Anderson-Fabry disease (AFD) is an X-linked storage disease characterized by multiorgan involvement and premature death attributable to cardiac failure, arrhythmia, stroke, and renal failure.1 The disease is caused by a deficiency in the enzyme $\alpha$-galactosidase A, which results in the accumulation of glycosphingolipid within lysosomes and, in some tissues, progressive fibrosis.2 Because treatment with recombinant enzyme has been shown to reverse or slow disease progression when initiated before reversible end-organ damage has occurred, early detection of glycosphingolipid deposition is imperative.3,4 At present, this can be achieved in the heart only by performing endomyocardial biopsy, which has several limitations, including the risk of myocardial perforation and sampling error.5 The most frequently used noninvasive surrogate for myocardial glycosphingolipid accumulation is an increase in left ventricular mass.4 Although this correlates with other markers of disease severity, it is a relatively late manifestation, typically appearing after the third decade in men and the fourth decade in women, and correlates poorly with myocardial glycophingolipid content.6

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Magnetic resonance imaging T1 relaxation time is a fundamental property of tissue that can now be assessed in the heart using recently created mapping sequences. Early results show that the native, noncontrast T1 lengthens with interstitial expansion caused by edema,7 infarction,8 amyloid infiltration,9 and fibrosis.10 This is believed to be the result of

Background—Anderson-Fabry disease (AFD) is a rare but underdiagnosed intracellular lipid disorder that can cause left ventricular hypertrophy (LVH). Lipid is known to shorten the magnetic resonance imaging parameter T1. We hypothesized that noncontrast T1 mapping by cardiovascular magnetic resonance would provide a novel and useful measure in this disease with potential to detect early cardiac involvement and distinguish AFD LVH from other causes.

Methods and Results—Two hundred twenty-seven subjects were studied: patients with AFD (n=44; 55% with LVH), healthy volunteers (n=67; 0% with LVH), patients with hypertension (n=41; 24% with LVH), patients with hypertrophic cardiomyopathy (n=34; 100% with LVH), those with severe aortic stenosis (n=21; 81% with LVH), and patients with definite amyloid light-chain (AL) cardiac amyloidosis (n=20; 100% with LVH). T1 mapping was performed using the shortened modified Look-Locker inversion sequence on a 1.5-T magnet before gadolinium administration with primary results derived from the basal and midseptum. Compared with healthy volunteers, septal T1 was lower in AFD and higher in other diseases (AFD versus healthy volunteers versus other patients, 882±47, 968±32, 1018±74 milliseconds; P<0.0001).

In patients with LVH (n=105), T1 discriminated completely between AFD and other diseases with no overlap. In AFD, T1 correlated inversely with wall thickness ($r=-0.51; P=0.0004$) and was abnormal in 40% of subjects who did not have LVH. Segmentally, AFD showed pseudonormalization or elevation of T1 in the left ventricular inferolateral wall, correlating with the presence or absence of late gadolinium enhancement (1001±82 versus 891±38 milliseconds; $P<0.0001$).

Conclusions—Noncontrast T1 mapping shows potential as a unique and powerful measurement in the imaging assessment of LVH and AFD. (Circ Cardiovasc Imaging. 2013;6:392-398)
the increase in free fluid associated with these pathophysiological states. Because fat is known to possess a very low T1, we hypothesized that the left ventricular myocardial non-contrast T1 could be used as a surrogate marker to detect myocardial glycosphingolipid storage before the development of left ventricular hypertrophy (LVH) has occurred. We also hypothesized that in patients with established LVH, T1 would allow AFD to be differentiated from other more common causes of LVH because of the presence of glycosphingolipid in this condition.

Methods

The research received approval from the local research ethics committee, and all participants provided written informed consent. Forty-four consecutive genetically proven AFD patients were prospectively recruited from an inherited cardiac disease unit (39% men; median age, 49 years; range, 21–78 years). Thirty-four patients (77%) had received enzyme replacement therapy for 78±40 months. Nine (90%) of those not on therapy were women. Six patients (14%, 5 women) had a clinical diagnosis of hypertension and AFD. Twenty-four patients (55%), of whom 58% were men, had LVH, defined as an elevated indexed left ventricular mass calculated from cardiac magnetic resonance (CMR) steady-state free-precession cine images.11 All these patients also had a maximal left ventricular wall thickness on CMR of >12 mm (which previous guidelines and publications have used to define the presence of LVH in AFD using echocardiography).12 Participant baseline data are shown in the Table. The results were compared with 67 healthy volunteers (45% men; median age, 46 years; range, 24–88 years) recruited from our local hospital, university, and general practice. All volunteers underwent clinical cardiovascular history, examination, 12-lead ECG, and clinical CMR to ensure that there was no evidence of cardiovascular disease.

Comparison was also made to patient T1 data from subsets of other disease-specific studies, the results of which have been or will be presented (in full cohorts) elsewhere; 41 patients with hypertrophic cardiomyopathy (55% men; median age, 42 years; range, 21–72 years; 24% with LVH), in whom the diagnosis was based on recommendations from national guidelines, and 34 patients with hypertrophic cardiomyopathy (76% men; median age, 55 years; range, 21–84 years; 68% asymmetrical septal hypertrophy; 26% apical predominant hypertrophy; and 6% concentric hypertrophy; mean maximal wall thickness, 20±4 mm).11,13–15 The diagnosis was based on international guidelines.16 Twenty-one patients with severe aortic stenosis were awaiting open valve replacement (71% men; median age, 72 years; range, 59–83 years; 81% with LVH). The indications for surgery were those recommended in international guidelines.17 Twenty patients had definite cardiac involvement in amyloid light-chain (AL) amyloidosis (70% men; median age, 67 years; range, 42–78 years; 100% with LVH) on the basis of conventional clinical criteria.18

All patients underwent CMR (1.5 T, Avanto, Siemens Healthcare, Erlangen, Germany). This included standard steady-state free-precession cine imaging to assess cardiac volumes and left ventricular mass and late gadolinium enhancement (LGE) imaging (using a fast, low-angle, single-shot inversion recovery sequence)19 to delineate focal fibrosis with the contrast agent Dotarem (Guerbet, Paris, France) at 0.1 mmol/kg.

Left ventricular volumes, ejection fraction, and mass were calculated using a thresholding method on CMR tools software (Cardiovascular Imaging Solutions Ltd, London, UK). Myocardial feature tracking was also performed on the short-axis cine stack of the healthy volunteers and patients with AFD using software that was recently approved by the Food and Drug Administration (2-dimensional performance analysis magnetic resonance, Tomtec, Unterschleissheim, Germany). After manual drawing around the endocardial border of the left ventricle, the software allows the quantitative assessment of wall motion, similar to echocardiographic speckle tracking. The deformation data are presented as global left ventricular myocardial longitudinal and circumferential strain, the most reproducible of the software outputs.20

Before contrast administration, T1 mapping was performed using the shortened modified Look-Locker inversion recovery (Sh-MOLLI) sequence in the basal and mid–short-axis planes.7 The resulting pixel-by-pixel color T1 maps were displayed using a customized 12-bit look-up table, where normal myocardium was green, increasing T1 was red, and decreasing T1 was blue. The color map is visible immediately after data acquisition (Figure 1).

For the septal T1, a region of interest in the basal and midseptum was drawn, and the average T1 was obtained, taking care to clearly avoid the blood-myocardial boundary. For segmental analysis, a custom macro for ImageJ (National Institutes of Health, Bethesda, MD) divided the left ventricular myocardium in the 2 slices into 6 segments on the basis of the American Heart Association model and gave the mean T1 of each segment.21

Six patients with AFD who were not administered gadolinium contrast, either because of renal impairment if the epidermal growth factor receptor was <30 mL/min (n=4) or patient preference (n=2).

The only exclusion criteria for the study were pregnancy or contraindication to CMR.

Results

were analyzed using SPSS (version 19; Chicago, IL). The normal range of T1 was defined as ±2 SD from our healthy volunteer mean. All T1 values were found to be normally distributed (Kolmogorov-Smirnov test; P>0.05 for each data set) and thus were expressed as mean±SD. Subgroup results were compared by either a 2-tailed t test or 1-way ANOVA with post hoc analysis using the Games-Howell procedure (differing variances) or Bonferroni correction if not. A value of P<0.05 was considered significant. Correlations were evaluated using Pearson coefficients.

Results

All patients completed the study. Baseline healthy volunteer and patient data are shown in the Table. The mean septal T1 in patients with AFD was much lower than in healthy volunteers, whereas patients with no AFD had higher T1 (AFD versus healthy volunteers versus other patients, 882±47, 968±32, 1018±74 milliseconds; P<0.0001).

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Of note, the comparator populations represent subsets of other disease-specific studies, the results of which have been or will be presented (in full cohorts) elsewhere. LVH indicates left ventricular hypertrophy.
In patients with LVH (n=105), there was absolute discrimination with no overlap of AFD with other diseases (858±37 versus 1038±76 milliseconds; P<0.0001; Figure 2). In all 4 patients with AFD with an epidermal growth factor receptor of <30 mL/min and 5 of the 6 patients with AFD and hypertension, the mean septal T1 was less than the lower limit of the normal range.

In patients with AFD without LVH (n=20), the mean septal T1 was lower than in healthy volunteers or LVH-negative patients with non-AFD (910±43 versus 968±32 versus 965±26 milliseconds; P<0.0001). Forty percent of patients with AFD without LVH had T1 below the lower limit of the normal range (<904 milliseconds; Figure 3). Of the 18 patients with negative LVH who underwent contrast imaging, 4 had LGE in the basal inferolateral wall, but their mean septal T1 was not different from that of the other patients with negative LVH (921 versus 905 milliseconds; P=NS).

In patients with AFD not on enzyme replacement therapy, the mean septal T1 was higher than in those receiving treatment (906±34 versus 875 ms±48 milliseconds; P=0.04) but lower than that of healthy volunteers (P=0.0004).

When considering the whole AFD group, the male mean septal T1 was lower than the female mean septal T1 (851±39 versus 901±42 milliseconds; P=0.0003). T1 correlated inversely with both indexed left ventricular mass (r=−0.41; P=0.006) and the maximal left ventricular wall thickness (r=−0.51; P=0.0004; Figure 4). There was no significant difference in circumferential or radial strain between healthy volunteers and patients with AFD. However, in the latter, there was a correlation between mean septal T1 and circumferential (r=0.35; P=0.02) and radial (r=−0.4; P=0.007) strain.

Segmental T1 analysis in AFD showed normal or even elevated T1 in the left ventricular inferolateral wall in some patients. This was associated with the presence (n=17; 45%) or absence (n=21; 55%) of LGE (1001±82 versus 891±38 milliseconds, respectively; P<0.0001; Figure 1). Segmental analysis of all other diseases and healthy volunteers did not show this pattern of elevated inferolateral wall T1, except in...
cardiac amyloidosis, in which a uniform elevation in T1 of all segments was found.

Discussion

We have shown that CMR noncontrast myocardial T1 mapping demonstrates a low mean septal T1 in AFD. Furthermore, in patients with LVH, T1 absolutely distinguishes AFD from other common causes with no apparent overlap. In AFD without LVH or fibrosis, the T1 may still be lower than normal, suggesting that it may be a marker of early cardiac involvement. The results held in both female patients and patients with an epidermal growth factor receptor of <30 mL/min.

AFD causes the accumulation of glycosphingolipid in myocytes.2 One explanation for the observed results would be that this will lower T1 and not be offset by potential prolongation from fibrosis because this appears absent in the septum of most patients with AFD with LVH,22–24 unlike some other forms of LVH.25 Histologically, the vacuolation (by light microscopy) and extent of lamellar bodies (by electron microscopy) can be substantial, yet extraction experiments obtain only a few percent by weight of the glycosphingolipid.26 The T1 lowering shown here (up to 200 milliseconds) would potentially require substantial lipid (≥10% by volume) if the effect were from protons on the CH2 groups of the glycosphingolipid or associated other lipids forming part of the storage phenomenon. Therefore, simple fat-based T1 shortening may be a too simplistic explanatory model. The lamellar body structure of AFD storage may behave like the myelin sheaths of white matter in the brain, which have a similar structure. Water constraint and water-lipid and water-protein interactions have been shown to cause T1 lowering in myelin, rather than a direct signal from lipid protons, and it may be that these mechanisms also drive the T1 decrease in AFD.27 Further work is required to elucidate this mechanism.

The T1 prolongation in other diseases has been described by our group and others. Focal and diffuse fibrosis has been shown to increase T1,10 with recent preliminary work demonstrating a correlation between the latter and myocardial collagen volume fraction from myocardial biopsy in severe aortic stenosis.13 A similar effect has been noted in AL amyloidosis,9 with impressive T1 elevation but significant overlap, unlike the apparent specificity of the T1 shortening.
in AFD. The AFD exception in this study was in the inferolateral wall, where T1 was significantly higher than in the other segments if LGE was present, potentially allowing identification of focal fibrosis without the need for a contrast agent to be administered in this disease. This is particularly useful in AFD because a significant percentage of patients have renal involvement. The administration of gadolinium contrast agents in patients with an epidermal growth factor receptor of <30 mL/min is considered a risk factor for the development of nephrogenic systemic fibrosis and is therefore generally avoided in this group, although newer cyclic agents (such as Dotarem) seem safer.

We hypothesize that the inferolateral wall myocardium in AFD undergoes a 4-phase transition from normal (pre-detectable storage) to low (storage) to pseudonormalization (storage+fibrosis) to elevation (fibrosis). Serial study of patients with negative LVH may elucidate this in the future. The specificity of T1 lowering in this study is striking, as it needs to be for a clinical test that would compare AFD to other more common diseases which can cause LVH. The prevalence of AFD is 1 in 40,000,28 so this study of 44 AFD and 227 participants in total is large but inadequate to fully define the sensitivity and specificity of the test and clinical use, except in scenarios in which the pretest probability is much higher (eg, unexplained LVH or in dialysis patients).

We suggest 3 possible future roles for noncontrast T1 mapping in AFD. First, AFD is believed to be both late and underdiagnosed, often decades after symptom onset and after multiple medical reviews.29 Significant prevalence is found in certain populations such as patients on dialysis30 and middle-aged men with late-onset hypertrophic cardiomyopathy.31 Identification of those patients with a potential diagnosis of AFD is important both for the individual (because he or she then requires specialist care and may be a candidate for enzyme replacement therapy) and for family members. In patients with LVH undergoing CMR, the finding of a low T1 should prompt referral for specialist testing for AFD. Second, identification of patients who will benefit from costly enzyme replacement therapy can be challenging. At present, clinical identification of myocardial involvement in AFD primarily uses echocardiographic assessment of the maximal left ventricular wall thickness.12 However, this is not an early marker. Recent work has suggested an additive role for CMR with LGE, with 1 study finding that 17% of women with AFD had LGE despite no evidence of LVH.24 Some authorities suspect that patients with established fibrotic cardiac disease may not respond as well to therapy. In the present study, the T1 of patients without LVH (85% women, 22% had LGE) was significantly lower than in healthy volunteers, with 40% being >2 SD below the normal mean. The finding of a low T1 is therefore likely to be an earlier CMR marker of cardiac involvement. It is possible that patients with low T1 but no LVH or fibrosis have the most to gain from enzyme replacement therapy in terms of potentially intervening at an earlier stage in the disease process. However, more work is needed to investigate the natural history of this group and the effects of therapy on them. Finally, there is currently no accepted cardiac end point for clinical trials assessing new therapies in AFD. The noninvasive method of CMR T1 assessment would show early potential for this role, but further work is needed to assess the reproducibility of the technique, the progression of T1 in untreated individuals, and the effects of enzyme replacement therapy on it.

There are several limitations in this study. Only 1 T1 mapping sequence, Sh-MOLLI, was used. At present, there are ≥4 other sequences that have been evaluated in clinical studies.14,32,33 Nearly all of them (including Sh-MOLLI) are Look-Locker inversion recovery–based sequences. Both phantom and clinical work has found good agreement and correlation in the T1s obtained by the different Look-Locker sequences.3,34 We believe there are scenarios in which myocardial noncontrast T1 measurement could be misleading. First, AFD can enter a progressive disease phase in which extensive myocardial scarring occurs, including in the septum, which could either pseudonormalize or elevate T1. We had no such patients in our cohort and did not find an increase in septal extracellular volume (which, if elevated, would have suggested the presence of fibrosis) using CMR in our previous AFD study.23 LGE was also a rare finding in a large cohort of patients with AFD scanned by another group.24 Previous autopsy work in 3 cases of severe cardiac involvement in AFD found very little fibrosis in basal septum.22 Focal fibrosis in the AFD septum is therefore uncommon even in advanced disease; however, we recommend regions of interest be drawn on noncontrast T1 maps in AFD to avoid any areas subsequently shown to have LGE. Second, scar from any cause (infection, cardiomyopathy) can have fatty metaplasia present, which would give a low T1. Third, myocardial T1 may be lowered by other infiltrative or storage diseases such as those that cause myocardial siderosis (eg, iatrogenic iron overload in thalassemia).35 In this study, we performed T2* mapping to exclude iron loading on 8 of our patients with AFD with low T1. All had no evidence of myocardial iron (T2* >20 milliseconds). Fourth, there may be CMR T1 mapping sequence acquisition errors beyond concurrent sensitivity to T2 and T2* such as poor shimming, susceptibility, breathing, sequence timing, and reconstruction artifacts, which can give rise to errors in T1 measurement. Inspection of the original images and reconstructed T1 error maps (which are produced as a part of the Sh-MOLLI sequence) enables exclusion of most measurement artifacts. Other limitations include that most patients were on enzyme replacement therapy. This study also has no correlation of results with non-CMR disease markers, no histological validation, no spectroscopy, and no assessment of technique reproducibility. Further work will address these limitations and potential future developments in CMR tissue characterization in this disease.

In conclusion, noncontrast T1 septal assessment is a simple, safe, quick, and useful add-on to clinical CMR, providing a new parameter that seems to be useful in the diagnostic workup of LVH and the detection of early cardiac involvement in AFD, with potential for therapy monitoring.

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Disclosures

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References


**CLINICAL PERSPECTIVE**

Anderson-Fabry disease is a rare but underdiagnosed intracellular lipid disorder that can cause left ventricular hypertrophy (LVH). Assessment of myocardial T1 can now be performed using sequences that require 1 short breath-hold per slice. In this study, we show that in patients with LVH, the finding a low noncontrast myocardial T1 allows differentiation of Anderson-Fabry disease from the other common causes of this presentation with an absolute cutoff value found. Furthermore, in Anderson-Fabry disease, T1 lowering is an earlier marker of cardiac involvement than any other present cardiac magnetic resonance imaging parameter. This study therefore shows the use of myocardial T1 in the diagnostic assessment of patients with LVH. In Anderson-Fabry disease, the finding of low noncontrast myocardial T1 before the occurrence of LVH may allow improved targeting of patients who would benefit the most from the administration of enzyme replacement therapy (before myocardial scarring or LVH has developed) and could facilitate monitoring of treatment response.
Identification and Assessment of Anderson-Fabry Disease by Cardiovascular Magnetic Resonance Noncontrast Myocardial T1 Mapping

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