Contrast-enhanced echocardiography improves agreement on the assessment of ejection fraction and left ventricular function. A multicentre study

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Introduction

Analysis of global and regional left ventricular function has important therapeutic and prognostic implications. Several imaging modalities are used to define left ventricular function and left ventricular volumes as well as regional function, among them echocardiography, cine-ventriculography, radionuclide ventriculography and magnetic resonance imaging (MRI). Cardiac MRI has evolved in recent years as the gold standard for determination of left ventricular mass, volumes and left ventricular function owing to the high image quality allowing clear endocardial and epicardial border definition in volumetric data sets.

Echocardiography is the most frequently used modality in clinical practice to define global and regional left ventricular function. Limited endocardial border definition with subsequent moderate reproducibility and accuracy are the major limitation of 2-D echocardiography. Contrast echocardiography in combination with recent innovations in ultrasound technology like Harmonic Imaging has been shown to significantly improve endocardial border delineation especially in patients with difficult imaging conditions which was unattainable before.

The SonoVue LV Function Group evaluated in a European multicentre study consisting of two parts the utility of contrast-enhanced echocardiography for assessment of global and regional left ventricular function. Results obtained by contrast-enhanced echocardiography were compared for this purpose with those of unenhanced echocardiography, cineventriculography and magnetic resonance imaging (MRI) in a multicentre acquisition setting with blinded on-site and off-site reading of each imaging technique.

Study design

This was a European multicentre study with acquisition of non-contrast and contrast-enhanced echocardiography, biplane cineventriculography and cardiac MRI for determination of left ventricular volumes as well as global and regional left ventricular function on the same patient, allowing within-patient comparisons (Fig. 1). The 8 centres contributing to the image acquisition were provided detailed protocols for carrying out the imaging examinations. Adherence to these guidelines was monitored. Each of the four imaging techniques was assessed by one on-site reader blinded to clinical characteristics and the results of the other imaging techniques and by two off-site readers at independent core centres.

The study enrolled 115 patients with a mean age of 62.5±11.5 years, evenly distributed over three groups with different ejection fractions (EF): >55%, 35-55%, <35%, based on results from cineventriculography (Table 1). Because not all centres were equipped for all imaging modalities, biplane cineventriculography was performed in 100 patients and MRI was performed in 55 patients. Imaging procedures were as follows:

- **Echocardiography:** Two-dimensional echocardiography was performed using Tissue Harmonic
Contrast-enhanced echocardiography improves agreement on the assessment of EF and LV function

Fig. 1. Multimodality comparison of left ventricular function analysis in a patient with prior inferior myocardial infarction. There was concordance among cardiac magnetic resonance imaging (cMRI), cineventriculography (CINE) and contrast-enhanced echocardiography (CE) in the detection of an inferior/posterior wall motion abnormality, which was not detected on unenhanced echocardiography (UE) due to limited visualization of the inferior/posterior wall. LAO: left anterior oblique, RAO: right anterior oblique. (Reproduced with permission from the Journal of the American College of Cardiology.)

Imaging and contrast-specific imaging for left ventricular opacification. Apical 4-Chamber, 2-Chamber and 3-Chamber views were acquired without contrast enhancement and with contrast enhancement. Great care was taken to avoid apical foreshortening and to maximize the length from base to apex.

For contrast-enhanced assessment of left ventricular function SonoVue® (Bracco, Italy) was administered with a starting infusion rate of 1 ml/min and subsequent adjustment in order to reach homogeneous cavity opacification without attenuation. Echo machine settings were optimized for contrast-specific imaging. Transmit power had to be set low (MI < 0.4) and dynamic range had to be adjusted in order to achieve optimal contrast between cardiac walls and left ventricular cavity.

- **Cineventriculography:** Standard biplane cineventriculography was performed using a 30° RAO projection and a 60° LAO projection with injection of at least 30 cc of contrast medium within 2 seconds.
- **Magnetic resonance imaging:** ECG-triggered MRI investigations at a field strength of 1.5 T during...
breath hold were performed for assessment of cardiac function. 4-Chamber, 2-Chamber, 3-Chamber as well as short-axis views with a slice thickness of 10 mm were acquired in baso-apical direction with a temporal resolution $\leq 50$ ms.

- **Reading of images**: Diagnostic images were read by the on-site reader as well as the two off-site readers according to standardized recommendations. Left ventricular volumes were determined in each method by manual tracing of endocardial contours using the Simpson rule. Ejection fraction was calculated from end diastolic and end systolic volumes. Regional wall motion abnormalities were defined based on a 16-segment model for unenhanced and contrast-enhanced echocardiography as well as for MRI. For cineventriculography a 7-segment model was applied. For each analyzed segment regional wall motion was defined as either normokinetic, hypokinetic, akinetic or dyskinetic. Presence of a regional wall motion abnormality was defined as hypokinesia, akinesia or dyskinesia in at least one segment.

To define a standard of truth for the existence of regional wall motion abnormalities, a consensus decision was made for each patient between 2 independent panelists based on clinical data, ECG, coronary angiography and results of all image readings. To define the standard of truth, the 2 panelists adhered to a predefined decision algorithm.

### Analysis of global left ventricular function

The first part of the study focused on analysis of global left ventricular function, in terms of end systolic and diastolic volumes and ejection fraction. Table 2 displays end diastolic and end systolic volumes as well as EF for the four different imaging techniques as determined by off-site-reader 1 of each technique. As expected, left ventricular end systolic and end diastolic volumes were relatively large defined by cineventriculography and MRI and small by unenhanced echocardiography while volumes determined by contrast-enhanced echocardiography were of intermediate magnitude. This trend was also observed for ejection fraction values. Compared with unenhanced echocardiography, results obtained by contrast-enhanced echocardiography were closer to those of cineventriculography and MRI. The mean difference between EF defined by echocardiographic images and EF by cineventriculography was significantly lowered when using contrast-enhanced echocardiographic images compared to unenhanced images. Similarly, the correlation between EF defined by echocardiography and EF defined by cineventriculography was better if contrast-enhanced echocardiography was used instead of unenhanced echocardiography (Table 3). When this comparison was made for MRI, contrast enhancement improved the correlation coefficient but did not reduce the mean difference in ejection fraction measurements. Analysis of the inter-method agreement on ejection fraction measurements was performed for individual patients using the Bland–Altman method. It demonstrated narrower ranges in the differences between ejection fraction measurements obtained by contrast-enhanced echocardiography vs MRI and cineventriculography compared to measurements obtained by unenhanced echocardiography.

For the four imaging methods the inter-observer variability in the determination of ejection fraction was defined. The mean percentage of error (MPE) between the on-site reader and the two blinded off-site readers was greatest for unenhanced echocardiography and lowest for MRI and contrast-enhanced echocardiography. The pattern of inter-observer agreement was confirmed for all three readers by calculation of the intra-class correlation coefficient, which was 0.91 for contrast-enhanced echocardiography, 0.86 for MRI, 0.80 for cineventriculography and 0.79 for unenhanced echocardiography (Fig. 2). Thus, it was significantly higher for contrast-enhanced echocardiography compared to cineventriculography and unenhanced echocardiography.

<table>
<thead>
<tr>
<th>Patients (n)</th>
<th>End diastolic volume (ml)</th>
<th>End systolic volume (ml)</th>
<th>EF (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cineventriculography</td>
<td>100</td>
<td>187±105</td>
<td>90±84</td>
</tr>
<tr>
<td>Magnetic resonance imaging</td>
<td>55</td>
<td>174±50</td>
<td>84±45</td>
</tr>
<tr>
<td>Unenhanced echocardiography</td>
<td>115</td>
<td>115±53</td>
<td>62±48</td>
</tr>
<tr>
<td>Contrast-enhanced echocardiography</td>
<td>115</td>
<td>147±60</td>
<td>73±56</td>
</tr>
</tbody>
</table>
Contrast-enhanced echocardiography improves agreement on the assessment of EF and LV function

Table 3
Inter-method agreement on left ventricular ejection fraction measurements between the two echocardiographic modalities and cineventriculography as well as MRI for echo off-site readers 1 and 2. For each comparison, the mean difference in individual patient’s values of ejection fraction is reported, as is Pearson’s correlation coefficient r.

<table>
<thead>
<tr>
<th>Reader</th>
<th>Echocardiography</th>
<th>MRI vs echo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unenhanced</td>
<td>Contrast-enhanced</td>
</tr>
<tr>
<td></td>
<td>Difference (%)</td>
<td>Difference (%)</td>
</tr>
<tr>
<td>Cineventriculography vs echo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Off-site reader 1</td>
<td>5.4</td>
<td>2.4</td>
</tr>
<tr>
<td>Off-site reader 2</td>
<td>6.8</td>
<td>1.9</td>
</tr>
<tr>
<td>MRI vs echo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Off-site reader 1</td>
<td>-0.7</td>
<td>-4.6</td>
</tr>
<tr>
<td>Off-site reader 2</td>
<td>-0.3</td>
<td>-4.7</td>
</tr>
</tbody>
</table>

Fig. 2. Inter-observer variability between off-site reader 1 and off-site reader 2 on determination of left ventricular ejection fraction for each imaging modality given as mean percentage of error (MPE, squares). Interobserver agreement between all three observers (on-site reader, off-site reader 1 and off-site reader 2) on determination of left ventricular ejection fraction for each imaging modality given as intraclass correlation coefficient (ICC, circles).

Analysis of regional left ventricular function

The second part of the study focused on the detection of regional wall motion abnormalities. Regional wall motion abnormalities are currently assessed in clinical practice by visual analysis. Thus, sufficient image quality is a fundamental need for adequate analysis.

This part of the study included only 100 patients due to the lack of biplane cineventriculography in the remaining 15 patients. Overall, regional wall motion abnormalities were detected in 58% to 86% of patients, depending on the imaging modality and on the readers’ subjective evaluations (Table 4). The three readers of echocardiographic images found similar rates of patients with abnormalities (63-67%) for unenhanced and contrast-enhanced echocardiography. There were greater variabilities between the three readers of cineventriculograms and in particular between the three readers of the MRI images. Mean inter-observer agreement between all three readers of an imaging modality was lowest for unenhanced echocardiography and highest for contrast-enhanced echocardiography while MRI...
and cineventriculography had intermediate levels (Fig. 3). The inter-method agreement regarding the presence of regional wall motion abnormalities was relatively poor (<0.59) between all imaging modalities used. In particular, inter-method agreement between unenhanced echocardiography and cineventriculography was 0.28, while it was 0.29 between unenhanced echocardiography and MRI. The use of a contrast agent increased the inter-method agreement noticeably: with MRI it was 0.46 while with cineventriculography it was 0.59.

To determine the accuracy of each imaging modality in the analysis of regional left ventricular function, results were compared to the standard of truth on presence of regional wall motion abnormalities defined by an expert panel with the help of a decision algorithm. The expert panel judged 67 of 100 patients to have regional wall motion abnormalities. The kappa value considering the findings of all three readers of a method and agreement with the panel decision of presence of RWMA was highest for contrast echocardiography, at 0.71 (Fig. 3). Agreement between the panel decision and contrast echocardiography was higher than the agreement between panel decision and unenhanced echocardiography. Considering the panel decision on the presence of regional wall motion abnormalities as standard, sensitivity, specificity and accuracy for assessment of regional wall motion abnormalities was on a high level for all imaging modalities, with a trend towards better diagnostic performance for cardiac MRI and contrast echocardiography (Fig. 4). Considering only those patients with all four imaging modalities being performed, the mean accuracy in the detection of a regional wall motion abnormality was 88.2% for contrast-enhanced echocardiography vs 79.5% for unenhanced echocardiography (p = 0.018).
Contrast-enhanced echocardiography improves agreement on the assessment of EF and LV function

Fig. 4. Sensitivity, specificity and accuracy of the four imaging modalities to detect panel-defined wall motion abnormalities.

Conclusions

The study demonstrated with respect to global left ventricular function analysis that (a) unenhanced echocardiography significantly underestimates left ventricular volumes compared to cineventriculography and MRI while contrast-enhanced echocardiography significantly improves determination of left ventricular volumes and ejection fraction; (b) unenhanced echocardiography is associated with a large inter-observer variability in the determination of ejection fraction while contrast enhancement improves inter-observer variability on determination of ejection fraction to a level observed for MRI; and (c) cineventriculography is associated also with a high inter-observer variability.

With respect to regional left ventricular function analysis the study demonstrated that (a) inter-observer agreement on presence of regional wall motion abnormalities is only moderate using unenhanced echocardiography and cineventriculography while it is considerably higher with contrast-enhanced echocardiography; (b) inter-method agreement on presence of regional wall motion abnormalities is only moderate if unenhanced echocardiography is compared with cineventriculography or cMRI, and is higher if contrast enhancement is applied; (c) contrast-enhanced echocardiography reaches a close agreement in regional wall motion abnormality assessment when compared to an expert panel decision considered as "standard of truth".

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References