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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 trans-tricuspid 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

Table 2
Comparison of clinical and biochemical data between patient groups.

Variable	Female (n = 73)	Male (n = 74)	p value
Age (years)	59 ± 13	63 ± 9	0.02
Smoking (%)	12	50	<0.001
Diabetes (%)	33	38	0.72
Arterial hypertension (%)	66	53	0.15
LBBB (%)	25	16	0.41
Preserved EF (%)	32	19	0.09
Body-mass index	29 ± 5	27 ± 4	0.04
Waist/hip ratio	0.9 ± 0.1	1.0 ± 0.1	<0.001
NYHA class	2.4 ± 0.6	2.3 ± 0.6	0.09
Fasting glucose (mmol/L)	7.3 ± 3.3	7 ± 3.3	0.69
Total cholesterol (mmol/L)	4.5 ± 1.4	4.2 ± 1.1	0.24
Triglycerides (mmol/L)	2.0 ± 1.2	1.5 ± 0.4	0.047
Urea (mmol/L)	9.7 ± 4.6	10 ± 4.2	0.61
Creatinine (μmol/L)	100 ± 39	118 ± 42	0.02
Hemoglobin (gm/dL)	12.5 ± 2.2	13 ± 2.4	0.27
Heart rate (beats/minute)	79 ± 13	77 ± 14	0.51
Six minute walk distance (m)	266 ± 107	268 ± 112	0.91

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

of the limited 6-MWT distance. Total isovolumic time (p = 0.003) and LV EF (p = 0.02) remained independent predictors of limited 6-MWT distance, in multivariate analysis, in male patients.

Table 3
Comparison of echocardiographic data between patient groups.

Variable	Female (n = 73)	Male (n = 74)	p value
Systolic LV function			
Ejection fraction (%)	42 ± 15	35 ± 13	0.006
Interventricular septum (cm)	1.12 ± 0.2	1.07 ± 0.2	0.238
Left atrium (cm)	4.5 ± 0.7	4.8 ± 0.7	0.007
LV EDD (cm)	5.9 ± 1.1	6.6 ± 1	<0.001
LV ESD (cm)	4.7 ± 1.3	5.5 ± 1.1	<0.001
Septal long axis amplitude (cm)	0.85 ± 0.3	0.87 ± 0.3	0.74
Septal S′ wave (cm/s)	6 ± 2.3	6.3 ± 1.9	0.31
Lateral long axis amplitude (cm)	1.1 ± 0.3	1.1 ± 0.3	0.99
Lateral S′ wave (cm/s)	6.2 ± 2.3	6.5 ± 2.6	0.65
LV posterior wall (cm)	1.05 ± 0.4	1.0 ± 0.1	0.19
Aortic root (cm)	3.28 ± 0.3	3.6 ± 0.3	<0.001
Diastolic LV function			
A wave velocity (cm/s)	62 ± 25	60 ± 25	0.68
Lateral A′ wave (cm/s)	7.8 ± 3.4	7.2 ± 3	0.33
E wave deceleration time (ms)	151 ± 65	157 ± 55	0.53
Lateral E′ wave (cm/s)	6.2 ± 2.3	6.8 ± 3.1	0.19
E/A ratio	1.4 ± 1	1.3 ± 0.9	0.85
Septal A′ wave (cm/s)	8 ± 3	8.9 ± 5	0.36
Septal E′ wave (cm/s)	5.4 ± 1.7	6.3 ± 1.8	0.09
E wave velocity (cm/s)	67.5 ± 26	68 ± 26	0.94
LA area	21 ± 10	30 ± 9.7	0.16
Global LV function			
t-IVT	13.3 ± 7	12.9 ± 5	0.68
Tei index	0.65 ± 0.4	0.68 ± 0.3	0.71
IVRT	108 ± 32	111 ± 32	0.68
E/E′ ratio	13 ± 8	12 ± 6	0.28
RV function			
A wave velocity (cm/s)	51 ± 17	54 ± 20	0.42
E wave deceleration time (ms)	46 ± 12	52 ± 21	0.05
Right long axis amplitude (cm)	2.1 ± 0.5	1.96 ± 0.6	0.29
PSAP (mm Hg)	41 ± 20	46 ± 21	0.31
Right E′ wave (cm/s)	8 ± 3	10 ± 4	0.04
Right A′ wave (cm/s)	13 ± 4	15 ± 6	0.31
Right S′ wave (cm/s)	11 ± 3	11.3 ± 3	0.68
EDD (cm)	3.2 ± 0.8	3.3 ± 0.9	0.53

LV: left ventricle; RV: right ventricle; A: atrial diastolic velocity; E: early diastolic filling velocity; EDD: end-diastolic dimension; ESD: end-systolic dimension; t-IVT: total isovolumic time; IVRT: isovolumic relaxation time; S′: systolic myocardial velocity, E′: early diastolic myocardial velocity; A′: late diastolic myocardial velocity.

5. Discussion

5.1. Findings

In this study we found that 6-MWT distance was not different between genders, irrespective of its length, despite the fact that female patients with stable chronic HF were younger. NYHA class and all cardiac functional echocardiographic parameters including those of filling pressures, global dyssynchrony and right ventricular function were not different between males and females. Of note, females had smaller LV and LA dimensions, and higher LV EF, compared with males. Predictors of 6-MWT distance, however, were quite different between the two groups. While markers of global LV dyssynchrony, measured by t-IVT, and LV EF predicted exercise capacity in males, NYHA functional class was the only predictor of poor 6-MWT in females.

5.2. Data interpretation

In our study, male and female HF patients had equal exercise capacity, compared to healthy subjects in whom males have better exercise ability than females [29,30]. Our data show that in this group of HF patients with limiting exertional symptoms gender differentiates between patients with respect to the underlying mechanisms for limited exercise capacity, irrespective of the 6 MW distance. Apart from the slightly raised EF in females, the rest of the cardiac functional parameters were not different between genders. Even global measures of LV dyssynchrony as well as right ventricular structure and function were all not different between males and females. Strikingly though, predictors of poor 6-MWT were quite different, while markers of LV systolic function (EF) and global dyssynchrony (total isovolumic time) predicted exercise capacity in males, it was only NYHA class in females that independently predicted poor exercise capacity. Etiological factors unfortunately, did not help in explaining such difference between genders, since the prevalence of ischemic heart disease was similar as well as other co-morbidities, even NYHA class was not different between groups. Such different mechanistic explanation of exercise intolerance matches what we previously found in normal exercise, with peak oxygen consumption being determined by stroke volume in males and by raised left atrial pressure in females [29]. Despite being in HF, our patients followed a similar pattern with males' exercise capacity determined by ventricular

Table 4
Comparison of clinical and biochemical data between patient groups with limited exercise capacity (<6 minute walk distance).

Variable	Female (n = 50)	Male (n = 37)	p value
Age (years)	57 ± 13	63 ± 9	0.008
Smoking (%)	14	49	<0.001
Diabetes (%)	27	40	0.19
Arterial hypertension (%)	64	53	0.36
LBBB (%)	23	17	0.49
Preserved EF (%)	32	19	0.17
Body-mass index	29.5 ± 6	27.5 ± 3	0.08
Waist/hip ratio	0.9 ± 0.1	1.0 ± 0.1	<0.001
NYHA class	2.4 ± 0.6	2.4 ± 0.6	0.91
Fasting glucose (mmol/L)	7 ± 3.4	7.1 ± 3.7	0.88
Total cholesterol (mmol/L)	4.5 ± 1.4	4.2 ± 1.1	0.24
Triglycerides (mmol/L)	2.0 ± 1.2	1.5 ± 0.4	0.047
Urea (mmol/L)	9.4 ± 4.5	11.3 ± 5.3	0.10
Creatinine (μmol/L)	103 ± 46	121 ± 55	0.14
Hemoglobin (gm/dL)	12.7 ± 2.2	13.3 ± 2.4	0.21
Heart rate (beats/minute)	77 ± 15	81 ± 11	0.26
Six minute walk distance (m)	209 ± 66	172 ± 73	0.02

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

Table 5
Comparison of echocardiographic data between patient groups with limited exercise capacity (<6 minute walk distance).

Variable	Female (n = 50)	Male (n = 37)	p value
Systolic LV function			
Ejection fraction (%)	42 ± 15	36 ± 12	0.05
Interventricular septum (cm)	1.11 ± 0.2	1.09 ± 0.2	0.74
Left atrium (cm)	4.5 ± 0.7	4.7 ± 0.6	0.06
LV EDD (cm)	6 ± 1.1	6.5 ± 1	0.02
LV ESD (cm)	4.8 ± 1.2	5.4 ± 1.1	0.02
Septal long axis amplitude (cm)	0.98 ± 0.3	0.78 ± 0.3	0.03
Septal S′ wave (cm/s)	6.8 ± 2.6	7.1 ± 1.1	0.75
Lateral long axis amplitude (cm)	1.2 ± 0.3	1.1 ± 0.4	0.17
Lateral S′ wave (cm/s)	6.4 ± 2	6 ± 2	0.34
LV posterior wall (cm)	1.1 ± 0.3	1.0 ± 0.1	0.85
Aortic root (cm)	3.3 ± 0.3	3.6 ± 0.4	<0.001
Diastolic LV function			
A wave velocity (cm/s)	61 ± 25	55 ± 22	0.28
Lateral A′ wave (cm/s)	7.5 ± 3.7	7.3 ± 3	0.87
E wave deceleration time (ms)	153 ± 71	143 ± 52	0.52
Lateral E′ wave (cm/s)	6.7 ± 2.4	6 ± 2.4	0.22
E/A ratio	1.4 ± 1	1.5 ± 1	0.57
Septal A′ wave (cm/s)	9.5 ± 5	7.8 ± 3	0.65
Septal E′ wave (cm/s)	6.1 ± 2.9	6.5 ± 1.8	0.73
E wave velocity (cm/s)	67 ± 22	70 ± 28	0.63
Global LV function			
t-IVT	11 ± 6.0	13 ± 5.0	0.71
Tei index	0.7 ± 0.6	0.7 ± 0.3	0.90
IVRT	103 ± 30	111 ± 34	0.43
E/E′ ratio	12.4 ± 5.3	14.7 ± 10	0.24
RV function			
E wave velocity (cm/s)	46 ± 11	53 ± 22	0.15
A wave velocity (cm/s)	53 ± 19	52 ± 19	0.89
E wave deceleration time (ms)	183 ± 82	137 ± 58	0.006
Right long axis amplitude (cm)	2.0 ± 0.7	1.9 ± 0.5	0.49
PSAP (mm Hg)	38 ± 20	49 ± 19	0.08
Right E′ wave (cm/s)	9 ± 4	9.5 ± 5	0.77
Right A′ wave (cm/s)	13.8 ± 5	14.5 ± 4	0.77
Right S′ wave (cm/s)	11 ± 3	11.7 ± 4	0.78
EDD (cm)	3.2 ± 0.5	3.3 ± 1	0.85

LV: left ventricle; RV: right ventricle; A: atrial diastolic velocity; E: early diastolic filling velocity; EDD: end-diastolic dimension; ESD: end-systolic dimension; t-IVT: total isovolumic time; IVRT: isovolumic relaxation time; S′: systolic myocardial velocity, E′: early diastolic myocardial velocity; A′: late diastolic myocardial velocity.

Table 6
Predictors of limited 6 minute walk test in female patients.

Variable	Odds ratio (95% CI)	p value (<)
Clinical univariate predictors		
Hemoglobin	1.005 (0.979–1.031)	0.72
Heart rate	1.031 (0.993–1.070)	0.11
NYHA class	2.228 (0.974–5.100)	0.06
Creatinine	1.008 (0.995–1.022)	0.23
Urea	1.055 (0.945–1.179)	0.34
Body-mass index	1.029 (0.941–1.124)	0.53
Diabetes mellitus	1.224 (0.418–3.590)	0.71
Age	0.995 (0.958–1.034)	0.81
Echocardiographic univariate predictors		
t-IVT	0.959 (0.882–1.042)	0.32
Tei index	0.755 (0.230–2.478)	0.64
IVRT	0.987 (0.963–1.011)	0.29
LV EF	0.983 (0.951–1.016)	0.31
E/A ratio	1.435 (0.886–2.325)	0.14
LV EDD	1.063 (0.683–1.066)	0.79
Right long axis amplitude	1.832 (0.885–3.791)	0.11
LV ESD	1.136 (0.770–1.676)	0.52
Left atrium	1.816 (0.855–3.857)	0.12
E wave deceleration time	0.999 (0.991–1.007)	0.76
E/E′ ratio	1.021 (0.959–1.087)	0.51
Lateral long axis amplitude	0.461 (0.080–2.664)	0.39
Septal long axis amplitude	0.436 (0.063–3.001)	0.39
Multivariate predictors		
t-IVT	0.961 (0.844–1.095)	0.55
LV ejection fraction	1.002 (0.947–1.061)	0.94
E/A ratio	1.386 (0.686–2.804)	0.36
Hemoglobin	1.017 (0.980–1.054)	0.37
Urea	1.055 (0.915–1.217)	0.46
Age	1.007 (0.946–1.071)	0.83
Body-mass index	1.073 (0.933–1.233)	0.32
Diabetes	1.425 (0.275–7.374)	0.67
NYHA class	4.439 (2.213–16.24)	0.02

LV: left ventricle; A: atrial diastolic velocity; E: early diastolic filling velocity; EDD: end-diastolic dimension; ESD: end-systolic dimension; t-IVT: total isovolumic time; IVRT: isovolumic relaxation time; S′: systolic myocardial velocity, E′: early diastolic myocardial velocity; A′: late diastolic myocardial velocity.

function (EF and synchrony) and females by the extent of subjective breathlessness (which potentially reflects left atrial pressure). We and others [17,31,32] have previously shown that reduced global systolic function predicts poor 6-MWT through compromised stroke volume and cardiac output. Likewise dyssynchrony compromises the stroke volume entering and ejected by the ventricle [33,34] which is known to exaggerate with age [35]. Thus, our results support the previously reported findings showing significant differences in the pattern of exercise intolerance in stable heart failure patients [32,36-39].

5.3. Limitations

We did not have BNP or NT-pro-BNP data in the studied cohort, which could have helped in better patient stratification in terms of severity of ventricular dysfunction and raised wall stress. We however, relied on our stringent clinical assessment of patients and NYHA classing. We did not have invasive measurements of left atrial pressures but relied on Doppler measurements, which are known to be highly reproducible and to closely correlate with invasive pressure measurements [38].

5.4. Clinical implications

In addition to LV EF as the first marker of ventricular dysfunction in heart failure patients, markers of global cavity dyssynchrony (t-IVT) should be routinely used in assessing patients with exercise intolerance, particularly males. Until more objective measures of exercise intolerance are available in females, NYHA classing remains the only predictor.

5.5. Conclusions

Despite similar exercise capacity, gender determines the pattern of underlying cardiac disturbances; ventricular dyssynchrony and LV systolic dysfunction in males and subjective NYHA class in female heart failure patients as independent predictors of limited exercise capacity.

Disclosure

None.

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Table 7
Predictors of limited 6 minute walk test in male patients.

Variable	Odds ratio (95% CI)	p value (<)
Clinical univariate predictors		
Hemoglobin	1.023 (0.997–1.050)	0.09
Heart rate	1.021 (0.979–1.066)	0.33
NYHA class	1.246 (0.603–2.578)	0.55
Creatinine	0.998 (0.985–1.010)	0.71
Urea	0.999 (0.885–1.127)	0.98
Body-mass index	0.978 (0.862–1.109)	0.73
Diabetes mellitus	0.772 (0.282–2.116)	0.61
Age	0.988 (0.938–1.040)	0.64
Echocardiographic univariate predictors		
t-IVT	0.887 (0.790–0.996)	0.04
Tei index	0.126 (0.012–1.299)	0.08
IVRT	0.961 (0.934–0.990)	0.008
LV EF	0.938 (0.895–0.983)	0.007
E/A ratio	1.435 (0.886–2.325)	0.14
LV EDD	0.971 (0.882–1.070)	0.55
Right long axis amplitude	1.034 (0.457–2.341)	0.94
LV ESD	1.447 (0.917–2.283)	0.11
Left atrium	1.139 (0.588–2.203)	0.70
E wave deceleration time	0.995 (0.986–1.004)	0.26
E/E′ ratio	0.989 (0.907–1.079)	0.81
Lateral long axis amplitude	0.901 (0.219–3.709)	0.88
Septal long axis amplitude	0.418 (0.0634–2.717)	0.36
Multivariate predictors		
t-IVT	0.699 (0.552–0.886)	0.003
LV ejection fraction	0.908 (0.835–0.987)	0.023
E/A ratio	1.151 (0.459–2.884)	0.76
Hemoglobin	1.028 (0.990–1.068)	0.15
Urea	0.994 (0.806–1.228)	0.96
Age	0.961 (0.867–1.066)	0.45
Body-mass index	0.926 (0.729–1.177)	0.53
Diabetes	0.898 (0.183–4.417)	0.89
Age	0.961 (0.867–1.066)	0.45
NYHA class	0.490 (0.108–2.230)	0.34

LV: left ventricle; A: atrial diastolic velocity; E: early diastolic filling velocity; EDD: end-diastolic dimension; ESD: end-systolic dimension; t-IVT: total isovolumic time; IVRT: isovolumic relaxation time; S′: systolic myocardial velocity, E′: early diastolic myocardial velocity; A′: late diastolic myocardial velocity.

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