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博 士 （医 学） 学 位 論 文

Feasibility of left ventricular volume measurements by three-dimensional speckle tracking echocardiography depends on image quality and degree of left ventricular enlargement: Validation study with cardiac magnetic resonance imaging

(三次元心エコー法による左室容積解析の可用性は左室拡大と取得画質に依存する：心臓 MRI を用いた検討)

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筑波大学大学院博士課程

人間総合科学研究科・博士（医学）

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Feasibility of left ventricular volume measurements by three-dimensional speckle tracking echocardiography depends on image quality and degree of left ventricular enlargement: validation study with cardiac magnetic resonance imaging

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Abstract

Background: Novel 3-dimensional echocardiography with speckle tracking imaging (3D-STE) may have advantages in assessing left ventricular (LV) volume through a cardiac cycle. The feasibility of 3D-STE may be affected by image quality and LV morphology.

Methods and results: We studied 64 patients (38 men, age 55 ± 12 years) who underwent cardiac magnetic resonance imaging (CMRI) and 3D-STE on the same day. LV end-diastolic volume (EDV) and end-systolic volume (ESV) were measured by both modalities. Imaging qualities were quantified in each of 6 LV segments by an imaging quality score (IQS) of 1 to 3, and scores were averaged (mean IQS) at end-diastole and end-systole. Compared to CMRI, 3D-STE showed a tendency to underestimate LV volume measurements, but not significantly (EDV: bias = -18 ± 37 ml; ESV: bias = -10 ± 34 ml), and measurements correlated well with those by CMRI (EDV: R = 0.80, ESV: R = 0.86, ejection fraction: R = 0.75, p <0.001). The absolute differences of LVEDV and ESV between 3D-STE and CMRI correlated significantly with mean IQS (LVEDV, R=-0.35, p=0.005; LVESV, R=-0.30, p=0.02). Based on the medium value of LVEDV by CMRI (127 ml), subjects were classified into the small (<127 ml) and large LVEDV (≧127 ml) groups. In the large LVEDV group, mean IQS significantly correlated with the absolute differences of LVEDV (mean IQS, r = -0.45, p = 0.01), despite of no significant correlation in the small LVEDV group.

Conclusion: 3D-STE could measure LV volume as well as CMRI, however, its accuracy depends on the quality of the acquired image and particularly on enlargement of the left ventricle.

Introduction

One limitation of conventional 2-dimensional (2D) echocardiography is the "through plane" phenomenon. Because the entire heart is moving in various directions at the same time, the fixed cross-sectional echo window permits only faulty measurements [1-5]. In contrast, 3-dimensional (3D) echocardiography may compensate for this limitation by obtaining 3D information [6-8]. We have previously validated left ventricular (LV) strain measurements by 3D speckle tracking echocardiography (3D-STE) in an animal model [9]. In principle, however, acquiring and analyzing 3D data requires more computational resources, and that gives rise to more restrictions in spatial and temporal resolution compared with 2D echocardiography. Accordingly, this may cause substantially inadequate precision. Nesser et al. [10] validated the ability of 3D-STE to measure LV volume in a comparison study with cardiac magnetic resonance imaging (CMRI). They reported favorable accuracy and reproducibility over measurements by 2D echocardiography, but they limited their analysis to subjects with adequate imaging quality. However, it is not always possible to expect acceptable imaging quality, which may affect actual results of measurements in the real-world clinical setting. Therefore, the aims of this study of consecutive patients who underwent CMRI were 1) to compare LV volume measurements between 3D-STE and CMRI and 2) to evaluate factors that relate with the differences of LV volume measurements between 3D-STE and CMRI.

Methods

Study subjects

This study enrolled 68 consecutive patients who underwent echocardiographic examination within 1 hour after CMRI examination. The intrinsic cardiac rhythm in all patients was sinus rhythm. The study was approved by the local research ethics committee, and all patients gave their written informed consent.

Conventional LV volume measurements

All echocardiographic data was obtained with an Aplio Artida^{TM} echocardiographic system (Toshiba Medical Systems, Tochigi, Japan). In conventional 2D echocardiographic examinations, LV end-diastolic volume (LVEDV) and end-systolic volume (LVESV) were measured by the bi-plane modified Simpson's method [11].

LV volume measurements by 3D-STE

All 3D echocardiographic examinations also were performed with the Artida^{TM} ultrasound system. Full-volume ECG-gated 3D data sets were acquired from apical positions using a matrix array 2.5-MHz transducer. To obtain these data sets, 6 sectors were scanned and automatically integrated into a wide-angle (70° x 70°) pyramidal data image covering the entire LV. Frame rate of each image was set at approximately 30 Hz.

The data were stored and transferred to a personal computer-based workstation for off-line analysis. The images were analyzed with the Advanced Cardiology Package software

(Toshiba Medical Systems Co.) specifically designed for analysis of data acquired with the Artida^{TM} system. A representative case is shown in Figure 1. The 3D data sets were displayed as multiplanar reconstruction (MPR) images corresponding to apical 2-chamber and 4-chamber views and 3 short-axis levels. In the MPR display, the ventricular long axis was adjusted so that the longest chamber lengths for the 4-chamber view in panel A and 2-chamber view in panel B of Figure 1 were obtained. After adjustment of the planes, the endocardial contours were traced for the respective views. Each contour was verified in the reconstructed short-axis views at the levels of the apical, mid, and basal sections in panels C3, C5, and C7, respectively, so that the contour exactly traced the endocardium. The papillary muscles were not included in the LV cavity. The 3D-STE system automatically followed the transformation of the left ventricle during the measured cardiac cycle, and the transitions of the LV contour were verified visually throughout the cardiac cycles. If this procedure failed to track the transition of the wall motion, the procedure was repeated until valid tracings were obtained. LV volume was measured directly from the tracked 3D endocardial surface information obtained by 3D-STE, and volumes were obtained from a single cardiac cycle with no assumptions about LV structure. LVEDV was defined as the LV volume at end-diastole, and LVESV was defined as the minimum LV volume measured during the cardiac cycle. LV ejection fraction (LVEF, %) was calculated by the formula (LVEDV - LVESV) × 100 / LVEDV [9].

Quantification of 3D-STE imaging quality

3D-STE imaging quality was classified into 3 states according to the feasibility of determining segmental endocardial continuity by defining an imaging quality score (IQS). Score 3 indicates that the contour is clearly visible and easily traced, score 2 indicates that the

contour is not clearly visible but can be determined from the echo information of adjacent tissue, and score 1 indicates that the contour can hardly be seen. In Figure 1, the apical 2-chamber view was divided into 3 combined regions: first, combined with basal and mid anterior walls; second, apical anterior and apical inferior walls, and third, basal and mid inferior walls. Similarly, in the apical 4-chamber view, the image was divided into 3 combined regions: first, combined with basal and mid lateral walls; second, apical lateral and apical septal walls; and third, basal and mid septal walls. Each region was evaluated at the end-diastolic and end-systolic phases by two different experienced observers (R.K., Y.S.). Image quality was calculated as the mean total score (mean IQS) of the scores assessed at end-diastole and at end-systole. An example of scoring at end-diastole is shown in Figure 2.

CMRI acquisition

CMRI examinations were performed with a 1.5-Tesla superconducting unit (NT/Intera 1.5T Master R12; Philips, Best, Netherlands) with a phased-array cardiac coil. First, ECG-gated cine mode images with a steady-state free precession (Balanced Turbo Field Echo) were obtained in long- and short-axis views of the left ventricle at 10-mm slice thickness without an intersection gap. The repetition time and echo time were 2.845 and 1.4225 msec, respectively, the flip angle was 70°, and the imaging matrix was 160 x 229. Acquisition time was from 10 to 16 seconds long during breath holding.

CMRI analysis

The images obtained by the CMRI scanner were stored on an optical disk in DICOM format. The data were analyzed off-line with a personal computer-based system using

commercial analysis software (ViewForum R5.1V1L1; Philips). The software loaded serial short-axis sections of the left ventricle, and the first basal slice, which showed the circular LV wall construction throughout the cardiac cycle, and the last apical slice, which showed the LV cavity, were set manually. In the end-diastolic frame of the first slice, the inner contour was manually traced, and the software automatically recognized the contour of subsequent frames. The same procedure was performed on each slice until the final apical slice. If incorrect tracing was apparent, the contour was corrected manually in the appropriate frames. The intraventricular volume was calculated as the total sum of the product of the area within each contour and the thickness between the each slice (i.e., 10 mm). The EDV was set as the volume at the time of R-wave onset on the ECG, and the ESV was set as the smallest volume measured throughout the cardiac cycle. These data were used as the reference values for echocardiographic measurements.

Reproducibility analysis

Reproducibility of the measurements from both modalities was determined by analyzing random samples from 10 cases by the same investigator at least 1 month after the first analysis to determine intra-observer variability and by a separate investigator (H.N.) to determine inter-observer variability. The other investigator was blinded to the results of the first observer. Reproducibility was analyzed as the coefficient of variability defined as the ratio of the standard deviation (SD) and the mean of absolute readings for each echocardiographic parameter.

Statistical analyses

Results are expressed as number or the mean value ± SD. The echocardiographic data were compared with the data obtained from CMRI as the reference. The data were statistically analyzed by simple linear regression and by Bland-Altman analysis to determine the bias and limits of agreement between the modalities. The significance of the difference between the groups was tested by one-way analysis of variance (ANOVA). When significant difference was detected, significance was tested by Scheffé's post-hoc test.

Simple linear regression analyses were performed to assess factors that have significant interactions with absolute differences of volume measurements between 3D-STE and CMRI. If the absolute differences of LV volume measurements between 3D-STE and CMRI were more than a 75 percentile point of the absolute differences, the measurements by 3D-STE were defined as data with significant error. The area under the receiver-operating characteristics (ROC) curve (AUC) was used to quantify the ability to predict a significant error. The best cutoff value was defined as the point with the highest sum of sensitivity and

specificity. A p value of <0.05 was considered to indicate statistical significance. All calculations were performed with SPSS ver. 20 (SPSS Inc., Chicago, IL).

Results

Of the 68 patients, 4 patients were excluded because of inadequate imaging quality even in the 2D echocardiographic examinations. Finally, 64 patients were studied fully (Table 1). Secondary myocardial disease included cardiac sarcoidosis in 6 patients. Arrhythmia-related diseases included Brugada syndrome in 2 patients, arrhythmogenic right ventricular cardiomyopathy in 2, long QT syndrome in 1, and idiopathic ventricular tachycardia in 1 patient. These 6 patients were in sinus rhythm during the CMRI and echocardiographic examinations.

Comparisons of LV volume measurements and EF between methods

Volumetric measurements are summarized in Table 2. 3D-STE showed a tendency for underestimation of LV volume measurements, which did not differ significantly from those by CMRI. In contrast, 2D echocardiography significantly underestimated both LVEDV and LVESV. Consequently, LVEF by 2D echocardiography was significantly different from LVEF by CMRI.

Comparisons of regional IQS

The mean IQS of the 6 LV regions at end-diastole was significantly lower than the mean IQS at end-systole (2.2 ± 0.6 vs. 2.0 ± 0.5, $p < 0.001$), showing strong correlation between both mean IQSs ($r = 0.92$, $p < 0.001$). IQS in each region at end-diastole and end-systole are shown in Figure 3. There were significant differences in IQS between regions at both end-diastole and end-systole. IQSs in the septal and inferior regions were higher, whereas IQSs in

the anterior and apical regions in the 2-chamber view were lower than those of other regions. In the comparison of corresponding regions between end-diastole and end-systole, IQS at end-systole was significantly higher ($p < 0.05$) in all regions except for the septal region.

IQS and LV volume measurements

Correlations of the measurements by 3D-STE with those by CMRI are shown in Figure 4.

First, the subjects were classified into 3 groups based on tertile points of mean IQS. The first and second tertile IQS points at end-diastole were 1.8 and 2.3, and those at end-systole were 2.0 and 2.5, respectively. Bland-Altman plots revealed a wide range of 95% CI values in the first tertile group compared to the second and third tertile groups. Subsequently, absolute differences of volume measurements between 3D-STE and CMRI were modestly correlated with mean IQS (Figure 5).

Related factors of differences in volume measurements

The relations with absolute differences of volume measurements are summarized in Table 3. The both absolute difference of LVEDV and LVESV correlated with LVEDV and LVESV measured by CMRI, mean IQS, and IQS in the apical and septal regions at end-diastole.

Accuracy of LV volume measurements and the enlarged left ventricle

Based on the medium value of LVEDV by CMRI (127 ml), subjects were classified into the small (<127 ml) and large LVEDV (≧127 ml) groups. In the small LVEDV group, LVEDV and mean IQS did not correlate with the absolute differences of LVEDV. In contrast,

in the large LVEDV group, only mean IQS significantly correlated with the absolute differences of LVEDV (mean IQS, r = -0.45, p = 0.01). The quartile points of the absolute differences of LVEDV were as follows: 25 percentile was 12.4 ml, medium 26.0 ml; 75 percentile was 32.7 ml, maximum 133.7 ml and minimum 1.0 ml. Then, an absolute difference of LVEDV of ≥33 ml was defined as a significant error of LVEDV measurement by 3D-STE. In ROC analysis to detect significant error of LVEDV measurement, the AUC was 0.64 for LVEDV (p = 0.75), and 0.57 for mean IQS (p = 0.35). However, in the large LVEDV group, the AUC for mean IQS was 0.73 (p = 0.02), with a sensitivity of 0.88 and specificity of 0.50 under the cut-off point of 1.5.

As for LVESV, based on the medium value of LVESV by CMRI (63 ml), subjects were classified into the small (<63 ml) and large LVESV (≥63 ml) groups. As with LVEDV, in the small LVESV group, mean IQS at both end-diastole and end-systole did not correlate with absolute differences of LVESV, and in the large LVESV group, mean IQS at end-systole, but not end-diastole, significantly correlated with the absolute differences of LVESV (mean IQS, r = -0.41, p = 0.02).

The quartile points of the absolute differences of LVESV were as follows: 25 percentile was 7.5 ml, medium 18.5 ml; 75 percentile was 33.6 ml, maximum 115.6 ml and minimum 0.3 ml. An absolute difference of LVESV of ≥33.7 ml was defined as a significant error of LVESV measurement. In ROC analysis, the AUC to detect significant error of LVESV measurement was 0.77 for LVESV (p = 0.002) with a sensitivity of 0.69 and specificity of 0.81 under the cut-off point of 109 ml. In contrast, the AUC was 0.63 for mean IQS (p = 0.11). In the large LVESV group as well, the AUC for LVESV was 0.75 (p = 0.02), with a sensitivity of 0.83 and specificity of 0.60 under the cut-off point of 116 ml; however, the AUC was 0.62 for mean IQS (p = 0.22).

Reliability of LVEF by 3D-STE

Correlations of LVEF by 3D-STE with those by CMRI are shown in Figure 4. In addition, there were no significant relations between absolute differences of LVEF and the variables shown in Table 3. However, absolute differences of LVEF modestly correlated only with an absolute difference of LVESV ($r = 0.30$, $p = 0.01$).

Reproducibility

In regard to reproducibilities of CMRI- and 3D-STE-derived LVEDV and LVESV measurements, all inter- and intra-observer variabilities were below 10%. Inter-observer variability was higher than intra-observer variability for each measurement. The highest inter-observer variability was that of 3D-STE-derived LVESV (9.7 ± 6.4%) followed by CMRI-derived LVESV (8.3 ± 3.7%).

Discussion

The present study showed that 3D-STE could measure LV volume through the cardiac cycle more accurately than could measurement by standard 2D echocardiography. Because 3D-STE is a novel modality that uses an endocardial tracking system to estimate the LV border, our findings confirmed the reliability of myocardial tracking. However, as we hypothesized that the accuracy of measurements was dependent on the quality of the acquired images as well as on enlargement of the left ventricle.

LV volume measurement is an advantage of 3D echocardiography. However, the system used in previous studies did not use STE to detect the LV border [6-8]. STE was developed as a modality for myocardial function analysis. We previously reported a validation study for 3D-STE in assessing regional myocardial deformation [9]. However, unlike regional myocardial strain analysis, tracking of the entire LV endocardial border with STE has remained challenging. Indeed, favorable accuracy and reproducibility may be obtained by limiting analysis to subjects with adequate imaging quality [10]. We hypothesized that the important factor influencing the concordance between LV volumes measured by CMRI and 3D-STE would be the quality of the acquired images. In fact, LV volumes measured by 3D-STE were significantly affected by image quality based on the correlations with LV volumes measured by CMRI. In addition, differences of LV volume measurements between CMRI and 3D-STE were related to image quality, particularly in the setting of a larger LV volume. These findings suggest that since LV volume measurements may have a significant role in assessing pathophysiology in cardiac disease with LV remodeling, image quality should be taken into considerations when interpreting LV volume data from 3D-STE.

Better image quality of 3D-STE was necessary to accurately estimate LV volume. Inadequate image quality due to the lower spatio-temporal resolution of 3D-STE is the first

concern related to inaccuracy in measurement. In particular, a lower IQS in the anterior region followed by the lateral region indicates a limitation of resolution in the peripheral regions in a 3D image as compared with the IQS in the septal and inferior regions, which are located at the round center of the image. However, lower image quality in the septal and inferior regions, which should be visualized, may affect the accuracy of LV volume measurements as shown in Table 3.

We showed that 3D-STE has a limitation in evaluating diseases with cardiac chamber enlargement. A large LV volume itself was a strong determinant of differences in LV volume measurements between 3D-STE and CMRI, as correlation coefficients between 3D-STE and CMRI were under 1.0. However, in patients with larger LV volume, image quality was also an independent determinant of accurate LV volume measurements. The main reason is limitation of the permitted angle to obtain 3D-pyramidal data sets, which could strongly affect image quality of the peripheral regions.

The present study also showed that 3D-STE had good reproducibility. Reproducibility of the measurements, as indicated by both intra- and inter-observer variability of <10%, was clinically acceptable. Intra-observer variability was smaller than inter-observer variability, and variability of LVESV measurements was larger than that of LVEDV measurements. The reason for the difference in reproducibility could be caused by the quite vague definition for determining the endomyocardial contour, making it difficult to unify the procedure between examiners. The difference in variability could be explained by the fact that the contour of the end-diastolic phase is determined manually, whereas that of the end-systolic phase is the result of automated tracking of the contour.

Conclusion

In comparison with CMRI, 3D-STE was shown to be a feasible method of quantifying LV volume. However, this novel technique is still thought to be limited to cases in which the imaging quality is adequate, particularly in patients with a large LV volume. These results will help clinicians to select appropriate patients for examination and to make the most of the abilities of 3D-STE.

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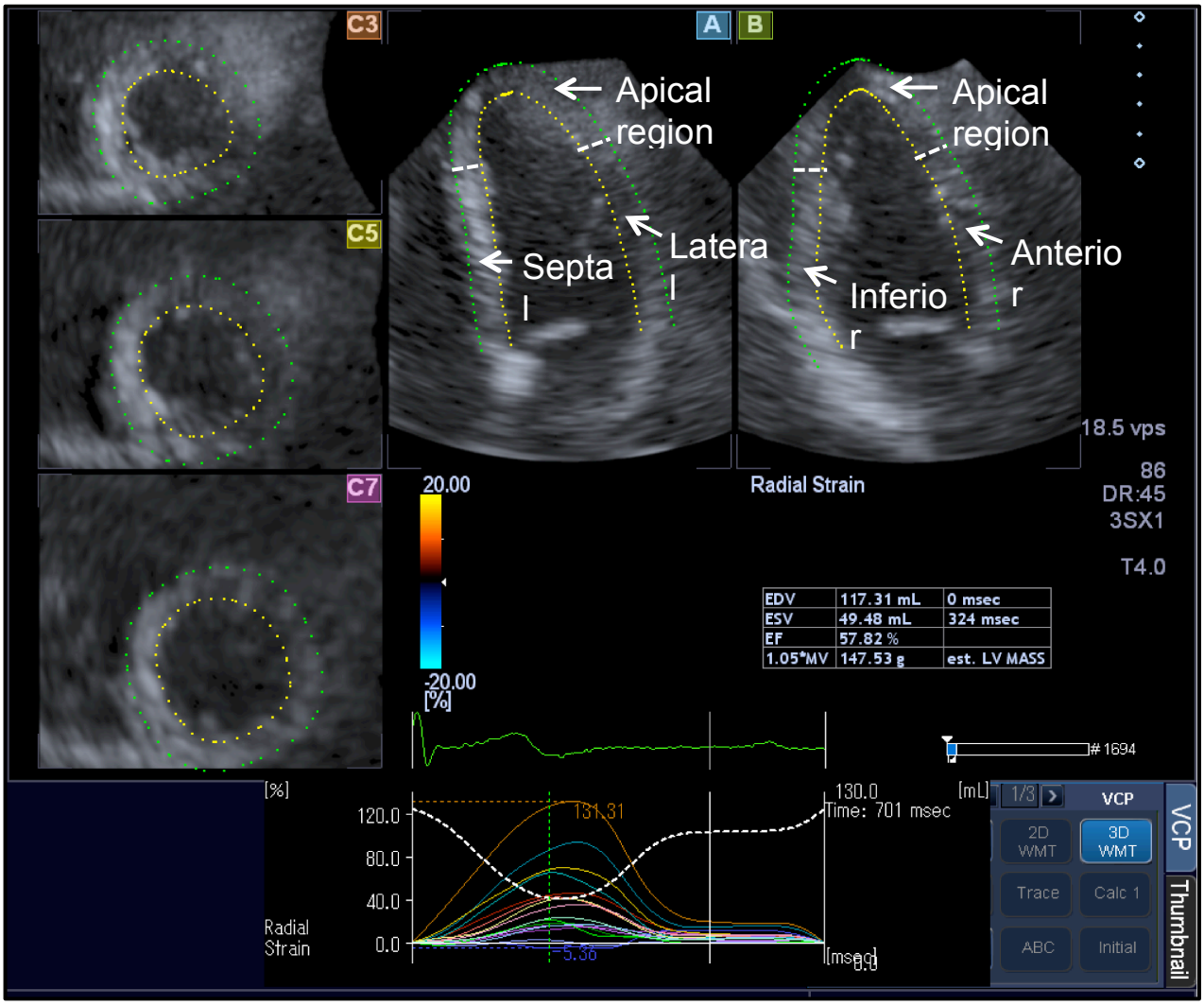
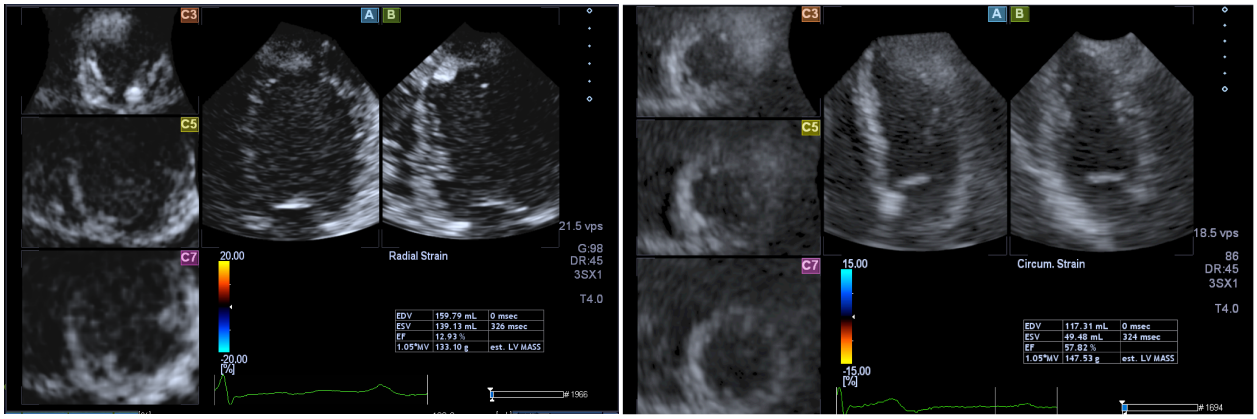
Figure Legends

Figure 1. Left ventricular volume measurement with 3-dimensional speckle tracking echocardiography and division of the left ventricular wall in assessing imaging quality score.



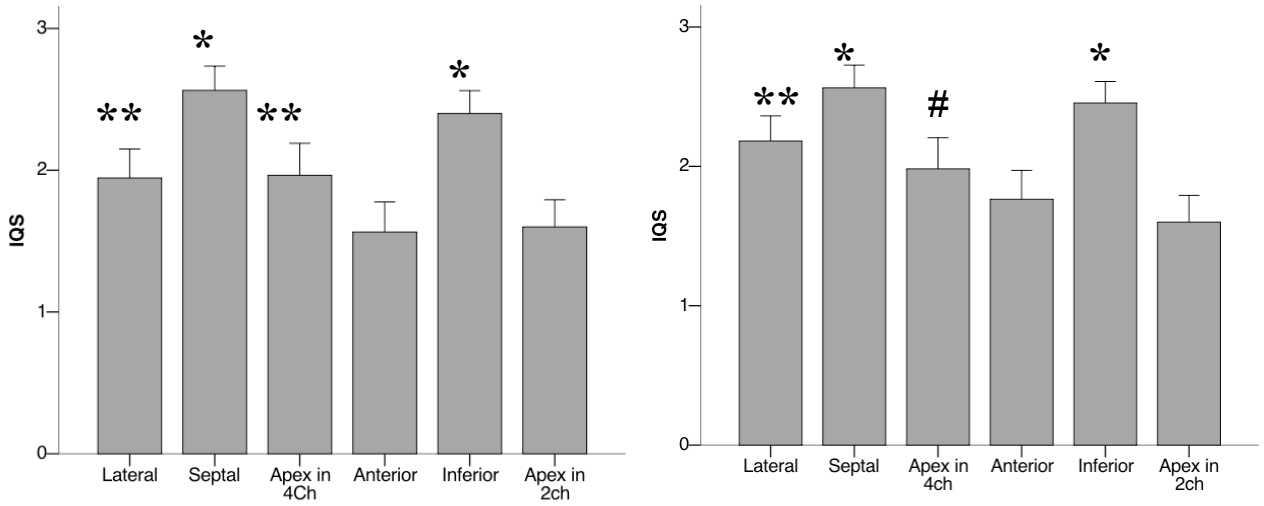
In the multiplanar reconstruction display, panel A (top center) and panel B (top right) show apical 4-chamber and 2-chamber views of the left ventricle, and panels C3 (top left), C5 (middle left), and C7 (bottom left) show short-axis images of the left ventricle at the level of the apex, mid ventricle, and base, respectively. Labeling and positioning of the panels are controlled by the vendor and are shown as originally output. 4ch, 4-chamber view; 2ch, 2-chamber view. See text for details.

Figure 2. Representative cases for assessing imaging quality score (IQS).



In the left images, the end-myocardial border of the septal region in panel A and the anterior region in panel B (as defined in Figure 1) are hardly seen and are thus scored as 1. In contrast, in the right image, the end-myocardial border of the anterior, apical, and inferior regions in panel B and the lateral and septal regions in panel A can be easily determined and are scored as 3, whereas the end-myocardial border of the apical region in the 4-chamber view can be determined by the adjacent contour and is scored as 2.

Figure 3. Imaging quality scores between left ventricular regions. 4ch, 4-chamber view; 2ch, 2-chamber view.

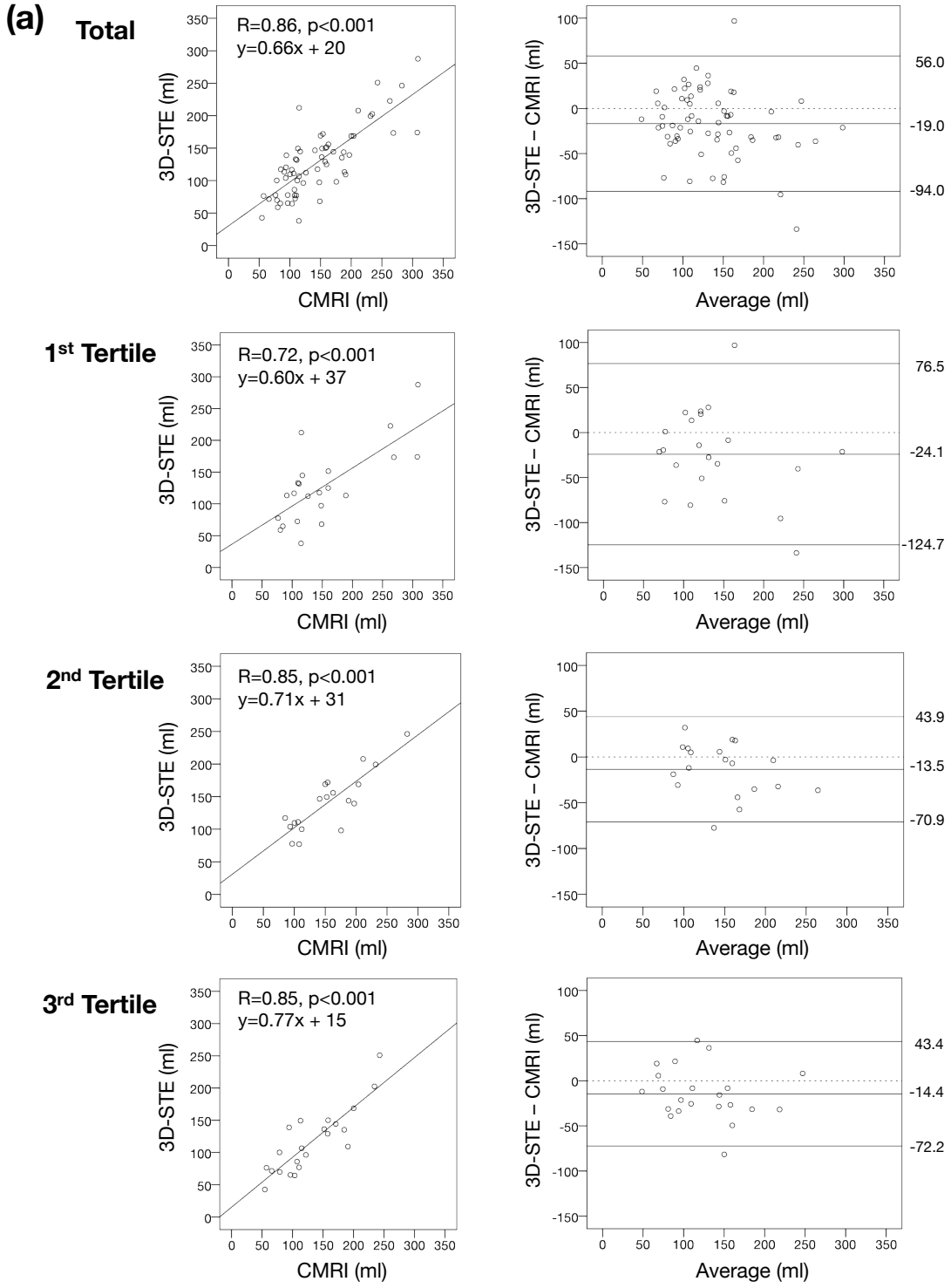


*p <0.001 vs. Lateral, Apex in 4ch and Anterior, Apex in 2ch;

**p <0.01 vs. Anterior, Apex in 2ch;

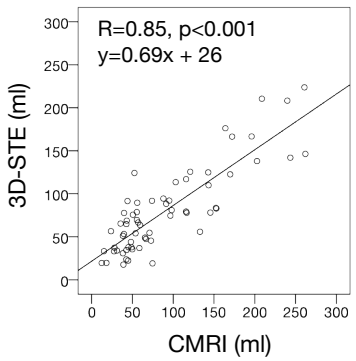
#p <0.05 vs. Anterior, Apex in 2ch.

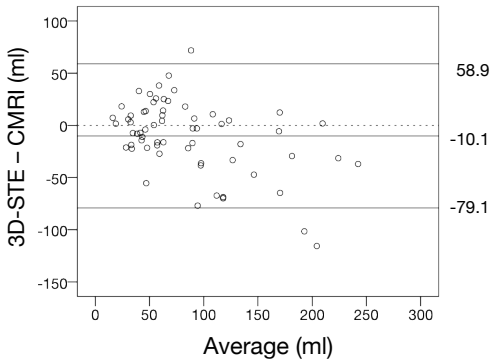
Figure 4. Correlations of volume measurements and ejection fraction between cardiac magnetic resonance imaging (CMRI) and-3-dimensional speckle tracking echocardiography (3D-STE): (a) left ventricular end-diastolic volume, (b) left ventricular end-systolic volume, and (c) left ventricular ejection fraction.



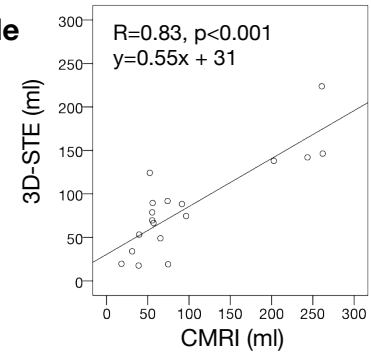
(b)

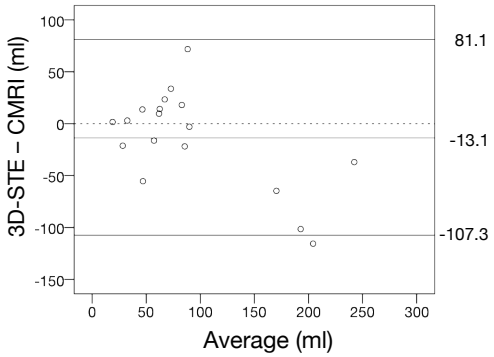
Total



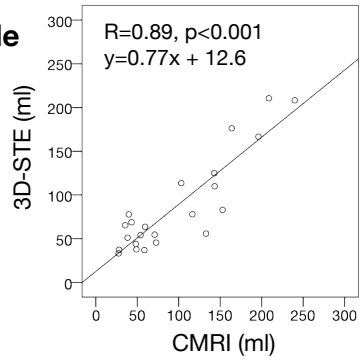


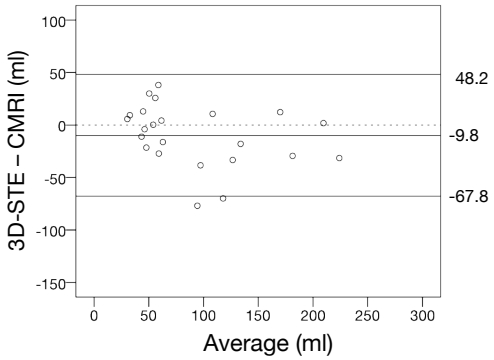
1st Tertile



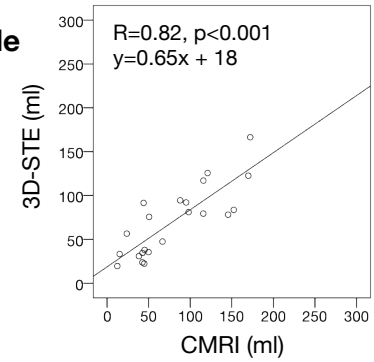


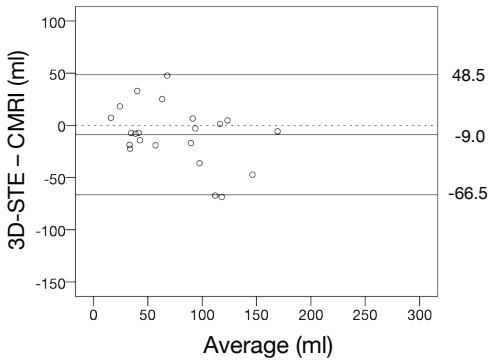
2nd Tertile

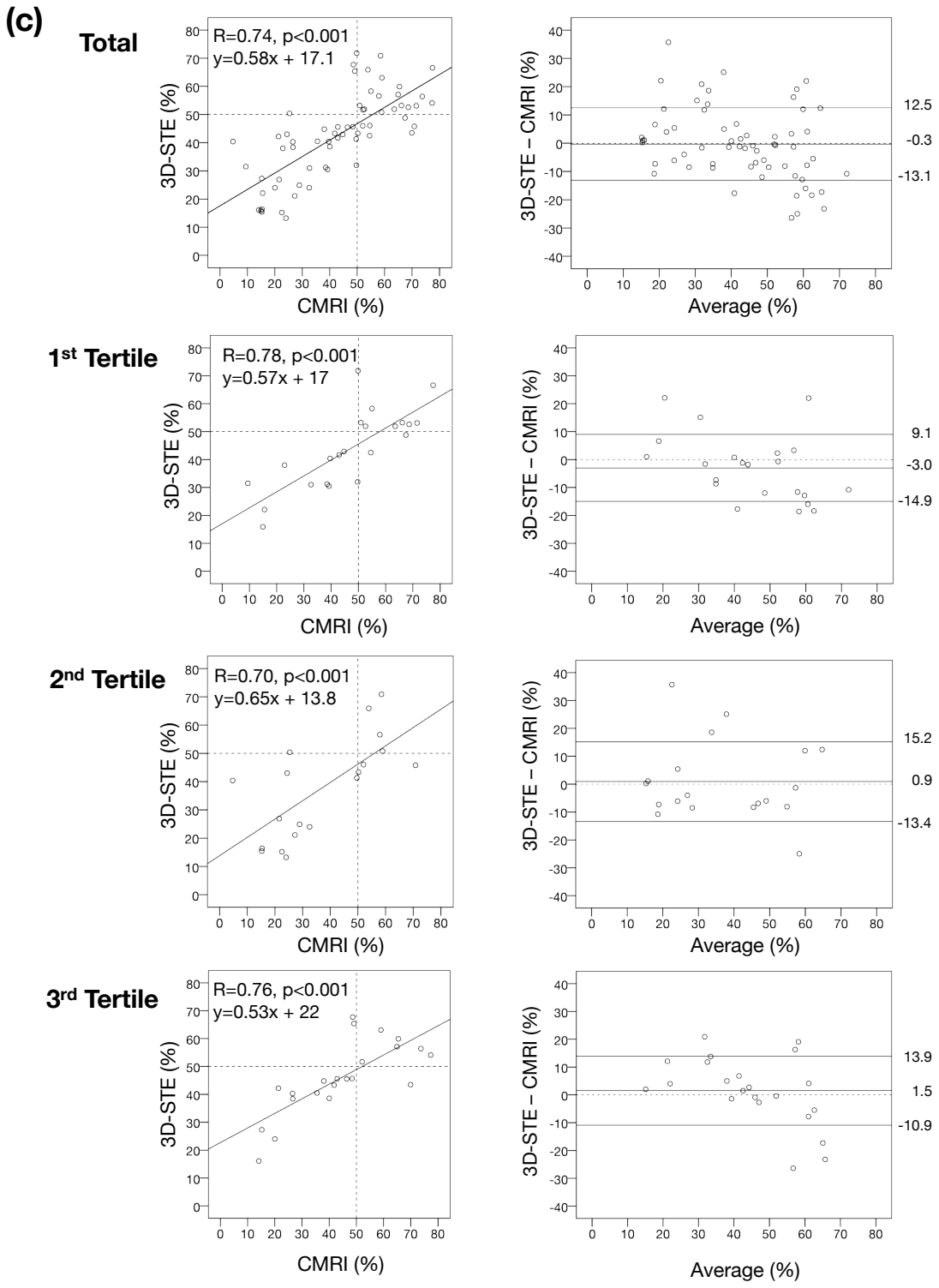




3rd Tertile

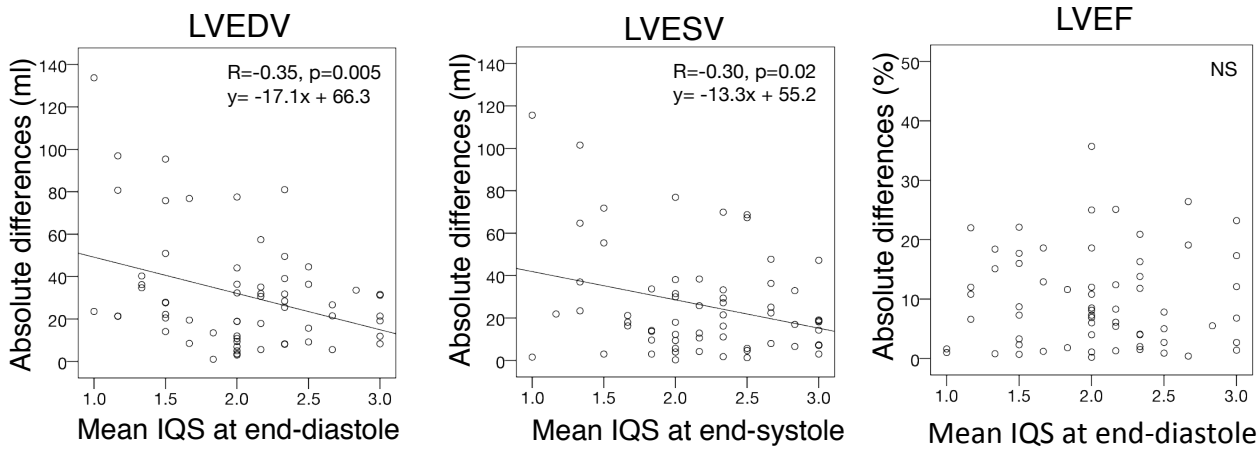






Scatter plots in the left panels show the correlation between the modalities. Bland-Altman plots in the right panels show the biases and limits of agreement. Lines and numbers in the right panels indicate ±95% confidence intervals and biases of the two modalities.

Figure 5. Correlations of IQS and absolute volume differences for left ventricular volume measurements.



CMRI, cardiac magnetic resonance imaging; IQS, imaging quality score; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; 3D-STE, 3-dimensional speckle tracking echocardiography.

Table 1
Clinical characteristics and echocardiographic data.

Sex (female/male), n	26/38
Age, years	55 ± 12 (range 17-80)
Dilated cardiomyopathy, n	17
Secondary myocardial diseases, n	14
Hypertrophic cardiomyopathy, n	12
Ischemic heart disease, n	8
Arrhythmia diseases, n	7
Hypertensive heart disease, n	4
Aortic stenosis, n	2
Heart rate, bpm	64 ± 13
End-diastolic dimension, mm	51 ± 9.7
End-systolic dimension, mm	38 ± 12
Interventricular septum thickness, mm	10 ± 5.8
Posterior wall thickness, mm	9.4 ± 2.3
Values are n or mean ± SD (range)	

Table 2
Volumetric measurements by CMRI, 2D echocardiography, and 3D-STE.

	CMRI	2D echocardiography	3D-STE
LVEDV (ml)	144 ± 60	113 ± 47*	125 ± 53
LVESV (ml)	89 ± 64	58 ± 43*	78 ± 49
EF (%)	44 ± 19	52 ± 17*†	43 ± 15

Values are mean ± SD. CMRI, cardiac magnetic resonance imaging; 3D-STE, three-dimensional speckle tracking echocardiography; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; EF, left ventricular ejection fraction.

*$p < 0.05$ vs. CMRI,

†$p = 0.006$ vs. 3D-STE.

Table 3
Relations with differences in volume measurements.

Variables	LVEDV		LVESV	
	r	*p*	*r*	*p*
Age	-	0.71	-	0.2
Body mass index	-	0.26	-	0.2
Heart rate	-	0.76	-	0.7
LVEDV by CMRI	0.41	0.001	0.52	<0.001
LVESV by CMRI	0.39	0.002	0.52	<0.001
LVEF by CMRI	-0.23	0.06	-0.42	<0.001
LVDd by 2D echo	0.26	0.05	0.31	0.01
LVDs by 2D echo	-	0.38	-	0.8
IQS at end-diastole				
Mean	-0.35	0.005	-0.27	0.03
Anterior region	-	0.22	-	0.12
Apical region in 2ch	-0.30	0.02	-	0.08
Inferior region	-0.31	0.01	-	0.16
Lateral region	-	0.51	-	0.81
Apical region in 4ch	-0.33	0.008	-0.28	0.03
Septal region	-0.33	0.009	-0.27	0.03
IQS at end-systole				
Mean			-0.30	0.02
Anterior region			-	0.12
Apical region in 2ch			-0.25	0.06
Inferior region			-0.27	0.03
Lateral region			-	0.24
Apical region in 4ch			-	0.24
Septal region			-0.31	0.02

LVEDV, left ventricular end-diastolic volume; CMRI, cardiac magnetic resonance imaging; LVESV, left ventricular end-systolic volume; LVEF, left ventricular ejection fraction; LVDd, left ventricular end-diastolic dimension; LVDs, left ventricular end-systolic dimension; 2ch, apical 2-chamber view; 4ch, apical 4-chamber view; IQS, image quality score.

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