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Anabolic hormones and heart failure with preserved ejection fraction: looking for Ariadne’s thread

Mariarosaria De Luca, Giulia Crisci, Federica Giardino, Valeria Valente, Ilaria Amaranto, Olimpia Iacono, Roberta D’Assante, Francesco Giallauria, Alberto M. Marra

1. Department of Translational medical Sciences, “Federico II” University, Naples, Italy
2. Faculty of Sciences and Technology, University of New England, Armidale, NSW, Australia
3. Center for Pulmonary Hypertension, Thoraxklinik at Heidelberg University Hospital, Heidelberg, Germany

Address for correspondence: Dr. Alberto M. Marra, MD, PhD, Department of Translational Medical Sciences, “Federico II” University Hospital and School of Medicine, Via Pansini 5, I-80131 Napoli, Italy. Tel. +39.081.7463492. E-mail: albertomaria.marra@unina.it

Abstract
Heart failure with preserved ejection fraction (HFpEF) is a complex clinical syndrome that accounts for more than half of all heart failure patients. Identification, early diagnosis and management of patients are still complex, and no targeted treatment is available, since all tested drugs were not able to lower hard clinical outcomes. A multi-hormonal deficiency syndrome has been described in HFpEF patients suggesting that different hormones may represent new biomarkers of the disease, but their clinical utility is still debated. The natriuretic peptides are the cornerstone biomarker in heart failure, predicting cardiovascular death and heart failure hospitalization. Testosterone and DHEA-S deficiencies have been reported in HFpEF and associated with right ventricular impairment and diastolic dysfunction. IGFBP-1/IGF-1 axis correlates with echocardiographic parameters of HFpEF patients and with several prognostic biomarkers including NT-proBNP and C reactive protein. Low triiodothyronine syndrome is frequently found in HFpEF and thyroid hormones should represent a potential biomarker of risk stratification and prognosis.

Key words: Anabolic hormones, biomarkers, diagnosis, heart failure preserved ejection fraction, prognosis, risk stratification, outcomes.
Introduction

Heart Failure (HF) is a complex clinical syndrome characterized by typical symptoms and signs (dyspnea, fatigue, pulmonary crackles, peripheral oedema) that result from structural and functional cardiac impairment at rest or during stress. It represents a major public health problem, with an incidence of ≈1,000,000 in 2014 in persons ≥55 years of age, progressively increasing in industrialized countries with ageing populations (1). Current classification of HF is based on Left Ventricular Ejection Fraction (LVEF) and includes distinct clinical profiles with different etiologies, demographics, co-morbidities and responses to therapies: HF with reduced ejection fraction (HFrEF): symptomatic HF with LVEF ≤40%; HF with mildly reduced ejection fraction (HFmrEF): symptomatic HF with LVEF 41-49%; HF with preserved ejection fraction (HFpEF): symptomatic HF with LVEF ≥50%; and HF with improved ejection fraction (HFimpEF): symptomatic HF with a baseline LVEF ≤40%, a ≥10 point increase from baseline LVEF, and a second measurement of LVEF > 40% (2). Diastolic dysfunction is the main mechanism involved in HFpEF: left atrial and right ventricular dysfunction, pulmonary hypertension and increased vascular stiffness are involved (3) (4). Although HFpEF accounts for more than half of all HF patients, identification, early diagnosis and management of patients are still complex, with severe implications for patient’s health and treatment costs. Furthermore, differently to HFrEF no targeted treatment is available, since all tested drugs were not able to lower hard clinical outcomes in randomized controlled trials. For this reason, several authors speculated that different phenotypes are included under the HFpEF category. These difficulties impose to the scientific community the incessant research for biomarkers that might represent a possible treatment target in a cluster of HFpEF patients, given its complex pathophysiology. Biomarkers are defined as any measured characteristic representing an indicator of normal biological or pathogenic processes or responses to an exposure or intervention (5, 6). Some biomarkers have already been successfully identified and integrated into the clinical routine (7, 8); others are currently under discussion (Table 1) (9-11). In particular, biomarkers associated with HFpEF are related with inflammation and angiogenesis, confirming their role in the pathophysiology of the disease (12). Catabolic mechanisms correlate with mortality and morbidity in HF and a multi-hormonal deficiency syndrome has been described both in HFrEF and in HFpEF patients, although less pronounced in HFpEF (13-16). These studies suggest that different hormones may represent biomarkers with a crucial role in disease management (Table 2) (Figure 1).

Aim of this review is to examine and summarize the current evidence on the role of hormonal biomarkers and to evaluate their clinical utility in each phase of HFpEF disease.
Natriuretic Peptides (NPs)

The natriuretic peptides (NPs), B-type natriuretic peptide (BNP) and N-terminal pro-BNP (NT-proBNP), are the cornerstone biomarker in HF disease. Their role is crucial in diagnosis and risk stratification. BNP is a peptide hormone released by cardiomyocytes in response to stretching derived by increased ventricular volume or pressure overload, NT-proBNP is the inactive protein cleaved from the prohormone of BNP. Guidelines establish the upper limit cut-off of normal in the non-acute setting in 35 pg/mL for BNP and 125 pg/mL for NT-proBNP, undistinguishing HFpEF from HFrEF even if NPs levels are lower in HFpEF in respect of HFrEF (2). NPs plasmatic levels may represent an initial diagnostic test, especially when echocardiography is not immediately available, and have demonstrated a very high negative predictive values but a low positive predictive value: patients with normal NPs concentrations are unlikely to have HF, vice versa, the only presence of abnormal NPs values does not allow the diagnosis of HF. Recently the European Society of Cardiology suggested a new score for the diagnosis of HFpEF: The Heart Failure Association Pre-test assessment, Echocardiography & natriuretic peptide, Functional testing, Final etiology (HFA-PEFF) score (17), which is a stepwise approach that incorporates NPs evaluation to hypothesize HFpEF diagnosis. Several conditions impact on NPs levels: higher levels can be observed in the elderly, in women, in atrial fibrillation, and in renal dysfunction (18). Differently, obese individuals show reduced NPs levels as compared to general population (19). It would seem prudent to use NPs for diagnosis together with a combination of clinical, biochemical, electrocardiographic, and imaging data. The rationale for using NPs in HF-pEF diagnosis is that their levels are related to the presence of diastolic dysfunction, which in turn is associated with increased LV filling pressure and consequently pressure overload to left atria (20, 21). The relationship between NPs levels and diastolic dysfunction was observed also in the preclinical phase (22) so that, besides their diagnostic utility, NPs levels might be used in community-based screening programs for detecting HFpEF (23). Moreover, NPs play a key prognostic role in patients with HFpEF. The i-PRESERVE and the PEP-CHF studies demonstrated that NT-proBNP values and their change from baseline correlate with mortality and heart failure rehospitalizations (24, 25).

Dehydroepiandrosterone-sulfate (DHEA-S) and Testosterone

Testosterone deficiency represents a fundamental element in the pathophysiology of chronic heart failure, resulting in a reduction of muscle mass, impaired use of energy, dyspnea and fatigue (26, 27). Lower plasma levels of total testosterone and DHEA-S were associated with an increased risk of incident HF, both in HFpEF and HFrEF (28), suggesting a possible use in community-based screening programs. The relationship between DHEA-S, testosterone and HFpEF has been poorly
investigated. Salzano et al. (13) reported testosterone and DHEA-S deficiencies in a population of mild-to-moderate chronic HFpEF. Subsequent studies have confirmed the association between DHEA-S and testosterone deficiency with right ventricular impairment and diastolic dysfunction in patients with HFpEF (29): patients with testosterone deficiency showed lower E wave, higher systolic pulmonary artery pressure and tricuspid peak velocity values (29). Moreover, testosterone may improve endothelial function and insulin resistance, by acting on muscle insulin sensitivity or visceral adipocytes metabolism, and testosterone supplementation may increase HDL-cholesterol (26). MDHEA-S and testosterone showed to influence antioxidant levels measured as the appearance of the chromogen ABTS (30, 31). Actually, there is no evidence that low testosterone and DHEA-s levels are associated with a worse prognosis in HFpEF patients due to the lack of large longitudinal studies.

**Insulin-like growth factor 1 (IGF-1)**

The insulin-like growth factor-1 (IGF-1) is an essential mediator in the regulation of growth and cellular differentiation in many tissues. Its activity is neutralized by IGF-binding protein 1 (IGFBP-1). Alterations in IGF-1/IGFBP-1 system were associated with a worse clinical course contributing to diastolic disfunction via increased collagen deposition and myocardium fibrosis (30). In addition, it has been demonstrated that human heart shifts from IGF-1 production to utilization in chronic heart failure (32). In HFrEF patients, IGF-1 has demonstrated a prognostic role, predicting clinical outcomes (33-35), while its importance in HFpEF is still discussed (36). Barroso et al. described a correlation between IGFBP-1/IGF-1 axis and echocardiographic left ventricular (LV) diastolic parameters in HFpEF patients (37). Similarly, patients with IGF-1 deficiency showed higher left atrial volume (29-30), higher systolic pulmonary artery pressure and tricuspid peak velocity and lower tricuspid annular plane systolic excursion (29). Moreover, IGF-1 and IGFBP-1/IGF-1 ratio seem to be positively correlated with prognostic biomarkers including NT-proBNP and C reactive protein (CRP) (30, 37-38). Only one study has not confirmed IGF-1 deficiency in HFpEF, demonstrating a positive correlation of the hormone levels with the prognosis in HFrEF but not in HFpEF patients (38). No other studies have correlated IGF-1 deficiency with cardiovascular prognosis in HFpEF.

**Thyroid hormones**

Thyroid hormones impact on cardiovascular system and their alterations increase cardiovascular risk through genomic and non-genomic mechanisms (39-40). A local cardiac hypothyroidism may be present even if plasmatic thyroid hormones are normal due to an upregulation of type 3
iodothyronine deiodinase (40). Both clinical and subclinical hypothyroidism increase risk of HF (41), and data from epidemiological studies described low triiodothyronine (T3) syndrome in about 22% of HFpEF patients and subclinical hypothyroidism in 10 to 20% (29) (42). T3 levels seems to be inversely associated with BNP and D-Dimer, markers of HFpEF severity, and correlate with echocardiographic parameters of diastolic dysfunction (42). HFpEF patients with T3 deficiency also showed higher right ventricular mid cavity diameter values (29). Disthyroidism affects the cardiovascular system also modifying oxygen consumption: patients with hyperthyroidism show a lower increment of heart rate between rest and anaerobic threshold, and lower VO₂ and oxygen pulse at anaerobic threshold when performing cardiopulmonary exercise test (43). These data suggest that thyroid hormones should represent a potential biomarker of risk stratification and prognosis in HFpEF patients even if we do not dispose of trials specifically focused. Furthermore, it may be assumed that thyroid hormone supplementation improves diastolic function of HFpEF patients, as suggested by clear evidence in HFrEF (44). According this hypothesis, T3 should represent a promising therapeutic target in this setting of HF patients.

Other Biomarkers
In addition to the above-mentioned hormones, several other molecules have shown a potential clinical utility in HFpEF patients. Patients with HFpEF have significantly higher levels of soluble suppression of tumorigenesis-2 (sST2) and high sensitivity troponin T (hsTnt) and their values predict overall survival and HF rehospitalizations (45). De Boer et al. demonstrated that Galectin-3 increases HF hospitalization and all-cause mortality (46). Similar data were obtained with osteopontin and neuropilin (12). It has been demonstrated that trimethylamine N-oxide (TMAO) adds to risk stratification, when combined with BNP (47). Inflammation concurs to the pathophysiology of HFpEF and inflammatory cytokines IL1, IL6, IL8, and CRP are elevated in HFpEF patient (8, 48). TNF-α and its specific receptors TNF-R1 and TNF-R2 contribute directly to the development and progression of heart failure, by determining ventricular remodeling, interstitial fibrosis, and cardiomyocyte apoptosis. The role of TNFα antagonists on TNFα cardiotoxicity is still debated with conflicting findings between animal model investigations and early clinical trials (49, 50). Finally, Cystatin C, a strong predictor of cardiovascular disease, is associated with poor prognosis in patients with acute heart failure, regardless of renal function (51).

Conclusions
Despite recent progresses, HFpEF morbidity and mortality are still too high due to the complex pathophysiology, the heterogeneous presentation and the lack of effective treatments. A multi-
hormonal deficiency syndrome has been described both in HFpEF and HFrEF. Only few biomarkers have already been successfully identified and introduced in the routine practice, but their clinical perspective are extremely interesting. Different hormones may represent an *Ariadne’s thread* in understanding the complex pathophysiology of HFpEF and, at the same time, biomarkers useful not only for screening, diagnosis, and prognosis of the disease, but also for clinical management and assessment of response to treatment. Finally, anabolic deficiencies represent possible therapeutic targets, considering positive results from preliminary reports (52-57). Further studies need to be carried out in order to identify main anabolic biomarkers and their exact clinical utility.

**Abbreviations:** BMI: Body Mass Index BNP: B-type natriuretic peptide; CRP: C reactive protein. DHEA-s: Dehydroepiandrosterone-sulfate EF: Ejection Fraction; HF: Heart Failure, HFpEF: Heart Failure with Preserved Ejection Fraction; HFrEF: Heart Failure with Reduced Ejection Fraction; hsTnt: high sensitivity troponin T; IGF-1: insulin-like growth factor-1; IGFBP-1: IGF-binding protein 1; NPs natriuretic peptides; NT-proBNP: N-terminal pro-BNP. T3: triiodothyronine. sST2: soluble suppression of tumorigenesis 2.

**References**


44. Virtanen, VK, Saha, HH, Groundstroem, KW, et al. Thyroid hormone substitution therapy rapidly enhances left-ventricular diastolic function in hypothyroid patients. Cardiology 2001;96:59–64.
Table 1. Predictive value of the main biomarkers in heart failure with preserved ejection fraction.

<table>
<thead>
<tr>
<th>First Author, year</th>
<th>Hormonal Biomarker</th>
<th>Setting</th>
<th>Follow up duration (median)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cleland et al., 2006 (58)</td>
<td>NT-proBNP</td>
<td>375 HFpEF patients</td>
<td>1 year</td>
<td>If ↑: ↑all-cause death ↑HF hospitalization</td>
</tr>
<tr>
<td>Anand et al., 2011 (25)</td>
<td>NT-proBNP</td>
<td>2612 HFpEF patients</td>
<td>6 months</td>
<td>If ↑: ↑cardiovascular death ↑HF hospitalization</td>
</tr>
<tr>
<td>Zhao et al., 2020 (28)</td>
<td>DHEA-S and Testosterone</td>
<td>4107 men and 4839 women</td>
<td>19.2 years</td>
<td>If ↓: ↑risk of incident HFpEF</td>
</tr>
<tr>
<td>Shah et al., 2011 (59)</td>
<td>sST2</td>
<td>200 patients with dyspnea and normal LV systolic function</td>
<td>1 year</td>
<td>If ↑: ↑all-cause mortality</td>
</tr>
<tr>
<td>De Boer et al., 2011 (46)</td>
<td>Galectin-3</td>
<td>114 HFpEF patients</td>
<td>18 months</td>
<td>If ↑: ↑all-cause mortality ↑HF hospitalization</td>
</tr>
<tr>
<td>Carrasco-Sánchez et al., 2011 (51)</td>
<td>Cystatin C</td>
<td>218 HFpEF patients</td>
<td>1 year</td>
<td>If ↑: ↑all-cause mortality</td>
</tr>
</tbody>
</table>
Table 2. Correlation between hormonal biomarkers and cardiac structure and function in heart failure with preserved ejection fraction.

<table>
<thead>
<tr>
<th>First Author, year</th>
<th>Hormonal biomarker deficiency</th>
<th>Setting</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Favuzzi et al. 2020 (29)</td>
<td>Testosterone</td>
<td>40 patients with HFpEF</td>
<td>↑ SPAP ↑ TPV</td>
</tr>
<tr>
<td></td>
<td>DHEA-S</td>
<td></td>
<td>↑ LAVI</td>
</tr>
<tr>
<td>Barroso et al. 2016 (37)</td>
<td>IGF-1</td>
<td>77 patients with HFpEF</td>
<td>↑ E/e’ ratio ↑ LAVI</td>
</tr>
<tr>
<td>Bruno et al. 2020 (30)</td>
<td>IGF-1</td>
<td>84 patients with HFpEF</td>
<td>↑ LAV ↑ LAVI</td>
</tr>
<tr>
<td>Favuzzi et al. 2020 (29)</td>
<td>IGF-1</td>
<td>40 patients with HFpEF</td>
<td>↑ LAV ↑ SPAP ↓ TAPSE ↑ TPV</td>
</tr>
<tr>
<td>Selvaraj et al. 2012 (42)</td>
<td>T3</td>
<td>89 patients with HFpEF without a prior diagnosis of thyroid dysfunction</td>
<td>↑ E ↑ E/e’ ratio ↓ E deceleration time</td>
</tr>
</tbody>
</table>

LAVI, left atrial volume index; SPAP, systolic pulmonary artery pressure; TAPSE, tricuspid annular plane systolic excursion; TPV, tricuspid peak velocity values.
Figure 1. Clinical utility of hormonal biomarkers in heart failure with preserved ejection fraction.