Clinical Usefulness of Low-Dose Dobutamine Stress Real-Time Myocardial Contrast Echocardiography for Detection of Viable Myocardium

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ABSTRACT: Objectives. To evaluate and compare the diagnostic accuracy of semi-quantitative and quantitative real-time myocardial contrast echocardiography (RT-MCE) with low-dose dobutamine stress echocardiography (LD-DSE) in detecting viable myocardium.

Methods. Thirty in-patients with coronary artery disease and regional wall motion abnormalities underwent RT-MCE without and with LD-DSE. Percutaneous coronary intervention was performed within 1 week after RT-MCE in all patients. Myocardial perfusion was evaluated from \( A_1 \), \( b_1 \), and \( A_3b_3 \) indices from microbubble replenishment curves. The motion of each myocardium segment was observed by routine echocardiography 1, 3, and 6 months after percutaneous coronary intervention and its improvement over time was the criterion of viable myocardium.

Results. RT-MCE sensitivity and specificity for the assessment of viable myocardium were 71.7% and 69.8%, rising to 81.3% and 76.7% \((p < 0.05)\) when combined with LD-DSE. Using quantitative RT-MCE with cutoff values of \( A_1 \), \( b_1 \), and \( A_3b_3 \), the sensitivity and specificity were 75.6%, 78.8%, 82.1%, and 82.4%, 77.9%, 78.6%, respectively. When combined with LD-DSE, the sensitivity and specificity were 86.0%, 83.2%; 88.9% and 84.1%; 89.6%, 79.9%, respectively.

Conclusions. Quantitative RT-MCE analysis yielded higher sensitivity and specificity than semi-quantitative RT-MCE with or without LD-DSE for the detection of viable myocardium. © 2012 Wiley Periodicals, Inc. J Clin Ultrasound 00:000–000, 2012; Published online in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/jcu.20891

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Real-time myocardial contrast echocardiography (RT-MCE) is a novel method that uses microbubbles to produce continuous myocardial echo enhancement at very low-power ultrasound.\(^{1,2}\) Compared with other imaging modalities of MCE, RT-MCE allows the simultaneous assessment of global and regional myocardial structure, motion, and perfusion. Previous studies showed that preservation of microvascular integrity after myocardial ischemia was associated with viable myocardium.\(^3\)

RT-MCE is a useful tool for tissue perfusion and myocardial viability assessment. Single-photon emission computed tomography (SPECT) and positron emission tomography (PET) are much more complex, costly, and irradiant techniques. Nevertheless, semi-quantitative RT-MCE remains subjective and requires experienced investigators. Several software developments have been aimed at the quantitative analysis of RT-MCE data, offering more accurate and objective results.\(^4–7\)

Several clinical studies have demonstrated the concordance between qualitative or semi-quantitative RT-MCE and SPECT in the assessment of
coronary artery disease (CAD). Although some studies showed an interest of RT-MCE for the detection of CAD and the demonstration of viable myocardium, very few studies evaluated RT-MCE combined with low-dose (10 \( \mu g/kg \cdot min \)) dobutamine stress echocardiography (LD-DSE) for the detection of viable myocardium. In the present study, we sought to evaluate the feasibility of RT-MCE with LD-DSE in patients undergoing percutaneous coronary intervention (PCI) and to detect viable myocardium in patients with CAD whose regional wall motion abnormalities were detected by RT-MCE perfusion parameters.

METHODS

Study Population

A total of 30 patients with CAD (18 men, mean age 51 years, range 36–67 years) were enrolled in this study. Eighteen patients presented with unstable angina and 12 patients presented with old myocardial infarction in whom PCI had been performed 0.5–6 years earlier. Inclusion criteria were unstable angina or myocardial infarction diagnosed on anamnesis, electrocardiography, echocardiography, and coronary angiography (CAG). Regional wall motion abnormalities of the left ventricle (LV) were detected by routine echocardiography.

All the patients had the indication for PCI according to current guidelines. Exclusion criteria were severe cardiac arrhythmia; rheumatic valvular heart disease; cardiomyopathy; and severe obstructive pulmonary disease. Each patient was informed of the investigative nature of the study and gave written, informed consent before enrollment. The study was approved by the regional ethics committee of the affiliated hospital of Xu Zhou Medical College.

Contrast Agent

An experienced nurse diluted 59 mg of second-generation contrast agent Sonovue (Bracco, Milano, Italy) in 5 ml saline and injected intravenously 2.5 ml of the resulting mixture through a 20 g vial in a proximal forearm vein at the speed of 1 ml/min. We used the same dose in adult and elderly patients regardless of their body weight, according to the manufacturer’s instructions. The infusion parameters were carefully adjusted to optimize myocardial enhancement and minimize far field attenuation.

RT-MCE Acquisition

Imaging was performed with an IE33 ultrasound system (Philips Healthcare, DA Best, The Netherlands) equipped with a 1–5 MHz sector scanning transducer, with a low-emitting power preset, in pulse inversion power Doppler mode at a rate of 20–22 frames/s. The optimal balance between myocardial contrast enhancement and attenuation was achieved at a very low mechanical index (0.1). The time gain compensation was adjusted to obtain homogenous signal intensity (SI) and to reduce noise. The setting was adjusted for each patient to ensure optimal myocardial enhancement.

Apical four-chamber, two-chamber, and long-axis views were acquired by an experienced echocardiographer. Wall-by-wall imaging was done to optimize contrast detection and avoid artifacts as attenuation and rib shadowing. Special care was taken to avoid out-of-plane imaging and LV long-axis foreshortening. Once the cavity of LV and myocardial contrast enhancement reached a steady state, a brief burst (flash) of eight frames at high mechanical index for transient microbubble destruction was applied during end expiration. There was an automatic return to low mechanical index for continuous imaging of microbubble replenishment for at least 10 cardiac cycles immediately after the flash frames. The procedure was repeated at least twice for every scan view, and 15 cardiac cycles of every destruction-replenishment sequence were captured and stored as raw data.

The acquired RT-MCE sequences were digitally transferred to an off-line computer for quantitative analysis by using QLAB (Advanced Quantification Software, Philips Healthcare). Using electrocardiographically triggered analysis, the end-systolic frames (end of T wave) were selected from all cardiac cycles of the replenishment sequence. Mean SI was automatically measured in regions of interest (ROI), which were manually positioned using a standard 16-segment model. The ROIs positioned on the first postflash end-systolic frame were automatically copied onto all subsequent selected frames, and these were manually realigned frame-by-frame to maintain a central position within the wall during the entire replenishment sequence.

The segmental contrast SI was plotted against time \((t)\), and the subsequent refilling curve was fitted to the exponential function: \[ y(t) = A \cdot \left(1 - \exp(-\beta t)\right) + C, \]

where \( y \) was SI at any time during contrast replenishment, \( A \) was the peak plateau of SI representing myocardial blood volume (MBV), \( \beta \) was the rate of SI increase.
reflecting the mean velocity of myocardial blood flow (MBF), and C was the intercept on the time axis reflecting background tissue SI. The \( t_0 \) was set at the initial postflash moment of minimal myocardial contrast enhancement. The ROIs were positioned and anchored for each frame before curve fitting was applied. Segmental values of A, \( \beta \), and the product A \( \times \beta \), which was regarded as an indicator of MBF, were derived from the replenishment curves and averaged for each coronary territory.

Semi-quantitative analysis was achieved by attributing 0, 0.5, or 1 score when myocardial perfusion was absent, poor, or normal, respectively. Stress RT-MCE was then performed with dobutamine at 10 \( \mu \)g/kg \( \cdot \) min. Segments whose motion improved (for at least 1 scale degree) after dobutamine stress were regarded as viable myocardium.

**PCI and Gold Standard in Detecting Viable Myocardium**

All patients underwent routine echocardiography, and every segment was semi-quantitatively and quantitatively analyzed. Regional wall motion was scored according to a standard 16-segment model and graded on a five-point scale (1 = normal, 2 = hypokinetic, 3 = akinetic, 4 = dyskinetic, 5 = aneurysmal). Wall motion score index was calculated as the sum of all segments of wall motion score divided by the number of segments. Complete revascularization was performed in all patients within 1 week, and no PCI was performed in unrelated vessels. Wall motion was evaluated in the same segments by routine echocardiography after 1, 3, and 6 months after PCI. Myocardium was considered viable in a given segment when its motion improved from at least 1 scale degree after PCI.

Left ventricle ejection fraction (LVEF) was calculated by two-dimensional echocardiography according to Simpson’s formula.\(^{14}\) Left ventricular end-diastolic volume was measured. Wall thickness was measured and averaged on the left ventricle anterior, inferior, posterior, lateral, and septal wall by M-mode echocardiography.\(^{14}\)

**Statistical Analysis**

Continuous variables were presented as mean \( \pm \) SD. Grouped data were tested for normal distribution and compared using two-tailed \( t \) tests. Unpaired tests were used for comparison of independent data. For more than two groups, analysis of variance was used, considering territorial and patient interaction terms. \( p \) values <0.05 were defined to be statistically significant. Receiver operating characteristic curves were used to calculate the predictive value of RT-MCE.

**RESULTS**

A total of 43 coronary artery stenoses (more than 50% of diameter) were detected by CAG. Quantitative computer analysis of CAG data demonstrated 21 cases of 75%–79%, 15 cases of 80%–89%, and 7 cases of 90%–100% stenosis. Patient baseline characteristics and CAG data are summarized in Table 1.

**Viable Myocardium**

A total of 446/480 segments in 30 patients were analyzed (34 poor image acquisition segments were excluded). We studied 88 segments in the anterior, 20 in the inferior, 18 in the posterior, 42 in the lateral, and 50 in the septal ventricle wall. Wall motion was normal in 228 and abnormal in 218 segments. There were 105 hypokinetic, 66 akinetic, 42 dyskinetic, and 5 aneurysmal segments. After PCI, 82 hypokinetic, 42 akinetic, 21 dyskinetic, but no aneurysmal segment, improved. Therefore, 145 myocardium segments were viable and 73 segments were nonviable (Figure 1) at the end of the 6 months of follow-up after PCI. Improvement was detected in 76 segments at 1 month, 43 segments at 3 months, and 26 segments at 6 months after PCI. The degree of improvement was 1 in 99 segments, 2 in 43
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FIGURE 1. Myocardium segments characteristics in 30 patients with CAD.

TABLE 2
Echocardiographic Data Before and After Percutaneous Coronary Intervention (PCI) in the Population Sample

<table>
<thead>
<tr>
<th></th>
<th>EF (%)</th>
<th>WMSI</th>
<th>LVEDV (ml)</th>
<th>Wall Thicknesses</th>
<th>Posterior Wall (mm)</th>
<th>Septal Wall (mm)</th>
<th>LV Mass (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before PCI</td>
<td>32.6 ± 15.4%</td>
<td>1.76 ± 0.54</td>
<td>118.7 ± 17.6</td>
<td>8.23 ± 2.20</td>
<td>8.11 ± 2.37</td>
<td>7.66 ± 1.34</td>
<td>267.5 ± 43.5</td>
</tr>
<tr>
<td>After PCI</td>
<td>46.5 ± 13.5%*</td>
<td>1.23 ± 0.36*</td>
<td>92.3 ± 15.8*</td>
<td>9.72 ± 2.54*</td>
<td>8.62 ± 2.76*</td>
<td>8.64 ± 2.11*</td>
<td>275.6 ± 45.2*</td>
</tr>
</tbody>
</table>

*p < 0.05 versus before PCI.

Abbreviations: EF: ejection fraction; LV: left ventricle; LVEDV: left ventricle end-diastolic volume; WMSI: wall motion score index.

TABLE 3
Semi-Quantitative Real-Time Myocardial Contrast Echocardiography (RT-MCE) versus Improvement of Segmental Wall Motion Over Time at Follow-Up Echocardiography (n = 218 segments)

<table>
<thead>
<tr>
<th>Improvement of segment motion over time</th>
<th>Semi-quantitative RT-MCE</th>
<th>Viable</th>
<th>Nonviable</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viable</td>
<td>104</td>
<td>22</td>
<td>126</td>
<td></td>
</tr>
<tr>
<td>Nonviable</td>
<td>41</td>
<td>51</td>
<td>92</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>145</td>
<td>73</td>
<td>218</td>
<td></td>
</tr>
</tbody>
</table>

TABLE 4
Low-Dose Dobutamine Stress Echocardiography (LD-DSE) with Semi-Quantitative Real-Time Myocardial Contrast Echocardiography (RT-MCE) (n = 218 segments)

<table>
<thead>
<tr>
<th>Improvement of segment motion over time</th>
<th>LD-DSE with Semi-Quantitative RT-MCE</th>
<th>Viable</th>
<th>Nonviable</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viable</td>
<td>111</td>
<td>14</td>
<td>125</td>
<td></td>
</tr>
<tr>
<td>Nonviable</td>
<td>34</td>
<td>59</td>
<td>93</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>145</td>
<td>73</td>
<td>218</td>
<td></td>
</tr>
</tbody>
</table>

segments, and 3 in 3 segments. LVEF improved from 32.6 ± 15.4% to 46.5 ± 13.5% (p < 0.05). Left ventricular end-diastolic volume and wall thicknesses also improved after PCI (Table 2).

Semi-Quantitative RT-MCE

Among the 218 segments with abnormal wall motion, myocardium was judged viable in 126 segments by RT-MCE (sensitivity 71.7%, specificity 69.8%) (Table 3) and in 125 segments by semi-quantitative LD-DSE (sensitivity 76.7%, specificity 81.3%) (Table 4, Figure 2).

Quantitative RT-MCE

In the 218 segments with abnormal wall motion, A, β, and A × β were 3.85 ± 1.24, 0.44 ± 0.16, and 1.53 ± 0.31, respectively, with RT-MCE, and 3.90 ± 1.18, 0.56 ± 0.21, and 1.86 ± 0.37, respectively, when RT-MCE was combined with LD-DSE. There were significant differences between RT-MCE and RT-MCE combined with LD-DSE as
for β (0.44 ± 0.16 versus 0.56 ± 0.21) and A × β (1.53 ± 0.31 versus 1.86 ± 0.37) (Table 5).

The cutoff values of quantitative RT-MCE for detection of viable myocardium were 3.66, 0.38, and 1.39, respectively, of A, β, and A × β, with a sensitivity and specificity of 75.6%, 82.4%, 78.8% and 82.1%, 77.9%, 78.6%, respectively. The cutoff values of RT-MCE combined with LD-DSE were 3.88, 0.49, and 1.74, respectively, for A, β, and A × β, with a sensitivity and specificity of 86.0%, 83.2%, 88.9% and 84.1%, 89.6%, 79.9%, respectively, for the detection of viable myocardium (Figure 3A–F). The area under the curve and 95% confidence interval of A, β, and A × β of quantitative RT-MCE showed different values in detecting viable myocardium (Table 6). Quantitative was better than semi-quantitative RT-MCE analysis. RT-MCE combined with LD-DSE yielded better results than RT-MCE alone (Table 7).

### DISCUSSION

The availability of an accurate, noninvasive method for identifying viable myocardium in patients with CAD is very important for clinical decision-making and prognostic evaluation. In recent years, several studies showed that the presence of tissue-level perfusion at RT-MCE was predictive of viable myocardium in patients with CAD. However, semi-quantitative RT-MCE remains subjective and requires experienced investigators. Shimoni et al showed that quantitative RT-MCE offered better sensitivity and specificity than TI201 nuclear scintigraphy and DSE for detecting myocardial hibernation. Similarly, Korosoglou et al showed that RT-MCE and fluorodeoxyglucose-18 PET had comparable diagnostic value in detecting myocardial viability in patients with CAD. MRI was shown to be a good method for tissue characterization and viability assessment, and to be significantly correlated with MCE. RT-MCE offers the advantages of being a relatively simple and non-irradiant technique over SPECT and PET. Therefore, RT-MCE can be a useful tool to assess tissue perfusion and detect myocardial viability. Dedicated software has been developed to quantitatively analyze RT-MCE data, improving its accuracy and objectivity.

Our study illustrated the possibilities and limits of very low power MCE to assess contrast replenishment after transient bubble destruction in real-time. A very few studies reported the relationship between RT-MCE and RT-MCE combined with LD-DSE. We used RT-MCE combined with LD-DSE to improve the accuracy of viable myocardium identification.

Associating semi-quantitative RT-MCE with LD-DSE improved specificity. Quantitative RT-MCE had higher sensitivity and specificity than semi-quantitative RT-MCE for the detection of viable myocardium. When quantitative RT-MCE was combined with LD-DSE, the specificity of A and A × β was similar to those of quantitative RT-MCE, but their sensitivity was even higher.
and the sensitivity of $\beta$ was comparable to that of quantitative RT-MCE, with even higher specificity. This may be due to the fact that these indices reflected the dobutamine-induced increase in coronary artery blood flow. RT-MCE is a promising method for the noninvasive detection of viable myocardium because of its excellent spatial and temporal resolution, portability, widespread availability, and relatively low cost. Several factors may affect the accuracy of RT-MCE in detect-
ing viable myocardium. First, CAD patients with impaired left ventricular systolic function often show islands of viable myocardium surrounded by fibrotic or necrotic tissue. Second, unrecognized myocardial infarction is common in patients with CAD. Nonviable segments do not improve functionally after revascularization, and this echocardiographic finding may be very useful in detecting viable myocardium during routine clinical practice.

Our patients showed improved LVEF after PCI, demonstrating that increasing coronary blood flow allowed for better LVEF. RT-MCE also showed improved myocardial perfusion and quantitative RT-MCE provided better sensitivity and specificity. The motion of each segment was observed by routine echocardiography at 1, 3, and 6 months after PCI, enabling the detection of those segments of viable myocardium that recovered slowly. Dobutamine is an adrenoreceptor agonist, and low-dose dobutamine could improve myocardial blood flow by dilating feeding arteries, resulting in better contrast perfusion. In our study, the sensitivity and specificity of quantitative RT-MCE with LD-DSE were better than RT-MCE or LD-DSE alone in detecting viable myocardium, and the variable $A \times \beta$ of RT-MCE with LD-DSE offered the best sensitivity while variable $\beta$ with LD-DSE offered the best specificity.

Large-scale studies on 26,774 patients have demonstrated the value of RT-MCE for the detection of viable myocardium. It demonstrated that RT-MCE with low-dose dobutamine was safe and feasible in detecting viable myocardium. A recent study has demonstrated sensitivity and specificity of quantitative RT-MCE in detecting viable myocardium to be 83.0%, 80.2%, 84.9% and 84.5%, 74.6%, 79.5% for $A$, $\beta$, and $A \times \beta$, respectively. The present study showed that, associated or not with LD-DSE, quantitative RT-MCE yielded higher sensitivity and specificity than semi-quantitative RT-MCE in detecting viable myocardium. Overall, combining RT-MCE with LD-DSE can improve the sensitivity and specificity in detecting viable myocardium.

### Study Limitations

In our study, intravenous injection was continued until all images had been acquired, allowing relatively stable contrast concentration to be maintained during the image acquisition period. This may result in the lack of significant differences in plateau $A$ between baseline and under stress. There was a large proportion of diabetes mellitus patients in our study, probably because of the small sample size. We chose to evaluate the diagnostic ability of RT-MCE in prediction of viable myocardium assessed by repeated echocardiography and did not correlate to a reference perfusion method as SPECT.

### CONCLUSIONS

Our results indicated that RT-MCE could be used as an effective measure to detect viable myocardium. $A$, $\beta$, and $A \times \beta$ derived from low-power RT-MCE can accurately detect viable myocardium in selected patients. LD-DSE was safe and easy to use and could improve the value of RT-MCE for the detection of viable myocardium. The sensitivity and specificity of quantitative RT-MCE analysis were higher than semi-quantita-
tive RT-MCE. However, this technique is still limited by imaging artifacts and time-consuming analysis. A more robust contrast detection technique and simplified data analysis and display are required to increase clinical applicability, and different RT-MCE techniques need to be compared in larger scale studies.

REFERENCES


