

Contrast Enhancement and Image Quality Influence Two- and Three-dimensional Echocardiographic Determination of Left Ventricular Volumes: Comparison With Magnetic Resonance Imaging

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ABSTRACT

PURPOSE: To evaluate the effect of image quality and contrast enhancement (CE) on left ventricular (LV) volume determination by two- (2D) and three-dimensional (3D) echocardiography (2DE/3DE).

METHODS: We studied 32 post-myocardial infarction (MI) patients without (2DE/3DE) and with CE (CE2DE/CE3DE), in comparison with cardiac magnetic resonance imaging (CMR).

RESULTS: Two-dimensional echocardiography showed the largest negative bias versus CMR for diastolic and systolic volumes (−59, −28 mL, respectively) with lower biases for CE2DE (−37, −22 mL), 3DE (−31, −17 mL), and CE3DE (−17, −11 mL). Bias for ejection fraction (EF) ranged from −2.1% for 2DE to +1.4% for CE3DE. Agreement (intraclass correlation coefficient, ICC) for EF between CMR and 3DE (0.86 without and 0.85 with contrast) was better than for 2DE (0.73 without and 0.69 with contrast). The inter-/intra-observer coefficients of variation for EF varied from 16%/10% (2DE) to 6.9%/6.6% (CE2DE), and 8.3%/4.8% (3DE) to 6.7%/6.8% (CE3DE), respectively. The agreement (ICC) with CMR for EF measured by 2DE/3DE changed from 0.64/0.84 with poor image quality to 0.81/0.87 with moderate to good image quality.

CONCLUSIONS: Three-dimensional echocardiography was more accurate than 2DE for estimating LV volumes, with less inter-/intra-observer variability in EF values. Contrast enhancement improved accuracy for both 2DE and 3DE and improved the inter-observer variability of EF estimates for 2DE and 3DE. Image quality had more impact on the agreement of EF values with CMR for 2DE than for 3DE. Our results emphasize the importance of using the same technique for longitudinal studies of LV EF and specially LV volumes.

KEYWORDS: 2D echocardiography, 3D echocardiography, cardiac magnetic resonance imaging, left ventricular volume, left ventricular ejection fraction, contrast echocardiography

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Introduction

Myocardial infarction (MI) may cause left ventricular (LV) remodeling, manifested as changes in size, shape, and function of the left ventricle. Several studies have shown that increased LV volume after an acute MI is associated with increased mortality and that there is a strong correlation between the LV ejection fraction (EF) and mortality in MI patients.^{1–5} Moreover, information about LV function is crucial to guide further treatment and secondary preventive measures in MI patients as well as in heart failure.^{6–9}

Two-dimensional echocardiography (2DE) is the most frequently used method for the assessment of LV function, although it has limitations in both accuracy and reproducibility

because of various factors such as image quality, geometric assumptions, and image plane errors.¹⁰ The use of contrast enhancement and the development of three-dimensional echocardiography (3DE) have been proposed to improve accuracy and variability in previous studies.^{11–16} However, only few studies have performed a head-to-head comparison of LV volumes and EF by all four echocardiographic methods (2DE and 3DE with and without contrast enhancement) with cardiac magnetic resonance imaging (CMR).^{17–19} Furthermore, no definitive conclusion about superiority of 3DE over contrast-enhanced two-dimensional echocardiography (CE2DE) has been drawn, and contrast-enhanced three-dimensional echocardiography (CE3DE) is not yet recommended in current European



guidelines because of limited number of studies.^{20,21} Therefore, the main aim of our study was to compare the accuracy of 2DE, 3DE, CE2DE, and CE3DE in the assessment of LV volumes and EF, using CMR as a reference method, in a patient population following an acute MI. We also aimed to assess the impact of echocardiographic image quality on the accuracy of EF determination.

Methods

Study population

The study population was recruited via a randomized study on patients with a first-time acute MI treated with percutaneous coronary intervention (PCI), performed at the Karolinska University Hospital in 2007.²² From this study, 32 consecutive patients were included in this study. The mean age of the patients was 63 ± 12 years; 30 of the 32 participants were men. The patients underwent transthoracic echocardiography and CMR ≥ 3 months after PCI (mean time frame 11 months). Both two- (2D) and three-dimensional (3D) echocardiographic examinations were performed on the same occasion. Cardiac magnetic resonance imaging was performed within a mean time of 32 days from the echocardiography. All measurements were completed in all patients, and poor image quality of the echocardiography was not considered an exclusion criterion, as the impact of image quality on results was one of the study aims. None of the patients had atrial fibrillation or pacemaker. Informed, written consent was obtained from all participants, and the study was approved by the Regional Ethics Review Board in Stockholm.

Transthoracic echocardiography

The 2DE and 3DE studies were performed using a Philips iE33 ultrasound scanner (Philips Medical Systems, Bothell, WA, USA). The images were obtained with the patient in a left lateral decubitus position. All examinations were performed by one sonographer with long experience in 2DE, 3DE, and contrast enhancement. All images were stored digitally on a server for off-line analyses (Xcelera, Philips). For 3DE, a matrix array 3DE-transducer (X3-1, Philips) was used. Image acquisition was done from the apical transducer position over four or seven consecutive cardiac cycles during breath-holding, generating a full-volume data set. Care was taken to include the entire LV volume, and the size of the volume in 3DE images was adjusted accordingly. The 2DE acquisitions were made using a transducer with tissue harmonic imaging (S5-1, Philips). Apical four- and two-chamber views were acquired over two heartbeats. Care was taken to avoid foreshortening of the LV image and to adjust gain settings for optimal image quality.

Contrast enhancement

A commercially available contrast agent containing sulfur hexafluoride microbubbles (SonoVue; Bracco Imaging S.p.A.,

Milan, Italy) was used. This was prepared according to the manufacturer's recommendations and was administered intravenously as a bolus injection of 1 mL and repeated if needed for optimal delineation of the LV cavity.²¹ The CE2DE and CE3DE images were then acquired.

Off-line analyses

The 2DE and 3DE data were analyzed offline using dedicated software (Xcelera R3.2L1, Philips and Q-lab 10 with option 3DQ Advanced, Philips) by an experienced reader (J.J.), who was blinded to the results of CMR and other echocardiographic results.

3DE volume analysis

The long-axis and rotational angle of two orthogonal planes were adjusted to yield four- and two-chamber views. The end-diastolic (first frame) and end-systolic (smallest cavity) frames were identified, and then five points were placed manually in the two frames adjacent to the lateral, medial, anterior, and inferior parts of the mitral valve annulus, and one point at the apex. The endocardial surface was then outlined using an automated contour detection algorithm. The surface was examined in multiple sagittal and transverse planes and manually adjusted if necessary. Papillary muscles and fine trabeculations were included in the cavity. The volume enclosed by the generated surface was computed by the program, yielding the end-diastolic volume (EDV) and end-systolic volume (ESV) for each data set. Ejection fraction was calculated by the program using the standard formula. The contrast-enhanced images were analyzed similarly to the description above; however, in these data sets, the outer border of the contrast in the LV cavity was outlined and adjusted manually, since the automated algorithm was not optimized for analysis of contrast images. In cases where there was shadowing of the basal segments, echoes from the mitral annulus were used as landmarks to identify where to draw the contour.

2DE analysis

The 2DE images were analyzed for determinations of the LV systolic and diastolic volumes using the biplane method of disks from the apical four- and two-chamber images. The tracings of the blood-tissue interface in LV images were performed including papillary muscles and trabeculations in the cavity in accordance with echocardiographic guidelines.²³ The EF was calculated using the standard formula.

Image quality index

Image quality in endocardial definition was assessed in all echocardiography studies using a 17-segment model,²⁴ with each segment assessed on a 0-4 grade scale as follows: grade 0, no visible endocardium; 1, endocardial border not visible in the

Table 1. Left ventricular volumes and ejection fractions measured by 2DE and 3DE compared with cardiac MR in 32 patients.

	CMR	2DE	CE2DE	3DE	CE3DE	MIXED MODEL OVERALL	
						F	P
EDV (mL)	181 ± 41.7	122 ± 31.3 ^a	144 ± 31.8 ^{a,c}	150 ± 34.9 ^a	164 ± 33.3 ^b	53 (4, 124)	<.001
ESV (mL)	90.9 ± 30.9	63.1 ± 22.2 ^a	69.2 ± 19.8 ^{a,c}	73.6 ± 23.0 ^a	79.7 ± 25.5 ^b	23 (4, 62)	<.001
SV (mL)	89.8 ± 17.2	58.4 ± 17.8 ^a	74.4 ± 17.8 ^{a,c}	76.1 ± 18.6 ^a	84.0 ± 16.5	38 (4, 124)	<.001
EF (%)	50.7 ± 8.26	48.6 ± 11.5	52.1 ± 7.24	51.3 ± 8.20	52.1 ± 8.60	1.9 (4, 70)	.12

Abbreviations: CMR, cardiac magnetic resonance imaging; 2DE, two-dimensional echocardiography; 3DE, three-dimensional echocardiography; CE2DE, contrast-enhanced two-dimensional echocardiography; CE3DE, contrast-enhanced three-dimensional echocardiography; EDV, end-diastolic volume; EF, ejection fraction; ESV, end-systolic volume; SV, stroke volume.

Values are expressed as mean ± SD; *P*-values from post hoc *t*-tests using a Bonferroni correction; mixed model overall differences in related means by a general linear mixed model.

^a*P* < 0.001 versus CMR;

^b*P* < 0.01 versus CMR;

^cCE2DE non-significant versus 3DE.

whole segment; 2, endocardial border just visible; 3, endocardial border easily visible; and 4, endocardium visible, including clearly defined trabeculations. For 2DE, only the segments in the two- and four-chamber views were assessed, as these are the two views necessary for volume calculation.

The scores for all segments were averaged to yield an LV image quality index for each study. The study was considered as having “poor” image quality if the image quality index was ≤2. The scores for each segment without and with contrast were compared for 2DE and 3DE, respectively, to assess the change in image quality.

Cardiac magnetic resonance imaging

The CMR investigations were performed with an eight-channel cardiac coil by means of a 1.5T system (Signa Excite TwinSpeed, General Electric Healthcare, Waukesha, WI, USA) during vector-electrocardiographic monitoring. The image protocol included scouting images, localization of the short axis, and then covering the whole LV with retrospectively gated cine steady-state free precession (SSFP) images. Around 10 to 12 short-axis views and 2-, 3-, and 4-chamber views were obtained. Typical parameters for CMR were as follows: SSFP (echo time 1.58 ms, repetition time 3.61 ms, flip angle 60°, 25 phases, 8-mm slice, no gap, matrix 226 × 226). Cardiac magnetic resonance imaging images were analyzed offline using freely available segmentation software (Segment V.1.8 R0857).²⁵ In the short-axis images, EDV and ESV were measured in the phase that had the largest and smallest LV volumes, respectively. The LV outflow tract, papillary muscles, and trabeculations were included in the LV volume. All measurements were made by an experienced investigator (P.S.), who was blinded to the echocardiographic data.

Measurement variability

To determine the intra-observer variability for 2DE, 3DE, CE2DE, and CE3DE, measurements were repeated >1 month later on 15 randomly selected cases by an observer (J.J.), who

was blinded to the results of the previous measurements. To determine the inter-observer variability, measurements were repeated by a second observer (M.J.E.), who was blinded to the results obtained by the first. The two observers were equally experienced.

Statistical analysis

Continuous variables are expressed as the mean ± standard deviation. Correlations between measurements were assessed by calculating Pearson's correlation coefficient *r*. Agreement between imaging methods and between readings were assessed by calculating the intraclass correlation coefficient (ICC) and analyzed using Bland-Altman plots.²⁶ The ICC was assessed qualitatively as poor (<0.20), fair (0.21-0.40), moderate (0.41-0.60), good (0.61-0.80), or very good (>0.80).²⁷ Intra- and inter-observer variability was assessed by calculating the coefficient of variability (CV), expressed as the within-subject SD as a percentage of the mean. Differences in related means were analyzed by a general linear mixed model and post hoc analyses with paired sample *t*-tests using a Bonferroni correction. Difference between related samples of ordinal data was assessed by Wilcoxon signed-rank test. A two-tailed *P* value of <0.05 was considered statistically significant. Statistical analysis was performed using IBM SPSS Statistics (version 25; IBM Corp, Armonk, NJ, USA).

Results

The LV volumes, stroke volumes, and EF values for all methods are presented in Table 1. The EDV and ESV values obtained by CMR were significantly larger than were those obtained by 2DE and 3DE, both with and without contrast, whereas no significant differences were observed in EF values between the CMR and any of the four echocardiographic methods. We compared specifically 3DE and CE2DE volumes by post hoc analysis and found no significant difference between the two methods.

Table 2. Agreement between echocardiographic methods and cardiac MR regarding left ventricular volumes and ejection fraction.

	<i>R</i> (<i>P</i>)	ICC	BIAS ± SD	
2DE				
EDV (mL)	0.80 (<.01)	0.34	-59	±25
ESV (mL)	0.86 (<.01)	0.53	-28	±16
EF (%)	0.78 (<.01)	0.73	-2.1	±7.2
2DE + contrast				
EDV (mL)	0.76 (<.01)	0.49	-37	±27
ESV (mL)	0.84 (<.01)	0.57	-22	±18
EF (%)	0.70 (<.01)	0.69	1.3	±6.1
3DE				
EDV (mL)	0.75 (<.01)	0.56	-31	±28
ESV (mL)	0.88 (<.01)	0.70	-17	±15
EF (%)	0.86 (<.01)	0.86	0.55	±4.3
3DE + contrast				
EDV (mL)	0.79 (<.01)	0.71	-17	±25
ESV (mL)	0.87 (<.01)	0.80	-11	±15
EF (%)	0.85 (<.01)	0.85	1.4	±4.6

Abbreviations: 2DE, two-dimensional echocardiography; 3DE, three-dimensional echocardiography; EDV, end-diastolic volume; EF, ejection fraction; ESV, end-systolic volume; ICC, intraclass correlation coefficient; *r*, Pearson's correlation coefficient.

2D echocardiography with and without contrast

Correlations and agreement between LV volumes and EF determined by 2DE and CMR are presented in Table 2, and by Bland-Altman plots in Figure 1. There was good correlation between 2DE and CMR for EDV and ESV, both with and without contrast. However, the ICC was low for both EDV (0.34) and ESV (0.53), without contrast, and increased only slightly to 0.49 and 0.57, respectively, after contrast, indicating poor to moderate agreement between the methods. There was a negative bias of -59 mL in EDV and -28 mL in ESV compared with CMR, which improved when contrast was applied to -37 and -22 mL, respectively. The bias in diastolic and systolic volumes had a skewed distribution both with and without contrast with increasing differences with increasing volumes. The EF showed good correlation between 2DE and CMR, both with and without contrast ($r=0.78$ and 0.70 , respectively). The ICC was 0.73 without contrast and 0.69 with contrast. The mean bias compared with CMR was -2.1 EF units for 2DE and 1.3 EF units for 2DE with contrast.

3D echocardiography with and without contrast

Correlations and agreements between LV volumes and EF values determined by 3DE and CMR are presented in Table 2. There was good correlation between LV volumes determined by 3DE and CE3DE compared with CMR, with similar correlation coefficients. Without contrast, the ICC was 0.56 for EDV and 0.70 for ESV, which increased to 0.71 and 0.80, respectively, with contrast. The agreements with CMR are shown as Bland-Altman plots in Figure 2. There was less negative bias of both diastolic and systolic volumes for CE3DE compared with 3DE (-17.0 vs -37.0 mL and -11.2 vs -17.3 mL). The bias in diastolic and systolic volumes had a skewed distribution with and without contrast, with an increasing difference with increasing volumes. However, for EF, there was no significant difference between 3DE and CE3DE, and both had a small positive bias (+0.55 and +1.4, respectively; $P=0.4$).

Image quality

The image quality index was 2.03 (± 0.53) for 2DE and 1.96 (± 0.48) for 3DE on a scale from 0-4. After contrast enhancement, image quality index increased to 2.47 (± 0.49 , $P<0.001$ for the difference) for CE2DE and 2.20 (± 0.57 , $P<0.05$ for the difference) for CE3DE.

The segmental image quality for 2DE and 3DE with and without contrast are presented in Figure 3. For 2DE, contrast enhancement resulted in an increase in image quality from poor (<2) to visible or better (≥ 2) in four additional segments and significantly improved image score within 7 segments. For 3DE, contrast enhancement resulted in an increase in image quality from <2 to ≥ 2 in the mid anterolateral, mid inferolateral, and three apical segments, whereas it decreased to <2 in the mid inferior and two basal segments due to shadowing of the contrast. A significant improvement was seen in five segments. Figure 4 shows representative 3DE images with shadowing of basal lateral segments in comparison with 2DE.

The data for 2DE and 3DE were categorized into two groups based on the image quality index in the non-enhanced images using 2 as the cut-off value, representing better or worse than moderate image quality. For 2DE, the agreement of EF with CMR values increased from borderline moderate (ICC 0.64) in the group with an image quality index <2 to very good (ICC: 0.81) in the group with an image quality index ≥ 2 . For 3DE, there was a similarly very good agreement to CMR in both groups (ICC: 0.84 vs 0.87).

Measurement variability

Intra- and inter-observer variability and agreement for the determination of LV volumes and EF values are presented in Table 3 and Figures 5 and 6. The intra-observer CV decreased with contrast enhancement for all parameters for 2DE, whereas

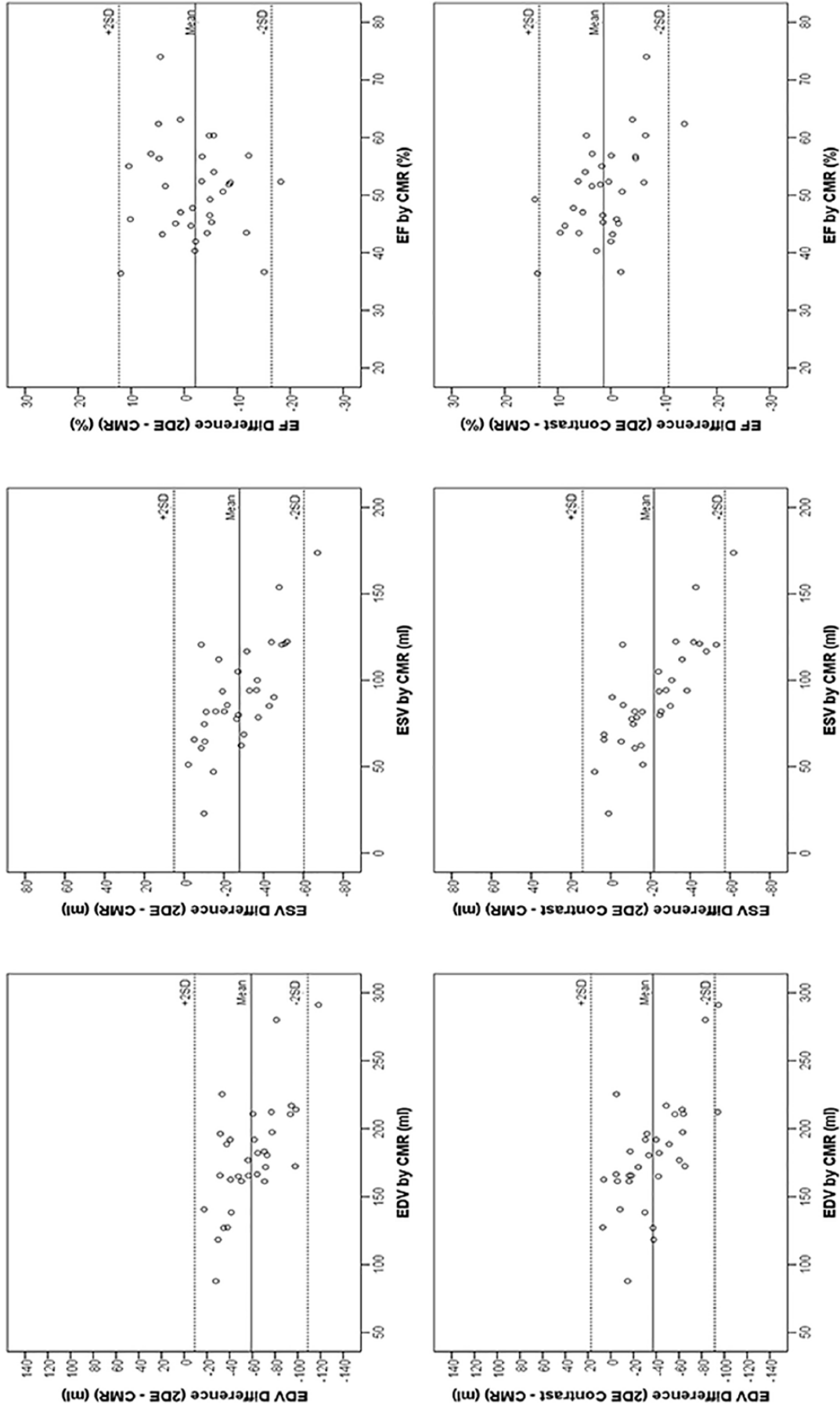


Figure 1 Bland-Altman analyses of (top) 2DE- and (bottom) CE2DE-derived left ventricular volumes and ejection fraction against CMR values. Abbreviations: EDV, end-diastolic volume; ESV, end-systolic volume; EF, ejection fraction.

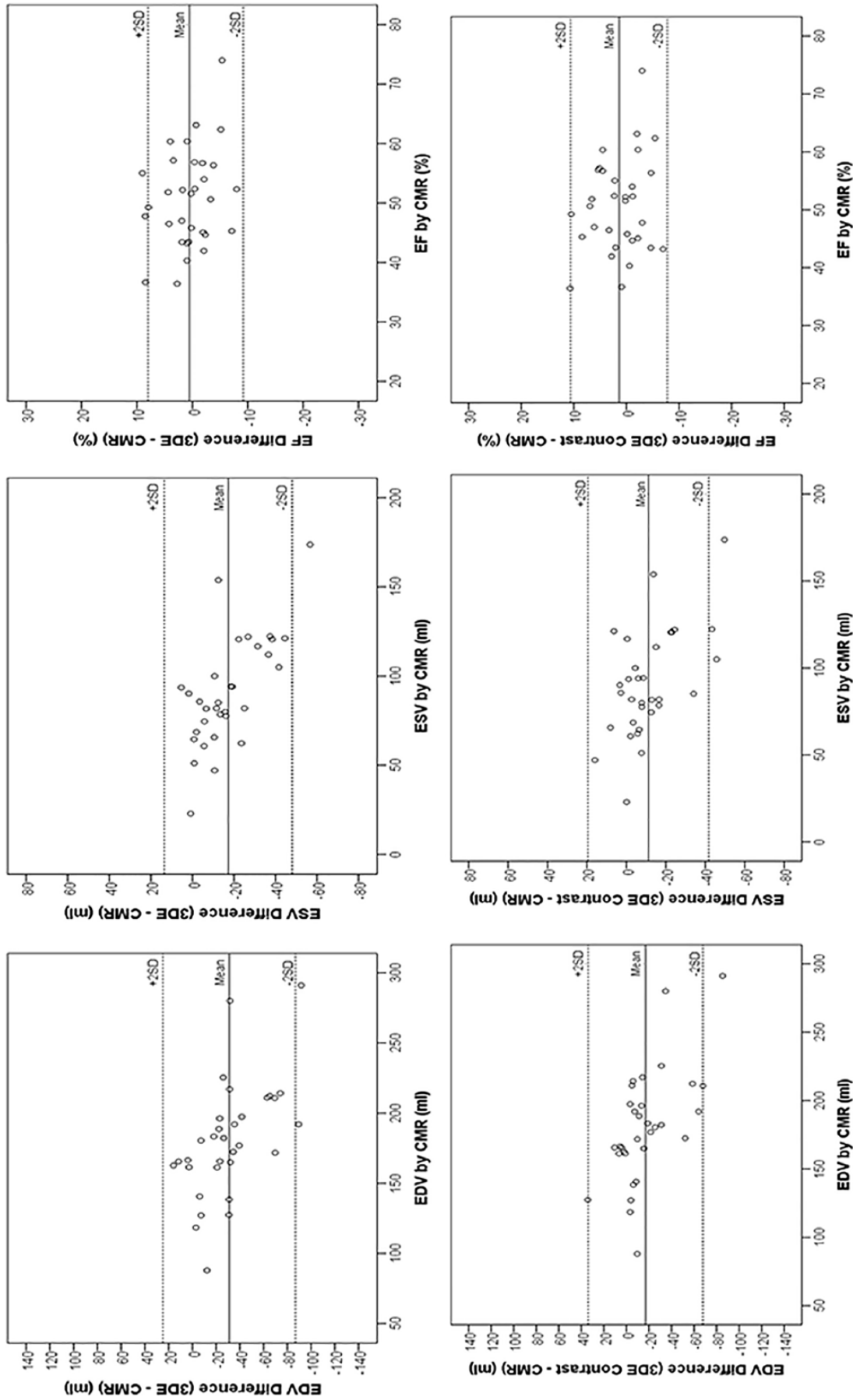


Figure 2. Bland-Altman analyses of (top) 3DE- and (bottom) CE3DE-derived left ventricular volumes and ejection fraction against CMR values. Abbreviations: EDV, end-diastolic volume; EF, ejection fraction; ESV, end-systolic volume.

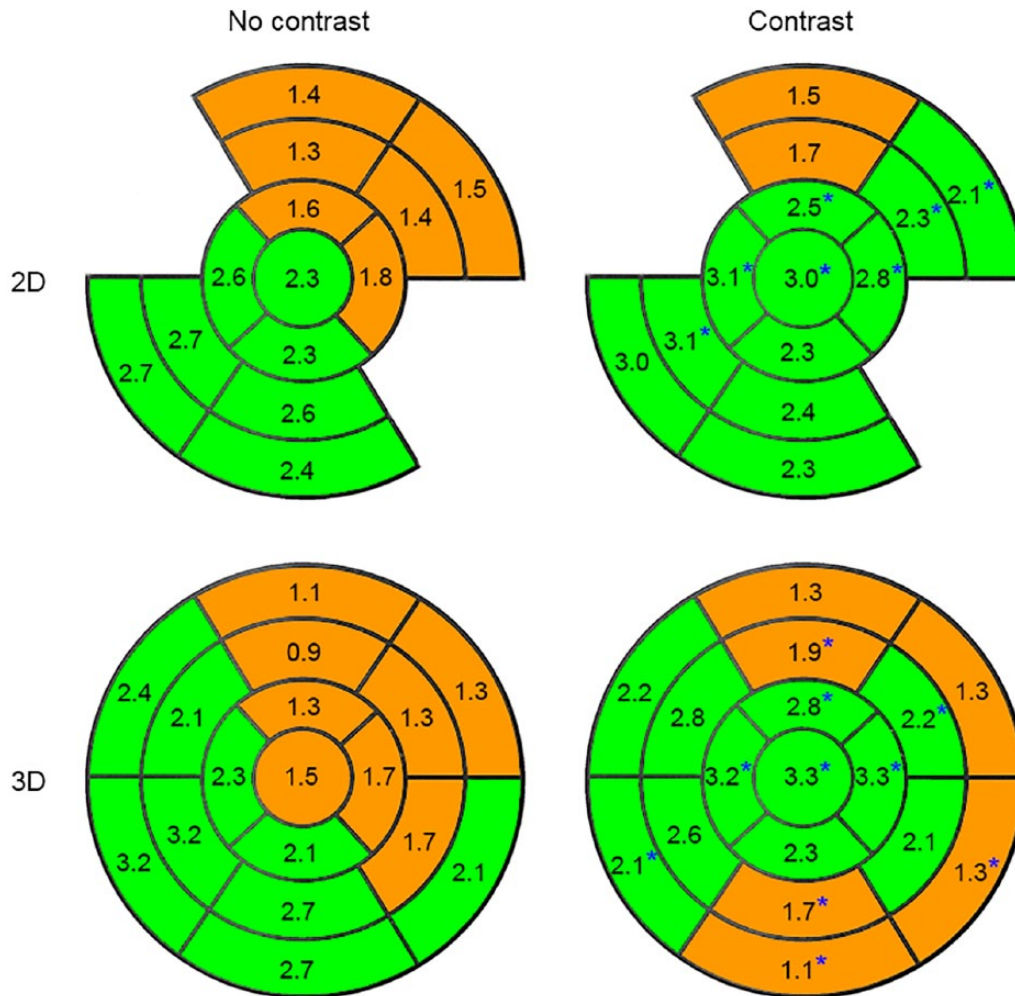


Figure 3. Average of image quality score in each myocardial segment assessed on a scale from 0 (no visible endocardium) to 4 (endocardium visible, including clearly defined trabeculations): (Top) 2D echocardiography, (bottom) 3D echocardiography, (left column) without contrast, and (right column) with contrast. Asterisk (*) denotes significant differences between contrast-enhanced and non-enhanced images assessed by Wilcoxon signed-rank test using Bonferroni correction for multiple comparisons.

for 3DE, this CV increased slightly for EDV (9.1% vs 9.4%), ESV (11% vs 13%), and EF (4.8% vs 6.8%). The inter-observer CV decreased with contrast enhancement for all 2DE parameters and was most pronounced for the EF values (16% vs 6.9%). For 3DE, contrast enhancement reduced the CV for the EF value (8.3 vs 6.7%) but had little effect on the CV for EDV and ESV.

Discussion

In this head-to-head study of 2DE and 3DE with and without contrast enhancement, we found that 3DE was better for the assessment of LV volumes and function than 2DE in our post-MI cases. This was caused by less systematic bias in LV volumes and better inter-observer agreement in EF for 3DE compared with 2DE. Contrast enhancement improved the delineation of the endocardial border, as expressed by an increase in the image quality index and a decrease in the systematic negative bias in LV volumes for both 2DE and 3DE compared with CMR. However, for the evaluation of EF,

contrast enhancement had only a small impact on accuracy and did not improve agreement with CMR for neither 2DE nor 3DE. The main advantage of contrast enhancement was the improved inter-observer agreement for both 2DE and 3DE in the determination of EF. Since EF is used more frequently than the LV volumes in making clinical decisions, this might be more relevant in serial follow-up of these patients. Regarding the comparison between 3DE and CE2DE, the two methods did not differ significantly in the estimation of LV volumes nor EF. In addition to the established 2DE, CE2DE, and 3DE methods, we included also a less studied technique, that is, CE3DE, in the study of measurement agreement and variability in comparison to the golden standard CMR. Among all four echocardiographic methods CE3DE showed the best agreement with CMR for LV volumes and EF in terms of ICC. The inter-observer agreement was overall in favor of CE2DE. Our results, in general, are consistent with previous studies that have found LV volumes measured by 3DE to correlate well with CMR and with less bias than 2DE and that

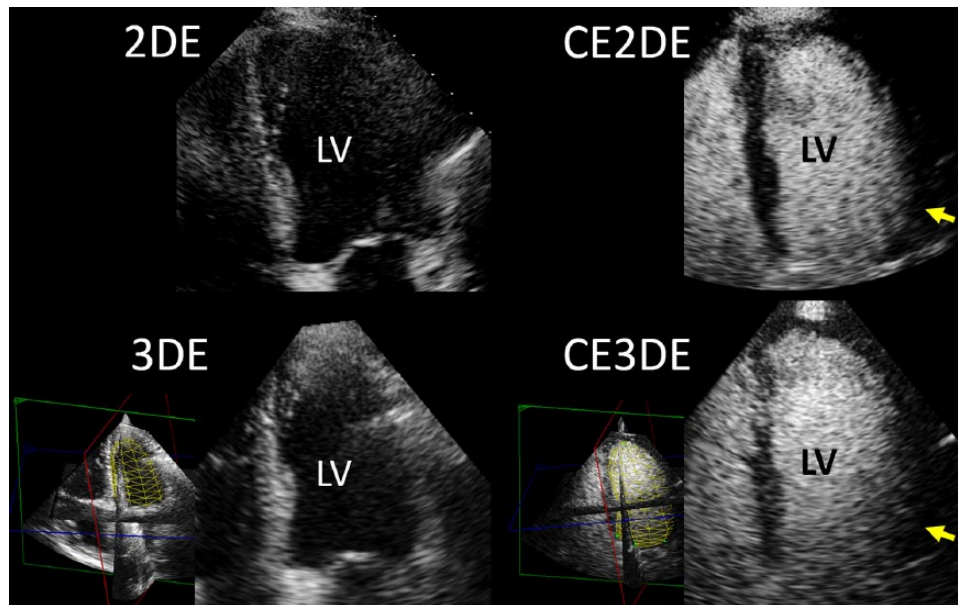


Figure 4. Typical example showing four chamber views with non-contrast-enhanced versus contrast-enhanced 2D images (top row). Corresponding images extracted from 3D full-volume data set (bottom row).

Abbreviations: 2DE, two-dimensional echocardiography; 3DE three-dimensional echocardiography; CE2DE, contrast-enhanced two-dimensional echocardiography; CE3DE, contrast-enhanced three-dimensional echocardiography; LV, left ventricle.

Arrows denote shadowing in the basal lateral segments in contrast-enhanced images. All images were acquired from the same subject.

Table 3. Intra- and inter-observer variability of 2DE and 3DE measurements with and without contrast enhancement (n=15).

	2DE				2DE + CONTRAST				3DE				3DE + CONTRAST			
	ICC	MEAN DIFF ± SD	CV (%)		ICC	MEAN DIFF ± SD	CV (%)		ICC	MEAN DIFF ± SD	CV (%)		ICC	MEAN DIFF ± SD	CV (%)	
EDV (mL)																
Intra	0.90	-9.5 ±11	8.9		0.96	-3.5 ±10	5.4		0.86	6.6 ±17	9.1		0.82	1.3 ±21	9.4	
Inter	0.86	6.7 ±15	10		0.87	14 ±13	10		0.60	22 ±22	17		0.65	25 ±21	16	
ESV (mL)																
Intra	0.94	-4.7 ±7.4	10		0.92	-1.2 ±9.4	9.9		0.91	2.1 ±11	11		0.87	1.5 ±14	13	
Inter	0.85	5.6 ±12	17		0.91	7.6 ±6.7	12		0.80	8.5 ±12	16		0.81	11 ±12	17	
EF (%)																
Intra	0.87	0.30 ±7.3	10		0.87	-0.45 ±5.1	6.6		0.93	0.02 ±3.8	4.8		0.86	-0.5 ±5.3	6.8	
Inter	0.61	-2.3 ±11	16		0.84	-1.2 ±1.4	6.9		0.76	2.2 ±5.9	8.3		0.86	0.67 ±5.2	6.7	

Abbreviations: 2DE, two-dimensional echocardiography; 3DE, three-dimensional echocardiography; CV, coefficient of variation; EDV, end-diastolic volume; EF, ejection fraction; ESV, end-systolic volume; ICC, intraclass correlation coefficient; Intra, intra-observer variability; Inter, inter-observer variability.

2DE and 3DE consistently underestimate LV volumes compared with CMR.^{14,28-32} The reasons for this are multifactorial. While for 2DE geometric assumptions and foreshortening have been identified as limiting factors, for 3DE the delineation of the LV endocardial border seems of major importance. The convention in CMR is to include not only papillary muscles but also trabeculations in the LV cavity.³³ This is in contrast to 3DE, where trabeculations might not be readily discernible and are therefore lumped together with the

myocardium instead of being included in the cavity, leading to systematic underestimation of LV volumes.³⁴ Left ventricular foreshortening is not a problem in 3DE as long as the whole LV is included in the data set. However, in our data, there was a trend toward increased disagreement between 3DE and CMR for the measurements of larger LV volumes due to difficulties in obtaining echocardiographic acquisitions of the whole LV volume in larger hearts, which has also been observed by others.^{35,36} Jenkins et al¹⁸ studied post-acute myocardial

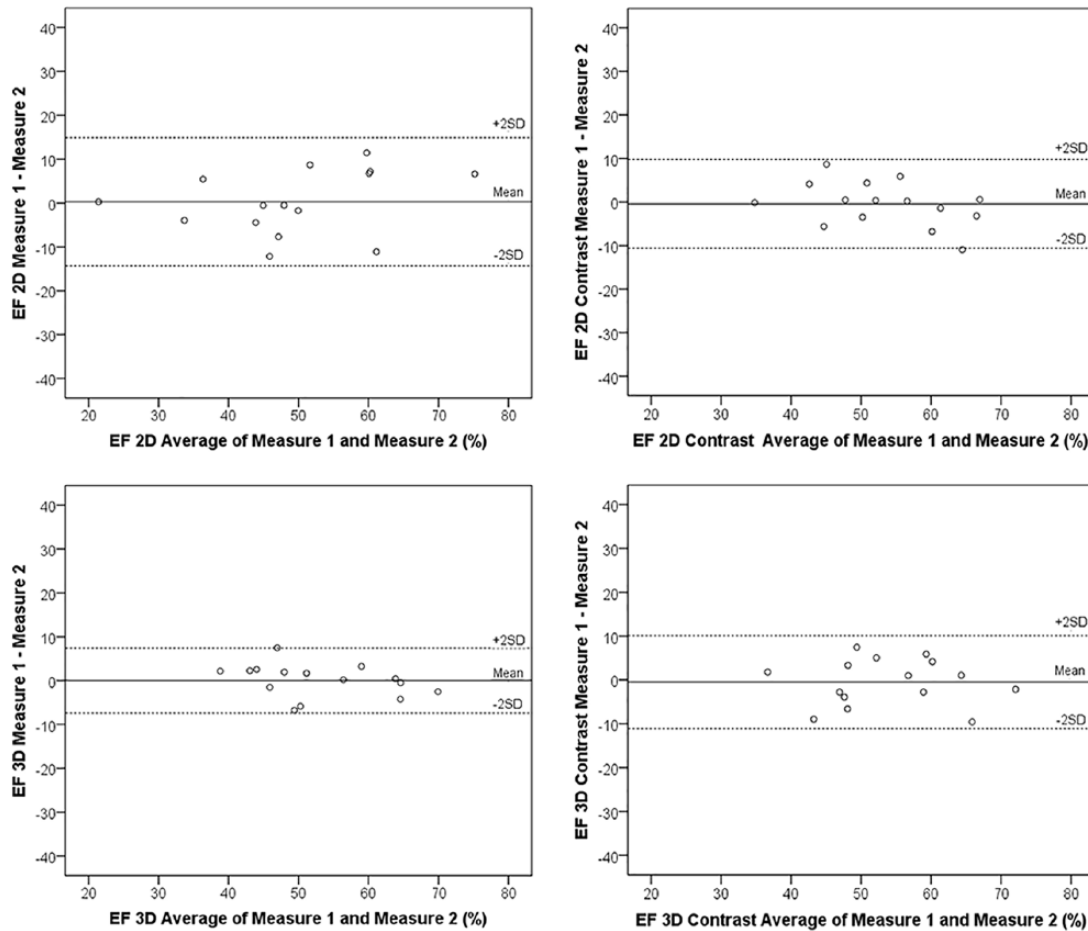


Figure 5. Intra-observer variability for EF measured by 2DE with and without contrast (top), and by 3DE with and without contrast (bottom); n = 15. Abbreviation: EF, ejection fraction.

infarction cases and reported a progressively less negative bias in the determination of EDV and ESV using 2DE, CE2DE, 3DE, and CE3DE in comparison with CMR; however, when EF was calculated, there was a small and equal bias for 2DE and CE2DE, as well as 3DE and CE3DE, which is consistent with our findings.

For 2DE, the systematic underestimation of LV volumes might arise in part also from an inability to identify the interface accurately between the compacted myocardium and the LV cavity, analogous to 3DE. Contrast enhancement facilitates identification of the true endocardial border, as it fills the intertrabecular space. However, as shown in our study, even with contrast, there is still a systematic negative bias that can be attributed to other sources of error, including inherent geometric assumptions in the biplane method of disk generation used for volume calculations, as well as image foreshortening and image plane errors.^{36,37} Nosir et al³⁸ reported that using the apical long-axis view instead of the apical two-chamber view in biplane calculation of LV volumes resulted in a reduction in bias compared with 3DE, as well as reduced observer variability.

In our study, contrast enhancement provided higher overall image quality. However for 3DE, the increased visualization was confined mainly to the apical segments, whereas it was

either unchanged or decreased for most basal segments, which was due to a shadowing phenomenon by the contrast. One mechanism of shadowing may be increased contrast bubble destruction caused by the high density of scan lines in 3DE compared with 2DE and also the increased contrast exposure to ultrasound because the contrast bubbles are exposed for a longer period of time within the scanned volume in CE3DE as opposed to within a single slice plane in CE2DE.³⁹ Continuous infusion of contrast instead of bolus injections may facilitate a more evenly distributed opacification of the LV.²¹ As we administered contrast using bolus injection, it could be hypothesized that a higher initial concentration compared with continuous infusion would be associated with increased bubble destruction, particularly for 3DE. However, for CE2DE, it has been demonstrated that bolus and continuous administration are associated with similar prevalence of contrast destruction.⁴⁰ The fact that shadowing, when it occurs, mainly affects the basal portions of the left ventricle is likely also explained by the large amount of reflective contrast between this area and the probe.

Others have studied the effect of contrast enhancement in 3DE on a segmental level. Nucifora et al⁴¹ found that contrast enhancement increased the number of segments with complete visualization from 66% to 84% and that the intra- and

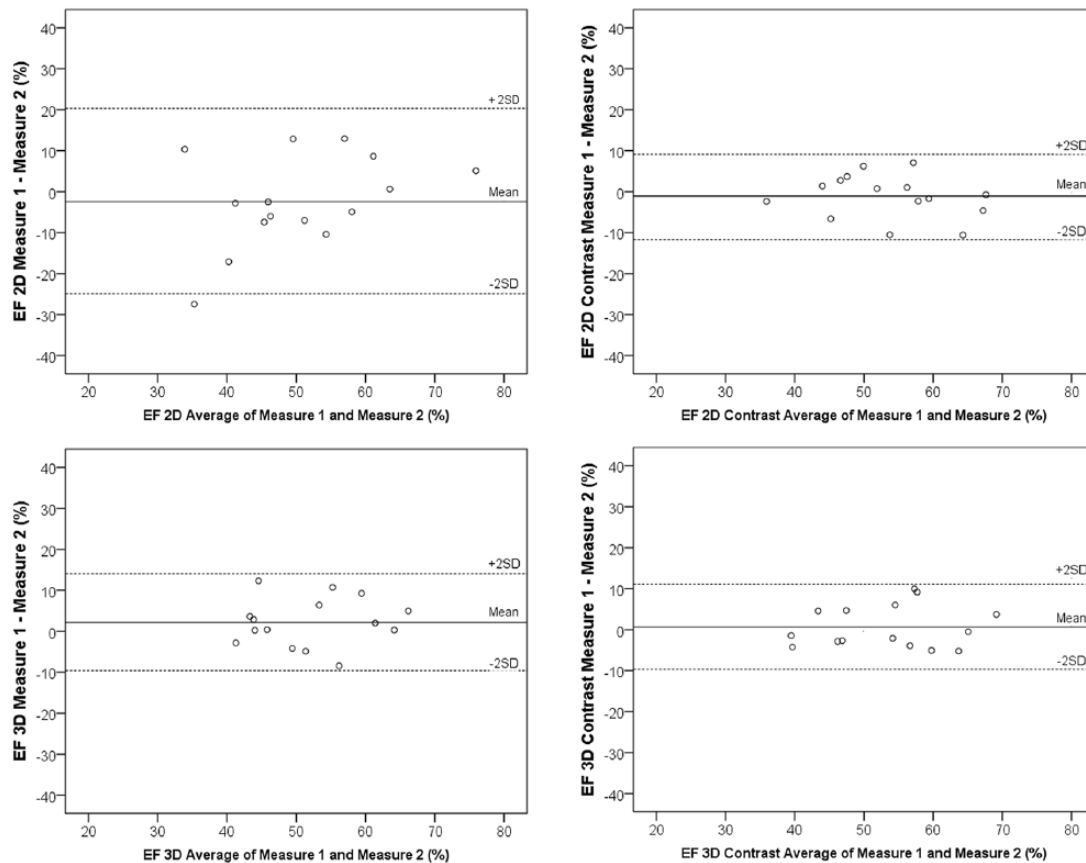


Figure 6. Inter-observer variability for EF by 2DE with and without contrast (top), and by 3DE with and without contrast (bottom); $n = 15$. Abbreviation: EF, ejection fraction.

inter-observer agreement for the grading of regional LV wall motion abnormalities also increased. In a study by Hoffmann et al,⁴² comparing 2DE and 3DE, the inter-observer agreement on the presence of regional wall motion abnormalities improved with contrast enhancement for both modalities and was higher for CE2DE than for CE3DE. These results are similar to ours, where contrast enhancement improved the segmental visualization more for 2DE than for 3DE. Indeed, there was also an increase in overall agreement with contrast enhancement regarding LV volumes when compared with CMR for both 3DE and 2DE in our study. Furthermore, in a subgroup of patients with poor image quality, the addition of contrast increased the agreement of EF with CMR for 2DE, whereas for 3DE, the agreement remained similarly very good in both groups, suggesting that contrast enhancement might be more beneficial in 2DE than in 3DE. These findings are in line with a study by Corsi et al⁴³ who reported that 3DE image analysis was feasible regardless of poor endocardial visualization in 2DE and may be explained by the ability to make better assumptions regarding the endocardial surface based on adjacent anatomical information during volumetric analysis of 3DE data, as opposed to being restricted to two cross-sectional planes in 2DE.

Regarding the impact of contrast enhancement on inter-observer agreement, only few studies have made a head-to-head comparison of all four modalities, that is, 2DE and 3DE,

both with and without contrast and the results have been somewhat diverging. Hoffmann et al¹⁷ reported the inter-observer agreement on EF for CE3DE to be higher than for CE2DE; however, the actual difference was small (limits of agreement 27.4 vs 27.9%). Interestingly, they also found the inter-observer agreement for 2DE to be somewhat higher than for 3DE (limits of agreement 39.4% vs 40.7%). Jenkins et al¹⁸ found the inter-observer agreement on EDV for CE3DE to be higher than for 3DE, which in turn was higher than for CE2DE and 2DE. Similar results were reported from a study using tri-plane analysis as opposed to full-volume analysis of 3D data.¹⁵ Another study by Thavendiranathan et al¹⁶ compared all four modalities and found the inter-observer variability regarding determination of EF to be smallest for 3DE, followed by CE3DE, 2DE, and surprisingly the highest variability was reported for CE2DE.

Our results showed the highest inter-observer agreement on LV volumes for CE2DE followed by CE3DE, 3DE, and 2DE, whereas for the determination of EF, the highest agreement was found for CE3DE followed by CE2DE, 3DE, and 2DE. However, the difference in inter-observer agreement between CE3DE and CE2DE was small (ICC 0.86 vs 0.84) regarding EF. Based on these results, and the ease of use, CE2DE may be the preferred method in serial follow-up of patients when changes in LV volumes and EF over time are of importance. Although CE3DE showed overall best agreement on LV

volumes with CMR, commercially available software for 3D analysis are not yet generally optimized for use with CE3DE data sets, which may currently limit its use in clinical practice.

Study limitations

A limitation of our study is the relatively small size of the study group. However, the main findings of the study reached statistical significance even in this group. There were only two women in the study population (vs 30 men), but we did not expect gender effects, and to rule out such would require a considerably larger study population.

The semi-automated software used for 3DE analysis was not optimized for use of contrast-enhanced images, resulting in the need for more manual tracing in these studies. This may potentially have affected the variability measurements compared with non-CE3DE. Software adaptations and development may facilitate these analyses in the future.

Echocardiography and CMR were not performed on the same occasion for all patients, which might have had an impact on the agreement between methods. However, the mean time from the initial cardiac event was 11 months, and changes in LV volumes and function occur mainly during the first month following an MI,⁴⁴ LV volumes were therefore likely stable at the time of echocardiography and CMR.

Translational commentary

Currently, we see a trend to implement semi-automatic endocardial out-lining for echocardiographic evaluation of LV volumes. This speeds up the evaluation process and reduces variability, but it does not necessarily improve the accuracy of measurements. For this purpose, contrast provides an important, but still for various reasons underused,⁴⁵ possibility to visualize LV borders in the not-so-rare situation when image quality is suboptimal.⁴⁶ Our use of contrast for LV opacification has increased substantially, partly triggered by this study, and recent recommendations by the European Association of Cardiovascular Imaging (EACVI) are helpful in this respect.²¹ However, there are still issues which we think necessitate further research and development in this area to optimize work flow and increase clinical relevance.

The development of semi-automatic LV endocardial border detection algorithms applicable also to 2D contrast images would be of great value in clinical practice. Our results have also encouraged us to apply 3DE to a larger extent. However, we would like to see improvements in the 3DE user interfaces, further development of semi-automatic or automatic volume determination algorithms for 3DE and better-optimized software for the evaluation of CE3DE data sets.

An important factor that hamper the use of contrast enhancement for LV volume quantification is the lack of reference values,^{21,23,47} so there is a need for large prospective studies to define normal ranges for LV volumes measured with CE2DE and CE3DE.

The cost-efficiency of CE2DE has been established in several studies in different patient groups and diagnoses.^{21,47} For CE3DE however, cost-efficiency analyses based on large-scale studies are still lacking. Another area of interest for future studies is to determine the prognostic value of CE3DE in comparison to non-enhanced imaging and CE2DE. This is of particular interest when serial assessments of LV volume and function are essential for clinical decision-making, for example, in valvular heart disease, cardiomyopathies, and during cancer treatment.

Conclusions

In this post-MI study population, 3DE was more accurate than 2DE for the determination of LV volumes and showed lower intra- and inter-observer variability in determination of EF. Contrast enhancement improved accuracy for the determination of LV volumes for both 2DE and 3DE, by improving overall endocardial definition. Contrast enhancement further decreased inter-observer variability in the determination of EF for both 2DE and 3DE. Poor echocardiographic image quality had a more negative impact on the measurement of EF by 2DE than 3DE in comparison with CMR. Understanding the difference in echocardiographic results depending on modality used is crucial in decision-making. Our results underline again the importance of choosing the same technique for clinical follow-up or longitudinal studies of LV EF and especially when LV volumes are considered.

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Author Contributions

JJ: Conceptualization and design, methodology, data acquisition, analysis and interpretation, writing original draft, revising the manuscript, final approval. PS: CMR methodology, CMR Data acquisition, analysis and validation, revising the manuscript, final approval. JP: Revising the manuscript, final approval. KC: Conceptualization and design, supervision, revising the manuscript, final approval. MJE: Conceptualization and design, supervision, data analysis and interpretation, revising the manuscript, final approval.

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