The relationship between global longitudinal strain, myocardial storage and hypertrophy in cardiac Fabry disease

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ABSTRACT

Introduction: Detecting early cardiac involvement in Fabry disease (FD) is important because therapy may alter disease progression. Cardiovascular magnetic resonance (CMR) can detect T1 lowering, representing myocardial sphingolipid storage. In many diseases, early mechanical dysfunction may be detected by abnormal global longitudinal strain (GLS). We explored the relationship of early mechanical dysfunction and sphingolipid deposition in FD.

Methods: An observational study of 221 FD and 77 healthy volunteers (HV) who underwent CMR (LV volumes, mass, native T1, GLS, late gadolinium enhancement), ECG, and blood biomarkers, as part of the prospective multicenter Fabry400 study.

Results: All FD had normal LV ejection fraction (EF 73±8%). Mean indexed LV mass (LVMi) was 89±39g/m^2 in FD and 55.6±10g/m^2 in HV. 102 (46%) FD participants had left ventricular hypertrophy (LVH). There was a negative correlation between GLS and native T1 in FD patients ($r=-0.515$, $p<0.05$). In FD patients without LVH (early disease), as native T1 reduced there was a reduction in GLS ($r=-0.285$, $p<0.05$), but only in males and not females (males: low T1 -18.3±1.6ms vs. normal T1 -20.0±1.0ms, $p<0.05$). ECG changes were not associated with impaired GLS.

Conclusions: Fabry males have changes in myocardial deformation before the onset of LVH associated with sphingolipid deposition; females display mechanical dysfunction only once they develop LVH, supporting possible sex dimorphism in the early myocardial functional response to storage.

KEY QUESTIONS

What is already known about the subject?

Cardiac involvement in Fabry disease is characterized by progressive LVH, myocardial fibrosis and heart failure. Impairment of systolic strain measured using speckle-tracking echocardiography has previously been described in Fabry disease. CMR imaging with T1 mapping can identify cardiac involvement earlier in the disease process, however, there is only limited data investigating the relationship between myocardial strain and sphingolipid deposition.

What does this study add?

This is the first study evaluating T1 mapping and myocardial systolic strain using CMR feature-tracking in a large cohort of patients with Fabry disease. It shows that Fabry males have impaired myocardial deformation before the onset of LVH supporting a possible sex dimorphism in the early myocardial functional response to storage.

How might this impact on clinical practice?

This study highlights that CMR feature-tracking is a sensitive imaging biomarker that is able to identify myocardial mechanical changes in the early stages of cardiac Fabry disease.

INTRODUCTION

Fabry disease (FD) is a X-linked lysosomal storage disorder caused by mutations in the gene (*GLA*) encoding for α-galactosidase A. The progressive accumulation of complex sphingolipids, predominantly globotriaosylceramide[1] affects multiple organs, including the heart where it results in left ventricular hypertrophy (LVH), progressive cardiomyopathy, myocardial fibrosis and arrhythmias.[2] Cardiac involvement is a major contributor to morbidity and mortality in FD.[3] Evidence suggests that best outcomes may occur with early initiation of enzyme replacement therapy (ERT).[4] Early cardiac involvement is difficult to detect and the identification of early phenotypic markers is required. Change in myocardial deformation – systolic strain – offers potential. Impairment of global longitudinal strain (GLS) has been described in FD using speckle tracking echocardiography in those with and without LVH.[5,6,7] Impaired GLS precedes any reduction in ejection fraction and is linked to worse functional status.[8]

Cardiovascular magnetic resonance (CMR) imaging can quantify myocardial strain using feature-tracking (FT-CMR) but there is a paucity of knowledge regarding its application in FD. We aimed to determine whether early storage (low T1 measured using T1 mapping) would alter myocardial contractility (measured using FT-CMR) before the development of LV hypertrophy. Additionally, we aimed to evaluate if electrical abnormalities (detected on the 12-lead ECG) alter with cardiac contractility during this earlier phase of the disease process.

METHODS

Study Population

Participants were recruited from four Fabry clinics as part of the prospective, multicenter international observational Fabry400 study (NCT03199001) - United Kingdom (UK): Royal Free Hospital London, National Hospital for Neurology and Neurosurgery London, Queen Elizabeth Hospital Birmingham; Australia: Westmead Hospital Sydney. The study was approved by the relevant Research Ethics Committees and conformed to the principles of the Helsinki Declaration. Written informed consent was obtained from all participants. Inclusion criteria for the FD cohort included: gene-positive Fabry disease and adults ≥18 years. The healthy volunteer controls (HV) were prospectively recruited and had no history of cardiovascular disease (normal health questionnaire, no cardioactive medication unless for primary prevention). Exclusion criteria included standard contraindications to CMR. All participants underwent CMR, ECG, and blood samples during the same study visit. High-sensitivity cardiac troponin T (UK) and I (Australia) (hs-TnT and hsTnI) was measured using an electrochemiluminescence-immunoassay (Roche, Basel, Switzerland; normal range 0-14ng/l and 0-15ng/l respectively).

CMR imaging

All participants underwent CMR at 1.5 Tesla (Avanto (UK), Aera (Australia); Siemens Healthcare, Erlangen, Germany) using a standard protocol including LV cines in short axis (SAX), 4-chamber, 2-chamber and 3-chamber views. Native T1 mapping was performed pre-contrast on basal and mid left ventricular SAX slices using a shortened modified Look-Locker inversion recovery (ShMOLLI) sequence.[9] The resulting pixel by-pixel T1 color maps were displayed using a customized 12-bit

lookup table, where normal myocardium was green, increasing T1 was red, and decreasing T1 was blue. Late Gadolinium enhancement (LGE) imaging was performed using phase sensitive inversion recovery (bolus administration of gadolinium 0.1 mmol/kg body weight, Gadoterate meglumine, Dotarem, Guerbet S.A., France)

CMR analysis

All images were centralized and analyzed using CVI42 software (Circle Cardiovascular Imaging Inc., Calgary, Canada). Cardiac chamber volumes and LV mass (LVM) (papillary muscles included in mass) were quantified on all subjects from a pre-contrast breath-held SAX stack of balanced steady-state free precession cine images, using previously described manual contouring methodologies.[10] Left ventricular hypertrophy (LVH) was defined as increased indexed LVM on CMR according to age and gender matched normal reference ranges.[11] Maximum wall thickness (MWT) was evaluated using semi-automated measurement on CVI42 software and a value greater than 12 mm was classified as being LVH positive.

Strain – Analysis of 2D global longitudinal strain (GLS) was obtained using CVI42, version 5.3.4. Smooth epicardial and endocardial borders were manually drawn on the end-diastolic frame of all long axis images (4-chamber, 2-chamber and 3-chamber views), and then strain (peak GLS, the most negative value during systole) was obtained from the applied automatic FT algorithm (example, Figure 1a). FT evaluates myocardial strain by utilizing a deformable 2D model and translating this onto all 2D cine slices selected over the entirety of the cardiac cycle. The extent of deformation is determined by motion of an imaginary line placed between endo- and epicardial

boundaries, which are tracked throughout the cardiac cycle by a pre-determined algorithm as previously described.[12,13] The accuracy of FT was confirmed manually for each case (by RV), and to ensure reproducibility a maximum of five operator corrections were performed.

Intra-observer reproducibility was performed by observer 1 (RV) carrying out CMR reanalysis in random subset of 30 study patients. For inter-observer variability, observer 2 (BL) independently analysed a randomly determined subset of 20 CMR scans.

Native T1 – visual inspection of T1 color maps has shown sphingolipid deposition to be variable within the myocardium, and consequently four regions of interest (ROI) were drawn in the septal and lateral LV wall at basal and mid cavity level, taking care to avoid the blood-myocardial boundary[14] (example, Figure 1b). Since T1 is known to vary between field strength, acquisition technique and site, and gender (females typically have higher T1 than males),[14] the normal ranges of T1 values were defined as mean ± 2 standard deviations based on site-specific healthy controls from each individual center (London: males mean 956±27ms, lower limit 902ms; females mean 978±34ms, lower limit 910ms. Birmingham: males mean 947±28ms, lower limit 890ms; females mean 958±30ms, lower limit 898ms. Sydney: males mean 947±24ms, lower limit 893ms; females mean 965ms±31ms, lower limit 903ms).

ECG

Abnormal ECGs included the presence of any irregularities (prolonged or shortened PR interval, QRS duration >120ms, the presence of LVH by Sokolow and Lyon

criteria, T wave inversion in at least two contiguous leads, or the presence of ventricular ectopy).

Statistical Analysis

Statistical analyses were carried out using SPSS 22 (IBM, Armonk, NY). Continuous variables are expressed as mean ± standard deviation, categorical as frequencies or percentages. Normality was checked using the Shapiro-Wilk test. Groups were compared using the independent-samples t-test (normally distributed variables) or the Mann-Whitney U test (non-normally distributed). Chi-squared testing was utilized when comparing proportions of a variable between two groups. Troponin values were analyzed after log transformation using parametric testing. Linear regression analysis (stepwise backward method) was utilized to evaluate the relationship between multiple continuous variables and the study outcome. A p-value of <0.05 was considered statistically significant. Intra- and inter-observer reproducibility was determined by calculating mean bias and 95% confidence intervals using Bland-Altman analyses and intra-class correlation coefficient (ICC) for absolute agreement.

RESULTS

Participant Characteristics

There were 298 participants in total (221 FD and 77 HV). This included (155 from London, 37 from Birmingham, and 29 from Sydney). Baseline demographics are demonstrated in Table 1. The mean FD age was 45±15 years with 85 males (38.5%) and 136 females (61.5%). The HV population was age-matched (± 2 years) with a mean age of 49.4±14 years (males 51.9%). All FD had normal LVEF (73±8.0%). Mean indexed LV mass (LVMi) was 89.0±39g/m^2 in FD and 55.6±10g/m^2 in HV.

MWT was significantly higher in FD compared with HV (12±5.0mm vs. 9±1.6mm respectively, $p<0.01$). There was significant correlation between LVMi and MWT in both groups (FD: $r=0.9$ and HV: $r=0.7$, $p<0.001$). 70.8% of patients had a classical mutation and the remaining 29.2% non-classical. There were 102 (46%) FD participants with LVH.

Global Myocardial Strain

Adequate tracking quality was obtained for all study participants. Left ventricular ejection fraction (LVEF) did not correlate with LVMi ($r=0.004$, $p=0.9$). However, GLS became increasingly impaired (values becoming less negative) as LVMi increased ($r=0.728$, $p<0.001$, Figure 2a and b). GLS was impaired in the LVH-positive FD group compared to LVH-negatives and HV (table 2, $p<0.05$). This was similar when split by sex; however the difference was greater in the male cohort (table 2). Similar relationships were observed when correlating LVEF and GLS with MWT as a marker of myocardial hypertrophy (supplementary table 1).

Myocardial Native T1 and Strain

In the total FD cohort, 72% (n=159/221) had a low native T1 – 91% in the LVH positive subgroup (n=93/102) compared to 56% in the LVH negative subgroup (n=66/119). There was a significant negative correlation between GLS and native T1 in the total FD cohort ($r=-0.515$, $p<0.05$) as shown in Figure 3a.

LVH Negative FD Population

There were 119 FD participants who were LVH negative when classified by LVMi (53.8% of total FD population). The mean age was 37±13.4 years, which was

significantly lower than the LVH positive group (53±11.7 years, $p<0.05$). 81.5% of the LVH negative cohort were female and 68.6% had a classical mutation. Mean LVMi was higher in this group than in HV (62±10.4g/m2 vs. 55.6±10.1g/m2, $p<0.05$), but maximum wall thickness (MWT) was similar (8.8±1.7mm vs. 9.0±1.6mm, $p=0.5$). GLS in LVH negative FD was lower (less impaired) when compared to HV (-20.3±2.9 and -19.3±2.0, $p<0.05$). When split by sex however, no significant differences were seen (table 2).

In the LVH-negative FD subgroup, as native T1 reduced there was also an impairment in GLS ($r=-0.285$, $p<0.05$) as shown in Figure 3b. When split by sex, only males and not females demonstrated impairment in GLS as native T1 reduced (figure 4, table 2). When classifying LVH by a MWT similar significant trends were observed (supplementary figure 1 and table 2).

Multivariable linear regression analysis demonstrated that LVMi and GLS were both independent predictors of a reduction in native T1 and a reduction in GLS. This was found in both the total population and the LVH negative cohort (supplementary table 3).

ERT

Of the total FD cohort 54.3% were on ERT and there was a significant difference in peak GLS in those taking ERT compared to those not on therapy (on ERT vs. ERT naïve: -17.6±3.8 vs. -19.7±2.9, $p<0.01$). When split by gender this difference was only present in the female population (female: on ERT -19.2±3.5 vs. ERT naïve -20.4±2.5, $p<0.05$; male: on ERT -16.2±3.5 vs. ERT naïve -16.9±2.5, p=NS). Of the LVH negative cohort 36.1% were on ERT, however no significant differences in systolic strain were seen when compared to those not on any therapy.

LGE

183 participants were given Gadolinium-based contrast agents (GBCA) and of these 77 (34.8%) had LGE. There was a significant difference in mean GLS between FD with and without LGE (LGE: -17.1±3.7 vs. no LGE: -19.7±2.5, $p<0.05$; LGE: -17.1±3.7 vs. HV: 19.3±2.0, $p<0.05$). In the LVH negative group, there were 14 out of 84 participants who had LGE (16.7%, all females) and there was no change in mean GLS measured (LGE: -20.4±2.2 vs. no LGE: -20.1±2.2 vs. HV: 19.3±2.0, $p=0.6$).

ECG

An abnormal ECG was found in 52.9% of the FD cohort. Of this, there were 18.6% in the LVH negative subgroup and 34.3% in the LVH positive subgroup. In the LVH negative sub-group, GLS did not correlate with the presence of ECG abnormalities and GLS values were similar to HV (table 2). This was also the case when evaluating GLS split by gender and in those participants with ECG abnormalities in combination with a low native T1 (table 2).

Biomarkers

Of the FD population 156 (70.6%) had high sensitivity troponin measured (hsTnT or hsTnI), with 27.6% having an elevated level above center-specific reference ranges. Median troponin in the total study population was 6.0µg/L (interquartile range: 1-31µg/L). An increasing level of troponin was associated with impairment in GLS in the total FD population ($r=0.516$, $p<0.05$). Of the LVH negative population 87 patients (73.1%) had hsTnT or hsTnI measured and only five had an elevated serum level with all others having a value <5ug/L. No significant relationship was

demonstrated between strain and troponin in the LVH negative group (r=0.169, p=0.118).

Reproducibility

Intra-observer reproducibility analysis performed following repeat evaluation of 30 CMR scans by observer 1 (RV) demonstrated a mean absolute bias of 0.7±0.6 with an intra-class correlation (ICC) for single measures of 0.98 (95% CI: 0.96-0.99). Reproducibility biases were similar when assessing inter-observer reproducibility following analysis of a subset of 20 CMR scans by observer 2 (BL) – mean absolute bias 0.6±0.5 and ICC for single measures of 0.99 (95%CI: 0.97-1.0).

DISCUSSION

The main findings of this study include:

1. Impaired GLS occurs in FD in the absence of reduced LVEF. The impairment in deformation is proportionate to an increase in LVM and storage in the overall FD cohort, and correlates with myocardial damage as shown by both LGE and biomarker evidence of cell necrosis troponin.

2. In LVH-negative FD (early disease), impaired GLS is associated with low native T1 in males, but not in females, suggesting that Fabry males have mechanical dysfunction before the onset of LVH when there is evidence of sphingolipid deposition (low T1). Interestingly, females only display mechanical dysfunction once they have LVH.

3. ECG changes do not follow impairment in GLS – suggesting electrical changes are independent of mechanical changes. This is important since a change either in

conduction and/or mechanical function may therefore serve as triggers for drug/enzyme intervention.

4. In LVH-positive FD, impaired GLS is associated with other signs of overt cardiac involvement namely increasing LVMi and the presence of LGE.

Fabry disease affects the heart. The obvious manifestations have been ECG abnormalities, hypertrophy, and, in late stage disease, impairment and thinning.[21, 22] Biomarkers are also elevated [23, 24, 25] and valve disease can be present, but the latter is rarely a clinically significant finding. CMR has also identified LGE in early disease, which characteristically affects the basal infero-lateral wall. This was initially thought to reflect only fibrosis; however, recent developments using advanced tissue characterisation with CMR parametric mapping (T1 and T2 mapping) has provided further insights. Native T1 is low in FD, representing sphingolipid accumulation [15, 19] in 85% of FD with LVH, and in 40-50% of LVH-negative patients, suggesting storage occurs early before the establishment of hypertrophy.[15, 20] When LGE is present without thinning, this has been shown to be associated with T2 elevation and hs-TnT release suggesting an inflammatory process.[24] Thus, the order and processes of phenotype development are being pieced together. ECG changes may precede echocardiographic LVH, and latest results suggest there is a pre-LVH phenotype with storage, ECG abnormalities, slight elevation of LV mass and LVEF clustering.[16]

Here, we introduce a new biomarker of myocardial mechanical dysfunction that is more sensitive than the ejection fraction to early changes in myocardial performance - GLS. This study supports the echocardiographic literature about impaired GLS in overt cardiac involvement in FD (LVH-positive disease), but offers new insights into LVH-negative disease. We have previously shown impaired GLS by speckle tracking

echocardiography in a small sample (n=25) of LVH-negative FD with low T1 compared to LVH-negative with normal T1.[15, 26] This current study expands on these findings by using a much larger cohort and is the first study to assess myocardial strain by CMR in conjunction with T1 mapping to show a sex difference.

Sex dimorphism in the FD response to storage has been previously proposed by us in patients with overt disease.[16] That is, in addition to apparent faster storage in hemizygous males, LVH positive males appear to have reduced T1 lowering with increasing LV mass in the LVH range – suggesting the dilution of the T1 lowering sphingolipid signal by the presence of triggered sarcomeric protein. A further example, found here is that LGE can be present in LVH negative females but rarely in males.[17 18] Here, mechanical dysfunction appears also to have sex dimorphism with female LVH-negative patients tolerating storage better than males – females had normal GLS, whereas males had impaired GLS with T1 lowering. The male patients within the LVH negative cohort all had a significantly lower T1 time compared with females. This may be indicative of a higher degree of sphingolipid storage within the myocardium of males, which is poorly tolerated; consequently leading to earlier functional impairment.

The limitations of this study include that it is only a single time point study with no follow-up data, but it is multicenter with a relatively large number of participants for a rare disease. A further limitation is that this study is only evaluating 2D longitudinal strain and not 3D strain. Preliminary results included assessment of 3D circumferential and radial strain, both of which demonstrated similar patterns to 2D GLS. However, when using LV short axis images to assess 3D strain parameters in

FD patients with LVH and cavity obliteration, there was significant impairment in myocardial border tracking, thus excluding a large proportion of the study cohort. Consequently, this study only assessed 2D GLS. Histological validation of T1 mapping for storage is lacking and it is likely that T1 mapping will miss the earliest storage due to the presence of a detection threshold in this technique. Further studies are also required to establish whether early institution of ERT based on a low T1 or impaired GLS in the absence of LVH affects the development of cardiac involvement.

CONCLUSIONS

In FD with LVH, myocardial strain (measured by GLS) reduces with hypertrophy, storage (measured by a low T1) and scar (measured by LGE). In early disease (pre-LVH), GLS is reduced in males and preserved in females when T1 is low, suggesting a possible sex difference in the myocardial functional response to storage.

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DISCLOSURES

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Table 1. Participant demographics and basic CMR findings

	Healthy volunteers	Fabry Total	Fabry Males	Fabry Females	p*
Sample size (n, %)	77 (100)	221 (100)	85 (38.5)	136 (61.5)	-
Age (y)	49.4±14.4	45±15.0	45±14.8	44±15.3	NS
LVEF (%)	70.2±5.6	73±8.0	71±9.0	74±7.2	<0.05
LVEDV (ml)	132.1±28.4	131±31.7	146±37.3	121±22.7	<0.05
LVESV (ml)	39.6±11.9	36±17.1	43±21.0	32±12.6	<0.05
GLS	-19.3±2.0	-18.5±3.6	-16.3±3.3	-19.9±3.0	<0.05
Native T1 (ms)	955.2±29.9	879±64.3	838.8±51.5	904.6±58.4	<0.05
LGE (n,%)	0 (0)	77 (100)	36 (46.8)	41 (53.2)	<0.05
LVH-positive (n,%)	0 (0)	102 (100)	63 (61.8)	39 (38.2)	<0.05
LVMi (g/m^2)	55.6±10.1	89±39.3	116±42.6	71±24.9	<0.05
MWT (mm)	9±1.6	12±5.0	15±5.1	10±3.8	<0.05

*p-value is for Fabry male-to-female comparisons.

Table legend: LVEF – left ventricular ejection fraction, LVEDV – left ventricular end-diastolic volume, LVESV – left ventricular end-systolic volume, GLS – global longitudinal strain, LGE – late gadolinium enhancement, LVH – left ventricular hypertrophy, LVMi – indexed left ventricular mass, MWT – maximum wall thickness, NS – non-significant.

Table 2a. Mean global longitudinal strain values in various subcohorts of the total study population

HV total	HV males	HV females		Fabry total	Fabry males	Fabry females	p
-19.3±2.0	-18.5±1.8	-20.2±1.9	LVH positive (n=102	-16.4±3.6	-15.5±3.4	-17.8±3.5	<0.05 *
			LVH negative (n=119)	-20.3±2.9	-18.7±1.7	-20.7±2.3	NS **

*p-value comparing Fabry vs. HV in all groups **p-value comparing Fabry males/females vs. HV males/females.

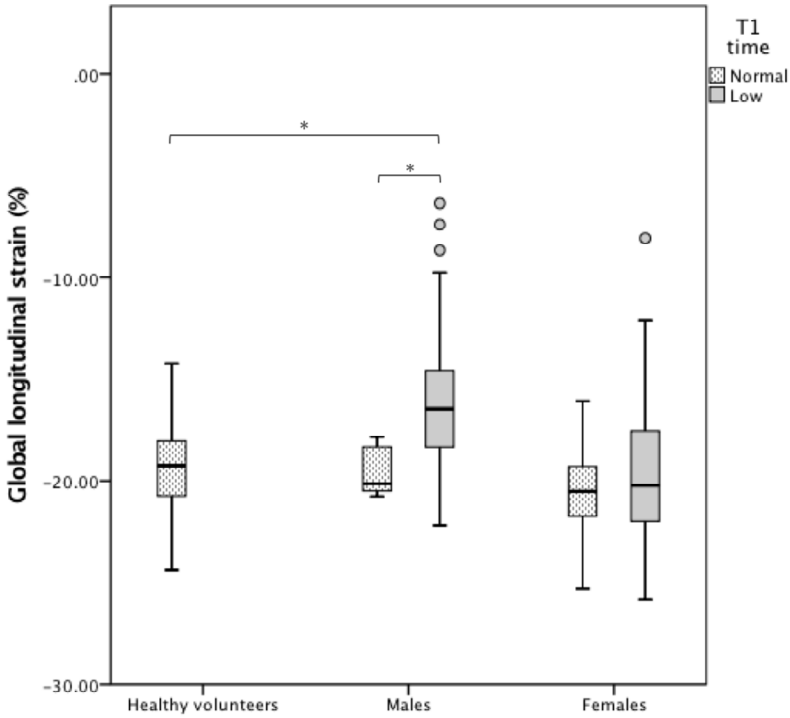
Table 2b. Mean global longitudinal strain values in various subcohorts of the LVH negative Fabry population

	Subcohort 1	**Subcohort 2**	P*
	Normal T1	**Low T1**	
Fabry total	-20.5±1.9	-20.2±2.6	NS
Fabry males	-20.0±1.0	-18.3±1.6	<0.05
Fabry females	-20.6±2.0	-20.9±2.5	NS
	Low T1 + ECG normal	Low T1 + ECG abnormal	
Fabry total	-20.4±2.8	-19.9±2.4	NS
Fabry males	-18.1±1.9	-18.9±1.1	NS
Fabry females	-21.2±2.5	-20.3±2.7	NS

*p-value is comparing subcohort 1 vs. subcohort 2 in all groups.

Table legend: HV – healthy volunteers, LVH – left ventricular hypertrophy, ECG – electrocardiogram, NS – non-significant.

Figure 4. The relationship between global longitudinal strain and native T1 in LVH negative Fabry and healthy volunteers.



*Indicates p-value <0.05.
Graph represents the mean peak GLS with standard deviation error bars. Of the LVH negative Fabry cohort, there is significant impairment in mean GLS in male patients with a low T1 time compared to those with a normal T1 and healthy volunteers.

Figure legend: LVH – left ventricular hypertrophy, GLS – global longitudinal strain.

Supplementary table 1. Correlation between different variables in the total population and the LVH negative cohort.

Variables	Correlation coefficient (R^2)	p
LVMi + MWT	0.9	<0.001
MWT + LVEF	0.1	<0.05
MWT + GLS	0.7	<0.01
LVH negative (n=131)*		
T1 + GLS	-0.3	0.03

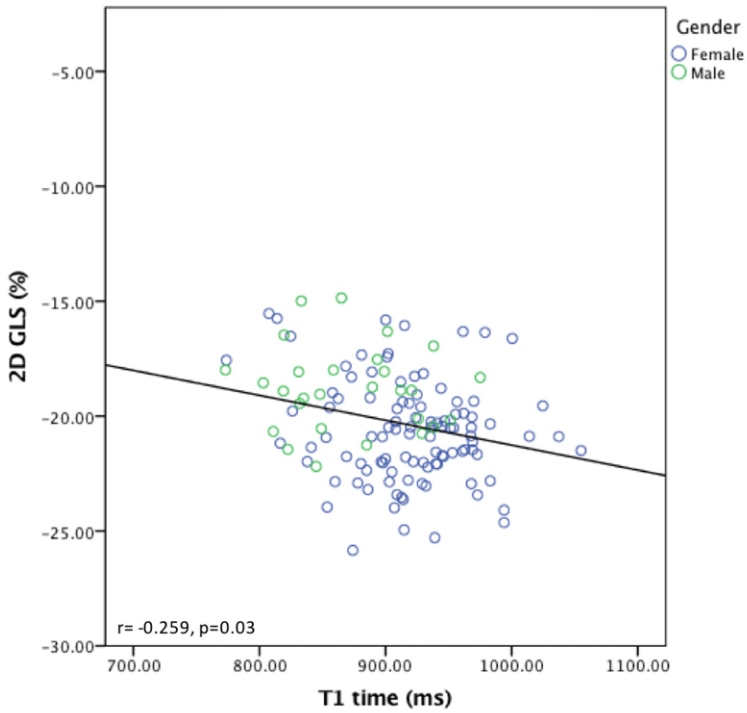
*LVH negative classified as MWT ≤12mm

Table legend: LVMi – indexed left ventricular mass, MWT – maximum wall thickness, LVEF – left ventricular ejection fraction, GLS – global longitudinal strain, LVH – left ventricular hypertrophy.

Supplementary table 2. Mean GLS in Fabry males and females who are LVH negative.

	Low T1	Normal T1	p
Males	-18.6±1.9	-20.0±1.0	0.03*
Females	-20.8±2.5	-20.6±1.9	0.67

Supplementary figure 1. Scatter plot showing the relationship between native T1 and 2D GLS in the LVH negative cohort.



LVH negative has been defined as a MWT ≤12 mm.

Supplementary table 3. The relationship of GLS and native T1 with baseline clinical characteristics (linear regression analysis)

Dependent variable	Independent variables	Uni-variable analysis				Multivariable model			
		Coefficient	95% CI	p	R^2	Coefficient	95% CI	p	R^2
Total population (n=221)									
GLS (%)	Age (years)	0.35	0.05-0.11	<0.01	0.12				
	LVMi (g/m^2)	0.68	0.05-0.07	<0.01	0.46	0.60	0.04 to 0.07	<0.01	0.49
	LGE	0.36	1.62-3.11	<0.01	0.13	-0.15	-2.04 to 0.08	0.069	
	Male gender	0.35	1.04-1.98	<0.01	0.12				
	Troponin	0.52	1.80-3.11	<0.01	0.27				
	T1 time (ms)	-0.47	-0.03-0.18	<0.01	0.22	0.27	-0.02 to 0.006	<0.01	
T1 time (ms)	LVMi (g/m^2)	-0.58	-1.20 to -0.86	<0.01	0.34	-0.22	-0.70 to -0.07	0.016	0.35
	GLS (%)	-0.47	-11.59 to -7.44	<0.01	0.22	-0.27	-8.50 to -1.94	0.002	
	Age (years)	-0.35	-2.02 to -9.6	<0.01	0.12	-0.17	-1.29 to -0.17	0.011	
	LGE	-0.53	-91.15 to -61.38	<0.01	0.28				
	ERT	-0.46	-76.10 to -48.49	<0.01	0.21	-0.13	-32.92 to -0.27	0.046	
LVH negative (n=119)									
GLS (%)	Age (years)	-0.15	-0.06 to 0.005	0.096	0.024				
	LVMi (g/m^2)	0.386	0.05 to 0.12	<0.01	0.15	0.35	0.03 to 0.12	0.001	0.22
	Male gender	0.34	1.00 to 3.03	<0.01	0.12				
	T1 time (ms)	-0.29	-0.02 to -0.01	0.002	0.081	-0.20	-0.17 to 0.00	0.058	
	Troponin	0.17	-0.23 to 2.03	0.118	0.03				
T1 time (ms)	LVMi (g/m^2)	-0.40	-2.99 to -1.20	<0.01	0.16	-0.28	-2.48 to -0.52	0.003	0.29
	GLS (%)	-0.29	-11.10 to -2.64	0.002	0.08	-0.18	-9.14 to -0.52	0.047	
	Age (years)	-0.10	-1.18 to 0.33	0.267	0.01	-0.30	-74.53 to -20.76	0.001	
	LGE	-0.29	-75.21 to -16.38	0.03	0.09				
	ERT	-0.22	-45.58 to-4.33	0.18	0.05	-0.19	-41.0 to -1.89	0.032	

Table legend: CI – confidence interval, GLS – global longitudinal strain, LVMi – indexed left ventricular mass, LGE – late gadolinium enhancement, LVH – left ventricular hypertrophy, ERT – enzyme replacement therapy.