Electrical Changes in Resting, Exercise, and Holter Electrocardiography in Fabry Cardiomyopathy

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Abstract *Background:* In Fabry cardiomyopathy, little is known about the interaction between its key feature of myocardial replacement fibrosis and changes in resting, Holter, and exercise electrocardiography (–ECG).

Methods and Results: Resting ECG, 24-h Holter ECG, and exercise ECG were performed in 95 patients (50 women) with Fabry disease, staged using cardiac magnetic resonance imaging to measure left ventricular fibrosis. With resting ECG, T alterations were seen in patients with cardiac fibrosis, while time intervals and rhythm were unchanged (except for a longer QRS duration in patients with severe fibrosis). All patients with severe fibrosis showed T inversion, ST alteration, or both. With Holter ECG, maximum and minimum heart rate did not differ with fibrosis severity. Patients without fibrotic tissue showed less ventricular premature beats (VPB) (median 5/24 h) compared to those with mild (median 11/24 h) or severe fibrosis (median 115/24 h; $P < 0.05$, respectively). Fibrosis was a

strong predictor of VPB burden ($r^2 = 0.5$; $P < 0.001$). During exercise, patients with severe fibrosis had the least increase in systolic blood pressure (sBP) (47 ± 22 mmHg vs. 62 ± 25 mmHg, $P < 0.05$) and the lowest maximum heart rate (113 ± 18 /min; $P < 0.05$). Patients with mild fibrosis had a high sBP during exercise (198 ± 37 mmHg; $P < 0.05$). Decreased diastolic blood pressure (>10 mmHg) occurred in some patients with no (3/41) or mild fibrosis (3/34) but not in patients with severe fibrosis (0/20; $P < 0.01$).

Conclusions: Our data suggest that cardiac replacement fibrosis is responsible for repolarization abnormalities on resting ECG and increased VPB with Holter ECG. During exercise ECG, advanced cardiomyopathy is characterized by chronotropic incompetence with limitations on blood pressure and heart rate increase.

Introduction

Fabry disease (FD) is an X-linked lysosomal storage disorder based on deficiency of the enzyme alpha-galactosidase A, which results in multisystemic disease mainly affecting the heart, kidney, and nervous system (Zarate and Hopkin 2008). In general, effects on the heart are well described as a concentric hypertrophic cardiomyopathy with reduced regional myocardial function (Breunig et al. 2003; Weidemann et al. 2010; Linhart et al. 2000). Another key feature is myocardial replacement fibrosis, detected with cardiac magnetic resonance imaging (cMRI) (Moon et al. 2003, 2006). In early reports, a short P–R interval was described as one of the typical alterations on electrocardiography (ECG) (Roudebush et al. 1973), but a large cross-sectional study failed to confirm this finding (Niemann et al. 2013). So far, information about electrical alterations

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Fig. 1 A typical cMRI picture which shows the late enhancement (the *arrow* indicates the fibrotic area in the inferolateral wall) and the left ventricular hypertrophy. *cMRI* cardiac magnetic resonance imaging

has been largely derived from cross-sectional studies, and exercise testing is not regularly used for clinical evaluation in FD (Koskenvuo et al. 2010).

For this reason, a detailed examination of the different ECG modalities according to the stage of the cardiomyopathy has not yet been reported. In this study, we sought to evaluate the relevance of resting ECG, Holter ECG, and exercise ECG in the routine surveillance of FD cardiomyopathy according to cMRI-based staging of the disease.

Methods

Study Population

A total of 185 patients were initially screened at their first visit to the Fabry center in Würzburg, Germany. Inclusion criteria were (1) genetically proven FD, (2) no contraindications for magnetic resonance imaging with contrast agent, (3) no enzyme-replacement therapy (ERT), (4) absence of coronary artery disease, and (5) informed consent for all examinations and participation in the study.

Ultimately, 95 patients (50 women) were included. Reasons for exclusion were contraindications for cMRI such as claustrophobia, hip implant, pacemakers, or severe renal dysfunction ($\text{eGFR} < 30 \text{ mL/min/1.73 m}^2$), lack of consent, or ERT at baseline. At the first visit, gadolinium-contrast cMRI of the heart was performed in all patients. In addition, resting ECG, 24-h Holter ECG, and exercise ECG

were performed within 2 days of this visit. Clinical examination was performed in the context of a standard clinical investigation program for Fabry patients. According to the Declaration of Helsinki, written informed consent was obtained from all patients or their guardians.

Patient myocardial fibrosis was analyzed according to the amount of late enhancement (LE) in the left ventricular (LV) myocardium (for quantification methods, see below). The mean amount of myocardial fibrosis in LE-positive patients was $1.9 \pm 0.2\%$. A value of $\geq 2\%$ was chosen to distinguish between patients with mild ($n = 34$; $\text{LE} < 2\%$) and severe fibrosis ($n = 20$; $\text{LE} \geq 2\%$) according to the quartiles of distribution of LE. Forty-one patients showed no fibrosis on cMRI.

Magnetic Resonance Imaging and Assessment of Fibrosis

cMRI was performed after intravenous injection of gadopentetate dimeglumine 0.2 mmol/kg (Magnevist, Schering AG, Berlin, Germany) on a 1.5 T scanner (Magnetom Symphony Quantum, Siemens Medical Systems, Erlangen, Germany). Pictures were acquired with inverse recovery sequences (8-mm slice thickness, breath hold, field of view $240 \times 320 \text{ mm}^2$, matrix size 165×256 , repetition time 7.5 ms, echo time 3.4 ms, flip angle 25°). All consecutive short axis slices were used for manually measuring the area with pathological mid- or transmural LE (Fig. 1). The sum of areas was multiplied by the slice thickness and then set in relation to LV myocardium volume. Every segment

of the employed 17 segment model was scanned separately for the occurrence of pathological LE.

Resting ECG, Holter ECG, and Exercise ECG

Twelve-lead surface resting-ECG measurements were recorded manually at a sweep of 25 mm/s and, if necessary, 50 mm/s. Readouts were analyzed by a reader blinded to disease stage. Standard criteria were applied as follows: normal PR interval, 120–200 ms, and normal QRS duration, 70–110 ms. LV hypertrophy was assessed using the Sokolow–Lyon index adding the S wave in lead V1 or V2 (whichever was larger) and the R wave in lead V5 or V6 (whichever was larger), with a cutoff of 3.5 mV. Right ventricular (RV) hypertrophy was assessed using the RV Sokolow index adding the R wave in lead V1 and the S wave in lead V5 or V6 (whichever was larger), with a cutoff of 1.05 mV. The QT interval (normal 300–440 ms) was measured from the beginning of the QRS complex to the end of the T wave, defined as the intersection of the tangent to the down slope of the T wave and the isoelectric line. Corrected QT duration (normal <440 ms) was calculated using Bazett's formula. For inverted 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 of ≥ 2 mm in precordial leads and ≥ 1 mm in limb leads. ST-segment decline was defined as a J-point decline of ≥ 1.5 mm in precordial leads and ≥ 1 mm in limb leads.

Holter ECG was started between 8 and 10 a.m. and continued for a mean of 22.3 h, followed by data analysis by a reader blinded to disease stage. Premature beat counts were performed automatically with manual correction. All counts were then corrected to a fictive duration of exactly 24 h by multiplying with the ratio of 24:00 h and exact recording time. Premature beats were classified by ventricular (VPB) or supraventricular (SVPB) origin and ranked as single, couplet, triplet, or run. Runs were defined as more than three consecutive VPB. Tachycardic episodes (i.e., periods with heart rate >100/min) were also counted.

Exercise ECG was performed with physical stress on a bicycle ergometer. Work load was increased every 2 min by 25 W until target heart rate (180 minus age) was achieved or stopping criteria were reached. The latter included apparent physical exhaustion, angina pectoris, dizziness, dyspnea, or ST decline ≥ 3 mV, ST elevation ≥ 1 mV, sustained ventricular tachycardia, or >20 mmHg decrease in systolic blood pressure (sBP). Analysis of these data was also performed by researchers blinded to the disease stage.

Statistical Analysis

Values are presented as absolute numbers (%), mean (SD), or median (quartiles, as appropriate). Differences between two groups were tested using paired or unpaired *t* tests, Chi-square test, or Fisher's exact test, as appropriate. Two-way ANOVA was used for comparisons of three or more groups, with Duncan post hoc analysis or with Kruskal–Wallis test followed by a Bonferroni-corrected Mann–Whitney *U*-test.

P values <0.05 or corrected values in multiple testing were considered to indicate statistical significance. Data were analyzed using SPSS version 22 (SPSS Inc., Chicago, IL).

Results

The clinical characteristics of the entire cohort are shown in Table 1. Mean age was 38 ± 12 years, and 53% of the FD patients were women. All calculations were performed under separate exclusion of patients under vasoactive drugs (beta-blocker, ACE inhibitors, calcium antagonists). With no changes in the results, we abstained from separate presentation.

Resting ECG

All resting-ECG results are presented in Table 2. Data for resting ECG showed no significant differences between different stages of the cardiomyopathy in terms of rhythm, vector, P duration, and PR time. QRS duration was elongated in patients with severe fibrosis (105 ± 16 vs. 92 ± 18 ms; $P < 0.05$). QT time and QTc time also did not differ among cardiomyopathy stages. In contrast, T inversion in V5 and V6 (representing the posterolateral wall) were more frequent in patients with fibrosis (no fibrosis 9.7% vs. fibrosis 52%; $P < 0.05$) but showed only a trend for a difference among patients with mild (41%) and severe fibrosis (70%; $P = 0.065$). ST-segment depression and elevation were common in patients with fibrosis (Table 2). All patients with severe fibrosis showed either T-wave inversion, ST-segment alteration, or both ($P < 0.05$, respectively). The LV Sokolow–Lyon index was elevated in all patients according to increasing LV mass as assessed by cMRI, and a higher percentage of patients with severe fibrosis had a right bundle branch block (3/20) compared with patients with mild (0/34) and without fibrosis (1/41; $P < 0.01$, respectively).

Table 1 Basic characteristics of Fabry patients

<i>Basic data</i>	
Sex (female/male)	50/45 (53/47)
Alpha-galactosidase activity (nmol/min/mg)	0.14 (0.07)
Age (years)	38 (12)
Height (m)	1.72 (0.10)
Weight (kg)	69 (14)
BMI (kg/m ²)	23.4 (4.2)
<i>Medication</i>	
Beta-blocker (<i>n</i>)	8 (8.4)
Calcium channel blocker (<i>n</i>)	2 (2.1)
ACE inhibitor (<i>n</i>)	22 (23)
Aspirin (<i>n</i>)	14 (15)
<i>cMRI, left ventricular assessment</i>	
Amount of fibrosis (%)	1.1 (1.7)
Mass (g/m ²)	82 (32)
End-diastolic volume (mL/m ²)	77 (23)
End-systolic volume (mL/m ²)	29 (14)
Stroke volume (mL/m ²)	48 (13)
Ejection fraction (%)	63 (8)
Cardiac index (L/min/m ²)	3.2 (0.9)
Septal wall thickness (mm)	11 (0.4)

Data are absolute numbers (%) or mean (SD)

ACE angiotensin-converting enzyme, BMI body mass index

Holter ECG

Results for the Holter ECG are presented in Table 3. Holter ECG was recorded for a mean of 22.3 h. Average, maximum, and minimum heart rate did not differ between patients with or without fibrosis. Patients with severe fibrosis had fewer tachycardic episodes (heart rate >100/min; 4.7 ± 5.5) compared to those without fibrosis (8.9 ± 7.8 ; $P < 0.05$) but a longer total time with tachycardia (65 ± 22 min vs. 12 ± 9 ; $P < 0.01$).

Patients with severe fibrosis had a higher median of SVPB with 47 (3–132) than patients with mild fibrosis (19 (4–43); $P < 0.01$) and patients with no fibrosis with a median of 9 (4–20); $P < 0.01$). The difference between no fibrosis and mild fibrosis was significant ($P < 0.05$). Interestingly, the median number of supraventricular couplets did not differ between the mild and severe fibrosis patients (2 (1–9) vs. 1 (1–4), respectively; $P = 0.12$) but differed from those without fibrosis (0 (0–2); $P < 0.05$, respectively). Supraventricular runs occurred only in patients with fibrosis.

VPB frequency was the most apparent difference among the groups (Fig. 2). Patients with severe fibrosis had a median of 115 (45–181) VPB in 24 h compared to a median of 11 (5–21) in those with mild fibrosis ($P < 0.01$)

and a median of 5 (2–18) in those with no fibrosis ($P < 0.01$). No patient in the advanced stages of fibrosis had fewer than 20 VPB. Ventricular couplets accumulated only in severely fibrotic hearts (2 (2–5) 11 ± 40 vs. mild fibrosis, 0 (0–1) 0.5 ± 0.9 , $P < 0.01$; and no fibrosis, 0 (0–0) 0.5 ± 1.0 , $P < 0.01$). Ventricular triplets and runs occurred only in patients with fibrosis but did not significantly differ among the various severity groups. Pearson's correlation coefficient for total fibrosis relative to VPB count was 0.71 ($P < 0.01$). Received operating characteristic analysis identified VPB on Holter ECG as a good noninvasive predictor of the existence of LV LE and thus for Fabry cardiomyopathy stage (area under the curve = 0.87; $P < 0.001$).

Exercise ECG

The results of exercise ECG are presented in Table 4 and indicate a decreased working capacity in advanced cardiomyopathy stages. Patients with severe fibrosis had lower maximum working capacity (97 ± 30 W) compared to patients without fibrosis (129 ± 33 W; $P < 0.05$) while those with no or mild fibrosis (114 ± 42 W) did not differ significantly ($P = 0.11$). Maximum heart rate under stress was lower in patients with severe fibrosis (113 ± 18 /min)

Table 2 Data of resting ECG grouped by stage of the cardiomyopathy according to LE-positive myocardium

	No fibrosis (<i>n</i> = 41)	Mild fibrosis (<i>n</i> = 34)	Severe fibrosis (<i>n</i> = 20)	Total (<i>n</i> = 95)
Female	28 (68)	16 (47)	6 (30)	50 (53)
Age (years)	33 (13)	39 (10) ^a	46 (9) ^b	38 (11)
<i>Rhythm</i>				
Sinus rhythm	41 (100)	33 (97)	19 (95)	93 (98)
Atrial flutter	0	0	0	0
Atrial fibrillation	0	1 (3)	1 (5)	2 (2)
<i>QRS axis vector</i>				
Indifferent	18 (44)	16 (47)	9 (45)	43 (45)
Vertical	19 (46)	13 (38)	6 (30)	38 (40)
Left	4 (9.7)	4 (12)	4 (20)	12 (13)
Right	0	1 (2.9)	1 (5.0)	2 (2.1)
LBBB	1 (2.4)	0	0	1 (1.0)
RBBB	1 (2.4)	0	3 (15) ^b	4 (4.2)
P duration (ms)	97 (12)	95 (18)	98 (18)	97 (16)
PR interval (ms)	138 (22)	131 (30)	131 (26)	135 (26)
QRS duration (ms)	92 (18)	99 (13) ^a	105 (16) ^b	97 (17)
QT duration (ms)	383 (36)	388 (32)	388 (36)	388 (34)
QTc duration (ms)	409 (33)	409 (27)	404 (31)	409 (31)
ST segment elevation	13 (32)	19 (56) ^a	14 (70) ^b	46 (48)
ST segment depression	2 (4.8)	6 (18)	6 (30) ^b	14 (15)
T wave inversion (<i>n</i>)	4 (9.7)	14 (41) ^a	14 (70) ^b	32 (34)
ST segment and/or T wave alteration (<i>n</i>)	13 (32)	20 (58) ^a	20 (100) ^{b, c}	53 (56)
SVPB count (<i>n</i>)	0	0	0 (0–1)	0 (0–0)
VPB count (<i>n</i>)	0	0	0 (0–1)	0 (0–0)
LV Sokolow index (mm)	24 (10)	31 (12) ^a	34 (5) ^b	29 (13)
RV Sokolow index (mm)	5 (9)	6 (4)	8 (5)	6 (4)

No fibrosis (0%); mild fibrosis ($\leq 2\%$); severe fibrosis ($> 2\%$)

Data are absolute numbers (%) or mean (SD)

ECG electrocardiogram, LBBB left bundle branch block, LE late enhancement, LV left ventricle, RBBB right bundle branch block, RV right ventricle, SVPB supraventricular premature beat, VPB ventricular premature beat

^a*p*-value < 0.05 for no fibrosis vs. mild fibrosis

^b*p*-value < 0.05 for no fibrosis vs. severe fibrosis

^c*p*-value < 0.05 for mild fibrosis vs. severe fibrosis

compared to those with mild ($132 \pm 25/\text{min}$) and no fibrosis ($144 \pm 26/\text{min}$; $P < 0.05$, respectively). Induced VPB more often occurred in patients with fibrosis (severe fibrosis, 2 (1–2); mild fibrosis, 1 (0–2) than those without it (0 (0–2); $P < 0.05$, respectively).

Differences among groups also were observed in blood pressure behavior during exercise. Patients with severe fibrosis had the highest sBP at rest (132 ± 70 mmHg) compared to those with mild (124 ± 18 mmHg) or no fibrosis (121 ± 21 mmHg; $P < 0.05$, respectively). Maximum sBP during exercise was significantly higher with mild fibrosis (198 ± 37 mmHg) compared to no fibrosis (183 ± 32 mmHg; $P < 0.05$), whereas patients with severe fibrosis showed the lowest maximum sBP (180 ± 28

mmHg; $P < 0.05$). In addition, sBP increase during exercise was lowest in patients with severe fibrosis (47 ± 22 mmHg) compared to those with no (62 ± 24 mmHg; $P < 0.01$) or mild fibrosis (76 ± 34 mmHg; $P < 0.01$). The sBP increase per watt was elevated only in the mild fibrosis group (0.7 ± 0.4 mmHg/W; $P < 0.05$, respectively).

An increase in sBP of more than 50 mmHg was more frequent in patients without fibrosis (71%) compared to those with mild (52%; $P < 0.05$) and severe fibrosis (40%; $P < 0.05$), and sBP declines did not occur (Fig. 3). Mean diastolic blood pressure (DBP) at rest or during exercise did not differ among groups (Table 4). Interestingly, a decline in DBP (> 10 mmHg) occurred only in patients with no (3/

Table 3 Data of Holter ECG grouped by stage of the cardiomyopathy according to LE-positive myocardium

	No fibrosis (<i>n</i> = 41)	Mild fibrosis (<i>n</i> = 34)	Severe fibrosis (<i>n</i> = 20)	Total (<i>n</i> = 95)
Duration (h:min)	21:53 (2:46)	22:39 (0:54)	22:22 (0:54)	22:31 (1:20)
HR average (min ⁻¹)	73 (12)	71 ±(9)	70 (10)	71 (10)
HR maximum (min ⁻¹)	129 (25)	127 (20)	117 (25)	125 (24)
HR minimum (min ⁻¹)	51 (9)	52 (9)	53 (9)	52 (9)
Bradycardic episodes, count	5 (2–11)	4 (2–10)	4 (1–10)	4 (2–10)
Tachycardic episodes, count	8 (3–17)	9 (4–13)	1 (0–8) ^b	5 (1–13)
Longest pause (ms)	0	0 (0–214) ^a	0 (0–50) ^{b, c}	0 (0–24)
SVPB count (<i>n</i>)	9 (4–20)	19 (4–43) ^a	47 (3–132) ^{b, c}	14 (64)
SV couplets (<i>n</i>)	0 (0–2)	2 (1–9) ^a	1 (1–4) ^c	0 (0–4)
SV triplets (<i>n</i>)	0 (0–0)	0 (0–1)	0 (0–1)	0 (0–0)
SV runs (<i>n</i>)	0	0 (0–2) ^a	0 (0–1) ^b	0 (0–1)
VPB count (<i>n</i>)	5 (2–18)	11 (5–21) ^a	115 (45–181) ^{b, c}	14 (4–40)
V couplets (<i>n</i>)	0 (0–0)	0 (0–1)	2 (2–5) ^{b, c}	0 (0–1)
V triplets (<i>n</i>)	0	0 (0–0) ^a	0 (0–1) ^b	0 (0–0)
V runs (<i>n</i>)	0	0 (0–1) ^a	0 (0–0) ^b	0 (0–0)

Data are mean (SD) or median (quartiles)

No fibrosis: LE = 0%; mild fibrosis: LE ≤ 2%; severe fibrosis: LE > 2%

ECG electrocardiogram, HR heart rate, LE late enhancement, SV supraventricular, PB premature beat, V ventricular

^a*p*-value <0.05 for no fibrosis vs. mild fibrosis

^b*p*-value <0.05 for no fibrosis vs. severe fibrosis

^c*p*-value <0.05 for mild fibrosis vs. severe fibrosis

Fig. 2 Scatter plot of ventricular premature beats (VPB) count within 24 h in relation to the amount of myocardial fibrosis on cMRI. Green, patients with no fibrosis; yellow, mild fibrosis; red, severe fibrosis. cMRI cardiac magnetic resonance imaging, VPB ventricular premature beats

Table 4 Data of exercise ECG grouped by stage of the cardiomyopathy according to LE-positive myocardium

	No fibrosis (<i>n</i> = 41)	Mild fibrosis (<i>n</i> = 34)	Severe fibrosis (<i>n</i> = 20)	Total
Load at start (W)	37 (13)	31 (11) ^a	29 (10) ^b	33 (12)
Load at end (W)	129 (33)	114 (42)	97 (30) ^c	116 (38)
HR at rest (min ⁻¹)	71 (14)	71 (13)	70 (16)	70 (14)
HR at maximum stress (min ⁻¹)	144 (26)	132 (25) ^a	113 (18) ^{b, c}	132 (26)
<i>Premature beats</i>				
VPB count (<i>n</i>)	0 (0–2)	1 (0–2) ^a	2 (1–2) ^b	0.1 (0.4)
V couplets (<i>n</i>)	0	0	0	0
V triplets (<i>n</i>)	0	0	0	0
V runs (<i>n</i>)	0	0	0	0
<i>Blood pressure</i>				
sBP at rest (mmHg)	121 (21)	124 (18) ^a	132 (70) ^{b, c}	125 (19)
max. sBP at stress (mmHg)	183 (32)	198 (37) ^a	180 (28) ^b	188 (34)
sBP increase (mmHg)	62 (24)	76 (34) ^a	47 (22) ^{b, c}	63 (29)
sBP drop (>15 mmHg)	0	0	0	0
sBP increase (>50 mmHg)	24 (71)	11 (52) ^a	8 (40) ^{b, c}	43
SBP increase/watt (mmHg/W)	0.5 (0.2)	0.7 (0.4) ^a	0.5 (0.2) ^b	0.6 (0.3)
dBp at rest (mmHg)	83 (12)	85 (9)	83 (10)	84 (10)
max.dBP at stress (mmHg)	91 (14)	90 (16)	90 (11)	91 (14)
dPB increase (mmHg)	8.6 (15)	4.1 (16)	8.6 (10)	7 (14)
dBP increase/watt (mmHg/W)	0.07 (0.15)	0.05 (0.15)	0.08 (0.17) ^b	0.07 (0.15)
dBP drop (>15 mmHg)	3 (5.4)	3 (6.7)	0 ^{b, c}	6 (6.3)
dBP increase (>15 mmHg)	12 (32)	7 (23)	6 (29)	25 (26)

Data are absolute numbers (%), mean (SD), or median (quartiles) as appropriate

No fibrosis, LE = 0%; mild fibrosis, LE ≤ 2%; severe fibrosis, LE > 2%

ECG electrocardiogram, HR heart rate, dBP diastolic blood pressure, LE late enhancement, sBP systolic blood pressure, VPB ventricular premature beat, V ventricular

^a*p*-value <0.05 for no fibrosis vs. mild fibrosis

^b*p*-value <0.05 for no fibrosis vs. severe fibrosis

^c*p*-value <0.05 for mild LE vs. severe fibrosis

Fig. 3 Scatter plots of blood pressure regulation during exercise in relation to the amount of fibrosis. *Left*, diastolic blood pressure (DBP). *Red*, patients with DBP decrease >10 mmHg. *Right*, systolic blood

pressure (SBP). *Red*, patients with fibrosis ≥2% and <50 mmHg increase, *DBP* diastolic blood pressure, *SBP* systolic blood pressure

41; 5.4%) or mild fibrosis (3/34; 6.7%) but not in patients with severe fibrosis (0/20; 0%; $p < 0.01$, respectively).

Discussion

Main Findings

The present study describes changes in resting ECG, Holter ECG, and exercise ECG in relation to cardiomyopathy stage in a large sample of patients with untreated FD. Results might be influenced by patients with severe stages of disease, which had to be excluded from this study because pacemaker and renal dysfunction are contraindications for cMRI with contrast agent. With resting ECG, the main finding is that T inversion seems to be a typical indirect nonquantitative feature of replacement fibrosis, whereas this alone cannot discriminate the stage of the Fabry cardiomyopathy. For Holter ECG, the main finding is that the frequency of VPB and SVPB correlates with the amount of LE-positive myocardium in the cMRI, indicating an influence of replacement fibrosis mainly on ventricular but also partly on supraventricular arrhythmias. Regarding exercise ECG, this testing was clinically uninformative in terms of disease stage or coronary heart disease diagnosis; however, blood pressure and heart rate during exercise showed characteristics that were specific to the cardiomyopathy. These changes might be part of the Fabry-related autonomic neuropathy.

Resting ECG

Results of the resting ECG correspond to those of previous studies identifying atrioventricular conduction (Niemann et al. 2013; Namdar et al. 2010), ventricular depolarization (Kampmann et al. 2002), and an increased LV Sokolow–Lyon index as a nonquantitative measure for hypertrophy (Linhart et al. 2001; Weidemann et al. 2005). Repolarization abnormalities are common in FD, as confirmed in previous studies (Niemann et al. 2013; Namdar et al. 2011). T inversion could be a sign of pathological LE and thus of replacement fibrosis. Consequently, in patients with T inversion, advanced diagnostics with cMRI should be discussed.

Interestingly, the QT time was not prolonged in patients with myocardial fibrosis. Because the burden of myocardial fibrosis is predictive for malignant ventricular arrhythmia (Krämer et al. 2014), QT time is not a useful marker for the prediction of malignant arrhythmias in FD.

Holter ECG

The current data clearly show a strong relation between the burden of cardiac fibrosis and the number of clinically relevant arrhythmias on Holter ECG. In this context, both VPB and SVPB were detected in advanced stages of the cardiomyopathy with a clear increase above a fibrotic load of 2% of LV mass. Thus, these data are in concordance with previous findings (Krämer et al. 2014) and again emphasize the importance of cardiac replacement fibrosis for cardiomyopathy and clinical outcome. In addition, these results are in agreement with a recent report that patients with replacement fibrosis can die because of malignant arrhythmias (Krämer et al. 2014). Thus, together with other data (Shah et al. 2005), the current findings emphasize the importance of regular Holter-ECG heart rhythm surveillance in patients with FD, particularly given that clinically relevant arrhythmias are not detectable on resting ECG. From a clinical perspective, the threshold of ventricular arrhythmias justifying the implantation of an automatic cardioverter defibrillator is still under debate but should be regarded as a prioritized research topic. Holter ECG, however, cannot evaluate all aspects of the autonomic nervous system and autonomic regulation of Fabry cardiomyopathy. Indeed, patients with severe cardiac fibrosis showed fewer phases with tachycardia ($>100/\text{min}$) during the day, but the average minimum and maximum heart rate did not differ significantly among the groups. These autonomic effects could be detected only with exercise ECG.

Exercise ECG

An important aspect of the current study is the finding of chronotropic incompetence in advanced stages of FD, which has been frequently discussed but not systematically investigated and is poorly understood (Lobo et al. 2008). During exercise ECG, the stress-induced heart rate increase was limited, especially in fibrotic hearts. This failure of chronotropic response might – at least partly – explain the limited increase in working capacities, implying limitations during exercise for affected Fabry patients.

During the exercise test, both sBP and dBP showed some interesting changes. Patients without myocardial fibrosis had normal blood pressure regulation, whereas patients with severe fibrosis had the most limited increase in sBP during exercise. Fewer than half of the patients in the severe stages had an increase exceeding 50 mmHg during exercise, which partly explains the reduced working

capacity and frequently displayed dizziness or fainting under physical stress (Ramaswami et al. 2006; Bouwman et al. 2012). A dBP decline occurred only in patients with no (3/41) or mild fibrosis on cMRI (3/34). Patients with severe fibrosis showed no significant declines, which again also might be explained by the influence of the autonomic nervous system on blood vessel dilation, leading to blood pressure declines for improvement of peripheral supply only in the early disease stages.

Conclusion

The current data clearly show the different contributions that resting ECG, Holter ECG, and exercise ECG can make to our understanding of FD-related cardiomyopathy. It seems that myocardial fibrosis is related to these electrical abnormalities, but it is unclear if the observed fibrosis is the original trigger for these abnormalities or if other factors such as globotriaosylceramide storage, hypertrophy, or pathological conduction system changes are primarily involved. In addition, the current data demonstrate that each of these methods detects different aspects of FD-related cardiomyopathy. Although all three clinical methods focus on the cardiomyopathy, these results also provide evidence that the autonomic nervous system is altered and affects the fibrotic heart. The influence of the autonomic nervous system was especially apparent during the exercise test, which showed chronotropic incompetence and changes in blood pressure regulation related to cardiomyopathy stage.

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Take-Home

Cardiac replacement fibrosis is responsible for clinical relevant electrical changes and seems to influence exercise intolerance in patients with Fabry disease.

Compliance with Ethics Guidelines

The authors state that the article has not been and will not be published elsewhere in substantially the same form. The submitting author has circulated the article and secured final approval of the version to be peer-reviewed from all coauthors prior to article submission.

This includes confirmation of absence of previous similar or simultaneous publications, their inspection of

the manuscript, their substantial contribution to the work, and their agreement to submission.

Conflict of Interest Disclosures

F. Weidemann, J. Krämer, and C. Wanner have received speaker honoraria from Genzyme Corporation and Shire. F. Weidemann and C. Wanner are members of the Fabry Registry European Board of Advisors and have received travel assistance and speaker honoraria. The institution has received research grants from Genzyme Corporation and Shire.

Peter Nordbeck, Stefan Störk, Christian Ritter, and Georg Ertl declare that they have no conflict of interest.

Contributorship Statement

Johannes Krämer, first draft, concept of the manuscript, data interpretation, statistical analysis; Peter Nordbeck, interpretation of the data, concept manuscript, revision manuscript; Stefan Störk, statistical analysis, revision manuscript; Christian Ritter, magnetic resonance imaging, revision manuscript; Georg Ertl, revision manuscript, supervision; Christoph Wanner, interpretation of the data, revision manuscript; Frank Weidemann, interpretation of the data, concept manuscript, revision manuscript, supervision.

Informed Consent

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. Informed consent was obtained from all patients for being included in the study. This article does not contain any studies with human or animal subjects performed by the any of the authors.

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