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Usefulness of tissue Doppler on early detection of cardiac disease in Fabry patients and potential role of enzyme replacement therapy (ERT) for avoiding progression of disease

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Aims Cardiac involvement, including progressive cardiomyopathy, is common in Fabry disease and is a leading cause of premature mortality. We sought to determine if tissue Doppler imaging (TDI) could identify Fabry disease patients at risk for the development of cardiomyopathy and if enzyme replacement therapy (ERT) with agalsidase alfa might slow or prevent the progression of cardiac involvement.

Methods and results Fabry disease patients were enrolled in this prospective, observational study. Echocardiography was performed at baseline and periodically throughout the study. A single investigator, blinded to both the type of assessment (baseline or follow-up) and enzyme replacement status of the patient, evaluated all echocardiograms. Seventy-six patients (26 male, 50 females) were enrolled in the study. Twenty men and 13 women were treated with agalsidase alfa during the study. At baseline, increasing interventricular septum thickness was significantly associated with decreasing TDI velocities. Twenty-nine patients >18 years old (23 females) had no evidence of cardiac involvement at baseline (normal LVM and normal TDI velocities). In this cohort, 80% (16 of 20) of patients not on ERT progressed to demonstrating an abnormal TDI velocity during follow-up, whereas only 33% (3 of 9) of patients on ERT progressed to TDI abnormalities ($P = 0.031$).

Conclusion In Fabry disease, reduced TDI velocity seems to be the initial sign of cardiac involvement that occurs before the development of cardiac hypertrophy. ERT with agalsidase alfa delays the onset of cardiac involvement and should be considered at an earlier stage of the disease, even in the absence of left ventricular hypertrophy.

Keywords Fabry disease • Cardiomyopathy • Enzyme replacement therapy

Introduction

Fabry disease (OMIM 301500) is a rare, inherited, X-linked deficiency in the activity of the lysosomal enzyme α-galactosidase A (α-Gal A).[1,2] In affected individuals, cellular accumulation of the principal enzyme substrate, globotriaosylceramide (Gb3), occurs and contributes to the signs and symptoms of the disease. In males, the onset of signs and symptoms of Fabry disease occurs in childhood and adolescence and is characterized by acroparesthesias and neuropathic pain, gastrointestinal problems including pain and diarrhea, hypohydrosis and heat intolerance, angiokeratoma, and characteristic corneal opacities.[3–5] As the disease progresses, kidney dysfunction, cardiac involvement, and stroke increase in prevalence and contribute to premature mortality in men.[6] Although women have been considered to be mere carriers of the mutation, it has recently become evident

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that they could experience nearly all the signs and symptoms of Fabry disease, but with a later onset and a more variable expression than seen in men.[7,8]

Cardiac involvement is common in patients with Fabry disease and includes left ventricular hypertrophy (LVH), valvular dysfunction, and conduction abnormalities.[9–11] Left ventricular (LV) wall thickening is the most common cardiac sign of Fabry disease, with increases in mass sometimes so large as to mimic hypertrophic cardiomyopathy.[9,12] As the disease progresses, interstitial fibrosis is commonly observed,[12–14] resulting in systolic and diastolic dysfunction.

Tissue Doppler imaging (TDI) is emerging as an accepted method for identifying the early stages of several forms of inherited cardiomyopathy.[15,16] TDI has been reported to distinguish between patients with Fabry disease with and without LVH and relatives without the Fabry disease mutation.[17] We have recently reported that TDI measurements can distinguish between Fabry disease patients with and without LVH, as well as between Fabry disease patients without LVH and healthy subjects without the disease.[18] However, to date, no prognostic information of TDI measurements has been reported in patients with Fabry disease. Thus, this longitudinal study was performed to investigate the prognostic information provided by tissue Doppler echocardiography in patients with Fabry disease and to evaluate the effect of enzyme replacement therapy (ERT) on the progression of Fabry disease cardiomyopathy.

Methods

This study was a prospective, blinded, observational study of male and female patients with a confirmed diagnosis of Fabry disease. In the male patients, diagnosis was made by a biochemical demonstration of a reduction in the activity of α-Gal A in peripheral leukocytes. DNA analysis was used to confirm Fabry disease in female patients. Patients were recruited into the study without regard for current or past use of ERT. All patients gave their informed written consent prior to enrolling in the study, and the study protocol was reviewed and approved by the ethics committee of the San Carlos University Hospital in Madrid, Spain. All patients were evaluated at least two times during this study, first at study entry (baseline) and thereafter at 6- to 12-months intervals. At each study evaluation, the following assessments were made: medical history, physical examination, supine 12-lead electrocardiogram, and echocardiography. Echocardiography was performed with a Philips 5500 or iE33 ultrasound system. Standard two-dimensional, M-mode, spectral and color Doppler, and Doppler tissue interrogation were performed. A single investigator who was blinded to the patient information, the type of assessment (baseline or follow-up), and the patient ERT status performed all the echocardiographic measurements. Septal and LV wall thickness and LV end-diastolic and end-systolic dimensions were determined by 2D images according to established criteria. LV mass (LVM) was calculated by the method of Devereux.[19] LVH was defined as having an interventricular septum or left ventricular posterior wall thickness $\geq$12 mm. Tissue Doppler was applied in the pulsed Doppler mode to record mitral annulus velocities at the septal and lateral corners. Systolic (Sa), early diastolic (Ea), and late diastolic (Aa) tissue Doppler velocities were measured. An abnormal TDI velocity was defined as Sa or Ea $<$ 8 cm/s at either the septal or lateral corner. This value was based on the approximate mean values reported for Fabry patients without LVH.[17]

Statistical analysis

Methods of descriptive statistics were applied. The relationship between Ea-septal and interventricular septum thickness was evaluated with linear regression. Fisher's exact test was used to analyse the relationship between ERT status and progression of TDI velocities during follow-up. Correlations were done using Spearman test. Patients $<$18 years old were not included in this analysis because cardiomyopathy is rare in children with Fabry disease.

Results

A total of 76 patients (26 men and 50 women) with Fabry disease were enrolled in the study. Twenty of the men and 13 of the women were being treated with agalsidase alfa (Replagal®, Shire Human Genetic Therapies, Cambridge, MA, USA) at a dose of 0.2 mg/kg infused intravenously every other week. The infusion period was 40 min, and premedication was not reported at the time of enrollment nor throughout the study. Follow-up data were available for 63 patients, and of these, 55 patients were $>$18 years old: 36 female (12 treated) and 19 males (16 treated). Agalsidase alfa is human cell line-derived α-gal A that is indicated for long-term ERT in Fabry disease.[20] Baseline echocardiographic data from some of these patients have been previously described.[18]

Echocardiography

Baseline 2D echocardiography measurements are presented in *Table 1*. As expected, the prevalence of LVH was higher in ERT-treated men and women than in the untreated men and women. This data are in accordance with the scientific evidence, as

Table 1 Baseline two-dimensional echocardiographic measurements in Fabry patients

	N	Age (years)	IVSd (mm)	PWTd (mm)	LVH prevalence (%)
Untreated men	6	31.3 ± 29.4 (5.0–75.6)	10.6 ± 5.5 (6–20)	10.0 ± 3.8 (6–16)	1/6 (16.7%)
Untreated women	37	28.8 ± 16.6 (3.6–69.6)	9.1 ± 2.0 (6–17)	9.1 ± 2.0 (6–16)	1/37 (2.7%)
Treated men	20	37.1 ± 12.7 (13.1–65.3)	13.4 ± 3.3 (8–19)	13.5 ± 3.3 (7–20)	11/20 (55.0%)
Treated women	13	42.9 ± 13.6* (19.8–61.7)	11.5 ± 2.3* (9–16)	11.0 ± 2.0* (8–15)	5/13 (38.5%)

Values are mean ± standard deviation (range). IVSd, interventricular septum thickness measured during diastole; PWTd, posterior wall thickness measured during diastole.
*$P < 0.05$ compared with untreated women (*t*-test).

Table 2 Baseline tissue Doppler imaging measurements

	N	Sa-s (cm/s)	Ea-s (cm/s)	Aa-s (cm/s)	Sa-l (cm/s)	Ea-l (cm/s)	Aa-l (cm/s)	Prevalence abnormal TDI (%)
Untreated men	6	8.0 ± 1.8	11.6 ± 2.0	6.9 ± 3.1	10.8 ± 2.3	16.8 ± 4.8	9.3 ± 2.6	1/6 (16.7%)
Untreated women	37	8.5 ± 1.4	10.7 ± 3.0	7.8 ± 1.7	11.5 ± 2.1	15.6 ± 5.2	10.1 ± 2.6	6/37 (16.2%)
Treated men	20	7.6 ± 2.0	7.9 ± 4.0	8.5 ± 1.0	10.1 ± 3.3	12.0 ± 5.2	8.9 ± 2.8	15/20 (75.0%)
Treated women	13	8.2 ± 1.6	8.7 ± 3.1	7.9 ± 1.5	8.8 ± 2.5*	9.7 ± 4.5*	8.9 ± 1.8	7/13 (53.8%)

Values are mean ± standard deviation. Sa, systolic; Ea, early diastolic; Aa, lateral diastolic; s, septal; l, lateral.
*$P < 0.05$ compared with untreated women (*t*-test).

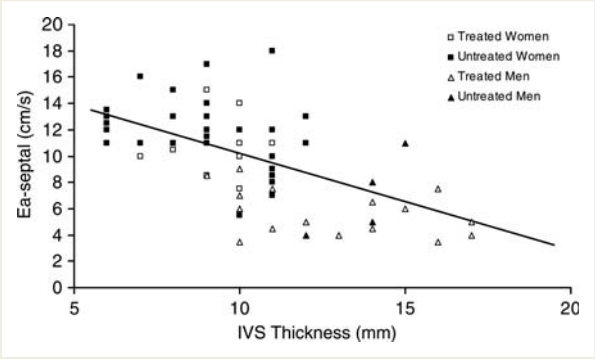

Figure 1 The association at baseline between interventricular septum thickness (IVS) and early diastolic-septal in men and women with Fabry disease. The solid line represents the results of regression analysis for the entire study population at baseline: early diastolic-septal velocity = 17.51 − 0.733 · IVS thickness ($r^2 = 0.379$, $P < 0.0001$).

according to current Fabry guidelines LVH is a clear marker to start ERT treatment, and very few patients actually start ERT before LVH is present, what sometimes could be too late for a beneficial effect. Ejection fraction was normal in both treated and untreated men and women. Over the course of up to 4.9 years of follow-up examinations, no significant changes in average 2D echocardiographic measurements were found. For example, untreated women demonstrated an average change from baseline of interventricular septum thickness measured during diastole (IVSd) of 0.29 ± 1.73 mm (mean ± SD) after a median of 2.9 years of follow-up.

Baseline TDI assessments are presented in *Table 2*. ERT-treated women had significantly lower Ea-lateral and Sa-lateral velocities compared with their untreated counterparts. A higher percentage of ERT-treated men (75.0%) and women (53.8%) were designated as having an abnormal TDI velocity than untreated men (16.7%) and women (16.2%).

The association between Ea-septal TDI velocity and interventricular septum thickness at baseline in the entire study population is presented in *Figure 1*. Ea-septal TDI velocity was inversely associated with interventricular septum thickness over the entire range of baseline values ($P < 0.0001$, regression analysis).

The abnormal TDI identified patients who were at risk for developing LVH during the longitudinal follow-up. TDI images from a patient with normal TDI velocities at baseline who progressed to abnormal TDI velocities are shown in *Figure 2*. At baseline, 23 women >18 years old had both normal TDI velocities and normal LVM, 7 women had abnormal TDI velocities and normal LVM, and 6 had both abnormal TDI velocities and an increased LVM. After a median 2.9 years of follow-up, this distribution had changed to 8 normal, 18 with abnormal TDI, and 10 with both abnormal TDI and LVH. A similar shift was seen in men. At baseline, 6 men had normal TDI velocities and normal LVM, 5 had abnormal TDI velocities and normal LVM, and 8 had both abnormal TDI velocities and LVH. After a median 3.4-year follow-up, the distribution had shifted to 3, 5, and 11 men, respectively.

The influence of ERT with agalsidase alfa on the progression of cardiac involvement in Fabry disease was very important. In the cohort of patients who had no evidence of cardiac involvement at baseline, 80% (16 of 20 patients) of patients not on ERT progressed to demonstrating an abnormal TDI velocity during follow-up, whereas only 33% (3 of 9) of patients on ERT progressed to TDI abnormalities ($P = 0.031$; *Tables 3* and *4*).

Assessment of diastolic dysfunction has also been studied. Of interest *E*/e' ratio was lower in the lateral annulus, which may be due to the interaction of the right ventricle at the mid-annulus (*Table 5*) and diastolic dysfunction was more present in those patients receiving ERT (*Table 6*). This may be related to the more frequency of LVH among the treated patients.

Discussion

In this study, echocardiography was performed on both male and female patients with Fabry disease. Our results showed that TDI velocities were inversely related to LVM (*Figure 1*). In addition, the serial follow-up echocardiographic examinations clearly demonstrated that abnormal TDI velocities were evident prior to the development of LVH. Moreover, ERT was significantly associated with preventing the development of abnormal TDI velocities in patients without evidence of cardiac involvement at baseline.

The TDI velocities of patients with Fabry disease in this study are of the magnitude previously reported in Fabry patients with or without LVH.[17,21,22] For example, Pieroni *et al.*[17] reported that septal Sa was 5.84 ± 0.61 cm/s and septal Ea was 5.33 ±

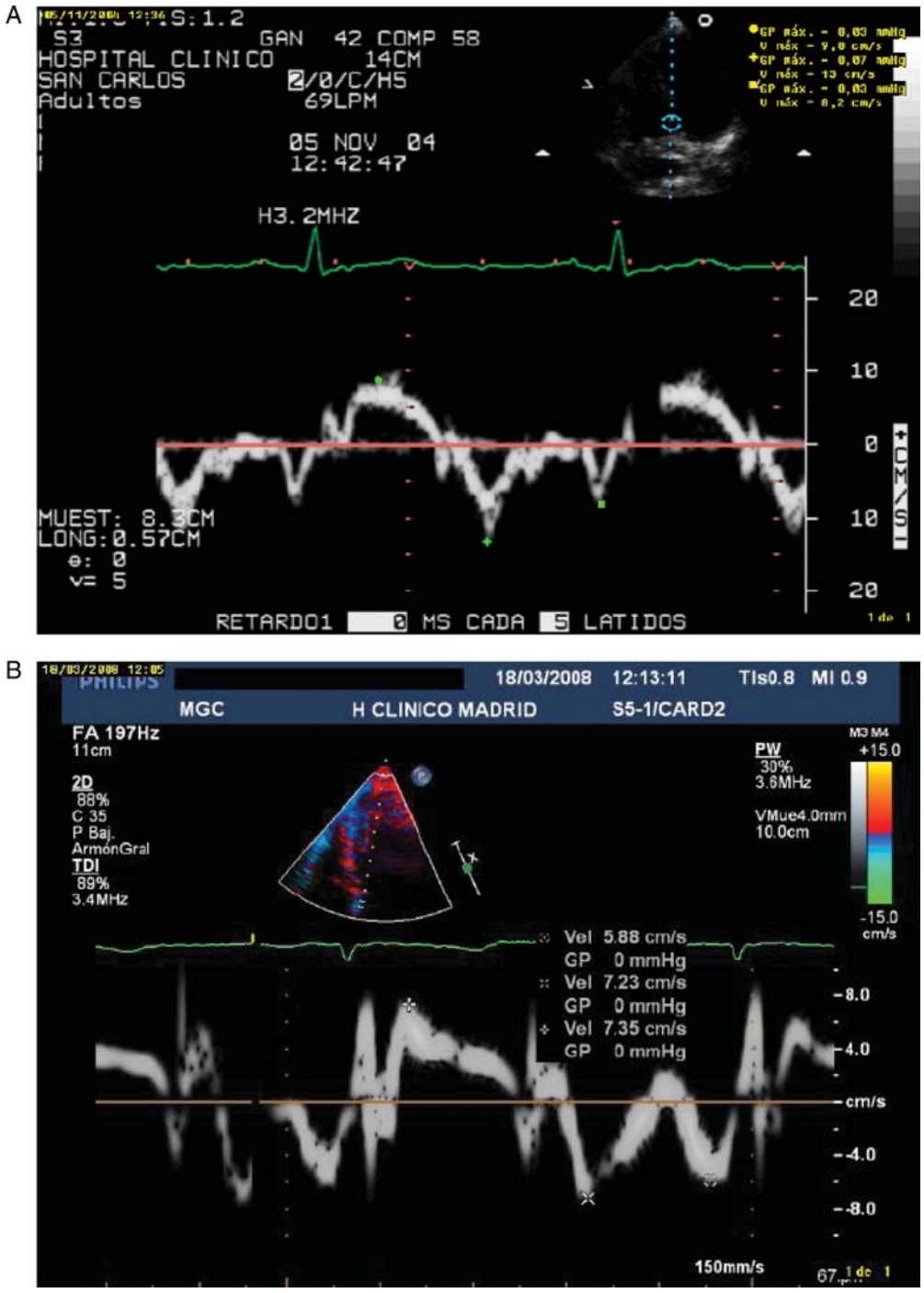

Figure 2 Baseline and follow-up tissue Doppler images in a patient who progressed from normal tissue Doppler imaging velocities (*A*) to abnormal tissue Doppler imaging velocities (*B*) during treatment with agalsidase alfa.

0.38 cm/s in 10 Fabry patients with LVH. In the present study, septal Sa and Ea were 6.71 ± 1.10 and 5.68 ± 1.98 cm/s, respectively, in the 18 patients with LVH at baseline. In the Pieroni study, all 20 patients with Fabry disease with or without LVH demonstrated lateral and septal Sa and Ea velocities <10 cm/s. In the present study, an abnormal TDI velocity was clearly a risk factor for progression to LVH. A similar prognostic value of TDI velocities has been reported in patients who have mutations causing hypertrophic cardiomyopathy.[23]

Previous studies have identified reduced TDI velocities in Fabry patients without echocardiographic evidence of Fabry-related cardiomyopathy.[17,18,22] The observation that TDI velocities are

Table 3 DTI data at follow-up (55 patients >8 years old)

	Female	Male	Total
Total number of patients.	36 (12t)	19 (16t)	55 (28t)
Echo normal	23 (5t)	6 (4t)	29 (9t)
LVH normal – TDI alt.	7 (2t)	5 (4t)	12 (6t)
LVH and TDI alt.	6 (5t)	8 (8t)	14 (13t)

Total number of patients (treated patients). t, treated patients.

Table 4 The influence of enzyme replacement therapy on progression cardiac involvement in Fabry patients without evidence of cardiac involvement at baseline

		No ERT	On ERT	Total
Evolution to DTI alt.	No	4	6	10
	Yes	16	3	19
		20	9	29

ERT, enzyme replacement therapy; DTI, doppler tissue imaging. $P = 0.031$ (Fisher's exact test).

Table 5 Diastolic parameters at baseline and follow-up: *E*/*é* ratios of lateral and medial wall baseline and end of study period values

E/*e*'	Mean	SD	*P*
Basal			
Septal	8.84	2.60	0.018
Lateral	6.28	3.36	
Final ($n = 57$)			
Septal	10.06	3.57	<0.001
Lateral	7.50	6.79	

For all the patients included ($n = 76$).

further reduced in Fabry patients with LVH has suggested that TDI abnormalities might be an initial finding of cardiac involvement in Fabry disease. The present study is the first to use TDI to longitudinally follow individual Fabry disease patients, and has documented that indeed, reduced TDI velocities appear to precede the development of LVH in all cases.

Cardiac involvement is common in both men and women with Fabry disease. Gb3 accumulates within all components of the heart (e.g. cardiomyocytes, conduction system, valvular cells, vascular endothelial cells, smooth muscle cells).[10] It is thought that this accumulation of Gb3, which represents only 1–2% of the total cardiac mass, stimulates the activation of other signalling pathways that lead to the hypertrophy and fibrosis.[10]

Fabry-related cardiomyopathy is characterized by concentric remodelling usually progressing to a concentric hypertrophy.[9,24] A recent report from the Fabry Outcome Survey found that the prevalence of LVH diagnosed by echocardiography increased with age in both men and women.[11] About 25% of all men were diagnosed with LVH by about age 42 years; the diagnosis of LVH in women occurred about 10 years later.[11] Although the onset of clinical heart disease in men with Fabry disease usually occurs in the third decade of life, cardiac involvement has been reported in boys as young as 6 years old.[4] Similarly, cardiac disease has been reported in female Fabry patients as young as 15 years old.[3] Cardiac involvement is a common cause of death in both male and female Fabry disease patients.[11]

Management of Fabry disease has historically been directed at symptoms; however, the development of human α-Gal A for ERT has opened the possibility of treating this genetic disease.[20,25] Two forms of human α-Gal A have been developed: agalsidase alfa, which is produced in a continuous human cell line and agalsidase beta (Fabrazyme®, Genzyme, Cambridge, MA, USA), which is produced in Chinese hamster ovary cells. These two forms of the enzyme have identical amino acid sequences, but have different glycosylation patterns due to the different cell cultures used in their manufacture, and this difference may reflect the difference in safety profile and different dosage seen for each drug.[26] Both forms of the enzyme have been reported to slow the progression of kidney dysfunction.[27,28]

Agalsidase alfa has been reported to reduce the severity of neuropathic pain.[20] In studies directly related to the present results,

Table 6 Conventional diastolic grading baseline and end of study period values by enzyme replacement therapy/no enzyme replacement therapy

		ERT	No ERT	*P*
Basal	*E*/*A* < 1 [% (*n*/*N*)]	32.25 (10/31)	9.68 (3/31)	0.029
	DT (mean ± SD)	0.21 ± 0.04	0.17 ± 0.038	0.003
Final	*E*/*A* < 1 [% (*n*/*N*)]	42.31 (11/26)	16.13 (5/31)	0.028
	DT (mean ± SD)	0.21 ± 0.04	0.17 ± 0.04	<0.001
Total [% (*n*/*N*)]		43.42 (33/76)	56.58 (43/76)	
		Basal	Final	*P*
E/*A* < 1 [% (n/N)]		20.97 (13/62)	28.07 (16/57)	0.367
DT, *n* (mean ± SD)		53 (0.19 ± 0.05)	48 (0.19 ± 0.05)	0.537

agalsidase alfa has been reported to reduce LVM in adult male[29] and adult female[30,31] Fabry disease patients with baseline LVH and to improve heart rate variability in adolescent male patients.[32] Agalsidase beta also has been tested for its ability to influence Fabry-related cardiomyopathy, with some studies finding a reduction in LVM[33,34] and others reporting no or mixed response.[34–38]

The variation in response to ERT seen in some patients has led investigators to suggest that ERT may be less effective in slowing or stopping the progression of Fabry disease when used in patients in an advanced stage of the disease.[27,29,39,40] However as seen in our cohort, that included patients with different burden of the disease, prevalence of LVH was higher in ERT-treated men and women than in the untreated men and women, suggesting that treatment is still started only when there is organ damage, that could be late in some patients for seeing a beneficial effect of ERT, being early diagnosis a crucial point. The influence of age is still a controversial issue. On the one hand it could of course contribute to the abnormal findings as patients treated are normally older and more affected than untreated patients due to the progressive course of the disease. However, it is also important to mention that as there is no clear correlation between genetic mutations and burden of the disease, patients affected may sometimes be younger than unaffected ones.

The observations in the present study confirm that to slow or prevent the progression of organ damage, it is important to identify patients at an early stage of the disease, and to initiate ERT at an early stage, because some of the pathological changes are potentially irreversible (e.g. myocardial fibrosis).[39,40]

Current guidelines indicate that all males over the age of 16 years should be offered ERT,[41] a strategy that should ensure the initiation of ERT before major organ damage has progressed to irreversible stages in most patients. However, for women with Fabry disease, the same guidelines state that ERT should only be initiated if significant symptoms develop or if evidence of progression of organ involvement is detected. In the case of the heart, delaying ERT until clinically significant cardiac involvement is present may be too late to positively influence its progression.

The results of the present study indicate that signs of cardiomyopathy can be detected by TDI before it is clinically evident, and suggest that ERT may slow the progression of cardiac involvement before irreversible changes occur if started early enough. Of the Fabry patients without evidence of cardiac involvement (i.e. normal TDI) at baseline, 80% of the untreated patients progressed to demonstrating abnormal TDI velocities during follow-up, whereas only 33% of patients treated with ERT showed similar progression. This is an important observation because it supports early initiation of ERT, even before TDI abnormalities can be detected. To clearly understand the potential benefits of early ERT on the heart it is of utmost importance to recognize that nearly all Fabry patients progress to LVH[40] and cardiac involvement contributes substantially to disease-related morbidity and mortality in men and is the major cause of premature death in heterozygous females.[11,42]

Study limitations

Although the investigators performing and evaluating the echocardiographic examinations were blinded to the ERT status of the study participants, the study was otherwise open and observational in nature. Study subjects were not randomly selected for ERT, and they were at a more advanced stage of cardiac involvement compared with the untreated patients. Because some patients were treated with agalsidase alfa upon entry to the study, no pretreatment measurements were available for these patients. Thus, the initial response of TDI velocities or 2D echocardiographic measurements to agalsidase alfa could not be evaluated. Future controlled clinical studies will be required to confirm whether early initiation of ERT in women or men before TDI velocities have declined can slow or stop the progression of Fabry-related cardiomyopathy.

Conclusions

In Fabry patients, disease progression and the degree of organ involvement at the time ERT is initiated are crucial for prognosis and response to therapy. In Fabry disease, the appearance of reduced TDI velocities may be the initial sign of cardiac involvement and occurs before LVH can be detected.

Early institution of ERT with agalsidase alfa appeared to slow the progression of cardiac involvement in Fabry disease. Our data suggest that ERT should be considered at an early stage of the disease to avoid further progression of the cardiac disease.

Author contributions

All authors participated in the study and review of the manuscript and are fully responsible for its content.

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The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology.

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