Improvement of Cardiac Function During Enzyme Replacement Therapy in Patients With Fabry Disease
A Prospective Strain Rate Imaging Study

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Background—Enzyme replacement therapy (ERT) has been shown to enhance microvascular endothelial globo-briaosylceramide clearance in the hearts of patients with Fabry disease. Whether these results can be translated into an improvement of myocardial function has yet to be demonstrated.

Methods and Results—Sixteen patients with Fabry disease who were treated in an open-label study with 1.0 mg/kg body weight of recombinant α-Gal A (agalsidase β, Fabrazyme) were followed up for 12 months. Myocardial function was quantified by ultrasonic strain rate imaging to assess radial and longitudinal myocardial deformation. End-diastolic thickness of the left ventricular posterior wall and myocardial mass (assessed by magnetic resonance imaging, n=10) was measured at baseline and after 12 months of ERT. Data were compared with 16 age-matched healthy controls. At baseline, both peak systolic strain rate and systolic strain were significantly reduced in the radial and longitudinal direction in patients compared with controls. Peak systolic strain rate increased significantly in the posterior wall (radial function) after one year of treatment (baseline, 2.8±0.2 s⁻¹; 12 months, 3.7±0.3 s⁻¹; P<0.05). In addition, end-systolic strain of the posterior wall increased significantly (baseline, 34±3%; 12 months, 45±4%; P<0.05). This enhancement in radial function was accompanied by an improvement in longitudinal function. End-diastolic thickness of the posterior wall decreased significantly after 12 months of treatment (baseline, 13.8±0.6 mm; 12 months, 11.8±0.6 mm; P<0.05). In parallel, myocardial mass decreased significantly from 201±18 to 180±21 g (P<0.05).

Conclusions—These results suggest that ERT can decrease left ventricular hypertrophy and improve regional myocardial function. (Circulation. 2003;108:1299-1301.)

Key Words: Fabry disease ■ enzymes ■ hypertrophy ■ imaging

Fabry disease is an X-linked lysosomal storage disorder caused by a deficiency of the enzyme α-galactosidase (α-Gal A). The enzymatic deficit results in progressive intracellular accumulation of glycosphingolipids (mainly globo-briaosylceramide) in different tissues. Cardiac involvement is frequent, with left ventricular (LV) hypertrophy as the most common finding. A variety of cardiac symptoms, including angina pectoris, arrhythmias, and progressive dyspnea, typically occur late in the course of the disease, and many patients die from heart failure.¹

Recently, a new therapeutic approach of enzyme replacement therapy (ERT) with recombinant α-Gal A was introduced.²⁻³ First clinical studies have shown that ERT cleared microvascular deposits of globo-briaosylceramide from the kidneys, the skin, and the heart.² Whether ERT can prevent the progression of LV hypertrophy and, in parallel, improve myocardial function is not known.

Echocardiographic measurements of global LV function such as ejection fraction (EF) are not sensitive enough to detect impaired myocardial function.⁴ Strain rate imaging, a new technique based on ultrasonic Doppler myocardial imaging, quantifies changes in regional myocardial deformation very precisely.⁵ A recent report has shown that Doppler myocardial imaging can detect reduced myocardial function even before LV hypertrophy in patients with Fabry disease occurs.⁴

Thus, in the present study, we sought to determine whether ERT can reduce myocardial hypertrophy and whether strain rate imaging can detect an improvement of myocardial function after 12 months of therapy.
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A period of 12 months. All patients underwent bicycle stress tests and
were used. CDMI data were analyzed using dedicated software
radial function of the posterior wall, parasternal long-axis views
longitudinal function (GE Vingmed Vivid V; 3.5 MHz). To assess
ventricular septum and the LV lateral, inferior, and anterior walls
Real-time 2-dimensional CDMI data were recorded from the inter-
deceleration time (DT), and isovolumetric relaxation time (IVRT).

extract the ratio of early to late diastolic flow velocity (E/A),

Age*/

Study Protocol
α-Gal A (agalasidase beta; Fabrazyme, Genzyme) was given at a dosage
1 mg per kilogram of body weight intravenously every 2 weeks for
6 Longitudinal strain rates in the basal, mid,

Radial function of the posterior wall, parasternal long-axis views

LV end-diastolic thickness of the posterior wall was measured using
standard M-mode echocardiographic methods from parasternal long-
axis views. EF was calculated using the modified Simpson method.

A value of \( P<0.05 \) was considered to indicate significance.

Results
The baseline characteristics of the Fabry patients are presented in
the Table. The major clinical limitation at study entry and after
1 year of ERT was acroparesthesias. Exercise capacity (bicycle
stress) did not change during ERT (1.3±0.1 versus 1.3±0.1
W/kg body weight, baseline versus 12 months).

Standard Echocardiographic Measurements
LV end-diastolic thickness of the posterior wall was measured using
standard M-mode echocardiographic methods from parasternal long-
axis views, EF was calculated using the modified Simpson method.
Blood pool pulsed Doppler of the mitral valve inflow was used to
extract the ratio of early to late diastolic flow velocity (E/A),
deceleration time (DT), and isovolumetric relaxation time (IVRT).

Color Doppler Myocardial Imaging
Real-time 2-dimensional CDMI data were recorded from the inter-
ventricular septum and the LV lateral, inferior, and anterior walls
using standard apical 4-chamber and 2-chamber views to evaluate
longitudinal function (GE Vingmed Vivid V; 3.5 MHz). To assess
radial function of the posterior wall, parasternal long-axis views
were used. CDMI data were analyzed using dedicated software
(TVI, GE Ultrasound). Longitudinal strain rates in the basal, mid,
and apical segments of each wall and radial strain rates of the
posterior wall were estimated by measuring the spatial velocity
gradient. Strain rate profiles were averaged over 3 consecutive
cardiac cycles and integrated over time to derive natural strain
profiles using end-diastole as the reference point (Speqle). From the
resulting strain rate and strain curves, peak systolic strain rate
(SR\(_{SYS}\)) and systolic strain (\(\epsilon_{SYS}\)) were measured. Data for longitudi-

Magnetic Resonance Imaging
Cine-MRI was performed in 10 patients with Fabry disease. Analysis
of LV mass was performed by manual segmentation of the endocar-
dial and epicardial borders of the end-diastolic and end-systolic
frame as previously described.

Statistics
Data are presented as mean±SEM. Differences between controls and
patients with Fabry disease were tested using two-tailed, unpaired
Student’s \( t \) test. For the comparison between baseline and follow-up,
two-way analysis of variance for repeated measurements was per-
formed. A value of \( P<0.05 \) was considered to indicate significance.

Methods
Study Population
Sixteen patients (42±3 years of age) with genetically confirmed Fabry
disease were included in a nonrandomized, open-labeled prospective
study (Table). In addition, none of the Fabry patients was receiving ERT
at study entry. Clinical symptoms of cardiac involvement are listed in
the Table. The data from the Fabry group were compared with those
from 16 age-matched healthy controls. The investigation conformed
with the principles outlined in the Declaration of Helsinki, and informed
consent was obtained from the patients.

Study Protocol
α-Gal A (agalasidase beta; Fabrazyme, Genzyme) was given at a dosage
of 1 mg per kilogram of body weight intravenously every 2 weeks for
a period of 12 months. All patients underwent bicycle stress tests and
standard echocardiographic and color Doppler myocardial imaging
(CDMI) studies at baseline, 6 months, and 12 months.

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<th>Family</th>
<th>Genotype</th>
<th>Exon/Intron Location</th>
<th>Enzyme Activity(*)</th>
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AH indicates arterial hypertension; AP, angina pectoris; and LVH, left ventricular hypertrophy.
\*Age at diagnosis, given in years.
†Enzyme activity in nmol/min per milligram protein.
treatment, the wall thickness decreased significantly to 11.8±0.6 mm (P<0.05). In Fabry patients, myocardial mass at study entry (n=10) averaged 201±18 g and decreased significantly after 12 months of ERT by 10% (180±21 g; P<0.05).

Radial Function
In the Fabry group, radial SR_SYS averaged 2.8±0.2 s⁻¹ and ε_SYS averaged 34±3%. These measurements were significantly lower as compared with controls (SR_SYS=4.1±0.1 s⁻¹, ε_SYS=60±3%; P<0.001 versus Fabry). After 6 months of treatment, SR_SYS and ε_SYS tended to increase, and after 12 months, the two parameters were significantly higher compared with baseline measurements (SR_SYS=3.7±0.3 s⁻¹, ε_SYS=45±4%; P<0.05 versus baseline) (Figure).

Longitudinal Function
As for radial function, longitudinal SR_SYS and εSYS in patients were significantly lower than in controls (Fabry: SR_SYS=1.1±0.1 s⁻¹, εSYS=13.4±0.7%; controls: SR_SYS=1.7±0.1 s⁻¹, εSYS=24.3±0.6%; P<0.001 versus Fabry). After 6 months of ERT, both parameters tended to increase, and after 12 months, SR_SYS and εSYS were significantly higher than at baseline (SR_SYS=1.4±0.1 s⁻¹, εSYS=17.2±0.6%; P<0.05 versus baseline).

Discussion
The safety and effectiveness of ERT have been well documented for Gaucher’s disease. This prospective study evaluates the impact of ERT in a second lysosomal disorder, Fabry disease. The presented data show for the first time that 12 months of ERT in these patients resulted in a combined morphological and functional cardiac improvement.

ERT in Fabry Disease
Safety of ERT was documented in two preclinical studies. Furthermore, Eng et al demonstrated in a placebo-controlled, double-blind study that ERT resulted in a histological clearance of the deposits of globotriaosylceramide in cardiomyocytes. Our study suggests that this clearance of globotriaosylceramide due to ERT leads to a regression of LV hypertrophy, which was documented by echocardiography and confirmed by MRI. The fact that QRS-complex duration decreases with ERT suggests that in addition to morphological changes, functional changes also occur. The present study demonstrates that both radial and longitudinal function of the LV improve after 12 months of treatment. Notably, the documented improvement of myocardial function was more pronounced in the last 6 months of ERT.

These findings parallel the histological observation that in contrast to other tissue (kidney and skin), the maximal clearance for globotriaosylceramide in the cardiomyocytes extends 6 months of therapy. Because many patients die from heart failure, improvement of myocardial function should be the primary cardiac aim when doing ERT. Nevertheless, we could not demonstrate that diastolic function and exercise capacity improved during ERT.

Assessment of Myocardial Function
In Fabry patients, LVEF as parameter of global ventricular function was normal at study entry. This is in accordance with many other studies showing that conventional measurements of global LV function are not sensitive enough to detect impaired myocardial function. A recent study using Doppler myocardial imaging showed that myocardial velocities are reduced in hypertrophic and even in nonhypertrophic segments. In the present study, strain rate imaging as a more sensitive method was used to quantify regional myocardial function. When compared with myocardial velocities, strain rate imaging has been shown to be less influenced by overall cardiac motion and tethering effects. Because it is known that SR_SYS is more related to regional contractility and εSYS more to stroke volume, these data suggest that ERT has an impact on both of these cardiac performance indices. In particular, the increase of SR_SYS confirms the improvement of inotropic function, as this parameter is more independent from myocardial wall thickness. In contrast, the increase in systolic deformation (strain) is necessary to maintain the same ejection fraction in the presence of reduced LV wall thickness. Thus, the increase of strain does not necessarily represent an increase in inotropy.

Conclusions
ERT in Fabry patients resulted in a decrease of LV hypertrophy associated with an improvement of LV function. This therapy concept appears to be a promising treatment approach in advanced stages of Fabry disease.

References
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