

## Echocardiography in Fabry disease

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### Abstract

Fabry disease is an X-linked lysosomal storage disorder caused by alpha-galactosidase A deficiency. The genetic defect leads to progressive intracellular accumulation of G13 in various tissues, including heart, kidney, vascular endothelium and the nervous system. Cardiac involvement is frequent and since renal transplantation therapy became standard most Fabry patients die due to cardiac reasons. Left ventricular hypertrophy is the morphological hallmark of the disease. Hypertrophy can be accompanied by various other cardiac findings, which can be visualized using echocardiography. Especially the left ventricular geometry and the regional myocardial function can show major alterations during disease progression. This review provides echocardiographic guidance in Fabry disease and highlights possible alterations of the hearts components visualizable with echocardiography. The main findings are summarized in the *Take home message* sections.

### Introduction

Fabry disease (FD) is an X-linked lysosomal storage disorder caused by  $\alpha$ -galactosidase A deficiency.<sup>1</sup> The genetic defect leads to progressive intracellular accumulation of G13 in various tissues, including heart, kidney, vascular endothelium and the nervous system.<sup>2</sup> Cardiac involvement is frequent and since renal transplantation therapy became standard most Fabry patients die due to cardiac reasons.<sup>3</sup> Moreover, a so-called *cardiac variant* has been reported with the heart being the sole affected organ.<sup>4</sup> Left ventricular hypertrophy (LVH) is the morphological hallmark of the disease.<sup>5</sup> Hypertrophy is accompanied by various other findings on echocardiography during disease progression. This review provides echocardiographic guidance in Fabry disease and highlights possible alterations of the hearts components visualizable with echocardiography. The main findings are summarized in the *Take home message* sections.

### Aortic dimensions

Some of the early echocardiographic reports on Fabry cardiomyopathy showed an increased aortic root diameter of male patients compared to female patients and healthy controls.<sup>6,7</sup> In recent days a study by Barbey *et al.*<sup>8</sup> found a high prevalence of ascending aortic dilation, predominantly in male Fabry patients. According to these data male Fabry patients seem to be at risk to develop ascending aortic dilation around the 5<sup>th</sup> decade of life. However, it has to be noted that a real aneurysm (>5 cm) is a rare finding as well as moderate or severe aortic regurgitation and that there has been no report about aortic dissection or rupture in Fabry disease. Nevertheless a *prominent bulbous aortae* of 40-44 mm is very common in middle-aged Fabry patients and might be linked to tissue alterations induced by G13 storage (Figure 1).

### Take home message

Mildly dilated aortic root is common in Fabry disease.

### Atria

Atrial dilatation is not a pathognomonic sign in Fabry disease as it is in cardiac amyloidosis. Comparable to aortic dilation the dilation of the left ventricular atrium is often mild to moderate. A distance measured from *edge to edge* in the parasternal longitudinal view of 40-45 mm in middle-aged male patients is frequent (Figure 1). In our cohort severe dilation was only seen in the rare case of severe mitral prolapse syndrome with flail leaflet (1 out of 180 patients). A severe tricuspid regurgitation is seldom observed in Fabry disease; thus, right atrial dilatation is not a frequent finding, either.

### Take home message

Atrial dimensions are mildly to moderately altered.

### Valve disease

Valve abnormalities are observed frequently in Fabry patients.<sup>9-11</sup> We systematically investigated 111 patients with genetically confirmed Fabry disease.<sup>12</sup> Overall, no patient had severe heart valve abnormalities. The most frequent findings were mild aortic (n=17 out of 111), mitral (n=57 out of 111) and tricuspid (n=38) valve regurgitation. Only two patients showed mild aortic valve stenosis. Moderate aortic

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(n=1), mitral (n=2) or tricuspid (n=1) regurgitation were rarely detected. Thirty patients had completely normal valve function.<sup>12</sup> The mild alterations seem to be no major limitation for the Fabry heart. Only if other morphological alterations are observed additionally (like mitral prolapse), higher degree variations are seen. Calcified aortic valve stenosis seems to play no role in Fabry disease because of the reduced life expectancy.

### Take home message

Although G13 storage is present in valve tissue, valve abnormalities are only mild.

### Right ventricle

The deposition of globotriaosylceramides can be found in both, the left and the right ventricle. Hypertrophy of the right ventricle can be found in around 50-70% of all patients with Fabry disease (dependent on gender and age).<sup>13,14</sup> Right ventricular involvement largely parallels left ventricular involvement when assessed with standard echocardiographic parameters.<sup>13,15</sup> Interestingly the right ventricle develops no fibrosis when assessed with cardiac magnetic resonance imaging. The regional right ventricular function of the lateral free wall (assessed with tissue Doppler imaging) is especially reduced in patients already presenting left ventricular replacement fibrosis.<sup>14</sup> When following patients under

enzyme replacement therapy by echocardiography no change in right ventricular regional function can be observed.<sup>14</sup> Interestingly, there is no reduction in right ventricular hypertrophy under enzyme replacement therapy, which is in contrast to the response of the left ventricle.<sup>14</sup> The tricuspid annular systolic plan excursion (TAPSE), the standard parameter for global right ventricular function is often normal in patients with Fabry disease, even in some patients with advanced stages of the disease.

### Take home message

Right ventricular involvement largely parallels left ventricular involvement.

## Left ventricle geometry

### Hypertrophy and fibrosis

The most prominent finding in Fabry cardiomyopathy is left ventricular hypertrophy, which starts with concentric left ventricular remodeling. The resulting hypertrophy usually also presents concentric and starts around the patients' mid thirties.<sup>16</sup> In rare cases other pattern of hypertrophy (excentric, regional) can be seen, but it should be doubted if this is solely due to Fabry disease (e.g. septal bulge in hypertensive heart disease, coexistence of sarcomeric hypertrophic cardiomyopathy or left ventricular non-compaction). Moreover, in end-stage cardiac disease regional myocardial fibrosis of the left ventricular inferior-lateral wall mimics asymmetrical left ventricular hypertrophy. It is known that up to 61% of patients with FD display left ventricular hypertrophy<sup>17</sup> and that the amount of left ventricular hypertrophy increases with age. Left ventricular outflow tract obstruction has not been regarded as an important finding in Fabry disease, because of low incidence under resting conditions. An interesting report was published recently where in a small cohort of 13 Fabry patients half of them developed dynamic left ventricular outflow tract obstruction >50 mmHg during exercise, although not present at rest.<sup>18</sup> The mechanism was complete systolic anterior motion of the mitral valve leaflets in 5 and in one the result of a narrow LV outflow tract, the presence of a tendon running between the septum and the papillary muscles and contact between the mitral valve leaflet and the septum.<sup>18</sup> However, it still has to be proven in a larger cohort if this finding is clinically relevant.

Takenaka *et al.* investigated end stage patients with the cardiac variant of Fabry disease.<sup>19</sup> They could show that there is a thinning of the posterior-lateral basal segment of the left ventricle, due to spreading replacement fibrosis.<sup>19</sup> In advanced stages this fibro-

sis leads to wall motion abnormalities that can be visualized even with standard echocardiography (Movies 1-3). It is of note that late enhancement in cardiac magnetic resonance can be seen even in some non-hypertrophic females, although there is no evidence of wall motion abnormality on echo.

Monitoring cardiac therapy responses, e.g. monitoring enzyme replacement therapy – available since 2001, is particularly done by echocardiography. Several studies showed a reduction of left ventricular hypertrophy in early disease stage, especially in the first years, and a stabilization thereafter.<sup>5,20,21</sup> However, the wall thinning in end stage patients under enzyme replacement therapy seems to be caused by the development and progression of fibrosis and seems to be no beneficial therapy effect.

### Take home message

Left ventricular hypertrophy is the hallmark of Fabry cardiomyopathy and can be useful to monitor enzyme replacement therapy.

### Endocardium

A binary appearance of the endocardium was first reported by Pieroni *et al.* in 2006.<sup>22</sup> They suggested this marker to detect patients with Fabry disease among patients with unclear left ventricular hypertrophy and proposed a linkage between the binary appear-

ance and the storage of G13 in the subendocardium.<sup>22</sup> Other studies doubted the feasibility of binary appearance to screen for Fabry disease or the ability to distinguish between Fabry cardiomyopathy and other hypertrophic diseases.<sup>23-25</sup> In our cohort of 180 Fabry patients the binary sign is seen rarely and is not associated with any stage of disease (Niemann and Weidemann, 2013, unpublished data). Thus, we do not suggest this sign as a useful marker to screen for Fabry disease.

### Take home message

Binary appearance is rare.

### Papillary muscles

From autopsy studies, it is known that the papillary muscle hypertrophies, too - like the wall of the left ventricle does (Movie 4).<sup>26</sup> In a recent study it could be shown that the absolute papillary muscle area as well as the ratio of the papillary muscle area and the left ventricular circumference is enlarged in Fabry disease.<sup>27</sup> This is in contrast to other hypertrophic cardiomyopathies like Friedreich ataxia, hypertrophic non obstructive cardiomyopathy or amyloidosis.<sup>27</sup>

### Take home message

Prominent papillary muscles are typical.

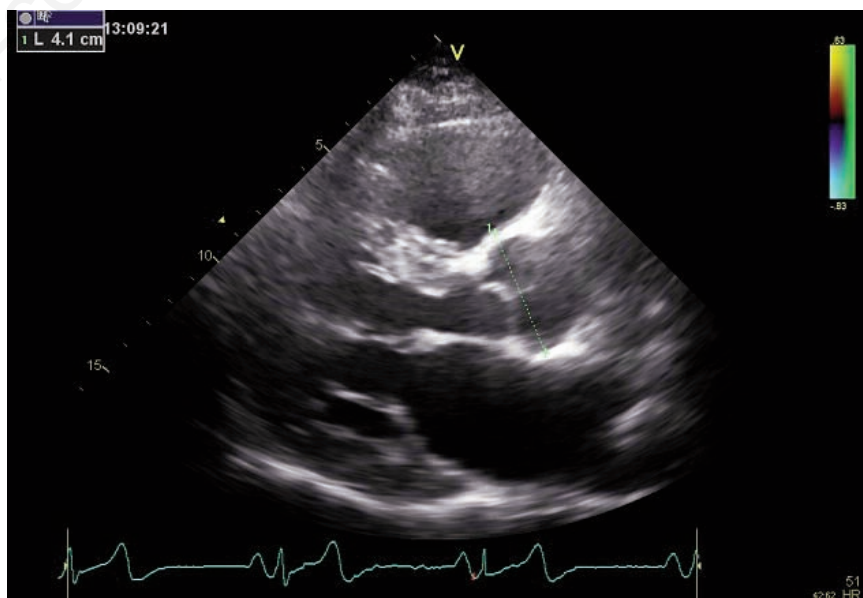


Figure 1. A parasternal long axis view of a Fabry patient's heart. Please note the mildly dilatated aortic root and left atrium.

## Global systolic function

The global left ventricular ejection fraction (EF) is typically preserved in Fabry disease (Movie 4).<sup>5,20</sup> Even when replacement fibrosis is already detectable the ejection fraction is often compensated. When ejection fraction finally decreases this is associated with high mortality.<sup>17,28</sup>

### Take home message

EF is preserved in Fabry disease.

## Diastolic function

For years and even today, Fabry cardiomyopathy has often been labeled as restrictive diastolic dysfunction (see Braunwald's *Textbook of Cardiovascular Medicine* and the *Oxford Handbook of Cardiology*). When the diastolic function of Fabry patients is investigated systematically a restrictive pattern turns out to be extremely rare: in a cohort of 100 patients only one patient (male, 51-year old) had the typical restrictive filling pattern with a high filling pressure.<sup>29</sup> These findings are also supported by a study by Linhart *et al.*, which showed that even in Fabry patients with left ventricular hypertrophy no restrictive filling pattern was observed.<sup>30</sup> In general, relaxation abnormalities are common, pseudo normalization being observed in more advanced stages (Figure 2).<sup>29</sup> More *advanced* methods for the evaluation of diastolic function (mitral annulus tissue Doppler imaging/pulmonary vein Doppler)<sup>31</sup> can detect mild diastolic dysfunction in patients with preserved LV systolic function earlier than the mitral inflow analysis. These two investigations are also very helpful to differentiate a normal from a pseudo

normal-filling pattern. Thus, the pulmonary vein Doppler and the mitral annulus tissue Doppler should be performed in every Fabry patient. Whether diastolic dysfunction is a direct consequence of G13 storage or is more influenced by reactive hypertrophy can only be speculated.

### Take home message

Diastolic function: relaxation abnormalities and pseudonormalization are found frequently.

## Combined analysis of global left ventricular diastolic and systolic function

A possibility to assess systolic and diastolic function in combination is the use of the so-called Tei-index or myocardial performance index. The Tei-index is dimensionless derived by dividing the sum of isovolumic contraction and relaxation times by the ejection time. A value below 0.4 is considered to be normal. It was shown in a large cohort of Fabry patients that the Tei-index is higher in patients with evidence of LVH and/or late enhancement (LE) on cardiac magnetic resonance than without.<sup>32</sup> Moreover, a significant positive correlation was observed between Tei index and LVH but not with the presence of LE on cardiac magnetic resonance. Thus, this tool is able to mirror morphological changes with functional measurements, but, as Pieroni states in a readworth comment on this paper, it can not substitute tissue Doppler imaging or cardiac magnetic resonance imaging in Fabry disease.<sup>33</sup>

### Take home message

Tei index can detect advanced stages of Fabry disease.

## Regional myocardial function

### Mitral annulus velocities

Tissue Doppler imaging (TDI) velocities of the septal and lateral mitral annulus were inversely related to left ventricular mass in a cohort of 76 Fabry patients.<sup>34</sup> In addition, follow up studies showed that the TDI velocity abnormalities were evident earlier than the development of left ventricular hypertrophy. There seems to be additional information that ERT might prevent the development of abnormal TDI velocities in patients without evidence for a cardiomyopathy at baseline.<sup>34</sup>

### Take home message

TDI measurements provide better information about systolic function than EF.

### Strain and strain rate imaging

Although in advanced stages of the Fabry cardiomyopathy ejection fraction can be normal, it is nowadays clear that even in early stages of cardiac involvement systolic myocardial performance shows subtle impairment that can be assessed by strain rate imaging and speckle tracking.<sup>28,33</sup> It could even be documented that there is reduced strain and strain rate in Fabry cardiomyopathy in the absence of any other echocardiographic sign of cardiomyopathy. Typically, the lateral basal segments are the first to develop regional functional abnormalities. In general longitudinal function is first reduced and radial function is initially preserved.<sup>28</sup> Strain and strain rate imaging can be used to monitor effects of enzyme replacement therapy. There is data that only early disease stage (without presence of replacement fibrosis detected by late enhancement on cardiac magnetic resonance) shows an improvement in regional myocardial function under enzyme replacement therapy.<sup>5</sup> A recent study

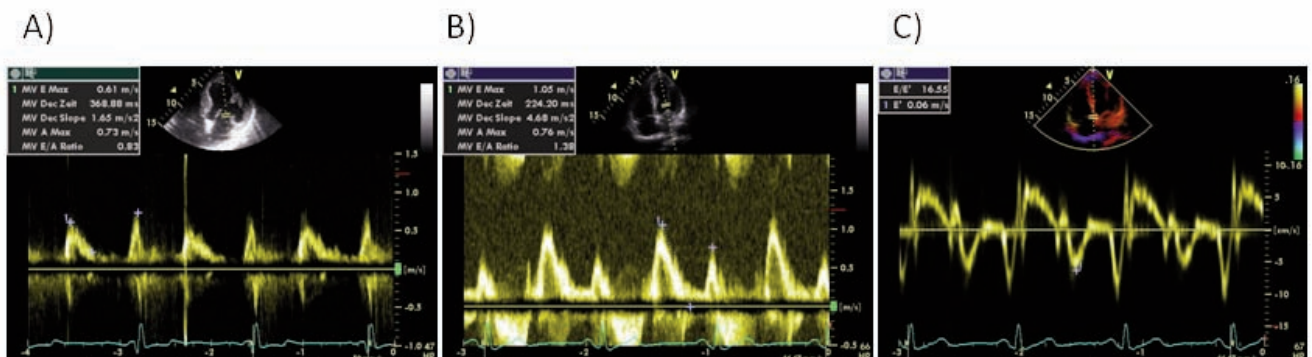


Figure 2. Typical diastolic pattern observed in Fabry patients: A) relaxation abnormalities; B) pseudonormal pattern C) typical E/E' value of 16.



by Gruner *et al.* showed that patients with Fabry disease lose the normal base to apex circumferential strain gradient.<sup>35</sup> This was in difference to patients with non-obstructive hypertrophic cardiomyopathy where the circumferential strain was indeed increased. One additional advantage of functional imaging is that the development of fibrosis, starting always in the mid layers of the inferolateral basal segments, can be indirectly visualized using strain rate imaging.<sup>36</sup>

### Take home message

Deformation imaging can visualize even subtle involvement in Fabry disease.

## Role of echocardiography in everyday Fabry disease management

Echocardiography and its findings (as listed above) play a major role in the diagnostic and therapeutic setting of patients with Fabry disease. The primary consulted cardiologist/echocardiographer should be aware of the main Fabry cardiomyopathy findings, summarized in the *Take home message* sections. Especially a left ventricular hypertrophy of unknown origin and typical echocardiographic markers like a prominent papillary muscle should serve as *red flags* – especially in combination with a typical clinical presentation (hypohidrosis, typical pain presentation). A second or third level center than has to confirm or rule out Fabry disease. Moreover these centers have to assess the severity of the cardiomyopathy, echocardiography being the pivotal investigation. The last important task concerning echocardiography in Fabry disease should be reserved to centers with great experience in diagnosing and monitoring Fabry disease patients: they must monitor disease progression, enzyme replacement therapy results and determine the need for concomitant therapy in addition to ERT.

## Conclusions

Echocardiography can be used to visualize the morphological and functional changes in Fabry disease, from early to late stage: i) *e.g.* it is applicable to detect early disease stage especially by the use of deformation imaging; ii) various echocardiographic techniques can be used to monitor and follow patients with left ventricular hypertrophy; iii) the end-stage patient is characterized by the coexistence of myocardial hypertrophy, myocardial thinning and the presence of wall motion abnormalities.

## Movies

Four movies are available at: [www.cardiogenetics.org](http://www.cardiogenetics.org)

*Movie 1-3:* A long axis view (Movie 1), apical 4-chamber view (Movie 2) and a 3-chamber view (Movie 3) of a patient with an advanced Fabry cardiomyopathy. Please note the wall thinning in the posterior-lateral segments.

*Movie 4:* A 4-chamber view of a patient with a cardiomyopathy and left ventricular hypertrophy. Please note the prominent papillary muscle.

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