Clinical research

The variation of morphological and functional cardiac manifestation in Fabry disease: potential implications for the time course of the disease

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Received 24 June 2004; revised 17 December 2004; accepted 23 December 2004; online publish-ahead-of-print 23 February 2005

Aims The aim of this clinical cross-sectional study was to investigate the cardiac inter-relation of morphological and functional abnormalities in patients with Fabry disease.

Methods and results Fifty-one patients (5–78 years) were compared with 25 controls (8–77 years). In all subjects, end-diastolic thickness of the left ventricle was measured by echocardiography and ultrasonic peak systolic strain rate (SR) was extracted to assess regional myocardial function. Magnetic resonance imaging was performed to assess late-enhancement for the detection of myocardial fibrosis in Fabry patients (n = 39). In patients, women <20 years of age had no hypertrophy, no late-enhancement, and normal radial and longitudinal function (SR longitudinal = −1.7 ± 0.5 s⁻¹; P = n.s. compared with controls). Ten women, >20 years of age, had no hypertrophy, no late-enhancement, normal radial and longitudinal function in the septal wall, but reduced longitudinal function in the lateral wall (SR = −1.4 ± 0.5 s⁻¹). All male patients without hypertrophy and no late-enhancement had normal radial function but reduced longitudinal function in both the septal and lateral walls (SR = −1.3 ± 0.3 s⁻¹). Patients with hypertrophy but without late-enhancement (n = 13) had reduced radial and longitudinal function. Twelve patients displaying hypertrophy and late-enhancement had severely reduced radial and longitudinal function (SR = −1.1 ± 0.5 s⁻¹). Two of them with the worst impairment of regional function (SR = −0.8 ± 0.6 s⁻¹) died in the follow-up period.

Conclusion These results illustrate the variation of morphological changes and its functional consequences in Fabry cardiomyopathy.

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Introduction

Fabry disease is an X-linked lysosomal storage disorder caused by α-galactosidase (α-GalA) deficiency. The enzymatic deficit results in progressive intracellular accumulation of glycosphingolipids (mainly globotriaosylceramide) in different tissues. Cardiac involvement is frequent, with left ventricular (LV) hypertrophy as the most common finding. In addition, histological and clinical studies suggest that some of these patients have focal LV fibrosis. Despite normal global LV function, regional myocardial function is impaired in both male and female patients and many patients die from heart failure. Thus, using conventional echocardiography it is challenging to recognize the cardiac involvement of the disease. The evaluation of the individual cardiac involvement in patients with Fabry disease is important as, with enzyme replacement therapy, specific therapeutic strategies are now available. One remaining clinical question concerns the early assessment of cardiac involvement, which might require specific therapy.

To date, cardiac studies in patients with Fabry disease were done either with relatively small patient samples or by focusing on details of either morphological or functional abnormalities. The aim of this cross-sectional study was to describe comprehensively morphological and functional cardiac abnormalities in a larger group of Fabry patients across a wide age range. Using this information, an algorithm is proposed to classify the individual cardiac involvement and the potential implications for the progression of the disease.

Methods

Study population

Fifty-one patients with genetically (n = 50) or biopsy (n = 1) confirmed Fabry disease were included in the study. None of the Fabry patients had received enzyme replacement therapy prior to study entry. A subgroup of 16 patients received enzyme replacement therapy afterwards and their echocardiographic baseline data have already been published. The Fabry group was compared with 25 healthy controls recruited from hospital staff and their relatives. Care was taken to recruit controls from similar age ranges (+/-5 years) and to include the same proportion of females as in patients (Table 1).

Echocardiography and magnetic resonance imaging (MRI) studies were performed on the same day. In three patients on haemodialysis, both imaging studies were performed on the day of the study. In addition, histological and clinical studies suggest that some of these patients have focal LV fibrosis. Despite normal global LV function, regional myocardial function is impaired in both male and female patients and many patients die from heart failure. Thus, using conventional echocardiography it is challenging to recognize the cardiac involvement of the disease. The evaluation of the individual cardiac involvement in patients with Fabry disease is important as, with enzyme replacement therapy, specific therapeutic strategies are now available. One remaining clinical question concerns the early assessment of cardiac involvement, which might require specific therapy.

To date, cardiac studies in patients with Fabry disease were done either with relatively small patient samples or by focusing on details of either morphological or functional abnormalities. The aim of this cross-sectional study was to describe comprehensively morphological and functional cardiac abnormalities in a larger group of Fabry patients across a wide age range. Using this information, an algorithm is proposed to classify the individual cardiac involvement and the potential implications for the progression of the disease.

Standard echocardiographic measurements

LV end-diastolic (LVEDD) and LV end-systolic dimensions (LVESD) and end-diastolic thickness of the inferolateral wall (WT) were measured using standard M-mode echocardiographic methods from parasternal LV long axis images. LV fractional shortening (FS) was calculated from the LV end-diastolic and end-systolic diameters. The end-diastolic wall thickness was corrected for body surface area. Blood pool pulsed Doppler traces of the mitral valve inflow were used to extract the early diastolic flow velocity (E).

MRI

Cine-MRI was carried out in 39 patients with Fabry disease. The remaining 12 patients could not be examined because of claustrophobia, missing consent, or other specific contraindications for MRI. Analysis of LV ejection fraction (EF) was performed by manual segmentation of the endocardial and epicardial borders of the end-diastolic and end-systolic frame as previously described. The late enhancement technique (8 mm slice thickness, breathhold, short and long heart axis) was applied to detect changes of tissue integrity in LV myocardium. Images were acquired 10–15 min after the injection of gadopentetate dimeglumine (Magnevist, Schering, Berlin, Germany; 0.2 mmol/kg of body weight) by using an inversion recovery sequence (field of view 240 × 320 mm²; matrix 165 × 256).

Colour doppler myocardial imaging for regional ventricular function

Real time two-dimensional colour Doppler myocardial imaging (CDMI) data were recorded from the interventricular septum, the LV lateral and the right ventricular (RV) free wall using a standard apical four-chamber view to evaluate longitudinal function (i.e. myocardial thinning in systole and thickening in diastole) (GE Vingmed Vivid V, Horten, Norway; 2.5 MHz). To assess radial function of the inferolateral wall (=myocardial thickening in systole and thinning in diastole), parasternal long axis views were used. CDMI data were analysed using dedicated software as previously described (TVi®, GE Ultrasound). Longitudinal strain rates in the basal, mid, and apical segments of each wall and radial strain rates of the inferolateral wall were estimated by measuring the spatial velocity gradient. Strain rate profiles were averaged over three consecutive cardiac cycles and integrated over time to derive natural strain profiles using end-diastole as the reference point (Spoele®, K.U. Leuven, Belgium). From the resulting strain rate and strain curves, peak systolic strain rate (SR) and systolic strain (ε) were measured. Data for longitudinal function are presented as the mean of the interrogated wall. In addition, the early diastolic
velocity of the mitral annulus ($E_a$) was extracted to assess the early diastolic transmitral velocity/mitral annular velocity ratio ($E/E_a$). The intra-observer variability (expressed in per cent of the mean) for this method was recently published and averaged 10% for $E$ and 11% for $E_a$.

**Data analysis**

Data are presented as mean ± standard deviation. The relation between regional strain rate or strain and end-diastolic wall thickness was described using the Spearman correlation coefficient. Since Fabry disease is a sex-related disorder and functional and morphological abnormalities are expected to vary with time of exposure, all comparisons between controls and Fabry patients were made using a linear regression model with fixed adjustment for sex and age. The assumption of normality and constant variance was checked by inspection of residual plots, and log-normalized data were used in case of violation. No further adjustments were made to the significance level due to the exploratory nature of the study. Within patients, predictors for presence of myocardial fibrosis (i.e. late enhancement) were sought by logistic regression analysis using age, sex, hypertrophy, and posterior strain and strain rate as independent variables, and odds ratios (OR) and 95% confidence intervals (CI) are reported.

**Results**

Fifty-one patients with Fabry disease were included in the study. The mean age was 44 ± 14 years (range 5–78 years) and 25 were female. Three patients (all females) had predominant cardiac involvement (cardiac variant). From the complete patient cohort, 31 patients (61%) showed the typical clinical symptoms of acroparaesthesia (61%) and 30 patients had renal disease (59%). The major cardiac symptom was dyspnoea. Clinical symptoms of cardiac involvement are listed in Table 1.

**Standard echocardiographic measurements**

The LVEDD and LVESD did not differ between patients (LVEDD = 47.4 ± 6.1 mm, LVESD = 28.7 ± 6.3 mm) and controls (LVEDD = 47.0 ± 5.0 mm, LVESD = 28.7 ± 3.9 mm). The wall thickness was significantly higher in patients when compared with controls (12.2 ± 2.6 vs. 7.5 ± 1.1 mm; $P < 0.001$). According to studies on end-diastolic wall thickness corrected for body surface area, 34 patients were classified as hypertrophic. Fractional shortening as a parameter for global LV function was normal in patients (39.5 ± 10.5%) and in controls (38.6 ± 8.5%). $E/E_a$ increased with incremental wall thickness, indicating abnormal diastolic function. Measurement values of the subgroups are given in Table 2.

**MRI**

Cine-MRI was carried out in 39 patients with Fabry disease. The EF as a marker of global LV systolic function was normal in patients with Fabry disease (EF = 60.9 ± 10.6%). Late enhancement as a marker for fibrotic tissue was detected in 12 patients (2 female and 10 male). In these patients it was restricted to the inferolateral wall, but two of them showed additional late enhancement in antero-septal segments. No late enhancement was detected in the RV. Nine patients had intramural and three patients subepicardial late enhancement. A typical example is shown in Figure 1.

**Regional ventricular function**

**Radial function**

LV radial SR as a parameter for the velocity of systolic thickening of the inferolateral wall was significantly lower in patients when compared with controls (3.0 ± 1.0 vs. 4.2 ± 0.9 s⁻¹; $P < 0.001$) (Figure 2). Consistently, regional radial $e$ as a parameter for the total amount of systolic thickening of the inferolateral wall was also significantly reduced in patients (43.8 ± 15.1 vs. 58.6 ± 12.1%; $P < 0.001$). Both SR ($r = 0.84, P < 0.001$) and $e$ ($r = 0.88, P < 0.001$) showed a close correlation with the end-diastolic wall thickness of the inferolateral wall (Figure 3).

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### Table 2  Baseline characteristics of the Fabry subgroups and controls

<table>
<thead>
<tr>
<th></th>
<th>No LV-Hypertrophy</th>
<th>With LV-Hypertrophy</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Control (n = 25)</td>
<td>LE negative (n = 10)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>39 ± 15 f</td>
<td>31 ± 11 f</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>65 ± 11 f</td>
<td>70 ± 11 f</td>
</tr>
<tr>
<td>LVEDD (mm)</td>
<td>47 ± 5 f</td>
<td>46 ± 4 f</td>
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<tr>
<td>LV PW (mm)</td>
<td>7.5 ± 1.1 f</td>
<td>9.3 ± 1.7 f</td>
</tr>
<tr>
<td>FS (%)</td>
<td>39 ± 10 f</td>
<td>48 ± 11 f</td>
</tr>
<tr>
<td>$E/E_a$</td>
<td>7.0 ± 3.2 f</td>
<td>8.3 ± 3.2 f</td>
</tr>
<tr>
<td>LV EF (%)</td>
<td>65 ± 3 f</td>
<td>56 ± 8 f</td>
</tr>
</tbody>
</table>

bpm, beats per minute; f, female; LV PW, left ventricular posterior wall; FS, fractional shortening; LE, late enhancement; EF, ejection fraction (by MRI and in controls by echocardiography); m = male.

* $P < 0.01$ vs. control.

* $P < 0.05$ within females vs. no LV hypertrophy and LE negative.

* $P < 0.01$ within males vs. no LV hypertrophy and LE negative.
Longitudinal function

LV longitudinal SR as a marker for the velocity of systolic shortening of a segment was significantly reduced in the septal (−1.3 ± 0.3 vs. −1.7 ± 0.4 s⁻¹; P < 0.001) and lateral walls (−1.1 ± 0.5 vs. −1.7 ± 0.5 s⁻¹; P < 0.001) in patients when compared with controls. In addition, in patients LV longitudinal ε as a parameter for the total amount of systolic shortening was also reduced in both walls (septal: −18.4 ± 7.8 vs. −24.9 ± 6.2%; lateral: −13.5 ± 8.2 vs. −23.0 ± 6.7%; P < 0.001). In contrast to the LV, longitudinal SR of the RV was normal (−2.4 ± 0.9 vs. −2.3 ± 0.7 s⁻¹; P = 0.96). In addition, RV longitudinal ε showed no difference between patients and controls (−35.9 ± 13.1 vs. −36.9 ± 11.1%; P = 0.60).

Predictors of late enhancement

All subjects who showed late enhancement also had LV hypertrophy, rendering LV hypertrophy a very strong predictor. Sex (OR 6.67, CI 1.55–31.23, P = 0.010), age per 10 years (OR 4.03, CI 1.69–11.15, P = 0.007), strain rate (OR 0.13, CI 0.03–0.51, P = 0.004), and strain (OR 0.01, CI 0.00–0.03, P = 0.001) were each strong predictors of late enhancement in univariate logistic regression. If these variables were entered into a multivariable logistic model, they explained 84% of the variation of the variable late enhancement (Nagelkerke R² = 0.844).

LV function in subgroups

To classify Fabry patients according to their state of cardiac functional impairment, we used information on sex and morphology criteria (LV hypertrophy and late enhancement). The proposed algorithm is shown in Figure 4. Applying this algorithm to our data, the following results emerged: female patients without LV hypertrophy and no late enhancement (n = 10) showed normal radial function (SR = 4.0 ± 0.6 s⁻¹) and normal septal longitudinal function (SR = −1.5 ± 0.5 s⁻¹) but reduced lateral function (SR = −1.4 ± 0.5 s⁻¹). Male patients without LV hypertrophy and no late enhancement (n = 4) showed normal radial function (SR = 3.9 ± 0.9 s⁻¹) but reduced longitudinal function in both septal (SR = −1.4 ± 0.3 s⁻¹, P = 0.042) and lateral walls (SR = −1.3 ± 0.3 s⁻¹). There was no patient without LV hypertrophy who showed late enhancement. The female patients with LV hypertrophy but no late enhancement (n = 5) had reduced radial (SR = 2.4 ± 0.5 s⁻¹) and also longitudinal function (SR = −1.1 ± 0.3 s⁻¹). Consistently, in males, radial (SR = 3.1 ± 0.6 s⁻¹) and longitudinal function (SR = −1.1 ± 0.4 s⁻¹) was lower in patients with LV hypertrophy but without late enhancement (n = 8) when compared with controls. Only two female patients had LV hypertrophy and were late enhancement positive. These two patients had severely reduced radial (SR = 1.8 ± 0.5 s⁻¹) and longitudinal function (SR = −1.2 ± 0.3 s⁻¹). Similarly, male patients with LV hypertrophy and late enhancement (n = 10) had severely reduced radial (SR = 2.1 ± 0.7 s⁻¹) and longitudinal function (SR = −1.1 ± 0.5 s⁻¹). For each subgroup, the individual radial SR values (displayed as dots) are shown in Figure 5. The extremes can be illustrated as follows: four females <20 years of age had no LV hypertrophy, no late enhancement, and normal radial and longitudinal function in the septal and lateral wall. In contrast, two patients of the cohort died in the follow-up period. Both had LV hypertrophy, late enhancement, and the worst radial (SR = 1.7 ± 0.6 s⁻¹) and longitudinal function (SR = −0.8 ± 0.6 s⁻¹). One of them was autopsied and histology confirmed fibrotic tissue in the inferolateral wall.

Discussion

Characteristics of Fabry cardiomyopathy, such as late enhancement and functional abnormalities, have been reported separately in limited patient sample sizes and have not been linked so far. The present cross-sectional study shows all aspects from a very early to the final stage of the disease in a larger patient cohort and thus has potential implication for the understanding of Fabry cardiomyopathy. The main findings regarding this progression in cardiac involvement are: (i) functional abnormalities tend to occur more often in the LV lateral wall, (ii) LV longitudinal function appears to be impaired earlier than radial function, (iii) the end-stage of Fabry cardiomyopathy is characterized by the coexistence of LV hypertrophy, late enhancement as a marker of myocardial fibrosis, and severely reduced regional LV function, and (iv) concerning regional ventricular dysfunction, only the LV but not the RV seems to be involved.

Morphological aspects

Similar to other studies on morphological abnormalities in Fabry disease, the typical finding of LV hypertrophy was frequently detected. The increase of myocardial wall thickness appears to be an early marker indicating...
definite morphological change as a consequence of glycosphingolipid accumulation. The second typical morphological finding was late enhancement in the LV which is discussed as a marker for myocardial fibrosis. Our finding is in accordance with the recent study by Moon et al., who also showed that 50% of their patients had late enhancement predominantly in the LV inferolateral wall. The underlying mechanism for this mainly intramural pattern of late enhancement is unknown. An ischemic pathology is unlikely since previous studies excluded coronary artery disease in this group of patients and ischemic necrosis usually starts at the subendocardium, finally inducing a decrease in wall thickness in the chronic phase. It is known that LV work load is highest in the inferolateral wall. This might initiate development of myocardial fibrosis in these segments because a high work load may increase local wall stress.

**Functional abnormalities**

In accordance with other studies, global LV function was normal and regional LV function was impaired in Fabry patients. Our data suggest that prior to the development of morphological changes, functional abnormalities could be detected. Interestingly, these abnormalities also seem to start in the LV inferolateral wall. Thus, in Fabry disease, the inferolateral wall appears to be the most affected LV segment for reasons which are currently unknown. It is here that a minor functional abnormality over time may progress toward the irreversible state of myocardial fibrosis. However, the LV walls without late enhancement (suggesting no fibrosis) also tend to develop severe functional abnormalities with increasing age. In contrast, the RV showed normal regional myocardial function although the deficiency of α-Gal A is also present in myocytes of the RV. The reason for this anatomical preference of a systemic disorder may lie in the combination of higher intraventricular pressure together with higher myocardial oxygen consumption in the LV when compared with the RV.

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**Figure 2** SR (mean and 95% CI of mean) in Fabry patients and controls. Note that the values are negative for longitudinal and positive for radial strain rate.

**Figure 3** Scatter plot and Spearman’s correlation coefficient for end-diastolic myocardial wall thickness (morphology) and radial systolic SR (function) of the inferolateral wall in patients with Fabry disease.
Clinical implications

As with enzyme replacement therapy, a specific strategy is now available and the early evaluation of individual cardiac involvement in patients with Fabry disease is critical.\textsuperscript{21,22} The present study shows that early cardiac impairment can be detected using advanced echocardiographic techniques. This might enable us to determine the optimal starting point for enzyme replacement therapy. Thus, early treatment may prevent myocardial damage more effectively than starting therapy late in the course of the disease. The measurements of global LV function (i.e. ejection fraction) and end-diastolic wall thickness, which are the routine techniques to assess cardiac involvement, seem to be insufficiently sensitive to detect early cardiac impairment. Also, new global diastolic indices like $E/Em$ only detect impaired myocardial function in those patients who have already developed LV hypertrophy. In principle, our data confirm the statement by Pieroni et al. that subclinical cardiac involvement can be detected prior to the occurrence of LV hypertrophy. However, in their study, pure velocity of mitral annular motion was assessed. In contrast, in our current study, regional deformation was measured allowing description of regional heterogeneity of LV function. Using this technical approach the functional abnormalities could be matched to those myocardial segments displaying late enhancement as a potential marker of myocardial fibrosis.

Figure 4  Clinical algorithm to classify patients with Fabry disease according to sex, LV hypertrophy, and late enhancement. For each subgroup, radial and longitudinal (long.) function is described semi-quantitatively. The strength of arrows is based on strain rate values in comparison with controls. Note that there is a progressive deterioration of LV function from female patients without hypertrophy and no late enhancement (left side) to male patients with hypertrophy and late enhancement (right side) emphasized by the large arrow at the bottom. $\uparrow$, normal function assessed by systolic SR; $\downarrow$, reduced longitudinal function only in the lateral wall; $\downarrow\downarrow$, moderately reduced function in the septal and lateral wall (longitudinal) or inferolateral wall (radial); $\downarrow\downarrow\downarrow$, severely reduced function in the septal and lateral wall (longitudinal) or inferolateral wall (radial).

Figure 5  Individual radial strain rate values for the control group and the different Fabry groups based on gender, left ventricular hypertrophy, and late enhancement. $\text{LVH}^-$, without late enhancement; $\text{LVH}^+$, with late enhancement; $\text{LVH}^-$, without left ventricular hypertrophy; $\text{LVH}^+$, with left ventricular hypertrophy.
Limitations

Coronary artery disease was not excluded by invasive catheterization because it was considered ethically inappropriate. In addition, endothelial dysfunction of the coronary arteries was not investigated, which may affect regional myocardial function. Also, due to ethical reasons, we did not undertake myocardial biopsies in the patients to determine the underlying histologic morphology. The small numbers in subgroups of Fabry patients open the possibility of unstable point estimates. However, the algorithm to classify Fabry patients was proposed predominantly on clinical grounds. The statistics employed in this study seem to support this concept, although larger cohort and follow-up studies and an external validation of the proposed algorithm are needed to prove it. Another limitation is that the control group is not matched for renal function which might have an impact on myocardial morphology and function.

Conclusions

Using regional strain rate imaging, functional changes preceding LV hypertrophy can be detected at an early stage in Fabry patients. Morphological and functional abnormalities in Fabry patients strongly depend on age and sex. Using information on sex, LV hypertrophy, and late enhancement, individual Fabry patients may be characterized according to their functional and structural abnormalities. This information may prove useful in guiding treating physicians to classify their patient regarding the severity of cardiac involvement and may support the decision to offer enzyme replacement therapy to those patients who may gain the most from an early start of therapy. An external validation of the proposed algorithm and future studies are needed to prove that using this information will affect long-term outcome in Fabry patients.

Acknowledgement

We wish to thank our colleagues of the Cardiac Ultrasound Research Group at the University of Leuven, Belgium, for providing us with the SPEQLE software package used during the data analysis in this study.

References