Journal of the American College of Cardiology Vol. 56, No. 16, 2010

Published by Elsevier Inc.
ISSN 0735-1097/$36.00
doi:10.1016/j.jacc.2010.03.090

Testosterone Therapy in Women With Chronic Heart Failure

A Pilot Double-Blind, Randomized, Placebo-Controlled Study

Ferdinando Iellamo, MD,*† Maurizio Volterrani, MD,* Giuseppe Caminiti, MD,* Roger Karam, MD,‡ Rosalba Massaro, MD,* Massimo Fini, MD,* Peter Collins, MD, PHD,*§ Giuseppe M. C. Rosano, MD*

Roma, Italy; Cinncinati, Ohio; and London, United Kingdom

Objectives The primary objective of this study was to assess the effect of a 6-month testosterone supplementation therapy on functional capacity and insulin resistance in female patients with chronic heart failure (CHF).

Background Patients with CHF show decreased exercise capacity and insulin sensitivity. Testosterone supplementation improves these variables in men with CHF. No study has evaluated the effects of testosterone supplementation on female patients with CHF.

Methods Thirty-six elderly female patients with stable CHF, (ejection fraction 32.9 ± 6) were randomly assigned (2:1 ratio) to receive testosterone transdermal patch (T group, n = 24) or placebo (P group, n = 12), both on top of optimal medical therapy. At baseline and after 6 months, patients underwent 6-min walking test (6MWT), cardiopulmonary exercise test, echocardiogram, quadriceps maximal isometric voluntary contraction, dynamic quadriceps isokinetic strength (peak torque), and insulin resistance assessment by homeostasis model.

Results Distance walked at 6MWT as well as peak oxygen consumption significantly improved in the T group, whereas they were unchanged in the P group ($p < 0.05$ for all comparisons). The homeostasis model was significantly reduced in the T group in comparison with the P group (−16.5% vs. +5%, respectively; $p < 0.05$). Maximal voluntary contraction and peak torque increased significantly in the T group but did not change in the P group. Increase in distance walked at 6MWT was related to the increase in free testosterone levels ($r = 0.593$, $p = 0.01$). No significant changes in echocardiographic parameters were observed in either group. No side effects requiring discontinuation of T were detected.

Conclusions Testosterone supplementation improves functional capacity, insulin resistance, and muscle strength in women with advanced CHF. Testosterone seems to be an effective and safe therapy for elderly women with CHF.
(J Am Coll Cardiol 2010;56:1310–6) © 2010 by the American College of Cardiology Foundation

Chronic heart failure (CHF) is a complex syndrome in which several pathophysiological mechanisms, in addition to primary heart disease, are involved. Therapeutic strategies targeted to the pathophysiological mechanisms sustaining the progression and worsening of heart failure (HF), mainly the prolonged neurohumoral activation, have been shown to improve quality of life and survival rate. Chronic heart failure is also characterized, in addition to neurohumoral activation, by metabolic disorders including testosterone (T) deficiency (1), insulin resistance (2), and a metabolic shift favoring catabolism and impairment in skeletal muscle bulk and function, the latter being involved not only in symptoms development but even in the pathophysiology of the HF syndrome (3). Low plasma levels of T have been reported in patients with CHF (1,4,5), 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 CHF (6). Indeed, anabolic hormone

See page 1317

From the *Centre for Clinical and Basic Research, Cardiovascular Research Unit, Department of Medical Sciences, Istituto di Ricovero e Cura a Carattere Scientifico San Raffaele Roma, Roma, Italy; †Department of Internal Medicine, University of Rome Tor Vergata, Roma, Italy; ‡Procter and Gamble Pharmaceuticals, Inc., Cincinnati, Ohio; and the §Brompton Hospital, Imperial College of Science and Technology, London, United Kingdom. This study was supported by the Italian Ministry of Health, as a part of Finalized Research 2005 grant. Dr. Karam was a Procter and Gamble employee at the time the study was performed. He contributed to the conception of the study but had no access to collection, analysis, or interpretation of data. He did not contribute in the writing of the report. Procter and Gamble Pharmaceuticals did not provide any financial support other than furnishing the drug. All other authors have reported that they have no relationships to disclose.

Manuscript received December 30, 2009; revised manuscript received February 17, 2010, accepted March 2, 2010.

depletion is relatively common in CHF and would also 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 that sustains the progression of the disease, possibly affecting survival (7). In keeping with this concept, several studies (6,8,9) and 1 recently by our group (10) reported that T supplementation given on top of optimal medical therapy improved exercise capacity, ventilatory efficiency, muscle strength, and insulin sensitivity in elderly men with moderately severe CHF without major side effects.

Similar to the gradual decline of T observed with aging in men, an age-dependent decline in endogenous total and free T occurs also in women (11), and in both sexes T therapy augments anabolic function, leading to increased muscle mass and physical strength. In recent investigations, T replacement therapy at physiological levels increased muscle mass and improved some cardiovascular risk factors, including insulin resistance, in women with androgen deficiency due to hypopituitarism (12,13).

However, until now, the effects of T supplementation in post-menopausal elderly women with CHF have never been assessed.

Accordingly, the aim of this proof-of-concept study was to assess the effects of low-dose T supplementation on functional capacity and insulin resistance in elderly women with moderate to severe HF. We also addressed the effect of T on quadriceps muscle performance to test the hypothesis that T supplementation could improve functional capacity through an improvement of muscle performance.

Methods

Patient population and study design. Patients were screened and randomized between December 2006 and November 2007, and the final patient completed the study in April 2008. Patients were included in the study if they had symptomatic HF with functional New York Heart Association functional class III, left ventricular ejection fraction <40%, and no hospital admission for HF in the previous 3 months. Patients were excluded if they had unstable angina or recent acute myocardial infarction, severe liver or kidney diseases, neoplasias, post-menopausal hormone therapy, androgen therapy, bilateral oophorectomy, or hysterectomy. From a total of 48 patients screened, 36 met the inclusion criteria and were included in the study. Eight patients were not included because of renal failure (creatinine clearance <30 mg/dl); 3 patients had hematocrit >50%; and 1 patient had undergone hysterectomy. All patients gave written informed consent to participate in the study, which was approved by the local ethics committee.

After the completion of baseline testing, patients were randomly allocated in a 2:1 ratio to receive either transdermal patch of T (300 μg Intrinsa, Procter and Gamble, Cincinnati, Ohio) or transdermal patch of placebo (P). Patches were applied twice/week to the abdominal skin between 8:00 AM and 10:00 AM for 24 weeks. Testosterone and P were dispensed by the Pharmacologic Department, which was also responsible for the randomization codes. Randomization was blinded to investigators and subjects. Subjects returned for follow-up study visits 1 month and 3 and 6 months after baseline testing.

At baseline and at the end of the study, patients underwent a 6-min walking test (6MWT), cardiopulmonary exercise test (CPET), echocardiographic examination, and muscle strength assessment. A blood sample was drawn from an antecubital vein after an overnight fast for determination of serum hormones and routine laboratory analyses. Serum T, free T, glucose, insulin, total cholesterol, high-density lipoprotein cholesterol, triglycerides, alanine aminotransferase, aspartate aminotransferase, hemoglobin, and creatinine were measured. Total T and sex hormone-binding globulin (SHBG) were measured by chemiluminescent magnetic microparticle immunoassay (analytical sensitivity 0.08 ng/ml and <0.1 nmol/l for T and SHBG, respectively) with inter- and intra-assay variability coefficients of <8% and <5% for T and <10% and <5% for SHBG, respectively. Free T concentration was calculated from T and SHBG with the validated equation of Vermeulen et al. (14).

Abbreviations and Acronyms

6MWT = 6-min walking test
CHF = chronic heart failure
CPET = cardiopulmonary exercise test
HF = heart failure
HOMA-IR = homeostasis model assessment
MVC = maximal voluntary contraction
P = placebo
SHBG = sex hormone-binding globulin
T = testosterone
VE = ventilation
VCO_2 = carbon dioxide production
VO_2 = oxygen consumption

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, as previously described (10).

Assessment of functional capacity and cardiorespiratory indexes. Functional capacity was assessed by means of 6MWT and CPET. The 6MWT was performed according to standardized procedures (15). The CPET was performed with an electrically braked bicycle ergometer with monitoring of gas exchange (Vmax 29 C, SensorMedics, Yorba Linda, California) as previously described (10) until exhaustion. Peak oxygen consumption (VO_2) was defined as the highest VO_2 averaged for the last 30 s of exercise. Respiratory exchange ratio is calculated at the same time point. A value >1.10 was taken to represent adequate effort. The ventilation (VE)/carbon dioxide production (VCO_2) slope, which relates the rate of increase in VE/unit increase in carbon dioxide was calculated with the whole exercise period. A 12-lead electrocardiogram was recorded continuously, and blood pressure was measured every 2 min by a sphygmomanometer.

Muscle performance assessment. Assessment of leg muscle strength was performed by means of a computer-based multifunctional dynamometer system (REV 9000, Technogym, Gambettola, Italy) in the seated position. Muscle strength was determined during both maximal isometric (maximal voluntary contraction [MVC]) and isokinetic (peak torque during dynamic leg flex-extension) effort, as recently described (10).

Insulin resistance. Glucose and insulin were measured after 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) (16).

Statistical analysis. There were no studies on which to calculate a power equation, because there are no previous reports on the effects of T supplementation on the selected end points in women with CHF. We recently examined the effect of T replacement therapy in 70 CHF men and reported a significant improvement in both 6MWT and insulin resistance as measured by HOMA-IR (10). On the basis of that study, we estimated that a therapeutic effect could be demonstrated with 30 patients to obtain the same effect size, with 80% power and 5% significance assuming a dropout rate of 10%.

Differences in baseline characteristics between treatment and P groups were evaluated by chi-square and unpaired *t* tests. Within-group changes in the reported variables were evaluated by paired *t* test or Wilcoxon signed rank test for non-normally distributed variables. Between-groups comparisons were performed by unpaired *t* test and Mann-Whitney rank sum test (10). Relations between variables were assessed by Pearson product-moment correlation or Spearman's rank test for non-normally distributed data (9,10). The primary end points were the treatment effect of T versus P on the 6MWT distance in meters and insulin resistance. Secondary end points were MVC and peak torque.

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).

Table 1 Baseline Characteristics of Patients in the 2 Groups

	Testosterone (n = 20)	Placebo (n = 12)
Age, yrs	68.2 ± 6.85	69.1 ± 8.6
Diabetes	11 (55)	6 (50)
Hypertension	11 (55)	5 (42)
Dyslipidemia	13 (65)	8 (67)
Atrial fibrillation	6 (30)	3 (25)
Concomitant therapy		
Beta-blockers	17 (85)	9 (75)
ACE inhibitors/ARBs	18 (90)	11 (92)
Diuretics	16 (80)	9 (75)
Aldosterone receptor blockers	12 (60)	7 (58)
Digoxin	6 (30)	4 (33)
Antiplatelet agents	20 (100)	12 (100)
Statins	17 (85)	8 (70)

No significant differences were found for any of the comparisons shown. Variables are reported as absolute numbers and percentage, unless otherwise indicated.
ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker.

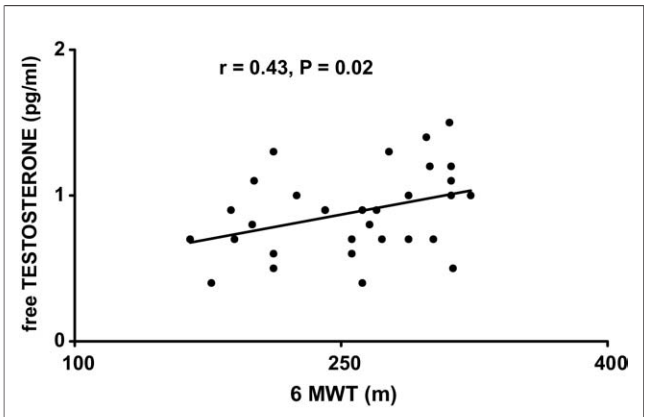

Figure 1 Relation Between Free Testosterone Levels and Distance Walked at 6MWT at Baseline

At baseline, there was a significant direct relationship between free testosterone levels and the distance walked in the 6-min walking test (6MWT).

Results

Four patients in the T group discontinued the study after 1 to 2 months. The reason for discontinuation was in every case the willingness of the patient to escape from the study (e.g., logistic reasons and decision to discontinue the protocol not related to T supplementation).

Baseline characteristics of the patients are reported in Table 1. There were no significant differences between the treatment and the P groups with respect to all variables.

The etiology of CHF was ischemic heart disease in all subjects. Patients were considered on top of medical therapy (Table 1), and medications were not altered throughout the study.

At baseline, all patients had total T levels within the normal range (0.09 to 1.3 ng/ml); 13 patients (41%), 9 in the treatment group and 4 in the P group, had free T levels below the normal range (0.9 to 4.0 pg/ml). Patients with low T levels (0.63 ± 0.13 pg/ml) had a significantly lower distance-walked at the 6MWT than patients with normal T levels (226.5 ± 41 m vs. 271.4 ± 43 m, p = 0.006), and baseline free T levels correlated with distance walked in the 6MWT (Fig. 1).

The effect of T supplementation on the different variables is reported in Tables 2 and 3. Distance walked at the 6MWT improved in both groups, but the increase in 6MWT was significant only in patients under T supplementation. Peak VO_2 significantly increased and VE/VCO_2 slope significantly decreased in patients receiving T (n = 13),

Table 2 Cardiorespiratory, Echocardiography, and Muscular Results Before and After 6 Months of Testosterone Supplementation Therapy

	Testosterone Group		Placebo Group		Changes (Δ)	
	Before	After	Before	After	Testosterone	Placebo
6MWT, m	260.6 ± 52	357.2 ± 43	254.9 ± 39	291.3 ± 22	96.6 ± 14.5*	36.4 ± 11.9
Peak VO_2, ml/kg/min	10.5 ± 1.0	13.2 ± 1.8	10.0 ± 1.9	10.1 ± 1.3	2.8 ± 0.06*	0.1 ± 0.03
VE/VCO_2 slope	34.6 ± 5.0	31.1 ± 7.0	35.8 ± 6.0	34.2 ± 8.4	−3.5 ± 0.1*	−1.6 ± 0.8
SBP, mm Hg	115.2 ± 18	113.8 ± 23	113.4 ± 19	112.6 ± 20	−2.2 ± 0.04	−1.3 ± 0.06
DBP, mm Hg	79.2 ± 9	80 ± 7	77.2 ± 11	78.6 ± 13	1.0 ± 0.03	1.4. ± 0.04
Resting HR, beats/min	67.8 ± 13	66.5 ± 11	68.6 ± 11	68.0 ± 13	−1.3 ± 0.05	−0.6 ± 0.02
MVC, n	65.0 ± 15	92.1 ± 20	65.4 ± 14	69.9 ± 16	27.1 ± 4.7*	4.5 ± 2.1
PTmax, Nm	41.3 ± 17.4	74.2 ± 14.8	43.6 ± 11.6	49.1 ± 9.2	32.9 ± 8.4*	5.5 ± 1.2
EF, %	32.3 ± 8.1	32.1 ± 7.2	31.8 ± 7.3	31.5 ± 7.7	−0.2 ± 0.03	−0.3 ± 0.07
LVEDD, mm	62.7 ± 12	63.5 ± 13	61.9 ± 13	62.4 ± 11	−0.8 ± 0.05	−0.5 ± 0.02

Data are expressed as mean ± SD. *Between-group differences at $p < 0.05$.

DBP = diastolic blood pressure; EF = ejection fraction; HR = heart rate; LVEDD = left ventricular end-diastolic diameter; MVC = isometric maximal voluntary contraction; PTmax = isokinetic power torque; SBP = systolic blood pressure; VCO_2 = carbon dioxide production; VE = ventilation; VO_2 = oxygen consumption; 6MWT = 6-min walking test.

whereas no significant changes in these variables were detected in the P group (n = 8). Seven patients in the T group and 4 in the P group did not complete CPET, because they did not tolerate the mouth-piece/nose clip apparatus. New York Heart Association functional class improved from III to II in 7 of 20 patients in the T group and in 2 of 12 in the P group ($p = 0.03$). Total T and free T both increased with treatment but remained within the normal physiological range for post-menopausal women, whereas no significant change was observed in the P group (Table 3).

The increase (Δ) in free T levels in the treatment group was positively correlated with the increase in distance walked at the 6MWT ($r = 0.593$, $p = 0.01$). The improvement in 6MWT in the treated group was greater in patients with low as compared with normal baseline T levels (125.2 ± 60.3 m vs. 68.8 ± 53.1 m, $p = 0.05$). The MVC and peak torque significantly improved in T-treated patients but remained unchanged in the P group (Table 2).

No significant changes in left ventricular ejection fraction, left ventricular end-diastolic diameter, heart rate, or systolic and diastolic blood pressure were detected in either group.

Metabolic and hormonal data are summarized in Table 3. The HOMA-IR decreased significantly in the T group, whereas it increased in the control group. High-density lipoprotein cholesterol as well as hemoglobin level significantly increased in the T as compared with the P group. No significant change in body weight or body mass index was detected in either the T or the P groups.

Two patients in the T group discontinued the study, 1 because of generalized prurigo (without skin lesions), and the other for her willingness to escape the study, the latter reason being the same for discontinuation therapy in 2 patients in the P group. Discontinuation occurred between 3 and 6 months after baseline evaluation. No sign of virilization was detected in the T group at intermediate and final visits, and patients did not report adverse effects related to T administration.

Table 3 Metabolic and Hormonal Results Before and After 6 Months of Testosterone Supplementation Therapy

	Testosterone Group		Placebo Group		Changes (Δ)	
	Before	After	Before	After	Testosterone	Placebo
BMI, kg/m^2	27.9 ± 4.0	28.6 ± 4.4	27.8 ± 3.7	27.9 ± 3.6	0.7 ± 0.04	0.1 ± 0.03
Body weight, kg	69.5 ± 9.2	71.2 ± 8.4	70.2 ± 8.3	70.5 ± 9.9	1.7 ± 0.06	0.2 ± 0.02
Fasting glycemia, mg/dl	109.3 ± 26	106.2 ± 31	114.1 ± 4.3	111.6 ± 27	−3.1 ± 0.4	−2.5 ± 0.2
Fasting insulinemia, μU/ml	12.6 ± 2.0	10.5 ± 1.0	11.8 ± 4.0	12.7 ± 3.0	−1.9 ± 0.06*	0.9 ± 0.02
HOMA-IR	3.47 ± 0.4	2.90 ± 0.03	3.32 ± 0.07	3.49 ± 0.04	−0.57 ± 0.03*	0.17 ± 0.02
Total cholesterol, mg/dl	138.5 ± 29	140.2 ± 36	140.5 ± 42	143.0 ± 48	1.7 ± 0.05	2.5 ± 0.2
HDL cholesterol, mg/dl	31.3 ± 7.1	36.0 ± 5.7	37.0 ± 6.2	36.6 ± 6.9	4.7 ± 0.9	−0.4 ± 0.05
Triglycerides, mg/dl	128.2 ± 31	131.4 ± 28	129.1 ± 30	124.3 ± 32	3.2 ± 0.3	3.6 ± 0.1
Free testosterone, pg/ml	0.95 ± 0.4	2.2 ± 0.8	0.93 ± 0.2	0.65 ± 0.3	1.2 ± 0.04*	−0.3 ± 0.05
Total testosterone, ng/ml	0.4 ± 0.05	1.0 ± 0.04	0.4 ± 0.07	0.3 ± 0.08	0.6 ± 0.05*	−0.1 ± 0.02
Hemoglobin, g/dl	11.0 ± 2.3	12.7 ± 2.4	10.7 ± 2.7	10.2 ± 3.1	1.7 ± 0.06*	−0.5 ± 0.03
Hematocrit, %	24.3 ± 2.1	27.4 ± 2.9	24.7 ± 2.4	25.2 ± 2.6	3.1 ± 0.2*	0.5 ± 0.2
Creatinine, mg/dl	1.32 ± 0.07	1.36 ± 0.06	1.34 ± 0.1	1.35 ± 0.08	0.4 ± 0.03	0.1 ± 0.02

Data are expressed as mean ± SD. *Between-group differences at $p < 0.05$.

BMI = body mass index; HDL = high-density lipoprotein; HOMA-IR = homeostasis model assessment.

During follow-up, 2 patients in the T group and 2 in the P group had worsening HF that was treated with increased doses of diuretics. Six patients in the T group and 2 in the P group referred mild skin irritation in the site of the patch application that did not require discontinuation of therapy.

Discussion

This is to our knowledge the first study to address the potential benefits of T administration in women with CHF. The results show that physiological T replacement therapy improves functional capacity and insulin resistance in women with CHF. The relevance of this finding should be placed in the context of the established evidence indicating the adverse prognostic role of low functional capacity and insulin resistance in patients with CHF.

Established evidence indicates that CHF is a syndrome involving not only the failing heart, but also peripheral skeletal muscles as well as neurohumoral, endocrine, and metabolic systems. These include a decrease in T levels and insulin sensitivity (17), possibly related to each other (18). Approximately 25% of men with CHF have biochemical evidence of T deficiency, and low levels have been related to disease progression in HF (18). Relative T deficit reflects 1 aspect of anabolic insufficiency that leads to a metabolic shift favoring catabolism, a major underlying mechanism for tissue wasting seen in CHF. The prevalence of insulin resistance in CHF and its role on CHF development have been elucidated (19,20). Indeed, more than 40% of HF patients, including women (21), have manifest disorders of glucose metabolism (17); insulin resistance, leading to an inability of insulin to promote glucose transport into skeletal muscles, has been proposed as a mediator of skeletal muscle fatigue and wasting of CHF, linking these processes directly to the metabolic disturbances in HF patients (22).

Our recent (10) as well as previous studies (6,8,9,23) reported that T supplementation therapy improves exercise capacity, insulin sensitivity, ventilatory efficiency, and muscle strength in elderly men with moderately severe CHF, even in those with normal T levels (10).

The secretion of T decreases with aging also in women (11), whereas the incidence of HF also rises in older women as well as older men. However, no study addressed the effect of T supplementation in elderly women with CHF.

The present study shows that low-dose T supplementation given in addition to optimal medical therapy improves functional capacity, insulin sensitivity, and large-muscles strength in elderly women with CHF. The increase in functional capacity was related to the increase in plasma levels of T and not related to changes in left ventricular function, confirming previous studies in men (8,10).

These results obtained with transdermal patch extend to women the findings that we (10) and others (6,8) have reported in elderly men with CHF after T supplementation therapy.

We demonstrated a significant improvement—like in men—in 6MWT, VO_2, and ventilatory efficiency, all of which carry a negative prognosis in CHF (24). The significant correlation between the increase in T level and the increased distance walked at 6MWT, a finding also reported in men (8,10), would support the hypothesis that the improvement in functional capacity was linked to T administration. The lack of any change in the P group would be consistent with this assumption. Testosterone supplementation improved insulin sensitivity in women with CHF as well as in men (9,10).

This study confirms that T supplementation in women, like in men (10), also improves both static and dynamic muscular performance of large, weight-bearing muscles, which are more relevant to the effort intolerance of the CHF syndrome.

The improvement in 6MWT was greater in women with lower baseline T levels. However, the improvements in insulin sensitivity, ventilatory efficiency, VO_2, and muscular performances did not differ significantly between patients with low T levels and those with normal T levels. This would indicate that the benefits of T supplementation are not entirely confined to female CHF patients with low baseline T, although a greater improvement in some physiological parameters in the latter would be expected, similar to what occurred in men (10).

The mechanisms through which T supplementation would affect cardiorespiratory parameters and insulin resistance is still unclear, and this study, by its design, cannot directly answer to this question.

However, some tentative explanations can be advanced. We observed a significant increase in both static and dynamic leg performance in the testosterone-treated group. These effects would depend on the action of T at the muscular level. Objective morphological and functional abnormalities, relatively independent of reduced blood flow, are present in the muscle of CHF patients (25) and include fiber atrophy and a prevalence of type II fibers with a predominance of glycolytic over oxidative metabolism, which are involved not only in symptoms development, but even in the pathophysiology and worsening of the HF syndrome, the so-called "muscle hypothesis" (3). In short, by this hypothesis, muscle alterations occurring in CHF would elicit over time an enhanced muscle metaboreflex (also called "ergoreflex") (26) activation even at moderate levels of exercise, which in turn would be responsible for the prolonged neurohumoral activation and abnormal cardiorespiratory responses to exercise that characterize CHF (26–28). 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 improve functional capacity (25,26). The increase in leg muscle performance observed in the present investigation after T supplementation, which reflects an improvement in muscle function, might have acted in the same manner by decreasing the muscle metaboreflex overactivity.

Anabolic administration at replacement doses has been shown to accelerate fast- to slow-oxidative fiber type conversion (29)—which is typically reduced in CHF patients (25)—and to increase the number and size of type I slow oxidative fibers (30), which implies an improved oxidative capacity of skeletal muscles and a higher aerobic potential with delayed fatigue. Improved insulin sensitivity, with the attendant increased availability of glucose as an energy source for the skeletal muscle cells, might have contributed to the reduced fatigability and might have also acted by promoting peripheral vasodilation, resulting in an increase in blood flow to exercising muscle.

The mechanism by which T reduces insulin resistance is uncertain. An effect of T on muscle insulin sensitivity has been suggested (31). Another potential mechanism would be an action of T on visceral adipocytes metabolism (9,32,33). Uncertainty is even greater in women, because to our knowledge no study has addressed this issue.

We cannot compare our results with those of other studies, because no investigation has been performed on the effects of T replacement therapy in women with CHF. The only comparison we can draw is with studies on the effect of T supplementation in men with CHF (6,8,10): even though T doses in male studies are 10 to 20 times the replacement doses appropriate for women, the magnitude of changes in 6MWT, VO_2, VE/VCO_2, and MVC observed in women in the present investigation was closely similar to that observed in men (6,8,10).

In our study there was high compliance, with only 2 patients discontinuing T therapy, like in the P group. This low percentage of dropout as compared with studies using transdermal patches in men with CHF (8) might be ascribed to the shorter follow-up period but mainly to the lower rate of patches application (only twice/week). No androgenic side effects were detected, confirming previous studies employing transdermal patches (25,34,35).

Study limitations. Some limitations of the present investigation deserve comment. The sample size was small, and the follow-up was short, so we cannot comment on clinical outcome. However, the present study would indicate that T supplementation therapy improves clinical measures that carry adverse effects and negative prognosis in CHF. In addition, this is a proof-of-concept study. Clinical outcome was not the main focus of the study, and as such, any uncertainty relating to clinical outcomes should not detract from the novelty of the study. Finally, T supplementation should be regarded at present only as an adjunctive therapy, and the results we obtained cannot be extrapolated at all in less severely ill and/or obese CHF patients. Larger long-duration studies are needed to determine long-term efficacy and safety of such a replacement strategy in women with CHF.

Conclusions

This proof-of-concept study indicates that T supplementation therapy improves functional capacity, insulin sensitivity, and muscle strength in elderly female patients with CHF. The lack of effects of T on left ventricular function in women, like in men, seems to confirm that T acts only through peripheral mechanisms.

Reprint requests and correspondence: Dr. Ferdinando Iellamo, Cardiovascular Research Unit, Department of Medical Sciences, IRCCS San Raffaele–Roma, via della Pisana 235, 00163 Roma, Italy. E-mail: iellamo@med.uniroma2.it.

REFERENCES

1. Kontoleon PE, Anastasiou-Nana MI, Papapetrou PD, et al. Hormonal profile in patients with congestive heart failure. Int J Cardiol 2003;87:179–83.
2. Witteles RM, Fowler MB. Insulin-resistant cardiomyopathy: clinical evidence, mechanisms, and treatment options J Am Coll Cardiol 2008;51:93–102.
3. Coats AJ, Clark AL, Piepoli M, Volterrani M, Poole-Wilson PA. Symptoms and quality of life in heart failure: the muscle hypothesis. Br Heart J 1994;72:S36–9.
4. Anker SD, Chua TP, Ponikowski P, et al. Hormonal changes and catabolic/anabolic imbalance in chronic heart failure and their importance for cardiac cachexia. Circulation 1997;96:526–34.
5. Moriyama Y, Yasue H, Yoshimura M, et al. The plasma levels of dehydroepiandrosterone sulfate are decreased in patients with chronic heart failure in proportion to the severity. J Clin Endocrinol Metab 2000;85:1834–40.
6. Pugh PJ, Jones RD, West JN, Jones TH, Channer KS. Testosterone treatment for men with chronic heart failure. Heart 2004;90:446–7.
7. Jankowska EA, Biel B, Majda J, et al. Anabolic deficiency in men with chronic heart failure prevalence and detrimental impact on survival. Circulation 2006;114:1829–37.
8. Malkin CJ, Pugh PJ, West JN, Van Beek EJR, Jones TH, Channer KS. Testosterone therapy in men with moderate severity heart failure: a double-blind randomized placebo controlled trial. Eur Heart J 2006;27:57–64.
9. Malkin CJ, Jones TH, Channer KS. The effect of testosterone on insulin sensitivity in men with heart failure. Eur J Heart Fail 2007;9:44–50.
10. Caminiti G, Volterrani M, Iellamo F, et al. 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. J Am Coll Cardiol 2009;54:919–27.
11. Martin-Du Pan R. Androgen deficiency in women: indications and risks of treatment with testosterone or DHEA. Rev Med Suisse 2007;3:792–6.
12. Miller K, Biller B, Beauregard C, et al. Effects of testosterone replacement in androgen-deficient women with hypopituitarism: a randomized, double-blind, placebo-controlled study. J Clin Endocrinol Metab 2006;91:1683–90.
13. Miller KK, Biller BM, Schaub A, et al. Effects of testosterone therapy on cardiovascular risk markers in androgen-deficient women with hypopituitarism. J Clin Endocrinol Metab 2007;92:2474–9.
14. Vermeulen A, Verdonck L, Kaufman JM. A critical evaluation of simple methods for the estimation of free testosterone in serum, J Clin Endocrinol Metab 1999;84:3666–72.
15. American Thoracic Society. ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med 2002;166:111–7.
16. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and β-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985;28:412–9.
17. von Haehling S, Doehner W, Anker SD. Nutrition, metabolism, and the complex pathophysiology of cachexia in chronic heart failure. Cardiovasc Res 2007;73:298 –309.
18. Malkin CJ, Jones TH, Channer KS. Testosterone in chronic heart failure. Front Horm Res 2009;37:183–96.

19. Swan JW, Anker SD, Walton C, et al. Insulin resistance in chronic heart failure: relation to severity and etiology of heart failure. J Am Coll Cardiol 1997;30:527–32.
20. Ingelsson E, Sundström J, Arnlöv J, Zethelius B, Lind L. Insulin resistance and risk of congestive heart failure. JAMA 2005;294:334–41.
21. Suskin N, McKelvie RS, Burns RJ, et al. Glucose and insulin abnormalities relate to functional capacity in patients with congestive heart failure. Eur Heart J 2000;21:1368–75.
22. Doehner W, Gathercole D, Cicoira M, et al. Reduced glucose transporter GLUT4 in skeletal muscle predicts insulin resistance in non-diabetic chronic heart failure patients independently of body composition. Int J Cardiol 2010;138:19–24.
23. Pugh PJ, Jones TH, Channer KS. Acute haemodynamic effects of testosterone in men with chronic heart failure. Eur Heart J 2003;24:909–15.
24. Swedberg K, Cleland J, Dargie H, et al. Guidelines on the diagnosis and treatment of chronic heart failure: executive summary (update 2005). The task force for the diagnosis and treatment of chronic heart failure of the European Society of Cardiology. Eur Heart J 2005;26:1115–40.
25. Hambrecht R, Fiehn E, Yu J, et al. Effects of endurance training on mitochondrial ultrastructure and fiber type distribution in skeletal muscle of patients with stable chronic heart failure. J Am Coll Cardiol 1997;29:1067–73.
26. Piepoli M, Clark AL, Volterrani M, Adamopoulos S, Sleight P, Coats AJS. Contribution of muscle afferents to the hemodynamic, autonomic, and ventilatory responses to exercise in patients with chronic heart failure: effects of physical training. Circulation 1996;93:940–9.
27. Piepoli MF, Kaczmarek A, Francis DP, et al. Reduced peripheral skeletal muscle mass and abnormal reflex physiology in chronic heart failure. Circulation 2006;114:126–34.
28. Ponikowski PP, Chua TP, Francis DP, Capucci A, Coats AJS, Piepoli MF. Muscle ergoreceptor overactivity reflects deterioration in clinical status and cardiorespiratory reflex control in chronic heart failure. Circulation 2001;104:2324–30.
29. Czesla M, Mehlhorn G, Fritzsche D, Asmussen G. Cardiomyoplasty-improvement of muscle fibre type transoformation by anabolic steroid. J Mol Cell Cardiol 1997;29:2989–96.
30. Ustünel I, Akkoyunlu G, Demir R. The effect of testosterone on gastrocnemius muscle fibres in growing and adult male and female rats: a histochemical, morphometric and ultrastructural study. Anat Histol Embryol 2003;32:70–9.
31. Holmäng A, Björntorp P. The effects of testosterone on insulin sensitivity in male rats. Acta Physiol Scand 1992;146:505–10.
32. Kapoor D, Goodwin E, Channer KS, Jones TH. Testosterone replacement therapy improves insulin resistance, glycaemic control, visceral adiposity and hypercholesterolaemia in hypogonadal men with type 2 diabetes. Eur J Endocr 2006;154:899–906.
33. Pitteloud N, Mootha VK, Dwyer AA, et al. Relationship between testosterone levels, insulin sensitivity, and mitochondrial function in men. Diabetes Care 2005;28:1636–42.
34. Shifren J, Davis S, Moreau M, et al. Testosterone patch for the treatment of hypoactive sexual desire disorder in naturally menopausal women: results from the INTIMATE NM1 study. Menopause 2006;13:770–9.
35. Braunstein G, Sundwall D, Katz M, et al. Safety and efficacy of a testosterone patch for the treatment of hypoactive sexual desire disorder in surgically menopausal women: a randomized, placebo-controlled trial. Arch Intern Med 2005;165:1571–2.

Key Words: congestive heart failure ■ exercise capacity ■ female ■ glucose metabolism ■ testosterone.