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Phantom-Validated Reference Values of Myocardial Mapping and Extracellular Volume at 3T in Healthy Koreans

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Original Article

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Purpose: Myocardial T1 and T2 relaxation times are affected by technical factors such as cardiovascular magnetic resonance platform/vendor. We aimed to validate T1 and T2 mapping sequences using a phantom; establish reference T1, T2, and extracellular volume (ECV) measurements using two sequences at 3T in normal Koreans; and compare the protocols and evaluate the differences from previously reported measurements.

Materials and Methods: Eleven healthy subjects underwent cardiac magnetic resonance imaging (MRI) using 3T MRI equipment (Verio, Siemens, Erlangen, Germany). We did phantom validation before volunteer scanning: T1 mapping with modified look locker inversion recovery (MOLLI) with 5(3)3 and 4(1)3(1)2 sequences, and T2 mapping with gradient echo (GRE) and TrueFISP sequences. We did T1 and T2 mappings on the volunteers with the same sequences. ECV was also calculated with both sequences after gadolinium enhancement.

Results: The phantom study showed no significant differences from the gold standard T1 and T2 values in either sequence. Pre-contrast T1 relaxation times of the 4(1)3(1)2 protocol was 1142.27 ± 36.64 ms and of the 5(3)3 was 1266.03 ± 32.86 ms on the volunteer study. T2 relaxation times of GRE were 40.09 ± 2.45 ms and T2 relaxation times of TrueFISP were 38.20 ± 1.64 ms in each. ECV calculation was 24.42% ± 2.41% and 26.11% ± 2.39% in the 4(1)3(1)2 and 5(3)3 protocols, respectively, and showed no differences at any segment or slice between the sequences. We also calculated ECV from the pre-enhancement T1 relaxation time of MOLLI 5(3)3 and the post-enhancement T1 relaxation time of MOLLI 4(1)3(1)2, with no significant differences between the combinations.

Conclusion: Using phantom-validated sequences, we reported the normal myocardial T1, T2, and ECV reference values of healthy Koreans at 3T. There were no statistically significant differences between the sequences, although it has limited statistical value due to the small number of subjects studied. ECV showed no significant differences between calculations based on various pre- and post-mapping combinations.

Keywords: Cardiac MRI; Cardiac mapping; Reference value; ECV; T1 mapping, native T1, T2 mapping

INTRODUCTION

Myocardial-tissue mapping by means of cardiovascular magnetic resonance (CMR) allows non-invasive characterization of myocardial tissue (1). T1 and T2 relaxation times as well as image-based T1 and T2 mapping values are also helpful in understanding the characteristics of the myocardium. Moreover, the extracellular volume (ECV), obtained from pre-contrast T1 (pre-T1), post-contrast T1 (post-T1), and hematocrit, gives information on myocardial fibrosis and edema (2).

However, T1 and T2 relaxation times are affected not only by the intensity of the magnetic field, but also by other technical factors, such as CMR platform/vendor, type of sequence, details of image post-processing, local factors, and the physical and chemical environment of water protons in the tissue (1, 3). Because of these factors, it is difficult to compare mapping values between different vendors and hospitals. Furthermore, reference values have been previously presented in many published papers, but they are derived from limited protocols, with most measurements done at 1.5T. Moreover, most of the previous studies were conducted in Western countries; so selection bias may have been present. Recently, efforts have been undertaken for standardization using a reference phantom to overcome these differences.

The goals of our study were 1) to validate T1 and T2 mapping sequences using phantoms, 2) to establish T1, T2, and ECV reference measurements using two sequences at 3T in normal Koreans, and 3) to compare the protocols and evaluate the differences from previously reported measurements.

MATERIAL AND METHODS

Study Population

This prospective study was approved by the Institutional Review Board of our institution. Informed consent was obtained from all participants (IRB No. KC16OIS10720). Between 2017-10-12 and 2018-10-16, we recruited 12 healthy subjects, aged between 28 and 56 years. We considered subjects healthy if they had:

(i) an uneventful medical history,
(ii) absence of symptoms indicating cardiovascular dysfunction,
(iii) normal electrocardiogram (ECG), and
(iv) normal myocardial tissue assessed by late gadolinium enhancement (LGE).

One woman dropped out of the study because of claustrophobia, so 11 volunteers were eventually included (6 men and 5 women). Table 1 shows the characteristics of the volunteers of this study. The subjects underwent cardiac magnetic resonance (MR) imaging on a 3T MR scanner (Verio, Siemens, Erlangen, Germany), equipped with a 16-channel cardiac radiofrequency coil and ECG for cardiac gating.

Table 1. Characteristics of the Volunteers

No	Age	Sex	Systolic BP/ diastolic BP	HR (T1)	HR (T2)	Height	Weight	BMI	BSA	Smoking	Glucose	Total cholesterol	TG	HDL	LDL	Hct
1	47	M	125/80	66	66	173	83	27.7	1.97	no	93	227	65	57	150	44.3
2	56	M	120/80	57	63	174	72	23.8	1.86	no	89	162	91	48	97	46.1
3	45	M	116/76	47	47	173	73	24.4	1.87	no	83	186	59	38	133	44.7
4	39	M	128/84	58	60	175	78	25.5	1.93	no	85	209	112	50	130	41.8
5	41	M	135/87	58	57	170	83	28.7	1.95	no	86	158	174	54	64	45.4
6	45	F	117/70	59	57	160	61	23.8	1.63	no	85	201	99	46	121	41.2
7	44	F	130/75	66	66	170	73	25.3	1.84	no	84	237	57	61	159	41.6
8	46	F	144/79	46	94	158	54	21.6	1.54	no	99	163	86	42	99	46.8
9	34	M	125/75	75	75	169	70	24.5	1.8	no	109	143	68	50	73	47.2
10	28	F	101/60	61	57	161	50	19.3	1.51	no	88	175	45	61	100	41
11	32	F	100/64	70	65	162	50	19.1	1.51	no	105	112	56	48	48	36.1

BMI = body mass index; BP = blood pressure; BSA = body surface area; Hct = hematocrit; HDL = high-density lipoprotein; HR (sequence) = average heart rate of the patient at the time of sequence; LDL = low-density lipoprotein; TG = triglyceride

Phantom Validation

We did phantom validation first. Twelve $NiCl_2$ and $MnCl_2$ sample phantoms were prepared; the two sets of samples were stacked in a round box, which was filled with tap water to obtain suitable models (Fig. 1).

Mapping values from two types of modified look locker inversion recovery (MOLLI) (4(1)3(1)2, 5(3)3) were compared with the gold standard T1 mapping method (inversion recovery weighted turbo spin echo). The MR parameters of each sequence are listed in Table 2.

In the T2 mapping protocol, we compared T2 mapping based on the gradient enhancement (GRE) and TrueFISP methods with the multi-spin-echo method, considered as the gold standard. The MR parameters of each sequence are listed in Table 3. We measured the mapping value of the phantom by drawing of the region of interest (Fig. 2).

CMR Examination: Imaging Parameters of the T1 and T2 Mapping Sequences

To assess left ventricular (LV) myocardial function and mass, we acquired 10-12 consecutive 8-mm short-axis images of the LV using a cine balanced steady-state free-precession sequence (b-SSFP). The imaging parameters were as follows: repetition time (TR) 3.3 ms, echo time (TE) 1.2 ms, flip angle (FA) 31°, field of view (FOV) 360 × 357 mm^2, matrix 224 × 155, slice thickness 8 mm, receiver bandwidth (BW) 970 Hz/px, parallel imaging using GRAPPA reconstruction (R = 2), and 25 cardiac phases.

Three-ventricular short-axis images (base, mid-ventricle, and apex) and modified look locker (MOLLI) images were then acquired for T1 mapping using 5(3)3 and 4(1)3(1)2 sequences. The imaging parameters are reported in Table 4.

For T2 mapping, we acquired data in the apex, midventricular, and basal short-axis view (SAX) planes using a T2-prepared single-shot SSFP technique. The imaging parameters are reported in Table 4.

To calculate the ECV, we acquired T1 mapping data in the basal, midventricular, and apical SAX planes, 10-15 minutes after administration of 0.15 mmol/kg i.v. meglumine gadopentetate (MRBest®, Accuzen, Taejoon Pharm Co., Seoul, Korea). We did LGE imaging in the same planes as b-SSFP CINE imaging using a segmented inversion-recovery gradient-echo sequence beginning 10-15 minutes after contrast administration. The inversion time (TI) was repeatedly adjusted to appropriately set the myocardium signal during LGE image acquisition. The imaging parameters were: TR = 5.3 ms, TE = 2.0 ms, FA = 20°, FOV 340 × 340 mm^2, matrix 256 × 179, slice thickness 8 mm, BW 285 Hz/px, GRAPPA acceleration factor 2.

CMR Image Analysis

All CMR analyses with manual myocardium contouring using available software (ISP, Philips, Best, the Netherlands) were done by two observers, with a 15-year and 1-year history of CMR image analysis. T1, T2, and post T1 mapping analyses were in the three LV short-axis slices. Endocardial

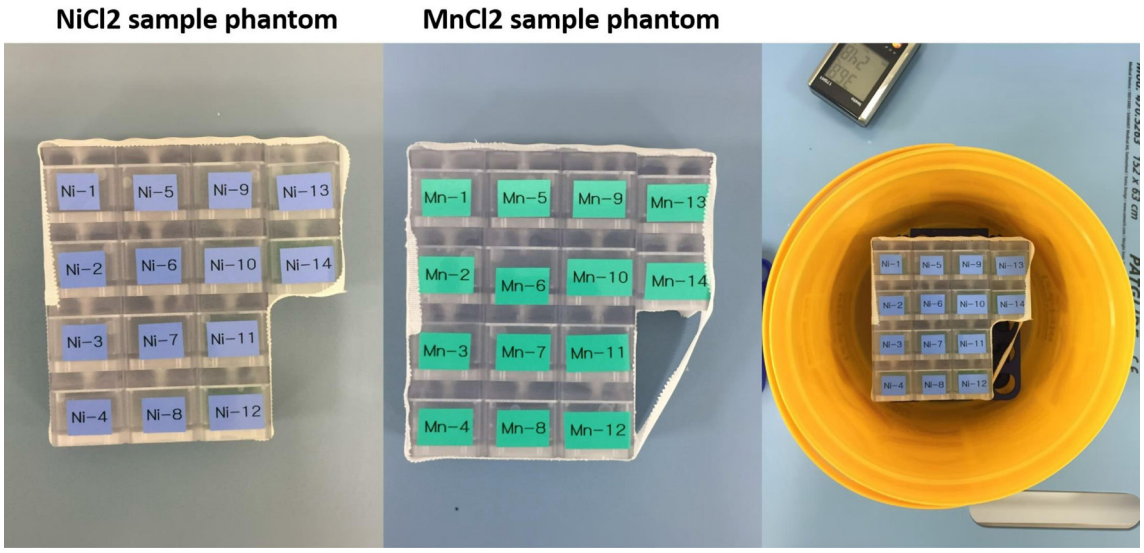


Fig. 1. Phantom model. The phantoms, consisting of various amounts of $NiCl_2$ and $MnCl_2$, were provided by the Korean Research Institute of Standards and Science (KRISS). Both phantoms were stacked in the middle of a jar, which was filled with tap water to prevent any image distortion.

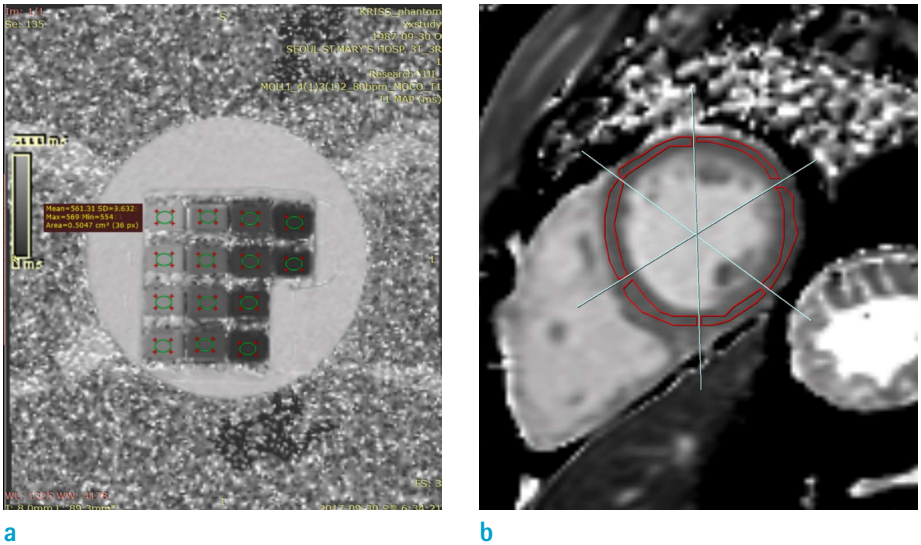
Table 2. T1 Mapping Protocols for Validation

3T Siemens Verio	Gold standard (GSTD)* T1 mapping	Modified look-locker inversion recovery (MOLLI)	
Sequence	Inversion Recovery weighted Turbo Spin Echo	4(1)3(1)2	5(3)3
Scan plane	Coronal	Coronal	Coronal
Thickness	8 mm	8 mm	8 mm
TR	6000 ms	414.62 ms	414.62 ms
TE	8.2 ms	1.22 ms	1.22 ms
FA	180 deg	35 deg	35 deg
Inversion time (ms)	30, 60, 150, 300, 600, 1000, 1500, 2000, 3000	Min TI = 129 ms Inc. TI = 80 ms	Min TI = 129 ms Inc. TI = 80 ms
Averages	1	1	1
Echo train length	4	1	1
Pixel size (mm × mm)	0.98 × 0.98	1.17 × 1.17	1.17 × 1.17

Table 3. T2 Mapping Protocols for Validation

3T Siemens Verio	Gold standard (GSTD)* T2 mapping	T2 preparation based T2 mapping	
Sequence	Multiple echo spin echo	T2map GRE	T2map TrueFISP
Scan plane	Coronal	Coronal	Coronal
Thickness	8 mm	8 mm	8 mm
TR	6000 ms	311.19 ms	310.13 ms
TE	8.8, 17.6, 26.4, 35.2, 44.0, 52.8, 61.6, 70.4, 79.2 ms	1.12 ms	1.06 ms
FA	180 deg	12 deg	35 deg
Averages	1	1	1
Echo train length	1	1	1
Pixel size (mm × mm)	0.98 × 0.98	1.87 × 1.87	1.87 × 1.87

FA = flip angle; TE = echo time; TR = repetition time



a b

Fig. 2. Examples of T1 mapping measurements in the phantom and a healthy volunteer. (a) Phantom. The region of interest of the phantom was measured by drawing 36 pixels for one homogeneous part in the center of the box. (b) Healthy volunteer. T1 mapping measurements of the mid-left ventricle myocardium in short-axis view with the epicardium, endocardium, and blood pool excluded. Myocardial segmentation was done using the American Heart Association standard (16 segmentation model).

Table 4. T1 and T2 Mapping Imaging Parameters

	T1 4(1)3(1)2	T1 5(3)3	T2 GRE	T2 TrueFISP
TR (ms)	2.7	2.7	2.8	2.5
TE (ms)	1.12	1.12	1.12	1.06
FA (degree)	35	35	12	35
FOV (mm^2)	307 × 360	307 × 360	288 × 360	288 × 360
Matrix	256 × 144	256 × 144	116 × 192	116 × 192
Slice thickness (mm)	8	8	8	8

FA = flip angle; FOV = field of view; TE = echo time; TR = repetition time

and epicardial contours were traced manually. We did myocardial segmentation using the American Heart Association standard (16 segmentation model) (4). Results are presented both per segment and averaged per slice. The measurements were limited to regions of interest (ROIs) containing only myocardium to avoid contamination by signals from blood or epicardial soft tissue (Fig. 2).

We calculated the ECV using the known formula (2).

$$ECV=(1-haematocrit)\frac{\frac{1}{post\ contrast\ T1\ myo}-\frac{1}{native\ T1\ myo}}{\frac{1}{post\ contrast\ T1\ blood}-\frac{1}{native\ T1\ blood}}$$

Inter- and Intra-Observer Variability

We tested inter- and intra-observer variability in three subgroup of randomly selected subjects (48 myocardial segments, 27% of total subject). For inter-observer variability, the two independent observers did post-processing blinded to each other's results. For intra-observer variability, one observer repeated the measurements using the identical method six months later.

Statistical Analysis

Statistical analyses used SAS, version 9.4, and a $P < 0.05$ was considered statistically significant in all tests. We computed descriptive statistics, such as average and 95% confidence interval, for the total, slice, and segment characteristics of each protocol. We used Spearman's correlation analysis to find the correlations between each pre-T1, post-T1, T2, and ECV protocol, the intra-class correlation coefficient to evaluate the agreement between protocols, and the Wilcoxon rank-sum test to compare male and female subjects. Inter- and intra-observer variability were tested by inter-class correlation coefficient (ICC) and coefficient of variation (CV, %).

RESULTS

Phantom Validation

When T1 mappings were compared, the measurement error was smaller in $NiCl_2$ samples, which reported longer T1 than did $MnCl_2$ samples as the heart rate increased. $NiCl_2$ was thus more appropriate for the comparison of T1 values (Fig. 3).

When we compared the MOLLI 4(1)3(1)2 and 5(3)3 sequences within $NiCl_2$ samples, the T1 error according to the heart rate of the 5(3)3 sequence was smaller than that of 4(1)3(1)2. However, the 4(1)3(1)2 sequence also showed small errors in the short-T1 samples.

In T2 mapping, changes of T2 with increasing heart rate were not observed in either $NiCl_2$ or $MnCl_2$ samples, and $MnCl_2$ samples showed a linear increase of T2. In particular, T2 showed a linear trend with the normal myocardial T2 range around 50 ms.

When we compared GRE and TrueFISP sequences, all samples showed similar trends, and T2 differences between the two methods were not observed. Therefore, the analysis confirmed that GRE or TrueFISP can be selected based on the image artifacts (Fig. 4).

Results on Healthy Volunteers

After we confirmed the appropriateness of the mapping by means of phantom validation, we analyzed 3T images from 11 healthy participants. Between the 352 segments obtained, four were not suitable for analysis, because of susceptibility artifacts and were thus excluded, so 344 segments were eventually eligible for analysis.

(1) Left ventricular myocardial function and mass

Global and regional left ventricular function was normal in all volunteers (mean ejection fraction ± SD, 65.9 ± 7.9%; LVEDV ± SD, 103.2 ± 17.1 mL, LVEDV index, 56.5 ± 10.7 mL/m^2; LV mass, 82.5 ± 20.9g; LV mass index, 44.3 ± 8.9 g/m^2). LGE MR images did not show myocardial scar in any of the participants.

(2) T2 mapping

The T2 relaxation times were 40.09 ± 2.45 ms and 38.20 ±1.64 ms on GRE and TrueFISP, respectively. T2 relaxation times for each segment and slice are shown in Supplementary material 1 and Figure 5.

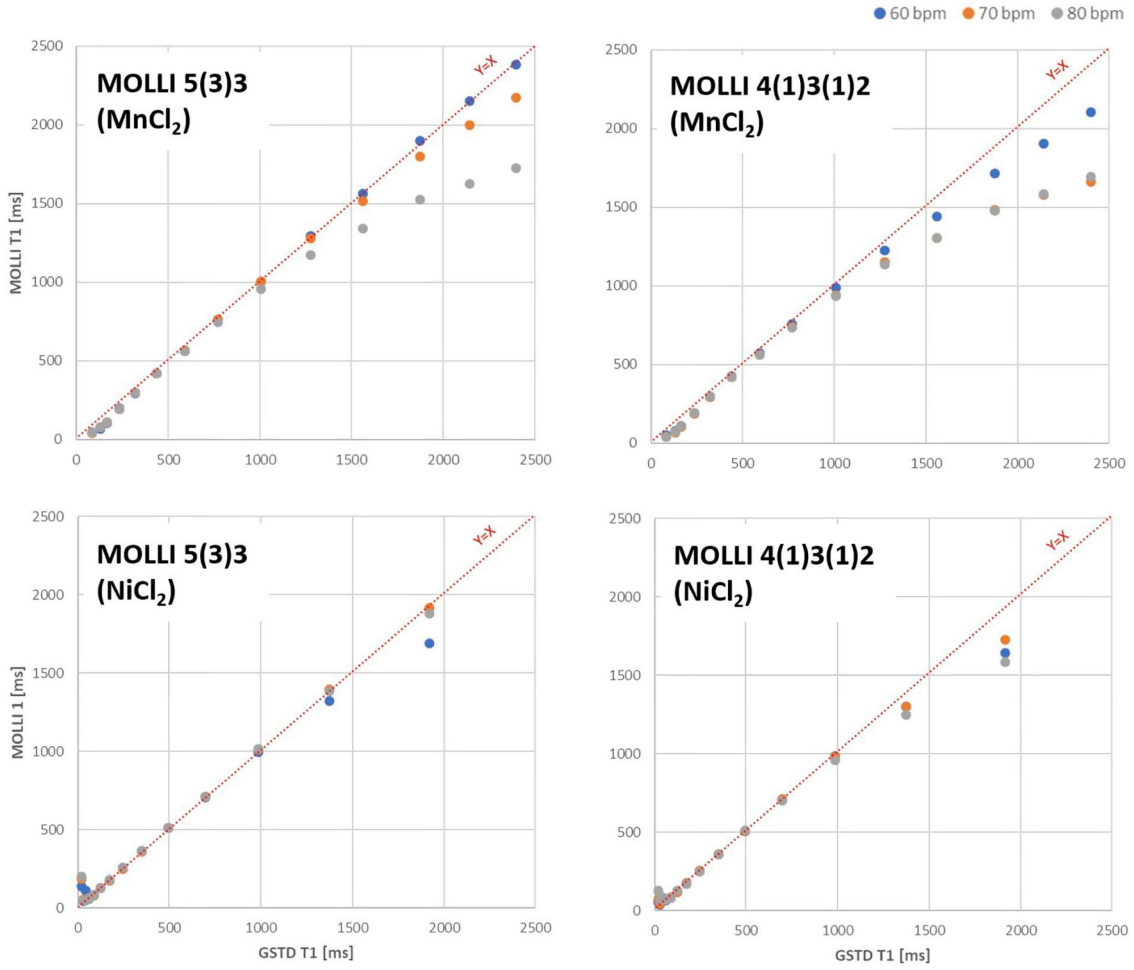


Fig. 3. T1 mapping result of phantom. The measurement error is smaller in $NiCl_2$ as the heart rate increased, suggesting that $NiCl_2$ is more appropriate for the comparison of T1 values. When comparing the MOLLI 4(1)3(1)2 and 5(3)3 sequences within $NiCl_2$ samples, the T1 error according to the heart rate of the 5(3)3 sequence is smaller than that of 4(1)3(1)2. However, the 4(1)3(1)2 sequence also shows small errors in the short-T1 samples.

Specifically, the mean T2 values on GRE were 38.88 ± 2.65 ms (base), 40.12 ± 3.04 ms (middle), and 41.86 ± 5.50 ms (apex), whereas TrueFISP gave T2 mean values of 37.93 ± 2.82 ms (base), 38.39 ± 1.59 ms (middle), and 38.32 ± 2.64 ms (apex).

When we compared the T2 mapping values obtained from GRE and TrueFISP, no statistically significant differences were revealed in any slice value or in the total value (Supplementary material 2).

(3) Pre-contrast T1 mapping

The pre-contrast T1 relaxation times were 1142.27 ± 36.64 ms and 1266.03 ± 32.86 ms in the 4(1)3(1)2 and 5(3)3 protocols, respectively, as shown in Supplementary material 1 and Figure 5.

Specifically, the mean values in the 4(1)3(1)2 protocol were 1140.38 ± 32.86 ms (base), 1143.34 ± 41.24 ms (middle), and 1143.52 ± 49.26 ms (apex), whereas in the 5(3)3 protocol, the mean values were 1265.37 ± 29.61 ms (base), 1263.98 ± 34.93 ms (middle), and 1270.10 ± 65.18 ms (apex).

There was no statistically significant difference in slice-specific pre-T1 mapping values obtained using the two protocols ($P > 0.05$) (Supplementary material 2).

(4) Post-contrast T1 mapping

The post-contrast T1 relaxation times were 599.68 ± 31.95 ms and 613.39 ± 37.49 ms for the 4(1)3(1)2 and 5(3)3 protocols, respectively. The post-contrast T1 relaxation times per slice are shown in Supplementary material 1 and Figure 5.

Specifically, the mean values in the 4(1)3(1)2 protocol

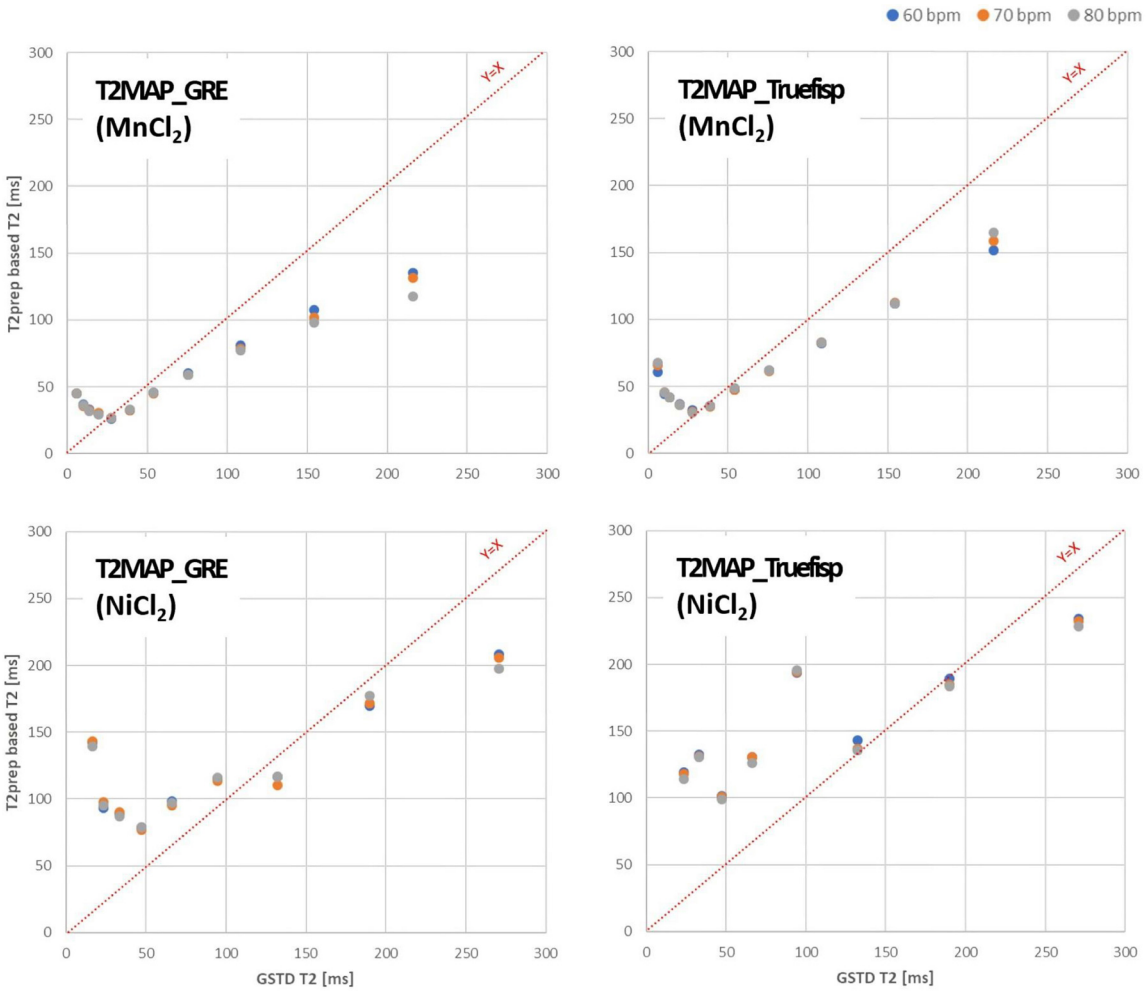


Fig. 4. T2 mapping result of phantom. Changes of T2 with increasing heart rate are not noted in either $NiCl_2$ or $MnCl_2$ samples, and $MnCl_2$ samples show a linear increase of T2. In particular, T2 showed a similar linear trend with the normal myocardial T2 range around 50 ms. When GRE and TrueFISP sequences are compared, all samples show similar trends, and T2 differences between the two methods are not observed.

were 603.10 ± 31.32 ms (base), 603.04 ± 36.62 ms (middle), and 589.49 ± 30.10 ms (apex), whereas those in the 5(3)3 protocol were 626.51 ± 34.53 ms (base), 612.64 ± 41.06 ms (middle), and 594.85 ± 45.23 ms (apex).

On post-contrast T1 mapping, the apical T1 relaxation time was smaller than the basal one in both protocols. However, there was no statistically significant difference in slice-specific post-T1 mapping values obtained using the two different protocols ($P > 0.05$) (Supplementary material 2).

(5) Extracellular volume

The ECV values were 24.42 ± 2.41% and 26.11 ± 2.39% in the 4(1)3(1)2 and 5(3)3 protocols, respectively. The ECV per slice are shown in Supplementary material 1 and Figure 6.

Specifically, the 4 (1)3(1)2 protocol mean values were 24.25 ± 2.79% (base), 23.92 ± 1.89% (middle), and 25.42 ± 3.32% (apex), whereas those in the 5(3)3 protocol were 25.32 ± 2.06% (base), 25.99 ± 2.76% (middle), and 27.47 ± 3.58% (apex) (Supplementary material 1).

When we compared the ECV values obtained by the 4(1)3(1)2 and 5(3)3 protocols, no statistical difference was found in the values for any segment or slice or in the total value (Supplementary material 2).

In addition, we evaluated the combined ECV, derived from the pre-T1 relaxation time of MOLLI 5(3)3 and the post-T1 relaxation time of MOLLI 4(1)3(1)2. The mean values of this combined ECV were 27.31 ± 2.86% (base), 26.72 ± 2.08% (middle), and 27.89 ± 3.5% (apex) (Supplementary material 1). No statistically significant difference was found

when we compared these values with those obtained from the 4(1)3(1)2 and 5(3)3 protocols in any segment or slice (Supplementary material 2).

We also evaluated the combined ECV from the pre-T1 relaxation time of MOLLI 4(1)3(1)2 and the post-T1 relaxation time of MOLLI 5(3)3, denoted as ECV-combined_

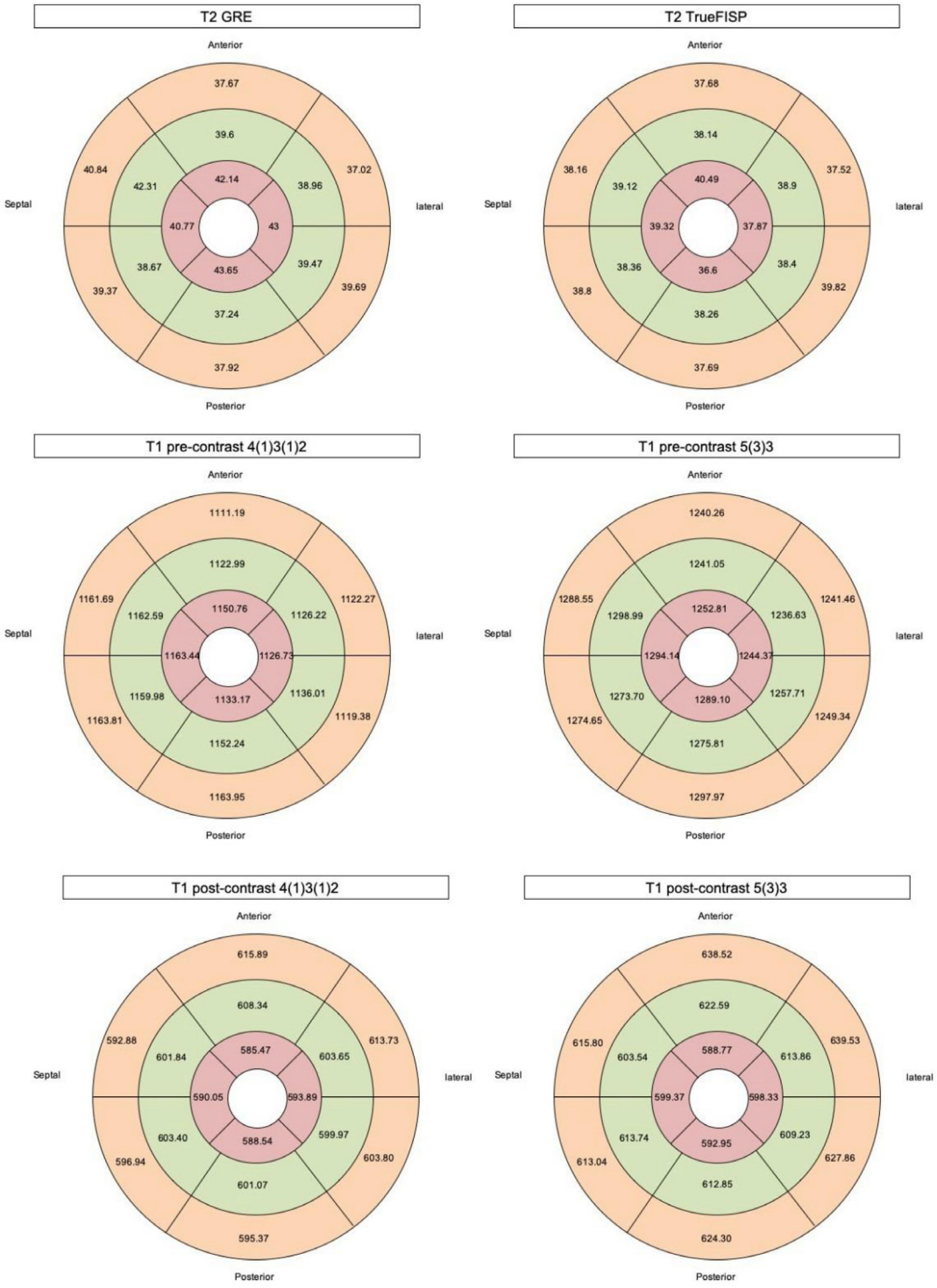


Fig. 5. Mean T2 and T1 relaxation times. T2 and T1 relaxation times (ms) for each myocardial segment illustrated as bulls-eye plots representing 16 segments of the basal (outer ring), mid-ventricular (middle ring), and apical (central ring) short-axis plane.

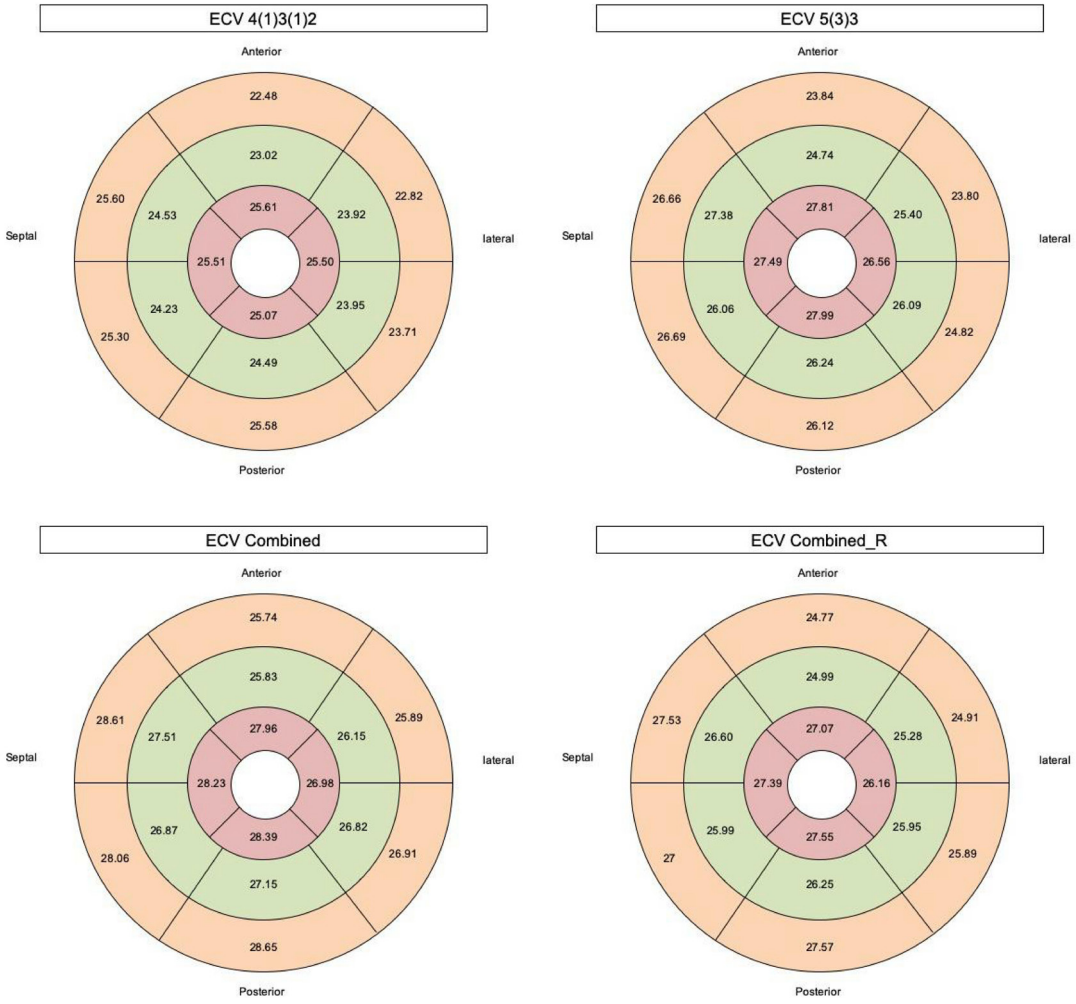


Fig. 6. Mean value of the extracellular volume (%). Extracellular volume (ECV) for each myocardial segment from two different protocols illustrated as a bulls-eye plot representing 16 segments of the basal (outer ring), mid-ventricular (middle ring), and apical (central ring) short-axis plane.

R (Supplementary material 1). The mean values of this ECV-combined_R were 26.28 ± 2.83% (base), 25.84± 1.82% (middle), and 27.04 ± 3.05% (apex). Also, in this case, we found no statistically significant differences when comparing these results with those of ECV 4(1)3(1)2, ECV 5(3)3 or ECV-combined for any segment or slice (Supplementary material 2).

(6) Sex comparison of pre-T1 and ECV

We evaluated sex-related differences in pre-T1 and ECV in each protocol. No significant differences between the sexes were detected using the 4(1)3(1)2 protocol. In contrast, in the 5(3)3 protocol, women showed longer pre-T1 relaxation time and larger ECV (Table 5). Also, the ECV-combined and ECV-combined_R showed larger values in women.

Table 5. Gender Comparison of Pre- T1 and Extracellular Volume (ECV)

Protocol	Sex		P-value
	Male (n = 6)	Female (n = 5)	
Pre T1 4(1)3(1)2 (ms)	1126.3 ± 39.08	1161.44 ± 24.6	0.1709
Pre T1 5(3)3 (ms)	1242.17 ± 24.65	1294.67 ± 24.88	0.0137
ECV 4(1)3(1)2 (%)	23.1 ± 1.41	26 ± 2.5	0.1207
ECV 5(3)3 (%)	24.56 ± 1.71	27.96 ± 1.63	0.0225
ECV combined (%)	24.79 ± 1.01	28.13 ± 2.25	0.0137
ECV combined_R (%)	25.54 ± 1.26	29.27 ± 2.21	0.0081

ECV combined: Pre T1 5(3)3 and Post T1 4(1)3(1)2, ECV combined R: Pre T1 4(1)3(1)2 and Post T1 5(3)3

P-value by Wilcoxon's rank sum test

(7) Inter- and Intra-Observer Variability

We evaluated the intra- and inter-observer variability for pre T1 4(1)3(1)2, pre 5(3)3, ECV 4(1)3(1)2, ECV 5(3)3, T2 GRE, and T2 TrueFISP. All global and slice values of each protocol showed good reproducibility (ICCs > 0.7) (Supplementary material 3).

DISCUSSION

The T1 and T2 relaxation times are fundamental magnetic features, which depend on tissue composition and field strength (4). However, the values *in vivo* are also affected by various factors, including the machine used, the type of pulse sequence, and the scan algorithm. Machine and sequence validation using phantom is necessary to set up the reference values of T1 and T2 mapping in each institution. However, it is not routinely done, because test phantoms for mapping are not widely available, and the phantom test is quite laborious. However, the need for phantom validation is increasing because of the increased use of cardiac mapping and the need for multicenter and multivendor studies using cardiac mapping.

We did all the steps required for the evaluation of the normal values of various mapping sequences at our institution, including the phantom study; such a procedure might be helpful in setting up multicenter and multivendor studies. Moreover, the normal ranges reported in our study allow for better detection of pathologic conditions and contribute to the standardization of CMR.

Phantom validation of the MOLLI 5(3)3 and MOLLI 4(1)3(1)2 sequences did not show significant differences from the gold standard T1 values; so both sequences could be considered to be suitable for measurement. The measurement error according to the heart rate of MOLLI 5(3)3 was smaller than that of 4(1)3(1)2. Validation of T2 mapping also showed no significant differences in the T2 relaxation times between the two methods, suggesting that method selection could be based on image artifacts.

Our study reported the normal reference values of cardiac T1 (using the two MOLLI protocols 4(1)3(1)2 and 5(3)3), T2 (using the two protocols GRE and TrueFISP), and ECV values in healthy volunteers aged 28-56 years at 3T. Although there are many ways to obtain T1 mapping values, we chose the MOLLI 4(1)3(1)2 and 5(3)3 sequences, because these protocols are widely available, enable short breath hold, and show heart rate insensitivity, precision, few image artifacts, and reproducibility (5).

Our study measured the pre-contrast T1 relaxation times of the 4(1)3(1)2 protocol to be 1142.27 ± 36.64 ms, whereas that of the 5(3)3 protocol was 1266.03 ± 32.86 ms. Regarding the native T1 values, Dall'Armellina et al. (6) reported a normal T1 mapping value of 1196 ± 56 ms at 3T with shMOLLI, whereas Piechnik et al. (7) reported a value of 1166 ± 60 ms with the same protocol; With the 3(3)3(5) protocol at 3T, reported T1 values had ranged from 1052 ms to 1158.7 ms (8-10). T1 values with various sequences at 3T are summarized in Table 6 (6-12). These differences could reflect influences from different scanners, populations, sample sizes, or age groups. Even though the myocardial T1 relaxation times we report can be regarded as reference values specific for this cohort and mapping techniques, our results with the 4(1)3(1)2 sequence are comparable to the ranges reported in other studies. We found that all the T1 relaxation times of 5(3)3 were higher than those found on 4(1)3(1)2. However, there was no statistical significance of any T1 relaxation times between 5(3)3 and 4(1)3(1)2 (P > 0.05) (Supplementary 2), perhaps because we had few subjects to study. In addition, the apical T1 relaxation time tends to be larger than the basal one in both protocols. Partial-volume effects owing to the curvature of the left ventricle can most probably explain this finding, with blood signals being included in the voxels (8).

T2 relaxation time of our study on GRE was 40.09 ± 2.45 ms and on TrueFISP was 38.20 ± 1.64 ms at 3T. von Knobelsdorff-Brenkenhoff et al. (8) reported the T2 relaxation time on GRE to be 39.6 ms at 3T, whereas Markl et al. (13) reported a range of 50.5-51.6 ms on GRE at 1.5T. We also found that the apical T2 relaxation time was larger than the basal slice in both protocols, again perhaps because of partial volume effects, although there was no statistical significance (8).

Since the ECV is a unique characteristic of the cells of the myocardium, there should be no significant differences in the values obtained with the various protocols. Indeed, our study reported no significant differences in ECV for any segment or slice in either sequence. In addition, according to Schelbert et al. (14), the sample from the 5th heart beat was unnecessary with the MOLLI sequence, because most post-contrast T1 values were approximately 500 ms or less, meaning that 99% of the magnetization had recovered by four heart beats. Hence, most institutions now adopt a pre-T1 5(3)3 sequence and a post-enhancement 4(1)3(1)2 sequence as the default MOLLI sequences. However, we wonder whether ECV from classic pre- and post-same MOLLI sequences would be different from ECV from

Table 6. T1 Mapping Values According to Various Acquisition Sequences at 3T

T1 Mapping (Ref.)	Pattern	TR (ms)	TE (ms)	FA (°)	Voxel Size (mm^3)	Acceleration imaging	Study population	Native T1 value (ms)	ECV	Contrast media
ShMOLLI (6)	5(1)1(1)1	2.14	1.07	35	1.8 × 1.8 × 8	GRAPPA = 2	41 patients (STEMI 32, NSTEMI 9): normal unaffected segments	1196 ± 56	N/A	Gadodiamide, 0.01 mmol/kg
ShMOLLI (7)	5(1)1(1)1	2.14	1.07	35	0.9 × 0.9 × 8	GRAPPA = 2	10 healthy volunteers (70% male, 35 years)	1066 ± 60	N/A	Gadodiamide, 0.03 mmol/kg
MOLLI (8)	3(3)3(3)5	2.6-2.7	1.0-1.1	35	1.6-1.8 × 1.6-1.8 × 8	GRAPPA = 2	60 healthy volunteers (50% male, 20-80 years)	1158.7	N/A	Gadobutrol, 0.1, 0.15, or 0.2 mmoL/kg
MOLLI (9)	3(3)3(3)5	3.3	1.64	50	1.8 × 1.8 × 8	SENSE = 2	32 healthy volunteers (53% male, 41 ± 17 years)	1052 ± 23	0.26 ± 0.04	Gadobutrol, 0.1, 0.15, or 0.2 mmoL/kg
MOLLI (10)	3(3)3(3)5	3.4	1.7	60	1.8 × 1.8 × 8	SENSE = 2	38 healthy volunteers (65% male, 49 ± 13 years)	1087 ± 60	N/A	Gadobutrol, 0.2 mmol/kg
MOLLI (11)	5(3)3	2.9	1.12	35	2.4 × 1.8 (spatial resolution)	GRAPPA = 2	69 healthy volunteers (51% male, 18-76 years)	1202 ± 45	0.27 ± 0.03	Gadopentetate Dimeglumine, 0.15 mmoL/kg
MOLLI (12)	3(3)3(3)5	3.3	1.57	50	0.9 × 0.9 × 8	SENSE = 2	30 healthy volunteers (63% male, 43 ±9 years)	1070 ± 55	0.27 ± 0.1	Gadobutrol, 0.2 mmol/kg
MOLLI (our study)	4(1)3(1)2	3.3	1.2	31	1.2 × 2.5 × 8	GRAPPA = 2	11 healthy volunteers (55% male, 28-56 years)	1142 ± 37	0.24 ± 0.02	Meglumine gadopentetate, 0.15 mmol/kg
MOLLI (our study)	5(3)3	3.3	1.2	31	1.2 × 2.5 × 8	GRAPPA = 2	11 healthy volunteers (55% male, 28-56 years)	1266 ± 33	0.26 ± 0.02 0.27 ± 0.03 (ECV combined)	Meglumine gadopentetate, 0.15 mmol/kg

ECV = extracellular volume fraction; FA = flip angle; GRAPPA = generalized autocalibrating partially parallel acquisition; MOLLI = modified Look-Locker inversion recovery; NSTEMI = non ST-elevation myocardial infarction; SENSE = sensitivity encoding for fast MRI; ShMOLLI = shortened MOLLI; TE = echo time; TR = repetition time; STEMI = ST-elevation myocardial infarction, ECV combined: Pre T1 5(3)3 and Post T1 4(1)3(1)2

pre- and post-combined MOLLI sequences or not. When compared with the standard ECV values obtained by the MOLLI 4(1)3(1)2/5(3)3 protocols, neither ECV-combined nor ECV-combined_R showed significant differences in any segment or slice. This result suggests that the theoretically known T1 shortening after contrast injection seems to have little effect on the acquisition of 4(1)3(1)2 or 5(3)3 sequences in the human body. We suspect that the various combinations of data from the pre-T1 MOLLI 5(3)3 and post-T1 MOLLI 4(1)3(1)2, as well as from the pre-T1 MOLLI 4(1)3(1)2 and post-T1 MOLLI 5(3)3, might be used interchangeably.

The existence of sex differences in pre-T1 and ECV values is controversial. Piechnik et al. (15) reported that T1 is longer by 24 ms in women up to the age of 45 years, after which there was no significant difference from that in men. In the MESA study, higher native T1 values were found in females in a multi-ethnic middle- to older-aged population (16). However, Dabir et al. (9) used MOLLI 3(3)3(3)5 on 1.5T/3T and reported no significant sex differences in T1 values or ECV. von Knobelsdorff-Brenkenhoff et al. (8) did not show gender differences in native T1 or ECV with MOLLI 3(3)3(3)5 on 3T. Our study showed that pre-T1 and ECV values were higher in women only when using 5(3)3 sequences. The ECV-combined and ECV-combined_R, which showed higher ECV in women, were both affected by the high pre-T1 values in the 5(3)3 sequence. It is hard to explain why T1 changes with sex only in the 5(3)3 sequence, but our having only a few subjects of each sex may have affected the result. Another hypothesis is that with 4(1)3(1)2 sequences, magnetization might not fully recover after 4 heart beats with a long T1 condition. According to an autopsy study of gender and aging, females showed a constant number of myocytes, size, and interstitium,

whereas males showed increased myocardial size, myocyte fusion, and loss of interstitium. The larger interstitium of the female might be a factor of the longer T1 and ECV value (17). Further investigation is necessary.

This study has some limitations. First, it was done in a single center, using a single vendor. Second, the number of subjects was small; so the result may be less statistically significant, especially for evaluating the differences in T1 and T2 mapping values according to each protocol. Further studies with a larger number of subjects are needed. Also, because we had limited software on only one device, study with a saturation recovery pulse sequence was not possible.

In conclusion, using various phantom-validated sequences, we successfully evaluated the normal myocardial T1, T2, and ECV reference values of healthy Koreans on 3T CMR. We found no statistically significant differences between T1 values obtained with the MOLLI 4(1)3(1)2 and MOLLI 5(3)3 sequences, or between the T2 values obtained with GRE and TrueFISP, although our findings have limited statistical value due to small sample size. When ECV was evaluated with every combination of pre-T1 and post-T1 MOLLI 5(3)3 and MOLLI 4(1)3(1)2 sequences, no significant differences were found.

Supplementary Materials

The Data Supplement is available with this article at https://doi.org/10.13104/imri.2020.24.3.141

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