Comparison of Two- and Three-Dimensional Unenhanced and Contrast-Enhanced Echocardiographies Versus Cineventriculography Versus Cardiac Magnetic Resonance for Determination of Left Ventricular Function

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Contrast enhancement has been shown to improve detection of regional wall motion abnormalities (RWMA) in 2-dimensional (2D) echocardiography. This study determined the use of contrast enhancement in the setting of 3-dimensional (3D) echocardiography for definition of left ventricular RWMA compared with 2D echocardiography, cineventriculography, and cardiac magnetic resonance (CMR). In 63 patients, unenhanced and contrast-enhanced (SonoVue; Bracco Imaging S.p.A., Milan, Italy) 2D and 3D echocardiographies, CMR, and cineventriculography were performed. Hypokinesia in ≥1 segment defined the presence of RWMA. Interreader agreement (IRA) between 2 blinded off-site readers on presence of RWMA was determined within each imaging technique. Intermethod agreement among imaging techniques was analyzed. A standard of truth for the presence of RWMA was obtained by an independent expert panel decision. IRA on presence of RWMA expressed as Cohen's κ coefficient was 0.27 for unenhanced 3D echocardiography, 0.40 for unenhanced 2D echocardiography, 0.57 for CMR, and 0.51 for cineventriculography. The use of contrast increased IRA on RWMA to 0.42 for 3D echocardiography and to 0.56 for 2D echocardiography. Agreement with CMR on RWMA increased for 3D echocardiography when contrast enhancement was used (κ 0.40 vs 0.22 for unenhanced 3D echocardiography). Similarly, agreement of 2D echocardiography with CMR on RWMA increased with contrast enhancement (κ 0.50 vs 0.32). Accuracy to detect expert panel−defined RWMA was highest for CMR (84%) followed by 2D contrast echocardiography (78%) and 3D contrast echocardiography (76%). It was lesser for 2D and 3D unenhanced echocardiographies. In conclusion, analysis of RWMA is characterized by considerable interreader variability even using high-quality imaging techniques. IRA on RWMA is lower with 3D echocardiography compared with 2D echocardiography. IRA on RWMA and accuracy to detect panel-defined RWMA improve with contrast enhancement irrespective of the 2D or 3D echocardiography use. **(Am J Cardiol 2014;113:395−401)**

The objectives of this multicenter study were to (1) determine the interreader agreement (IRA) in the definition of regional wall motion abnormalities (RWMA) for unenhanced and contrast-enhanced 3-dimensional (3D) echocardiographies compared with unenhanced and contrast-enhanced 2-dimensional (2D) echocardiographies, cineventriculography, and cardiac magnetic resonance (CMR), (2) determine the agreement between the different imaging techniques in the definition of RWMA, and (3) evaluate for each of the imaging techniques the agreement and accuracy of determined RWMA related to the standard of truth on regional left ventricular (LV) function as defined by an expert panel decision (EPD) based on clinical, electrocardiographic (ECG), angiographic, and imaging data. The design of this study allowed a direct comparison of the techniques during resting conditions on the same patients. Blinded readings using experienced independent core laboratories were performed for each imaging technique according to defined standards.

Methods

This multicenter open-label study used intrasubject comparison of 3D unenhanced and contrast-enhanced echocardiographies with 2D echocardiography, biplane cineventriculography, and CMR for determination of RWMA. Coronary angiography for suspected coronary

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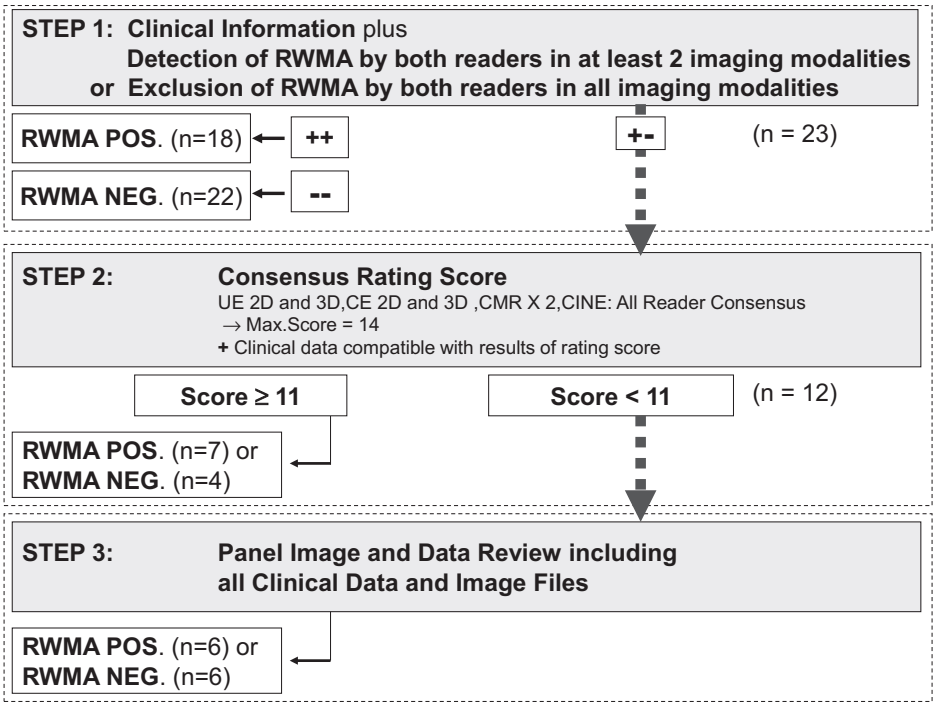

Figure 1. Three-step decision algorithm used to define the standard of truth (EPD) on the presence of RWMA. CE = contrast-enhanced echocardiography; CINE = cineventriculography; UE = unenhanced echocardiography.

Table 1
Patient baseline characteristics

Characteristic	Value, n = 63 (%)
Age (yrs)	63.8 ± 10.4
History of previous myocardial infarction	20 (32)
Previous percutaneous coronary intervention	33 (52)
Previous coronary bypass surgery	7 (11)
Significant coronary artery disease	48 (76)
Coronary stenosis in left anterior descending	35 (56)
Coronary stenosis in left circumflex branch	40 (63)
Diabetes mellitus	6 (10)
Hypertension	44 (70)
Hypercholesterolemia	21 (33)
Ejection fraction by cineventriculography	
<35%	10 (16)
35%–55%	16 (25)
>55%	37 (59)

Hypertension: blood pressure >140/90 mm Hg or medically treated; hypercholesterolemia: total cholesterol level >200 mg/dl or medically treated.

artery disease was performed in all patients. Immediate revascularization after coronary angiography was an exclusion criterion. All imaging techniques were performed within 72 hours with the patient being in stable hemodynamic conditions.

For each imaging technique, recommendations on the performance of image acquisition were defined to secure uniform and interpretable image data sets from all participating institutions. The adherence to the predefined imaging protocols of this multicenter trial by the performing physicians was monitored during the enrollment period.

The analysis of image data sets for RWMA was performed for each imaging technique by 2 independent off-site readers not affiliated to the participating centers who were unaware of the clinical data and the results of the other imaging techniques. All off-site readers had at least 5 years of experience in the evaluated imaging technique. Guidelines were defined and provided on the evaluation of regional LV function for each imaging technique to the unaffiliated off-site readers of the independent core laboratories (see Appendix). Regional wall motion of each analyzed segment was defined as either normokinetic, hypokinetic, akinetic, or dyskinetic. Whenever the regional function could not be defined because of insufficient image quality, the function was assumed to be normal. Although regional function was determined for each LV segment, the presence of an RWMA was reported on a patient basis, and a comparison of methods was performed on detection of RWMA on a patient basis. The study was conducted according to the Good Clinical Practice and in compliance with local regulatory requirements. The research protocol was approved by the applicable central and local institutional ethics committees. All patients gave written informed consent to participate in the study.

Sixty-five patients were enrolled at 4 European centers with balanced contribution. Patient enrollment was stratified at each center based on results from angiographic ventriculography to achieve a balanced distribution within 3 predefined LV ejection fraction groups (>55%, 35% to 55%, and <35%). An interpretable cineventriculography with availability of at least 2 consecutive nonextrasystolic cardiac cycles during ventriculographic contrast administration was a prerequisite for inclusion into the study. Two patients had to be excluded from the study because of

Table 2
Percentage of left ventricular segments found to be nonevaluable for segmental function because of low image quality

Variable	Imaging (%)	Contrast-Enhanced Imaging (%)	p
2D echocardiography			
Off-site 1	11.8	0.5	
Off-site 2	2.9	1.1	<0.001
Reconstructed planes from 3D echocardiography			
Off-site 1	31.5	3.0	
Off-site 2	16.8	6.4	<0.001
3D full-volume echocardiography			
Off-site 1	6.3	3.6	
Off-site 2	7.4	6.3	<0.001
Cardiac magnetic resonance			
Off-site 1	2.2		
Off-site 2	1.8		
Cineventriculography			
Off-site 1		9.7	
Off-site 2		1.2	

Table 3
Frequency of regional wall motion abnormalities detected by each of the imaging techniques

Imaging Technique	Off-Site Reader 1 (%)	Off-Site Reader 2 (%)	p
Unenhanced 2D echocardiography	61	45	0.116
Reconstructed planes from unenhanced 3D echocardiography	63	52	0.287
Unenhanced 3D full-volume echocardiography	76	41	0.007
Contrast-enhanced 2D echocardiography	56	42	0.113
Reconstructed planes from contrast-enhanced 3D echocardiography	60	46	0.149
Contrast-enhanced 3D full-volume echocardiography	61	41	0.053
Cardiac magnetic resonance	57	52	0.726
Cineventriculography	31	56	<0.001

claustrophobia during the CMR imaging procedure. Thus, 63 patients formed the study group.

Two-dimensional and 3D echocardiographies using tissue harmonic imaging for unenhanced and contrast-specific imaging for contrast-enhanced echocardiography were performed with a commercially available ultrasound scanner (IE 33; Philips, Andover, Massachusetts). Written recommendations were provided for the uniform use of equipment presets, imaging conventions, imaging sequence, and annotations. Two-dimensional apical 4-chamber, 2-chamber, and 3-chamber views as well as 3D full-volume data sets from the apical position were acquired without and with contrast enhancement. For unenhanced imaging, harmonic imaging (mechanical index 1.6, gain 50%, compression 70%) was used, whereas for contrast-specific imaging, a low mechanical index of 0.3 was preselected (gain 60%, compression 15%). Optimization of imaging conditions for endocardial border definition was performed by modulation of transmit power, gain, focus, and dynamic range, as required. Great care was taken to avoid apical foreshortening and to maximize the length from base to apex. A 3D full-volume data set of the ventricle was obtained with gated (5 beats) acquisition. Sector size and depth were optimized to obtain the highest possible volume rates reaching 17 to 20 frames/s in the contrast 3D full-volume mode.

For contrast-enhanced echocardiography, a 20Fr intravenous catheter was introduced into the right antecubital vein. Sulfur hexafluoride microbubbles (SonoVue; Bracco Imaging S.p.A., Milan, Italy) were administered with a starting infusion rate of 1 ml/min followed by subsequent rate adjustments to reach homogeneous LV cavity opacification without attenuation. Before acquiring 2D and 3D echocardiographic images, the infusion rate was separately adjusted if necessary to obtain adequate contrast enhancement.

In each patient, regional wall motion analysis was performed based on 2D images without contrast, 2D images with contrast enhancement, apical 2D image views reconstructed from 3D data sets, full-volume 3D images without contrast, and 3D images with contrast enhancement. The analysis of the 4 echocardiographic techniques in each patient was performed independently and in random order to prevent mutual bias. For each of the 17 LV segments defined by Cardiac Imaging Committee of the Council on Clinical Cardiology of the American Heart Association, regional systolic LV function was determined.[1] For analysis of 2D and 3D echocardiographic images, a dedicated workstation was used (TomTec, Unterschleißheim, Germany) with application of Image Arena to analyze 2D data sets and 4D CardioView and 4D LV Analysis softwares for processing and analysis of 3D recordings.

Standard biplane cineventriculography was performed in all patients using a 30° right anterior oblique projection and a 60° left anterior oblique projection with injection of at least 30 ml of contrast medium at a flow rate of 12 to14 ml/s using 5Fr to 6Fr pigtail catheters. Frame rate was set at 30 Hz. Regional systolic LV function was determined for each of 7 segments (anterolateral, anterobasal, apical, posterobasal, posterolateral, diaphragmal, and septal).[2]

ECG-triggered CMR investigations at a field strength of 1.5 T during breath hold were performed using a special volume-adapted surface coil. To assess LV function, standard steady-state free-precession cine imaging (spatial resolution 1.4 × 1.4 × 8 mm, 35 phases per cardiac cycle, repetition time 3.1 ms, echo time 1.6 ms, flip angle 55°) was performed in short repetitive end-expiratory breath holding. Four-chamber, 2-chamber, 3-chamber, and short-axis views with a slice thickness of 10 mm were acquired in basoapical direction using a special volume-adapted surface coil. Regional systolic function was determined for each of the 17 segments considering wall thickening during systole and endocardial inward motion.[1]

Considering even the limitations of CMR in the assessment of RWMA with considerable interobserver variability,[3,4] an EPD on the presence of RWMA considering more information than only CMR was used. To define this standard of truth for the presence of RWMA, an EPD was made for each patient between 2 independent panelists (RH and SvB) based on clinical data (known cardiomyopathy,

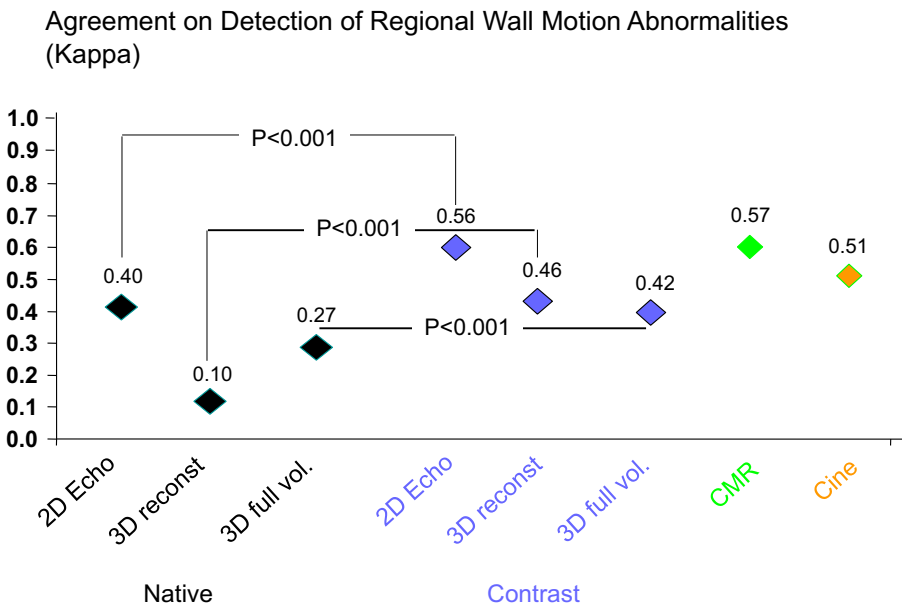

Figure 2. IRA on detection of regional wall motion abnormalities for each imaging technique as described by the κ value. There is significant improvement in IRA for each echocardiographic imaging technique by contrast application.

history of myocardial infarction, and previous revascularization procedure), electrocardiography, coronary angiography, and results of all off-site image readings. To define the standard of truth, the 2 panelists adhered to a predefined 3-step decision algorithm (Figure 1). In the first step, they had to consider clinical information and the results of the given reads. Known cardiomyopathy, history of myocardial infarction in combination with ECG abnormalities, angiographically proved significant coronary artery disease or previous coronary revascularization, and RWMA in at least 2 imaging methods by both readers indicated evidence for RWMA. No history of myocardial infarction in combination with normal test results in electrocardiography, no previous coronary revascularization, angiographic exclusion of coronary artery disease, and in all imaging techniques, no RWMA by both readers were indicative for no RWMA. If no decision could be made based on the first step, the results of all imaging reads were considered in the second step. At least 11 points (1 point per reader, echocardiographic imaging technique, and cineventriculography reader and 2 points per CMR reader) on a consensus scale of 14 points had to be reached to obtain a result on the presence of an RWMA. This was obtained by consensus of at least 11 of the 14 readings (6 imaging techniques and 2 readers per imaging technique, 2 points per CMR reading to balance against the greater number of echocardiographic imaging techniques). Furthermore, clinical data had to be compatible with this result. In 12 cases, the achieved consensus score was inconclusive. In these cases, the 2 panelists were provided with all imaging cine loops for reassessment. Subsequently, the panelists reached a consensus agreement in all cases.

Statistical analysis was performed by MEDIDATA (Konstanz, Germany) using the SPSS software package (IBM SPSS Statistics, Armonk, New York). Continuous variables are presented as mean ± SD. The presence of RWMA is reported on a patient basis. To evaluate the diagnostic performance of each imaging technique in terms of detection of RWMA, sensitivity, specificity, and accuracy were estimated using the panel decision as the gold standard. Sensitivities, specificities, and accuracies were compared using McNemar test for dependent samples. The Cohen's κ coefficient was calculated to evaluate IRA for each pair of readers.[5] Cohen's κ was also obtained to evaluate intermethod agreement on detection of RWMA evaluated by off-site reader 1 of each imaging technique. The same analyses were performed for the agreement between off-site reader and panel decision in terms of RWMA within each individual imaging technique. The Cohen's κ coefficient of agreement was graded as follows: 0 to 0.2 = poor to slight; 0.21 to 0.4 = fair; 0.41 to 0.6 = moderate; 0.61 to 0.8 = substantial; 0.81 to 1.0 = nearly perfect. p Value <0.05 was considered statistically significant.

Results

Sixty-three patients (mean age 63.8 ± 10.4 years, 51 men) were included in this study. Patient characteristics are listed in Table 1. In all patients, all imaging techniques were performed as per protocol. The SonoVue infusion rate needed for optimal image quality was 1.13 ± 0.19 ml/min. After receiving the contrast agent, 1 adverse event with hypotension was reported in 1 of the subjects.

Table 2 lists the percentage of LV segments defined as nonevaluable. There was a significant difference between the imaging techniques in the percentage of LV segments defined as nonevaluable because of low image quality or insufficient endocardial border delineation. Although 3% to 12% of segments were nonevaluable with unenhanced 2D echocardiography and full-volume 3D analysis, up to 32% of segments were assessed as nonevaluable using reconstructed planes from the 3D full-volume data sets. Contrast enhancement resulted in a significant reduction of the

Table 4
Agreement between regional wall motion abnormality detected by an imaging technique and panel-defined presence of a wall motion abnormality

Imaging Technique	κ	95% CI
Unenhanced 2D echocardiography	0.46	0.24−0.68
Reconstructed planes from unenhanced 3D data sets	0.24	0.03−0.52
Unenhanced 3D full-volume echocardiography	0.28	0.04−0.51
Contrast-enhanced 2D echocardiography	0.56	0.35−0.76
Reconstructed planes from contrast-enhanced 3D data sets	0.44	0.28−0.60
Contrast-enhanced 3D full-volume echocardiography	0.53	0.32−0.74
Cardiac magnetic resonance	0.67	0.48−0.86
Cineventriculography	0.58	0.37−0.79

CI = confidence interval.

Table 5
Sensitivity, specificity, and accuracy of each imaging technique to detect panel-defined regional wall motion abnormalities

Imaging Technique	Sensitivity (%)	Specificity (%)	Accuracy (%)
Unenhanced 2D echocardiography	84	63	73
Contrast-enhanced 2D echocardiography	84	72	78
Unenhanced 3D full-volume echocardiography	90	38	63
Contrast-enhanced 3D full-volume echocardiography	87	66	76
Cardiac magnetic resonance	90	74	84
Cineventriculography	71	89	80

number of segments found to be nonevaluable. Visibility of LV segments was found to allow analysis of segmental function in almost all cases using CMR. Contrast-enhanced 2D and 3D full-volume data set analyses reached a visibility of LV segments comparable with CMR.

Table 3 lists the frequency of RWMA detected with the 4 different echocardiographic imaging techniques as well as for cineventriculography and CMR for each of the 2 readers. Considering reader 1, in 16 patients, RWMA were detected by unenhanced 3D full-volume echocardiography but not by unenhanced 2D echocardiography, and in 6 patients, RWMA were detected by unenhanced 2D echocardiography but not by unenhanced 3D full-volume echocardiography. In 5 patients, RWMA were detected by contrast-enhanced 3D echocardiography but not by unenhanced 3D echocardiography, and in 15 patients, RWMA were detected by unenhanced 3D echocardiography but not by contrast-enhanced 3D echocardiography. The frequency of detected RWMA varied between the 2 readers of each imaging technique.

Figure 2 displays the intramethod agreement between off-site readers 1 and 2 for each imaging technique on the presence of RWMA expressed as a κ value. Considering unenhanced echocardiography, the κ value was highest with 2D echocardiography. It was lowest for unenhanced echocardiography using the reconstructed views from the 3D data set. With contrast enhancement, the IRA on RWMA improved significantly for each echocardiographic image technique. The IRA for CMR was $\kappa = 0.57$ and for cineventriculography, a κ of 0.51 was determined.

In the analysis of intermethod agreement on detection of RWMA, the results of off-site reader 1 were used for each imaging technique. Agreement on the presence of RWMA was only fair if unenhanced 2D or full-volume 3D echocardiography was compared with CMR ($\kappa = 0.32$ and 0.22, respectively). Contrast-enhanced 2D and full-volume 3D echocardiographies were associated with improved agreement to CMR ($\kappa = 0.50$ and 0.40, respectively) compared with unenhanced echocardiography. Agreement between 3D unenhanced and contrast-enhanced echocardiographies with CMR on RWMA tended to be lower compared with 2D unenhanced and contrast-enhanced echocardiographies. The agreement between cineventriculography and CMR on RWMA was also only fair ($\kappa = 0.39$). The κ value on agreement between contrast-enhanced 2D echocardiography and CMR was higher than that between 3D full-volume unenhanced echocardiography and CMR ($p = 0.0324$).

Considering clinical data, electrocardiography, coronary angiography, and the results of all imaging techniques, 31 patients were determined by EPD to have an RWMA. The agreement between panel decision and findings of off-site reader 1 of a method on the presence of an RWMA was highest for CMR ($\kappa = 0.67$, 95% confidence interval 0.48 to 0.86; Table 4). Agreement between panel decision and unenhanced 2D as well as 3D echocardiographies was lower than agreement between panel decision and contrast-enhanced 2D and 3D echocardiographies. The agreement of unenhanced 3D echocardiography with the panel decision was lower than that of unenhanced 2D echocardiography.

Considering the EPD on the presence of RWMA as the standard, the sensitivity, specificity, and accuracy of off-site reader 1 of each method in detecting an RWMA were calculated for each imaging method. Sensitivity, specificity, and accuracy for detection of RWMA were on a high level for all imaging techniques. Accuracy was highest for CMR, cineventriculography, and 2D contrast echocardiography (Table 5). Although accuracy of CMR for detection of RWMA was significantly greater than that of 2D and 3D unenhanced echocardiographies ($p < 0.05$), 2D and 3D contrast-enhanced echocardiographies were noninferior to CMR in the detection of RWMA.

Discussion

This is the first multicenter study comparing 2D and 3D echocardiographic methods for assessment of regional LV function with CMR and cineventriculography. It demonstrates that (1) contrast administration results in a reduction of nonevaluable LV segments, which is similar for 3D echocardiography to those of 2D echocardiography, (2) IRA on RWMA using 3D echocardiograms is lower than that using 2D echocardiograms, (3) IRA on RWMA using 3D echocardiography improves with contrast administration but remains lower than with 2D contrast echocardiography, (4) intermethod agreement on RWMA detected by CMR is higher using 2D echocardiography compared with 3D echocardiography and considering contrast-enhanced versus unenhanced echocardiography, and (5) contrast-enhancement results in improved accuracy to detect expert panel−defined RWMA using 2D and 3D echocardiographies.

Interreader variability is a well-known problem in the interpretation of cardiac imaging tests.[3,6–8] In particular, assessment of RWMA is based on subjective visual analysis contributing to reader variability. However, adequate and consistent patient management is based on accurate and reliable test interpretation with minimal operator dependence. The major issue of this study was to define in a multicenter study with several readers whether 3D echocardiography allows interpretation of RWMA with a reliability and accuracy as good as 2D echocardiography or better. Three-dimensional echocardiography has been shown to improve accuracy in the assessment of LV volumes.[9–13] Three-dimensional echocardiography has also been used for the analysis of regional function including stress echocardiography and analysis of LV dyssynchrony.[9,14] However, low visibility of the endocardial border is frequently affecting 3D echocardiography with potential negative impact on regional function assessment. Segmental visibility was shown to be lesser with 3D echocardiographic imaging techniques compared with 2D echocardiographic imaging techniques in this study. This may have contributed to the lower IRA on RWMA with 3D echocardiographic imaging techniques compared with IRA on 2D echocardiographic imaging techniques. The lower intermethod agreement on RWMA between 3D echocardiographic imaging techniques and CMR as well as the expert panel–defined RWMA may also be interpreted by the lower segmental visibility compared with 2D echocardiography. IRA on RWMA with 2D echocardiography, CMR, and cineventriculography was on a level similar to that reported in a previous multicenter study.[6] IRA on RWMA using unenhanced 2D echocardiography has been reported with a κ of 0.43 at rest and of 0.37 during 2D stress echocardiography.[3,6] For CMR, IRA on RWMA expressed as κ has been reported to be 0.43 in a multicenter study in 55 patients.[6] In a stress CMR study on 150 patients, a mean κ of 0.55 on test interpretation among 3 expert readers of different centers has been reported.[4] In another study that involved only readers from 1 center, the κ value on interpretation of stress CMR studies was 0.70.[15] Thus, although CMR is known for its high accuracy and reproducibility in the assessment of LV volumes and ejection fraction, IRA for RWMA was found to be far from perfect in several studies. Previous studies had already demonstrated that contrast enhancement improves analysis of regional LV function with 2D echocardiographic imaging.[6,16,17] In this study, contrast administration increased the level of IRA on the definition of RWMA using 2D and 3D echocardiographic techniques. The increase of agreement for 3D echocardiography was of a magnitude similar to that found for 2D echocardiography, beginning from a lower baseline level than for 2D echocardiography.

Although previous studies demonstrated already that IRA on regional wall motion assessment is method and image quality dependent, this study extends these results to 3D echocardiography. Considering CMR for comparison, intermethod agreement was rather poor for unenhanced echocardiography, whereas fair agreement was found if contrast-enhanced echocardiography was applied. Three-dimensional echocardiography–based analysis of RWMA was found to result in lower levels of intermethod agreement to CMR than 2D echocardiography considering unenhanced and contrast-enhanced imaging. This confirms the greater difficulties of 3D echocardiography compared with 2D echocardiography in the accurate and reliable definition of RWMA. It also underlines that previous findings on analysis of RWMA using 2D echocardiography cannot be transferred to 3D echocardiography. However, contrast administration resulted also with 3D echocardiography in improved intermethod agreement with CMR.

To get an even greater insight into the value of each imaging technique in the analysis of RWMA, a standard of truth on RWMA was defined by 2 experienced cardiologists based on a clearly defined decision algorithm. This approach was selected to allow the assessment of accuracy in the definition of RWMA for each of the applied imaging techniques. Three-dimensional echocardiography failed to reach the level of agreement with the standard of truth and the accuracy to define RWMA, which was found for 2D echocardiography. This result was found for unenhanced and contrast-enhanced 3D echocardiographies. CMR and 2D contrast echocardiography were the methods of highest agreement with the standard of truth on RWMA and the methods with greatest accuracy to define RWMA.

Administration of contrast clearly improved the agreement with the standard of truth on RWMA and should be applied with 3D echocardiography as much as with 2D echocardiography if reproducible, and accurate analysis of regional LV function is requested. This analysis included only 63 patients. However, a well-defined and strictly monitored study protocol was applied in all the patients of this multicenter study. Furthermore, independent analysis of imaging techniques was performed at a total of 6 core laboratories considering CMR, echocardiography, and cineventriculography. This allowed a reliable analysis and comparison of 8 different imaging techniques. The number of segments used to evaluate regional LV function by cineventriculography was only 7 compared with 17 for the other imaging techniques. This is in part related to the biplane display of LV function instead of a triplane or full-volume display using echocardiography and CMR. However, the presence of an RWMA was reported on a patient basis and not on a segment basis.

There is no objective gold standard for the definition of RWMA to which each imaging technique could be easily compared with. CMR has been considered as the gold standard in some circumstances. However, because of the considerable interreader variability proved in previous studies and this analysis, it has significant limitations. To circumvent this problem, we tried to define a “standard of truth” based on a panel decision between 2 blinded expert cardiologists considering all available information in a well-defined decision algorithm. All readers in this study were trained experts. The reported reader agreement and accuracy to detect RWMA are likely to reflect the best possible level, whereas it may not reflect a setting with less-trained readers.

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Disclosures

Christian Greis is an employee of Bracco Imaging Deutschland. He contributed to the design and organized the performance of the study. He had no influence on data analysis or interpretation. The other authors do not have anything to disclose.

Appendix: Participating Institutions and Investigators for the SonoVue Study Group

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