Testosterone deficiency in men with heart failure: pathophysiology and its clinical, prognostic and therapeutic implications

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HEART FAILURE: A CARDIOGERIATRIC SYNDROME

Heart failure (HF) is a disease syndrome characterised by large incidence and prevalence, which has been estimated in the developed countries at 5–10/1000 persons per year and 1–2%, respectively [1], with a clear rise of these indices with age [2–4]. In the British Hillingdon study [2], the incidence of HF among subjects aged 25–34 years was only 0.02/1000 persons per year, rising to 11.6/1000 persons per years among subjects aged ≥ 85 years. Similar trends were observed for the prevalence of HF which was less than 1% among subjects aged 55–64 years but exceeded 10% among subjects aged ≥ 85 years in the Rotterdam Study [4]. In the United States, HF is the major diagnostic group in hospitalised patients aged > 65 years [5, 6], and British data indicate that nearly 5% of acute admissions are related to HF [7]. Age is an adverse prognostic factor in patients with HF [1], including de novo HF [8], and in the ADHERE registry [9], acute decompensations of HF were observed mostly among the elderly. With these characteristics, HF has been considered a cardiogeriatric syndrome by some experts [10] and is major medical and socioeconomical problem in modern aging populations [11–14].

Despite recent advances in cardiac investigations and therapy, outcomes in HF continue to be unacceptably poor. According to the data from the European Society of Cardiology (ESC) HF-Pilot registry [15], annual re-hospitalisation rate and mortality among outpatients with chronic HF has been estimated at 31.9% and 7.2%, respectively. Thus, new therapeutic approaches are needed to reverse these adverse epidemiological trends. In the recent years, this search for new therapies for HF has focused on pathogenetic concepts related to non-cardiac disturbances and abnormalities in HF [16, 17]. In the current research on the pathophysiology and natural history of HF, attention has been paid to renal dysfunction [18–20], hepatic dysfunction [21, 22], immune activation [23], autonomic sympathetic/parasympathetic imbalance [24], skeletal muscle dysfunction [16, 25, 26], anaemia [27–29], iron deficiency [30–33] and insulin resistance [34]. Another important feature of the pathophysiology of HF is impaired hormone metabolism [35], with anabolic/catabolic balance shifted towards the latter [17, 36, 37]. In the most extreme form, cardiac cachexia develops which significantly worsens already poor outcomes in this patient group (18-month mortality among patients with cachexia is 50% compared to 17% in those without cachexia) [38].

In this paper, we presented the most important data on the role of testosterone in normal functioning of the cardiovascular system (CVS) and summarised pathophysiological, clinical, and prognostic implications of testosterone deficiency in men with HF, along with available data on the effects of testosterone administration in men with HF.

TESTOSTERONE FRACTIONS AND THE EFFECT OF AGING ON TESTOSTERONE SYNTHESIS

Three main anabolic axes play major physiological roles in men, including the gonadal (involved in testosterone production, mainly in the testes), adrenal (dehydroepiandrosterone...
production in the adrenal glands), and somatotropin axis (growth hormone production in the hypothalamus, and synthesis of its tissue mediators, mainly insulin-like growth factor 1 produced mostly by hepatocytes) [39–41].

Testosterone is the most important endogenous androgen and anabolic hormone in men [42, 43]. It is synthesized by the interstitial cells of Leydig (producing more than 90% of plasma testosterone) and transported in blood mostly in a protein-bound form (98%; mainly bound to sex hormone binding globulin [SHBG], and to a lesser extent to albumins) [42–46]. Only 1–2% of testosterone circulates in blood as free testosterone (FT) but this fraction exhibits the most potent biological activity [46]. However, both FT and albumin-bound testosterone are readily available for peripheral tissues, comprising so-called bioavailable testosterone (BT) fraction [46]. Testosterone and its derivative, dihydrotestosterone (DHT), which is the most biologically active androgen synthesized from testosterone by 5α-reductase, exert their effects on peripheral tissues by interacting with the androgen receptor. Some biological effects of testosterone are a result of its aromatisation to oestra diol and subsequent interaction with the oestrogen receptor [47, 48].

The preferred method for measuring total testosterone (TT) is extraction and chromatography followed by mass spectrometry, although immunoenzymatic methods, including ELISA, are routinely used [49]. The gold standard laboratory method for FT level determination is equilibrium dialysis [50, 51]. However, this method is expensive and time-consuming, which significantly reduces its routine use outside specialised laboratories [51]. Blood FT pool may also be estimated (estimated FT [eFT]) using a formula proposed by Vermeulen et al. [51], based on blood TT, SHBG, and albumin levels (a sample calculator is available online at http://www.issam.ch/freetesto.htm). Use of this formula has been approved in the current guidelines of the Endocrine Society on testosterone treatment in men with androgen deficiency, although experts have indicated that the reliability of eFT largely depends on the quality of TT and SHBG assays [52]. Of note, FT estimates have been used in large population studies on male hypogonadism [53].

For the evaluation of BT, the level of this fraction is measured by ammonium sulfate precipitation, or estimated using the formula of Vermeulen et al. [51, 52].

A gradual age-related decrease in circulating testosterone by about 1% per year begins in men in the third decade of life [46]. In the population-based Massachusetts Male Aging Study (MMAS) [54] including 1709 men (age at baseline: 40–70 years; duration of follow-up: 7–10 years), it has been shown using continuous models that TT, FT, and albumin-bound testosterone decreases with age in men by 1.6%, 2.8%, and 2.5% per year, respectively. This age-related decrease in testosterone level was significantly higher compared to that found in cross-sectional analyses (at baseline, by 0.3%, 1.0%, and 0.9% per year, respectively) [54]. The authors suggested that this may indicate an effect of other factors (e.g., coexisting diseases) on acceleration of age-related decrease in circulating testosterone level [54]. In the MMAS study [54], an increase in serum SHBG level by 1.3% per year was also noted in continuous models (a value comparable to estimates in cross-sectional analyses), which implicates a need for comprehensive evaluation of blood testosterone level in the clinical practice, i.e. taking into account its fractions and not only TT (although TT may be within normal levels, FT and BT may reduced due to age-related changes in SHBG level) [46]. In another study in 890 men, the Baltimore Longitudinal Study of Aging (BLSA) [55], an age-related decrease in TT level was also noted, along with low serum TT levels (defined as < 11.3 nmol/L) found in 12%, 19%, 28% and 49% of men aged 50–59, 60–69, 70–79 and ≥ 80 years, respectively.

DEFINITION OF TESTOSTERONE DEFICIENCY

There are controversies regarding the exact laboratory definition of testosterone deficiency in the general male population. In general, 2 methodological approaches have been used to determine the cutoff value of low TT level. Some experts believe [52, 56–58] that in all adult men regardless of age, a fixed cutoff value of decreased TT level should be determined based on, e.g., a specified percentile (2.5th, 5th, or 10th) in young healthy men. Such a definition was used in the BLSA study [55], in which hypogonadal TT level was defined in all men as < 2.5th percentile in the 21–45 years age group in the same study, i.e. < 11.3 nmol/L (to convert for ng/mL, a value in nmol/L should be divided by 3.467, which in this case gives < 3.26 ng/mL). A deficiency of FT may also be calculated using the same approach. An alternative methodological approach is based on the assumption that values defining TT and FT deficiency should be defined for specific age groups (e.g. decades) separately, e.g., as < 2.5th percentile among healthy men of the same age [59]. Undoubtedly, an advantage of the latter approach is the fact that it takes into account physiological, age-related decrease in blood testosterone level. From the clinical point of view, androgen deficiency syndrome has been defined in the current guidelines of the Endocrine Society as a constellation of specific signs and symptoms accompanied by low serum testosterone level. [52]. A detailed list of signs and symptoms suggesting androgen deficiency in men (categorised as more or less specific) has been included in these guidelines [52]. Determination of TT level is clearly indicated when more specific signs are present including abnormalities of sexual development, sexual dysfunction, gynaecomastia, small testicular size, infertility, and low-energy fractures [52]. Experts also suggest consideration of TT level measurements in patients with less specific symptoms, such as attention and sleep problems, depressive mood etc. [52]. For initial evaluation, morning TT level should be determined, with repeated measurements to confirm the diagnosis [49, 52]. According to the expert panel of the Endocrine Society, the cutoff value
for decreased TT level should be defined as the lower limit of normal values among healthy young men in a given laboratory [52]. At the same time, determination of FT and/or BT level has been recommended in the guidelines when the measured TT level is difficult to interpret (e.g., close to the lower limit of the reference range), concomitant conditions are present (e.g., obesity, diabetes, thyroid dysfunction), or the patient is treated with drugs potentially affecting SHBG level (e.g., anticonvulsants, glucocorticosteroids) [52].

**TESTOSTERONE AND THE CVS, METABOLISM AND INFLAMMATORY PROCESSES**

Testosterone, enzymes that metabolise testosterone, and androgen receptors are present in CVS structures including cardiomyocytes [60–64]. Similarly to metabolic processes that occur in testes, skin, and skeletal muscle, testosterone in the heart may also be reduced to DHT [65–67] and aromatised to oestradiol [42]. Also similarly to other tissues, both DHT and testosterone exert biological effects in cardiomyocytes through an interaction with androgen receptors [67], and testosterone-derived oestradiol through an interaction with oestrogen receptors [42]. It was shown that steroid hormones act in the CVS and nervous system not only via the classical genomic mechanism but also through interactions with cytoplasmic and membrane structures, leading to changes in the spatial configuration of membrane channels and modulation of cellular signalling [68–73]. Multiple experimental studies showed a major importance of testosterone for normal CVS functioning [74]. Changes seen in surgically or pharmacologically castrated male rodents include smaller heart mass [75], systolic and diastolic dysfunction [75, 76], changes in proportions between different types of myosin heavy chains (MHC) in cardiomyocytes, with an increase in MHC-β and a decrease in MHC-α [77], and a decrease in the amount of mRNA for androgen receptors, Na+ /Ca2+ ion channels, L type calcium channels, and β-adrenergic receptors in cardiomyocytes [78, 79]. Most aforementioned disturbances normalise following testosterone supplementation [76–79]. Testosterone also modulates electrical activity of the myocardium [80], e.g. through an effect on membrane Ca2+ and K+ channels that was shown experimentally [81–83]. This steroid also has vasodilating properties in the CVS, both in the systemic and pulmonary arterial beds [84–91].

Some evidence indicates that testosterone may prevent or reverse pathological myocardial remodelling in experimental models [92–96], although this was not confirmed by some authors [97–101]. A potential beneficial effect of testosterone on the myocardium may be related to its anti-inflammatory [102] and antioxidant [103] properties. Administration of testosterone and DHT to healthy male rats decreases interleukin-6 level in the myocardium [102], while castration reduces myocardial activity of superoxide dismutase (an important element of cellular antioxidative system [103]) and activates matrix metalloproteases [104]. In addition, a protective effect of testosterone on the myocardium was shown in an experimental model of ischaemia and reperfusion [93, 95, 96].

**TESTOSTERONE DEFICIENCY IN MEN WITH HF: PREVALENCE, PATHOMECHANISM, AND CLINICAL AND PROGNOSTIC IMPLICATIONS**

Testosterone has a major effect on the overall mental and physical well-being of men during the whole ontogenetic process [42, 43], and its deficiency is associated with a number of adverse clinical and prognostic consequences which are summarised in Figure 1. Evidence from clinical and experimental studies indicates a significant relationship between testosterone deficiency in men and incidence and/or progression of cardiovascular disease [105]. An initial report on hormonal disturbances in men with HF was published in 1979 [106]. Tappler and Katz [106] showed that low testosterone level correlated with decreased cardiac output, and digoxin treatment improved both haemodynamic parameters and circulating testosterone level. However, subsequent studies in small groups of HF patients yielded divergent results. Anker et al. [37, 107] did not confirm TT deficiency in men with HF, while Kontoleon et al. [108] showed that FT level in 23 men with dilated cardiomyopathy (mean age 51 ± 9 years) was significantly lower compared to healthy men of the same age. Interesting results were also reported by Noirhomme et al. [109] who showed that mechanical circulatory support in patients with severe HF not only improved haemodynamic parameters but also normalised blood testosterone level.

In 2006, we reported a large study on deficiencies of anabolic hormones including testosterone in an unselected group of 208 men with stable systolic HF [35]. TT and eFT levels (the latter estimated using the formula by Vermeulen et al. [51]) were compared with a reference group of 366 healthy men inhabiting the same area [35]. TT and eFT deficiency (defined as blood levels ≤ 10th percentile in a population of healthy men of the same age) was found in 39%, 17%, 13%, and 27% (TT), and 62%, 22%, 17%, and 36% (eFT) of men with HF aged ≤ 45, 46–55, 56–65, and ≥ 66 years, respectively [35]. Most recent data from our centre indicate that in a group of 382 men with systolic HF treated according to the current standards, TT and eFT deficiency (defined as blood levels ≤ 10th percentile in a population of healthy men of the same age) was found in 23% and 30% of men with HF aged < 60 years, and 23% and 34% of men aged ≥ 60 years, respectively [110]. Similar rates of testosterone deficiency in HF were reported by other authors [111]. In a group of 175 men with systolic HF aged ≥ 60 years, TT and eFT deficiency (defined as levels < 10th percentile in healthy peers) was found in 22% and 27% of patients, respectively [111]. Güder et al. [112] found TT and eFT deficiency (defined based on the lower reference limit in a local laboratory: TT — 1.8 ng/mL in the age group > 50 years and 2.6 ng/mL in
Abnormalities of the gonadal anabolic axis may be related to damage involving the central nervous system (CNS) [113–117], the anterior lobe of the hypothalamus [113–115, 118] or the Leydig cells [113, 114]. The pathogenesis of testosterone deficiency in men with HF is unclear. The mechanism of reduced secretion of this androgen in HF has been postulated to be similar to the mechanism that operates during aging. Increased systemic inflammation is believed to be the major cause of age-related impairment of gonadal steroidogenesis. Macrophages play a major role in maturation of the Leydig cells and regulation of their function [119, 120] but their activation also results in release of proinflammatory cytokines (tumour necrosis factor-α, interleukin-1) and free oxygen radicals which inhibit enzymes involved in steroidogenesis [119]. Through this mechanism, excessive macrophage activation along with local gonadal increase in inflammation leads to inhibition of androgen synthesis [119–121]. In this context, increased inflammation, which is the important pathogenic component of HF [122], may significantly contribute to gonadal dysfunction in men with this cardiac disease. It has also been believed that a common mechanism of impaired gonadal steroidogenesis in both aging and HF may be progressive insulin resistance which impairs endocrine activity of the Leydig cells [123–125]. Testosterone deficiency in HF may also be secondary to the cardiac disease. One pathogenetic theory holds that myocardial damage leads to reflex activation of inflammatory processes in the autonomic CNS centres (so-called microglial neuroinflammation) which result in impaired autonomic balance [126]. As the Leydig cells are linked to these centres via autonomic nervous fibres, inflammation in the CNS may result in impaired gonadal steroidogenesis [126]. It cannot also be excluded that testosterone deficiency in HF is related to the use of specific medications (e.g. spironolactone has an antiandrogenic effect [127]) or co-morbidities that potentially lead to secondary hypogonadism (e.g. obesity and diabetes [43]), although these hypotheses are only partially supported by our results [110].

Testosterone deficiency in men with HF is associated with a number of adverse clinical consequences that are summarised in Figure 2. Hypoestrogenaemia is also associated with the severity of cardiac disease. Low TT level was found to correlate with higher severity of HF symptoms (higher New York Heart Association [NYHA] functional class [35]) and neurohormonal activation (higher level of N-terminal pro-B type natriuretic peptide [NT-proBNP] [111]), and worse renal function (lower estimated glomerular filtration rate [35]). Associations were also shown between low eFT level and higher NYHA class [35, 112, 110], higher NT-proBNP level [111, 112], impaired renal function [35], and higher degree of inflammation (higher level of C-reactive protein [112]). However, an association between low testosterone level and long-term mortality in men with HF remains unclear. In three published large cross-sectional studies that overall included 574 men with HF, in univariate analyses both TT and eFT deficiency were found to be adverse long-term prognostic factors in this group of patients [35, 111, 112]. When additional
clinical prognostic factors were also included, however, results became less evident [35, 111, 112] and in only one of these studies (in 208 men with systolic HF, median age 63 years, 3-year follow-up [35]) low TT and eFT levels were shown to be independent adverse prognosticators. Of note, HF is also associated with other disturbances than involving the gonadal anabolic axis. If disturbances of the adrenal axis (dehydroepiandrosterone sulfate deficiency) and the somatotropin axis (insulin-like growth factor 1 deficiency) are also included in survival analyses, a relation is noted between an increasing number of disturbed anabolic axes in men with systolic HF and increasing long-term mortality [35]. In addition, low eFT level in men referred for coronary angiography predicted increased mortality due to HF during long-term follow-up (median duration 7.7 years) in the German LURIC study [128].

**TESTOSTERONE TREATMENT IN PATIENTS WITH HEART FAILURE**

Evidence of effectiveness and safety of testosterone treatment in patients with HF is limited, and in most studies testosterone was administered regardless of the baseline hormonal status of the patients [129–135] (except for the study by Stout et al. [133] which included patients with systolic HF, low TT level, and symptoms of hypogonadism). Thus, these studies dealt not with androgen supplementation but rather with testosterone treatment in men with HF. Table 1 summarises results of at least single-blind randomised controlled trials (RCT) with a placebo control group that evaluated testosterone therapy in men with systolic HF. In a metaanalysis of four RCTs [131, 132, 134, 137] on the effect of testosterone therapy on exercise tolerance in patients with systolic HF (n = 198; 84% of men, mean age 67 years) that was published in 2012 by Toma et al. [136], therapy with this androgen (a suspension of testosterone esters or long-acting testosterone undecanoate administered intramuscularly and transcutaneous systems, treatment duration ranging from 12 weeks to 12 months) was associated with a significant improvement in exercise tolerance (measured by the 6-min walking test or incremental shuttle walking test or peak oxygen consumption (peakVO₂)) [131, 132, 134, 136, 137]. Among studies included in the metaanalysis, particularly interesting findings were reported by Caminiti et al. [134]. These authors showed that testosterone treatment resulted in a better improvement of exercise tolerance (measured by peakVO₂) in men with HF and low baseline testosterone level (< 12 nmol/L [ < 3.46 ng/mL]) compared to men with normal testosterone level at baseline [134]. Toma et al. [136] also evaluated safety of testosterone treatment and showed similar incidence of adverse cardiovascular events in the testosterone and placebo groups. In addition, no increase in prostate-specific antigen (PSA) level following hormonal treatment was noted in either of the three studies performed in men [131, 132, 134] (the fourth study included 32 women with HF [137]). However, no large RCT has been performed yet that would clearly prove long-term benefits and safety of testosterone treatment in men with HF and low baseline testosterone level [17], and this therapy has not been included in the current ESC guidelines on the diagnosis and treatment of acute and chronic HF [138]. In addition, poorly controlled HF has been listed as a contraindication for testosterone administration in the Endocrine Society guidelines [52]. Other conditions in which testosterone therapy should not be used include metastatic prostate cancer, breast cancer, some unevaluated prostate lesions, lower urinary tract symptoms associated with benign prostatic hyperplasia, PSA level > 4 ng/mL (> 3 ng/mL in patients at high risk of prostate cancer), and haematocrit > 50% [52].
### Table 1. Beneficial effects of testosterone treatment in men with systolic heart failure (HF)

<table>
<thead>
<tr>
<th>No.</th>
<th>Authors, year, reference no.</th>
<th>Study group</th>
<th>Route of administration and dose of testosterone</th>
<th>Study design</th>
<th>Duration of study</th>
<th>Beneficial effects of testosterone treatment</th>
<th>Tolerance and adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Malkin et al., 2007 [129]</td>
<td>13 men with systolic HF (LVEF 24–38%), age 74 ± 2 years</td>
<td>Suspension of testosterone esters (Sustanon 250) administered subcutaneously 2 times 2 weeks apart</td>
<td>Single-blind, crossover, placebo-controlled</td>
<td>12 weeks (2 phases with a washout period)</td>
<td>Improved insulin sensitivity, increased body mass with reduced fat, indicating an increase in muscle mass</td>
<td>Drug well tolerated; no electrolyte disturbances were noted</td>
</tr>
<tr>
<td>2</td>
<td>Malkin et al., 2003 [130]</td>
<td>20 men with systolic HF; patients receiving testosterone (n = 10): age 62 ± 3 years, LVEF 33 ± 3%; patients receiving placebo: age 61 ± 2 years, LVEF 37 ± 2%</td>
<td>Suspension of testosterone esters (Sustanon 100) administered subcutaneously every 2 weeks</td>
<td>Double blind, randomised, placebo-controlled</td>
<td>12 weeks</td>
<td>Reduced dispersion of corrected QT interval</td>
<td>No data</td>
</tr>
<tr>
<td>3</td>
<td>Malkin et al., 2006 [131]</td>
<td>76 men with systolic HF, age 64 ± 10 years, LVEF 32 ± 11%</td>
<td>Transdermal patches (5 mg/24 h)</td>
<td>Double blind, randomized, placebo-controlled</td>
<td>12 months</td>
<td>Reduced severity of clinical symptoms (evaluated using the NYHA classification), increased distance in incremental shuttle walking test, increased forearm muscle strength, increased haematocrit</td>
<td>Similar incidence of serious adverse events in testosterone and placebo groups. Cutaneous reactions in 42 (55%) patients, 19 patients discontinued treatment for this reason. No changes in PSA level or haematocrit during follow-up</td>
</tr>
<tr>
<td>4</td>
<td>Pugh et al., 2004 [132]</td>
<td>20 men with systolic HF, median age 62 years, LVEF 35 ± 8%</td>
<td>Suspension of testosterone esters (Sustanon 100) administered subcutaneously every 2 weeks</td>
<td>Double blind, randomised, placebo-controlled</td>
<td>12 weeks</td>
<td>Improved quality of life, trend towards reduction of depressive symptoms (evaluated using the BDI), increased distance in incremental shuttle walking test</td>
<td>Drug well tolerated. No effect on heart rate and blood pressure. No increase in PSA level or changes of haematological parameters</td>
</tr>
<tr>
<td>5</td>
<td>Stout et al., 2012 [133]</td>
<td>28 men with systolic HF, symptoms of hypogonadism and low baseline TT level, i.e. &lt; 4.32 ng/mL; patients receiving testosterone (n = 15): age 68 ± 5 years, LVEF 21 ± 10%; patients receiving placebo: age 66 ± 9 years, LVEF 28 ± 6%</td>
<td>Suspension of testosterone esters (Sustanon 100) administered subcutaneously every 2 weeks</td>
<td>Double blind, randomised, placebo-controlled — testosterone or placebo administered during a 12-week physical rehabilitation programme</td>
<td>12 weeks</td>
<td>Increased physical fitness and muscle strength, reduced severity of depressive symptoms, beneficial effect on symptoms of androgen deficiency</td>
<td>No study-related adverse events were noted</td>
</tr>
</tbody>
</table>
SUMMARY

Impaired anabolic/catabolic balance and testosterone deficiency are important components of the pathophysiology and the clinical presentation of HF in men. It has not been clearly established whether testosterone deficiency in this patient group only reflects severe chronic systemic disease or is an independent predictor of poor outcomes and thus constitutes an important therapeutic target. Results of the available studies on testosterone administration in relatively small groups of men with HF showed beneficial effects and safety of such therapy. Thus, a large clinical trial would be warranted to determine value of testosterone therapy in this patient group.

This work was supported as a part of the statutory activity of the Laboratory for Applied Research on Cardiovascular System, Department of Heart Diseases, Wroclaw Medical University, Wroclaw, Poland (ST-436).

Conflict of interest: none declared

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