Early Myocardial Dysfunction in Patients with Fabry Disease Assessed by Tissue Doppler Imaging

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Abstract

Fabry disease (FD) is a rare X-linked recessive chromosomal disease with a deficiency of the enzyme α-galactosidase A, which leads to an accumulation of glycolipid substrate in skin, nervous system, kidney, cornea and heart. Cardiac involvement is characterized by conduction disorders, left ventricular (LV) hypertrophy, valvular thickening, and development of restrictive or hypertrophic cardiomyopathy. The present study was aimed to assess the extent of changes in cardiac function and morphology in six FD patients. Twelve healthy subjects were included as controls. Both groups were investigated by 2D-Doppler Echocardiography and Tissue Doppler Imaging (TDI). All FD patients had preserved global LV ejection fraction. In four of them (with history of arterial hypertension) a mild LV hypertrophy and features of diastolic dysfunction were detected. In all six FD patients significantly reduced telesystolic global longitudinal strain and average velocities of medial and lateral mitral annulus were demonstrated by TDI. These findings suggest TDI might be a useful method for a detection of early myocardial dysfunction in FD.

Keywords: Fabry disease, Early myocardial dysfunction, 2D-Echocardiography, Tissue Doppler Imaging.

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I. INTRODUCTION

Fabry disease (FD), also known as angiokeratoma corporis diffusum universale, is a rare X-linked genetic disorder with recessive inheritance, which gene is located at Xq 22 chromosome. It belongs the family of accumulation diseases with inherited deficiency or attenuated activity of alfa galactosidase A (alfa Gal A) [1,2,3].

FD was simultaneously described by Johannes Fabry and William Anderson in 1898 [4]. The first clinical signs of the disease include: angiokeratoma in childhood, acroparesthesia, hypohidrosis as well as ocular abnormalities (cornea verticillata). FD prevalence is estimated to be 1:40000 in males and 1:117000 in general population [5,6,7]. The disease can affect both genders unlike the most sex-related inherited disorders, but it is more common and with more severe clinical manifestation in men, where alfa Gal A activity is very low or even absent. To date 431 mutations have been reported for the Gal A gene and more than 57% of them are missense mutations with residual enzyme activity [8,9]. Most often so-called “private” mutations are available, i.e. typical for each FD family [5]. According to MacDermot et al. the median cumulative survival of FD patients is 50 years, which represents an approximately 20-year reduction of life span [10]. The most severely affected organs appear to be heart muscle, kidney and central nervous system. A pathological accumulation of globotriasylceramide is detected in vascular endothelium of different tissues. Patients with FD can be presented clinically with chronic neuronopathic pain, gastrointestinal disturbances, a specific skin finding called angiokeratoma, progressive renal impairment, restrictive and hypertrophic cardiomyopathy, and premature myocardial infarction or stroke [9,11,12].

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Fig. 1. Representative Pulse-wave Doppler and TDI of a patient with FD.
Cardiac involvement can also include: left ventricular hypertrophy (LVH), abnormalities of electrical conduction and mild aortic or mitral regurgitations, whereas severe valvular disorders are rare [13,14,15]. The ventricular walls are thickened due to a deposition of globotriaosylceramide in the cardiomyocytes and cellular hypertrophy, which can cause mild decrease of the diastolic compliance, usually with normal systolic function [1]. Cardiac disorders and fatal cardiac complications are the leading cause of mortality in women with FD and the second most frequent in men. It is also likely that cardiac disease contributes to the dismal prognosis of patients with FD and end-stage renal failure [16]. Therefore, early recognition of cardiac involvement is crucial for optimal treatment and for delaying its progression [4,17,18].

The aim of our study was to assess the extent of changes in cardiac function and morphology in Bulgarian patients with FD using 2D-Echocardiography (2D-EchoCG) and Tissue Doppler Imaging (TDI).

### II. METHODS

**Study population:** To our knowledge there are altogether twelve patients with genetically confirmed FD in Bulgaria. Six of them (4 men and 2 women, aged 19-60 years) with histologically proven chronic glomerulonephritis and preserved renal function were involved in this study. Four of these patients had well-controlled and treated arterial hypertension (AH) according to the ESC/ESH Guidelines, two of them suffered from bronchial asthma and one – from small joints polyarthritis and angiookeratoma. Twelve normal subjects without AH and LVH (aged 23-55 years) were included into a control group.

**Echocardiographic studies:** All subjects underwent complete standard echocardiographic examinations in accordance with current guidelines of the American Society of Echocardiography [19]. The following parameters were measured by 2D-EchoCG and pulse-wave (PW) Doppler:

- **Parameter**
  - **Age (years)**
  - **Heart rate (bpm)**
  - **Systolic BP (mmHg)**
  - **Diastolic BP (mmHg)**
  - **EF (%)**
  - **SV (ml)**

**Table 1.** Baseline characteristics of six patients with Fabry disease and controls.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Fabry patients</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>38 ± 12</td>
<td>36 ± 15 *</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>69 ± 7</td>
<td>67 ± 10 *</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>126 ± 14</td>
<td>124 ± 9 *</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>85 ± 4</td>
<td>83 ± 7 *</td>
</tr>
<tr>
<td>EF (%)</td>
<td>61 ± 6</td>
<td>64 ± 5 *</td>
</tr>
<tr>
<td>SV (ml)</td>
<td>66 ± 11</td>
<td>72 ± 18 *</td>
</tr>
</tbody>
</table>

* p = NS. Data expressed as mean ± SD; BP: blood pressure; EF: ejection fraction; SV: stroke volume.

end-diastolic interventricular septum thickness and left ventricular posterior wall thickness, early (E) and late (A) mitral inflow velocities, early myocardial relaxation velocity (e’) and deceleration time (DT), LV ejection and shortening fractions.

**TDI:** In all six patients and twelve aged matched controls a telo-stysolic global longitudinal strain (GLS) and average peak velocities of the medial and lateral mitral annulus were evaluated by TDI (Fig. 1).

**Statistical Analysis:** Statistical analyses were performed by SPSS Statistics version 12.0. The data were expressed as mean values ± SD. For comparison of quantitative variables a Fisher’s exact test was used. P < 0.05 was accepted as a level of statistical significance.

### III. RESULTS

In the group of six evaluated FD patients the clinical and echocardiographic findings could be summarized as follows: 1. The general characteristics (age, heart rate, systolic and diastolic blood pressure), as well as global ejection fraction and stroke volume were comparable between FD patients and controls (p=NS); (Table 1).

2. Four FD patients with AH, irrespective of sex and age had mild LVH (mean interventricular septum thickness: 12.4 mm; mean LV posterior wall thickness: 12.0 mm (both p<0.05 vs controls). The pulse-wave Doppler and TDI data showed statistically significant disturbances in diastolic LV function (decreased E/A ratio and increased E/e’ ratio) only in these 4 FD patients with AH and LVH (p<0.01); (Table 2, Fig. 2)

3. In all six FD patients:
   - A significantly decreased global longitudinal strain (mean -6% vs mean -21.6% in controls, p<0.01) was detected by TDI; (Table 3, Fig. 2)
   - The average peak velocities of the lateral mitral annulus in FD were also diminished (p<0.01 vs controls); (Table 3, Fig. 2). Changes in the velocities of the medial mitral annulus in FD were similar to these of the lateral one.

**Table 2.** PW-Doppler and TDI measurements in four FD patients with arterial hypertension and LV hypertrophy vs controls.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Fabry patients</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>IVSd (cm)</td>
<td>1.24 ± 0.2</td>
<td>0.90 ± 0.3 *</td>
</tr>
<tr>
<td>LVPWd (cm)</td>
<td>1.2 ± 0.3</td>
<td>0.93 ± 0.2 *</td>
</tr>
<tr>
<td>E/A ratio</td>
<td>0.71 ± 0.38</td>
<td>1.40 ± 0.36 #</td>
</tr>
<tr>
<td>E/e’ ratio</td>
<td>10.39 ± 1.25</td>
<td>5.19 ± 1.93 #</td>
</tr>
</tbody>
</table>

* p < 0.05; # p < 0.01. Data expressed as mean ± SD; IVSd: end-diastolic interventricular septum thickness; LVPWd: left ventricular end-diastolic posterior wall thickness; A: transmitral A velocity; E: transmitral E velocity; e’: velocity of mitral annulus (lateral wall).
Our study was aimed to investigate the type and the extent of changes in LV morphology and function in six FD patients with higher frequency of cardiac morbidity associated with this disease. Classically, a cardiac manifestation of FD involves a diffuse myocardial wall thickening [16,22]. However, it is crucial to identify the patients with FD at a stage, preceding LVH, since some of them could have lysosomal storage of globotriaosylceramide in the absence of hypertrophy, established by conventional image technologies [3,23]. The presence of LVH is associated with higher frequency of cardiac symptoms and is related independently to gender, age and renal function [16]. Recent reports have shown that TDI (before development of LVH) is an accurate and sensitive method for identifying subjects with familial hypertrophic cardiomyopathy mutations [20,24,25]. The majority of FD studies involve patients with already developed LVH and disturbed diastolic function [26,27]. Wu et al. described a cohort of 139 Fabry patients with a high prevalence of cardiovascular complications. A left ventricular hypertrophy was found in up to 84% of these cases. The presence of LVH was associated with lower alfa Gal A activity and higher rate of cardiovascular symptoms, i.e. more severe form of the disease. The concentric LVH was a predominant cardiac pathology in these FD patients [28]. At its advanced stage Fabry cardiomyopathy is characterized by reduced myocardial contraction and development of systolic dysfunction.

Our study was aimed to investigate the type and the extent of changes in LV morphology and function in six FD patients of both sexes (a half of all Bulgarian FD cases). All of them were presented with preserved global LV ejection fraction and stroke volume. It should be pointed out the PW-Doppler data of diastolic dysfunction were obtained only in 4 FD patients with arterial hypertension and LVH, whereas the global longitudinal strain and average velocities of lateral mitral annulus were found to be significantly reduced in all six patients (with and without AH and LVH), when compared to aged-matched controls. Actually, our data are similar to the findings of Pieroni et al. [29]. They reported reduced myocardial contraction and relaxation velocities at TDI before the development of LVH and alterations of global systolic function. Patients with LVH showed higher peak A velocity, lower E/A ratio, longer isovolumic relaxation time and deceleration time than the other two groups. There were no significant differences between hemizygote male and heterozygote female subjects. Chimenti et al. confirmed the current understanding that TDI could reveal diastolic and systolic LV dysfunction in FD even before the development of wall thickening. These authors analysed the mechanical properties of isolated cardiomyocytes, the degree of glycosphingolipid accumulation and the extent of fibrosis in endomyocardial biopsy samples of FD patients. Their results showed a positive correlation of these measurements with the parameters of LV function, assessed by TDI [30]. In a recent study subtle, but significant changes of global LV motion and deformation in the early stages of cardiac involvement in FD were detected by 3D Speckle tracking. It was proved that this method is another feasible and reproducible tool in this setting [4,24]. FD clinical recognition has long been discouraging due to the lack of opportunities to influence its natural and often unfavourable course [31]. Nowadays, using TDI, clinicians could be able to indicate the need for an implementation of enzymatic therapy in FD patients, as well as for an early and accurate evaluation of the treatment efficacy.

The main limitation of our study is the very small number of included patients (six). Indeed, the entire cohort of genetically confirmed FD cases in Bulgaria encompasses twelve patients.

### Table 3. Results of average velocity of the lateral mitral annulus and global longitudinal strain, evaluated by TDI in six patients with Fabry disease vs controls.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Fabry patients</th>
<th>Controls</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average velocity of the lateral mitral annulus (cm/s)</td>
<td>e': 4.1 ± 1.4</td>
<td>e':11.1 ± 2.0</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Global longitudinal strain (%)</td>
<td>-6.0 ± 3.6</td>
<td>-21.6 ± 4.4</td>
<td>&lt; 0.01</td>
</tr>
</tbody>
</table>

**IV. DISCUSSION**

2D-EchoCG is now the most commonly used noninvasive method for evaluation of cardiac anatomy and function. Moreover, Tissue Doppler Imaging EchoCG is an important tool to assess the early systolic and diastolic LV dysfunction and thus could provide a preclinical diagnosis of a myocardial involvement [20]. Albeit described over a century ago, FD still remains a challenge for diagnosis and treatment [21]. It has been reported a high prevalence of cardiac morbidity, associated with this disease. Classically, a cardiac manifestation of FD involves a diffuse myocardial wall thickening [16,22]. However, it is crucial to identify the patients with FD at a stage, preceding LVH, since some of them could have lysosomal storage of globotriaosylceramide in the absence of hypertrophy, established by conventional image technologies [3,23]. The presence of LVH is associated with higher frequency of cardiac symptoms and is related independently to gender, age and renal function [16]. Recent reports have shown that TDI (before development of LVH) is an accurate and sensitive method for identifying subjects with familial hypertrophic cardiomyopathy mutations [20,24,25]. The majority of FD studies involve patients with already developed LVH and disturbed diastolic function [26,27]. Wu et al. described a cohort of 139 Fabry patients with a high prevalence of cardiovascular complications. A left ventricular hypertrophy was found in up to 84% of these cases. The presence of LVH was associated with lower alfa Gal A activity and higher rate of cardiovascular symptoms, i.e. more severe form of the disease. The concentric LVH was a predominant cardiac pathology in these FD patients [28]. At its advanced stage Fabry cardiomyopathy is characterized by reduced myocardial contraction and development of systolic dysfunction.

![Fig. 2. Comparative analysis of the main 2D-EchoDoppler in 4 FD patients and TDI in all 6 FD patients measurements vs controls.](image-url)
Unfortunately, we were able to investigate only these ones, who had been monitored in the University Clinic of Nephrology and Transplantation in Sofia. In this setting our data might not be applicable to the whole Bulgarian FD population. Moreover, this was a cross-sectional study, i.e. the involved six patients were not followed up for development of cardiac or non-cardiac events, as well as for mortality rate.

V. CONCLUSIONS

In the present study we showed overt diastolic dysfunction in 4 FD patients with arterial hypertension. However, the TDI evaluation revealed significantly diminished global longitudinal strain and average velocities of lateral mitral annulus in all six FD patients (in comparison to normal subjects), i.e. even in absence of LV hypertrophy and diastolic abnormalities. Thus, this approach might be useful for detection of early myocardial dysfunction in FD patients, but needs further research for clarification of its reliability.

REFERENCES