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Differentiation between Fabry disease and hypertrophic cardiomyopathy with cardiac T1 mapping

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Abstract

Purpose. To evaluate the potential of non-contrast myocardial T1 mapping on cardiovascular magnetic resonance examination (CMR) in differentiating patients with Fabry disease (FD) from those with hypertrophic cardiomyopathy (HCM) and healthy control subjects.

Materials and methods. Seventeen patients with FD (8 men, 9 women; mean age, 48 years \pm 18; [range: 19-73 years]; 53% with left ventricular hypertrophy [LVH]) were matched with 36 patients with hypertrophic cardiomyopathy (HCM) (22 men, 14 women; mean age, 57 years \pm 16 [SD] [range: 22-85 years]) and 70 healthy control subjects (34 men, 36 women; mean age, 38 years \pm 15 [SD]; [range: 18-65 years]). Cardiac T1 mapping was performed using the modified Look-Locker inversion (MOLLI[®]) sequence on a 1.5-T magnet. T1 values were calculated, on midventricular section, for septal left ventricular segments (S8-S9) and all mid-ventricular ones (global T1 values; S7-S12). Statistical analysis included unpaired Mann-Whitney test, receiver operating characteristic curve and likelihood ratios.

Results. Septal native T1 values were significantly decreased in patients with AFD (889 \pm 61 [SD] ms; range: 784-980 ms) compared to those with HCM (995 \pm 48 [SD] ms; range: 935-1125 ms) ($P < 0.001$) and versus healthy controls (965 \pm 29 [SD] ms; range: 910-1028 ms) ($P < 0.001$). Global native T1 values were also significantly decreased in patients with AFD (891 \pm 49 [SD] ms; range 794-970 ms) compared to those with HCM (995 \pm 34 [SD] ms; range: 952-1086 ms) ($P < 0.001$) and versus healthy controls (966 \pm 27 [SD] ms; range: 920-1042 ms) ($P < 0.001$). A septal left ventricular native T1 cutoff value of 940 ms could distinguish AFD from HCM with 88% sensitivity (95% CI: 73-100%) and 92% specificity (95% CI: 83-100%). Positive likelihood ratio was 11, negative likelihood ratio was 0.12. Compared to controls, the same threshold could distinguish AFD with 88% sensitivity (95% CI: 73-100%) and 86% specificity (95% CI: 78-94%). Positive likelihood ratio was 6.3, negative likelihood ratio was 0.14. T1 value was abnormal in 4 of 8 (50%) of FD patients who did not have LVH.

Conclusion. Native T1 values are significantly lower in patients with AFD compared with HCM and healthy volunteers.

Keywords: Cardiac magnetic resonance imaging (MRI); Fabry disease; Left ventricular hypertrophy; Hypertrophic cardiomyopathy

List of abbreviations

FD: Fabry disease

LVH: left ventricular hypertrophy

ERT: enzyme replacement therapy

CMR: cardiac magnetic resonance

LVM: left ventricular mass

LGE: late gadolinium enhancement

LV: left ventricle

MRI: magnetic resonance imaging

HCM: hypertrophic cardiomyopathy

CI: confidence interval

SD: standard deviation

Introduction

Fabry disease (FD) is a rare multisystem X-linked lysosomal storage disorder of glycosphingolipid metabolism due to complete or partial deficiency of the lysosomal enzyme α -galactosidase A (α -Gal A) caused by mutations in the *GLA* gene (located on Xq 22) [1]. More than 600 pathogenic mutations have been identified, most of them being private, occurring in individual families [2]. Disease severity in patients with FD is inversely related to α -Gal A activity. As a result, progressive intracellular accumulation of glycosphingolipids occurs in multiple organs. Premature death is the consequence of cardiac failure, arrhythmia, stroke and renal failure [1]. Progressive left ventricular hypertrophy (LVH) and myocardial fibrosis may induce systolic/diastolic dysfunction, valvular heart disease, arrhythmias and heart failure [2].

The incidence of FD has been estimated 1 in 40,000 to 1 in 117,000 live births for males [1]. Screening of patient populations at risk of FD (*i.e.*, those with cardiomyopathy [3-4], stroke [5], or renal failure [6]), has identified a low but not negligible prevalence of FD in the general symptomatic population. Recently, studies in high-risk patient cohorts suggested that FD was much more common and accounted for at least 3% of unexplained LVH in middle aged men [1, 7]. The diagnosis of FD is often delayed by as much as 14 years in males

and 16 years in females although the first signs of FD, such as acroparaesthesia, usually appear in childhood in affected patients.

The assessment of cardiac involvement in patients with FD is crucial because early enzyme replacement therapy (ERT) is likely to postpone the progression of LVH and development of myocardial fibrosis and maintain functional capacities [8, 9]. Cardiac magnetic resonance (CMR) examination is now the gold standard imaging technique to assess myocardial anatomy, regional and global function and approach tissue characterization. CMR examination has emerged as a key imaging modality to provide both quantitative and qualitative assessment of cardiomyopathies [10-12]. In the context of FD, CMR examination helps identify and quantify increased left ventricular mass (LVM) and the presence of scarring on late images obtained after intravenous administration of a gadolinium chelate (*i.e.*, “late gadolinium enhancement” [LGE]). However, those anomalies are neither sensitive nor specific of FD [13]. As glycosphingolipids are supposed to decrease the T1 longitudinal relaxation time, we hypothesized that native myocardial T1 values would be significantly lower in patients with FD compared to those with hypertrophic cardiomyopathy (HCM) or healthy subjects. In this regard, Sado et al. have shown that native myocardial T1 values were substantially lower in patients with FD compared to those with other causes of LVH [14].

The goals of this study were to evaluate the potential of non-contrast myocardial T1 mapping for differentiating patients with FD from those with HCM and healthy controls.

Materials and Methods

Patient selection

Seventeen patients with clinically and genetically confirmed FD, who underwent a CMR examination from May 2013 to March 2018 were retrospectively included. Four of them were receiving ERT. Patients with usual magnetic resonance imaging (MRI) contraindication such as pregnancy, or legal protection were excluded. Thirty-six patients with HCM were also included in the same period of time. The diagnosis of HCM was defined as a LVH (wall thickness > 15 mm or 13 mm in the context of documented familial disease) associated with a non-dilated left ventricle (LV) and required the absence of another cardiac or systemic disease [15]. The diagnosis of HCM was established based on international guidelines [16]. Exclusion criteria included documented coronary artery disease, hypertension, aortic valvular disease, and significant renal dysfunction with estimated

glomerular filtration rate $< 30 \text{ mL/min/1.73m}^2$ and usual contraindications to MRI examination.

Concomitantly, 70 asymptomatic healthy control participants with no documented history of cardiovascular disease and normal CMR findings formed a control group. Healthy control participants were enrolled from the “Heart Map Study”, a study performed in our center to determine the normal T1, T2 and T2* values of the myocardium in a cohort of 175 healthy volunteers (ClinicalTrials.gov Identifier: NCT01712581) [17]. All healthy volunteers gave written informed consent to participate in the study. The institutional review board approved this retrospective study, and informed consent was waived. Clinical and demographic data were obtained from the electronic patient records.

No patients were excluded. The final cohort consisted of 17 patients with gene-positive FD; there were 8 men and 9 women (mean age, 48 ± 18 [SD] years; range: 19-73 years) (Table 1). Four patients with FD (24%) were receiving ERT. Thirty-six patients with HCM were included; there were 22 men and 14 women (mean age, 57 ± 16 [SD] years; range: 22-85 years). Finally, 70 healthy volunteers were included; there were 34 men and 36 women (mean age, 38 ± 15 [SD] years; range: 18-65 years). Figure 1 shows patients inclusion.

CMR protocol

CMR examinations were performed on a 1.5 T Avanto[®] unit (Siemens Healthineers) with a cardiac 32 channel-coil for signal reception and electrocardiographic (ECG) gating. CMR examinations included cardiac function assessment, native T1 mapping and LGE images.

Cardiac function assessment was performed using cine-MRI sequences obtained with retrospectively ECG-gated balanced steady-state-free precession (SSFP) sequences in long axis and short axis providing full coverage of the LV. The following parameters were used: TR, 36 ms; TE, 1.5 ms; flip angle, 60° ; field of view (FOV), 360x420 mm; matrix size, 216x256; slice thickness, 6 mm; interslice gap, 3mm; cardiac phases per cardiac cycle, 20-25.

Mid ventricular native T1 mapping was performed in the short axis plane (S7-12) in all patients. Modified Look-Locker inversion recovery (MOLLI[®]) technique was used to evaluate T1 values. Inversion groupings acquisition scheme 3(3)3(3)5 was applied [18]. For patients with AFD, three short-axis sections were acquired at the base, mid-ventricle, and apex before intravenous administration of gadobutrol (Gadovist[®], Bayer Healthcare) at a dose of 0.1 mmol/kg of body weight [19]. Imaging parameters were as follows: TR, 3.7 ms; TE,

1.1 ms; flip angle, 35°; matrix acquisition size, 256 x 128; FOV, 360 x 270 mm; slice thickness, 8 mm; TI, 75-750 ms; trigger delay, 300 ms; and views per segment, 24. Images were processed with a curve fitting technique to generate T1 maps.

LGE sequences were performed 10 minutes after the intravenous administration of gadobutrol to identify regional fibrosis using a T1-weighted inversion recovery gradient echo technique. Imaging parameters were as follows: TR, 7.1 ms; TE, 3.1 ms; slice thickness, 8 mm; matrix acquisition size, 256 x 192; with an inversion time individually determined to null the myocardial signal. LGE sequences were performed using standard long-axis and short-axis views of the LV. Healthy volunteers were not injected.

Image analysis

All CMR images were analysed using SyngoVia® (Siemens Healthineers) by one observer (E.D.) with an experience of two years in cardiac MRI.

Evaluation of LV function and wall thickness

LV short-axis epicardial and endocardial borders were semi-automatically contoured at end-diastole and end-systole for determining end-diastolic and end-systolic volumes, LV ejection fraction and LVM. The papillary muscles were included as part of the LV cavity volume. Maximum end-diastolic LV wall thickness was manually determined on short axis cine steady-state free precession images. LVH was considered when LVM indexed to body surface area was above 85 g/m² in men and 81 g/m² in women [20].

Evaluation of myocardial T1 values

For each short-axis image, and for each myocardial segment, a region of interest (ROI) was manually drawn within the LV myocardium to calculate T1 values, excluding papillary muscles. Care was taken to avoid LV cavity blood pool and potential partial volume effects at the endocardial and epicardial borders. A total of six segments per patient were analysed. T1 values comparisons were established on the short axis midventricular section as it was the only available one in healthy volunteers. Segments 8 and 9 of the American Heart Association were considered for estimating septal T1 values while global T1 values were inferred from segments 7-12. As midwall myocardial MOLLI® T1 was shown to be reproducible, with intra-individual, intra- and inter-MRI variability $\leq 2\%$ [21], we did not perform reproducibility testing. The relatively long duration of T1 mapping sequences occasionally led to some

undesired breathing motion, which generated artifacts and non-evaluable segments. Less than 1% of all segments were excluded and these segments were not used for the analysis. An analysis with short axis slice used in the study is described in Figure 2.

Evaluation of LGE images

The LGE images were visually examined for the presence of regional fibrosis. LGE was considered present only if identified in two orthogonal views and excluding RV insertion points [22]. Presence or absence of LGE was mentioned for each myocardial segment. The analysis of LGE sequences was performed independently from the T1 analyses. Fourteen patients with FD received an intravenous administration of gadolinium chelate; of these, one patient had not interpretable CMR because of artifacts so that 13 CMR examinations could be analyzed for LGE findings.

Statistical analysis

Quantitative variables were expressed as mean \pm standard deviation (SD) and ranges. Qualitative variables were expressed as raw numbers, proportions and percentages. Comparison of continuous variables was performed using unpaired Mann-Whitney test. Comparison of proportions was done with chi-squared (χ^2) test. Receiver operating characteristic curves (ROC) were created to evaluate the ability of native T1 values to discriminate between the three groups. Areas under the receiver operating characteristic curve (AUC) for native T1 values were tested for equality [23]. Bivariate correlations were searched for using Pearson correlation test, with $r < 0.3$ indicating none or very weak correlation, $0.3 < r < 0.5$ a weak correlation, $0.5 < r < 0.7$ a moderate correlation and $r > 0.7$ a strong correlation. For all comparisons, a P value < 0.05 was considered to indicate significance. Statistical analyses were performed using the website BiostatTGV[®] (<https://biostatgv.sentiweb.fr/?module=tests>).

Results

Study population

A total of 123 patients were evaluated during the study period, including 17 patients with FD, 70 asymptomatic control subjects and 36 patients with HCM. The 4 patients with

FD (24%) under ERT were not excluded from the analysis. Patients' characteristics are presented in Table 1.

CMR imaging findings

CMR imaging findings are shown in Table 2. Nine of 17 patients (53 %) with FD and 19 of 36 patients with HCM (53 %) had LVH. Basal inferolateral LGE was more common in patients with FD (5 of 13; 38 %) than in those with HCM (3 of 36; 8 %) ($P = 0.02$). Basal inferolateral LGE was present in 5 out of the 6 patients with FD showing LGE (83 %).

Native T1 findings

In discriminating patients with FD from those with HCM, septal T1 values yielded an AUC of 0.930 (95% confidence interval [CI]: 0.813-0.976). The AUC of global T1 values was 0.989 (95 % CI: 0.938-0.998) (Figs. 3, 4). A septal T1 cutoff value of 940 ms yielded 88% sensitivity (15 of 17; 95 % CI: 73-100 %), 92% specificity (33 of 36; 95% CI: 83-100 %), positive likelihood ratio of 11 and negative likelihood ratio of 0.12 in distinguishing FD from HCM.

In the identification of patients with FD from healthy controls (*i.e.*, allowing detection of FD patients in general population), the AUC of septal T1 was 0.877 (95% CI: 0.726-0.921). The AUC of global T1 was 0.925 (95 % CI: 0.824-0.970) (Figs. 4, 5). Using a cutoff of 940 ms for septal LV native T1 value, CMR examination had 88 % sensitivity (15 of 17; 95 % CI: 73-100 %), 86 % specificity (60 of 70; 95 % CI: 78-94 %), positive likelihood ratio of 6.3 and negative likelihood ratio of 0.14 for discriminating between patients with FD and healthy volunteers.

Relationship between T1 values and functional parameters in patients with AFD

When considering the whole FD group, we observed a strong positive correlation between septal native T1 values and non-septal native T1 values ($r = 0.85$; $P < 0.001$). Septal native T1 values did not differ significantly between men (886 ± 59 [SD] ms) and women (893 ± 67 [SD] ms) ($P = 0.61$) (Fig. 5). Fifty percent of patients with FD and no LVH had T1 values under the limit of 907 ms (normal values - 2SD). T1 values were weakly and inversely correlated with indexed LVM ($r = -0.483$; $P = 0.049$) and was also moderately and inversely correlated with the maximal LV wall thickness ($r = -0.572$; $P = 0.016$). Septal native T1

values did not differ significantly between patients with FD whether they were on ERT or not (respectively $872 \text{ ms} \pm 54 \text{ [SD]}$ vs. $895 \text{ ms} \pm 64 \text{ [SD]}$) ($P = 0.395$). Normal or even elevated T1 in the LV inferolateral wall was shown in some patients with FD (Fig. 2). This variation was observed in patients with ($n=5$; 38 %) or without ($n=8$; 62 %) LGE (respectively $978 \text{ ms} \pm 22 \text{ [SD]}$ vs. $917 \text{ ms} \pm 52 \text{ [SD]}$) ($P = 0.009$) (Table 2).

Discussion

Differentiating FD from HCM on conventional MRI remains challenging. Our study confirmed that myocardial native T1 mapping helps differentiate between patients with FD and healthy subjects and those with HCM. At 1.5-T and using MOLLI[®], a septal native T1 cutoff value of 940 ms can distinguish patients with FD from those with HCM with a high sensitivity and specificity. Two prior studies reported that native T1 values obtained with shortened MOLLI[®] and saturation recovery single-shot acquisition (SASHA[®]) schemes at 1.5-T were lower in patients with FD than in healthy control subjects and patients with other causes of LVH. Sado et al. reported that a native septal T1 value of 940 ms using shortened MOLLI[®] (without exclusion of LGE areas) could distinguish FD from non-FD causes of LVH [14]. Using SASHA[®], Thompson et al. reported global native T1 cutoff points of 1146 ms in women and 1120 ms in men [24].

By comparison to MOLLI[®] and ShMOLLI[®], Roujol et al. reported that SASHA[®] and SAPHIRE[®] had better accuracy, lower precision, and similar reproducibility. They found that MOLLI[®] and ShMOLLI[®] led to underestimating myocardial T1 values in both phantom and healthy subject studies. These underestimations were found to be more prominent with higher T1 values [25]. In our study we chose to use MOLLI[®] for several reasons; first, we had experience with the technique. Secondly, we had carried out a study in a population of 175 healthy volunteers (NCT01712581) [17]. Finally, the midwall myocardial native T1 drawn from MOLLI[®] sequence was shown to be reproducible with an intra-individual, intra- and inter-MRI variability $\leq 2\%$ [21].

A large-scale study including more than 1,200 subjects and using ShMOLLI[®] reported that patients with FD had significantly lower native T1 ($863 \pm 23 \text{ [SD]}$ ms) compared to patients with normal CMR examination or the normal reference myocardium in patients with other cardiovascular disease [26]. Another recent study reported that patients with FD and LVH had reduced native T1 values and more positive circumferential strain compared to those without LVH. They showed that the basal septum could be the most appropriate region

for measuring native T1 values because of a smaller standard deviation. They also showed that basal septal T1 value was superior to circumferential strain in discriminating among patients with LVH [27].

In a previous publication that compared native myocardial T1 values at 3.0 T between patients with FD and those with HCM, a septal native T1 cutoff point value of 1220 ms was defined [28, 29, 30]. This cutoff value allowed distinguishing patients with FD from those with HCM with high sensitivity (29 of 30 [97 %]), specificity (28 of 30 [93 %]), and accuracy (57 of 60 [95 %]). Although global T1 values had slightly better reproducibility compared with septal LV native T1 values, septal T1 values were recommended in the setting of patients with suspected FD, because of better discriminating capabilities and ease of measurements [28]. Regarding the potential of evaluating global vs. septal T1 values, our results did not bring definite conclusion although the global AUCs appeared more discriminating than septal ones. The values of T1 did not differ significantly between men and women in our study as well as in data from the literature [31].

The decrease in myocardial T1 values in patients with FD could be explained by the accumulation of glycosphingolipids in myocytes [32]. On the other hand, we noted a pseudo-normalization of T1 values in the lateral-inferior basal segment in patients with a focal fibrous scar visualized on the LGE sequences. A significant percentage of patients with FD having renal dysfunction, this paradoxical increase in T1 values could make it possible to identify focal fibrosis without contrast injection. Although this could be of interest in this population at risk of gadolinium-induced complications, further studies are needed to confirm this trend. Septal T1 values do not seem to be affected by the development of fibrosis; previous autopsy work found very little amount of fibrosis in the septum in 3 cases of severe cardiac involvement in FD [14, 24, 33]. We observed that in patients with concentric hypertrophy, the fibrous scar on LGE images has most often an inferior-lateral-basal location and this was recently demonstrated by Deva et al. in 39 patients [34].

As reported by Wilson et al., the study of myocardial strain in patients with FD using cine sequences could be a useful addition to T1 mapping [35]. Nordin et al. suggested that inflammation could contribute to LGE in patients with FD [36]. T2 mapping and troponins could be assessed to evaluate inflammation, stratify the risk and monitor therapies. It has been shown that in the absence of myocardial fibrosis, ERT could improve myocardial morphology, function and exercise capacity [9]. Today, as there is no available morphological or functional biomarker of treatment effectiveness, we are performing a prospective

multicentric research (ClinicalTrials.gov Identifier: NCT02956954) in order to try to address this question.

Our study has several limitations. First, it is retrospective single center study that included a limited number of patients with FD. However, FD is a rare disease and considering the significantly lower native T1 values compared to control subjects, only a small sample size was sufficient to detect significant changes. Previous sample size calculations have been performed showing that 7 patients were required to detect a 40 ms difference [37]. Considering the small number of patients with FD, we could not divide them into sub groups (*e.g.*, patients without hypertrophy or patients with ERT). Also, we did not measure the extracellular volume in our population. Deva et al. reported that in the case of non-concentric hypertrophy, the topography of LGE was different and most often multiple [34]. We were unable to reproduce this result in our study as the vast majority of patients with FD had concentric hypertrophy. Reproducibility of T1 values measurements was not assessed because previous studies had shown it to be excellent [21, 38]. A single operator performed all ROI tracings accordingly with rules of good practice. Multivariate analysis (age, sex and heart rate) was not possible considering the limited number of patients. A previous study showed that the heart rate was the only physiological factor that had a small effect on myocardial T1 values (-6 ms/10 bpm) [24]. This study involved only the MOLLI[®] technique while at least 4 other T1 mapping schemes have been assessed [39, 40]. However, in different Look-Locker sequences, T1 values were shown to correlate in clinical studies [26]. In accordance with a recent study, our results may potentially only apply to our equipment given the inter-equipment variability [41].

In conclusion, native CMR imaging T1 values at 1.5 T are reduced in FD patients compared with HCM patients and healthy volunteers; therefore, this imaging biomarker could be instrumental in the early identification of cardiac involvement in patients with FD. Finding a low T1 value should be considered as a possible hint of FD and should refer the patient to a specialist in order to confirm the diagnosis.

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Disclosure of interest

No potential conflict of interest relevant to this article was reported.

Conflicts of interest

The authors have no conflicts of interest to disclose in relation with this study.

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Figure Legends

Figure 1. Flowchart of the study.

Figure 2. 50 year-old woman with Fabry disease. A, Short axis T1 map reveals decreased T1 value in the septum (915 ms) and pseudo-normalized T1 value in the infero lateral wall (1006 ms). B, Late gadolinium enhancement image shows typical scar in the infero-lateral segment (arrow) indicating fibrosis.

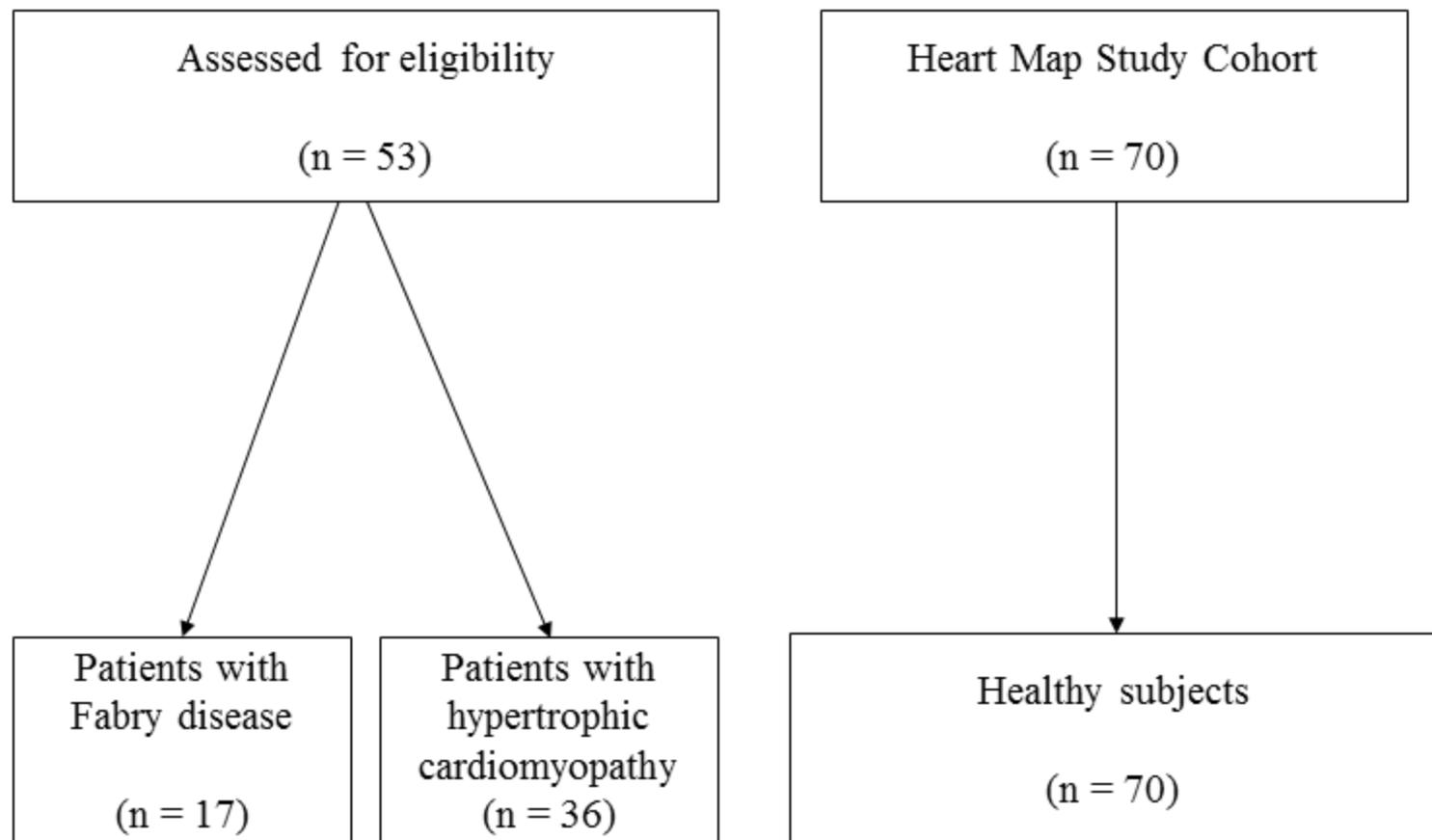
Figure 3. Graph shows mean septal left ventricular T1 values (in ms) in the three study groups. Healthy indicates healthy control subjects; HCM indicates hypertrophic cardiomyopathy; FD indicates Fabry disease.

Figure 4. Graph shows mean global left ventricular T1 values (in ms) in the three study groups. Healthy indicates healthy control subjects; HCM indicates hypertrophic cardiomyopathy; FD indicates Fabry disease.

Figure 5. Graph shows mean global left ventricular T1 values (in ms) in men and women with Fabry disease.

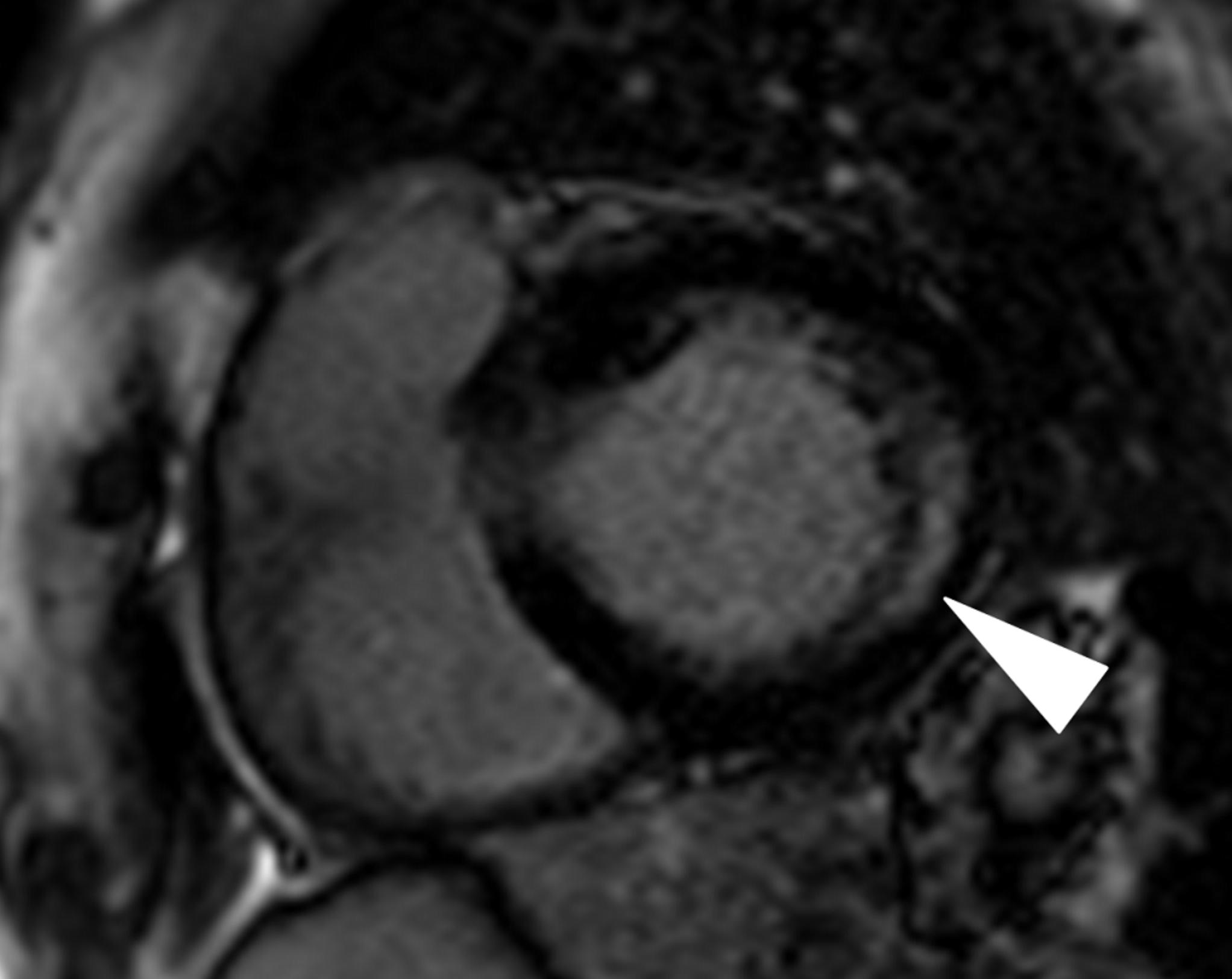
Table 1. Baseline characteristics in patients with Anderson-Fabry disease, patients with hypertrophic cardiomyopathy and healthy volunteers.

Table 2. Cardiac MR imaging findings.



ROI20_1
Mean/SD: 915,27 /34,62
Area: 5,21 cm2

ROI21_1
Mean/SD: 1006,59 /33,93
Area: 2,17 cm2



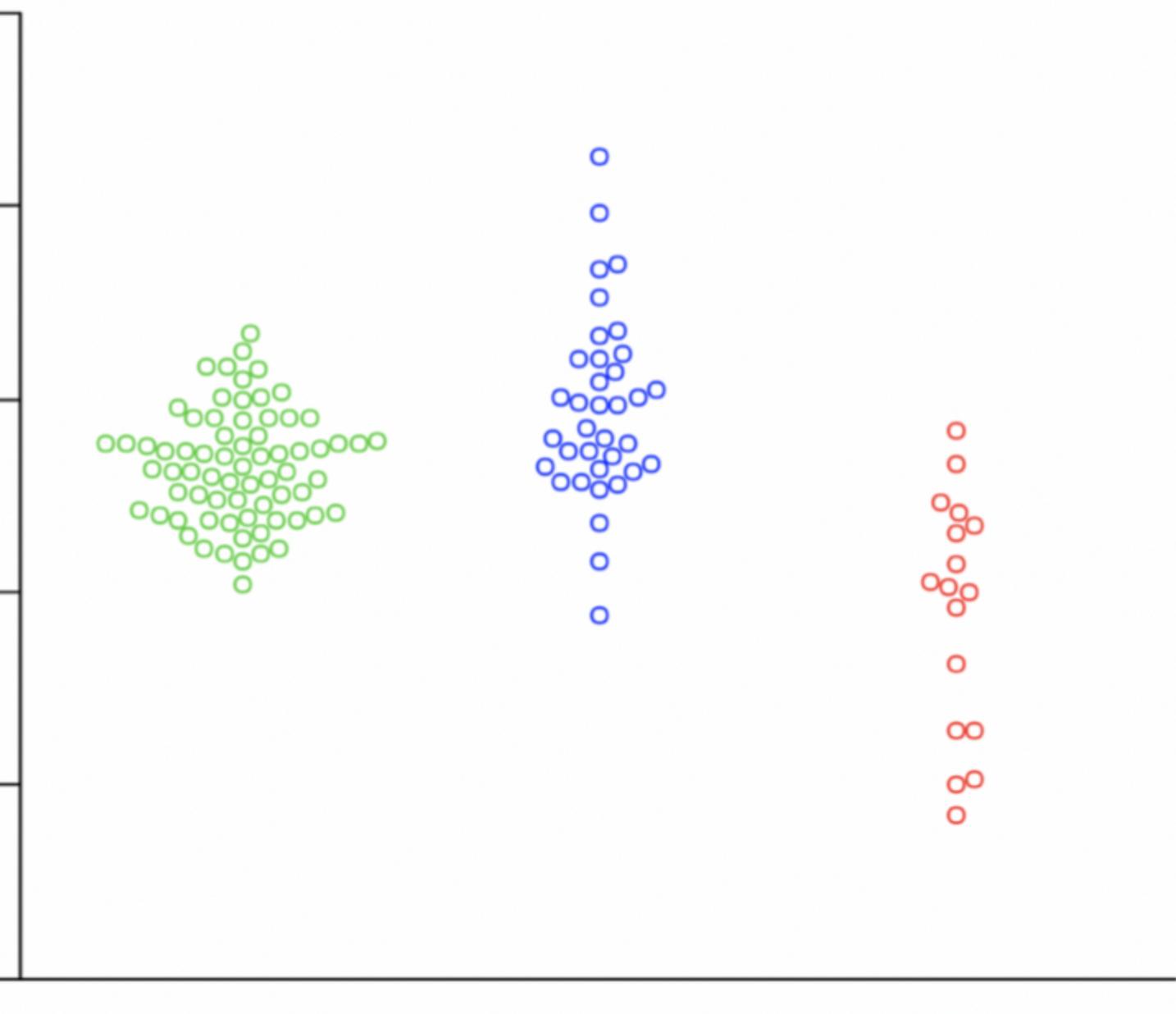
Septal T1 mapping (in ms)

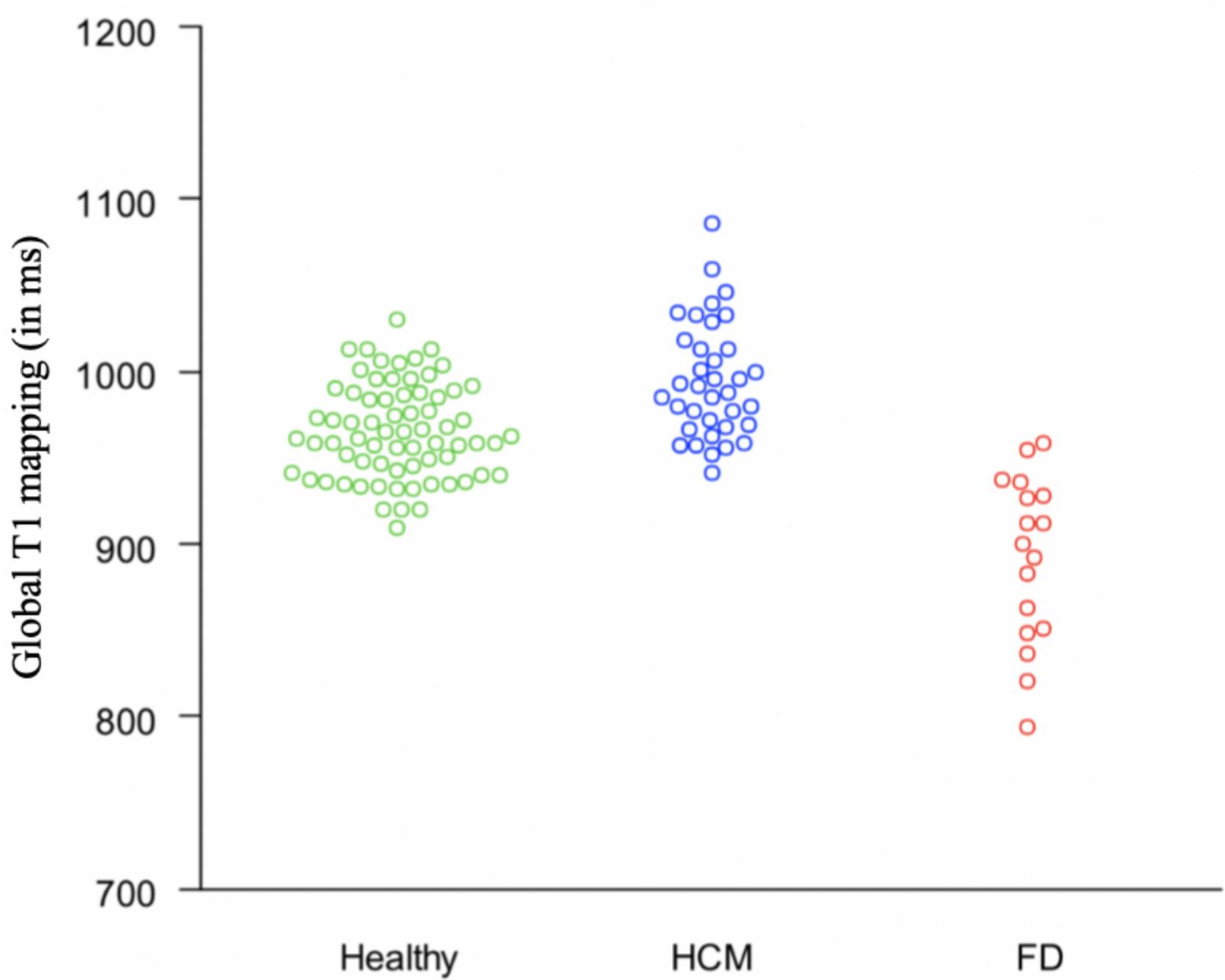
1200
1100
1000
900
800
700

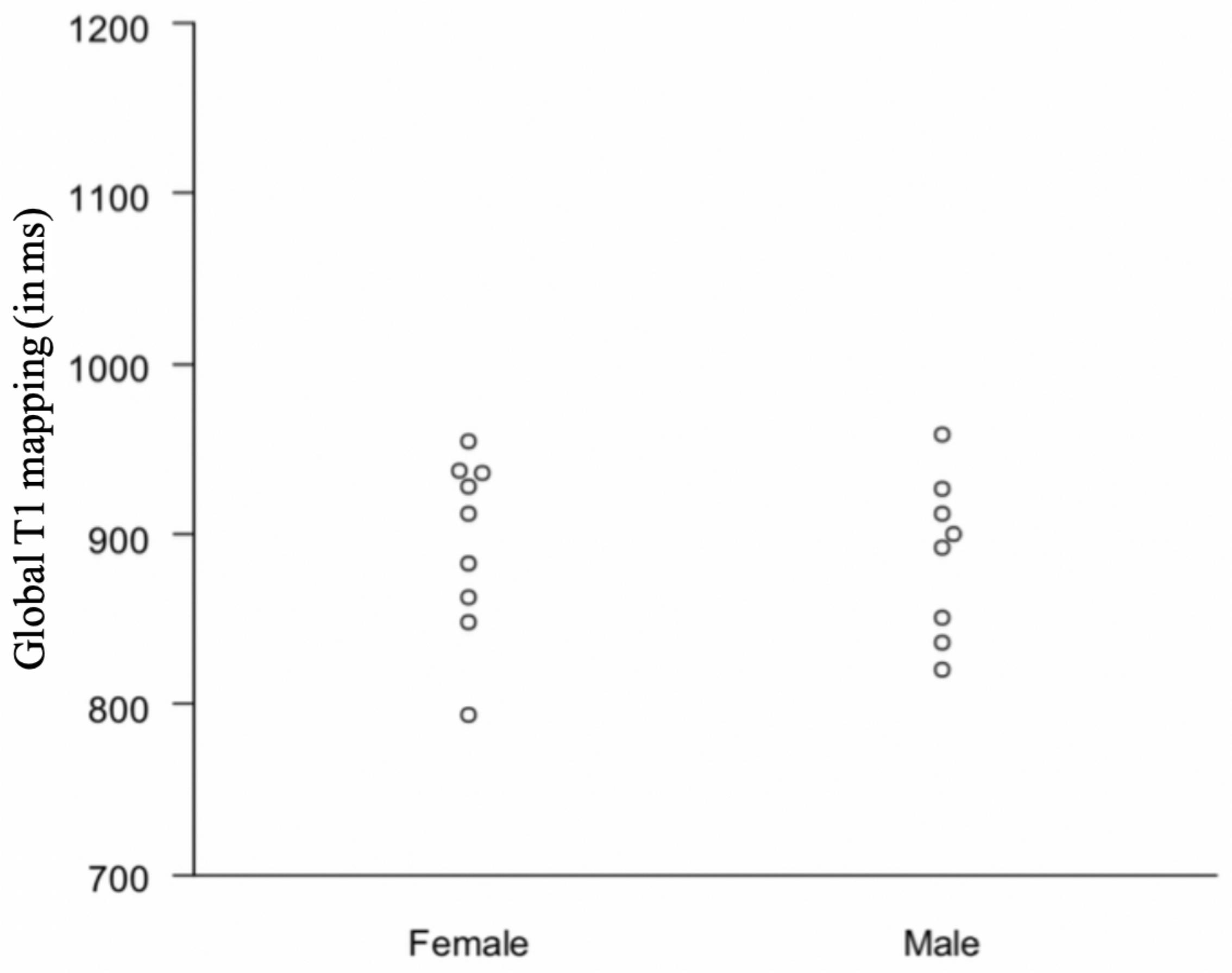
Healthy

HCM

FD







Variables	FD (n = 17)	HCM (n = 36)	P value (FD vs. HCM)	Controls (n= 70)	P value (FD vs. HV)
Age	48 ± 18 [19-73]	57 ± 16 [22-85]	< 0.001	38 ± 15 [18-65]	< 0.001
Sex			0.38		> 0.99
<i>Male</i>	8 (47%)	22 (61%)		34 (48%)	
<i>Female</i>	9 (53%)	14 (39%)		36 (52%)	
BMI (kg/m²)	25.2 ± 3.9 [20.4-35.1]	28.1 ± 3.8 [22.1-36.4]	< 0.001	23.1 ± 3.2 [19.2-32.4]	< 0.001
BSA (m²)	1.8 ± 0.2 [1.6-2.1]	1.9 ± 0.2 [1.6-2.2]	0.45	1.8 ± 0.2 [1.6-2.4]	> 0.99
HR (bpm)	71 ± 14 [50-104]	74 ± 12 [54-106]	0.006	73 ± 12 [50-100]	0.04

Quantitative variables are expressed as means ± standard deviation; numbers in brackets are ranges.

Qualitative variables are expressed as raw numbers, numbers in parentheses are percentages.

FD = Fabry disease; HCM = Hypertrophic cardiomyopathy; HV = healthy volunteers; BMI = Body mass index; BSA = Body surface area; HR = Heart rate (in bpm).

Variables	FD (n=17)	HCM (n=36)	P value (FD vs. HCM)	HV (n=70)	P value (FD vs. HV)
LVEDV (mL)	150 ± 41 [104-238]	138 ± 48 [84-213]	0.25	140 ± 30 [74-216]	0.57
LVEDV_i (mL/m²)	83 ± 22 [57-110]	74 ± 25 [52-108]	0.05	78 ± 13 [49-100]	0.70
LVESV (mL)	63 ± 32 [30-166]	41 ± 39 [34-85]	<0.001	51 ± 13 [19-75]	0.27
LVESV_i (mL/m²)	35 ± 18 [17-95]	18 ± 6 [17-41]	<0.001	29 ± 6 [13-35]	0.34
LVEF (%)	59 ± 11 [30-75]	72 ± 10 [55-79]	<0.001	63 ± 5 [50-75]	0.19
LVM (g)	176 ± 79 [83-350]	179 ± 84 [67-167]	0.78	102 ± 28 [62-131]	<0.001
LVM_i (g/m²)	97 ± 41 [50-184]	95 ± 47 [38-79]	0.83	56 ± 10 [41-72]	< 0.001
Left atrial volume (mL)	88 ± 27 [43-148]	90 ± 55 [34-237]	0.34	102 ± 32 [36-150]	0.19
Maximum LV wall thickness (mm)	15 ± 6 [8-28]	20 ± 3 [14-26]	0.13	8 ± 2 [5-11]	< 0.001
LVH	9 (53%)	19 (53%)	1	0 (0%)	N.A.
Any LGE *	6/13 (46%)	25 (69%)	0.18	N.A.	N.A.
Basal infero-lateral LGE*	5/13 (38%)	3 (8%)	0.02	N.A.	N.A.
Septal LV native T1 (ms)	889 ± 61 [784-980]	995 ± 48 [935-1125]	< 0.001	965 ± 29 [910-1028]	< 0.001
Global LV native T1	891 ± 49 [794-970]	995 ± 34 [952-1086]	< 0.001	966 ± 27 [920-1042]	< 0.001
Mean infero-lateral native T1 (ms)	925 ± 48 [825-960]	1010 ± 59 [880-1115]	< 0.001	N.A.	N.A.
LGE Yes *	978 ± 22 [856-991]	1062 ± 64 [1005-1131]	N.A.	N.A.	N.A.
LGE No *	917 ± 52 [813-949]	1004 ± 56 [872-1136]	N.A.	N.A.	N.A.

Note : Quantitative variables are expressed as means ± standard deviation; numbers in brackets are ranges. Qualitative variables are expressed as raw numbers, numbers in parentheses are percentages. FD = Fabry disease; HCM = Hypertrophic cardiomyopathy; HV = Healthy volunteers; LGE = Late gadolinium enhancement; LV = Left ventricle; LVEDV = Left ventricular end diastolic volume; LVEDV_i = LVEDV indexed to body surface area; LVEF = Left ventricular ejection fraction; LVESV = Left ventricular end systolic volume; LVESV_i = LVESV indexed to body surface area; LVH = Left ventricular hypertrophy; LVM = Left ventricular mass; LVM_i = LVM indexed to body surface area; vs. = versus; N.A. = Not applicable.

* Only 14 patients of the AFD Group received an injection of gadolinium chelate, one examination was not interpretable.