Gender Differences in Native Myocardial T1 in a Healthy Chinese Volunteer Cohort

Heerajnarain Bulluck¹,², Jennifer A Bryant¹, Jonan Zhien Tan¹, Yun Yun Go¹, Thu-Thao Le¹, Ru San Tan¹, Tiong Keng Lim¹, Hak Chiaw Tang¹, Narayan Lath¹, Adrian Shoen Low¹, Calvin Woon-Loong Chin¹, Stuart A Cook¹,³, Derek J Hausenloy¹,²,³,4,5,6

¹National Heart Research Institute Singapore, National Heart Centre Singapore, Singapore, Singapore
²The Hatter Cardiovascular Institute, Institute of Cardiovascular Science, University College London, London, UK
³Cardiovascular and Metabolic Disorders Program, Duke-National University of Singapore, Singapore, Singapore
⁴The National Institute of Health Research, University College London Hospitals, Biomedical Research Centre, London, UK
⁵Yong Loo Lin School of Medicine, National University Singapore, Singapore, Singapore
⁶Barts Heart Centre, St Bartholomew’s Hospital, London, UK

Objective: T1 mapping cardiovascular magnetic resonance (CMR) is emerging as a promising imaging biomarker. However, there are conflicting reports on whether myocardial T1 is affected by age, gender, heart rate, and blood T1. Therefore, the aim of this study was to assess the influence of these parameters on myocardial T1 at 1.5T in a healthy Chinese cohort.

Materials and Methods: 101 healthy Chinese volunteers underwent CMR (Siemens Aera 1.5T scanner). A mid-ventricular short axis modified Look-Locker inversion recovery T1 map was acquired. The images were analyzed on CVI42. Manual regions of interest were drawn in the inferior septum and in the blood pool.

Results: Participants’ mean age was 46±13 (range 21 to 68) years and 51 out of 101 patients (51%) were males. Females in this study had significantly higher myocardial T1 and blood T1 values than males (1025±26 ms vs. 1001±23 ms, p<0.001; and 1659±60 ms vs. 1577±54 ms, p<0.001 respectively). There was no correlation between myocardial T1 and age. Blood T1 and heart rate correlated with myocardial T1 in females, but not in males and both were significantly associated with myocardial T1 in a multivariate analysis. After adjusting myocardial T1 for heart rate and blood T1 in females, the standard deviation reduced by 12% but the gender difference was still present.

Conclusion: Gender-specific T1 values should be established by each center, and heart rate and blood T1 should be taken into account in female participants. This would be important in order to reliably detect small changes in native T1 in pathologies with diffuse interstitial fibrosis.

Key words Magnetic resonance imaging ∙ Myocardium ∙ Reference values ∙ Sex ∙ Healthy volunteers.

INTRODUCTION

Contrast-enhanced cardiovascular magnetic resonance (CMR) is considered the gold standard for the non-invasive detection of focal myocardial fibrosis [1,2]. Over the past decade, more in-depth tissue characterization has become possible using T1 mapping CMR [3]. This technique allows the non-invasive detection of diffuse interstitial myocardial fibrosis [4-6], amyloid deposits [7-9], edema [10-12], intramyocardial fat [13,14], and iron deposits [15]. In pathologies such as amyloidosis and Anderson-Fabry’s disease, where the changes in myocardial T1
values are large, T1 mapping is already being used in the clinical setting [16]. However, in conditions with diffuse interstitial myocardial fibrosis such as hypertensive heart disease [17], diabetic cardiomyopathy [18], and aortic stenosis [19], where the changes in myocardial T1 values are relatively small, more work needs to be done before this technique can be used for diagnosis, prognosis, disease surveillance, and assessment of response to therapies.

Initial methods of T1 measurement involved multiple breathholds to obtain the recovery curve at different time points. The Look–Locke sequence was then introduced [20] to measure the T1 relaxation time at multiple time points after an initial excitation pulse and then subsequently adapted as the modified Look–Locke inversion recovery (MOLLI) [21] sequence. Colored, pixel-wise T1 maps are generated automatically by the scanner, whereby each pixel carries the measured T1 value [3].

In order for native T1 mapping CMR to be established as a robust marker, the influence of the physiological changes on myocardial T1 due to age [22,23], gender [22–26], and heart rate [22,27] need to be addressed. There have been conflicting reports on whether a gender difference exists [22,28]. In a small study of 40 healthy individuals, the gender difference in myocardial T1 was eliminated after normalizing for blood T1 [26]. There are also conflicting reports on whether T1 increases [24,29] or decreases with age [22]. Other factors such as blood T1 (either due to the intravascular compartment or partial volume effects) [30] and heart rate have also been shown to influence myocardial T1 values [27]. Furthermore, T1 mapping values in an Asian cohort have not yet been reported and the Society for CMR and CMR Working Group of the European Society of Cardiology consensus statement [31] highlighted the need for site and vendor-specific reference values.

Therefore, the aim of this study was to assess the influence of age, gender, heart rate, and blood T1 on myocardial T1 at 1.5T in a healthy Chinese volunteer cohort.

MATERIALS AND METHODS

The study was approved by the Singhealth Centralized Institutional Review Board and all participants provided written informed consent. Healthy Chinese Singaporean volunteers free of a history or symptoms of cardiovascular disease, diabetes, or hypertension were recruited via local advertisement.

CMR acquisition

CMR scans were performed on a 1.5T scanner (Magnetom Aera; Siemens Medical Solutions, Erlangen, Germany) using a 60-channel cardiac phased array receiver coil. The imaging protocol included standard steady state free precession cines and mid-ventricular short axis native MOLLI T1 mapping as part of MyoMaps available on the scanner [21]. The sampling protocol involved 11 heart beats in total, with the acquisition of 5 images after the first inversion pulse, followed by a recovery phase of 3 heart beats and acquisition of the final 3 images after the second inversion pulse. This sampling protocol is referred to as the 5(3)3 sampling protocol throughout the manuscript. The acquisition parameters were as follows: pixel bandwidth=1085 Hz/pixel; flip angle=35°; matrix=256×144; slice thickness=8 mm; echo time=1.1 ms; repetition time=280 ms; typical field of view=360 mm; voxel size=1.5×1.5×8 mm; field of view phase=85%; acceleration factor for parallel imaging=2; acquisition time=11 heartbeats. Non-rigid motion correction was performed to align the set of images acquired at different inversion times and a non-linear least-square curve fitting was used to generate a pixel-wise colored T1 map in-line by the scanner. All CMR scans were screened for any structural abnormalities by Level 3 CMR cardiologists and radiologists.

Imaging analysis

All CMR scans were analyzed using specialist software (Circle Cardiovascular Imaging, Version 5.3.4, Calgary, Canada). Cine images were analyzed based on the current recommendations [2]. A region of interest (ROI) was manually drawn in the inferior septum (=0.5 cm²) and the left ventricular blood pool (=1.5 cm²) of the mid-ventricular short axis native MOLLI T1 map. The width of the ROI line in the inferior septum was 3 pixels and care was taken to avoid the inferior right ventricular insertion points and the blood pool by allowing for the myocardium to be visible (visually equivalent to at least more than an ROI line width–3 pixels) between the blood pool and ROI. For the blood pool ROI, care was taken to avoid the papillary muscles. Fig. 1 illustrates 2 mid ventricular short axis T1 maps from a male and a female volunteer with ROIs drawn on the inferior septum and blood.

Fig. 1. Example of the manual region of interest delineation in the inferior septum and the blood pool with representative values of two mid-ventricular MOLLI T1 maps from a male and a female volunteer. MOLLI: modified Look-Locker inversion recovery.
20 T1 maps were randomly chosen for inter-observer and intra-observer variability of T1 measurements.

Statistical analyses
Statistical analyses were performed using SPSS (Ver 22, IBM Co., IL, USA). Normality was assessed using the Shapiro-Wilk Test. Continuous data was expressed as mean±standard deviation (SD) or median (interquartile range), and categorical data was reported as frequencies and percentages. Groups were compared using the paired Student t-test, Wilcoxon signed rank test and unpaired Student t-test or Mann Whitney U test where appropriate. Correlation was assessed using either Pearson’s correlation coefficient for normally distributed data or Spearman’s rho for non-normally distributed data. Interobserver and intraobserver variability was assessed using the intraclass correlation coefficient (ICC). Factors significant on univariate linear regression analysis were included in a multivariate linear regression analysis. All statistical tests were two-tailed, and p<0.05 was considered statistically significant.

RESULTS

101 healthy Chinese volunteers completed the study protocol and were included in the analysis. The mean age was 46±13 (range 21 to 68) years and 51 of the 101 patients (51%) were males. Only 4 volunteers (4%) were smokers. Further details on the clinical and CMR characteristics are presented in Table 1.

Interobserver and intraobserver variability
There was excellent interobserver and intraobserver agreement for myocardial T1 (ICC 0.940, 95% CI 0.850–0.976 and ICC 0.978, 95% CI 0.944–0.991, respectively) and blood T1 measurements (ICC 0.997, 95% CI 0.980–0.999 and ICC 0.997, 95% CI 0.992–0.999, respectively) using manual ROI delineation.

Myocardial and blood T1 of the cohort
The mean myocardial T1 and blood T1 of the whole cohort were 1013±27 ms and 1618±70 ms, respectively. Females had significantly higher myocardial T1 and blood T1 values than males (1025±36 ms vs. 1001±33 ms, p=0.001; and 1659±60 ms vs. 1577±54 ms, p<0.001, respectively).

Impact of age, heart rate, gender, and blood T1 on myocardial T1
There was no correlation between myocardial T1 and age for both genders as shown in Fig. 2A. There was no difference in heart rate between the genders (female: 62±19 bpm, range 45–90 bpm; male: 62±11 bpm, range 45–90 bpm, p=0.84). However, blood T1 and heart rate were significantly correlated with myocardial T1 in females (blood T1 versus myocardial T1 R² 0.11, p=0.02, heart rate versus myocardial T1 R² 0.12, p=0.016), but not in males as shown in Fig. 2B and C.

Myocardial T1 adjusted for heart rate and blood T1 in females
In females, factors significantly associated with myocardial T1 on univariate linear regression analysis (heart rate and blood T1) were included in a multivariate linear regression analysis, and both factors remained significantly associated with myocardial T1. Using the slope derived from the multivariate linear regression analysis, myocardial T1 was adjusted for blood T1 and heart rate in females using the equation below adapted from Reiter et al. [26]:

\[
\text{Adjusted myocardial T1} = \text{measured myocardial T1} + \text{slope}_{\text{blood T1}} \times \text{blood T1} + \text{slope}_{\text{heart rate}} \times \text{heart rate} - \text{actual heart rate}
\]

Where slope_{blood T1}=0.18; slope_{heart rate}=0.79; mean heart rate=62 beats per minute; mean blood T1=1659 ms.

The mean adjusted myocardial T1 in females was 1025±23 ms and was similar to the non-adjusted myocardial T1 (1025±26 ms, p=0.95). The gender difference was still present (adjusted

Table 1. Clinical and CMR characteristics of the Chinese participants

<table>
<thead>
<tr>
<th></th>
<th>Males (n=51)</th>
<th>Females (n=50)</th>
<th>p</th>
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</thead>
<tbody>
<tr>
<td>Clinical</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Age (years)</td>
<td>48±14</td>
<td>44±13</td>
<td>0.14</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>131±16</td>
<td>121±16</td>
<td>0.003</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>79±9</td>
<td>73±9</td>
<td>0.002</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>62±11</td>
<td>62±9</td>
<td>0.84</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>171±6</td>
<td>159±7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>69±12</td>
<td>57±10</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI (kg m⁻²)</td>
<td>24±4</td>
<td>22±4</td>
<td>0.09</td>
</tr>
<tr>
<td>BSA (m²)</td>
<td>1.81±0.18</td>
<td>1.59±0.15</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CMR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVEDV (mL)</td>
<td>139±21</td>
<td>110±19</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVEDVi (mL m⁻²)</td>
<td>77±9</td>
<td>69±9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVESV (mL)</td>
<td>54±13</td>
<td>41±11</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVESVi (mL m⁻²)</td>
<td>30±6</td>
<td>26±6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVMass (g)</td>
<td>95±18</td>
<td>70±16</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVMass (g m⁻²)</td>
<td>52±8</td>
<td>44±7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>61±6</td>
<td>63±6</td>
<td>0.06</td>
</tr>
<tr>
<td>Blood T1 (ms)</td>
<td>1577±54</td>
<td>1659±60</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Myocardial T1 (ms)</td>
<td>1001±23</td>
<td>1025±26</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

BP: blood pressure, bpm: beats per minute, CMR: cardiovascular magnetic resonance, LVEDV: left ventricular end diastolic volume, LVEDVi: indexed left ventricular end diastolic volume, LVESV: left ventricular end systolic volume, LVESVi: indexed left ventricular end systolic volume, LVMass: left ventricular mass, LVMass: indexed left ventricular mass, LVEF: left ventricular ejection fraction.
myocardial T1 in females: 1025±23 ms, myocardial T1 males: 1001±23 ms, p<0.001). However, there was a 12% (3 ms) reduction in the SD for myocardial T1 in the female cohort.

**DISCUSSION**

The main findings of our study are; firstly, there was no change in myocardial T1 with age in this Chinese cohort up to 68 years of age. Secondly, myocardial T1 was influenced by heart rate and blood T1 in females but not in males. Furthermore, despite adjusting myocardial T1 for these 2 parameters, the gender difference persisted. Lastly, adjusting myocardial T1 for heart rate and blood T1 in females reduced the variability in this cohort by 12%.

Whether fibrosis increases with age remains a topic of debate. Sado et al. [32] previously showed in a cohort of 81 healthy volunteers that extracellular volume fraction (ECV) derived from native and post-contrast T1 did not change with age. However, they used the previous laborious technique for T1 measurement rather than the latest generation T1 mapping techniques. Most recently, Rosmini et al. [25], in a conference abstract involving 94 healthy volunteers and using the latest MOLLI T1 and ECV mapping technique, showed that T1 values fell with age, but there was no correlation between age and ECV. In a larger healthy volunteer cohort of 342 participants using the shortened MOLLI (ShMOLLI) T1 mapping technique, Piechnik et al. [22] also showed a reduction in T1 with age, but in females only. Rauhalammi et al. [23] recently showed that myocardial T1 by the MOLLI T1 mapping 3(3)3(3)5 sampling protocol was negatively correlated with age in females, but not in males in 84 participants. The impact of age on myocardial T1 has also been investigated in non-healthy volunteer cohorts. Ugander et al. [29] reported an increase in ECV with age in 60 patients with cardiovascular disease, but no scars. In the MESA cohort involving 1231 participants aged 54 to 93 years and with cardiovascular risk factors (the largest cohort of T1 mapping reported so far), Liu et al. [24] also showed an increase in T1 and ECV with age (more pronounced in males than females). However, in a sub-group of patients with reduced exposure to cardiovascular risk factors (n=235), there was no correlation between age and ECV. We also found no correlation between age and myocardial T1 in healthy hearts, but the maximum age of our cohort was 68 years.

The gender difference in myocardial T1 and ECV has been reported by several groups [22-26] and of note, all these studies were performed on Siemens scanners. In a multi-centre study using MOLLI T1 mapping on Philips scanners by Dabir et al. [28], no gender difference in myocardial T1 was observed. However, their study included a mixture of healthy individuals (n=102) and low-risk patients (n=113) and used the 3(3)3(3)5 MOLLI sampling protocol. We used the optimized 5(3)3 MOLLI sampling protocol which has been shown to have improved accuracy compared to the 3(3)3(3)5 MOLLI sampling protocol [27]. It is already recognized that differences in androgen levels between genders influence the cardiac geometry and lead to thicker hearts in females 

![Fig. 2. Correlation between myocardial T1 and (A) age; (B) heart rate; (C) blood T1, stratified according to gender. NS: not statistically significant.](image)
Heart rate is known to affect the MOLLI T1 maps due to loss of spatial resolution at higher heart rates, which then leads to an increase in motion and an increase in partial volume effects [27]. Piechnik et al. [22] previously reported an increase of 6 ms in ShMOLLI T1 values for every 10 bpm increase in heart rate. In our study, despite no significant difference in heart rate between genders, heart rate was positively associated with myocardial T1 in females, but not in males. This is likely due to females having thinner myocardium and therefore may be more prone to in-plane partial volume effects [22]. In a study of 40 healthy volunteers [27], myocardial T1 adjusted for blood T1 eliminated the gender difference. That study had a smaller number of participants compared to our study and furthermore, the MOLLI sampling protocol was 5(4)2 and different from the commonly used sampling protocols. In our study of 101 healthy volunteers, the gender difference was still present after adjusting for blood T1 and heart rate using the 5(3)3 MOLLI sampling protocol. However, the variability in myocardial T1 in females reduced by 12% and may likely represent a reduction in partial volume effects.

Liu et al. [24] explored the impact of ethnicity and found no difference in myocardial T1 values among Caucasian, African, Chinese, and Hispanic groups. The T1 values reported in our cohort of healthy Chinese Singaporeans were similar to the values reported in a UK cohort [25] using a similar sampling protocol on a Siemens platform at 1.5T (our cohort myocardial T1: males 1001±23 ms and females: 1025±26 ms; UK cohort: males 1008±33 ms and females 1043±37 ms).

The implications of this study are firstly, in centers using MOLLI T1 mapping on a Siemens platform at 1.5T with the 5(3)3 sampling protocol, T1 reference values should be derived for each gender separately. Secondly, myocardial T1 values in females should be adjusted to blood T1 and heart rate, which would reduce variability. The impact of gender, blood T1, and heart rate on myocardial T1 may not be significant in pathologies with big changes in T1 values, e.g., myocarditis [37], acute myocardial infarction [11], and amyloidosis [7]. However, in pathologies where myocardial T1 changes are subtler, e.g., hypertensive heart disease [17], diabetic cardiomyopathy [18], and aortic stenosis [19], the impact of gender, blood T1, and heart rate may be more significant and must be taken into account.

Limitations
We only recruited Chinese participants in this study, as they are the predominant ethnicity in Singapore. We did not administer contrast to rule out late gadolinium enhancement, but a normal scan was confirmed based on normal wall thickness and normal wall motion in a healthy volunteer cohort free of risk factors. For the same reason, ECV data was not available in this cohort. Hemoglobin and hematocrit results were not collected and therefore we could not adjust for these factors. Manual ROIs were drawn in the septum for representative T1 values rather than calculating mean segmental T1 values. This was to provide reference values using a method that can be easily performed in a clinical setting. We only used one vendor and one T1 mapping sequence at 1.5T. The variability in myocardial T1 may be multi-factorial due to a combination of biological, physiological, and technical factors, and warrants further investigation.

Conclusion
There was no correlation between age and myocardial T1 by MOLLI using the 5(3)3 sampling protocol up to an age of 68 years. In females, myocardial T1 was significantly associated with heart rate and blood T1. Adjusting myocardial T1 for heart rate and blood T1 did not eliminate the gender difference, but reduced the variability of myocardial T1 in females. Therefore, centers using MOLLI T1 mapping should provide gender-specific reference values for myocardial T1. Furthermore, heart rate and blood T1 should be taken into account in female participants, as this may be important when investigating small changes in native T1 in pathologies such as hypertensive heart disease, aortic stenosis, and diabetic cardiomyopathy, in order to detect diffuse interstitial fibrosis more reliably.

Conflicts of Interest
The authors declare that they have no conflict of interest.

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