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Left ventricular markers of global dyssynchrony predict limited exercise capacity in heart failure, but not in patients with preserved ejection fraction

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Abstract

Background: The aim of this study was to prospectively examine echocardiographic parameters that correlate and predict functional capacity assessed by 6 min walk test (6-MWT) in patients with heart failure (HF), irrespective of ejection fraction (EF).

Methods: In 147 HF patients (mean age 61 ± 11 years, 50.3% male), a 6-MWT and an echo-Doppler study were performed in the same day. Global LV dyssynchrony was indirectly assessed by 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 based on the 6-MWT distance (Group I: ≤300 m and Group II: >300 m), and also in two groups according to EF (Group A: LVEF ≥ 45% and Group B: LVEF < 45%).

Results: In the cohort of patients as a whole, the 6-MWT correlated with t-IVT (r = −0.49, p < 0.001) and Tei index (r = −0.43, p < 0.001) but not with any of the other clinical or echocardiographic parameters. Group I had lower hemoglobin level (p = 0.02), lower EF (p = 0.003), larger left atrium (p = 0.02), thicker interventricular septum (p = 0.02), lower A wave (p = 0.01) and lateral wall late diastolic myocardial velocity a' (p = 0.047), longer isovolumic relaxation time (r = 0.003) and longer t-IVT (p = 0.03), compared with Group II. In the patients cohort as a whole, only t-IVT ratio [1.257 (1.071-1.476), p = 0.005], LV EF [0.947 (0.903-0.993), p = 0.02], and E/A ratio [0.553 (0.315-0.972), p = 0.04] independently predicted poor 6-MWT performance (<300 m) in multivariate analysis. None of the echocardiographic measurements predicted exercise tolerance in HFpEF.

Conclusion: In patients with HF, the limited exercise capacity, assessed by 6-MWT, is related mostly to severity of global LV dyssynchrony, more than EF or raised filling pressures. The lack of exercise predictors in HFpEF reflects its multifactorial pathophysiology.

Keywords: Six-minute walk test, Doppler echocardiography, LV function and dyssynchrony

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Background

Heart failure (HF) has become a major public health problem [1], and its incidence is increasing [2], particularly that caused by systolic left ventricular (LV) dysfunction, which is known to have poor prognosis [3,4]. In patients with systolic HF, systolic [5] and diastolic [6,7] LV velocity parameters, as well as right ventricular [8] function have been shown to correlate with functional capacity. However, detailed assessment of cardiac function timing [9] has shown that similar clinical limitation could be seen in patients with isolated diastolic myocardial abnormalities in the presence of preserved LV ejection fraction (EF) (HFpEF) [10]. Irrespective of EF, the morbidity and mortality of patients with HF remain high, despite advances in pharmacological and non-pharmacological treatments [11,12], suggesting a need for identifying other functional parameters that guide towards optimum management and better clinical outcome.

Ventricular dyssynchrony has been shown to contribute to clinical deterioration of HF and resynchronization therapy has proved the opposite [13-15]. LV segmental and global dyssynchrony can easily be assessed by Doppler echocardiography [16-18], with its parameters not only predicting prognosis but also the extent of exercise tolerance. Six-minute walk test (6-MWT) is very popular for objective assessment of exercise capacity in HF [19], particularly in secondary and tertiary referral centers [20,21]. We have previously shown that echocardiographic markers of raised left atrial pressure and those of ventricular dyssynchrony predict limited exercise capacity in patients with poor LV EF [22]. However, the predictive role of echocardiography in assessing limited exercise capacity in patients with HFpEF has not been thoroughly investigated. The aim of this study was to prospectively examine predictors of functional capacity, assessed by 6-MWT in a consecutive group of patients irrespective of EF. This objective is based on the rationale that HFpEF patients have multi-factorial causes for limited exercise capacity therefore difficult to identify breathlessness related mechanisms using Doppler echocardiography.

Methods

Study population

We studied 147 patients (mean age 61 ± 11 years, 50.3% male) with clinical diagnosis of congestive heart failure, and New York Heart Association (NYHA) functional class I-III, secondary to ischemic heart disease or non-ischemic etiology. Patients were referred to the Service of Cardiology, Internal Medicine Clinic, University Clinical Centre of Kosovo, between December 2005 and April 2011. At the time of the study all patients were on optimum cardiac medications, optimized at least 2 weeks prior to enrollment, based on patient's symptoms and renal function: 81% were receiving ACE inhibitors or ARB, 70% beta-blockers, 11% digoxin, 46% spironolactone, 64% diuretics. Patients with reduced LV EF had ischemic etiology in 42%, hypertensive in 25%, and unknown etiology in 33%. Patients with preserved LV EF had ischemic aetiology in 44% and hypertensive in 56%. All patients were in sinus rhythm. Fifty seven patients had LV EF <45% (HFpEF), and the remaining 90 patients had LV EF ≥45% (Table 1). Patients with clinical evidence for cardiac decompensation, limited physical activity due to factors other than cardiac symptoms (e.g. arthritis), more than mild mitral regurgitation, more than mild renal failure, chronic obstructive pulmonary disease (COPD) 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.

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 tests. Estimated body mass index (BMI) was calculated from weight and height measurements. Waist, hip measurements were also made and waist/hip ratio calculated.

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. End-systole and end-diastole LV dimensions were made 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 2 and 4 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 [23] 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 were calculated. Left atrial diameter was measured from aortic root recordings with the

Table 1 Comparison of echocardiographic data between patient's groups

Variable	Limited performance (n = 90)	Good performance (n =57)	P
Systolic LV function			
Ejection fraction (%)	34 ± 12	41 ± 15	0.003
Interventricular septum (cm)	1.06 ± 0.1	1.11 ± 0.2	0.07
Left atrium (cm)	4.8 ± 0.7	4.5 ± 0.7	0.02
LV EDD (cm)	6.4 ± 1.3	6.1 ± 1.1	0.15
LV ESD (cm)	5.3 ± 1.0	4.9 ± 1.1	0.08
Septal long axis amplitude (cm)	0.8 ± 0.3	0.9 ± 0.3	0.21
Septal s' wave (cm/s)	6.3 ± 1.4	7 ± 2.6	0.24
Lateral long axis amplitude (cm)	.05 ± 0.3	1.1 ± 0.3	0.24
Lateral s' wave (cm/s)	6.1 ± 2.4	6.5 ± 2.5	0.51
LV posterior wall (cm)	1.0 ± 0.1	1.0 ± 0.4	0.86
Aortic root (cm)	3.4 ± 0.3	3.4 ± 0.4	0.94
Diastolic LV function			
A wave velocity (cm/s)	58 ± 21	72 ± 29	0.009
Lateral a' wave (cm/s)	7 ± 2.5	8.3 ± 3.5	0.047
E wave deceleration time (ms)	146 ± 57	168 ± 65	0.08
Lateral e' wave (cm/s)	6 ± 2.3	6.4 ± 2	0.28
E/A ratio	1.2 ± 0.8	1.6 ± 1.1	0.045
Septal a' wave (cm/s)	8.2 ± 2.5	8.7 ± 5	0.64
Septal e' wave (cm/s)	6 ± 2.2	6 ± 2.8	0.71
E wave velocity (cm/s)	69 ± 24	70 ± 32	0.75
Left atrial area	27 ± 8.2	28 ± 8.6	0.88
Global LV function			
T-IVT	14.1 ± 3.8	11.8 ± 4.4	0.03
Tei index	0.74 ± 0.5	0.6 ± 0.3	0.07
IVRT	121 ± 35	99 ± 24	0.003
E/e' ratio	12.6 ± 6.6	11.6 ± 5.6	0.41
RV function			
A wave velocity (cm/s)	51 ± 15	54 ± 22	0.44
E wave deceleration time (ms)	154 ± 68	157 ± 71	0.84
Right long axis amplitude (cm)	2 ± 0.61	2 ± 0.6	0.93
PSAP (mmHg)	44.3 ± 23	44.4 ± 17	0.99
Right e' wave (cm/s)	9.7 ± 4.3	9 ± 3.8	0.57
Right a' wave (cm/s)	15 ± 5.6	13 ± 4.7	0.24
Right s' wave (cm/s)	10.6 ± 2.9	11.2 ± 3.2	0.52
EDD (cm)	3.2 ± 0.9	2.8 ± 0.6	0.06

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.

M-mode cursor positioned at the level of the aortic valve leaflets.

Diastolic function of the LV and RV was assessed from 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 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 of more than 40 mm in transverse diameter [24].

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 Doppler flow velocity. Total isovolumic time (t-IVT) was calculated as 60 - (total ejection time + total filling time) and was expressed in s/min [25]. Tei index was calculated as the ratio between t-IVT and ejection time [26]. 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 them was calculated [26].

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 [27]. Likewise, tricuspid regurgitation was assessed by color Doppler and continuous-wave Doppler. Retrograde trans-tricuspid pressure drop > 35 mmHg was taken as an evidence for pulmonary hypertension [28]. All M-mode and Doppler recordings were made at a fast speed of 100 mm/s with a superimposed ECG (lead II).

Six minute walk test
Within 24 h of the echocardiographic examination a 6-MWT was performed on a level hallway surface for all patients and was administered by a specialized nurse blinded to the results of the echocardiogram. According to the method of Gyatt et al. [29] patients were informed of the purpose and protocol of the 6 MWT which was conducted in a standardized fashion while patients on their regular medications [30,31]. A 15 m flat, obstacle-

free corridor was used and patients were instructed to walk as far as they can, turning 180° after they have 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 the 6 min the supervising nurse measured the total distance walked by the patient. Pulse and blood pressure were measured before and at the end of the walking test.

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 and limited exercise performance groups [32], and were compared using unpaired Student t-test. Also, patients with maintained HFpEF were compared with those with reduced EF (<45%) using unpaired t-test.

Results

Patients mean age was 61 ± 11 years, and 50.3% were females (Table 2). The etiology of heart failure was ischemic in 68 patients (46%), idiopathic in 44 (30%) and hypertensive in 35 (24%) patients. The studied patients as a whole exercised for a mean of 265 ± 111 m and had to stop because of breathlessness and/or tiredness. Patients with HF and reduced EF exercised for 241 ± 107

Table 2 Baseline patient's data in study patients

Sex (female, in%)	49.7
Age (years)	61 ± 11
Smoking (%)	31
Diabetes (%)	33
LBBB (%)	25
Body-mass index	28 ± 5
Waist/hips 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
Hemoglobine (g/L)	128 ± 23
Heart rate (beats/min)	78 ± 13

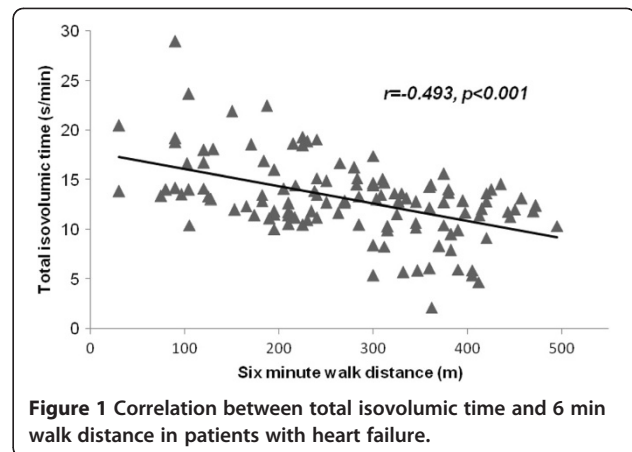Data are mean ± standard deviation. NYHA = New York Heart Association.

Figure 1 Correlation between total isovolumic time and 6 min walk distance in patients with heart failure.

m compared to 275 ± 112 m in those with HFpEF, (p = 0.09).

Clinical and echocardiographic correlates of 6 MWT distance

Out of the list of Doppler echocardiographic measurements, only markers of global dyssynchrony, t-IVT (r = −0.49, p < 0.001) and Tei index (r = −0.43, p < 0.001) correlated with the 6-MWT distance using Pearson's correlation model (Figure 1 & 2).

Patients with limited vs. good 6 MWT performance

Hemoglobin (p = 0.03) and smoking (p = 0.04) were the only clinical finding that was different between the two groups of patients with good and limited exercise performance (Table 3). Patients with limited 6-MWT performance had lower EF (p = 0.003), larger left atrium (p = 0.02), lower A wave (p = 0.009) and lateral myocardial velocity a' (p = 0.047), but longer isovolumic relaxation time (p = 0.003) and longer t-IVT (p = 0.03, Table 1).
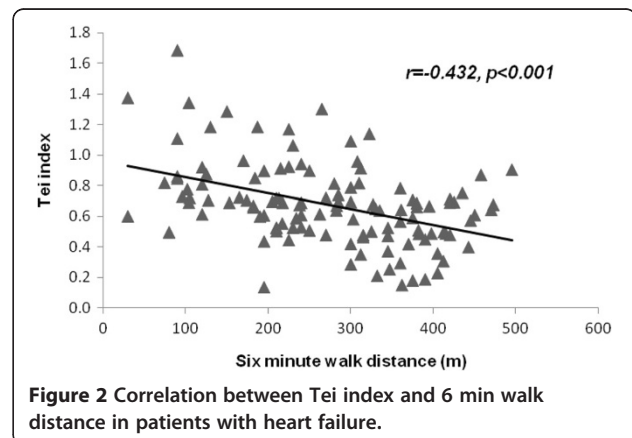

Figure 2 Correlation between Tei index and 6 min walk distance in patients with heart failure.

Table 3 Comparison of clinical and biochemical data between patient's groups

Variable	Limited performance (n = 90)	Good performance (n = 57)	P value
Sex (female, in%)	53	43	0.26
Age (years)	61 ± 12	61 ± 10	0.81
Smoking (%)	25	44	0.04
Diabetes (%)	34	30	0.67
LBBB (%)	24	26	0.75
Preserved EF (%)	30	40	0.24
Body-mass index	28 ± 5	28 ± 4	0.91
Waist/hips ratio	0.95 ± 0.1	0.97 ± 0.1	0.28
NYHA class	2.3 ± 0.6	2.5 ± 0.7	0.09
Fasting glucose (mmol/L)	6.9 ± 3.3	7.1 ± 2.7	0.84
Total cholesterol (mmol/L)	4.2 ± 1.2	4.3 ± 1.3	0.16
Triglycerides (mmol/L)	1.8 ± 1.2	1.6 ± 0.4	0.25
Urea (mmol/L)	9.9 ± 4.3	9.5 ± 5.2	0.66
Creatinine (µmol/L)	111 ± 36	108 ± 55	0.74
Haemoglobine (g/L)	123 ± 28	133 ± 16	0.03
Heart rate (beats/min)	79 ± 13	77 ± 14	0.51

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

Predictors of limited 6 MWT distance

Univariate predictors of limited 6 MWT distance

From the biochemical and clinical findings, only low haemoglobin level (p = 0.047) predicted limited 6-MWT distance. Prolonged t-IVT (p < 0.001), high Tei index (p < 0.001), prolonged isovolumic relaxation time (p = 0.005), low LV EF (p = 0.007) and high E/A ratio (p = 0.03), were the echocardiographic predictors of limited distance (Table 4).

Multivariate predictors of limited 6 MWT distance

In multivariate analysis [odds ratio 95% confidence interval], prolonged t-IVT [1.257 (1.071-1.476), p = 0.005], low LV EF [0.947 (0.903-0.993), p = 0.02], and high E/A ratio [0.553 (0.315-0.972), p = 0.04], independently predicted the limited 6-MWT distance (Table 4). A t-IVT of 12.5 s/min had a sensitivity of 70% and specificity of 65% (AUC on ROC analysis of 73%) for predicting limited performance (Figure 3).

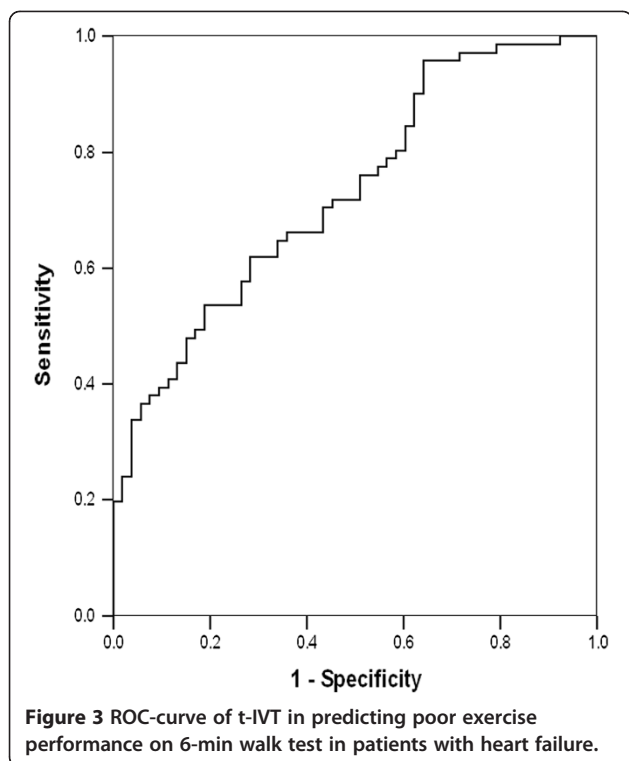#### Patients with EF < 45% vs patients with HFpEF

We further divided the whole cohort into patients with reduced EF (<45%) and those with HFpEF and compared their clinical and echocardiographic parameters, as well as exercise capacity and its predictors.

Table 4 Predictors of limited 6 min walk test

Variable	Odds ratio (95% CI)	P value (<)
Clinical univariate predictors		
Hemoglobin	1.020 (1.000-1.041)	0.047
Heart rate	1.027 (0.999-1.056)	0.06
NYHA class	1.535 (0.878-2.685)	0.13
Gender	1.502 (0.734-3.073)	0.27
Creatinine	1.003 (0.995-1.012)	0.47
Urea	1.030 (0.950-1.117)	0.47
Body-mass index	1.028 (0.947-1.117)	0.51
Diabetes mellitus	0.847 (0.394-1.820)	0.67
Age	1.004 (0.973-1.036)	0.81
Echocardiographic univariate predictors		
T-IVT	0.743 (0.646-0.855)	<0.001
Tei index	0.038 (0.007-0.219)	<0.001
IVRT	0.974 (0.957-0.992)	0.005
LV EF	1.049 (1.013-1.087)	0.007
E/A ratio	1.526 (1.035-2.251)	0.03
LV EDD	0.714 (0.483-1.055)	0.09
Right long axis amplitude	1.832 (0.885-3.791)	0.11
LV ESD	0.781 (0.562-1.086)	0.14
Left atrium	1.272 (0.763-2.120)	0.36
E wave deceleration time	0.997 (0.991-1.003)	0.39
E/e' ratio	1.036 (0.943-1.140)	0.46
Lateral long axis amplitude	0.708 (0.197-2.554)	0.59
Septal long axis amplitude	0.794 (0.857-3.404)	0.76
Multivariate predictors		
T-IVT	1.257 (1.071-1.476)	0.005
LV Ejection Fraction	0.947 (0.903-0.993)	0.02
E/A ratio	0.553 (0.315-0.972)	0.04
Haemoglobin	0.974 (0.947-1.001)	0.06
Gender	0.535 (0.188-1.523)	0.24
Age	1.022 (0.975-1.072)	0.37

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.

Heart rate was the only clinical variable slightly lower in patients with HFpEF compared to those with low EF (p = 0.04). LV EDD, LV ESD and left atrium were all smaller in HFpEF patients (p < 0.001, for all). Interventricular septum was thicker (p = 0.01) and septal long axis amplitude of motion (p = 0.049) were both higher in HFpEF patients. LV filling A wave was higher (p = 0.002), E wave deceleration time longer p = 0.03, and E/A ratio lower (p = 0.008) in HFpEF patients (Table 1). None of clinical or echocardiographic parameters independently predicted the limited exercise in patients with HFpEF.

Figure 3 ROC-curve of t-IVT in predicting poor exercise performance on 6-min walk test in patients with heart failure.

Discussion

Findings

In this study we identified markers of global LV dyssynchrony, measured by t-IVT and Tei index but not pre-ejection time which correlated with the 6 MWT distance in a group of patients with clinically stable HF irrespective of EF. A long t-IVT, a low LV EF and high transmitral E/A ratio predicted limited exercise performance in multivariate analysis. Low hemoglobin, a univariate predictor, failed to independently predict limited exercise performance. In a small subgroup of patients with HFpEF none of the clinical parameters or functional echocardiographic measurements predicted limited 6MWT distance.

Data interpretation

In the absence of musculoskeletal disorders, increased body weight or chronic obstructive pulmonary disease, limited exercise performance is commonly related to cardiac dysfunction, in the form of reduced systolic function (EF) or raised filling pressures [22,33]. These two common findings have similar consequences, in the form of raised pulmonary pressure, causing exertional breathlessness. Our studied patients show this disturbed pathophysiology, even partially, having shown reduced LV EF and global LV dyssynchrony as independent predictors of limited exercise performance. Global dyssynchrony in the form of prolonged t-IVT and high Tei index restrict effective phases of the cardiac cycle,

required for LV filling and ejection. This results in compromised stroke volume and consequently cardiac output and exercise performance as previously shown [33]. In addition, limited left atrial emptying is bound to increase pulmonary venous pressure and hence breathlessness [34] and limited exercise capacity. In individual patients, a t-IVT cut off value of 12.5 s/m clearly discriminated good from limited exercise capacity, having identified over 50% of patients. It must be mentioned that normal exercise capacity is dictated by limited stroke volume or raised left atrial pressure, based on gender [35]. Theoretically therefore, correcting LV synchronous function in heart failure patients by cardiac resynchronisation therapy (CRT), in the absence of evidence for a need for revascularization, is bound to reverse such disturbed physiology and cardiac symptoms [36]. On the other hand when segregating the cohort into patients with reduced EF and those with HFpEF such predictive power of cardiac measurements for 6MWT distance was lost, suggesting the presence of other mechanisms for breathlessness, even in a minority of patients, which diluted the relationship we found above. It also confirms the lack of uniformity of such patients, currently combined under one diagnosis 'HFpEF' as has recently been shown not to respond to one and the same medical protocol [37]. This finding confirms our hypothesis stated in the introduction above.

Limitations

We did not obtain Doppler echocardiographic measurements at peak exercise, when patients became symptomatic, since the objective of the study was to simply determine predictors of ordinary walking exercise limitation rather than an exercise echocardiogram that should have required a different protocol. 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]. We avoided using segmental measurements of dyssynchrony, based on the recent doubt of their accuracy [31]. We did not have BNP ant NT-pro-BNP data in our patients. However, as the aim of the study was the assessment of echocardiographic predictors of exercise capacity in heart failure patients, we believe that the lack of these data will not weaken the results.

Clinical implications

Patients with HF, particularly those in NYHA class III and IV are known to have significantly limited exercise tolerance. Although EF is the most popular measure of LV function, and is considered the corner stone for recruiting patients for various treatment modalities,

markers of global LV dyssynchrony should be considered as part of the conventional protocol of the follow-up of such patients. Despite exertional breathlessness in HF patients is multi-factorial, identifying specific patterns of cardiac dysfunction should guide towards optimum management of individual patients, e.g. vasodilators in patients with raised left atrial pressure and cardiac resynchronisation therapy in those with ventricular dys-synchrony, particularly when there is evidence for irre-versible dyssynchrony. Those with HFpEF need individualistic approach in assessing their exercise cap-acity and management.

Conclusions

Patients with heart failure who appear to be clinically stable may have significantly limited exercise ability. In these patients, markers of global ventricular dyssyn-chrony are as important, if not more, than markers of systolic LV dysfunction, in predicting limited exercise performance. Results of the small subgroup of patients with HFpEF cannot be generalised without being tested in a larger cohort.

Authors contributions
GB, EH and MH designed the study; GB, AB, AP, AA, RO and ZV, made the protocol of study; GB, VH, BM, PR, DV, RT and EH, examined the patients; AB, AA, AP, EH, ZV, RO, PR, RT, DV and BM wrote the paper. GB and MH made critical review of the paper; All authors read and approved the final manuscript.

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