Analysis of myocardial perfusion or myocardial function for detection of regional myocardial abnormalities. An echocardiographic multicenter comparison study using myocardial contrast echocardiography and 2D echocardiography

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Abstract  Background: Echocardiography based myocardial perfusion imaging and regional wall motion analysis are used for evaluation of coronary artery disease and regional myocardial abnormalities.
Aim: This study sought to compare myocardial contrast echocardiography (MCE) and 2D echocardiography with regard to interobserver variability and detection of regional myocardial abnormalities.
Methods: In 70 patients evenly distributed between three ejection fraction groups based on biplane cineventriculography (>55%, 35–55%, <35%), unenhanced and contrast enhanced 2D echocardiography and myocardial contrast echocardiography.
Introduction

The effects of coronary artery disease on left ventricular (LV) myocardium are defined by perfusion abnormalities and subsequent contractile malfunction. Visual analysis of regional left ventricular function by 2D echocardiography is the most frequently used approach to evaluate regional LV myocardial abnormalities. It is associated with a complex process which incorporates endocardial inward motion as well as wall thickening analysis. The subjective nature of regional function assessment and a substantial reader variability are the main limitations using 2D echocardiography. Contrast enhanced 2D echocardiography has been shown to improve endocardial border definition and thereby confidence as to the analysis of regional wall motion abnormalities (RWMA).

Myocardial perfusion imaging is a different approach to get insight into the effects of coronary artery disease on the LV myocardium. Analysis of myocardial contrast echocardiography in clinical practice involves also a subjective interpretation process. There are much less data on the use of MCE for assessment of regional myocardial abnormalities. In particular, there are no data which have compared within the same patient group 2D echocardiography with and without contrast enhancement as well as MCE with regard to the interobserver agreement in image interpretation and the potential of these methods to detect myocardial abnormalities at rest due to chronic ischemic disease or previous myocardial infarction. The objective of this study was: (1) to compare MCE to 2D echocardiography with and without contrast enhancement with regarding to the interobserver agreement (IOA) on test abnormalities; and (2) to assess the adequacy of determined RWMA or regional myocardial perfusion abnormalities related to a "standard of truth" on regional myocardial abnormalities. The "standard of truth" being defined by an expert-panel based on clinical, electrocardiographic, angiographic and imaging data. The design of this study allowed a direct comparison of the three techniques on the same patients. This study is a substudy of a larger multicenter study on the comparison of cineventriculography, 2D echocardiography and cMRI for assessment of LV function. Blinded on-site and off-site readings using experienced core laboratories was performed for each imaging technique according to prospectively defined standards.

Methods

This multicenter, open label study utilizing intra-subject comparison assessed the interobserver agreement (IOA) among 2 readers was determined within each imaging modality. To define a standard of truth for the presence of segmental myocardial disease an independent expert-panel decision was obtained based on clinical data, ECG, coronary angiography and blinded information from the imaging modalities. Regional wall motion and myocardial perfusion were assessed referring to a 16 segment model. Interobserver agreement (IOA) among 2 readers was determined within each imaging modality. To define a standard of truth for the presence of segmental myocardial disease an independent expert-panel decision was obtained based on clinical data, ECG, coronary angiography and blinded information from the imaging modalities.

Results: Regional wall motion assessment was possible in 98.1% of segments using contrast enhanced 2D echocardiography and in 87.2% using unenhanced 2D echocardiography (p < 0.001), while perfusion assessment was possible in 90.1% of segments (p < 0.001). IOA on presence of any regional wall motion abnormality expressed as Kappa coefficient was 0.71 (95% CI 0.53–0.89) for contrast enhanced echocardiography and 0.37 (95% CI 0.14–0.59) for unenhanced echocardiography. IOA on presence of any perfusion abnormality was 0.53 (95% CI 0.34–0.73). For MCE there was high IOA for the apical segments (kappa = 0.57) and lower IOA for the basal segments (kappa = 0.14), while no such gradient was found for the IOA on wall motion abnormalities. Mean accuracy to detect expert-panel defined myocardial abnormalities was 80.6% for unenhanced echocardiography, 85.0% for contrast enhanced 2D echocardiography and 80.6% for MCE.

Conclusions: MCE is inferior to contrast enhanced 2D echocardiography with regard to visibility of all LV segments and appears slightly inferior with regards to IOA, while both are superior to unenhanced 2D echocardiography. The methods demonstrated high accuracy in detection of panel defined regional myocardial abnormalities.

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variability of unenhanced and contrast-enhanced 2D echocardiography and MCE.

All echocardiographic imaging modalities were performed immediately after each other. Recommendations on the performance of image acquisition were prospectively defined for each imaging modality to secure uniform and interpretable image datasets from all participating institutions. Adherence to the predefined imaging protocols was monitored during the enrolment period of this multicenter trial.

Analysis of RWMA on 2D echocardiographic image datasets as well as perfusion abnormalities on MCE was performed for each imaging technique by 1 on-site reader as well as 1 independent off-site reader who was unaware of the clinical data and the results of the other imaging techniques. Recommendations on the evaluation of regional LV function as well as regional myocardial perfusion were prospectively defined and provided as guidelines to the on-site readers at the study sites and to the unaffiliated off-site reader using an independent core laboratory (see Appendix). Evaluations were performed according to well defined standards and after formal training. For each analyzed segment regional wall motion was defined as either normokinetic, hypokinetic, akinetic or dyskinetic and regional myocardial perfusion was defined as normal or abnormal. Analysis of regional wall motion had to consider delayed contraction as abnormal. Myocardial perfusion had to be considered as abnormal if there was incomplete, patchy or delayed contrast enhancement.

The study was conducted according to Good Clinical Practice and in compliance with local regulatory requirements considering the Declaration of Helsinki. 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.

Patients

Five European centers experienced in the applied imaging techniques enrolled 70 patients planned for routine coronary angiography due to suspected coronary artery disease. Patients with acute myocardial infarction within the last 14 days were excluded. At each center consideration was taken in patient enrollment for an even distribution within 3 pre-defined ejection fraction groups (>55%, 35–55%, <35%) based on results from cine-ventriculography. This distribution was selected to secure different levels and extent of RWMA and myocardial perfusion abnormalities. Inclusion into the study required sinus rhythm and an interpretable cineventriculography with at least 2 consecutive non-extrasystolic cardiac cycles during ventriculographic contrast administration.

2D echocardiography

Two-dimensional echocardiography using tissue harmonic imaging for unenhanced and contrast specific imaging for contrast enhanced echocardiography was performed with a commercially available ultrasound scanner (SONOS 5500, Philips, Andover, Massachusetts). Written recommendations were provided for the uniform use of equipment presets, imaging conventions, imaging sequence and annotations. Apical 4-chamber, 2-chamber and 3-chamber views were acquired with and without contrast enhancement. For unenhanced imaging harmonic imaging (mechanical index [MI] 1.6, Gain 50%, Compression 70%) was used, whereas for contrast specific imaging with a MI 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. Five consecutive cardiac cycles of each view were acquired during breathhold and digitally stored. Great care was taken to avoid apical foreshortening and to maximize the long axis length of the left ventricle.

A 20 gauge intravenous catheter was introduced into the right antecubital vein. Sulphur hexafluoride microbubbles (SonoVue®, Bracco Imaging, S.P.A., Milan, Italy) was administered with a starting infusion rate of 1 ml/min followed by subsequent rate adjustments in order to reach homogenous LV cavity opacification without attenuation. Additional bolus injections were administered if required to achieve sufficient contrast saturation.

For each of the 16 LV segments defined by the American Society of Echocardiography regional systolic LV function was determined.11

Myocardial contrast echocardiography

Two-dimensional myocardial perfusion echocardiography using contrast specific imaging settings was performed in all patients. Written recommendations were provided for the uniform use of equipment presets, imaging conventions, imaging sequence and annotations. Apical 4-chamber, 2-chamber and 3-chamber views were acquired for myocardial perfusion imaging. The machine settings were switched to low power real time perfusion
imaging (MI < 0.2) with adjustment of transmit power, gain, dynamic range and line density to achieve optimal and artefact-free visualisation of myocardial perfusion. Infusion rate of SonoVue® was adjusted for optimal visualisation of myocardial perfusion. Contrast refill-kinetics using replenishment flashes were evaluated visually. Myocardial perfusion was assessed on a segmental level using a 16-segment model. First, imaging was categorized as diagnostic or non-diagnostic (due to attenuation artifact, rib shadowing, or insufficient myocardial contrast) for each segment. Diagnostic segments were divided into those with normal and abnormal perfusion (perfusion defect, delayed perfusion, reduced perfusion or reduced and delayed perfusion).

Cineventriculography

Standard biplane cineventriculography was performed using a 30° Right Anterior Oblique (RAO) projection and a 60° Left Anterior Oblique (LAO) projection with injection of at least 30 cc of contrast medium at a flow rate of 12–14 cc/s. Frame rate was set at 30 Hz. Written recommendations were provided for the uniform use and documentation of image projections, contrast medium flow and image storage. Cineventriculograms were evaluated at an independent core lab (see Appendix).

Definition of true regional left ventricular abnormalities

To define a standard of truth for the presence of regional LV abnormalities, a consensus decision was made for each patient between 2 independent panelists not involved in the on-site and off-site reading based on clinical data (history of myocardial infarction and prior revascularization procedure), ECG, coronary angiography, cineventriculography and results of MCE as well as both 2D echocardiographic modalities (from the on-site and off-site reader).

To define the standard of truth, the 2 panelists adhered to a predefined decision algorithm (Fig. 1). They had to consider primarily the clinical information including ECG and coronary angiography and then the results of the given reads. Known history of myocardial infarction in combination with ECG abnormalities, angiographically proven significant coronary artery disease or previous coronary revascularization and regional abnormalities in all three imaging methods (in the same left ventricular perfusion area) by at least one reader indicated evidence for regional myocardial abnormalities. No history of

**Figure 1** Three step decision algorithm used to define the standard of truth (expert panel decision) on the presence of regional myocardial abnormalities. Clinical information used in step 1 relates to clinical history, ECG, angiography. The consensus rating score applied in step 2 considered echocardiographic results from the two readers of all three applied modalities. In the panel review applied in step 3 all clinical and imaging data were reviewed by the panel. CE: contrast echocardiography, MCE: myocardial contrast echocardiography, UE: unenhanced echocardiography.
myocardial infarction in combination with normal ECG, no previous coronary revascularization, angiographic exclusion of coronary artery disease, and in all imaging modalities no myocardial abnormalities by at least one reader was indicative for no regional myocardial abnormality. In case no decision could be made based on these data the results of all imaging reads were considered. At least 4 points (one point per reader and imaging modality) on a consensus scale of 6 points had to be reached in order to obtain a result on the presence of a regional myocardial abnormality. Clinical data had to be compatible with this result.

In 9 cases the achieved consensus score was inconclusive, to determine either the presence or the absence of a regional myocardial abnormality. In these cases the 2 off-site panelists were provided with all imaging cine loops for reassessment. Subsequently, the panelists reached a consensus agreement in all cases.

For each imaging technique obtained results by each reader were compared with the defined standard of truth on the presence of a regional myocardial abnormality.

Statistics

Statistical analysis was performed using the SPSS software package (SPSS 12.0, SPSS Inc, U.S.A). Continuous variables are presented as mean ± SD. The Cohen’s kappa coefficient was calculated to evaluate interobserver agreement for each pair of observers. Cohen’s Kappa was also obtained to evaluate intermethod agreement on detection of regional myocardial abnormality evaluated by the off-site reader of each imaging modality. The same analyses were performed for the agreement between off-site/on-site reader and the panel decision in terms of regional myocardial abnormality within each individual imaging modality (Fig. 2). The Kappa 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 0.99 = nearly perfect; 1.0 = perfect. To evaluate the diagnostic performance of each imaging modality in terms of detection of regional myocardial abnormalities, sensitivity, specificity, and accuracy were estimated using the panel decision as gold standard.

End-diastolic

Unenhanced 2D Echo

Contrast-enhanced 2D Echo

Myocardial Contrast Echo

End-systolic

Figure 2 Multimodality comparison for detection of a regional myocardial abnormality in a 48 year old patient with prior anterior myocardial infarction and occluded left anterior descending artery. Ejection fraction was abnormal (46%). There was concordance among unenhanced 2D echocardiography, contrast enhanced 2D echocardiography and myocardial contrast echocardiography in the detection of an abnormality of the anteroseptal myocardium. Unenhanced and contrast enhanced 2D echocardiography allowed detection of a regional wall motion abnormality while MCE allowed detection of a myocardial perfusion defect.
Sensitivities, specificities and accuracies were compared using chi-square statistics, with two sided test and alpha level $= 0.05$.

**Results**

**Baseline characteristics**

70 patients (54 male) were included in this study. Patient characteristics are given in Table 1. Cineventriculography, unenhanced and contrast enhanced echocardiography as well as MCE was performed in all patients.

The SonoVue® infusion rate needed for optimal contrast enhanced 2D and myocardial contrast echocardiographic image quality was $1.35 \pm 0.44$ ml/min. During contrast imaging one non-serious adverse event of mild intensity was reported (single ventricular extrasystoles, resolving spontaneously without any sequel).

**Regional wall motion**

Both readers agreed that analysis of regional myocardial function by 2D echocardiography was possible in 98.1% of segments using contrast enhanced echocardiography and in 87.2% of segments using unenhanced echocardiography ($p < 0.001$). There was no significant difference between the 16 segments in the visualization using contrast enhanced echocardiography. For unenhanced echocardiography visualization ranged from 79.3% for the apico-anterior segment to 95.5% for the midventricular septal segment ($p < 0.01$). The frequency of detected RWMA ranged from 5.7% to 31.4% between the different segments for the two readers using contrast enhanced echocardiography and between 6.2% to 30.4% using unenhanced echocardiography. Any RWMA was detected in 57.7% of patients by reader 1 and in 54.9% of patients by reader 2 with contrast enhanced echocardiography. Considering unenhanced echocardiography any RWMA was detected in 57.7% of patients by reader 1 and in 53.5% of patients by reader 2. The IOA on any RWMA within a patient defined by the kappa value was 0.71 (95% CI 0.53–0.89) using contrast enhanced echocardiography and 0.37 (95% CI 0.14–0.59) using unenhanced echocardiography. Considering IOA for each of the LV segments there were no significant differences between the different LV areas using contrast enhanced 2D echocardiography. Table 2 displays the IOA on wall motion abnormalities between the two readers for each LV segment using contrast enhanced echocardiography.

**Myocardial contrast echocardiography**

Both readers agreed that analysis of regional myocardial perfusion by MCE was possible in 90.1% of segments; significantly less ($p < 0.001$) than with contrast enhanced 2D echocardiography. The visualization ranged from 78.2% for the apico-basal segment to 96.1% for the midventricular septal segment ($p < 0.01$). The frequency of detected segmental myocardial perfusion abnormalities ranged from 4.3% to 41.1% between the different segments. Any perfusion abnormality was detected in 50.0% of patients by reader 1 and in 62.0% of patients by reader 2. The IOA on any perfusion abnormality within a patient defined by the kappa value was 0.53 (95% CI 0.32–0.73). Considering IOA for each of the LV segments, there was a significant ($p < 0.05$) apico-basal gradient with high IOA for the apical segments (kappa = 0.57; 95% CI 0.47–0.67 for the combined four apical segments) and lower IOA for the basal segments (kappa = 0.14; 95% CI –0.09–0.37 for the combined six basal segments). Table 2 displays the IOA on myocardial perfusion between the two readers for each LV segment.

**Intermethod agreement on segmental myocardial normality**

Considering both readers of each method there was an agreement defined by the kappa value of 0.61 (95% CI 0.48–0.74) between RWMA by contrast enhanced 2D echocardiography and regional myocardial perfusion analysis by MCE on presence of a myocardial abnormality.

<table>
<thead>
<tr>
<th>Table 1 Patient baseline characteristics</th>
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<tbody>
<tr>
<td>Age, years</td>
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<tr>
<td>History of prior myocardial infarction, %</td>
</tr>
<tr>
<td>Prior coronary angioplasty, %</td>
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<tr>
<td>Prior coronary bypass surgery, %</td>
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<tr>
<td>Coronary stenosis in LAD</td>
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<tr>
<td>Coronary stenosis in LCX/RCA</td>
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<tr>
<td>Diabetes mellitus, %</td>
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<tr>
<td>Hypertension</td>
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<tr>
<td>Hypercholesterolemia, %</td>
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<tr>
<td>Ejection fraction by cineventriculography, %</td>
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</tbody>
</table>

LAD: left anterior descending artery, LCX: circumflex branch of the left coronary artery, RCA: right coronary artery.

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Agreement with consensus definition of regional left ventricular normality

Considering clinical data, ECG, coronary angiogram and the results of all imaging modalities, 44 patients (63%) were determined by panel decision to have a regional myocardial abnormality. Considering the findings of both readers of an imaging modality, the agreement between panel decision on presence of a myocardial abnormality and MCE was $\kappa = 0.53$ (95% CI 0.37–0.69). In comparison, the mean agreement between panel decision on presence of a myocardial abnormality and both reader defined contrast enhanced 2D echocardiographic findings was $\kappa = 0.67$ (95% CI 0.53–0.80), and it was for the unenhanced 2D echocardiographic findings $\kappa = 0.57$ (95% CI 0.42–0.71).

Considering the panel decision on the presence of a segmental myocardial abnormality, a mean sensitivity, specificity and accuracy of both readers in the detection of a segmental myocardial abnormality was calculated for MCE as well as 2D echocardiography. Mean sensitivity of contrast enhanced wall motion analysis for detection of panel defined myocardial abnormalities was 80.8%, while it was 78.1% for myocardial perfusion analysis and 80.0% for wall motion analysis without contrast enhancement. Mean specificity of contrast enhanced wall motion analysis for detection of panel defined myocardial abnormalities was 97.2%, while it was 85.7% for myocardial perfusion analysis and 80.0% for unenhanced echocardiography. Mean accuracy for detection of panel defined myocardial abnormalities was 85.0% for contrast enhanced 2D echocardiography based wall motion analysis, 80.6% for unenhanced wall motion analysis and 80.6% for myocardial perfusion analysis (Fig. 3).

Discussion

The present study demonstrates that: (a) analysis of myocardial perfusion by MCE is possible in a lower number of segments than regional function assessment by contrast enhanced 2D echocardiography; (b) IOA on MCE tends to be lower than IOA on contrast enhanced 2D echocardiography but higher than for unenhanced 2D echocardiography; (c) for MCE there is a segmental gradient with high IOA for apical segments and low IOA for the basal segments, while there is no such gradient for segmental wall motion analysis; (d) agreement

<table>
<thead>
<tr>
<th>Basal segments</th>
<th>IOA – wall motion analysis</th>
<th>IOA – perfusion analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal anterior-septal segment</td>
<td>0.19</td>
<td>0.19</td>
</tr>
<tr>
<td>Basal anterior segment</td>
<td>0.30</td>
<td>0.17</td>
</tr>
<tr>
<td>Basal lateral segment</td>
<td>0.28</td>
<td>0.14</td>
</tr>
<tr>
<td>Basal posterior segment</td>
<td>0.36</td>
<td>0.14</td>
</tr>
<tr>
<td>Basal inferior segment</td>
<td>0.43</td>
<td>0.08</td>
</tr>
<tr>
<td>Basal septal segment</td>
<td>0.38</td>
<td>0.19</td>
</tr>
<tr>
<td>Combined basal segments</td>
<td>0.31</td>
<td>0.14</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Midventricular segments</th>
<th>IOA – wall motion analysis</th>
<th>IOA – perfusion analysis</th>
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</thead>
<tbody>
<tr>
<td>Mid anterior-septal segment</td>
<td>0.43</td>
<td>0.42</td>
</tr>
<tr>
<td>Mid anterior segment</td>
<td>0.36</td>
<td>0.33</td>
</tr>
<tr>
<td>Mid lateral segment</td>
<td>0.19</td>
<td>0.12</td>
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<tr>
<td>Mid posterior segment</td>
<td>0.27</td>
<td>0.09</td>
</tr>
<tr>
<td>Mid inferior segment</td>
<td>0.23</td>
<td>0.11</td>
</tr>
<tr>
<td>Mid septal segment</td>
<td>0.52</td>
<td>0.29</td>
</tr>
<tr>
<td>Combined midventricular segments</td>
<td>0.32</td>
<td>0.22</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Apical segments</th>
<th>IOA – wall motion analysis</th>
<th>IOA – perfusion analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apical anterior segment</td>
<td>0.39</td>
<td>0.61</td>
</tr>
<tr>
<td>Apical lateral segment</td>
<td>0.44</td>
<td>0.59</td>
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<tr>
<td>Apical inferior segment</td>
<td>0.34</td>
<td>0.57</td>
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<tr>
<td>Apical septal segment</td>
<td>0.37</td>
<td>0.49</td>
</tr>
<tr>
<td>Combined apical segments</td>
<td>0.38</td>
<td>0.57</td>
</tr>
</tbody>
</table>

Given data are kappa-values.
between myocardial function defined by contrast enhanced echocardiography and myocardial perfusion defined by MCE is substantial; and (e) both methods demonstrate high accuracy in the detection of expert panel defined regional myocardial abnormalities.

Analysis of regional myocardial abnormalities

The effects of coronary artery disease on LV myocardium relate to perfusion as well as function abnormalities. Assessment of myocardial function or myocardial perfusion are very different approaches to get insight into the effect of coronary artery disease on the LV myocardium.13-16 Analysis of regional systolic function is the commonly performed method to detect regional myocardial abnormalities. Detection of RWMA at rest has considerable implications for patient management and prognosis. Resting RWMA may indicate scar formation after myocardial infarction as well as chronic myocardial ischemia or stunning. In the analysis of regional LV function different parameters come into play, in particular, endocardial border inward motion and myocardial wall thickening, mainly due to circumferential fibers contraction. Interpretation thresholds for rating regional LV function as abnormal are subjective. Interobserver variability is a well known problem as interpretation thresholds for rating abnormal regional LV function are subjective.1,17,18 Obviously, the image quality has an important impact upon the ability to define RWMA.1,10,18,19 Contrast echocardiography has been shown in several studies to significantly improve endocardial border delineation and thereby reader confidence in global LV function analysis.2,4,20

Myocardial perfusion imaging is a different approach to get insight into the effect of coronary artery disease on the LV myocardium. MCE allows the assessment of perfusion defects after acute myocardial infarction as well as in chronic ischemic heart disease.6,7,9,21 In addition, MCE may be used to define inducible perfusion defects during stress testing.13,15,16 Detection of differences in myocardial grayscale with contrast administration is the main analysis parameter. Although analysis of MCE is commonly performed also on a visual subjective basis it might be less vulnerable to interobserver variability than the complex regional wall motion analysis but this hypothesis has remained unproven so far.

Current study

The first aspect of this study was the IOA between two readers of one imaging modality. For unenhanced echocardiography the kappa between the two readers was 0.37. In stress echocardiographic studies kappa values have been reported to be between 0.37 and 0.55 using contrast unenhanced imaging.1,17 For contrast enhanced echocardiography a higher level of IOA on the definition of RWMA was found. Previous studies had already indicated that contrast enhancement improves analysis of global LV-function but has also a positive impact on regional function analysis.2-5,10,20,22 In a comparative multicenter study on 100 subjects agreement in the detection of wall motion abnormalities was kappa = 0.41 using unenhanced imaging and increased to kappa = 0.77 using contrast echocardiography.22 MCE was found to have a slightly lower level of IOA than contrast enhanced 2D echocardiography. Both imaging modalities tended to have a higher IOA than unenhanced 2D echocardiography. In principle, the detection of myocardial grayscale differences between normal and abnormal segments using MCE may be easier and request a less complex evaluation process than the analysis of regional function abnormalities. However, ambiguous intermediate findings do occur also in the analysis of myocardial perfusion and are likely to have contributed to the observers’ disagreement in a considerable number of cases. For regional wall motion analysis it is known that IOA is lowest for intermediate findings such as mild hypokinesia in which overreaders may detect an abnormality while underreaders still define normokinesia. Furthermore, MCE may be affected by greater differences in image quality, a variability in local patterns of contrast enhancement (intensity, homogeneity, temporal course) and contrast-specific
problems such as signal attenuation resulting in higher number of segments with insufficient visualization as compared to contrast enhanced 2D echocardiography.

There are only few data on IOA in the interpretation of MCE. Dubart et al. reported IOA on interpretation of MCE to be good with a kappa of 0.72. However, compared to this study the observers came from the same department and a higher number of segments (18%) was excluded from the analysis. In the present study there was a significant gradient for MCE in the segmental IOA with high IOA for the apical segments and low IOA for the basal segments. This finding should be explained by significantly greater difficulties to assess myocardial perfusion by MCE in the basal segments due to potential attenuation and shadowing affecting in particular the basal segments and resulting in heterogeneity of segmental contrast enhancement. In contrast, no such gradient was found for the IOA on segmental wall motion assessment. The low IOA for the basal segments should caution the diagnosis of coronary artery disease if perfusion abnormalities are seen only in the basal segments. The results of myocardial perfusion in the apical segments should always be considered reflecting the perfusion beds of the coronary arteries.

The second aspect evaluated in the study was the agreement between MCE and contrast enhanced 2D echocardiography. Intermethod agreement between MCE and contrast enhanced 2D echocardiography was fair. This finding indicates that in patients with stable coronary artery disease at rest and conditions regional myocardial perfusion abnormalities and regional myocardial function abnormalities occur simultaneously in most instances. The concurrence should be explained by impaired function and perfusion after previous myocardial infarction. This finding probably does not apply to patients with impaired LV function not related to coronary artery disease or patients with unstable angina.

There is no objective gold standard for the definition of regional myocardial abnormalities to which each imaging modality could be easily compared with. We tried to circumvent this problem by defining a “standard of truth” based on a panel decision between two blinded expert cardiologists considering all available information in a well defined decision algorithm in order to allow the assessment of accuracy in the definition of regional myocardial abnormalities for each of the applied imaging techniques. It should be acknowledged that the obtained “standard of truth” was used only because a real gold standard for regional myocardial abnormality is not available.

2D echocardiography without contrast enhancement tended to be less accurate in the detection of myocardial abnormalities compared to contrast enhanced 2D echocardiography. Obviously, the higher quality in endocardial border definition improved the accuracy in detection of myocardial abnormalities. Myocardial perfusion analysis using MCE was found to have also a high level of accuracy in the evaluation of myocardial abnormalities.

This study evaluated only wall motion and myocardial perfusion at rest. Thus, results may give some clues as to analysis of tests during stress conditions. However, they should not be transferred unreflected to stress testing.

**Study limitations**

While the analysis of regional wall motion has become established and is performed in a relatively standardized fashion, the performance of MCE as well as reading of myocardial perfusion echocardiography is much less standardized. Thus, the findings of this study may not be translated to all available MCE protocols using different techniques, for instance bolus injection of contrast agents. MCE performed as low power, real time perfusion imaging allows to obtain simultaneous information on regional myocardial function although limited in quality. Thus, the reader of the MCE datasets was not completely blinded to regional function information. Demonstration of still perfusion images might have circumvented this problem at cost of introducing an artificial reading mode, not comparable to actual clinical practice. Moreover, the interpretation of real time perfusion imaging with the use of flashes relates in particular to the refilling phase which can be displayed only by complete datasets. Still, although a combination of perfusion and function information might have resulted in superior IOA, the additional regional function information within the real time perfusion imaging datasets was obviously not sufficient to control differences in perfusion assessment between the observers.

Visual analysis of MCE is certainly limited by its subjective nature. Quantitative analysis of MCE would certainly have been an approach which allows more objective and probably more accurate analysis of myocardial perfusion. However, the techniques for quantitative analysis of MCE vary and quantitative analysis of MCE is not routinely used in clinical practice.

All readers in this study were trained experts. The reported reader agreement and accuracy to
detect RWMA is likely to reflect the best possible level while it may not reflect a setting with less trained readers. This study used the 16-segment model instead of the 17-segment model more recently proposed by the American cardiology societies. This was done as the apical segment within the 17-segment model is difficult to evaluate both for wall motion analysis as well as myocardial perfusion imaging.

Conclusions

MCE is limited by more frequent imaging failure compared to contrast enhanced 2D echocardiography. Analysis of regional myocardial perfusion using MCE is characterized by a fair IOA, which is slightly inferior to those obtained for analysis of regional myocardial function using contrast enhanced 2D echocardiography but tends to be superior to those of unenhanced 2D echocardiography. For MCE, there is a segmental gradient with high IOA on perfusion abnormalities in the apical segments and low IOA for the basal segments.

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Appendix

Participating Institutions and Investigators for the SonoVue Study Group

Clinical Centers (number of patients included):
University RWTH Aachen, Aachen, Germany (15): Rainer Hoffmann, MD, Harald Kühl, MD; University Charite, Berlin, Germany (14): Adrian C. Borges, MD, Thorsten Walde, MD; Medical University of Lodz, Poland (12): Jaroslaw D. Kasprzak, MD; Deutsches Herzzentrum, Munich, Germany (14): Christian Firschke, MD, Marek Orban, MD, Petr Tousek, MD; Cliniques Universitaires Saint-Luc, Brussels, Belgium (15): Jean-Louis Vanoverschelde, MD, Agnes Pasquet, MD.

Core Laboratories:
Echocardiography:
University RWTH Aachen, Germany.
Cineangiography:
University Clinic Munich, Germany.

References


