Anabolic Status and Functional Impairment in Men With Mild Chronic Heart Failure

Francisco J. Pastor-Pérez, MD[a,*], Sergio Manzano-Fernández, MD, PhD[a], Iris P. Garrido Bravo, MD[a], Francisco Nicolás, MD[b], Pedro L. Tornel, MD, PhD[b], Antonio Lax, PhD[b], Gonzalo de la Morena, MD, PhD[a], Mariano Valdés, MD, PhD[a], and Domingo A. Pascual-Figal, MD, PhD[a]

The purpose of this study was to establish the role of hormonal anabolic deficiencies in exercise intolerance in patients with chronic heart failure One hundred four consecutive men (mean age 53.1 ± 10.6 years) with established diagnoses of chronic heart failure were included. At enrollment, blood samples were taken, and echocardiography and cardiopulmonary exercise testing were carried out. Exercise capacity was expressed as peak oxygen consumption (Vo_2), predicted peak Vo_2, and the ventilatory response to exercise (VE/Vco_2) slope. The mean left ventricular ejection fraction was 29.7 ± 11.9%, and most patients (86%) were in New York Heart Association class I or II, with a mean peak Vo_2 of 18 ml/min/kg. According to the age-adjusted reference values, hormonal deficiencies were present in 29% for total testosterone, 39% for estimated free testosterone, 34% for insulin-like growth factor–1, and 61% for dehydroepiandrosterone sulfate. Dehydroepiandrosterone sulfate showed a significant correlation with peak Vo_2 ($r = 0.29$, $p = 0.007$), predicted peak Vo_2 ($r = 0.28$, $p = 0.006$), and VE/Vco_2 slope ($r = -0.39$, $p < 0.001$), whereas total testosterone, estimated free testosterone, and insulin-like growth factor–1 were not significantly correlated. After adjusting in a multivariable model, dehydroepiandrosterone sulfate remained an independent predictor of each exercise parameter. In conclusion, in a cohort of patients with mild chronic heart failure, exercise capacity objectively measured using cardiopulmonary exercise testing was related to anabolic impairment of the adrenal rather than the somatotropic or peripheral axis. **(Am J Cardiol 2011;108:862–866)**

Chronic heart failure (CHF) is a multiple metabolic and hormonal deficiency syndrome with anabolic-catabolic imbalance. The impairment of the 3 major anabolic axes (adrenal, gonadal, and somatotropic) is widely present in men with CHF and is associated with greater severity of symptoms, and more important, it represents a powerful predictor of poor outcome.[1] Functional impairment is a hallmark in the severity of heart failure and has long been recognized as a prognostic marker of the disease. Cardiopulmonary exercise testing has become an important clinical tool to objectively evaluate exercise capacity and predict outcomes in patients with CHF.[2] Recently, Jankowska et al[3] demonstrated that the gonadal axis, reflected by a reduction of circulating testosterone, is related to cardiopulmonary exercise capacity in men with CHF. However, these findings have not been widely confirmed in other studies. Therefore, we aimed to establish the clinical determinants and hormonal anabolic deficiencies that could explain exercise intolerance in a cohort of patients with CHF.

Methods

The study group consisted of 104 consecutive patients with established diagnoses of CHF[4] who were followed up in an outpatient specialized clinic. The selection criteria were a left ventricular ejection fraction (LVEF) <40%, clinically stable condition (defined as the absence of hospitalization or signs of acute cardiac decompensation in the previous 4 weeks), and optimized medical therapy for CHF, which were all unchanged for ≥4 weeks (100% angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, 100% β blockers, 84% loop diuretics, 58% digoxin, 55% spironolactone). For each patient, all procedures of the study were performed in the same morning. Blood samples were taken after a fasting period of ≥12 hours and a rest period of 20 minutes. We prospectively recorded all clinical variables, and transthoracic echocardiography (Sonos 5500; Philips Medical Systems, Andover, Massachusetts) was carried out. The LVEF was calculated using the modified Simpson's rule using second-harmonic imaging. Finally, symptom-limited cardiopulmonary exercise testing was performed. The study protocol was approved by the local ethics committee, and informed consent was obtained from each patient.

[a]Heart Failure Unit, Cardiology Department, and [b]Biochemistry Department, University Hospital Virgen de la Arrixaca, University of Murcia, Murcia, Spain. Manuscript received March 23, 2011; revised manuscript received and accepted May 6, 2011.

This study was supported in part by Grant-2007 from Fundación Seneca – Agencia de Ciencia y Tecnología de la Region de Murcia (Proyecto 05822/PPC/07) and by the national network of investigation in heart failure "REDINSCOR," Ministerio de Sanidad y Consumo (exp. RD06/0003/0013).

*Corresponding author: Tel: 34-968-369445; fax: 34-968-369662.

E-mail address: franpastor79@hotmail.com (F.J. Pastor-Pérez).

All patients underwent symptom-limited cardiopulmonary exercise testing using the modified Bruce protocol on a Marquette treadmill (GE Medical Systems, Milwaukee, Wisconsin). Pulmonary gas exchange and ventilatory variables were obtained from calibrated signals derived from rapidly responding gas analyzers and a pneumotachograph (CPX System; Medical Graphics Corporation, St. Paul, Minnesota) with the assessment of minute ventilation (VE), oxygen consumption (V_{O_2}), and carbon dioxide production (V_{CO_2}) every 10 seconds using a mass spectrometer (Amis 2000, MedGraphics Cardio2 System; Innovision A/S, Odense, Denmark). Patients were encouraged to exercise to exhaustion, and all patients reached the anaerobic threshold and a respiratory ratio (V_{CO_2}/V_{O_2}) >1.05. Continuous 12-lead electrocardiographic monitoring was used. Blood pressure was recorded every minute using a sphygmomanometer cuff. All participants stopped exercise because of breathlessness and/or fatigue. None experienced chest pain or developed ST-segment deviation. Peak V_{O_2} was established as the highest value in the terminal phase of exercise. Peak V_{O_2} was expressed in milliliters per kilogram per minute and also as a percentage of the normal predicted peak V_{O_2}. Predicted peak V_{O_2} was calculated on the basis of gender, age, and weight using the formulas proposed by Oudiz et al.[5] The slope of the relation between VE and V_{CO_2} (VE/V_{CO_2}) was calculated as the ventilatory response to exercise.[6] Platelet-poor plasma and serum fraction were obtained by centrifugation at 2,200g for 20 minutes. Aliquots were stored at −80°C for bath analysis. Total testosterone (TT) was measured using electrochemiluminescence immunoassay kits in a Modular Analytics E 170 module (Roche Diagnostics GmbH, Mannheim, Germany) (range 0.02 to 15.0 ng/ml). Estimated free testosterone (eFT) was calculated using the equation of Vermeulen et al,[7] taking into account TT, albumin, and sex hormone–binding globulin. Sex hormone–binding globulin was measured using immunoradiometric assay kits (Orion Diagnostica, Espoo, Finland) in an LKB luminometer (Wallac, Turku, Finland) (range 6.25 to 200 nmol/L). Dehydroepiandrosterone sulfate (DHEA-S) was determined by immunometric assay (Immunotech, Marseille, France) in an LKB luminometer (range 0 to 1,000 μg/100 ml). Insulin-like growth factor–1 (IGF-I) was determined using immunoradiometric assay kits (Immunotech) in an LKB luminometer (range 0 to 1,200 ng/ml). N-terminal pro–B-type natriuretic peptide (NT–pro-BNP) was measured using electrochemiluminescence immunoassay using a Modular Analytics E 170 module (range 5 to 35,000 pg/ml). C-reactive protein was measured using immunoturbidimetric assay in a Modular P 800 analyzer (Roche Diagnostics GmbH) (range 0.1 to 25.8 mg/dl). For each hormone, the presence of hormone deficiency was defined using the normal limit for the gender- and age-adjusted value provided by the manufacturer. The estimated glomerular filtration rate was calculated using the simplified Modification of Diet in Renal Disease (MDRD) equation ($186.3 \times$ plasma creatinine $- 1.154 \times$ age $- 0.203$; the correction factor for women was 0.742).[8]

Continuous variables were tested for a normal distribution using the Kolmogorov-Smirnov test. Normally distributed data are presented as mean ± SD and non-normally distributed variables as medians with interquartile ranges; the latter were log transformed, which made it possible to normalize their distribution for statistical analysis. Categorical variables are expressed as percentages. Single-predictor and multivariate regression analysis were applied to establish variables determining hormone levels, peak V_{O_2}, predicted peak V_{O_2}, and VE/V_{CO_2} slope. In the single-predictor

Table 1
Baseline characteristics of patients (n = 104)

Variable	Value
Age (years)	53.1 ± 10.6
Body mass index (kg/m^2)	27.6 ± 3.9
Nonischemic cause	86 (83%)
Ischemic cause	18 (17%)
CHF duration (months)	53 (18–97)
New York Heart Association class	2.0 ± 0.6
I	14
II	72
III	14
IV	0
Sinus rhythm	79 (77%)
Bundle branch block	51 (49%)
Echocardiography	
LVEF (%)	29.7 ± 11.9
Left atria (mm)	47.8 ± 9.5
Left ventricular end-diastolic volume (ml)	206 (65–284)
Left ventricular end-diastolic diameter (mm)	65.5 (58–71)
Biochemistry	
Estimated glomerular filtration rate (ml/min/1.73 m^2)	72.6 ± 24.8
Hemoglobin (g/dl)	14.8 ± 3.3
Sodium (mg/dl)	139 ± 3.4
Potassium (mg/dl)	4.7 ± 0.5
NT–pro-BNP (pg/ml)	668 (183–1,745)
Uric acid (mg/dl)	7.1 ± 2.0
Total cholesterol (mg/dl)	184 ± 40
C-reactive protein (mg/dl)	0.30 (0.10–0.50)
Cardiopulmonary exercise test	
Peak V_{O_2} (ml/min/kg)	18.6 ± 5.1
Predicted peak V_{O_2} (%)	55.3 ± 15.0
VE/V_{CO_2}	33 (30–37)

Data are expressed as mean ± SD, as median (interquartile range), or as number (percentage).

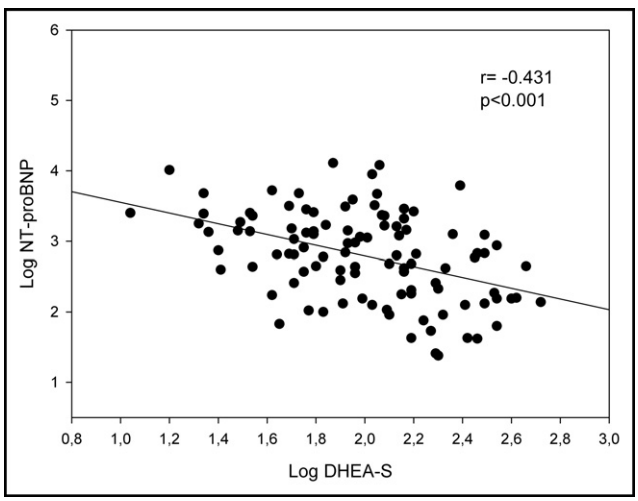

Figure 1. Scatterplot of the levels of NT–pro-BNP versus DHEA-S.

Table 2
Associations between clinical and hormonal variables and exercise parameters (single-predictor models)

Determinant	Peak Vo_2		Peak Vo_2 Predicted		VE/Vco_2 Slope	
	r	p Value	r	p Value	r	p Value
Age	−0.50	<0.001	—	—	0.31	0.007
Body mass index	−0.27	0.011	0.07	0.535	−0.15	0.186
LVEF	0.01	0.365	0.26	0.015	−0.25	0.034
CHF duration	−0.15	0.193	−0.43	<0.001	0.39	0.01
Log_{10}(NT–pro-BNP)	−0.27	0.010	0.42	<0.001	0.43	<0.001
Log_{10}(hemoglobin)	0.18	0.100	0.29	0.012	−0.14	0.223
Estimated glomerular filtration rate	0.27	0.014	0.24	0.029	−0.16	0.179
Uric acid	−0.26	0.017	−0.17	0.139	0.35	0.003
Diabetes mellitus	$t = -0.17$	0.125	$t = -0.10$	0.373	$t = 0.29$	0.010
TT	0.06	0.572	0.05	0.652	0.11	0.350
Log_{10}(eFT)	0.07	0.514	0.09	0.425	0.10	0.938
Log_{10}(DHEA-S)	0.29	0.007	0.29	0.008	−0.39	<0.001
IGF-1	−0.03	0.852	−0.15	0.300	−0.04	0.817
Sex hormone–binding globulin	0.03	0.793	−0.03	0.763	−0.05	0.639

Table 3
Associations between clinical and hormonal variables and exercise parameters (multivariate model)

Variable	Peak Vo_2		Peak Vo_2 Predicted		VE/Vco_2 Slope	
	β	p Value	β	p Value	β	p Value
Age	−0.24	0.002	—	—	0.15	0.161
Body mass index	−0.43	<0.001	—	—	—	—
LVEF	—	—	0.04	0.704	−0.08	0.490
CHF duration	—	—	−0.27	0.019	0.08	0.486
Log_{10}(NT–pro-BNP)	−0.21	0.046	−0.30	0.033	0.26	0.034
Log_{10}(hemoglobin)	0.20	0.027	0.39	<0.001	—	—
Estimated glomerular filtration rate	0.06	0.566	0.22	0.045	—	—
Uric acid	−0.08	0.426	—	—	0.23	0.041
Diabetes mellitus	—	—	—	—	0.12	0.263
Log_{10}(DHEA-S)	0.27	0.009	0.22	0.051	−0.25	0.039
Corrected r^2	0.45		0.40		0.39	

analysis, we included clinical parameters (age, body mass index, LVEF, and CHF duration), major co-morbidities (renal function assessed by the estimated glomerular filtration rate, anemia assessed by hemoglobin level, and the presence of diabetes mellitus), and serum levels of uric acid, C-reactive protein, and NT–pro-BNP. We also included sex hormone–binding globulin and anabolic hormones (TT, eFT, DHEA-S, and IGF-1) to determine cardiopulmonary exercise test parameters. During the construction of multivariate models, we included all the variables that had been shown to be significant determinants in single-predictor models. Forward and backward stepwise multivariate analysis was applied, with $p = 0.10$ for the inclusion and exclusion of variables in the model. A p value <0.05 was considered statistically significant. The statistical analysis was performed using SPSS version 15.0 for Windows (SPSS, Inc., Chicago, Illinois).

Results

A total of 104 men with CHF were included in this study. Table 1 lists the clinical characteristics and the nonhormonal laboratory parameters. Anabolic hormonal levels were as follows: TT 4.35 ± 2.54 ng/ml, eFT 75.2 pg/ml (interquartile range 52.0 to 101.3), DHEA-S 1,045 ng/ml (interquartile range 560 to 1,707), and IGF-1 127.5 ± 52 ng/ml. According to the age-adjusted reference values, hormonal deficiencies were present in 29% for TT, 39% for eFT, 34% for IGF-1, and 61% for DHEA-S. At least 1 anabolic deficiency was present in 74% of patients: 39% had 1, 15% had 2, and 19% had 3 anabolic deficiencies.

DHEA-S levels were correlated inversely with age ($r = -0.37$, $p < 0.001$), CHF duration ($r = -0.26$, $p = 0.011$), NT–pro-BNP ($r = -0.43$, $p < 0.001$; Figure 1) and uric acid ($r = -0.23$, $p = 0.021$). After adjusting in a multiple linear regression analysis, only NT–pro-BNP remained an independent predictor of DHEA-S levels ($\beta = 0.30$, $p = 0.01$). TT showed negative correlations with body mass index ($r = -0.22$, $p = 0.021$) and LVEF ($r = -0.2$, $p = 0.045$) and borderline correlations with hemoglobin ($r = 0.18$, $p = 0.07$) and NT−pro-BNP ($r = 0.17$, $p = 0.08$). However, only hemoglobin ($\beta = 0.22$, $p = 0.029$) remained an independent predictor after multiple linear regression analysis. IGF-1 and eFT did not show any significant correlations with variables at baseline ($p > 0.05$ for all analyses).

In the single-predictor models (Table 2), peak Vo_2 was positively correlated with age, body mass index, NT–pro-

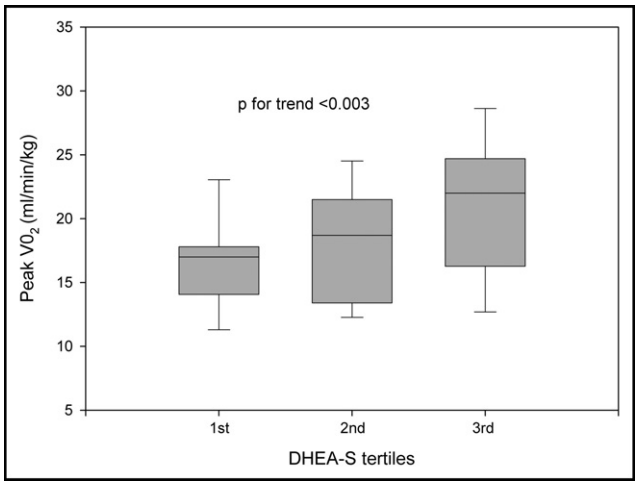

Figure 2. Box plots of peak Vo_2 across tertiles of DHEA-S.

BNP, estimated glomerular filtration rate, and uric acid. Predicted Vo_2 was correlated with LVEF, duration of CHF, NT–pro-BNP, hemoglobin, and estimated glomerular filtration rate, whereas VE/Vco_2 slope was correlated with age, LVEF, CHF duration, NT–pro-BNP, uric acid, and the presence of diabetes mellitus. Among hormonal parameters, DHEA-S showed a significant correlation with peak Vo_2 ($r = 0.29$, $p = 0.007$), predicted peak Vo_2 ($r = 0.28$, $p = 0.006$), and VE/Vco2 slope ($r = -0.39$, $p < 0.001$), but TT, eFT, and IGF-1 showed no significant correlations with any of these variables. After adjusting in the multivariate model (Table 3), DHEA-S remained an independent predictor of each exercise parameter. Significant impairment was found across tertiles of DHEA-S in terms of peak Vo_2 (Figure 2), predicted peak Vo_2, and VE/Vco_2 slope ($p < 0.003$ for all parameters), but we did not find any significant differences across tertiles of TT, eFT, and IGF-1.

Discussion

The main finding of this study is that of the 3 anabolic axes, only the suppression of the adrenal axis reflects the observed functional impairment in our population of patients with mild CHF.

Heart failure is a clinical syndrome that develops in response to an insult resulting in a decrease in the pumping capacity of the heart. This is subsequently characterized by the continuous interaction between the underlying myocardial dysfunction and the compensatory neurohumoral mechanisms and cytokine activation. The milieu of cytokines and hormones in CHF is a maladaptive response that lends to a proinflammatory state that favors catabolism.[9–11] Currently, the strategies for controlling this maladaptive response are limited to the inhibition of the renin-angiotensin-aldosterone system and sympathetic blockade, although recent data support the restoration of the anabolic-catabolic balance as a therapeutic target in CHF.[12–15]

The prevalence of anabolic hormone deficiency is variable in CHF, although most cross-sectional studies and trials report a percentage ranging from 25% to 30%.[11,12,15] Jankowska et al[16] demonstrated that multiple anabolic deficiency in gonadal (testosterone), adrenal (DHEA-S), and somatotropic (IGF-1) hormones is common in men with CHF and that it is also associated with worse survival. We also found a significant proportion of patients with hormonal deficiency, especially in the adrenal axis, affecting 61% of patients. The adrenally produced dehydroepiandrosterone and its sulfated ster are the most abundant steroid hormones found in the circulation. They are weak androgens and precursors of the more potent androgens testosterone and dihydrotestosterone, after conversion in peripheral tissues.[17] Epidemiologic studies have suggested a role for DHEA-S in cardiovascular disease. Indeed, DHEA-S deficiency is an independent risk factor of ischemic heart disease and a predictor of increased all-cause and cardiovascular mortality in a general male population.[18,19] In the setting of CHF, Anker et al[10] were the first to describe lower levels of DHEAS in CHF patients compared to control subjects. Moriyama et al[20] confirmed lower levels in 49 patients with CHF compared to 32 age-matched controls and found that DHEA-S levels were related to the severity of CHF. In line with these data, we have found similar results, with DHEA-S inversely correlated with NT–pro-BNP levels. A possible explanation for these findings was suggested by Liang et al[21] in a study in which they demonstrated that B-type natriuretic peptide opposes angiotensin II–stimulated adrenal steroidogenesis via multiple steps.

Cardiopulmonary exercise testing has become an important clinical tool for evaluating exercise capacity and predicting outcomes in patients with CHF. The limitation of exercise capacity is 1 of the cardinal manifestations of CHF, varying directly with the severity of the disease. Thus, decreased maximal exercise capacity is associated with decreased patient survival.[2] Although anabolic hormones are determinants of male exercise capacity in the general population, in men with CHF, only low circulating testosterone levels had been independently related to impaired exercise intolerance.[3] In contrast to previous data by Jankowska et al,[3] we found that DHEA-S but not testosterone level was an independent determinant of functional capacity measured by cardiopulmonary exercise test in terms of peak Vo_2, predicted Vo_2, and VE/Vco_2 slope. These apparently discordant results could be attributed to the differences between the populations studied. Indeed, our patients were younger (mean age 53 vs 60 years) and had less severity of CHF, reflected by better functional capacity (86% of patients in New York Heart Association class I or II vs 64%, peak Vo_2 18 vs 15 ml/min/kg) and lower levels of NT–pro-BNP (median 668 vs 2,890 pg/ml). Therefore, we hypothesize that at early stages of the disease, when DHEA-S levels are not severely decreased, the adrenal rather than the gonadal axis may better reflect the functional impairment associated with CHF. This is important because anabolic derangement is considered a hallmark of patients at advanced stages. Our data support that hormonal anabolic status is also affected at earlier stages, mainly reflected by a deficiency in the adrenal axis, which is a main determinant of functional impairment in patients with mild CHF.

Our study included male ambulatory patients with systolic CHF and extremely well-managed (100% β-blocker and angiotensin-converting enzyme inhibitors or angiotensin II receptor blocker use and nearly 60% aldosterone blockade) and lower risk (age, functional class, and median

NT–pro-BNP levels lower than in many reports of CHF) population. Therefore, our results could not be extrapolated to other patient profile, but they are complementary to other CHF cohorts.

1. Sacca L. Heart failure as a multiple hormonal deficiency syndrome. *Circ Heart Fail* 2009;2:151–156.
2. Albouaini K, Egred M, Alahmar A, Wright DJ. Cardiopulmonary exercise testing and its application. *Postgrad Med J* 2007;83:675–682.
3. Jankowska EA, Filippatos G, Ponikowska B, Borodulin-Nadzieja L, Anker SD, Banasiak W, Poole-Wilson PA, Ponikowski P. Reduction in circulating testosterone relates to exercise capacity in men with chronic heart failure. *J Card Fail* 2009;15:442–450.
4. Dickstein K, Cohen-Solal A, Filippatos G, McMurray JJ, Ponikowski P, Poole-Wilson PA, Stromberg A, van Veldhuisen DJ, Atar D, Hoes AW, Keren A, Mebazaa A, Nieminen M, Priori SG, Swedberg K, Vahanian A, Camm J, De CR, Dean V, Dickstein K, Filippatos G, Funck-Brentano C, Hellemans I, Kristensen SD, McGregor K, Sechtem U, Silber S, Tendera M, Widimsky P, Zamorano JL, Tendera M, Auricchio A, Bax J, Bohm M, Corra U, della BP, Elliott PM, Follath F, Gheorghiade M, Hasin Y, Hernborg A, Jaarsma T, Komajda M, Kornowski R, Piepoli M, Prendergast B, Tavazzi L, Vachiery JL, Verheugt FW, Zamorano JL, Zannad F. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). *Eur J Heart Fail* 2008;10:933–989.
5. Oudiz RJ, Barst RJ, Hansen JE, Sun XG, Garofano R, Wu X, Wasserman K. Cardiopulmonary exercise testing and six-minute walk correlations in pulmonary arterial hypertension. *Am J Cardiol* 2006; 97:123–126.
6. Chua TP, Ponikowski P, Harrington D, Anker SD, Webb-Peploe K, Clark AL, Poole-Wilson PA, Coats AJ. Clinical correlates and prognostic significance of the ventilatory response to exercise in chronic heart failure. *J Am Coll Cardiol* 1997;29:1585–1590.
7. 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;84:3666–3672.
8. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D; Modification of Diet in Renal Disease Study Group. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. *Ann Intern Med* 1999;130:461–470.
9. Agarwal M, Naghi J, Philip K, Phan A, Willix RD Jr, Schwarz ER. Growth hormone and testosterone in heart failure therapy. *Expert Opin Pharmacother* 2010;11:1835–1844.
10. Anker SD, Chua TP, Ponikowski P, Harrington D, Swan JW, Kox WJ, Poole-Wilson PA, Coats AJ. Hormonal changes and catabolic/anabolic imbalance in chronic heart failure and their importance for cardiac cachexia. *Circulation* 1997;96:526–534.
11. Kontoleon PE, Anastasiou-Nana MI, Papapetrou PD, Alexopoulos G, Ktenas V, Rapti AC, Tsagalou EP, Nanas JN. Hormonal profile in patients with congestive heart failure. *Int J Cardiol* 2003;87:179–183.
12. Caminiti G, Volterrani M, Iellamo F, Marazzi G, Massaro R, Miceli M, Mammi C, Piepoli M, Rosano M, Fini GM. 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;54:919–927.
13. Tomoda H. Effect of oxymetholone on left ventricular dimensions in heart failure secondary to idiopathic dilated cardiomyopathy or to mitral or aortic regurgitation. *Am J Cardiol* 1999;83:123–125.
14. Pugh PJ, Jones RD, West JN, Jones TH, Channer KS. Testosterone treatment for men with chronic heart failure. *Heart* 2004;90:446–447.
15. Malkin CJ, Pugh PJ, West JN, van Beek EJ, 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.
16. Jankowska EA, Biel B, Majda J, Szklarska A, Lopuszanska M, Medras M, Anker SD, Banasiak W, Poole-Wilson PA, Ponikowski P. Anabolic deficiency in men with chronic heart failure: prevalence and detrimental impact on survival. *Circulation* 2006;114:1829–1837.
17. Sanderson JT. The steroid hormone biosynthesis pathway as a target for endocrine-disrupting chemicals. *Toxicol Sci* 2006;94:3–21.
18. Barrett-Connor E, Khaw KT, Yen SS. A prospective study of dehydroepiandrosterone sulfate, mortality, and cardiovascular disease. *N Engl J Med* 1986;315:1519–1524.
19. Mitchell LE, Sprecher DL, Borecki IB, Rice T, Laskarzewski PM, Rao DC. Evidence for an association between dehydroepiandrosterone sulfate and nonfatal, premature myocardial infarction in males. *Circulation* 1994;89:89–93.
20. Moriyama Y, Yasue H, Yoshimura M, Mizuno Y, Nishiyama K, Tsunoda R, Kawano H, Kugiyama K, Ogawa H, Saito Y, Nakao K. The plasma levels of dehydroepiandrosterone sulfate are decreased in patients with chronic heart failure in proportion to the severity. *J Clin Endocrinol Metab* 2000;85:1834–1840.
21. Liang F, Kapoun AM, Lam A, Damm DL, Quan D, O'Connell M, Protter AA. B-type natriuretic peptide inhibited angiotensin II-stimulated cholesterol biosynthesis, cholesterol transfer, and steroidogenesis in primary human adrenocortical cells. *Endocrinology* 2007;148: 3722–3729.