Relation of Burden of Myocardial Fibrosis to Malignant Ventricular Arrhythmias and Outcomes in Fabry Disease☆

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The aim of this study was to investigate the impact of myocardial fibrosis in Fabry disease. Seventy-three patients with genetically confirmed Fabry disease were followed for 4.8 ± 2.4 years. In accordance with current guidelines, 57 patients received enzyme replacement therapy (ERT) after study inclusion, whereas 16 did not. At baseline and latest possible follow-up, myocardial fibrosis was assessed noninvasively by cardiac magnetic resonance, and biomarkers of collagen metabolism were determined. Holter electrocardiography and clinical follow-up at yearly intervals were used to monitor malignant ventricular arrhythmias (MVAs; nonsustained and sustained ventricular tachycardia and sudden cardiac death). In total, 48 patients (66%) showed fibrosis assessed by late enhancement (LE) at baseline, and 4 patients developed new LE during follow-up, 2 of them despite ERT. The 2 patients receiving ERT (1.4 ± 1.9% vs 2.5 ± 2.6%, p <0.001) and the patients not receiving ERT (0.5 ± 0.8% vs 0.7 ± 1.0%, p = 0.035) showed a progression of LE during follow-up. None of the patients displayed reductions of LE during follow-up. Collagen biomarkers were elevated in patients with and without LE but did not correlate with LE amount. Thirteen LE-positive patients at the baseline examination had documented MVAs (including 5 sudden cardiac deaths), whereas none of the patients without LE had MVAs. The yearly increase in fibrosis was 0.9 ± 0.6% in patients with MVAs and 0.2 ± 0.3% in patients without MVAs (p <0.001). Logistic multivariate regression analysis revealed that the annual increase in fibrosis during follow-up was the only independent predictor of MVAs. In conclusion, myocardial fibrosis in Fabry disease is progressive, apparently not modified by ERT, and a crucial outcome determinant. **(Am J Cardiol 2014;114:895−900)**

Fabry disease is an X-linked lysosomal storage disorder caused by a deficiency of α-galactosidase A.[1] Cardiac involvement is characterized by the accumulation of globotriaosylceramide in cells, causing left ventricular (LV) hypertrophy and finally leading to myocardial replacement fibrosis in the hearts of patients with Fabry disease.[2] The dominant cardiac symptoms are arrhythmias and heart failure, which determine the reduced life expectancy observed in patients with Fabry disease.[3,4] The reference standard for noninvasively assessing myocardial fibrosis is cardiac magnetic resonance (CMR) using the late enhancement (LE) technique,[5,6] and various studies have successfully used this tool to investigate myocardial fibrosis in patients with Fabry disease.[7−11] Although LE was used to stage patients with Fabry disease, a prospective longitudinal study to quantify the development of myocardial fibrosis is lacking, especially in patients receiving enzyme replacement therapy (ERT). Moreover, the prognostic relevance of myocardial fibrosis in Fabry disease needs further evaluation. We hypothesized that the fibrotic progression in the Fabry cardiomyopathy has an impact on prognosis. Thus, we investigated the impact of myocardial fibrosis in this disease using CMR LE imaging and collagen biomarkers and determined the occurrence of malignant ventricular arrhythmias (MVAs).

Methods

In total, 171 referred patients were screened at their first visits to the Fabry center in Würzburg (Figure 1). All of the following criteria had to be met for inclusion in this observational study: (1) genetically proved Fabry disease, (2) the ability to undergo CMR imaging with contrast agent, (3) no ERT before this study, (4) no ERT therapy switch during follow-up, (5) a minimum follow-up time of 1 year with 2 corresponding CMR scans or death during follow-up, and (6) informed consent. Overall, 73 consecutive patients with Fabry disease (35 female) fulfilled all these criteria and were included. Recruitment started in January 2001 and ended in September 2009. The treatment decision for ERT was reviewed at study start, and in accordance with current guidelines,[12] 57 patients received ERT and 16 did not. In accordance with the Declaration of Helsinki, written informed consent from all patients or their guardians was

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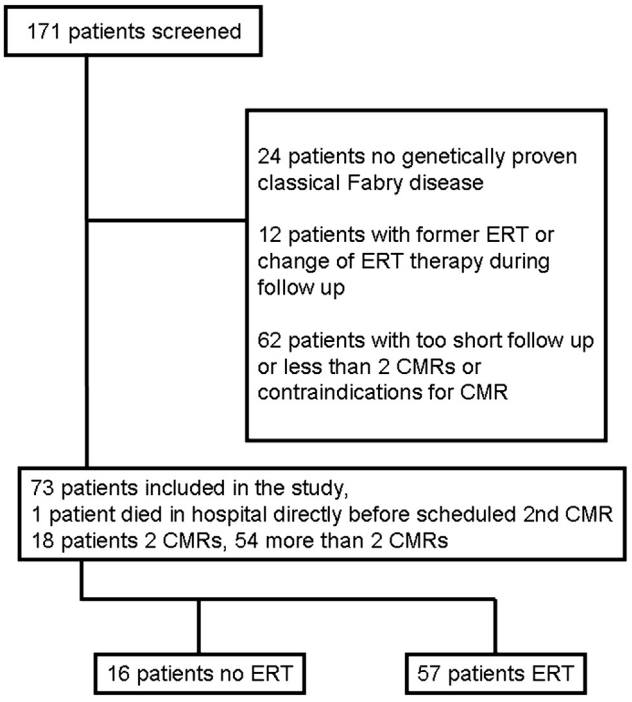

Figure 1. Flowchart of the complete screened group and the study cohort.

obtained, and the local ethics board approved the protocol. Several patients from the present study cohort have been included in other open-cohort studies from our center.

CMR was performed at first presentation and latest possible follow-up with intravenous injection of gadobenate dimeglumine 0.1 mmol/kg (MultiHance; Bracco Diagnostics, Milan, Italy) on a 1.5-T scanner (Magnetom Symphony Quantum; Siemens Medical Systems, Erlangen, Germany). Standard steady-state free precession cine breath-hold short-axis 4-, 3-, and 2-chamber images were used to determine wall thickness, cardiac mass, and the ejection fraction. LE images (Figure 2) were acquired with inverse recovery sequences (slice thickness 8 mm, breath hold, field of view 240 × 320 mm^2, matrix size 165 × 256, repetition time 7.5 ms, echo time 3.4 ms, flip angle 25°). Care was taken to use the same settings for the follow-up scan.

The analysis was done blinded to all clinical data by an experienced CMR specialist (>15 years' experience in CMR, >10 years' experience with Fabry disease). Inter- and intraobserver variability was recently published by our group.[13]

All consecutive short-axis slices were used for measuring the area with pathologic LE. The sum of areas was multiplied by the slice thickness and then set in relation to LV myocardial volume (the amount of LV fibrosis as a percentage). To calculate the percentage change in fibrosis over time in a single patient, we subtracted the percentage of fibrosis determined in the last available CMR examination from the result taken from the baseline CMR examination. Any CMR examinations performed between these times points were omitted from the analysis.

Peripheral venous blood samples were obtained after 30 minutes of rest in the supine position at baseline and latest possible follow-up. Blood samples were immediately centrifuged at 4°C at 10g for 10 minutes. Afterward, aliquots of 100 to 250 ml serum were stored at −20°C for ≤3 days until final storage in a freezer at −80°C. All aliquots were analyzed at the end of the study period. Serum procollagen type III aminoterminal propeptide, procollagen type I carboxyterminal propeptide, and collagen type I carboxyterminal telopeptide levels were quantified using a radioimmunoassay technique using commercially available kits from USCN Life Science Inc. (Wuhan, China), as previously described.[14]

The occurrence of MVAs (nonsustained and sustained ventricular tachycardia [VT] and sudden cardiac death) was determined in annual intervals by Holter electrocardiography of ≥24 hours in duration (mean 28 ± 5.5 hours). All available Holter electrocardiograms for each patient were analyzed for the detection of arrhythmias. Sudden cardiac death was defined as an unexpected arrest of presumed cardiac origin within 1 hour after the onset of any symptoms that could be interpreted as being cardiac in origin.

All values are presented as absolute number (percentage) or mean ± SD. Differences between 2 groups were tested using paired or unpaired *t* tests, chi-square tests, or Fisher's exact tests, as appropriate. Higher group numbers were tested using 2-way analysis of variance with Duncan's post hoc analysis and Bonferroni's correction. A Kaplan-Meier curve was plotted for visualizing the event-free rate of MVAs of patients with and without fibrosis as indicated by LE, and a log-rank test was performed to statistically compare the 2 survival curves. Predictors of MVAs were sought using logistic regression analysis. The multivariate regression analysis included percentage LV fibrosis, LV mass, septal wall thickness, blood pressure, annual increase of LV mass, and annual increase of percentage LV fibrosis, all selected on the basis of univariate predictors of MVAs. The multivariate logistic regression analysis was performed with fixed adjustment for age, gender, kidney function, and ERT status. A p value <0.05 or corrected values in multiple testing were deemed to indicate statistical significance. Data were analyzed using SPSS versions 20 and 21 (SPSS, Inc., Chicago, Illinois).

Results

Seventy-three consecutive patients with Fabry disease were included in this observational study and followed for 4.8 ± 2.4 years. Table 1 lists the general clinical data of the complete cohort, indicating reasonably preserved kidney and global LV function and moderate LV hypertrophy. In total, 48 patients (66%) exhibited fibrosis as assessed by LE on CMR at baseline. Table 2 lists the baseline CMR and biomarker data, split into groups of patients with and without fibrosis. There was no difference in the ejection fraction; however, significant differences were seen in LV wall thickness and LV mass. Collagen biomarkers were elevated in the 2 groups compared with healthy controls reported in the published research[14] but did not differentiate between groups. During follow-up, patients with and those without ERT showed progressive LE, as evidenced by an increase in percentage LV fibrosis on repeat CMR (Table 3). Those with ERT showed an increase from 1.4 ± 1.9% at baseline to 2.5 ± 2.6% at follow-up (p <0.001); those without ERT showed an increase from 0.5 ± 0.8% to 0.7 ± 1.0% (p = 0.035). None

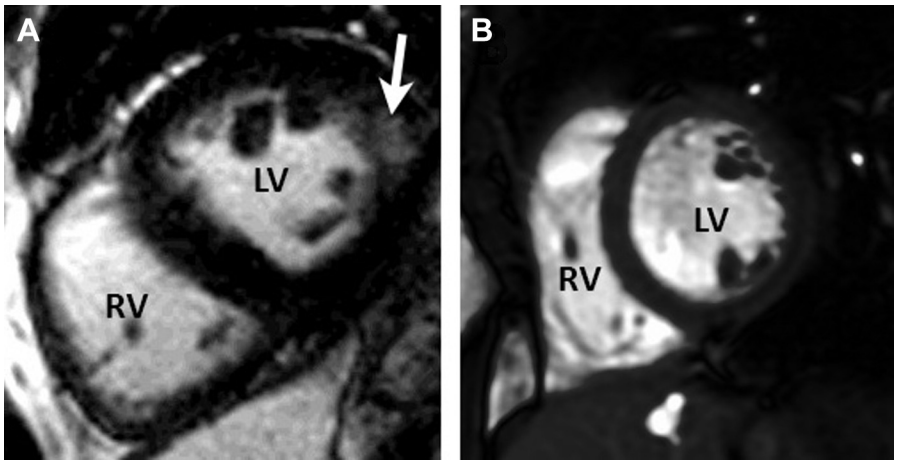

Figure 2. CMR short-axis images of patients with Fabry disease. A male patient with severe LE in the basal posterolateral wall segment (*arrow*) and hypertrophy *(A)* and a female patient without LE *(B)*. LV = left ventricle; RV = right ventricle.

Table 1
Clinical baseline characteristics of the Fabry patients (n = 73)

Male/Female	38/35 (48%/52%)
Age (years)	39 ± 11
Height (cm)	172 ± 10
Weight (kg)	68 ± 13
Heart rate (1/min)	66 ± 14
Systolic blood pressure (mmHg)	123 ± 18
Diastolic blood pressure (mmHg)	81 ± 12
Abnormal sweating	50 (67%)
Heat or cold intolerance	49 (67%)
Chronic diarrhea	30 (41%)
Sudden deafness	18 (25%)
Angiokeratomata	30 (41%)
Dialysis	7 (10%)
Kidney transplantation	6 (8%)
Serum creatinine (mg/dl)	1.5 ± 2.1
Diethylene triamine pentaacetic acid clearance (ml/min)	93 ± 32
Stroke/transitory ischemic attack	9 (12%)
Typical neuropathic pain	51 (79%)
Chronic pain syndrome	32 (44%)
Depression	11 (15%)
Left-ventricular mass (g/m^2)	85 ± 32
Left-ventricular ejection fraction (%)	63 ± 8
Septal wall thickness (mm)	11.3 ± 3.8
Amount of fibrosis (% of left-ventricular mass)	1.2 ± 1.7

Table 2
Cardiac Magnetic Resonance, biomarker results and events of patients with and without fibrosis

	No Fibrosis (n = 25)	Fibrosis (n = 48)
Left-ventricular mass (g/m^2)	70 ± 16	93 ± 36*
Septal wall thickness (mm)	9.4 ± 2.4	12.2 ± 4.0*
Ejection fraction (%)	62 ± 7	64 ± 9
Amount of fibrosis (% of left-ventricular mass)	0	1.8 ± 1.8*
Procollagen type I carboxy-terminal propeptide (ng/ml)	308 ± 399	302 ± 361
Collagen type I carboxy-terminal telopeptide (ng/ml)	8.3 ± 15.3	8.0 ± 12.9
Procollagen type III amino-terminal propeptide (μg/l)	5.9 ± 2.4	6.8 ± 3.7
Malignant ventricular arrhythmias	0 (0%)	13 (27%)
Sudden cardiac death	0 (0%)	5 (10%)

* Significant vs. "No fibrosis", p <0.05.

of the patients showed reductions in LE at follow-up. Four patients developed new fibroses at rates of +0.9% after 8 years (no ERT), +0.7% after 6 years (no ERT), +1.7% after 7 years (ERT), and +1.0% after 5 years (ERT). There was no significant change in any of the biomarkers in either the ERT-naive or in the ERT group. Results are listed according to ERT status in Table 3.

Annually repeated Holter electrocardiography (407 Holter studies in total, i.e., 4 or 5 per patient) and clinical follow-up was used to search for MVAs. No patients without LE showed MVAs during follow-up, whereas 13 patients with LE experienced MVAs (Table 2). Five of these patients experienced sudden cardiac death; 1 of those had an implantable cardioverter-defibrillator (ICD) placed after the detection of VT and showed multiple adequately terminated episodes of sustained VT during an in-hospital stay before he died because of VT; another patient with VT had an ICD implanted and experienced multiple episodes of sustained VT adequately terminated by the ICD. The 7 remaining patients had nonsustained VT. One of these patients with nonsustained VT was the sixth patient who died. He died presumably not because of cardiac reasons but because of sepsis with acute or chronic kidney failure. However, he presented with LE of 5.2% at latest follow-up and, as stated earlier, had documented nonsustained VT on Holter electrocardiography. In general, all indications for the implantation of an ICD in patients participating in this study were based on the documentation of VT during Holter electrocardiography to prevent sudden cardiac death.

On Kaplan-Meier analysis for MVAs in the 2 groups (LE vs no LE), a significant difference between the 2 curves could be observed (log-rank p = 0.017; Figure 3). Logistic regression analysis revealed that the annual increase in fibrosis (percentage) during follow-up was the only independent predictor of MVAs in our cohort (p = 0.038). The

Table 3
Cardiac Magnetic Resonance and biomarker results of patients with and without Enzyme replacement therapy at baseline and at follow up

	No Enzyme Replacement Therapy;		Enzyme Replacement Therapy;	
	Baseline (n = 16)	Follow-Up (n = 16)	Baseline (n = 57)	Follow-Up (n = 56)*
Left-ventricular mass (g/m^2)	59 ± 11	61 ± 14	92 ± 33†	90 ± 30‡
Septal wall thickness (mm)	8.0 ± 1.6	8.6 ± 1.9	12.2 ± 3.7†	12.3 ± 3.7‡
Ejection fraction (%)	60 ± 6	59 ± 8	64 ± 9	63 ± 9
Amount of fibrosis (% of left-ventricular mass)	0.5 ± 0.8	0.7 ± 1.0§	1.4 ± 1.9†	2.5 ± 2.6‡§
Procollagen type I carboxy-terminal propeptide (ng/ml)	319 ± 362	194 ± 290	299 ± 377	240 ± 346
Collagen type I carboxy-terminal telopeptide (ng/ml)	9.9 ± 18.4	6.2 ± 14.7	6.2 ± 14.7	9.8 ± 15.0
Procollagen type III amino-terminal propeptide (µg/l)	5.7 ± 1.6	5.9 ± 1.7	5.9 ± 1.7	6.8 ± 3.1

* Only one patient died before he could get a regular follow up with cardiac magnetic resonance and biomarkers.
† Significant vs. No ERT, BS; p <0.05.
‡ Significant vs. No ERT, FU; p <0.05.
§ Significant vs. same group baseline; p <0.05.

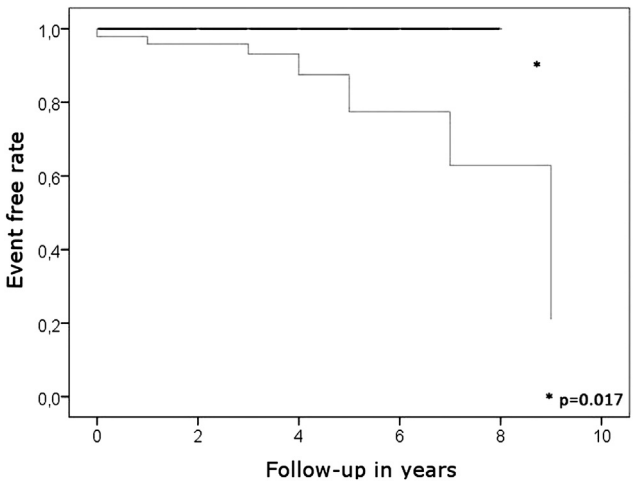

Figure 3. Kaplan-Meier survival plot of the occurrence of MVAs in patients with (*grey*) and without (*black*) LE at baseline examination. Note that in the follow-up time of nearly 5 years, no events occurred in patients without LE at baseline. Five of the ventricular arrhythmias in the group with LE were fatal.

annual increase in fibrosis was 0.9 ± 0.6% in patients with MVAs and 0.2 ± 0.3% in patients without MVAs (p <0.001).

Discussion

Myocardial fibrosis is 1 of the hallmarks of Fabry cardiomyopathy.[2,8,10,11] Clinical and registry data suggest that patients with Fabry disease may experience MVAs and die predominantly because of cardiac reasons, but a causal relation has been hypothetical so far.[3,4,15] We conducted the first systematic investigation of the longitudinal quantification of cardiac fibrosis via CMR and its relation to cardiac arrhythmias and clinical events in a large Fabry cohort. The main findings are as follows: (1) myocardial fibrosis is a common feature in Fabry cardiomyopathy; (2) regardless of ERT, cardiac fibrosis progresses over time, with no possibility of regression; (3) established blood biomarkers for fibrosis are elevated in patients with Fabry but are not helpful for either characterizing cardiomyopathy or staging the disease; and (4) myocardial fibrosis relates to MVA, and subjects with a high annual increase in LV fibrosis are at risk for sudden cardiac death.

Gadolinium is an extracellular agent that cannot cross intact cell membranes.[16] Late gadolinium enhancement is an observed phenomenon that occurs when myocardial damage is present; T1-weighted LE images can reveal information useful for the noninvasive assessment of myocardial fibrosis.[16] In early stages, the nonischemic cardiomyopathy LE distribution pattern mostly spares the subendocardial region and is limited to the midwall and epicardial regions.[16] With disease progression, this pattern can change to transmural LE.[11] This nonischemic LE pattern is also characteristic of patients with Fabry cardiomyopathy but typically starts at the lateral basal region.[10,17] Adabag et al[18] showed that LE in hypertrophic cardiomyopathy increases susceptibility to arrhythmias. Recently, 2 independent studies consistently found that a large amount of LE predicts major adverse cardiac events in patients with hypertrophic cardiomyopathy.[19,20] According to current hypertrophic cardiomyopathy guidelines, however, this CMR-derived risk information does not (yet) establish an indication for ICD implantation.[21]

Moon et al[8] were the first to describe LE as a marker of myocardial fibrosis in patients with Fabry disease. Subsequently, it became evident that LE starts in the posterolateral wall in Fabry cardiomyopathy.[2,7–11,16,22] Treatment studies showed that the recovery of regional myocardial function and the regression of LV wall thickness depend on the extent of LE at the initiation of ERT.[10] In patients with high LE burden, only a stabilization of regional LV function and a mild beneficial decrease in septal wall thickness were observed.[10] The present data strongly suggest that the development of myocardial fibrosis cannot be stopped or reversed by ERT. In contrast, the amount of fibrosis in relation to the LV myocardial volume doubled in the course of 5 years in our study, despite ERT. The fact that none of the ERT-treated patients showed a reduction in the amount of fibrosis might indicate that Fabry cardiomyopathy, and perhaps Fabry disease in general, is a progressive fibrotic disease, starting early in patients' lives and progressively worsening over time. This hypothesis is also supported by data on collagen biomarkers, which exhibit elevated levels in the groups with and without LE. The fact that patients receiving ERT showed a greater LE

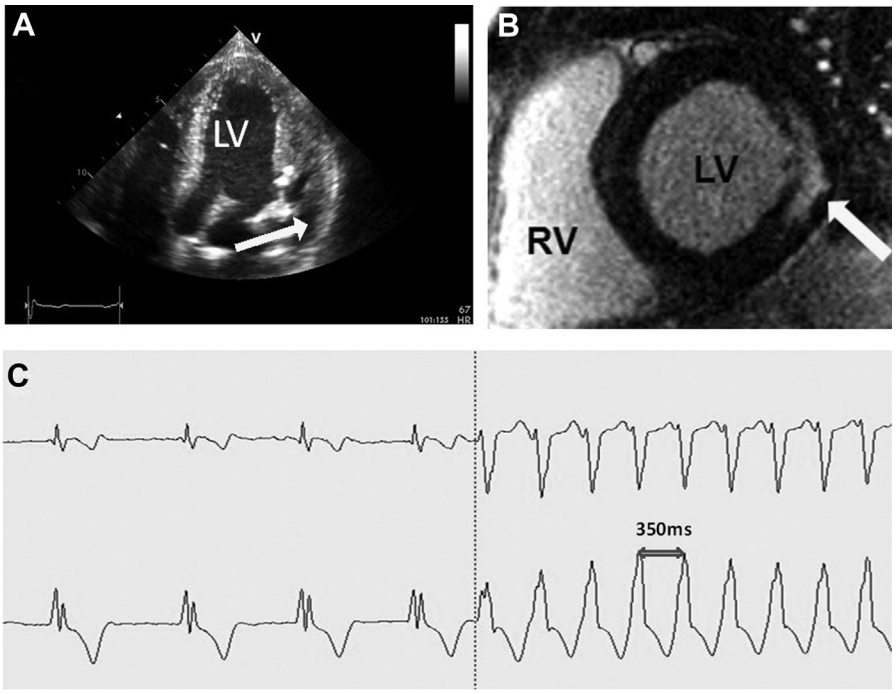

Figure 4. A typical echocardiographic 4-chamber view of a patient with Fabry disease *(A)* with left ventricular hypertrophy, a prominent papillary muscle, and wall thinning lateral. *(B)* The corresponding CMR image with LE (the *arrow* indicates the fibrotic area in the inferolateral wall). In this patient, nonsustained ventricular arrhythmia was documented *(C)* during annual follow-up (Holter electrocardiography), and an ICD was implanted. LV = left ventricle; RV = right ventricle.

increase over time in comparison with patients not receiving ERT might indicate that the fibrotic remodeling is worsened or accelerated in sicker patients.

In 2005, Shah et al[15] were the first to publish that ventricular arrhythmias might affect the outcomes of patients with Fabry disease. In addition, it was shown that the causes of death in patients with Fabry disease are dominated by cardiac causes, namely, sudden cardiac death, since kidney replacement therapy has become widely available.[3,4] Higashi et al[23] suggested that the origin of ventricular arrhythmia might be the posterolateral basal wall, that is, the area where LE usually originates. This morphologic-electrical interaction theory fits very well with the present finding that patients with Fabry disease with LE and high annual increases of fibrotic burden are prone to MVAs and are at risk for sudden cardiac death. Findings for a typical patient with LE and an MVA are shown in Figure 4.

Fabry guidelines recommend echocardiography as the imaging technique of choice when evaluating a patient for cardiac involvement.[12] However, because only CMR can detect cardiac fibrosis, this technique should be used to document or rule out clinically relevant LE. In hearts without LE, MVAs are very unlikely to occur. As soon as LE is detected, careful clinical monitoring for MVA is required. Especially in hearts with large LE-positive areas, annual Holter electrocardiography, as recommended by current guidelines,[12] might not suffice, and advanced techniques such as an event recorder should be considered. In addition, our data corroborate the view that as soon as MVAs are detected in "fibrotic hearts," an ICD should be implanted to prevent sudden cardiac death. The present data further suggest that every fibrotic heart in a patient with Fabry disease is at risk for MVA as soon as a specified amount of fibrosis is exceeded. To recommend the implantation of an ICD without documentation of MVA, further studies are required. We recommend regular monitoring of those patients at risk for arrhythmias and suggest the implantation of an event recorder.

Another very important fact must be considered when following patients with Fabry over time: even with ERT, patients can develop new LE, thus mandating a regular CMR monitoring algorithm. In addition, patients who are already LE positive at the initiation of ERT may progress to advanced fibrotic cardiomyopathy stages, requiring extension of therapy. This is emphasized by the fact that the only independent predictor of MVA in our cohort was the annual increase in fibrotic burden. Thus, patients who were LE negative at baseline also require follow-up magnetic resonance imaging.

The analysis of collagen markers in our work did not result in clear findings in patients with hypertrophic cardiomyopathy, such as those provided in the work of, for example, Ho et al.[24] This might partly be because Fabry disease can be regarded as a "general" fibrotic disease, meaning that not only the heart but also the kidneys and other organs might be involved in the fibrotic process. Reduced kidney function might also play a role in collagen marker clearance.

In recent years, it has become evident that a 24-hour Holter electrocardiography once a year might not be sufficient for monitoring patients with Fabry disease. Thus, with the methods used, we might have missed some MVAs.

Disclosures

Drs. Weidemann, Niemann, and Krämer have received speaker's honoraria from Genzyme Corporation, Cambridge, Massachusetts. Drs. Weidemann and Niemann have received speaker's honoraria from Shire Plc., Dublin, Ireland. Drs. Weidemann and Wanner are members of the Fabry Registry European Board of Advisors and have received travel assistance and speaker's honoraria. Research grants were given to the institution by Genzyme Corporation and Shire Plc.

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