Accuracy of Dipyridamole Myocardial Contrast Echocardiography for the Detection of Residual Stenosis of the Infarct-Related Artery and Multivessel Disease Early After Acute Myocardial Infarction

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OBJECTIVES
We aimed to evaluate the ability of vasodilator myocardial contrast echocardiography (MCE) to detect significant infarct-related artery (IRA) stenosis and multivessel disease (MVD) after thrombolysis.

BACKGROUND
The detection of residual IRA stenosis subtending significant viable myocardium and the identification of MVD may help to triage patients who may benefit from mechanical revascularization after acute myocardial infarction (AMI) and thrombolysis.

METHODS
Patients with AMI underwent low-power MCE at rest and after dipyridamole stress during SonoVue infusion seven to 10 days after thrombolysis.

RESULTS
Of the 73 patients, 61 demonstrated significant myocardial viability, of whom 57 (93%) showed significant IRA stenosis. Sensitivities to detect >50% IRA stenosis and MVD were 88% and 72%, respectively. The accuracy of detecting significant coronary stenosis in the anterior (left anterior descending coronary artery) versus inferoposterior (right coronary artery/left circumflex artery) circulation was similar for both IRA (85% vs. 91%) and remote territories (91% vs. 81%). Quantitative peak contrast intensity (p = 0.02), microbubble velocity (p < 0.0001), and myocardial blood flow (p < 0.0001) were significantly lower in patients with significant coronary stenosis during dipyridamole compared with rest. Only beta reserve discriminated various grades of coronary stenosis.

CONCLUSIONS
Use of MCE accurately predicted significant IRA stenosis and MVD after thrombolysis. This information is valuable for identifying patients who may benefit from mechanical revascularization. (J Am Coll Cardiol 2004;43:2247–52) © 2004 by the American College of Cardiology Foundation

Despite successful thrombolysis, complete patency of the infarct-related artery (IRA) is not always achieved in patients after acute myocardial infarction (AMI) (1). Residual IRA stenosis is predictive of an adverse outcome in patients with jeopardized myocardium and inducible ischemia (2). The presence of multivessel disease (MVD) further adversely affects the outcome (3). Thus, patient outcome may be improved by the early detection of jeopardized viable myocardium in the infarct zone and detection of MVD (2,3). Myocardial contrast echocardiography (MCE) utilizing an intravenous contrast agent that traverses the microvasculature has been shown to accurately assess myocardial viability at rest (4) and flow-limiting coronary artery stenosis during vasodilator stress (5). Thus, the aim of the study was to determine the accuracy of vasodilator MCE early after AMI to detect the presence of flow-limiting coronary artery disease (CAD) in the IRA and non-IRA territory.

METHODS

Study design. Consecutive hemodynamically stable and asymptomatic patients were enrolled after their first presentation of ST-segment elevation AMI and thrombolysis. All patients gave written, informed consent. The local Institutional Review Board approved the protocol. Dipyridamole MCE was performed at a mean of 7 ± 2 days after thrombolysis. All patients underwent coronary angiography before hospital discharge, independent of the results of the MCE study. All images were interpreted by an observer who was unaware of the clinical, electrocardiographic (ECG), and angiographic data.

Myocardial contrast echocardiography. The MCE study was performed in the apical four-, two-, and three-chamber views, using a low-power technique at a mechanical index of 0.1 after the assessment of systolic wall thickening, with tissue harmonic imaging (SONOS 5500, Philips Medical Systems, Best, the Netherlands). SonoVue (Bracco Research SA, Geneva, Switzerland), which consists of microbubbles (mean diameter of 2.5 μm) filled with sulfur hexafluoride, an inert gas, stabilized by a phospholipid monolayer, was infused at 50 to 70 ml/h using Vueject (BR-INF 100, Bracco Research SA). During imaging at rest, end-systolic frames up to 15 cardiac cycles after
microbubble destruction (mechanical index of 1.7) were digitally captured in each view (3 sequences in each). Stress MCE images were similarly acquired 1 min after dipyridamole administration (0.56 mg/kg over 4 min).

**Qualitative MCE.** A semi-quantitative contrast scoring system (previously validated) was used following a destructive pulse: 2 = homogeneous opacification; 1 = reduced or heterogeneous opacification; 0 = minimal or absent contrast opacification utilizing the 16-segment left ventricular model (6). Nine segments were assigned to the left anterior descending coronary artery (LAD; anterior) and seven to the right coronary artery/left circumflex artery (RCA/LCx; inferoposterior) arterial distributions. Myocardial viability was considered to be absent when no contrast uptake was noted transmurally at rest, even after 15 cardiac cycles following a destructive pulse (6). A reversible perfusion defect was considered to be present when myocardial replenishment was incomplete 1 s after destructive imaging following vasodilator stress (5). For the IRA territory, only patients with significant myocardial viability (i.e., at least 20% of segments with homogeneous contrast enhancement in the IRA territory) were assessed (6), whereas MVD was assessed in all patients.

**Quantification of MCE.** Regions of interest were placed across the entire thickness of the myocardium in the four apical segments, mid-anterior septum, and mid-anterior segment pertaining to the anterior coronary circulation and in the mid-inferior, mid-posterior, and mid-lateral segments pertaining to the posterior circulation at rest and stress. The QLab software (Philips Medical Systems) automatically constructed background-subtracted plots of peak myocardial contrast intensity, A (representing capillary blood volume), versus pulsing intervals, from which the slope of the replenishment curve depicting mean microbubble velocity, beta reserve, and myocardial blood flow (MBF) (A × beta) (7) were derived. Coronary flow reserve (CFR) (i.e., stress MBF/rest MBF) and beta and A reserve were calculated.

**Coronary angiography.** The IRA was identified on the basis of the acute ECG changes and wall thickening abnormality. Significant CAD was defined as the presence of >50% luminal diameter narrowing of one or more major epicardial artery or its major branches. Multivessel CAD was defined as CAD involving both anterior and inferoposterior circulations.

**Statistical analysis.** All categorical variables are expressed as percentages, and continuous variables as the mean value ± SD. The paired t-test was used to compare continuous variables between rest and stress. One-way analysis of variance was used to compare the MCE variables among various grades of stenosis. Receiver-operator characteristic (ROC) curves were plotted to determine the best cut-off values for predicting significant CAD. Sensitivity, specificity, and positive and negative predictive values for detecting significant CAD were also calculated. Accuracy was derived by adding the true positive and negative results and dividing the sum by the total number considered. All statistical tests were two-sided. A value of p < 0.05 was considered significant. Analyze-it software (version 1.62, Leeds, U.K.) was used for analysis.

**RESULTS**

**Patient characteristics.** Of the 80 consecutive patients enrolled, 7 patients did not undergo dipyridamole stress (3 patients were hemodynamically unstable and 4 had bronchospasm). The clinical variables of the 73 patients are shown in Table 1. Of the 61 patients demonstrating 50% luminal diameter narrowing of one or more major epicardial artery or its major branches. Multivessel CAD was defined as CAD involving both anterior and inferoposterior circulations.

**Table 1.** Patient Characteristics (n = 73)

<table>
<thead>
<tr>
<th>Age (yrs)</th>
<th>Males</th>
<th>Diabetes</th>
<th>Hypertension</th>
<th>Smoking</th>
<th>Hypercholesterolemia</th>
<th>Family history of coronary disease</th>
<th>Anterior/inferior infarcts</th>
<th>Q-wave infarcts</th>
<th>Peak creatine kinase (IU/l)</th>
<th>Time to thrombolysis (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>61 ± 10</td>
<td>57 (78%)</td>
<td>21 (29%)</td>
<td>25 (34%)</td>
<td>30 (41%)</td>
<td>34 (47%)</td>
<td>23 (32%)</td>
<td>51 (70%)/22 (30%)</td>
<td>53 (73%)</td>
<td>1,542 ± 1,165</td>
<td>184 ± 110</td>
</tr>
</tbody>
</table>

Data are presented as the mean value ± SD or number (% of patients).

**Table 2.** Accuracy of Myocardial Contrast Echocardiography to Detect Residual Infarct-Related Artery Stenosis (>50%)

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
<th>Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>88%</td>
<td>75%</td>
<td>98%</td>
<td>30%</td>
<td>87%</td>
</tr>
<tr>
<td>LAD (n = 39)</td>
<td>86%</td>
<td>75%</td>
<td>97%</td>
<td>38%</td>
<td>85%</td>
</tr>
<tr>
<td>RCA/LCx (n = 22)</td>
<td>91%</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
</tbody>
</table>

*All of these 22 patients demonstrated >50% residual stenosis. IRA = infarct-related artery; LAD = left anterior descending coronary artery; LCx = left circumflex artery; NPV = negative predictive value; PPV = positive predictive value; RCA = right coronary artery.
significant myocardial viability, residual IRA stenosis (>50%) was found in 57 (93%), of whom 35 had LAD stenosis. The mean IRA diameter stenosis was 89.7%. The remote non-IRA demonstrated significant CAD in 32 patients (44%) (21 in the LAD and 11 in the RCA/LCx). No significant differences in heart rate or blood pressure were noted after dipyridamole administration. No serious adverse events occurred.

Detection of IRA stenosis and MVD (Tables 2 and 3). Myocardial contrast echocardiography detected IRA stenosis and MVD in 50 (88%) of the 57 patients and 23 (72%) of the 32 patients, respectively. It correctly detected the absence of IRA stenosis and MVD in 3 of the 4 (75%) and 38 (93%) of the 41 patients, respectively. The sensitivity of MCE showed a trend toward an increase with increasing severity of stenosis, both for IRA and remote non-IRA (Fig. 1). Detection of CAD in the anterior and posterior circulations was similar.

Quantitative MCE (Fig. 2). Peak contrast intensity (dB), beta (dB/s), MBF (dB²/s) were significantly lower (p < 0.001, p < 0.0001, and p < 0.0001, respectively) during stress (8.3 ± 2.3, 0.3 ± 0.1, 2.6 ± 1.5) than at rest (9.3 ± 2.1, 0.7 ± 0.4, 6.0 ± 4.0) in territories with significant CAD. On the other hand, while the peak contrast intensity was similar (p = 0.07) during stress (10.4 ± 1.6) compared with rest, beta (1.6 ± 1.1) and MBF (17.0 ± 5.8) increased significantly (p = 0.003 and p = 0.002, respectively) in vascular territories with <50% stenosis. Although all the three quantitative parameters showed a significant reduction during stress in patients with >50% stenosis compared with patients with no stenosis, only beta discriminated various grades of stenosis. Myocardial blood flow just failed to reach significance (p = 0.07). The areas under the ROC curve for A reserve, beta reserve, and CFR were 0.76, 0.93, and 0.94, respectively (Fig. 3). A CFR of 1.1 and beta reserve of 1.5 provided a sensitivity and specificity of 90% and 87% and 92% and 80%, respectively.

Figure 4 shows examples of MCE at rest and stress. The images demonstrate the ability of both qualitative and quantitative MCE to detect the presence of residual IRA stenosis and MVD.

Intra- and interobserver variability. The intra- and interobserver agreements for qualitative MCE to detect >50% coronary stenosis were 90% (kappa = 0.77) and

<table>
<thead>
<tr>
<th></th>
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<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
<th>Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients (n = 73)</td>
<td>72%</td>
<td>93%</td>
<td>89%</td>
<td>81%</td>
<td>84%</td>
</tr>
<tr>
<td>LAD (n = 22)</td>
<td>82%</td>
<td>100%</td>
<td>100%</td>
<td>85%</td>
<td>91%</td>
</tr>
<tr>
<td>RCA/LCx (n = 51)</td>
<td>64%</td>
<td>93%</td>
<td>88%</td>
<td>77%</td>
<td>81%</td>
</tr>
</tbody>
</table>

Abbreviations as in Table 2.

Figure 1. Sensitivity of myocardial contrast echocardiography to detect varying degrees of coronary stenosis. Solid bars = infarct-related artery; open bars = non-infarct-related artery.

Figure 2. Relationship between quantitative myocardial contrast echocardiography parameters at stress and detection of coronary stenosis: (A) peak contrast intensity; (B) microbubble velocity; (C) myocardial blood flow. *Normal versus coronary artery disease. †Between varying grades of stenosis.
80% (kappa = 0.72), respectively. The intra- and interobserver variabilities for quantitative peak contrast intensity were 8% and 12%; for beta, they were 6% and 9%, respectively.

**DISCUSSION**

This study is the first to evaluate the accuracy of qualitative MCE, supported by quantitation for the detection of residual IRA stenosis and MVD after thrombolysis in stable patients with AMI and no clinical evidence of ischemia. It showed that MCE is accurate in identifying patients with residual IRA stenosis and MVD. Quantitative MCE further accurately discriminated grades of coronary stenosis.

**Mechanism of detection of CAD by MCE.** During continuous infusion of microbubbles, when the entire ultrasound beam is fully replenished with microbubbles, the peak contrast intensity represents the myocardial blood volume.
During dipyridamole administration, the myocardium subtended by <50% coronary luminal diameter stenosis will exhibit a three- to fivefold increase in MBF, whereas those subtended by >50% coronary stenosis will show an attenuated hyperemic response (9). In the absence of any significant increase in heart rate, myocardial blood volume does not increase in normal myocardium, while beta invariably increases (8). Conversely, in the myocardium subtended by...
>50% stenosis, both myocardial blood volume and beta reserve decrease, as compared with myocardium subtended by no stenosis (7). In our study, quantitative parameters exactly mimicked the experimental data.

Although visual assessment of regional differences in video intensity is hampered by differences in the concentration of microbubbles between rest and stress studies, acoustic heterogeneity, and artifacts, assessment of beta is relatively independent of the aforementioned factors. Using visual assessment of beta, we have shown that MCE was accurate in predicting significant IRA and non-IRA stenosis. Furthermore, quantitative beta accurately predicted various grades of coronary stenosis.

**Clinical implications.** Previous noninvasive studies after AMI have shown that identification of jeopardized myocardium at the infarct site and the detection of MVD can risk-stratify stable patients better than coronary angiography alone (3,10). Based on this study, MCE may now be used to triage stable post-AMI patients after thrombolysis to either medical therapy or revascularization.

**Study limitations.** The high prevalence of residual IRA stenosis (probably because only 59% received tissue plasminogen activator; the rest received streptokinase) explains the low negative predictive value of qualitative MCE to detect IRA stenosis and also makes the assessment of specificity less meaningful. Furthermore, this study is applicable mainly in countries where thrombolytic therapy after AMI is the initial intervention of choice rather than percutaneous intervention.

**Conclusions.** Dipyridamole MCE accurately detected residual IRA stenosis and MVD in stable patients early after AMI and thrombolytic therapy and thus may help guide appropriate management.

**REFERENCES**