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Reference parameters for left ventricular wall thickness, thickening, and motion in stress myocardial perfusion CT: Global and regional assessment

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ABSTRACT

Purpose: To use adenosine-induced stress CT myocardial perfusion imaging (CT-MPI) to determine normal reference values for left ventricle (LV) wall thickness (WT) and motion parameters.

Methods: This study included 106 Korean subjects (52 men and 54 women) who underwent CT-MPI due to chest pain, but were not found to have any detectable mild or severe coronary artery disease or myocardial perfusion defect. The following quantitative parameters were assessed on the CT-MPI according to a 17-segment model: LV myocardial thickness at end-systolic (WT_{ES}) and end-diastolic (WT_{ED}) phases, systolic wall thickening (SWT), and wall motion (WM). The associations of the measured parameters with the subjects' demographic characteristics and comorbidities were also analyzed.

Results: Septal wall (7.2 mm) and basal-level (7.7 mm) LV myocardium demonstrated significantly higher WT ($p < 0.001$). SWT was highest in lateral (77.8%, $p < 0.014$) and apical (78.9%, $p = 0.009$) myocardium, while lateral (7.7 mm) and basal (6.7 mm) myocardium exhibited the greatest WM ($p < 0.001$). WT was significantly higher in men and younger (< 60 years) subjects (all, $p < 0.001$). Hypertensive individuals presented with significantly higher SWT (79.9%, $p = 0.024$). LV WT exhibited statistically significant correlations (all positive, except for age) with age, height, weight, body surface area, body mass index, and systolic blood pressure (all, $p < 0.010$).

Conclusions: The present study provides CT-MPI reference values for LV myocardial WT, SWT, and WM measured on an adult Korean population. Knowledge of such normal reference measurements would be beneficial for the efficient interpretation of CT-MPI examinations in populations of Asian ethnicity.

1. Introduction

Ischemic heart disease and other cardiovascular disorders are one of the leading causes of death worldwide, and early diagnosis and precise treatment planning are major challenges in the contemporary medical environment [1]. Although direct coronary catheterization has been the only conclusive diagnostic method for coronary artery disease in the past, coronary computed tomography angiography (CCTA) has become a popular alternative diagnostic tool owing to the pronounced technological advances and its improved clinical availability [2,3]. With the adoption of electrocardiography (ECG) gating and multi-detector CT technology, the spatial and temporal resolutions have markedly improved over the past decade [4,5]. Therefore, in addition to the evaluation of coronary artery status, the accurate and reliable assessment of cardiac function can also be achieved with cardiac CT examinations [6].

The assessment of left ventricle (LV) function with cardiac CT has been validated in multiple prior studies, and has shown a similar accuracy to cardiac magnetic resonance imaging (MRI) or echocardiography [7,8]. The retrospective reconstruction of CT at 5% or 10% intervals of the cardiac cycle allows for efficient qualitative and quantitative evaluation of cardiac function, especially with commercially

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available post-processing workstations, which commonly facilitate an automated or semi-automated workflow. Initially, the analysis of cardiac function mainly concentrated on global LV function expressed as changes in ventricular volume; however, the detection of wall motion (WM) abnormalities and the localization of diseased segments provide essential information on the functional state and viability of the myocardium [9]. Myocardial perfusion abnormality is another important prognostic factor in ischemic heart disease, and adenosine-induced stress CT myocardial perfusion imaging (CT-MPI) has become an established diagnostic tool for the detection of myocardial ischemia [10]. When CT-MPI is performed with retrospective ECG gating, a diverse range of other quantitative parameters can be simultaneously obtained in a semi-automatic manner, using the CT vendor-provided workstation. These parameters include the phase-specific myocardial wall thickness (WT), systolic wall thickening (SWT), and systolic WM. The determination of normal reference values is crucial for the precise interpretation of these measured quantitative parameters, and such reference values for cardiac function are known to exhibit significant differences between imaging modalities and between subjects of different ethnicities and genders [11–13]. To the best of our knowledge, normal CT-MPI reference values for LV WT, SWT, and WM have not been reported. Therefore, the purpose of this study was to determine normal reference values for CT-MPI-measured LV WT and motion parameters in a healthy Korean population, and in accordance with the 17-segment model of the American Heart Association (AHA).

2. Materials and methods

2.1. Study population

From September 2012 to May 2014, 372 consecutive patients who underwent CT-MPI examinations and were registered in a multicenter myocardial perfusion CT registry (data blinded for peer-review) were initially reviewed. This CT-MPI registry consisted of patients who presented with chest pain or other angina-like symptoms, and all of the patients were at least 18 years of age. After a thorough review, a total of 106 patients with normal or minimal coronary artery stenosis and normal myocardial perfusion imaging on CT-MPI were finally included in this study, and their general demographic characteristics and relevant comorbidities such as hypertension and diabetes mellitus were recorded. Written informed consent was obtained from all patients, and our institutional review board approved the study.

2.2. Cardiac CT protocol

All cardiac CT examinations were performed with a dual-source 128-detector-row CT scanner (Somatom Definition Flash; Siemens, Forchheim, Germany), with the CT protocol being established in concordance with the Asian Society of Cardiovascular Imaging guideline [14]. A detailed CT scanning parameters have been published in a previous study [15]. In short, stress-state cardiac CT was performed after a 5 minute adenosine infusion and rest-state CT was performed after another 10 minute rest with the administration of an oral spray of isosorbide dinitrate. Both stress- and rest-state CT images were acquired with a retrospective ECG-gated technique, with a standard cardiac kernel (B26f) being used for coronary artery evaluation and a smooth kernel (B10f) being used for cardiac function and myocardial perfusion analyses. The average value of the documented total effective-dose was 12.9 mSv. All multiphase data sets were analyzed for detailed quantitative analyses with a vendor-specific software (*syngo*. via, version VB10A; Siemens Healthineers, Forchheim, Germany) for detailed quantitative analyses.

2.3. Assessment of coronary artery and myocardial perfusion status

CT data acquired during the rest phase were reconstructed with 0.6 mm slice thickness with 0.4 mm increment using a standard cardiac filter (B26f) for evaluation of coronary artery stenosis. The degree of stenosis was graded into five categories on the basis of the relative decrement of the coronary artery diameter: normal, minimal (< 30%), mild (30–49%), moderate (50–69%), and severe (≥70%). A single reader with 11 years of experience with CCTA interpreted the CT images, and subjects with coronary artery stenosis rated greater than mild were excluded from the study. The visual assessment of myocardial perfusion CT images was performed by the same reader. An area of low attenuation that persisted throughout the reconstructed cardiac cycle was defined as a myocardial perfusion defect. Low-attenuation myocardial areas that disappeared during a different cardiac phase were considered to be imaging artifacts. Although the reader was able to change the slice thickness of the multiplanar reconstruction (MPR) images for the evaluation of a myocardial perfusion defect, a thickness of 10 mm was initially provided for each exam. Patients with detectable myocardial perfusion defects were also excluded from the current study.

2.4. Quantitative assessment of myocardial thickness and motion

Quantitative assessments were carried out by two readers in consensus, using a dedicated post-processing workstation. CT images acquired in the adenosine-induced stress state were retrospectively reconstructed at 10% intervals of the cardiac cycle, and freely manipulatable multi-planar reformation (MPR) images of the heart were generated. The LV endocardial and epicardial borders were automatically traced in all reconstructed cardiac phases, although the automatically drawn LV myocardial outlines were manually modified by the readers if considered necessary (Fig. 1). The defined LV myocardium was then automatically segmented according to the 17-segment model of the AHA.

Following the segmentation, the LV blood volume was automatically calculated and the end-systolic (ES) and end-diastolic (ED) phases were determined as the minimal and maximum LV volumes, respectively. The ventricular WT was measured as the distance between the endocardial and epicardial border, and was recorded twice at both the ES and ED phase. SWT was defined as the relative incremental percentile value of WT at the ES phase (WT_{ES}) compared with WT at the ED phase (WT_{ED}), and was calculated as follows: $SWT = \frac{WTES - WTED}{WTED} \times 100\%$. Lastly, the absolute movement of the epicardial outline of the LV wall between the ES and ED phases (measured in mm) was defined as the WM. The global and regional parameters were displayed on a color-coded 17-segment bulls-eye map.

2.5. Statistical analysis

All documented continuous variables were expressed as the mean ± standard deviation. Differences in the measured parameters between the various anatomical locations within the LV wall were analyzed with one way ANOVA tests. Independent *t*-tests were performed to estimate the influence of gender, hypertension, diabetes, and old age (equal to or above the age of 60) on the measured LV functional parameters. The associations between the measured quantitative LV parameters and the continuous clinical variables such as age, height, weight, body surface area (BSA), body mass index (BMI), and systolic blood pressure were assessed with Pearson's correlation analysis. A p-value < 0.05 was considered to indicate statistical significance. All statistical analyses were performed using SPSS software version 21.0 (SPSS Inc., Chicago, IL, USA).

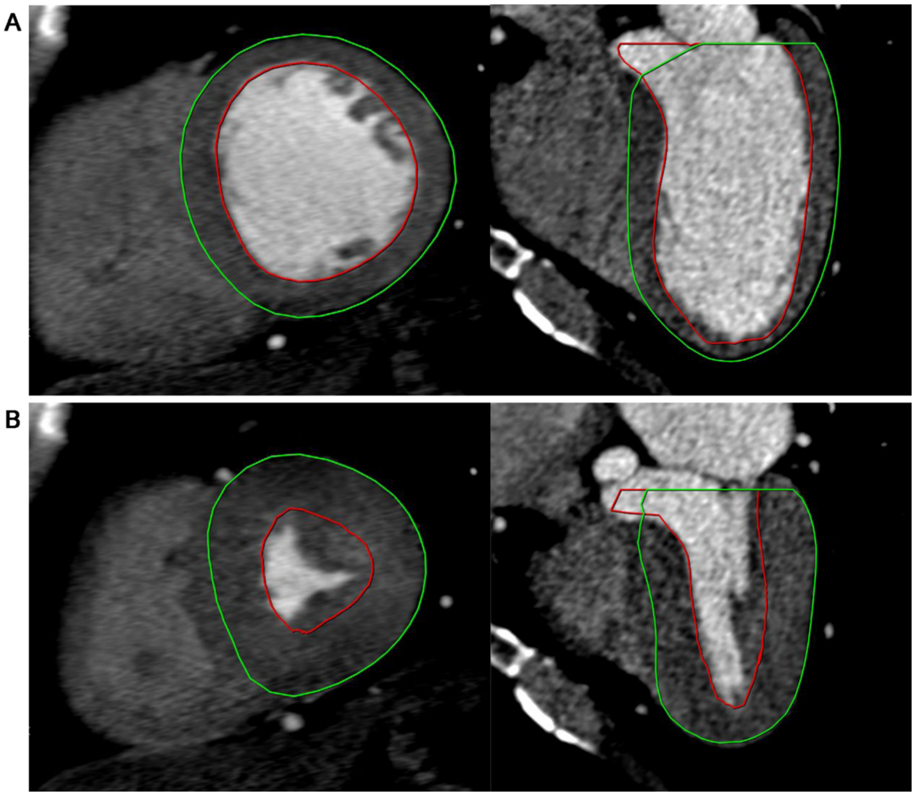

Fig. 1. Automatically traced LV endocardial and epicardial borders.
The LV endocardial (red line) and epicardial (green line) borders were automatically traced in all reconstructed cardiac phases, including end-diastolic (A) and end-systolic (B) phases. Note that the papillary muscles were excluded when tracing the endocardial borders. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

3. Results

3.1. Study population

The patient characteristics are displayed and summarized in Table 1. A total of 106 patients were included in the present study. The mean age of the patients was 60.7 ± 9.5 years, and 52 (49.1%) patients were of male gender. Approximately half (54 out of 106) of the study population were hypertensive, and 17 patients had diabetes. The global LV functional parameters such as LV ejection fraction, systolic volume, and cardiac output were all within normal ranges. None of the study population had established diagnosis of valvular heart disease.

Table 1
Baseline characteristics of 106 patients.

Characteristics	Total	Male	Female	p
Age (yr)	60.7 ± 9.48	57.0 ± 9.3	64.2 ± 8.3	0.000
Gender	106(100)	52(49.1)	54(50.9)	0.000
Height (cm)	160.7 ± 9.0	167.8 ± 6.2	153.4 ± 4.5	0.000
Weight (kg)	66.15 ± 11.13	74.02 ± 8.85	153.4 ± 4.5	0.000
BMI (kg/m^2)	25.48 ± 2.74	26.27 ± 2.84	24.7 ± 2.4	0.004
BSA (m^2)	1.70 ± 0.18	1.84 ± 0.13	1.6 ± 0.1	0.000
SBP (mm Hg)	130.9 ± 15.4	132.2 ± 15.9	129.6 ± 14.8	0.385
Smoking				0.000
Never	44 (41.5)	10 (19.2)	34 (63.0)	
Ex-smoker	21 (19.8)	21 (40.4)	0 (0.0)	
Current	11 (10.4)	8 (15.4)	3 (5.6)	
Hypertension	54 (50.9)	23 (44.2)	31 (57.4)	0.245
Diabetes mellitus	17 (16)	7 (13.5)	10 (18.5)	0.657

Note - Continuous variables are presented as mean ± standard deviation. Unless otherwise specified, data are numbers of patients, with percentages in parentheses. BMI, body mass index; BSA, body surface area; SBP, systolic blood pressure.

3.2. Regional variations

Detailed information on the mean values of the measured quantitative parameters for each of the 16 anatomic segments (segment 17 was excluded) are displayed as bulls-eye maps in Fig. 2. The quantitative parameters were compared according to their anatomical locations on short-axis views of the LV wall (anterior, septal, inferior, and lateral) and longitudinal levels (basal, mid, and apical). In all subjects, the image quality of CT-MPI was acceptable for quantitative analysis. The measured values of LV WT, SWT, and WM all showed significant regional variations (Table 2, Fig. 3). The septal WT was significantly greater than in the other segments in both the ED (7.16 ± 1.99 mm, $p < 0.001$) and ES (11.87 ± 2.74 mm, $p < 0.001$) phases. The average measured ventricular WT was highest at the basal level (ED, 7.74 ± 1.77 mm; ES, 12.91 ± 2.55 mm) and lowest at the apical level (ED, 5.41 ± 1.29 mm; ES, 9.38 ± 2.45 mm; both, $p < 0.001$). Among the short-axis segments, the lateral LV wall demonstrated the maximum SWT and WM values (SWT, 77.82%; WM, 7.73 ± 2.09 mm). The septal wall showed the minimal WM (4.55 ± 1.82 mm, $p < 0.001$), while the anterior wall (68.73 ± 38.06 mm, $p = 0.014$) showed the minimum SWT. The basal-level LV myocardium exhibited the maximum WM measurement (6.66 ± 2.72 mm, $p < 0.001$), while the apical myocardium showed the maximum SWT (78.89 ± 43.89 mm, $p = 0.009$).

3.3. Influence of clinical parameters

Both WT_{ED} (7.35 ± 1.25 mm vs. 6.33 ± 0.78 mm, $p < 0.001$) and WT_{ES} (12.30 ± 2.12 mm vs. 10.68 ± 1.64 mm, $p < 0.001$) showed significant differences between male and female patients, with the former exhibiting thicker myocardium (Table 3). Additionally, an age of 60 years or over was related to a meaningful decrease in WT_{ED} (6.43 ± 0.89 mm vs. 7.33 ± 1.25 mm, $p < 0.001$) and WT_{ES} (10.77 ± 1.68 mm vs. 12.33 ± 2.14 mm, $p < 0.001$) in comparison with subjects < 60 years of age. However, the SWT and WM

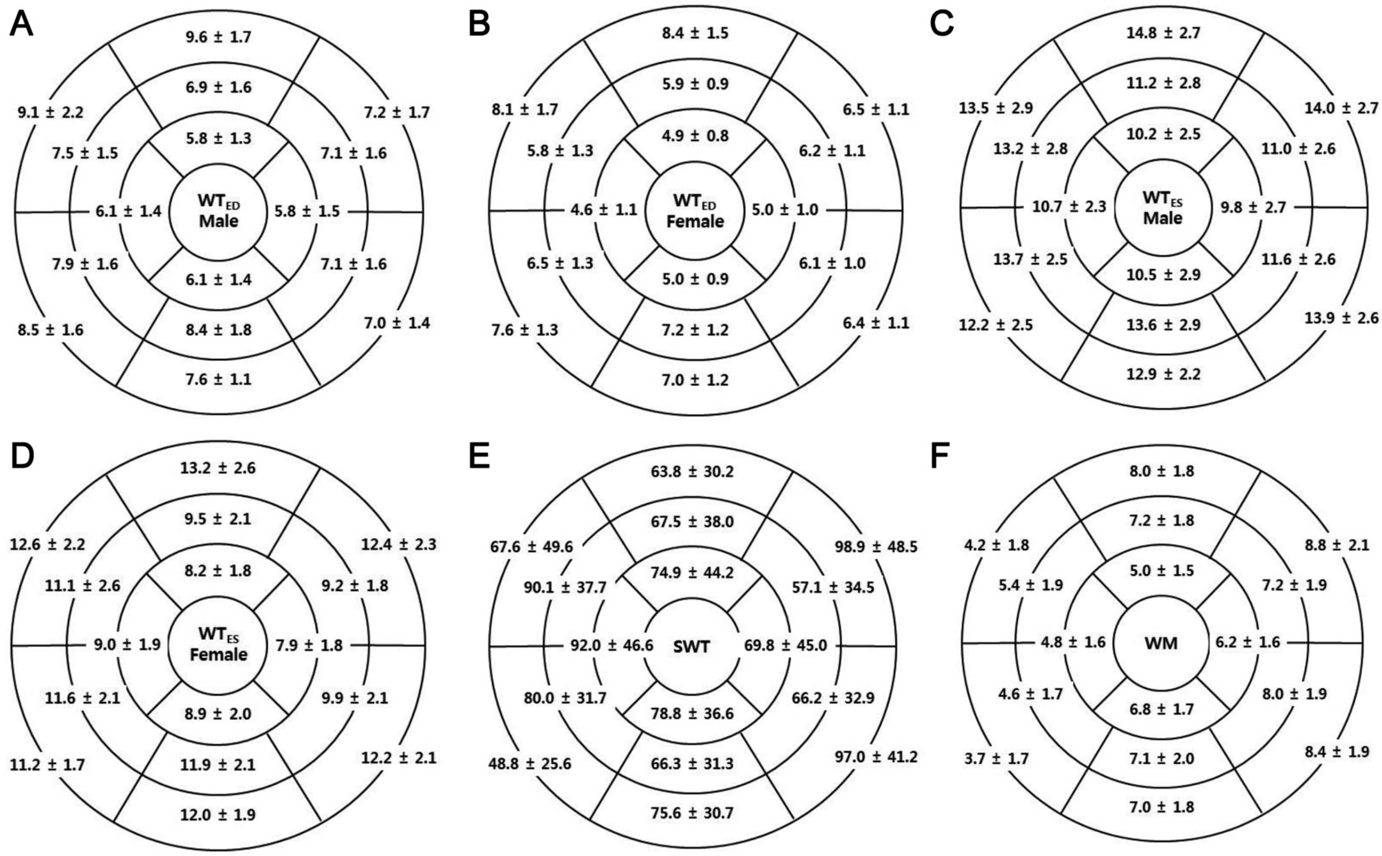

Fig. 2. Mean and standard variation of the measured quantitative parameters expressed according to the American Heart Association 17-segment map. Measured normal reference values for wall thickness at end-diastolic phase in males (mm) (A), and females (B). Wall thickness at end-systolic phase in males (mm) (C), and females (D). Systolic wall thickening (%) (E), and wall motion (mm) (F) are also shown.

measurements were not influenced by differences in gender or age. Individuals diagnosed with hypertension showed an association with higher SWT (79.95% vs. 69.17%, $p = 0.024$). Otherwise, the presence of comorbidities was not associated with significant dissimilarities in the measured quantitative parameters.

LV myocardial WT_{ED} exhibited a statistically significant correlation with all of the clinical variables, which were age, height, weight, BSA, BMI, and systolic blood pressure (all, $p < 0.01$; Supplementary Table 1). The strongest correlation found was with BSA ($R = 0.522$), which was followed by height ($R = 0.492$) and weight ($R = 0.475$). The age of the patient was negatively correlated with WT_{ED} ($R = -0.384$). The average LV-WM showed a weak positive correlation with individual weight ($R = 0.204$, $p = 0.042$) and BMI ($R = 0.265$, $p = 0.009$). No statistically meaningful correlation was found between SWT and the clinical variables.

4. Discussion

Normal reference values for the quantitative LV myocardial thickness and WM parameters obtained on CT-MPI are presented as the major finding of this study. Knowledge of the normal reference measurements for WM parameters may contribute to more accurate and reproducible assessments of WM abnormalities detected on CT-MPI. The accurate identification of myocardial WM abnormalities associated with a hemodynamically significant coronary artery stenosis could improve the diagnostic performance for ischemic heart disease. In a prior study [15], visual assessment of WM abnormalities using CT-MPI demonstrated a high specificity (100%) for detection of significant

Table 2
Regional variations of measured parameters.

Variables	WT_{ED} (mm)	p	WT_{ES} (mm)	p	SWT (%)	p	WM (mm)	p
LV wall		< 0.001		< 0.001		0.014		< 0.001
Anterior	6.9 ± 1.2		11.2 ± 2.3		68.7 ± 30.8		6.7 ± 1.4	
Septal	7.2 ± 1.9		11.9 ± 2.7		75.7 ± 42.3		4.6 ± 1.8	
Inferior	6.9 ± 1.2		11.6 ± 2.1		73.6 ± 25.4		6.9 ± 1.5	
Lateral	6.4 ± 1.3		11.2 ± 2.2		77.8 ± 32.7		7.7 ± 1.6	
LV level		< 0.001		< 0.001		0.009		< 0.001
Basal	7.7 ± 1.2		12.9 ± 2.1		75.3 ± 26.3		6.7 ± 1.1	
Mid	6.9 ± 1.4		11.4 ± 2.4		71.2 ± 26.7		6.6 ± 1.2	
Apical	5.4 ± 1.2		9.4 ± 2.3		78.9 ± 34.4		5.7 ± 1.1	

Note - Variables are presented as mean ± standard deviation. The displayed values are averages of different myocardial segments included at a certain myocardial region or level. WT_{ED}, wall thickness at end-diastolic phase; WT_{ES}, wall thickness at end-systolic phase; SWT, systolic wall thickening; WM, wall motion, LV, left ventricle.

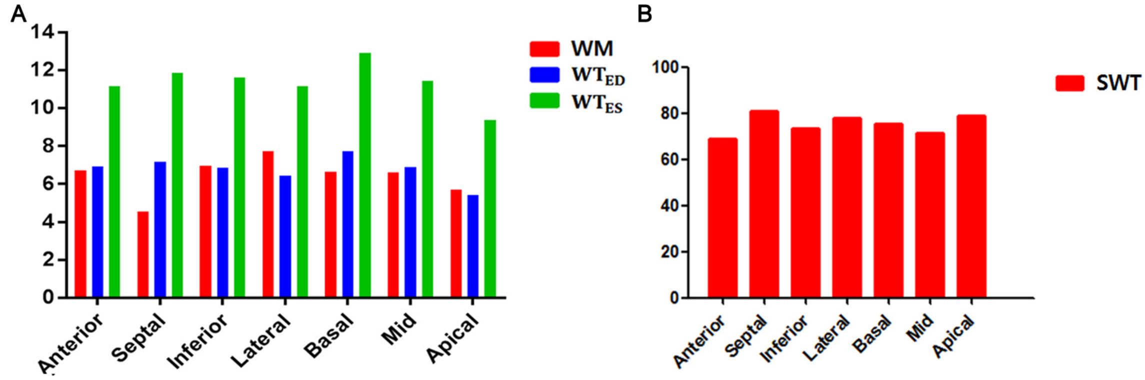

Fig. 3. Mean values of the measured LV parameters according to the axial segments and zonal levels.
A. Mean values for wall thickness (mm) and wall motion (mm) are shown in the graph.
B. Mean values for systolic wall thickening (%) are shown in the graph.

coronary artery disease, although a poor sensitivity (18%) was observed. This poor sensitivity may have resulted from the innate limitations of the qualitative assessment used; the quantitative assessment of WM abnormalities using the reference values documented in this study may aid in increasing the diagnostic performance of CT-MPI examinations. In addition, documentation of the normal range of WT and WM parameters would be beneficial in the evaluation of the myocardial geometry alterations that often occur with various structural heart diseases, including hypertrophic cardiomyopathy and valvular heart diseases [16].

Echocardiography is the most widely used imaging modality for the routine evaluation of LV function, because it is relatively cheap, easy, and safe; however, its use may be limited by the poor acoustic window and substandard proficiency of the operator [17]. Cardiac MRI is currently considered to be the gold standard method for cardiac functional analysis, demonstrating excellent performance [18]. However, cardiac MRI is a relatively expensive and time-consuming procedure, and patients with claustrophobia or implanted metallic devices are not eligible candidates for cardiac MRI examination. Although the use of CT is limited by the risk resulting from the radiation exposure, CT offers a number of potential advantages as a noninvasive imaging tool for various cardiac diseases: 1) a relatively shorter acquisition time, 2) superior clinical availability, 3) less inter-observer variability, and 4) full quantification potential with the use of available workstations [19]. In this context, CT-MPI has been shown to be reliable in the detection of hemodynamically significant myocardial perfusion defects, and the number of CT-MPI examinations performed has increased in recent years [20]. As the retrospective ECG-gating method is commonly adopted in CT-MPI examinations, CT images can be reconstructed at various points of the cardiac cycle, and diverse quantifiable parameters of cardiac function such as WT, SWT, and WM, can be simultaneously obtained in a semi-automatic manner using readily available post-processing workstations.

Normal reference values for WT, SWT, and WM measured with CT-MPI during an adenosine-induced stress state in a Korean population have never been reported in prior studies. Although numerous studies have measured various LV parameters using MRI or CT, the ethnicities of the subjects, methods of measurement, imaging modalities used, and quantitative parameters measured vary markedly across the studies. For example, even though the measurement modality and subjects' ethnicity were similar, Kang et al. presented substantially higher WT_{ED} values than those found in the present study (septal WT_{ED}: 10.8 ± 1.8 mm vs. 7.8 ± 1.7 mm) [21]. Such discordance may be the result of a larger male percentage and single-level measurements in the study of Kang et al. Therefore, the direct application of such reference values to another study population would be largely inappropriate, because quantitative LV parameters demonstrate systemic differences among imaging modalities, and the demographic characteristics of the patients have also been found to have a significant influence on imaging-based measurements [11–13].

The measured WT, SWT, and WM values all demonstrated significant differences across the distinct anatomical regions and levels of the LV. In concordance with previous reports, the septal wall demonstrated the greatest myocardial thickness, with the difference being significantly larger at the ED phase of the cardiac cycle [21]. To the contrary, the septal wall showed the least myocardial movement between the ED and ES phases. The LV lateral wall, also known as the free wall, was associated with maximum SWT and WM. The measured LV WT demonstrated a trend of decrease at the more apical levels of the myocardium, which was in agreement with previous results measured on MRI [22].

In concordance with previous reports, a significant gender-related

Table 3
Influence of gender, comorbidities, and age on measured parameters.

Variables	WT_{ED} (mm)	p	WT_{ES} (mm)	p	SWT (%)	p	WM (mm)	p
Sex		< 0.001		< 0.001		0.554		0.752
Male	7.4 ± 1.3		12.3 ± 2.1		73.2 ± 26.3		6.4 ± 1.0	
Female	6.3 ± 0.8		10.7 ± 1.6		76.1 ± 23.2		6.4 ± 0.9	
Hypertension		0.704		0.142		0.024		0.214
Yes	6.8 ± 0.8		11.8 ± 1.9		79.9 ± 26.4		6.5 ± 0.9	
No	6.9 ± 1.4		11.2 ± 2.2		69.2 ± 21.8		6.3 ± 0.9	
Diabetes		0.905		0.687		0.525		0.412
Yes	6.8 ± 0.8		11.7 ± 2.1		78.2 ± 23.0		6.6 ± 1.0	
No	6.8 ± 1.2		11.4 ± 2.1		74.0 ± 25.1		6.4 ± 0.9	
Age	< 0.001		< 0.001	0.761		0.761		0.906
60 ≥ (n = 58)	6.4 ± 0.9		10.8 ± 1.7		76.0 ± 26.2		6.4 ± 0.9	
< 60 (n = 48)	7.3 ± 1.3		12.3 ± 2.1		73.1 ± 22.9		6.4 ± 0.9	

WT_{ED}, wall thickness at end-diastolic phase; WT_{ES}, wall thickness at end-systolic phase; SWT, systolic wall thickening, WM, wall motion.

difference in the LV myocardial thickness was found in both ED and ES phases [12,23–26]. The male gender was associated with higher WT values than the female gender, with this distinction being slightly more prominent at the ES phase. We also observed lower LV WT in the elderly group (age ≥60). Age-related changes in LV WT in non-stressed myocardium have been evaluated in previous studies, but the present study is the first to document myocardial thickness during a pharmacologically induced stress state. The age-related discrepancy in LV WT was greater in the ES phase than in the ED phase (1.56 mm vs. 0.9 mm). Systolic LV myocardial thickening is considered to be a quantitative marker of LV contractile function, and shows good correlation with regional WM abnormalities diagnosed on echocardiography or MRI [27]. The average SWT in the present study was 73.95%, which is considerably higher than the values given in previous reports, which average around 44–47% [28,29]. This difference is likely to due to the induction of a pharmacologic stress state as part of the routine protocol in our CT-MPI examinations. No gender-related difference of measured SWT was documented, similar to a prior non-stress induced quantitative cardiac MRI study [25].

LV myocardial WT measured without pharmacologic stress has been reported to have a significant association with various demographic features [21,22,30], and consistent results were obtained in the current study performed with CT-MPI. The weight and BMI of individuals were correlated with the LV-WM under pharmacologically induced stress, but the correlations were weak. The measured SWT was generally uninfluenced by all of the documented clinical parameters.

The current study had several limitations that must be addressed. First, the number of subjects included in this study was relatively small, and therefore the interpretation of the statistical significance and subgroup analyses may be subject to some restrictions. Second, because of the single-CT-vendor study design, the results from the present study may not be applicable to CT-MPI performed in different institutions with different imaging protocols or CT manufacturers. However, CT-MPI protocol of the present study was not substantially different from the currently adopted protocols, and evaluation of normal reference values and their regional variations forms the required first step in the proper interpretation of WM parameters obtained on CT-MPI examinations. Third, certain degrees of selection bias may have occurred, as the present study was retrospectively performed by reviewing medical records and archived CT-MPI data. Fourth, this study included patients with minimal coronary artery stenosis without visible perfusion defects. Although these patients did not reveal detectable perfusion defects and thus were presumed to have normal wall motion, the exact impact of minimal coronary artery stenosis on ventricular wall motion parameters are not completely clear. Lastly, individuals with comorbidities such as hypertension and diabetes were included in this study. However, hypertension and diabetes are highly prevalent diseases in the general population, and according to our analysis, such comorbidities had a minimal influence on the measured quantitative parameters.

In conclusion, normal CT-MPI reference values for LV myocardial WT, SWT, and WM for an adult Korean population are provided in the present study. These values take into account gender-related and cardiac region-related variations. Knowledge of such normal reference measurements would be beneficial in efficient interpretation of CT-MPI examinations in populations of Asian ethnicity.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clinimag.2019.04.002.

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