Noninvasive Evaluation of Coronary Reperfusion by Transthoracic Doppler Echocardiography in Patients With Anterior Acute Myocardial Infarction Before Coronary Intervention

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Background—Transthoracic Doppler echocardiography (TTDE) enables evaluation of distal left anterior descending coronary artery (LAD) flow. The purpose of this study was to test whether TTDE can differentiate coronary reperfusion with Thrombolysis in Myocardial Infarction (TIMI) grade 3 from TIMI grade ≤ 2 in patients with anterior acute myocardial infarction (AMI).

Methods and Results—In 46 consecutive patients with a first anterior AMI in the acute phase before emergent coronary intervention, the presence of antegrade distal LAD flow and its diastolic peak velocity were evaluated by color and pulsed TTDE and compared with TIMI grades by subsequent coronary angiography performed 29 ± 12 minutes later. Nineteen patients had TIMI 0 reperfusion, 4 had TIMI 1, 10 had TIMI 2, and 13 had TIMI 3. Visual antegrade distal LAD flow was present in 22 of the 46 patients. TIMI 2 and 3 reperfusions were both generally visualized by color TTDE. However, peak distal LAD flow velocity by pulsed TTDE was significantly greater in patients with TIMI 3 compared with those with TIMI 2 (40 ± 10 vs 20 ± 6 cm/s, P < 0.0001). The diagnosis of TIMI 3 based on diastolic peak distal LAD flow velocity ≥ 25 cm/s by TTDE had a sensitivity, specificity, and accuracy of 77%, 94%, and 89%, respectively.

Conclusion—TTDE enables noninvasive differentiation of TIMI 3 from TIMI ≤ 2 coronary reperfusion in patients with AMI in the acute phase before emergent coronary intervention. (Circulation. 2003;108:2763-2768.)

Key Words: echocardiography • myocardial infarction • reperfusion

Suboptimal coronary reperfusion with Thrombolysis in Myocardial Infarction (TIMI) grade ≤ 2 in acute myocardial infarction (AMI) adversely affects patient prognosis and requires additional procedures, such as thrombolysis and/or percutaneous coronary intervention (PCI).2–5 Thus, a rapid, noninvasive diagnosis of coronary reperfusion is important for decision making. Although currently available noninvasive tools that evaluate coronary reperfusion, including the resolution of ST-segment elevation and the rapid washout of serum cardiac biomarkers, are accurate,6–9 they are indirect and require serial evaluation requiring 90 minutes to several hours.

Recent advances in transthoracic Doppler echocardiography (TTDE) have enabled the direct evaluation of coronary flow, especially in the distal left anterior descending coronary artery (LAD),10–20 and the culprit lesion of an anterior AMI is proximal to the middle LAD in most patients. Therefore, TTDE can potentially enable direct evaluation of coronary reperfusion at a site distal to the culprit lesion in anterior AMI. We hypothesized that good reperfusion would be associated with less reduction in coronary flow and therefore, would have (1) better antegrade flow visualization by color TTDE and (2) less reduced antegrade flow velocity by pulsed TTDE. Because the feasibility of TTDE to evaluate coronary reperfusion has not been fully investigated, the purpose of the present study was to test this hypothesis by comparing the TTDE findings of distal LAD flow and TIMI grades by angiography in patients with anterior AMI.

Methods

The subjects included 50 consecutive patients with a first anterior AMI. Inclusion criteria were as follows: (1) typical chest pain lasting > 30 minutes and ≤ 12 hours from onset, which was not relieved by standard antianginal therapy; (2) ST-segment elevation > 0.2 mV in precordial leads; and (3) subsequent increase in serum creatine kinase ≥ 2 times the upper limit of normal. Four patients with blood pressure ≤ 80 mm Hg were excluded because of anticipated diffi-
Difficulty in evaluating LAD flow. Consequently, the remaining 46 patients were prospectively enrolled in the study. The institutional committee of Kagoshima City Hospital approved the study protocol. After written, informed consent was obtained, all patients underwent emergent TTDE and subsequent coronary angiography. Intravenous thrombolysis was performed before the TTDE in 14 patients, but no thrombolysis was performed between the emergent TTDE and angiography.

Transthoracic Doppler Echocardiography

Standard 2-dimensional and Doppler echocardiography was performed in the supine or left lateral decubitus position with a digital ultrasound system (HDI-3000, ATL Ultrasound) with a 2- to 3-MHz transducer. After the standard examination, distal LAD flow was evaluated with a 4- to 7-MHz transducer. The transducer was placed at the fourth or fifth intercostal space between the cardiac apex and the parasternal area, and the anterior interventricular groove was visualized in the short-axis view. Then the transducer was rotated to visualize the long axis of the groove, and color TTDE with a Nyquist limit of ±19 to ±24 cm/s was applied to visualize the LAD flow with relatively low velocity; its velocity was measured by pulsed TTDE (Figure 1). Transducer position and direction were adjusted to make the Doppler beam as parallel as possible to LAD flow, and an angle correction was performed. When the distal LAD flow was retrograde by color Doppler or was not visualized within 5 minutes, antegrade LAD flow was considered to be absent, and the TTDE coronary study was discontinued. Studies were recorded on super-VHS videotape. Observers blinded to the patients’ data reviewed the TTDE recordings. As pulsed Doppler parameters of LAD flow, the peak and mean velocity, the velocity time integral, and the deceleration time of diastolic flow velocity were measured with an analyzer incorporated into the ultrasound system. These parameters were calculated for 3 consecutive beats and averaged.

Coronary Angiography

Coronary angiography was performed immediately after the TTDE study by the femoral approach with a 6F standard catheter and an INNOVA 2000 (GE Medical Systems). All patients received oral aspirin (162 mg), intravenous heparin (5000 U), and intracoronary isosorbide dinitrate (2 mg). Several views of the LAD were digitally acquired, and the minimum lumen diameter of the culprit lesion, the reference vessel diameter, and the percent diameter stenosis were quantified with a commercially available system (Cardiac QCA, GE Medical Systems) with a 6F catheter as the reference. The angiographic TIMI grade was evaluated according to a previous study that used initial coronary angiography. TIMI grade 0 (no perfusion) denoted absent antegrade flow beyond the obstruction; TIMI grade 1 (penetration without perfusion) denoted flow beyond the obstruction but incomplete filling of the distal vessel; TIMI grade 2 (partial perfusion) denoted patent vessels with slow filling and/or slow emptying; and TIMI grade 3 (complete perfusion) denoted normal brisk flow. The angiographic TIMI grade of the LAD was evaluated by using a cardiac review station equipped with a frame counter, as previously described. The frame rate was 30 frames/s. The degree of angiographic collateral circulation was also evaluated by using the Rentrop grading system. Two independent, blinded observers reviewed these angiograms.

Comparison of LAD Flow Velocity Profiles by TTDE and Doppler Guidewire

In 9 patients with TIMI 2 or 3, intracoronary Doppler guidewire (FloWire, Jomed, Inc) was also performed before PCI. Diastolic peak velocity and deceleration time of the distal LAD flow by pulsed TTDE were compared with the values obtained by Doppler guidewire.

Reproducibility

Two observers measured the diastolic peak distal LAD flow velocity in 10 patients to determine interobserver variability. The same observer repeated the measurements to determine intraobserver variability.

Statistical Analysis

The results are expressed as mean±SD. The χ² test was used to compare the incidence of categorical variables. Continuous variables...
were compared between 2 groups by the Mann-Whitney U test. The ability of peak LAD flow velocity to indicate TIMI 3 was analyzed by receiver operating characteristic curves. Statistical analysis was performed with StatView software (Abacus Concepts, Inc). A value of $P < 0.05$ was considered significant.

## Results

### Patient Characteristics

The patients’ profiles are summarized in Table 1. Of the 46 patients, 19 (41%) had TIMI 0, 4 (9%) had TIMI 1, 10 (22%) had TIMI 2, and 13 (28%) had TIMI 3 reperfusion. The culprit lesion was proximal to the middle LAD in all patients.

<table>
<thead>
<tr>
<th>Risk factors, n (%)</th>
<th>Total (n=46)</th>
<th>0 (n=19)</th>
<th>1 (n=4)</th>
<th>2 (n=10)</th>
<th>3 (n=13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>18 (39)</td>
<td>6 (32)</td>
<td>2 (50)</td>
<td>3 (30)</td>
<td>7 (54)</td>
</tr>
<tr>
<td>Hypercholesterolemia (&gt;220 mg/dL)</td>
<td>16 (35)</td>
<td>5 (26)</td>
<td>2 (50)</td>
<td>6 (60)</td>
<td>3 (23)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>17 (37)</td>
<td>8 (42)</td>
<td>0 (0)</td>
<td>5 (50)</td>
<td>4 (31)</td>
</tr>
<tr>
<td>Current smoking</td>
<td>23 (50)</td>
<td>10 (53)</td>
<td>1 (25)</td>
<td>6 (60)</td>
<td>6 (46)</td>
</tr>
<tr>
<td>Time from onset to TTDE, h</td>
<td>4.8±3.0</td>
<td>4.3±2.6</td>
<td>5.9±3.9</td>
<td>4.7±2.8</td>
<td>5.2±3.6</td>
</tr>
<tr>
<td>Time from TTDE to angiography, min</td>
<td>29±12</td>
<td>27±8</td>
<td>26±6</td>
<td>25±6</td>
<td>35±18</td>
</tr>
<tr>
<td>Peak CPK, IU/L</td>
<td>3600±2920</td>
<td>5160±2970</td>
<td>3745±2268</td>
<td>2369±3112</td>
<td>2344±1896</td>
</tr>
<tr>
<td>Q-wave infarction, n (%)</td>
<td>31 (67)</td>
<td>17 (89)*</td>
<td>4 (100)*</td>
<td>6 (60)</td>
<td>4 (31)</td>
</tr>
<tr>
<td>IVCT, n (%)</td>
<td>14 (30)</td>
<td>3 (16)*</td>
<td>1 (25)</td>
<td>4 (40)</td>
<td>6 (46)</td>
</tr>
<tr>
<td>Segment 6/segment 7</td>
<td>26/20</td>
<td>11/8</td>
<td>3/1</td>
<td>6/4</td>
<td>6/7</td>
</tr>
<tr>
<td>RD, mm</td>
<td>2.9±0.5</td>
<td>2.9±0.5</td>
<td>2.8±0.1</td>
<td>2.8±0.6</td>
<td>2.9±0.5</td>
</tr>
<tr>
<td>MLD, mm</td>
<td>0.4±0.7</td>
<td>0*</td>
<td>0.1±0.1*</td>
<td>0.2±0.2*</td>
<td>1.4±0.9</td>
</tr>
<tr>
<td>DS, %</td>
<td>88</td>
<td>100*</td>
<td>99±0.4*</td>
<td>93±7*</td>
<td>57±27</td>
</tr>
<tr>
<td>CTFC</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>52±13*</td>
<td>23±6</td>
</tr>
<tr>
<td>Collateral grade 0–1</td>
<td>43</td>
<td>16</td>
<td>4</td>
<td>10</td>
<td>13</td>
</tr>
<tr>
<td>Collateral grade 2</td>
<td>3</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

BMI indicates body mass index; HR, heart rate; SBP, systolic blood pressure; CPK, creatine phosphokinase; IVCT, intravenous coronary thrombolysis; RD, reference diameter; MLD, minimal lumen diameter; DS, diameter stenosis; and CTFC, corrected TIMI frame count. Other abbreviations are as defined in text.

* $P < 0.05$ vs TIMI 3.

Compared with patients with TIMI 0 to 2, patients with TIMI 3 had a significantly less severe percent diameter stenosis and a greater minimum lumen diameter. The corrected TIMI frame count of patients with TIMI 2 and 3 was, by definition, significantly different.

### Visual LAD Flow by Color TTDE Versus Angiographic TIMI Grade

By color TTDE, visual antegrade distal LAD flow was present in 22 of the 46 patients (Table 2). Of the 22 patients with visual LAD flow, 19 had TIMI 2 or 3 flow; however, the

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**TABLE 1. Patient Characteristics**

<table>
<thead>
<tr>
<th>TIMI Grade</th>
<th>Total (n=46)</th>
<th>0 (n=19)</th>
<th>1 (n=4)</th>
<th>2 (n=10)</th>
<th>3 (n=13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>67±13</td>
<td>69±12</td>
<td>66±13</td>
<td>63±15</td>
<td>67±14</td>
</tr>
<tr>
<td>Male/female</td>
<td>33/13</td>
<td>11/8</td>
<td>4/0</td>
<td>9/1</td>
<td>9/4</td>
</tr>
<tr>
<td>BM, kg/m²</td>
<td>23.1±2.9</td>
<td>23.3±3.0</td>
<td>23.7±2.9</td>
<td>22.2±2.5</td>
<td>23.2±3.2</td>
</tr>
<tr>
<td>HR, bpm</td>
<td>85±15</td>
<td>81±13</td>
<td>83±12</td>
<td>82±17</td>
<td>89±15</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>128±17</td>
<td>121±14</td>
<td>133±19</td>
<td>130±16</td>
<td>127±19</td>
</tr>
</tbody>
</table>

**TABLE 2. Color and Pulsed TTDE Findings vs Angiographic TIMI Flow Grade**

<table>
<thead>
<tr>
<th>TIMI Grade</th>
<th>Total (n=46)</th>
<th>0 (n=19)</th>
<th>1 (n=4)</th>
<th>2 (n=10)</th>
<th>3 (n=13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visual distal LAD flow (+)</td>
<td>22</td>
<td>3</td>
<td>0</td>
<td>8</td>
<td>11</td>
</tr>
<tr>
<td>Visual distal LAD flow (-)</td>
<td>24</td>
<td>16</td>
<td>4</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Visual flow (+) and PV ≥25 cm/s</td>
<td>12</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>Visual flow (-) or PV &lt;25 cm/s</td>
<td>34</td>
<td>19</td>
<td>4</td>
<td>8</td>
<td>3</td>
</tr>
</tbody>
</table>

PV indicates peak velocity. Other abbreviations are as defined in text.
remaining 3 patients had TIMI 0 flow at the time of angiography. Of the 24 patients without visual LAD flow by TTDE, 16 had TIMI grade 0, whereas the other 8 had TIMI 1 to 3. Therefore, both TIMI 2 and 3 flows were generally visualized as antegrade flow by color TTDE, whereas TIMI 0 and 1 flows were usually not visualized. The diagnosis of TIMI 2 or 3 based on the presence of antegrade distal LAD flow by color TTDE had a sensitivity, specificity, and accuracy of 83%, 87%, and 85%, respectively. However, the diagnosis of TIMI 3 by the same criteria was only fair, with a sensitivity, specificity, and accuracy of 85%, 67%, and 72%, respectively.

Distal LAD Flow Velocity by Pulsed TTDE Versus Angiographic TIMI Grade
The distal LAD flow velocity was measured by pulsed TTDE in all 22 patients who had visual flow by color Doppler. In the 22 patients, there were no differences between patients with TIMI ≤2 and TIMI 3 in heart rate (81±14 vs 87±14 bpm; NS) and systolic or diastolic blood pressure (systolic, 128±15 vs 126±20 mm Hg, NS; diastolic, 77±12 vs 76±10 mm Hg, NS). However, patients with TIMI 3 had a significantly higher diastolic peak distal LAD flow velocity (P<0.001), a higher mean velocity (P=0.0002), a greater velocity time integral (P=0.0004), and a shorter diastolic deceleration time (P<0.05) compared with patients with TIMI ≤2 (Figure 2). No patient had a “no-reflow” pattern characterized by an early diastolic preserved peak velocity and a very short diastolic deceleration time. Diastolic peak flow velocity of the LAD showed a significant inverse correlation with the percent diameter stenosis of the culprit lesion by quantitative coronary angiography (Figure 3). On the basis of receiver operating characteristic curve analysis, the optimal cutoff point of diastolic peak velocity to differentiate TIMI 3 from TIMI 0 to 2 was 25 cm/s. The diagnosis of TIMI 3 based on the presence of visual antegrade distal LAD flow with a diastolic peak velocity ≥25 cm/s by TTDE had a sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of 77%, 94%, 83%, 91%, and 89%, respectively (Table 2). Figure 4 shows representative patients with TIMI 2 and 3 reperfusions with smaller and larger visual color flow signals and slower and faster diastolic peak velocities, respectively.

Comparison of Distal LAD Flow Velocity Profiles by TTDE and Doppler Guidewire
The diastolic peak velocity and diastolic deceleration time of LAD flow by TTDE had a significant correlation with the values by Doppler guidewire (P<0.001; Figure 5).

Reproducibility of Measurements
The interobserver variability of peak diastolic LAD flow velocity was 1.1±0.9 cm/s, or 4±4% of the mean value, and the intraobserver variability was 0.8±1.0 cm/s, or 3±4% of the mean value.

Discussion
This study demonstrated that TTDE enables the noninvasive differentiation of angiographic TIMI 3 from TIMI ≤2 in patients with anterior AMI in the acute phase before PCI. The presence of antegrade distal LAD flow by color TTDE generally indicates either TIMI 2 or 3 flow and is therefore, not specific to TIMI 3. On the other hand, in TIMI 3 patients, distal LAD flow velocity was preserved or even increased compared with previously reported normal values (23±5 cm/s), whereas the flow velocity in patients with TIMI ≤2 tended to be reduced. Consequently, in most cases, diastolic peak distal LAD flow velocity ≥25 cm/s by pulsed TTDE indicates TIMI 3, whereas flow velocity <25 cm/s indicates TIMI ≤2 flow. Therefore, the current study demonstrated a novel, noninvasive, nonprovocative tool that differentiates anterior AMI patients with and without preserved coronary perfusion and thus, determines which patients need additional acute-phase procedures before emergent PCI.

Relation to Previous Studies
Since the initial coronary flow study with TTDE by Fusejima, TTDE has been applied to evaluate many aspects of coronary
pathophysiology, including epicardial coronary stenosis, coronary vasodilatory function, coronary obstruction with collateral flow, and intramyocardial small coronary artery flow dynamics. The present study confirmed the feasibility of TTDE to evaluate coronary pathophysiology and further demonstrated its utility to differentiate TIMI 0 to 2 and TIMI 3 reperfusion in patients with anterior AMI.

Previous intracoronary Doppler guidewire studies, whose results are comparable to ours, showed that the distal coronary flow velocity is preserved or even increased in patients with TIMI 3, with a diastolic peak velocity of $36 \pm 11$ cm/s, whereas flow velocity is reduced in patients with TIMI 0 to 2.23,24 The present study confirms these previous results with a noninvasive method.

In this study, before PCI, no patient demonstrated a typical no-reflow pattern, characterized by preserved diastolic flow velocity and a very shortened diastolic deceleration time. This enabled the preserved diastolic peak distal LAD flow velocity to indicate TIMI 3. These results confirm previous proposals that (1) mechanical dilation by PCI contributes to the distal embolism of thrombus and plaque components and causes no reflow, which explains why no reflow before PCI is rare, and (2) TIMI 2 before PCI is caused by low flow velocity owing to severe coronary stenosis and not by no reflow. Therefore, for most patients before PCI, TIMI 3 can be diagnosed on the basis of a higher peak diastolic LAD flow velocity. However, no reflow can develop in a small number of patients before PCI, with a potential for finding TIMI 2 flow with a preserved diastolic peak velocity even before the PCI. In such patients, the current criteria could present a problem, and in such cases, the diastolic deceleration time or the velocity time integral will likely be useful in differentiating TIMI 3 from TIMI 2.

Limitations
In the present study, patients with right coronary or left circumflex artery disease were excluded. In addition, in the emergent situation, the LAD flow signals by TTDE were occasionally suboptimal. We did not use contrast agents to enhance Doppler signals, because the use of contrast agents is not permitted in patients with AMI in Japan. Thus, further technical innovations of TTDE with contrast agents are expected to expand the feasibility of evaluating the LAD and other vessels.

Inclusion to the present study was limited to patients with an anterior AMI that had developed within 12 hours, with potential need for emergent PCI. The preservation of distal LAD flow velocity might be related to a hyperemic response after reperfusion, which can potentially last for several hours. Therefore, the current method might not be feasible many hours after reperfusion or in patients with AMI that developed >12 hours earlier.

Although the present study demonstrated the feasibility of TTDE to differentiate TIMI 0 to 2 from TIMI 3 reperfusion in patients with anterior AMI before PCI, the criterion of diastolic peak flow velocity $\geq 25$ cm/s needs prospective validation in a larger number of patients. In addition, there were some discrepancies between the reperfusion evaluated by TTDE and that by angiography. One explanation might be the dynamic nature of coronary reperfusion. Recanalization or reocclusion in the culprit lesion might have developed between TTDE and angiography. Yet another possibility is the technical difficulty of detecting distal LAD flow with TTDE. The relatively low sensitivity of TTDE to diagnose TIMI 3 might reflect this technical difficulty. Nevertheless,
the purpose of the present study was achieved by demonstrating the feasibility of TTDE to differentiate TIMI 0 to 2 and TIMI 3 flow in patients with anterior AMI in the acute phase before emergent PCI.

Acknowledgments
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References
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