Pathology and Function of Conduction Tissue in Fabry Disease Cardiomyopathy

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Background—Cardiac arrhythmias are common in Fabry disease (FD) and may occur in prehypertrophic cardiomyopathy suggesting an early compromise of conduction tissue (CT). Therefore, FD X-linked and CT may be variously involved in male and female patients with FD cardiomyopathy, affecting CT function.

Methods and Results—Among 74 patients with endomyocardial biopsy diagnosis of FD cardiomyopathy, 13 (6 men; 7 women; mean age, 50.1±13.5 years; maximal wall thickness, 16.7±3.7 mm) had CT included in histological specimens and 6 also at electron microscopy. CT glycolipid infiltration was defined as focal, moderate, extensive, or massive, if involved ≤30%, ≤50%, >50%, or 100% of cells; identified as loosely arranged small myocytes positive to HCN4 immunostaining, supplied by a centrally placed thick-walled arteriole. CT involvement was correlated with age, sex, and α-Gal gene mutation. CT function was evaluated by electrophysiological study and arrhythmias at Holter registration. CT infiltration was focal/moderate in 4 women with no arrhythmias and normal electrophysiological study, extensive in 3 women with atrial or ventricular arrhythmias and short HV interval, and massive in 6 men with atrial fibrillation or ventricular arrhythmias and short HV. Short PR/AH with increased refractoriness was additionally found in 3 patients with extensive/massive CT infiltration. A male patient with the shortest HV presented infra-Hissian block during decremental atrial stimulation. There was no correlation with age, maximal wall thickness, and type of gene mutation.

Conclusions—CT infiltration in FD cardiomyopathy is constant in men and variable in women because of skewed X-chromosome inactivation; its extensive/massive involvement causes accelerated conduction with prolonged refractoriness and electric instability. (Circ Arrhythm Electrophysiol. 2015;8:799-805. DOI: 10.1161/CIRCEP.114.002569.)

Key Words: arrhythmias, cardiac ▪ cardiomyopathies ▪ Fabry disease ▪ microscopy, electron ▪ mutation

Fabry disease (FD) is an X-linked lysosomal storage disorder caused by deficiency of the enzyme α-galactosidase A, leading to progressive intracellular deposition of globotriaosylceramide (Gb3) and related neutral glycosphingolipids in multiple organ systems, including skin, kidneys, vascular endothelium, ganglion cells of peripheral nervous system, and heart.1 Cardiac involvement is common both in homozygous men and in heterozygous women and contributes substantially to disease-related morbidity and mortality.2,3 Noteworthy, the heart can be the only organ involved in the so-called cardiac Fabry variant,4 raising specific diagnostic problems with hypertrophic cardiomyopathy.5

Indeed, GB3 accumulates in all cardiac cell types, including microvacular endothelial and smooth muscle cells, fibroblasts, and cardiomyocytes, leading to myocardial ischemia, valve abnormalities, and myocardial hypertrophy that mimic the morphological and clinical picture of hypertrophic cardiomyopathy.3,6

Conduction tissue (CT) is believed to be specifically affected, as well as supraventricular and ventricular arrhythmias are common and may manifest even in the prehypertrophic phase of FD cardiomyopathy (FDCM).7,8 Pathology of CT in FDCM is poorly understood and may vary with sex of patients because of the X-chromosome localization of α-Gal gene and the skewed inactivation of X-chromosome in women and type of gene mutation resulting in isolated cardiac or systemic manifestation. Severity of CT infiltration by Gb3 may reflect on CT function and arrhythmic profile of FD subjects requiring in the advanced stage of disease major therapeutic interventions, including pacemaker and implantable cardioverter defibrillator implantation.

In the present report, pathology of CT included in endomyocardial biopsy specimens from patients with FDCM is described. Severity of CT involvement is correlated with patients’ age, sex, and mutation (classical or variant) of α-Gal gene. The effects of CT infiltration have been evaluated by electrophysiological study and Holter monitoring.

Materials and Methods

Patient Population
From 1998 to 2013, 74 patients with clinical phenotype of hypertrophic cardiomyopathy (idiopathic left ventricular [LV] hypertrophy with maximal wall thickness [MWT] ≥15 mm), unexplained LV
WHAT IS KNOWN

- Cardiac arrhythmias are common in patients with Fabry disease cardiomypathy and may occur even in the prehypertrophic phase of the disease suggesting an early compromise of conduction tissue.
- A short PR interval on ECG has been reported in 15% of subjects with Fabry disease, without the presence of an accessory pathway.

WHAT THE STUDY ADDS

- Conduction tissue infiltration with globotriaosylceramide and related neutral glycosphingolipids in Fabry disease cardiomypathy is constant in men and variable in women because of X-chromosome skewed inactivation.
- The extensive infiltration in the conduction tissue causes accelerated conduction with prolonged refractoriness and electric instability.

Immunohistochemistry for HCN4

Immunohistochemistry was performed on formalin/paraformaldehyde-fixed paraffin-embedded sections of endomyocardial samples to identify HCN4 positive CT. To expose target proteins, heat-induced antigen retrieval was performed using 10 mmol/L of sodium citrate (pH 6.0) buffer microwaved for 15 minutes. After antigen retrieval, tissues were blocked in 3% BSA-PBS for 30 minutes at room temperature. Tissues were then probed at a dilution of 1:20 with a rat monoclonal antibody recognizing HCN4 (Pierce Antibody Products, Thermo Fisher Scientific Inc) or without primary antibody (negative control) overnight at 4°C in a humidified chamber. Tissues were washed extensively with PBS, and detection was performed using a biotin-conjugated secondary antibody and Streptavidin–horseradish peroxidase (UCS Diagnostics S.r.l) at room temperature for 10 minutes. Samples were washed and incubated by colorimetric detection using 3,3′-diaminobenzidine (DAB, Dako), counterstained with hematoxylin, and mounted with a quick-hardening mounting medium (Eukitt, Bio-Optica S.p.A).

Electrophysiological Study

For electrophysiological study (EPS), 2 catheters were introduced through the right femoral vein. The first was a steerable decapolar catheter (Bard, Inc Dynamic, Deca, MA) and was positioned in the coronary sinus; the second was a quadripolar steerable catheter with 4-mm tip electrode (Biosense Webster, Inc Diamond Bar, CA) and was applied, in turn, in the right ventricular and His region. EPS evaluated the duration of AH and HV intervals basically and after atrial and ventricular stimulation. If short PQ was revealed, the presence of an anomalous pathway was investigated.

Statistics

Normal distribution of variables was assessed with Kolmogorov–Smirnov test. Quantitative measurements were expressed as mean±SD. Difference between 2 groups was determined by unpaired t test for continuous variables and Fisher exact test for categorical data. Correlations were analyzed by Pearson correlation coefficient. A 2-tailed P value of <0.05 was considered statistically significant.

Results

Main characteristics of single patients are summarized in Table.

Cardiac Studies

ECG showed increased QRS voltages with alterations of ST segment or T wave in 11 of 13 patients. Short PR (Figures 1 and 3A) was identified in 3 patients (patients 2, 3, and 10). In 11 patients, 2-dimensional echocardiography revealed a diffuse myocardial hypertrophy more pronounced in the LV (LVMWT, 16.7±3.7 mm) but extended also to the right ventricle (RV) where the free wall was between 8 and 12 mm. In 2 patients, the examination was normal. RV and LV hypertrophy was usually symmetrical but was localized in 1 subject (patient 9) in the LV apex being paralleled by giant negative T wave in the V3–V5 electrocardiographic leads, mimicking the clinical phenotype of apical hypertrophic cardiomyopathy. Cardiac magnetic resonance confirmed the magnitude and distribution of myocardial hypertrophy and, in addition, showed a subependimal delayed enhancement in the inferolateral LV wall, after Gadolinium infusion, in 7 of 13 subjects with FDCM, particularly evident in those with an MWT of >15 mm. At cardiac catheterization, RV and LV end-diastolic pressures were elevated (>8 and >12 mm Hg, respectively). Coronary angiography showed a normal network with slow flow in 6 patients. No major complications related to cardiac

Histology and Electron Microscopy

For histological analysis, the endomyocardial samples were fixed in 10% buffered formalin and paraffin embedded. Sections of 5-μm thickness were stained with hematoxylin and eosin, Masson trichrome, and Miller’s Elastic Van Gieson. Histochemistry with periodic acid-Schiff and Sudan black stains was obtained in frozen sections to evaluate the presence of intracellular glycolipid material. A quantitaive evaluation of the severity of CT infiltration was assessed counting the percent of infiltrated cells on total number of CT cells in at least 3 serial sections. The infiltration was defined as focal in the presence of <30% of affected cells, moderate with <50%, extensive with >50%, and massive in the presence of 100% of cell affected.

For transmission electron microscopy, additional samples were fixed in 2% glutaraldehyde in 0.1 mol/L phosphate buffer, at pH 7.3, postfixed in osmium tetroxide, and processed after a standard schedule for embedding in Epon resin. Ultrathin sections were stained with uranyl acetate and lead hydroxide. A Philips CM-10 transmission electron microscopy was used for observation and photographic analysis.

Cardiac Studies

Extensive clinical examination, including assessment of FD systemic manifestations, noninvasive (resting ECG, Holter monitoring, echocardiography with tissue Doppler analysis, and cardiac magnetic resonance), and invasive cardiac studies were performed in all patients. Invasive cardiac examinations were performed, including cardiac catheterization, selective coronary angiography, LV angiography, and biventricular or LV endomyocardial biopsy. Endomyocardial biopsies (4 to 5 each ventricular chamber) were performed in the septal-apical region of left or both ventricles. Myocardial samples were processed for routine histological and histochemical analysis and for transmission electron microscopy.

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catheterization and biopsy have been observed: in 1 patient, a transient left bundle branch block after LV biopsy was reported. Holter monitoring (24 hours for at least 2 registrations) revealed no significant ventricular arrhythmias in 4 female patients with FDCM (Lown class, 1–2) and atrial fibrillation or significant ventricular arrhythmias (Lown class, 3–4A) in 3 women and 1 male (Lown class, 3–4B; Table).

We did not find statistical significant correlation between severity of ventricular arrhythmias (Lown class) and age ($P=0.18$; $r^2=0.08$). Occurrence of atrial fibrillation was not associated with age ($P=0.65$) or severity of cardiac hypertrophy ($P=0.09$). Patients with cardiac variant (N215S and R227Q mutations) did not show increase in the severity of ventricular arrhythmias ($P=0.06$) or severity of cardiac hypertrophy ($P=0.52$; $r=0.15$) or severity of cardiac hypertrophy ($P=0.34$; $r^2=0.08$).

Pathology of Myocardium and CT
Cardiomyocytes were regularly arranged and enlarged with clear perinuclear and cytoplasmic vacuoles that in the advanced disease occupied >50% of cell surface. These vacuoles were periodic acid-Schiff and Sudan Black positive at histochemistry of frozen sections, suggesting an accumulation of glycolipid material. The interstitium was widened because of intercellular, perivascular, and replacement fibrosis. Myocardial arterioles presented a lumen narrowing with thickened wall because of hypertrophy and hyperplasia of smooth muscle cells showing perinuclear vacuoles suggesting a vascular Gb3 infiltration. Semithin sections from epon-embedded samples showed massive accumulation of glycolipid bodies in vessel, myocytes, and CT (Figure 1D) at ultrastructural examination cell vacuoles consisted of large lysosomes containing myelin bodies (Figure 1C).

Cardiac CT was observed mostly in LV biopsy fragments (specifically in 2 samples from RV and 9 from LV). CT was identified at histology as loosely arranged small myocytes, positive to HCN4 immunostaining (Figure 1C, inset) supplied by a centrally placed thickened wall arteriole, circumscribed by a fibrous membrane in a fascicle configuration (Monckeberg and Aschoff criteria; Figure 1C and 1D). At ultrastructural examination, CT appeared as small myocytes containing sparse myofibrils, a large number of endocytic vesicles, and particularly rich lateral gap junctions (Figure 1E). CT cells were variably vacuolated in relationship with patients' sex. In particular, in 3 women, <30% of cells were affected and vacuoles were confined to perinuclear area (Table; Figure 2C and 2D). In 1 female patient, the number of affected and unaffected cells was balanced (=50% in patient 8). In 3 women, vacuoles involved >50% of cells and expanded toward the cytoplasm (Figure 1C–1E). In 6 men, 100% CT cells were homogeneously infiltrated and vacuoles occupied nearly the entire cell surface (Figure 3C and 3D). Severity of CT infiltration in women failed to correlate with age ($P=0.52$; $r=0.08$) and with severity of LV hypertrophy ($P=0.96$; $r^2=0.00$). Female patients with cardiac variant (N215S and R227Q mutations) did not have a more severe CT infiltration compared with noncardiac variant ($P=0.16$). CT arterioles in men and women with extensive CT infiltration were affected with thickened walls and hypertrophied smooth muscle cells containing glycolipid accumulation (Figures 1, 3, and 3D).

Electrophysiological Study
Four women (patients 4, 7, 8, and 11 of Table) had normal PR (>120 ms) and normal basal intervals (AH, 90±20 ms;
HV, 45±10 ms) with normal functional intervals (Wenckebach point, 350±50 ms; effective refractory period of atrioventricular node was 600/400±20 ms and of right atrial was 600/240±20 ms). Ventricular stimulation was decremental and concentric. This cohort had no palpitation or arrhythmias at Holter monitoring.

Three women (patients 2, 9, and 10) had a short (<35 ms) HV interval and 2 patients (2 and 10) also a short AH ($\leq$ 90 ms). This group presented an abnormal (>400 ms) Wenckebach point and a nodal atrioventricular increased refractory period (>600/400 ms). These patients manifested supraventricular or ventricular arrhythmias. The presence of accessory pathway was ruled out because of concentric retroconduction during decremental stimulation from RV apex with VA dissociation at elevated intervals.

The 6 male patients had short HV, and patient 3 also had a short PR and AH. This last patient presented the shortest HV interval (20 ms) and an infra-Hissian block at 390-ms cycle during decremental atrial stimulation (Figure 3B). This patient cohort manifested supraventricular or ventricular arrhythmias, and patient 1 needed an implantable cardioverter defibrillator implantation because of an episode of sustained ventricular tachycardia.

The presence of accessory pathway was ruled out because of concentric retroconduction during decremental stimulation from RV apex with VA dissociation at elevated intervals.

**Correlation Between EPS and CT Pathology**

EPS was normal in 3 women with focal (<30%) and 1 female patient with moderate CT cell involvement. It showed an

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**Figure 1.** A, ECG showing short PR with ST/T-wave changes. B, Electrophysiological study showing short AH and HV intervals. C, General view of conduction tissue (CT) involvement in glycolipid accumulation; paraffin-embedded and hematoxylin and eosin–stained section. A large number of clear vacuoles is visible. Inset shows positive immunostaining for HCN4 confirming the morphological identification of CT. D, Epon-embedded and toluidine blue–stained semithin section. Glycolipid bodies are metachromatically stained by toluidine blue, infiltrate CT, vessel components, and myocardiocytes. E, Electron microscopy showing glycolipid infiltration of a small CT myocyte and vessel cellular components. A indicates arteriole; and M, myocardiocyte.
accelerated conduction with short HV interval in the 3 women with extensive infiltration and in all male patients with FDCM. In addition, a short PR (<120–209 ms) at ECG and short AH interval at EPS were observed in 2 women with extensive (patients 2 and 10) and in 1 male patient (3) with massive CT infiltration. Noteworthy, a prolonged refractory period with an abnormal Wenckebach point was documented in a female FDCM patient with extensive CT infiltration. Infiltration of CT showed a significant correlation with the short HV value ($P<0.01; r=-0.6576$).

Discussion
Cardiac arrhythmias are common in FD$^7,8$ and may occur in the prehypertrophic phase of FDCM, in the absence of myocardial fibrosis, suggesting an early compromise of CT. Indeed, lone atrial fibrillation,$^9$ cryptogenic ventricular arrhythmias, and sudden death$^{10}$ have been reported as a first manifestation of FDCM in the absence of clinical (systemic symptoms), electrocardiographic (high QRS voltages and ST segment/T-wave changes), and cardiac imaging (2D-echo, cardiac magnetic resonance) abnormalities. A recent report on endomyocardial biopsy sections of CT has shown that lone ventricular arrhythmias are associated with a prominent infiltration of CT in comparison with working myocytes. The reason for this pathological discrepancy is actually unclear although a higher energy metabolism in CT cells with a lower availability of the lysosomal enzyme, $\alpha$-galactosidase A, and a degradation of subcellular ultrastructure have been hypothesized. Overall, CT involvement seems to play a major role in the generation of cardiac arrhythmias in FDCM. However, the pathology of CT is poorly understood as systematic postmortem studies are lacking and inclusion of CT in endomyocardial biopsies is rare. In this study, we report the histological examination of CT in 13 patients with FDCM, identified by Monckeberg and Aschoff morphological criteria and positive immunostaining for the molecular marker HCN4.$^{11}$ The relatively high prevalence of CT inclusion in endomyocardial biopsy specimens (17% of 74 subjects with FDCM) may be due to the biventricular approach with withdrawal of 8 to 10 fragments per patient. In addition, CT was mostly found in biopsies from the LV, a common site of investigation in our laboratory for patients with cardiomyopathies$^{12}$ allowing an easier approach of the interventricular septum where CT branches are expected to be more represented in comparison with cardiac apex, as well as RV and LV free wall. As far as CT involvement in FDCM is concerned, it might be assumed that its compromise would vary with age, sex, severity of LV hypertrophy, and type (classical or variant) of $\alpha$-Gal gene mutation. Our study shows that CT is indeed variably affected in patients with FDCM and that the

Figure 2. A, Normal ECG. B, Electrophysiological study showing normal AH and HV intervals. C, Focal glycolipid accumulation in female patients; paraffin embedded and hematoxylin and eosin–stained section of conduction tissue (CT). Arrows indicate affected cells of CT. D, Transmission electron microscopy detail of perinuclear glycolipid body (GB) accumulation in a small conductive myocyte.
extent of its involvement is essentially related to patients’ sex. In particular, male subjects had all CT cells affected (Figure 3C and 3D), whereas women with FDCM presented focal (<30%; Figure 2C and 2D), moderate (≈50%, patient 8), or extensive (>50%; Figure 1C–1E) cell infiltration as a consequence of a skewed inactivation of X-chromosome. On the other hand, CT infiltration in female patients was not correlated with age, severity of LV hypertrophy, and type of gene mutation (classical versus cardiac variant). This is exemplified in 2 sisters aged 58 and 60 years (patients 10 and 11 of Table) with a classical gene mutation and similar MWT. CT was extensively infiltrated in the younger subject although it was focally affected in the older one. Finally, in our study, the degree of CT infiltration seemed to influence atrioventricular conduction, refractoriness, and severity of cardiac arrhythmias. In fact, patients with focal/moderate CT involvement had a normal EPS and no arrhythmias, whereas patients with extensive or massive CT infiltration manifested a short HV interval (in 3 patients also a short PR/AH) with supraventricular or ventricular arrhythmias requiring an implantable cardioverter defibrillator implantation in a male patient with sustained ventricular tachycardia.

The pathophysiological basis of accelerated atrioventricular conduction in FDCM is still speculative and is essentially correlated with the physicochemical properties of glycosphingolipids. Indeed, the latter are implicated in the impulse transmission in neurons, and we speculate that they may cause the short PR and increased QRS voltages in FDCM. In particular, short PR firstly indicated by Roudebush in 1973 as a characteristic of FD is reported with a prevalence of ≈15% in large series. In the absence of accessory pathways, it is attributed to Gb3 infiltration of the atrioventricular node. In our report, 3 of 13 patients with FDCM (23%) had short PR.

Likewise, increasing of ECG voltages is paralleled by a progressive myocyte infiltration of Gb3 that may completely replace the myocyte myofibrillar content. The positive relationship between Gb3 accumulation and QRS voltages is explained with an enhanced myocardial conduction provided by glycosphingolipids.

Interestingly, FDCM with accelerated atrioventricular conduction showed at EPS a prolonged refractory period with a lower Wenckebach point. In addition, 1 male subject with associated short PR and very short HV interval had an abnormal infra-Hissian block at decremental atrial stimulation. This apparent functional contradiction probably reflects, in CT cells, the degradation of myofilaments, the toxic effects of Gb3 on energy metabolism (through oxidative mitochondrial damage), and Gb3
hindrance to creatine-phosphate diffusion with consequent dysfunction of membrane pumps. These last considerations explain the occurrence in the advanced disease of the bradyarrhythmias and the need of pacemaker implantation in some patients.

The effect of enzyme replacement therapy on CT dysfunction is actually controversial. Normalization of atrioventricular conduction with prolongation of PR interval and reduction of QRS duration has been occasionally reported after enzyme replacement therapy administration. Further studies are needed to clarify whether early administration and enhanced dosage may make enzyme replacement therapy more effective.

Limitations of the Study

Patient selection in our study reflects essentially CT inclusion in endomyocardial biopsy samples and may not be representative of the general FDCM population. Nevertheless, male and female patients with FDCM are equally represented with different ages and various degrees of LV hypertrophy, as well as in the prehypertrophic state covering a wide range of clinical situations.

Conclusions

CT infiltration in FDCM is constant in men and variable in women consistent with variable X-chromosome inactivation; its extensive/massive involvement causes accelerated conduction with prolonged refractoriness and electric instability.

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Disclosures

None.

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