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ORIGINAL ARTICLE

Cardiac performance during exercise in patients with Fabry's disease

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ABSTRACT

Background Fatigability and dyspnoea on effort are present in many patients with Fabry's disease. We assessed the determinants of cardiac performance during exercise in patients with Fabry's disease and preserved left ventricular ejection fraction at rest.

Materials and methods Sixteen patients with Fabry's disease and 16 control subjects underwent radionuclide angiography at rest and during exercise, tissue Doppler echocardiography and magnetic resonance imaging at rest.

Results The exercise-induced change in stroke volume was +25 ± 14% in controls and +5·8 ± 19% in patients with Fabry's disease ($P < 0{\cdot}001$). In 10 patients (group 1), the stroke volume increased (+19 ± 10%), and in 6 patients (group 2) it decreased (–16 ± 9%) with exercise. Patients of group 2 were older, had worse renal function, higher left ventricular mass and impaired diastolic function compared to group 1. The abnormal stroke volume response to exercise in group 2 was associated with a decrease in end-diastolic volume ($P < 0{\cdot}001$) and a lack of reduction of end-systolic volume ($P < 0{\cdot}01$) compared with both controls and group 1. The ratio of peak early-diastolic velocity from mitral filling to peak early-diastolic mitral annulus velocity was the only independent predictor of exercise-induced change in stroke volume (B –0·44; SE 0·119; β –0·70; $P < 0{\cdot}005$).

Conclusions The majority of patients with Fabry's disease were able to augment stroke volume during exercise by increasing end-diastolic volume, whereas patients with more advanced cardiac involvement may experience the inability to increase cardiac output by the Frank Starling mechanism.

Keywords Exercise stress test, Fabry cardiomyopathy, left ventricular function.

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Introduction

Fabry's disease is an X-linked storage disorder caused by a deficient activity of lysosomal hydrolase α-galactosidase A and characterized by a progressive accumulation of glycosphingolipids in the vascular endothelium and in different tissues [1,2]. Cardiac involvement is frequent, due to cytoplasmatic deposits of glycosphingolipids within myocytes, fibroblasts and endothelial cells. Focal myocardial fibrosis has also been documented in Fabry's disease patients, and cardiac hypertrophy with preserved left ventricular (LV) ejection fraction represents the most common clinical feature of the disease [3–7]. Many patients with Fabry-related cardiomyopathy complain for chronic symptoms of easy fatigability and dyspnoea on effort [2,5]. In patients with heart failure or essential hypertension and preserved LV systolic function at rest, exercise tolerance may depend on diastolic function [8,9]. However, the relationship between cardiac performance during exercise and diastolic function has not been investigated in patients with Fabry's disease. Therefore, we assessed the determinants of the cardiac response to physical exercise in a cohort of patients with Fabry's disease and preserved LV ejection fraction at rest.

Methods

Study population

We prospectively studied 16 consecutive patients (9 men, mean age 37 ± 11 years) with genetically confirmed Fabry's disease. None of the patients received enzyme replacement therapy prior to study entry. Inclusion criteria were sinus rhythm and the ability to undergo exercise test. Patients were not included in the study if they had valvular stenosis or severe valvular regurgitation. Silent coronary artery disease was ruled out using stress myocardial perfusion imaging. Each patient underwent a detailed clinical

assessment of Fabry's disease manifestations. Sixteen age- and gender-matched (9 men, mean age 42 ± 10 years) healthy volunteers were recruited to serve as control subjects. All controls had a normal history, normal physical examination, and normal maximal exercise electrocardiogram. In all patients and controls, glomerular filtration rate was estimated using the modified diet in renal disease equation [10]. None of the Fabry's disease patients had concomitant diseases relevant for diastolic dysfunction such as hypertension or diabetes, except one patient with mild hypertension. At the time of the study, nine patients were under treatment with low-dose angiotensin-converting enzyme inhibitors. All patients and controls underwent on the same day venous blood sampling, echocardiography, magnetic resonance imaging (MRI), and equilibrium radionuclide angiography. Our institutional review board approved the investigation and informed consent was obtained from each participant.

Laboratory procedures

After the patients had been at rest for at least 20 min in the supine position, blood samples for determination of N-terminal fragment of the B-type natriuretic peptide (NT-proBNP) were collected, centrifuged and plasma stored at –80 °C until analysis. Plasma concentrations of NT-proBNP were measured by a sandwich immunoassay on an Elecsys 2010 (Roche Diagnostics, Basel, Switzerland). The intra-assay variation is below 3·0% and the total coefficient of variation ranges from 2·2% to 5·8% in low and high ranges of NT-proBNP.

MRI

Standard cine-MRI was performed using a 1·5 Tesla MRI system (Gyroscan Intera, Philips Medical System, Best, the Netherlands) equipped with master gradients, as previously described in detail [11]. Additionally, a segmented inversion recovery sequence was obtained 15–20 min after the intravenous administration of gadolinium–diethylene triamine pentaacetic acid at a standard dose of 0·1 mmol kg^{-1} (maximum dose, 15 mL). Four-chamber horizontal long-axis, vertical long axis and biventricular short axis views were acquired with attention to the inversion time that was iteratively modified to obtain maximal nulling of the LV myocardium, with an average value of 225 ms. Post-processing was performed on a dedicated workstation (Viewforum, Philips Medical System) and analysis of LV mass (LVM) was performed as previously described [11]. LVM was normalized for body surface area and expressed as LVM index (LVMi). Late-enhancement MRI was used to assess the myocardium for an abnormal increase in signal intensity.

Echocardiography

A comprehensive *trans*-thoracic echocardiography study was performed with a Sonos 5500 ultrasound system (Philips Medical Systems, Andover, MA, USA). Tissue Doppler imaging program was set to the pulsed wave Doppler mode and was used to record lateral mitral annular velocities. Doppler recordings were obtained at a sweep speed of 100 mm s^{-1}. Interpretable Doppler recordings of *trans*-mitral flow and pulmonary flow velocity curves were obtained in all patients and controls. The acquisitions were digitally stored and a single observer who had no knowledge of exercise results analysed the study. Peak early (E) and late (A) *trans*-mitral filling velocities, E/A ratio, deceleration time of E velocity, and isovolumic relaxation time were measured from mitral inflow velocities. The mitral A velocity duration minus pulmonary venous reversal velocity duration (Ar) difference (Adur – Ardur) was calculated. Systolic (Sa), early diastolic (Ea), and late diastolic (Aa) velocities were measured, and the Ea/Aa and E/Ea were computed. For each measurement, three beats were averaged. Reproducibility of Doppler measurements from our laboratory has been previously reported [7].

Radionuclide angiography

In vivo labelling of red blood cells was performed with 555 MBq Tc-99 m. Equilibrium radionuclide angiography was performed at rest and during physical exercise as previously described [9]. A small field of view gamma camera (Elscint Apex SP-4 H, Haifa, Israel) equipped with a low–energy, all-purpose collimator was used. Exercise studies were performed using a bicycle ergometer and workload was increased by 25 watts every 2 min until angina, limiting dyspnoea or fatigue developed. Heart rate and blood pressure were monitored during exercise at each stage. Radionuclide angiography was performed using a standard commercially available software system. Indices of LV function were derived by computer analysis of the background-corrected time-activity curve. Ejection fraction was computed on the basis of relative end-diastolic and end-systolic counts, both peak ejection rate and peak filling rate were computed in LV counts per second normalized for the number of counts at the end-diastole and expressed as end-diastolic volume per second (EDV/s). When normalized for end-diastolic volume, peak ejection rate and peak filling rate are influenced directly by the magnitude of ejection fraction [9]. To minimize the influence of the magnitude of ejection fraction, we also calculated the ratio peak filling rate/peak ejection rate. End-diastolic volume, end-systolic volume and stroke volume were measured according to the attenuation-corrected count-based distance method [12]. The exercise-induced change in end-diastolic volume, end-systolic volume and stroke volume were also expressed as percentage of rest value.

Statistical analysis

Statistical analysis was performed by SPSS 12·0 statistical software (SPSS Inc., Chicago, IL, USA). Continuous data are presented as mean ± standard deviation. Categorical variables are presented as

percentage. Differences between groups were analysed by the two-sample Kolmogorov–Smirnov test, Kruskal–Wallis test or chi-squared test as appropriate. A P-value of $< 0{\cdot}05$ was considered significant. Regression analysis was used to assess the predictors of exercise-induced change in stroke volume. The variables showing significant univariate association were considered for the multivariate analysis.

Results

The demographic data and clinical characteristics of Fabry's disease patients are reported in Table 1. All women included in the study presented clinical manifestations of the disease. Glomerular filtration rate was lower in patients compared to controls (83 ± 36 mL · min^{-1} 1·73 m^{-2} and 140 ± 17 mL · min^{-1} 1·73 m^{-2}, respectively; $P < 0{\cdot}001$). However, a high number of patients exhibited a glomerular filtration rate greater than 90 mL · min^{-1} 1·73 m^{-2}.

Laboratory, MRI and echocardiographic data

Plasma levels of NT-proBNP were higher in patients than in controls (558 ± 1008 and 47 ± 18 pg mL^{-1}, respectively; $P < 0{\cdot}01$). LVMi was greater in patients compared to controls (110 ± 32 and 65 ± 7 g m^{-2}, respectively; $P < 0{\cdot}001$). Late enhancement was present in four (25%) of the patients and in none of the controls ($P < 0{\cdot}001$). The results of tissue Doppler echocardiography in controls and patients are reported in Table 2. As compared to controls, patients showed lower Adur – Ardur, Sa, Ea and Ea/Aa (all $P < 0{\cdot}001$) and greater E/Ea ($P < 0{\cdot}005$).

Table 1 Demographic data and clinical characteristics for patients with Fabry's disease

Age (years)	37 ± 11
Male gender	9
Angiokeratoma	12
Cornea verticillata	14
Arthralgia/myalgia	12
Proteinuria	12
Stages of chronic kidney disease	
Stage 1	11
Stage 2	2
Stage 3	1
Stage 4	1
Stage 5	1
New York Heart Association functional class	1·5 ± 0·6

Data are presented as mean value ± standard deviation or number of patients.

Exercise stress test and radionuclide angiographic data

All patients and controls completed the exercise test. None experienced high-grade ventricular arrhythmia necessitating interruption of test. The haemodynamic parameters recorded at rest and at peak exercise are reported in Table 3. The test was interrupted because of fatigue in four controls (25%) and five

Table 2 Tissue Doppler echocardiography data for control subjects and patients

	Controls ($n = 16$)	Patients ($n = 16$)	P value
E (cm s^{-1})	68 ± 7	54 ± 14	NS
A (cm s^{-1})	52 ± 6	66 ± 15	NS
E/A	1·35 ± 0·2	1·01 ± 0·31	NS
E deceleration time (ms)	214 ± 32	226 ± 46	NS
Isovolumic relaxation time (ms)	75 ± 10	80 ± 15	NS
Adur – Ardur (ms)	27 ± 7	–1·5 ± 27	< 0·001
Sa (cm s^{-1})	10 ± 2·7	6·8 ± 2	< 0·001
Ea (cm s^{-1})	13 ± 3·8	8 ± 3·2	< 0·001
Aa (cm s^{-1})	9·4 ± 2·2	10·8 ± 2·2	NS
Ea/Aa	1·4 ± 0·3	0·75 ± 0·3	< 0·001
E/Ea	5·4 ± 1·5	8·7 ± 3·3	< 0·005

Data are presented as mean value ± standard deviation. E, early diastolic peak velocity on mitral inflow; A, late diastolic peak velocity on mitral inflow; Adur – Ardur, late diastolic peak velocity on mitral inflow duration minus pulmonary venous reversal velocity duration; Sa, systolic peak velocity on mitral annular Doppler imaging; Ea, early diastolic on mitral annular Doppler imaging; Aa, late diastolic peak velocity on mitral annular Doppler imaging.

Table 3 Haemodynamic parameters recorded at rest and at peak exercise in control subjects and patients

	Controls ($n = 16$)		Patients ($n = 16$)	
	Rest	Exercise	Rest	Exercise
Heart rate (beats per minute)	73 ± 10	145 ± 25*	69 ± 16	130 ± 28*
Systolic blood pressure (mmHg)	128 ± 11	165 ± 24*	137 ± 17	155 ± 32*
Diastolic blood pressure (mmHg)	76 ± 13	82 ± 15*	72 ± 19	86 ± 23*
Exercise duration (min)	12 ± 4		9 ± 4†	
Maximal exercise level (%)	75		45†	

Data are presented as mean value ± standard deviation or percentage. *$P < 0{\cdot}01$ vs. rest; †$P < 0{\cdot}05$ vs. controls.

Table 4 Radionuclide angiography data at rest and at peak exercise in control subjects and patients

	Controls ($n = 16$)		Patients ($n = 16$)	
	Rest	Exercise	Rest	Exercise
End-diastolic volume (mL)	100 ± 8	108 ± 18*	85 ± 30	86 ± 30†
End-systolic volume (mL)	38 ± 11	31 ± 9*	25 ± 11†	24 ± 11
Stroke volume (mL)	61 ± 18	78 ± 15*	58 ± 28	61 ± 23†
Ejection fraction (%)	66 ± 4	73 ± 6*	70 ± 9	75 ± 9
Peak ejection rate (EDV/s)	3·95 ± 0·7	4 ± 1·2	4·1 ± 1	4·3 ± 2
Peak filling rate (EDV/s)	3 ± 0·4	3·5 ± 0·7	3·2 ± 0·7	3·4 ± 1·4
Peak filling rate/peak ejection rate	0·77 ± 0·16	0·74 ± 0·12	0·8 ± 0·18	0·7 ± 0·2

Data are presented as mean value ± standard deviation. *$P < 0{\cdot}01$ vs. rest; †$P < 0{\cdot}05$ vs. controls.

patients (30%) and because of shortness of breath and angina in four patients (25%). At rest, end-diastolic volume, stroke volume, ejection fraction, peak ejection rate, and indices of left ventricular filling were similar in controls and patients. However, end-systolic volume at rest was lower ($P < 0{\cdot}05$) in patients compared to controls (Table 4). At peak exercise, end-diastolic volume and stroke volume were lower (both $P < 0{\cdot}05$) in patients compared to controls, while ejection fraction and end-systolic volume were not different.

Exercise-induced change in stroke volume

The exercise-induced change in stroke volume in controls and in patients is reported in Fig. 1. The Fabry's disease patients were classified into two groups according to their stroke volume response to exercise. In 10 patients (group 1), the stroke volume increased with exercise. In the other 6 patients (group 2), the stroke volume decreased with exercise. The characteristics of patients of groups 1 and 2 are presented in Table 5. Interestingly, all patients with late enhancement at MRI belonged to group 2. There were no differences in pharmacological treatment between patients of groups 1 and 2. The abnormal stroke volume response to exercise in group 2 was associated with a decrease in end-diastolic volume (Fig. 2) and a lack of reduction of end-systolic volume (Fig. 3) during exercise compared with both controls and group 1.

Predictors of exercise-induced change in stroke volume

At univariate analysis, a significant relationship between exercise-induced change in stroke volume and the following variables was found: age ($P < 0{\cdot}001$), LVMi ($P < 0{\cdot}05$), Sa ($P < 0{\cdot}05$), Adur – Ardur ($P < 0{\cdot}001$) and E/Ea ($P < 0{\cdot}001$). At multivariate regression analysis, only E/Ea was independently associated with exercise-induced change in stroke volume (B –0·44; SE 0·119; β –0·70; $P < 0{\cdot}005$).

Discussion

Patients with Fabry's disease often complain for exercise intolerance [2,5]. Musculoskeletal pain, poor heat tolerance, respiratory function impairment, chronic renal failure and cardiac involvement may account for such a compromised adaptation to physical exercise. This is the first study demonstrating that patients with Fabry's disease may exhibit a limited ability to increase stroke volume during exercise.

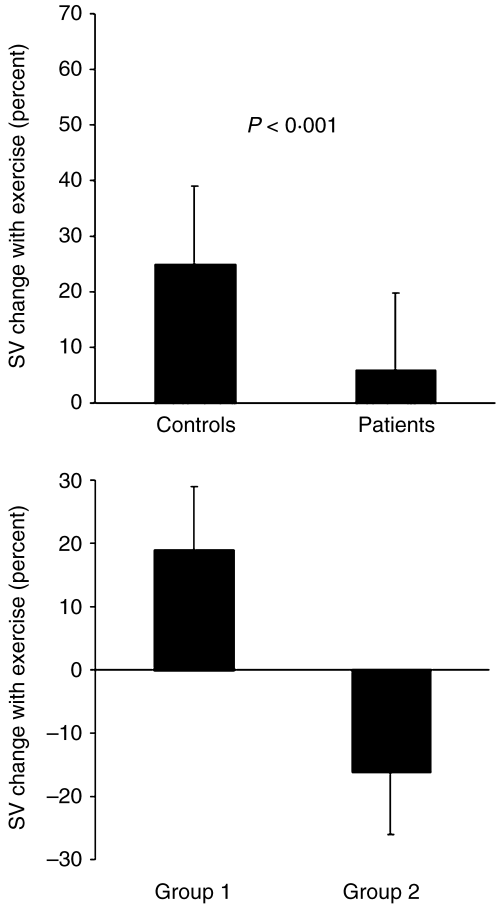

Figure 1 Stroke volume (SV) response to exercise in control subjects and patients with Fabry's disease (upper panel) and in the two groups of patients divided according to their SV response to exercise (lower panel). Group 1: 10 patients with an increase in SV with exercise; group 2: 6 patients in whom SV decreased with exercise.

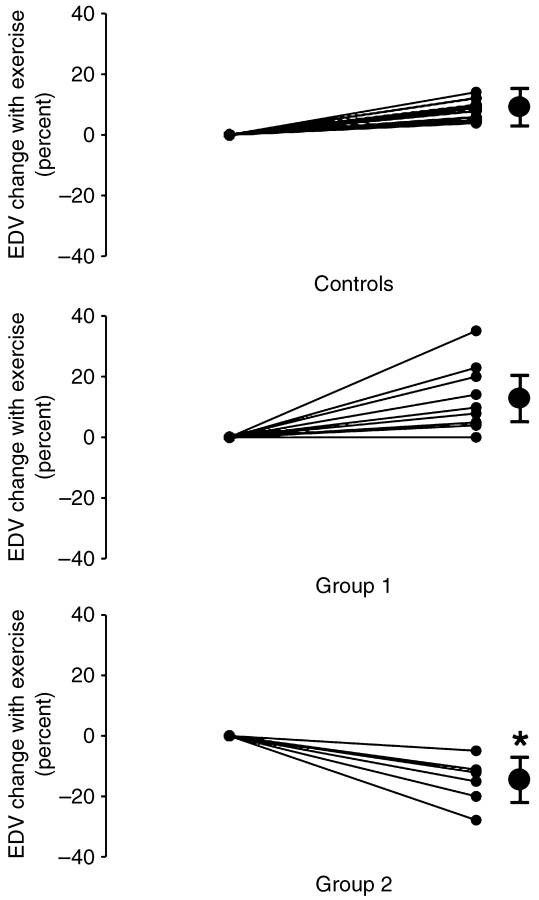

Figure 2 Plots of individual changes in end-diastolic volume (EDV) during exercise in control subjects and in the two groups of patients. *$P < 0{\cdot}01$ vs. controls and group 1. Large closed circles = mean values.

In patients with Fabry's disease, lysosomal storage of globotriasylceramide leads to cardiac hypertrophy and release of growth factors, mainly affecting extracellular matrix collagen biosynthesis and degradation [13]. In a normal heart, during exercise, the stimulatory effects of the sympathetic nervous system and circulating catecholamine enhance ventricular relaxation on the basis of both inactivation and load-dependent mechanisms [14]. The increased rate and extent of relaxation, in turn, augments the pressure gradient between left atrium and left ventricle in early diastole, thereby facilitating ventricular filling during exercise and allowing for augmented stroke volume despite the marked reduction in diastolic filling time that occurs at high heart rates. However, in the setting of LV hypertrophy, this mechanism to increase cardiac output may be inoperative, because the rate of isovolumic pressure decay or chamber compliance may be reduced, resulting in impairment of both active and passive mechanisms of LV filling. As compared with normal subjects, patients with Fabry's disease experienced a lower decrease of end-systolic volume at peak exercise. However, the majority of them were able to augment stroke volume and ejection fraction by increasing end-diastolic volume. Otherwise, some patients showed a dramatic fall of end-diastolic volume at peak exercise, yet they could not utilize the Frank-Starling mechanism to increase stroke volume. They were older than the patients with preserved exercise stroke volume and exhibited greater LVM. Additionally, four out of six patients (66%) displayed a late enhancement at gadolinium MRI. This enhancement likely reflects the presence of connective (fibrotic) tissue. Therefore, LV hypertrophy and interstitial fibrosis seem to have important implications in the mechanisms underlying stroke volume impairment during

Table 5 Characteristics of patients with stroke volume increase (group 1) and stroke volume decrease (group 2) with exercise

	Group 1 ($n = 10$)	Group 2 ($n = 6$)	*P* value
Age (years)	34 ± 3	48 ± 10	< 0·05
Male gender	5	4	NS
New York Heart Association functional class	1·2 ± 0·4	2·1 ± 0·4	< 0·001
Exercise duration (min)	11 ± 2	7 ± 1	< 0·01
GFR (mL · min^{-1} 1·73 m^{-2})	109 ± 8	47 ± 28	< 0·001
LVMi (g m^{-2})	100 ± 13	138 ± 9	< 0·05
Late enhancement	0	4	< 0·005
NT-proBNP (pg mL^{-1})	346 ± 522	3413 ± 5880	NS
Sa (cm s^{-1})	7·4 ± 1·5	5·4 ± 1·7	NS
Ea (cm s^{-1})	8·5 ± 4·3	6·6 ± 1·3	NS
E/Ea	7·0 ± 0·2	12·0 ± 0·2	< 0·001
Adur – Ardur (ms)	16 ± 13	–26 ± 15	< 0·001

Data are presented as mean value ± SD or number of patients. GFR, glomerular filtration rate; LVMi, left ventricular mass index; NT-proBNP, N-terminal fragment of the B-type natriuretic peptide; Sa, systolic peak velocity on mitral annular Doppler imaging; E, early diastolic peak velocity on mitral inflow; Ea, early diastolic on mitral annular Doppler imaging; Adur – Ardur, late diastolic peak velocity on mitral inflow duration minus pulmonary venous reversal velocity duration.

exercise, likely, by increasing LV stiffness with detrimental effects on cardiac reserve. Subclinical systolic dysfunction, as detected by tissue Doppler imaging, also appeared to play a role presumably by affecting end-systolic volume decrease. We did not perform direct measure of LV pressure; however, it was possible to assume that the decreased chamber volume at peak exercise would lead to an upward/leftward shift of end-diastolic pressure/volume relationship. This hypothesis was supported by the results of Doppler echocardiography. In details, Adur – Ardur and E/Ea were inversely correlated with exercise-induced change stroke volume. Adur – Ardur represents a sensitive method for the detection of reduced LV compliance and increased end-diastolic pressure either in patients with systolic dysfunction or in those with preserved ejection fraction [15–17]. Similarly, the ratio E/Ea strongly correlates with LV filling pressure, as it has been demonstrated within a wide range of clinical conditions [18–20]. In the present study, E/Ea was the only independent predictor of exercise-induced change in stroke volume.

The limited ability of NT-proBNP in predicting the response to exercise of Fabry's disease patients may be explained by the fact that natriuretic peptides may be elevated by increased LVM, independent on LV diastolic function [21]. Cardiomyopathy related to Fabry's disease may mimic to some extent hypertrophic cardiomyopathy. However, the changes we observed in the present study were different from those reported in patients with hypertrophic cardiomyopathy. In these latter patients, myocardial ischaemia during exercise may induce LV dysfunction and represents the primary reason of stroke volume decrease [22,23]. We could exclude that the abnormal response to exercise of Fabry's disease patients would arise from myocardial ischaemia, because exercise-induced ischaemia is characterized by an increase in end-diastolic volume with a proportionately greater increase in end-systolic volume [24]. We rather assumed that marked cardiac stiffness and increased external constraint to LV filling (as a result of diastolic ventricular interaction and pericardial constraint) might contribute to impaired use of Frank-Starling mechanism in this group of patients [25].

The number of patients included in this study was relatively small. However, it should be considered that Fabry's disease is a rare condition and this was a single-centre study. Although LV filling pressures have not been directly measured by invasive method and either duration difference or E/Ea are just surrogates for LV end-diastolic pressure, the results of previous studies support the use of non-invasive approaches to assess LV diastolic function [19,20].

Conclusions

The results of the present study highlight a cardiac mechanism causing exercise intolerance in some patients with Fabry's disease. Patients with less severe cardiac involvement are able to augment stroke volume during exercise, by increasing end-diastolic volume. On the other hand, patients with more advanced disease may exhibit inability to utilize the Frank-Starling mechanism. The abnormal stroke volume response to exercise is associated with high LV filling pressures at rest. It is yet to be demonstrated whether enzyme replacement therapy is effective in improving LV filling in patients with end-diastolic volume fall during exercise,

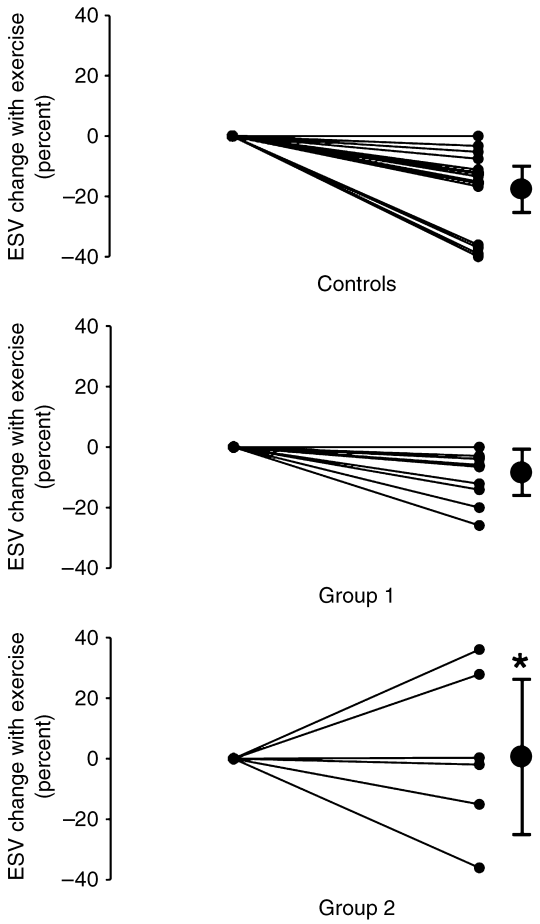

Figure 3 Plots of individual changes in end-systolic volume (ESV) during exercise in control subjects and in the two groups of patients. *$P < 0{\cdot}01$ vs. controls and group 1. Large closed circles = mean values.

or at least in preventing cardiac function worsening in those with preserved stroke volume response.

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References

1 Desnick RJ, Ioannou YA, Eng CM. α-Galactosidase A deficiency: Fabry disease. In: Scriver CR, Beaudet AL, Sly WS *et al*. editors. *The Metabolic and Molecular Bases of Inherited Disease*. New York: McGraw-Hill; 2001. 3733–74.
2 MacDermot KD, Holmes A, Miners AH. Anderson-Fabry disease: clinical manifestations and impact of disease in a cohort of 98 hemizygous males. *J Med Genet* 2001;**38**:750–60.
3 Pieroni M, Chimenti C, Ricci R, Sale P, Russo MA, Frustaci A. Early detection of Fabry cardiomyopathy by tissue Doppler imaging. *Circulation* 2003;**107**:1978–84.
4 Moon JC, Sachdev B, Elkington AG, McKenna WJ, Mehta A, Pennell DJ *et al*. Gadolinium enhanced cardiovascular magnetic resonance in Anderson-Fabry disease. Evidence for a disease specific abnormality of the myocardial interstitium. *Eur Heart J* 2003;**24**:2151–5.
5 Linhart A, Palecek T, Bultas J, Ferguson JJ, Hrudová J, Karetová D *et al*. New insights in cardiac structural changes in patients with Fabry's disease. *Am Heart J* 2000;**139**:1101–8.
6 Weidemann F, Breunig F, Beer M, Sandstede J, Turschner O, Voelker W *et al*. Improvement of cardiac function during enzyme replacement therapy in patients with Fabry disease. *Circulation* 2003;**108**:1299–301.
7 Spinelli L, Pisani A, Sabbatini M, Petretta M, Andreucci MV, Procaccini D *et al*. Enzyme replacement therapy with agalsidase β improves cardiac involvement in Fabry's disease. *Clin Genet* 2004;**66**:158–65.
8 Kitzman DW, Higginbotham MB, Cobb FR, Sheikh KH, Sullivan MJ. Exercise intolerance in patients with heart failure and preserved left ventricular systolic function: failure of the Frank-Starling mechanism. *J Am Coll Cardiol* 1991;**17**:1065–72.
9 Cuocolo A, Sax FL, Brush JE, Maron BJ, Bacharach SL, Bonow RO. Left ventricular hypertrophy and impaired diastolic filling in essential hypertension. Diastolic mechanisms for systolic dysfunction during exercise. *Circulation* 1990;**81**:978–86.
10 Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med* 1999;**130**:461–70.
11 Sandstede J, Lipke C, Beer M, Hofmann S, Pabst T, Kenn W *et al*. Age- and gender-specific differences in left and right ventricular cardiac function and mass determined by cine magnetic resonance imaging. *Eur Radiol* 2000;**10**:438–42.
12 Starling MR, Dell'Italia LJ, Walsh RA, Little WC, Benedetto AR, Nusynowitz ML. Accurate estimates of absolute left ventricular volumes from equilibrium radionuclide angiographic count data using a simple geometric attenuation correction. *J Am Coll Cardiol* 1984;**3**:789–98.
13 Barbey F, Brakch N, Linhart A, Rosenblatt-Velin N, Jeanrenaud X, Qanadli S *et al*. Cardiac and vascular hypertrophy in Fabry disease: evidence for a new mechanism independent of blood pressure and glycosphingolipid deposition. *Arterioscler Thromb Vasc Biol* 2006;**26**:839–44.
14 Karliner JS, Lewinter M, Mahler F, Engler R, O'Rourke RA. Pharmacologic and hemodynamic influences on the rate of

isovolumic left ventricular relaxation in the normal conscious dog. *J Clin Invest* 1977;**60**:511–21.
15 Rossvoll O, Hatle LK. Pulmonary venous flow velocities recorded by transthoracic Doppler ultrasound: relation to left ventricular diastolic pressures. *J Am Coll Cardiol* 1993;**21**:1687–96.
16 Appleton CP, Galloway JM, Gonzalez MS, Gaballa M, Basnight MA. Estimation of left ventricular filling pressures using two-dimensional and Doppler echocardiography in adult patients with cardiac disease. Additional value of analyzing left atrial size, left atrial ejection fraction and the difference in duration of pulmonary venous and mitral flow velocity at atrial contraction. *J Am Coll Cardiol* 1993;**22**:1972–82.
17 Yamamoto K, Nishimura RA, Chaliki HP, Appleton CP, Holmes DR, Redfield MM. Determination of left ventricular filling pressure by Doppler echocardiography in patients with coronary artery disease: critical role of left ventricular systolic function. *J Am Coll Cardiol* 1997;**30**:1819–26.
18 Garcia MJ, Ares MA, Asher C, Rodriguez L, Vandervoort P, Thomas JD. An index of early left ventricular filling that combined with pulsed Doppler peak E velocity may estimate capillary wedge pressure. *J Am Coll Cardiol* 1997;**29**:448–54.
19 Nagueh SF, Middleton KJ, Kopelen HA, Zoghbi WA, Quinones MA. Doppler tissue imaging: a noninvasive technique for evaluation of left ventricular relaxation and estimation of filling pressures. *J Am Coll Cardiol* 1997;**30**:1527–33.
20 Ommen SR, Nishimura RA, Appleton CP, Miller FA, Oh JK, Redfield MM *et al*. Clinical utility of Doppler echocardiography and tissue Doppler imaging in the estimation of left ventricular filling pressures: a comparative simultaneous Doppler-catheterization study. *Circulation* 2000;**102**:1788–94.
21 Luchner A, Burnett JC, Jougasaki M, Hense HW, Heid IM, Muders F *et al*. Evaluation of brain natriuretic peptide as marker of left ventricular dysfunction and hypertrophy in the population. *J Hypertens* 2000;**18**:1121–8.
22 Yoshida N, Ikeda H, Wada T, Matsumoto A, Maki S, Muro A *et al*. Exercise-induced abnormal blood pressure responses are related to subendocardial ischemia in hypertrophic cardiomyopathy. *J Am Coll Cardiol* 1998;**32**:1938–42.
23 Ciampi Q, Betocchi S, Lombardi R, Manganelli F, Storto G, Losi MA *et al*. Hemodynamic determinants of exercise-induced abnormal blood pressure response in hypertrophic cardiomyopathy. *J Am Coll Cardiol* 2002;**40**:278–84.
24 Jones RH, McEwan P, Newman GE, Port S, Rerych SK, Scholz PM *et al*. Accuracy of diagnosis of coronary artery disease by radionuclide management of left ventricular function during rest and exercise. *Circulation* 1981;**64**:586–601.
25 Moore TD, Frenneaux MP, Sas R, Atherton JJ, Morris-Thurgood JA, Smith ER *et al*. Ventricular interaction and external constraint account for decreased stroke work during volume loading in CHF. *Am J Physiol* 2001;**281**:H2385–91.