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Left atrial emptying fraction predicts limited exercise performance in heart failure patients

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ABSTRACT

Aim: We aimed in this study to assess the role of left atrial (LA), in addition to left ventricular (LV) indices, in predicting exercise capacity in patients with heart failure (HF).
Methods: This study included 88 consecutive patients (60 ± 10 years) with stable HF. LV end-diastolic and end-systolic dimensions, ejection fraction (EF), mitral and tricuspid annulus peak systolic excursion (MAPSE and TAPSE), myocardial velocities (s′, e′ and a′), LA dimensions, LA volume and LA emptying fraction were measured. A 6-min walking test (6-MWT) distance was performed on the same day of the echocardiographic examination.
Results: Patients with limited exercise performance (≤300 m) were older ($p = 0.01$), had higher NYHA functional class ($p = 0.004$), higher LV mass index ($p = 0.003$), larger LA ($p = 0.002$), lower LV EF ($p = 0.009$), larger LV end-systolic dimension ($p = 0.007$), higher E/A ratio ($p = 0.03$), reduced septal MAPSE ($p < 0.001$), larger LA end-systolic volume ($p = 0.03$), larger LA end-diastolic volume ($p = 0.005$) and lower LA emptying fraction ($p < 0.001$) compared with good performance patients. In multivariate analysis, only the LA emptying fraction [0.944 (0.898–0.993), $p = 0.025$] independently predicted poor exercise performance. An LA emptying fraction <60% was 68% sensitive and 73% specific (AUC 0.73, $p < 0.001$) in predicting poor exercise performance.
Conclusion: In heart failure patients, the impaired LA emptying function is the best predictor of poor exercise capacity. This finding highlights the need for routine LA size and function monitoring for better optimization of medical therapy in HF.

1. Introduction

Heart failure (HF) is a clinical syndrome, which is becoming a major problem in public health in recent decades [1,2]. Despite many new achievements in pharmacological and non-pharmacological treatments, the morbidity and mortality associated with HF still remain high [2–6]. Several echo-parameters were tested previously [7–15] for clinical outcome prediction in patients with HF. Different indices were also, proposed as predictors of survival [11–17], quality of life [11–15] and exercise capacity [22–26] in these patients. Six-minute walk test (6-MWT) has been introduced as an accurate tool for assessing exercise capacity in HF patients, being safe, simple to perform and its results can predict clinical outcomes [18–21].

Left ventricular (LV) systolic function indices [22,23] and those of global mechanical dyssynchrony [24–26] have been shown to independently predict exercise capacity in HF patients. However, the left atrial (LA) function indices and their relationship with exercise markers have not been completely tested yet in this setting. Therefore, we aimed to test LA total emptying fraction as a potential predictor of exercise capacity in HF patients in comparison with other clinical and echocardiographic parameters.

2. Methods

2.1. Study population

We studied 88 patients (mean age 60 ± 10 years, 61% female) with clinical diagnosis of HF, and New York Heart Association (NYHA) functional class I–class III. Patients were referred to the Service of Cardiology, Internal Medicine Clinic, University Clinical Centre of Kosovo, between February 2013 and November 2013. At the time of the study, all patients were on conventional medical treatment, optimized at least 2 weeks prior to enrollment, based on patient's symptoms and renal function:

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84.6% were receiving ACE inhibitors or ARB, 70.5% beta-blockers, 55% diuretics, 77% aspirin and 20.5% Ca-blockers. Of the studied cohort, 19% had ischemic etiology, 65.5% hypertension, 7.14% valve disease and 8.3% unknown etiology.

Patients with clinical evidence for cardiac decompensation, limited physical activity due to factors other than cardiac symptoms (e.g. arthritis), chronic renal failure with a stage >2 (glomerular filtration rate ≥ 89 mL/min), 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.

2.2. Data collection

Detailed history and clinical assessment were obtained in all patients, in whom routine biochemical tests were also performed including, lipid profile, blood glucose level and kidney function tests. Estimated body mass index (BMI) was calculated from weight and height measurements. Waist and hip measurements were also made and waist/hip ratio 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. LV end-systole and end-diastole dimension measurements 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. MAPSE and TAPSE were studied by placing the M-mode cursor at the lateral and septal angles of the mitral annulus and the lateral angle of the tricuspid annulus.

Total amplitude of long axis motion (MAPSE or TAPSE) was measured as previously described [27] 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 pulsed wave Doppler sample volume placed at the basal part of LV lateral and septal segments as well as RV free wall. Systolic (s′) and 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.

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 as the ratio between transmitral E wave and mean lateral and septal e′ wave velocities. 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 [28].

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 [29]. Likewise, tricuspid regurgitation was assessed by color Doppler and continuous-wave Doppler. Retrograde transtricuspid pressure drop >35 mmHg was taken as an evidence for pulmonary hypertension [30]. All M-mode and Doppler recordings were made at a fast speed of 100 mm/s with a superimposed ECG (lead II).

2.4. Measurements of left atrial dimensions and function

LA diameter was measured from aortic root recordings with the M-mode cursor positioned at the level of the aortic valve leaflets. LA volumes were measured using area-length method from the apical four and two chamber views, according to the guidelines of the American Society of Echocardiography [31]. Left atrial maximum volume (LA end-systolic volume) was measured at the end of LV systole, just before the opening of the mitral valve, LA minimum volume (LA end-diastolic volume) was measured at end diastole, right after the closure of the mitral valve, and left atrial total emptying fraction (LA emptying function) was calculated automatically [31,32].

2.5. 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. [33], 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 [34,35]. A 15-m flat, obstacle-free corridor was used, and patients were instructed to walk as far as they can, turning 180° after reaching 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.

2.6. Statistical analysis

Data are presented as mean ± SD or proportions (% of patients). Continuous data were compared with two-tailed unpaired Student 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 [36] and were compared using unpaired Student t test.

3. Results

Patients' mean age was 60 ± 10 years, and 61% were females (Table 1). The patients group as a whole exercised for a mean of 298 ± 109 m.

Table 1
Baseline patient's data.

Clinical data	
Sex (female, %)	61
Age (years)	60 ± 10
Smoking (%)	21.5
Diabetes (%)	29
Body mass index	29 ± 3.5
Body surface area	1 ± 0.2
Waist/hip ratio	0.95 ± 0.5
NYHA class	1.8 ± 0.8
LBBB	19
Fasting glucose (mmol/L)	7 ± 2.9
Total cholesterol (mmol/L)	4.6 ± 1.2
Triglycerides (mmol/L)	1.7 ± 1
Urea (mmol/L)	8.8 ± 6
Creatinine (mmol/L)	93 ± 29

NYHA: New York Heart Association; LBBB: left bundle branch block.

3.1. Patients with limited vs. good exercise performance

Forty-five patients had good exercise, and the remaining 43 patients had limited exercise. Patients with limited exercise capacity (6-MWT < 300 m) were older ($p = 0.01$) and had higher creatinine level ($p = 0.03$), higher NYHA class ($p = 0.004$) and lower systolic and diastolic blood pressure ($p = 0.001$, for both) compared with those with good exercise performance (Table 2).

Patients with limited exercise performance also had higher LV mass index ($p = 0.003$), larger LA ($p = 0.002$), lower LV EF ($p = 0.009$), larger LV end-systolic dimension ($p = 0.007$), higher E/A ratio ($p = 0.03$), reduced septal MAPSE ($p < 0.001$), larger LA end-systolic volume ($p = 0.03$), larger LA end-diastolic volume ($p = 0.005$) and lower LA emptying fraction ($p < 0.001$) compared with good performance patients (Table 3). Nine of the 43 with limited exercise had restrictive LV filling pattern compared to 2 of 45 patients with good exercise performance, the difference of this incidence between groups was not significant.

3.2. Correlation of 6-MWT distance with echo parameters

From the list of echocardiographic measurements, only LA emptying fraction ($r = 0.26$, $p = 0.01$), LV EF ($r = 0.22$, $p = 0.03$), MAPSE septal ($r = 0.33$, $p = 0.002$) and Septal s′ ($r = 0.26$, $p = 0.02$) correlated with the 6-MWT distance (Table 4).

3.3. Predictors of limited 6-MWT distance

From the biochemical and clinical findings, only age ($p = 0.01$) and NYHA class ($p = 0.007$) predicted limited 6-MWT distance in univariate analysis. However, low LV EF ($p = 0.01$), higher LV mass index ($p = 0.006$), larger LV end-systolic dimension ($p = 0.01$) and end-diastolic dimension ($p = 0.04$), reduced septal MAPSE ($p = 0.001$), higher E/A ratio ($p = 0.03$), larger LA dimension ($p = 0.006$) and lower LA emptying fraction ($p = 0.001$) were univariate echocardiographic predictors of limited exercise capacity (Table 5). In multivariate analysis, only LA emptying fraction [0.944 (0.898–0.993), $p = 0.025$] independently predicted poor exercise performance (Table 5). An LA emptying fraction <60% was 68% sensitive and 73% specific (AUC 0.73, $p < 0.001$) in predicting poor exercise performance (Fig. 1).

4. Discussion

4.1. Findings

Our findings show that beyond LV EF and its longitudinal systolic function, the LA emptying function correlated with the 6-MWT distance in a group of patients with clinically stable HF. It was also the only independent predictor of limited exercise capacity, assessed by 6-MWT, in these patients.

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

Variable	Good performance (>300 m distance) N = 45	Limited performance (≤300 m distance) N = 43	P
Age (years)	58 ± 8.0	63 ± 10	0.01
Body mass index (kg/m^2)	29 ± 3.7	28 ± 3.3	0.52
Body surface are	1.1 ± 0.3	1.0 ± 0.2	0.40
Waist/hip ratio	0.95 ± 0.5	0.96 ± 0.5	0.36
SBP (mmHg)	145 ± 24	128 ± 21	0.001
DBP (mmHg)	90 ± 13	81 ± 12	0.001
NYHA class	1.5 ± 0.8	2.1 ± 0.8	0.004
Fasting glucose (mmol/L)	6.1 ± 2.0	7.9 ± 3.9	0.05
Total cholesterol (mmol/L)	4.7 ± 1.2	4.6 ± 1.3	0.83
Tryglycerides (mmol/L)	2.0 ± 1.3	1.5 ± 0.7	0.05
Urea (mmol/L)	7.7 ± 6	10 ± 6	0.12
Creatinine (mmol/L)	82 ± 22	99 ± 32	0.03

Data are mean ± standard deviation. NYHA: New York Heart Association; SBP: systolic blood pressure; DBP: diastolic blood pressure.

Table 3
Comparison of echocardiographic data between patient's groups.

Variable	Good performance (>300 m distance) N = 45	Limited performance (≤300 m distance) N = 43	P
LV dimensions and mass			
LV mass index (g/m $^{2.7}$)	50 ± 19	65 ± 26	0.003
LV EDD (cm)	5.1 ± 0.6	5.6 ± 1.3	0.036
LV ESD (cm)	3.4 ± 0.8	4.1 ± 1.5	0.007
IVSd (cm)	1.16 ± 0.3	1.21 ± 0.3	0.5
LVPWd (cm)	0.97 ± 0.1	1.04 ± 0.1	0.04
EDV (ml)	127 ± 27	165 ± 97	0.01
ESV (ml)	54 ± 34	93 ± 86	0.006
LV systolic function			
LV ejection fraction (%)	59 ± 12	51 ± 17	0.009
LV shortening fraction (%)	32 ± 8.3	27 ± 11	0.01
MAPSE septal (cm)	1.2 ± 0.2	0.9 ± 0.3	<0.001
Septal s′ (cm/s)	4.8 ± 1.1	4.2 ± 1.2	0.06
MAPSE lateral (cm)	1.3 ± 0.2	1.3 ± 0.3	0.15
Lateral s′ (cm)	5.4 ± 1.3	5.0 ± 1.3	0.18
E/e′ ratio	10 ± 4.7	12 ± 9.0	0.29
LV diastolic function			
E wave (cm/s)	58 ± 18	67 ± 24	0.07
A wave (cm/s)	70 ± 16	65 ± 26	0.33
E/A ratio	0.9 ± 0.4	1.3 ± 1.1	0.02
E wave DT (ms)	188 ± 46	160 ± 51	0.01
Lateral e′ (cm/s)	6.4 ± 2.4	7.0 ± 2.8	0.33
Lateral a′ (cm/s)	8.5 ± 2.9	6.6 ± 2.0	0.009
Septal e′ (cm/s)	5.8 ± 1.7	5.5 ± 2.3	0.45
LA dimensions and function			
LA diameter (cm)	3.4 ± 0.7	4.6 ± 1.3	0.002
LA transversal diameter (cm)	3.9 ± 0.8	4.7 ± 1.4	0.004
LA longitudinal diameter (cm)	5.7 ± 0.8	6.1 ± 1.3	0.09
LA end systolic volume (ml)	56 ± 36	80 ± 62	0.03
LA end diastolic volume (ml)	23 ± 25	43 ± 40	0.005
LA total EF (%)	62 ± 12	50 ± 16	<0.001

LV: left ventricle; EDD: end-diastolic dimension; ESD: end-systolic dimension; IVSd: interventricular septum in diastole; PWd: parietal wall in diastole; s′: systolic myocardial velocity; MAPSE: mitral annular plane systolic excursion; A: atrial diastolic velocity; E: early diastolic filling velocity; LA: left atrial; LA total; EF: left atrial total emptying fraction; DT: deceleration time.

Table 4
Correlations of clinical and echocardiographic variables with 6-min walk distance.

Variable	*R*	*P*
Clinical correlates		
Age	−0.29	0.01
Body mass index	−0.35	0.01
Creatinine	−0.06	0.62
Echocardiographic correlates		
LA total EF	0.26	0.01
LV ejection fraction	0.22	0.03
E wave velocity	−0.09	0.38
A wave velocity	0.01	0.93
E/A ratio	−0.13	0.24
E wave DT	0.18	0.09
MAPSE lateral	0.21	0.06
MAPSE septal	0.33	0.002
Septal e′	0.19	0.07
Septal a′	0.11	0.32
Septal s′	0.26	0.02

LV: left ventricle; LA total EF: left atrial total emptying fraction; E: early diastolic filling velocity; A: atrial diastolic filling velocity; E′: early diastolic myocardial velocity; MAPSE: mitral annular plane systolic excursion.

Table 5
Predictors of limited exercise performance.

Variable	Odds ratio (95% CI)	*P*
Clinical univariate predictors		
Age	1.066 (1.013–1.122)	0.01
Body mass index	0.958 (0.841–1.092)	0.52
Body surface are	0.410 (0.052–3.254)	0.39
NYHA class	2.346 (1.268–4.341)	0.007
Fasting glucose	1.214 (0.988–1.490)	0.06
Urea	1.097 (0.970–1.240)	0.14
Creatinine	1.026 (0.999–1.053)	0.56
Echocardiographic univariate predictors		
LV mass index (g/m 2.7)	1.039 (1.011–1.067)	0.006
LV EDD (cm)	1.047 (1.001–1.095)	0.04
LV ESD (cm)	1.053 (1.011–1.097)	0.01
LV ejection fraction (%)	0.963 (0.935–0.992)	0.01
MAPSE septal (cm)	0.043 (0.007–0.256)	0.001
Septal s′ (cm/s)	0.707 (0.490–1.020)	0.06
MAPSE lateral (cm)	0.317 (0.078–1.293)	0.10
Lateral s′ (cm)	0.796 (0.570–1.111)	0.18
E wave (cm/s)	1.018 (0.998–1.039)	0.08
A wave (cm/s)	0.989 (0.968–1.011)	0.32
E/A ratio	2.313 (1.047–5.111)	0.03
LA diameter (cm)	2.223 (1.260–3.923)	0.006
LA total EF (%)	0.936 (0.902–0.971)	<0.001
Multivariate predictors		
Age	1.036 (0.970–1.107)	0.29
Gender	1.082 (0.303–3.859)	0.90
NYHA class	1.673 (0.745–3.752)	0.21
LVMI (gm/2.7)	1.013 (0.984–1.044)	0.38
LV EF	1.019 (0.972–1.069)	0.43
MAPSE septal	0.470 (0.043–5.113)	0.53
LA total EF	0.944 (0.898–0.993)	0.02

LV: left ventricle, EDD: end-diastolic dimension, ESD: end-systolic dimension, s′: systolic myocardial velocity, MAPSE: mitral annular plane systolic excursion, A: atrial diastolic velocity, E: early diastolic filling velocity, t-IVT: total isovolumic time, LA: left atrial, LA total EF: left atrial total emptying fraction.

4.2. Data interpretation

The main exercise limiting symptom in heart failure is breathlessness, for which a number of mechanisms have been identified, including compromised stroke volume and cardiac output, raised LV filling pressures, mitral regurgitation, secondary pulmonary hypertension and inadequate peripheral muscle oxygen supply and demand. In our patients, numerous parameters of cardiac function differentiated the two groups of patients according to the 6-MW distance. Obviously, LV global and segmental function were worse in patients with limited exercise capacity as were markers of filling pressures; however, the frequency of patients with restrictive filling pattern was not different between the two groups. In addition, the left atrium was significantly larger in patients with limited exercise capacity, and its function was quite disturbed, as shown by the reduced total emptying fraction with a value of <60% predicting limited exercise. While the contribution of low LV ejection fraction to exertional breathlessness is easily understood on the basis of compromised stroke volume [36] and cardiac output, that of the LV long axis function (MAPSE) requires further explanation. LV long axis function is supported by the longitudinal myocardial fibers located subendocardially. They have been shown to contribute significantly to the overall myocardial fattening and hence contractile function as shown by thickening fraction and ejection fraction [37]. In our patients, LV long axis function indeed correlated with exercise capacity and univariately predicted poor performance. Furthermore, during exercise, the magnitude of long axis excursion normally increases in order to allow reciprocal increase in left atrial volume and consequently venous return [38]. This behavior was, again, suboptimal in our patients because of the abnormal long axis function, at rest, and the enlarged left atrium with its stiff myocardium. Finally, the left atrial emptying function proved to be the only independent predictor of limited exercise capacity. This could be explained on the basis of the chronically enlarged left atrial cavity with the potential loss of adequate contractile function, on the plateau of Frank–Starling curve [39,40], irrespective of the severity of raised pressures. The perpetual increase of left atrial pressure secondary to raised LV end-diastolic pressure and mitral regurgitation results eventually into stretched LA myocardium with fibrosis, which limits the cavity ability to fill and empty [41]. This causes pulmonary venous hypertension and consequently breathlessness with exertion.

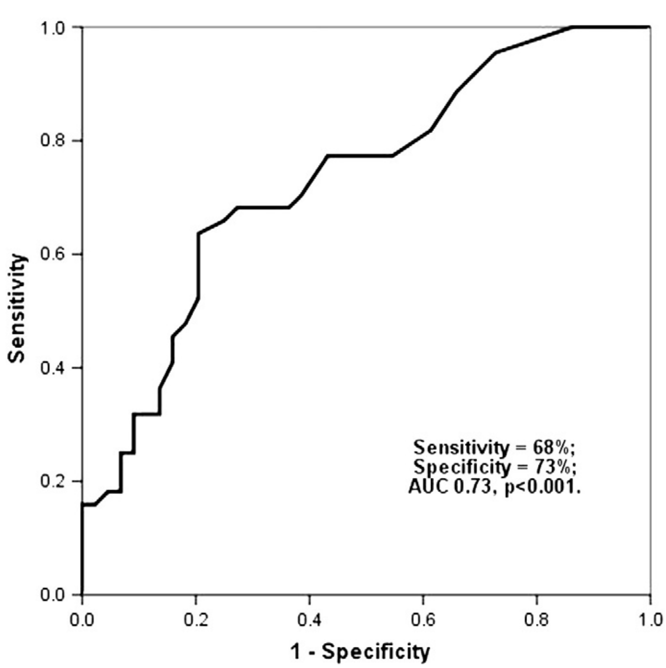

Fig. 1. An LA total EF <60% was 68% sensitive and 73% specific (AUC 0.73, $p < 0.001$) in predicting poor exercise performance.

4.3. Clinical implications

While restrictive LV filling has been well documented as an explanation of exercise intolerance in heart failure, our findings show that impaired LA emptying function, irrespective of restrictive filling, could explain patient's exertional breathlessness. Regular incorporation of LA function assessment in heart failure follow-up protocol should assist in identifying patients who need aggressive left atrial pressure offloading therapy to save them developing restrictive filling, which in many patients might be irreversible and is known for its poor clinical outcome [42]. Our findings show that LV EF should not be taken solely as an accurate measure of subtle functional changes in heart failure patients. Furthermore, our results are supported by Terzi S et al. [43], who demonstrated similar relationship between LA function and objective measurements of exercise capacity by VO_2.

4.4. Limitations

We did not assess left atrial intrinsic myocardial function in this study, using strain and strain rate measurements. They would have shed light on explaining our findings. Our comments on raised left atrial pressure were based on Doppler findings, which are well validated, rather than direct measurements of left atrial pressures, which would have needed clinically unjustifiable invasive techniques. The modest predictive value of individual measurements might be due to the small patient's number, as well as the known heterogeneity of this syndrome.

4.5. Conclusion

In stable heart failure patients, the intrinsic left atrial function seems to be the best predictor of exercise capacity, assessed by 6-MWT distance, irrespective of the presence of restrictive filling pattern. These findings suggest a potential use of left atrial emptying fraction as a sign of early function disturbances, which might recover with optimum adjustment of left atrial pressure offloading therapy.

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

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