European Journal of Echocardiography (2009) **10**, 400–405
doi:10.1093/ejechocard/jen297

Echocardiographic predictors of functional capacity in endomyocardial fibrosis patients

Vera M.C. Salemi[1]*, João J. Leite[2], Michael H. Picard[3], Leila M. Oliveira[2], Soraya F. Reis[1], Jose L.B. Pena[1], and Charles Mady[1]

[1]*Cardiomyopathy Unit, University of São Paulo Medical School;* [2]*Pulmonary Division from Heart Institute (InCor), University of São Paulo Medical School, São Paulo, Brazil; and* [3]*Cardiology Division and Cardiac Ultrasound Laboratory, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA*

Received 29 April 2008; accepted after revision 5 October 2008; online publish-ahead-of-print 24 October 2008

KEYWORDS
Endomyocardial fibrosis;
Restrictive cardiomyopathy;
Echocardiography;
Diastole;
Ergoespirometry and prognosis

Aims Endomyocardial fibrosis (EMF) is a restrictive cardiomyopathy manifested mainly by diastolic heart failure. It is recognized that diastole is an important determinant of exercise capacity. The purpose of this study was to determine whether resting echocardiographic parameters might predict oxygen consumption (VO_{2p}) by ergoespirometry and the prognostic role of functional capacity in EMF patients.
Methods and results A total of 32 patients with biventricular EMF (29 women, 55.3 ± 11.4 years) were studied by echocardiography and ergoespirometry. The relationship between the echocardiographic indexes and the percentage of predicted VO_{2p} ($\%VO_{2p}$) was investigated by the 'stepwise' linear regression analysis. The median VO_{2p} was 11 ± 3 mL/kg/min and the $\%VO_{2p}$ was $53 \pm 9\%$. There was a correlation of $\%VO_{2p}$ with an average of A′ at four sites of the mitral annulus (A′ peak, $r = 0.471$, $P = 0.023$), E′/A′ of the inferior mitral annulus ($r = -0.433$, $P = 0.044$), and myocardial performance index ($r = -0.352$, $P = 0.048$). On multiple regression analysis, only A′ peak was an independent predictor of $\%VO_{2p}$ ($\%VO_{2p} = 26.34 + 332.44 \times$ A′ peak). EMF patients with $\%VO_{2p} < 53\%$ had an increased mortality rate with a relative risk of 8.47.
Conclusion In EMF patients, diastolic function plays an important role in determining the limitations to exercise and $\%VO_{2p}$ has a prognostic value.

Introduction

Endomyocardial fibrosis (EMF) is a rare restrictive cardiomyopathy of unknown origin. It is characterized by fibrous tissue deposition in the endocardium and, to a lesser extent, in the myocardium, in the inflow tract, and apex of one or both ventricles.[1] It results in a reduced ventricular cavity size leading to a filling restriction. The fibrous compromise of papillary muscles, and chordae tendinae leads to mitral and/or tricuspid regurgitation. Systolic performance is normal or slightly depressed in patients with EMF. In contrast, diastolic dysfunction is mainly responsible for the development of severe cardiac failure. Previous studies have emphasized the importance of left ventricular (LV) diastolic dysfunction in limiting the exercise capacity of patients with heart failure.[2] The aim of the present study was to examine the relationship between resting echocardiographic indices and exercise capacity in patients with EMF and to analyse the prognostic role of functional capacity in EMF patients.

Methods

Patient population

We prospectively studied 32 patients with biventricular EMF (29 women, mean age 55.3 ± 11.4 years) and no other systemic disease. Each patient was evaluated by a detailed clinical history, physical examination, electrocardiography, two-dimensional Doppler echocardiography, and ergoespirometry. Inclusion criteria were a clinical diagnosis of diastolic heart failure and an echocardiogram showing apical biventricular obliteration (*Figure 1*, see supplementary material *Video 1*). The diagnosis in each patient was confirmed by cardiac catheterization, patients continued to receive optimal pharmacological therapy during the study, and no acute decompensation was observed at least 1 month before the study inclusion. The degree of ventricular obliteration was qualitatively classified as mild, moderate, or severe based on its echocardiography and cineventriculography, as previously described.[3,4] Patients remaining in New York Heart Association (NYHA) functional

* Corresponding author. Tel/fax: +55 11 3556 9832.
E-mail address: verasalemi@uol.com.br

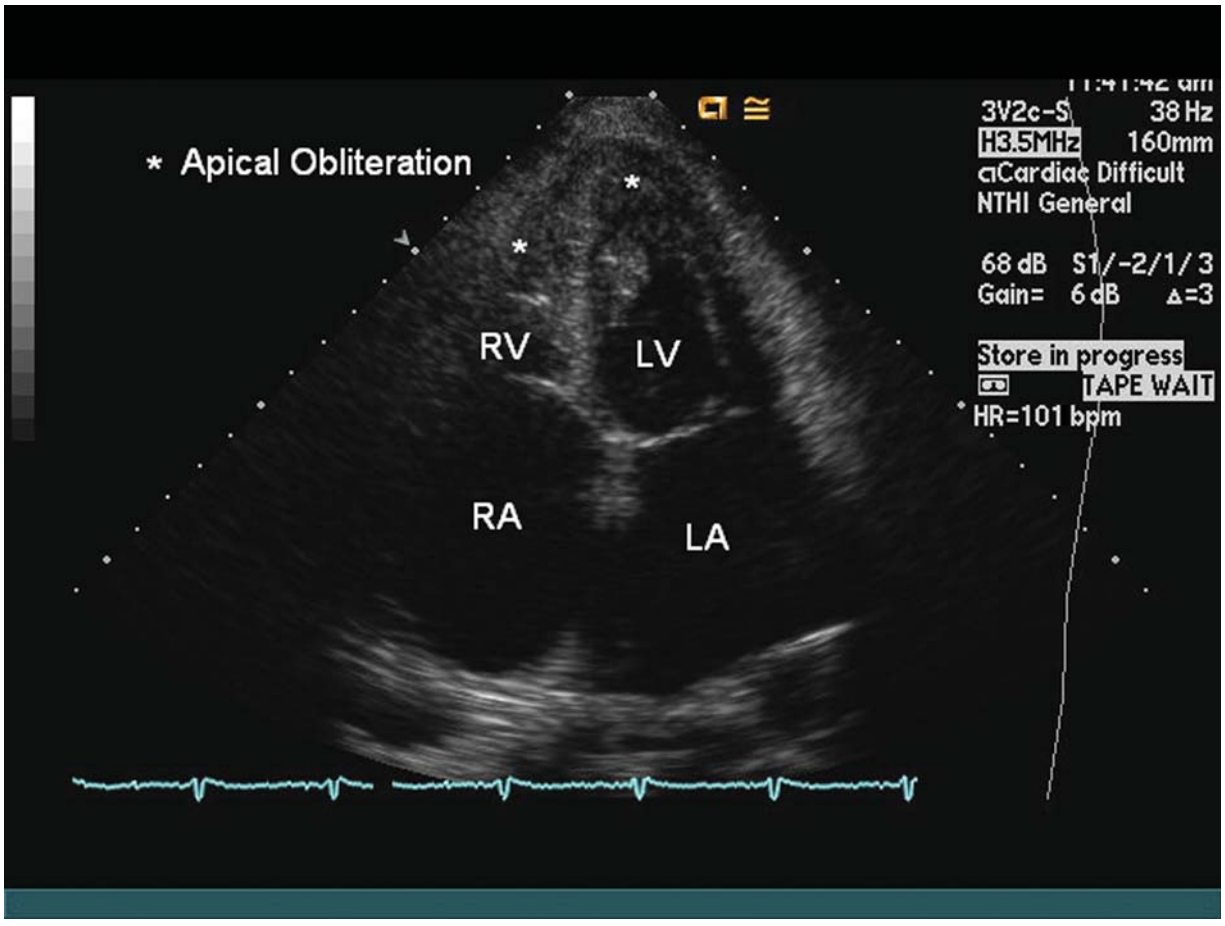

Figure 1 Apical, four-chamber, two-dimensional echocardiogram of a patient with endomyocardial fibrosis showing apical obliteration of both ventricles. RA, right atrium; RV, right ventricle; LA, left atrium; LV, left ventricle.

classes III and IV after medical therapy were offered surgical resection.

Our institutional review board approved this study, and informed consent was obtained from all patients.

Echocardiographic studies

Complete echocardiographic studies were performed with a Sequoia 512 ultrasound machine (Acuson, Mountain View, CA, USA) with a 2.5 MHz harmonic imaging transducer. From the apical acoustic window, two-dimensional images of the left atrium (LA) and LV were traced to calculate end-diastolic and end-systolic biplane volumes corrected by body surface area (BSA), using a modified form of Simpson's biplane method, as well as the LA and LV ejection fractions were calculeted.[5] LV mass was calculated by the M-mode echocardiography on the short-axis view, according to Devereux *et al*.[6] The diastolic function was assessed from pulsed-wave Doppler of the mitral and pulmonary venous flow velocities,[7] tissue Doppler imaging of the septal, lateral, anterior, and inferior mitral annulus, and the average myocardial peak velocity at four sites of the early diastole (E′ peak), late diastole (A′ peak), and systole (S′ peak).[8]

The myocardial performance index (MPI), defined as the sum of the isovolumetric contraction time and isovolumetric relaxation time divided by the ejection time, also was determined by the pulsed-wave Doppler.[9] Mitral regurgitation was quantified by planimetry of the colour Doppler area of the regurgitant jet relative to the area of the LA.[10] Systolic pulmonary artery pressure was determined from the continuous-wave Doppler tricuspid regurgitation peak velocity, using the simplified Bernoulli's equation and adding 10 mmHg of estimated right atrial pressure.[11] Pericardial effusions were classified as mild, moderate, or severe based on the distance between the epicardium and pericardium. The cardiac rhythm in nine patients was atrial fibrillation (AF); in these cases, the cycles chosen for analysis were based on the quality of Doppler recordings, the presence of a cycle with a heart rate ranging between 60 and 100 bpm, and an interval $\geq$70 ms between the end of mitral flow and the onset of the QRS.[12]

Exercise oxygen consumption determination

Ergoespirometry was carried out the same day as the echocardiography. This examination was performed on a bicycle ergometer (model CardiO_2), using a 10 W ramping protocol, with the breath-by-breath gas exchange analysis. The peak oxygen uptake (VO_{2p}) was expressed in milliliter per kilogram per minute, and the percentage of predicted VO_{2p} (%VO_{2p}) was derived from Wasserman's formulae.[13]

Statistical analysis

All data are expressed as mean $\pm$ SD or frequency (%) for discrete variables.

Comparisons of gender, rhythm, and functional class with %VO_{2p} were performed with the *t* test; and the degree of mitral regurgitation, pericardial effusion, right or LV fibrotic tissue involvement by one-way analysis of variance. The Pearson correlation coefficients were determined to evaluate relationships between the echocardiographic indexes and %VO_{2p} in all patients, as well as those in sinus rhythm and with AF. The variables that presented a *P*-value of $\leq$0.10 at Pearson's correlation were used in the 'stepwise' multiple linear regression to identify the independent echocardiographic

predictors of $\%VO_{2p}$. The Kaplan–Meier method was used for survival curves with the log-rank test with a median $\%VO_{2p}$ of 53% used as a cut-off value. $P < 0.05$ was considered statistically significant. Statistical analysis was performed with SPSS v 15 (SPSS Inc., Chicago, IL, USA).

Results

The mean VO_{2p} was 11 ± 3 mL/kg/min (5–21) and the mean $\%VO_{2p}$ was $53 \pm 9\%$ (25–84). Gender was not related to $\%VO_{2p}$ ($P > 0.05$), but NYHA functional class II presented a $\%VO_{2p}$ of $59 \pm 12\%$ and functional class III a $\%VO_{2p}$ of $44 \pm 13\%$ ($P = 0.002$). Patients in sinus rhythm presented a $\%VO_{2p}$ of $52.06 \pm 13.98\%$ and those in AF presented a $\%VO_{2p}$ of $50.31 \pm 15.47\%$ ($P = 0.759$). Degree of mitral regurgitation, pericardial effusion, and LV fibrotic tissue involvement were not related to $\%VO_{2p}$, but the degree of RV involvement was related to $\%VO_{2p}$ ($P = 0.024$). Resting heart rate, systolic and diastolic blood pressure at rest and at peak exercise, age, and BSA did not correlate with $\%VO_{2p}$ ($P > 0.05$). Peak heart rate presented a positive correlation with $\%VO_{2p}$ ($r = 0.36$, $P = 0.04$).

Table 1 summarizes the assessed echocardiographic indices, as well as any correlations between these indices and $\%VO_{2p}$. There was a correlation of $\%VO_{2p}$ with an average of A′ peak of the septal, lateral, inferior, and anterior mitral annulus (A′ peak, $r = 0.471$, $P = 0.023$), E′/A′ of the inferior mitral annulus ($r = -0.433$, $P = 0.044$), and MPI ($r = -0.352$, $P = 0.048$).

On multiple regression analysis, only A′ peak was an independent predictor of $\%VO_{2p}$ ($\%VO_{2p} = 26.34 + 332.44 \times$ A′ peak).

Figure 2 shows the linear regression of $\%VO_{2p}$ related to A′ peak. Ten patients (31%) died in 50 months, nine from cardiac causes. Considering nine deaths, we found that $\%VO_{2p} < 53\%$ was associated with a greater mortality rate ($P = 0.017$), with a relative risk of 8.47 (*Figure 3*).

Discussion

Sex preponderance is a variable depending on the region considered. In Brazil, EMF presents a female preponderance, as seen in our study. Male preponderance is found in Kerala, Mozambique, and Nigeria, whereas female is in Uganda.[1,4] In this study, $\%VO_{2p}$ was determined in addition to VO_{2p} to correct for individual factors such as age, weight, height, and mainly gender (due to large number of women).[13]

A previous study has shown that survival curves of patients with EMF are better for those in NYHA functional class I or II.[3] However, the widely used NYHA functional class is a subjective approach to assessing functional status, whereas quantitative exercise testing represents a more objective approach. In this study, there was a relation between the NYHA functional class and the exercise capacity ($P = 0.002$), allowing the use of this classification in assessing functional status.

Although we found no relationship between the resting heart rate and exercise capacity, the peak heart rate was positively correlated with the $\%VO_{2p}$. This may occur in EMF as a result of an increased cardiac output at exercise, which is highly dependent on an increase in heart rate and not an increase in diastolic volumes. An increase in diastolic volume, in turn, is limited by the fibrous thickening of the endocardium that irregularly penetrates the myocardium.[14] Therefore, the normal increase in cardiac output which occurs with exercise may be limited by the Frank–Starling curve in these patients, leading to an increase in pulmonary capillary pressure.[1]

The exercise capacity and ejection fraction are the most important prognostic indicators in patients with heart failure, but their correlation is weak. A limited exercise capacity is common in patients with EMF.[15] In our study, we found the $\%VO_{2p} < 53$ is related to long-term mortality. This parameter may be a useful prognostic marker in the follow-up of the EMF patients. Many experimental and human studies have shown that the magnitude of the reduction in the LV ejection fraction does not correlate with the degree of functional impairment, whereas parameters of the LV diastolic function are important in limiting exercise capacity.[16–18] EMF is characterized by fairly normal myocardium; yet stiffness of the ventricle is markedly increased (due to thickening and scarring of the endocardium), leading to slow relaxation of the underlying myocardium. Consistent with this, patients with EMF present with a spectrum of ventricular filling abnormalities, ranging from abnormal relaxation to a restrictive pattern.[19,20] In the present study, the LV ejection fraction did not correlate with functional capacity but the A′ peak did. A prior invasive study revealed that the A′ is positively correlated with LA contractility ($r = 0.67$) and LA relaxation ($r = 0.73$) but is inversely correlated with LV end-diastolic pressure ($r = -0.53$).[21] In our study, A′ peak was an independent predictor of $\%VO_{2p}$, reflecting the importance of global atrial function, as it represents the average of four annular sites, and demonstrate that the LA dysfunction may limit the exercise capacity in EMF patients. The inverse relationship of E′/A′ inferior and $\%VO_{2p}$ may also reflect the importance of atrial function on the exercise capacity. Donal *et al.*[22] have also shown the importance of late diastolic myocardial peak velocity recorded at the lateral site of mitral annulus, that added predictive value of rest echocardiography to exercise capacity in patients with heart failure. This relatively load-independent index of regional myocardial velocity, which allows the characterization of atrial function, is easy to acquire and is also considered a prognostic index for heart failure patients when < 5 cm/s.[23]

Permanent AF, defined as AF present for at least 1 year with no interruption, is reported to occur in at least 20% of the patients with heart failure, and it is associated with poor prognosis and reduction in exercise capacity.[24] However, previous study showed that cardioversion improves exercise capacity by ~5%, suggesting that the underlying heart disease had a greater influence on exercise capacity than AF.[25] In EMF patients, AF is also a predictor of worse prognosis.[26] Previous study showed that EMF patients with AF presented a higher mortality rate than those who did not have AF ($P = 0.0195$), but not among those who allowed to fibrous tissue resection.[26] In our study, 28% of the patients presented AF, and we did not find any differences in $\%VO_{2p}$ for patients with AF and sinus rhythm. Also, in our study, patients with AF, but not in sinus rhythm, the MPI presents inverse and high correlation with $\%VO_{2p}$ ($r = -0.689$, $P = 0.04$, *Table 1*). The MPI evaluates global LV performance, systolic, and diastolic.[8] However, in our study, the mean global ejection fraction was normal,

Table 1 Echocardiographic variables of patients with endomyocardial fibrosis and their relationship to $\%VO_{2p}$

Echocardiographic variables	All patients ($n = 32$)		SR ($n = 23$)		AF ($n = 9$)	
	Mean ± SD	r	Mean ± SD	r	Mean ± SD	r
LV mass index (g/m^2)	103 ± 46	0.097	101 ± 42	0.136	108 ± 56	0.038
Relative wall thickness	0.33 ± 0.07	−0.197	0.31 ± 0.07	−0.200	0.37 ± 0.08	−0.168
LV diastolic volume/BSA (mL/m^2)	46 ± 14	0.164	43 ± 14	0.340	52 ± 12	−0.251
LV systolic volume/BSA (mL/m^2)	19 ± 10	0.130	18 ± 9	0.296	24 ± 11	−0.145
LV ejection fraction (%)	59 ± 10	−0.109	60 ± 8	−0.192	55 ± 14	−0.028
LV/LA diastolic volume	1.3 ± 0.6	0.283	1.5 ± 0.6	0.319	0.9 ± 0.5	0.217
LV/LA systolic volume	1.0 ± 0.4	0.381**	1.0 ± 0.4	0.381**	–	–
LA diastolic volume/BSA (mL/m^2)	48 ± 38	−0.113	34 ± 16	−0.028	82 ± 54	−0.187
LA systolic volume/BSA (mL/m^2)	21 ± 13	−0.061	21 ± 13	−0.061	–	–
LA ejection fraction (%)	40 ± 13	0.095	40 ± 13	0.095	–	–
Pulmonary artery systolic pressure (mmHg)	47 ± 26	0.051	39 ± 22	0.392	60 ± 30	−0.500
E peak velocity (cm/s)	77 ± 37	−0.059	63 ± 25	−0.038	114 ± 49	−0.021
Acceleration time of E (ms)	69 ± 19	0.116	69 ± 22	0.132	69 ± 6	0.086
Deceleration time of E (ms)	165 ± 53	0.193	181 ± 52	0.220	121 ± 24	0.103
A peak velocity (cm/s)	51 ± 21	0.386**	51 ± 21	0.386**	–	–
A duration (ms)	137 ± 35	0.0	137 ± 35	0.0		
E/A	1.6 ± 11	−0.238	1.6 ± 11	−0.238	–	–
Isovolumetric relaxation time (ms)	98 ± 38	0.104	110 ± 39	0.073	70 ± 10	0.337
S peak velocity (cm/s)	40 ± 15	0.174	44 ± 15	0.203	29 ± 11	0.013
D peak velocity (cm/s)	49 ± 22	−0.131	44 ± 20	−0.313	60 ± 23	0.271
S/D	1.1 ± 0.7	0.228	1.2 ± 0.7	0.287	0.6 ± 0.4	−0.051
Ar peak velocity (cm/s)	24 ± 10	−0.264	24 ± 10	−0.264	–	–
Ar duration (ms)	120 ± 42	−0.311	120 ± 42	−0.311	–	–
Myocardial performance index	64 ± 34	−0.352*	49 ± 20	−0.291	101 ± 33	−0.689*
E′ peak velocity—septum (cm/s)	8 ± 2	−0.127	8 ± 2	−0.074	8 ± 2	−0.249
A′ peak velocity—septum (cm/s)	8 ± 3	0.400**	8 ± 3	0.400**	–	–
E′/A′ septum	1.1 ± 0.7	−0.371**	1.1 ± 0.7	−0.371**	–	–
E/E′ septum	10 ± 5	0.053	9 ± 4	0.056	15 ± 5	0.195
S′ peak velocity—septum (cm/s)	7 ± 2	0.126	7 ± 2	0.277	5 ± 2	−0.408
E′ peak velocity—lateral (cm/s)	11 ± 3	−0.068	10 ± 3	−0.197	12 ± 3	0.267
A′ peak velocity—lateral (cm/s)	8 ± 3	0.408**	8 ± 3	0.408**	–	–
E′/A′ lateral	1.6 ± 1.0	−0.338	1.6 ± 1.0	−0.338	–	–
E/E′ lateral	7 ± 3	−0.074	6 ± 2	0.114	10 ± 5	−0.221
S′ peak velocity—lateral (cm/s)	8 ± 2	0.197	9 ± 2	0.119	7 ± 2	0.445
E′ peak velocity—inferior (cm/s)	9 ± 3	−0.243	8 ± 2	−0.413**	11 ± 3	−0.044
A′ peak velocity—inferior (cm/s)	9 ± 3	0.419**	9 ± 3	0.419**	–	–
E′/A′ inferior	1.2 ± 0.9	−0.433*	1.2 ± 0.9	−0.433*	–	–
E/E′ inferior	9 ± 3	0.108	8 ± 3	0.235	11 ± 4	−0.009
S′ peak velocity—inferior (cm/s)	7 ± 2	0.152	8 ± 2	0.353	6 ± 2	−0.480
E′ peak velocity—anterior (cm/s)	9 ± 3	−0.204	9 ± 3	−0.187	10 ± 3	−0.226
A′ peak velocity—anterior (cm/s)	7 ± 2	0.383**	7 ± 2	0.383**	–	–
E′/A′ anterior	1.3 ± 0.7	−0.363**	1.3 ± 0.7	−0.363**	–	–
E/E′ anterior	9 ± 4	0.104	8 ± 3	0.102	12 ± 6	0.227
S′ peak velocity—anterior (cm/s)	7 ± 2	−0.258	7 ± 2	−0.232	6 ± 1	−0.508
E′ peak (cm/s)	9 ± 2	−0.170	9 ± 2	−0.213	10 ± 3	−0.047
A′ peak (cm/s)	8 ± 2	0.471*	8 ± 2	0.471*	–	–
E′/A′	1.3 ± 0.7	−0.409**	1.3 ± 0.7	−0.409**	–	–
E/E′	8 ± 4	0.029	7 ± 2	0.128	12 ± 5	−0.002
S′ peak (cm/s)	7 ± 2	0.085	8 ± 1	0.183	6 ± 1	−0.316

Data are expressed as mean ± SD. SR, sinus rhythm; AF, atrial fibrillation; LV, left ventricular; BSA, body surface area; LA, left atrium; Ar, pulmonary vein atrial reverse velocity; E′ peak, average peak velocity of the early diastolic mitral annular velocities determined at four sites (septum, lateral, inferior, and anterior); A′ peak, average peak velocity of the late diastolic mitral annular velocities determined at four sites (septum, lateral, inferior, and anterior).

*$P < 0.05$.

**$0.05 \leq P \leq 0.10$.

suggesting that an increase in MPI could reflect diastolic dysfunction.

Several limitations to our study do exist. First, our patients did not show the typical pattern of restrictive diastolic dysfunction, because probably, they were allowed to continue their usual medications. In addition, patients with mild LV fibrotic involvement were included, which limits the evaluation of diastolic function. However, our data do support the notion that resting echocardiographic parameters might be useful for predicting functional capacity in EMF patients.

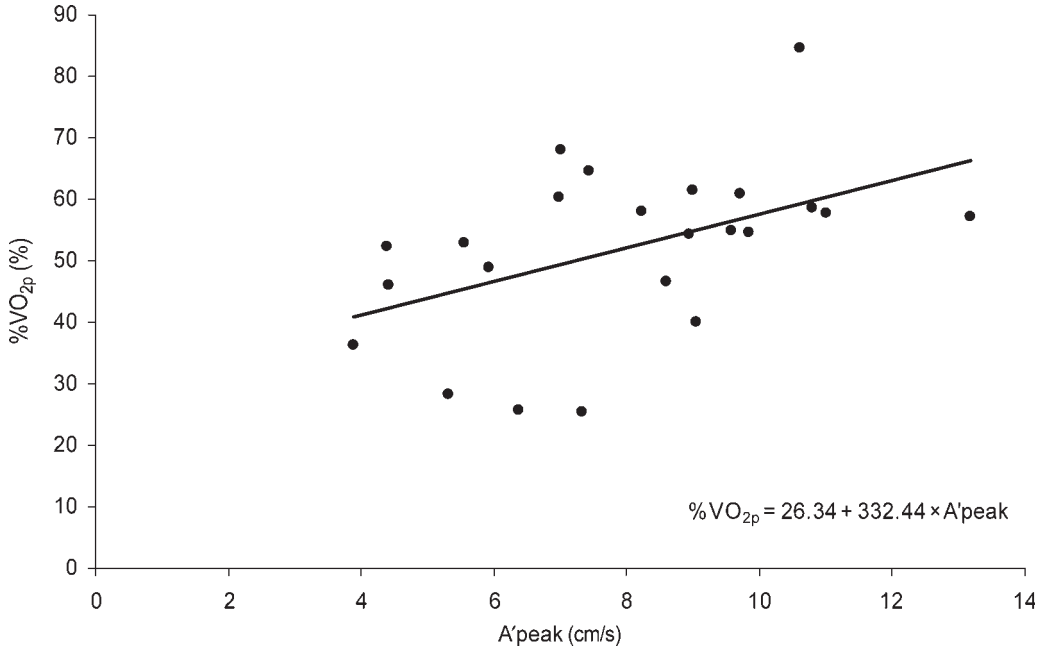

Figure 2 Relation between percentage of predicted VO_{2p} and average A′ peak of the septum, lateral, inferior, and anterior mitral annulus.

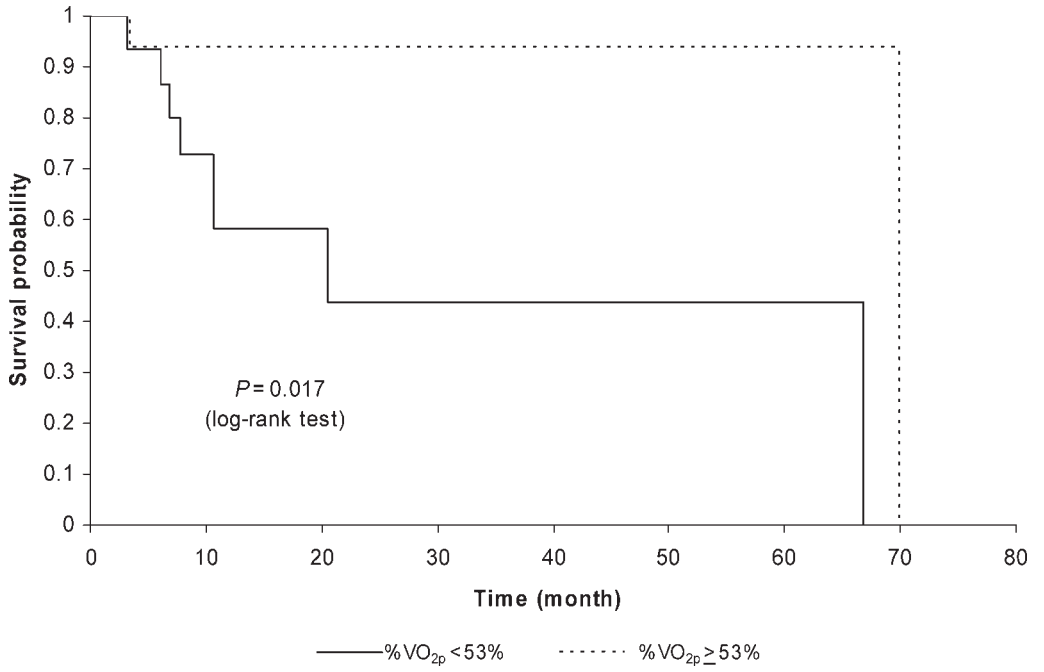

Figure 3 Worse survival rate of patients with the percentage of predicted $VO_{2p} < 53\%$.

Supplementary data

Supplementary data are available at *European Journal of Echocardiography* online.

Acknowledgements

We thank Julia K. Fukushima for the statistical analysis.

Conflict of interest: none declared.

References

1. Mocumbi AO, Yacoub S, Yacoub MH. Neglected tropical cardiomyopathies: II. Endomyocardial fibrosis: myocardial disease. *Heart* 2008;**94**: 384–90.
2. Kitzman DW, Little WC, Brubaker PH, Anderson RT, Hundley WG, Marburger CT *et al*. Pathophysiological characterization of isolated diastolic heart failure in comparison to systolic heart failure. *JAMA* 2002; **288**:2144–50.
3. Barretto AC, da Luz PL, de Oliveira SA, Stolf NA, Mady C, Bellotti G *et al*. Determinants of survival in endomyocardial fibrosis. *Circulation* 1989;**8**: I-177–82.

4. Mocumbi AO, Ferreira MB, Sidi D, Yacoub MH. A population study of endomyocardial fibrosis in a rural area of Mozambique. *N Engl J Med* 2008; **359**:43–9.
5. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA *et al*. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr* 2005;**18**:1440–63.
6. Devereux RB, Alonso DR, Lutas EM, Gottlieb GJ, Campo E, Sachs I *et al*. Echocardiographic assessment of left ventricular hypertrophy: comparison to necropsy findings. *Am J Cardiol* 1986;**57**:450–8.
7. Oh JK, Appleton CP, Hatle LK, Nishimura RA, Seward JB, Tajik AJ. The noninvasive assessment of left ventricular diastolic function with two-dimensional and Doppler echocardiography. *J Am Soc Echocardiogr* 1997;**10**:246–70.
8. Garcia MJ, Thomas JD, Klein AL. New Doppler echocardiographic applications for the study of diastolic function. *J Am Coll Cardiol* 1998;**32**: 865–75.
9. Tei C. New non-invasive index for combined systolic and diastolic ventricular function. *J Cardiol* 1995;**26**:394–404.
10. Helmcke F, Nanda NC, Hsiung MC, Soto B, Adey CK, Goyal RG *et al*. Color Doppler assessment of mitral regurgitation with orthogonal planes. *Circulation* 1987;**75**:175–83.
11. Yock PG, Popp RL. Noninvasive estimation of right ventricular systolic pressure by Doppler ultrasound in patients with tricuspid regurgitation. *Circulation* 1984;**70**:657–62.
12. Nagueh SF, Kopelen HA, Quiñones MA. Assessment of left ventricular filling pressures by Doppler in the presence of atrial fibrillation. *Circulation* 1996;**94**:2138–45.
13. Wasserman K, Hansen JE, Sue DY, Casaburi R, Whipp BJ. Normal values. In:*Principles of Exercise Testing and Interpretation*. 3rd ed. Baltimore, MD: Lippincott Willians & Wilkins; 1999. p143–64.
14. Iglezias SD, Benvenuti LA, Calabrese F, Salemi VM, Silva AM, Carturan E *et al*. Endomyocardial fibrosis: pathological and molecular findings of surgically resected ventricular endomyocardium. *Virchows Arch* 2008; **453**:233–41.
15. Mady C, Barretto AC, Mesquita ET, Silva PR, Cardoso RH, Bellotti G *et al*. Maximal functional capacity in patients with endomyocardial fibrosis. *Eur Heart J* 1993;**14**:240–2.
16. Little WC, Kitzman DW, Cheng CP. Diastolic dysfunction as a cause of exercise intolerance. *Heart Fail Rev* 2000;**5**:301–6.
17. Guazzi M, Brenner DA, Apstein CS, Saupe KW. Exercise intolerance in rats with hypertensive heart disease is associated with impaired diastolic relaxation. *Hypertension* 2001;**37**:204–8.
18. Barmeyer A, Müllerleile K, Mortensen K, Meinertz T. Diastolic dysfunction in exercise and its role for exercise capacity. *Heart Fail Rev* 2008 (in press).
19. Keren A, Popp RL. Assignment of patients into the classification of cardiomyopathies. *Circulation* 1992;**86**:1622–33.
20. Salemi VM, Picard MH, Mady C. Assessment of diastolic function in endomyocardial fibrosis: value of flow propagation velocity. *Artif Organs* 2004;**28**:343–6.
21. Nagueh SF, Sun H, Kopelen HA, Middleton KJ, Khoury DS. Hemodynamic determinants of the mitral annulus diastolic velocities by tissue Doppler. *J Am Coll Cardiol* 2001;**37**:278–85.
22. Donal E, Raud-Raynier P, De Place C, Gervais R, Rosier A, Roulaud M *et al*. Resting echocardiographic assessments of left atrial function and filling pressure interest in the understanding of exercise capacity in patients with chronic congestive heart failure. *J Am Soc Echocardiogr* 2008;**21**: 703–10.
23. Yamamoto T, Oki T, Yamada H, Tanaka H, Ishimoto T, Wakatsuki T *et al*. Prognostic value of the atrial systolic mitral annular motion velocity in patients with left ventricular systolic dysfunction. *J Am Soc Echocardiogr* 2003;**16**:333–9.
24. De Ferrari GM, Klersy C, Ferrero P, Fantoni C, Salerno-Uriarte D, Manca L *et al*. Atrial fibrillation in heart failure patients: prevalence in daily practice and effect on the severity of symptoms. *Eur J Heart Fail* 2007;**9**: 502–9.
25. Ueshima K, Myers J, Morris CK, Atwood JE, Kawaguchi T, Froelicher VF. The effect of cardioversion on exercise capacity in patients with atrial fibrillation. *Am Heart J* 1993;**126**:1021–4.
26. Barretto AC, Mady C, Nussbacher A, Ianni BM, Oliveira SA, Jatene A *et al*. Atrial fibrillation in endomyocardial fibrosis is a marker of worse prognosis. *Int J Cardiol* 1998;**67**:19–25.