in the gastrocnemius (namely MHC1, slow aerobic; MHC2a, fast oxidative; and MHC2b, fast glycolytic), the severity of the heart failure syndrome,11 and EC expressed in terms of peak \( \dot{V}O_2 \) and VT.12 ACE inhibitors (ACEi) have been shown to reduce morbidity and mortality and improve EC in patients with congestive heart failure (CHF), left ventricular dysfunction, and previous myocardial infarction.13 These changes have been mostly attributed to the favorable effects of the blockade of the renin-angiotensin system15 or to a decreased bradykinin breakdown.14 Improvements in EC because of pharmacological treatment or training have been accompanied by mechanical, metabolic, and biochemical changes in the skeletal muscle.15–22 Moreover, there are still no explanations for improved EC after ACEi because neither central hemodynamic nor skeletal muscle blood flow seems to

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correlate with improved EC. Studies that examine skeletal muscle changes after treatment with ACEi have led to controversial results.23,24 Recently, AII antagonists (AIIa) have been introduced for the treatment of CHF. They improve EC24–25 and even decrease mortality.26 Although several comparisons with ACEi have been performed, similarities and differences between these 2 therapeutic options remain to be elucidated. In the present study, we have compared the magnitude of improvement in EC after 6 months’ treatment with enalapril (E) with those occurring with losartan (L).

Since we have postulated that changes in skeletal muscle fibers may contribute to it, we correlated the net improvement in EC with biochemical changes occurring in the leg skeletal muscles. We took MHCs as skeletal muscle biochemical markers and gas exchanged during maximal cardiopulmonary exercise testing as an objective measurement of EC.

Methods

Patients

We studied 16 male patients with CHF in different NYHA classes. The cause of CHF was diagnosed with clinical criteria, ECG, echocardiogram, cardiac catheterization, and coronary angiogram. Clinical characteristics are described in Table 1. Symptoms of heart failure had been present at least 2 months before they entered the study, and these included dyspnea, orthopnea, peripheral edema, and gallop. All patients except 2 were on frusemide with dosage ranging from 20 to 120 mg/d. Diuretic treatment was optimized and stabilized before randomization. None of them had previous treatment with ACEi or AIIa. None had diabetes mellitus, peripheral vascular disease (excluded by a Winson ankle/brachial index ≥1.1), neuromuscular diseases, heart valve disease, or lung disease. Patients underwent echocardiogram, maximal treadmill cardiopulmonary exercise testing, and medial gastrocnemius needle biopsy and were afterward randomly assigned either to E or to L treatment so that 2 groups of 8 patients were formed. Patients randomized to L started with 25 mg once a day, which was titrated up to 50 mg after a week, whereas patients randomized to E were started on 5 mg twice a day, which was titrated up to 10 mg after a week. After 6 months’ treatment, all the patients had another echocardiogram, maximal cardiopulmonary exercise testing, and second needle biopsy. Eight age-matched, detrained, sedentary, healthy volunteers with negative medical history and physical examination, normal blood pressure (BP), and resting ECG functioned as controls and underwent gastrocnemius biopsy. The study was approved by the ethics committee of the Venice City Hospital, and written informed consent was obtained.

Diuretic consumption score was assigned to each patient according to the following classes: class 1, no diuretic; class 2, 20 to 40 mg/d frusemide or a thiazide diuretic; class 3, ≥40 mg/d frusemide; class 4, ≥80 mg/d; and class 5, ≥120 mg/d.27

Cardiopulmonary Exercise Testing

All CHF patients underwent maximal symptom-limited cardiopulmonary exercise testing with a modified Naughton protocol.22 A Schiller Cardiovit CS100 with a 1308 capnograph was used. Oxygen consumption at maximum exercise was expressed as peak oxygen consumption (peak \( \dot{V}O_2 \)). Defined as the mean oxygen consumption of the last 30 seconds of an incremental exercise test. The anaerobic ventilatory threshold (VT) was automatically calculated by use of Wasserman’s criteria.28 The degree of muscle atrophy was expressed as the gastrocnemius cross-sectional area (CSA)/body mass index (BMI). The CSA was calculated on a CT scan slice obtained one-third distal to the right popliteal space.29

Skeletal muscle needle biopsies were taken from the right medial gastrocnemius with a 17-gauge soft-tissue Menghini needle (Sterylab Histo-cut). With this method,11,12 we were able to obtain 50 to 200 \( \mu \)g of tissue that was immediately frozen in liquid nitrogen. The electrophoretic separation of MHCs was carried out with the method described by Carraro.26 Samples were solubilized in 2.3% SDS, 10% glycerol, 0.5% mercaptoethanol, and 62.5 mmol/L Tris-HCl pH 7.6 and loaded on a 7% polyacrylamide slab gel. Gels containing ≈0.2 \( \mu \)g of protein per band are usually stained with 0.1% Coomassie’s Brilliant Blue in 5% acetic acid/40% methanol. Gels with <0.1 \( \mu \)g protein were stained with the silver method. Individual MHCs were identified by immunoblotting the gel bands with a panel of monoclonal antibodies (gift of Prof S. Schiaffino, University of Padua, Italy).11,12,30 The percent distribution of MHCs was determined by gel densitometry (Hofer Scientific GS300 transmittance reflectance scanner connected to a McIntosh SE Apple computer). Data were analyzed with GS370 densitometry software. A linear response was attained on densitometry when 0.1 to 2 \( \mu \)g of individual MHC was analyzed.29 Within this range, there was no variability in MHC percent distribution when different protein concentrations of the same sample were loaded. Quantitative densitometry was performed by use of internal MHC standards with known percent distribution of MHCs. The coefficient of variation for interassay and intra-assay (same sample tested on different gels and the same sample tested on the same gel, respectively) was <2%. The reproducibility of the biopic sampling is fairly high and is the coefficient of variation in CHF patients of 5% for MHC1, 5% for MHC2a, and 6% for MHC2b, as previously shown in 5 biopsies taken on consecutive days from the same patient.11

<table>
<thead>
<tr>
<th>TABLE 1. Clinical Characteristics of Patients at Baseline and After 6 Months’ Treatment</th>
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<tr>
<td>Age</td>
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<tr>
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<tr>
<td>Ischemic heart disease</td>
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<td>Class III</td>
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<td>Class IV</td>
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<td>P=NS</td>
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### Relationship Between Muscle Strength and Size

In 7 other patients with CHF of different causes (1 from congenital heart disease; 3 from DCM; and 3 from ischemic heart disease) and different NYHA classes (4, class II; 2, class III; and 1, class IV), gastrocnemius isometric strength in the dominant leg was measured with a CYBEX ORTHOTRON device. A maximum of 5 voluntary contractions was accepted as maximal strength. This was expressed
in newtons. Gastrocnemius CSA was measured on CT scan sections and the strength/unit area was calculated. A skeletal muscle biopsy was taken from the same muscle immediately afterward. The correlation between MHC composition, muscle strength, muscle CSA, and strength/unit area was then calculated.

**Statistical Analysis**
Mean ± SD was used. Student's t test for paired and unpaired data was used when appropriate. Linear regression was also used. A 5% difference was considered statistically significant.

**Results**

**Control Patients**
Mean age of control subjects was 55.4 ± 8.5 (P = NS versus CHF). The gastrocnemius MHC composition showed the prevalence of MHC1 (73.0 ± 4.6%, P = 0.03 versus CHF baseline). MHC2a was 16.13 ± 7.04 (P = 0.33) and MHC2b 11.12 ± 5.54 (P = 0.015). These data are similar to those previously reported by our group. 11

**CHF Patients**

**Baseline**

Patient Characteristics
The 2 groups of patients did not differ in terms of baseline demographics, and clinical parameters (age, body weight, and systolic and diastolic blood pressure) (Tables 1 and 2). In terms of the cause of heart failure, NYHA class, and diuretic class the 2 groups were well balanced.

Measurements
Measurements showed no statistically different values between L and E for EF, LVEDD, and LVESD. Gas exchange measurements of peak VO2, VT, and VE were not significantly different between L and E. O2 pulse was also similar (12.1 ± 3.0 mL · kg⁻¹ · min⁻¹ · hr⁻¹ in L group versus 11.9 ± 2.5 mL · kg⁻¹ · min⁻¹ · hr⁻¹ [P = NS] in E group). Exercise duration was also similar in E and L. MHC composition of the medial gastrocnemius was almost identical for all 3 isoforms in L and E groups. For CSA/BMI, the degree of gastrocnemius atrophy was sim-

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**Table 2. Comparison Between Losartan and Enalapril at Baseline and After 6 Months’ Treatment**

<table>
<thead>
<tr>
<th></th>
<th>Losartan Baseline</th>
<th>Losartan Treatment</th>
<th>Enalapril Baseline</th>
<th>Enalapril Treatment</th>
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<tbody>
<tr>
<td>SBP, mm Hg</td>
<td>141.2±16.2</td>
<td>138.1±12.8</td>
<td>134.9±12.1</td>
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<td>DBP, mm Hg</td>
<td>91.5±10.8</td>
<td>88.1±7.3</td>
<td>86.9±9.8</td>
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<td>EF, %</td>
<td>28.6±7.3</td>
<td>33.9±4.3</td>
<td>29.0±6.3</td>
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<td>LVEDD, mm</td>
<td>72.4±6.9</td>
<td>71.5±7.6</td>
<td>68.4±5.5</td>
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<td>LVESD, mm</td>
<td>57.2±8.0</td>
<td>54.8±10.3</td>
<td>54.2±8.8</td>
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<tr>
<td>Exercise duration, min</td>
<td>8.6±2.6*</td>
<td>12.4±2.8*</td>
<td>6.6±2.4†</td>
<td>10.6±3.6†</td>
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<td>Vmax, L/min</td>
<td>33.4±13.7</td>
<td>38.5±17.1</td>
<td>34.2±14.2</td>
<td>40.4±14.2</td>
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<td>Peak VO2, mL · kg⁻¹ · min⁻¹</td>
<td>21.0±4.7‡</td>
<td>27.6±4.3‡</td>
<td>17.5±5.0§</td>
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<tr>
<td>VT, mL</td>
<td>15.0±4.0∥</td>
<td>19.9±4.9∥∥∥∥</td>
<td>12.0±1.9∥∥∥</td>
<td>15.4±3.5∥∥∥∥</td>
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<td>MHC</td>
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<td>60.6±13.1**</td>
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<td>12.9±4.4††</td>
<td>19.9±7.8‡‡</td>
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<tr>
<td>2b, %</td>
<td>17.5±6.5§§</td>
<td>11.7±5.2§§</td>
<td>19.5±6.7</td>
<td></td>
</tr>
</tbody>
</table>

SBP indicates systolic blood pressure; and DBP, diastolic blood pressure.
*P = 0.03, †P = 0.03, ‡P = 0.011, §P = 0.014, ¶P = 0.009, ¶¶P = 0.039, #P = 0.012, **P = 0.006, ††P = 0.05, ‡‡P = 0.06, §§P = 0.07, |||P = 0.0015, ¶¶¶P = 0.04.

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**Figure 1.** Peak VO2 at baseline and after 6 months’ treatment. Los Base indicates L baseline; En Base, E baseline; Los Treat, L treatment; and En Treat, E treatment.

**Figure 2.** Ventilatory threshold (VT) at baseline and after 6 months’ treatment. Abbreviations as in Figure 1.
ilar in both L and E groups (0.63±0.18 versus 0.60±0.21, \(P=\text{NS}\)).

**Six Months’ Treatment**

**Patient Characteristics**

Body weight and systolic and diastolic blood pressure were substantially similar in the 2 treatment groups (Tables 1 and 2). NYHA classes in the L group were I in 3 patients, II in 3, and III in 2, whereas in the E group they were I in 1 patient, II in 4, III in 2, and IV in 1. Similarly, there were no differences in diuretic class between the 2 treatment groups.

Measurements

EF, LVEDD, and LVESD did not show differences between L and E. Peak \(\dot{V}O_2\), VT, and \(\dot{V}E\) were not different in L and E groups. \(\dot{O}_2\) pulse was also similar (15.3±4.11 versus 13.00±3.4 mL·kg\(^{-1}\)·min\(^{-1}\)·hr\(^{-1}\), \(P=\text{NS}\)). The exercise duration was 12.2±2.8 minutes for L versus 10.6±3.6 minutes for E (\(P=\text{NS}\)). None of the 3 MHC isoforms differed between L and E. The degree of muscle atrophy after 6 months’ treatment was similar in L and E (0.64±0.16 versus 0.62±0.21, \(P=\text{NS}\)) and therefore substantially unchanged when compared with baseline values.

**Figure 3.** SDS-PAGE of MHCs. Arrows indicate the 3 isoforms separated on the basis of their relative mobility: in order from the fastest to the slowest, MHC1, MHC2a, and MHC2b. Lanes a and b: L, baseline; c and d, E baseline; a’ and b’, L after 6 months’ treatment; and c’ and d’, E after 6 months’ treatment.

**Figure 4.** MHC composition at baseline and after 6 months’ treatment. A, MHC1; B, MHC2a; C, MHC2b. Abbreviations as in Figure 1.

**Figure 5.** Correlation between peak \(\dot{V}O_2\) and MHC composition at baseline. A, MHC1; B, MHC2a; C, MHC2b.
Comparison of Baseline and 6 Months’ Treatment

**Losartan**

Blood pressure was statistically unchanged after 6 months' treatment, though a slight trend toward lower values was observed both for systolic and diastolic BP. EF showed a slight, though not significant, increase after 6 months’ treatment. LVEDD and LVESD were not significantly different. After 6 months’ treatment, there was a significant increase in EC in that the mean exercise time was significantly increased. This was reflected by a significant improvement in peak VO\(_2\) (Figure 1) and VT (Figure 2). There was also a trend for VE to be significantly increased (P < 0.5). MHC composition is shown in Figure 3. The percent distribution of the MHCs in the medial gastrocnemius showed a significant increase of the MHC1 after 6 months’ treatment (P < 0.012) (Figure 4a). This was paralleled by a decrease of both MHC2a (P < 0.05) (Figure 4b) and MHC2b (P < 0.07) (Figure 4c).

**Enalapril**

Blood pressure decreased after 6 months’ treatment without reaching statistical significance for systolic or diastolic pressures. There was a slight, though not significant, increase in EF. Ventricular diameters did not show any significant change. Similar to L treatment, 6 months’ E treatment produced an increase in EC. Exercise duration (P = 0.03), peak VO\(_2\) (P = 0.014) (Figure 1), and ventilatory threshold (VT) (P = 0.039) (Figure 2) increased significantly. VE showed only a trend to significance (P = 0.4). MHC composition is shown in Figure 3. As it did with L, 6 months’ treatment with E produced an increase in the percent of MHC1 (P = 0.006) (Figure 4a) and a decrease in both MHC2a (P = 0.06) (Figure 4b) and MHC2b (P = 0.0015) (Figure 4c).

**Correlation Between Changes in MHCs and Cardiopulmonary Exercise Test Measurements**

At baseline, we found a significant correlation between peak VO\(_2\) and the percent distribution of MHCs. The correlation was positive for MHC1 (P = 0.007) (Figure 5a) and negative for MHC2a (Figure 5b) (P = 0.008) and MHC2b (P = 0.058) (Figure 5c). When data were analyzed for the single L and E groups, there was an equally positive correlation between peak VO\(_2\) and MHC1 (r\(^2\) = 0.59, P = 0.026 for L and r\(^2\) = 0.36, P = 0.1 for E), and MHC2a (r\(^2\) = 0.73, P = 0.007 for L and

r\(^2\) = 0.32, P = 0.1 for E). At baseline, there was a trend for MHCs to be correlated with VT and VE (MHC1 versus VT, P = 0.11; MHC2a versus VT, P = 0.11; MHC2b versus VT, P = 0.4; MHC1 versus VE, P = 0.5; MHC2a versus VE, P = 0.6; and MHC2b versus VE, P = 0.6). We also correlated the absolute changes in MHC (ΔMHC) composition after treatment with the changes in peak VO\(_2\) (ΔVO\(_2\)), and VT (ΔVT). ΔVO\(_2\) was correlated with ΔMHC1 (P = 0.029) (Figure 6) and ΔMHC2a (P = 0.06), whereas for ΔMHC2b it did not reach statistical significance (P = 0.3). When the ΔVO\(_2\) was correlated with ΔMHC1 for L and E groups separately, it was r\(^2\) = 0.57, P = 0.05 and r\(^2\) = 0.28, P = 0.2, respectively. The correlation between ΔVT and ΔMHCs was r\(^2\) = 0.2, P = 0.6 for ΔMHC1; r\(^2\) = 0.21, P = 0.8 for ΔMHC2a; and r\(^2\) = 0.11, P = 0.7 for ΔMHC2b.

Statistically, NYHA class at baseline was highly correlated with peak VO\(_2\) (r\(^2\) = 0.54, P < 0.001). We could not find any correlation between EF, LVEDV, LVESV, diuretic score, and indexes of cardiopulmonary exercise testing. Similar results
were obtained for the 2 groups of treatment when analyzed separately. NYHA class at baseline was negatively correlated with MHC1 ($r^2=0.26$, $P=0.05$) and positively with MHC2a and MHC2b ($r^2=0.28$, $P=0.04$). After 6 months’ treatment, there was no correlation between the hemodynamic indexes (EF, LVEDD, and LVESD) and gas measurements (peak $V_O_2$, VT, and $V_E$). $\Delta$EF, $\Delta$LVEDD, and $\Delta$LVESD did not correlate with $\Delta$ VO$_2$ or with $\Delta$MHCs. NYHA class was, however, still significantly correlated ($r^2=0.45$, $P=0.004$) with peak $V_O_2$.

**Relationship Between Skeletal Muscle Strength and MHC Composition**

In the 7 patients in whom gastrocnemius strength was measured, MHC composition was similar to that of CHF patients randomized either to L or E (MHC1 59.4±8.9%, MHC2a 18.3±8.5%, and MHC2b 22.3±5.5%). We could not find any relationship between MHC composition and muscle strength, CSA, or strength/unit area. In fact, for MHC1 this was $r^2=0.1$, $P=0.5$ for strength (Figure 7a); $r^2=0.2$, $P=0.3$, for CSA (Figure 7b); and $r^2=0.3$, $P=0.2$ for strength/unit area (Figure 7c). There was an even lower correlation between MHC2a and MHC2b and the same parameters.

**Discussion**

ACEi have been shown to improve EC, quality of life, and survival in CHF. Recently, similar data have been reported for ARB.25,26 In this article, we describe an improved EC of similar magnitude after 6 months’ treatment with L and E. This is demonstrated by NYHA class and exercise duration but especially by the objective measurements of EC such as peak $V_O_2$, VT, and $V_E$. Since the treatment groups look homogeneous in terms of demographics, clinical characteristics, and causes, the differences appear true. The reason why ACEi produce favorable changes in EC are not entirely clear. Central hemodynamics improve with therapy but do not correlate with peak $V_O_2$. The modulation of the neurohormonal cascade, the decrease in peripheral resistances, the improvement in skeletal muscle blood flow,31 and the local increase of the bradykinin concentration25 have been proposed as possible mechanisms. We can speculate that the latter mechanism is unlikely to be involved in that L, though showing similar effects of E, does not possess this therapeutic property.

CHF is characterized by skeletal muscle myopathy accompanied by a reduced number of type I, slow, aerobic, fatigueresistant fibers that express MHC1, and by an increased number of type 2a and 2b fast fibers, which express MHC2a and MHC2b, respectively.9,33–37 These latter fibers reach anaerobic metabolism earlier and are more prone to fatigue. It has been recently demonstrated that there is a close correlation between indexes of EC and muscle characteristics, and we have hypothesized that skeletal muscle MHC composition plays an important role in determining EC in CHF.12 In this study, at baseline, patients with different degrees of CHF show the presence of typical skeletal muscle myopathy with a statistically significant correlation between MCH composition, clinical and functional parameters of CHF, and expiratory gases. After 6 months’ treatment with L and E, the skeletal muscle MHC composition of the gastrocnemius reverts toward MHC1. This occurred in both treatment groups, and the results were statistically significant for all 3 MHC components; the magnitude was the same. Schaufelberger et al13 found that 3 months’ therapy with E was able to increase skeletal muscle fiber size without changes in fiber-type distribution. The present study was twice as long and looked at MHC distribution rather than fibers distribution, and this can account for the observed differences. Our data are, however, in agreement with Munzel et al,24 who showed that with ACEi an increased concentration of mitochondria per fiber correlated with an increased endurance to fatigue. Our results are consistent with changes in fiber type obtained with 6 months’ physical training in patients with CHF; EC was improved and paralleled by an increase in type I fibers.19 Low-intensity exercise training has also been shown to improve EC and oxidative metabolism by increasing mitochondria concentration.29 We observed a statistically significant correlation between $\Delta$PEAK $V_O_2$ and $\Delta$MHCs and a trend toward significance for $\Delta$ VT, which suggests that the reshift of the MHC pattern toward the slow, more fatigue-resistant, aerobic MHCs could be, at least in part, responsible for the improvement in cardiopulmonary parameters that closely reflect the EC in CHF patients. These data are supported by our previous observations11,12 and also by those of Massie et al.38 who found that in the skeletal muscle of patients with CHF there was an inverse relationship between the appearance of fatigue and the fiber type II excess. The correlation between $\Delta$PEAK $V_O_2$ and $\Delta$MHC1 was present in the E and L groups separately, which suggests that both drugs were able to produce the same biological effects. If this is because of a common mechanism of action, it cannot be established by the present study. We can speculate that these drugs could act directly on the muscle fibers, or they could modulate circulating substances. The sympathetic drive to the skeletal muscle and the AII-mediated norepinephrine release could be reduced with consequent savings in oxidative substrates.40 E and L could also block tumor necrosis factor-α41 or insulin-like growth factor42 that have been shown to produce contractile protein waste in the CHF myopathy.43 As previously observed,44,45 central hemodynamic parameters do not seem to interfere with EC or with fiber-type composition; in fact, in our study, none of them changed with treatment and no correlation was found with respect to clinical parameters, gas exchange measurements, and MHC pattern. Muscle atrophy has been postulated to limit EC in CHF,46,47 which suggests a correlation with muscle function.48 We did not observe substantial changes in muscle trophism after 6 months’ treatment, in keeping with the hypothesis that disuse atrophy may not play a role in the genesis of the CHF myopathy.11,30,49 In fact, we could not find any relationship between MHC composition and muscle strength, CSA, or strength/unit area. It is known that MHC composition in the skeletal muscle does not account for force, but it determines speed of shortening and relaxation, ATP, and oxygen consumption.50 Muscle strength is known to be related to muscle mass, and strength/unit area does not change in leg muscle in CHF,51 except in cardiac cachexia.43 Gastrocnemius CSA/BMI did not change significantly in our patients and we
therefore assume that muscle strength did not change after 6 months’ treatment. The contribution of the observed changes in MHC pattern to improving EC has to be ascribed to the enhanced muscle endurance derived from intrinsic characteristics of MHC1 that are more fatigue resistant.

Conclusions

In conclusion, the present study shows that L and E improve EC in patients with CHF due to different causes and with different levels of severity. The improvement in EC is paralleled by a reshift of the contractile proteins toward more fatigue-resistant, oxidative fibers. Since there is a correlation between the magnitude of isoymic shift and net improvement in peak $V\dot{O}_2$, it can be argued that the increased EC could be explained (in part) by the favorable biochemical changes occurring in the skeletal muscle.

Limitations of the Study

This study was done with 16 patients. A larger sample could have led to statistically significant differences for those parameters that only showed trends to significance (such as $\Delta V\dot{O}_2$ and $\Delta MHC2b$ or $\Delta V T$ and $\Delta MHC$s), which would have eventually strengthened our hypothesis. We think that the lack of central hemodynamic data did not bias or weaken our study because of the known absence of correlation between central hemodynamics, severity of CHF syndrome, and severity of myopathy.55 Whether the increased expression of MCH1 after L and E is a direct effect of the drugs on the skeletal muscle or is secondary to other factors, such as improvement in exercise activity, is something that can only be speculated. Further studies are needed.

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