CHAPTER 12

Real-time 3-dimensional echocardiography early after acute myocardial infarction: incremental value of echo-contrast for assessment of left ventricular function

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ABSTRACT

Objectives: Accurate and reproducible assessment of left ventricular (LV) systolic function is important in patients with acute myocardial infarction (AMI). Real time three-dimensional echocardiography (RT3DE) is an accurate technique, but it relies heavily on good image quality. Aim of the present study was to evaluate the incremental value of contrast-enhanced RT3DE.

Methods: A total of 140 consecutive patients (58±11 years; 78% men) with ST-elevation AMI clinically underwent non-enhanced and contrast-enhanced RT3DE within 24 hours from AMI to evaluate global and regional LV systolic function. Endocardial border definition was graded for each of the 16 LV segments as: 0 = border invisible; 1 = border visualized only partially and 2 = complete visualization of the border. Three image quality groups (good, fair and uninterpretable) were identified. LV volumes and ejection fraction were measured off-line. Wall motion was graded for each visible segment as: 1 = normal; 2 = hypokinetic; 3 = akinetic and 4 = dyskinetic.

Results: During contrast-enhanced RT3DE, as compared to non-enhanced RT3DE, the number of segments with complete visualization of the endocardial border increased from 66% to 84% (p <0.001) and the number of patients with a good quality echocardiogram increased from 59% to 94% (p <0.001). Intra- and inter-observer agreement for assessment of global and regional LV systolic function improved during contrast-enhanced RT3DE, as compared to non-enhanced RT3DE.

Conclusions: Assessment of LV systolic function in AMI patients with RT3DE is frequently hampered by suboptimal echocardiographic quality. Contrast-enhanced RT3DE is of incremental value, improving the endocardial border visualization and the reproducibility of LV function assessment.
INTRODUCTION

The assessment of global and regional left ventricular (LV) systolic function is extremely important among patients with acute myocardial infarction (AMI), since it carries significant therapeutic and prognostic implications 1–6. Recently, real time three-dimensional echocardiography (RT3DE) has been introduced for assessment of LV function and volumes. RT3DE has been validated against magnetic resonance imaging and found to be more accurate and reproducible as compared to two-dimensional echocardiography (2DE) 7–13. However, even more than 2DE, RT3DE relies heavily on the presence of good image quality 14,15.

The use of intravenous contrast agents during 2DE has been shown to be of incremental value, improving LV endocardial border visualization among patients with suboptimal image quality and increasing the accuracy and reproducibility of LV systolic function measurements 16–22. In contrast, data regarding the use of echo contrast during RT3DE are scarce 14,23–25. In particular, no specific data exist about the efficacy of contrast-enhanced RT3DE performed early after AMI; the safety of contrast-enhanced echocardiography early after AMI was reported recently with 2DE 26. Aim of the present study was therefore to investigate, in a large cohort of consecutive patients with AMI, the potential incremental value of contrast-enhanced RT3DE over non-enhanced RT3DE for assessment of LV function and volumes.

METHODS

Patient population

The patient population consisted of 140 patients admitted to the coronary care unit because of ST-elevation AMI. The diagnosis of ST-elevation AMI was made on the basis of typical ECG changes and/or ischemic chest pain associated with elevation of cardiac biomarkers 27.

All patients underwent immediate coronary angiography and primary percutaneous coronary intervention. As part of the clinical work-up, RT3DE (with echo contrast) was performed in the coronary care unit within 24 hours from patients’ admission to accurately evaluate global and regional LV systolic function.

Echocardiography

Patients were imaged in left lateral decubitus position with a commercially available system (Vivid 7, GE Healthcare, Horten, Norway) equipped with a 3V phased array transducer (2.5 MHz). First, apical full volume 3D data sets were acquired in harmonic mode, integrating,
during a brief breath-hold, 8 R-wave-triggered sub-volumes into a larger pyramidal volume (90° by 90°) with a complete capture of the LV. Thereafter, the same acquisition was repeated during echo contrast administration (Luminity®, Bristol-Myers Squibb Pharma, Bruxelles, Belgium) to optimize LV border delineation. Each patient received an intravenous infusion of 1.3 ml of echo contrast diluted in 50 ml of 0.9% NaCl solution; the rate of infusion was initially set at 4.0 ml/min and then titrated to achieve optimal LV chamber opacification and endocardial border delineation. Contrast-enhanced RT3DE was performed in harmonic mode at low mechanical index (0.26), and care was taken to record the images at a phase when echo contrast flow was relatively stable with absent or minimal swirling in the apex. The 3D data sets were digitally stored for the off-line analysis.

**Echocardiographic analysis**

The 3D data sets were analyzed on-line for the analysis of LV chamber opacification and off-line for the analysis of LV endocardial border definition and LV volumes and function. The off-line analysis was performed using a dedicated software (4D LV-Analysis©; TomTec, Munich, Germany) by an observer who had no knowledge of the patient’s identity, medical history and symptom status. As described elsewhere, the software automatically displays in a quad-screen the 4-chamber view, as a reference view, the 2- and 3-chamber views with default interplane angles at 60 degrees and a short-axis view (Figure 1). The interplane angles can be manually modified in order to obtain adequate orientation of the 3 apical views and their meeting point can be adjusted in the middle of the LV cavity in order to avoid LV foreshortening. This procedure can also be used to evaluate regions between the 3 adjacent conventional apical views.

![Figure 1. Left panel. Example of fair quality echocardiogram during non-enhanced RT3DE. Right panel. Optimal left ventricular chamber opacification and improved endocardial border definition during contrast-enhanced RT3DE in the same patient. The 3 apical views are shown with the 4-chamber as a reference view in the top right and the 2- and 3-chamber views in the bottom left and bottom right, respectively. Top left: short-axis view.](image-url)
LV chamber opacification

The degree of LV chamber opacification during echo contrast administration was graded according to a 5-point rating scale: 0 = no contrast enhancement; 1 = weak or little contrast enhancement; 2 = adequate contrast enhancement that facilitates image interpretation; 3 = full contrast enhancement that definitely aids image interpretation; 4 = excessive contrast enhancement that hampers interpretation. The percentage of patients with adequate-to-full contrast enhancement was calculated. The mean time needed to achieve adequate-to-full contrast enhancement was measured.

LV endocardial border definition

Qualitative assessment of the endocardial border was performed both in non-enhanced and contrast-enhanced images. A standard 16-segment model was used. Adequacy of LV endocardial border definition was graded for each of the 16 cardiac segments as follows: 0 = border invisible; 1 = border visualized only partially throughout the cardiac cycle and/or incomplete segment length, and 2 = complete visualization of the border. A global endocardial visualization score was calculated as the sum of each LV segment’s score.

On basis of the global score, 3 image quality groups were defined: good (score 25-32), fair (score 17-24) and uninterpretable (score ≤16). Uninterpretable echocardiograms were deemed non-diagnostic and further analyses of LV volumes and global and regional LV functions were considered not feasible.

LV volumes and global systolic function

The algorithm used by the software to calculate LV end-diastolic volume (EDV), LV endsystolic volume (ESV) and LVEF is described in detail elsewhere. Briefly, the endocardial border is manually traced in the 3 apical views (including LV trabeculations and papillary muscles within the cavity) in both the end-diastolic and end-systolic frames. Subsequently, the software automatically identifies the endocardial border in the entire 3D dataset; further manual adjustments are possible in approximately 30 coronal and sagittal planes. Finally, a reconstruction of the LV model is generated and LV volumes and LVEF are obtained.
LV regional function

Qualitative assessment of the regional wall motion was performed both in non-enhanced and contrast-enhanced images, according to the same 16-segment model used for the evaluation of LV endocardial border definition. Segments with invisible endocardial border were excluded from this analysis. Wall motion was graded for each of the visualized segments as follows: 1 = normal; 2 = hypokinetic; 3 = akinetic and 4 = dyskinetic. A global wall motion score index (WMSI) was calculated as the sum of each LV segment’s score divided by the number of visualized segments.

Reproducibility of RT3DE measurements

The datasets of 20 patients with a good quality echocardiogram and 20 patients with a fair quality echocardiogram during non-enhanced RT3DE were randomly selected and analyzed again 1 month later by the original observer and by a second observer who was blinded to the results of the previous analysis. Intra- and inter-observer agreement was assessed for the measurements of LV volumes and LVEF and the grading of regional wall motion.

Statistical analysis

Continues variables are expressed as mean and standard deviation. Categorical data are presented as absolute numbers and percentages.

The global endocardial visualization score and the measurements of LV volumes, LVEF and WMSI were compared between the 2 imaging techniques with the paired t-test. To determine whether there was a statistically significant difference in the comparison between categorical variables, the McNemar test was performed for binary data and the marginal homogeneity test for multinomial response data. Intra- and inter-observer agreement in the measurements of LV volumes and LVEF were assessed using Bland-Altman analysis and expressed as the mean difference between the 2 measurements ±2 standard deviations. To evaluate intra- and inter-observer agreement in the grading of regional wall motion, weighted Kappa test was used and the level of agreement was interpreted 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; and 0.81 to 1.0 = nearly perfect. A p-value <0.05 was considered statistically significant. Statistical analysis was performed using the SPSS software package (SPSS 15.0, Chicago, Illinois).
RESULTS

Patient population

Baseline characteristics of the patient population are summarized in Table 1. Mean age of the patients was 58±11 years; 109 (78%) were male. Fifteen (11%) patients had a history of myocardial infarction and 12 (9%) had previous surgical or percutaneous myocardial revascularization. The infarct-related artery was the left anterior descending coronary artery in 60 (43%) patients, the left circumflex coronary artery in 19 (13%) and the right coronary artery in 61 (44%). Obstructive multi-vessel disease (i.e. more than 1 vessel with a luminal narrowing ≥70%) was present in 51 (36%) patients.

Table 1. Clinical and echocardiographic patient characteristics (n = 140).

<table>
<thead>
<tr>
<th>Clinical and echocardiographic characteristics (n = 140)</th>
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<tbody>
<tr>
<td>Age (years)</td>
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<tr>
<td>Gender (male/female)</td>
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<tr>
<td>Diabetes</td>
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<tr>
<td>Family history of coronary artery disease</td>
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<tr>
<td>Hypercholesterolemia</td>
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<tr>
<td>Hypertension</td>
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<tr>
<td>Current or previous smoking</td>
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<tr>
<td>Previous myocardial infarction</td>
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<tr>
<td>Previous myocardial revascularization</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
</tr>
<tr>
<td>Current anterior myocardial infarction</td>
</tr>
<tr>
<td>Current infarct-related artery</td>
</tr>
<tr>
<td>- left anterior descending coronary artery</td>
</tr>
<tr>
<td>- left circumflex coronary artery</td>
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<tr>
<td>- right coronary artery</td>
</tr>
<tr>
<td>Multi-vessel coronary artery disease</td>
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</table>

Echocardiography

The mean infusion rate of echo contrast was 3.0±0.6 ml/min and the total infusion dose was on average 16 µl/kg.

LV chamber opacification

Adequate-to-full enhancement during echo contrast infusion was noted in 130 (93%) patients. Weak or little contrast enhancement was observed in 9 (6%) patients and excessive
contrast enhancement in 1 (1%) patient. The mean time needed to achieve adequate-to-full LV contrast enhancement was 65±20 sec.

**LV endocardial border definition**

During non-enhanced RT3DE, from the total number of 2240 LV segments, the endocardial border was invisible in 243 (11%) and visualized only partially in 509 (23%). A complete visualization of the border was possible in 1488 (66%) segments (Table 2). The mean global endocardial visualization score was 25±6. A total of 82 (59%) patients had a good quality echocardiogram, while 44 (31%) and 14 (10%) had a fair quality and uninterpretable echocardiogram, respectively (Figure 2).

During contrast-enhanced RT3DE, a complete visualization of the border was possible in 1890 (84%) segments (p <0.001 as compared to non enhanced RT3DE) (Table 2). The LV endocardial border definition significantly improved in the segments of each LV wall (Table 2). As compared to non-enhanced RT3DE, the mean global endocardial visualization score improved to 29±3 (p <0.001). A total of 131 (94%) patients had a good quality echocardiogram, while 7 (5%) and 2 (1%) had a fair quality and uninterpretable echocardiogram, respectively (p <0.001 in comparison to non-enhanced RT3DE) (Figure 2).

An example of LV chamber opacification and improved endocardial border definition during contrast-enhanced RT3DE, as compared to non-enhanced RT3DE is displayed in Figure 1.
Contrast-enhanced RT3DE after AMI

LV volumes and global systolic function

Non-enhanced RT3DE provided significantly lower values of LVEDV as compared to contrast-enhanced RT3DE (107±28 ml vs. 113±27 ml, p <0.001). The values of LVESV were not statistically different between the 2 techniques (59±21 ml vs. 61±20 ml, p = ns). Accordingly, non-enhanced RT3DE provided slightly, but significantly lower values of LVEF (45±9% vs. 47±9%, p = 0.003).

LV regional systolic function

WMSI assessed on non-enhanced and contrast-enhanced images were 1.8±0.4 and 1.7±0.4, respectively (p = 0.04).
Reproducibility of RT3DE measurements

Intra- and inter-observer agreement for the measurements of LV volumes, LVEF and the grading of regional wall motion obtained with the 2 techniques are shown in Tables 3 and 4. The weakest agreements were observed among patients with a fair quality echocardiogram. Contrast-enhanced RT3DE improved intra- and inter-observer agreement both in good and fair echocardiograms.

Table 3. Intra- and inter-observer agreements for the measurements of left ventricular volumes and left ventricular global function, in relation to image quality during non-enhanced RT3DE.

<table>
<thead>
<tr>
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<th>Good quality echocardiogram during non-enhanced RT3DE</th>
<th>Fair quality echocardiogram during non-enhanced RT3DE</th>
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<tbody>
<tr>
<td>Intra-observer agreement</td>
<td></td>
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<tr>
<td>LVEDV</td>
<td>-1.5±28.0</td>
<td>-4.5±42</td>
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<tr>
<td>LVEF</td>
<td>-0.1±10.0</td>
<td>1.7±14.8</td>
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<tr>
<td>LVEF</td>
<td>-0.7±6.8</td>
<td>0.2±5.4</td>
</tr>
<tr>
<td>LVEF</td>
<td>-4.5±42</td>
<td>1.7±14.8</td>
</tr>
<tr>
<td>Inter-observer agreement</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV EDV</td>
<td>-6.1±36.2</td>
<td>-6.6±44.2</td>
</tr>
<tr>
<td>LV ESV</td>
<td>-4.2±20.2</td>
<td>-6.4±36.2</td>
</tr>
<tr>
<td>LV EF</td>
<td>-1.0±12.8</td>
<td>2.2±22.4</td>
</tr>
<tr>
<td>LV EF</td>
<td>-0.7±7.4</td>
<td>-1.4±8.8</td>
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Intra- and inter-observer agreements for the measurements of LV volumes and LVEF were assessed using the method proposed by Bland and Altman and expressed as the mean difference between the 2 measurements±2 standard deviations. EDV: end-diastolic volume; EF: ejection fraction; ESV: end-systolic volume; LV: left ventricle; RT3DE: real-time three-dimensional echocardiography.

Table 4. Intra- and inter-observer agreements for the grading of left ventricular regional wall motion, in relation to image quality during non-enhanced RT3DE.

<table>
<thead>
<tr>
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<th>Good quality echocardiogram during non-enhanced RT3DE</th>
<th>Fair quality echocardiogram during non-enhanced RT3DE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intra-observer agreement</td>
<td></td>
<td></td>
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<tr>
<td>LV RWM</td>
<td>0.77</td>
<td>0.69</td>
</tr>
<tr>
<td>Inter-observer agreement</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV RWM</td>
<td>0.65</td>
<td>0.54</td>
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</table>

Intra- and inter-observer agreements for the grading of LV RWM were assessed using the weighted Kappa test and expressed as weighted Kappa value. LV: left ventricle; RT3DE: real-time three-dimensional echocardiography; RWM: regional wall motion.
DISCUSSION

The current results show that, among unselected patients in the early stage of AMI, contrast-enhanced RT3DE has a high feasibility (93%), and is of incremental value for the assessment of LV systolic function. Specifically, as compared to non-enhanced RT3DE, 1) it significantly increased the number of LV segments with a complete visualization of the endocardial border (from 66% to 84%); 2) it increased the number of good quality echocardiograms (from 59% to 94%); and 3) it reduced the number of fair quality and uninterpretable echocardiograms (from 41% to 6%). Moreover, intra- and inter-observer agreement for the measurements of global and regional LV systolic function improved during contrast-enhanced RT3DE, particularly among patients with fair quality echocardiogram during non-enhanced RT3DE.

Advantages and limitations of RT3DE

The most commonly used imaging modality for the evaluation of global and regional LV systolic function is 2DE. However, 2DE relies on significant geometric assumptions, resulting in modest agreement with reference methods and fair reproducibility 17,31.

More recently, RT3DE has been proposed to overcome the above mentioned limitations of 2DE; RT3DE correlated well with magnetic resonance imaging for assessment of LV volumes and LV ejection fraction 8–11. In addition, it has been suggested that RT3DE has potential advantages for the evaluation of regional LV function in regions/planes that could not be adequately visualized with 2DE 7;13.

Because of its higher accuracy and reproducibility, RT3DE could be extremely useful for serial assessment of systolic function 32. RT3DE would be particularly useful in AMI patients, in whom accurate assessment of LV function and volumes is important for prediction of future adverse events 2,3.

However, RT3DE has still several limitations; particularly, RT3DE image quality is highly dependent on the acoustic window, due to a lower spatial and temporal resolution as compared to 2DE 11,24. Accordingly, adequate endocardial border delineation may be difficult on RT3DE still frames, even in the presence of relatively good quality 2DE 33. Due to this limitation, most of the previous RT3DE studies included only patients with an optimal acoustic window 8–10. Few studies explored the feasibility of RT3DE, in relation to the image quality, for the assessment of LV systolic function in unselected population and reported a prevalence of uninterpretable or poor quality RT3DE images in the range of 35% 15,24. This issue may be even more prominent in patients with AMI, in whom adequate assessment of LV function and volumes is important for prognosis, but in whom RT3DE data acquisition may be hampered by reduced patient mobility 12,24. In the present study, 41% of 140 consecutive patients referred to RT3DE within 24 hours from AMI had a fair quality or uninterpretable echocardiogram. This
percentage is in line with previous studies and may also be related to technical limitations associated to the performance of RT3DE in the coronary care unit, as well as the high body mass index of our study population.

**Incremental value of contrast-enhanced RT3DE**

In the subset of patients with inadequate RT3DE images, contrast agents could improve LV endocardial border visualization, increasing the feasibility, accuracy and reproducibility of LV function assessment as previously reported with 2DE.

Thus far, few small studies (16, 20, 39 and 50 patients, respectively) previously assessed the accuracy of contrast-enhanced RT3DE, reporting a good agreement between contrast-enhanced RT3DE and magnetic resonance imaging for assessment of LV function and volumes. However, data regarding the feasibility of contrast-enhanced RT3DE and its incremental value over non-enhanced RT3DE (in terms of improved image quality) have not been shown. In the present study, we reported our experience on the feasibility and efficacy of contrast-enhanced RT3DE in a large, unselected cohort of patients in the early stage of AMI. Echo contrast infusion ensured optimal LV opacification in 93% of the patients. Moreover, the definition of the endocardial border significantly increased with the use of echo contrast, allowing more reliable and reproducible assessment of regional wall motion abnormalities. Of note, visualization of the anterior and anterolateral walls particularly improved with the use of echo contrast.

Overall, the prevalence of good quality echocardiograms increased from 59% to 94% with the intravenous contrast. The prevalence of fair image quality and uninterpretable echocardiograms decreased from 31% to 5% and from 10% to 1%, respectively.

**Study limitations**

The present study has some limitations that should be acknowledged. First, the semi-automated algorithm used for LV volume analysis requires manual tracing of the endocardial border in the 3 apical planes, which is a subjective procedure that could alter the reproducibility of the technique. Second, an independent gold standard (e.g. magnetic resonance imaging) was not performed and therefore data about accuracy of contrast-enhanced RT3DE could not be provided.
CONCLUSIONS

In patients with recent AMI, the use of echo contrast significantly improved the endocardial border visualization and the reproducibility of measurements of global and regional LV systolic function.
REFERENCES


30. Lang RM, Bierig M, Devereux RB et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography’s Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association


