Anabolic Deficiency in Men With Chronic Heart Failure
Prevalence and Detrimental Impact on Survival

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Background—The age-related decline of circulating anabolic hormones in men is associated with increased morbidity and mortality. We studied the prevalence and prognostic consequences of deficiencies in circulating total testosterone (TT) and free testosterone, dehydroepiandrosterone sulfate (DHEAS), and insulin-like growth factor-1 (IGF-1) in men with chronic heart failure (CHF).

Methods and Results—Serum levels of TT, DHEAS, and IGF-1 were measured with immunoassays in 208 men with CHF (median age 63 years; median left ventricular ejection fraction 33%; New York Heart Association class I/II/III/IV, 19/102/70/17) and in 366 healthy men. Serum levels of free testosterone were estimated (eFT) from levels of TT and sex hormone binding globulin. Deficiencies in DHEAS, TT, eFT, and IGF-1, defined as serum levels at or below the 10th percentile of healthy peers, were seen across all age categories in men with CHF. DHEAS, TT, and eFT were inversely related to New York Heart Association class irrespective of cause (all P<0.01). DHEAS correlated positively with left ventricular ejection fraction and inversely with N-terminal pro-brain natriuretic peptide (both P<0.01). Circulating TT, eFT, DHEAS, and IGF-1 levels were prognostic markers in multivariable models when adjusted for established prognostic factors (all P<0.05). Men with CHF and normal levels of all anabolic hormones had the best 3-year survival rate (83%, 95% CI 67% to 98%) compared with those with deficiencies in 1 (74% survival rate, 95% CI 65% to 84%), 2 (55% survival rate, 95% CI 45% to 66%), or all 3 (27% survival rate, 95% CI 5% to 49%) anabolic endocrine axes (P<0.0001).

Conclusions—In male CHF patients, anabolic hormone depletion is common, and a deficiency of each anabolic hormone is an independent marker of poor prognosis. Deficiency of >1 anabolic hormone identifies groups with a higher mortality. (Circulation. 2006;114;&NA;-.)

Key Words: heart failure ■ anabolic hormones ■ prognosis

A nabolic/catabolic imbalance, which favors catabolism, is a key pathological feature of patients with severe chronic heart failure (CHF). The imbalance is related to activation of the neuroendocrine and inflammatory systems, symptoms, exercise intolerance, and the occurrence of cardiac cachexia.1,2 Anabolic deficiency is an important component of the imbalance and has traditionally been expressed as an impairment of the GH/IGF-1 (growth hormone/insulin-like growth factor-1) axis.3–6 But anabolic impairment is a multifaceted phenomenon and is related to abnormalities in at least 3 key anabolic endocrine axes: gonadal, adrenal, and somatotropic. The clinical significance of reduced activity in multiple anabolic pathways in men with heart failure has not been established.

Clinical Perspective p ●●●

Patients with CHF develop GH resistance, which results in depletion of IGF-1 in peripheral tissues, thereby promoting skeletal muscle apoptosis.5,6 Reduced circulating IGF-1 identifies those patients in whom, despite the absence of classic markers of disease severity, detrimental changes in body composition and cytokine and neurohormonal activation are present.4 Early studies reported androgen status in a small number of patients with CHF but did not make a comparison with age-matched reference values from a healthy male population.1,2,7–9 In healthy men, such endocrine abnormalities constitute a crucial element of the normal aging process, albeit with unfavorable health consequences, such as sexual dysfunction, cognitive impairment, depression, visceral obe-
sity, metabolic syndrome, and cardiovascular diseases. In the general male population, deficiencies in circulating dehydroepiandrosterone sulfate (DHEAS) and IGF-1 are related to increased risk of all-cause and cardiovascular death, and reduced IGF-1 levels promote development of heart failure in an elderly community. The purpose of the present study was to evaluate prospectively the prevalence and prognostic consequences of multiple anabolic hormone deficiencies in a cohort of unselected men with CHF.

Methods

Study Population

The study was conducted between October 2001 and November 2002 among male patients with CHF who were hospitalized or attended the outpatient clinic. The criteria for study inclusion were as follows: (1) a >6 month documented history of CHF; (2) left ventricular ejection fraction (LVEF) <45% as assessed by echocardiography; and (3) clinical stability and unchanged medications for at least 1 month preceding the study. Diagnosis of systolic CHF was based on the following criteria recommended by the European Society of Cardiology: (1) presence of CHF symptoms; (2) evidence of left ventricle systolic dysfunction (as documented by LVEF <45%); and (3) positive response to CHF-specific therapy. Exclusion criteria included (1) acute coronary syndrome or coronary revascularization within the 6 months preceding the study, (2) any acute/chronic illness that might influence hormonal metabolism, and (3) any hormonal treatment, either at the time of the study or in the past. We prospectively identified 208 patients who were suitable for the study and who agreed to participate.

The reference population consisted of 366 healthy men aged 35 to 80 years living in the same area, who were examined in the year 2000 in the Silesian Centre for Preventive Medicine (DOLMED, Wroclaw, Poland). These individuals had no history of any chronic disease and no abnormalities on physical examination. These healthy subjects were included to provide a reference for cutoffs and were not pooled with those with CHF in any formal statistical analyses.

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 Helsinki Declaration.

Serum Levels of Anabolic Hormones and Laboratory Measurements

In all patients and healthy men, 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 IGF-1 were measured with immunoassays (Diagnostic Products Corp, San Francisco, Calif) and expressed in nanograms per milliliter. The interassay and intraassay variability coefficients were 12.0% and 6.8% for DHEAS, 9.8% and 7.4% for TT, and 6.2% and 3.1% for IGF-1, respectively.

Anabolic deficiency with regard to TT (gonadal androgen deficiency), DHEAS (adrenal androgen deficiency), and IGF-1 was defined prospectively as a serum hormone level less than or equal to the 10th percentile calculated for the equivalent age categories in the cohort of healthy men, as described elsewhere. The 10th percentiles of assessed hormone levels for healthy men from the reference population in the present study aged ≥45, 46 to 55, 56 to 65, and ≥66 years, respectively, were 3.2, 3.0, 2.7, and 2.6 ng/mL for serum TT; 1411, 1048, 709, and 310 ng/mL for serum DHEAS; and 258, 227, 216, and 168 ng/mL for serum IGF-1.

To estimate a circulating fraction of free testosterone, which may express more accurately the biological activity of circulating testosterone, we also measured serum level of sex hormone binding globulin (SHBG) in all subjects using an immunoassay (Diagnostic Products Corp), and SHBG was expressed in nanomoles per liter. The interassay and intraassay variability coefficients were 5.2% and 3.0%, respectively. Serum level of estimated free testosterone (eFT) was calculated with the validated equation of Vermeulen et al.

Gonadal androgen deficiency was defined as serum eFT level less than or equal to the 10th percentile calculated for the equivalent age categories in the cohort of healthy men. The 10th percentiles of eFT for healthy men from the present reference population aged ≥45, 46 to 55, 56 to 65, and ≥66 years were 77, 64, 59, and 52 pg/mL, respectively.

Plasma levels of N-terminal pro-brain natriuretic peptide (NT-proBNP; pg/mL) were measured with immunoassay based on electrochemiluminescence on the Elecsys 1010/2010 System (Roche Diagnostics GmbH, Mannheim, Germany). In our laboratory, the upper limit of normal values of plasma NT-proBNP for male subjects was 125 pg/mL. Renal function was assessed with the estimated glomerular filtration rate (GFR; mL · min⁻¹ · 1.73 m²), calculated from the Cockcroft-Gault formula.

Clinical Follow-Up

Patients were seen regularly by the study investigators in the outpatient CHF clinic, with a follow-up duration of at least 3 years. Information regarding survival (as of November 30, 2005) was obtained directly from patients or their relatives, from the CHF clinic database, or from the hospital system. No patient was lost to follow-up. The primary end point for the analysis was all-cause mortality.

Statistical Analysis

Most variables had a skewed distribution and were expressed as medians with lower and upper quartiles. The intergroup differences were tested with the Mann-Whitney U test, the χ² test, or the Kruskal-Wallis ANOVA where appropriate. Correlations between variables were assessed with Spearman rank test (r).

The associations between analyzed variables and survival were assessed by Cox proportional hazards analysis (both single-predictor and multivariable models). In the single-predictor analyses, we included clinical parameters (age; New York Heart Association [NYHA] class; LVEF; plasma NT-proBNP; CHF origin; major comorbidities, ie, renal dysfunction, assessed with GFR, or anemia, assessed with hemoglobin level; and presence of diabetes mellitus) and serum levels of anabolic hormones (TT, DHEAS, IGF-1, and eFT). We also considered a number of anabolic deficiencies as a separate categorical variable to express information about the magnitude of anabolic deficiency within all 3 endocrine axes (ranging from 0 = no deficiency to 3 = deficiency in all 3 axes). During the construction of multivariable models, we included all variables that had been shown to be significant predictors of survival in single-predictor regression models. Forward and backward stepwise multivariable analyses were applied with P=0.20 used for both inclusion and exclusion of variables into the model. The assumptions of proportional hazard were tested for all the covariates.

To estimate the effect of severity of anabolic deficiency (expressed as the number of reduced anabolic hormones) on 3-year mortality rates, Kaplan-Meier curves for cumulative survival were constructed for CHF men with no anabolic deficiency or deficiency in 1, 2, or all 3 anabolic axes, respectively. Differences in survival rates were tested with the Cox-Mantel log-rank test. A value of P<0.05 was considered statistically significant. Statistical analyses were performed with StatView 5.0 for Windows (Abacus Concepts, Berkley, Calif) and Stata 9.1 (College Station, Tex).

The authors had full access to the data and take full responsibility for their integrity. All authors have read and agreed to the manuscript as written.

Results

Prevalence of Anabolic Deficiency in Men With CHF

The baseline clinical characteristics of 208 white men with CHF are given in Table 1. The reference group consisted of 366 healthy men. Median age of the reference male population was 51 (44 to 58) years, and median body mass index...
was 26.9 (24.9 to 29.3) kg/m² (median with lower and upper quartiles; P<0.0001 and P>0.2, respectively, compared with a group of men with CHF).

Reduced circulating levels of DHEAS and IGF-1 were consistently seen across all age categories, whereas both eFT and TT levels were reduced in men with CHF aged ≤45 years and those aged ≥66 years (Table 2). When we applied prospectively established criteria, the prevalence of anabolic deficiencies in men with CHF differed across age categories. Deficiency in circulating testosterone was most frequent in the youngest and oldest groups of men with CHF, when assessed with both TT (39% and 27%, respectively) and eFT (62% and 36%, respectively), whereas marked deficiencies in DHEAS and IGF-1 were present in all age groups among men with CHF (Table 2). Figure 1 presents serum levels of anabolic hormones of all individual men with CHF compared with normal values (10th, 33rd, 50th, 66th, and 90th percentiles) of healthy men in the corresponding age categories.

Among men with CHF, deficiencies in none, 1, 2, and 3 main anabolic axes were found in 23 (11%), 85 (41%), 85 (41%), and 15 (7%), respectively. In men with CHF, serum TT weakly correlated with serum DHEAS (r=0.14, P<0.05), whereas serum IGF-1 was related neither to DHEAS nor to TT (both P>0.2). Serum eFT correlated with DHEAS (r=0.22, P<0.01), IGF-1 (r=0.28, P<0.0001), and TT (r=0.78, P<0.0001). In healthy men, serum IGF-1 correlated with serum DHEAS (r=0.24, P<0.0001), whereas serum TT was related neither to DHEAS nor to IGF-1 (both P>0.2). Serum eFT was related to DHEAS (r=0.24, P<0.0001), IGF-1 (r=0.11, P<0.05), and TT (r=0.77, P<0.0001). Age was inversely related to DHEAS (r=−0.30, P<0.0001, and r=−0.60, P<0.0001, respectively, for men with CHF and healthy peers), IGF-1 (r=−0.18, P<0.01, and r=−0.38, P<0.0001), TT (r=−0.20, P<0.01, and r=−0.10, P=0.07), and eFT (r=−0.28, P<0.0001, and r=−0.35, P<0.0001).

### Table 1: Baseline Characteristics of Men With CHF

<table>
<thead>
<tr>
<th>Variables</th>
<th>Men With CHF (n=208)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>63 (54–71)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>26.5 (23.8–29.6)</td>
</tr>
<tr>
<td>Ischemic CHF cause, n (%)</td>
<td>169 (81)</td>
</tr>
<tr>
<td>NYHA class I/II/III/IV, n (%)</td>
<td>19/102/70/17 (9/49/34/8)</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>33 (28–38)</td>
</tr>
<tr>
<td>Plasma NT-proBNP, pg/mL</td>
<td>1824 (729–4216)</td>
</tr>
<tr>
<td>GFR, mL · min⁻¹ · 1.73 m⁻²</td>
<td>52.4 (42.7–65.6)</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>58 (28)</td>
</tr>
<tr>
<td>Treatment, n (%)</td>
<td>202 (97)</td>
</tr>
<tr>
<td>ACE inhibitors or ARB</td>
<td>181 (87)</td>
</tr>
<tr>
<td>β-Blockers</td>
<td>166 (80)</td>
</tr>
<tr>
<td>Diuretics</td>
<td>50 (24)</td>
</tr>
<tr>
<td>Digoxin</td>
<td>166 (80)</td>
</tr>
<tr>
<td>Acetylsalicylic acid</td>
<td>129 (62)</td>
</tr>
</tbody>
</table>

BMI indicates body mass index; ACE, angiotensin-converting enzyme; and ARB, angiotensin receptor blockers.
Values are presented as medians (with lower and upper quartiles) or n (%) where appropriate.

### Table 2: Serum Levels of Anabolic Hormones and the Prevalence of Anabolic Deficiencies in Men With CHF and Healthy Male Subjects in Equivalent Age Categories

<table>
<thead>
<tr>
<th>Healthy male subjects, n</th>
<th>Men Aged ≤45 y</th>
<th>Men Aged 46–55 y</th>
<th>Men Aged 56–65 y</th>
<th>Men Aged ≥66 y</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum TT level, ng/mL</td>
<td>4.30 (3.60–5.10)</td>
<td>4.20 (3.30–5.00)</td>
<td>4.10 (3.30–5.10)</td>
<td>4.10 (3.10–5.80)</td>
</tr>
<tr>
<td>Serum eFT level, pg/mL</td>
<td>103 (86–119)</td>
<td>90 (76–109)</td>
<td>81 (69–101)</td>
<td>81 (63–99)</td>
</tr>
<tr>
<td>Serum DHEAS level, ng/mL</td>
<td>2331 (1707–2986)</td>
<td>1625 (1188–2199)</td>
<td>991 (813–1430)</td>
<td>651 (342–1168)</td>
</tr>
<tr>
<td>Serum IGF-1 level, ng/mL</td>
<td>334 (279–383)</td>
<td>297 (256–344)</td>
<td>276 (242–321)</td>
<td>256 (182–299)</td>
</tr>
</tbody>
</table>

Men with CHF

| Serum TT level, ng/mL    | 3.60 (2.36–4.49)† | 4.35 (3.57–5.27) | 4.42 (3.31–5.53) | 3.59 (2.56–4.55)‡ |
| Prevalence of TT deficiency, % | 39†               | 17               | 13               | 27†             |
| Serum eFT level, pg/mL   | 72 (64–108)‡      | 90 (68–126)      | 92 (67–125)      | 67 (45–91)‡     |
| Prevalence of eFT deficiency, % | 62*               | 22‡              | 17               | 36‡             |
| Serum DHEAS level, ng/mL | 1000 (553–1850)*  | 723 (398–1210)*  | 420 (308–670)*   | 328 (183–845)*  |
| Prevalence of DHEAS deficiency, % | 62*               | 63*              | 78*              | 44‡             |
| Serum IGF-1 level, ng/mL | 204 (187–213)*    | 193 (158–211)*   | 185 (165–211)*   | 173 (126–204)*  |
| Prevalence of IGF-1 deficiency, % | 92*              | 80*              | 78*              | 43†             |

Results are presented as median (with upper and lower quartiles) or % where appropriate.

*P<0.0001, †P<0.01, ‡P<0.05, men with CHF vs healthy male subjects in the same age categories.
between male CHF patients with ischemic origins and those with nonischemic origins of CHF (all \(P < 0.2\)).

LVEF correlated positively with DHEAS (\(r = 0.18, P = 0.01\)) but not with TT, eFT, or IGF-1 (all \(P > 0.2\)). There was an inverse correlation between elevated plasma NT-proBNP level and reduced DHEAS (\(r = -0.19, P < 0.01\)), with no relationships with TT, eFT, or IGF-1 (all \(P > 0.2\)). Circulating levels of all hormones correlated with renal function expressed as GFR (TT \(r = 0.18, P < 0.01\); eFT \(r = 0.17, P < 0.05\); DHEAS \(r = 0.23, P < 0.001\); and IGF-1 \(r = 0.24, P < 0.001\)). In men with CHF, body mass index was not related to any anabolic hormone level (all \(r < 0.1, P > 0.2\)).

**Anabolic Deficiency and Prognosis in Men With CHF**

At the end of follow-up (mean follow-up duration 930±434 days; median 1144 days, limits 12 to 1370 days; >3 years in all who survived), there were 75 deaths (36%). All deaths were cardiovascular. The cumulative survival of all patients was 83%, 72%, and 64% at 1, 2, and 3 years, respectively. The proportionality assumption and the assumption of a log-linear relationship between the prognosticators and the hazard function were fulfilled for all tested variables.

**Single-Predictor Analyses**

In single-predictor Cox proportional hazards models, the following variables were related to increased mortality in men with CHF: age (per 1 year: hazard ratio [HR] = 1.04, 95% CI 1.01 to 1.06, \(P = 0.002\)), NYHA class (per NYHA class, with NYHA I as a reference group: HR = 2.83, 95% CI 2.08 to 3.85, \(P < 0.0001\)), LVEF (per 1%: HR = 0.92, 95% CI 0.89 to 0.95, \(P < 0.0001\)), plasma NT-proBNP (per 500 pg/mL: HR = 1.05, 95% CI 1.03 to 1.06, \(P < 0.0001\)), GFR (per 5 mL·min\(^{-1}·1.73\)m\(^2\): HR = 0.83, 95% CI 0.77 to 0.90, \(P < 0.0001\)), and hemoglobin level (per 1 g/dL: HR = 0.81, 95% CI 0.71 to 0.92, \(P = 0.001\)) but neither the cause of CHF nor the presence of diabetes mellitus (both \(P > 0.2\); Table 3).

In single-predictor analyses, reduced serum levels of TT, eFT, DHEAS, and IGF-1 were predictors of poor outcome in men with CHF (TT [per 1 ng/mL]: HR = 0.72, 95% CI 0.62 to 0.84, \(P < 0.0001\); eFT [per 10 pg/mL]: HR = 0.89, 95% CI 0.84 to 0.95, \(P = 0.0002\); DHEAS [per 100 ng/mL]: HR = 0.87, 95% CI 0.81 to 0.93, \(P < 0.0001\); and IGF-1 [per 10 ng/mL]: HR = 0.94, 95% CI 0.90 to 0.98, \(P = 0.002\)). In addition, a number of anabolic deficiencies predicted survival (per each additional deficiency: HR = 1.73, 95% CI 1.31 to 2.27, \(P = 0.0001\); Table 3).

**Multivariable Analyses**

In trivariable models, reduced serum levels of TT, DHEAS, and IGF-1 were predictors of poor outcome in men with CHF (TT [per 1 ng/mL]: HR = 0.75,
95% CI 0.65 to 0.86, P<0.0001; DHEAS [per 100 ng/mL]: HR=0.88, 95% CI 0.83 to 0.94, P=0.0001; and IGF-1 [per 10 ng/mL]: HR=0.94, 95% CI 0.90 to 0.98, P=0.005; χ² of the trivariable model=41.32, P<0.0001). Similar results were obtained when in an analogous trivariable model, serum TT was replaced by serum eFT (eFT [per 10 pg/mL]: HR=0.92, 95% CI 0.87 to 0.97, P=0.004; DHEAS [per 100 ng/mL]: HR=0.88, 95% CI 0.83 to 0.94, P=0.0001; and IGF-1 [per 10 ng/mL]: HR=0.96, 95% CI 0.92 to 1.00, P=0.08; χ² of the trivariable model=32.38, P<0.0001).

In multivariable models of Cox proportional hazard, we included all variables that were significantly related to sur-

**TABLE 3. Single-Predictor Models of Cox Proportional Hazard Analyses in Men With CHF**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Units</th>
<th>HR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>y</td>
<td>1.04</td>
<td>1.01–1.06</td>
<td>0.002</td>
</tr>
<tr>
<td>NYHA class</td>
<td>I/II/III/IV</td>
<td>2.83</td>
<td>2.08–3.85</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CHF origin</td>
<td>CAD/non-CAD</td>
<td>1.40</td>
<td>0.73–2.65</td>
<td>0.31</td>
</tr>
<tr>
<td>LVEF</td>
<td>1%</td>
<td>0.92</td>
<td>0.89–0.95</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Plasma NT-proBNP</td>
<td>500 pg/mL</td>
<td>1.05</td>
<td>1.03–1.06</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>GFR</td>
<td>5 mL · min⁻¹ · 1.73 m⁻²</td>
<td>0.83</td>
<td>0.77–0.90</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>g/dL</td>
<td>0.81</td>
<td>0.71–0.92</td>
<td>0.001</td>
</tr>
<tr>
<td>Presence of diabetes mellitus</td>
<td>Yes/no</td>
<td>1.03</td>
<td>0.62–1.70</td>
<td>0.91</td>
</tr>
<tr>
<td>Serum TT</td>
<td>1 ng/mL</td>
<td>0.72</td>
<td>0.62–0.84</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Serum eFT</td>
<td>10 pg/mL</td>
<td>0.89</td>
<td>0.84–0.95</td>
<td>0.0002</td>
</tr>
<tr>
<td>Serum DHEAS</td>
<td>100 ng/mL</td>
<td>0.87</td>
<td>0.81–0.93</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Serum IGF-1</td>
<td>10 ng/mL</td>
<td>0.94</td>
<td>0.90–0.98</td>
<td>0.002</td>
</tr>
<tr>
<td>No. of anabolic deficiencies</td>
<td>0/1/2/3</td>
<td>1.73</td>
<td>1.31–2.27</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

CAD indicates coronary artery disease.
vival in single-predictor analyses. In the stepwise analyses, both when forward and backward approaches were applied, the final model consisted of 7 significant independent predictors (listed in order of decreasing predictive power), namely: LVEF (per 1%: HR = 0.95, 95% CI 0.92 to 0.99, P = 0.007), plasma NT-proBNP (per 500 pg/mL: HR = 1.03, 95% CI 1.01 to 1.04, P = 0.008), NYHA class (per NYHA class, with NYHA I as a reference group: HR = 1.60, 95% CI 1.11 to 2.33, P = 0.01), GFR (per 5 mL · min⁻¹ · 1.73 m⁻²: HR = 0.91, 95% CI 0.84 to 0.98, P = 0.02), serum DHEAS (per 100 ng/mL: HR = 0.92, 95% CI 0.87 to 0.99, P = 0.02), serum TT (per 1 ng/mL: HR = 0.84, 95% CI 0.72 to 0.97, P = 0.02), and serum IGF-1 (per 10 ng/mL: HR = 0.95, 95% CI 0.91 to 0.99, P = 0.03; χ² of the 7-variable model = 90.74, P < 0.0001; Table 4). Similar results were obtained when, during a construction of the best-fitted multivariable model, serum TT was replaced by serum eFT. Similar to serum TT, in a multivariable model, serum eFT remained an independent predictor of survival (per 10 pg/mL: HR = 0.94, 95% CI 0.89 to 0.99, P = 0.01).

**Graded Relation Between Severity of Anabolic Deficiency and Survival**

There was a relationship between deficiencies of multiple anabolic hormones and mortality in men with CHF (χ² = 26.12, P < 0.0001). Men with CHF and normal circulating levels of all anabolic hormones had the best 3-year survival rate (83%, 95% CI 67% to 98%) compared with those with deficiencies in 1 (74%, 95% CI 65% to 84%), 2 (55%, 95% CI 45% to 66%), or 3 (27%, 95% CI 5% to 49%) anabolic endocrine axes (Figure 3).

**Discussion**

The present study presents 2 major findings. In an unselected cohort of men with CHF, we have demonstrated a high prevalence of reduced serum concentrations of anabolic hormones. The 3 hormones studied reflect the major anabolic endocrine axes, namely, gonadal, adrenal, and somatotropic. We have also found that reduced levels of multiple serum anabolic hormones (TT, DHEAS, and IGF-1) constitute strong markers of a poor prognosis independent of conventional risk predictors.

Published data on anabolic status in male patients with CHF, assessed on the basis of serum concentrations of TT, DHEA, or IGF-1, are sparse and equivocal. Some reports have shown deficiencies of testosterone, DHEAS, and IGF-1, whereas others have not. We have found marked endocrine deficiencies in all 3 main anabolic hormonal axes reflected in measurements of serum concentrations of TT, DHEAS, and IGF-1. A major problem in making comparisons between studies is the definition of hormonal deficiency. We prospectively defined an anabolic hormone deficiency as below or equal to the 10th percentile calculated separately for TT, DHEAS, and IGF-1 levels in age groups from a large population of 366 healthy male subjects. Because age is the major determinant of anabolic hormone levels in men, a definition of anabolic deficiency should not be based on threshold values that are constant across the entire age spectrum.

Testosterone deficiency was most evident in the youngest group of men with CHF (≤45 years old) regardless of

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**Table 4. Multivariable Stepwise Models of Cox Proportional Hazard Analyses in Men With CHF**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Units</th>
<th>HR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum TT</td>
<td>ng/mL</td>
<td>0.84</td>
<td>0.72–0.97</td>
<td>0.02</td>
</tr>
<tr>
<td>Serum DHEAS</td>
<td>ng/mL</td>
<td>0.92</td>
<td>0.87–0.99</td>
<td>0.02</td>
</tr>
<tr>
<td>Serum IGF-1</td>
<td>ng/mL</td>
<td>0.95</td>
<td>0.91–0.99</td>
<td>0.03</td>
</tr>
<tr>
<td>NYHA class</td>
<td>I/II/III/IV</td>
<td>1.60</td>
<td>1.11–2.33</td>
<td>0.01</td>
</tr>
<tr>
<td>LVEF</td>
<td>%</td>
<td>0.95</td>
<td>0.92–0.99</td>
<td>0.007</td>
</tr>
<tr>
<td>Plasma NT-proBNP</td>
<td>pg/mL</td>
<td>1.03</td>
<td>1.01–1.04</td>
<td>0.008</td>
</tr>
<tr>
<td>GFR</td>
<td>mL · min⁻¹ · 1.73 m⁻²</td>
<td>0.91</td>
<td>0.84–0.98</td>
<td>0.02</td>
</tr>
<tr>
<td>No. of anabolic deficiencies</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>year</td>
<td>1.04</td>
<td>1.01–1.07</td>
<td>0.02</td>
</tr>
<tr>
<td>NYHA class</td>
<td>I/II/III/IV</td>
<td>1.59</td>
<td>1.09–2.33</td>
<td>0.02</td>
</tr>
<tr>
<td>LVEF</td>
<td>%</td>
<td>0.94</td>
<td>0.91–0.98</td>
<td>0.002</td>
</tr>
<tr>
<td>Plasma NT-proBNP</td>
<td>pg/mL</td>
<td>1.02</td>
<td>0.99–1.04</td>
<td>0.12</td>
</tr>
<tr>
<td>GFR</td>
<td>mL · min⁻¹ · 1.73 m⁻²</td>
<td>0.93</td>
<td>0.85–1.01</td>
<td>0.09</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>g/dL</td>
<td>0.88</td>
<td>0.77–1.01</td>
<td>0.07</td>
</tr>
</tbody>
</table>
whether testosteronemia was expressed as TT or as eFT (39% or 62%, respectively, of CHF men demonstrated a testosterone level below the 10th percentile of their healthy peers). In this age group, testosterone deficiency is of particular clinical significance because androgen deficiency significantly affects patients’ quality of life. Testosterone deficiency was also found in approximately one third of men aged \( \geq 66 \) years, an age group in which heart failure is more common. Deficiencies in DHEAS and IGF-1 were present in the majority of CHF patients in all age groups \( \leq 65 \) years, with a lower prevalence in the oldest group. Endocrine activity of somatotropic and adrenal axes was deranged, predominantly in younger and middle-aged men with CHF.

Anabolic hormone deficiency in men with CHF is not a simple surrogate of disease severity. The only meaningful association was a decrease in TT, eFT, and DHEAS levels in patients with more advanced CHF symptoms, as assessed by NYHA class; however, these relationships, although statistically significant, were rather weak in magnitude. IGF-1 levels remained low regardless of NYHA class. The underlying cause of CHF did not determine anabolic status. Neither TT, eFT, nor IGF-1 levels correlated with echocardiographic (LVEF) or humoral (NT-proBNP) indices of left ventricle function. LVEF and plasma NT-proBNP were only related to circulating DHEAS levels, which confirms a previous report.\(^9\) Again, all of these correlations for DHEAS were not strong. Impaired anabolic metabolism may be a generalized phenomenon seen in the course of CHF that begins at an early stage of disease and accelerates the endocrine changes that normally occur in the course of male aging.

We have shown that the presence of multiple hormone deficiencies in men with CHF carries a worse prognosis. DHEAS deficiency is an independent risk factor of ischemic heart disease\(^{25} \) and a predictor of increased all-cause and cardiovascular mortality in a general male population.\(^{14} \) There are no data on the relationship between TT level and mortality in men. Reduced circulating IGF-1 levels are related to increased total\(^{16} \) and cardiovascular mortality in men and to an increased incidence of heart failure in community settings.\(^{17} \) In the present study, reduced levels of TT, eFT, DHEAS, and IGF-1 were related to an unfavorable outcome in men with CHF, even when adjusted for conventional clinical prognostic markers, such as plasma NT-proBNP. Additionally, we showed a progressive association between the number of impaired anabolic axes and all-cause 3-year mortality. Patients with multiple insufficiency that affected at least 2 endocrine anabolic axes had the worst survival, i.e., 3-year mortality rates of approximately 50% and 75% in those with 2 and 3 impaired anabolic axes, respectively. The present findings demonstrate the clinical utility of the evaluation of all 3 anabolic axes for the assessment of long-term prognosis in men with CHF in addition to such parameters as NYHA class, ejection fraction, NT-proBNP, and renal function.

Studies performed in groups of elderly men with testosterone or dehydroepiandrosterone deficiency suggest that pharmacological augmentation of anabolic drive can result in favorable changes in the body composition, sexual function, and psychological status of aging men.\(^{26,27} \) Recently, Malkin et al\(^{28} \) showed that a 12-month testosterone replacement therapy regimen in men with CHF was followed by improvement in NYHA class and functional capacity, as assessed by an incremental shuttle walk test. There is no evidence that gonadal or adrenal androgen supplementation can improve survival.

**Study Limitations**

The observational character of the present study needs to be acknowledged. The study was not designed to elucidate the underlying mechanisms of anabolic deficiency in CHF. The origin of the age-related decline in anabolic hormones in aging men remains uncertain.\(^{12} \) One hypothesis is that male
aging is accompanied by a steady exacerbation of inflammatory processes, with elevated circulating proinflammatory cytokines, which inhibit the secretion of sex steroids by gonadal and adrenal glands.\textsuperscript{29,30} Reported relationships between high cytokine and reduced anabolic hormone levels\textsuperscript{1,4} might suggest the existence of an analogous phenomenon in CHF. It is presumed that reduced DHEA secretion in CHF, at least, may be due to insulin resistance and hyperinsulinemia, because it is a frequent metabolic derangement found in CHF patients.\textsuperscript{31} Insulin is a physiological inhibitor of DHEA secretion in healthy subjects.\textsuperscript{32}

The evaluation of testosterone deficiency in men with CHF was based on serum levels of TT with appropriate reference limits. This approach, although recommended for clinical practice in some guidelines,\textsuperscript{33,34} may have potential disadvantages. There is no consensus regarding which fraction of circulating testosterone should be routinely measured. Free testosterone reflects the most active fraction of circulating gonadal androgen, which reflects direct biological effects on target tissues. Nevertheless, a preferable measurement is the assessment of free testosterone by equilibrium dialysis.\textsuperscript{22,23} This technique is complex, time-consuming, and available only in specialized centers.

To overcome these problems, we measured SHBG levels in all subjects so as to be able to estimate serum levels of free testosterone using a well-established and validated equation published by Vermeulen et al and recommended for clinical use by the International Society for the Study of the Aging Male.\textsuperscript{23} We have confirmed that eFT predicted survival in CHF men in both single-predictor and multivariable models, and the replacement of TT by eFT in constructed multivariable models did not significantly influence the clinical meaning of the results.

Conclusions
The present study demonstrates that in an unselected cohort of male CHF patients, multiple anabolic deficiencies occur frequently and predict long-term outcome. Whether pharmacological correction of anabolic deficiencies might constitute a therapeutic approach in men with CHF remains a subject for further clinical investigation.

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Disclosures
None.

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**CLINICAL PERSPECTIVE**

Deficiency in anabolic hormones strongly predicts high morbidity and mortality in a general male population. In chronic heart failure (CHF), strong evidence indicates that the balance between anabolic and catabolic processes is severely disturbed, which constitutes a key pathophysiological feature of this syndrome. Until now, however, in CHF, this imbalance has been investigated only selectively in the context of augmented catabolic drive. The present study demonstrates that multiple anabolic depletion, defined as reduced serum levels of key anabolic hormones (testosterone, dehydroepiandrosterone sulfate, and insulin-like growth factor-1), identifies CHF patients with high long-term mortality. The higher the number of deficient anabolic hormones, the worse the prognosis. Further studies should elucidate the mechanisms responsible for the protective role of anabolic signaling in this group of patients. Our results constitute premises for the selective supplementation of deficient anabolic hormones, which may become a novel therapeutic approach in CHF. Its safety and effectiveness need to be verified in future clinical trials.