Early Detection of Fabry Cardiomyopathy by Tissue Doppler Imaging

Maurizio Pieroni, MD; Cristina Chimenti, MD, PhD; Roberta Ricci, MD; Patrizio Sale, MD; Matteo Antonio Russo, MD; Andrea Frustaci, MD

Background—Fabry cardiomyopathy is diagnosed by detection of left ventricular hypertrophy (LVH) in patients with α-Galactosidase A deficiency. Conventional noninvasive tools are unable to provide a preclinical diagnosis allowing prompt institution of enzymatic therapy.

Methods and Results—We studied three groups of patients: 10 patients with causal mutations for Fabry disease and LVH, 10 mutation-positive patients without LV, and 10 healthy relatives without causal mutations and no LVH. All patients with LVH and 6 patients with Fabry disease without LVH with complex repetitive ventricular arrhythmias underwent biventricular endomyocardial biopsy to assess cardiac involvement. In all patients 2-dimensional echocardiography with tissue Doppler analysis in the pulsed Doppler mode was performed: systolic (Sa), early diastolic (Ea), and late diastolic (Aa) velocities were measured, and the Ea/Aa ratio and the dimensionless parameter E/Ea were computed at both corners of the mitral annulus. All mutation-positive patients had significant reduction of Sa, Ea, and Aa velocities at both corners of the mitral annulus compared with normal control subjects. Ea/Aa ratio was significantly lower and E/Ea ratio significantly higher in mutation-positive patients than in control subjects. Patients with LVH showed significantly lower contraction and relaxation tissue Doppler velocities, lower Ea/Aa ratio, and higher E/Ea ratio in comparison with mutation-positive patients with no LVH.

Conclusions—Fabry cardiomyopathy is characterized by reduced myocardial contraction and relaxation tissue Doppler velocities, detectable even before development of LVH. Tissue Doppler imaging can provide a preclinical diagnosis of Fabry cardiomyopathy, allowing early institution of enzyme replacement therapy. (Circulation. 2003;107:1978-1984.)

Key Words: cardiomyopathy • hypertrophy • echocardiography • tissue • biopsy

Fabry disease is an X-linked disorder caused by deficiency of lysosomal enzyme α-galactosidase A (α-Gal A), responsible for the hydrolysis of terminal α-galactosyl residues from glycolipids and glycoproteins. The disorder is caused by mutations in the α-Gal A gene located in the X chromosomal region Xq22. The enzymatic deficit results in progressive intracellular accumulation of glycosphingolipids (mainly globotriaosylceramide) in different tissues, including skin, kidneys, vascular endothelium, ganglion cells of peripheral nervous system, and heart.1

Cardiac involvement is very common and is the most important cause of death in affected patients.1,2 Moreover, the heart can be the only organ involved in male patients with specific gene mutations1 and in female carriers provided by low enzymatic activity,4 the so-called “cardiac Fabry variant.” This is characterized by progressive severe left ventricular hypertrophy (LVH) that mimics an obstructive or nonobstructive hypertrophic cardiomyopathy,5 so that in some series a cardiac Fabry variant has been identified in up to 6% of patients with a clinical diagnosis of hypertrophic cardiomyopathy.6 The differential diagnosis between the two entities has become particularly important because effective enzyme replacement therapy has been recently made available.7

The clinical impact of enzymatic therapy is strictly correlated with an early detection of cardiac involvement because myocyte and endothelial dysfunction occurring in the preclinical stage of Fabry disease can cause both electrical instability and thromboembolic complications.8 Conventional noninvasive tools as ECG, 2D-echocardiography, and even MRI are unable to identify the preclinical phase of Fabry cardiomyopathy.9

Recent reports have shown at tissue Doppler imaging (TDI) reduced myocardial contraction and relaxation velocities in patients with familial hypertrophic cardiomyopathy, demonstrating that TDI, before and independent of LVH, is an accurate and sensitive method for identifying subjects who are positive for familial hypertrophic cardiomyopathy mutations.10,11

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In this study, we sought to determine whether patients with cardiac Fabry disease have reduced myocardial contraction and relaxation velocities and whether TDI, compared with endomyocardial biopsy findings, could provide an early diagnosis of Fabry cardiomyopathy before the development of LVH.

**Methods**

**Study Population**

Study population included 3 groups of patients from 9 families with Fabry disease: 10 Fabry patients with mutation in α-Gal A gene and LVH; 10 patients who had a mutation with no evidence of LVH; a control group of 10 healthy relatives (sex- and age-matched with patients with mutation but no LVH) who did not carry the causal mutation, asymptomatic, with normal α-Gal A activity in the blood, and normal ECG and echocardiogram. Causal mutations had been previously identified by direct sequencing in all 9 families.

At the time of the study, no patient was receiving cardiovascular drugs that could influence echocardiographic and TDI findings, and no one had yet begun enzyme replacement therapy.

**Biochemical Studies**

Peripheral blood enzymatic activity was assessed in all patients, as previously described. Normal values were considered between 3929.8 to 1672.0 nmol/h per milligram of protein.

**Clinical Studies**

All mutation-positive patients underwent an extensive clinical and instrumental screening for the assessment of Fabry disease manifestations, including neurological, opthalmologic, audiovestibular and dermatological evaluation, cardiac nuclear magnetic resonance, Holter monitoring, renal ultrasound, and assessment of glomerular filtration rate.

**Cardiac Catheterization and Endomyocardial Biopsy**

All invasive cardiac procedures were performed after informed patient consent and approval by the ethics committee of our institution.

All patients with LVH and 6 patients (4 mol/L, 2 women) with mutation of α-Gal A gene but no LVH presenting with complex and repetitive ventricular ectopic beats (Lown class III-IVa) were submitted to cardiac catheterization with coronary angiography and biventricular endomyocardial biopsy.

Endomyocardial biopsies (3 to 4 from each ventricular chamber) were performed in the septal-apical region of both ventricles. Myocardial samples were processed for routine histological and histochemical analysis and for transmission electron microscopy. Two to three samples were immediately frozen in OCT compound with isopentane cooled in liquid nitrogen. For light microscopy, specimens were fixed in 10% buffered formalin and embedded in paraffin, and 5-µm sections were stained with hematoxylin and eosin, Miller's elastic Van Gieson stain, and Masson's trichrome. Frozen sections were stained with periodic acid–Schiff and Sudan black. For transmission electron microscopy, myocardial samples were fixed in 2% glutaraldehyde in 0.1 m phosphate buffer (pH 7.3) and embedded in Epon resin. Ultrathin sections were stained with uranyl acetate and lead hydroxide.

**Echocardiographic Studies**

Echocardiographic studies were performed with an Agilent Sonos 5500 ultrasound system. Patients were imaged, and data were analyzed by a single observer who had no knowledge of genotype and histology. Septal and posterior left ventricular (LV) wall thickness, LV end-diastolic and end-systolic diameters, and LV mass and left atrial volumes were determined from 2D images, according to published criteria. LV ejection fraction (EF) was calculated by using the modified Simpson's method. Peak early (E) and late (A) transmitral filling velocities, E/A ratio, deceleration time of E velocity, and isovolumic relaxation time were measured from mitral inflow velocities. Peak, duration, and time-velocity integral of pulmonary vein flow velocities were measured, and systolic filling fraction and difference between atrial reversal and mitral A wave duration were calculated.

Tissue Doppler was applied in the pulsed Doppler mode to record mitral annulus velocities at septal and lateral corners. Systolic (Sa), early diastolic (Ea), and late diastolic (Aa) TD velocities were measured, and the Ea/Aa ratio and the dimensionless parameter E/Ea were computed at both corners of the mitral annulus. The E/Ea index has been demonstrated to be a good estimate of LV filling pressures in patients with familial hypertrophic cardiomyopathy. For each measurement, 5 beats were averaged.

**Statistical Analysis**

Echocardiographic variables were compared among the 3 groups by ANOVA with Bonferroni t test correction. Statistical significance was defined as P<0.05.

**Results**

Causal mutations identified in the 9 families are reported in Table 1. Each group included patients from at least 4 different families. Clinical characteristics, signs and symptoms of cardiac involvement, and extracardiac manifestations are reported in Tables 2 and 3. Both the two groups of patients with α-Gal A mutation included 7 hemizygotes men and 3 heterozygous women (Table 4). In all male patients, α-Gal A enzymatic activity was very low (mean value, 83.98; range, 9.2 to 360.43 nmol/h per milligram of protein). Among heterozygote women, 4 showed intermediate values of α-Gal

### Table 1. Causal Mutations in α-Gal Identified in the 9 Fabry Families Studied

<table>
<thead>
<tr>
<th>Family</th>
<th>Exon/Intron Location</th>
<th>Nucleotide Change</th>
<th>Effect on Coding Sequence</th>
<th>Genotype</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Exon 6</td>
<td>c946 delG</td>
<td>Frameshift/stop codon</td>
<td>c946 del G</td>
<td>Morrone 2002</td>
</tr>
<tr>
<td>II</td>
<td>Exon 2</td>
<td>c334 C&gt;T</td>
<td>Amino acid change</td>
<td>R112C</td>
<td>Ishii 1992</td>
</tr>
<tr>
<td>III</td>
<td>Exon 7</td>
<td>c1133G&gt;A</td>
<td>Amino acid change</td>
<td>C378Y</td>
<td>Topaloglu 1999</td>
</tr>
<tr>
<td>IV</td>
<td>Intron3</td>
<td>IVS3+1G&gt;A</td>
<td>Splicing defect</td>
<td>IVS3+1G&gt;A</td>
<td>Aston-Prolla 2000</td>
</tr>
<tr>
<td>V</td>
<td>Exon 1</td>
<td>c119 C&gt;T</td>
<td>Amino acid change</td>
<td>P40L</td>
<td>Aston-Prolla 2000</td>
</tr>
<tr>
<td>VI</td>
<td>Exon 6</td>
<td>c982 G&gt;A</td>
<td>Amino acid change</td>
<td>G628R</td>
<td>Ishii 1992</td>
</tr>
<tr>
<td>VII</td>
<td>Exon 7</td>
<td>del CT</td>
<td>Frameshift/stop codon</td>
<td>L344-X17,Stop</td>
<td>Germain 1996</td>
</tr>
<tr>
<td>VIII</td>
<td>Exon 5</td>
<td>c680A&gt;T</td>
<td>Amino acid change</td>
<td>R227G</td>
<td>Eng 1993</td>
</tr>
<tr>
<td>IX</td>
<td>Exon 1</td>
<td>c126–127 insCATG</td>
<td>Frameshift/stop codon</td>
<td>c126–127 insCATG</td>
<td>Morrone 2002</td>
</tr>
</tbody>
</table>

del indicates deletion; IVS, intervening sequence; ins, insertion.
A activity (mean value, 971.38; range, 905.15 to 1030.15 \text{nmol/h per milligram of protein}) and had isolated cardiac disease (2 with and 2 without LVH). In the remaining 2 patients, plasmatic activity was lower than in the other 4 women (134.12 and 589.10 \text{nmol/h per milligram of protein}, respectively), and they showed cardiac, ocular, and peripheral nervous system involvement. In particular one young girl (patient 1 of Table 3) showed enzymatic activity and initial multiorgan clinical manifestations comparable to those of young affected male subjects of the same family (Table 3).

Complex and repetitive ventricular extrasystoles (Lown class III-IVa) were present at Holter monitoring in 6 patients with LVH and in 6 asymptomatic patients without LVH. Cardiac magnetic resonance confirmed the presence or absence of LVH but failed to show signal intensity abnormalities in all patients.

Extracardiac manifestations were present in 7 patients with LVH and in 6 patients without LVH. Acroparesthesias caused by peripheral nerve lesions were present in 12 patients, representing in all of them the first onset of the disease in the childhood. Eye involvement was detected in 11 cases, mainly characterized by corneal (\textit{cornea verticillata}) and lenticular opacities but also by glycolipid deposition in the retina. Skin lesions in the form of angiokeratomas were present in 8 patients, ranging from isolated typical localization at the scrotum or umbilicus to wider extension to inguinal and perianal regions, hips, back, and arms. Evidence of audi vestibular dysfunction with signs of cochlear and neural damage, causing dizziness, vertigo, and hearing loss was found in 7 patients. Hypohidrosis with heat intolerance was present in 4 patients. Renal function impairment with proteinuria and reduced glomerular filtration rate was documented in 4 patients, all male, in the group with LVH. Signs of central nervous system involvement were documented in 2 male patients with LVH.

### Cardiac Catheterization

Coronary arteries were normal in all patients. LV angiography was normal with preserved contractile function and no abnormalities of segmental wall motion in all patients. LV end-diastolic pressure was increased in all patients, including

### TABLE 2. Genetic, Enzymatic, and Clinical Characteristics of Patients With Fabry Disease and LVH

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age/Sex</th>
<th>Family</th>
<th>Enzymatic Activity,* \text{nmol/h per mg Protein}</th>
<th>Cardiac Manifestations</th>
<th>Extracardiac Manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>44/M</td>
<td>I</td>
<td>20.90±1.46</td>
<td>Dyspnea, chest pain, VA</td>
<td>Skin, eyes, ears, kidneys, CNS, AP, H</td>
</tr>
<tr>
<td>2</td>
<td>53/F</td>
<td>I</td>
<td>589.10±6.25</td>
<td>Dyspnea</td>
<td>Eyes, ears, AP, H</td>
</tr>
<tr>
<td>3</td>
<td>44/M</td>
<td>II</td>
<td>30.56±6.33</td>
<td>Dyspnea, VA</td>
<td>Skin, eyes, ears, kidneys, CNS, AP, H</td>
</tr>
<tr>
<td>4</td>
<td>31/M</td>
<td>III</td>
<td>103.08±13.51</td>
<td>VA</td>
<td>AP, skin, eyes</td>
</tr>
<tr>
<td>5</td>
<td>37/M</td>
<td>IV</td>
<td>360.43±16.34</td>
<td>...</td>
<td>AP, skin, eyes</td>
</tr>
<tr>
<td>6</td>
<td>33/M</td>
<td>V</td>
<td>9.2±0.19</td>
<td>...</td>
<td>AP, skin, eyes</td>
</tr>
<tr>
<td>7</td>
<td>41/M</td>
<td>VI</td>
<td>136.00±21.1</td>
<td>Dyspnea, chest pain, VA</td>
<td>...</td>
</tr>
<tr>
<td>8</td>
<td>47/F</td>
<td>VII</td>
<td>1027.10±56.47</td>
<td>Dyspnea</td>
<td>...</td>
</tr>
<tr>
<td>9</td>
<td>50/F</td>
<td>VIII</td>
<td>923.15±73.00</td>
<td>Dyspnea, VA</td>
<td>...</td>
</tr>
<tr>
<td>10</td>
<td>46/M</td>
<td>IX</td>
<td>70.26±9.55</td>
<td>Dyspnea, VA</td>
<td>Skin, eyes, H</td>
</tr>
</tbody>
</table>

*Values are mean±SD results of 3 independent determinations on peripheral blood lymphocytes.
VA indicates ventricular arrhythmias (Lown class III-Va); CNS, central nervous system; AP, acroparesthesias; H, hypohidrosis.

### TABLE 3. Genetic, Enzymatic, and Clinical Characteristics of Patients With Fabry Disease and No LVH

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age/Sex</th>
<th>Family</th>
<th>Enzymatic Activity,* \text{nmol/h per mg Protein}</th>
<th>Cardiac Manifestations</th>
<th>Extracardiac Manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>15/F</td>
<td>I</td>
<td>134.12±21.68</td>
<td>...</td>
<td>AP, eyes, ears</td>
</tr>
<tr>
<td>2</td>
<td>21/M</td>
<td>I</td>
<td>28.29±6.52</td>
<td>VA</td>
<td>AP, eyes, ears</td>
</tr>
<tr>
<td>3</td>
<td>24/M</td>
<td>I</td>
<td>17.05±3.68</td>
<td>VA</td>
<td>AP, eyes, ears, skin</td>
</tr>
<tr>
<td>4</td>
<td>34/F</td>
<td>II</td>
<td>905.15±52.11</td>
<td>VA</td>
<td>...</td>
</tr>
<tr>
<td>5</td>
<td>40/F</td>
<td>II</td>
<td>1030.15±78.05</td>
<td>VA</td>
<td>...</td>
</tr>
<tr>
<td>6</td>
<td>20/M</td>
<td>VII</td>
<td>23.79±4.14</td>
<td>...</td>
<td>AP, skin, ears, eyes</td>
</tr>
<tr>
<td>7</td>
<td>25/M</td>
<td>VIII</td>
<td>99.00±19.09</td>
<td>VA</td>
<td>AP</td>
</tr>
<tr>
<td>8</td>
<td>28/M</td>
<td>VIII</td>
<td>7.00±1.95</td>
<td>VA</td>
<td>AP</td>
</tr>
<tr>
<td>9</td>
<td>27/M</td>
<td>IX</td>
<td>123.04±40.27</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>10</td>
<td>28/M</td>
<td>IX</td>
<td>84.20±17.87</td>
<td>...</td>
<td>...</td>
</tr>
</tbody>
</table>

*Values are mean±SD results of 3 independent determinations on peripheral blood lymphocytes.
VA indicates ventricular arrhythmias (Lown class III-Va); AP, acroparesthesias.
those without LVH (mean value, 20.2±4.8 mm Hg and 15.6±2.4 mm Hg, respectively).

### Histology and Electron Microscopy Studies
Endomyocardial biopsy specimens consisted of regularly arranged and hypertrophied myocardial fibers containing systematically cell vacuoles that on frozen sections positively stained with periodic acid–Schiff and Sudan black, suggesting the accumulation of glycolipid material (Figure 1). At electron microscopy, these vacuoles appeared to be represented by concentric, lamellar figures in single membrane-bound vesicles (Figure 2) that were consistent with the diagnosis of Fabry disease. The extent of cell hypertrophy and of intracellular vacuole accumulation paralleled the severity of LV thickening. In particular, in patients without LVH, myocardiocytes were mildly hypertrophied (mean diameter at nuclear level, 18±2 μm) and contained small vacuoles mostly confined to the perinuclear zone (Figures 1 and 2). In patients with LVH, myocardiocytes were larger (mean diameter at nuclear level, 38±9 μm) and contained bigger vacuoles,

![Figure 1](image1.png)

**Figure 1.** Left ventricular endomyocardial biopsy of patient 2 (Table 3) showing mildly enlarged myocardiocytes containing perinuclear vacuoles (arrows). Hematoxylin and eosin stain; original magnification ×250.

![Figure 2](image2.png)

**Figure 2.** Transmission electron micrographs of LV endomyocardial biopsy of patient 2 (Table 3) showing at low (A) (arrows) and high (B) magnification perinuclear vacuoles that consist of single membrane-bound vesicles containing concentric, lamellar, electron-dense figures, typical of glycolipid storage disease. A, Magnification ×1250 (scale bar represents 10 μm; B, magnification ×11,000 (scale bar represents 1 μm).
extending from the perinuclear into the cytoplasmic area. The interstitium was normal or mildly widened because of intercellular fibrosis and tiny areas of fibrous replacement in patients without LVH, whereas it was moderately to severely increased because of scar tissue in patients with LVH. At ultrastructural analysis, storage vacuoles were observed in endothelial and smooth muscle cells of intramural vessels and in the endocardial layer of all patients.

**Echocardiographic Studies**

There were no differences among groups in LVEF and LV end-diastolic and end-systolic dimensions. LV septum and posterior wall thickness, LV mass, and LV atrial volume were increased in patients with Fabry disease and LVH compared with patients without LVH and control subjects. Patients with LVH showed higher peak A velocity, lower E/A ratio, longer isovolumic relaxation time and deceleration time, increased systolic filling fraction and atrial reversal velocity, and longer atrial reversal duration than the other two groups (Table 4). There were no significant differences between hemizygote male subjects and heterozygote female subjects. With regard to the pattern of hypertrophy, 8 patients showed a concentric hypertrophy and 2 patients an asymmetric septal hypertrophy without typical outflow gradient. Two-dimensional and traditional Doppler measurements were not significantly different in mutation-positive patients without LVH and control subjects. No patient showed mitral or aortic valve function abnormalities.

**Tissue Doppler Studies**

All patients with mutation in the α-Gal A gene had significant reduction of Sa, Ea, and Aa velocities at both corners of the mitral annulus compared with normal control subjects, with TD velocities being lowest in patients with LVH (Figure 3). At both lateral and septal corners, the mitral annulus Ea/Aa ratio was significantly lower and E/Ea ratio significantly higher in mutation-positive patients than in control subject. In particular, in patients with LVH and even in the 6 patients without LVH submitted to cardiac catheterization, septal E/Ea ratio predicted the presence of elevated LV end-diastolic pressure, in accordance with previous findings in patients with hypertrophic cardiomyopathy.14 Patients with LVH showed significantly lower contraction and relaxation TD velocities, lower Ea/Aa ratio, and higher E/Ea ratio in comparison with mutation-positive patients with no LVH (Table 5).

Lateral and septal Sa <10 cm/s both showed a sensitivity and specificity of 100% in identifying mutation-positive subjects without LVH. Similarly, lateral Ea <10 cm/s and septal Ea <10 cm/s had a sensitivity of 100% and specificity of 90% and 100%, respectively.

**Discussion**

Fabry cardiomyopathy is characterized by progressive LVH that may mimic hypertrophic cardiomyopathy in its nonobstructive and more rarely obstructive form.5,8 It is the most important cause of death not only in hemizygote male subjects but also in female heterozygote carriers with defi-
cy of α-Gal A, with a reduction of life-expectancy of approximately 20 and 15 years, respectively.3

Its clinical recognition has long been discouraging for the poor possibility to influence its natural and often unfavorable course. Recently, both enzyme activity enhancement12 and enzyme-replacement therapy7 have been revealed effective in reducing glycosphingolipids accumulation and in clearing existing deposits with improvement and even regression of the cardiomyopathy. Therefore, early diagnosis of Fabry cardiomyopathy has become crucial to allow prompt institution of the treatment and prevent cardiovascular complications as cardiac arrhythmias, ischemic heart disease, and systemic thromboembolic events.

In the present study, we report that Fabry cardiomyopathy is characterized by reduced myocardial contraction and relaxation velocities at TDI and that such abnormalities are detectable before the development of LVH and alterations of traditional echocardiographic parameters of diastolic function, thus providing a preclinical diagnosis of cardiac involvement. The gold standard for the diagnosis of Fabry cardiomyopathy was represented by histologic and ultrastructural findings obtained through endomyocardial biopsy in all patients with LVH and in 6 of 10 patients without LVH.

In our series, all patients with a mutation in the α-Gal A gene showed reduced myocardial contraction and relaxation TD velocities independent of their gender and type of mutation. Myocardial TD dysfunction was more pronounced in patients with LVH than in patients without LVH. This difference was consistent with the pathologic findings described in the two groups. In fact, in patients with LVH, histological and ultrastructural examination showed more extensive accumulation of storage material and more prominent myocardocyte hypertrophy in comparison with subjects without LVH, in whom mildly hypertrophied myocardocytes contained focal perinuclear vacuoles.

It can be argued that for the latter patients there is a discrepancy between TDI abnormalities and limited extent of pathological lesions. However, similar TDI changes have been previously documented in patients with genetic diagnosis of hypertrophic cardiomyopathy and no LVH. In addition, TDI abnormalities in our patients were systematically paralleled by an increase of LV filling pressure detected during cardiac catheterization, a less sophisticated but also more objective measure. We can then speculate that both in Fabry and hypertrophic cardiomyopathy, beyond the mechanical reflexes of storage material or abnormal protein synthesis, there would be a functional interference with the relaxation/contraction cycle of normal sarcomeres, thus producing secondary cellular hypertrophy and reduced contraction and relaxation TDI velocities. These abnormalities are to be considered the sign of initial intrinsic myocardial impairment not yet manifesting as LVH and conventional parameters of diastolic or even systolic dysfunction. In our series, only 6 of 10 patients without LVH showed extracardiac manifestations of Fabry disease: In the remaining 4 patients, TDI abnormalities were the first clinical sign of the disease. Thus, TDI screening of mutation-positive patients can allow the recognition of a preclinical cardiac damage.

With regard to the therapeutic impact of an early detection of Fabry cardiomyopathy, there is no definite indication to the ideal time to start with the enzyme replacement therapy, an expensive and even expensive option. However, Fabry disease is known to be characterized by an endothelial dysfunction that can be unpredictably complicated by devastating thromboembolic events, whereas myocardial involvement, since its initial stage, can manifest with complex and even severe arrhythmias. Indeed, in our series both invasive procedures and subsequent indication to enzymatic treatment were prompted by the occurrence of complex and repetitive ventricular extrasystoles in young people with genetic and biochemical diagnosis of Fabry disease and abnormal TDI findings and by the reluctance to use antiarrhythmic drugs, a palliative solution potentially aggravated in 5% to 8% of cases by proarrhythmic events.

In addition, TDI can be useful in female carriers, often without systemic manifestations and usually considered spared by the disease. In our study, heterozygote female subjects showed Fabry cardiomyopathy in 6 cases, 3 with and 3 without LVH, confirming previous observations that female carriers can present various degrees of the disease ranging from completely healthy subjects to classically affected patients with multiorgan involvement.4 The presence and extent of clinical manifestations strongly depend on the rate of inactivation of the X chromosome carrying the nonmutated gene in different tissues: An unfavorable lyonization can lead to very low enzymatic activity with clinical manifestations resembling those of hemizygote male subjects.4,15

The detection of TDI abnormalities in female carriers can represent a hint for invasive assessment of cardiac involvement and therefore for eventual enzymatic therapy.

In conclusion, our data suggest that Fabry cardiomyopathy is characterized by reduced myocardial contraction and relaxation TD velocities. TD abnormalities are detectable before the development of wall thickening and traditional echocardiographic signs of diastolic dysfunction and are a specific and sensitive marker of initial cardiac involvement.

TDI can indicate the need for a prompt institution of enzymatic therapy in patients with Fabry disease. Further TDI endomyocardial biopsy—based studies in patients undergoing

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**TABLE 5. Tissue Doppler Velocities in the Three Groups**

<table>
<thead>
<tr>
<th></th>
<th>Mutation+/LVH+ (n=10)</th>
<th>Mutation+/LVH− (n=10)</th>
<th>Control Group (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lateral Sa, cm/s</td>
<td>6.11±0.60*</td>
<td>7.98±0.55†</td>
<td>14.54±1.26</td>
</tr>
<tr>
<td>Lateral Ea, cm/s</td>
<td>6.00±0.72*</td>
<td>8.21±0.53†</td>
<td>15.66±1.02</td>
</tr>
<tr>
<td>Lateral Aa, cm/s</td>
<td>6.78±1.23*</td>
<td>8.59±0.83†</td>
<td>9.76±0.47</td>
</tr>
<tr>
<td>Lateral Ea/Aa, cm/s</td>
<td>0.89±0.07*</td>
<td>0.96±0.13†</td>
<td>1.60±0.13</td>
</tr>
<tr>
<td>Lateral E/Ea, cm/s</td>
<td>12.58±0.71†</td>
<td>9.62±1.11†</td>
<td>4.95±0.44</td>
</tr>
<tr>
<td>Septal Sa, cm/s</td>
<td>5.84±0.61*</td>
<td>7.91±0.58†</td>
<td>14.40±1.33</td>
</tr>
<tr>
<td>Septal Ea, cm/s</td>
<td>5.33±0.38*</td>
<td>8.22±0.55†</td>
<td>15.2±1.00</td>
</tr>
<tr>
<td>Septal Aa, cm/s</td>
<td>6.1±0.72*</td>
<td>8.31±0.26†</td>
<td>9.72±0.31</td>
</tr>
<tr>
<td>Septal Ea/Aa, cm/s</td>
<td>0.88±0.09*</td>
<td>0.99±0.06†</td>
<td>1.56±0.11</td>
</tr>
<tr>
<td>Septal E/Ea, cm/s</td>
<td>14.17±1.65*</td>
<td>9.61±1.12†</td>
<td>5.11±0.52</td>
</tr>
</tbody>
</table>

*P<0.001 vs normal control subjects.
†P<0.01 vs Mutation+/LVH+.
‡P<0.001 vs Mutation+/LVH−.

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enzyme replacement therapy will define the possible role of TDI for an early and accurate evaluation of treatment efficacy.

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References
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