

Diastolic function is associated with quality of life and exercise capacity in stable heart failure patients with reduced ejection fraction

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Abstract

Exercise capacity and quality of life (QOL) are important outcome predictors in patients with systolic heart failure (HF), independent of left ventricular (LV) ejection fraction (LVEF). LV diastolic function has been shown to be a better predictor of aerobic exercise capacity in patients with systolic dysfunction and a New York Heart Association (NYHA) classification \geq II. We hypothesized that the currently used index of diastolic function E/e' is associated with exercise capacity and QOL, even in optimally treated HF patients with reduced LVEF. This prospective study included 44 consecutive patients aged 55 ± 11 years (27 men and 17 women), with $LVEF < 0.50$ and NYHA functional class I-III, receiving optimal pharmacological treatment and in a stable clinical condition, as shown by the absence of dyspnea exacerbation for at least 3 months. All patients had conventional transthoracic echocardiography and answered the Minnesota Living with HF Questionnaire, followed by the 6-min walk test (6MWT). In a multivariable model with 6MWT as the dependent variable, age and E/e' explained 27% of the walked distance in 6MWT ($P = 0.002$; multivariate regression analysis). No association was found between walk distance and LVEF or mitral annulus systolic velocity. Only normalized left atrium volume, a sensitive index of diastolic function, was associated with decreased QOL. Despite the small number of patients included, this study offers evidence that diastolic function is associated with physical capacity and QOL and should be considered along with ejection fraction in patients with compensated systolic HF.

Key words: Echocardiography; Left ventricular dysfunction; Six-minute walk test; Dyspnea

Introduction

Heart failure (HF) is a leading cause of death in many countries (1). Mortality is as high as 80% in the 5-year period following the first decompensation event (2,3). Exercise intolerance and decreased quality of life have been demonstrated to be markers of poor prognosis in these patients, independent of left ventricular (LV) ejection fraction (LVEF) (4-7).

Evidence indicates that exercise capacity and quality of life are related to LV filling pressure, mainly for patients with diastolic HF, that is, those with an $LVEF > 0.50$ (8,9). It has been suggested that, when the LVEF is low, the resulting symptoms are related to both systolic and diastolic dysfunction (10). LV early diastolic function has been shown to be a better predictor of aerobic exercise capacity in patients with systolic dysfunction and a New York Heart Association (NYHA) classification I-III (11-13). On the other hand, the effect of diastolic function on quality of life in compensated patients with LV systolic

dysfunction has not been fully addressed. During the last decade, the assessment of diastolic function has been enhanced by the use of tissue Doppler-derived indexes in combination with normalized left atrial volume (LAV) (14).

Therefore, assuming that HF symptoms are greatly affected by LV diastolic pressure filling (15,16), we hypothesized that exercise intolerance and decreased quality of life can be predicted by diastolic function indexes in stable HF patients with reduced LVEF. To address this question, the aim of this study was to analyze the association of both systolic and diastolic LV function with the quality of life and exercise tolerance in these patients.

Material and Methods

Study design and population

This prospective study included 44 consecutive patients over 18 years of age (age range, 55 ± 11 years;

27 men and 17 women) who were treated in the Ambulatório de Insuficiência Cardíaca of our institution for HF and reduced LVEF. The inclusion criteria were as follows: men and women with functional class I-III according to the NYHA classification, a stable clinical condition shown by the absence of dyspnea exacerbation for at least 3 months, LVEF less than 0.5, and ability to cooperate and understand the information they were given.

Patients with any of the following conditions were excluded: HF due to primary valve disease, chest pain or unstable angina, high blood pressure, acute dyspnea, cardiac arrhythmias, clinically manifested pulmonary diseases, more than mild valve dysfunction, orthopedic disease, physical limitation, or signs of infection.

The procedures were approved by the Ethics Committee of the Faculdade de Medicina de Botucatu (OF.405/2009-CEP) and were conducted in accordance with the Declaration of Helsinki. All participants gave written informed consent.

Study protocol

Clinical evaluation. Gender, age, comorbidities (diabetes mellitus, obesity/overweight, dyslipidemia, thyroid dysfunction, and renal failure), tobacco use, symptoms, and pharmacological treatments were recorded. Blood pressure and heart rate were determined as the average of three replicate measurements after at least 10 min of rest in a supine position.

Echocardiography. Immediately after clinical evaluation, all exams were performed by the same cardiologist (SGZB), following standard procedures for recording images and making measurements (17,18). The ultrasound equipment used was a Philips HDI5000 (USA). LV mass was estimated from linear dimensions as follows: $LV\ mass\ (g) = 0.8X\{1.04[(LVDd + PWTd + SWTd)^3 - (LVDd)^3]\} + 0.6$, where LVDd, PWTd, and SWTd represent diastolic LV diameter, posterior wall thickness, and septal wall thickness, respectively. LV mass was indexed for body surface area (g/m^2). LV systolic function was assessed by LVEF using the modified Simpson's rule and tissue Doppler-derived average systolic mitral annular motion (S' , cm/s). Diastolic function was evaluated using pulsed Doppler recordings of mitral inflow velocities E and A waves (cm/s), deceleration time (ms), isovolumic relaxation time (ms), LAV normalized to body surface area (LAVI, mL/m^2), as well as tissue Doppler-derived average diastolic mitral annular motion (e' , cm/s) and the E/e' ratio. The variable e' was analyzed as the average of the medial and lateral annulus motion.

Minnesota Living with Heart Failure Questionnaire (MLWHFQ). In a quiet and private place, all participants answered the 21 questions related to symptoms and physical and psychosocial functions with respect to the impact of the disease on his/her life in the previous month. The total score ranges from 0 (optimal) to 105 (extremely poor) points (19,20).

Six-minute walk test (6MWT). Each patient performed the test, following the recommendations of the American Thoracic Society (21). The participants were asked to walk as fast as they could for 6 min, with the option to interrupt the test at any time. Standardized motivational comments were made at 1-min intervals during the walk. The test course was 30 m long, with markers every 3 m. The final result was the total distance walked, in meters, during the established time. The same researcher carried out the 6MWT and MLWHFQ.

Statistical analysis

Data management and analysis were performed using SYSTAT 12.0 (SYSTAT Software, Inc., USA). Summary data are reported as means \pm SD, unless otherwise specified. Linear regression was used to predict distance walked during the 6MWT and MLWHFQ scores. Independent variables included in the univariate model were gender, age, body surface area, left chamber dimensions, and LV systolic and diastolic function indexes. Significant associations indicated by simple linear regression were included in the multivariate linear regression. Colinearity was avoided by removing from the model those variables with a significant correlation coefficient and selecting those with the greatest clinical relevance. Pearson's correlation was used to analyze the association between LV systolic function indexes and E/e' . The level of significance was set at $P < 0.05$.

Results

Patients

Of the 195 patients who visited the Ambulatório de Insuficiência Cardíaca, Hospital das Clínicas de Botucatu, from January 2008 to January 2010, 151 presented one or more of the exclusion criteria; therefore, 44 patients (27 men and 17 women) were finally included in the study.

Underlying causes of HF and characteristics of the study population are presented in Table 1. Myocardial ischemia was the cause of ventricular dysfunction in 22.7% of the population (10 cases). Twelve patients presented hypertensive heart disease, 11 dilated cardiomyopathy, 8 Chagas' disease, and the remaining 3 HF due to other causes. At the time of entry into the study, 19 patients had no other disease leading to HF, 19 presented one comorbidity, and 6 presented two or more comorbidities. Ten individuals reported tobacco use.

The average age was 55 ± 11 years, and the average body mass index was $26 \pm 5\ kg/m^2$. The average myocardial mass ($155 \pm 41.8\ g/m^2$), LV diastolic and systolic diameters (6.4 ± 0.85 and 5.2 ± 0.93 cm, respectively), and LAVI ($54 \pm 15.8\ mL/m^2$) were all increased above normal values. The LVEF ($36 \pm 8\%$) was below 30% in 12 patients. The average 6MWT distance was 444 ± 63.7 m, and the average MLWHFQ score was 28.7 ± 21.17 .

The cardiovascular drugs used in this population were

Table 1. Characteristics of the study population.

Parameters	Values
Female/male	17/27
Age (years)	55 ± 11
Body mass index (kg/m ²)	26 ± 5
Systolic blood pressure (mmHg)	125 ± 17.2
Diastolic blood pressure (mmHg)	83 ± 13.2
Heart rate (bpm)	71 ± 14.1
Underlying cause of heart failure (n)	
Hypertensive heart disease	12
Ischemic heart disease	10
Dilated cardiomyopathy	11
Chagas' disease	8
Others	3
Comorbidities (n)	
Diabetes	16
Dyslipidemia	11
Hypothyroidism	1
Echocardiography	
LVEF (%)	36 ± 8
LV mass (g/m ²)	155 ± 41.8
LAVI (mL/m ²)	54 ± 15.8
E (cm/s)	76 ± 27.2
A (cm/s)	69 ± 23.5
S' (cm/s)	7.6 ± 1.19
e' (cm/s)	10.2 ± 1.71
E/e' (cm/s)	7.6 ± 2.96
6MWT distance (m)	444 ± 63.7
MLWHFQ score	28.7 ± 21.17

Data are reported as means ± SD or number of cases. LV: left ventricle; LVEF: LV ejection fraction; LAVI: normalized left atrium volume; S': average systolic mitral annular motion; e': average diastolic mitral annular motion; E/e': mitral inflow E velocity to tissue Doppler e' ratio; 6MWT: 6-min walk test; MLWHFQ: Minnesota Living with Heart Failure Questionnaire.

oral diuretics (88.6%), angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers (95.5%), beta blockers (88.6%), spironolactone (56.8%), digoxin (56.8%), aspirin (40.9%), statin (29.5%), and warfarin (11.4%).

Physical capacity and quality of life

Univariate analysis revealed that a number of variables were significantly related to distance walked (Table 2). Colinearity was found between E/e', LV mass, and LAVI; multivariate regression analysis included age and E/e'. After adjusting for age, walk distance was significantly associated with E/e' (P=0.015). LVEF and S' did not show any association with walk distance, even though these systolic function indexes were associated with E/e' (LVEF: R=-0.583, P<0.001, and S': R=-0.607, P<0.001, Pearson's correlation). Table 3 shows that, among the continuous variables analyzed by simple linear regression, only LAVI, an index of diastolic dysfunction, was significantly associated with the MLWHFQ score. None of the systolic function indexes was associated with quality of life. Gender, tobacco use, and diabetes did not influence either the walk distance or the quality of life of the patients.

Discussion

In the present study, it was found that diastolic function but not LVEF or tissue Doppler mitral systolic velocity was associated with exercise tolerance in patients with stable functional class I-III HF and reduced LVEF. In addition, increased LAVI but not the degree of systolic dysfunction was associated with decreased quality of life.

Although ventricular systolic/diastolic dysfunction may decrease exercise tolerance, indexes of LV systolic function have been shown to be poor predictors of exercise capacity (13), while diastolic function indexes have not been fully studied. In the last decade, several

Table 2. Estimating walking distance in reduced ejection fraction heart failure patients from age, body mass index, and echocardiography by simple linear regression.

Variable	Coefficient	95%CI	R	P
Age	-2.36	-4.11 to -0.61	0.387	0.009
BMI	-0.10	-4.00 to 3.00	0.077	0.618
LAVI	-0.78	-1.50 to -0.056	0.318	0.035
LV mass	-0.49	-0.94 to -0.04	0.319	0.035
LVEF	165	-75 to 405	0.209	0.173
S'	10.2	-6.66 to 27.14	0.185	0.228
e'	5.44	-7.67 to 18.54	0.128	0.407
E/e'	-7.53	-13.81 to -1.24	0.349	0.020
E/e'*	-7.34	-13.16 to -1.52	0.516	0.015

BMI: body mass index; LAVI: normalized left atrium volume; LV: left ventricle; LVEF: LV ejection fraction; S': average systolic mitral annular motion; e': average diastolic mitral annular motion; E/e': mitral inflow E velocity to tissue Doppler e' ratio. *Adjusted by age.

Table 3. Estimating quality of life in reduced ejection fraction heart failure patients from age, body mass index, exercise capacity, and echocardiography by simple linear regression.

Variable	Coefficient	95%CI	R	P
Age	-0.414	-1.03 to -0.203	0.204	0.183
BMI	-0.10	-2.38 to 0.197	0.255	0.095
6MWT	-0.071	-0.172 to 0.030	0.215	0.162
LAVI	0.274	0.036 to 0.513	0.337	0.025
LV mass	0.040	-0.266 to 0.345	0.040	0.795
LVEF	-23.3	-104.7 to 58.1	0.089	0.567
S'	-1.80	-7.49 to 3.89	0.098	0.527
e'	1.38	-2.44 to 5.21	0.112	0.470
E/e'	1.902	-0.248 to 4.052	0.266	0.081

BMI: body mass index; 6MWT: 6-minute walk test; LAVI: normalized left atrium volume; LV: left ventricle; LVEF: LV ejection fraction; S': average systolic mitral annular motion; e': average diastolic mitral annular motion; E/e': mitral inflow E velocity to tissue Doppler e' ratio.

authors have described associations between exercise capacity and diastolic function more accurately using tissue Doppler indexes (22-24). However, little is known about the association between diastolic function and quality of life and exercise capacity in optimally treated and compensated patients with systolic HF (11-13,22-24).

In the present study, although the LVEF and E/e' indexes were directly correlated, there was no association between LVEF and distance walked during the 6MWT, in accordance with others (25). On the other hand, walk distance was influenced by age and E/e'. Gardin et al. (13) also found a correlation between diastolic function and exercise tolerance in a large population of HF patients with reduced LVEF and NYHA functional class \geq II. In that study it was suggested that mitral valve E/A and E/e' indexes were more strongly related to exercise performance than was LVEF. Brucks et al. (11) and Fukata and Little (12) showed that, regardless of LVEF and the severity of symptoms, the degree of diastolic dysfunction was closely associated with prognosis and exercise intolerance in HF patients in class \geq II. We included stable patients whose performance on the 6MWT suggested mild or moderate physical limitation. Despite the simplicity of the 6MWT, its use has been validated in the literature, because it can predict the exercise tolerance in patients with HF and reduced LVEF (26,27). Also, Carvalho et al. (28) showed a correlation between the 6MWT and cardiopulmonary exercise tests in patients with HF (NYHA I-II).

Our findings indicated that patients with systolic HF who are oligosymptomatic with pharmacologic treatment have a reduced physical capacity associated with decreased LV diastolic function. A possible explanation for our results is that physical activity increases heart rate, impairing atrial emptying and thus raising the pressure in the left atrium. These events would cause pulmonary congestion and exercise intolerance (29,30). Diastolic function was evaluated using tissue Doppler imaging

(TDI) of mitral annular motion (E/e'). This index has been shown to be an excellent predictor of diastolic filling in subsets of patients. In addition, the TDI parameter that had the best correlation with the invasive mean LV diastolic pressure was the E/e' ratio; this correlation was better in patients with LVEF $<$ 50% (14). Therefore, limitations on exercise would more likely be related to dyspnea caused by increased pressure in the left atrium than to a reduced oxygen supply related to decreased cardiac output.

Despite the evidence that LV function affects exercise capacity, reports indicate that ventricular function indexes do not affect a patient's reported quality of life (31). We found a positive association between LAVI and MLWHFQ scores. Specifically, the enlargement of the left atrium, indicating diastolic dysfunction, was associated with a higher MLWHFQ score, suggesting a decreased quality of life. We did not find a significant association between the systolic function index and the MLWHFQ score, in accordance with others (6,32-34). On the contrary, there is a paucity of information on the association between quality of life and LAV or other index of diastolic function in HF patients with reduced LVEF.

It is worthy mentioning that E/e' did not correlate with quality of life and that LAVI did not correlate with walking distance. We believe that this asymmetry is caused by the variability of the indexes and the small number of patients included in the study. It is possible that, if we had a larger number of patients, then both indexes would be correlated with either quality of life or walking distance.

Interestingly, our results did not indicate a correlation between the MLWHFQ score and the 6MWT distance, indicating that diastolic dysfunction, rather than walk distance, plays a major role in decreasing quality of life. This finding is in contrast with those of other studies that used the same questionnaire (34,35). A possible explanation for the disagreement is that the patients included in the earlier studies may have had more severe systolic

dysfunction, further increasing LV filling pressure and reducing their 6MWT distance. Unfortunately, those studies did not evaluate diastolic function.

It is important to note that HF patients with systolic dysfunction and reduced cardiac output may have decreased respiratory and skeletal muscle performance, which would reduce their ability to perform exercise (36,37). This condition decreases oxidative type I fibers and increases glycolytic type IIb fibers. Other consequences that have been described include impaired endothelial function, negative changes in vasodilatory capacity, excessive sympathetic stimulation causing vasoconstriction, decreased blood flow to skeletal

muscles, and an enhanced ergoreflex response (38). In the present study, because these alterations were not evaluated, we are unable to draw conclusions concerning their effects on the patients' physical capacity.

We conclude that, despite the small number of patients, this study offers evidence that diastolic function is associated with physical capacity and quality of life and should be considered along with ejection fraction in patients with compensated systolic HF.

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