Usefulness of an Implantable Loop Recorder to Detect Clinically Relevant Arrhythmias in Patients With Advanced Fabry Cardiomyopathy

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Patients with genetic cardiomyopathy that involves myocardial hypertrophy often develop clinically relevant arrhythmias that increase the risk of sudden death. Consequently, guidelines for medical device therapy were established for hypertrophic cardiomyopathy, but not for conditions with only anecdotal evidence of arrhythmias, like Fabry cardiomyopathy. Patients with Fabry cardiomyopathy progressively develop myocardial fibrosis, and sudden cardiac death occurs regularly. Because 24-hour Holter electrocardiograms (ECGs) might not detect clinically important arrhythmias, we tested an implanted loop recorder for continuous heart rhythm surveillance and determined its impact on therapy. This prospective study included 16 patients (12 men) with advanced Fabry cardiomyopathy, relevant hypertrophy, and replacement fibrosis in "loco typico." No patients previously exhibited clinically relevant arrhythmias on Holter ECGs. Patients received an implantable loop recorder and were prospectively followed with telemedicine for a median of 1.2 years (range 0.3 to 2.0 years). The primary end point was a clinically meaningful event, which required a therapy change, captured with the loop recorder. Patients submitted data regularly (14 ± 11 times per month). During follow-up, 21 events were detected (including 4 asystole, i.e., ECG pauses ≥3 seconds) and 7 bradycardia events; 5 episodes of intermittent atrial fibrillation (>3 minutes) and 5 episodes of ventricular tachycardia (3 sustained and 2 nonsustained). Subsequently, as defined in the primary end point, 15 events leaded to a change of therapy. These patients required therapy with a pacemaker or cardioverter−defibrillator implantation and/or anticoagulation therapy for atrial fibrillation. In conclusion, clinically relevant arrhythmias that require further device and/or medical therapy are often missed with Holter ECGs in patients with advanced stage Fabry cardiomyopathy, but they can be detected by telemonitoring with an implantable loop recorder. **(Am J Cardiol 2016;118:264−274)**

Fabry disease is an X-linked lysosomal storage disorder that results from a deficiency in alpha-galactosidase A.[1] The cardiac pathogenetic correlate is the accumulation of globotriaosylceramides in cells, which causes left ventricular (LV) hypertrophy and finally leads to myocardial replacement fibrosis.[1–7] In these fibrotic hearts, life-threatening arrhythmias can develop.[8] Thus, patients at risk should be evaluated regularly for potential arrhythmia treatments. The current recommendations[9] for managing patients with confirmed Fabry disease include an annual Holter electrocardiogram (ECG) assessment to detect different types of advanced arrhythmias that indicate a potential need to switch therapy. The Holter ECG covers only a relatively short period; therefore, it might be beneficial to implement continuous surveillance for potential arrhythmias in patients at high risk for severe arrhythmias. Several implantable devices are available for continuous rhythm surveillance, such as the Reveal XT device (Medtronic, Minneapolis, Minnesota). These devices reliably facilitate the detection of cardiac arrhythmias in routine clinical care.[10] However, the role of these devices in improving the detection of relevant cardiac arrhythmias that require a change in clinical management, such as ventricular tachycardia (VT), bradycardia, and atrial fibrillation (AF), remains to be determined in patients with Fabry disease. Therefore, the present study

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aimed to investigate whether an implantable loop recorder with telemonitoring capabilities could reveal events that required a change in clinical management in patients at risk of developing clinically relevant arrhythmias associated with advanced Fabry cardiomyopathy.

Methods

Study recruitment started in June 2012 and ended in September 2014. A total of 120 consecutive patients with Fabry cardiomyopathy were screened in the Fabry centers in Würzburg and Berlin. Criteria for inclusion were (1) genetically proved Fabry disease, (2) signs of severe LV fibrosis (defined in the following section), (3) no previous detectable clinically relevant arrhythmia (defined in the following section) on Holter ECG, (4) stable treatment with enzyme replacement therapy for at least 12 months, and (5) informed consent for examinations and participation in the study. All these criteria had to be met for enrollment in the study. Exclusion criteria were (1) anticoagulation treatment due to AF, (2) an implanted pacemaker or cardioverter−defibrillator (ICD), and (3) signs of AF or VT in the past.

Severe fibrosis was defined as the presence of at least 2 segments of late enhancement (LE) during cardiac magnetic resonance imaging (cMRI) or wall motion abnormalities combined with wall thinning in at least 2 LV segments after exclusion of coronary artery disease (CAD) with heart catheterization. In all patients with signs or symptoms of CAD (i.e., by a stress test), a heart catheterization was performed to rule out CAD. We defined a clinically relevant arrhythmia as (1) bradycardia with a heart rate $\leq$40 beats/min during the day, which indicated a need for pacing therapy; (2) an electrical ventricular pause $\geq$3 seconds during the day, which indicated a need for pacing therapy; (3) sustained (>30 seconds) or symptomatic nonsustained (<30 seconds) VT, which indicated a need for an ICD; or (4) AF that lasted at least 3 minutes, which indicated a need for anticoagulation.[11,12]

Of the 120 patients screened, 22 fulfilled the inclusion criteria, and 6 refused to participate. Consequently, this prospective study included 16 consecutive patients (4 women) who were considered "at risk" of developing clinically relevant arrhythmias. At baseline, before loop recorder implantation, an echocardiography, cMRI (when not contraindicated), Holter ECG, and clinical assessment were performed in all patients. A yearly follow-up was conducted with the same assessments performed in the baseline visit. All patients were asked to transmit data from the loop recorder by telephone as often as possible. The loop recorder was explanted when a patient required implantation of an ICD or pacemaker. According to the Declaration of Helsinki, we obtained written informed consent for all patients or their guardians. The local institutional ethics board approved the study protocol.

We performed LV parasternal long-axis imaging with M-Mode echocardiography (Vivid 7, GE Vingmed Ultrasound AS, Horten, Norway) to determine the end-diastolic septal (interventricular septal wall thickness at end diastole [IVSd]) and posterior wall thicknesses. In addition, we measured the left atrial (LA) diameter, and we calculated the LV ejection fraction with Simpson's formula. We used blood pool pulsed Doppler of the mitral valve inflow to quantify the ratio of early-to-late (E/A) diastolic flow velocity and the deceleration time. The transmitral flow was determined by placing the Doppler window between the tips of the mitral valve leaflets; we measured the peak flow velocities in early (E wave) and late (A wave) systole. In addition, tissue Doppler was performed for measuring the ratio between early transmitral flow and peak early tissue Doppler velocity (E/E′). Measurements were averaged over 3 cycles.

We performed 2-dimensional speckle tracking with an EchoPAC (GE Vingmed Ultrasound AS, Horten, Norway) to acquire standard apical views of the LV for off-line quantification of myocardial deformation. After manually selecting the Region of Interest, speckles were applied automatically and then confirmed by the user. We used semiautomatic postprocessing to extract the longitudinal systolic strain of the 17 LV segments.

We performed cMRI to quantify myocardial mass and cardiac volumes with standard, steady state free precession cine imaging sequences on a 1.5 T whole body scanner (Magnetom Avanto, Siemens Medical Systems, Erlangen, Germany). To detect myocardial fibrosis, we acquired delayed enhancement images after an intravenous injection of gadopentetate dimeglumine (0.2 mmol/kg; Magnevist, Schering AG, Berlin, Germany). We used a T1-weighted inversion recovery sequence with the breath hold technique (field of view 240 × 320 mm^2, matrix size 165 × 256, slice thickness 8 mm, repetition time 7.5 ms, echo time 3.4 ms, and flip angle 25°). Care was taken to use identical settings in the baseline and follow-up examinations for a given patient. All consecutive, short-axis slices covering the whole heart were used to measure the area with pathological LE. The sum of areas that showed LE was multiplied by the slice thickness, and then expressed as a percentage of the LV myocardium volume.

Twelve-lead surface resting ECGs were recorded at a sweep of 50 mm/s. ECGs were measured manually and analyzed by a reader who was blinded to the disease stage. Standard criteria for ECG findings were applied, as follows: A normal PR interval was defined as 120 to 200 ms. A normal QRS duration was defined as 70 to 110 ms. LV hypertrophy was assessed with the Sokolow−Lyon index, where the S wave in lead V1 or V2 (whichever was larger) was added to the R wave in lead V5 or V6 (whichever was larger), with a minimum cutoff of 3.5 mV. The QT interval (normal 300 to 440 ms) was measured from the beginning of the QRS complex to the end of the T wave, which was defined as the point where the tangent to the downslope of the T wave intersected the isoelectric line. The corrected QT duration (normal <440 ms) was calculated with the Bazett's formula. For negative or biphasic T waves, the peak was measured from the nadir of the T wave. ST-segment elevation was defined as a J point elevation that was $\geq$2 mm in the precordial leads and $\geq$1 mm in the limb leads. ST-segment decrease was defined as a J point decrease that was $\geq$1.5 mm in the precordial leads and $\geq$1 mm in the limb leads.

The Holter ECG was started between 8 A.M. and 10 A.M. and continued for a mean of 22.3 hours. The data were

Table 1
Baseline characteristics of all Fabry patients

Patient number	Genetics	Age (years)	Sex	Height (cm)	Weight (kg)	Gal-A activation (nmol/min/mg)	lysoGb3 (ng/ml)	ERT for (years)	Kidney TX	Dialysis	GFR (MDRD) (ml/min/1.73 m^2)	TIA/Stroke*	Dyshidrosis	Angiokeratoma
1	Exon7. Mutation E341 K	53	M	185	57	0.03	63.1	10	0	0	83	+	+	+
2	Exon 7. Del c.1221 delA	58	F	163	56	0.14	18.7	3	0	0	55	0	0	0
3	Exon3. Mutation D136 E	70	F	165	71	0.15	11.2	10	0	0	76	0	0	0
4	Intron 3. IVS3+1 G > A	45	M	184	75	0.04	21.2	12	+	0	47	0	+	0
5	Exon 7. Mutation E341 K	49	M	180	72	0.02	65.7	11	0	0	110	0	+	0
6	Exon7. Mutation c.1208.del	45	M	184	84	0.02	15.0	11	+	+	58	0	+	+
7	Exon 7. Deletion 354 fs Del 15 bp	54	F	165	64	0.19	10.1	9	0	0	82	0	+	+
8	Transition c664A > G; Mutation N215S	67	M	170	63	0.13	6.0	2	0	0	103	0	+	+
9	Exon 1. c.162 del T	54	M	177	78	0.08	30.6	13	+	0	40	+	+	+
10	Exon 7. Mutation c.1208 del	49	M	178	72	0.03	28.1	12	0	0	85	0	+	0
11	Exon 1. C134T > C [L45P]	36	M	193	83	0	63.4	3	0	0	100	+	+	0
12	Exon 3. Mutation D136 E	48	M	182	83	0.02	15.1	11	+	0	74	0	+	0
13	Intron 6 Trans IVS6-10G > A Splice-Site-Mutation Mut c.1000-10G > A	36	M	187	86	0.04	30.3	2	0	0	80	0	0	+
14	Exon 6. c. 973 G > A Mutation G325S	73	F	156	52	0.23	7.2	3	0	0	39	0	0	0
15	c.747A > G	56	M	170	60	0.03	74.7	2	0	0	102	0	0	+
16	c.982 G > C	43	M	148	68	0.02	114	4	0	0	116	0	0	+

ERT = enzyme replacement therapy; F = female; GFR = glomerula filtration rate; M = male; TIA = transistoric ischemic attack; TX = transplantation.
* All TIA and stroke were not due to documented atrial fibrillation.

analyzed by a reader blinded to the disease stage. Premature ventricular beats (PVBs) were counted automatically, with manual correction. All counts were then corrected to a fictive duration of exactly 24 hours. PVB were classified as ventricular or supraventricular in origin, and they were ranked as a singlet, couplet, triplet, or run. A run was defined as more than 3 PVBs in a row.

All patients received identical loop recorders with telemedicine capabilities (Reveal XT; Medtronic). Immediately before the surgical procedure, patients were screened for an eligible implant position in the body with the vendor-supplied dermal ECG vector measurement tool. All patients showed good signal quality at the parasternal left position. After aseptic preparation and local anesthesia, an incision approximately 3 cm long was made parasternal left. Then, a subfascial pouch 8 to 10 cm long in the caudal direction was prepared with blunt dissection. The Reveal device was inserted and fixed by muscular ligation with Mersilene. The incision was closed with Vicryl subcutan and Prolene intracutan. Then, the device was interrogated and activated with the external programmer. Directly after the implantation procedure, the settings were programmed according to the study specifications (fast ventricular tachycardia: detection: on; ECG recording: on; interval: 290 ms, 30/40 beats; VT: detection: on; ECG recording: on; interval: 370 ms, 16 beats; asystole: detection: on; ECG recording: on; bradycardia: detection: on; ECG recording: on; interval: 1,500 ms, 4 beats; symptoms: detection: on; ECG recording: 3 episodes − 7.5 minutes; atrial tachycardia/AF: detection: on; ECG recording: on - all episodes). All patients received a corresponding transmitter. We requested that they should transfer data daily, whenever possible. Transmitted data were interrogated at the study center daily (on workdays) through an electronic internet platform.

Continuous data are presented as the mean (SD); categorical variables are presented as numbers (percentages). Categorical data were compared across groups with the chi-square test. A 2-tailed probability value <0.05 was considered significant. Statistical analysis was performed with IBM SPSS, version 22 for Windows (SPSS, IBM, Chicago, Illinois).

Results

Table 1 lists the genetic and clinical data for every individual patient and information about their typical Fabry organ involvement. Fifteen patients had a classical mutation, and one patient had a late-onset mutation, which typically presents as a cardiac variant. Most patients were men (75%), and all had markedly elevated levels of globotriaosylsphingosine (Lyso-Gb3; mean 36.3 ± 32 ng/ml). The mean age was 52 ± 11 years, and all were on enzyme replacement therapy for at least 2 years. All patients submitted the data regularly, at a rate of 14 ± 11 times per month. After device implantation, patients were prospectively followed with telemedicine for a median of 1.2 years (range 0.3 to 2.0 years), and no patient died during follow-up.

In Table 2, all individual echocardiographic and cMRI data are shown with the average values. All patients showed LV hypertrophy (IVSd ≥11 mm), and all but one had visible papillary muscle thickening. One patient had a reduced ejection fraction. Seven patients had an E/E′ above 15, which suggested elevated diastolic filling pressure. The global systolic strain averaged −13 ± 5%, and systolic strain in the basal lateral wall was markedly reduced to −9±6%, a sign of both reduced regional LV function and replacement fibrosis in loco typico.

Three patients did not receive cMRIs, due to claustrophobia; one was not eligible due to terminal renal insufficiency/dialysis. All patients with cMRIs (n = 12) showed replacement fibrosis in loco typico. All patients who did not receive cMRIs had visible and quantifiable thinning of the posterior wall (defined as LV posterior wall thickness at end diastole ≥2 mm thinner than the IVSd). Figure 1 shows representative examples of echocardiography and cMRI.

Table 3 lists the results from the ECGs at rest. Only 2 patients had a prolonged QTc interval. Seven patients had a positive LV Sokolov index for LV hypertrophy, and 11 patients had T negativities in V5 and V6. Figure 1 shows a typical ECG at rest.

All patients were in sinus rhythm for both the resting and Holter ECG recordings. During the Holter ECG, the mean heart rate was 68 ± 10 during the day and 57 ± 6 during the night. No relevant bradycardia or VT was detected. Three patients had ventricular runs for <10 beats. Eight patients had supraventricular runs with maximums of <25 beats.

Table 4 lists all the clinically relevant events recorded. Three male patients had a documented asystole that prompted a recommendation for pacing therapy. One patient experienced syncope, one experienced dizziness, and the third patient had no noticeable symptoms. Because these 3 patients had also at least one VT documented with the event recorder, the final recommendation was an ICD implant, which had an implemented pacing function. One female patient experienced 6 events of asystole, and the longest electrical ventricular pause lasted 3.4 seconds. Because she was completely asymptomatic, she was not scheduled for a device implantation; instead, she received a careful watch and wait regime. Figure 2 shows typical recordings for 2 patients with asystole.

One male patient experienced several episodes of symptomatic bradycardia; thus, pacemaker implantation was recommended. One male patient experienced bradycardia of 26 beats/min, and he experienced syncope. Because this patient had severe cardiac hypertrophy and a large area of fibrosis (3.21% of the LV), a prophylactic ICD was recommended. In another male patient who had been taking a β blocker, we detected one asymptomatic bradycardia of 27 beats/min. The recommendation for this patient was termination of beta-blocker therapy. In addition, 4 patients (1 woman and 3 men) had several documented episodes of asymptomatic bradycardia. Based on these events, a careful watch and wait regime was recommended. However, later, 3 of these patients (all men) had a documented VT; thus, an ICD was recommended. Figure 2 shows typical intracardiac electrograms (IEGMs) from 2 patients with bradycardia.

In 3 male and 2 female patients, the loop recorder documented intermittent asymptomatic AF that lasted at least 3 minutes. Because all 5 patients had hypertrophic cardiomyopathy, therapeutic anticoagulation was recommended. Figure 3 shows typical IEGM data from 2 patients with intermittent AF.

Table 2
Organ specific values

Patient number	Echocardiography												Magnetic Resonance Imaging					
	LVDd (mm)	LVDs (mm)	IVSd (mm)	LVPWd (mm)	EF (%)	LA (mm)	DT (ms)	E/E′	AO root (mm)	LV hypertrophy	Thick papillary muscle	Posterior wall thinning	LVMI (g/m^2)	LVED Vol. (ml)	LVES Vol. (ml)	Stroke Vol. (ml)	Cardiac output (l/min)	Fibrosis (%)
1	45	27	12	12	59	38	283	15	39	+	+	0	146	152	37	115	6.9	1.23
2	39	20	18	16	63	41	160	12	32	+	+	0	205	115	34	81	4.6	1.21
3	46	35	11	7	61	37	228	19	35	+	+	+	NA	NA	NA	NA	NA	NA
4	54	36	12	13	55	36	197	12	43	+	+	0	127	179	77	102	5.9	2.14
5	45	29	11	11	73	36	224	13	37	+	+	0	77	135	35	100	6.6	0.74
6	60	31	11	10	76	41	187	11	33	+	+	0	109	198	36	162	9	1.12
7	47	28	12	10	54	40	195	18	32	+	+	0	117	130	39	91	5.6	2.8
8	55	42	13	7	59	42	181	10	42	+	+	+	NA	NA	NA	NA	NA	NA
9	51	24	13	13	55	36	275	14	35	+	+	0	131	117	36	81	6.1	4.27
10	39	24	13	11	68	37	301	14	34	+	+	+	NA	NA	NA	NA	NA	NA
11	64	50	11	11	51	40	135	12	41	+	0	0	107	263	140	123	6.6	0.65
12	50	32	12	9	71	38	352	20	39	+	+	+	111	180	58	122	6.3	3.92
13	42	27	12	13	67	28	268	10	32	+	+	0	85	156	53	103	7.7	1.03
14	47	23	14	13	70	41	181	16	28	+	+	0	133	110	26	84	5.9	1.86
15	37	23	20	15	60	38	208	16	31	+	+	+	NA	NA	NA	NA	NA	NA
16	39	25	17	18	63	36	256	19	34	+	+	0	183	107	33	70	4.8	3.21
Mean	48 ±8	30 ±8	13 ±3	12 ±3	63 ±7	38 ±3	233 ±58	14 ±3	35 ±4	+=16 (100%)	+=15 (64%)	+=5 (31%)	124 ±36	149 ±44	49 ±30	101 ±24	6.5 ±1.2	1.86 ±1.33

AO = aortic; DT = deceleration time; EF = ejection fraction; LV = left ventricular; LVDd = left ventricular diastolic diameter; LVED = left ventricular end-diastolic; LVES = left ventricular end-systolic; LVMI = left ventricular mass index; LVSd = left ventricular systolic diameter; LVPWd = left ventricular posterior wall thickness at diastole; IVSd = interventricular septal wall thickness at diastole; NA = not available.

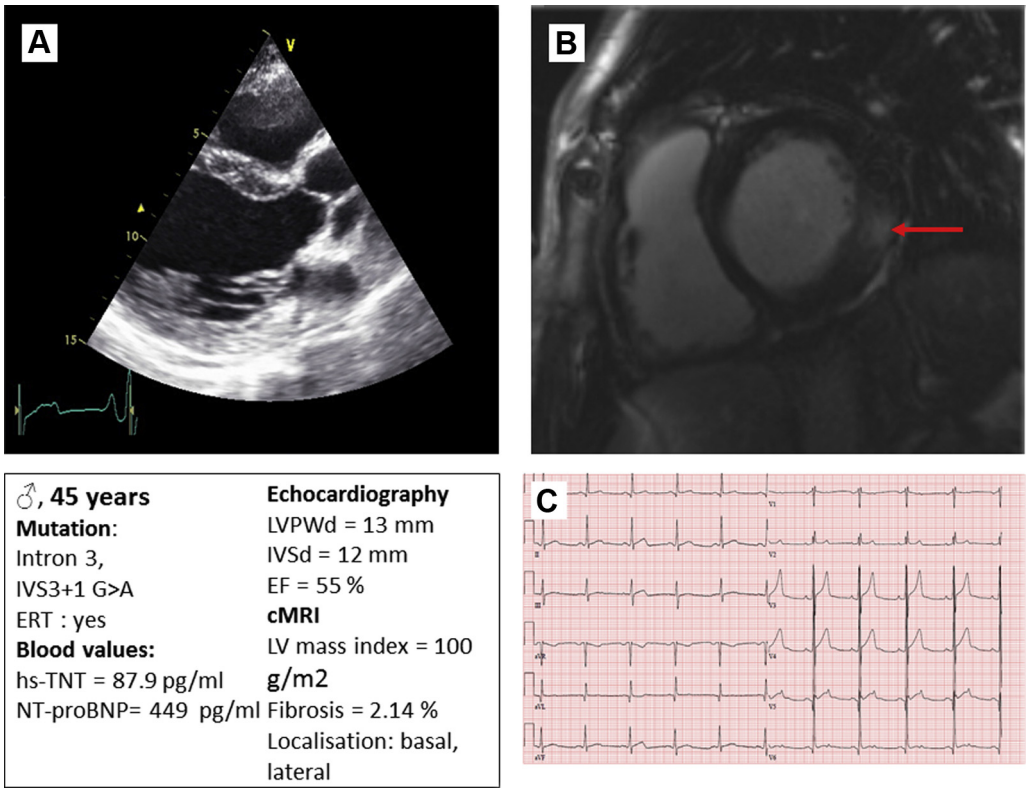

Figure 1. Example of a 45-year-old male patient with typical, advanced Fabry cardiomyopathy. In this patient, bradycardia, asystole, intermittent AF, and sustained VT were detected with an implanted loop recorder. *Left (A)*: representative echocardiography from a parasternal long-axis viewpoint shows eccentric hypertrophic cardiomyopathy. *Right top (B)*: representative cardiac magnetic resonance image in the short-axis orientation. The *red arrow* indicates a large area with positive LE, which indicates replacement fibrosis. *Right bottom (C)*: 12-lead, resting electrocardiograph with signs of LV hypertrophy in advanced Fabry cardiomyopathy. EF = ejection fraction; hs-TNT = highly sensitive troponin; LV = left ventricle; LVPWd = left ventricular posterior wall thickness at end diastole; NT-proBNP = N-terminal propeptid of the brain natriuretic peptide.

Table 3
Electrocardiography

Patient number	Heart rhythm	Heart axis	Heart rate (min^{-1})	P- dur. time (ms)	PQ dur. (ms)	QRS dur. (ms)	QTc dur. (ms)	Sokolow index (+/0)	T-wave negativity (+/0)	ST elevation (+/0)
1	SR	Vertical	56	100	120	130	425	+	+	0
2	SR	Intermediate	54	80	100	100	588	+	+	0
3	SR	Intermediate	68	80	120	80	383	0	+	0
4	SR	Intermediate	64	100	150	100	427	+	0	0
5	SR	Intermediate	64	100	120	100	392	0	0	0
6	SR	Intermediate	52	100	140	90	400	+	0	0
7	SR	Intermediate	50	110	140	120	420	+	+	0
8	SR	Left	52	80	160	130	437	0	+	0
9	SR	Intermediate	91	90	110	100	394	+	+	0
10	SR	Intermediate	78	80	80	100	388	0	0	0
11	SR	Intermediate	52	110	180	120	382	+	0	0
12	SR	Left	72	100	110	110	427	0	+	0
13	SR	Left	54	100	110	100	379	0	+	0
14	SR	Left	58	100	160	160	492	0	+	0
15	SR	Intermediate	64	90	150	110	434	0	+	0
16	SR	Intermediate	80	80	130	100	439	0	+	0
Mean			63±12	95±11	130±26	109±19	426±53	+=7(44%)	+=11(67%)	+=0 (0%)

Dur = duration; SR = sinus rhythm.

VTs were documented in 4 male patients. Of these, 3 had sustained VTs, with syncope in one, chest pain in another, and no symptoms in the third; accordingly, ICDs were recommended. The fourth patient had 2 nonsustained asymptomatic VTs, and the longer episode lasted 16 seconds at a heart rate of 200 beats/min. This patient also

Table 4
Events detected by implantable loop recorder separated for clinical relevance (= changing therapy, n = 15) and irrelevance (= watch and wait, n = 6)

Event: Asystole					
Patient number	Numbers	Type of Event	Max. duration (sec)	Time	Recommendation
6	4x	Asystole	3.7	6-9 am	ICD-Implantation*
4	3x	Asystole	3.3	10 pm-9am	ICD-Implantation*
1	53x	Asystole	4.4	10 pm-12 am	ICD-Implantation*
2	6x	Asystole	3.3	10 pm-6am	Watch and wait
Event: Bradycardia					
Patient number	Numbers	Event	Min. frequency (1/min)	Time	Recommendation
5	19x	Bradycardia	39	10 pm-12 am	Pacemaker-Implantation
9	1x	Bradycardia	27	6-9 am	Termination of β-Blockers
16	1x	Bradycardia	26	9-12 am	ICD-Implantation†
3	1x	Bradycardia	54	10 pm-6 am	Watch and wait
4	>1700x	Bradycardia	37	10 pm-9 am	Watch and wait
6	>1400x	Bradycardia	38	9 pm-12 am	Watch and wait
8	>5000x	Bradycardia	36	10 pm-9 am	Watch and wait
Event: Atrial Fibrillation					
Patient number	Event		Max. frequency (1/min)	Max. time (sec)	Recommendation
1	Intermittent AF		46	>85000	Anticoagulation
3	Intermittent AF		105	7200	Anticoagulation
6	Intermittent AF		103	1560	Anticoagulation
4	Intermittent AF		120	240	Anticoagulation
7	Intermittent AF		122	1560	Anticoagulation
Event: Ventricular Tachycardia					
Patient number	Numbers	Event	Max. frequency (1/min)	Max. time (sec)	Recommendation
1	3x	VT	188	48	ICD-Implantation
4	5x	VT	200	360	ICD-Implantation
6	2x	VT	200	16	ICD-Implantation
8	3x	VT	206	45	ICD-Implantation
3	1x	VT	200	4	Watch and wait

AF = atrial fibrillation; ICD = implantable cardioverter–defibrillator; VT = ventricular tachycardia.
* Because of additional ventricular tachycardia.
† Because of large area of fibrosis.

presented with episodes of bradycardia, which suggested a pacing indication. Therefore, the final decision was to implant an ICD. In addition, one female patient had an asymptomatic nonsustained VT, which lasted 4 seconds. In this patient, a careful watch and wait regime was recommended. Figure 3 shows typical IEGM examples from 2 patients with VTs.

When comparing clinically relevant events and the evaluated general and cardiomyopathy parameters, no significant correlation for any parameter was detected in these patients who were by the definition of inclusion criteria advanced cardiomyopathies.

Discussion

It is well established that patients with Fabry disease can develop clinically relevant arrhythmias; in addition, most die due to cardiac complications.[8,13] However, no previous study has systematically investigated both the frequency and the kind of arrhythmias in patients at risk. The present prospective study focused on detecting relevant arrhythmias that could change clinical management in patients with advanced Fabry cardiomyopathy. Our main findings were: (1) modern technology has made it feasible to provide permanent telemonitoring for all types of arrhythmias; (2) a high number of clinically relevant arrhythmias were detected over time in Fabry hearts with advanced replacement fibrosis, despite negative results from an initial Holter ECG; (3) we found both supraventricular and ventricular arrhythmias; consequently, a specific treatment was necessary in most patients to prevent stroke, syncope, and sudden cardiac death.

Advanced Fabry cardiomyopathy is characterized by LV hypertrophy and replacement fibrosis in the basal posterolateral wall.[2,6,7,14–16] The present study focused on patients with Fabry disease that showed either a direct sign of replacement fibrosis (2 LE positive segments) or an indirect sign of severe fibrosis (regional wall motion abnormalities in the posterolateral wall). The presence of fibrosis was the main inclusion criterion, because a recent study showed a

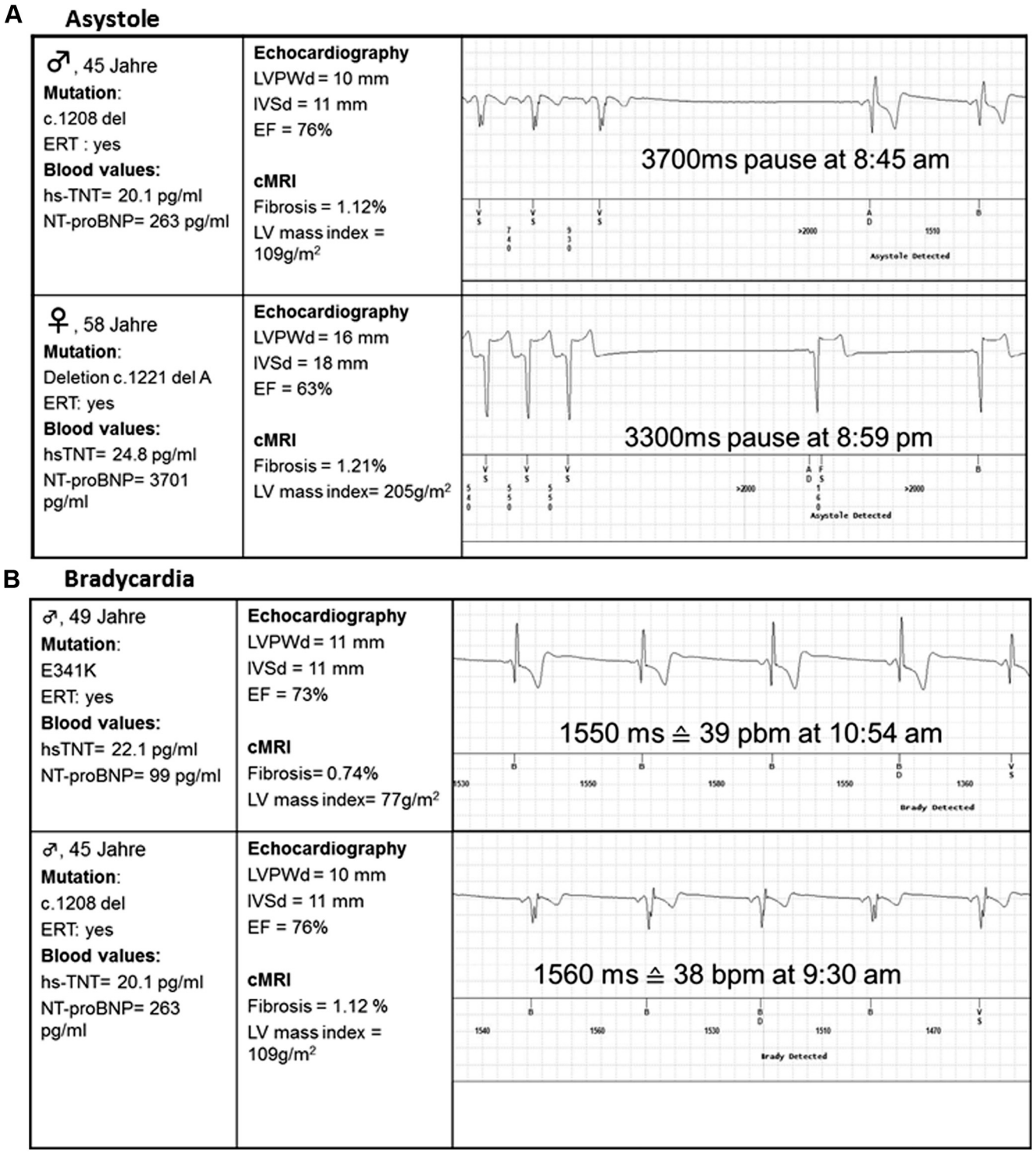

Figure 2. Examples of arrhythmias detected in patients with Fabry who received an implanted loop recorder. ECGs show: *(A)* 2 patients with asystole and *(B)* 2 patients with bradycardia. EF = ejection fraction; HR = heart rate; hs-TNT = highly sensitive troponin; LV = left ventricle; LVPWd = left ventricular posterior wall thickness at end diastole; NT-proBNP = N-terminal propeptid of the brain natriuretic peptide.

close correlation between the burden of fibrosis and malignant arrhythmias in patients with Fabry cardiomyopathy.[9] In these patients, considered at risk, careful monitoring is desirable. An implantable loop recorder, such as the Reveal XT device, is an expedient tool for permanent telemonitoring.[10] By transmitting all detected arrhythmias through telephone to the Fabry center, it was possible to securely diagnose, and subsequently, treat all relevant arrhythmias. The loop recorder detected different types of supraventricular arrhythmias, including AF, bradycardia,

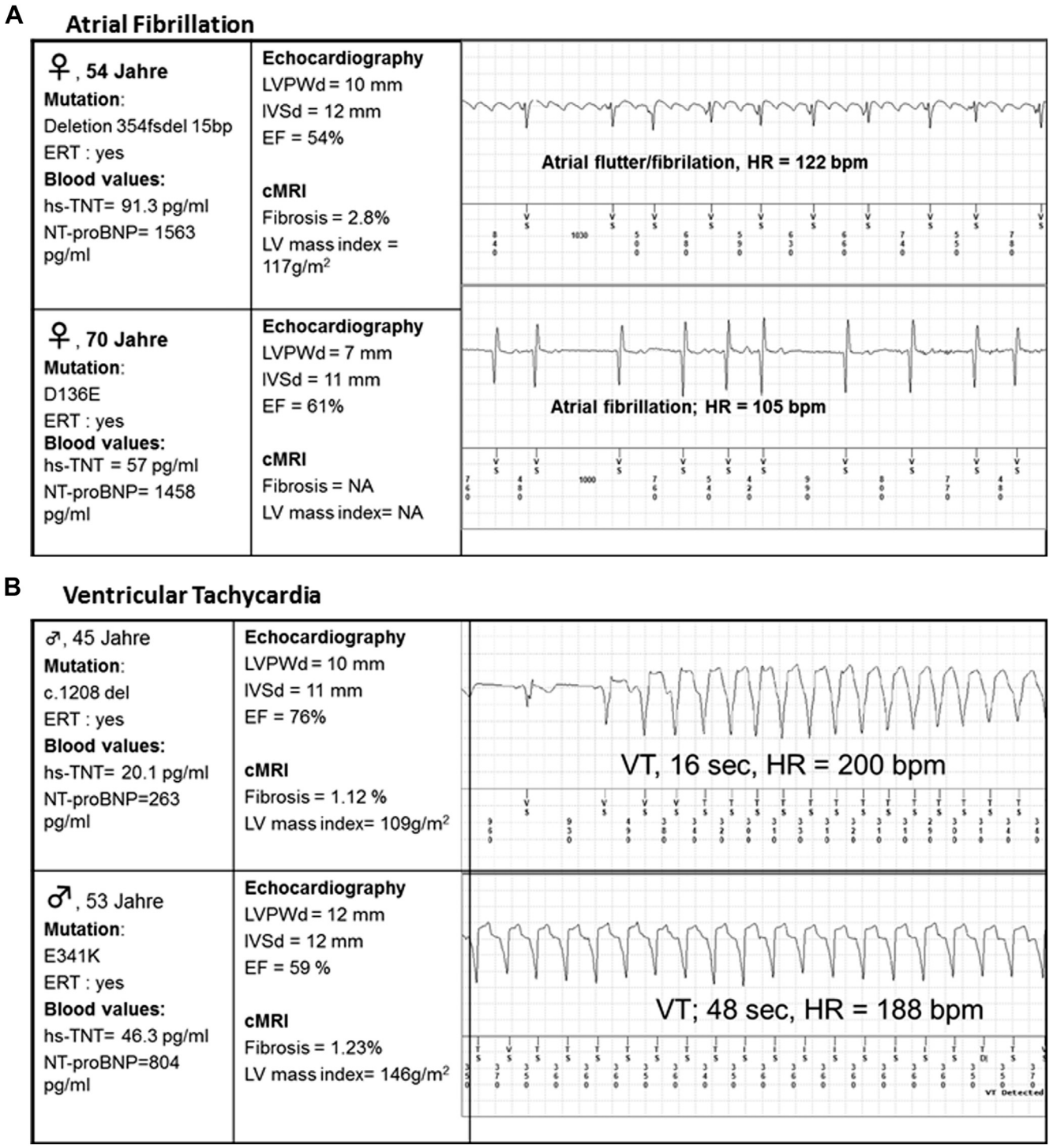

Figure 3. Examples of arrhythmias detected in patients with Fabry who received an implanted loop recorder. ECGs show: *(A)* 2 patients with intermittent AF and *(B)* 2 patients with VT. EF = ejection fraction; HR = heart rate; hs-TNT = highly sensitive troponin; LV = left ventricle; LVPWd = left ventricular posterior wall thickness at end diastole; NT-proBNP = N-terminal propeptid of the brain natriuretic peptide.

and sinus arrest. Although all patients had sinus rhythm at baseline (an inclusion criterion), the E/E′ was above 10 in all patients, which suggested elevated LA pressure. In addition, LA size was increased in a lot of patients. Consistent with clinical experience, it was not surprising to find that a dilated LA with increased pressure was vulnerable to supraventricular arrhythmias. These morphologic and electrical LA abnormalities are typical for advanced hypertrophic cardiomyopathy in patients with general and Fabry cardiomyopathies.[13,17–19]

More dangerous than atrial arrhythmias, we frequently detected ventricular arrhythmias, such as nonsustained and

sustained VTs, in patients considered at risk. Interestingly, none of the patients with a documented VT exhibited prolonged QT intervals on the ECG at rest. Although all these patients with VT had myocardial fibrosis, based on the inclusion criteria, they did not have the largest volumes of fibrosis. Thus, neither the ECG at rest nor the total quantities of fibrosis were good predictors for the VTs later documented. When asked, only 1 patient reported that he experienced syncope during the VT. Thus, it seemed clear that many potentially life-threatening arrhythmias are not recognized by patients with progressive Fabry disease. The exact origin of these VTs remains an open question. Recent studies in ischemic and dilated cardiomyopathy have shown that the presence of midventricular LE/fibrosis was closely associated with the development of VTs. That finding suggested that these tachycardias are often generated at the border zone of myocardial fibrosis or a scar.[20−22] Thus, it can be speculated that the VTs may originate at the basal posterolateral wall, where cMRI data indicated that all patients had replacement fibrosis; consequently, progressive fibrosis visualized with MRI may be an indicator of generalized electrical instability of the heart. In this study, all patients with a sustained VT received an implanted ICD for primary prophylaxis of sudden cardiac death.

Current guidelines for managing patients with Fabry recommend an annual Holter ECG.[9] However, our results suggested that the Holter ECG might not be sufficient for patients at risk. Instead, in patients with severe Fabry cardiomyopathy, continuous surveillance with an implanted loop recorder and telemonitoring should be preferred.

Stroke is also a very common clinical event in patients with early and advanced Fabry.[23,24] Our data confirmed that many patients with advanced cardiomyopathy develop intermittent AF, which may explain the potential for thromboembolic stroke. Thus, in patients at risk, a thorough search for AF should be performed, and in case of a positive finding, therapeutic anticoagulation should be discussed.

The worst clinical event in Fabry disease is sudden cardiac death, which has been described as a major factor in the diminished life expectancy of these patients.[9,25] The present study confirmed previous studies,[8,13] which showed that patients with advanced cardiomyopathy frequently develop VT. Based on other forms of hypertrophic cardiomyopathy, it is well known that rhythm events, such as VT and ventricular fibrillation, are primarily responsible for sudden cardiac death.[17] This suggests that, whenever a sustained VT is documented in a patient with Fabry, an ICD should be discussed. Further studies must determine whether this intervention will effectively prolong life expectancy in these patients.

This prospective study focused on detecting clinically relevant arrhythmias. Thus, we did not primarily aim to investigate advanced pharmaceutical and device-related therapy for arrhythmias in patients with Fabry.

Although 120 Fabry patients were screened, the total number of patients included in the present study was relatively low. This was because we only included patients with very advanced Fabry cardiomyopathy. Because large numbers of events were detected in most of the selected patients, despite negative initial 12-channel and Holter ECGs, we speculated that the inclusion criteria may have been too strict. In this context, it is very interesting that in these advanced cardiomyopathy hearts, no significant correlation for any parameter with the events was detected, even not for the gender. Thus, further studies should use an implanted loop recorder to focus on the earlier stages of Fabry cardiomyopathy.

Disclosures

Drs. Weidemann, Canan-Kühl, and Wanner received speaker honoraria from Genzyme and from Shire Corporation. Drs. Weidemann and Wanner are members of the Fabry Registry European Board of Advisors and have received travel assistance and speaker honoraria. Research grants were given to the Institution by Genzyme and Shire Corporations. Drs. Maier and Becher received speaker honoraria and research funding from Medtronic GmbH, Germany. The other authors have no conflicts of interest to disclose.

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