T₁ Mapping with CMR Is Highly Sensitive for Fabry Disease Independent of Hypertrophy and Gender

Thompson et al: T₁ mapping with CMR in Fabry Disease

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Abstract

Background—Fabry disease (FD) is an X-linked disorder of lysosomal metabolism affecting multiple organs with cardiac disease being the leading cause of death. Current imaging evaluations of the heart are suboptimal. The goals of the current study were to evaluate the potential of quantitative T\textsubscript{1} mapping with CMR as a disease-specific imaging biomarker.

Methods and Results—31 patients with FD, 23 healthy controls and 21 subjects with concentric remodeling or hypertrophy (CR/H) underwent CMR to measure left ventricular morphology, function, delayed enhancement as well as myocardial T\textsubscript{1} values and derived parameters (extra-cellular volume fraction (ECV)). All subjects had LVEF >50\% and similar volumes. FD and CR/H had similarly increased mass, wall thickness and mass/volume as compared to controls. 16 of 31 FD subjects and 10 of 21 CR/H subjects had LVH. Non-contrast myocardial T\textsubscript{1} values were substantially lower in FD as compared to controls and CR/H (1077±43ms, 1177±34ms and 1207±33, p<0.001) but ECV was similar in all groups (21.7±2.4\%, 22.2±3.1\% and 21.8±3.9\%). Single-voxel NMR spectroscopy in 4 FD and 4 healthy control subjects showed a significant negative linear relationship between lipid content and non-contrast T\textsubscript{1} values (r=−0.9, p=0.002). Female subjects had lower LV mass and wall thickness, longer myocardial T\textsubscript{1} values and larger ECV suggesting a key gender difference in cardiac remodeling.

Conclusions—Reduced non-contrast myocardial T\textsubscript{1} values are the most sensitive and specific CMR parameter in patients with FD irrespective of gender and LV morphology and function.

Key Words: CMR, hypertrophy, Fabry disease, cardiomyopathy, T1-weighted MRI
Fabry disease (FD) is an X-linked glycolipid storage disease caused by a deficiency of alpha-galactosidase A enzyme resulting in progressive intracellular accumulation of glycosphingolipids in different tissues. Cardiac involvement is characterized by progressive left ventricular (LV) hypertrophy, heart failure, valvular heart disease and arrhythmias. Importantly, subclinical cardiac involvement may represent the first sign of organ damage, particularly in female carriers. Large-scale genetic screening studies have shown a high incidence of late-onset FD in diverse groups of patients although the phenotypic penetrance of these findings remains to be determined.

Fabry’s cardiomyopathy is one of the most common causes of death in these patients with the importance of renal disease as a cause of death in patients with FD decreasing. The assessment of myocardial lipid deposition and heart disease in patients with FD is critical as early enzyme replacement therapy is likely to delay the progression of LV hypertrophy and appearance of myocardial fibrosis, and maintains exercise capacity.

Cardiovascular magnetic resonance imaging (CMR) has emerged as a key imaging modality to provide both quantitative and qualitative assessment of cardiomyopathies and is now the gold standard imaging technique to assess myocardial anatomy, regional and global function, and tissue characterization. Adverse myocardial remodeling and left ventricular hypertrophy can result from diverse acquired and genetic etiologies with varying diagnostic, prognostic and treatment strategies. However, current imaging evaluations of the heart including left ventricular ejection fraction, hypertrophy and the presence of scar, as identified on late gadolinium enhancement, are not sensitive or specific to FD. The goals of the current study were to evaluate the potential of non-contrast myocardial T₁ (longitudinal relaxation time) mapping to identify FD independent of the presence of patterns of concentric remodeling or hypertrophy (CR/H), gender or systolic function.
Methods

Study Population

Thirty-one patients with clinical and genetically confirmed FD were recruited from the metabolic clinics in Edmonton and Calgary with eighteen patients receiving enzyme replacement therapy. A healthy control group as well as a group with increased left ventricular wall thickness but with normal end-diastolic volumes (concentric hypertrophy) were included from an ongoing study of heart failure with a preserved ejection fraction (Alberta HEART). As an integral component of the Alberta HEART study, a thorough history and physical examination, 12-lead ECG, transthoracic echocardiogram and CMR were obtained from all patients. For the healthy control group, 23 subjects with no history of cardiovascular disease or risk-factors and with a normal 12-lead ECG and transthoracic echocardiogram were selected to provide an age range and gender distribution similar to the FD group. The concentric remodeling or concentric hypertrophy group, termed the CR/H group in this study, consisted of 21 subjects with LVEF >50% and with normal end-diastolic volumes but increased ratio of left ventricular mass (M) to end-diastolic volume (V) (M/V) greater than 1.5 standard deviations than the healthy control population, for both men and women. The mean and standard deviations for M/V for male and female control subjects, which were used to define the CR/H group, were 0.71±0.07 and 0.83±0.07, respectively. All subjects were imaged with a contrast-enhanced CMR exam including quantitative T1 mapping both at baseline and following contrast agent injection. This study was approved by the University of Alberta and University of Calgary health ethics research board and informed consent was obtained from all subjects.
Magnetic Resonance Imaging

CMR was performed on 1.5T Siemens Sonata or Avanto scanners (Siemens Medical Solutions, Erlangen, Germany) with cardiac array coils for signal reception and electrocardiogram gating. Standard balanced steady-state free precession (SSFP) short-axis and long-axis cines provided full coverage of the left ventricle (echo time, TE 1.24 ms, repetition time, TR 2.89 ms, flip angle 51º, 8 mm slice thickness, 2 mm gap, matrix size 256×144, field of view 360×270 mm, 13 views per segment and 30 reconstructed cardiac phases). T₁ mapping of the left ventricle was performed in a basal and mid-ventricular short axis slice using the SAturation-recovery single-SHot Acquisition (SASHA) SSFP pulse sequence.13-15 For SASHA acquisitions, single-shot images were acquired during diastasis in sequential heartbeats, with a single non-saturation image followed by 9 images with saturation recovery times (TS) spanning the interval from the QRS to diastasis. Typical pulse sequence parameters: TE 1.39 ms, TR 2.78 ms, flip angle 70º, 8 mm slice thickness, matrix size 192×108, field of view 360×270 mm, 75% phase partial Fourier, and 9 TS values between 120-900 ms for a heart rate of 60 bpm. T₁ maps were acquired at baseline and 15 minutes after a bolus injection of 0.15 mmol/kg gadopentetate dimeglumine (Magnevist, Bayer Inc., Toronto, Canada).

Conventional late gadolinium enhancement imaging was performed 7 minutes after contrast injection using a phase sensitive inversion recovery (PSIR) sequence in the short-axis, 2-, 3-, and 4-chamber views to match the cine slice locations.

In order to evaluate the relationship between non-contrast myocardial T₁ values and myocardial glycosphingolipid accumulation, single-voxel ¹H NMR spectra were acquired in a subset of 8 FD patients and healthy controls to directly measure lipid content in the myocardium. Similar to previous ¹H NMR studies, spectra were acquired using cardiac gating with a trigger delay of 500-600 ms from the R-wave to ensure acquisition during diastasis.16,17 Acquisitions were
from 4 averages with 4 seconds of recovery between acquisitions within a single breath-hold using a PRESS (point-resolved spectroscopy) pulse sequence with dimensions of 10 × 30 × 30 mm centered on the ventricular septum (TE\textsubscript{1} = 10 ms and TE\textsubscript{2} = 14 ms).\textsuperscript{18,19} The 4 seconds of recovery between acquisitions limited the potential T\textsubscript{1}-weighting of the water reference signal by allowing >97% recovery of the signal. Acquisitions with and without water suppression were acquired in sequential breath holds.

**Data Analysis**

Quantification of left ventricular end-systolic (LVESV) and end-diastolic (LVEDV) volumes and mass were performed using in-house software\textsuperscript{20} to calculate LV ejection fraction, LVEF = (LVEDV-LVESV)/LVEDV. Papillary muscles were included in muscle volume and excluded from the left ventricular cavity volume. Mass was calculated as the LV muscle volume corrected for specific gravity of the tissue (1.05 g/ml). Mass and volumes were indexed to body surface area (BSA), and average wall thickness in diastole was indexed to height (mm/m). A corrected BSA in each subject, using ideal adjusted body weight\textsuperscript{21}, was used for the CR/H group to account for obesity in this group. Identification of left ventricular hypertrophy used indexed mass as defined by Hudsmith \textit{et al.}\textsuperscript{22}

Epicardial and endocardial contours were traced for T\textsubscript{1} analysis using custom software (MATLAB), following registration of all 10 images to correct for in-plane motion during the breath hold. The myocardial region was automatically segmented into 18 circumferential segments, referenced to the inferior right ventricular insertion point, in each of which the signal was averaged prior to fitting of signal intensity (Supplemental Figure 1). The signal intensity was fit using a two-stage Nelder-Mead simplex direct search algorithm to a three-parameter mono-
exponential recovery curve, \( S = k \times (1 - \eta \times \exp(-TS/T_1)) \), \( S \): signal intensity, \( k \): a constant, \( \eta \): saturation efficiency, \( TS \): saturation recovery times and \( T_1 \): spin-lattice relaxation time, Supplemental Figure 1). A region of interest drawn in the LV cavity was used to measure the blood \( T_1 \). In each of the 18 segments, the extracellular volume fraction (ECV), which is the volume in which gadolinium contrast agent is distributed, was estimated using the calculated concentrations of contrast agent in the blood and tissue.\(^{23}\) The contrast agent concentrations are proportional to the difference in \( 1/T_1 \) values from baseline to after contrast delivery, resulting in the standard expression: \( ECV = [1/T_1(\text{myocardium}_{\text{post}}) - 1/T_1(\text{myocardium}_{\text{pre}})] / [1/T_1(\text{blood}_{\text{post}}) - 1/T_1(\text{blood}_{\text{pre}})] \times (1-Hct) \), where Hct is blood hematocrit, measured on the same day as imaging in the current study.\(^{23}\) The contrast agent was assumed to be in equilibrium between the vascular and interstitial space by 15 minutes after injection, at the time of post-contrast \( T_1 \) measurement.\(^{24}\) All results for \( T_1 \) and derived ECV are the average of best-fit values from the 18 segments.

Statistical Analysis

All continuous variables were reported as mean ± standard deviation. Spearman’s correlation was used to determine the relationship between continuous variables. Group (FD, CR/H and control) differences were evaluated using ANOVA with post-hoc comparison of CR/H and controls as compared to the FD group. Multiple linear regressions were used to evaluate the dependence of LV mass, wall thickness/height, mass/volume, LVEF, non-contrast \( T_1 \) and ECV on group (FD, CR/H or control) and gender adjusted for age, BSA and SBP, with post-hoc analysis of group differences of CR/H and control groups as compared to the FD group. We first confirmed that our data obtained for key variables (LV mass, \( T_1 \) values and BMI) were normally distributed (Shapiro-Wilk statistic; \( p<0.05 \)), and then performed statistical analyses noted above. Statistical significance
was considered at p<0.05. All statistical analyses were performed using SPSS for Windows (SPSS Inc, Chicago, version 19).

Results

The subject characteristics in each of the healthy control, FD and CR/H groups are summarized in Table 1. There were no significant differences between the control and FD groups in gender, age, height, weight, BSA, blood pressure heart rate or hematocrit, but the CR/H group was significantly older with higher BSA and systolic blood pressures. Systolic and diastolic blood pressures in the healthy controls were 128±8 and 75±6 mmHg, respectively. Female subjects had a lower hematocrit, 0.38±0.03, as compared to men, 0.43±0.03. Importantly, diabetes and coronary artery disease were not present in the healthy control and FD groups. In contrast to the FD group, the adverse myocardial remodeling and hypertrophy in the CR/H group is likely driven by a combination of hypertension, mild obesity and diabetes mellitus (Table 1). Corrected BSA in the CR/H group, calculated using the corrected ideal body weight, was similar to control and FD group. All groups had similar end-systolic and end-diastolic volumes (p>0.05), and while LVEF was lower in the CR/H group, it was normal on average (59.8±7.2%) and >50% in all subjects, by study design (Table 2). The CR/H and FD groups had similar wall thickness/height, LV mass, indexed mass and M/V. As compared to the FD group, the control group had significantly lower LV mass, indexed mass, wall thickness and M/V (p<0.001 for all). 5 of 16 female subjects and 11 of 15 male FD subjects were positive for LVH (Table 2). Similarly, 3 of 9 female and 7 of 12 male CR/H subjects were positive for LVH, while no control subjects were positive. The mean and standard deviations for M/V for male and female control subjects, which were used to define the CR/H group, were 0.71±0.07 and 0.83±0.07, respectively.
$T_1$ mapping showed significantly reduced baseline (non-contrast) myocardial $T_1$ values in FD subjects (1070±50 ms) compared to the control (1177±27 ms) and CR/H groups (1207±33 ms), $p<0.001$ for both comparisons (Table 3). Baseline $T_1$ values were increased in CR/H compared to controls ($p<0.05$). However, all other $T_1$ values, including baseline blood $T_1$ values, and both blood and myocardial $T_1$ values post-contrast, were similar in all three groups ($p>0.05$). The derived ECV values were also similar in all three groups (controls 22.2±3.1%, FD 21.7±3.0%, CR/H 21.8±3.9%, $p>0.05$). Sample baseline $T_1$ pixel maps from each group highlights the globally reduced $T_1$ values in the FD patients compared to both control and CR/H patients (Figure 1). The histograms of $T_1$ values from within the indicated septal regions of interest further highlight the distinctly reduced $T_1$ values in FD group as compared to the other groups, with minimal overlap in values even when individual pixels are represented.

The average baseline myocardial $T_1$ values in all individual subjects by group is shown in Figure 2A. In the FD group, the average percentage of myocardial mass that was positive for late gadolinium enhancement was 6.0±4.2%, with 13 out of 29 studies positive (45%), with the most common location being the basal lateral wall. There were no wall motion abnormalities associated with regions that were positive for late gadolinium enhancement in the FD group. Late enhancement studies were not performed in 2 subjects due to poor kidney function precluding the use of contrast agents. In the CR/H group, 7 of 21 subjects (33%) were positive for late gadolinium enhancement. Figure 2B shows a late gadolinium enhancement image from a FD subject illustrating a pronounced region of gadolinium enhancement in the lateral wall, with the corresponding non-contrast $T_1$ map indicating increased $T_1$ values in this region (Figure 2C). Consistent with previous studies, $T_1$ values from regions of late enhancement showed significantly
increased T$_1$ values, as compared to remote myocardium (Figure 2D).$^{25}$ All myocardial regions that were positive for late enhancement in FD and CR/H subjects were excluded from T$_1$ analysis.

We hypothesize that the reduced T$_1$ values in FD can be causally linked to increased myocardial glycosphingolipid accumulation. $^1$H NMR spectroscopy experiments were performed on 4 FD and 4 healthy control subjects, with representative water and water-suppressed lipid spectra shown in Figure 3A and 3B, respectively. The $^1$H NMR findings for all 8 subjects showed a significant linear relationship between lipid content, expressed as a percentage of the water peak, and the myocardial T$_1$ values (Figure 3C). The BMIs of the spectroscopy subgroups were in the normal healthy range and similar between the groups (ranging from 22 to 25.5 kg/m$^2$). The reported T$_1$ values are the average of recordings from the septum from each subject, to match the region covered by the single voxel $^1$H acquisition.

Figure 4 summarizes the group and gender differences for several parameters using two-way ANOVA analysis with group and gender as fixed factors. There was no significant interaction between group and gender for any of the parameters. Left ventricular mass and wall thickness were larger in male subjects and in FD subjects as compared to controls (p<0.001), but was similar in CR/H and FD subjects (Figure 4A and B). Similarly, M/V was larger in the male subjects (p=0.017) and in FD subjects as compared to controls (p<0.001), but similar in CR/H and FD subjects (Figure 4C). LVEF was significantly smaller in male subjects and in the male CR/H group (Figure 4D). Baseline myocardial T$_1$ values were reduced in FD independent of gender as compared to both control and CR/H groups, but were also lower in men as compared to women (p<0.001), with a mean difference of 32.7 ms between genders (Figure 4E). Finally, ECV was similar in all three groups, but significantly lower in men as compared to women ($20.7\pm3.2\%$ vs. $23.1\pm3.0\%$, p<0.001; Figure 4F). Gender differences in non-contrast T$_1$ and ECV were
independent of wall thickness. Finally, non-contrast blood $T_1$ values were significantly larger in women as compared to men (1711±135 ms vs. 1560±121 ms).

Figures 5A and 5B show the non-contrast $T_1$ values in the female and male subjects, respectively, in each of the three groups, as a function of age. The solid lines in each figure show the threshold $T_1$ value that best separates the FD group from the healthy control and CR/H groups, with cut off values of 1146 ms for the female group and 1120 ms for the male group, which provides complete separation of the FD group for both genders. Incidence of late enhancement in FD was 45% (13/29) was similar to the rates in CR/H (33%) (7/21), and thus does not offer good discrimination of these groups. By study design, the FD and CR/H groups have similar distributions of LVH, 16/31 of FD subjects (52%) and 10/21 of CR/H subjects (48%).

Discussion

Novel imaging modalities continue to improve our diagnostic and prognostic ability in patients with cardiovascular disease. CMR has emerged as the gold standard imaging technique to assess myocardial anatomy, regional and global function, and tissue characterization. Importantly, CMR has the ability to differentiate and diagnose different types of cardiomyopathies thereby influencing clinical decision making and therapeutic applications. Fabry disease is characterized by typically preserved LVEF, variable and gender dependence of LVH, and moderate prevalence of late gadolinium enhancement. Longitudinal strain has been shown to be reduced in FD, even with preserved LVEF, but a similar relationship is also observed in other types of hypertrophic cardiomyopathy. Contrast enhanced $T_1$ mapping with CMR, for the calculation of myocardial ECV, provides novel disease-specific information, however with limited added value in FD, where ECV is similar to healthy subjects. The finding of normal ECV in the current
study and recent work by Sado et al\textsuperscript{23} is consistent with a previous autopsy study in three FD subjects, which shows limited fibrosis in the septum.\textsuperscript{34}

The major finding of the current study is the significantly reduced non-contrast T\textsubscript{1} values in the FD group compared to healthy subjects and a group of patients with similar patterns of concentric remodeling or concentric hypertrophy. Our results are in good general agreement with Sado et al, who recently showed similar discrimination of FD patients from several other conditions with similar patterns of LV hypertrophy using non-contrast T\textsubscript{1} mapping of the myocardium with CMR.\textsuperscript{33} T\textsubscript{1} mapping using CMR without gadolinium contrast is particularly attractive for FD due to the co-existence of advanced renal disease failure in these patients which often precludes the use of contrast. The use of CMR with non-contrast T\textsubscript{1} mapping shows the potential to be used as a diagnostic tool in patients with unexplained LV hypertrophy to screen for FD. T\textsubscript{1} mapping can also serve as a useful non-invasive monitoring tool since the early initiation of enzyme replacement therapy in patients with FD can prevent long-term adverse remodeling.\textsuperscript{8}

The reduced non-contrast myocardial T\textsubscript{1} values in FD are potentially the consequence of increased glycosphingolipid concentration in the myocardium, where lipids have characteristically lower T\textsubscript{1} values, \textasciitilde250 ms at 1.5T, which would thus reduce the apparent tissue T\textsubscript{1} values. In support of this lipid hypothesis, significantly increased myocardial lipid content was directly measured in a subset of FD patients (2.6±0.9\%), as compared to healthy age-matched controls (0.7±0.3\%), and with correspondingly reduced non-contrast T\textsubscript{1} values in the FD group (1037±15 ms versus 1161±20 ms in healthy subjects). The healthy subject lipid content is similar to a previous study.\textsuperscript{17} Pathology studies have shown relatively high myocardial concentrations of the glycolipid, ceramide trihexoside (CTH) of 11.5 to 16.5 mg/g of tissue (up to 1.5\% lipid by weight) in patients with FD.\textsuperscript{35} These CTH concentrations, in combination with normal triglycerides and
phospholipids are in line with the elevated total lipid values found in the current study. In contrast to our findings, a previous $^1$H NMR study of FD measured myocardial lipids in comparison to healthy controls and showed no increase in the lipid to water ratio.$^{36}$ Given these findings, and our relatively small number of subjects from which lipid spectra were acquired, larger future studies are needed to determine a definitive relationship between lipid content and non-contrast T$_1$ values.

Previous reports of reduced non-contrast T$_1$ values in disease-specific states are limited to the Sado et al. study of FD$^{33}$ and a recent study of patients with thalassemia.$^{37}$ The opposite trend, of increased non-contrast T$_1$ values with heart disease, has been shown in acute myocardial edema$^{38}$, with injury in myocardial infarction$^{39}$ and identification of the area at risk$^{40}$, where increased values are associated with increased water mobility, and thus represent a distinct mechanism from the reduced T$_1$ values in the current study. While reduced post-contrast T$_1$ values have been reported in heart failure$^{41}$ and diabetes$^{42}$, these contrast-enhanced T$_1$ values are a surrogate for increased ECV in these populations and are not directly related to non-contrast T$_1$ values. Previous non-contrast T$_1$ values of 1175.2±27.6 ms$^{13}$ in healthy subjects, measured with the same SASHA T$_1$ mapping method used in the current study, are in close agreement the control group values reported here (1177±27 ms). However, a wide range of values have been reported with other T$_1$ mapping methods. Wacker et al measured non-contrast T$_1$ values of 1219 ms with a saturation-recovery approach similar to the SASHA method$^{43}$, while the commonly used MOLLI family of pulse sequence has reported values ranging from 939 to 1029 ms at 1.5 T.$^{11, 24, 38, 44-48}$ A previous direct comparison of MOLLI and SASHA methods in 10 healthy subjects yielded non-contrast T$_1$ values that match this trend, with MOLLI values of 935.5±24.9 ms and SASHA values of 1175.2±27.6 ms, respectively.$^{13}$ Sado et al recently reported uniformly lower non-contrast T1 values of 968±27.6 ms in healthy subjects and 858±27.6 ms in FD$^{33}$ as compared to our currently
reported T₁ values. Importantly, they reported absolute mean differences between FD and healthy controls 110 ms which is similar to our reported mean difference of 107 ms.

The findings of normal ECV in FD as compared to the healthy control group are in agreement with a recent study by Sado et al, suggesting no diffuse fibrosis, and in agreement with an autopsy study from three FD patients showing normal fibrotic burden in the septum. However, if increased lipid content is the source of the reduced non-contrast T₁ values in FD, then the conventional equations that relate contrast-agent concentration at baseline and post-contrast delivery to ECV, which are based on a single pool T₁ values, may not be accurate for FD. Regions of late gadolinium enhancement were excluded from T₁ analysis to avoid contamination by the longer T₁ values measured in these regions. The burden of LGE of 6% is similar to previously reported values in FD and the prevalence of 45% was also similar to previous studies. We also showed a gender dependence of non-contrast myocardial T₁ and ECV. The lower non-contrast T₁ values measured in male as compared to female subjects, 32.6 ms lower on average, are similar to the recent findings of Piechnik et al, although they found that the gender differences were not significant in older subjects (>45 years). When age was included as a co-factor in the multiple regression analysis, the gender dependence of non-contrast T₁ remained significant (p=0.002). The lower myocardial ECV values in male subjects as compared to female subjects (20.7±3.2% versus 23.1±3.0%, p<0.001) are similar, in the magnitude of their difference, to a recent T₁ mapping study. Importantly, gender differences in ECV and non-contrast T₁ were also independent of wall thickness, hematocrit, height, weight and heart rate with significant gender differences when each of these was included as a co-factor. The larger non-contrast blood T₁ values in women as compared to men is similar to previous reports, with similar differences in T₁ values, and is likely a consequence of the lower hematocrit in the female (0.38±0.03) as
compared to male (0.43±0.03) subjects. The characterization of gender differences in T1 mapping values is important given the different presentation of FD in men and women. While FD is an X-linked disease, female carriers also show significant heart disease with a different type of remodeling compared to males.2, 27, 51 Indeed, genetic testing is currently recommended as essential for the diagnosis of FD in women51, and our findings imply that a CMR with T1 mapping is likely to add further diagnostic potential while also providing useful information on cardiac structure and function.

Our study is limited by the relative small and diverse group of CR/H subjects. The excellent sensitivity and specificity of non-contrast T1 values for the identification of FD was defined only in comparison to this group, and thus there is potential for T1 overlap with other patient groups not represented here. Since healthy controls were not evaluated with clinical biochemical testing, we cannot be entirely certain as to the absence of diabetes or dyslipidemia. However, the recent FD study by Sado et al showed similar discriminatory capability of non-contrast T1 mapping in comparison to larger well-defined disease groups with LV hypertrophy.33 Future studies should also consider the specificity of these findings in other patient populations in which myocardial lipid content maybe altered such as obesity and diabetes.52 However, our study revealed no relationship between either BSA or the presence of diabetes and non-contrast T1 in the CR/H group and within the CR/H group, myocardial T1 values in the 8 diabetic patients (1211±40 ms) were similar to non-diabetic subjects (1204±29 ms). The current study is also potentially limited by incomplete coverage of the heart with T1 mapping, with all data reported as the average from two short-axis slices from the mid and basal locations. However, all of our data indicates the reduced T1 values in FD are spatially uniform in these two slices, excluding regions positive for late gadolinium enhancement, and thus the detection of disease does not appear to be limited by
spatial coverage. The absence of contrast enhancement in the septum in all cases confirms it as a standardized location for measurement of $T_1$. In conclusion, non-contrast $T_1$ mapping offers a novel imaging test for the detection of FD, and potentially for monitoring response to enzyme replacement therapy. $T_1$ mapping pulses sequences such as the SASHA method reported in the current study, or alternatively the MOLLI sequence, similarly can measure $T_1$ within a single breath-hold per slice, and thus are readily appended to a standard clinical CMR exam, without the requirement of contrast agents.

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Disclosures

None.

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Table 1. Subject Characteristics

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†p < 0.05 for ANOVA. *p<0.01 compared to FD subjects from post-hoc analysis. BSA value in brackets is the corrected BSA for ideal body weight, to account for obesity. SBP=systolic blood pressure; DBP=diastolic blood pressure; MABP=mean arterial blood pressure; CAD=coronary artery disease. $CAD was defined by the presence of angina, history of previous myocardial infarction and/or presence of Q-waves on the 12-lead ECG consistent with a previous MI.
Table 2. Left Ventricular Morphology

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<th></th>
<th>Controls</th>
<th>FD</th>
<th>CR/H</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEDV (ml/m²)</td>
<td>75.4±13.1</td>
<td>75.9±16.1</td>
<td>78.9±18.1</td>
</tr>
<tr>
<td>LVESV (ml/m²) †</td>
<td>27.1±5.7</td>
<td>29.3±7.4</td>
<td>31.9±10.1</td>
</tr>
<tr>
<td>LVSV (ml)</td>
<td>87.9±19.5</td>
<td>92.4±24.1</td>
<td>87.1±21.9</td>
</tr>
<tr>
<td>LVEF (%) †</td>
<td>63.8±4.2</td>
<td>66.8±5.3</td>
<td>59.8±7.2***</td>
</tr>
<tr>
<td>LV Mass (g) †</td>
<td>110.4±30.6***</td>
<td>159.8±55.2</td>
<td>147.0±35.2</td>
</tr>
<tr>
<td>LV Mass (g/m²) †</td>
<td>59.9±14.3***</td>
<td>87.5±27.9</td>
<td>78.5±14.7</td>
</tr>
<tr>
<td>Mass/LVEDV (g/ml)†</td>
<td>0.77±0.10***</td>
<td>1.18±0.41</td>
<td>1.02±0.19</td>
</tr>
<tr>
<td>Wall Thickness (mm) †</td>
<td>7.6±1.3***</td>
<td>10.1±2.1</td>
<td>9.9±1.4</td>
</tr>
<tr>
<td>Wall Thickness / Height (mm/m) †</td>
<td>4.4±0.6***</td>
<td>6.0±1.2</td>
<td>5.8±0.7</td>
</tr>
<tr>
<td>LVH (male/female) †</td>
<td>0/0</td>
<td>11/5</td>
<td>7/3</td>
</tr>
</tbody>
</table>

†p < 0.05 for ANOVA. *p<0.05, **p<0.01 and ***p<0.001 compared to FD subjects from post-hoc analysis. Indexed values for CR/H group are using the ideal body weight BSA.

Table 3. Myocardial T₁ and Extra Cellular Volume

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>FD</th>
<th>CR/H</th>
</tr>
</thead>
<tbody>
<tr>
<td>T₁ Baseline (Myo) (ms) †</td>
<td>1177±27***</td>
<td>1070±50</td>
<td>1207±33***</td>
</tr>
<tr>
<td>T₁ Baseline (Blood) (ms)</td>
<td>1624±96</td>
<td>1620±192</td>
<td>1643±164</td>
</tr>
<tr>
<td>T₁ Post Contrast (Myo) (ms)</td>
<td>559±51</td>
<td>541±42</td>
<td>537±45</td>
</tr>
<tr>
<td>T₁ Post Contrast (Blood) (ms)</td>
<td>331±45</td>
<td>314±51</td>
<td>294±42</td>
</tr>
<tr>
<td>Lambda</td>
<td>38.9±4.4</td>
<td>35.4±4.4</td>
<td>37.1±5.8</td>
</tr>
<tr>
<td>ECV (%)</td>
<td>22.2±3.1</td>
<td>21.7±3.0</td>
<td>21.8±3.9</td>
</tr>
</tbody>
</table>

†p < 0.05 for ANOVA. *p<0.05, **p<0.01 and ***p<0.001 compared FD subjects from post-hoc analysis.
Figure Legends

Figure 1. Sample baseline (pre-contrast) T₁ pixel maps in control, FD and CR/H subjects are shown in B). The corresponding non-saturated image from the SASHA acquisition is shown in A). Histograms of pixel T₁ values, from the septal regions indicated on the pixel maps, are shown in C). FD histograms are overlaid (dashed lines) on control and CR/H groups to highlight the differences in T₁ values. FD=Fabry disease and CR/H=concentric remodeling or hypertrophy.

Figure 2. A) Baseline myocardial T₁ values in all subjects by group. T₁ is different between groups (p<0.001, ANOVA) and all groups have significantly different T₁ values on post-hoc analysis (p<0.001 between FD and control, p<0.001 between FD and CR/H and p = 0.01 between control and CR/H). Late gadolinium enhancement image of a FD subject with late gadolinium enhancement in the lateral wall (B) and the corresponding baseline myocardial T₁ map (C), showing increased T₁ values in the late enhancement region, as visualized with the T₁ histogram (D). FD=Fabry disease and CR/H=concentric remodeling or hypertrophy.

Figure 3. Representative water and water suppressed ¹H NMR spectra from healthy control (A) and Fabry disease (B) subjects. Water suppressed spectra are shown in the insets, showing the lipid peak in the range of 1.3-1.7 ppm. The ratio of the lipid peak area to water peak area is 0.5% for the healthy subject and 3.0% for the Fabry disease subject. Comparison of baseline myocardial T₁ values with the myocardial lipid to water ratio in 4 healthy controls and 4 Fabry disease subjects, showing a significant correlation between lipid content and reduced T₁ values (r=-0.9, p=0.002) (C). NMR=nuclear magnetic resonance spectroscopy.
Figure 4. Gender and group (control, FD, CR/H) comparisons of A) LV mass, B) LV wall thickness corrected for height, C) M/V, D) LVEF, E) baseline myocardial T1 and F) myocardial ECV. P values for ANOVA are shown in each figure with along with post-hoc differences from the FD group. There was no significant interaction between group and gender for all results (p>0.1). *p<0.001 post-hoc comparison with the FD group. FD=Fabry disease, CR/H=concentric remodeling or hypertrophy, M/V=LV mass corrected for volume, LVEF=LV ejection fraction and ECV=extracellular volume.

Figure 5. Scatter plots show the baseline myocardial T1 values in all three groups (control, FD, CR/H) as a function of age, separately for female (A) and male (B) subjects. The solid horizontal line on each figure shows the cut off T1 value that optimally separate the FD group from the healthy control and CR/H groups. FD=Fabry disease, CR/H=concentric remodeling or hypertrophy.
T₁ Mapping with CMR Is Highly Sensitive for Fabry Disease Independent of Hypertrophy and Gender
Richard B. Thompson, Kelvin Chow, Aneal Khan, Alicia Chan, Miriam Shanks, Ian Paterson and Gavin Y. Oudit

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Supplemental Material

\[ T_1 \text{ mapping with CMR is highly sensitive for Fabry disease independent of hypertrophy and gender} \]

Richard B. Thompson PhD, Kelvin Chow, Aneal Khan MSc, MD, Alicia Chan MD, Miriam Shanks MD, Ian Paterson MD, Gavin Y. Oudit MD, PhD
Supplementary Figure 1. SASHA T₁ mapping method. On each of 10 saturation recovery images, the endocardium, epicardium and a region of interest in the blood are identified. The myocardium is divided into 18 circumferential segments and T₁ values are calculated in each segment by fitting a saturation recovery curve. S is the measured signal intensity normalized to the non-saturated image intensity, η is the best-fit saturation efficiency, TS are saturation recovery times and T₁ is the best fit T₁ value. Sample saturation recovery data from 18 myocardial segments and a blood pool region are shown from a FD patient.