Hormonal Alterations in Heart Failure: Anabolic Impairment in Chronic Heart Failure – Diagnostic, Prognostic and Therapeutic Issues

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Abstract
Chronic heart failure represents a leading cause of mortality and health care expenditure in developed countries. In the last 20 years, medical therapy of heart failure has dramatically changed thanks to the introduction of agents able to significantly reduce the neurohormonal hyperactivation that underpins the syndrome, and to the growing opportunities of electrical therapies. Although major advances in terms of improved survival and quality of life have been achieved, the reduction in the burden of heart failure is still the primary goal of cardiovascular societies. In the last decades, other research lines have also grown to complement the neurohormonal paradigm. It is increasingly evident that several hormonal systems are down-regulated or impaired in patients with heart failure, including growth and thyroid hormones, androgens and insulin. These abnormalities could be considered interrelated and linked, in turn, to the neurohormonal and cytokine hyperactivation. Since most of these alterations provide prognostic information, these new lines of evidence support the extension of the classical neurohormonal scheme to a more comprehensive pathophysiological model that includes multiple hormonal and metabolic deficiencies. This chapter examines the evidence in support of this concept. Preliminary experience concerning targeted hormonal supplementation or metabolic modulation is also briefly reviewed in this article.

Chronic heart failure (CHF) represents the common end point of virtually each cardiac disease (ischemic heart disease, valvular disease, arrhythmia and pericardial disease) and is characterized by the inability to deliver oxygen at a rate commensurate with the requirements of the metabolizing tissues, despite normal filling pressures or at the expense of increased filling pressures [1]. CHF is a leading cause of mortality, morbidity and high health costs in European countries. Approximately 1–2% of the adult population is affected by CHF in developed countries with a remarkably higher prevalence in the elderly (10% of men and 8% of women over the age of 60) [2, 3]. The
prognosis of patients affected largely differs depending on the etiology, New York Heart Association class, age and comorbidities. Despite the prognostic improvement in the last decades, mean survival in CHF is around 50% at 5 years, i.e. worse than that of many cancers, and up to 50% of patients are readmitted for CHF within 6 months of discharge [4]. The relentless increase in cardiovascular mortality and the heart failure epidemic prompt the quest for novel pathophysiological mechanisms and innovative therapeutic strategies. In this chapter, available evidence about the hormonal impairment occurring in CHF patients is reviewed. Experience with hormonal therapies is also reported.

**Neurohormonal and Multiple Hormonal Deficiency Models in Chronic Heart Failure**

The current model adopted to explain the pathophysiological substrate and the progressive worsening in CHF is rooted in the overexpression of several metabolic and neurohormonal molecules. This paradigm includes the enhanced activity of both the renin-angiotensin-aldosterone system and the adrenergic pathway. Although in the early stage of CHF this hormonal storm is helpful to adapt the cardiac output to the needs of peripheral tissues and organs, it turns harmful in the long term and leads to pathological left ventricular (LV) remodeling and disease progression [5]. In the 1990s, large trials testing molecules inhibiting such hyperactivated pathways in CHF have definitely demonstrated the clinical value of the neurohormonal model and paved the way for the routine use of several agents, including β-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers and aldosterone receptor antagonists. Besides the renin-angiotensin-aldosterone system and adrenergic overactivity, a relevant contribution to the CHF syndrome is also brought about by low-grade inflammation and cytokine activation [6]. The ‘cytokine hypothesis’ somehow parallels the neurohormonal model and is based on the observation that many features of the CHF syndrome can be induced by proinflammatory cytokines (TNF-α, IL-6 and IL-10) [6]. Although it is not likely that cytokines are sufficient inductors of CHF, their overexpression may play an important role in CHF progression. Inhibition of TNF-α by monoclonal antibodies was tested in several multicenter trials, but most of these were terminated prematurely for lack of benefit or even increased mortality.

Although the neurohormonal approach in the clinical setting has led to invaluable advantages in terms of reduced mortality and hospitalization, it clearly shows several pitfalls manifested by the still high figures of mortality. Such gaps have not been completely filled by the recent optimization of the ‘traditional’ medical approach employing implantable cardioverter defibrillators and/or resynchronization therapy in eligible patients.

In the last two decades, growing efforts coming from different research teams provided adequate evidence of reduced anabolic drive and enhanced catabolism in heart
failure patients [7]. Although these impairments are clearly detectable in the end stage of CHF (cardiac cachexia), it is increasingly evident that some degree of anabolic/catabolic imbalance is also present at earlier stages. Although sometimes conflicting, evidence of common abnormalities in steroids, growth hormone (GH) axis and other hormonal pathways are emerging and leading to a novel comprehensive pathophysiologic scenario that has been termed multiple hormonal deficiencies syndrome [7]. In the following paragraphs, we provide evidence for reduced drive of the main anabolic axes in CHF as well as for beneficial effects of hormone replacement therapies.

**Androgens in CHF**

*Physiology*

The main androgens in the systemic circulation are testosterone, dihydrotestosterone, androstenedione, dehydroepiandrosterone and its sulfate (DHEA-S). From a biological standpoint, a pivotal role is played by testosterone. The function of androstenedione is limited to the transformation in testosterone, whereas dihydrotestosterone originates from conversion of testosterone by 5-reductase in the peripheral target tissues, and exerts testosterone-like actions. Testosterone is secreted almost exclusively by the testes and partially produced by the conversion from precursors. It is largely bound to plasma proteins: 40–50% is weakly bound to albumin, 50–60% is strongly bound to the sexual hormones binding globulins, and the free fraction accounts for about 1–2%. Unbound testosterone diffuses passively through the cell membrane and binds to specific cytoplasmic androgen receptors, although direct, receptor-independent actions are also recognized [8].

DHEA-S represents by far the most abundant androgen in the serum. Although DHEA-S is partially converted to testosterone, there is preliminary evidence about its direct actions, which are independent from androgen receptors, on several tissues including endothelial cells and mediators of atherosclerosis [9].

Although usually related only to skeletal muscle anabolism and male sexual performance, androgens are endowed with distinct cardioactive properties at different levels. The discovery of testosterone receptors in myocardial tissue dates back to the early 1980s, and since then numerous cardiovascular actions of testosterone have been described, both mediated by specific receptors and resulting from direct interaction with ionic channels. Studies performed in rats showed that testosterone supplementation might contribute to the reduction in myocardial infarction size by decreasing cardiomyocyte apoptosis rate, probably via increased expression of K_{ATP}, a mitochondrial K⁺ channel enhancing the stability of the mitochondrial membrane during ischemia. Moreover, several in vitro reports displayed that testosterone may be endowed with antiarrhythmic properties mediated by the reduction in action potential...
duration and QTc interval length. Finally, indirect beneficial effects on the cardiovascular system are secondary to its modulation of body composition (individuals with higher endogenous testosterone levels tend to display greater lean mass and decreased fat mass) and the cardiovascular risk profile. The wide spectrum of the metabolic syndrome, including hyperglycemia, hypertension, dyslipidemia and visceral obesity, was beneficially affected by testosterone supplementation in a rabbit model, and testosterone supplementation ameliorated main metabolic parameters in hypogonadal men with the metabolic syndrome [10].

Androgens and Incidence of Heart Failure in the General Population

Large population-based studies have demonstrated a significant association between testosterone levels and measures of clinical outcome. In particular, the EPIC-Norfolk study documented that individuals with serum testosterone levels ranging in the higher quartile (>19.6 nmol/L) had a 25–30% lower risk of all-cause and cardiovascular mortality than the ones in the lowest quartile (<12.5 nmol/L) [11]. While some studies provided evidence for increased cardiovascular mortality in patients with lower androgen levels, others failed at demonstrating a direct relation between testosterone levels and heart disease [12, 13]. In a selected male population referred for coronary angiography, with or without LV function impairment, free testosterone (but not total testosterone) was independently associated with mortality for CHF after a mean follow-up of 7.7 years [14].

Epidemiologic studies have suggested a role for DHEA-S in cardiovascular disease. Indeed, DHEA-S deficiency is a predictor of increased all-cause and cardiovascular mortality in a male population aged >50, and an independent risk factor of ischemic heart disease [15].

Although the evidence reported above supports the detrimental effect of low testosterone levels on several cardiovascular outcome measures, including cardiovascular mortality in some studies, there is no direct evidence that low testosterone activity may predispose to CHF. Similarly, there are no studies demonstrating an association between incident heart failure and low circulating DHEA-S levels.

Testosterone in Patients with Chronic Heart Failure

Approximately one quarter of men with CHF display biochemical evidence of testosterone deficiency when compared with age-matched healthy individuals [16]. In some studies, the levels of testosterone were directly related to functional measures of CHF, including distance at the 6-min shuttle test and peak oxygen consumption [17]. The pathophysiological underpinning for worse exercise tolerance of patients with low testosterone levels is related to impaired skeletal muscle function, whereas
cardiovascular hemodynamics appears relatively unaffected. Higher reduction in testosterone levels over time was also associated with stronger disease progression \[18\].

Several studies have shown that circulating DHEA-S levels are decreased in CHF compared with control subjects. Although a definite prevalence of DHEA-S deficiency is not available, it was found to range between 44 and 78% depending on the age category in one study \[16\].

More importantly, androgens showed prognostic impact in CHF patients. In the study by Jankowska et al. \[16\], the authors assessed baseline levels of total testosterone, DHEA-S and insulin-like growth factor-1 (IGF-1) in male CHF patients. Deficiency in each anabolic hormone was an independent marker of a poor prognosis, and multiple deficiencies identified groups with a higher mortality. Specifically, the 3-year survival rate was 83% in patients with no deficiencies, 74% in patients with one deficit, 55% with two and 27% with deficiencies in all axes. Although androgen deficiency may indicate a poor outcome in patients with CHF and there are data linking low levels of testosterone to worse surrogate end points, there is no direct evidence that hypotestosteronemia alone may lead to a worse survival in CHF patients.

**Testosterone Therapy in Patients with Chronic Heart Failure**

In view of such preliminary evidence, some investigators have tested testosterone therapy in patients with CHF. Although no study was powered to assess survival in treated patients, all of them showed significant beneficial effects. A pioneering study by Pugh et al. \[17\] showed that testosterone administration (100 mg, different esters of testosterone, i.m. every 2 weeks) for 12 weeks improved the distance walked measured by the shuttle walking test. Subsequently, a 12-week, double-blind, placebo-controlled trial with long-acting testosterone supplementation (1,000 mg, long-acting testosterone undecanoate, i.m. every 6 weeks) confirmed and expanded such preliminary findings displaying improvement in more robust surrogate end points, including peak oxygen consumption and ventilator efficiency (VE/VCO2 slope), and muscle strength \[18\].

In the above-mentioned studies, significant correlations were found between increased testosterone levels by supplementation and improvement in functional variables. Although no studies adopted the testosterone deficiency as inclusion criterion, subgroup analysis of one of these studies demonstrated that patients with a baseline value consistent with testosterone deficiency showed a significantly higher clinical response to supplemental therapy than patients with baseline values in the normal range. Of note, testosterone administration is also metabolically advantageous insofar as it appears to improve insulin resistance (IR), a very common defect in CHF \[19\].