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Short Report

Enzyme replacement therapy with agalsidase β improves cardiac involvement in Fabry's disease

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Fabry's disease is an X-linked lysosomal storage disease caused by a deficiency of α-galactosidase that results in an accumulation of neutral glycosphingolipids throughout the body, including the cardiovascular system. Fabry cardiomyopathy, characterized by progressive severe concentric left ventricular (LV) hypertrophy, is very frequent and is the most important cause of death in affected patients. Enzyme replacement therapy (ERT) allows a specific treatment for this disease, however, there are very few data on the effectiveness of therapy on cardiac involvement. Nine patients with Fabry cardiac disease were studied on basal condition and after 6 and 12 months of treatment with algasidase β (Fabrazyme®). A complete clinical, electrocardiographic and echocardiographic evaluation was performed in all patients. Interpretable Doppler recordings of transmitral flow and pulmonary flow velocity curves were also acquired. At baseline, the patients with Fabry's disease had increased LV septum and posterior wall thickness, normal LV fractional shortening, LV ejection fraction, normal Doppler parameters of mitral inflow but a duration of pulmonary vein flow velocity wave exceeding that of the mitral wave at atrial systole. ERT did not affect heart rate and arterial pressure. LV internal diameters did not change, there was a slight but not significant decrease in the LV posterior wall thickening and a progressive decrease in the interventricular septum thickening ($p < 0.025$) and in LV mass ($p < 0.001$) The difference in duration between pulmonary vein flow velocity wave and mitral wave at atrial systole significantly decreased ($p < 0.001$). These results suggest that ERT in patients with Fabry cardiomyopathy is able to reduce the LV mass and ameliorate the LV stiffness.

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Fabry's disease is an X-linked recessive disorder of glycosphingolipid metabolism caused by deficiency of the lysosomal enzyme α-galactosidase. It is a rare panethnic disorder with an estimated frequency of 1 in 1,17,000 male births (1). In fact, a recent evaluation in Italy indicates about 150 subjects with a confirmed diagnosis of the disease. The disease is characterized by the progressive intracellular accumulation of neutral glycosphingolipids throughout the body, with prominent involvement of the skin, vascular endothelium, kidney, nervous system, and heart (2). The median survival for hemizygous males is 50 years and 70 for obligate females with death secondary to cerebrovascular disease and myocardial infarction (3, 4). Fabry cardiomyopathy is very frequent and is the most important cause of death in affected patients (2, 5). Moreover, the cardiac involvement can be the sole manifestation of disease in male patients with specific gene mutations and in female carriers with low enzymatic activity ('cardiac Fabry variant') (6, 7). The isolated cardiac variant seems to be more common than previously thought, and around 3% of

male patients with an unexplained left ventricular hypertrophy (LVH) may suffer from this disease variant (8). However, most patients with Fabry's disease do not experience cardiac symptoms until late in the disease course. A common feature of the Fabry cardiomyopathy is an LVH in the presence of a diastolic dysfunction with preserved systolic function (9). Echocardiography allows to obtain a reliable assessment of left ventricular mass and of systolic and diastolic function. Namely, the simultaneous analysis of mitral and pulmonary vein flow velocity curves provides information on left ventricular filling dynamics (10, 11). Doppler-derived parameters of the first diastolic phase are influenced by left ventricular systolic function and are predictive of filling pressures only in patients with depressed left ventricular ejection fraction. On the contrary, Doppler measurements of late diastole reflect left ventricular end-diastolic pressure regardless of systolic function (12).

Recent advances in molecular biology and genetic engineering have enabled the development of enzyme replacement therapy (ERT) in Fabry's disease. Results from independent therapy studies are indeed promising: the infusion of enzyme preparation seems to be well tolerated and effective in catabolizing the lipid deposits (13, 14). This ERT could be one of the first examples for causal treatment of LVH. The availability of genetically engineered enzyme offers an effective targeted treatment approach, but also emphasizes the need for surrogate markers to monitor the efficacy of ERT. Few data are until now available on the impact of therapy on cardiac involvement (15, 16). In this study, we aimed to characterize left ventricular diastolic function by Doppler echocardiography in asymptomatic patients with Fabry cardiomyopathy and to detect the impact of ERT on myocardial hypertrophy and on left ventricular function.

Materials and methods

Study population

Between July and December 2001, 20 subjects from six families with Fabry's disease were screened at the Nephrology Department of Medical School 'Federico II' of Naples. Two male subjects did not have the mutation, one affected male refused the study (he was a dialysis patient and hemiplegic after a stroke episode). Eleven subjects (seven males, four females) were identified as affected by Fabry cardiomyopathy: as two female patients were not eligible, due to atrial fibrillation, nine patients were enrolled in the study. The remaining six subjects were female (one was 46 years old, three were under 20 years of age, two were over seventy) and did not show any evidence of Fabry's disease throughout the observation period of the study. The Fabry cardiomyopathy was defined by echocardiographic signs of increased thickness of the interventricular septum and/or LV posterior wall. The diagnosis of Fabry's disease was confirmed by peripheral blood α-galactosidase activity measurement, less than 1.5 nmol/ml/h (normal: 8–19), in male patients. Causal mutation was identified by direct sequencing in all six families. Each patient underwent a detailed clinical and instrumental screening of assessment of Fabry's disease manifestations, including neurological, ophthalmologic, dermatological, renal, and cardiac evaluation. After informed consent and approval by the ethics committee of our institution, the patients were treated with ERT, consisting of intravenous infusion of recombinant α-galactosidase A (r-hαGalA; agalsidase β; Fabrazyme®; Genzyme, Cambridge, MA) at the dose of 1 mg/kg/BW every 2 weeks. Before starting ERT and after 6 and 12 months, all patients underwent a complete electrocardiographic and echocardiographic evaluation in order to detect the effect of ERT on left ventricular mass and function. Ten healthy subjects, age- and gender-matched, were studied as the control group for the basal evaluation of left ventricular function.

Echocardiography

Echocardiographic studies were performed by the same operator using an ultrasound system (Sonos 2000, Hewlett-Packard, Andover, MA) equipped with a 2.5 MHz transducer, with the patient held in left lateral decubitus.

Left ventricular chamber dimensions, septum, and posterior wall thickness were measured utilizing two-dimensional guided M-mode recordings. The images were stored on videotape and reading was made in a blinded fashion by two independent observers (LS and MP), unaware of the temporal sequence of the recordings. Each observer read the all the 37 exams twice and intraobserver reproducibility was calculated. Left ventricular mass was calculated by the Penn Convention based on 3–5 averaged measurements (17). Left ventricular mass index was obtained by dividing left ventricular mass by body surface area.

LVH was considered to be present if left ventricular (LV) mass was above 130 g/m^2 for male and above 110 g/m^2 for female. Relative wall thickness (RWT) was calculated as (IVSth + PWth)/LVdd where IVSth and PWth and LVdd indicated thickness of interventricular septum, LV

posterior wall and internal diameter of the left ventricle at the end of diastole, respectively. Left ventricular concentric remodeling or concentric hypertrophy was defined as RWT > 0.45. LV volumes were measured with an application of the biplane Simpon's rule (18). Fractional shortening (FS) and ejection fraction were used as measures of LV systolic function.

The transmitral flow velocities were obtained by pulsed Doppler interrogation, from a four-chamber apical view, with the sample volume placed at the level of the mitral valve leaflet tips. Continuous wave Doppler echocardiography was used to simultaneously obtain the transmitral flow velocity curve and aortic valve closure click. The pulmonary vein flow velocities were recorded with the sample volume 0–1 cm into the right superior pulmonary vein. Continuous wave Doppler echocardiography was used to simultaneously obtain the transmitral flow velocity curve and aortic valve closure click. Doppler velocity curves were recorded at a horizontal sweep speed of 100 mm/s on videotape with the patient held in expiration and measured by two observers using electronic pointer device. For each measurement, three consecutive beats were averaged. The transmitral flow velocity curve was analyzed for the measurement of early diastolic (E) and late diastolic (A) peak velocities, the deceleration time of the mitral E wave velocities (DT), and the mitral A duration. The ratio between early diastolic peak velocity and late diastolic peak velocity on the mitral flow velocity curve was also calculated (E/A ratio). Isovolumic relaxation time (IRT) was measured as the interval from the aortic closure click to E wave onset. The pulmonary vein flow velocity curves was analyzed for measurement of the peak velocity and velocity–time integral (VTI) of systolic (PVs) and diastolic (PVd) forward waves. The peak velocity and the duration of the pulmonary venous flow wave at atrial contraction (PVa) were also determined. Finally, the difference between the duration of PVa and the duration of A (Δ duration) was calculated. Reproducibility of Doppler measurements from our laboratory has been previously reported (19).

Statistical analysis

Continuous data are expressed as mean ± SD. To assess the interobserver variability for the LV measurements, the Pearson correlation coefficient was calculated. Moreover, the percent difference between the measurements made by the two observers was calculated as the numerical average of the absolute difference between two measurements divided by the mean.

Student *t*-test and repeated measures analysis of variance (ANOVA) were performed to compare the Fabry patients and the control group and to detect changes over time during ERT, respectively. A two-tailed p-value < 0.05 was considered statistically significant.

Results

Demographic data, clinical characteristics, symptoms of cardiac involvement, and extracardiac manifestations of the nine patients included in the study are reported in Table 1. In all patients, α-galactosidase A enzymatic activity was very low. None of the patients had symptoms of heart failure. Extracardiac manifestations were present in all patients. Acroparesthesias caused by peripheral nerve lesions were present in six patients. Skin lesions in the form of angiokeratomas were present in five patients, with localization in lips, fingertips, palm of the hands, and toes. Hypohidrosis with heat intolerance was present in six patients. In all but two of the patients, a renal impairment was documented, two patients were on maintenance hemodialysis, and one received a renal transplant 8 years prior to the start of ERT. Two patients were hypertensive, and only one was treated with angiotensin-converting enzyme inhibitors at least 10 months before starting ERT. In all patients, blood pressure values and the anti-hypertensive drugs were not changed during the observation period.

In the Table 2, the mean values of the echocardiographic and Doppler variables of control and Fabry patients at baseline are listed. All patients had interpretable Doppler recordings of transmitral flow and pulmonary flow velocity curves. As compared with the control group, the patients with Fabry's disease had increased thickness of the interventricular septum and of the LV posterior wall and increased LV mass index and RWT, while LV end-diastolic and end-systolic dimensions, LV fractional shortening and LV ejection fraction were similar. In eight patients, a LV concentric hypertrophy was detectable, while one patient showed a concentric remodeling without an abnormally increased mass.

The mean values of E/A ratio, DT, and IRT were similar in the two groups; patients with Fabry's disease, however, had greater peak velocity and VTI of PVa, and a greater Δ duration. Therefore, in spite of the lack of abnormalities in Doppler parameters of early left ventricular filling, presence of diastolic dysfunction could be detected at baseline.

Table 1. Characteristics of patients

Patient	Family	Age/sex	Genotype/exon	Protein (nmol/h/mg)	Clinical manifestations	Kidney involvement	Blood pressure (mmHg)	Hemoglobin (g/dl)
1	I	25/male	G749A/exon 5	0.2	Skin, eyes, kidney, acroparesthesias, hypohidrosis	proteinuria	130/70	14.5
2	I	32/male	G749A/exon 5	0.3	Skin, eyes, hypohidrosis, acroparesthesias	–	130/70	14.2
3	I	53/female	G749A/exon 5	2.1	Eyes, kidney, angina pectoris	proteinuria	110/70	12.9
4	II	32/male	512 del A/exon 3	0.2	Skin, eyes, kidney, acroparesthesias, hypohidrosis	reduced GFR in renal transplantation (46.4 ml/min)	140/80	11.8
5	III	47/male	T483C/exon 3	0.2	Eyes, kidney, acroparesthesias	hemodialysis	110/70	12.8
6	IV	32/male	C1133G/exon 7	0.1	Skin, eyes, kidney, acroparesthesias, hypohidrosis	reduced GFR (24 ml/min)	140/85	11.2
7	V	61/female	G274S/exon 6	0.1	Eyes, kidney	hemodialysis	140/80	11.8
8	V	32/male	G274S/exon 6	0.1	Eyes, kidney, acroparesthesias, hypohidrosis	reduced GFR (48 ml/min)	140/85	12.8
9	VI	54/male	G1085A/exon 7	0.2	Eyes	–	120/70	13.2

GFR, glomerular filtration rate.
Results of three independent determinations on peripheral blood.

Table 2. Echocardiographic and Doppler measurements in Fabry patients at baseline

Variable	Control	Fabry patients
LA dimension (mm)	34 ± 3.5	39.2 ± 6.6[a]
Ao diameter (mm)	32 ± 2.3	37.9 ± 4.4
IVSth (mm)	9.1 ± 1.6	13.9 ± 2.2[a]
PWth (mm)	8.9 ± 1.8	13.3 ± 1.4[a]
LVdd (mm)	49 ± 3.5	49.5 ± 6.2
LVsd (mm)	27 ± 2.8	29.1 ± 5.4
RTW	0.39 ± 0.03	0.54 ± 0.10[a]
LVMi (g/m^2)	84.4 ± 21	183 ± 44.5[a]
FS (%)	42.4 ± 2.5	41 ± 0.06
LV ejection fraction (%)	66 ± 4	56.2 ± 4.2
RR interval (ms)	940 ± 38	1133 ± 108.4
E/A ratio	1.2 ± 0.9	1.38 ± 0.5
DT (ms)	188 ± 6	248 ± 70[a]
IRT (ms)	85 ± 8	92.5 ± 17
PVs (cm/s)	55 ± 14.4	56.8 ± 12.2
PVd (cm/s)	59 ± 11.5	49.3 ± 12
PVa (cm/s)	22.1 ± 4	36.1 ± 8.4[a]
PVs VTI (cm)	13.7 ± 2.4	15.7 ± 2.28
PVd VTI (cm)	11 ± 1.8	12.1 ± 1.89
PVa VTI (cm)	1.3 ± 0.08	2.52 ± 0.70[a]
Δ duration (ms)	-9 ± 3.5	8.6 ± 10.3[a]

[a]$p < 0.05$ (minimum) control subjects *vs* Fabry patients.

ERT did not induce changes in heart rate (RR = 1033 ± 108 ms, 1016 ± 55 ms, 1001 ± 103 ms at baseline and after 6 and 12 months of ERT, respectively). No significant change was observed in LV internal diameters (LVdd = 49 ± 6 mm, 48 ± 3 mm, 50 ± 6 mm; LVsd = 29 ± 5 mm, 29 ± 6 mm at baseline and after 6 and 12 months of ERT, respectively), in FS ($41 \pm 0.06\%$, $40 \pm 0.05\%$, $42 \pm 0.08\%$, at baseline and after 6 and 12 months of ERT, respectively) and in LV ejection fraction ($56 \pm 4\%$, $57 \pm 6\%$, $59 \pm 4.5\%$, at baseline and after 6 and 12 months of ERT, respectively). Results showed a slight but non-significant decrease in the LV posterior wall thickness (13.3 ± 1.6 mm, 13 ± 2.5 mm, 12.4 ± 1.5 mm at baseline and after 6 and 12 months of ERT, respectively) and a significant decrease in interventricular septum thickness, in RWT and LV mass index (Fig. 1a,b,c). After 12 months of treatment with algasidase β, left ventricular mass index (LVMi) was significantly reduced in all but two of the patients (Fig. 1d). One of them had left ventricular concentric remodeling (with only an initial cardiac involvement), whereas the other had a renal transplant with a history of severe hypertension in the past and a marked increase of left ventricular mass.

With regard to echo-Doppler-derived variables IRT (86 ± 17 ms, 90 ± 21 ms, 82 ± 16 ms at baseline and after 6 and 12 months of ERT, respectively) and DT (248 ± 70 ms, 230 ± 48 ms, 234 ± 60 ms at baseline, and after 6 and 12 months of ERT, respectively), PVs, PVd did not change during the 12 months of treatment. There was a

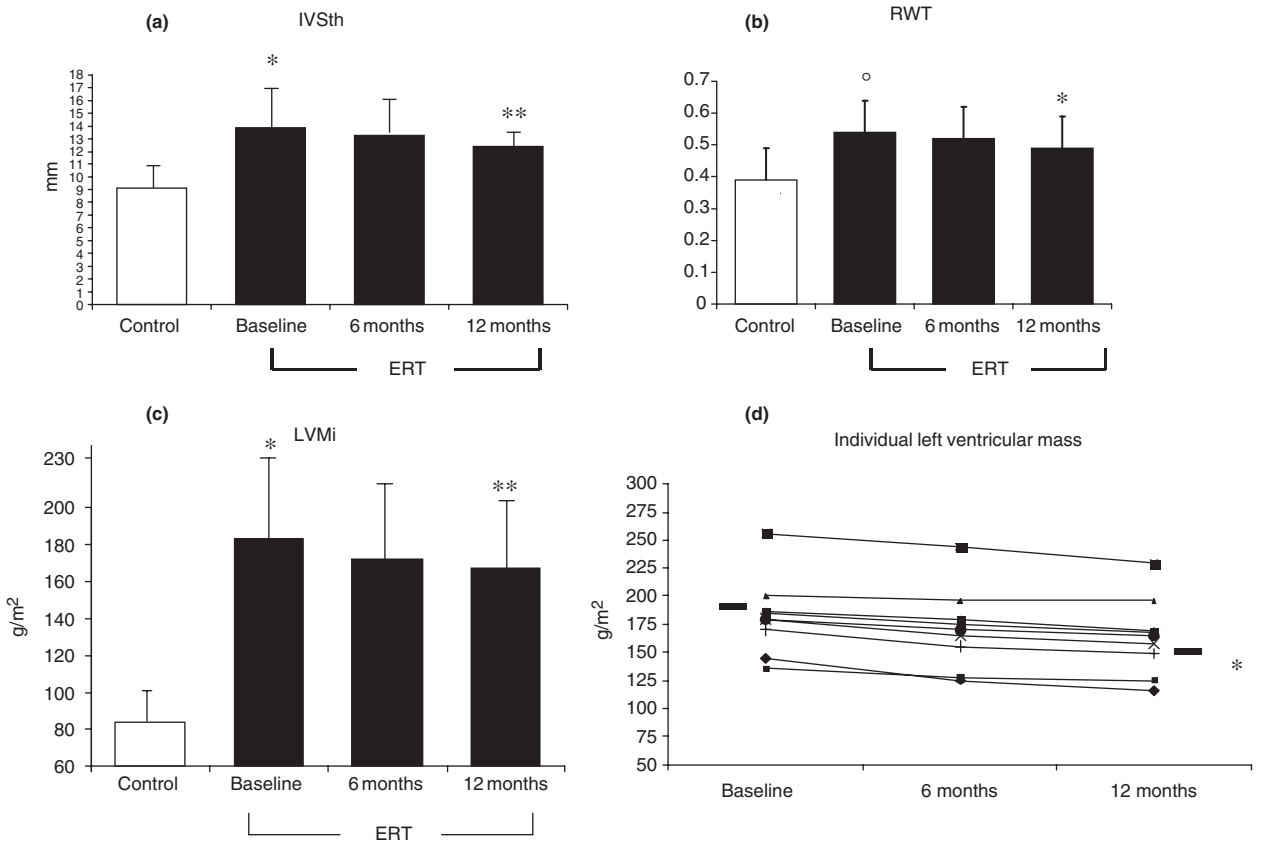

Fig. 1. Echocardiographic parameters before and after 6 and 12 months of treatment with Fabrazyme. (a) Thickness of interventricular septum (IVSth), (b) Relative wall thickness (RWT), (c) LVMi, (d) Individual changes in LVMi. Fabry patients baseline *vs* control subjects (*$p < 0.05$), 12 months of enzyme replacement therapy (ERT) *vs* baseline (**$p < 0.01$).

slight decrease in PVa (32.6 ± 8.46 cm/s, 29.5 ± 6.64 cm/s, 28.5 ± 6.64 cm/s at baseline and after 6 and 12 months of ERT, respectively) and VTI PVa (2.52 ± 0.70 cm, 2.23 ± 0.62 cm, 2.21 ± 0.52 cm at baseline and after 6 and 12 months of ERT, respectively), while E/A ratio

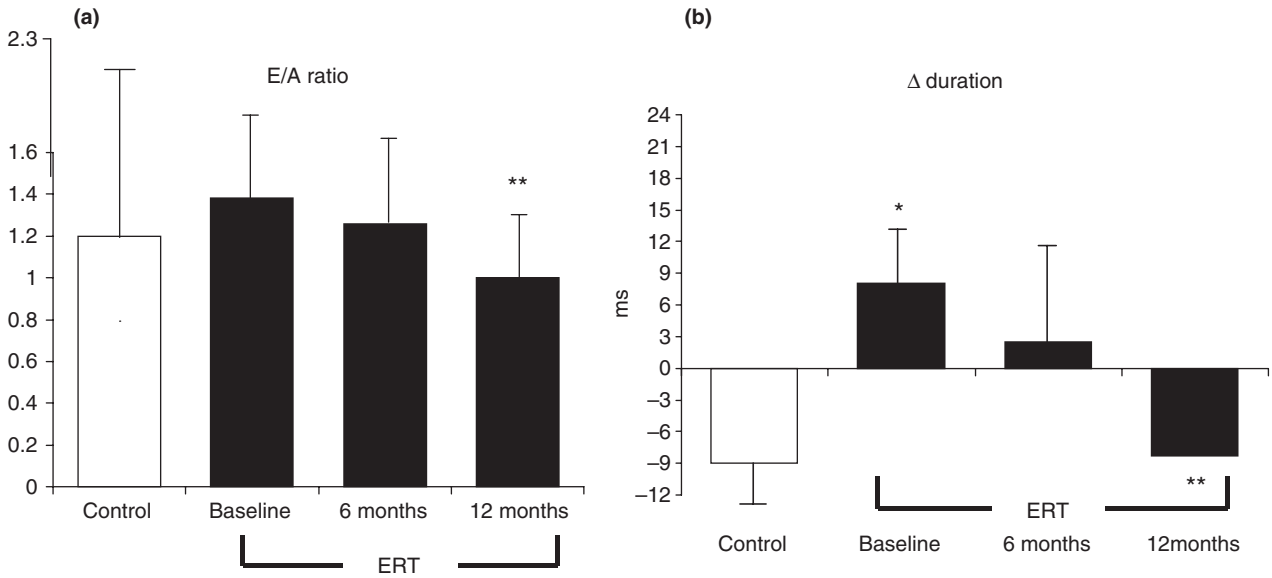

Fig. 2. Echo-Doppler parameters before and after 6 and 12 months of treatment with Fabrazyme. (a) E/A ratio and (b) Δ duration. Fabry patients baseline *vs* control subjects (*$p < 0.05$), 12 months ERT *vs* baseline (**$p < 0.01$).

and Δ duration resulted significantly reduced during therapy (Fig. 2). After one year of ERT, only one patient exhibited a reverse pulmonary vein flow velocity wave longer than mitral A wave.

Reproducibility

In the Table 3, the mean values of the readings made by the two observers and for the interventricular septum thickness, LV posterior wall thickness, LVdd and LV mass index and interobserver variability are shown. Interobserver variability was expressed as percent difference of the measurements and the Pearson correlation coefficient.

Discussion

During the past decade, the safety and the efficacy of ERT for the lysosomal storage disease, Gaucher type 1, have been demonstrated: the infusion of recombinant acid β glucosidase is able to metabolize the accumulated substrate and reverse the disease-related abnormalities (20, 21) and is representing the standard of treatment for this disorder. A report by the International Collaborative Fabry Disease Study Group demonstrated the efficacy of treatment with agalsidase β to reverse the accumulation of microvascular endothelial deposits of globotriaosylceramide in the kidney, heart, and skin in patients with Fabry's disease (13). Long-term, double-blind, controlled studies would be necessary in order to demonstrate the impact of ERT on the prevention and, possibly, the reversion of organ damage in Fabry's disease. However, the availability on the market of enzyme and its effectiveness in removing lipid deposition (13) makes very hard and even unethical to perform such a study. Furthermore, based upon former studies on the effect of therapy on LVH (22), hundreds of patients in each arm would be necessary to demonstrate its efficacy with such a protocol. The present study indicates that ERT in patients with Fabry cardiomyopathy after 12 months of treatment reduces left ventricular mass and ameliorates the left-ventricular stiffness, in comparison with the basal condition.

The enzymatic defect of Fabry's disease leads to the accumulation of uncleaved glycosphingolipids primarily but non-exclusively in the vascular endothelium of skin, kidney, nervous system, eye, and heart (2–7). Cardiac abnormalities are common and may be the only clinical manifestation of disease in some patients (6, 8). The cardiomyopathy in Fabry's disease is a progressive hypertrophic infiltrative cardiomyopathy, with peculiar features: glycosphingolipids lysosomal storage, in fact, represents about 1% of the increase in left ventricular mass (23, 24). Although globotriaosylceramide is the main glycosphingolipid to accumulate, glycolipid biosynthesis and other cellular pathways may also be deregulated. Other sphingolipids that mimic the biological function of cytokines, growth factors, and stress-signaling molecules, accumulate in tissues and could act as a second messenger and potentiate the hypertrophy of the myocardium (2, 9). Of note, increased plasma endotelin-1 levels have been reported (25). Therefore, hypertrophic cardiomyopathy in Fabry's disease is due to a lysosomal storage and to a true increase in heart muscle mass, related to an additional neurohormonal activation. Although most of Fabry patients do not experience symptoms until late in the disease course, LVH may cause congestive heart failure, myocardial ischemia, life-threatening arrhythmias, and death. Cardiac involvement represents, thus, the first cause of death for this disease (2–5). To date, few studies suggest a positive effect of ERT on LVH. A randomized trial by US National Institutes of Health demonstrated a decrease in QRS-complex duration after ERT, suggesting an improvement in intraventricular conduction and/or a decrease in LV mass (14). In the present study, echocardiography has been utilized to assess changes in left ventricular mass. In order to maximize the reliability of the method, we have accurately tested the reproducibility of the measurements with a blinded reading made by two independent observers. Results of the current study, showing a decrease in LV mass of about 10%, are consistent with those recently published by Weidemann et al. (16) and obtained using magnetic resonance imaging. In all but two of the patients, we observed a significant reduction in left ventricular mass during treatment with agalsidase β. One of the two patients had only

Table 3. Reproducibility: interobserver variability for echocardiographic measurements

Measurement	Observer A	Observer B	Percent difference (%)	Pearson correlation coefficient
IVSth (mm)	13.32 ± 1.78	13.42 ± 1.61	4.3	0.941
PWth (mm)	12.92 ± 2.16	12.99 ± 2.00	3.5	0.977
LVdd (mm)	47.7 ± 2.69	48.10 ± 2.56	2.4	0.893
LVMi (g/m^2)	169.4 ± 43.7	168.7 ± 41.4	4.1	0.986

Values are mean ± standard deviation.

left ventricular concentric remodeling without an increased mass, this indicating that this patient was in an early phase of Fabry cardiomyopathy. The other patient had a renal transplant and a history of severe hypertension with blood pressure values non-optimally controlled by the therapy. The presence of hypertension or of comorbidity in such patients, requires specific therapeutic measures and represents a potential confounding factor in assessing whether ERT is effective. Considering the progressive nature of cardiac involvement in Fabry's disease, the lack of increase in left ventricular mass over 12 months could be assumed as a positive effect of the ERT.

To date, no study reported the effect of ERT on Doppler parameters of late diastole in Fabry's disease patients. Doppler echocardiography is a reliable tool to assess left ventricular diastolic function. The analysis of transmitral and pulmonary venous flow velocity waves at atrial contraction is a validated tool to non-invasively detect the increase in left ventricular stiffness and end-diastolic pressure. High LV resistance to filling in late diastole, due to reduced ventricular compliance, results in increased pressure into the left atrium, yielding a prolongation of the duration of reverse pulmonary vein flow at atrial systole. Both pulmonary vein and mitral A duration are related to ventricular compliance and they change in an opposite manner. Differently from Doppler-derived parameters of the first diastolic phase, which are influenced by left ventricular systolic function and are predictive of filling pressures only in patients with depressed left ventricular ejection fraction, Doppler measurements of late diastole reflect left ventricular end-diastolic pressure, regardless of systolic function. Therefore, they are suitable for patients affected by Fabry cardiomyopathy whose cardiac involvement is characterized by LVH and diastolic dysfunction in presence of preserved systolic function. As the little overlap of values between patients with and without increased LV end-diastolic pressure, the difference in duration of the pulmonary venous flow velocity wave and mitral flow velocity wave at atrial contraction is an index clinically useful in individual patients (12). Our results demonstrate that left ventricular diastolic dysfunction may be present in Fabry patients with myocardial hypertrophy even in absence of symptoms. Although diastolic impairment was not able to limit daily life activities, it is likely that it could become a limiting factor for exercise capacity whenever a greater exercise performance was required. The exercise tolerance was not specifically addressed in the present study and it should an important subject for future studies. According to Doppler evidence of increased filling pressure, Fabry patients exhibited a larger left atrium, an anatomic hallmark of diastolic dysfunction. High values of LV end-diastolic pressure have been previously observed in Fabry patients, with mutation in α-galactosidase A gene and LVH (26).

ERT induced a significant improvement in diastolic function, as demonstrated by the significant reduction in the difference between the duration of the pulmonary vein and mitral A wave at atrial contraction, suggesting a decrease in the left ventricular filling pressures. After 12 months of therapy, only one patient exhibited a pulmonary vein A wave longer than mitral A wave. This patient was carrying a kidney transplant and did not show the regression of the left ventricular mass.

The current results indicate the effectiveness of the ERT in eliciting a reduction in left ventricular stiffness along with a decrease in left ventricular mass in Fabry cardiac disease. It is reasonable to postulate that the decrease in left ventricular mass, that we and others observed, and the improvement in left ventricular compliance were due to a reverse substrate storage in the lysosomes of myocardial cells. Histological clearance of the deposits of globotraosylceramide in the vascular endothelium of the heart has been demonstrated after 20 weeks of ERT (13). In one case of cardiac variant of Fabry's disease and residual a-galactosidase A activity, intravenous infusions of galactose enhanced the stability and the residual enzyme activity and induced a decrease in the endomyocardial storage vacuoles along with a reduction of left ventricular mass (27).

These data emphasize the role of ERT in Fabry cardiomyopathy. However, although our results are encouraging, they were obtained in patients without evidence of hemodynamic compromise, therefore long-term follow-up data are necessary to ascertain the real impact of ERT on the natural history of this disease and on the survival of patients with Fabry's disease.

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