Fabry disease (FD) is an X-linked glycolipid storage disease caused by a deficiency of α-galactosidase A enzyme resulting in progressive intracellular accumulation of glycosphingolipids in different tissues. Cardiac involvement is characterized by progressive left ventricular hypertrophy (LVH), 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 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 because early enzyme replacement therapy is likely to delay the progression of LVH and appearance of myocardial fibrosis and maintains exercise capacity.

Cardiovascular MRI (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 LVH can result from diverse acquired and genetic pathogeneses with varying diagnostic, prognostic, and treatment strategies. However, current imaging evaluations of the heart, including LV ejection fraction (LVEF), LVH, and the presence of scar, as identified on late gadolinium enhancement (LGE), are not sensitive or specific to FD. The goals of the current study are to evaluate the potential of noncontrast myocardial $T_1$ (longitudinal relaxation time) mapping to identify FD independent of the presence of patterns of concentric remodeling or hypertrophy (CR/H), sex, or systolic function.

**Key Words:** CMR • hypertrophy • Fabry disease • cardiomyopathies

Clinical Perspective on p 645

© 2013 American Heart Association, Inc.

Circ Cardiovasc Imaging is available at http://circimaging.ahajournals.org

DOI: 10.1161/CIRCIMAGING.113.000482

637
Methods

Study Population
Thirty-one patients with clinically and genetically confirmed FD were recruited from the metabolic clinics in Edmonton and Calgary with 18 patients receiving enzyme replacement therapy. A healthy control group, as well as a group with increased LV wall thickness but with normal end-diastolic volumes (concentric hypertrophy), was included from an ongoing study of heart failure with a preserved EF (Alberta Heart Failure Etiology and Analysis Research Team [HEART]). As an integral component of the Alberta HEART study, a thorough history and physical examination, 12-lead ECG, trans-thoracic 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 trans-thoracic echocardiogram were selected to provide an age range and sex distribution similar to the FD group. The CR/H group consisted of 21 subjects with LVEF >50% and with normal end-diastolic volumes but increased ratio of LV mass (M) to end-diastolic volume (V; M/V) >1.5 SD than the healthy control population, for both men and women. The mean and SD 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 examination, including quantitative T1 mapping, both at baseline and after 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.

MRI
CMR was performed on 1.5T Siemens Sonata or Avanto scanners (Siemens Medical Solutions, Erlangen, Germany) with cardiac array coils for signal reception and ECG gating. Standard balanced steady-state–free precession short-axis and long-axis cines provided full coverage of the left ventricle (echo time [TE], 1.24 ms; repetition time, 2.89 ms; flip angle, 51°; 8-mm slice thickness; 2-mm gap; matrix size, 256x144; field of view, 360x270 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 SAuration-recovery single-Shot Acquisition (SASHA) steady-state–free precession pulse sequence.\cite{15-17} For SASHA acquisitions, single-shot images were acquired during diastasis in sequential heartbeats, with a single nonsaturation 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; repetition time, 2.78 ms; flip angle, 70°; 8-mm slice thickness; matrix size, 192x108; field of view, 360x270 mm; 75% phase partial Fourier; and 9 TS values between 120 and 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 LGE imaging was performed 7 minutes after contrast injection using a phase sensitive inversion recovery sequence in the short-axis, 2-, 3-, and 4-chamber views to match the cine slice locations.

To evaluate the relationship between noncontrast myocardial T1 values and myocardial glycosphingolipid accumulation, single-voxel 1H NMR spectra were acquired in a subset of 8 patients with FD and healthy controls to measure lipid content directly in the myocardium. Similar to previous 1H NMR studies, spectra were acquired using cardiac gating with a trigger delay of 500 to 600 ms from the R wave to ensure acquisition during diastasis.\cite{16,17} Acquisitions were from 4 averages with 4 seconds of recovery between acquisitions with a single breath hold using a point-resolved spectroscopy pulse sequence with dimensions of 10x30x30 mm centered on the ventricular septum (TE =10 ms and TE =14 ms).\cite{18,19} The 4 seconds of recovery between acquisitions limited the potential T1-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 LV end-systolic and end-diastolic volumes and mass was performed using in-house software\cite{20} to calculate LVEF=[LV end-diastolic volume–LV end-systolic volume]/LV end-diastolic volume. Papillary muscles were included in muscle volume and excluded from the LV 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,\cite{21} was used for the CR/H group to account for obesity in this group. Identification of LV wall thickness indexed to height was performed by Handelsman.\cite{22}

Epicaldian and endocardial contours were traced for T1 analysis using custom software (MATLAB) after 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 before fitting of signal intensity (Figure 1 in the online-only Data Supplement). The signal intensity was fit using a 2-stage Nelder–Mead simplex direct search algorithm to a 3-parameter monoeponential recovery curve, S=So×(1−exp(−TS/T1)), where S denotes signal intensity, k denotes a constant, η denotes saturation efficiency, TS denotes saturation recovery times, and T1 denotes spin-lattice relaxation time (Figure 1 in the online-only Data Supplement). A region of interest drawn in the LV cavity was used to measure the blood T1. In each of the 18 segments, the extracellular volume (ECV) fraction, 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.\cite{23} The contrast agent concentrations were proportional to the difference in 1/T1 values from baseline to after contrast delivery, resulting in the standard expression: ECV=[1/T1(myocardium−pre)−1/T1(myocardium−post)]/[1/T1(blood−post)−1/T1(blood−pre)]; where Hct denotes blood hematocrit, measured on the same day as imaging in the current study.\cite{24} The contrast agent was assumed to be in equilibrium between the vascular and interstitial space by 15 minutes after injection, at the time of postcontrast T1 measurement.\cite{25} All results for T1 and derived ECV were the average of best-fit values from the 18 segments.

Statistical Analysis
All continuous variables were reported as mean±SD. Spearman 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 with the FD group. Multiple linear regressions were used to evaluate the dependence of LV mass, wall thickness/height, mass/volume, LVEF, noncontrast T1, and ECV on group (FD, CR/H, or control) and sex adjusted for age, BSA, and systolic blood pressure, with post hoc analysis of group differences of CR/H and control groups as compared with the FD group. We first confirmed that our data obtained for key variables (LV mass, T1 values, and body mass index) 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 (version 19; SPSS Inc, Chicago, IL).

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 the FD groups in sex, 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 with men, 0.43±0.03. Importantly, diabetes mellitus and coronary artery disease were not present in
CAD was defined by the presence of angina, history of previous myocardial infarction and presence of Q-waves on the 12-lead ECG consistent with a previous MI. BMI indicates body mass index; BSA, body surface area; CAD, coronary artery disease; CR/H, concentric remodeling or hypertrophy; DBP, diastolic blood pressure; FD, Fabry disease; MABP, mean arterial blood pressure; MI, myocardial infarction; and SBP, systolic blood pressure.

### Table 1. Subject Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>FD</th>
<th>CR/H</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects (men/women)</td>
<td>23 (11/12)</td>
<td>31 (15/16)</td>
<td>21 (12/9)</td>
</tr>
<tr>
<td>Age, y†</td>
<td>42±15</td>
<td>41±12</td>
<td>64±11*</td>
</tr>
<tr>
<td>Height, m</td>
<td>1.70±0.09</td>
<td>1.70±0.10</td>
<td>1.70±0.09</td>
</tr>
<tr>
<td>Weight, kg†</td>
<td>71.5±15.5</td>
<td>70.2±13.4</td>
<td>88.3±19.0*</td>
</tr>
<tr>
<td>BSA, m²†</td>
<td>1.84±0.23</td>
<td>1.82±0.19</td>
<td>2.06±0.25*</td>
</tr>
<tr>
<td>BMI, kg/m²†</td>
<td>24.4±4.8</td>
<td>24.7±5.4</td>
<td>30.6±5.9*</td>
</tr>
<tr>
<td>SBP, mmHg‡</td>
<td>122±9</td>
<td>113±15</td>
<td>140±19*</td>
</tr>
<tr>
<td>DBP, mmHg‡</td>
<td>78±11</td>
<td>70±10</td>
<td>76±15</td>
</tr>
<tr>
<td>MABP, mmHg‡</td>
<td>93±10</td>
<td>84±12</td>
<td>97±14</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>64±7</td>
<td>63±10</td>
<td>63±10</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>0.42±0.04</td>
<td>0.39±0.04</td>
<td>0.41±0.05</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>0/23</td>
<td>0/31</td>
<td>8/21</td>
</tr>
<tr>
<td>CAD</td>
<td>0/23</td>
<td>0/31</td>
<td>4/21</td>
</tr>
</tbody>
</table>

*P<0.01 compared with FD subjects from post hoc analysis. BSA value in brackets is the corrected BSA for ideal body weight, to account for obesity.
†P<0.05 for ANOVA.

In the healthy control and FD groups. In contrast to the FD group, the adverse myocardial remodeling and hypertrophy in the CR/H group was 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 with the FD group, the control group had significantly lower LV mass, indexed mass, wall thickness, and M/V (P<0.001 for all). A total of 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, whereas no control subjects were positive. The mean and SDs 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.

The average baseline myocardial T1 values in all individual subjects by group are shown in Figure 2A. In the FD group, the average percentage of myocardial mass that was positive for LGE was 6.0±4.2%, with 13 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 LGE in the FD group. Late enhancement studies were not performed in 2 subjects because of poor kidney function precluding the use of contrast agents. In the CR/H group, 7 of 21 subjects (33%) were positive for LGE. Figure 2B shows a LGE image from a FD subject illustrating a pronounced region of gadolinium enhancement in the lateral wall, with the corresponding noncontrast T1 map indicating increased T1 values in this region (Figure 2C). Consistent with previous studies, T1 values from regions of late enhancement showed significantly increased T1 values, as compared with remote myocardium (Figure 2D). All myocardial regions that were positive for late enhancement in FD and CR/H subjects were excluded from T1 analysis.

### Table 2. Left Ventricular Morphology

<table>
<thead>
<tr>
<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>LVSW, 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 (men/women)†</td>
<td>0/0</td>
<td>11/5</td>
<td>7/3</td>
</tr>
</tbody>
</table>

BSA indicates body surface area; CR/H, concentric remodeling or hypertrophy; CAD, coronary artery disease; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVH, left ventricular hypertrophy; and LVSW, left ventricular stroke volume.

histograms of T1 values from within the indicated septal regions of interest further highlighted the distinctly reduced T1 values in FD group as compared with the other groups with minimal overlap in values even when individual pixels were represented.

The average baseline myocardial T1 values in all individual subjects by group are shown in Figure 2A. In the FD group, the average percentage of myocardial mass that was positive for LGE was 6.0±4.2%, with 13 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 LGE in the FD group. Late enhancement studies were not performed in 2 subjects because of poor kidney function precluding the use of contrast agents. In the CR/H group, 7 of 21 subjects (33%) were positive for LGE. Figure 2B shows a LGE image from a FD subject illustrating a pronounced region of gadolinium enhancement in the lateral wall, with the corresponding noncontrast T1 map indicating increased T1 values in this region (Figure 2C). Consistent with previous studies, T1 values from regions of late enhancement showed significantly increased T1 values, as compared with remote myocardium (Figure 2D). All myocardial regions that were positive for late enhancement in FD and CR/H subjects were excluded from T1 analysis.

### Table 3. Myocardial T1 and ECV

<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 postcontrast (myo), ms‡</td>
<td>559±51</td>
<td>541±42</td>
<td>537±45</td>
</tr>
<tr>
<td>T1 postcontrast (blood), ms‡</td>
<td>331±45</td>
<td>314±51</td>
<td>294±42</td>
</tr>
<tr>
<td>λ</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>

CR/H indicates concentric remodeling or hypertrophy; ECV, extracellular volume; and FD, Fabry disease.

*P<0.05, **P<0.01, and ***P<0.001 compared with FD subjects from post hoc analysis. †P<0.05 for ANOVA.
We hypothesize that the reduced T₁ values in FD can be causally linked to increased myocardial glycosphingolipid accumulation. ¹H 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 ¹H NMR findings for all 8 subjects showed a significant linear relationship between lipid content, expressed as a percentage of the water peak, and

![Figure 1](http://circimaging.ahajournals.org/)

Figure 1. A. Sample baseline (precontrast) T₁ pixel maps in control, Fabry disease (FD), and concentric remodeling or hypertrophy (CR/H) subjects. B. The corresponding nonsaturated image from the SATuration-recovery single-Shot Acquisition. C. Histograms of pixel T₁ values, from the septal regions indicated on the pixel maps. FD histograms are overlaid (dashed lines) on control and CR/H groups to highlight the differences in T₁ values.

![Figure 2](http://circimaging.ahajournals.org/)

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 Fabry disease [FD] and control; P<0.001 between FD and concentric remodeling or hypertrophy [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).
the myocardial $T_1$ values (Figure 3C). The body mass indexes 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 sex differences for several parameters using 2-way ANOVA analysis with group and sex as fixed factors. There was no significant interaction between group and sex for any of the parameters. LV mass and wall thickness were larger in male subjects and in FD subjects as compared with controls ($P<0.001$), but was similar in CR/H and FD subjects (Figure 4A and 4B). Similarly, $M/V$ was larger in the male subjects ($P=0.017$) and in FD subjects as compared with 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 sex as compared with both control and CR/H groups, but were also lower in men as compared with women ($P<0.001$), with a mean difference of 32.7 ms between sexes (Figure 4E). Finally, ECV was similar in all 3 groups but significantly lower in women as compared with men ($20.7\pm3.2\%$ versus $23.1\pm3.0\%; P<0.001$; Figure 4F). Sex differences in non-contrast $T_1$ and ECV were independent of wall thickness. Finally, noncontrast blood $T_1$ values were significantly larger in women as compared with men ($1711\pm135$ versus $1560\pm121$ ms).

Figure 5A and 5B shows the noncontrast $T_1$ values in the female and male subjects, respectively, in each of the 3 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 cutoff 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 sexes. Incidence of late enhancement in FD was 45% (13/29) that was similar to the rates in CR/H (33%; 7/21) and thus does not allow 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.10–12,26 Importantly, CMR has the ability to differentiate and diagnose different types of cardiomyopathies, thereby influencing clinical decision making and therapeutic applications. FD is characterized by typically preserved LVEF, variable and sex dependence of LVH,27 and moderate prevalence of LGE.28,29 Longitudinal strain has been shown to be reduced in FD, even with preserved LVEF,30 but a similar relationship is also observed in other types of hypertrophic cardiomyopathy.30 Contrast-enhanced $T_1$ mapping with CMR, for the calculation of myocardial ECV, provides novel disease-specific information,31,32 however, with limited added value in FD, where ECV is similar to healthy subjects.33 The
finding of normal ECV in the current study and recent work by Sado et al.\textsuperscript{33} is consistent with a previous autopsy study in 3 FD subjects, which shows limited fibrosis in the septum.\textsuperscript{34} The major finding of the current study is the significantly reduced noncontrast T1 values in the FD group compared with healthy subjects and a group of patients with similar patterns of LVH. Our results are in good general agreement with Sado et al.,\textsuperscript{33} who recently showed similar discrimination of patients with FD from several other conditions with similar patterns of LVH using noncontrast T1 mapping of the myocardium with CMR. T1 mapping using CMR without gadolinium contrast is particularly attractive for FD because of the coexistence of advanced renal disease in these patients which often precludes the use of contrast. The use of CMR with noncontrast T1 mapping shows the potential to be used as a diagnostic tool in patients with unexplained LVH to screen for FD. T1 mapping can also serve as a useful noninvasive monitoring tool because the early initiation of enzyme replacement therapy in patients with FD can prevent long-term adverse remodeling.\textsuperscript{8}

The reduced noncontrast myocardial T1 values in FD are potentially the consequence of increased glycosphingolipid concentration in the myocardium, where lipids have...
characteristically lower $T_1$ values, ≈250 ms at 1.5T, which would thus reduce the apparent tissue $T_1$ values. In support of this lipid hypothesis, significantly increased myocardial lipid content is directly measured in a subset of patients with FD (2.6±0.9%), as compared with healthy age-matched controls (0.7±0.3%), and with correspondingly reduced noncontrast $T_1$ values in the FD group (1037±15 versus 1161±20 ms in healthy subjects). The healthy subject lipid content is similar to a previous study. Pathology studies have shown relatively high myocardial concentrations of the glycolipid, ceramide trihexoside (CTH) of 11.5 to 16.5 mg/g of tissue (≤1.5% lipid by weight) in patients with FD. 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 1H NMR study of FD measures myocardial lipids in comparison with healthy controls and shows no increase in the lipid-to-water ratio. Given these findings, and our relatively small number of subjects from which lipid spectra are acquired, larger future studies are needed to determine a definitive relationship between lipid content and noncontrast $T_1$ values.

Previous reports of reduced noncontrast $T_1$ values in disease-specific states are limited to the study of Sado et al. of FD and a recent study of patients with thalassemia. The opposite trend, of increased noncontrast $T_1$ values with heart disease, has been shown in acute myocardial edema, with injury in myocardial infarction and identification of the area at risk, where increased water mobility and thus represent a distinct mechanism from the reduced $T_1$ values in the current study. Although reduced postcontrast $T_1$ values have been reported in heart failure and diabetes mellitus, these contrast-enhanced $T_1$ values are a surrogate for increased ECV in these populations and are not directly related to noncontrast $T_1$ values. Previous noncontrast $T_1$ values of 1175.2±27.6 ms in healthy subjects, measured with the same SASHA $T_1$ mapping method used in the current study, are in close agreement with the control group values reported here (1177±27 ms). However, a wide range of values has been reported with other $T_1$ mapping methods. Wacker et al. measured noncontrast $T_1$ values of 1219 ms with a saturation-recovery approach similar to the SASHA method, whereas the commonly used modified look-locker inversion-recovery family of pulse sequence has reported values ranging from 939 to 1029 ms at 1.5T. A previous direct comparison of modified look-locker inversion-recovery and SASHA methods in 10 healthy subjects yielded noncontrast $T_1$ values that match this trend, with modified look-locker inversion-recovery values of 935.5±24.9 ms and SASHA values of 1175.2±27.6 ms. Sado et al. recently reported uniformly lower noncontrast $T_1$ values of 968±27.6 ms in healthy subjects and 858±27.6 ms in FD as compared with our currently reported $T_1$ values. Importantly, they reported absolute mean differences between FD and healthy controls 110 ms that is similar to our reported mean difference of 107 ms.

The findings of normal ECV in FD as compared with 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 3 patients with FD showing normal fibrotic burden in the septum. However, if increased lipid content is the source of the reduced noncontrast $T_1$ values in FD, then the conventional equations that relate contrast agent concentration at baseline and postcontrast delivery to ECV, which are based on a single pool $T_1$ values, may not be accurate for FD. Regions of LGE are excluded from $T_1$ analysis to avoid contamination by the longer $T_1$ values measured in these regions. The burden of LGE of 6% is similar to previously reported values in FD, and the prevalence of 45% is also similar to previous studies. Wacker et al. measured noncontrast $T_1$ values in male as compared with female subjects, 32.6 ms lower on average, are similar to the recent findings of Piechnik et al., although they found that the sex differences were not significant in older subjects (≥45 years). When age was included as a cofactor in the multiple regression analysis, the sex dependence of noncontrast $T_1$ remained significant ($P=0.002$). The lower myocardial ECV values in male subjects as compared with 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 $T_1$ mapping study. Importantly, sex differences in ECV and noncontrast $T_1$ were also independent of wall thickness, hematocrit, height, weight, and heart rate with significant sex differences when each of these was included as a cofactor. The larger noncontrast blood $T_1$ values in women as compared with men are similar to previous reports, with similar differences in $T_1$ values, and is likely a consequence of the lower hematocrit in the female (0.38±0.03) as compared with male (0.43±0.03) subjects. The characterization of sex differences in $T_1$ mapping values is important given the different presentations of FD in men and women. Although FD is an X-linked disease, female carriers also show significant heart disease with a different type of remodeling compared with males. Indeed, genetic testing is currently recommended as essential for the diagnosis of FD in women, and our findings imply that a CMR with $T_1$ 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 noncontrast $T_1$ values for the identification of FD were defined only in comparison with this group, and thus there is potential for $T_1$ overlap with other patient groups not represented here. Because healthy controls were not evaluated with clinical biochemical testing, we cannot be entirely certain as to the absence of diabetes mellitus or dyslipidemia. However, the recent FD study by Sado et al. showed similar discriminatory capability of noncontrast $T_1$ mapping in comparison with larger well-defined disease groups with LVH. 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 mellitus. However, our study revealed no relationship between either BSA or the presence of diabetes mellitus and noncontrast $T_1$ in the CR/H group and within the CR/H group, myocardial $T_1$ values in the 8 patients with diabetes mellitus (1211±40 ms) were similar to nondiabetic subjects (1204±29 ms). The current study is also potentially limited by incomplete coverage of the heart with $T_1$ mapping, with all data reported as the average from 2 short-axis slices from the mid and the basal locations. However, all
of our data indicate that the reduced T₁ values in FD are spatially uniform in these 2 slices, excluding regions positive for LGE, and thus the detection of disease does not seem 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 T₁. In conclusion, noncontrast T₁ mapping offers a novel imaging test for the detection of FD and potentially for monitoring response to enzyme replacement therapy. T₁ mapping pulses sequences, such as the modified look-locker inversion-recovery sequence similar to the SASHA method reported in the current study, or alternatively the modified look-locker inversion-recovery sequence similarly can measure T₁ within a single breath hold per slice and thus are readily appended to a standard clinical CMR examination, without the requirement of contrast agents.

Acknowledgments
We acknowledge the use of healthy controls and the patient cohort with CR/H from the Alberta Heart Failure Etiology and Analysis Research Team (HEART) study.

Sources of Funding
Our study received financial support from the University Hospital Foundation and Alberta Innovates-Health Solutions.

Disclosures
None.

References


**CLINICAL PERSPECTIVE**

Fabry disease (FD) is an X-linked disorder of lysosomal metabolism affecting multiple organs with cardiac disease being the leading cause of death. We evaluated the potential of quantitative T1 mapping with cardiovascular MRI as a disease-specific imaging biomarker in 31 patients with FD, 23 healthy controls, and 21 subjects with concentric remodeling or hypertrophy. All subjects had preserved left ventricular ejection fraction (>50%) and similar volumes. FD and concentric remodeling or hypertrophy had similarly increased mass, wall thickness, and mass/volume as compared with controls. Noncontrast myocardial T1 values were substantially lower in FD as compared with controls and concentric remodeling or hypertrophy (1077±43, 1177±34, and 1207±33, respectively; P<0.001), but myocardial extracellular volume was similar in all groups. Single-voxel NMR spectroscopy showed a significant negative linear relationship between lipid content and noncontrast T1 values. Female subjects had lower left ventricular mass and wall thickness, longer myocardial T1 values, and larger extracellular volume suggesting a key sex difference in cardiac remodeling. Reduced noncontrast myocardial T1 values are the most sensitive and specific cardiac MRI parameter in patients with FD irrespective of sex and left ventricular morphology and function. Noncontrast T1 mapping offers a new sensitive and specific test for the detection of FD, and potentially for monitoring response to enzyme replacement therapy. These results illustrate the ability of cardiac MRI coupled with NMR spectroscopy to further characterize substrate for cardiomyopathy and serve as an imaging-based biomarker.
T₁ Mapping With Cardiovascular MRI Is Highly Sensitive for Fabry Disease Independent of Hypertrophy and Sex
Richard B. Thompson, Kelvin Chow, Aneal Khan, Alicia Chan, Miriam Shanks, Ian Paterson and Gavin Y. Oudit

Circ Cardiovasc Imaging. 2013;6:637-645; originally published online August 6, 2013;
doi: 10.1161/CIRCIMAGING.113.000482
Circulation: Cardiovascular Imaging is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2013 American Heart Association, Inc. All rights reserved.
Print ISSN: 1941-9651. Online ISSN: 1942-0080

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circimaging.ahajournals.org/content/6/5/637

Data Supplement (unedited) at:
http://circimaging.ahajournals.org/content/suppl/2013/08/06/CIRCIMAGING.113.000482.DC1

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation: Cardiovascular Imaging can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation: Cardiovascular Imaging is online at:
http://circimaging.ahajournals.org//subscriptions/
Supplemental Material

T$_1$ 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 $T_1$ 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 $T_1$ 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, $\eta$ is the best-fit saturation efficiency, TS are saturation recovery times and $T_1$ is the best fit $T_1$ value. Sample saturation recovery data from 18 myocardial segments and a blood pool region are shown from a FD patient.