Myocardial T1 and extracellular volume fraction measurement in asymptomatic patients with aortic stenosis: reproducibility and comparison with age-matched controls

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Aims
(i) To establish the test–retest reproducibility of myocardial T1 and extracellular volume (ECV) fraction measurement in asymptomatic patients with moderate–severe aortic stenosis (AS), (ii) to compare reproducibility using motion-corrected (MOCO) parametric T1 maps for analysis vs full MOLLI series of images, and (iii) to compare T1 and ECV between patients and age-matched controls.

Methods and results
3 T cardiac MRI was performed twice on 10 patients (median interval 7 days) to assess reproducibility. An additional 40 patients and 22 asymptomatic controls underwent a single MRI. Native T1 and ECV were calculated by outlining the myocardium on T1 maps generated inline, and using an offline T1 fit on the MOCO multiple inversion-time raw image series, in the reproducibility cohort (n = 10). Reproducibility was excellent using the inline T1 maps (CoVs for T1: 1.77%; ECV: 6.52%) and good using the full MOLLI series (CoVs for T1: 8.52%; ECV: 12.98%). On comparing AS and controls, who were well matched for age, gender and co-morbidities, there was no significant difference in the native T1 or ECV (T1 = 1103.32 ± 33.07 vs. 1092.27 ± 34.29; ECV = 0.243 ± 0.019 vs. 0.251 ± 0.026 in patients and controls, P > 0.05), which was maintained even after splitting the patients into moderate and severe AS subgroups.

Conclusion
The test–retest reproducibility of myocardial T1 quantification using MOLLI is excellent in patients with AS and is highest using inline generated T1 maps for analysis. There was no difference in native myocardial T1 or ECV between asymptomatic patients with moderate–severe AS and age-matched controls without valve disease.

Keywords
cardiac magnetic resonance imaging • T1 mapping • ECV • aortic stenosis

Introduction
T1 mapping from cardiac magnetic resonance imaging (MRI) has emerged as a tool for quantifying myocardial extracellular volume (ECV) fraction, which is a marker of diffuse interstitial fibrosis.1 Diffuse interstitial fibrosis is a key pathophysiological process involved in the development of both systolic and diastolic dysfunction in aortic stenosis (AS).2 ECV has also been shown to be a predictor of short-term mortality in patients having clinically indicated cardiac MRI scans.1,4 The most widely used technique for myocardial T1 quantification is the Modified Look-Locker Inversion Recovery (MOLLI) sequence.5 While the inter- and intra-observer variability of ECV measurement has consistently been shown to be excellent, there is scarce data assessing test–retest reproducibility, especially in patient groups, which is particularly important when monitoring treatment effects or disease progression in longitudinal studies. True test–retest reproducibility of ECV has mainly been assessed in healthy volunteers with no co-morbidities.6–8 Many studies have also demonstrated the utility of T1 mapping in differentiating disease states such as AS,9,10 heart failure,11 cardiomyopathy,12 and amyloidosis6,13 from healthy controls. However, most studies in patients with AS have used a younger cohort of

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Previous studies have employed various methods of defining the myocardial regions of interest (ROIs) to obtain average myocardial T1 values, including outlining the epicardial and endocardial borders on the full series of images with multiple inversion times produced by the scanner,\textsuperscript{11,12} as well as outlining on a single T1\textsuperscript{7,8,14} or R1\textsuperscript{15} map produced by the scanner or in-house software. Analysing a single T1 map generated inline on the scanner has the advantage of being less time consuming and may be less prone to variation than analysing the full MOLLI series (typically 11 images). No previous study has directly compared these two techniques.

**Objectives**

We sought to assess the test–retest reproducibility, inter-observer and intra-observer variability of T1 quantification, and ECV measurement using MOLLI at 3 T, in asymptomatic patients with moderate-to-severe AS, outlining the myocardium on the T1 maps generated inline after motion correction and on each of the 11 images in the MOLLI series. Finally, we compared T1 and ECV values between patients with moderate-to-severe AS and age-matched asymptomatic controls without valve disease.

**Methods**

**Study population**

Patients participating in the ‘Prognostic importance of microvascular dysfunction in AS’ (PRIMID-AS) study\textsuperscript{16} were prospectively recruited from a single centre. Inclusion criteria were (i) asymptomatic and (ii) moderate or severe AS (based on two or more echocardiographic criteria).\textsuperscript{17} Exclusion criteria were (i) contraindication to MRI, (ii) eGFR < 30, (iii) ejection fraction (EF) < 40%, (iv) other valve disease of more than moderate severity, and (v) recent myocardial infarction or previous coronary artery bypass grafting. The patient group was split into moderate and severe AS subgroups according to European Society of Cardiology (ESC) guidelines\textsuperscript{17} for further analysis.

The local research and ethics committee approved the study, and written informed consent was obtained from subjects before participation. Cardiac MRI was performed twice on 10 asymptomatic patients with moderate to severe AS, at a median interval of 7 days, to assess reproducibility. An additional 40 patients (giving a total of 50 patients with AS) and 22 age-matched asymptomatic controls without valve disease underwent a single cardiac MRI scan. All controls were recruited through advertising, and none were referred for a clinical MRI, which subsequently turned out to be normal. Other common co-morbidities such as hypertension, hyperlipidaemia, and diabetes were not excluded in the controls, since we wanted to assess the incremental effect of AS on the myocardial T1 and ECV values.

**Image acquisition**

Imaging was performed using a 3T scanner (Magnetom Skyra, Siemens AG, Healthcare Sector, Erlangen, Germany) using an 18-channel phased-array anterior coil using an identical protocol in patients and controls. T1 data were acquired using a prototype, breath-held, end-expiratory, ECG-gated single-shot MOLLI sequence,\textsuperscript{5} with the 3(3)(3)(3) sampling pattern, and the following typical parameters: slice thickness 8 mm, field of view 300 × 400 mm, flip angle 50°, minimum TI 120 ms, inversion-time increment 80 ms. MOLLI images were acquired at the mid short-axis level before and 20 min after 0.15 mmol/kg of Gadobutrol contrast agent (Gadovist, Bayer Pharma AG, Germany). The contrast dose was split, as all subjects underwent a stress and rest perfusion (0.04 mmol/kg) protocol followed by a top-up (0.07 mmol/kg) after rest perfusion. Blood was taken to determine the haematocrit (Hct). To minimize artefacts, acquisition was performed with the ROI at iso-centre, a small shim volume was applied around the myocardium, a large FOV (≥ 400 mm) was used, and imaging was repeated after changing the phase-encode direction or resonance offset frequency if artefacts persisted. Identical parameters were used on the repeat scan in the reproducibility cohort. Late gadolinium enhancement (LGE) imaging was undertaken at least 10 min after the last contrast injection and prior to the post-contrast MOLLI imaging.

The MOLLI sequence produces a series of 11 images with different inversion times, with data collected over 17 heart beats. The Siemens software (Syngo MR D13) then employs a built-in post-processing image registration technique to produce a motion-corrected (MOCO) series of images to account for misregistration caused by breathing, patient movement, or mistriggering.\textsuperscript{18} In addition, the inline reconstruction software also produces a T1 parametric map, with pixel-by-pixel computation of the T1 values.

**Image analysis**

Analysis was performed using CMR42 (Circle Cardiovascular Imaging, Calgary, Alberta, Canada) software. The calculation of myocardial ECV requires the definition of ROIs for the myocardium and the blood pool, from which R1 (=1/T1) values are derived, which are used to calculate the partition coefficient (λ) and the ECV, taking account of the blood Hct level:\textsuperscript{15}

$$\lambda = \frac{R1_{myo\ post} - R1_{myo\ pre}}{R1_{blood\ post} - R1_{blood\ pre}}$$

and

$$ECV = \lambda (1 - Hct),$$

where the subscripts myo and blood refer to the R1 values in the myocardium and blood, respectively, and the subscripts pre and post refer to the pre-contrast and post-contrast values, respectively.

Mean blood and myocardial T1 values were obtained from the parameter maps as well as the full MOCO MOLLI series in the reproducibility cohort (n = 10) for comparison of test–retest reproducibility of the two analysis methods. ROIs were drawn to delineate the myocardium and the LV blood pool (avoiding the papillary muscle) on the pre- and post-contrast T1 maps (Figure 1B), to obtain the mean pre- and post-contrast T1 values in each region. Any segment with clear artefact was excluded from the myocardial ROI. For the MOLLI series of images, the epicardial and endocardial borders were drawn on the image with the most contrast between blood pool and myocardium, as well as an ROI in the blood pool, and propagated to the other images, with manual adjustment if required (Figure 1A). The analysis software uses a three-parameter least-squares fitting technique, with heart rate (HR) correction, to generate the average T1 value for the whole of the myocardium as outlined.

Two observers (A.S. and S.B.) analysed scan-1 and one observer (S.B.) repeated the contours on scan-1, using both techniques, to assess the inter-observer and intra-observer variability. One observer (A.S.) also analysed scan-2 to assess the test–retest reproducibility. For comparison of AS patients with healthy controls, one observer (A.S.) contoured the T1 maps of all 50 AS patients and 22 controls. All analysis was performed offline blinded to the patient details. We also compared the effect of HR correction in 10 patients, by generating T1 values with and without HR correction (built-in option in the analysis software) from the MOLLI
series of images, as no HR correction was applied when the T1 maps were calculated on the scanner console.

The LGE images were reviewed by two observers (A.S. and G.P.M.) and graded for the presence or absence of LGE. If present, the location of LGE was recorded and graded as infarct or non-ischaemic (typically mid wall or epicardial), as well as if LGE was present in the slice used for MOLLI imaging. Segments with LGE present were not excluded from T1 analysis.

**Statistical analysis**

Statistical tests were performed using SPSS 20.0 software (Statistical Package for the Social Sciences, Chicago, IL, USA). Normality was assessed using the Shapiro–Wilk test, histograms, and Q–Q plots. Continuous data are expressed as mean (standard deviation). Inter-observer, intra-observer, and test–retest reproducibility were assessed using the Bland and Altman method and coefficient of variation (CoV). Pearson’s correlation coefficient was used for assessment of correlation between the two measurement techniques. Patients and control values were compared by independent t-tests or analysis of variance (ANOVA). The test–retest reproducibility results were used to calculate the sample sizes needed to detect a 5 and 2.5% (relative) change in T1 and ECV, with a power of 90% and alpha error of 0.05.

**Figure 1** An example of outlining of the myocardial and blood pool ROIs on (A) Full MOCO MOLLI series, with corresponding graphs showing the fitted relaxation curves produced pre- and post-contrast injection and (B) T1 maps pre- (left) and post-contrast (right) injection.
Results

The demographic data for the AS patient group as a whole and split according to severity, as well as for the control group, are shown in Table 1. There was no significant difference in the demographic data between patients and controls. LGE was present more frequently in AS patients (seven subendocardial infarcts and eight non-ischaemic) vs. controls (all four non-ischaemic), \( P = 0.295 \). The distribution of LGE was confined to one area in all subjects, and enhancement in the mid short-axis slice was present in only two AS patients (1 infarct, 1 mid wall) and no controls.

Effect of HR correction

Since analysis of the full MOLLI series employed HR correction, while this was not done for the T1 maps, we generated T1 values with and without HR correction from the MOLLI series of images in 10 patients. There was no significant difference between T1 values or ECV on paired \( t \)-test (T1 = 1101.39 ± 42 vs. 1086.19 ± 20, \( P = 0.132 \); ECV = 0.233 ± 0.04 vs. 0.230 ± 0.04, \( P = 0.134 \) with and without HR correction, respectively), and significant correlations were present on Pearson’s correlation. Additionally, we found no correlation between HR and native T1 value in our overall patient group (\( r^2 = 0.005, P = 0.642 \)).

Table 1

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Asymptomatic controls ( (n = 22) )</th>
<th>All AS patients ( (n = 50) )</th>
<th>( P )-value ( (\text{all AS patients vs. controls}) )</th>
<th>Moderate AS ( (n = 21) )</th>
<th>Severe AS ( (n = 29) )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>67.5 ± 8.8</td>
<td>65.9 ± 13.2</td>
<td>0.615</td>
<td>63.0 ± 16.3</td>
<td>68.0 ± 10.2</td>
</tr>
<tr>
<td>Male (n, %)</td>
<td>15 (68%)</td>
<td>39 (78%)</td>
<td>0.375</td>
<td>19 (90%)</td>
<td>20 (69%)</td>
</tr>
<tr>
<td>Hct</td>
<td>0.430 ± 0.037</td>
<td>0.419 ± 0.030</td>
<td>0.198</td>
<td>0.429 ± 0.028</td>
<td>0.413 ± 0.030</td>
</tr>
<tr>
<td>Echocardiographic data</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AV Vmax (m/s)</td>
<td>1.4 ± 0.28</td>
<td>3.9 ± 0.62</td>
<td>&lt;0.001</td>
<td>3.5 ± 0.26</td>
<td>4.2 ± 0.62</td>
</tr>
<tr>
<td>MPG (mmHg)</td>
<td>4.1 ± 1.7</td>
<td>36.2 ± 14.3</td>
<td>&lt;0.001</td>
<td>26.8 ± 5.0</td>
<td>43.1 ± 14.9</td>
</tr>
<tr>
<td>AVA (cm²)</td>
<td>3.18 ± 0.63</td>
<td>1.10 ± 0.30</td>
<td>&lt;0.001</td>
<td>1.32 ± 0.20</td>
<td>0.94 ± 0.27</td>
</tr>
<tr>
<td>Haemodynamic data</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>72.4 ± 8.3</td>
<td>72.6 ± 11.1</td>
<td>0.937</td>
<td>69.8 ± 9.2</td>
<td>74.7 ± 12.1</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>152.3 ± 22.6</td>
<td>151.1 ± 24.0</td>
<td>0.838</td>
<td>146.9 ± 24.5</td>
<td>154.2 ± 23.7</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>81.7 ± 9.2</td>
<td>76.9 ± 10.5</td>
<td>0.065</td>
<td>76.5 ± 11.2</td>
<td>77.1 ± 10.1</td>
</tr>
<tr>
<td>Past medical and drug history</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>7 (32%)</td>
<td>26 (52%)</td>
<td>0.113</td>
<td>8 (38%)</td>
<td>18 (62%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2 (9%)</td>
<td>6 (12%)</td>
<td>0.717</td>
<td>1 (5%)</td>
<td>5 (17%)</td>
</tr>
<tr>
<td>Hyperlipidaemia</td>
<td>2 (9%)</td>
<td>11 (22%)</td>
<td>0.190</td>
<td>6 (29%)</td>
<td>5 (17%)</td>
</tr>
<tr>
<td>CAD</td>
<td>0 (0%)</td>
<td>5 (10%)</td>
<td>0.124</td>
<td>3 (14%)</td>
<td>2 (7%)</td>
</tr>
<tr>
<td>ACE-I/ARB</td>
<td>5 (23%)</td>
<td>22 (44%)</td>
<td>0.086</td>
<td>8 (38%)</td>
<td>14 (48%)</td>
</tr>
<tr>
<td>Statin</td>
<td>10 (46%)</td>
<td>32 (64%)</td>
<td>0.141</td>
<td>13 (62%)</td>
<td>19 (66%)</td>
</tr>
<tr>
<td>BB</td>
<td>1 (5%)</td>
<td>16 (32%)</td>
<td>0.012</td>
<td>4 (18%)</td>
<td>12 (41%)</td>
</tr>
<tr>
<td>CCB</td>
<td>4 (18%)</td>
<td>13 (26%)</td>
<td>0.472</td>
<td>5 (24%)</td>
<td>8 (28%)</td>
</tr>
<tr>
<td>MRI data</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVMi (g/m²)</td>
<td>44.3 ± 7.4</td>
<td>56.9 ± 13.1</td>
<td>&lt;0.001</td>
<td>54.2 ± 8.7</td>
<td>58.9 ± 15.4</td>
</tr>
<tr>
<td>LVEDVI (mL/m²)</td>
<td>77.7 ± 9.4</td>
<td>82.4 ± 17.1</td>
<td>0.141</td>
<td>83.6 ± 14.2</td>
<td>81.6 ± 19.2</td>
</tr>
<tr>
<td>LVESVI (mL/m²)</td>
<td>31.7 ± 4.8</td>
<td>35.0 ± 9.7</td>
<td>0.056</td>
<td>35.8 ± 7.7</td>
<td>34.5 ± 11.0</td>
</tr>
<tr>
<td>LVMi/LVEDVI (g/mL)</td>
<td>0.57 ± 0.08</td>
<td>0.70 ± 0.12</td>
<td>&lt;0.001</td>
<td>0.66 ± 0.10</td>
<td>0.73 ± 0.13</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>59.1 ± 3.5</td>
<td>57.9 ± 4.8</td>
<td>0.270</td>
<td>57.4 ± 3.9</td>
<td>58.2 ± 5.4</td>
</tr>
<tr>
<td>LGE (%)</td>
<td>4 (18%)</td>
<td>15 (30%)</td>
<td>0.295</td>
<td>9 (43%)</td>
<td>6 (21%)</td>
</tr>
<tr>
<td>Native Myo T1 (ms)</td>
<td>1092.27 ± 34.28</td>
<td>1103.32 ± 33.03</td>
<td>0.201</td>
<td>1091.95 ± 21.66</td>
<td>1111.55 ± 37.57</td>
</tr>
<tr>
<td>ECV</td>
<td>0.251 ± 0.026</td>
<td>0.243 ± 0.019</td>
<td>0.147</td>
<td>0.2368 ± 0.019</td>
<td>0.2468 ± 0.018</td>
</tr>
</tbody>
</table>

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; AVA, aortic valve area; AV Vmax, peak velocity across aortic valve; BB, beta blocker; bpm, beats per minute; CAD, coronary artery disease; CCB, calcium channel blocker; ECV, extracellular volume fraction; Hct, haematocrit; HR, heart rate; LGE, late gadolinium enhancement; LVEDV, left-ventricular end-diastolic volume indexed; LVEF, left-ventricular ejection fraction; LVESV, left-ventricular end-systolic volume indexed; LVMi, left-ventricular mass indexed; MPG, mean pressure gradient; MRI, magnetic resonance imaging; Myo, myocardial; PPG, peak pressure gradient; SBP, systolic blood pressure.
myocardial T1 and ECV, using the T1 maps and full MOLLI series for analysis. Reproducibility was excellent using the T1 maps for assessment and good using the full MOLLI series.

**Comparison of T1 map analysis vs. MOLLI series**

The reproducibility of the T1 map analysis using the full MOLLI series was better than that of the full MOLLI series, with lower CoVs and narrower Bland–Altman limits of agreement (Figure 2). T1 maps were therefore used for further comparison between AS and controls.

Looking at the inter-technique agreement, the CoVs were good (<10%) for agreement between the two methods, but there was a small negative bias for the T1 map technique, which gave slightly lower raw T1 values compared with the full MOLLI series (mean native T1 = 1086.61 ± 22.67 vs. 1118.42 ± 55.40, mean ECV = 0.234 ± 0.018 vs. 0.239 ± 0.029, respectively). However, this difference was not statistically significant for ECV.

**Sample size calculation**

The test–retest reproducibilities were used to calculate the sample size needed to detect a 2.5% and 5% relative change in T1 and ECV, with a power of 90% and alpha error of 0.05 (Table 3). As can be seen, a much smaller sample size would be needed to demonstrate a significant change if T1 maps are used for analysis, instead of the full MOLLI series, for a 2.5% change to be demonstrated.

**Comparison of AS and controls**

There was no significant difference between patients and controls in age, gender, HR, and systolic blood pressure (SBP), and they had similar incidences of other co-morbidities (Table 1). Patients with AS had a significantly higher left-ventricular mass index (LVMI) compared with controls, with no significant difference in LV volume, leading to a significantly increased mass to volume ratio.

There was no significant difference in the native T1 value or ECV between asymptomatic patients with moderate-to-severe AS and matched healthy controls in our study: mean native myocardial T1 = 1103.32 ± 33.07 in all patients vs. 1092.27 ± 34.29 in controls; mean ECV = 0.243 ± 0.019 in all patients vs. 0.251 ± 0.026 in controls, P > 0.05.

**Moderate and severe AS**

The mean native T1 value was very similar between controls and the moderate AS group, with a non-significant trend (P = 0.055 on ANOVA test) for this to be higher in patients with severe AS, though there was significant overlap between all groups (Figure 3). There was also no significant difference in the ECV value between the three groups (P = 0.089). The mean Hct was lower in the severe AS group though not statistically significantly (Table 1).

**Discussion**

This is the first study to assess test–retest reproducibility of ECV measurement in patients with AS. Additionally, we compared...
values obtained from different post-processing methods: one outlining the myocardium on the series of 11 MOCO MOLLI images and the other using the inline T1 map. Previous studies have used different T1 mapping sequences and field strengths to examine T1 and ECV in controls and AS. Native T1 values measured using MOLLI have been shown to be higher than with the shortened MOLLI (ShMOLLI) sequence in healthy controls at 1.5 T\(^{20,21}\) while no difference was found at 3 T.\(^{21}\) Relatively lower T1 values have also been demonstrated in AS using ShMOLLI.\(^{10}\) However, there was no difference in the ECV when assessed using these two sequences.\(^{20}\) Native myocardial T1 values also increase with increased field strength,\(^{21,22}\) and therefore, results are not comparable between studies conducted at 1.5 and 3 T.

**Test–retest reproducibility in AS**

While test–retest reproducibility of T1 mapping has previously been assessed in healthy volunteers and one small study of 7 patients with amyloidosis\(^8\) using ShMOLLI and multi-breath-hold T1 mapping, this is the first study to assess it in patients with AS. Our reproducibility values using T1 maps compare favourably with those previously demonstrated for healthy volunteers with MOLLI at 3 T. For native

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**Figure 2** Scatter plots and Bland–Altman plots for test–retest reproducibility of ECV in moderate-to-severe aortic stenosis.

**Table 3** Sample sizes needed to detect a 5 or 2.5% change in parameter with a power of 90% and alpha error of 0.05

<table>
<thead>
<tr>
<th>Technique</th>
<th>Parameter</th>
<th>Required sample size (5% diff, 90% power)</th>
<th>Required sample size (2.5% diff, 90% power)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1 map</td>
<td>Native T1</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>ECV</td>
<td>20</td>
<td>72</td>
</tr>
<tr>
<td>MOLLI series</td>
<td>Native T1</td>
<td>33</td>
<td>125</td>
</tr>
<tr>
<td></td>
<td>ECV</td>
<td>73</td>
<td>285</td>
</tr>
</tbody>
</table>

Abbreviations as in Table 2.
myocardial T1, previous CoVs have been between 2.5 and 8.4%,\textsuperscript{6,22} compared with 1.8% in this report. For ECV, the CoV was 6.4% in Liu’s study\textsuperscript{6}, compared with ours of 6.5%. Therefore, the high reproducibility of T1 and ECV does suggest that this technique could be used reliably for serial monitoring of AS patients.

**T1 map vs. MOLLI series**

On comparing the reproducibility using T1 maps vs. full MOLLI series, we found higher reproducibility and narrower standard deviations for the inline T1 maps. This resulted in lower calculated sample sizes needed to demonstrate a significant difference, which is an important consideration for future longitudinal studies. This technique was also less time consuming, since the myocardium was outlined on a single image as opposed to 11 in the MOLLI series.

**Comparison of AS and controls**

We found no significant difference in the native myocardial T1 value or ECV between asymptomatic patients with moderate to severe AS and matched asymptomatic controls without valve disease. This finding is contrary to others who have demonstrated significantly higher T1 and ECV in patients with AS than healthy controls.\textsuperscript{7,10,13} However, the healthy control groups in most studies were not age matched to the patient group,\textsuperscript{6–8} and controls with any history of hypertension, diabetes, or other cardiovascular risk factors were excluded.\textsuperscript{9,10} A correlation between age and ECV has been demonstrated in one study,\textsuperscript{15} but not in others.\textsuperscript{9,13} We age matched and deliberately included controls with common co-morbidities, since we wanted to see the true effect of AS in addition to that of ageing and other possible effects of co-morbidities. Another recent study also did not demonstrate any significant difference in the native T1 value between AS and controls (1191 ± 34 vs. 1180 ± 28 ms respectively, $P = 0.29$), and although the ECVs were higher in the AS group, their controls were significantly younger.\textsuperscript{7} Their absolute values of the native T1 and ECV were higher than ours (T1 = 1191 vs. 1103, ECV = 0.28 vs. 0.24), but their AS cohort were slightly older and had a greater proportion of females, who have been shown to have higher ECV.\textsuperscript{23}

In Bull’s study, where the controls were age matched to the overall patient population, there was no difference found in the native T1 values between controls and patients with moderate AS, and there was a large overlap between moderate and asymptomatic severe AS. This is similar to our findings of no significant difference even after splitting the patient group into moderate and severe AS. In their study, Bull et al. also found a significant difference between asymptomatic severe AS and symptomatic severe AS.\textsuperscript{10} All patients in our study were asymptomatic at the time of scanning. Our AS cohort demonstrated a >25% increase in LVMI compared with controls despite no difference in volume or systolic function. This suggests the presence of significant pressure overload with compensated hypertrophy phase of LV remodelling. We did demonstrate a trend for the native T1 to be higher in the severe AS group, but they also tended to have a lower Hct value, which led to ECVs being equal across all groups. This finding highlights the importance of not relying solely on native T1 value for assessment.

We did not exclude patients with areas of LGE in the mid short-axis slice. This only occurred in two subjects and would tend to underestimate diffuse fibrosis (ECV) in the patients and therefore does not alter the main result that ECV is not significantly increased in asymptomatic AS patients than controls. It is possible that lower capillary density in patients with moderate AS and LVH\textsuperscript{2} may result in lower T1 values due to less blood per unit of myocardium, which may mask underlying diffuse interstitial fibrosis.

There are some limitations to this study. The numbers were relatively small, but similar to other studies assessing test–retest reproducibility of MRI measured parameters. The flip angle used in the earlier version of the MOLLI prototype used for this study was higher than the current recommendation (35°), which may have led to underestimation of the absolute T1 value,\textsuperscript{24} but as the same

![Figure 3](image-url)
protocol was used in all subjects studied, we do not believe this affects the validity of the results. Similarly, an older version of the MOLLI sequence (3,3,5) was used in this cohort, compared with which newer versions may produce more reliable T1 values, particularly at higher field strength. Another technical confounding factor could be the increased possibility of partial volume in controls with no LVH, leading to falsely higher T1 values, though a narrow myocardial ROI was used in these cases to minimize this effect.

The Holy Grail in the management of asymptomatic AS patients is to reliably identify those with incipient symptoms, with a view to offering aortic valve replacement. The lack of any significant difference between asymptomatic patients with severe AS and age-matched controls makes it very unlikely that T1 mapping will be sufficiently accurate to identify individual patients. However, longitudinal data are keenly awaited.

Conclusions

The test--retest reproducibility of T1 quantification using MOLLI is excellent in patients with AS and is higher when outlining the myocardium on a single T1 map rather than on each individual MOLLI image. There was no difference in native myocardial T1 or ECV demonstrated between asymptomatic patients with moderate to severe AS and age-matched controls without valve disease. Longitudinal studies are required to determine whether T1 mapping will be useful in the management of asymptomatic patients with severe AS.

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References