

## Research Article

# Myocardial Dysfunction in Anderson-Fabry Disease (AFD) without Ventricular Hypertrophy

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## Keywords

- Fabry disease
- Echocardiography
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- Myocardial dysfunction

## Abstract

Cardiac involvement in Anderson-Fabry Disease, a rare X-linked genetic lysosomal storage disorder, is common and more than 50% of patients develops a concentric non-obstructive left ventricle hypertrophy.

**Aim:** Aim of study was to identify early signs of myocardial involvement in patients with Fabry Disease without hypertrophy, using 2D Speckle Tracking Echocardiography to evaluate the Left Ventricle Longitudinal Strain (GLS).

We evaluated Echocardiograms of 21 patients (7 males, 14 females) with diagnosis of Fabry Disease. For this study we reported the values of the LV mass indexed by body surface area (LVMI), E wave of mitral flow, the systolic (S') and early diastolic myocardial velocity (E') of tissue Doppler at mitral annulus, E/E' ratio and GLS. Patients were grouped according to the presence or absence of LV hypertrophy in two groups: with LVMI >115 g/m<sup>2</sup> (LVH) and with LVMI ≤115 g/m<sup>2</sup> (noLVH); the data were compared to normal group (N) matched for age and BSA. LVH pts (2M-3F, 53 ± 9y) showed: Enzyme activity 1,54 ± 1,98; LVMI g/m<sup>2</sup> 150 ± 23,6; E cm/s 70,4 ± 23,7 (vs. p<0,196); S'cm/s 5,4 ± 1,1 (vs. p<0,001); E' 5,2 ± 2,7 (vs. p<0,001); E/E' 16,96 ± 11,8 (vs. p<0,0005); GLS% -11,7 ± 5,4. (vs. p<0,001). NoLVH pts (5M-11F, 33 ± 19y) showed: Enzyme activity 3,43 ± 3,03; LVMI g/m<sup>2</sup> 70 ± 16,4 (vs. p<0,719); E cm/s 82,1 ± 29,6 (vs. p<0,807); S' cm/s 7,2 ± 1,6 (vs. p<0,001); E' 12 ± 4,1 (vs. p<0,204); E/E' 8 ± 3 (vs. p<0,0005); GLS% - 18,4 ± 2,8 (vs. p<0,02). Our study shows that even in patients without hypertrophy, then in the pre-clinical stage, the longitudinal ventricle function, expressed by GLS is already precociously altered.

## ABBREVIATIONS

AFD: Anderson-Fabry Disease; BSA: Body Surface Area; CMR: cardiac magnetic resonance; DTI: Tissue Doppler Imaging, E: Early velocity wave of mitral flow; E': Early diastolic myocardial velocity of tissue Doppler at mitral annulus, ECG: electrocardiogram, FPS: Frames per seconds; Gb3: Globotriaosylceramide; GLA: α-galactosidase A; GLS: Global Longitudinal Strain; LV: Left Ventricle; LVMI: LV mass indexed by body surface area; LVH: Left Ventricle Hypertrophy; MPI: Cardiac performance index; N: Normal Health Group; S': Systolic myocardial velocity of tissue Doppler at mitral annulus; TTE: Transthoracic Echocardiography; TIA: Transient Ischemic Attack; 2D-STE: Two-Dimensional Speckle Tracking Echocardiography.

## INTRODUCTION

Anderson-Fabry disease (ASD) is a rare X-linked genetic

disease of the lysosomal metabolism. It has an incidence of 1: 40,000 and is caused by a mutation of the gene coding for the α-galactosidase A (GLA), with an absent or reduced enzymatic activity causing progressive intralysosomal accumulation of glycosphingolipids, particularly of globotriaosylceramide (Gb3), in different cell types.

ASD may present with its wide variety of clinical phenotypes, from "classical" severe with multisystem involvement, as cardiomyopathy, stroke, renal failure, to asymptomatic forms. Males, homozygous, have the most severe form with earlier onset in childhood and adolescence; females, mosaics because of the lyonization, express the disease with greater phenotypic variability [1]. Cardiac involvement in Fabry disease is very common and more than 50% of patients develop a characteristic pattern called "Fabry cardiomyopathy". The most common cardiac abnormalities include concentric non-obstructive

left ventricular hypertrophy, prominent papillary muscles, electrocardiogram (ECG) abnormalities, arrhythmias, aortic and mitral regurgitation, early stages of diastolic dysfunction with preserved global ejection fraction, intramyocardial fibrosis which typically affects the basal postero-lateral wall of the left ventricle [2,3]. In the myocardium GB3 can be accumulated in cardiomyocytes, conduction system, endothelium and in vascular cells.

The traditional non-invasive techniques to identify the cardiac involvement in patients with Fabry disease, such as ECG, conventional echocardiography and cardiac magnetic resonance (CMR), are useful in patients with manifested cardiomyopathy, but are not suitable to detect early subclinical myocardial alterations. The potential benefits of early enzymatic therapy, makes it important early diagnosis to modify the natural history of the disease.

The advanced echocardiographic examination with Tissue Doppler Imaging (DTI) and Speckle-Tracking Echocardiography (STE) is able to evaluate the assessment of myocardial deformation and provides incremental information in the clinical setting [4]. The main areas of application of these techniques have been assessment of myocardial mechanics and in detecting subclinical myocardial dysfunction in cardiomyopathies, in patients undergoing chemotherapy for cancer or in those affected by heart valve diseases [5].

Aim of this study was to identify early signs of myocardial involvement in patients with Fabry disease, by analysing the left ventricular longitudinal strain, using 2D STE, in patients with AFD but without left ventricular hypertrophy.

## MATERIALS AND METHODS

21 patients (7 males, 14 females), 12 probands and 9 relatives all with diagnosis of AFD, based on plasma and leucocytes  $\alpha$ -galactosidase A enzyme activity and sequencing of the GLA gene, were evaluated from January 2010 to April 2016.

All patients were evaluated using resting 12-lead ECG, standard Transthoracic Echocardiography (TTE) and considering the medical history and physical examination. TTE was performed using GE Vivid 7 (GE Healthcare, Horten, Norway) equipped with multifrequency S3-probe.

Echocardiographic variables included: left atrial volume, LV volumes and Ejection Fraction, posterior wall and interventricular septal thickness in diastole, LVmass (LVM) calculated from the Deveraux formula and indexed by body surface area (LVMi). By means Doppler PW at mitral valve were evaluate the mitral flow velocities (E and A waves) and, using Tissue Doppler at mitral annulus, the systolic (S') and early diastolic myocardial velocity (E'), as average of septal and lateral wall values, E/E' ratio and the cardiac performance index (MPI) in accordance to Tei formula. After image acquisition of apical four-, two- and long-axis chambers (60-80 fps), using a dedicated off-line software (Echo PAC, GE healthcare ver. 113.0.0), was evaluated GLS of left ventricular and of myocardial layers ENDO, MID, EPI. Speckle tracking was performed for the entire myocardial wall thickness outlined by the tracked ROI border: the centerline (MID) of the ROI represents the average values of the full value thickness;

the measurements for ENDO and EPI layers are the values at the inner and outer tracked ROI lines.

According to the presence or absence of LV hypertrophy, two groups were considered: group of patients with LVMi >115 g/m<sup>2</sup> (LVH) and patients with LVMi  $\leq$ 115 g/m<sup>2</sup> (noLVH) and compared to a group (N) of 91 normal healthy subjects (48 males and 43 females) matched for age and BSA

Data are presented as mean  $\pm$  standard deviation (m  $\pm$  SD). Differences between means were compared using the unpaired t-test and Bonferroni adjusted p value. Analysis of correlation was performed with the Pearson correlation coefficient. To differentiate the value with the highest impact multivariate logistic regression analysis was performed. A p value <0.05 was considered statistically significant. Statistical analysis was performed using SPSS 12.02.00.

## RESULTS

### Clinical features

The LVH group consisted of 5 patients (age 53  $\pm$  9y, all probands) including 2 males (mean age 45  $\pm$  7.07y) and 3 females (mean age 59  $\pm$  5.5y) (Table 1).

Signs correlate with AFD were present in all patients: one male showed alterations of the peripheral nervous system represented by acroparaesthesias, while alterations of the central nervous system were found in 3 patients: 1 male and 2 females, with previous stroke. Cornea verticillata was observed in 2 males and in 1 female patients and angiokeratomas were present in three patients, 1 male and 2 females. As for the renal involvement 2 males and 2 females have developed, during the course of the disease, chronic renal failure, which led to renal transplant in 3. Arrhythmias were found in 3 females: one had supraventricular tachycardia, another atrial fibrillation and the other atrial and ventricular ectopic beats. Enzyme activity in this group was 1,54  $\pm$  1,98 nmol/h/ml, more reduced in males than females.

The noLVH group consisted of 16 patients (7 probands and 9 relatives, with a mean age of 33  $\pm$  19y) including 5 males (mean age 38  $\pm$  28,8y) and 11 females (mean age 35  $\pm$  15,1). Signs correlate with Fabry disease were present in 13 patients: 2 males and 2 females showed acroparaesthesias, while alterations of the central nervous system were found in 4 females: 1 showed previous TIA, 2 history of stroke and another cerebrovascular disease detected on MRI. Cornea verticillata was found in 2 patients (1male and 1 female) and opacities of lens in another 2 (1male and 1 female). Cutaneous manifestations were present in 3 females: one showed angiokeratomas and 2 hypo-anhidrosis. Only one male patient showed renal manifestations represented by proteinuria. ECG alterations were observed in 6 patients: short PQ in one male, right bundle block in 2 females, atrial ectopic beats in one male e atrial fibrillation in one female. Enzyme activity in this group was 3,43  $\pm$  3,03 nmol/h/ml, more reduced in males than females.

The clinical manifestations AFD-related were present more in men than women but not significantly.

### Echocardiographic findings

LVH pts showed: LVMi g/m<sup>2</sup> 150  $\pm$  23,6; E cm/s 70,4  $\pm$  23,7(vs.

**Table 1:** Clinical features.

	LVH 5 pts		noLVH 16 pts	
	M (2 pts)	F (3 pts)	M (5 pts)	F (11 pts)
Age (y)	45 ± 7.1	59 ± 5.5	33 ± 27	32.6 ± 16.1
Enzyme activity (nmol/h/ml)	0.45 ± 0.64	2.23 ± 2.42	1.66 ± 2.45	4.24 ± 3.02
Peripheral nervous system manifestations (%)	50	-	40	18
Central nervous system manifestations (%)	50	67	-	36
Ocular manifestations (%)	100	33	40	18
Cutaneous manifestations (%)	50	67	-	27
Renal manifestations (%)	100	67	20	-
Arrhythmias (%)	-	100	60	27

**Abbreviations:** LVH: group with left ventricular hypertrophy; no LVH: group without left ventricular hypertrophy.

**Table 2:** Echocardiographic findings.

		N	LVH		noLVH	
		m±DS	m±DS	p	m±DS	p
LVMi	gr/m <sup>2</sup>	66 ± 17	150 ± 24	0,001	70 ± 16	0,719
E	cm/s	81 ± 17	70 ± 24	0,196	82 ± 30	0,807
E/A		1,44 ± 0,97	1,15 ± 0,51	0,725	1,69 ± 0,59	0,723
S'	cm/s	9 ± 1,7	5 ± 1,1	0,001	7 ± 1,6	0,001
E'	cm/s	13 ± 3,5	5 ± 2,7	0,001	12 ± 4,1	0,204
A'	cm/s	10 ± 2,3	5 ± 2,7	0,001	7 ± 2,6	0,00055
E/E'		6 ± 1,2	17 ± 11,8	0,001	8 ± 3	0,000492
MPI		0,39 ± 0,1	0,49 ± 0,1	0,00629	0,45 ± 0,1	0,00484
LV-GLS	%	-22 ± 6	-12 ± 5	0,001	-18 ± 3	0,020
LS-EPI	%	-20 ± 3	-10 ± 7	0,001	-14 ± 3	0,001
LS-MID	%	-22 ± 2	-15 ± 7	0,001	-16 ± 3	0,001
LS-ENDO	%	-25 ± 3	-18 ± 6	0,001	-19 ± 3	0,001

**Abbreviations:** N: Control Group; LVH: Group with Left Ventricular Hypertrophy; No LVH: Group without Left Ventricular Hypertrophy; LVMi: Left Ventricular Mass Indexed by Body Surface Area; E: Early Diastolic Mitral Flow Velocity; S': Systolic Myocardio Velocity at Mitral Annulus; E': Early Diastolic Myocardial Velocity At Mitral Annulus; MPI: Myocardial Performance Index; LV-GLS: Left Ventricular Global Longitudinal Strain; LS: Longitudinal strain of Myocardial Layer ENDO.

N p<0,196); S'cm/s 5,4 ± 1,1 (vs. N p<0,001); E' cm/s 5,2 ± 2,7 (vs. N p<0,001); A' cm/s 10 ± 2,3 (vs. N p<0,001); E/E' 16,96 ± 11,8 (vs. N p<0,0005); GLS% -11,7 ± 5,4. (Vs. N p<0,001) (Table 2).

NoLVH pts showed: LVMi g/m<sup>2</sup> 70 ± 16,4 (vs. N p<0,719); E cm/s 82,1 ± 29,6 (vs. N p<0,807); S'cm/s 7,2 ± 1,6 (vs. N p<0,001); E' 12 ± 4,1 (vs. N p<0,204); E/E' 8 ± 3 (vs. N p<0,0005); GLS% -18,4 ± 2,8 (vs. N p<0,02).

Compared to N group, the average values of S' wave is lower in both Fabry groups, while E' only in LVH. MPI showed higher values in both Fabry groups. The E/E' was higher in both Fabry groups: 4 LVH patients showed E/E' values 9 to 14 and in 1 >15. Other diastolic function parameters did not show significant differences between the two groups.

LV-GLS showed lower values in the Fabry groups compared to N, with the most significant differences in the LVH group and values < -19% in 62.5% of patient's no LVH. The analysis of the multilayer strain, showed reduced values of all layers in both group compared to normal, with a greater reduction proceeding

from endocardium (LS-ENDO) to epicardium (LS-EPI).

The GLS was related with LVMi (p<0, 00000), LS-ENDO with E/E' (p<0,006), LS-MID with E/E' and LVMi (p<0,005), LS-EPI with LAVi (p<0,02).

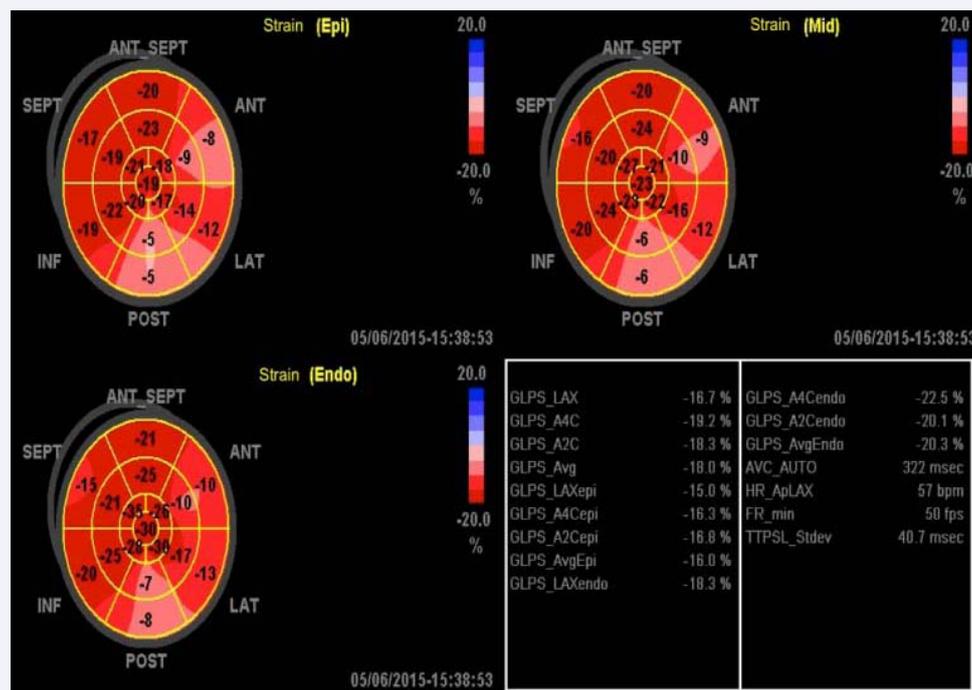
Figure (1) shows bulls-eye of multilayer strain in an AFD male without LVH (LVMi 95 g/m<sup>2</sup>). Figure (2) shows bulls-eye of multilayer strain in an AFD female with LVH (LVMi 162 g/m<sup>2</sup>).

The α-galactosidase A enzyme activity was lower in LVH group compared to NoLVH (p<0.02).

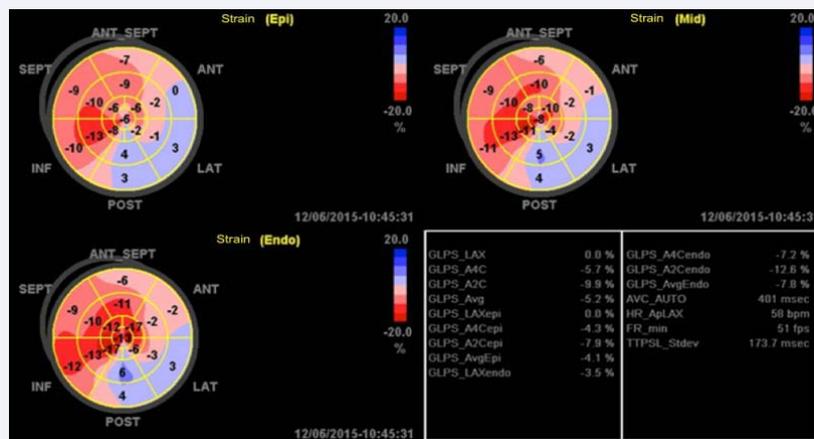
## DISCUSSION

Even if ECG, conventional echocardiography and CMR can identify patients with a clear cardiomyopathy, such techniques are not sufficiently sensitive in detecting silent and preclinical myocardial dysfunction.

In that intent is useful to complete the echocardiographic examination with parameters derived from Tissue Doppler



**Figure 1** Bulls-eye of multilayer strain and GLS (-18%) in an AFD male without LVH. GLS is more reduced at postero-lateral wall.



**Figure 2** Bulls-eye of multilayer strain and GLS (-5.2%) in an AFD female with LVH. GLS is reduced in all segments, more at postero-lateral wall.

Imaging. This method makes it possible to detect a diastolic dysfunction characterized by a reduction of the speed of contraction and relaxation of the septum and the lateral wall by detecting a sub-clinical involvement, before ventricular hypertrophy develops [6,7]. Both in patients with hypertrophy than in those who only have a genetic positivity for Fabry disease, can be detected a significant reduction in the S', E' and A' velocities, a E'/E' ratio significantly higher, than normal control subjects, indicative of diastolic dysfunction [8-11]. In addition, patients with LVH show contraction and relaxation speed significantly lower, lower ratio E'/A' and higher ratio E/E' compared to patients with genetic positivity for Fabry disease but without LVH [8]. In our study we observed that in patients with hypertrophy the E' is significantly lower and the E/E' is significantly higher

compared to normal. S' is significantly reduced in LVH group compared to N and also in 3 no LVH patients.

In the end-stages of Fabry cardiomyopathy an interstitial and substitutive fibrosis develops and it affects the basal part of the postero-lateral wall of the left ventricle [12]. This fibrous replacement is responsible for functional alterations, such as abnormalities of the "wall motion", myocardial stiffness and reduced regional systolic strain values [7,13]. It's possible that the interfaces between the fibrous skeleton of the heart and the LV midwall or mesocardial layer are sites of increased stress. The basal inferolateral segment is the most mobile of the basal segments and likely faces the most junctional stresses transmitted from the fibrous skeleton into the mesocardial layer. This hypothesis, recently proposed by Deva, may explain why

midwall basal inferolateral scar is the most common pattern of myocardial scar in AFD [14].

The analysis of longitudinal strain using 2D Speckle Tracking, allows to evaluate the early fibrotic myocardial dysfunction and to detect early and subclinical systolic dysfunctions. This technique offers many advantages over Doppler Tissue because its measurements are angle-independent. Saccheri showed reduced longitudinal strain in AFD patients with or without hypertrophy and in patients without LVH 70% of the segments with abnormal longitudinal strain were located in the basal regions [15]. Similarly, in our study we found a reduction of the global longitudinal strain of the ventricle in both groups, but we have not found altered segmental strain in AFD patients without hypertrophy.

Gruner showed signs of diastolic LV dysfunction and a significant reduction of Longitudinal and Circumferential Strain, at basal, mid ventricular and apical LV level, in patients with Fabry disease, either with or without hypertrophy compared with healthy controls, while conventional 2D echocardiographic parameters for the assessment of LV systolic function are still preserved [16].

Also in our study, 2D Speckle Tracking showed a reduction of LV-GLS, well as in patients with hypertrophy also in those without hypertrophy, and of values of all layers in both group compared to normal, with a greater reduction proceeding from endocardium (LS-ENDO) to epicardium (LS-EPI).

Unlike Saccheri, Speckle tracking in our study was performed for the entire myocardial wall thickness, from apical images and includes the strain of the whole ventricle, while the Circumferential Strain considered in only three levels.

The LV myocardium is not homogenous and is composed of 3 layers of fibers, consists of circumferential fibers in the mid-wall layer and longitudinal fibers in the endocardial and epicardial layers. Myofibers orientation changes continuously in the form of a right-handed helix in the subendocardium to a left-handed helix in the subepicardium. Therefore, LV strain is not uniform over the left ventricle; it varies through myocardial layers and levels with circular and longitudinal inhomogeneity [17,18]. Manaka et al., [19] demonstrated that myocardial systolic impairment, in hypertrophic heart, might originate at the endocardial side and extend to the epicardium. Tomberli et al., [20] showed in 30 AFD patients, with normal echocardiographic findings, a blunting of the vasodilator response to dipyridamole reflecting a coronary micro vascular dysfunction, as an early feature of cardiac involvement that precede left ventricular hypertrophy. The mechanisms remain unresolved, even though is in line with prior observations in a number of cardiomyopathies, particularly those related to storage or infiltrative disorders [21] and to our previous observations in Fabry disease [11]. Our finding of a relationship between reduction of strain and increase of end-diastolic pressure indices (E/E', LAVi) in the absence of hypertrophy, confirm the possibility of identifying an initial cardiac damage in Fabry disease.

## CONCLUSION

Data obtained from our study show that even in patients

without hypertrophy, and then in the pre-clinical stage, the longitudinal left ventricular function is already early altered, making it a sensitive instrument able to detect the early cardiac abnormalities in patients suffering from Fabry disease.

Although MRI is always the gold standard imaging technique that allows to identify areas of myocardial fibrosis, in the early stages, when it has not yet established left ventricular hypertrophy, there is no late gadolinium enhancement, the analysis of LV GLS can be a useful tool for early diagnosis.

The limitation of our study lies mainly in the small number of analysed patients, as result of the rarity of the disease itself. The further evolution of technology will lead to a better analysis of myocardial deformation parameters, such as the analysis of strain multilayer's, thus offering the possibility of a more complete physio-pathologic understanding of the disease.

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