Detection of TIMI-3 Flow Before Mechanical Reperfusion With Ultrasonic Tissue Characterization in Patients With Anterior Wall Acute Myocardial Infarction

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Background—Spontaneous coronary reperfusion with TIMI-3 flow is associated with favorable clinical outcomes in patients with acute myocardial infarction (AMI). We investigated the ability of analyzing cardiac cycle-dependent variation of myocardial integrated backscatter (IBS) for predicting spontaneous reperfusion in anterior AMI.

Methods and Results—We recorded IBS images on admission in 104 patients with first anterior wall AMI and subsequently performed coronary angiography and coronary intervention. We measured the cyclic variation of IBS within the infarct zone and expressed its magnitude as phase-corrected magnitude (PCM) by giving positive and negative values when it showed synchronous and asynchronous contraction, respectively. Twenty-three patients showing TIMI-3 flow at the initial coronary angiography had smaller peak creatine kinase value than 57 patients with initial TIMI-0/1 flow (864±961 versus 2358±1757 IU/L; P=0.0002) and better percent wall thickening within risk area (36.1±15.1% than those with TIMI-2 (16.7±12.8%, P<0.0001) or TIMI-0/1 (5.1±11.6, P<0.0001). The patients with initial TIMI-3 had higher PCM (2.7±1.3 dB) than those with TIMI-2 (−0.3±2.2 dB, P<0.0001) or those with TIMI-0/1 (−1.1±2.4 dB, P<0.0001). Using PCM=1.0 dB as the cutoff point, PCM detected TIMI-3 flow with 95.7% sensitivity and 90.1% specificity. Multivariable logistic regression analysis revealed that only PCM is an independent predictor for spontaneous reperfusion among the hemodynamic, echocardiographic, and electrocardiographic variables.

Conclusions—Analysis of myocardial IBS could detect spontaneous reperfusion noninvasively in the emergent stage of anterior AMI. (Circulation. 2003;107:3159-3164.)

Key Words: echocardiography ▪ myocardial infarction ▪ reperfusion

Early achievement of Thrombolysis in Myocardial Infarction trial (TIMI) grade 3 flow in infarct related artery plays a crucial role to obtain favorable outcomes after acute myocardial infarction (AMI). The patients with spontaneous TIMI-3 flow show better functional and clinical outcomes after percutaneous coronary intervention (PCI) than those without it. Thus, patency of infarct related artery at the early stage of AMI has an impact on the clinical course after reperfusion.

The interaction between ultrasound and tissue has been studied to characterize the histological state of tissue as the ultrasonic tissue characterization. Measuring quantitated integrated backscatter (IBS) from unprocessed radiofrequency signal, which is usually processed and displayed on the traditional echocardiographic images, is a unique approach to assess coronary perfusion and myocardial viability. Myocardial IBS shows cardiac cycle-dependent variation (CV), and it blunts during coronary occlusion and recovers much faster than wall motion after coronary reperfusion. We previously reported that the synchronous CV after coronary reperfusion implies adequate tissue perfusion and viable myocardium in the patients with AMI. In the present study, we investigated whether analyzing CV of IBS could detect spontaneous reperfusion in the patients with first, anterior wall AMI before angiography.

Methods

Study Population

Between January 2000 and July 2001, 122 consecutive patients were admitted to our hospital within 24 hours of the symptom onset and diagnosed as having first anterior wall AMI. Diagnosis of AMI was made if the patient showed at least 2 of the following: prolonged chest pain (>30 minutes), ST segment elevation ≥2 mm in at least 2 precordial electrocardiographic leads, and ≥3-fold increase in serum creatine kinase (CK)-MB level. Location of infarct area was confirmed with ECG or with echocardiography in each patient. Eighteen patients were excluded because of inadequate echocardi-
Protocol After the admission, we recorded a 12-lead ECG and monitored the multiplane echocardiograms with a commercially available echocardiograph (SONOS 5500, Philips Medical Systems). We determined the risk segments as myocardial segments showing dyskinesia, akinesia, or severe hypokinesia in this baseline study. Then we recorded 2D IBS images of the short-axis view at the mid-papillary muscle level using acoustic densitometry package and stored consecutive 60 frames (30 frames/s) on the magnetic optical disc.  

Analysis of IBS Data Two independent observers blinded to patients’ data evaluated wall motion in echocardiogram on admission and at the follow-up study. Percent systolic wall thickening (%SWT) within risk area and at remote normal segments was determined on short-axis image as the difference in the wall thickness at end systole and at end diastole divided by end diastolic thickness.

Analysis of Echocardiographic Data Two independent observers blinded to patients’ data evaluated wall motion in echocardiogram on admission and at the follow-up study. Percent systolic wall thickening (%SWT) within risk area and at remote normal segments was determined on short-axis image as the difference in the wall thickness at end systole and at end diastole divided by end diastolic thickness.

Analysis of IBS images. Left, The ovoid region of interest (Arrow) was placed at the center of the segments at risk to reconstruct a curve of IBS versus time. Right, The magnitude of cyclic variation of IBS was determined as the difference between the minimal and maximal values in a cardiac cycle (A). The interval from the upstroke of QRS complex to the nadir of the cyclic variation (B) was divided the value by QT interval (C) to determine the normalized delay.

≤1.2, the phase-corrected magnitude is the same as the measured magnitude value.

Analysis of Coronary Angiography Two experienced interventional cardiologists blinded to patients analyzed CAG and determined patency of culprit lesion before PCI with TIMI flow grade. If TIMI flow grade ≥2 was observed in left anterior descending coronary artery (LAD), TIMI frame count was determined as the frame count required for dye to first opacify a standard distal landmark.  

Collateral channels were graded according to the report by Rentrop, and good collateral was defined as grade 2 or 3.

Analysis of Electrocardiography An experienced cardiologist blinded to patients’ data analyzed ECG recorded on hospital admission and just before CAG. Resolution of more than 70% of ST elevation in the precordial leads was considered as the electrographic signs of spontaneous reperfusion.

Reproducibility of Data We determined intraobserver and interobserver variability of measuring the magnitude and normalized delay value of cyclic variation of IBS by measuring the 2 variables in a randomly selected 10 records twice by the same observer and by 2 independent observers, respectively. Intraobserver and interobserver variabilities of the magnitude were 4.2±4.0% and 5.1±4.2% (absolute difference), respectively. Intraobserver and interobserver variabilities of normalized time delay were 4.2±3.2% and 4.7±2.4% (absolute difference), respectively.

Statistics All data are expressed as mean±SD. We made multiple comparisons by one-way ANOVA, and significance of difference was calculated with Scheffe’s F test. To analyze predictive value of variables, we constructed receiver operating characteristic curves and determined the suitable cutoff point where sensitivity is as nearly equal to specificity as possible. Multivariate logistic regression analysis was used to identify independent predictors for spontaneous recanalization. Differences were considered significant at P<0.05. Statistical analysis was performed with StatView 5.0 (SAS Institute).

Results Patients’ Characteristics Among the 104 study patients (mean age, 63±12 years; range, 40 to 91 years), 78 patients were men. The culprit...
lesion was at the proximal portion of LAD in 58 patients (55.8%) and at the middle portion in 46 patients. The mean time from the symptomatic onset to CAG was 7.4±5.4 hours, and peak creatine kinase level was 2142±1581 IU/L.

**Initial TIMI Flow Grade**

Among the 104 study patients, 23 patients (22.1%) showed TIMI-3 flow at the initial CAG. TIMI-2 was observed in 18 patients (17.3%), TIMI-1 in 6 patients (5.8%), and TIMI-0 in 57 patients (54.8%). TIMI frame count in TIMI-3 flow was significantly smaller than that in TIMI-2 flow (16±4 versus 37±10 frames, respectively; \(P<0.0001\)). The initial TIMI-3 and TIMI-2 groups had significantly lower pulmonary capillary wedge pressure (PCWP) than the TIMI-0/1 group, but no differences were observed between these 2 subsets (Table 1).

We performed PCI in all patients except for 1 patient with initial TIMI-2 flow and 6 with initial TIMI-3 and obtained successful coronary recanalization in all but 2 patients. After PCI, TIMI-3 flow was observed in 47 of 63 patients (74.6%) with initial TIMI-0/1, in 15 of 18 patients (83.3%) with initial TIMI-2, and in all patients (100%) with initial TIMI-3 flow \((P=0.03\) among the 3 subsets) (Table 1).

Patients with initial TIMI-3 or TIMI-2 flow had significantly lower peak CK and CK-MB values than those with TIMI-0/1 (Table 1), whereas there were no significant differences between the TIMI-3 and the TIMI-2 groups. The patients with initial TIMI-3 flow also had higher %SWT within risk area than the others. At the follow-up study, the initial TIMI-3 group showed significantly higher %SWT within risk area (36.1±15.1%) than the initial TIMI-2 (16.7±12.8%, \(P<0.0001\)) or TIMI-0/1 groups (5.1±11.6, \(P<0.0001\)). The incidence of in-hospital complications was lower in patients with initial TIMI-3 (4.3%) than those with initial TIMI-2 (27.8%) and with initial TIMI-0/1 (36.5%), although the difference did not reach the statistical significance. Two patients who died during hospital stay showed initial TIMI-0 flow.

**Prediction of Spontaneous Coronary Reperfusion**

Figure 2 shows waveforms of CV on admission. CV within the infarct zone shows synchronous contraction in the patient with initial TIMI-3 flow (left). In the patients with initial TIMI-0, CV showed its nadir in diastole, implying asynchronous contraction (right). Twenty-three patients with initial

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**Table 1. Clinical Characteristics of the Study Patients**

<table>
<thead>
<tr>
<th></th>
<th>All Patients</th>
<th>TIMI-0/1</th>
<th>TIMI-2</th>
<th>TIMI-3</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>104</td>
<td>63</td>
<td>18</td>
<td>23</td>
<td></td>
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<tr>
<td>Age, y</td>
<td>63±12</td>
<td>63±12</td>
<td>64±14</td>
<td>65±13</td>
<td>0.72</td>
</tr>
<tr>
<td>Gender, male/female</td>
<td>78/26</td>
<td>45/18</td>
<td>13/5</td>
<td>20/3</td>
<td>0.32</td>
</tr>
<tr>
<td>Risk factors</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>48.7</td>
<td>46.0</td>
<td>61.1</td>
<td>43.5</td>
<td>0.60</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>59.6</td>
<td>61.9</td>
<td>55.6</td>
<td>56.5</td>
<td>0.82</td>
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<tr>
<td>Hyperlipidemia, %</td>
<td>26.9</td>
<td>31.7</td>
<td>27.8</td>
<td>13.0</td>
<td>0.46</td>
</tr>
<tr>
<td>Smoking, %</td>
<td>53.8</td>
<td>50.8</td>
<td>61.1</td>
<td>53.8</td>
<td>0.81</td>
</tr>
<tr>
<td>Hemodynamic data</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>130±23</td>
<td>132±23</td>
<td>127±23</td>
<td>128±24</td>
<td>0.54</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>84±15</td>
<td>86±15</td>
<td>80±16</td>
<td>0.47</td>
<td></td>
</tr>
<tr>
<td>PCWP, mm Hg</td>
<td>12±6</td>
<td>14±6</td>
<td>10±7*</td>
<td>8±5‡</td>
<td>0.002</td>
</tr>
<tr>
<td>Cardiac index, L/min per m²</td>
<td>3.6±0.8</td>
<td>3.6±0.9</td>
<td>3.5±0.2</td>
<td>3.6±1.0</td>
<td>0.90</td>
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<tr>
<td>Symptom to CAG time, h</td>
<td>7.7±6.0</td>
<td>7.9±6.6</td>
<td>4.8±2.3</td>
<td>9.4±5.7</td>
<td>0.20</td>
</tr>
<tr>
<td>Proximal culprit, %</td>
<td>55.8</td>
<td>58.7</td>
<td>50.0</td>
<td>52.2</td>
<td>0.75</td>
</tr>
<tr>
<td>Stent implantation, %</td>
<td>45.2</td>
<td>46.0</td>
<td>44.4</td>
<td>43.5</td>
<td>0.98</td>
</tr>
<tr>
<td>TIMI-3 flow after PCI, %</td>
<td>81.7</td>
<td>74.6</td>
<td>83.3</td>
<td>100</td>
<td>0.03</td>
</tr>
<tr>
<td>Peak CK, IU/L</td>
<td>1855±1626</td>
<td>2358±1757</td>
<td>1361±1016†</td>
<td>864±961‡</td>
<td>0.0002</td>
</tr>
<tr>
<td>Peak CK-MB, IU/L</td>
<td>166±128</td>
<td>206±130</td>
<td>97±67‡</td>
<td>86±97</td>
<td></td>
</tr>
<tr>
<td>In-hospital complications, %</td>
<td>17.3</td>
<td>36.5</td>
<td>27.8</td>
<td>4.3</td>
<td>0.12</td>
</tr>
<tr>
<td>Echocardiographic study</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>%SWT: risk area</td>
<td>2.2±6.4</td>
<td>0.6±4.7</td>
<td>0.04±1.1</td>
<td>8.1±9.0*§$</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>%SWT: normal area</td>
<td>46.0±21.2</td>
<td>46.7±23.1</td>
<td>41.2±12.5</td>
<td>47.5±21.3</td>
<td>0.57</td>
</tr>
<tr>
<td>PCM: risk area, dB</td>
<td>-0.1±2.6</td>
<td>-1.1±2.4</td>
<td>-0.4±2.2</td>
<td>2.7±1.3‡</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PCM: normal area, dB</td>
<td>5.7±2.2</td>
<td>5.7±2.4</td>
<td>5.6±1.6</td>
<td>5.6±1.9</td>
<td>0.91</td>
</tr>
<tr>
<td>%SWT at follow-up study</td>
<td>12.7±17.0</td>
<td>5.1±11.6</td>
<td>16.7±12.8‡</td>
<td>36.1±15.1‡</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

\(P\) values for the differences among the TIMI-0/1, -2 and -3 groups. *\(P<0.05\), †\(P<0.02\), and ‡\(P<0.01\) vs TIMI-0/1; §\(P<0.05\), ||\(P<0.01\) vs TIMI-2.
TIMI-3 flow showed significantly higher PCM (2.7±1.3 dB) than those with initial TIMI-2 (−0.3±2.2 dB, P<0.0001) and those with initial TIMI-0/1 (−1.1±2.4 dB, P<0.0001) (Table 1). There were no significant differences in PCM between the initial TIMI-2 and the TIMI-0/1 groups. Among the 81 patients with initial TIMI-0/1 flow, TIMI frame count in LAD also showed a significant correlation with PCM within risk area (R=0.65, P<0.0001; Figure 4). Moreover, PCM was also correlated with TIMI frame count in the 19 patients with both TIMI-2 flow and %SWT=0 (R=0.59, P=0.02). These results suggested that PCM somehow reflected coronary flow independently from residual wall motion.

PCM within risk area also showed a significant but weak correlation with PCWP before CAG (R=0.29, P=0.004). Although a better correlation was observed in the initial TIMI-3 group (R=0.46, P=0.04), no correlation was observed in patients with TIMI-2 (R=0.004, P=0.98) or in those with TIMI-0/1 (R=0.14, P=0.30). No correlations were observed between PCM and other hemodynamic factors. Also there was no correlation between PCM and the elapsed time from symptom onset to CAG.

The receiver-operating characteristic analysis indicated that PCM=1.0 dB was the suitable cutoff point to detect initial TIMI-3 flow (Figure 5). Among 30 patients with PCM >1.0 dB, 22 patients (73.3%) showed TIMI-3 flow, whereas only 1 (1.4%) of 74 patients with PCM <1.0 dB showed TIMI-3 flow. Thus, PCM >1.0 dB before CAG predicted TIMI-3 flow with 95.7% sensitivity and 90.1% specificity. Patients with PCM >1.0 db showed lower peak CK value (1250±1377 versus 2537±1657 IU/L, P=0.0017) and better
%SWT on follow-up study (29.6±17.1 versus 6.7±12.3, \( P < 0.001 \)) than those with PCM \( \leq 1.0 \) db.

ST resolution was observed on ECG in 7 of 23 patients with the initial TIMI-3 (30.4%) and in 10 of 81 patients with initial TIMI-0/1/2 (12.3%, \( P = 0.04 \)), indicating ECG assessed spontaneous TIMI-3 reperfusion with only 30.4% sensitivity and 87.7% specificity.

We performed multivariate logistic regression analysis to determine the independent predictive factors for spontaneous coronary reperfusion using PCM, peak CK-MB, PCWP, %SWT within risk area, and ST resolution as variables. Among these variables, PCM was the only independent predictor for spontaneous coronary reperfusion (Table 2).

### Discussion

We investigated the effects of spontaneous coronary reperfusion on functional and clinical outcomes after AMI and the potential of myocardial IBS for predicting spontaneous reperfusion in the 104 patients with first, anterior wall AMI. Patients showing spontaneous reperfusion with TIMI-3 flow had lower peak CK value and better functional recovery than those with initial TIMI \( \leq 2 \). The patients with initial TIMI-3 had higher PCM in the infarct zone than those showing TIMI-0/1/2 flow. Using 1.0 dB as the cutoff point, PCM detected TIMI-3 spontaneous reperfusion with 95.7% sensitivity and 90.1% specificity. Multivariate logistic regression analysis indicated that PCM is only an independent predictor of spontaneous recanalization among echocardiographic and ECG variables.

#### Cyclic Variation of IBS at the Early Stage of AMI

Recently, Hancock et al.\(^{14}\) reported that CV of IBS measured 90 minutes after thrombolysis detects successful coronary reperfusion in the patients with AMI. The present study demonstrated that spontaneous reperfusion with TIMI-3 flow also could elicit similar quick recovery of CV, whereas TIMI-2 flow was not enough for the recovery of CV. The mechanism of CV of IBS has not been fully understood yet. Prior studies indicated that CV of IBS recovers after ischemia before wall motion recovery.\(^{7-10}\) In the present study, PCM showed weak but significant correlation with %SWT (Figure 3). However, CV was observed even in some of the 42 segments showing no visible wall motion. These results implied that PCM somehow reflects wall motion itself, but it is not the only mechanism of recovery of CV. The lower PCWP in the initial TIMI-3 group and a weak but significant correlation between PCWP and PCM suggested that PCWP also might affect CV, although its effect might be very limited. The significant correlation between PCM and TIMI frame count in LAD in the patients with initial TIMI \( \geq 2 \) flow implied that PCM also could somehow reflect coronary perfusion, though CV could be observed even in some patients with total coronary occlusion. The other possible explanation of presence of CV is that it could reflect intrinsic contraction of sarcomere that might not be enough for visible wall thickening.

The recent study reported that magnitude of CV without phase correction could detect successful reperfusion after thrombolysis.\(^{14}\) However, some segments within risk area showed asynchronous contraction or passive stretch, indicated as negative value in %SWT, and these segments showed highly delay in CV indicated as negative PCM (Figure 3). Previous studies indicated that not only the magnitude of CV but also changes in cyclic phase are important for analysis of ultrasonic tissue characterization.\(^{9,15}\) In the original phase-weighted amplitude, negative value is given to magnitude of CV if delay of phase of cyclic variation (\( \theta \)) is within 90 to 0 degrees, whereas it was multiplied with 60.
−cos(θ) if 0 degrees ≤ θ ≤ 90 degrees. Although this method would reflect the phase delay more accurately than PCM, it is too tedious for the clinical use. PCM is an easier way to assess both magnitude and phase delay of CV at the same time, and our previous studies demonstrated that it could be a good index for coronary reperfusion and myocardial viability. 10,11

Prediction of Spontaneous Reperfusion With PCM

The early detection of spontaneous TIMI-3 reperfusion could be important for clinical decision making after AMI. Although ST resolution in ECG has been used for the assessment of successful coronary reperfusion, it could detect spontaneous reperfusion with only modest accuracy in the present study. It might be because ST resolution takes some time to become apparent, as observed in the case of thrombolysis. 16 Spontaneous reperfusion was associated with significantly better %SWT in the present study. However, multivariate logistic regression analysis revealed that PCM could be an independent predictor for spontaneous reperfusion but not %SWT. As discussed above, PCM reflects not only visible myocardial contraction but also other factors related with coronary reperfusion, which might lead to more sensitive detection of spontaneous reperfusion than %SWT.

Study Limitations

We enrolled the patients who underwent PCI within 24 hours in the present study, and the relatively longer symptom to CAG time (7.7 ± 6.0 hours) might affect the present results. CV of IBS is dependent on the angle between fiber orientation and ultrasonic beam, called anisotropy. 17 We measured CV only in anterior and posterior (control) wall in the short-axis view, in which myocardial fiber is oriented nearly perpendicular to the ultrasound beam, to avoid problems with anisotropy as possible. It is unclear whether the results in the present study could be applied to inferior or lateral wall infarction because of anisotropy. Measurement of CV on apical views might be also useful for detecting coronary reperfusion to reduce anisotropy. 17 The quality of echocardiographic images also could affect analysis of IBS, and approximately 10% of the study patients were excluded because of inadequate echocardiographic images. This method might also not be applicable for the patients having prior myocardial infarction, bundle branch block, paced rhythm, or cardiomyopathy. Moreover, additional prospective studies would be required to validate the cutoff value of 1.0 dB to predict spontaneous recanalization in another patient population.

References

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