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Multiple hormone deficiency syndrome in heart failure with preserved ejection fraction

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The heart failure (HF) epidemic, its ominous prognosis (worse than that of many cancers), and the huge direct and indirect costs for health systems worldwide prompt the quest for novel pathophysiological mechanisms and innovative therapeutic strategies. In this regard, emerging evidence support the concept that multiple hormone deficiencies (MHD), particularly those affecting the anabolic drive, impact on HF progression [1,2]. However, whereas consistent data coming from several independent groups have documented the reduced activity of most anabolic axes in HF with reduced ejection fraction (HFrEF) [1–3], to date no study has addressed the presence and prevalence of the MHD Syndrome (MHDS) in HF with preserved ejection fraction (HFpEF). This information appears relevant considering that HFpEF currently accounts for >50% of all heart failure patients and its prevalence relative to heart failure with reduced ejection fraction (HFrEF) is rising at a rate of approximately 1% per year. Therefore, the purpose of the current study was to describe the prevalence of MHDS, in particular deficiencies of somatotropic, thyroid, adrenal, and gonadal axes in patients with HFpEF compared with HFrEF.

Thirty-six male consecutive subjects with HFpEF were enrolled in our tertiary referral center, and compared with 36 age-matched patients with HFrEF enrolled in the T.O.S.CA. Registry [4]. Particular care was given to select patients with comparable NYHA class. The diagnostic criteria for HFrEF and HFpEF were those published by the recent guidelines [5], and in addition, patients were aged >18 years, on stable medications for at least three months including ß-blocker. Patients undergoing an active hormone treatment, with known advanced kidney disease (eGRF <30 ml/min) or liver cirrhosis were excluded. All patients included in the study underwent evaluation of blood chemistry and circulating levels of total testosterone, dehydroepiandrosterone sulfate (DHEA-S), thyroid hormones, insulin-like growth factor-1 (IGF-1). Moreover, all patients performed a pituitary stimulatory test with GH releasing hormone plus arginine, EKG and a complete doppler echocardiographic study. Left Ventricular (LV) volumes and LV ejection fraction (LVEF) were calculated as previously described (Aplio XG imaging system, Toshiba, Japan) [6]. Peak oxygen consumption (peak VO_2) and ventilatory efficiency (VE/VCO_2 slope) were measured during a bicycle cardiopulmonary exercise test (CPET) with a ramp protocol of 10 W/min continued until limiting symptoms [2]. Informed consent was obtained from each patient. This study protocol was reviewed and approved by the local Ethics Committee (rif. 151/16). All blood samples were collected by venipuncture in fasting patients, total testosterone was measured by the DPC Coat-A-Count RIA kit; DHEA-S was measured by a solid-phase, competitive chemiluminescent enzyme immunoassay, while IGF-1 by a radioimmuno assay using a monoclonal

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Table 1
Clinical parameters, blood chemistry, hormonal evaluations, echocardiographic and CPET measures in HFpEF vs. HFrEF.

	HFpEF ($n = 36$)	HFrEF (n = 36)	p
Anthropometric			
Age (mean)	66 ± 14	66 ± 9	ns
BMI (kg/m^2)	29 ± 4	30 ± 5	ns
LVEF (%)	56 ± 2	30 ± 7	<0.01
Coronary artery disease (%)	30	56	<0.05
Hypertension (%)	80	45	<0.05
Diabetes (%)	51	43	ns
Atrial fibrillation (%)	58	33	<0.05
NYHA (I/II/III)	8/22/6	2/28/6	ns
Echocardiographic and CPET findings			
LVMi (g/m^2)	120 ± 27	146 ± 37	0.02
RWT	0.31 ± 0.05	0.28 ± 0.05	ns
LVEDd (mm)	59 ± 6	66 ± 9	0.05
e/a	1.01 ± 0.5	1.05 ± 0.5	ns
e/e'	11 ± 4	15 ± 7	0.05
Peak VO_2 (mL/kg/min)	18 ± 4	18 ± 3	ns
VO_2 AT (mL/kg/min)	13 ± 2.5	11.6 ± 4	ns
VE/VCO_2 slope	27 ± 7	28 ± 6	ns
Watt max (W)	88 ± 20	86 ± 30	ns
Hormonal data			
IGF-1 (ng/mL)	139 ± 44	101 ± 37	<0.01
Deficit IGF-1 (%)	8	15	ns
GH deficiency (%)	19	44	<0.05
Total Testosterone (ng/mL)	520 ± 143	382 ± 211	ns
Testosterone deficit (%)	14	38	<0.05
DHEA-S (ug/dL)	98 ± 86	78 ± 74	ns
Low DHEA-S (%)	41	45	ns
TSH (μU/mL)	2.1 ± 1.9	1.83 ± 1.7	ns
FT3 (pg/mL)	3.2 ± 1.4	2.71 ± 0.61	ns
FT4 (ng/mL)	1.3 ± 0.4	1.37 ± 0.2	ns
Low T3 (%)	6	4	ns

HFpEF: heart failure with preserved ejection fraction; HFrEF: heart failure with reduced ejection fraction; LVEF: left ventricle ejection fraction; BMI: body mass index; IGF-1: Insulin-like Growth Factor-1; NYHA: New York Heart Association; LVMi: Left Ventricle Mass indexed; RWT: relative wall thickness; LVEDd: left ventricle end-diastolic diameter; e/a; e/e'; VO_2: Oxygen uptake; AT: anaerobic threshold; VE: ventilation per minute; VCO_2: carbon dioxide production.
Continuous variables were expressed as mean ± SD.

antibody after acid-ethanol extraction. Continuous variables were expressed as mean ± SD. Categorical variables were expressed as percentage. Differences between subgroups were evaluated by a Student's *t*-test for unpaired data. Significance was set at 5%. Statistical analysis was performed using the SPSS 16.0 package (SPSS Inc., Chicago, IL). Rates and proportions were compared between groups of interest using the chi-square test. Biochemical hormone deficiencies (HD) were defined as previously reported [2]: DHEA-S and IGF-1 below the 10th percentile of our sex and age-matched control population; serum total testosterone levels below 300 ng/dL and free triiodotironine levels (T_3) below 2.0 pg/mL (in the presence of normal TSH levels), according to the reference limit of our laboratory and congruent with current guidelines. GH deficiency was diagnosed according to the Guidelines of the Italian National Health Care System (*nota 39*), using a Growth Hormone Releasing Hormone (GHRH) + Arginine test and BMI-adjusted cut-offs (peak GH below 9 μg/L for patients ≤30 kg/m^2 BMI and 4.1 μg/L for patients with BMI > 30 kg/m^2).

Clinical parameters, blood chemistry, hormonal evaluations, echocardiographic and CPET measures in the two groups of HF patients are shown in Table 1. As expected, HFpEF patients showed a mean LVEF of 56 ± 2% while HFrEF patients had a mean LVEF of 30 ± 7% ($p < 0.01$). Overall, patients with HFpEF displayed lower prevalence of coronary artery disease, higher percentage of systemic hypertension, atrial fibrillation and, with regard to therapy, decreased use of beta-blockers (72% vs 92% in HFrEF, data not shown). Patients with HFpEF also displayed MHDS as depicted in Fig. 1. However, the most striking difference between the two groups was that almost half of HFpEF patients (46%) did not display any HD, compared with only 4% in HFrEF. Also testosterone deficiency was more common in HFrEF vs. HFpEF subjects ($p < 0.05$). No differences were found with regard to low T_3 syndrome and DHEA-S deficiency. Specifically, both GH and testosterone deficiencies were more common in HFrEF than in HFpEF (respectively 44% vs. 19% and 38% vs 14% of enrolled patients, $p < 0.05$). Average circulating levels of IGF-1 and total testosterone were 18% and 27% lower in HFrEF compared with HFpEF, respectively. Peak oxygen consumption and other CPET parameters were similar in the two subgroups, confirming comparable degrees of HF. HFrEF patients showed a significantly higher value of LV mass index and LV end-diastolic diameter (Table 1). Moreover, HFrEF patients displayed higher LV filling pressures as suggested by e/e′ ratio compared to patients with HFpEF.

To the best of our knowledge, this is the first study to document the occurrence of anabolic deficiencies in HFpEF. Although lower than in HFrEF, prevalence of HD in HFpEF was remarkable in our population of mild-to-moderate CHF, considering that more than half of HFpEF had at least 1 hormone deficiency. Of note, GH/IGF-1 and testosterone were the most affected axes since DHEA-S and thyroid hormone values were not significantly different between the two groups. Although this study was not specifically designed at identifying the mechanisms of the observed differences in endocrine defects between the two study populations, one hypothesis can be put forward. Recently, it has been demonstrated that patients with HFpEF and HFrEF express different biomarkers, leading to speculation that different pathophysiological pathways are involved in the two clinical syndromes [7]. Specifically,

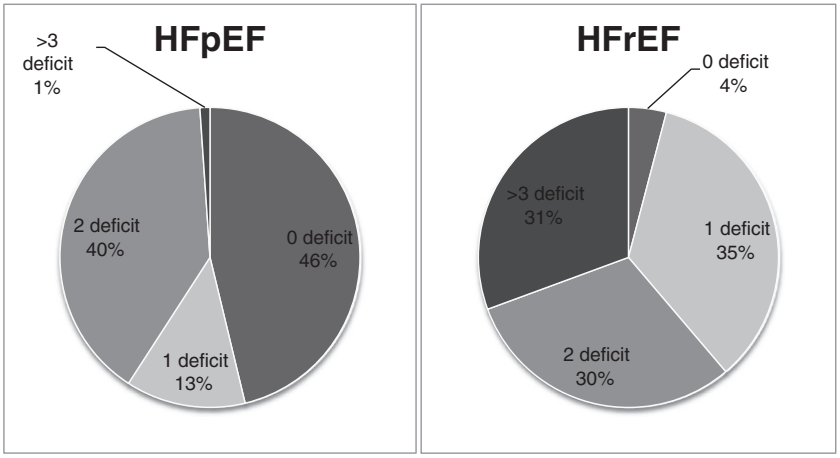

Fig. 1. Prevalence of hormone deficiencies in HFpEF vs. HFrEF.

HFrEF is associated with greater adrenergic activation [8] and increased indices of myocardial stress/injury, such as NT-proBNP and high sensitivity troponin T (hsTnT). Biomarkers of inflammation, fibrosis, and anemia are more prominent in HFpEF [7]. This contrasting biomarker profile observed in HFrEF may in turn lead to greater inhibition of anabolic hormone biosynthesis compared to HFpEF. It is also possible that the slightly lower mortality rates observed in HFpEF may be accounted for by the decreased impairment of the anabolic drive. Accordingly, higher levels of anabolic drive in HFpEF vs. HFrEF may be considered a further peculiarity supporting the emerging paradigm of a syndrome different from HFrEF. Comorbidities appear to play a pivotal role in HFpEF driving myocardial dysfunction and remodeling [9]. In several preliminary trials, MHDS correction was successfully tested in HFrEF and it would be of utmost interest to determine whether such a pharmacological approach may be beneficial also in HFpEF. When designing therapeutic strategies, anabolic deficiencies could represent additional biomarkers to evaluate the various phenotypes of HF [10,11].

In conclusion, we provide new evidence for the presence of MHDS in HFpEF, although the impairment of the anabolic drive is less pronounced than in patients with HFrEF. Further studies are needed to confirm the presence of anabolic deficiency in larger population of HFpEF and its prognostic implication.

Conflict of interest

None.

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