Effect of Long-Acting Testosterone Treatment on Functional Exercise Capacity, Skeletal Muscle Performance, Insulin Resistance, and Baroreflex Sensitivity in Elderly Patients With Chronic Heart Failure

A Double-Blind, Placebo-Controlled, Randomized Study

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Objectives

This study investigated the effect of a 12-week long-acting testosterone administration on maximal exercise capacity, ventilatory efficiency, muscle strength, insulin resistance, and baroreflex sensitivity (BRS) in elderly patients with chronic heart failure (CHF).

Background

CHF is characterized by a metabolic shift favoring catabolism and impairment in skeletal muscle bulk and function that could be involved in the pathophysiology of heart failure.

Methods

Seventy elderly patients with stable CHF—median age 70 years, ejection fraction 31.8 ± 7%—were randomly assigned to receive testosterone (n = 35, intramuscular injection every 6 weeks) or placebo (n = 35), both on top of optimal medical therapy. At baseline and at the end of the study, all patients underwent echocardiogram, cardiopulmonary exercise test, 6-min walk test (6MWT), quadriceps maximal voluntary contraction (MVC), and isokinetic strength (peak torque) and BRS assessment (sequences technique).

Results

Baseline peak oxygen consumption (VO2) and quadriceps isometric strength showed a direct relation with serum testosterone concentration. Peak VO2 significantly improved in testosterone but was unchanged in placebo. Insulin sensitivity was significantly improved in testosterone. The MVC and peak torque significantly increased in testosterone but not in placebo. The BRS significantly improved in testosterone but not in placebo. Increase in testosterone levels was significantly related to improvement in peak VO2 and MVC. There were no significant changes in left ventricular function either in testosterone or placebo.

Conclusions

These results suggest that long-acting testosterone therapy improves exercise capacity, muscle strength, glucose metabolism, and BRS in men with moderately severe CHF. Testosterone benefits seem to be mediated by metabolic and peripheral effects. (J Am Coll Cardiol 2009;54:919–27) © 2009 by the American College of Cardiology Foundation

Chronic heart failure (CHF) is a disease increasingly recognized as a health burden worldwide. An improvement in survival rate has been reported in CHF in the last decade (1), which should be ascribed mainly to therapeutic strategies targeted to the pathophysiological mechanisms sustaining the progression and worsening of the disease, mainly the prolonged neurohumoral activation. CHF is also characterized by, in addition to neurohumoral activation, a metabolic shift favoring catabolism and impairment in skeletal muscle...
that sustains the progression of the disease, possibly affecting survival (7).

In the last few years, some reports have suggested the effectiveness of testosterone supplementation in improving the hemodynamic status and New York Heart Association (NYHA) functional class of patients with CHF (6,8–10). These studies would seem promising as to the benefits of testosterone supplementation in patients with CHF; however, they were limited by the indirect assessment of individual functional capacity and by the evaluation of muscle performance of small muscle masses (e.g., forearm muscles). Until now, there were no data on the effect of testosterone replacement on standard measures of functional capacity and exercise tolerance that occur in the CHF syndrome (6). Indeed, anabolic hormone depletion has been reported to be relatively common in CHF and to carry a negative prognosis (7). Hence, improving the anabolic status of patients with CHF could represent an additional therapeutic target acting on a pathophysiological mechanism involved not only in symptoms (sensory) but also in homeostasis (physiological mechanism) involved in the impairment of skeletal muscle function and exercise tolerance, which occur in the CHF syndrome (6). In men, androgens are important determinants of anabolic function and muscle strength. Low plasma levels of testosterone have been reported in patients with CHF (3–5), and it has been hypothesized that a relative hypotestosteronemia could be involved in the impairment of skeletal muscle function and exercise tolerance that occur in the HF syndrome (6).

Methods
Patient population and study design. The study population included 70 elderly male patients with CHF. Patients were screened and randomized between October 2005 and November 2006, and the final patient completed the study in February 2007. Subject eligibility was determined at the initial screening visit. Patients were selected from the outpatient department of cardiology and were included in the study if they had left ventricular ejection fraction (LVEF) <40%, symptomatic HF with NYHA functional class II or III, and clinical stability without hospital admission for HF in the previous 3 months.

Patients were excluded if they had unstable angina or recent acute myocardial infarction, history of severe liver or kidney diseases, uncontrolled hypertension, significant pulmonary disease, erythrocytosis (hematocrit >50%), prostate cancer, prostate-specific antigen (PSA) >3 ng/ml, severe lower urinary tract symptoms and lower extremities vascular, or other diseases that could prevent a symptom limited exercise test. At baseline and at the end of the study, a blood sample was drawn from an antecubital vein after an overnight fast for determination of serum hormones and routine laboratory analyses. Serum testosterone, free testosterone, total and free PSA, alanine aminotransferase, aspartate aminotransferase, glucose, insulin, creatinine, total cholesterol, high-density lipoprotein cholesterol, and triglycerides were measured. At baseline and at the end of the study, each patient underwent echocardiographic examination, muscle strength assessment, and cardiopulmonary exercise test. A 6-min walk test (6MWT) was also performed. At baseline and at the end of the study, patients underwent BRS assessment in the supine position. All patients gave written informed consent to participate in the study, which was approved by the local ethics committee.

Patients were randomly allocated to receive, on top of optimal medical therapy, either intramuscular (IM) long-acting testosterone undecanoate (1,000 mg Nebido, Bayer-Schering, Berlin, Germany) or IM saline injection at baseline and at 6 and 12 weeks. Testosterone and placebo were dispensed by the Pharmachologic Department, which was also responsible for the randomization codes. The drug was administered by a nurse, and the investigators were kept blinded on patient treatment. Patients were followed clinically every month until the end of the study.

Echocardiographic examination. A complete 2-dimensional, M-mode, and Doppler echocardiogram was performed at baseline and at the end of the study by the same physicians unaware of clinical and study data, according to the recommendations of the American Society of Echocardiography (17), with an Acuson Sequoia device and a 2.5- to 4.25-MHz wide-angle phased-array transducer. Left ven-
tricular volumes were measured from the apical 4- and 2-chamber views. LVEF was calculated with the Simpson’s rule algorithm.

**Muscle performance assessment.** Assessment of leg muscle strength was performed by a computer-based multifunctional dynamometer system (REV 9000, Technogym, Gambettola, Forli, Italy) in the seated position (18). Muscle strength was determined during both isometric and isokinetic effort. Isometric strength was defined as the highest force developed by the patients in 3 5-s maximal voluntary contractions (MVCs) separated by 1 min rest. Isokinetic strength was assessed by evaluating the highest peak torque achieved in a 5-maximal repetition test of concentric knee extension/flexion performed at 90°/s (18). The range of motion was 70°. During the exercises, the lever arm of the dynamometer was placed parallel to the limb, with the axis of rotation coinciding as close as possible with the axis of rotation of the knee joint (19). The distal end of the lever arm was attached to the inferior third of the dominant leg, and the foot was not in contact with the floor. The noncontracting leg was maintained flexed at 90° at the knee and not in contact with the floor (18). Maximal strength tests were performed after 5 min of warm-up consisting of unloaded cycling and leg stretching. Twenty minutes were allowed between the maximal strength tests. Quadriceps muscle fatigue was automatically calculated by the dynamometer software program through a fatigue index (work performed last repetition/work performed first repetition × 100) along with power output.

**Assessment of functional capacity and cardiorespiratory indexes.** Functional capacity was assessed by the cardiopulmonary exercise test and 6MWT at baseline and at the end of the study. Cardiopulmonary exercise test was performed at the enrollment and at the end of the study with an electrically braked bicycle ergometer with monitoring of gas exchange (Vmax 29 C, SensorMedics, Yorba Linda, California). Exercise started with 1 min of unloading pedaling and increased by 10 W every minute until exhaustion (defined as the inability to keep the pedaling rate steady at 60 rpm). Peak VO\textsubscript{2} was defined as the highest VO\textsubscript{2} observed during exercise averaged for a 30-s recording during the last minute. Respiratory exchange ratio was calculated at the same time-point. A value >1.10 was taken to represent adequate effort. The ventilation/carbon dioxide output (VE/VCO\textsubscript{2}) slope, which relates the rate of increase in ventilation/unit increase in carbon dioxide, was calculated for the whole exercise period. A 12-lead electrocardiogram was recorded continuously, and blood pressure (BP) was measured every 2 min by a sphygmomanometer. The 6MWT was performed according to standardized procedures (20).

**Insulin resistance.** Glucose and insulin were measured after an overnight fasting. The blood samples were collected in 5-ml tubes, immediately placed on ice, and transferred to the biochemistry laboratory where samples were processed. Plasma insulin levels were measured by immunoradiometric assay with a commercially available kit (DiaSorin, Inc., Reutlinger, Germany). Insulin resistance was estimated by the homeostasis model assessment (HOMA-IR) (21).

**BRS assessment.** We also assessed BRS in a subgroup of patients by the sequences technique (22) by analyzing simultaneous recordings of noninvasive finger beat-by-beat BP (Finapres, Ohmeda 2350, Englewood, Colorado) and the electrocardiographic trace from a precordial lead at a sampling rate of 250 Hz (Biopac system, Goleta, California), as described in detail previously (23,24), during 10 min of supine rest. The sequences method allows a quantification of the BRS at the current prevailing levels of arterial pressure and R-R interval and reflects vagally mediated baroreflex responses (22,25,26). Additional exclusion criteria for BRS assessment were atrial fibrillation and/or frequent premature supraventricular or ventricular ectopic beats, which would have prevented reliable BRS measurements.

**Statistical analysis.** The sample size for the study was calculated on the basis of previous studies (9) showing that 3-month testosterone treatment led to a 70% increase in walking distance in CHF subjects versus control subjects. We estimated an overall need of 70 patients to obtain the same effect size with 80% power and 5% significance, assuming a dropout rate of 15%.

Differences in baseline characteristics between treatment and placebo groups were evaluated by the chi-square and unpaired t test. Within-group changes in the reported variables were evaluated by the paired t test or Wilcoxon signed rank test for non-normally distributed variables. Between groups comparisons were performed by the unpaired t test and Mann-Whitney rank sum test. Relations between variables were assessed by Pearson product-moment correlation or Spearman’s rank test for non-normally distributed data. Results are expressed as mean ± SD. A 2-tailed p value of <0.05 was considered significant. All analyses were performed with a commercially available statistical package (SPSS for Windows version 12.0, Chicago, Illinois).

**Results**

From a total of 96 patients screened, 70 met the inclusion criteria and were included in the study. Fourteen patients were not included, because of renal failure in advanced stage (creatinine clearance <30 mg/dl); 9 patients had PSA levels >3 ng/ml; 3 patients had hematocrit >50%. Of 70 patients, 64 completed the study protocol: 4 patients in the testosterone group and 2 in the placebo group discontinued the study. The reason for discontinuation, in every case, was the willingness of the patient to escape from the study (e.g., logistic reasons, moving to another region, autonomous decision to discontinue the protocol not related to testosterone supplementation).

Baseline characteristics of the patients are reported in Table 1. There were no significant differences between the
treatment and the placebo groups with respect to all variables. Most of the patients were receiving beta-blockers (86%), angiotensin-converting enzyme inhibitors or angiotensin receptor antagonists (92%), or diuretics (44%); 41% were taking aldosterone receptor blockers, and 33% were receiving digitalis. Medications were not altered throughout the study.

The effect of testosterone supplementation on the different variables is reported in Tables 2 and 3. Peak VO₂ and peak workload significantly increased, and VE/VCO₂ slope significantly decreased in patients receiving testosterone, whereas no significant changes in these variables were detected in the placebo group. Distance walked at the 6MWT and NYHA functional class (data not shown) improved in both groups, but the increase in the 6MWT was significant only in patients receiving testosterone supplementation (Table 2).

No significant change in LVEF was detected in either group. Both groups showed a tendency toward BP decrease, with significant results only for diastolic BP in the testosterone-treated group.

The MVC and PT significantly improved in testosterone-treated patients but remained unchanged in the placebo group. Similarly, both the work output (Δ +31.3 ± 16.2 J, p = 0.01) and the fatigue index (−42.4 ± 13.0%, p = 0.03) improved in the treatment group, whereas no significant changes were detected in the control group (data not shown).

At baseline, 21 patients (30%)—12 in the testosterone group and 9 in the placebo group—had total and free testosterone levels below the normal range (total testosterone <3.5 ng/ml, and free testosterone <2.5 pg/ml). Baseline total testosterone levels correlated with peak VO₂ (r = 0.43, p = 0.007), distance reached in the 6MWT (r = 0.31, p = 0.01), and isometric strength (r = 0.30, p = 0.002). Total testosterone and free testosterone both increased with treatment but remained within the normal physiological range (1.5 to 5.7 ng/ml), whereas no significant change was observed in the placebo group.

Changes in testosterone levels correlated significantly with changes in peak VO₂ and MVC (Figs. 1 and 2). There was no significant relation between basal total testosterone levels and LVEF.

The effects of testosterone supplementation in patients with low-normal (e.g., <12 ng/ml) in comparison with patients with normal testosterone levels are reported in Tables 4 and 5. In patients with low baseline testosterone levels, there was a greater improvement in peak VO₂ and

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### Table 1: Baseline Characteristics of Patients in the 2 Groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Testosterone (n = 35)</th>
<th>Placebo (n = 35)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs), median (interquartile range)</td>
<td>71 (67–76)</td>
<td>69 (66–74)</td>
<td></td>
</tr>
<tr>
<td>Cause of heart failure, CAD/IDC</td>
<td>26/9</td>
<td>28/7</td>
<td></td>
</tr>
<tr>
<td>NYHA functional class, II/III</td>
<td>18/17</td>
<td>20/15</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>9</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>21</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>11</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>14</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Hypogonadism</td>
<td>12</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Concomitant therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beta blockers</td>
<td>30</td>
<td>31</td>
<td></td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>32</td>
<td>34</td>
<td></td>
</tr>
<tr>
<td>Diuretics</td>
<td>16</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>Aldosterone receptor blockers</td>
<td>16</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Digiines</td>
<td>7</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Antplatelet agents</td>
<td>21</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>Anticoagulants</td>
<td>16</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Statins</td>
<td>29</td>
<td>26</td>
<td></td>
</tr>
</tbody>
</table>

Hypogonadism was defined as total testosterone <3.5 ng/ml and free testosterone <2.5 pg/ml. No significant differences were found for any of the comparisons shown. Variables are reported as absolute numbers.

ACE = angiotensin-converting enzyme; CAD = coronary artery disease; IDC = idiopathic dilated cardiomyopathy; NYHA = New York Heart Association.

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### Table 2: Cardiorespiratory and Muscular Results Before and After 3 Months of Testosterone Supplementation Therapy

<table>
<thead>
<tr>
<th>Variable</th>
<th>Testosterone Group (n = 31)</th>
<th>Placebo Group (n = 33)</th>
<th>Changes (Δ)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before</td>
<td>After</td>
<td>Before</td>
<td>After</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>26.4 ± 3.7</td>
<td>28.7 ± 4.3*†</td>
<td>26.1 ± 4.4</td>
</tr>
<tr>
<td>Body weight, kg</td>
<td>63.5 ± 13.7</td>
<td>66.8 ± 11.4*</td>
<td>64.7 ± 8.3</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>125.6 ± 6.2</td>
<td>121.3 ± 42.7</td>
<td>128.2 ± 46.3</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>92 ± 13.0</td>
<td>80 ± 12.0*</td>
<td>89 ± 11.7</td>
</tr>
<tr>
<td>Resting HR, beats/min</td>
<td>74.3 ± 7.2</td>
<td>70 ± 11.5</td>
<td>77.6 ± 8.2</td>
</tr>
<tr>
<td>Peak VO₂, ml/kg/min</td>
<td>13.4 ± 4.4</td>
<td>16.3 ± 1.7†</td>
<td>13.8 ± 3.2</td>
</tr>
<tr>
<td>VE/VCO₂ slope</td>
<td>33.6 ± 7.0</td>
<td>29.2 ± 5.1†</td>
<td>34.1 ± 9.5</td>
</tr>
<tr>
<td>Peak workload, W</td>
<td>78.3 ± 16.0</td>
<td>88.2 ± 18.7†</td>
<td>77.3 ± 14.2</td>
</tr>
<tr>
<td>6MWT, m</td>
<td>386.8 ± 121.0</td>
<td>472.8 ± 138.4†</td>
<td>390.9 ± 107.4</td>
</tr>
<tr>
<td>MVC, Nm</td>
<td>116.7 ± 26.3</td>
<td>135.6 ± 21.2†</td>
<td>116.7 ± 26.3</td>
</tr>
<tr>
<td>PTmax, Nm</td>
<td>74.0 ± 17.4</td>
<td>83.4 ± 16.3†</td>
<td>74.2 ± 14.4</td>
</tr>
<tr>
<td>EF, %</td>
<td>31.5 ± 9.9</td>
<td>32.1 ± 7.2</td>
<td>33.8 ± 6.5</td>
</tr>
<tr>
<td>LVEDD, mm</td>
<td>68.3 ± 35.7</td>
<td>66.9 ± 23.2</td>
<td>67.3 ± 27.2</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± SD. *Within groups differences; †between groups differences at p < 0.05.

6MWT = 6-min walking test; BMI = body mass index; DBP = diastolic blood pressure; EF = ejection fraction; HR = heart rate; LVEDD = left ventricular end-diastolic diameter; MVC = maximal voluntary contraction; Nm = Newton meter; PTmax = isokinetic power torque; SBP = systolic blood pressure; VE/VCO₂ = ventilation/carbon dioxide output; VO₂ = oxygen consumption.
MVC with testosterone supplementation, whereas the improvements in the other exercise performance and metabolic parameters as well as in VE/VCO₂ were not significantly different between patients with low versus normal baseline testosterone levels.

The testosterone group showed a significant increase in hematocrit in comparison with the placebo group (2.3 ± 0.8% vs. 0.8 ± 0.2%, respectively, p = 0.001).

The HOMA-IR decreased significantly in the testosterone group but remained unchanged in the control group. Body weight and body mass index significantly increased only in the testosterone group (from 63.5 ± 13.7 kg to 66.8 ± 11.4 kg, p = 0.021, and from 26.4 ± 3.7 kg/m² to 28.7 ± 4.3 kg/m², p = 0.032) but remained unchanged in the placebo group (from 64.7 ± 8.3 kg to 65 ± 12.9 kg, p = 0.09 and from 26.1 ± 4.4 kg/m² to 26.6 ± 3.6 kg/m², p = 0.12).

The BRS significantly increased in the testosterone group (n = 10) by 3.7 ± 0.9 ms/mm Hg from a baseline value of 6.0 ± 1.3 ms/mm Hg, whereas it did not change significantly in the placebo group (n = 12) (0.3 ± 0.8 ms/mm Hg from a baseline value of 6.4 ± 0.7 ms/mm Hg, p = 0.01).

The PSA levels, liver and renal functions, and hemoglobin levels were not significantly affected by treatment with testosterone. No side effect requiring discontinuation of testosterone supplementation occurred throughout the study. No patient died during the follow-up period.

Worsening HF occurred in 2 patients receiving testosterone and in 1 patient in the control group and was managed only by increasing the dose of furosemide in 2 patients (1 in the testosterone and 1 in the control group). Only 1 patient of the treated group required hospital stay.

Table 3  Metabolic and Hormonal Results Before and After 3 Months of Testosterone Supplementation Therapy

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Testosterone Group (n = 31)</th>
<th>Placebo Group (n = 33)</th>
<th>Changes (Δ)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
<td>Before</td>
</tr>
<tr>
<td>Fasting glycemia, mg/dl</td>
<td>114.8 ± 37.1</td>
<td>119.2 ± 33.5</td>
<td>111 ± 37.3</td>
</tr>
<tr>
<td>Fasting insulinemia, μU/ml</td>
<td>10.4 ± 2.0</td>
<td>7.9 ± 1.4†</td>
<td>11.0 ± 3.1</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>2.6 ± 1.4</td>
<td>1.8 ± 0.8†</td>
<td>2.5 ± 1.1</td>
</tr>
<tr>
<td>Total cholesterol, mg/dl</td>
<td>142.5 ± 43.7</td>
<td>148.5 ± 39.3</td>
<td>147.3 ± 54.2</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dl</td>
<td>36.3 ± 7.1</td>
<td>36.0 ± 5.7</td>
<td>37.0 ± 6.2</td>
</tr>
<tr>
<td>Triglycerides, mg/dl</td>
<td>131.2 ± 39.7</td>
<td>142.5 ± 44.1</td>
<td>138.6 ± 32.5</td>
</tr>
<tr>
<td>Total testosterone, ng/ml</td>
<td>2.3 ± 1.8</td>
<td>5.2 ± 2.2†</td>
<td>2.1 ± 2.1</td>
</tr>
<tr>
<td>Free testosterone, pg/ml</td>
<td>11.3 ± 5.6</td>
<td>32.0 ± 11.2†</td>
<td>12.1 ± 6.0</td>
</tr>
<tr>
<td>Total PSA, ng/ml</td>
<td>1.4 ± 1.1</td>
<td>1.5 ± 1.0</td>
<td>1.3 ± 0.7</td>
</tr>
<tr>
<td>Free PSA, ng/ml</td>
<td>0.4 ± 0.2</td>
<td>0.6 ± 0.3</td>
<td>0.4 ± 0.1</td>
</tr>
<tr>
<td>C-reactive protein, mg/dl</td>
<td>0.3 ± 0.2</td>
<td>0.3 ± 0.2</td>
<td>0.4 ± 0.2</td>
</tr>
<tr>
<td>Creatinine, mg/dl</td>
<td>1.4 ± 0.4</td>
<td>1.5 ± 0.3</td>
<td>1.4 ± 0.5</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± SD. *Within groups differences; †between groups differences at p < 0.05.

HDL = high-density lipoprotein; HOMA-IR = homeostasis model assessment (21); PSA = prostate-specific antigen.
Discussion

The results of this study indicate that testosterone supplementation improves VO$_2$, VE/VCO$_2$ slope, large-muscle performance, and BRS in patients with CHF. The relevance of these findings should be placed in the context of the established evidence indicating the adverse prognostic role of low functional capacity, ventilatory efficiency and BRS, and the peripheral muscle deterioration leading to early fatigue and limited exercise tolerance that characterize patients with CHF.

The present study shows that testosterone supplementation given on top of optimal medical therapy improves functional capacity, large-muscle strength, and glucose metabolism in elderly patients with CHF. The increase in functional capacity and muscular strength is related to the increase in plasma levels of testosterone and not related to changes in left ventricular function.

Until now only few studies have been conducted on the effect of testosterone therapy in CHF. In a 12-week pilot study of 20 CHF patients, Pugh et al. (6) showed that intramuscular testosterone therapy improved the distance walked at the shuttle walking test, without effects on forearm muscle strength. In a larger placebo-controlled trial, Malkin et al. (9) found that a 12-month testosterone replacement therapy improved both distance walked at the shuttle walking test and forearm muscle strength in men with moderately severe CHF. Assessment of exercise capacity by means of effort tolerance tests such as the 6MWT and incremental shuttle walk test is easy to perform, correlates with peak VO$_2$, and has been shown to be useful in prognostic stratification (27–30). However, these assessments do not reflect the overall cardiovascular performance (30) and do not provide any information as to the ventilatory efficiency and cardiopulmonary matching during exercise, which play a relevant pathophysiological and prognostic role in CHF (11,12,30,31).

We demonstrated a significant improvement of both peak VO$_2$ and ventilatory efficiency in CHF patients under testosterone supplementation therapy. This is relevant because VO$_2$ and VE/VCO$_2$ slope reflect different although related aspects of the integrated cardiorespiratory responses to exercise in HF. Although both VO$_2$ and VE/VCO$_2$ slope discriminate individuals at high and low risk for cardiac mortality in CHF, recent studies have indicated that VE/VCO$_2$ slope could be more useful than VO$_2$ in predicting future events (32). This has been explained by the inability of VO$_2$ to provide information on the ventilatory response to exercise, which is also markedly altered in CHF syndrome (33). Thus, the improvement in functional capacity and ventilatory efficiency induced by testosterone supplementation might positively affect the prognosis in patients with moderate HF. The significant correlation between testosterone level and VO$_2$ would support the hypothesis that the improvement in peak VO$_2$ was related to testosterone administration. The lack of any change in the placebo group is consistent with this assumption.

This study also extends to larger, weight-bearing muscles, the previous finding of a testosterone-induced increase in forearm muscle strength, which is more relevant to the effort intolerance of the CHF syndrome. This occurred for both static and dynamic muscular performance, this latter being never investigated before.

The improvement in VO$_2$ was greater in patients with lower baseline testosterone levels as it was the increase in static strength (i.e., MVC). However the improvements in ventilatory efficiency, 6MWT, dynamic muscular performance and insulin sensitivity did not differ significantly
between patients with low and normal testosterone levels. This would indicate that the benefits of testosterone supplementation are not entirely confined to HF patients with low baseline testosterone, although a greater improvement in some physiological parameters in these patients would be expected.

The mechanism(s) through which testosterone affects cardiorespiratory indexes is still unclear. However, our data on muscle performance might provide some insights. We observed a significant increase in both static and dynamic leg strength in addition to a reduced fatigue index and improved work output in the testosterone-treated group. These effects would depend on the action of testosterone at the muscular level. Objective morphological and functional abnormalities, relatively independent of reduced blood flow, are present in the muscle of CHF patients (34). These maladaptive changes in the muscles, which include fiber atrophy and a prevalence of type II fibers with a predominance of glycolytic over oxidative metabolism, are involved not only in symptoms development but even in the pathophysiology and worsening of the HF syndrome, the so-called “muscle hypothesis” (2). In short, by this hypothesis, muscle alterations occurring in CHF would elicit—in time—an enhanced muscle metaboreflex (also called ergoreflex) (35) activation even at moderate levels of exercise that in turn would be responsible for the prolonged neurohumoral activation and abnormal hemodynamic, autonomic, and ventilatory responses to exercise that characterize CHF (35–37). In this context, a strong link has been demonstrated between muscle metaboreflex overactivity and increased VE/VCO2 slope in CHF (38). Interventions specifically targeted at reversing peripheral muscle alterations such as exercise training have been shown to improve muscle structure and function and reduce muscle metaboreflex overactivity and ventilatory response to exercise in CHF in addition to improving VO2 (34,35,39).

The increase in leg muscle strength and work output observed in the present investigation after testosterone supplementation, which reflects an improvement in overall muscle function, might have acted in the same manner, by decreasing the muscle metaboreflex contribution to ventilatory response to exercise, thus reducing VE/VCO2 slope and improving ventilatory efficiency. Indeed, anabolic administration at replacement doses has been shown to accelerate fast- to slow-oxidative fiber type conversion (40)—which are typically reduced in CHF patients (34)—and increase the number and size of type I slow oxidative fibers (41), which imply an improved oxidative capacity of skeletal muscles and a higher aerobic potential with a delayed fatigue. In addition, the small but significant increase in hematocrit observed in the testosterone-treated group (42) might have also contributed to reduction of muscle metaboreflex activation and, in turn, the ventilatory response by improving oxygen availability to the exercising muscles. This would explain the similar improvement in VE/VCO2 slope in patients with low and normal testosterone levels.

As far as the metabolic profile is concerned, we found a significant reduction of insulin resistance in the testosterone-treated group. In recent years the prevalence of insulin resistance in CHF and its role on CHF development have been elucidated (43,44). Effects of testosterone replacement on insulin resistance have led to divergent findings, with either no changes (45) or significant improvements of HOMA-IR (46) being reported. In the only small study conducted in nondiabetic CHF patients, testosterone improved insulin sensitivity with an increase in total body mass and a reduction in fat mass (47), a finding confirmed in the present investigation on a larger sample size.

Another novel and potentially relevant finding of the present investigation is the significant increase in BRS detected in the testosterone-treated group. This would add further to the benefits of testosterone, because it is well known that BRS is depressed in CHF carrying a negative prognosis (16,48). Hence, any intervention capable of increasing BRS should be regarded as protective in CHF syndrome. The mechanism(s) through which testosterone would enhance BRS cannot be defined by the present investigation. Several animal studies have shown that testosterone facilitates baroreceptor control of heart rate through an enhancement of cardiac efferent vagal activity (13–15). This effect is likely to occur at central nervous system sites, because androgen receptors have been characterized in brainstem nuclei involved in baroreflex cardiac regulation (49), and a competitive androgen receptors blocking drug that penetrates the blood brain barrier was capable of attenuating BRS (15). Nevertheless, although limited by the small sample size, our finding of an increase in BRS induced by testosterone supplementation is in a direction that has been associated with a better outcome in CHF.

We did not find, in agreement with previous studies, any significant change in LVEF. The lack of effects of testosterone on left ventricular function seems to confirm that testosterone acts only through peripheral mechanisms.

In our study there was high compliance: overall only 8% of patients were lost during the follow-up, a much lower percentage than in the study of Malkin et al. (9). Possible explanations for these differences are the shorter follow-up period and, mainly, the route of administration of testosterone. Malkin et al. (9) used a transdermal patch that was poorly tolerated, with a substantial number of skin reactions (55% of cases). We used a very-long-acting IM testosterone, until now used only in the treatment of hypogonadism (50), which required only 3 administrations and as a consequence was well tolerated by all patients. More data are needed on long-term safety of testosterone supplementation in patients with CHF before such therapy could be widely employed in this patient population. However, our data on the safety of long-acting IM testosterone seem promising.
Study limitations. Although in our study testosterone supplementation therapy improved both VO₂ and VE/VCO₂ slope and BRS, 3 strong prognostic indicators in CHF, the follow-up was short, and we cannot comment on clinical outcome. This is the main limitation of the study. However, the present study would indicate that testosterone supplementation therapy improves clinical measures that carry adverse effects and negative prognosis in CHF. In addition, our data on BRS, although consistent, are limited to a small sample size. Finally, the increase of muscle strength and performance we observed after testosterone supplementation therapy was likely related to changes in skeletal muscle ultrastructure and biochemistry, but we have no direct data about these changes.

Conclusions

Long-term testosterone supplementation improves functional capacity and baroreflex control of heart rate, muscle strength, and glucose metabolism in elderly patients with CHF. Long-acting IM administration of the drug is well tolerated by CHF patients. Testosterone benefits on CHF seem to be mediated by metabolic and peripheral effects.

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