International Journal of Cardiology 146 (2011) 385–389

Contents lists available at ScienceDirect

International Journal of Cardiology

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

Left ventricular asynchrony and raised filling pressure predict limited exercise performance assessed by 6 minute walk test

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ARTICLE INFO

Article history:
Received 18 May 2009
Received in revised form 12 July 2009
Accepted 20 July 2009
Available online 20 August 2009

Keywords:
Six-minute walk test
Doppler echocardiography
Restrictive filling
Left ventricular asynchrony

ABSTRACT

Background: Six minute walking test (6-MWT) may serve as a reproducible test for assessing exercise capacity in heart failure (HF) patients and can be clinically predicted. We aimed in this study to ascertain if global markers of ventricular asynchrony can predict 6MWT distance in a group of patients with HF and left ventricular (LV) ejection fraction (EF) <45%.

Methods and results: This study included 77 consecutive patients (60 ± 12 years) with stable HF. LV end-diastolic and end-systolic dimensions, shortening fraction (SF), EF, myocardial velocities, t-IVT, and Tei index were measured, as well as 6-MWT distance.

Patients with limited exercise performance (≤300 m) had lower SF ($p = 0.02$) and EF ($p = 0.017$), longer t-IVT ($p = 0.001$), higher Tei index ($p = 0.002$) and higher E/E′ ratio ($p < 0.001$) compared with good performance patients. In multivariate analysis, only E/E′ ratio [0.800 (0.665–0.961), $p = 0.017$], and t-IVT [0.769 (0.619–0.955), $p = 0.018$] independently predicted poor exercise performance.

Conclusions: In heart failure patients, the higher the filling pressures and the more asynchronous the left ventricle, the poorer is the patient's exercise capacity. These findings highlight specific LV functional disturbances that should be targeted for better optimization of medical and/or electrical therapy.

1. Introduction

The syndrome of heart failure (HF) constitutes a major public health problem [1,2], being a common pathway for a number of clinical conditions. Left ventricular (LV) systolic dysfunction is the most common cause of HF, with high prevalence [3] and poor prognosis [4]. A number of other physiological disturbances have equally important impact on the quality of life of such patients and carry unfavorable prognosis [5] e.g diastolic abnormalities in the form of raised filling pressures [6,7]. Recently, segmental myocardial asynchrony has been shown as another factor behind exercise intolerance in HF patients [8]. Despite advances in pharmacological and non-pharmacological treatments, HF related morbidity and mortality remain high [9,10], suggesting a need for more accurate markers that may guide towards optimum management.

Doppler echocardiography is the main stay for assessing systolic and diastolic LV function [11–13]. We have previously shown that echocardiographic measurements of global ventricular asynchrony, which results in shortening of filling and ejection times, accurately predict exercise tolerance in dilated cardiomyopathy [14], prognosis in patients with raised filling pressures [15] and after coronary artery surgery [16] as well as response to cardiac resynchronization therapy [17]. Six-minute walk test (6-MWT) is widely used to assess functional status of patients with chronic HF [18] and is very popular in secondary and tertiary referral centres [19,20]. It was shown also as a strong independent long-term predictor in patients hospitalized with acute HF [21]. We aimed in this study to identify resting cardiac functional measurements, in particular those of global LV asynchrony, that correlate with exercise tolerance, assessed by 6 MWT in particular those of global LV asynchrony. We also planned to determine potential predictors of limited exercise performance that may guide towards best optimum management.

2. Methods

2.1. Study population

The study group included 77 consecutive patients with stable heart failure [New York Heart Association (NYHA) functional class I–III] secondary to ischemic heart disease or idiopathic dilated cardiomyopathy. Patients were referred to our Cardiology Department, between December 2005 and August 2008. All patients were on optimum cardiac medications at the time of the study which included ACE-inhibitors, β blockers, digoxin and diuretics. Medications were optimized for individual patients at least 2 weeks prior to enrollment, based on symptoms and renal function. All patients were in sinus rhythm and had clear evidence for LV dysfunction (EF <45%) assessed by a baseline echocardiogram. Patients with clinical evidence for cardiac decompensation, limited physical activity due to factors other than cardiac symptoms (e.g. arthritis), with severe mitral regurgitation, more than mild renal failure, chronic obstructive

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doi:10.1016/j.ijcard.2009.07.018

pulmonary disease as well as 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. Routine biochemical tests were performed which included hemoglobin, lipid profile, blood glucose level, and kidney function tests. Estimation of body mass index (BMI) was made from weight and height measurements. Waist, 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 dimensions at end-systole and end-diastole were made from the left parasternal cross-sectional recording of the minor axis with the M-mode cursor positioned by the tips of the mitral valve leaflets. LV volumes and ejection fraction 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 [22]. LV and right ventricular (RV) long axis myocardial velocities were also studied using Doppler tissue imaging technique. From the apical 4-chamber view, longitudinal velocities were recorded with the sample volume placed at the basal segment 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 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. Peak LV and RV early (E wave), and late (A wave) diastolic velocities were measured and E/A and E/E′ ratios were calculated. LV filling pattern was considered 'restrictive' when E/A ratio was >2.0, E wave deceleration time <140 ms and the left atrium dilated, >40 mm in transverse diameter [23].

2.4. Measurements of LV asynchrony

Indirect assessment of LV asynchronous function 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 [24]. Tei index was calculated as the ratio between t-IVT and ejection time [25]. 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, the time delay between them was calculated [25].

Mitral regurgitation severity was assessed by colour 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 [26]. Likewise, tricuspid regurgitation was assessed by colour Doppler and continuous-wave Doppler. Retrograde transtricuspid pressure drop >35 mm Hg was taken as an evidence for pulmonary hypertension [27]. 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; the test was administered by a specialized nurse blinded to the results of the echocardiogram, as well as clinical characteristics of the patients. According to the method of Gyatt et al. [28] patients were informed of the purpose and protocol of the 6-min walk test which was conducted in a standardized fashion while patients were on their regular medications [28–30]. 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.

2.6. 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-MW distance were identified with univariate analysis and multivariate logistic regression was performed by the Step-wise method, a significant difference was defined as $p<0.05$ (2-tailed). We included in the multivariate regression model the variables that were significant in univariate analysis, except those that interfere because of the small number of patients. Patients were divided according to their ability to walk >300 m into Good and Limited exercise performance groups [31], and were compared using unpaired Student *t*-test.

3. Results

Patients mean age was 60 ± 12 years, and 33.3% were female. The etiology of heart failure was ischemic cardiomyopathy in 50 patients and idiopathic dilated cardiomyopathy in 27 patients.

3.1. Clinical and echocardiographic correlates of 6 minute walk distance

Out of the whole list of Doppler echocardiographic measurements, the E′ wave ($r=0.61$, $p<0.001$), E/E′ ratio ($r=-0.49$, $p<0.001$), t-IVT ($r=-0.44$, $p<0.001$) and Tei index ($r=-0.43$, $p<0.001$) had the highest correlation with the 6-MW distance (Table 1, Figs. 1 and 2). Age, LV function and dimensions, and kidney function correlated poorly with 6-MWT (Table 1).

3.2. Patients with limited vs. good 6 minute walk performance

3.2.1. Clinical and biochemical differences

A number of clinical differences featured patients who had limited 6 MWT performance. They were older ($p<0.001$), had higher prevalence of smoking ($p=0.03$), had worse kidney function (higher urea, $p=0.019$ and creatinine, $p=0.027$), had worse degree of HF as shown by NYHA class ($p<0.001$) and higher prevalence of broad QRS >120 ms ($p=0.038$) compared with those with good performance. None of the other clinical parameters was significantly different between the two groups (Table 2).

3.2.2. Echocardiographic differences

Patients with limited 6-MWT performance had lower shortening fraction ($p=0.021$) and ejection fraction ($p=0.017$), longer t-IVT ($p=0.001$, Fig. 3) and higher Tei index ($p=0.002$), compared with those with good performance. They had also lower myocardial E′ ($p<0.001$), higher E/E′ ratio ($p<0.001$, Fig. 4) and higher prevalence of LV restrictive filling pattern ($p=0.02$). None of the LV structural or other functional measurements differentiated the two groups (Table 3).

3.3. Predictors of limited 6 minute walk performance

3.3.1. Univariate predictors of limited 6 minute walk performance

From biochemical and clinical findings, NYHA class ($p<0.001$), age ($p=0.003$), kidney function (urea: $p=0.029$, and creatinine: $p=0.039$) and smoking ($p=0.04$) predicted limited 6-MWT performance. LV E′ wave ($p<0.001$), E/E′ ($p=0.001$), t-IVT ($p=0.003$), Tei

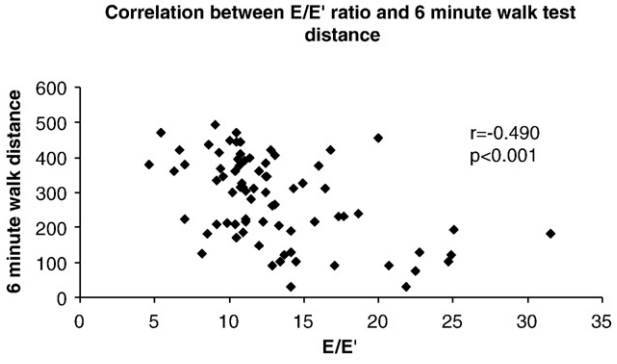

Fig. 1. Correlation between E/E′ ratio and 6 minute walk distance in patients with heart failure due to systolic dysfunction.