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Hormonal deficiencies in heart failure with preserved ejection fraction: prevalence and impact on diastolic dysfunction: a pilot study

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Abstract. – OBJECTIVE: In heart failure with reduced ejection fraction, catabolic mechanisms have a strong negative impact on mortality and morbidity. The relationship between anabolic hormonal deficiency, thyroid function, and heart failure with preserved ejection fraction (HFpEF) has still been poorly investigated. Therefore, we aimed to define the multi-hormonal deficiency prevalence in HFpEF patients and the relationships between hormonal deficiency and echocardiographic indexes.

PATIENTS AND METHODS: Plasma levels of N-terminal pro-brain natriuretic peptide, fasting glucose, thyroid-stimulating hormone, free triiodothyronine (T3), free thyroxine, insulin-like growth factor-1, dehydroepiandrosterone-sulfate (DHEA-S), total testosterone (only in male subjects) in 40 patients with HFpEF were evaluated. An echocardiographic evaluation was performed.

RESULTS: One (2.5%) patient (2.5%) had no hormonal deficiencies; 8 (20%) patients had deficits of one hormone, 18 patients (45%) of two axes, 12 patients (30%) of three axes, and one patient (2.5%) of all four axes. Among them, 97.5% had DHEA-S deficiency, 67.5% IGF-1 deficiency, 37% testosterone deficiency, 22.5% a "Low T3 syndrome", and 20% subclinical hypothyroidism. Patients with IGF-1 deficit showed higher left atrial volume values, systolic pulmonary artery pressure (SPAP), tricuspid peak velocity (TPV), and lower tricuspid annular plane systolic excursion (TAPSE) and TAPSE/SPAP ratio values.

Patients with testosterone deficiency had higher SPAP and TPV. Patients with low T3 syndrome had higher value of right ventricular mid cavity diameter. Hormonal dysfunction was independent from the presence of comorbidities and no difference between male and female subjects was noted.

CONCLUSIONS: Multi-hormonal deficiencies are associated with right ventricular dysfunction and diastolic dysfunction in patients with HFpEF.

Key Words:
Hormones, Diastolic dysfunction, Right ventricle, Heart failure with preserved ejection fraction.

Introduction

Anabolic hormones, in particular insulin-like growth factor-1 (IGF-1), dehydroepiandrosterone-sulfate (DHEA-S), testosterone (T), together with thyroid hormone triiodothyronine (FT3) have an important role on cardiac morphology and function. Each of these hormones can affect contraction-excitation mechanism or can regulate ionic channels[1-4].

Anabolic hormone deficiency, which can peak in cardiac cachexia, demonstrated detrimental impact on disease progression and mortality in heart failure with reduced ejection fraction (HFrEF)[5-11] ischemic heart disease.

About half of the patients affected by heart failure have a preserved ejection fraction (HFpEF)[12]. Diastolic dysfunction is the main mechanism involved, but several other alterations, as left atrial dysfunction, right ventricular dysfunction, pulmonary hypertension, and increased vascular stiffness, have been identified, which contribute to HFpEF[13-17]. Advanced age and comorbidities are the leading risk factors for HFpEF.

The relationship between anabolic hormone deficiency and HFpEF has been poorly investigated. A study of Salzano et al[18] showed a lower impact of anabolic drive deficiencies in HFpEF than HFrEF, although about half of the HFpEF patients demonstrated single or multiple hormonal deficiency. No correlation between hormone values and echocar-

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diographic patterns was reported. We performed an observational cross-sectional study to quantify anabolic hormonal deficiency prevalence, and to investigate the relationships between any anabolic alteration and diastolic dysfunction indexes, assessed by echocardiography, with the aim to gain insight into pathophysiology of HFpEF patients.

Patients and Methods

Chronic HFpEF patients with NYHA functional class I-III, admitted to the Department of Internal Medicine of the "Fondazione Policlinico Universitario A. Gemelli IRCCS" between April 2016 and May 2017 were recruited. The HFpEF diagnosis was based on current European Society of Cardiology guidelines[12]. Patients with symptoms and signs of HF (i.e., chronic fatigue, pretibial edema, dyspnea, exercise intolerance) elevated natriuretic peptides levels, such as the Brain Natriuretic Peptide (BNP) or the N-terminal proBNP (BNP > 35 pg/ml and/or NT-proBNP > 125 pg/ml, left ventricle EF > 50%) and echocardiographic evidence of diastolic dysfunction were considered. The echocardiographic criteria of diastolic dysfunction were defined as left atrial volume index (LAVI) > 34 ml/m^2, left ventricular mass index left atrial volume index (LAVI) >34 mL/m or a left ventricular mass index (LVMI) ≥ 115 g/m^2 for males, and ≥ 95 g/m^2 for females. Doppler parameters were a ratio of transmitral early filling velocity to tissue early diastolic mitral annular velocity (E/e′) ≥ 13 and a mean e' septal and lateral wall < 9 cm/s.

Patients with acute HF, NYHA class IV, end stage renal disease, liver cirrhosis, neoplastic or autoimmune diseases were excluded, as well as patients with known endocrinopathies, taking hormonal replacement therapy or previous/current amiodarone treatment.

Information about physiological and medical history, including the main risk factors for cardiovascular disease and pharmacological therapy, were acquired. Standard medical therapy, including loop diuretics, angiotensin converting enzyme inhibitors (ACEi), angiotensin II receptor blockers (ARB), and beta-blockers (BBs) had to be stable for at least 2 months. We investigated the prevalence of the following comorbidities: arterial hypertension, diabetes mellitus (DM), chronic obstructive pulmonary disease (COPD), renal failure, anemia, atrial fibrillation, peripheral artery disease or coronary artery disease.

Body weight was measured in light clothes with an electronic scale (Seca 910; Seca, Hamburg, Germany) to the nearest 0.1 kg and height was measured with a stadiometer (Seca 220 telescopic measured rod; Seca, Hamburg, Germany) to the nearest 0.1 cm. Body Mass Index (BMI) was calculated with the formula Body weight (kg)/(height (m))^2.

All patients signed written informed consent, according to the declaration of Helsinki. The study was approved by the Local Ethics Committee.

In all patients, venous blood samples were collected in lithium-heparin tubes in the morning after an overnight fast and after a supine rest of at least 15 minutes, in order to evaluate plasma levels of N-terminal pro-brain natriuretic peptide (NT-proBNP), plasma fasting glucose, thyroid-stimulating hormone (TSH), FT3, free thyroxine (FT4), IGF-1, DHEA-S. In male subjects, total testosterone (T) was also assayed. All samples were centrifuged within 2 hr after collection and separate plasma aliquots were stored at -80°C until assayed.

A complete echocardiography evaluation was performed (Affiniti 70c, Echocardiography Philips, Philips s.p.a. Milan, Italy), calculating the following parameters: left ventricular ejection fraction (LVEF), left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic diameter (LVESD), left ventricular end-diastolic volume (LVEDV), left ventricular end-systolic volume (LVESV), septal thickness (IVS), posterior wall thickness (PW), peak E-wave velocity (E), peak A-wave velocity (A), E/A ratio, pulsed-wave TDI E' velocity (E'), E/E' ratio, deceleration time (DT), left atrial volume (LAV), indexed left atrial volume (LAVI), systolic pulmonary artery pressure (SPAP), tricuspid annular plane systolic excursion (TAPSE), right ventricular mid cavity diameter value (RVEDV), TAPSE/SPAP ratio, and tricuspidal peak velocity (TPV).

NT-proBNP plasma concentrations, TSH, FT3, FT4, DHEA-S, T, and IGF-1 were measured using immunochemiluminometric assays on a Roche Modular E170 analyzer (Roche Diagnostics, Indianapolis, IN, USA). The intra-assay and inter-assay CV for all hormones were, < 5.0% and < 7.0%, respectively. Echocardiographic and hormonal parameters were obtained in a stable clinical condition.

Our laboratory considered the following ranges as normal: NT-proBNP (>126 pg/ml), TSH (0.4-3.2 uUI/ml), FT3 (2.4-4.2 pg/ml), FT4 (8.5-16.5 pg/ml), DHEA-S (800-3500 ng/ml), and T (2.5-8.4 ng/ml). Values equal or below the lower normal limit of normal were defined as deficiency. IGF-1 defi-

ciency was defined according to T.O.S.C.A. registry (i.e., 122 ng/ml for age range >55 years, 109 ng/ml for range 55-64 years, 102 ng/ml for range 65-74 years, 99 ng/ml for age >75 years), referring to the 33th percentile of a male population with Chronic Heart Failure due to age-related variations[19,20].

Statistical Analysis

Patients with normal values and hormonal deficiencies were identified for each single measured hormonal parameter. Mean and Standard Deviation (SD) were used to describe quantitative variables, absolute and relative frequencies for qualitative variables. Mann-Whitney U-Test was used to evaluate the differences in echocardiographic parameters, NT-proBNP values, BMI, and age between patients divided in groups according to the presence or absence of hormone deficiency (in particular, IGF-1 and testosterone deficiencies).

Kruskal-Wallis test was used to compare the same parameters between patients with Low T3 Syndrome and normal thyroid function. In order to investigate the associations between hormonal deficiency and comorbidities, Fisher's exact or Chi-squared test was used. Spearman correlation coefficient was used to investigate the association between hormone values (TSH, FT3, FT4, T, IGF-1, DHEA-S), NT-proBNP values, and echocardiographic parameters.

Furthermore, to predict diastolic dysfunction (mild to moderate) severity univariate logistic regression was used for the calculation of Odds Ratio (OR). Variables with *p*-values lower than 0.25 were included in a multivariate model with backward approach for the estimate of the adjusted ORs. A value of $p<0.05$ was considered statistically significant and the analysis was performed using Stata 13.

Results

Our population consisted of 40 patients, 27 men (67.5%) and 13 women (32.5%), aged between 59 and 92 years (mean ± SD: 78.33 ± 8.05 years).

BMI ranged from 21 kg/m^2 to 44 kg/m^2; in particular, 8 (20%) patients had normal weight, 19 (47.5%) were overweight and 13 (32.5%) were obese. We noted a mild renal impairment trend (mean glomerular filtration rate (GFR) 67.28 ml/min/1.73 m^2) in our study population. The average NT-proBNP value was 2726 ± 2662 ng/mL (Table I). Thirty-six patients (90%) showed moderate diastolic dysfunction degree, whilst four patients (10%) presented a mild degree. Twenty-nine patients (72.5%) were classified as functional NYHA III, 11 (27.5%) as NYHA II.

Thirty-six patients (90%) had three or more comorbidities, three patients (7.5%) at least two comorbidities and one patient (2.5%) only one comorbidity. Table II shows comorbidity prevalence and distribution in our cohort.

Eight (20%) patients had deficiency of at least one hormone, 18 (45%) were deficient in two hormonal axes, 12 (30%) had deficits of three axes and one (2.5%) patient showed deficits of all four

Table I. Features and mean values of clinical and hormonal parameters.

		Total population = 40 pts	%	Mean	SD
Males		27	67.5		
Females		13	32.5		
Age (years)				78.33	8.05
BMI (kg/m^2)				28.22	4.96
NYHA	II	11	27.5		
	III	29	72.5		
GFR* (ml/min/1,73 mq)				67.28	24.65
NT-proBNP (ng/ml)				2726.33	2662.03
IGF-1 (ng/ml)				91.73	37.20
TSH (ng/ml)				2.42	2.31
FT3 (pg/ml)				2.45	0.49
FT4 (pg/ml)				11.67	2.45
DHEA-S (ng/ml)				418.48	317.74
T (ng/ml)				2.66	1.29

DHEA-S = dehydroepiandrosterone-sulfate, FT3 = free triiodothyronine, FT4 = free thyroxin, GFR= glomerular filtration rate; IGF-1 = insulin-like growth factor-1, NT- proBNP = N-terminal pro-brain natriuretic peptide, T = total testosterone; TSH = serum thyroid-stimulating hormone. * GFR was calculated with MDRD formula.

Table II. Prevalence of hormonal alterations and comorbidities.

Hormonal deficits	Pts n	%
DHEA-S deficiency	39	97.5
IGF-1 deficiency	27	67.5
T deficiency	10	37
Low T3 syndrome	9	22.5
Subclinical hypothyroidism	8	20
Hypothyroidism	2	5
Subclinical hyperthyroidism	4	10
Comorbidities	**Pts n**	**%**
Hypertension	34	85
PAD/CHD	31	77.5
Anemia	31	77.5
COPD	22	55
Diabetes	18	47
Atrial fibrillation	17	42.5

DHEA-S = dehydroepiandrosterone-sulfate, IGF-1 = insulin-like growth factor-1, T = total testosterone; T3 = triiodothyronine, CHD: coronary heart disease; COPD chronic obstructive pulmonary disease; PAD: peripheral artery disease.

axes. Only one patient (2.5%) did not show hormonal deficiency. Among our patients, 97.5% had DHEA-S deficiency, 67.5% IGF-1 deficiency, 37% T deficiency, 22.5% a "Low T3 syndrome", 20% subclinical hypothyroidism, and 10% subclinical hyperthyroidism (Table II).

Patients with IGF-1 deficiency were older (mean age 81 *vs.* 72.77 years, $p < 0.05$) compared to patients without hormonal deficiencies. Patients with IGF-1 deficiency showed higher LAV (mean±SD 92.11±30.78 mL *vs.* 75.69±14.90 mL; $p<0.05$), SPAP (37.56 mmHg±8.14 *vs.* 33.62±7.86 mmHg; $p<0.05$) and TPV values (2.93±0.27 m/s *vs.* 2.65±0.35 m/s; $p<0.05$), but lower TAPSE values (20.74 mm *vs.* 23.69 mm; $p<0.05$) and a lower TAPSE/SPAP ratio (0.57 *vs.* 0.74; $p<0.05$) compared to patients with normal IGF-1 (Table III). T deficiency patients showed lower E (425.6 mm/s±202.50 *vs.* 578.7±165.82 mm/s; $p<0.05$), higher SPAP (39.10±5.95 mmHg *vs.* 33.35±7.42 mmHg, $p<0.05$), and TPV values (2.91±0.25 m/s *vs.* 2.64±0.34 m/s, $p<0.05$) compared to patients without deficit (Table IV). Patients with overt hypothyroidism had lower septal and posterior wall thickness. However, only two patients were part of this specific subgroup. Furthermore, patients with subclinical hypothyroidism were more frequently affected by atrial fibrillation (75% *vs.* 29.4%, $p<0.05$), but did not significantly differ in echocardiographic parameters. Patients with low T3 syndrome showed higher LVEDD (51.33±5.81 mm *vs.* 47.44±3.45 mm; $p<0.05$) and L/2 (30± 3.81 mm *vs.* 26.72±3.79 mm, $p<0.05$) compared to euthyroid patients and no difference was observed between patients with hyperthyroidism and patients without any thyroid dysfunction.

Mann-Whitney U-Test was not performed for DHEA-S deficiency patients, because only an isolated case was enrolled in our research. Regarding correlations between hormonal and echocardiographic parameters, we noted a negative correlation between DHEA-S and LAVI (r=-0.38, $p=0.01$). Concerning IGF-1, we observed a negative correlation with NT-proBNP (r=-0.39, $p=0.01$), E/E' ratio (r=-0.31, $p=0.05$), LAVI (r=-0.33, $p=0.04$), SPAP (r=-0.39, $p=0.01$), and TPV (r=-0.39, $p=0.01$), as well as a positive correlation with TAPSE/SPAP (r=0.36, $p=0.02$). The only predictive variable for diastolic dysfunction severity was E/e' (OR = 16.40; 95% CI 1.25 -217.69; $p= 0.033$), in multivariate analysis.

Finally, comorbidity prevalence was equal between patients with or without hormone deficiencies, except for the above-described difference in atrial fibrillation prevalence of subclinical hypothyroidism patients. We noted equal hormonal dysfunction prevalence between male and female patients (except for T, measured only in males).

Discussion

Mainly, we observed an elevated hormonal deficiencies prevalence, with one or multiple hormonal deficiencies in 97.5% of HFpEF patients compared to a recent study, reporting 54%[18]. Particularly, DHEA-S was below normal values in almost all patients (97.5%), followed by IGF-1 deficiency (67.5%), T deficiency (37%), and Low T3 syndrome (22.5%).

The increased hormonal deficiency prevalence can be explained with an increased average age in our cohort (78 *vs.* 66 years) and poorer clinical status, with 72.5% of patients classified as NYHA III, compared to 61% classified as NYHA II.

Furthermore, we noted a strong association between right ventricular function and hormonal deficiency parameters in IGF-1, T, and FT3 deficiency, singularly compared to patients with normal values. Patients with IGF-1 deficit had higher SPAP and TPV values, lower TAPSE values and an inferior TAPSE/SPAP ratio. Moreover, patients with T deficit had higher SPAP and TPV

Table III. Echocardiographic parameters in patients with or without IGF-1 deficiency.

	Normal IGF-1		IGF-1 deficiency		
	Mean	SD	Mean	SD	p
LVEDD (mm)	48.42	5.50	48.78	4.16	n.s
LVESD (mm)	30.25	7.12	31.11	4.85	n.s
LVEDV (mL)	98.23	18.84	91.37	13.39	n.s
LVESV (mL)	44.77	10.99	41.37	5.87	n.s
IVS (mm)	13.69	2.02	13.93	1.84	n.s
PW (mm)	10.77	1.30	10.85	1.23	n.s
E (mm/s)	530.77	209.86	523.56	222.22	n.s
A (mm/s)	583.54	267.87	629.48	255.46	n.s
Dt (ms)	240.31	71.89	248.81	131.78	n.s
EF (%)	57.69	4.73	61.00	28.20	n.s
E/A	0.94	0.14	0.88	0.26	n.s
E/E'	11.40	2.06	12.4	2.4	n.s
LAV (mL)	75.69	14.90	92.11	30.78	*0.04*
LAVI (mL/m^2)	41.31	8.76	49.37	16.69	n.s
TAPSE (mm)	23.69	2.75	20.74	3.19	*0.006*
RVEDV (mm)	28.33	3.61	27.41	3.59	n.s
SPAP (mmHg)	33.62	7.86	37.56	8.14	*0.018*
TPV (m/sec)	2.65	0.34	2.93	0.27	*0.01*
TAPSE/SPAP	0.74	0.20	0.57	0.16	*0.008*

A = Peak A-wave velocity, DT = Deceleration time, E = Peak E-wave velocity, E' = Pulsed-wave TDI E' velocity, E/A: E/A ratio, E/E' ratio, IVS = Septal thickness, LAV=left atrial volume, LAVI: left atrial volume indexed, LVEDD = left ventricular telediastolic diameter, LVEDV = left ventricular telediastolic volume, LVEF = left ventricular ejection fraction, LVESD = left ventricular telesystolic diameter, LVESV = left ventricular telesystolic volume, SPAP = Systolic pulmonary artery pressure, PW = Posterior wall thickness, RVEDV = right ventricular mid cavity diameter value, TAPSE = Tricuspid annular plane systolic excursion, TAPSE/SPAP: TAPSE/SPAP ratio, TPV = tricuspidal peak velocity.

values, while patients with low FT3 values had higher right ventricular diameter values. TAPSE is a contractile function measure of the right ventricle and correlates well with other right ventricular systolic parameters. Lower TAPSE values indicate right ventricular dysfunction[21]. SPAP and TPV are indicators for right intraventricular systolic pressure and relate to systolic/diastolic left ventricle dysfunction. TPV values are one of the parameters defining diastolic left ventricle dysfunction[22]. Instead, increased right ventricle diameter indicates increased pulmonary pressure.

Several scientific reports suggest the important role of right ventricular dysfunction in HFpEF[23,24]. In particular, right ventricle systolic dysfunction, as assessed by cardiac MRI, was associated with mortality and clinical status in 171 patients with HFpEF[25]. A recent review[23] showed a high prevalence of right ventricular dysfunction and pulmonary hypertension, both associated with poor HFpEF outcomes. In addition, a lower TAPSE/SPAP ratio is associated with increasing natriuretic peptide levels, worse hemodynamic status, lower exercise capacity, and lower ventilatory efficiency. Accordingly, the TAPSE/SPAP ratio, as a right ventricular function parameter, is proposed for risk stratification to identify HFpEF subgroups[26], as COPD patients, which may benefit from specific therapeutic right ventricular dysfunction strategies.

However, as proposed by Paulus et al[27"], HFpEF and HFrEF have a different pathophysiology. HFrEF processes start with primary ischemic or oxidative damage of cardiomyocytes. Instead, multiple co-morbidities increase systemic pro-inflammatory response, which triggers endothelial damage leading to microvascular coronary inflammation, and, ultimately, to myocardial dysfunction in HFpEF patients.

Furthermore, hormonal deficiency appears as an independent factor, since comorbidity prevalence was similar in patients with or without deficiencies. Only subclinical hypothyroidism demonstrated higher atrial fibrillation prevalence

Table IV. Echocardiographic parameters in patients with or without testosterone deficiency.

	Normal testosterone		Testosterone deficiency		
	Mean	SD	Mean	SD	p
LVEDD (mm)	48.59	3.87	48.20	4.05	ns
LVESD (mm)	29.47	6.38	31.90	4.15	ns
LVEDV (mL)	94.94	19.69	93.90	10.93	ns
LVESV (mL)	42.18	10.94	42.90	3.35	ns
IVS (mm)	13.94	2.33	13.60	1.84	ns
PW (mm)	11.24	1.30	10.60	1.26	ns
E (mm/s)	578.71	165.82	425.60	202.50	*0.02*
A (mm/s)	664.29	241.65	618.70	267.41	ns
Dt (ms)	239.82	77.72	283.90	204.53	ns
EF (%)	56.29	4.44	68.90	46.50	ns
E/e'	12.41	1.84	11.70	2.00	ns
E/A	0.91	0.21	0.77	0.30	ns
LAV (mL)	87.24	36.18	85.60	21.67	ns
LAVI (mL/m^2)	45.00	17.72	44.00	10.55	ns
TAPSE (mm)	21.65	3.66	21.20	3.29	ns
RVEDV (mm)	27.76	3.27	28.30	4.62	ns
SPAP (mmHg)	33.35	7.42	39.10	5.95	*0.04*
TPV (m/s)	2.64	0.34	2.91	0.25	*0.04*
TAPSE/SPAP	0.68	0.20	0.57	0.16	ns

A = Peak A-wave velocity, DT = Deceleration time, E = Peak E-wave velocity, E' = Pulsed-wave TDI E' velocity, E/A: E/A ratio, E/E' ratio, IVS = Septal thickness, LAV = left atrial volume, LAVI: left atrial volume indexed, LVEDD = left ventricular telediastolic diameter, LVEDV = left ventricular telediastolic volume, LVEF = left ventricular ejection fraction, LVESD = left ventricular telesystolic diameter, LVESV = left ventricular telesystolic volume, SPAP = Systolic pulmonary artery pressure, PW = Posterior wall thickness, RVEDV = right ventricular mid cavity diameter value, TAPSE = Tricuspid annular plane systolic excursion, TAPSE/SPAP: TAPSE/SPAP ratio, TPV = tricuspidal peak velocity.

without affecting echocardiographic parameters.

In our analysis, the most relevant and statistically significant results are those related to IGF-1 deficiency. IGF-1 and IGFBP-7, as a binding protein, are clinical outcome predictors in HFpEF patients[28]. A higher IGFBP/IGF-1 ratio was significantly associated with left atrial enlargement, increased E/e' ratio, and NT-proBNP levels. Therefore, IGF-1 decrease or IGFBP-7 increases were associated with a poor clinical course triggering fibrosis mechanism. This suggestion is based on different mechanisms present in other diseases, such as liver fibrosis[29]. IGF-1 deficiency or increased IGFBP-7/IGF-1 ratio could be associated with increased collagen deposition in the myocardium, contributing to fibrosis and increased stiffness, both causing diastolic dysfunction, similarly to mechanisms in the liver. In favor of this hypothesis, an elevated soluble suppression of tumorigenicity-2 (sST2), a known collagen synthesis marker from myocardial fibroblast[30], has been described in patients with higher IGFBP-7/IGF-1[28]. Other links between IGF-1 deficit and diastolic dysfunction were described. Patients with growth hormone (GH) and IGF-1 deficiencies exhibit endothelial dysfunction, reduced nitric oxide (NO) production, and high peripheral vascular resistance. Replacement GH therapy normalizes NO production and peripheral resistance[31]. Reduced NO production could contribute to reduced ventricular compliance in HfpEF patients.

Aging is one of the most important risk factors for HFpEF patients. Both aging and IGF-1 deficiency regulate diastolic dysfunction processes, leading to reduce NO production, increased reactive oxygen species (ROS) production, and mitochondrial dysfunction. Therefore, they could reciprocally potentiate in determining diastolic dysfunction.

Sex hormones are closely related to right ventricle structure and function[32]. In particular, DHEA stimulates both NO and endothelin-1, two important regulators of pulmonary hypertension, although

with antagonistic actions. Therefore, DHEA may have complex pleiotropic effects on pulmonary vascularization and right ventricular function.

Finally, concerning thyroid hormones, we observed different pictures, the most prevalent of which was low-T3, according to literature[33]. Despite subclinical hypothyroidism is reported to affect left ventricular, diastolic, and overall right ventricular function[34], we did not find significant echocardiographic alterations, probably due to the small group of patient (8/40) with such condition.

Medications might have influenced our study results although our patients had stable medications for at least 2 months before inclusion; moreover, HFpEF and HFrEF therapy is the same in both syndromes, including loop diuretics, ACEi or ARB and BBs. Giustina and Veldhuis[35] suppose a blunting effect of BBs on the GH/IGF-1 axis. However, results are conflicting[36]. According to data of Arcopinto et al[36] HF patients with normal or reduced GH secretion showed similar usage of BBs (78% in GH sufficient, and 75% in GH deficient patients) and of other classes of drugs: ACEi, ARB, Digoxin, Spironolactone, and diuretics.

About ACEi, 10 mg Enalapril twice a day for 8 weeks were demonstrated to increase IGF-1 levels in HFrEF patients, possibly as a consequence of the clinical improvement[37] however no studies on HFpEF patients are reported in literature.

Therapeutic implications of our observations could be hypothesized. Maison and Chanson[38] evaluated anabolic hormone effects in HFrEF patients. A meta-analysis, focused on GH treatment effects in HFrEF patients, highlighting the importance of GH on right ventricular function. Patients treated with recombinant GH showed a significantly reduced mean pulmonary systolic arterial pressure, increased cardiac output, and reduced peripheral vascular resistance. GH/IGF-1 axis deficiency may contribute to HFpEF aggravation because pulmonary hypertension, increased peripheral vascular resistance, and impaired ventricular arterial coupling are important pathophysiological mechanisms. Patients with IGF-1 deficit demonstrated also increased left atrial volume values. Atrial volume is related to left ventricular diastolic pressure, and it is a hospitalization risk predictor in HFpEF patients[39].

Effects of T administration are still debated. Long term epidemiological trials suggested a protective effect of T treatment in the reduction of major adverse cardiovascular events and mortality[40]. On the contrary, other raised doubts on this topic[41-44]. In fact, an increased risk has been claimed; a trial performed in elderly with limited lower extremity mobility was stopped because higher rate of cardiovascular events in the treated group *vs.* placebo occurred[45]. Another retrospective cohort analysis in male veterans[46] showed that T was associated with increase in events. Finally, a cohort study aimed to evaluate the risk of developing a nonfatal myocardial infarction after an initial prescription of T replacement therapy found an increased age-related risk[47]. A key point is that not all studies reported basal values of T; therefore, the term "replacement therapy" does not seem to be appropriate, as also remarked by the positive results reported in other studies[48].

Finally, few studies reported T3 administration effects in HFrEF, despite recognizing Low T3 syndrome as a poor prognostic indicator[49,50].

Short-term T3 administration in patients with dilated cardiomyopathy improved ventricular performance and the neuroendocrine profile, with reduction of NT-proBNP, aldosterone, and noradrenaline levels[51]. Similarly, a randomized, double blind, placebo-controlled study with stable chronic heart failure patients taking supplementary T3 for 6 weeks, showed beneficial effects in six-minute walking test, left ventricular EF, and NT-proBNP levels[52].

However, at the best of our knowledge, no trials about T3 supplementation have been reported in HFpEF. Our study could represent the pathophysiological basis for a personalized hormonal replacement therapy, based on the deficiencies observed in individual patients.

We collected our data in a single-center setting on a relatively small sample (a population of 40 patients). Nearly all HFpEF patients belonged to functional NYHA class III, a more advanced class compared to previously described studies. A larger population, including equally different NYHA functional classes would reveal more representative data.

Conclusions

Our data demonstrate high multihormonal deficiency prevalence in HFpEF patients and suggest hormonal impacts on diastolic dysfunction parameters. Furthermore, hormonal dysfunction seems to be independent from comorbidities in HFpEF patients, which appears to be a "multifactorial" syndrome, opening new management paths for HFpEF.

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Conflict of Interests

We have no conflicts of interest to declare.

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