International Journal of Cardiology 224 (2016) 245–251

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Correspondence

Circulating sex hormones, alcohol consumption and echocardiographic parameters of cardiac function in men with heart failure

Viktor Čulić [a,b,*], Željko Bušić [b], Marija Bušić [b]

[a] Department of Cardiology, University Hospital Center Split, Split, Croatia
[b] University of Split School of Medicine, Split, Croatia

ARTICLE INFO

Article history:
Received 11 August 2016
Received in revised form 24 August 2016
Accepted 15 September 2016
Available online 16 September 2016

Keywords:
Alcohol
Diastolic function
Echocardiography
Estradiol
Heart failure
Testosterone

Among the multiple hormonal alterations that accompany heart failure (HF) [1], lower endogenous testosterone levels are associated with poorer clinical status [2,3] and overall prognosis [4,5] in men with HF. Without affecting left ventricular ejection fraction (LVEF) [2,3,5–7], testosterone's beneficial mechanism in HF may include peripheral vasodilation which reduces cardiac afterload and increases cardiac output [2,3,7], increased baroreflex sensitivity [2,3], and prevention of diastolic dysfunction (DD) [8,9].

Approximately half of all HF patients have preserved LVEF, and DD underlies their symptoms [10,11]. Women are twice as likely to have HF with preserved LVEF as men, and postmenopausal loss of estrogen protection against DD has been linked to this phenomenon [11–13]. In animal male models, estrogen protected from adverse ventricular remodeling [14–17]. In men with HF, estrogen administration decreased pulmonary and systemic vascular resistance and improved cardiac output [18]. Yet, there is no clinical evidence about estrogen effects on systolic and diastolic function in men.

Excessive alcohol consumption is associated with alcoholic cardiomyopathy [19]. However, the beneficial effects of moderate alcohol consumption on cardiometabolic profile [20–24] may underlie a lower risk of incident HF [21–23]. At the same time, chronic heavy alcohol intake may lower circulating testosterone and increase estrogen levels by promoting the induction of aromatase and impairing estrogen metabolism in the liver [13]. Therefore, alcohol may affect the link between sex hormones and cardiovascular disease. The aim of the present study was to examine the associations of circulating sex hormones and alcohol consumption with echocardiographic parameters of systolic and diastolic function in men with HF.

Male patients hospitalized because of HF at the Department of Cardiology, University Hospital Center Split-Križine between October 2012 and December 2013 were eligible for enrollment in this prospective study. The inclusion criteria were: 1) clinical presentation suggestive of HF; 2) echocardiographic finding of either LVEF ≤45% or DD; 3) unchanged medications for at least 1 month preceding the study. Exclusion criteria were: 1) any current or previous hormonal treatment or drugs noticeably inhibiting hormone production; 2) cardiac surgery, acute coronary syndrome or coronary revascularization within the 6 months preceding the study; 3) previous myocardial infarction; 4) acute or chronic illness that might influence hormonal metabolism (all endocrine disorders, infectious, autoimmune or malignant diseases; circulating CRP levels under 10 mg/L may be regarded as clinically insignificant [26], and to account for a low-grade systemic inflammation which accompanies HF [27], we determined a maximum of 15 mmol/L, i.e. 50% increase, as a cutoff value for inclusion); 5) end-stage renal disease (i.e. peritoneal or hemodialysis); 6) primary liver disease or liver cirrhosis; and 7) a BMI < 18.5 kg/m^2 to adjust for possible frailty. Out of the 171 eligible patients, 67 were included in the analysis. The study complies with the Helsinki Declaration. The study protocol was approved by the Hospital Ethics Committee and all patients gave their written informed consent.

For each patient, a devoted questionnaire was administered by specially trained interns and medical students. The questionnaire covered questions on general and anthropometric data, presence of cardiovascular risk factors and diseases, NYHA class, medications used, and quantity of consumption of specific beverage items during the past 6 months. The patients were asked about their usual daily consumption of beer, wine, and spirits as separate items. To account for the alcohol content of a specific beverage, alcohol intake was assessed separately for each beverage and then summated for total alcohol consumption. A drink was considered to contain approximately 13 g to 15 g ethanol, i.e. approximately 3.5 dL (12 oz.) of beer, 1.5 dL (5 oz.) of wine, 0.5 dL (1.5 oz.) of 80-proof spirits, or 0.3 dL (1 oz.) of 100-proof spirits.

All subjects twice underwent standard transthoracic echocardiographic examination at rest during the first 2 days of hospitalization.

* Corresponding author at: Department of Cardiology, University Hospital Center Split-Križine, Šoltanska 1, 21000 Split-Križine, Croatia.
E-mail address: viktor.culic@st.t-com.hr (V. Čulić).

http://dx.doi.org/10.1016/j.ijcard.2016.09.050
0167-5273/

All echocardiographic parameters were obtained in accordance with the guidelines [28,29]. The LVEF were assessed by the biplane Simpson's method from the apical 4- and 2-chamber views. Color M-mode mitral inflow velocity of propagation, pulmonary venous flow, and flow-derived parameters of diastolic left ventricular function on pulsed-wave Doppler were also measured from the apical 4- and 2-chamber views. The early filling (E) and atrial (A) filling peak velocities, E/A ratio, E-wave deceleration time, and isovolumic relaxation time were measured from transmitral flow. Real time pulsed wave tissue-Doppler imaging, with the pulsed-Doppler sample volumes positioned within 1 cm of the septal and lateral insertion sites of the mitral valve leaflets was recorded. The sample volume and gain were optimized, the Nyquist limit was set to 15 to 20 cm/s, and septal and lateral diastolic é and á peak annular tissue velocities, the é/á ratio, and LV filling index E/é ratio were obtained. The severity of DD was assessed according to 4 basic grades [9,30].

Venous blood samples were taken within the first 24 h of hospitalization, in the morning between 8.30 and 11.00 AM after an overnight fasting. The serum was centrifugated, aliquoted and frozen at −70 °C until being analyzed. Serum concentrations of sex hormone binding globulin (SHBG, nmol/L), total testosterone (nmol/L), estradiol (pmol/L) and plasma N-terminal pro-B type natriuretic peptide (NT-proBNP, pmol/L) were measured by using chemiluminescence immunoassay (Roche Elecsys 2010/Elecsys 1010, Roche Diagnostics GmbH, Mannheim, Germany). For all hormone assays, the intra- and inter-assay variation coefficients were <9% and <13%, respectively. The estimated free testosterone was calculated using the Vermeulen's equation [31]. 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 [32].

Normally distributed continuous variables were presented as means ± standard deviations. Variables with a skewed distribution were expressed as medians with interquartile ranges. The intergroup differences for continuous variables were tested using the Student's t-test or Mann–Whitney U test where appropriate. The dichotomous variables were expressed as numbers with percentages and the inter-group differences were tested using the $\chi 2$ test. Correlations among continuous clinical variables were tested by linear regression analysis and expressed through the Pearson's correlation coefficient. To assess the shape of nonlinear associations between alcohol consumption and both LVEF and DD, the number of alcoholic drinks/day was modeled through a transformation using second (quadratic) and third (cubic) order polynomials. This special case of multiple linear regression fits a non-linear model to the data, for example in U-shaped relationship, but with significant improvements [33].

The independent variables were inspected for multicollinearity before conducting the multivariable analysis, and SHBG, triglycerides and laboratory liver findings were excluded because of strong correlations with both estradiol levels and alcohol consumption. The associations were investigated using the hierarchical linear regression and data were entered in 2 blocks. In Model 1, the adjustment was made for age and GFR because of their important role in pathophysiology, presentation and prognosis of HF [6,11,13,34], as well as for clinical variables that showed associations with LVEF and DD in the univariable analysis. The second block (Model 2) contained serum testosterone, serum estradiol and alcohol consumption. The change in R2 was evaluated for each block and individual contributions for each independent variable were calculated by squaring the semipartial correlation.

In average, patients with diabetes mellitus had a significantly lower LVEF and greater DD (Table 1). The relation between alcohol consumption and both LVEF and DD was slightly better accommodated with cubic than with quadratic polynomial regression model or with a linear regression model (Table 2). Both the peak for LVEF (Fig. 1) and the nadir for DD (Fig. 2) were observed at 2 to 3 drinks/day. Left ventricular size and NYHA class decreased whereas alkaline phosphatase (AF) increased with increasing LVEF (Table 2). The grade of DD increased with increasing age, urate and triglycerides level, left ventricular size and NYHA class, and with decreasing GFR, alanine aminotransferase (ALT), gamma-glutamyl transpeptidase (GGT) and AF (Table 2).

Serum total testosterone ($r = 0.600$, $p < 0.001$) and estradiol ($r = 0.488$, $p < 0.001$) increased with increasing SHBG. DD decreased with increasing SHBG, total and free testosterone, and estradiol. A positive correlation of LVEF with both SHBG and estradiol approached significance (Table 3). Both NT-proBNP and NYHA class increased with decreasing serum SHBG. Left ventricular and left atrium diameters, NT-proBNP and NYHA class increased with decreasing both serum total and free testosterone. Free testosterone increased with duration of HF. Estradiol increased with increasing left atrium diameter and decreased NYHA class. Serum SHBG, total testosterone and estradiol decreased with advancing age and decreasing GFR. Serum SHBG decreased with increasing BMI. Both serum SHBG and estradiol increased with increasing serum activity of aspartate aminotransferase (AST), ALT, GGT and direct bilirubin. Serum estradiol also increased with increasing AF, total and indirect bilirubin and with decreasing serum albumins. Free testosterone decreased with increasing activity of AST and GGT (Table 3).

With increasing alcohol consumption, serum estradiol increased whereas free testosterone showed a downward trend. HDL cholesterol increased and total triglycerides decreased with increasing estradiol. Serum sodium decreased with the increase of both SHBG and estradiol, and increased with free testosterone (Table 3). HDL cholesterol increased with increasing alcohol consumption ($r = 0.327$, $p = 0.007$). Men with HF who consumed 2 or more drinks per day had higher ALT, GGT, AF, and both total and direct bilirubin compared to those who consumed less than 2 drinks. There was no age or BMI difference between the groups (Table 4).

In the multivariable analysis, baseline variables showed no significant association with LVEF (Model 1, Table 5). The inclusion of serum estradiol, total testosterone and cubic regression-transformed alcohol

Table 1
The association of left ventricular ejection fraction (LVEF) and grade of diastolic dysfunction (DD) with cardiovascular risk factors and prehospital medication.

		LVEF (mean ± SD)			DD (mean ± SD)		
	Variable frequency N (%)	Yes	No	p	Yes	No	p
Never smoker	23 (34.3%)	44.6 ± 6.4	41.0 ± 12.7	0.21	3.0 ± 0.5	3.0 ± 0.7	0.84
Arterial hypertension	35 (52.2%)	41.3 ± 11.4	43.3 ± 10.6	0.45	3.1 ± 0.7	2.9 ± 0.6	0.42
Diabetes mellitus	52 (77.6%)	40.9 ± 11.3	46.9 ± 8.6	0.04	3.1 ± 0.7	2.7 ± 0.6	0.01
Loop diuretic	43 (64.2%)	42.7 ± 10.2	41.4 ± 12.5	0.65	3.1 ± 0.6	2.8 ± 0.8	0.11
Spironolactone	20 (29.9%)	44.2 ± 12.6	41.0 ± 9.6	0.16	2.8 ± 0.7	3.1 ± 0.6	0.10
Hygroton	5 (7.5%)	40.0 ± 8.6	42.3 ± 11.2	0.72	3.1 ± 0.7	2.9 ± 0.7	0.21
Digoxin	18 (26.9%)	44.7 ± 6.6	41.0 ± 12.1	0.12	3.1 ± 0.6	3.0 ± 0.7	0.81
Angiotensin converting enzyme inhibitor	22 (32.8%)	40.4 ± 12.5	43.2 ± 10.2	0.33	3.1 ± 0.6	2.9 ± 0.7	0.23
Angiotensin II receptor type-1 blocker	9 (13.4%)	44.7 ± 7.4	41.6 ± 11.4	0.20	3.0 ± 0.4	3.0 ± 0.7	0.92
ß-blocker	26 (38.8%)	41.4 ± 13.7	42.8 ± 9.0	0.63	3.1 ± 0.8	3.0 ± 0.6	0.28
Calcium channel antagonist	6 (9.0%)	42.5 ± 7.0	42.2 ± 11.4	0.95	3.2 ± 0.8	3.0 ± 0.7	0.38
Statin	9 (13.4%)	44.0 ± 7.4	41.7 ± 11.4	0.27	3.0 ± 0.4	3.0 ± 0.7	0.92

p values were obtained from the t test.