

Inverse Correlation between Testosterone and Ventricle Ejection Fraction, Hemodynamics and Exercise Capacity in Heart Failure Patients with Erectile Dysfunction

Edimar A. Bocchi, Vitor O. Carvalho, Guilherme V. Guimaraes

Laboratory of Heart Failure and Transplantation, Heart Institute, Incor, University of Sao Paulo, SP, Brazil

ABSTRACT

Background: Neurohormonal activation and abnormalities in growth hormone and testosterone concentrations have been reported in heart failure (HF). Erectile dysfunction(ED) is common in these patients and contributes to a low quality of life. No data are known regarding the correlation between testosterone and hemodynamics, exercise capacity and cardiac function in HF patients with ED, a marker of endothelial dysfunction. The aim of this study was to correlate testosterone levels with cardiac function, hemodynamic and exercise capacity in HF patients with ED.

Materials and Methods: Fifteen HF patients underwent a six-minute treadmill cardiopulmonary walking test (6'CWT) and, ten minutes later, a maximum cardiopulmonary exercise test. Also, testosterone and other hormones were determined at rest.

Results: Among hemodynamic variables only diastolic blood pressure on 6'CWT was correlated with testosterone levels($r = -0.66$, $p = 0.007$). The variables on exercise tests, VE/VCO₂ slope and oxygen consumption did not show any correlation, except the distance at 6'CWT ($r = 0.50$, $p = 0.047$). Right and left ventricle ejection fraction showed inverse correlation with testosterone ($r = -0.55$, $p = 0.03$ and $r = -0.69$, $p = 0.004$ respectively).

Conclusion: Testosterone levels correlated directly with distance at six-minute cardiopulmonary walk test and inversely with diastolic blood pressure, right and left ventricle ejection fraction in heart failure patients with erectile dysfunction. Further elucidation of mechanisms as regards testosterone action in these patients is warranted.

Key words: heart failure; hemodynamics; physical activity; testosterone; erectile dysfunction

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INTRODUCTION

Heart failure (HF) can be considered as the last stage of heart disease and a significant cause of mortality and morbidity worldwide (1). The left ventricular systolic dysfunction and limited exercise capacity manifested by breathlessness and fatigue are determinants of mortality and clinical events in the follow-up of HF patients. (2,3). Multiple mechanisms

have been reported to be related to exercise capacity including diastolic and systolic cardiac function, reflex, metabolic, vascular and muscular response (3). Sexual satisfaction is an important component that influences quality of life in HF patients. Erectile dysfunction (ED) affects 60 to 70% of HF clinic outpatients (4). Symptoms, hormonal abnormalities, hemodynamic status, medication side effects and psychological factors are the major contributors to this sexual disorder.

In the physiopathology of chronic HF, the neurohormonal hypothesis for progression of heart failure has been considered of greater interest than the original hemodynamic mechanisms (5). Activation of sympathetic nervous system, renin-angiotensin-aldosterone system, arginine vasopressin, and endothelins are considered as neurohormonal targets in the treatment of HF. However, other hormonal abnormalities have been reported in HF such as significant decrease in growth hormones, insulin-like growth factor I and testosterone concentrations (6). The hormonal and cytokine activation contributes to peripheral muscle tissue wasting as well as anabolic/catabolic imbalance (7). In men, testosterone seems to play a role in determining anabolic function, anti-inflammatory and vasodilator processes. No data has been reported as regards testosterone's effect on hemodynamics, cardiac function and exercise capacity in HF patients with ED.

The aim of this study was to evaluate the correlation between serum testosterone levels and cardiac function, hemodynamics, and exercise capacity in HF patients with ED. In addition, we determined a HF hormone profile: serum levels of prolactin, luteinizing hormone, follicle-stimulating hormone, resting norepinephrine, and thyroid hormones.

MATERIALS AND METHODS

Studied Population

Fifteen randomized chronic male HF patients, 50 ± 10 years with ED (Table-1) for at least four months, in a steady relationship and presenting interest in sex were included. ED was defined as the inability to achieve or maintain a durable erection to permit satisfactory sexual intercourse (the 5th-item of the International Index of Erectile Dysfunction) (8,9). Patients were in stable clinical condition for three months without testosterone replacement or drugs that could have affected testosterone levels, as finasteride, opiates, glucocorticoids and anticonvulsants. All patients were sedentary and did not have heavy alcohol consumption, nephrotic syndrome or liver cirrhosis history. All patients were evaluated for ED etiology such as arterial insufficiency, venous leakage or penile fibrosis. No etiology was found, except HF

syndrome. The protocol was approved by the Ethical Committee of the Heart Institute. Subjects provided written informed consent before participation. Exclusion criteria: ED secondary to causes other than HF, previous ED therapy, recent use of phosphodiesterase inhibitors, psychiatric or psychological disorders, unstable angina or recent myocardial infarction, syncope, high-risk arrhythmias, disease with limitation for exercise except HF, and symptomatic hypotension or systolic blood pressure (SBP) < 85 mm Hg.

Exercise Protocol

We measured systolic blood pressure (SBP) and diastolic blood pressure (DBP) with the patient in an upright position immediately before each exercise test, at the last minute of the six-minute walking test (6'WT), at maximum exercise peak, and at 1-minute recovery (10). Electrocardiography was continuously monitored. Pulmonary ventilation and gas exchange data were determined on a breath-by-breath basis with a computerized system (model Vmax 229 Sormedics). The six-minute walking test (6'WT) was performed using a programmable treadmill without inclination and with patient-controlled speed (Series 2000, Marquette Electronics) at least 2 hours after a light meal and with controlled room temperature (21°C to 23°C). The patients were oriented to walk according to Borg's scale, with exertion level ranging from light to somewhat hard, from 11 to 13. After return of heart rate (HR), SBP, DBP, and symptoms to basal condition, patients underwent a progressive exercise test using a modified Naughton protocol. They were encouraged to perform maximum exercise until exhaustion or the onset of non tolerated symptoms occurred and the respiratory exchange ratio exceeded 1.0. The peak oxygen consumption (peak VO_2) was considered the maximum reached VO_2 value.

Cardiac Function and Hormonal Determinations

The right ventricular and left ventricular ejection fraction (RVEF and LVEF, respectively), as a percentage, were determined by echocardiogram. Hormonal dosage at rest before the exercise test included determination of serum total testosterone (fluoroimmunoassay method), prolactin, luteinizing

Table 1 – Characteristics of patients with erectile dysfunction.

Characteristics of Heart Failure Patients	N of Patients (%) or Value
Etiology	
Ischemic	22
Chagasic	22
Idiopathic dilated cardiomyopathy	26
Hypertensive	26
Valvular	4
NYHA functional class	
II	83
III	13
IV	4
Diuretics	91
ACE inhibitor	67
Angiotensin II AT1 receptor antagonists	8
β-Adrenergic receptor blocker	61
Spironolactone	61
Amiodarone	17
Isosorbide 5-mononitrate (40 mg)	9
Total cholesterol, mg/dL	203 ± 49
HDL cholesterol, mg/dL	46 ± 13
LDL cholesterol, mg/dL	130 ± 41
Triglycerides, mg/dL	155 ± 145
Duration of ED symptoms, months	24 ± 19
Duration of CHF symptoms, months	61 ± 49

Values are mean ± SD or n (%); ACE = angiotensin-converting enzyme inhibitor; CHF-symptoms = congestive heart failure; ED = erectile dysfunction.

hormone, norepinephrine and follicle stimulating hormone. The normal value of testosterone in this study was 200-950 ng/dL. Lipid profile assessment was total cholesterol, HDL cholesterol, LDL cholesterol, Triglycerides. Due to hormonal circadian rhythms, all these tests were performed in the same period (early morning).

Statistical Analysis

The descriptive analysis was presented as mean and standard deviation. The variables studied underwent the non-parametric Spearman test for correlation, considering $p < 0.05$ (SPSS Statistical

Software for Windows version 11.5. Inc., Chicago, IL, USA).

RESULTS

All patients had total testosterone serum levels in the range for normal subjects (200-950 ng/dL). Four patients had prolactin serum levels below the normal range (2.5-11.5 ng/mL). One patient had hypothyroidism and the other hyperthyroidism. The cardiac function, left ventricular diameters, and hormonal values of patients are reported in Table-2. Table-3 shows the hemodynamic and exercise variables.

Table 2 – Cardiac function, left ventricular diameters and hormonal values in patients with erectile dysfunction.

Variables of Heart Failure Patients	Number of Patients or Value
LV ejection fraction (echo) %	23 ± 7
RV ejection Fraction (echo) %	28 ± 8
LV end-diastolic diameter (echo), mm	72 ± 16
LV end systolic diameter (echo), mm	58 ± 55
Hypothyroidism/hyperthyroidism	2 patients
Serum total testosterone, ng/dL (normal 200-950)	604 ± 203
Prolactin, ng/mL (normal 2.5-11.5)	4.2 ± 2.3
Luteinizing hormone, IU/L (normal 1.4-9.2)	3.6 ± 1.9
Follicle-stimulating hormone, IU/L (normal 1-12)	4.2 ± 2.8
Resting norepinephrine, pg/mL (normal 40-268)	448 ± 214

Values are mean ± SD or n (%); LV= left ventricular; RV= right ventricular.

Table 3 – Hemodynamic and exercise variables.

Variable	p Value
HR 6m	111 ± 105 bpm
SBP 6m	141 ± 133 mmHg
DBP 6m	74 ± 71 mmHg
HR max	134 ± 127 bpm
SBP max	138 ± 128 mmHg
DBP max	78 ± 74 mmHg
Distance 6m	0.20 ± 0.03 miles
Slope 6m	31.7 ± 7
VO ₂ 6m	11.9 ± 2.9 mL/Kg/min
Slope Max	34.3 ± 8.7
VO ₂ Max	17.8 ± 3.9 mL/Kg/min
Time Max	12.3 ± 8 min

HR 6m = Heart rate at last six minutes at six minutes cardiopulmonary walking test; SBP6m = systolic blood pressure at last six minutes on 6m cardiopulmonary walking test; DBP6m = BP at last six minutes on 6m cardiopulmonary walking test; HRmax = Heart rate at peak on maximum cardiopulmonary test; SBP max = SBP at peak on maximum cardiopulmonary test; DBP max = DBP at peak on maximum cardiopulmonary test. Distance 6m = distance on 6m cardiopulmonary walking test; Slope 6min = slope VE/VCO₂ on 6m cardiopulmonary walking test; VO₂ 6min = Oxygen consumption at six minutes of 6m cardiopulmonary walking test; SlopeMax = Slope VE/VCO₂ at maximum cardiopulmonary test; VO₂Max = VO₂ peak at maximum cardiopulmonary test; Time Max = Total time at maximum cardiopulmonary test.

Correlation between Testosterone Serum Levels and Cardiac Diameters, Cardiac Function, and Hemodynamic Data

Left ventricle ejection fraction (r = -0.69, p = 0.004) (Figure-1) and right ventricle ejection fraction (r = -0.55, p = 0.03) (Figure-1) showed inverse correlation with testosterone levels. SBP, DBP and heart rate during MCT (maximum cardiopulmonary test) did not show any correlation with testosterone levels or any hormonal serum levels except for DBP during the 6'WT that correlated with testosterone (r = -0.66, p = 0.007) (Figure-2). Left ventricular end diastolic diameter and left ventricular end systolic diameter did not show any correlation with testosterone levels either (Table-4)

Correlation between Hormonal Levels and Exercise Capacity Data

Exercise capacity variables on 6'CWT, VE/VCO₂ slope at six minutes, oxygen consumption at six minutes did not any show correlation with testosterone levels or hormonal serum levels. Only maximum distance at 6'CWT showed correlation (r = 0.50, p = 0.047) with testosterone levels. Also during the MCT, maximum VE/VCO₂ slope, maximum oxygen consumption and time of maximum test did not show correlation either (Table-4)

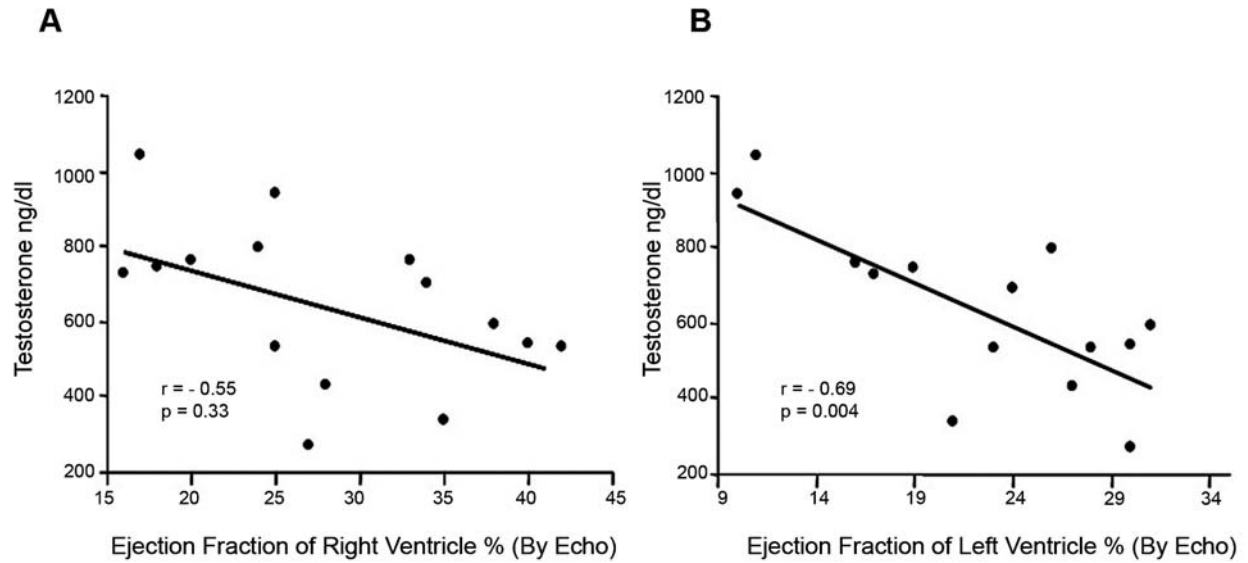


Figure 1 – A) Regression linear plots in all patients between total testosterone and right ventricular ejection fraction (% by echography). B) Regression linear plots in all patients between total testosterone serum levels and left ventricular ejection fraction (% by echography).

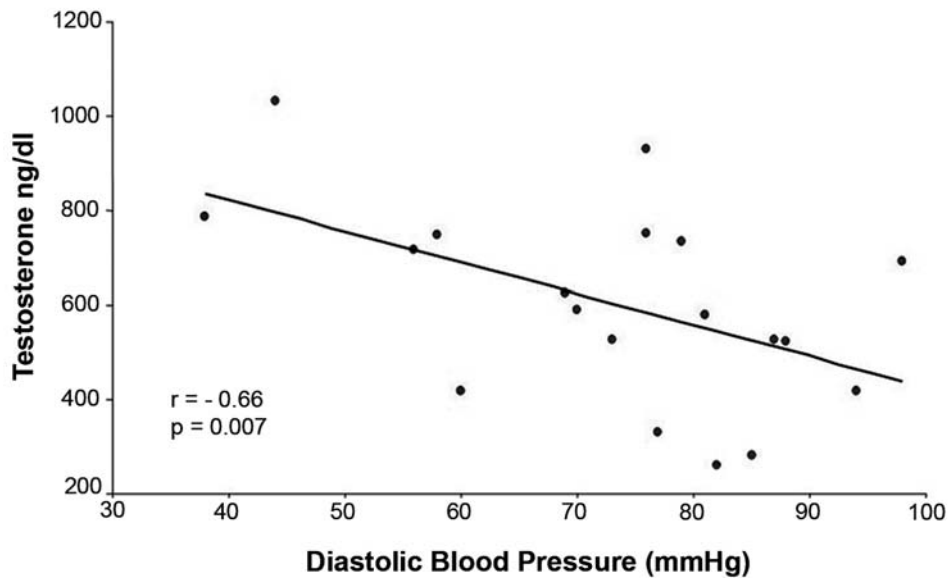


Figure 2 – Regression linear plots in all patients between total testosterone serum levels systemic diastolic blood pressure at the last minute of the 6 minutes walking test.

Table 4 – Linear regression results between total testosterone serum levels and cardiac function, and exercise variables.

Variable	r	p Value
LVEF (in %)	- 0.69	0.004
RVEF (in %)	- 0.55	0.03
LVEDD (in mm)	- 0.02	ns
LVESD (in mm)	0.04	ns
HR 6m	0.10	ns
SBP 6m	0.16	ns
DBP 6m	- 0.66	0.007
HR max	- 0.04	ns
SBP max	0.16	ns
DBP max	- 0.14	ns
Distance 6m	0.50	0.047
Slope 6m	- 0.11	ns
VO ₂ 6m	0.24	ns
Slope Max	- 0.21	ns
VO ₂ Max	0.02	ns
Time Max	0.00	ns

LVEF = Means left ventricular ejection fraction; RVEF = Right ventricular EF; LVEDD = LV end diastolic diameter; LVESD = LV end systolic diameter; HR 6m = Heart rate at last six minutes at six minutes cardiopulmonary walking test; SBP6m = systolic blood pressure at last six minutes on 6m cardiopulmonary walking test; DBP6m = BP at last six minutes on 6m cardiopulmonary walking test; HRmax = Heart rate at peak on maximum cardiopulmonary test; SBP max = SBP at peak on maximum cardiopulmonary test; DBP max = DBP at peak on maximum cardiopulmonary test; Distance 6m = distance on 6m cardiopulmonary walking test; Slope 6min = Slope VE/VCO₂ on 6m cardiopulmonary walking test; VO₂6min = Oxygen consumption at six minutes of 6m cardiopulmonary walking test; SlopeMax = Slope VE/VCO₂ at maximum cardiopulmonary test; VO₂Max = VO₂ peak at maximum cardiopulmonary test; Time Max = total time at maximum cardiopulmonary test.

COMMENTS

Ours results demonstrated that there was an inverse correlation between right and left ventricular function and total testosterone serum levels in patients with ED. Other hemodynamic and exercise variables did not show a correlation with testosterone serum

levels, except diastolic blood pressure and distance on 6'CWT. Other hormones abnormalities can be found in heart failure patients with erectile dysfunction.

Low testosterone levels were reported in severe stroke and acute myocardial infarction (11). In HF, the testosterone serum levels may be low or in the normal range depending of the severity of the disease (11). Also, it has been reported that plasma levels of dehydroepiandrosterone sulfate decreased in patients with chronic HF in proportion to the severity evaluated by marker of cardiac function (12). However, to our knowledge this is the first time that an inverse correlation was demonstrated between left and right systolic cardiac function and total testosterone serum levels in selected patients with HF and ED (6,13,14). It is also partially discordant that, after testosterone administration, serum total levels remained in the normal physiological range and no significant changes were found in BNP, TNF- α or LVEF. Also, there was also a positive correlation between testosterone and cardiac output (15). However, it was concordant with worsening of left ventricular remodeling with testosterone administration. The mechanisms to explain our findings are not clear. Effects of testosterone in the heart are controversial and alternative hypotheses could be proposed.

The first hypothesis is that the total testosterone serum blood levels could play a role in pathophysiology of HF, worsening cardiac function. This is concordant with the concept that anabolic steroids were considered as having cardiac toxicity with alterations of cellular pathology and organ physiology similar to those seen with heart failure and cardiomyopathy (16). In addition, testosterone treatment in very high supra-physiological doses causes myocardial hypertrophy and stiffening (17). Investigators administered physiologic doses of testosterone and found an increase in the left ventricular diameters, but did not find any change in the LVEF (18).

The second hypothesis, in contrast is that testosterone serum levels could have beneficial effects on HF, and a resistance for testosterone could be proposed in selected HF patients (6). In rats, androgen therapy has been reported to improve coronary blood flow and increased both fractional shortening, thereby improving cardiac function. In addition, animal stud-

ies demonstrated vasodilator effects of androgens with potential beneficial effects in endothelial dysfunction (19), increment in IGF-1 levels with reduction in hyperinsulinemia and insulin resistance (20). In addition, resistance to growth hormone (GH) was also proposed in severe HF patients based on higher GH concentrations in proportion with low IGF-1 concentration (21). However, the hypothesis of testosterone resistance needs to be proved in future investigations including mediators, nongenomic and genomic androgen action mechanisms (10).

Our method to include these patients in this study could have influenced our results because of specific factors related to erectile dysfunction in HF and higher severity of our patients in comparison with other studies (18). Patients with HF may experience erectile dysfunction for similar reasons to the general population, however, there are social, psychological, physiological, and drug-related consequences specific to HF (22). However, the influence of ED in our patients should be considered if the concept that this symptom is a marker of severity of HF and endothelial dysfunction is accepted (23). Endothelial dysfunction appears to affect all cardiac and peripheral circulation. Significant relationship between sexual performance and functional class and six-minute walk test has been reported (24). Moreover, as suggested for GH resistance in more severe patients, our results could have been influenced by these factors.

The correlation between total testosterone and exercise capacity is concordant with previous randomized, double blind, placebo-controlled parallel trial of testosterone replacement therapy. Exercise capacity significantly improved with testosterone therapy, compared with placebo (18). There are evidences in animal studies that anabolic androgens attenuate muscle fatigue in response to exercise, although the mechanism has not been identified (25). In addition, androgens may have different effects on heart and peripheral muscle (15).

Our correlation between testosterone and exercise, systemic DBP is in concordance with vasodilator effect of testosterone, but previous reports have speculated that for a vasodilatation effect of testosterone supra physiological concentrations are required (26,27). However, beyond the vessel relaxation testosterone effect, this may activate the

renin-angiotensin system (10,28). Also, vascular effects could be dose-dependent manner, with opposite effects according to the dose.

Despite previous reported improvement in New York Heart Association functional class and exercise capacity, the potential prescription of testosterone for HF should be evaluated. This potential prescription should consider our results and previous study that showed the increment of left diameters in HF patients after testosterone administration (17). Further investigations should be performed concerning elucidation of its action in the heart and to determine if it is safe. Acute hemodynamics, exercise and functional beneficial effects cannot guarantee a short and long-term benefit in cardiac function and primary endpoints for heart failure treatment (17,27).

Although this study is limited by the number of patients and did not include other markers of HF, nevertheless cardiac function could be considered as one of the main surrogate endpoints in heart failure. A better elucidation of testosterone mechanisms and action is warranted in a larger patient population.

CONCLUSION

Testosterone levels correlated directly with distance at six-minute cardiopulmonary walk test and inversely with diastolic blood pressure, right and left ventricle ejection fraction in heart failure patients with erectile dysfunction.

CONFLICT OF INTEREST

None declared.

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Correspondence address:

Dr. Vitor Oliveira Carvalho
Laboratório de ICC-Transplante
INCOR, HCFMUSP
Av. Dr. Enéas de Carvalho Aguiar
05403-000, Sao Paulo, SP, Brazil
Fax: + 55 11 3069-5419
E-mail: vitor.carvalho@usp.br

EDITORIAL COMMENT

Decreased testosterone level was reported throughout a 4-year follow-up in elderly patients with erectile dysfunction (ED) in addition to the association with an adverse metabolic profile (1). Testosterone deficiency is a common occurrence in men with chronic heart failure (CHF) and may underpin features of advanced disease, including reduced skeletal muscle mass and fatigue (2). Testosterone is known to act as a vasodilator in systemic, coronary and pulmonary vascular beds, as well as having anabolic properties (3). This effect could potentially lead to increased cardiac output and improved cardiovascular function that may contribute to the clinical benefit. Therefore,

administration of testosterone to men with chronic congestive heart failure may lead to hemodynamic alterations. Furthermore, testosterone deficiency is positively correlated with cardiac output and exercise capacity in patients with CHF, whereas a significant improvement in both these parameters has been observed following testosterone replacement therapy. Testosterone therapy has also been shown to reduce circulating levels of inflammatory markers, (TNF- α and IL-1 β) in patients with established coronary artery disease and testosterone deficiency (4).

Although the mechanisms are poorly understood, the improvement in exercise capacity was

shown to be positively correlated with the increase in serum testosterone level and was accompanied by a small increase in internal left ventricular length (2). As testosterone is a vasodilator, this could explain its anti-ischemic effects on cardiac function during exercise. However, it is currently unknown whether the vasodilatory effects of testosterone can influence the fatigability of skeletal muscle in a similar fashion. Therefore, adjunctive testosterone therapy might augment the positive effects of exercise rehabilitation on these clinical outcomes in hypogonadal males with stable CHF.

Currently, the main drawbacks in the design of clinical protocols and the inclusion of patients for the study of hormonal alteration lie in establishing the best assay for T measurement and in defining a baseline T cut off level. Although some limitations of the current study have been mentioned by the authors, the important feature of this study is that it addresses one timely and important issue, which is the correlation between serum testosterone levels and cardiac function, hemodynamic, and exercise capacity in HF patients with ED.

EDITORIAL COMMENT

In this study Bocchi, and his colleagues documented that testosterone (TT) levels correlated directly with distance at six-minute cardiopulmonary walk test and inversely with diastolic blood pressure, right and left ventricle ejection fraction in heart failure patients with erectile dysfunction (ED). Erectile dysfunction is considered an early sign of endothelial dysfunction and hence cardiovascular disorders while low TT levels are related to ED.

TT level is considered a marker of vascular reactivity and non-traditional risk factor (Bio Marker)

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Dr. Ahmed I. El-Sakka

Suez Canal University

School of Medicine

Ismailia, Egypt

E-mail: aielsakka@yahoo.com

Dr. Farid Saad

Bayer Schering Pharma

Scientific Affairs Men's Healthcare

Berlin, Germany

for coronary artery disease and peripheral arterial disease. It is also related to low arrhythmia threshold and prolonged QT intervals.

Low TT level is a predictor of cardiovascular mortality, and marker of low exercise tolerance and poor quality of life. So if used as an adjuvant in treatment of heart failure it may significantly improve the functional capacity and symptoms of heart failure.

Although the number of cases in this study is limited, as stated by the authors, the paper is interesting not only to the Urologist and Andrologists

but also to the cardiologist and general physicians. However, 61% of men included in this study were taking spironolactone, which is an anti-androgen rendering interpretation of the data a little bit difficult. Understanding the correlation between TT and cardiac functions will have a great beneficial effect on ED patients with heart failure.

Further studies using cardiac speckle technique and tissue Doppler imaging can provide more accurate assessment of cardiac function and perhaps demonstrate a correlation between TT levels and cardiac function.

Dr. Ahmed Asaad
*Cardiology Consultant
National Heart Institute
Cairo, Egypt*

Dr. Wael Zohdy
*Department of Andrology
Cairo University
Cairo, Egypt
E-mail: wzohdy62@hotmail.com*