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# Effects of enzyme replacement therapy in adult patients with Fabry disease on cardiac structure and function: a retrospective cohort study of the Fabry Münster Study (FaMüS) data

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## ABSTRACT

**Objective:** Fabry disease (FD) is an X-linked inborn error of glycosphingolipid catabolism caused by deficient lysosomal α-galactosidase A activity. Progressive accumulation of globotriaosylceramide and related glycosphingolipids in vascular endothelial lysosomes of the heart, kidneys and brain is responsible for the main disease manifestations. The aim of our study was to assess short-term and long-term effects of enzyme replacement therapy (ERT) on cardiac mass and function.

**Design:** Retrospective cohort study.

**Setting:** Hospital outpatient clinic.

**Participants:** 40 FD patients (21 men, 19 women) receiving agalsidase β-ERT.

**Outcome measures:** The focus at baseline and follow-up examinations was on structural, functional (Doppler-echocardiography) as well as electrical changes (ECG) and blood pressure.

**Results:** In the Early Group, systolic and diastolic blood pressures significantly decreased. Left-ventricular (LV) also decreased; however, wall thickness and LV mass index showed no further increase. VE as an indicator for diastolic function significantly improved (64±21 vs 75±27 cm/s, p=0.038). There were no significant changes of ECG parameters. There were few relevant changes in the Late Group, albeit systolic blood pressure significantly decreased and QRS duration significantly increased. In conclusion, echocardiographic left-ventricular mass index, interventricular septum thickness, left-ventricular posterior wall, left-ventricular end-diastolic dimension) and diastolic function parameters are valuable for follow-up and guidance of therapy.

**Conclusions:** The primary positive impact of ERT appears to be an early effect after the start of therapy, and early initiation of ERT should be recommended.

## ARTICLE SUMMARY

### Article focus

- Assessment of short-term and long-term effects of enzyme replacement therapy on cardiac structure and function in patients with Morbus Fabry.
- Assessment of long-term cardiovascular changes in patients with Morbus Fabry without enzyme replacement therapy.

### Key messages

- Early initiation of enzyme replacement therapy stops/reduces cardiovascular changes in patients with Morbus Fabry.
- Late initiation of enzyme replacement therapy does hardly result in significant cardiovascular changes in patients with Morbus Fabry.
- Cardiac hypertrophy develops early in the course of Morbus Fabry, thus enzyme replacement therapy should be initiated as early as possible.

### Strengths and limitations of this study

- Relatively large cohort study, long follow-up.
- Retrospective cohort study.

## INTRODUCTION

Morbus Fabry-Anderson disease (FD) is an X-chromosome-linked (Xq22.1) lysosomal storage disorder caused by the deficiency of α-galactosidase A, resulting in aberrant glycosphingolipid metabolism and accumulation of globotriaosylceramide (Gb3).[1–4] This progressive accumulation causes remarkable clinical consequences, mainly related to the involvement of vascular endothelial cells of the kidney, the brain and especially the heart.[5] FD is a multiorgan disease with severe effects on cardiac, renal, cerebrovascular, ocular and neural function.[3 5 6] Registry data suggests cardiac involvement is associated with increased morbidity.[7] Enzyme replacement therapy (ERT) with recombinant α-galactosidase appears to be one of the most effective current therapies for FD. The replacement of missing or insufficient

α-galactosidase in patients with FD might be a strategy to handle symptoms and overcome the enzyme deficiency in patients. Treatment with infusions of recombinant enzyme preparations aims to attenuate accumulation of the major enzyme substrate globotriaosylceramide (Gb3), particularly from capillary endothelial cells of the heart, kidney and skin.[8–13] The heart and cardiovascular system are severely affected structures in FD; left-ventricular hypertrophy, arrhythmias, ischaemia, cardiomyopathy or disturbance of electrical conduction are typical manifestations in most cases.[14–17] First signs of FD can appear in early childhood, or during adulthood, and often include acroparasthesia, angiokeratomas and/or hypohidrosis.[5] Women can be affected to a similar degree to men, but the onset of disease tends to be later and progression slower.[4 18–20] In this retrospective study, we focused on cardiac involvement and improvement under ERT. The aims of this study were to determine short-term and long-term effects of ERT on cardiac structure and function in Fabry patients of the Fabry Münster Study (FaMüS) cohort, to identify potential gender-related differences in this group, and to prove the importance of echocardiographic parameters in diagnosis and therapeutic decision-making.

## MATERIALS AND METHODS

### Study population and patient groups

FD patients from the Fabry outpatient clinic of the University Hospital of Münster between July 2001 and January 2009, matching the inclusion criteria (genetically proven FD and existing echocardiographic examination) were retrospectively included in this study. Exclusion criteria were patients without genetically proven FD or without echocardiographic examination. Group definitions: the Early Group (E0–E3) comprised 23 FD patients (11 men, 12 women), 22 treated with Fabrazyme (Genzyme GmbH, a Sanofi company, Neu Isenburg, Germany) and one with Replagal in their first 3 years of ERT after initial diagnosis of FD. The Late Group (E3-Late–E7) comprised 17 FD patients (10 men, seven women), 15 treated with Fabrazyme and two with Replagal, from a baseline examination in their first 3 years of ERT to a follow-up examination, which was performed during years 4–7 after starting ERT.

E0: Baseline examination of the Early Group before ERT.

E3: Follow-up examination of the Early Group in the first 3 years after beginning ERT.

E3-Late: examination in the first 3 years after beginning ERT as baseline examination of the Late Group.

E7: Follow-up examination of the Late Group in years 4–7 after beginning ERT.

A second cohort of FD patients, also from the Fabry outpatient clinic of the University Hospital of Münster, not undergoing ERT, who have partly been examined only once, was included before beginning ERT to check for age-dependent changes in patients with FD independent of ERT.

Informed written consent was obtained from all patients.

### Standard Doppler-echocardiographic examination

Doppler-echocardiographic studies were performed using clinical standard echocardiography platforms (General Electrics Vivid 7 (GE HealthcareGmbH, Solingen, Germany), Philips IE 33 (Philips Healthcare, Hamburg, Germany)) by a small number of experienced residents and consultants at the Department of Cardiology and Angiology of the University Hospital of Münster. Examinations were performed according to current guidelines of the American Society of Echocardiography. End-diastolic interventricular septum thickness (IVS), end-diastolic thickness of the posterior wall (LVPW), and left-ventricular end-diastolic and end-systolic dimensions (LVEDD and LVESD) were measured in a B-mode guided M-mode (parasternal long axis). PW Doppler of the mitral inflow was used to measure the ratio of the early-to-late diastolic flow velocity (E/A ratio); ejection fraction (EF) was calculated using standard formulae. Echocardiographic myocardial mass was calculated with the Penn-Cube formula[21] and indexed to the body surface area:

$$\text{LV mass index (LVMI)} = (1.04^{*}((\text{IVS} + \text{LVEDD} + \text{LVPW})^{3} - \text{LVEDD}^{3}) - 13.6)/\text{BSA}.$$

### Electrocardiogram

Standard 12-channel ECG for the measurement of PQ time, QRS time and Sokolow-Lyon index were digitally recorded using clinical electrocardiography platforms and analysed automatically. Analyses were controlled by experienced clinicians.

### Statistical analysis

Statistical analysis was performed using SPSS release V.16.0 (SPSS, Inc, Chicago, Illinois, USA) and graphics were generated using Microsoft Works Excel 2003 (Microsoft Corp., Redmond, Washington DC, USA). Continuous variables are presented as mean±SD. Before statistical testing, each continuous variable was analysed for normal distribution (Kolmogorov-Smirnov test). The Wilcoxon test was used for the comparison of non-parametric variables between dependent study groups. The Mann-Whitney U test was used for the comparison of nonparametric variables between independent study groups. The Kruskal-Wallis test was used for overall statistical analysis in the age-dependent separated cohort. Statistical significance was defined as $p<0.05$.

## RESULTS

Twenty-three patients were assigned to the Early Group. The mean age of the patients in this group was

45.6±11.6 years, and the mean time receiving ERT was 1.7±0.8 years. Seventeen patients could be assigned to the Late Group. The mean age of these patients was 50.2±17.9 years and the mean time receiving ERT was 2.8±0.8 years at E3-Late and 5.9±1.2 years at E7. Mean age was not significantly different between the Early and Late Groups. All but one patient had LVH at the point of inclusion in the study. Eight of the patients could be assigned to both Early and Late Groups. In the Early Group, 17 patients had missense mutations and six had non-sense mutations. In the Late Group, 13 patients had missense mutations and four had nonsense mutations. Relation of missense and nonsense mutations was not significantly different between Early and Late Groups. Patients were followed up for a maximum of 7 years. Measurements could be obtained in adequate quality in all patients.

In the Early Group, systolic and diastolic blood pressures significantly decreased within the initial year of ERT (128±16 vs 121±12, and 84±8 vs 79±7 mm Hg, p=0.02 and 0.04, table 1). LVESD significantly decreased (3.1±0.6 vs 2.8±0.5 cm, p=0.036), and there was a trend for decreased LVEDD values (4.9±0.5 vs 4.68±0.7 cm, p=0.056). Wall thickness did not change. The EF always stayed within the normal range. The velocity of the E-wave significantly increased (64±21 vs 75±27 cm/s, p=0.038), indicating improved diastolic function after years of ERT. No significant changes were found when comparing male patients to female patients.

In the Late Group, only systolic blood pressure significantly decreased (125±13 vs 114±14 mm Hg, p=0.045). Diameters of the left ventricle and wall thickness remained stable within the period of examination. QRS duration significantly increased (111±38 vs 118±37 ms, p=0.008) and PQ time tended to increase (128±23 vs 142±33 ms, p=0.063), albeit not significantly. No significant gender-specific differences were found when comparing male to female.

For the second cohort, 67 patients (24 men, 43 women, figure 1), mean age at diagnosis 43±16 years (men 35±13 years; women 49±16 years), were included. They were divided into four different age groups to assess the age-dependent progress of cardiovascular changes without the influence of ERT as follows: group 1, <21 years (nine patients: five men, four women); group 2, 21–40 years (22 patients: 13 men, nine women); group 3, 41–60 years (24 patients: five men, 19 women); group 4, >60 years (12 patients: one man, 11 women).

There was a progressive and considerable increase in IVS thickness with age (group 1 (n=8), 1.0±0.1 cm; group 2 (n=22), 1.1±0.2 cm; group 3 (n=22), 1.3±0.3 cm; group 4 (n=12), 1.7±0.6 cm, figure 1). Left-ventricular mass index also progressively increased with age (<21 years (n=8) 115±40 g/m$^2$; 21–40 years (n=18) 117±33 g/m$^2$; 41–60 years (n=20) 154±43 g/m$^2$; >60 years (n=11) 213±98 g/m$^2$, figure 1). The difference between groups 2 and 3 was highly significant (p=0.01 for both values); overall significance (Kruskal-Wallis test): IVS p=0.001, LVMI p=0.001 (figure 1). IVS thickness exceeded normal values in the 21–40 years age group. LVMI exceeded normal values, even in the youngest group, and continuously increased.

## DISCUSSION

The aim of this retrospective study was to show the short-term and long-term effects of ERT in FD patients of our FaMüS cohort. Furthermore, the clinical value of echocardiographic parameters in diagnosis and therapy control was assessed. In our study, ERT led to a significant reduction of systolic and diastolic blood pressures and LV diameters in the Early Group, while wall thickness and LV mass index did not increase further. VE as an indicator of diastolic function significantly improved. There were no clinically relevant changes in the Late Group.

**Table 1** Echo and ECG parameters (mean±SD)

| | Early Group | | | | Late Group | | | |
|---|---|---|---|---|---|---|---|---|
| | n | E0 | E3 | P | n | E3-Late | E7 | p |
| Blood pressure syst (mm Hg) | 23 | 128 ± 16 | 121 ± 12 | 0.02 | 17 | 125 ± 13 | 114 ± 14 | 0.045 |
| Blood pressure diast (mm Hg) | 23 | 84 ± 8 | 79 ± 7 | 0.044 | 17 | 79 ± 8 | 77 ± 8 | n.s. |
| LVEDD (cm) | 17 | 4.9 ± 0.5 | 4.6 ± 0.7 | 0.056 | 16 | 4.6 ± 0.4 | 4.6 ± 0.7 | n.s. |
| LVESD (cm) | 17 | 3.1 ± 0.6 | 2.8 ± 0.5 | 0.036 | 16 | 3.0 ± 0.6 | 2.9 ± 0.5 | n.s. |
| IVS (cm) | 18 | 1.4 ± 0.4 | 1.4 ± 0.4 | ns | 16 | 1.5 ± 0.4 | 1.5 ± 0.4 | n.s. |
| LVPW (cm) | 15 | 1.4 ± 0.3 | 1.4 ± 0.3 | ns | 16 | 1.4 ± 0.4 | 1.4 ± 0.3 | n.s. |
| LVMI (g/m$^2$) | 15 | 179 ± 69 | 167 ± 57 | ns | 15 | 185 ± 78 | 198 ± 80 | n.s. |
| LV-EF (%) | 17 | 68 ± 8 | 64 ± 6 | 0.049 | 14 | 59 ± 9 | 58 ± 10 | n.s. |
| VE (cm/s) | 15 | 64 ± 21 | 75 ± 27 | 0.038 | 14 | 73 ± 18 | 80 ± 12 | n.s. |
| VA (cm/s) | 13 | 56 ± 24 | 51 ± 21 | ns | 12 | 61 ± 12 | 60 ± 19 | n.s. |
| E/A ratio | 13 | 1.4 ± 0.9 | 1.6 ± 0.6 | 0.066 | 12 | 1.2 ± 0.5 | 1.5 ± 0.6 | n.s. |
| PQ-time (ms) | 14 | 143 ± 43 | 137 ± 37 | ns | 9 | 128 ± 23 | 142 ± 33 | 0.063 |
| QRS-time (ms) | 15 | 110 ± 33 | 109 ± 24 | ns | 9 | 111 ± 38 | 118 ± 37 | 0.008 |
| Sokolow-Lyon-index (mV) | 8 | 3.2 ± 1.5 | 2.9 ± 1.2 | ns | 7 | 3.0 ± 1.1 | 3.0 ± 1.1 | n.s. |

IVS, interventricular septum thickness; LVEDD, left-ventricular end-diastolic dimension; LV-EF, left-ventricular-ejection fraction; LVESD, left-ventricular end-systolic dimension; LVMI, left-ventricular mass index; LVPW, left-ventricular posterior wall; ns, not significant.

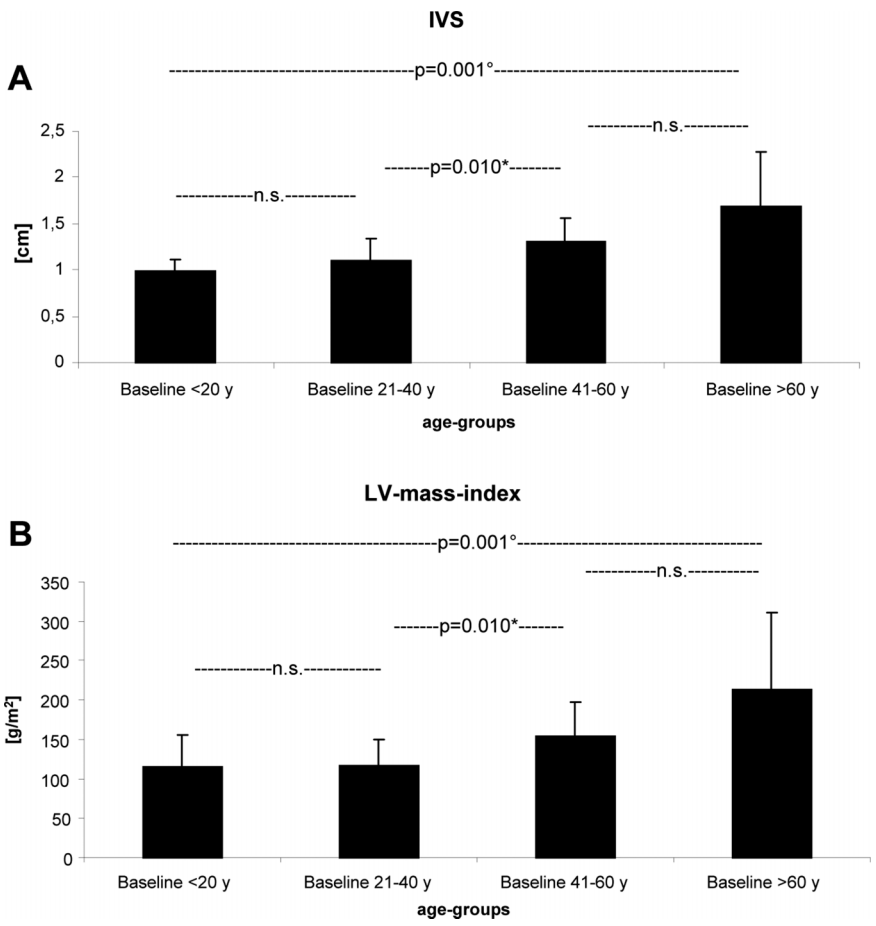


**Figure 1** Interventricular septum thickness and left-ventricular mass index dependent on age.

Systolic and diastolic blood pressures significantly decreased in the Early Group; in the Late Group, only the systolic blood pressure significantly decreased. These results are comparable with those of other studies in which a modulation of ACE activity by γ-galactosidase A, leading to decreased blood pressure levels, is suggested.[22 23]

In our cohort, wall thickness was stable in both Early and Late Group. These results are in agreement with the findings of Koskenvuo *et al*[24] and Kovacevic-Preradovic *et al*,[25] who also did not observe a decreased wall thickness. Other studies were able to identify a significant decrease in the wall thickness during ERT.[26 27] The difference between the results of Imbriaco *et al*[27] and Koskenvuo *et al*[24] might be explained by the younger mean age of the former study's patient cohort (35 years (Imbriaco) vs 41 years (Koskenvuo) vs 46 (EG) and 50 (LG) years (our population)).

LVMI tended to decrease in the Early Group, albeit not significantly (p=0.173). This is consistent with other studies showing a (significant) reduction of LV hypertrophy.[23 27–30] Regarding these findings, Eng *et al*[11] could demonstrate a histological clearance of Gb3 in myocardial endothelial cells. Therefore, other authors suggested that the clearance of Gb3 deposits induces a regression of LV hypertrophy.[29] By contrast, the Late Group showed a trend towards an increase in the LVMI, which was not significant (p=0.125). Hypertension could not have caused this process or the observed cardiac hypertrophy at the initial status, considering the normal blood pressure of the FD patients (table 1).[23 31] Mehta *et al*[23] demonstrated a slowing down of regression of LVMI during ERT from year-2-to-year-5 of therapy, which is consistent with the results of our Early and Late Groups. The increase in the LVMI in the Late Group in comparison to the results of Mehta *et al* could be explained by the higher age of our cohort (50 years) and by the longer duration of therapy, which may indicate a decrease of therapy impact with regard to the late therapy process.

LV diameters decreased in the Early Group, indicating improved systolic function, whereas they did not change in the Late Group. Spinelli *et al*[26] could not find any significant changes regarding LV internal diameters.

In the Early Group, the velocity of the early inflow into the LV significantly increased, indicating improved diastolic function. Toro *et al*[32] demonstrated that FD patients exhibited a reduction in VE velocity compared with that of normal control subjects. Therefore, velocity parameters should have particular significance, because they seem to have positive effects on FD-typical low contraction and relaxation Doppler velocities, as described in other studies.[32 33] There was no significant change in the Late Group.

QRS duration significantly, and PQ duration insignificantly, increased in the Late Group. ECG parameters did not change significantly in the Early Group. The significant increase of QRS duration in the Late Group could be due to a further accumulation of substrate in myocardial cells.[34]

The second cohort showed that diagnosis of FD was established more than 10 years later in women than in men (p=0.001). These results are consistent with the literature.[4] The majority of female patients were older (40–60 years) when diagnosed with FD than male patients, who were commonly diagnosed at the age of 30–40 years. Progression of LVMI and wall thickness mainly took place between age groups 2 and 3. Thus, it might be preferable to stop this progress in the early years following diagnosis by starting ERT early. Corresponding recommendations have been published by other authors.[30 35 36] Our results are in line with the findings of other authors who demonstrated a strong correlation between age and left-ventricular mass index and further growth of the LVMI relative to age with no influence of ERT.[36]

In the later stages of ERT (Late Group), the initial major benefit is barely noticeable. These results agree with the results of the analysis of large multinational observational databases by Mehta *et al*[23] Regarding different parameters, this study demonstrated that the improvement observed during the initial years of ERT decreased over time. This is in agreement with our findings. It remains questionable whether this advantageous effect in the initial years of ERT can be extended by an increase in the dosage of enzyme infusions in later years of therapy, or if this procedure will lead to no further recoveries or improvements.

## LIMITATIONS

Most of our patients were treated with Fabrazyme, with only a few receiving Replagal. In order to increase the number of patients, we pooled patients independent of the ERT used. However, exclusion of the patients on Replagal did not significantly change the results of statistical analyses. Owing to the retrospective nature of this study, some data are missing in some patients. For some values, there are relatively clear trends that did not reach significance; this is probably due to the relatively small sample size.

## CONCLUSION AND OUTLOOK

Echocardiographic parameters are valuable for follow-up and guidance of therapy before and during ERT in FD patients. Early treatment with ERT is recommended to prevent further cardiovascular deterioration. The primary positive impact of ERT seems to be an early effect after the start of therapy; during further ERT treatment, the initial major benefit seems to be lost and improvements slow down. Concentration of the few FD patients in FD centres is necessary to increase knowledge and to allow treatment of these patients according to the latest available level of knowledge.[17 37] Besides ERT, gene transfer could become a promising alternative treatment strategy in the future.[38 39]

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