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Gender related predictors of limited exercise capacity in heart failure

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ABSTRACT

Aim: The aim of this study was to investigate the impact of gender on the prediction of limited exercise capacity in heart failure (HF) patients assessed by 6 minute walk test (6-MWT).
Methods: In 147 HF patients (mean age 61 ± 11 years, 50.3% male), a 6-MWT and a Doppler echocardiographic study were performed in the same day. Conventional cardiac measurements were obtained and global LV dyssynchrony was indirectly assessed using total isovolumic time − t-IVT [in s/min; calculated as: 60 − (total ejection time − total filling time)] and Tei index (t-IVT/ejection time). Patients were divided into two groups according to gender, which were again divided into two subgroups based on the 6-MWT distance (Group I: ≤ 300 m, and Group II: > 300 m).
Results: Female patients were younger ($p = 0.02$), and had higher left ventricular (LV) ejection fraction − EF ($p = 0.007$) but with similar 6-MWT distance to male patients ($p = 68$). Group I male patients had lower hemoglobin level ($p = 0.02$) and lower EF ($p = 0.03$), compared with Group II, but none of the clinical or echocardiographic variables differed between groups in female patients. In multivariate analysis, only t-IVT [0.699 (0.552–0.886), $p = 0.003$], and LV EF [0.908 (0.835–0.987), $p = 0.02$] in males, and NYHA functional class [4.439 (2.213–16.24), $p = 0.02$] in females independently predicted poor 6-MWT distance (<300 m).
Conclusion: Despite similar limited exercise capacity, gender determines the pattern of underlying cardiac disturbances; ventricular dysfunction in males and subjective NYHA class in female heart failure patients.

1. Introduction

Heart failure (HF) has become a major public health problem [1], and its incidence, morbidity and mortality are increasing worldwide [2]. Despite recent advances in medical treatment, patients with persistent symptoms still manifest poor prognosis [3–6]. Many clinical and echocardiographic parameters have been shown as independent predictors of these patients [7–11], particularly the six-minute walk test (6-MWT) which is commonly used to objectively assess patient's exercise capacity [12–14]. We have previously shown that echocardiographic markers of raised left atrial pressure [15], right ventricular dysfunction [16] and ventricular dyssynchrony [17] correlate with exercise capacity in HF patients and predict 6-MWT distance results. However, the impact of gender on limited exercise capacity and its relationship to clinical and echocardiographic predictors of exercise in these patients have not been evaluated. The aim of this study therefore, was to investigate the impact of gender in predicting limited exercise capacity, assessed by 6-MWT, in HF patients.

2. Methods

2.1. Study population

We studied 147 patients (mean age 61 ± 11 years, 50.3% male, Table 1) with clinical diagnosis of congestive HF secondary to ischemic heart disease or non-ischemic etiology, who were in New York Heart Association (NYHA) functional classes I–III. Patients were referred to the Service of Cardiology, Internal Medicine Clinic, University Clinical Centre of Kosova, between December 2005 and April 2011. At the time of the study all patients were on full cardiac medications, optimized at least 2 weeks prior to enrollment, based on symptoms and renal function: 81% were receiving ACE inhibitors or ARB, 70% beta-blockers, 11% digoxin, 46% spironolactone, and 64% diuretics. Patients with reduced LV EF had ischemic etiology in 42%, hypertension in 25%, and unknown etiology in 33%. Patients with preserved LV EF had ischemic etiology in 44% and hypertension in 56%. All patients were in sinus rhythm and had symptoms of HF. Patients with clinical evidence of cardiac decompensation, limited physical activity due to factors other than cardiac symptoms (e.g. arthritis), obesity, more than mild valve regurgitation, more than mild renal failure, chronic obstructive pulmonary disease or those with recent acute coronary syndrome, stroke or anemia were excluded. Patients gave a written informed consent to participate in the study, which was approved by the local Ethics Committee.

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Table 1
Baseline clinical data.

Sex (female, in %)	49.7
Age (years)	61 ± 11
Smoking (%)	31
Diabetes (%)	33
LBBB (%)	25
Body-mass index	28 ± 5
Waist/hip ratio	0.95 ± 0.1
NYHA class	2.3 ± 0.6
Fasting glucose (mmol/L)	7 ± 3.3
Total cholesterol (mmol/L)	4.3 ± 1.3
Triglycerides (mmol/L)	1.7 ± 1
Urea (mmol/L)	9.9 ± 4.5
Creatinine (μmol/L)	109 ± 41
Hemoglobin	128 ± 23
Heart rate (beats/minute)	78 ± 13

Data are mean ± standard deviation. NYHA = New York Heart Association.

2.2. Data collection

Detailed history and clinical assessment were obtained in all patients, in whom routine biochemical tests were also performed including hemoglobin, lipid profile, blood glucose level, and kidney function. Estimated body mass index (BMI) was calculated from weight and height measurements. Waist and hip measurements were also made and waist/hip ratio was calculated.

2.3. Echocardiographic examination

A single operator performed all echocardiographic examinations using a Philips Intelligent E-33 system with a multi-frequency transducer, and harmonic imaging as appropriate. Images were obtained with the patient in the left lateral decubitus position and during quiet expiration according to the recommendations of the American Society of Echocardiography and European Association of Echocardiography [18,19]. End-systolic and end-diastolic LV dimensions were measured from basal LV M-mode recordings, taken from the left parasternal long axis view with the M-mode cursor positioned by the tips of the mitral valve leaflets. LV volumes and EF were calculated from the apical 4 and 2 chamber views using the modified Simpson's method. Ventricular long axis motion was studied by placing the M-mode cursor at the lateral and septal angles of the mitral ring and the lateral angle of the tricuspid ring. Total amplitude of long axis motion was measured as previously described [20] from peak inward to peak outward points. LV and right ventricular (RV) long axis myocardial velocities were also studied using Doppler myocardial imaging technique. From the apical 4-chamber view, longitudinal velocities were recorded with the sample volume placed at the basal part of LV lateral and septal segments as well as RV free wall. Systolic (S′), as well as early and late (E′ and A′) diastolic myocardial velocities were measured with the gain optimally adjusted. Mean value of the lateral and septal LV velocities was calculated. Left atrial diameter was measured from aortic root recordings with the M-mode cursor positioned at the level of the aortic valve leaflets. Diastolic function of the LV and RV was assessed from their filling velocities using spectral pulsed wave Doppler with the sample volume positioned at the tips of the mitral and tricuspid valve leaflets, respectively, during a brief apnea. Peak LV and RV early (E wave), and late (A wave) diastolic velocities were measured and E/A ratios were calculated. The E/E′ ratio was calculated from the transmitral E wave and the mean lateral and septal segments of E′ waves. The isovolumic relaxation time was also measured from aortic valve closure to mitral valve opening, on the pulsed wave Doppler recording. LV filling pattern was considered 'restrictive' when E/A ratio was >2.0, E wave deceleration time <140 ms and the left atrium dilated more than 40 mm in transverse diameter [21].

2.4. Measurements of LV dyssynchrony

Indirect assessment of LV dyssynchrony was obtained by measuring total isovolumic time (t-IVT), Tei index and LV–RV pre-ejection time delay. Total LV filling time was measured from the onset of the E wave to the end of the A wave and ejection time from the onset to the end of the aortic pulsed Doppler flow velocity. Total isovolumic time (t-IVT) was calculated as 60 − (total ejection time + total filling time) and was expressed in s/min [22]. Tei index was calculated as the ratio between t-IVT and ejection time [22,23]. LV and RV pre-ejection times were measured as the time interval between the onset of the q wave and the onset of the aortic and pulmonary forward flow velocities, respectively and the time delay between the two was calculated [24].

Mitral regurgitation severity was assessed by color and continuous wave Doppler and was graded as mild, moderate, or severe according to the relative jet area to that of the left atrium as well as the flow velocity profile, in line with the recommendations of the American Society of Echocardiography [25]. Likewise, tricuspid regurgitation severity was assessed by color Doppler and continuous-wave Doppler. Retrograde transtricuspid pressure drop >35 mm Hg was taken as an evidence for pulmonary hypertension [18], after excluding patients with more than mild tricuspid regurgitation. All M-mode and Doppler recordings were made at a fast speed of 100 mm/s with a superimposed ECG (lead II).

2.5. Six minute walk test

Within 24 h of the echocardiographic examination a 6-MWT was performed on a level hallway surface and was administered by a specialized nurse blinded to the results of the echocardiogram. According to the method of Guyatt et al. [26] patients were informed of the purpose and protocol of the 6-MWT which was conducted in a standardized fashion without interrupting patient's regular medications [27]. A 15 meter flat, obstacle-free corridor was used and patients were instructed to walk as far as they can, turning 180° after they had reached the end of the corridor, during the allocated time of 6 min. Patients walked unaccompanied so as not to influence walking speed. At the end of 6 min the supervising nurse measured the total distance walked by the patient.

3. Statistical analysis

Data are presented as mean ± SD or proportions (% of patients). Continuous data was compared with two-tailed unpaired Student's *t* test and discrete data with Chi-square test. Correlations were tested with Pearson coefficients. Predictors of 6-MWT distance were identified with univariate analysis and multivariate logistic regression was performed using the step-wise method, a significant difference was defined as $p < 0.05$ (2-tailed). Patients were divided according to their ability to walk >300 m into good (Group I) and limited (Group II) exercise performance groups [28], and were compared using unpaired Student *t*-test.

4. Results

4.1. Female vs. male patients (Tables 2 & 3)

Clinical findings: Female patients were younger ($p = 0.02$), had higher BMI ($p = 0.04$), but lower waist/hip ratio ($p < 0.001$), lower creatinine level ($p = 0.02$), and lower prevalence of smoking ($p < 0.001$) (Table 2). There were no gender related differences in the prevalence of diabetes, systemic hypertension or LBBB. Females had smaller aortic root diameter ($p < 0.001$), smaller left atrium ($p = 0.007$), LV EDD and LV ESD dimensions ($p < 0.001$ for both), and higher LV EF ($p = 0.006$) (Table 3). All other clinical and echocardiographic parameters were not significantly different between genders, neither was 6-MWT distance.

4.2. Female vs. male patients with limited exercise capacity (Tables 4 & 5)

Clinical findings: Female patients walked longer distance as compared with males in this subgroup with limited exercise capacity ($p = 0.02$). They were also younger ($p = 0.08$), had lower waist/hip ratio ($p < 0.001$), lower creatinine level ($p = 0.02$), and lower prevalence of smoking ($p < 0.001$) (Table 4). The prevalence of diabetes, systemic hypertension and LBBB did not differ between the two genders. Females had smaller aortic root diameter ($p < 0.001$), smaller LV EDD and LV ESD dimensions ($p = 0.02$ for both), longer E wave deceleration time ($p = 0.006$) and higher septal long axis amplitude ($p = 0.03$) (Table 5). All other clinical and echocardiographic parameters were not significantly different between the two subgroups.

4.3. Predictors of limited 6-MWT distance in female patients (Table 6)

None of the biochemical or clinical findings predicted the limited 6-MWT distance in the univariate analysis. However, in the multivariate analysis, functional NYHA class was the only independent predictor ($p = 0.02$) of limited 6-MWT distance in female patients.

4.4. Predictors of limited 6-MWT distance in male patients (Table 7)

In male patients, the univariate analysis showed LV EF ($p = 0.007$), isovolumic relaxation time ($p = 0.008$) and t-IVT (0.04) as predictors