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ORIGINAL ARTICLE

# Effect of Exercise Training and Testosterone Replacement on Skeletal Muscle Wasting in Patients With Heart Failure With Testosterone Deficiency

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## Abstract

**Objective:** To examine whether combined testosterone replacement and exercise training (ET) therapies would potentiate the beneficial effects of isolated therapies on neurovascular control and muscle wasting in patients with heart failure (HF) with testosterone deficiency.

**Patients and Methods:** From January 10, 2010, through July 25, 2013, 39 male patients with HF, New York Heart Association functional class III, total testosterone level less than 249 ng/dL (to convert to nmol/L, multiply by .03467), and free testosterone level less than 131 pmol/L were randomized to training (4-month cycloergometer training), testosterone (intramuscular injection of testosterone undecylate for 4 months), and training + testosterone groups. Muscle sympathetic nerve activity was measured using microneurography, forearm blood flow using plethysmography, body composition using dual X-ray absorptiometry, and functional capacity using cardiopulmonary test. Skeletal muscle biopsy was performed in the vastus lateralis.

**Results:** Muscle sympathetic nerve activity decreased in ET groups (training, $P<.01$; training + testosterone, $P<.01$), whereas no changes were observed in the testosterone group ($P=.89$). Forearm blood flow was similar in all groups. Lean mass increased in ET groups (training, $P<.01$; training + testosterone, $P<.01$), whereas lean mass decreased in the testosterone group ($P<.01$). The response of cross-sectional area of type I ($P<.01$) and type II ($P<.05$) fibers increased in the training + testosterone group as compared with the isolated testosterone group.

**Conclusion:** Our findings provide evidence for a superior effect of combined ET and testosterone replacement therapies on muscle sympathetic nerve activity, muscle wasting, and functional capacity in patients with HF with testosterone deficiency.

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Deficiency in anabolic hormones is associated with increased morbidity and mortality in male patients with heart failure (HF).[1] In fact, low circulating testosterone levels affects around 20% to 30% of male patients with HF, which is related to higher neurohormonal activation, skeletal muscle wasting, and lower functional capacity.[1-3]

Decreased muscle sympathetic nerve activity (MSNA) is a hallmark of HF, and it is an independent marker of mortality.[4] In addition, sympathetic hyperactivity in experimental models of HF is a major factor contributing to skeletal muscle wasting.[5] Consequently, weight loss (muscle wasting) has received special attention in patients with advanced HF.[3] In fact, muscle wasting has been associated with a negative response to drug treatment, poor quality of life, and mortality in humans with HF.[6,7] Therefore, the poor combination of decreased MSNA and skeletal muscle wasting could worsen the clinical status in patients with HF.

Either isolated testosterone replacement (TR)[8-10] or exercise training (ET)[11-13] has a positive effect on key health outcomes. For

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instance, isolated TR compared with placebo is associated with improved functional capacity and leg muscle strength,[8,9,14] whereas isolated ET decreases MSNA, increases functional capacity, and reduces both hospitalization and mortality in male patients with HF.[11,15] However, little is known about the combined effects of both therapies in patients with HF with testosterone deficiency.

The present study was undertaken to test whether combined TR and ET therapies would potentiate the beneficial effects of isolated therapies on neurovascular control and skeletal muscle wasting in patients with HF with testosterone deficiency. In addition, we tested the effect of combined therapies on total body composition, functional capacity, hormonal status, and quality of life.

## PATIENTS AND METHODS

In this prospective randomized study, we evaluated 162 male patients with HF who underwent blood testosterone measurement. Of those 162 patients, 70 patients (43%) exhibited normal testosterone levels being excluded from the protocol. In contrast, 92 patients (57%) exhibited testosterone deficiency (total testosterone level <249 ng/dL [to convert to nmol/L, multiply by .03467] and free testosterone level <131 pmol/L). Of those 92 patients, 39 patients (42%) agreed to participate in the protocol and were randomized according to a computer-generated list into 3 groups: training, testosterone, and training + testosterone. Of those 39 patients, 12 dropped out (31%) because of coronary artery bypass grafting (n=1), decompensated HF (n=3), discontinuing the protocol (n=2), and death from cardiac causes (n=6). Therefore, 27 patients completed the protocol (training, n=11; testosterone, n=8; and training + testosterone, n=8) (Figure 1).

Inclusion criteria were as follows: (1) history of HF greater than 6 months before the study; (2) New York Heart Association (NYHA) functional class III; (3) testosterone deficiency (total testosterone level less than 249 ng/dL and free testosterone level less than 131 pmol/L); (4) left ventricular ejection fraction (LVEF) less than 40% measured by echocardiography; (5) compensated HF with optimal medication; and (6) age range between 18 and 65 years. Exclusion criteria were as follows: (1) history of coronary revascularization or myocardial infarction less than 6 months before the study; (2) any hormonal treatment, including exogenous testosterone therapy, before or during the protocol; (3) arrhythmia; (4) atrial fibrillation; (5) biventricular pacemaker with or without implantable cardioverter-defibrillator; (6) kidney disease, liver disease, or diabetes; (7) obesity (body fat percentage, >29%; body mass index [BMI; calculated as the weight in kilograms

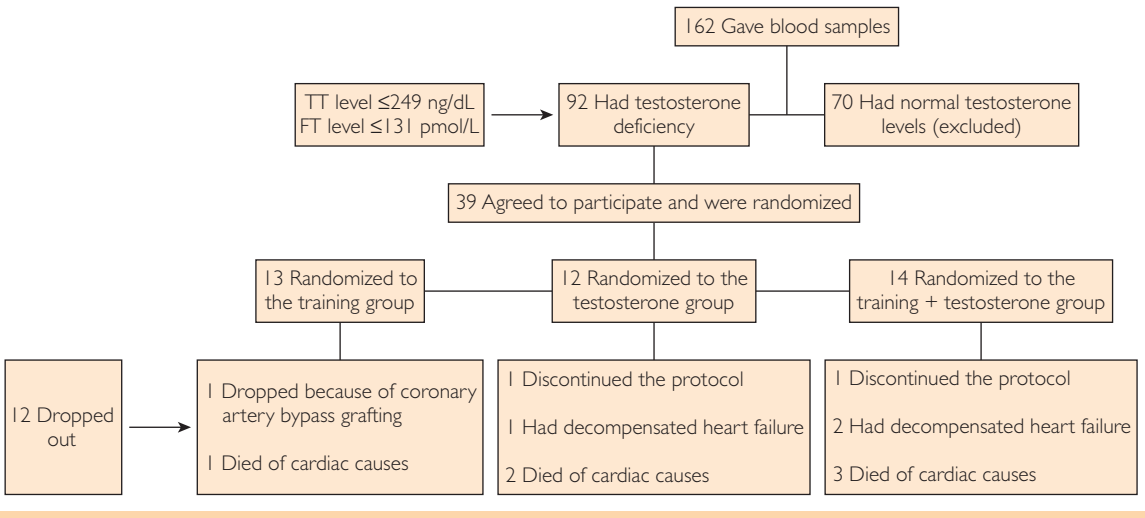


**FIGURE 1.** Flowchart of patients studied during the study. FT = free testosterone; TT = total testosterone. SI conversion factor: To convert to nmol/L, multiply by .03467.



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