

Research Article

Anabolic Hormone Deficiencies in Heart Failure with Reduced or Preserved Ejection Fraction and Correlation with Plasma Total Antioxidant Capacity

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Background. While anabolic hormone deficit is a common finding in heart failure with reduced ejection fraction (HFrEF), few data are available in heart failure with preserved ejection fraction (HFpEF). **Methods.** Blood samples were collected for metabolic (total cholesterol, HDL cholesterol, LDL cholesterol, creatinine, and glucose) and hormonal (IGF-1, DHEA-S, TSH, fT3, fT4, and T) determination, comparing 30 patients with HFpEF and 20 patients with HFrEF. Total antioxidant capacity was evaluated by using the spectrophotometric method using the latency time in the appearance of the radical species of a chromogen (LAG, sec) as a parameter proportional to antioxidant content of the sample. Echocardiographic parameters were also assessed in the two groups. **Results.** A high prevalence of testosterone (32% in HFrEF and 72% in HFpEF, $p < 0.05$) and DHEA-S deficiencies was observed in HFpEF patients. Echocardiographic parameters did not correlate with hormone values. A significant direct correlation between T ($r^2 = 0.25$, $p < 0.05$) and DHEA-S ($r^2 = 0.19$, $p < 0.05$) with LAG was observed only in HFpEF. **Conclusion.** Anabolic hormone deficiency is clearly shown in HFpEF, as already known in HFrEF. Although longitudinal studies are required to confirm the prognostic value of this observation, our data suggest different mechanisms in modulating antioxidants in the two conditions, with possible therapeutic implications.

1. Introduction

Chronic heart failure (CHF) is defined as a clinical syndrome based on an unbalance between cardiac output and metabolic requirements of organism [1]. Any structural or functional disorders such as coronary heart disease, hypertension, diabetes, cardiomyopathies, heart valve diseases, arrhythmias, congenital heart defects, anaemia, cocaine abuse, AIDS, thyroid disorders, radiation, and chemotherapy that reduce

the ability of the ventricle to fill with or eject an adequate volume of blood may be the cause of this condition. It is a staggering plague for our times since its prevalence is around 1-2% of the adult population in developed countries, with a peak $\geq 10\%$ among people >70 years of age [2-4].

The main classification of CHF relies on left ventricular ejection fraction (LVEF), evaluated by echocardiography, or, less frequently, myocardial scintigraphy and magnetic resonance of the heart; its measurement identifies three classes

of CHF: from the well known and classic heart failure with reduced ejection fraction (HFrEF), which includes patients with left ventricular ejection fraction (LVEF) <40%, to heart failure with preserved ejection fraction (HFpEF), which comprises patients with LVEF <50%, to the grey area of LVEF in the range of 40–49%, which describes the new entity of heart failure with midrange ejection fraction [1]. HFrEF and HFpEF are the most known subtypes, with a relevant and increasing literature concerning the last one [5, 6]. They are different syndromes, with different pathogenesis, pathophysiology, and therapy. In HFrEF, the hinge point is a direct damage to the heart that leads to reduced left ventricle contraction [7], whereas in HFpEF, diastolic dysfunction is the main mechanism involved, with other features contributing to this scenario such as left atrial dysfunction, right ventricular dysfunction, pulmonary hypertension, and increased vascular stiffness [8–12].

Both the conditions present with a high prevalence of multihormonal deficiencies [13, 14]. The impairment of major anabolic systems (somatotrophic, adrenal, and gonadal) does not appear to represent a mere epiphenomenon but is involved in the CHF pathophysiology; especially low serum testosterone (T), dehydroepiandrosterone-sulfate (DHEA-S), and insulin-like growth factor (IGF)-1 levels have been correlated to the symptoms severity and the adverse outcomes in men suffering from CHF [15–19]. On the contrary, T, DHEA-S, and IGF-1 are known to regulate oxidative stress in different manners [20], exerting pro-oxidative effects or exhibiting an antioxidant power. CHF is a syndrome in which inflammation and OS play a fundamental role, and, in turn, this may point to a pivotal role of these hormonal alterations both in the pathogenesis of CHF and in its treatment.

Total antioxidant capacity (TAC) expresses the whole effects of nonproteic nonenzymatic antioxidants, as widely discussed in previous studies [21, 22]. Previously, we have shown the modulatory action of anabolic hormones on this parameter and its variations in CHF [20, 23].

Thus, the aim of the present study was to explore the correlation between anabolic hormones, echocardiographic parameters, and TAC in HFpEF and HFrEF and correlate them with metabolic parameters (with the aim to better understand the possible molecular consequences of hormonal derangement in these conditions).

2. Materials and Methods

50 subjects involved in this study were admitted to the University Hospital “Policlinico Gemelli” Dept. of Internal Medicine and were enrolled after being given an explanation of purposes and nature of the study, conducted in accordance with the Declaration of Helsinki, as revised in 2013. The study protocol was approved by the Institutional review board of “Medical Pathology” of our University Hospital.

Twenty patients with HFrEF, aged 42–88 years (mean 69.5), and thirty patients with HFpEF, aged 59–90 years (mean 77.7), were recruited. The diagnosis of HFpEF was established according to the current guidelines of the European Society of Cardiology [1]. Patients with end-stage renal disease, liver cirrhosis, and neoplastic or autoimmune

diseases were excluded. All patients were nonsmokers or had stopped smoking for at least a year. Clinical, anthropometric, and echocardiographic evaluations were achieved, including the main risk factors for cardiovascular disease. Prevalence of comorbidities (T2DM, hypertension, atrial fibrillation, peripheral atherosclerosis, non-end-stage chronic kidney disease, and COPD) was evaluated. The two groups were not significantly different for age, BMI, and NYHA classes (all belonged to class II-III).

Between 08.30 and 09.00 a.m., after an overnight fast, a polyethylene catheter was inserted into the antecubital vein of one forearm and the blood was collected using a 6 mL vacutainer blood collection tube containing lithium heparin and immediately centrifuged (4°C at 3000 ×g for 15 min) with aliquots stored at –80°C until assayed.

We evaluated metabolic (glycaemia, insulinemia, and total-HDL-LDL cholesterol) and hormonal pattern (fT3, fT4, TSH, IGF-1, T, DHEA-S, and NT-proBNP).

Fasting glucose and insulin levels were quantified with commercial kits using ADVIA automatic analyser (Siemens, Italy).

Plasmatic concentrations of NT-proBNP, TSH, fT3, fT4, DHEA-S, T, and IGF-1 were measured by using immunochemiluminometric assays on a Roche Modular E170 analyser (Roche Diagnostics, Indianapolis, IN, USA). The intra- and interassay CV for all hormones were, respectively, <5.0% and <7.0%.

Normal ranges in our laboratory were NT-proBNP (>126 pg/ml), TSH (0.4–3.2 μUI/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 limit of normal ranges were used to define as deficiency. For IGF-1, due to the age-related variations, we applied, to define IGF-1 deficiency, criteria of the TOSCA registry referring to the 33th percentile of a population of men with chronic heart failure (i.e., 122 ng/ml for age range under 55 years, 109 ng/ml for age range 55–64 years, 102 ng/ml for age range 65–74, and 99 ng/ml for age range older than 75 years) [13, 17].

A complete echocardiographic evaluation was performed (Echocardiography Philips, Affiniti 70c), measuring the following parameters: left ventricular ejection fraction (EF), left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic diameter (LV-ESD), left ventricular end-diastolic volume (LVEDV), left ventricular end-systolic volume (LV-ESV), septal thickness (IVS), posterior wall thickness (LV-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), and tricuspid peak velocity (TPV).

Total antioxidant capacity (TAC) was evaluated with the method of Rice-Evans and Miller [21], modified as previously reported [24]. The method is based on the interaction between the system H₂O₂-metmyoglobin with the chromogen ABTS, whose radical form is spectroscopically detectable. The latency time (LAG in sec.) before the appearance of radical species is proportional to the antioxidant concentration in the sample.

HOMA-IR was used as an index of insulin resistance and was obtained from the fasting blood insulin (immunoreactive insulin (IRI)) concentration and the fasting blood sugar (FBS) level early in the morning, based on the following equation: $HOMA-IR = (IRI \times FBS) / 405$.

To estimate the sample sizes, the estimated decrease prevalence of T deficiency between the two groups was set at 20%, based on the only reported work that, at the best of our knowledge, evaluated these data in HFrEF vs HFpEF patients [14], with a type I error rate of 0.05 and a type II error rate of 0.20 (i.e., power of 0.80). Due to the expected effect size, a total of 44 patients were considered adequate.

The Mann-Whitney *U* test was employed to evaluate differences between the two groups of subjects. A *p* value of 0.05 was considered statistically significant. Linear regression analysis was employed to correlate TAC with hormonal parameters. The *X* square test was used to compare percent differences between the two groups, when considering the prevalence of hormone deficiencies and comorbidities.

3. Results

Table 1 shows the echocardiographic parameters: other than ejection fraction, which was different, by definition, other differences were found in LVEDV, LVESV, and LAV, all significantly higher in HFrEF ($p < 0.05$). On the contrary, the A wave was significantly higher in HFpEF ($p < 0.05$).

Comorbidities, as expected, were more prevalent in HFpEF patients (41% T2DM, 72% hypertension, 36% atrial fibrillation, 68% peripheral atherosclerosis, 63% non-end-stage chronic kidney disease, and 36% COPD) than in HFrEF patients (30% T2DM, 39% hypertension, 44% atrial fibrillation, 5% peripheral atherosclerosis, 33% non-end-stage chronic kidney disease, and 16% COPD). *X* square analysis showed a significant difference only in hypertension and peripheral atherosclerotic disease ($p < 0.05$).

Table 2 shows the metabolic and hormonal parameters in the two groups. Significant differences were observed in NT-proBNP, total cholesterol, and T, with higher levels in HFrEF. LAG values were not significantly different between the two groups despite higher prevalence of comorbidities in HFpEF.

Figure 1 shows the graphical representation of percent prevalence of T deficiency, and DHEA-S levels were under the normal range in all but two patients. The prevalence of T deficiency was significantly different between the two groups using the *X* square test ($p < 0.05$).

No significant correlation was present when correlating T or DHEA-S with echocardiographic parameters. On the contrary, both T and DHEA-S significantly correlated with LAG values, but only in patients with HFpEF (Figure 2).

4. Discussion

Our data confirm a high prevalence of anabolic hormones deficit in the two HF subgroups, thus expanding the concept that anabolic deficiencies are a common finding not only in HFrEF but also in HFpEF, a poorly explored condition in this concern. We found a significant difference in the

TABLE 1: Echocardiographic parameters in the two subgroups of heart failure, with preserved or reduced ejection fraction (HFpEF and HFrEF, respectively).

	HFpEF	HFrEF	<i>p</i>
LV-EDV (ml)	48.6 ± 1	146 ± 13	<0.05
LV-ESV (ml)	31.1 ± 1.8	91 ± 10	<0.05
LV-PW (mm)	10.9 ± 0.6	10.6 ± 0.6	n.s.
E (mm/s)	575.3 ± 74.6	347 ± 152	n.s.
A (mm/s)	789.6 ± 63.3	334 ± 110.74	<0.05
EF (%)	55.7 ± 0.8	36.91 ± 2	<0.05
E/A	0.8 ± 0.1	1.10 ± 0.38	n.s.
E/e'	11.9 ± 1.2	12.42 ± 2.86	n.s.
LAV (ml)	86.4 ± 8.9	117.86 ± 12	<0.05
TAPSE (mm)	21.3 ± 0.9	19.5 ± 1.21	n.s.
SPAP (mmHg)	35.9 ± 2.4	42 ± 4.84	n.s.

LV-EDV = left ventricular end-diastolic volume; LV-ESV = left ventricular end-systolic volume; LV-PW = left ventricular posterior wall thickness; E = E wave; A = A wave; e' = e' wave; EF = ejection fraction; LAV = left atrial volume; TAPSE = tricuspid annular plane systolic excursion; SPAP = systolic pulmonary arterial pressure.

TABLE 2: Mean ± SEM values of clinical, metabolic, and hormonal values in the two subgroups of heart failure, with preserved or reduced ejection fraction (HFpEF and HFrEF, respectively).

	HFpEF	HFrEF	<i>p</i>
NHYA class	II (<i>n</i> = 12) III (<i>n</i> = 18)	II (<i>n</i> = 10) III (<i>n</i> = 10)	
NT-proBNP (pg/ml)	2862.2 ± 488.5	7500.16 ± 2459.5	<0.05
Total cholesterol (mg/dl)	125.5 ± 6.9	153.6 ± 10.9	<0.05
HDL-C (mg/dl)	34.4 ± 2	44.47 ± 5.2	n.s.
LDL-C (mg/dl)	75.7 ± 7.3	91.36 ± 7.3	n.s.
Creatinine (mg/dl)	1.3 ± 0.1	1.27 ± 0.1	n.s.
Insulin (μUI/ml)	11.8 ± 1.4	25.32 ± 9.9	n.s.
Glucose (mg/dl)	88.5 ± 4.7	94.95 ± 8.4	n.s.
HOMA-IR	2.8 ± 0.5	3.68 ± 1.3	n.s.
BMI (kg/m ²)	28.7 ± 1.1	28.03 ± 1.2	n.s.
IGF-1 (ng/ml)	89.4 ± 7.1	112.78 ± 11.8	n.s.
DHEA-S (ng/ml)	438.9 ± 61.1	564.1 ± 140.3	n.s.
TSH (μU/ml)	2.5 ± 0.5	2.82 ± 1.0	n.s.
fT3 (pg/ml)	2.4 ± 0.1	2.5 ± 0.1	n.s.
fT4 (pg/ml)	11.3 ± 0.5	11.28 ± 0.5	n.s.
T (ng/ml)	2.4 ± 0.2	3.55 ± 0.5	<0.05
LAG (sec)	83 ± 6.7	75.77 ± 7.5	n.s.

prevalence of low T in HFpEF; this datum is not fully in agreement with the only report of hormone evaluation in HFpEF [13]; however, the difference in age of patients could contribute to these results. Nevertheless, ageing seems not to be the only factor influencing hormone picture in these patients since T levels correlated with LAG in this specific group, suggesting a possible link between T, oxidative stress, and cardiac function.

Focusing on T levels, there are several evidences that, in HFrEF, low levels can represent a bad prognostic sign [18, 25]. At the state of knowledge, the same conclusion in HFpEF cannot be sustained due to the lack of large longitudinal studies.

We have neither found correlations between T or DHEA-S levels and echocardiographic parameters nor

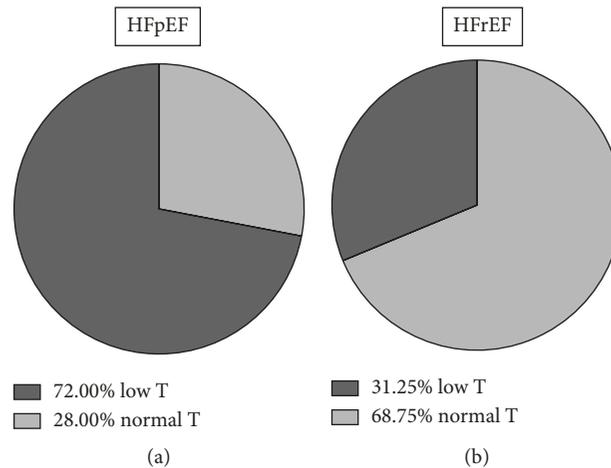


FIGURE 1: Percentage of patients with low testosterone levels in the two forms of heart failure (preserved or reduced ejection fraction, HFpEF and HFrEF, respectively).

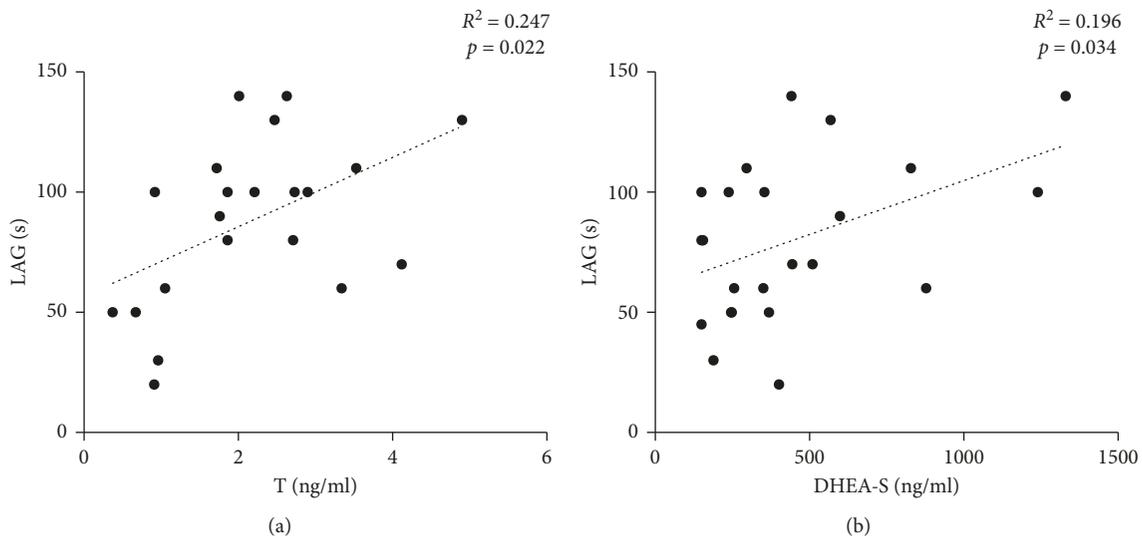


FIGURE 2: Graphical representation of correlation between LAG (latency time in the appearance of radical species, see text for the method), as a parameter of total antioxidant capacity and levels of testosterone T (a) or DHEA-S (b) in patients with heart failure with preserved ejection fraction (HFpEF).

differences comparing patients with low or normal T and low or normal DHEA-S.

On the contrary, interesting data emerge when correlating hormonal levels with TAC. Previously, we have shown that antioxidant systems can counteract OS in patients with HFrEF when one single hormonal deficit is detected, while such compensation is less effective when more deficits ensue [20].

This is the first report on TAC in HFpEF. We have found a significant correlation between T and DHEA-S with LAG in such model, while this is not evident in HFrEF.

Two consequences can be argued from these data: first, an important role of anabolic hormones in modulating antioxidant systems in HFpEF; second, different pathophysiological mechanisms underlying the two models of HF.

For both hormones, conflicting data are reported in literature showing pro-oxidant or antioxidant effects,

depending on concentration or different models studied. For instance, DHEA-S administration can induce oxidative stress in hearts of male wistar rats, defining various histologic cardiac lesions in rats, such as misshapen cell nuclei, leukocytic infiltrates, disorganized myocardial fibers, and echocardiographic alterations (increased LV-PW and LV-ESD) [26, 27], while it exerts a protective role in the liver of diabetic rats [28] and rats with obstructive jaundice [29]; in ovariectomized rats, it improves nitric oxide (NO) production, vascular function, and blood pressure levels [30]. The results of *in vivo* and *in vitro* studies have shown that DHEA-S limits lipid peroxidation [31, 32]. Moreover, oxidative stress parameters in plasma and in peripheral blood mononuclear cells in diabetic subjects are significantly decreased by DHEA-S treatment [33].

The same double-faced effects are attributed to T. In fact, ROS production in vascular smooth muscle cells in culture is

stimulated by T, especially in hypertensive animal models [34]; T also stimulates xanthine oxidase and therefore superoxide generation [35]; finally, acute administration of T in supraphysiological doses increased NO urinary metabolites in healthy subjects [36]. However, it well established a protective role in ischaemic cardiopathy [37–39]; it is also known that T has a vasodilatory property via nongenomic mechanisms [40].

The literature concerning the T evaluation in CHF has been extensively reviewed, also for the therapeutic implication. T deficiency has a key role in some pathophysiological aspects of CHF, such as reduced muscle mass, abnormal energy handling, dyspnoea, and fatigue [41]. The so-called “muscle hypothesis” is based on functional and structural alterations of myocytes, which are strongly influenced by anabolic hormones [42, 43]. Metabolic influence of T has been also reported [25, 44]. However, some data are still contrasting: total and free T levels have been shown to decrease in elderly patients and related to CHF severity, but they were not independent predictors for mortality [45]. Long-term epidemiological trials were in favour of a protective effect of T treatment in the reduction of major adverse cardiovascular events and mortality [44], even if other meta-analyses raised doubts on this topic [46–49].

Our study clearly shows the correlation of the two hormones with antioxidant systems and is therefore in favour of a positive role on OS, which is one of the main players in the pathophysiology of HF.

According to literature, our patients with HFpEF, with a higher prevalence of obesity and other metabolic comorbidities, exhibited a trend toward increased LAG values. It can be speculated that a further increase in oxidative stress condition could induce a compensatory increase in antioxidant systems, possibly influencing T levels with a reciprocal vicious circle due to the modulatory role of T itself on antioxidants. Such correlation is not evident in the HFrfEF group in which a worse cardiac performance or systemic catabolic status is present in CHF. Therefore, two different pathophysiological models seem to be involved in the two kinds of CHF. As recently proposed, in HFrfEF, the process starts with primary ischaemic or oxidative damage of cardiomyocytes, whereas in HFpEF, a cascade of events is increased by the systemic proinflammatory state related to multiple comorbidities. The resultant endothelial damage leads to microvascular coronary inflammation and, ultimately, to myocardial dysfunction [50].

Nevertheless, there are some potential limitations of the present study. Firstly, the number of subjects is relatively small, and our findings need to be validated in a larger cohort. It is not possible to express a cause-effect relation between anabolic hormones and antioxidant status. Moreover, only one parameter of antioxidant status has been evaluated although, in our previous study, the positive effect of T replacement therapy on TAC in hypogonadal patients was described [51].

In conclusion, deficit of anabolic hormones is clearly revealed in HFpEF, as already known in HFrfEF. Although longitudinal studies are needed to confirm a prognostic

value of this observation, our data suggest a different mechanism in modulating antioxidant systems in these two conditions. Moreover, a possible therapeutic role of antioxidants needs to be investigated, particularly when T therapy is contraindicated.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Disclosure

This manuscript was presented as abstract at the American Society of Andrology 44th Annual Conference, Chicago (IL, USA), April 6–9th 2019.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

References

- [1] P. Ponikowski, A. A. Voors, S. D. Anker et al., “2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure,” *European Heart Journal*, vol. 37, no. 27, pp. 2129–2200, 2016.
- [2] A. Mosterd and A. W. Hoes, “Clinical epidemiology of heart failure,” *Heart*, vol. 93, no. 9, pp. 1137–1146, 2007.
- [3] G. Bleumink, A. Knetsch, M. Sturkenboom et al., “Quantifying the heart failure epidemic: prevalence, incidence rate, lifetime risk and prognosis of heart failure—the Rotterdam study,” *European Heart Journal*, vol. 25, no. 18, pp. 1614–1619, 2004.
- [4] M. M. Redfield, S. J. Jacobsen, J. C. Burnett Jr., D. W. Mahoney, K. R. Bailey, and R. J. Rodeheffer, “Burden of systolic and diastolic ventricular dysfunction in the community,” *JAMA*, vol. 289, no. 2, p. 194, 2003.
- [5] B. A. Borlaug and W. J. Paulus, “Heart failure with preserved ejection fraction: pathophysiology, diagnosis, and treatment,” *European Heart Journal*, vol. 32, no. 6, pp. 670–679, 2011.
- [6] C. Andersson and R. S. Vasan, “Epidemiology of heart failure with preserved ejection fraction,” *Heart Failure Clinics*, vol. 10, no. 3, pp. 377–388, 2014.
- [7] M. W. Bloom, B. Greenberg, T. Jaarsma et al., “Heart failure with reduced ejection fraction,” *Nature Reviews Disease Primers*, vol. 3, no. 1, 2017.
- [8] C. S. P. Lam, V. L. Roger, R. J. Rodeheffer, B. A. Borlaug, F. T. Enders, and M. M. Redfield, “Pulmonary hypertension in heart failure with preserved ejection fraction. A community-based study,” *Journal of the American College of Cardiology*, vol. 53, no. 13, pp. 1119–1126, 2009.
- [9] B. A. Borlaug and D. A. Kass, “Ventricular-vascular interaction in heart failure,” *Cardiology Clinics*, vol. 29, no. 3, pp. 447–459, 2011.
- [10] P. H. Brubaker and D. W. Kitzman, “Prevalence and management of chronotropic incompetence in heart failure,” *Current Cardiology Reports*, vol. 9, no. 3, pp. 229–235, 2007.
- [11] T. T. Phan, G. N. Shivu, K. Abozguia et al., “Impaired heart rate recovery and chronotropic incompetence in patients with heart failure with preserved ejection fraction,” *Circulation: Heart Failure*, vol. 3, no. 1, pp. 29–34, 2010.

- [12] D. W. Kitzman, B. Nicklas, W. E. Kraus et al., "Skeletal muscle abnormalities and exercise intolerance in older patients with heart failure and preserved ejection fraction," *American Journal of Physiology-Heart and Circulatory Physiology*, vol. 306, no. 9, pp. H1364–H1370, 2014.
- [13] M. Arcopinto, A. Salzano, E. Bossone et al., "Multiple hormone deficiencies in chronic heart failure," *International Journal of Cardiology*, vol. 184, no. 1, pp. 421–423, 2015.
- [14] A. Salzano, A. M. Marra, F. Ferrara et al., "Multiple hormone deficiency syndrome in heart failure with preserved ejection fraction," *International Journal of Cardiology*, vol. 225, pp. 1–3, 2016.
- [15] P. E. Kontoleon, M. I. Anastasiou-Nana, P. D. Papapetrou et al., "Hormonal profile in patients with congestive heart failure," *International Journal of Cardiology*, vol. 87, no. 2–3, pp. 179–183, 2003.
- [16] J. E. Nettleship, R. D. Jones, K. S. Channer, and T. H. Jones, "Testosterone and coronary artery disease," *Frontiers of Hormone Research*, vol. 37, pp. 91–107, 2008.
- [17] M. Arcopinto, J. Isgaard, A. M. Marra et al., "IGF-1 predicts survival in chronic heart failure. Insights from the T.O.S.C.A. (Trattamento Ormonale Nello Scompensio CArdiaco) registry," *International Journal of Cardiology*, vol. 176, no. 3, pp. 1006–1008, 2014.
- [18] E. A. Jankowska, B. Biel, J. Majda et al., "Anabolic deficiency in men with chronic heart failure: prevalence and detrimental impact on survival," *Circulation*, vol. 114, no. 17, pp. 1829–1837, 2006.
- [19] Y. Moriyama, H. Yasue, M. Yoshimura et al., "The plasma levels of dehydroepiandrosterone sulfate are decreased in patients with chronic heart failure in proportion to the severity," *Journal of Clinical Endocrinology & Metabolism*, vol. 85, no. 5, pp. 1834–1840, 2000.
- [20] A. Mancini, E. Vergani, C. Bruno et al., "Oxidative stress as a possible mechanism underlying multi-hormonal deficiency in chronic heart failure," *European Review for Medical and Pharmacological Sciences*, vol. 22, no. 12, pp. 3936–3961, 2018.
- [21] C. Rice-Evans and N. J. Miller, "[241 total antioxidant status in plasma and body fluids," *Methods in Enzymology*, vol. 234, pp. 279–293, 1994.
- [22] A. Mancini, S. Raimondo, M. Persano et al., "Estrogens as antioxidant modulators in human fertility," *International Journal of Endocrinology*, vol. 2013, Article ID 607939, 6 pages, 2013.
- [23] A. Mancini, R. Festa, V. Donna et al., "Hormones and antioxidant systems: role of pituitary and pituitary-dependent axes," *Journal of Endocrinological Investigation*, vol. 33, no. 6, pp. 422–433, 2010.
- [24] A. Mancini, E. Leone, R. Festa et al., "Evaluation of antioxidant systems (coenzyme Q10 and total antioxidant capacity) in morbid obesity before and after biliopancreatic diversion," *Metabolism*, vol. 57, no. 10, pp. 1384–1389, 2008.
- [25] V. A. Giagulli, E. Guastamacchia, G. D. Pergola, M. Iacoviello, and V. Triggiani, "Testosterone deficiency in male: a risk factor for heart failure," *Endocrine, Metabolic & Immune Disorders-Drug Targets*, vol. 13, no. 1, pp. 92–99, 2013.
- [26] M. H. V. M. Jacob, D. d. R. Janner, A. Belló-Klein, S. F. Llesuy, and M. F. M. Ribeiro, "Dehydroepiandrosterone modulates antioxidant enzymes and Akt signaling in healthy Wistar rat hearts," *The Journal of Steroid Biochemistry and Molecular Biology*, vol. 112, no. 1–3, pp. 138–144, 2008.
- [27] E. Emer, O. Yildiz, M. Seyrek et al., "High-dose testosterone and dehydroepiandrosterone induce cardiotoxicity in rats: assessment of echocardiographic, morphologic, and oxidative stress parameters," *Human & Experimental Toxicology*, vol. 35, no. 5, pp. 562–572, 2016.
- [28] M. Aragno, E. Tamagno, V. Gatto et al., "Dehydroepiandrosterone protects tissues of streptozotocin-treated rats against oxidative stress," *Free Radical Biology and Medicine*, vol. 26, no. 11–12, pp. 1467–1474, 1999.
- [29] F. Çelebi, I. Yilmaz, H. Aksoy, M. Gümüş, S. Taysi, and D. Oren, "Dehydroepiandrosterone prevents oxidative injury in obstructive jaundice in rats," *Journal of International Medical Research*, vol. 32, no. 4, pp. 400–405, 2004.
- [30] J. P. G. Camporez, E. H. Akamine, A. P. Davel, C. R. Franci, L. V. Rossoni, and C. R. de Oliveira Carvalho, "Dehydroepiandrosterone protects against oxidative stress-induced endothelial dysfunction in ovariectomized rats," *The Journal of Physiology*, vol. 589, no. 10, pp. 2585–2596, 2011.
- [31] G. Bocuzzi, M. Aragno, M. Seccia et al., "Protective effect of dehydroepiandrosterone against copper induced lipid peroxidation in the rat," *Free Radical Biology and Medicine*, vol. 22, no. 7, pp. 1289–1294, 1997.
- [32] A. Khalil, J.-G. Lehoux, R. J. Wagner et al., "Dehydroepiandrosterone protects low density lipoproteins against peroxidation by free radicals produced by gamma-radiolysis of ethanol-water mixtures," *Atherosclerosis*, vol. 136, no. 1, pp. 99–107, 1998.
- [33] E. Brignardello, C. Runzo, M. Aragno et al., "Dehydroepiandrosterone administration counteracts oxidative imbalance and advanced glycation end product formation in type 2 diabetic patients," *Diabetes Care*, vol. 30, no. 11, pp. 2922–2927, 2007.
- [34] A. Z. Chignalia, E. Z. Schuldt, L. L. Camargo et al., "Testosterone induces vascular smooth muscle cell migration by NADPH oxidase and c-Src-dependent pathways," *Hypertension*, vol. 59, no. 6, pp. 1263–1271, 2012.
- [35] Y. Puttabyatappa, J. N. Stallone, A. Ergul et al., "Peroxynitrite mediates testosterone-induced vasodilation of microvascular resistance vessels," *Journal of Pharmacology and Experimental Therapeutics*, vol. 345, no. 1, pp. 7–14, 2013.
- [36] C. Skogastierna, M. Hotzen, A. Rane, and L. Ekström, "A supraphysiological dose of testosterone induces nitric oxide production and oxidative stress," *European Journal of Preventive Cardiology*, vol. 21, no. 8, pp. 1049–1054, 2014.
- [37] V. A. Cameron, T. J. Mocatta, A. P. Pilbrow et al., "Angiotensin type-1 receptor A1166C gene polymorphism correlates with oxidative stress levels in human heart failure," *Hypertension*, vol. 47, no. 6, pp. 1155–1161, 2006.
- [38] C. J. Howe, M. M. LaHair, J. A. McCubrey, and R. A. Franklin, "Redox regulation of the calcium/calmodulin-dependent protein kinases," *Journal of Biological Chemistry*, vol. 279, no. 43, pp. 44573–44581, 2004.
- [39] J. R. Erickson, M.-I. A. Joiner, X. Guan et al., "A dynamic pathway for calcium-independent activation of CaMKII by methionine oxidation," *Cell*, vol. 133, no. 3, pp. 462–474, 2008.
- [40] R. D. Jones, K. M. English, P. J. Pugh, A. H. Morice, T. H. Jones, and K. S. Channer, "Pulmonary vasodilatory action of testosterone: evidence of a calcium antagonistic action," *Journal of Cardiovascular Pharmacology*, vol. 39, no. 6, pp. 814–823, 2002.
- [41] M. Volterrani, G. Rosano, and F. Iellamo, "Testosterone and heart failure," *Endocrine*, vol. 42, no. 2, pp. 272–277, 2012.
- [42] A. J. S. Coats, A. L. Clark, M. Piepoli, M. Volterrani, and P. A. Poole-Wilson, "Symptoms and quality of life in heart failure: the muscle hypothesis," *Heart*, vol. 72, no. 2 Suppl, pp. S36–S39, 1994.

- [43] M. F. Piepoli, A. Kaczmarek, D. P. Francis et al., “Reduced peripheral skeletal muscle mass and abnormal reflex physiology in chronic heart failure,” *Circulation*, vol. 114, no. 2, 2006.
- [44] T. Jones and D. Kelly, “Randomized controlled trials—mechanistic studies of testosterone and the cardiovascular system,” *Asian Journal of Andrology*, vol. 20, no. 2, p. 120, 2018.
- [45] H.-Y. Wu, X.-F. Wang, J.-H. Wang, and J.-Y. Li, “Testosterone level and mortality in elderly men with systolic chronic heart failure,” *Asian Journal of Andrology*, vol. 13, no. 5, pp. 759–763, 2011.
- [46] R. A. Kloner, C. Carson, A. Dobs, S. Kopecky, and E. R. Mohler, “Testosterone and cardiovascular disease,” *Journal of the American College of Cardiology*, vol. 67, no. 5, pp. 545–557, 2016.
- [47] O. M. Calof, A. B. Singh, M. L. Lee et al., “Adverse events associated with testosterone replacement in middle-aged and older men: a meta-analysis of randomized, placebo-controlled trials,” *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences*, vol. 60, no. 11, pp. 1451–1457, 2005.
- [48] R. M. Haddad, C. C. Kennedy, S. M. Caples et al., “Testosterone and cardiovascular risk in men: a systematic review and meta-analysis of randomized placebo-controlled trials,” *Mayo Clinic Proceedings*, vol. 82, no. 1, pp. 29–39, 2007.
- [49] M. M. Fernández-Balsells, M. H. Murad, M. Lane et al., “Clinical review 1: adverse effects of testosterone therapy in adult men: a systematic review and meta-analysis,” *The Journal of Clinical Endocrinology & Metabolism*, vol. 95, no. 6, pp. 2560–2575, 2010.
- [50] W. J. Paulus and C. Tschöpe, “A novel paradigm for heart failure with preserved ejection fraction: comorbidities drive myocardial dysfunction and remodeling through coronary microvascular endothelial inflammation,” *Journal of the American College of Cardiology*, vol. 62, no. 4, pp. 263–271, 2013.
- [51] A. Mancini, E. Leone, R. Festa et al., “Effects of testosterone on antioxidant systems in male secondary hypogonadism,” *Journal of Andrology*, vol. 29, no. 6, pp. 622–629, 2008.



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