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Letter to the Editor

Testosterone may influence left ventricular diastolic function depending on previous myocardial infarction and smoking

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Testosterone has numerous cardiovascular functions including the impact on both cardiac and extracardiac structures [1–4]. Pathophysiological mechanisms that influence cardiomyocytes and other cardiac structures at the same time may affect left ventricular (LV) function. For example, in conditions of supraphysiological levels of chronic misuse of anabolic androgen steroids, such mechanisms induce myocardial hypertrophy, and systolic and diastolic dysfunction (DD) [5–7]. Somewhat paradoxically, in pathophysiological relations of heart failure (HF) with reduced LV ejection fraction, testosterone supplementation improves exercise capacity which is achieved without improvement in ejection fraction [3,8–10]. Moreover, clinical studies have not found a correlation between serum concentration of testosterone and LV ejection fraction [8–12].

In contrast to systolic function, the role of testosterone on LV diastolic function in HF is much less understood. The correlation between DD in HF patients and myocardial fibrosis [13] and beneficial effects of testosterone in attenuation of cardiac fibrosis [14] suggests a possible link between testosterone and diastolic function. This link is further supported by a testosterone's blocking effect on both the migration ability of cardiac fibroblasts and collagen production capability [15,16]. However, the same process may have an adverse impact on the healing process after myocardial infarction (MI) [17] which has been observed in an animal model [18].

We have recently reported that hormonal and hemodynamic mechanisms in obese male patients with HF are altered and may be based on lower serum testosterone levels (TL) [19]. This further supported the possibility that the effects of testosterone on overall hemodynamics are more important than its effects on LV systolic function. In the present report, we undertook a secondary analysis of that data in order to evaluate whether endogenous TL plays a role in diastolic function in men with HF and whether the presence of heart disease in the form of MI influences that role. We compared total TL with the grade of DD and other clinical parameters in male HF patients who have had versus those who have not had an old MI.

Male patients hospitalized because of acute HF at the Department of Cardiology, University Hospital Center Split-Križine between December 2011, and March 2014 were interviewed and a devoted questionnaire was filled out by specially trained medical students and interns. The diagnosis was established according to clinical presentation and echocardiographic findings of either systolic (LV ejection fraction <45% assessed by the Simpson method) or DD. Excluded were patients with acute coronary syndrome or coronary revascularization within the 6 months preceding the study, acute or chronic illness that might influence hormonal metabolism (including the patients with a body mass index <18.5 kg/m^2 for possible frailty) or any current or previous hormonal treatment or drugs noticeably affecting hormone levels [19].

Blood samples were taken within the first 24 h of hospitalization. Serum concentration of testosterone (in nmol/L) was measured by using immunoassays (Roche Diagnostics GmbH, Mannheim, Germany). Renal function was assessed by using the estimated glomerular filtration rate (GFR, in mL/min/1.73 m^2) calculated from the Modification of Diet in Renal Disease equation [20]. The study protocol was approved by the Hospital Ethics Committee and all patients gave written informed consent.

In addition to color M-mode mitral inflow velocity of propagation, the following flow-derived parameters of diastolic LV function were measured on pulsed-wave Doppler from the apical four-chamber view: peak mitral inflow E and A velocity waves, E/A ratio, E-wave deceleration time, isovolumic relaxation time, and pulmonary venous flow. Septal and lateral diastolic é and á peak annular tissue velocities, the é/á ratio, and LV filling index E/é ratio were obtained by tissue-Doppler imaging, where the pulsed-Doppler sample volumes were positioned within 1 cm of the septal and lateral insertion sites of the mitral valve leaflets. Echocardiographic parameters were obtained in accordance with the guidelines

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[21,22] and the severity of DD was assessed according to four basic grades [23] with the use of intermediate grades in appropriate cases.

Total TL and n-terminal pro brain natriuretic peptide (NT-proBNP) showed a skewed distribution and their values are expressed as median with interquartile range (IR). In a univariate analysis, the intergroup differences were tested using the χ^2 test, t test or Man Whitney U test, as appropriate. Risk factors and previous medication in all analyses were coded as dichotomous variables except smoking, where in the multivariate analysis we accounted for former smoking by introducing an intermediate category.

As the univariate analysis suggested that total TL is highly correlated with DD severity, a multiple regression analysis was used to estimate the independent predictive association of total TL and other clinical variables with DD in the total study group, and also separately for men with and without previous MI. Considering the presence of a relatively small group of patients with previous MI and that several clinical variables showed the impact of a borderline significance ($p \leq 0.10$) on DD, such variables were also included in the multivariate models. To keep a recommendable ratio of 10–15 cases per predictor [24,25], total TL and other variables of interest were adjusted for only one additional variable in each model.

Out of the 121 included men with HF, 31 (25.6%) had previous MI. They had a somewhat lower average NYHA class on admission, and significantly more often used aspirin, loop diuretic, spironolactone or beta-blocker compared to those without a previous MI (Table 1). There were no differences between the groups in average age, LV ejection fraction, cardiovascular risk factors or prehospital use of digoxin, angiotensin converting enzyme-inhibitor, angiotensin II receptor I blocker (ARB), calcium channel antagonist (CCA; all were dihydropiridines) or statin (Table 1). Admission laboratory findings revealed that patients with previous MI were characterized by a significantly lower both serum total TL and GFR (Table 2).

All patients had DD with the average grade of 2.68 ± 0.68. The severity of DD was also analyzed according to clinical characteristics and laboratory findings (Table 3). Although there were no statistically significant differences in average DD according to the history of cardiovascular risk factors or prehospital drug therapy, characteristics such as current smoking and use of an ARB or CCA showed differences of a borderline statistical significance (Table 3). DD showed a significant inverse correlation with total TL (Fig. 1), and the same trend was present in both men with ($r = -0.334$, $p = 0.067$) and without ($r = -0.198$, $p = 0.061$) previous MI. DD also showed positive correlations with NT-proBNP, serum uric acid, aspartate aminotransferase, gamma-glutamyl transpeptidase, and both total and direct bilirubin levels (Table 4).

Multivariate analysis revealed that in the total study group, both total TL and smoking (also accounting for former smoking) were significant predictors of DD severity (Table 5, Model 1). However, in the group of those with a previous MI, only smoking remained a strong independent predictor whereas in their counterpart group only total TL remained associated with DD severity (Table 5, Model 1). Both ARB and CCA showed no predictive significance for the DD, but they somewhat attenuated the effect of testosterone (Table 5, Models 2 and 3). Neither ARB nor CCA had an effect on the close correlation of smoking with the severity of DD among HF patients with previous MI (Table 5, Models 4 and 5).

The results of the present report suggest that lower TL could be an important factor in the development of DD in men with HF. This association seems to be confined to patients without previous MI. In contrast, in HF patients who have had a MI, smoking seems to be the chief factor in the progression of DD.

This is the first report that associates TL with DD in a specific subgroup of patients with HF. Our results suggest that TL is inversely related to the grade of DD in patients without previous MI. It has been suggested that testosterone-related impairment of activity and collagen production by cardiac fibroblasts [15,16] may attenuate myocardial fibrosis [14] and beneficially affect diastolic function. The same process, i.e., the blockade of myocardial fibrosis, may impair cardiac healing after a MI and in acute phase predispose to cardiac rupture [18]. The latter may be explained by an inverse relation of collagen content in MI area and the risk of ventricular rupture [26].

The beneficial effect on DD among our patients without previous MI but not among those who have had a MI may suggest that the presence of scar tissue, altered LV geometry or some other structural, histological or cellular consequences of MI block testosterone's beneficial effect on DD. Therefore, the present report supports the hypothesis that testosterone within a normal physiological concentration has beneficial cardiovascular effects only in relatively "healthy" individuals whereas in the case of diseased or aged hearts these effects may be altered [1]. In line with that, testosterone replacement given to aged rabbits to increase levels similar to those of young rabbits may have an arrhythmogenic effect due to enhanced adrenergic stimulation and mechanical dysfunction of the aged hearts [27].

Among smoke-related factors that may impair LV diastolic function, one of the most important is the pro-fibrotic effect of nicotine on myocardial tissue [28]. In addition, carbon monoxide and other constituents of cigarette smoke, via oxidative stress and inflammation, damage the extracellular matrix, myocyte contractile proteins, and can lead to cardiomyocyte death, fibrosis and cardiac remodeling [29,30]. Hemodynamic changes, mediated by neurohormonal activation and increased blood pressure, also participate in smoking-induced cardiac remodeling [31–34]. Finally, acute inhalation of cigarette smoke has been directly associated with DD [35].

In our patients with previous MI, smoking was most powerfully associated with DD which in multivariate analysis abolished the effect of antihypertensive medication and the effect of testosterone. Two possible scenarios may help explain this finding. The first is that MI, as an aftermath of smoking, changes the LV geometry and produces remodeling forces which are too powerful to be compensated for by either hormonal or medicamentous factors. The second scenario is that there is a subpopulation of patients generally more susceptible to smoking-associated cardiovascular consequences. In the present setting, they had smoking associated with both MI and more progressed DD. This subpopulation may consist of several genotypes, including the carriers of genes coding for the apolipoprotein

Table 1
Baseline characteristics of the study patients according to previous myocardial infarction.

	With previous MI (n = 31)	Without previous MI (n = 90)	p
Clinical characteristics			
Age (mean ± SD; years)	73.3 ± 7.6	74.2 ± 8.9	0.62
LVEF (mean ± SD; %)	42.1 ± 12.9	44.6 ± 14.7	0.41
NYHA class (mean ± SD)	3.2 ± 0.7	3.4 ± 0.7	0.09
Arterial hypertension (%)	71	54.4	0.12
Diabetes mellitus (%)	38.9	38.7	0.99
Hypercholesterolemia (%)	32.3	21.1	0.21
Hypertriglyceridemia (%)	22.6	22.2	0.97
Low HDL (%)	61.3	47.8	0.19
Current smoking (%)	29	31.1	0.83
Body mass index (mean ± SD)	28.3 ± 3.3	27.5 ± 4.4	0.35
Prehospital medication (%)			
Aspirin	54.8	27.0	0.005
Digoxin	22.6	24.7	0.81
ACEI	29.0	44.9	0.12
ARB	19.4	10.1	0.18
Loop diuretic	87.1	68.5	0.044
Spironolactone	35.5	18.0	0.044
ß-Blocker	77.4	52.8	0.016
Calcium channel antagonist	12.9	18.0	0.51
Statin	32.3	21.3	0.22

LVEF: left ventricular ejection fraction, NYHA: New York Heart Association, HDL: high-density lipoprotein, MI: myocardial infarction, ACEI: angiotensin converting enzyme-inhibitor, ARB: angiotensin II receptor I blocker.
p values were obtained from the t test or χ^2 test as appropriate.