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. Indeed, GB3 accumulates in all cardiac cell types, including microvascular 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.5,6

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 cardiomyopathy 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 globotriaosylsphingolipids in Fabry disease cardiomyopathy 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.

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 tissue structure and composition. Immunohistochemistry with monoclonal antibody against HCN4 (Pierce Antibody Products, Thermo Fisher Scientific Inc) was used for detection of HCN4 expression in the conduction system.

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 the second was a quadripolar steerable catheter with 4-mm tip electrode (Biosense Webster, Inc Diamond Bar, CA) and was positioned in the coronary sinus. Cardiac magnetic resonance imaging (CMR) was performed in all patients, and invasive cardiac studies were performed in 11 patients. The study was approved by the Ethical Committee of our Institute, and written informed consent was obtained from each patient before study entry.

Results

Main characteristics of single patients are summarized in Table. Cardiac studies showed increased QRS voltages with alterations of ST segment or T wave in 11 of 13 patients. Short PR interval (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 subepicardial 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 mmHg, respectively). Coronary angiography showed a normal network with slow flow in 6 patients. No major complications related to cardiac...
Table. Characteristics of 13 Patients With Fabry Disease Cardiomyopathy and Conduction Tissue Inclusion

<table>
<thead>
<tr>
<th>Patient</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
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<th>10</th>
<th>11</th>
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<tr>
<td>Age/Sex</td>
<td>43 men</td>
<td>58 women</td>
<td>39 men</td>
<td>64 women</td>
<td>53 men</td>
<td>52 men</td>
<td>59 women</td>
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<td>50 women</td>
<td>58 women</td>
<td>60 women</td>
<td>28 men</td>
<td>22 men</td>
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<td>Enzymatic activity*</td>
<td>20.9±1.5</td>
<td>15.2±0.8</td>
<td>50.2±89.0</td>
<td>79.2±84.5</td>
<td>378.4±160.8</td>
<td>558.5±40.6</td>
<td>150.7±7.2</td>
<td>50.2±5.6</td>
<td>923.2±73.0</td>
<td>256±77.8</td>
<td>980.2±33.0</td>
<td>22.5±5.4</td>
<td>25.4±8.5</td>
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<td>Extracardiac manifestations</td>
<td>E, S</td>
<td>E, M, CNS</td>
<td>E, PNS</td>
<td>K, S, E</td>
<td>S, CNS, K</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>E, S, CNS</td>
<td>E, K, S</td>
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<td>MWT, mm</td>
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<td>17.0</td>
<td>20.5</td>
<td>15.5</td>
<td>16.5</td>
<td>20.0</td>
<td>19.5</td>
<td>15.5</td>
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<td>19.0</td>
<td>18.5</td>
<td>10.0</td>
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<td>CT infiltration</td>
<td>M (100%)</td>
<td>E (70%)</td>
<td>M (100%)</td>
<td>E (78%)</td>
<td>M (100%)</td>
<td>M (100%)</td>
<td>F (25%)</td>
<td>M (48%)</td>
<td>F (28%)</td>
<td>E (68%)</td>
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<td>EPS PR, ms</td>
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<td>...</td>
<td>118</td>
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<td>AH, ms</td>
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<td>330</td>
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</table>

C indicates classic; CNS, central nervous system; CT, conduction tissue; E, eyes; EA, ears; EPS, electrophysiological study; E; extensive, F; focal; K, kidney; M, moderate; M, muscle; MWT, maximal wall thickness; NAVRP, effective refractory period of atrioventricular node; PNS, peripheral nervous system; S, skin; SVEB, supraventricular ectopic beats; V, variant; and VEB, ventricular ectopic beats.

*nmol/h per mg of protein; values are the mean (±SD) results of 3 independent determinations on peripheral blood lymphocytes.

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 all men (Lown class, 3–4B; Table).

We did not find statistical significant correlation between severity of ventricular arrhythmias (Lown class) and age (P=0.18; r²=0.15) or severity of cardiac hypertrophy (P=0.34; r²=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 in the occurrence of atrial fibrillation (P=0.39) compared with patients with classical mutation.

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 1E).

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; r²=0.08) and with severity of LV hypertrophy (P=0.96; r²=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, 3C, 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 (≤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 and ventricular arrhythmias.

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
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 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, cryptogenic ventricular arrhythmias, and sudden death 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, α-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 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 α-Gal gene mutation. Our study shows that CT is indeed variably affected in patients with FDCM and that the
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 197314 as a characteristic of FD is reported with a prevalence of ≈15% in large series.15,16 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 function of membrane pumps. These last considerations explain may make enzyme replacement therapy more effective.

Further studies are needed to clarify whether early administration and enhanced dosage 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/invasive involvement causes accelerated conduction with prolonged refractoriness and electric instability.

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**Disclosures**

None.

**References**

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