Reduction in Circulating Testosterone Relates to Exercise Capacity in Men With Chronic Heart Failure

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ABSTRACT

Background: We investigated whether anabolic deficiency was linked to exercise intolerance in men with chronic heart failure (CHF). Anabolic hormones (testosterone, dehydroepiandrosterone sulfate, insulin-like growth factor 1 [IGF1]) contribute to exercise capacity in healthy men. This issue remains unclear in CHF.

Methods and Results: We studied 205 men with CHF (age 60 ± 11 years, New York Heart Association [NYHA] Class I/II/III/IV: 37/95/65/8; LVEF [left ventricular ejection fraction]: 31 ± 8%). Exercise capacity was expressed as peak oxygen consumption (peak VO_2), peak O_2 pulse, and ventilatory response to exercise (VE-VCO_2 slope). In multivariable models, reduced peak VO_2 (and reduced peak O_2 pulse) was associated with diminished serum total testosterone (TT) ($P < .01$) and free testosterone (eFT; estimated from TT and sex hormone globulin levels) ($P < .01$), which was independent of NYHA Class, plasma N-terminal pro-brain natriuretic peptide, and age. These associations remained significant even after adjustment for an amount of leg lean tissue. In multivariable models, high VE-VCO_2 slope was related to reduced serum IGF1 ($P < .05$), advanced NYHA Class ($P < .05$), increased plasma NT-proBNP ($P < .0001$), and borderline low LVEF ($P = .07$). In 44 men, reassessed after 2.3 ± 0.4 years, a reduction in peak VO_2 (and peak O_2 pulse) was accompanied by a decrease in TT ($P < .01$) and eFT ($P \leq .01$). Increase in VE-VCO_2 slope was related only to an increase in plasma NT-proBNP ($P < .05$).

Conclusions: In men with CHF, low circulating testosterone independently relates to exercise intolerance. The greater the reduction of serum TT in the course of disease, the more severe the progression of exercise intolerance. Whether testosterone supplementation would improve exercise capacity in hypogonadal men with CHF requires further studies. (*J Cardiac Fail 2009;15:442–450*)

Key Words: Chronic heart failure, exercise intolerance, anabolic hormones.

Exercise intolerance is a cardinal symptom of chronic heart failure (CHF) associated with poor quality of life, high morbidity and mortality.[1–3] The underlying mechanisms are not fully understood, which partially explains why therapeutic interventions to improve exercise capacity in CHF patients are still limited. In recent years, it has become evident that apart from impaired hemodynamics, abnormal regulation of the periphery can adversely affect exercise capacity in patients with CHF.[4,5]

Anabolic hormones are determinants of male exercise capacity. Age-related decline in circulating testosterone, dehydroepiandrosterone sulfate (DHEAS), and insulin-like growth factor 1 (IGF1) contribute to gradually impaired exercise tolerance in elderly men.[6–9] Administration of anabolic androgenic steroids significantly increases lean mass and skeletal muscle strength and improves physical performance.[10,11]

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Anabolic/catabolic imbalance as evidenced by multiple anabolic deficiency reflecting impairment of 3 major anabolic axes (testosterone, DHEAS, IGF1) is often present in men with CHF, and is related not only to severity of symptoms but also to increased long-term mortality.[12] Although there are biologic reasons for anticipating pathophysiological links between multiple anabolic deficiency and impaired exercise capacity in men with CHF, so far these associations have not been clearly demonstrated. Therefore, we performed a study to establish whether deficiencies in circulating anabolic hormones (testosterone, DHEAS, IGF1) were related to exercise intolerance in men with CHF.

Methods

Study Population

Between October 2001 and September 2005, we evaluated male patients who were hospitalized in our department or attended the outpatient CHF clinic, and agreed to participate in our program of metabolic assessment. The criteria for study inclusion were: a >3-month documented history of CHF; left ventricular ejection fraction (LVEF) ≤40% as assessed by echocardiography; and clinical stability and unchanged CHF medications for ≥4 weeks preceding the study. Exclusion criteria included: acute coronary syndrome or coronary revascularization within the 6 months preceding the study; any acute/chronic illness which might influence hormone metabolism; and any hormonal treatment either at the time of the study or in the past.

During the study period, we prospectively identified 336 male patients who met these criteria and constituted the total population of our CHF metabolic program. In this study, we are reporting the prespecified analyses performed in those who additionally underwent the assessment of exercise capacity with cardiopulmonary exercise testing. All patients included in the metabolic program were asked to participate provided they did not have any pulmonary, musculoskeletal, or any other chronic disease that may significantly contribute to exercise intolerance. We prospectively identified 205 men. All men were Caucasian. Baseline characteristics of a study population are given in Table 1. Eighty-seven patients included into this study were also included in the previously published report.[12]

The study protocol was approved by the local ethics committee and all subjects gave written informed consent. The study was conducted in accordance with the Declaration of Helsinki.

Serum Levels of Anabolic Hormones and Laboratory Measurements

In all men with CHF, venous blood samples were taken in the morning after an overnight fast and after a supine rest of at least 15 minutes. After centrifugation, serum was collected and frozen at −70°C until being analyzed.

Serum levels of total testosterone (TT), DHEAS, and IGF1 were measured using immunoassays (Diagnostic Products Corp, San Francisco, CA), and expressed in ng/mL. The inter- and intra-assay variability coefficients were: DHEAS 12.0% and 6.8%, TT 9.8% and 7.4%, and IGF1 6.2% and 3.1%, respectively.

To estimate the circulating fraction of free testosterone, which may express more accurately the biological activity of circulating testosterone[13,14] in all subjects, serum level of sex hormone−binding globulin (SHBG) was measured using an immunoassay (Diagnostic Products Corp), and SHBG was expressed in nmol/L (the inter- and intra-assay variability coefficients were 5.2% and 3.0%, respectively). The serum level of estimated free testosterone (eFT) was calculated from TT and SHBG levels using the validated equation of Vermeulen et al.[14]

Table 1. Baseline Characteristics of Examined Men with CHF

Variables	Men with CHF (n = 205)
Age, years	60 ± 11
NYHA Class, I/II/III/IV, n (%)	37/95/65/8 (18/46/32/4)
Ischemic CHF etiology, n (%)	145 (71)
LVEF, %	31 ± 8
Plasma NT-proBNP, pg/mL	2890 ± 3572
Hemoglobin level, g/dL	14.3 ± 1.5
eGFR, mL·min·1.73m^2	72.8 ± 20.3
Diabetes mellitus, n (%)	59 (29)
Treatment:	
ACE inhibitors/ARB, n (%)	195 (95)
β-blocker, n (%)	183 (89)
Digoxin, n (%)	58 (28)
Diuretics, n (%)	168 (82)
Statin, n (%)	152 (74)
ASA, n (%)	109 (53)
Serum TT, ng/mL	4.55 ± 1.67
Serum eFT, pg/mL	91 ± 43
Serum DHEAS, ng/mL	884 ± 772
Serum IGF1, ng/mL	133.5 ± 65.6
Peak VO_2, mL·min·kg	15.6 ± 4.2
Peak VO_2, % of predicted values	53 ± 14
Peak O_2 pulse, mL/beat	11.2 ± 3.6
VE-VCO_2 slope	37.6 ± 10.6

CHF, chronic heart failure; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; eGFR, estimated glomerular filtration rate; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ASA, acetylsalicylic acid; TT, total testosterone; eFT, estimated free testosterone; DHEAS, dehydroepiandrosterone sulfate; IGF1, insulin-like growth factor 1; VO_2, minute oxygen consumption; VCO_2, minute carbon dioxide production; VE, minute ventilation. Values are presented as mean ± SD, or n (%) where appropriate.

Plasma levels of NT-proBNP (N-terminal-pro-brain natriuretic peptide, pg/mL) were measured using immunoassay based on electrochemiluminescence on the Elecsys 1010/2010 System (Roche Diagnostics GmbH, Mannheim, Germany).

Renal function was assessed using the estimated glomerular filtration rate (eGFR, mL·min·1.73 m^2), calculated from the Modification of Diet in Renal Disease equations.[15]

Cardiopulmonary Exercise Testing

After a period of 5-minute rest, all patients underwent a symptom-limited treadmill exercise test (modified Bruce's protocol) with respiratory gas exchange analysis. Minute ventilation (VE), oxygen consumption (VO_2), and carbon dioxide production (VCO_2) were assessed every 10 seconds (BREEZE EX, Cardiorespiratory Diagnostic Software 1991-1996, Medical Graphics, USA). Peak oxygen consumption (peak VO_2) was measured as an average of the last 30 seconds of exercise, and was expressed in mL·min·kg and as a percentage of predicted values of age- and weight-matched healthy men. Peak O_2 pulse was calculated as the ratio of peak VO_2 and peak heart rate, and was expressed in mL/beat. Ventilatory response to exercise (expressed as a VE-VCO_2 slope) was calculated as the regression slope relating VE to CO_2 during the whole exercise).[16,17] Percentage of age-, sex-, and