Noncontrast T1 Mapping for the Diagnosis of Cardiac Amyloidosis

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CME Objective for This Article: At the end of this activity the reader should be able to: 1) discuss the importance of cardiac involvement in AL amyloidosis; 2) recognise the limitations of noninvasive imaging tests to detect cardiac involvement in patients with AL amyloidosis; and 3) understand the role of noncontrast T1 myocardial mapping using CMR in the detection of cardiac involvement in patients with AL amyloidosis.
Noncontrast T1 Mapping for the Diagnosis of Cardiac Amyloidosis

OBJECTIVES  This study sought to explore the potential role of noncontrast myocardial T1 mapping for detection of cardiac involvement in patients with primary amyloid light-chain (AL) amyloidosis.

BACKGROUND  Cardiac involvement carries a poor prognosis in systemic AL amyloidosis. Late gadolinium enhancement (LGE) cardiac magnetic resonance (CMR) is useful for the detection of cardiac amyloid, but characteristic LGE patterns do not always occur or they appear late in the disease. Noncontrast characterization of amyloidotic myocardium with T1 mapping may improve disease detection. Furthermore, quantitative assessment of myocardial amyloid load would be of great value.

METHODS  Fifty-three AL amyloidosis patients (14 with no cardiac involvement, 11 with possible involvement, and 28 with definite cardiac involvement based on standard biomarker and echocardiographic criteria) underwent CMR (1.5-T) including noncontrast T1 mapping (shortened modified look-locker inversion recovery [ShMOLLI] sequence) and LGE imaging. These were compared with 36 healthy volunteers and 17 patients with aortic stenosis and a comparable degree of left ventricular hypertrophy as the cardiac amyloid patients.

RESULTS  Myocardial T1 was significantly elevated in cardiac AL amyloidosis patients (1,140 ± 61 ms) compared to normal subjects (958 ± 20 ms, p < 0.001) and patients with aortic stenosis (979 ± 51 ms, p < 0.001). Myocardial T1 was increased in AL amyloid even when cardiac involvement was uncertain (1,048 ± 48 ms) or thought absent (1,009 ± 31 ms). A noncontrast myocardial T1 cutoff of 1,020 ms yielded 92% accuracy for identifying amyloid patients with possible or definite cardiac involvement. In the AL amyloidosis cohort, there were significant correlations between myocardial T1 time and indices of systolic and diastolic dysfunction.

CONCLUSIONS  Noncontrast T1 mapping has high diagnostic accuracy for detecting cardiac AL amyloidosis, correlates well with markers of systolic and diastolic dysfunction, and is potentially more sensitive for detecting early disease than LGE imaging. Elevated myocardial T1 may represent a direct marker of cardiac amyloid load. Further studies are needed to assess the prognostic significance of T1 elevation. (J Am Coll Cardiol Img 2013;6:488–97) © 2013 by the American College of Cardiology Foundation
Amyloidosis is a group of diseases in which proteins misfold to form insoluble fibrils that accumulate in the extracellular space and disrupt the structure and function of many tissues and organs (1). Cardiac involvement is common and is a principal cause of morbidity and mortality particularly in primary amyloid light-chain (AL) amyloidosis (1–3). Although endomyocardial biopsy is the gold standard for demonstrating cardiac amyloid deposits, it is not routinely performed because it is invasive and, in practice, much reliance has been placed on the collective diagnostic value of clinical features, electrocardiography (ECG) and echocardiography, supported by the presence of amyloid in extracardiac sites (1).

Cardiac magnetic resonance (CMR) with late gadolinium enhancement (LGE) provides unique information on myocardial tissue characterization in patients with cardiac amyloidosis (4–8). A characteristic appearance of global, subendocardial LGE is the hallmark for identifying cardiac involvement, which substantially aids the noninvasive diagnosis of cardiac amyloid, and correlates with prognosis (4,6). However, the LGE technique has limitations in evaluating patients with suspected cardiac amyloidosis, many of whom have significant renal impairment making administration of a gadolinium-based contrast problematic. Furthermore, the pattern of LGE may be atypical and patchy, even in patients with life-threatening disease (1,4,7). Therefore, a reproducible, noncontrast CMR technique that could provide accurate identification of cardiac amyloidosis and, ideally, quantitative assessment of myocardial amyloid load would be of great value.

Measurement of myocardial T1 relaxation times using noncontrast magnetic resonance T1 mapping has the potential to be useful in the detection of interstitial expansion due to myocardial edema and fibrosis (9–12). In patients with systemic AL amyloidosis, alterations of T1 times in the liver, spleen, and fat have been described using low-field magnetic resonance imaging (13). Therefore, we hypothesized that noncontrast T1 mapping would provide diagnostic information in patients with suspected cardiac AL amyloidosis.

**METHODS**

**Study population.** Fifty-three patients with systemic (primary) AL amyloidosis and no contraindications for CMR were recruited from the United Kingdom National Amyloidosis Centre (Royal Free Hospital, London, UK) between 2010 and 2011. All patients had histological confirmation of systemic AL amyloidosis by Congo red and immunohistochemical staining, which was obtained through specimens of kidney (n = 15), bone marrow (n = 8), soft tissues (n = 8), fat (n = 5), rectum (n = 5), endomyocardium (n = 4), liver (n = 2), lymph node (n = 2), upper gastrointestinal tract (n = 1), lung (n = 1), bladder (n = 1), and peritoneum (n = 1). Participants were required to have glomerular filtration rate >30 ml/min since LGE was performed.

On the basis of a combination of clinical and echocardiographic features, amyloid patients were categorized as having no (n = 14), possible (n = 11), and definite (n = 28) cardiac involvement. The categorization into definite or no cardiac involvement was based on international consensus criteria (14). An additional category of possible involvement was created for patients with cardiac abnormalities in whom there were confounding features. The categorization was defined as follows: definite cardiac involvement includes either of the following: 1) left ventricular (LV) wall thickness of ≥12 mm in the absence of any other known cause; or 2) right ventricular (RV) free wall thickening coexisting with LV thickening in the absence of systemic or pulmonary hypertension. Possible cardiac involvement includes any of the following: 1) LV wall thickening in the presence of hypertension; 2) RV thickening in the presence of pulmonary hypertension; and 3) normal wall thickness with diastolic dysfunction and raised serum biomarkers. No suspected involvement is defined as normal wall thickness with normal serum biomarkers.

In addition, 17 patients with moderate to severe aortic stenosis according to established criteria (15), such as peak aortic valve gradient ≥36 mm Hg or valve area <1.5 cm², were recruited from cardiology outpatient clinics at the John Radcliffe Hospital in Oxford, UK. Thirty-six normal volunteers were also recruited. All healthy controls had no history or symptoms of cardiovascular disease and no risk factors (diabetes mellitus, hypertension). All patients and healthy controls underwent 12-lead ECG. The study was approved by the institutional ethics committees, and all patients and normal volunteers gave written

**ABBREVIATIONS AND ACRONYMS**

AL = amyloid light-chain  
CMR = cardiac magnetic resonance  
ECG = electrocardiography  
LGE = late gadolinium enhancement  
LV = left ventricular  
ROC = receiver-operating characteristic  
RV = right ventricular  
SHMOLLI = shortened modified look-locker inversion recovery
Informed consent. Table 1 shows the baseline characteristics of patients and controls.

**CMR protocol.** All subjects underwent CMR with a 1.5-T clinical scanner (Avanto, Siemens Healthcare, Erlangen, Germany). Images were acquired with the patient supine, using anterior and posterior phased-array surface coils. For cine CMR, from standard pilot images, short-axis cine images covering the entire left ventricle were acquired using a retrospectively ECG-gated balance steady-state free precession sequence. For T1 mapping, a midventricular short-axis and a 4-chamber long-axis plane were acquired using the shortened modified look-locker inversion recovery 4-chamber long-axis plane were acquired using the Siemens Medical Solutions) (18). For aortic stenosis patients, aortic valve area was determined by direct valve planimetry. For T1 measurements, the midventricular short-axis and the 4-chamber ShMOLLI image were manually contoured to outline the endocardium and epicardium, and the average T1 value over all available images was calculated using in-house software MC-ROI (myocardial regions of interest [programmed by S.K.P.], Interactive Data Language-IDL Version 6.1, ITT Exelix, McLean, Virginia), as previously described (16). The LGE images were visually analyzed for the presence or absence of enhancement from a reader blinded to T1 mapping results. The presence of LGE was classified as: 1) patchy; 2) circumferential in the subendocardium; 3) diffuse circumferential involving the subendocardium and extending to the epicardial layer; and 4) abnormal contrast handling on T1 scout with no discernible LGE, defined as myocardium nulling before blood on a 5-min post-contrast T1 scout.

### Table 1. Baseline Characteristics of the Cohort

<table>
<thead>
<tr>
<th></th>
<th>Normal (n = 36)</th>
<th>Amyloid, No Cardiac (n = 14)</th>
<th>Amyloid, Possible Cardiac (n = 11)</th>
<th>Amyloid, Definite Cardiac (n = 28)</th>
<th>Aortic Stenosis (n = 17)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs</td>
<td>59 ± 4</td>
<td>58 ± 12</td>
<td>65 ± 10</td>
<td>63 ± 10</td>
<td>63 ± 5</td>
<td>0.07</td>
</tr>
<tr>
<td>Male/female</td>
<td>22/14</td>
<td>8/6</td>
<td>7/4</td>
<td>20/8</td>
<td>12/5</td>
<td>0.85</td>
</tr>
<tr>
<td>BSA, m²</td>
<td>1.9 ± 0.2</td>
<td>2.0 ± 0.3</td>
<td>2.0 ± 0.2</td>
<td>1.9 ± 0.3</td>
<td>2.0 ± 0.1</td>
<td>0.42</td>
</tr>
<tr>
<td>NYHA functional class</td>
<td>&gt;III</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>eGFR, ml/min/1.73 m²</td>
<td>NA</td>
<td>85 ± 10</td>
<td>74 ± 32</td>
<td>77 ± 20</td>
<td>NA</td>
<td>0.42</td>
</tr>
<tr>
<td>Hemoglobin, g/dl</td>
<td>NA</td>
<td>13 ± 1</td>
<td>13 ± 2</td>
<td>13 ± 2</td>
<td>NA</td>
<td>0.95</td>
</tr>
<tr>
<td>LVEDV index, ml/m²</td>
<td>77 ± 13*</td>
<td>59 ± 11†‡</td>
<td>58 ± 9‡†</td>
<td>65 ± 11†‡</td>
<td>77 ± 10*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVESV index, ml/m²</td>
<td>20 ± 5</td>
<td>16 ± 5*‡</td>
<td>13 ± 5†‡</td>
<td>25 ± 8</td>
<td>23 ± 9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>74 ± 5*</td>
<td>73 ± 6*</td>
<td>77 ± 6*</td>
<td>62 ± 12†‡</td>
<td>71 ± 9*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LV mass index, g/m²</td>
<td>58 ± 11†‡</td>
<td>69 ± 20‡</td>
<td>77 ± 20†</td>
<td>118 ± 32†</td>
<td>104 ± 18†</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ShMOLLI T1, ms</td>
<td>958 ± 20*</td>
<td>1,009 ± 31†‡</td>
<td>1,048 ± 48†‡</td>
<td>1,140 ± 61†‡</td>
<td>979 ± 51*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>E/A ratio</td>
<td>NA</td>
<td>0.88 ± 0.15*</td>
<td>0.97 ± 0.38*</td>
<td>1.72 ± 0.81</td>
<td>NA</td>
<td>&lt;0.001</td>
</tr>
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<td>E/E’ ratio</td>
<td>NA</td>
<td>7.6 ± 2.3*</td>
<td>14.2 ± 4.5</td>
<td>15.4 ± 6.4</td>
<td>NA</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>E deceleration time, ms</td>
<td>NA</td>
<td>204 ± 42</td>
<td>231 ± 66*</td>
<td>174 ± 62</td>
<td>NA</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Values are mean ± SD or n. *Indicates p < 0.01 versus amyloid with definite cardiac involvement; †p < 0.01 versus normal; ‡p < 0.01 versus aortic stenosis.

A = peak late transmitral diastolic velocity; BSA = body surface area; E = peak early transmitral diastolic velocity; E’ = mitral annular early velocity; eGFR = estimated glomerular filtration rate; LV = left ventricular; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; NA = not applicable; NYHA = New York Heart Association; ShMOLLI = shortened modified look-locker inversion recovery.
Statistical analysis. Statistical analysis was performed using IBM SPSS Statistics Version 19 (IBM, Somers, New York) and MedCalc Version 12 (MedCalc Software, Mariakerke, Belgium). All continuous variables were normally distributed (Kolmogorov-Smirnov test) and are presented as mean ± SD. Comparisons between groups were performed by 1-way analysis of variance with post-hoc Bonferroni correction. The chi-square test or Fisher exact test was used to compare discrete data as appropriate. Receiver-operating characteristic (ROC) curve analysis was performed to define a T1 relaxation time cutoff value that identifies cardiac involvement with the greatest sum of sensitivity and specificity. Correlation between continuous variables was assessed using Pearson (r) test. Statistical significance was defined as p < 0.05.

RESULTS

Subject characteristics are described in Table 1. There were no differences in age, sex, and body surface area among the 5 groups of subjects. Subjects with definite cardiac amyloid had significantly increased LV mass index (p < 0.001) and smaller LV end-diastolic volume (p = 0.001) compared to healthy controls. The degree of LV hypertrophy was similar in patients with definite cardiac involvement and aortic stenosis (p = 0.11). Ejection fraction was slightly lower in patients with definite cardiac involvement compared to the other groups (p < 0.01 for all comparisons), although values remained within normal limits. Peak systolic aortic velocity in patients with aortic stenosis was 3.8 ± 0.5 m/s, and the mean valve area was 1.1 ± 0.2 cm². At the time of the CMR scan, only 1 patient with possible cardiac amyloidosis and 2 patients with definite cardiac amyloidosis were in New York Heart Association functional class III. All other patients were in New York Heart Association functional class I or II. There were no differences in renal function and hemoglobin among the 3 groups of systemic AL amyloidosis patients.

T1 relaxation times in amyloidosis, healthy controls, and aortic stenosis. There were significant differences in noncontrast myocardial ShMOLLI T1 relaxation times among the 5 subject groups (Fig. 1). Patients with definite cardiac AL amyloidosis had significantly elevated myocardial T1 times (1,140 ± 61 ms) compared to normal controls (958 ± 20 ms, p < 0.001) or aortic stenosis patients with comparable
Noncontrast ShMOLLI myocardial T1 cut-off value of 1,020 ms yielded an area under the ROC curve of 0.97 ± 0.01 (p < 0.0001), with 92% diagnostic accuracy for identifying cardiac involvement. Based on this cutoff, 0 of 28 patients with definite and 3 of 11 patients with possible cardiac amyloid would have been misclassified (false negatives, sensitivity 92%). False positive results occurred in 0 of 36 normals, 3 of 17 aortic stenosis patients, and 3 of 14 amyloid patients with no cardiac involvement (specificity 91%).

**LGE findings and T1 in cardiac amyloid.** The frequency of LGE or abnormal contrast handling increased from the no, possible, and definite cardiac involvement with rates of 0%, 54%, and 96%, respectively. The possible cardiac involvement group (n = 11) comprised 5 patients with no LGE, 4 with LGE (3 with typical circumferential subendocardial LGE, 1 with patchy LGE), and 2 with abnormal contrast handling. The definite cardiac involvement group (n = 28) contained 1 patient with no LGE, 26 with LGE (9 with typical circumferential subendocardial LGE, 6 with patchy LGE, 11 with extensive LGE), and 1 with abnormal contrast handling. Increased T1 times (above the threshold of 1,020 ms) were present in all patients with patchy or extensive LGE, 2 of 3 patients with abnormal contrast handling on T1 scout, and 4 of 6 patients with possible or definite cardiac involvement but no discernible LGE. Only 6 of 19 (32%) aortic stenosis patients showed mild patchy midwall enhancement in the lateral wall. None of the normal controls had LGE. Representative examples of the CMR scans are shown in Figure 3.

**T1 and myocardial function in cardiac amyloid.** There were significant correlations between noncontrast T1 relaxation times and indices of systolic and diastolic function in the AL amyloidosis cohort. As T1 relaxation times increased, LV ejection fraction decreased (r = −0.57, p < 0.001) and LV mass index increased (r = 0.58, p < 0.001), suggesting that the changes in myocardial T1 reflect to some extent the severity of cardiac involvement (Fig. 4). In addition, T1 times increased significantly as diastolic function worsened as shown by a positive correlation between T1 times and E/E’ ratio (r = 0.45, p = 0.001) and a negative correlation between T1 times and E deceleration time (r = −0.44, p = 0.002).

**DISCUSSION**

The major finding of this study is that patients with systemic AL amyloidosis show markedly increased noncontrast T1 relaxation times in the myo-
dium. The T1 times are also increased in many patients in whom currently used clinical investigations suggest cardiac involvement is uncertain or absent. Among amyloid patients with overt cardiac involvement, the T1 increases are more pronounced than in patients with aortic stenosis and a similar degree of ventricular wall thickening. Furthermore, noncontrast T1 relaxation times correlate well with markers of systolic and diastolic dysfunction, indicating that the elevation in myocardial T1 likely reflects the severity of cardiac involvement. Thus, T1 mapping may have potential as a valuable method for diagnosing and quantifying cardiac involvement in systemic AL amyloidosis.

Cardiac involvement (as assessed by current conventional methods) is associated with very poor prognosis in patients with AL amyloidosis, with a median survival of 8 months compared to about 4 years among patients in whom the heart is spared (19–22). Its presence increasingly informs the choice and intensity of chemotherapy with the availability of various novel agents, some of which have cardiac toxicities (1,23). The gold standard for diagnosis of cardiac involvement is cardiac biopsy but sampling error prevents quantification and can give rise to false negative results. Abnormalities of ECG such as low QRS voltages in limb leads (<0.5 mV) and poor R-wave progression in chest leads occur in as many as two-thirds of cardiac AL amyloid patients (20,24). Echocardiography may demonstrate wall thickening, poor longitudinal function, biatrial dilation, and early diastolic and late systolic dysfunction (25,26), but only in the advanced stage do these features become discriminatory over other diseases such as hypertensive heart. Biomarkers, particularly N-terminal pro-B-type natriuretic peptide, and high-sensitivity cardiac troponins are useful for prognosis (19) and elevate early but nonspecifically. Radiolabeled serum amyloid P component is unable to image amyloid in the motile myocardium, and technetium-99m 3,3-diphosphono-1, 2-propanodicarboxylic acid (99mTc-DPD) scintigraphy is frequently negative in cardiac AL amyloidosis (27,28).

Figure 3. Characteristic Examples From CMR Scans
Cardiac magnetic resonance (CMR) end-diastolic frame from cine (left panel), ShMOLLI noncontrast T1 map (middle panel), and late gadolinium enhancement (LGE) images (right panel) in normal volunteer, aortic stenosis patient, and cardiac amyloid patient. Note the markedly elevated myocardial T1 time in the cardiac amyloid patient (1,170 ms, into the red range of the color scale) compared to the normal control (955 ms) and the patient with aortic stenosis and left ventricular hypertrophy (998 ms). ED = end diastolic; other abbreviations as in Figures 1 and 2.
CMR provides additive information in cardiac amyloid through myocardial tissue characterization with contrast. The appearance of global, subendocardial LGE and associated dark blood-pool is characteristic and correlates with prognosis (4–8). Other LGE patterns may exist, and LGE may occur even without overt hypertrophy. However, LGE patterns may be nonspecific or only occur in later disease and require contrast, which may be contraindicated in patients with renal failure, common with amyloid (29).

With the degree of myocardial infiltration present in amyloid, noncontrast T1-mapping has the potential to detect and also quantify cardiac involvement and could become a clinically useful diagnostic test. Furthermore, the lack of need for contrast and the quantitative nature of T1 mapping are particularly appealing for assessing prognosis and the effects of treatment on amyloidosis patients. Changes in T1 times had previously been demonstrated in the liver, spleen, and fat in amyloidosis using low-field magnetic resonance imaging (13), and early results supported myocardial changes (30–32). Here, we build on these results using the more advanced shortened breath-hold T1 mapping technique, incorporating a single color T1 map (16) in a large cohort with robust controls, and demonstrate functional consequences and early disease detection. Although there are technical differences between CMR sequences used to measure T1 relaxation times, our results are in agreement with previous work from Hosch et al. (30) who found a 19% increase in T1 times in cardiac amyloid patients compared to normal controls. Furthermore, we found that the T1 elevation in amyloid with definite cardiac involvement and wall thickening was higher than in measurements in aortic stenosis with similar hypertrophy, providing specificity for the technique. The higher T1 values likely reflect either the increase in the proportion of amyloid compared to fibrosis for similar wall thickness increase, or greater T1 prolongation by amyloid compared to myocardial fibrosis. Our T1 results in patients with moderate-severe aortic stenosis should be interpreted with caution as it is likely that patients with more severe aortic stenosis and more fibrosis will exhibit a greater degree of T1 elevation. Further work will be needed to clarify this.

Measurement of myocardial T1 times using ShMOLLI has shown very good accuracy for the detection of cardiac involvement in AL amyloidosis and correlate well with the extent of systolic and diastolic dysfunction. It is tempting to speculate that noncontrast T1 mapping is more sensitive than LGE-CMR for the detection of cardiac involvement as all amyloid patients with nontypical patchy enhancement had increased T1 values. Further-
more, T1 values in the AL amyloid without cardiac involvement group were significantly increased compared to normal controls and patients with aortic stenosis, indicating that at least some of these patients may be at early stages of cardiac involvement when clinical, echocardiographic, and LGE characteristics fail to demonstrate specific changes. Elevated myocardial T1 times likely represent a direct marker of cardiac amyloid load and are potentially more sensitive to early changes than LGE imaging. These preliminary findings need further confirmation in large scale studies that will assess not only the diagnostic and prognostic value of noncontrast T1 mapping but also the effect of therapy on T1 values.

**Study limitations.** Study patients had histologically proven amyloid but had not systematically undergone endomyocardial biopsy, as is standard clinical practice in the UK National Amyloidosis Center. Therefore, no histological correlation with T1 values is available. This study explored noncontrast T1 mapping (applicable to even patients with renal failure) rather than extracellular volume quantification with contrast. Post-contrast T1 mapping and extracellular volume imaging have been shown to be useful in detecting diffuse interstitial fibrosis (33–35) and have recently provided interesting insights into cardiac amyloid (36). Two-dimensional T1 mapping is also subject to sampling error because it is not a 3-dimensional acquisition and endocardial T1 values may be affected by partial voluming of blood pool. However, multiple views and the thickened (infiltrated) myocardium in cardiac amyloid help to minimize these. A more comprehensive cover of the left ventricle will likely facilitate monitoring of disease progression and treatment. Motion-corrected MOLLI can also help reduce edge errors further (37). The prognostic significance of T1 elevation also remains to be evaluated. The study only explores AL amyloid, not transthyretin amyloid, and the translation of our findings to different amyloid types is unknown. Finally, as T1 mapping is still an evolving field, it is unclear whether patients with other infiltrative cardiomyopathies or hypertrophic cardiomyopathy and extensive fibrosis would exhibit similar degrees of noncontrast T1 times prolongation. Ongoing studies are expected to answer this question and clarify the specificity of our findings.

**CONCLUSIONS**

Noncontrast T1 mapping has high diagnostic accuracy for the detection of cardiac AL amyloidosis and correlates well with markers of systolic and diastolic dysfunction. It may be more sensitive than LGE imaging for identifying early cardiac disease, but further studies are needed to assess this and the prognostic significance of T1 elevation.

**REFERENCES**


Key Words: amyloid • cardiovascular magnetic resonance • T1 time.