The Impact of Contrast-enhanced Echocardiography to Improve Agreement on Assessment of Left Ventricular Function

a report by

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Analysis of global and regional left ventricular function has important therapeutic and prognostic implications. Echocardiography, cineventriculography, radionuclide-ventriculography and magnetic resonance imaging (MRI) are the imaging modalities most frequently used to define global and regional left ventricular function and left ventricular volumes. Cardiac MRI (cMRI) may be considered the gold standard for determination of left ventricular mass, volumes and left ventricular function due to the high image quality allowing clear endocardial and epicardial border definition in volumetric data sets.

While echocardiography is the most frequently used modality in clinical practice for defining global and regional left ventricular function, the limited endocardial border definition in many patients is the major limitation, resulting in moderate reproducibility and accuracy. Contrast echocardiography in combination with harmonic imaging allows improvement of endocardial border delineation, especially in patients with difficult imaging conditions, to a level that was unattainable before.

The utility of contrast-enhanced echocardiography for assessment of global and regional left ventricular function was determined in a multicentre study. Results on left ventricular function obtained by contrast-enhanced echocardiography were compared with those of unenhanced echocardiography, cineventriculography and MRI in a setting with blinded on-site and off-site reading of each imaging technique. The four imaging techniques were applied for determination of left ventricular volumes, as well as global and regional left ventricular function on the same patient, allowing patient comparisons. Eight centres contributing to the image acquisition process were provided with detailed protocols for carrying out the imaging examinations. 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.

Patients

Enrolled in the study were 155 patients with a mean age of 62.5±11.5 years, evenly distributed within three ejection fraction (EF) groups (>55, 35–55 and <35%) based on results from cineventriculography. As not all centres were equipped for all imaging modalities, biplane cineventriculography was performed in 100 patients and MRI was performed in 55 patients. The imaging procedures are described below.

Echocardiography

2D echocardiography was performed with the use of tissue harmonic imaging and contrast-specific imaging for left ventricular opacification. Apical 4-chamber, 2-chamber and 3-chamber views were acquired both with and without contrast enhancement. Great care was taken to avoid apical foreshortening and to maximise the length from base to apex. The contrast agent SonoVue® (Bracco S.A., Milan, Italy) was administered for contrast-enhanced assessment of left ventricular function. A starting infusion rate of 1ml/min and subsequent dose adjustment in order to reach homogenous cavity opacification without attenuation was used. Scanner settings were optimised for contrast-specific imaging. Transmit power had to be set low (myocardial infarction (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 in a 30° right anterior oblique (RAO) projection, and a 60° left anterior oblique (LAO) projection with injection of at least 30cc of contrast medium within two seconds.

Magnetic Resonance Imaging

Electrocardiograph (ECG)-triggered MRI investigations at a field strength of 1.5T during breathhold were performed. Short-axis views with a slice thickness of 10mm in baso-apical direction, as well as 4-, 2- and 3-chamber views, were acquired with a temporal resolution ≤50ms.

Reading of Images

Diagnostic images were read by the on-site reader and two off-site readers according to standardised recommendations. For each method, left ventricular volumes were determined by manual tracing of endocardial contours using the Simpson rule. EF was calculated from end-diastolic and end-systolic volumes. Based on a 16-segment model, regional left ventricular function was assessed by unenhanced and contrast-enhanced echocardiography, as well as by MRI. A seven-segment model was applied for cineventriculography. Segmental wall motion was defined as normokinetic, hypokinetic, akinetic or dyskinetic. Presence of a regional wall motion abnormality (RWMA) was defined as hypokinesia, akinesis or dyskinesia in at least one segment. A standard of truth on the existence of RWMA in a patient was determined based on a consensus decision between two independent panelists considering clinical data, ECG, coronary angiography and results of all image readings. The two panelists had to adhere to a pre-defined decision algorithm in order to determine existence of RWMA.

Impact of Contrast-enhanced Echocardiography on Global Left Ventricular Function Assessment

Global left ventricular function was determined based on end-systolic and end-diastolic volumes and EF. Table 1 displays end-diastolic and end-systolic volumes, as well as EF, for the four imaging techniques determined by off-site reader one for each technique. Left ventricular end-systolic and end-diastolic volumes determined by cineventriculography and MRI were relatively larger, whereas they were smaller when determined by unenhanced echocardiography. Volumes determined by contrast-
enhanced echocardiography were of intermediate magnitude. Similar results were observed for EF values. Compared with unenhanced echocardiography, results obtained by contrast-enhanced echocardiography were closer to those of cineventriculography and MRI. Analysis of the inter-method agreement on EF measurements was performed for individual patients using the Bland-Altman method, demonstrating narrower ranges in the differences between EF measurements obtained by contrast-enhanced echocardiography versus MRI, and cineventriculography compared with measurements obtained by unenhanced echocardiography. The inter-observer variability in the determination of EF for the four imaging methods expressed as 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 magnitude of inter-observer agreement was confirmed by calculation of the intra-class correlation coefficient considering all three readers. It was 0.91 for contrast-enhanced echocardiography, 0.86 for MRI, 0.80 for cineventriculography and 0.79 for unenhanced echocardiography. Thus, it was significantly higher for contrast-enhanced echocardiography compared with cineventriculography and unenhanced echocardiography.

Impact of Contrast-enhanced Echocardiography on Assessment of Regional Left Ventricular Function

Analysis of regional left ventricular function is of similar importance to global function assessment. RWMA were detected in 58–86% of patients, depending on the imaging modality and on the subjective evaluations of the readers. The three readers of echocardiographic images found similar rates of patients with abnormalities (63–67%) for unenhanced and contrast-enhanced echocardiography. There were greater variations between the three readers of cineventriculograms and, in particular, between the three readers of the MRI images. Mean inter-observer agreement among 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.

To determine the accuracy of each imaging modality in the analysis of regional left ventricular function, results were compared with a standard of truth on presence of RWMA defined by an expert panel. The panel of two expert cardiologists judged 67 of 100 patients to have RWMA based on a pre-specified decision algorithm. The kappa value considering the findings of all three readers of a method and agreement with the panel decision on presence of RWMA was highest, at 0.71, for contrast echocardiography. 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 RWMA as standard, other factors such as sensitivity, specificity and accuracy for assessment of RWMA were at a high level for all imaging modalities, with a trend towards better diagnostic performance for MRI and contrast echocardiography. The mean accuracy in the detection of RWMA considering only those patients with all four imaging modalities being performed was 88.2% for contrast-enhanced echocardiography versus 79.5% using unenhanced echocardiography (p=0.018) (see Table 2).

Conclusions

Considering global left ventricular function parameters, unenhanced echocardiography significantly underestimates left ventricular volumes compared with cineventriculography and MRI, while contrast-enhanced echocardiography significantly improves determination of left ventricular volumes and EF. Unenhanced echocardiography is associated with a large inter-observer variability in the determination of EF, while contrast enhancement improves inter-observer variability on determination of EF to a level observed for MRI. Cineventriculography is also associated with a high inter-observer variability on EF. With respect to regional left ventricular function analysis, inter-observer agreement on presence of RWMA is considerably higher with contrast-enhanced echocardiography, compared with only moderate results using unenhanced echocardiography and cineventriculography.

Table 2: Diagnostic Accuracy of Each Imaging Technique

<table>
<thead>
<tr>
<th>Only cMRI patients</th>
<th>Echo Unenhanced</th>
<th>Echo Contrast-enhanced</th>
<th>Cineventriculography</th>
<th>cMRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (n)</td>
<td>56</td>
<td>56</td>
<td>56</td>
<td>56</td>
</tr>
<tr>
<td>Sensitivity (%)</td>
<td>83.3</td>
<td>90.7</td>
<td>84.1</td>
<td>90.8</td>
</tr>
<tr>
<td>Specificity (%)</td>
<td>73.0</td>
<td>83.8</td>
<td>69.4</td>
<td>74.4</td>
</tr>
<tr>
<td>Accuracy (%)</td>
<td>79.5</td>
<td>88.2*</td>
<td>78.7</td>
<td>84.9</td>
</tr>
</tbody>
</table>

Method to define presence of regional wall motion abnormalities as defined by a panel decision. Presented sensitivities, specificities and accuracies given in this analysis relate to the mean from all three readers. cMRI = cardiac magnetic resonance imaging; echo: echocardiography; * p=0.018 versus echo unenhanced; # p=0.018 versus cineventriculography.

Table 1: Left Ventricular Volumes and Ejection Fraction

<table>
<thead>
<tr>
<th></th>
<th>Patients (n)</th>
<th>End-diastolic Volume (ml)</th>
<th>End-systolic Volume (ml)</th>
<th>Ejection Fraction (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cineventriculography</td>
<td>100</td>
<td>167±105</td>
<td>90±84</td>
<td>56.2±18.3</td>
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<tr>
<td>Magnetic resonance imaging</td>
<td>55</td>
<td>174±50</td>
<td>84±45</td>
<td>54.7±12.9</td>
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<tr>
<td>Unenhanced echocardiography</td>
<td>115</td>
<td>115±53</td>
<td>62±48</td>
<td>59.9±15.3</td>
</tr>
<tr>
<td>Contrast-enhanced echocardiography</td>
<td>115</td>
<td>147±60</td>
<td>73±56</td>
<td>54.6±16.8</td>
</tr>
</tbody>
</table>

Findings determined by cineventriculography, magnetic resonance imaging, unenhanced echocardiography and contrast-enhanced echocardiography. Data relate to those determined by blinded off-site reader one.