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Echocardiography

Two-Dimensional Speckle Tracking Echocardiography for Early Detection of Myocardial Damage in Young Patients with Fabry Disease

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Fabry disease (FD) is characterized by left ventricular hypertrophy (LVH). Conventional echocardiography is not sensitive enough to perform the preclinical diagnosis To assess whether longitudinal myocardial strain of the left ventricle (LV), using speckle tracking, is useful to detect early myocardial involvement in FD. Forty-four patients with FD who were diagnosed with genetic testing were prospectively included and were compared to a sex-matched control group. They were divided into three groups: 22 with LVH (Group I), 22 without LVH (Group II), and 22 healthy volunteers (Group III). LV longitudinal strain was measured from the apical views. An ANOVA test was used for multiple comparisons for variables with a normal distribution, and a Kruskal–Wallis test was used for variables with non-Gaussian distribution. Longitudinal LV strain was different in the three groups: it was $\geq -15\%$ in at least one segment in all Group I patients, in 50% of patients of Group II and in no patient of Group III. Seventy percent of the segments with abnormal strain in Group II were located in the basal regions (32/46). These findings show that the presence of at least one strain value $\geq -15\%$ demonstrates subclinical myocardial dysfunction in patients with preclinical FD. Longitudinal myocardial LV strain measured with speckle tracking is a useful tool to detect early myocardial involvement in young patients with FD. This information allows the detection and treatment of myocardial dysfunction at an early stage, which is of high clinical importance. (Echocardiography 2013;30:1069-1077)

Key words: echocardiography, Fabry disease

Fabry disease (FD) is a lysosomal storage disease, caused by mutations in the gene encoding the enzyme α-galactosidase A (α-Gal A), located in the long arm of chromosome X (Xq22.1), which results in a deficit in enzyme activity. It results in progressive accumulation of glycosphingolipids, especially globotriaosylceramide (Gb3) inside the lysosomes of various organs, with the resulting cardiac, renal, neurological, gastrointestinal, as well as eye and skin involvement;[1] which in turn will cause premature death due to renal failure, stroke and heart disease.

Cardiac involvement is quite frequent and is one of the main causes of death in patients with advanced FD.[2] Although FD affects multiple organs, the heart may be the main organ involved in male patients with some specific mutations[3] and in heterozygous women,[4] which is the so called "cardiac variant of Fabry disease."[5]

Cardiac involvement is characterized by progressive concentric left ventricular hypertrophy (LVH), which in most cases is symmetric and in some asymmetric; it correlates with disease severity[6] and leads to myocardial fibrosis and the end-stage phase of the disease with LV systolic dysfunction.[7]

Early treatment with enzyme replacement therapy (ERT) may result in decrease in LV mass and improvement of LV systolic function as long as the disease process has not reached an advanced stage.[7] The clinical impact of ERT correlates with

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the early detection of cardiac involvement, as initially, lysosomal deposition of Gb3 occurs in the absence of LVH on ECG or echocardiogram. Intervention with ERT at an early stage could result in a more effective treatment.[8–10]

In patients with FD, conventional diagnostic methods: ECG, cardiac Doppler echo, and even cardiac magnetic resonance (CMR), are not useful for the early diagnosis of myocardial damage, because they can only detect patients with an advanced stage of the disease.[1,8,11]

Speckle tracking is a new technique, which allows to measure myocardial strain using the two-dimensional (2D) echo signal[12] and offers several advantages over tissue Doppler imaging, because its measurements are angle-independent and allow for a regional assessment of all myocardial segments. Several studies have shown that 2D myocardial strain measurement may detect early abnormalities in patients with ventricular hypertrophy, reflecting underlying myocardial damage.[11,13,14]

The aim of our study was to assess whether in patients with FD without LVH, myocardial longitudinal strain measured with speckle tracking allows us to detect subclinical changes in regional systolic function.

Materials and Methods:

Patients:

In this prospective study performed at the "Argerich Hospital" over a 20-month period between September 2009 and May 2011, we assessed 44 consecutive patients with FD and compared them to a sex-matched control group. The study population was divided into 3 groups: 22 patients with FD with LVH (Group I: genotype+, LVH+), 22 patients with FD without LVH (Group II: genotype+/LVH−), and a control group of 22 normal subjects (Group III), similar in age to the asymptomatic patients with FD (Table I).

Inclusion criteria were as follows: decreased activity of α-Gal A enzyme in men, and DNA analysis with a mutation in the α-Gal A gene in both genders, confirming the diagnosis of FD.

FD patients were detected from 4 initial index cases. Of the 4 index cases, two were identified by cardiologists, one by a dermatologist and another by a clinician. Once the index case and gene mutation were identified, a family screening was performed, which led to the detection of 44 patients with FD that were included in this study.[15]

Of the 4 index cases with FD detected, two families had the same mutation, which had not been previously described (p.Cys174Gly). The mutations of the other two index cases were p.Asp155His and p.Thr194Ile. All were missense mutations.

The clinical stage was defined by the presence of left ventricular hypertrophy. The preclinical stage was defined by the absence of cardiovascular signs and symptoms of FD and normal ECG and 2D echo.

All patients signed an informed consent form, approved by the Research and Ethics Committees of the Argerich Hospital, to undergo the enzy-

TABLE I

Demographic, Clinical, and Echocardiographic Parameters

	Group I (G+/LVH+) (n = 22)	Group II (G+/LVH−) (n = 22)	Group III (control) (n = 22)	P Value I versus III	P Value II versus III
Age (years)	51 ± 12	25 ± 8	28 ± 10	<0.05	NS
Men/Women	12/10	9/13	12/10	NS	NS
HR (bpm)	62 ± 7	70 ± 11	68 ± 11	NS	NS
SBP (mmHg)	121 ± 11	119 ± 13	118 ± 12	NS	NS
BMI (kg/m^2)	25.7 ± 2.2	22.2 ± 4	23.4 ± 4	NS	NS
RV (mm)	17.3 ± 5	18.5 ± 3	18.6 ± 3	NS	NS
LVDD (mm)	51.1 ± 9	45.8 ± 4	47.8 ± 5	NS	NS
LVDD/BS	28.9 ± 3	28.5 ± 3	27.2 ± 2	NS	NS
LVSD (mm)	30.4 ± 1	25 ± 4	27.7 ± 3	NS	NS
FS (%)	41 ± 15	45 ± 7	42 ± 5	NS	NS
EF (%)	69 ± 19	76 ± 7	72 ± 6	NS	NS
IVS (mm)	18 ± 4	8.5 ± 0.7	7.8 ± 1.8	<0.05	NS
PW (mm)	13 ± 2	6.7 ± 1	6.7 ± 1.1	<0.05	NS
LVMI (g/m^2)	281 ± 91	76 ± 15	73 ± 22	<0.05	NS
LASD (mm)	42.5 ± 6	33.5 ± 3	35 ± 4	<0.05	NS
Aortic root (mm)	34 ± 5	27.6 ± 3	29 ± 4	<0.05	NS

G = genotype; HR = heart rate; SBP = systolic blood pressure; LVH = left ventricular hypertrophy; BMI = body mass index; LVDD = LV diastolic diameter; LVDD/BS = LV diastolic diameter normalized by body surface; LVSD = LV systolic diameter; FS = fractional shortening; EF = ejection fraction; IVS = interventricular septum in diastole; PW = posterior wall in diastole; LVMI = left ventricular mass index; LASD = left atrial systolic diameter.

matic and genetic tests as well as all the remaining ancillary exams.

At the time of the study, all patients in group 1 were receiving enzyme replacement therapy (ERT). The duration of ERT is shown in Table II. No patient in group 2 received ERT, because of absence of cardiovascular sign and symptoms of FD and the presence of normal ECG and 2D echocardiogram.

Enzymatic and Genetic Testing:
Assessment of α-Gal A enzyme activity was performed in leukocytes obtained from peripheral blood.[1]

Detection of a mutation in the GLA gene encoding for α-Gal A, was performed in blood anticoagulated with EDTA, from which the genomic DNA was isolated. Each of the 7 exons of the GLA gene was amplified, together with the adjacent intron regions. Amplification products were purified and later sequenced in both directions in a DNA sequencer (Applied Biosystems, Foster City, CA, USA).[1]

Patients with FD were studied with the AADELFA[1] protocol, which included: clinical and neurological evaluation (conduction velocity studies, sensitive thresholds, conduction velocity studies, brain MR, and pain scales), renal assessment (renal ultrasound, proteinuria, creatinine clearance, and glomerular filtration rate), cardiac assessment (electrocardiogram, 24-hour Holter, exercise test, color Doppler cardiac echo, and CMR with late gadolinium enhancement), dermatological, eye, and audiovestibular assessment.

TABLE II

Clinical Manifestations of the Population with Fabry Disease

Clinical Manifestations	Group I (G+/LVH+) (n = 22)	Group II (G+/LVH−) (n = 22)
Age (years)	51 ± 12	25 ± 8
Arterial hypertension n (%)	6 (27.3)	0
Neuropathic pain n (%)	14 (63.6)	10 (45.5)
Angiokeratomas n (%)	14 (63.6)	5 (22.7)
Proteinuria n (%)	8 (36.4)	0
CRF n (%)	2 (9.1)	0
Cornea verticillata n (%)	14 (63.6)	4 (18.2)
Gastrointestinal symptoms n (%)	10 (45.5)	8 (36.4)
LVH on ECG n (%)	18 (81.8)	0
TIA/Stroke n (%)	2 (9,1)	0
Abnormal brain MR	4 (18.2)	0
Cardiac MR with LGE n (%)	16 (72.7)	0
Duration of ERT (years)	3.3 ± 2.2	0

CRF = chronic renal failure; LVH = left ventricular hypertrophy; TIA = transient ischemic attack; MR = magnetic resonance; LGE = late gadolinium enhancement; ERT = enzyme replacement therapy.

Healthy Volunteers:
Twenty-two healthy volunteers, from 12 to 44 years of age, 12 male volunteers, were enrolled in the study from the community rather than from the diagnostic laboratory and were free from any known cardiovascular disease or cardiovascular risk factors. Detailed clinical evaluation, general physical examination, and cardiovascular examination, biochemistry, and conventional 2D and Doppler echocardiography were performed in each individual to exclude any underlying pathology that could alter cardiovascular structure and function.

Echocardiography:
The 2D echocardiograms were performed with a commercially available standard ultrasound scanner (Vivid 7, GE Medical Systems, Horten, Norway), with a 2.5 MHz transducer and digital storage of images. Data were analyzed by two independent observers who were unaware of the clinical data.

Standard left parasternal and apical views were obtained. For each view, 3 consecutive cardiac cycles were recorded during quiet respiration. The following parameters were measured from the M-mode echocardiography: LV end-diastolic and end-systolic diameters, diastolic septal and posterior wall thicknesses, fractional shortening, left atrial systolic diameter, and aortic root diameter, according to published criteria.[16] Left ventricular dilatation was defined as a LV diastolic diameter normalized by body surface > 32 mm/m^2. Aortic root dilatation was defined as a diameter >19 mm/m^2.

Left ventricular ejection fraction (EF) was calculated using Simpson's method, and LV dysfunction was defined as an EF <55%.

Left ventricular mass index was calculated using Devereux's formula.[17] According to the recommendations of the European and American Societies of Echocardiography,[16] LVH was defined as LV mass indexes to body surface area >115 g/m^2 in men and >95 g/m^2 in women.

Color Doppler recordings were performed to exclude valvular dysfunction.

Myocardial Longitudinal Strain Measured with Speckle Tracking:
Speckle tracking derived from the 2D echocardiogram is based on the frame-by- frame tracking of the speckles detected inside the myocardium during the cardiac cycle and subsequent measurement of LV myocardial longitudinal strain.[18] The frame rate was set in all patients between 60 and 80 frames/sec.

The three apical views were obtained (two-, three-, and four- chamber views) and the LV was divided into 18 segments. Strain (%) was defined as the change in wall dimension (length) between end-diastolic and end systolic diameters, normalized to its initial (normally the onset of the QRS complex). During this period, longitudinal strain values were negative as a consequence of myocardial fiber shortening. Doppler flow of the LV outflow tract was used to mark the aortic opening and closure. In each of the apical views, 3 points were placed inside the endocardial border, 2 in the basal segments along the mitral annulus and one in the LV apex. These 3 points triggered an automatic process which analyzed the myocardial motion inside the region of interest and measured systolic myocardial longitudinal strain in 6 segments of each view.

Longitudinal strain measurements were performed off line with dedicated automated software (EchoPAC PC, version 110.1.2, GE Vingmed, Horton, Norway). Global longitudinal peak strain (GLPS) was obtained from the average of segments analyzed. The results of the longitudinal strain of all segments were rendered in a "bull's-eye" format (Fig. 1).

Each LV wall was divided into 3 segments, and a tracking-quality (TQ) score was obtained for each myocardial segment. The TQ scores were derived with a block-matching algorithm to define the quality of speckle tracking, ranging between 1 (excellent tracking) and 3 (poor tracking). Segments with TQ measured as 3 were excluded from the analysis.

Intra- and Inter-observer Variability:
Offline two-dimensional longitudinal strain were performed by a single observer (TFC), who was blinded to the clinical features and genetic findings in the study cohort. Eleven studies were analyzed by another observer (JAL) for the assessment of inter-observer variability. The same

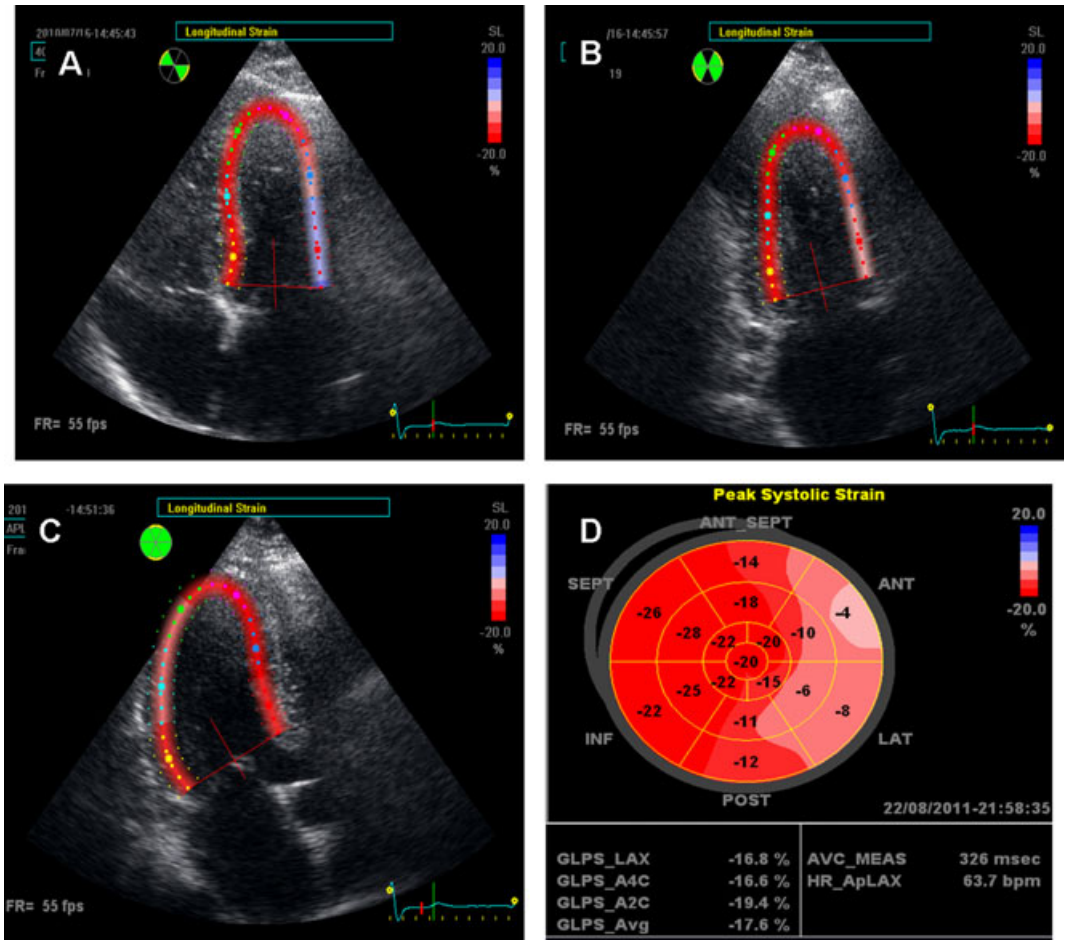

Figure 1. Apical four-chamber view **A.**, apical two-chamber view **B.**, apical three-chamber view **C.**, and a bull's-eye rendering **D.** of myocardial strain in a patient with Fabry disease with left ventricular hypertrophy (LVH). The bull's-eye shows an average longitudinal peak systolic strain (GLPS_Avg) of −17.6%. Normal strain is depicted in red and the decrease in strain (values lower than −15%) is depicted in pink.

observer (JAL) reanalyzed the same 11 studies 1 hour later for the assessment of intra-observer variability.

Statistical Analysis:
Results are expressed as mean ± standard deviation, or medians and interquartile intervals or proportions. The Shapiro–Wilk test was used to evaluate if the parameters fit a normal distribution. The ANOVA or Kruskal–Wallis tests were used according to whether the distribution was parametric or nonparametric. For comparison of the two groups, the *t*-test or Wilcoxon test was performed depending on whether the distribution was normal or not. A P value < 0.05 was considered statistically significant.

Results:

Characteristics of the Population:
The demographic, clinical, and echocardiographic characteristics of the 3 groups are summarized in Table I.

Among the 22 patients with FD and LVH (Group I: G+/LVH+), 12 were men (mean age: 51 ± 12 years, range 29–63 years), and among the group of 22 patients with FD and no LVH (Group II: G+/LVH−), 9 were male patients (mean age: 25 ± 8 years, range 14–40 years). Among the group of healthy subjects (Group III), 12 were male patients (mean age: 28 ± 10 years, range 12–44 years).

Patients with FD with LVH (Group I: G+/LVH+) were older than Group II (Table I) because the cardiac manifestations of the disease appear later, around age 30 years in men and even a decade later in women 1.[2,9,19]

All patients had a similar body mass index (Table I) and in all, heart rate and blood pressure were within normal ranges; all patients were in sinus rhythm.

Clinical manifestations of the population with FD are summarized in Table II.

CMR was performed in all patients with FD. In patients with LVH (Group I) CMR with gadolinium showed late enhancement in 16 (72.7%) patients suggesting myocardial fibrosis. CMR with gadolinium in patients without LVH (Group II) showed no delayed enhancement in any patient.

In patients with FD without LVH (Group II) some reported mild neuropathic pain, hypohidrosis, isolated episodes of gastrointestinal complaints (diarrhea and abdominal pain), vertigo, and tinnitus. One patient had bronchial asthma with adequate response to conventional treatment and two patients had cornea verticillata with normal visual acuity. None of these patients had test results with major criteria to begin enzyme replacement therapy. Significant coronary artery disease was ruled out with exercise stress testing.

Echocardiographic Analysis:
There were no differences among groups in fractional shortening, ejection fraction, or diastolic and systolic LV diameters.

Septal and posterior wall thickness, LV mass index, left atrial and aortic root diameters were greater in patients with G+/LVH+ compared to patients with G+/LVH− and to subjects in the control group (Table I).

Septal and posterior wall thicknesses were greater in Group I than in Group II (18 ± 4 mm and 13 ± 2 mm vs. 8.5 ± 0.7 mm and 6.7 ± 1 mm, respectively, $P < 0.0001$).

In group I, the LVH pattern was symmetric in 12 patients (54.6%) and septal asymmetric in 10 patients (45.4%). No patient had a dynamic subaortic gradient, either at rest or with the Valsalva maneuver.

The aortic root was dilated in 14 (63.6%) patients of Group I (21.2 ± 1.2 mm/m^2) and in 5 patients (22.7%) of Group II (19.8 ± 0.7 mm/m^2).

No patient had abnormal valve function or pulmonary hypertension.

Myocardial Longitudinal Strain Analysis:
Left ventricular longitudinal strain was measured from the apical views in the 18 segments in the 44 patients with FD and in the 22 normal subjects, with a total of 1.188 segments analyzed.

A speckle tracking quality <3 (good quality) was achieved in 1.152 (97%) of the 1.188 segments analyzed. Longitudinal strain could not be measured in 34 segments (2.9%) because speckle tracking-quality score was 3 (poor quality). None of the basal segments were excluded.

Table III illustrates longitudinal peak strain (LPS) in the 3 groups. All patients with G+/LVH+ had lower global longitudinal peak strain (GLPS) than those with G+/LVH− :−15.1% (−18.4% to − 9.4%) vs. −22.1% (−23.4% to −20.1%), $P < 0.0001$).

There were no differences in GLPS between patients with G+/LVH− and the control group. Differences were particularly pronounced in basal-lateral and basal-posterior LV segments, in which longitudinal peak strain dramatically decreased in patients with FD without LVH. Patients with G+/LVH−, when compared to healthy subjects, had a decrease in LPS in the basal-lateral and basal-posterior segments of the LV: −18% (−21 to −16%) and−19% (−21% to −16%) vs. −22% (−25% to −20%) and−23% (−25% to −18%). All values of longitudinal peak strain in normal group were higher than −15%, while 23 segments in group 2 and 206 segments

TABLE III

Measurements of LV Longitudinal Myocardial Strain with Speckle Tracking

	Group I (G+/LVH+) (n = 22)	Group II (G+/LVH−) (n = 22)	Group III (control) (n = 22)	P Value I vs III	P Value II vs III
Basal-inferosetal (%)	−10 (−14 to −6)	−19 (−21 to −16)	−20 (−21 to −19)	0.0002	NS
Mid-inferoseptal (%)	−15 (−17 to −10)	−22 (−22 to −19)	−22 (−23 to −18)	0.0006	NS
Apical-inferoseptal (%)	−22 (−23 to −18)	−25 (−29 to −22.5)	−24 (−30 to −22)	0.009	NS
Basal-lateral (%)	−12 (−16 to −5)	−18 (−21 to −16)	−22 (−25 to −20)	0.0001	0.01
Mid-lateral (%)	−13 (−16 to −5)	−21 (−23 to −20)	−21 (− 25 to −20)	0.0001	NS
Apical-lateral (%)	−20 (−20 to −12)	−25 (−28 to−22)	−24 (−29 to −22)	0.0001	NS
Basal-inferior (%)	−12 (−15 to −3)	−20 (−22 to−18)	−21 (−24 to −21)	0.0001	NS
Mid-inferior (%)	−13 (−16 to −11)	−21 (−23 to −19)	−22 (23 to −21)	0.0001	NS
Apical-inferior (%)	−18 (−21 to −16)	−24 (−26 to −22)	−25 (−27 to −22)	0.0003	NS
Basal-anterior (%)	−11 (− 16 to −4)	−21 (−24 to −20)	−23 (−25 to −17)	0.0002	NS
Mid-anterior (%)	−10 (−20 to −8)	−22 (−21 to −19)	−22 (28 to −20)	0.001	NS
Apical-anterior (%)	−20 (−25 to−14)	−23 (−26 to −20)	−23 (−27 to −21)	0.03	NS
Basal-posterior (%)	−7 (−15 to −3)	−19 (− 21 to −16)	−23 (−25 to −18)	0.0001	0.02
Mid-posterior (%)	−9 (−16 to −3)	−19 (−23 to −17)	−22 (−25 to −20)	0.0001	NS
Apical-posterior (%)	−18 (−20 to −12)	−24 (−27 to −22)	−25 (−26 to −24)	0.001	NS
Basal-anteroseptal (%)	−12 (−18 to−5)	−21 (−22 to −17)	−22 (−24 to −19)	0.0002	NS
Mid-anteroseptal (%)	−18 (−20 to −14)	−23 (−25 to −20)	−22 (25 to −22)	0.0004	NS
Apical-anteroseptal (%)	−21 (−23 to −16)	−25 (−27 to −21)	−25 (−28 to −23)	0.008	NS
GLPS A3C (%)	−15.6 (−17.6 to −8)	−21.8 (−23.7 to −18.6)	−21.9 (−24.5 to −21)	0.0001	NS
GLPS A4C (%)	−16.7 (−18.7 to −11.7)	−22.2 (−23.3 to −20.2)	−22 (−24 to −20)	0.0001	NS
GLPS A2C (%)	−13.2 (−19.4 to −9.2)	−21.6 (−24.6 to −20.2)	−22.1 (−26.8 to −20.1)	0.0001	NS
Average GLPS (%)	−15.1 (−18.4 to −9.4)	−22.1 (−23.4 to −20.1)	−22.3 (−24.2 to −21)	0.0001	NS

G = genotype; LVH = left ventricular hypertrophy; GLPS = global longitudinal peak systolic; A3C = apical three chamber view; A4C = apical four chamber view; A2C = apical two chamber view.

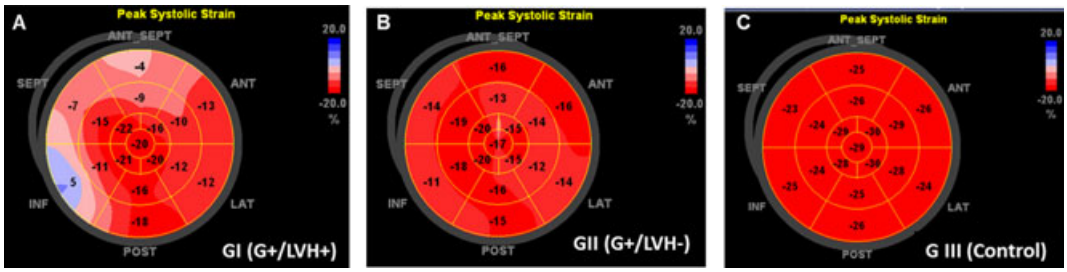

Figure 2. "Bull's-eye" rendering of the longitudinal strain of the LV obtained with "speckle tracking" from the apical four-chamber view. Values in each of the 17 segments indicate the peak systolic strain. **A.** Patient with Fabry disease with LVH (Group I: Genotype+ and LVH+) showing 9 segments with abnormal strain ($\leq -15\%$). **B.** Patient with Fabry disease without LVH (Group II: Genotype+ and LVH−) showing 6 segments with abnormal strain. **C.** Normal subject (Group III) showing all segments with a peak systolic strain higher than −15%.

in group 1 showed lower values of −15%. A cut-off $\geq -15\%$ allowed to discriminate patients with FD without LVH with sensitivity of 45% and specificity of 100%.

Figure 2 shows the "bull's-eye" rendering of the longitudinal strain of the LV obtained with "speckle tracking" from the apical four-chamber view in a patient with FD with LVH (Group I: Genotype+ and LVH+) showing 9 segments with abnormal longitudinal peak strain ($\geq -15\%$), in a patient with FD without LVH (Group II: Genotype+ and LVH−) showing 6 segment with abnormal longitudinal peak strain, and in a normal subject (Group III) showing all segments with a longitudinal peak systolic strain higher than −15%.

Left ventricular longitudinal strain differed in the 3 groups (Table IV and Fig. 3). Longitudinal strain was $\geq -15\%$ in at least one segment in all patients of Group I, in 50% of Group II and in no patient of Group III. Seventy percent of the segments with abnormal longitudinal strain in Group II were located in the basal segments (16/23).

These findings show that the presence of at least one segment with a longitudinal strain value

TABLE IV

Number of Patients with Decrease in Longitudinal Myocardial Peak Systolic Strain ($\leq -15\%$) in Each Segment in the 3 Groups

	Group I (G+/LVH+) (n = 22)	Group II (G+/LVH−) (n = 22)	Group III (control) (n = 22)
Basal-inferoseptal (n)	18	3	0
Basal-lateral (n)	18	4	0
Basal-inferior (n)	16	2	0
Basal-anterior (n)	16	1	0
Basal-posterior (n)	16	4	0
Basal-anteroseptal (n)	14	2	0
Mid-inferoseptal (n)	14	0	0
Mid-lateral (n)	14	2	0
Mid-inferior (n)	16	0	0
Mid-anterior (n)	12	0	0
Mid-posterior (n)	16	2	0
Mid-anteroseptal (n)	6	2	0
Apical-inferoseptal (n)	2	0	0
Apical-lateral (n)	8	0	0
Apical-inferior (n)	4	0	0
Apical-anterior (n)	8	1	0
Apical-posterior (%)	6	0	0
Apical-anteroseptal (n)	4	0	0

G = genotype; LVH = left ventricular hypertrophy.

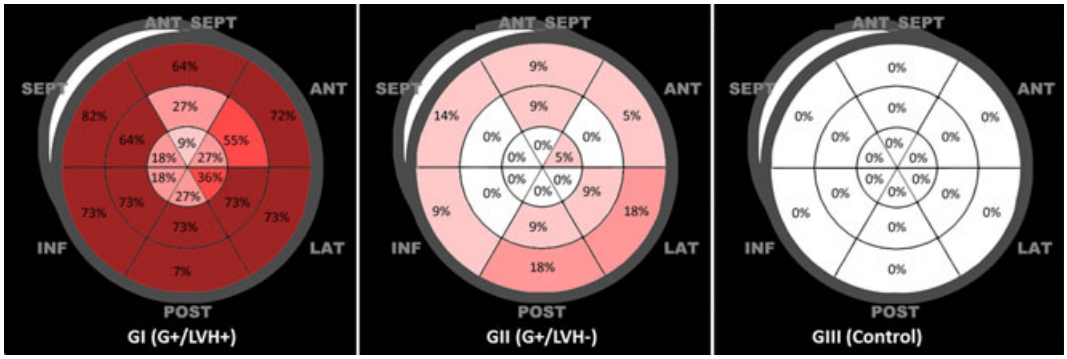

Figure 3. Schematic of the "bull's-eye" rendering of the percent of abnormal longitudinal strain ($\leq -15\%$) observed in the 3 groups. G = genotype; LVH = left ventricular hypertrophy.

$\geq -15\%$ demonstrates subclinical myocardial dysfunction in patients with FD without LVH.

Reproducibility:
Inter-observer agreement correlation coefficient was 0.94 for myocardial peak systolic longitudinal strain with 2SD of the percent difference of 10. Intra-observer agreement correlation coefficient was 0.96 for myocardial longitudinal peak systolic strain with 2SD of the percent difference of 9.

Discussion:
Our study demonstrates that myocardial longitudinal strain with speckle tracking is a useful technique for detecting FD in young people without myocardial hypertrophy, when a longitudinal basal-lateral strain value $\geq -20\%$ is present, with at least one another segment with $\geq -15\%$.

Dalen et al[20] in the Hunt study in healthy volunteers found a normal longitudinal systolic strain value in the basal-lateral segment of $-21.9 \pm 3.7\%$, and a global longitudinal systolic strain of $-21.6 \pm 2.3\%$. The average age of this population was 48.6 ± 3.6 years old, and the longitudinal strain was decreasing with age, so in the younger group the global values found were $-21.7 \pm 2.0\%$. Although, these values include healthy volunteers aged below 40 years with the lower limit of 34 years. Marwick et al.,[18] in another study on healthy population, age 51 ± 12 years, found a normal longitudinal basal-lateral strain value of $-17.8 \pm 5.0\%$ with a global longitudinal peak systolic strain of $-18.6 \pm 0.1\%$. In our

study, the mean age of patients with preclinical cardiac FD was clearly younger (Group II: 25 ± 8 years), as heart involvement occurs later, so our control healthy group was adjusted to that age (Group III: 28 ± 10 y.o.). Accordingly, normal values for basal-lateral wall and global longitudinal peak systolic strain are higher than those reported in other studies, as they correspond to a younger population, which agrees well with our study group.

There are few studies exploring the usefulness of the new speckle tracking technique in patients with FD without LVH.[21] To our knowledge, our study is the first to compare speckle tracking in a cohort of patients with FD with LVH and patients with FD without LVH and without clinical expression in any other organs.

Gruner et al.[21] studied 21 patients with FD without LVH, age 37 ± 13 years, and analyzed systolic myocardial function using vector velocity strain and demonstrated lower global longitudinal peak strain (GLPS) compared to normal subjects. Their conclusion was that patients with FD without LVH already show abnormal systolic myocardial function.

According to these findings, our study analyzed systolic myocardial function using speckle tracking echocardiography in a younger population with FD without LVH, age 25 ± 8 years. These patients showed normal GLPS, but we detected regional impairment of systolic function, manifested by a reduction in longitudinal peak strain in some segments. This finding may suggest that speckle tracking echocardiography in young patients with FD and normal GLPS, a reduction in longitudinal peak strain in some segments, could show the early onset of myocardial dysfunction.

In Group I, GLPS was decreased and demonstrated the presence of an abnormal longitudinal peak strain ($\geq -15\%$) in at least one segment in all patients of Group I. GLPS was normal in Group II and III, but abnormal longitudinal peak strain ($\geq -15\%$) in at least one segment was seen in 50% of Group II and no patient of Group III.

In patients with FD without LVH, 70% of the segments with abnormal longitudinal strain were located in the basal regions (16/23). These findings show that the presence of at least one segment with abnormal longitudinal peak strain demonstrates regional (but not global) subclinical myocardial dysfunction, in the early stage of FD without LVH. The basal segments involvement is concordant with the greater involvement of such segments in patients with FD and LVH with late enhancement in CMR in the same segments in patients with advanced stages of FD.[22]

Although average GLPS was similar in G+/LVH− and in healthy subjects, a decrease in longitudinal peak strain was seen in LV basal-lateral and basal-posterior segments. Similar findings were shown with speckle tracking in patients with a genetic diagnosis of hypertrophic cardiomyopathy (HCM) before the development of LVH.[23] It is possible that in both diseases, FD and HCM, beyond the lysosomal storage of glycosphingolipids or the abnormal synthesis of sarcomeric proteins, interference with sarcomere contraction and relaxation results in secondary LVH and decrease in myocardial longitudinal strain, as evidenced by speckle tracking.

Considering the findings of this study, showing that all patients who are G+/LVH+ exhibit changes in myocardial longitudinal strain, it is possible that a longitudinal strain value $\geq -15\%$ in young patients G+/LVH− may be a predictor of the development of LVH. Further research is needed to establish whether patients G+/LVH− with abnormal myocardial longitudinal strain values will ultimately develop LVH.

Until a decade ago, clinical recognition of FD was disappointing because of the slim chances of changing its unfavorable natural history and prognosis. Recently, ERT has proved useful in decreasing the lysosomal accumulation of glycosphingolipid, with improvement and even regression of cardiac involvement.[24] Hence, early diagnosis of cardiac involvement in FD is very important as it allows us to start ERT as soon as possible to prevent complications such as LVH and irreversible myocardial fibrosis, lethal arrhythmias, and coronary heart disease.[25] Further research is needed to establish whether patients G+/LVH− with abnormal myocardial longitudinal strain values will develop LVH.

Study Limitations:

Patients with FD and LVH who were included in this study were older than patients with FD without LVH, because the cardiac manifestations of the disease do not appear at an early age. This age difference is not a limitation because it has been shown[26] that neither gender nor age affects longitudinal systolic strain, although they do affect longitudinal early diastolic strain rate, a variable that was not measured in our study.

Although the number of patients studied is small, it should be considered that FD is a rare disease, with an incidence of 1/117,000 men. In our country, fewer than 285 patients with FD have been detected to date, so our population represents 11.6% of patients with FD in our country.

In this study we only study longitudinal strain, and we did not assess radial strain, circumferential strain, strain rate, rotation or torsion.

As the different speckle tracking software results in different strain values, the values

obtained in this study cannot be extrapolated to other variety of two-dimensional speckle tracking method.

Conclusion:

Longitudinal myocardial LV strain measured with speckle tracking is a useful tool to detect early myocardial involvement in young patients with FD. This information allows the detection and treatment of myocardial dysfunction at an early stage, which is of high clinical importance.

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