

# Native Myocardial Longitudinal ( $T_1$ ) Relaxation Time: Regional, Age, and Sex Associations in the Healthy Adult Heart

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**Purpose:** To use magnetic resonance imaging (MRI) at two field strengths to assess healthy adults' regional myocardial noncontrast (native)  $T_1$  relaxation time distribution, and global myocardial native  $T_1$  between sexes and across age groups.

**Materials and Methods:** In all, 84 healthy volunteers underwent MRI at 1.5T and 3.0T.  $T_1$  maps were acquired in three left ventricular short axis slices using an optimized modified Look–Locker inversion recovery investigational prototype sequence.  $T_1$  measurements in msec were calculated from 16 regions-of-interest, and a global  $T_1$  value from all evaluable segments per subject. Associations were assessed with a multivariate linear regression model.

**Results:** In total, 1297 (96.5%) segments were evaluable at 1.5T and 1263 (94.0%) segments at 3.0T. Native  $T_1$  was higher in septal than lateral myocardium (1.5T:  $956.3 \pm 44.4$  vs.  $939.2 \pm 54.2$  msec;  $P < 0.001$ ; 3.0T:  $1158.2 \pm 45.9$  vs.  $1148.9 \pm 56.9$  msec;  $P = 0.012$ ). Native  $T_1$  decreased with increasing age in females but not in males. Among lowest age tertile (<33 years) global native  $T_1$  was higher in females than in males at 1.5T ( $960.0 \pm 20.3$  vs.  $931.5 \pm 22.2$  msec, respectively;  $P = 0.003$ ) and 3.0T ( $1166.5 \pm 19.7$  vs.  $1130.2 \pm 20.6$  msec;  $P < 0.001$ ). No sex differences were observed in upper age tertile ( $\geq 55$  years) at 1.5T ( $937.7 \pm 25.4$  vs.  $934.7 \pm 22.3$  msec;  $P = 0.762$ ) or 3.0T ( $1153.0 \pm 30.0$  vs.  $1132.3 \pm 23.5$  msec;  $P = 0.056$ ). Association of global native  $T_1$  to age ( $P = 0.002$ ) and sex ( $P < 0.001$ ) was independent of field strength and body size.

**Conclusion:** In healthy adults, native  $T_1$  values are highest in the ventricular septum. Global native  $T_1$  was inversely associated with age in women, but not in men.

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Advances in magnetic resonance imaging (MRI) now enable the estimation of longitudinal (spin-lattice,  $T_1$ ) proton relaxation time in vivo using parametric mapping techniques. Non-contrast (native)  $T_1$  reflects myocardial water content and pathology, and  $T_1$  mapping has emerging clinical utility for detection of acute myocardial infarction,<sup>1</sup> acute myocarditis,<sup>2</sup> infiltrative cardiomyopathy,<sup>3,4</sup> and pressure-overload hypertrophy.<sup>5</sup>

$T_1$  can be measured in regions-of-interest (ROIs) in the heart.<sup>6</sup> However,  $T_1$  map acquisitions are susceptible to

artifacts, especially at higher magnetic fields, making their interpretation challenging.<sup>7</sup>  $T_1$  values also vary between scanner type and pulse sequence, and clinical guidelines recommend standardization of image acquisition and analysis.<sup>8</sup> Piechnik et al<sup>9</sup> described variation of native myocardial  $T_1$  in healthy subjects using the shortened modified Look–Locker inversion recovery (ShMOLLI) method at 1.5T in subjects aged 11–69 years (mean  $\pm$  standard deviation [SD] age  $38 \pm 15$ ) years. They observed that native  $T_1$  was associated with sex, body size, and hematocrit, but not age. The

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**TABLE 1. Typical Imaging Parameters at 1.5T and 3.0T**

|                        | 1.5T               | 3.0T               |
|------------------------|--------------------|--------------------|
| Bandwidth              | 1090 Hz/pixel      | 930 Hz/pixel       |
| Flip angle             | 35°                | 35°                |
| Echo time (TE)         | 1.1 msec           | 1.06 msec          |
| T1 of first experiment | 100 msec           | 100 msec           |
| TI increment           | 80 msec            | 80 msec            |
| Repetition time (TR)   | 788 msec           | 740 msec           |
| Parallel imaging       | 2                  | 2                  |
| Partial Fourier        | 6/8                | 6/8                |
| Matrix                 | 192 × 124 pixels   | 192 × 124 pixels   |
| Spatial resolution     | 2.2 × 1.8 × 8.0 mm | 2.2 × 1.8 × 8.0 mm |
| Scan time              | 17 heartbeats      | 17 heartbeats      |

current study is a further assessment of native  $T_1$  variation using a different  $T_1$  mapping method, at different MR field strengths, in older individuals, and involving gadolinium-based contrast MR to rule out incidental myocardial disease.

## Materials and Methods

### Volunteers

Healthy adults across a broad age range were enrolled based on responses to advertisements on public noticeboards and through personal contacts of the investigators. All subjects gave written informed consent after the nature of procedures had been fully explained, and ethical approval was granted for all study procedures (West of Scotland Research Ethics Service, reference 11/AL/0190). The inclusion criteria were age >18 years, no known history of cardiovascular disease or systemic illness, and a normal 12-lead electrocardiogram (ECG) recording. The exclusion criteria included prior history of cardiovascular or connective tissue disease, or treated hypertension or hypercholesterolemia. There was no upper age limit. For females, pregnancy or suspected pregnancy was also included as part of the exclusion criteria.

### MRI Protocol

MRI was performed at 1.5T (Magnetom Avanto, with a 12-element phased array surface coil, Siemens Healthcare, Erlangen, Germany) in a large regional hospital and at 3.0T (Magnetom Verio, with a 16-element phased array surface coil, Siemens Healthcare) in the university research center. The imaging protocol included cine MR with steady-state free precession (SSFP) and  $T_1$ -relaxometry (mapping) sequences. A cine short axis (SA) stack covered the full left ventricle (LV).  $T_1$  maps were acquired in three SA slices (basal, mid, and apical), using a motion-corrected optimized modified Look-Locker inversion recovery (MOLLI) investigational prototype sequence (Siemens Healthcare, works-in-progress method 448).<sup>10,11</sup> The MOLLI  $T_1$  cardiac-gated acquisition involved three inversion-recovery prepared inversion time (TI) scout experiments, with three heartbeats for recovery between each experiment, com-

bined within one protocol (3 (3) 3 (3) 5).<sup>12</sup> Typical imaging parameters are provided in Table 1.

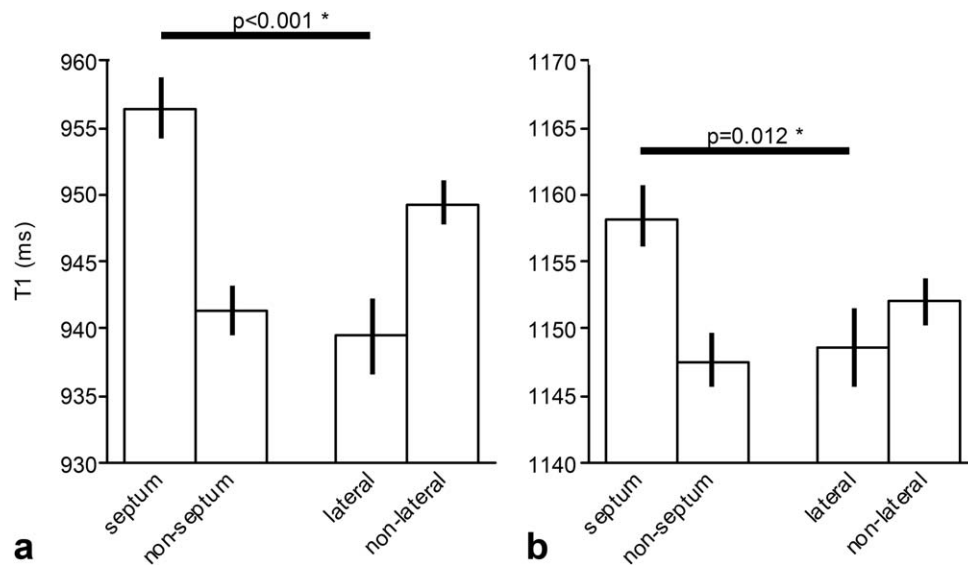
Participants over 45 years of age and an estimated glomerular filtration rate >30 mL/min underwent further contrast-enhanced imaging. Delayed-enhancement phase-sensitive inversion-recovery pulse sequences, covering the SA stack of a full LV,<sup>13</sup> and three (basal, mid, and apical) postcontrast  $T_1$  maps were acquired 10–15 minutes after intravenous contrast agent administration at 1.5T. Contrast was 0.15 mmol/kg of gadolinium diethyltriaminepentaacetic acid (Magnevist, Bayer Healthcare, Berlin, Germany). Volunteers aged >45 years, who did not receive contrast, were included in the other analyses.

Two phantoms (small: cylindrical, diameter 15 cm; large: box-shaped, 40 × 40 × 10 cm), containing water and contrast, were scanned at 1.5T and 3.0T. Phantoms were positioned centrally on the scanner table and axial  $T_1$  maps acquired with a simulated heart rate of 60 bpm.

### Image Analysis

Anonymized images were analyzed in a random order on a Siemens Healthcare (syngoMR) workstation by two MR-trained observers (S.R., D.C.) with 4 years of cardiac MR experience. The accuracy of all of the image analyses was reviewed by a cardiologist with over 10 years of experience (C.B.) in cardiac MR. The overall image quality was ranked as high, adequate, or nondiagnostic, based on: endo- and epicardial border definition (ie, ECG gating), success of motion correction image alignment, presence and severity of ghosting (ie, breathing) and SSFP off-resonance artifacts.

LV dimensions, volume, and ejection fraction were quantified using computer-assisted planimetry and an axial stack of images, and compared against well-established reference ranges.<sup>14</sup> The late gadolinium enhancement (LGE) images, covering the entire LV, were evaluated visually following current clinical guidelines,<sup>11,15</sup> and the absence of myocardial LGE was a requirement for inclusion of the participant in the analysis.



**FIGURE 1:** Regional differences in mean native  $T_1$  relaxation times (msec; mean, 95% CI) between septal vs. nonseptal ROIs and lateral vs. nonlateral ROIs, at: **a** = 1.5T and **b** = 3.0T.

Each  $T_1$  map was assessed separately by two observers (S.R., K.M.) for the presence of artifacts relating to susceptibility effects or cardiorespiratory motion, and evaluated against the original images. When there was discordance between the artifact scoring, a third observer (C.B.) acted as a blinded independent adjudicator. Artifacts related to off-resonance in MOLLI SSFP readout were included in susceptibility artifacts. When artifacts occurred and observers unanimously agreed that these would potentially contribute to variation in the  $T_1$  (msec), the affected segments were not included in the analysis. LV contours were delineated on the raw  $T_1$  image and copied onto the color-enhanced spatially coregistered maps.  $T_1$  maps were segmented according to the American Heart Association (AHA) 16-segment model, using the anterior right ventricular-LV insertion point as the reference point.<sup>16</sup> Segmental AHA ROIs were delineated by user-defined semiautomated border delineation (Argus, Siemens Healthcare). The ROIs were standardized to be of similar size and shape, containing at least 100 pixels in all of the segments. The  $T_1$  value was measured in each of the segments included, with particular care taken to delineate ROIs with adequate margins of separation from tissue interfaces prone to partial volume averaging, such as between blood-pool and myocardium.<sup>8,15</sup> The ROI from LV blood pool was also measured. ROIs were copied between the pre- and postcontrast  $T_1$  maps. Typical  $T_1$  maps are shown in Supplementary Fig. 1.

Septal  $T_1$  was calculated as a mean value of anteroseptal, inferoseptal, and septal AHA segments, while nonseptal  $T_1$  is the mean of the remaining AHA segments. Lateral  $T_1$  refers to the mean of inferolateral, anterolateral, and lateral AHA segments, and nonlateral to the remaining segments. Global averaged myocardial  $T_1$  relaxation times are presented as a mean value of all analyzable segments on a per-subject basis.

For the phantom analysis, ROIs containing at least 20 pixels were drawn to cover the entire area of the phantom  $T_1$  map. For the smaller phantom, 10 ROIs were used, and for the larger phantom 20 ROIs.

### Statistical Analysis

Categorical variables were expressed as number and percentage of observations. Normality was explored using residual plots and confirmed or excluded with the Ryan-Joiner statistic. Continuous variables with normal distribution are presented as means  $\pm$  SD unless otherwise mentioned. Extracellular volume (ECV) was calculated as  $ECV = (1-HCT) * ([1/T_{1myo\ post} - 1/T_{1myo\ pre}] / [1/T_{1blood\ post} - 1/T_{1blood\ pre}])$ .<sup>17</sup> When a blood sample for hematocrit (HCT) was not available, an estimation  $HCT = 0.88 - (T_{1blood} / 3240)$  was used.<sup>18</sup> Body surface area (BSA) was calculated using DuBois & DuBois method.<sup>19</sup> Correlation analyses were Pearson tests. Regional, sex, and age differences were assessed by the unpaired  $t$ -test, while comparisons between field strengths were undertaken with the paired  $t$ -test. In order to assess for associations between anthropometry and  $T_1$ , subjects were categorized by sex and age (tertiles with equal  $n$  values) and assessed using analysis of variance (ANOVA). No corrections were made for multiple testing. The univariate relationships between age, sex, height, weight, body mass index (BMI), and BSA were assessed, and univariate associates ( $P < 0.05$ ) were then included in a multivariate linear regression analysis. For regression models, male sex was coded as 1 and female sex as 0. For all of the analyses  $P < 0.05$  was considered statistically significant. Image analyst intra- and interobserver variability was tested in 30 volunteers selected at random per each field strength and assessed by Bland-Altman plots and 95% limits of agreement. The statistical analyses were performed using Minitab software (Minitab, State College, PA, v. 16.2.2).

### Results

In total, 86 healthy adults underwent MRI (1.5T and 3.0T) 1.4  $\pm$  1.4 days apart. Two subjects did not complete the MRI protocol. One male had an incidental finding of high  $T_1$  in the anterior wall of the left ventricle in the distribution of the left anterior descending coronary artery and,

| TABLE 2. Characteristics of the Healthy Volunteers |             |
|--|-------------|
| <b>Overall (n = 84)</b>                            |             |
| Mean ± SD age, years                               | 45 ± 18.0   |
| Male sex, n (%)                                    | 43 (49.4)   |
| Mean ± SD height, cm                               | 171.1 ± 9.9 |
| Mean ± SD weight, kg                               | 77.1 ± 14.8 |
| Mean ± SD body mass index, kg/m <sup>2</sup>       | 26.1 ± 3.9  |
| Mean ± SD body surface area, m <sup>2</sup>        | 1.8 ± 0.4   |

when retrospectively reviewed, had exertional chest pain suggestive of angina, which was not disclosed previously. One female experienced claustrophobia. The characteristics of the participants with complete  $T_1$  MRI ( $n = 84$ ) are shown in Table 2.

Native  $T_1$  values at 1.5T ( $P > 0.100$ ) and 3.0T ( $P > 0.100$ ) were normally distributed. The global mean native  $T_1$  relaxation time for all myocardial segments per subject was shorter at 1.5T ( $943.8 \pm 24.7$  msec) than at 3.0T ( $1154.7 \pm 26.2$  msec;  $P < 0.001$ ). There was a moderate correlation between the intraindividual global native  $T_1$  values measured at different field strengths ( $r = 0.577$ ;  $P < 0.001$ ) (Supplementary Fig. 2).

No correlation was found between the LV ejection fraction and global native  $T_1$  relaxation times at 1.5T ( $r = 0.112$ ;  $P = 0.343$ ) or 3.0T ( $r = 0.204$ ;  $P = 0.081$ ).

**Artifact Analysis**

Overall image quality was good (with 81.5% ranked as high, and 98.9% as high or adequate). After regional segmentation of the LV, 47 (3.5%) of 1344 segments imaged at 1.5T and 81 (6.0%) of 1344 segments at 3.0T were

excluded because of artifacts related to susceptibility effects (76, 5.7%) and cardiorespiratory motion (52, 3.9%). The majority of excluded segments were located at the distal LV, especially at 3.0T (Supplementary Table 1). Motion artifacts were most common among older individuals and susceptibility artifacts were more common in males than in females (Supplementary Table 2).

**Regional  $T_1$  Values**

We observed regional differences in mean native  $T_1$  relaxation times (Fig. 1, Supplementary Table 3). At 1.5T, mean native  $T_1$  values from septal segments ( $956.3 \pm 44.4$  msec) were longer than lateral segments ( $939.2 \pm 54.2$  msec;  $P < 0.001$ ). The regional differences were similar at 3.0T for septal vs. lateral segments ( $1158.2 \pm 45.9$  vs.  $1148.9 \pm 56.9$  msec;  $P = 0.012$ ).

For the regional differences within the phantom  $T_1$  map, at 1.5T coefficients of variation were 0.4 for the smaller phantom and 0.3 for the larger phantom, and at 3.0T 0.8 and 0.4, respectively.

**Associations Between  $T_1$  With Gender and Age**

The study population was categorized in tertiles of age (each  $n = 28$ ):  $<33$  years, 33–54 years,  $\geq 55$  years. In females, mean native  $T_1$  relaxation time reduced with increasing age (Fig. 2, Table 3). Native  $T_1$  did not vary with age in males. At 1.5T, global native  $T_1$  decreased by 5.50 msec for each additional decade ( $P = 0.014$ ). Native  $T_1$  was shorter in men than in women (Table 3) with an interaction for global native  $T_1$  between age and sex ( $P = 0.046$ ); ( $[\text{mean global native } T_1 \text{ (ms)}] = 976.0 - 0.550 \cdot [\text{age}] - 44.8 \cdot [\text{male sex}] + 0.619 \cdot [\text{age} \cdot \text{male sex}]$ ). Similar observations occurred at 3.0T (regression coefficient of  $-4.55$  msec/decade [ $P = 0.042$ ]). At 3.0T, global native  $T_1$  was shorter in males than in females ( $P = 0.001$ ), but there was no interaction for age and sex ( $P = 0.143$ ). Native  $T_1$

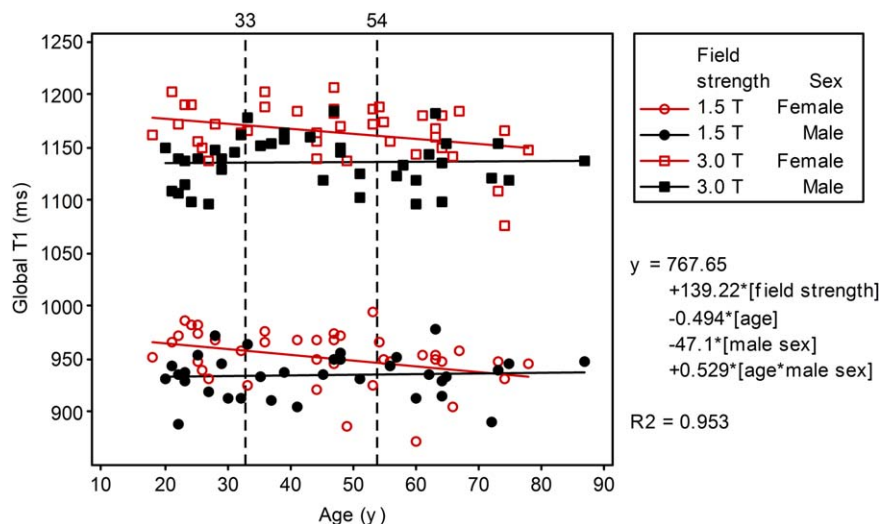


FIGURE 2: Global averaged myocardial native  $T_1$  relaxation times (mean, msec) displayed by age and sex at 1.5T and 3.0T.

**TABLE 3. Global Averaged Myocardial Native T<sub>1</sub> Relaxation Times (Mean ± SD, msec) Grouped by Age Tertiles and Sex at 1.5T and 3.0T**

|                                      | 1.5T         |              |                                      | 3.0T          |               |                                      |
|--------------------------------------|--------------|--------------|--------------------------------------|---------------|---------------|--------------------------------------|
|                                      | Males        | Females      | <i>P</i> -values (males vs. females) | Males         | Females       | <i>P</i> -values (males vs. females) |
| Age < 33, years<br>( <i>n</i> = 28)  | 931.5 ± 22.2 | 960.0 ± 20.3 | 0.003                                | 1130.2 ± 20.6 | 1166.5 ± 19.7 | <0.001                               |
| Age 33-54, years<br>( <i>n</i> = 28) | 936.8 ± 18.0 | 952.8 ± 28.5 | 0.093                                | 1149.4 ± 23.7 | 1176.0 ± 20.6 | 0.006                                |
| Age ≥ 55, years<br>( <i>n</i> = 28)  | 934.7 ± 22.3 | 937.7 ± 25.4 | 0.762                                | 1132.3 ± 23.5 | 1153.0 ± 30.0 | 0.056                                |
| <i>P</i> -value (tertiles)           | 0.828        | 0.092        |                                      | 0.079         | 0.045         |                                      |

was multivariably independent of height, weight, and BSA at both field strengths (Table 4). Univariate relationship between native T<sub>1</sub> and height, weight, and BSA was related to sex.

Global native T<sub>1</sub> was dependent on field strength (*P* < 0.001), and also on age (*P* = 0.002), sex (*P* < 0.001), and an interaction for native T<sub>1</sub> between age and sex included in the regression equation (*P* = 0.016); ([mean global native T<sub>1</sub> (msec)] = 767.65 + 139.22\*[field strength]-0.494\*[age]-47.1\*[male sex]+0.529\*[age\*male sex]).

#### Myocardial Extracellular Volume in Volunteers Aged >45 Years

In all, 37 (88.1%) of 42 volunteers aged >45 years underwent contrast-enhanced MRI. None of them had evidence of myocardial fibrosis (scar), based on the late gadolinium enhancement imaging. HCT was available for 26 (70.3%) volunteers aged >45 years, and an estimated HTC value used for 11 (29.7%) volunteers. There was no difference between actual (0.415 ± 0.026) and estimated (0.408 ± 0.034; *P* = 0.557) HCT values. ECV measurements were available

**TABLE 4. Relationships Between Global Native T<sub>1</sub> and Age, Sex, and Height, Weight, Body Mass Index, and Body Surface Area (*n* = 84)**

| Associations                 | 1.5T                    |                 | 3.0T                    |                 |
|------------------------------|-------------------------|-----------------|-------------------------|-----------------|
|                              | Coefficient (95% CI)    | <i>P</i> -value | Coefficient (95% CI)    | <i>P</i> -value |
| Univariable                  |                         |                 |                         |                 |
| Age, for 1 year difference   | -0.228 (-0.556, 0.101)  | 0.171           | -0.183 (-0.541, 0.174)  | 0.310           |
| Male sex                     | -17.05 (-28.01, -6.08)  | 0.003           | -28.55 (-39.51, -17.59) | <0.001          |
| Height, for 10 cm difference | -5.78 (-11.59, 0.030)   | 0.051           | -11.10 (-17.24, -4.96)  | 0.001           |
| Weight, for 1 kg difference  | -0.413 (-0.800, -0.026) | 0.037           | -0.430 (-0.848, -0.011) | 0.044           |
| BMI, for 1 kg/m <sup>2</sup> | -1.128 (-2.706, 0.451)  | 0.159           | -0.189 (-1.846, 1.469)  | 0.821           |
| BSA, for m <sup>2</sup>      | -30.4 (-56.9, -3.9)     | 0.025           | -40.6 (-69.2, -11.9)    | 0.006           |
| Multivariable associations   |                         |                 |                         |                 |
| Age, for 1 year difference   | -0.550 (-0.986, -0.115) | 0.014           | -0.455 (-0.893, -0.017) | 0.042           |
| Male sex                     | -44.8 (-74.0, -15.6)    | 0.003           | -49.5 (-79.3, -19.8)    | 0.001           |
| Age*male sex, interaction    | 0.619 (0.012, 1.225)    | 0.046           | 0.455 (-0.158, 1.068)   | 0.143           |
| Height, for 10 cm difference | -1.63 (-9.08, 5.83)     | 0.664           | -1.96 (-9.84, 5.92)     | 0.622           |
| Weight, for 1 kg difference  | -0.175 (-0.589, 0.238)  | 0.400           | 0.091 (-0.32, 0.502)    | 0.662           |
| BSA, for m <sup>2</sup>      | -12.4 (-42.8, 17.9)     | 0.415           | 2.1 (-29.1, 33.3)       | 0.894           |

for 514 of 592 (86.8%) segments. ECV values were normally distributed ( $P = 0.086$ ). The mean ECV fraction was similar in septal ( $25.3 \pm 3.1\%$ ) and lateral segments ( $25.5 \pm 2.9\%$ ;  $P = 0.776$ ). The mean global ECV fraction ( $25.0 \pm 2.3\%$ ) was not associated with sex ( $P = 0.071$ ), age ( $P = 0.147$ ), or body size (BMI:  $P = 0.760$ , BSA:  $P = 0.583$ ), with correlation for ECV fraction and age ( $r = -0.213$ ;  $P = 0.205$ ) remaining weak when grouped by sex (ECV% + male age:  $r = -0.248$ ;  $P = 0.322$ , and ECV% + female age:  $r = -0.165$ ;  $P = 0.499$ ).

### **Intra- and Interobserver Agreement of $T_1$ Measurements**

At 1.5T the intraclass correlation coefficient for reliability of mean  $T_1$  was 0.913 (95% confidence interval [CI]: 0.790, 0.960;  $P < 0.001$ ), and at 3.0T 0.909 (95% CI: 0.808, 0.958;  $P < 0.001$ ). Bland–Altman plots showed no evidence of bias. The intraobserver coefficients of variation for mean  $T_1$  were 2.07 (1.5T) and 2.21 (3.0T), and for interobservers 2.79 (1.5T) and 2.83 (3.0T). The intra- and interobserver coefficients of variation were slightly greater for lateral (vs. septal) regions at both field strengths (Supplementary Table 4).

### **Discussion**

We present information on myocardial native  $T_1$  values at 1.5T and 3.0T in 84 adults across a broad age range. The mean age in our study was older than in the largest other study of native  $T_1$  to date.<sup>9</sup> We used contrast-enhanced MRI to rule out the possibility of incidental myocardial disease in older subjects.

Native  $T_1$  was shorter at 1.5T vs. 3.0T, as would be expected. Whereas  $T_2$  relaxation times remain fairly constant,  $T_1$  relaxation times have been shown to be longer for most tissues at higher field strengths.<sup>20</sup> Our measurements of myocardial  $T_1$  values at different field strengths are consistent with those from other water-based tissues elsewhere in the body.<sup>20</sup> Our main observation was an age-related decline in global mean native  $T_1$  values in females. Myocardial native  $T_1$  relaxation times were longer in young females than in young males. Native  $T_1$  relaxation time was not associated with age in males. Second, native  $T_1$  relaxation times were longer in the LV septum vs. lateral wall. These differences were mostly consistent across both MRI field strengths. Third, we observed that the age- and sex-related associations were independent of field strength and body size. Fourth, as would be expected, we found that cardiorespiratory motion artifacts and susceptibility effects were more common at the higher field (3.0T vs. 1.5T) and predominated in the distal regions of the LV. A higher incidence of motion artifacts occurred in older patients ( $\geq 55$  years), and susceptibility artifacts were more common among males. Finally, the ECV fraction was not associated with myocardial region, age, or sex, in contrast to native  $T_1$  values.

Previous studies have reported conflicting information on age or sex associations of myocardial native  $T_1$  relaxation times.<sup>9,21–23</sup> Most of these investigations focused on comparisons between age groups, while we present regression analysis data independent of grouping and include an interaction term for age and male sex. Although we do not present paired longitudinal data for native  $T_1$  measurements over time in the same individuals, the data suggest an age-related decline in myocardial native  $T_1$  in females, in contrast to some previous studies.<sup>21,22</sup> These studies have interpreted an age-related elevation in myocardial native  $T_1$  values as a sign of increased myocardial fibrosis.<sup>24,25</sup> However, ECV values observed in our sample were not consistent with age-related myocardial fibrosis among older subjects, even though our sample included elderly subjects. Sex differences in age-related changes are especially relevant, as females develop cardiovascular disease on average 7–10 years later than men.<sup>26,27</sup> Our observations raise the question of whether sex hormone status may influence myocardial tissue characteristics as reflected by myocardial native  $T_1$ . Estrogen, progesterone, and androgens have effects on myocardial structure and function.<sup>28,29</sup> For example, sex-specific differences in myocardial hypertrophy have been recently associated with the regulatory role of estrogen pathways.<sup>30</sup> We present our results and interpretation as hypothesis generating and further research is warranted.

Our observation of regional differences in native myocardial  $T_1$  relaxation times are in line with previously reported findings.<sup>21,31</sup> Although B1 inhomogeneities may have a small effect, based on our phantom assessment they are unlikely to be the cause of regional differences observed in the myocardial  $T_1$  values. Instead, the lateral free wall is known to be more prone to motion artifacts,<sup>32</sup> which may partly explain the lower native  $T_1$  values in the lateral segments. As  $T_1$  maps are derived from a sequential series of images, motion during the acquisition may result in a poor  $T_1$  model fit and, consequently, in falsely low  $T_1$  values.<sup>1</sup> This seems to be further supported by our finding of a higher variation of  $T_1$  values in lateral (vs. septal) regions. The smaller spread of septal values (vs. lateral) supports the septal sampling approach proposed by Rogers et al for the standardization of native  $T_1$  measurements.<sup>31</sup>

Limited data are available about the reproducibility of myocardial  $T_1$  relaxation times at different field strengths. The sources of variation between myocardial  $T_1$  at different field strengths are likely to involve measurement errors in acquisition and analyses. Partial volume effects that are a recognized technical limitation<sup>9</sup> are likely to be more relevant in the distal LV and lateral wall where motion is greatest. MRI artifacts are more common at the higher magnetic field and affect especially distal LV.<sup>33,34</sup> Increased incidence of motion artifacts among older subjects may reflect a reduced propensity for breath-holding during the MRI

acquisition,<sup>32</sup> whereas the higher incidences of susceptibility artifacts among males may be related to the sex differences in LV dimensions.<sup>35</sup> Consistent with our findings, motion and susceptibility artifacts have been shown to be more prevalent at higher field strengths also in other body parts, such as the boundaries of para-nasal sinuses and bone–soft tissue interfaces in the spinal canal.<sup>36</sup> These artifacts are often subtle, calling for caution in clinical use.

The  $T_1$  mapping field is progressing rapidly with emerging clinical utility. The first  $T_1$  consensus statement of the Society for Cardiovascular Magnetic Resonance and CMR Working Group of the European Society of Cardiology<sup>8</sup> highlights the importance of representative local normal values for each site/scanner. Our data have a slightly lower spread of global and local mean  $T_1$  values than what has been reported in the myocardial reference ranges obtained before.<sup>37–39</sup> It is expected that in the future advances in MRI hardware and postprocessing will lower the spread even further.<sup>20</sup> A major limitation of our study is that we did not collect information on reproductive history, menopause, or sex hormone status. Considering the known precision of  $T_1$  measurements,<sup>39</sup> our finding of a relatively low correlation between  $T_1$  values at 1.5T and 3.0T raises some important questions. The lower than expected interscan reproducibility of  $T_1$  values may be partly related to the higher flip angle (35°) at 3.0T. A high flip angle may bias the  $T_1$  estimations with MOLLI sequences, especially at higher field strengths, and the use of smaller flip angles than what was applied in our study has been recently proposed (recommended: 1.5T: 30°, and 3.0T: 20°).<sup>35</sup> Further limitations include large but limited numbers of volunteers and the delay between the scans at different field strengths. Finally, MOLLI sequences are known to systematically underestimate true  $T_1$  values, since the later images are influenced by the previous inversions. Relying on R-R intervals for the timings<sup>12</sup> results in  $T_1$  estimations being easily affected by incomplete tissue recovery between inversions, especially at higher heart rates. Due to the effects of incomplete recovery, it has been suggested that different MOLLI schemes should be employed for native and postcontrast  $T_1$  measurements.<sup>40</sup>

In conclusion, native  $T_1$  values vary according to myocardial location. The explanation may be related to myocardial structure/function relationships as well as regional variation in artifacts. Sex difference in global myocardial mean native  $T_1$  relaxation times are observed among younger but not older subjects and this observation was consistent between MRI field strengths.

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