Predictive Factors for Development of the No-Reflow Phenomenon in Patients With Reperfused Anterior Wall Acute Myocardial Infarction

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OBJECTIVES
We sought to elucidate the clinical factors related to the development of no-reflow phenomenon after successful coronary reperfusion in patients with an acute myocardial infarction (AMI).

BACKGROUND
Myocardial contrast echocardiography revealed that the no-reflow phenomenon is observed in some patients with a reperfused AMI, and those patients usually have poor functional and clinical outcomes. It is still unknown what clinical factors are related to the development of the no-reflow phenomenon.

METHODS
Myocardial contrast echocardiography was performed 15 min after successful coronary reperfusion therapy in 199 patients with an anterior wall AMI who underwent successful coronary reperfusion with primary coronary angioplasty within 24 h after the onset of AMI. Multiple logistic regression analysis was used to identify independent predictors of the no-reflow phenomenon.

RESULTS
Seventy-nine patients showed the no-reflow phenomenon. Univariate analysis indicated that pre-infarction angina within 48 h before symptom onset, Killip class, Thrombolysis in Myocardial Infarction flow grade 0 on the initial coronary angiogram, the number of abnormal Q-waves and the wall motion score (WMS) on the echocardiogram obtained at hospital admission are related to the no-reflow phenomenon. Multivariate logistic regression analysis revealed that all of these factors, except for Killip class, are independent predictive factors of the no-reflow phenomenon.

CONCLUSIONS
Development of the no-reflow phenomenon is related to the severity of myocardial damage (number of Q-waves), the size of the risk area (WMS) and the occlusion status of infarct-related artery. In addition, ischemic preconditioning (pre-infarction angina) seems to be the factor that attenuates the no-reflow phenomenon. (J Am Coll Cardiol 2001;38:472–7)

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Coronary reperfusion therapy has improved the prognosis of patients with acute myocardial infarction (AMI). However, successful recanalization, as demonstrated by angiography, does not necessarily guarantee adequate myocardial salvage in all patients (1,2). We have used myocardial contrast echocardiography (MCE) to demonstrate that the no-reflow phenomenon is observed in ~30% of patients with a reperfused anterior wall AMI (3). These patients have poor functional recovery and more frequently manifest post-AMI complications, as compared with those with good reflow (4).

Several clinical factors, such as the age of the patient (5), the presence of congestive heart failure (5,6), the time elapsed from the onset of AMI to treatment (5,7), collateral circulation (7,8), pre-infarction angina (9,10) and ST segment re-elevation after coronary reperfusion (11,12), have been reported to affect the functional outcomes and clinical prognoses of patients with AMI. Although these factors may also affect the development of microvascular dysfunction, their relationship to the no-reflow phenomenon remains unknown. In the present study, we compared the clinical, hemodynamic and electrocardiographic (ECG) variables of patients with the no-reflow phenomenon with those of patients without it to derive the predictive factors of the no-reflow phenomenon after a reperfused anterior wall AMI.

METHODS
Study group. Between July 1992 and January 1999, 265 consecutive patients with their first AMI underwent primary percutaneous transluminal coronary angioplasty (PTCA) or stent implantation, or both, of the totally or subtotally occluded coronary artery (Thrombolysis In Myocardial Infarction [TIMI] flow grade 0 or 1) within 24 h of symptom onset of AMI and underwent MCE in the catheterization laboratory. The diagnosis of AMI was based on chest pain lasting ≥30 min, ST segment elevation ≥2 mm in at least two contiguous ECG leads and a greater than threefold increase in serum creatine kinase (CK) levels. Sixty-six patients were excluded because of a poor echocardiographic image (n = 33), spontaneous recanalization of the culprit lesion (TIMI flow grade ≥2) at the time of the initial coronary angiographic study (n = 20), allergy to
ioxaglate (n = 7) and unsuccessful angioplasty (n = 6). Therefore, the final study group consisted of 199 patients. The study protocol was approved by the hospital’s Ethics Committee. One of the investigators obtained written, informed consent from each patient before cardiac catheterization.

**Study protocol.** We recorded the 12-lead ECG on hospital admission and then performed two-dimensional echocardiography. We recorded the apical and parasternal views. We defined the risk area as myocardial segments showing dyskinesia, akinesia or severe hypokinesia.

Aspirin (243 mg) was given orally at least 30 min before coronary angiography. After administration of intravenous heparin (100 U/kg), we performed coronary angiography using the right femoral approach to determine the culprit lesion and collateral channels. Collateral channels were graded according to the report by Rentrop et al. (13), and good collateral flow was defined as grade 2 or 3. We performed PTCA on the culprit lesion by using appropriate-sized balloon catheters. We repeated PTCA or implanted a stent to achieve a residual diameter stenosis ≤50%. At a mean time of 15 min after the last PTCA, we performed MCE, as previously reported (3,4). In brief, we injected 2 ml of sonicated ioxaglate (Hexabrix-320, Tanabe, Tokyo, Japan) containing microbubbles of a mean size of 12 μm into the left coronary artery while recording the two-dimensional echocardiograms using a mechanical sector scanner (model SAL-38B, Toshiba, Tokyo, Japan or SONOS 100, Agilent Technologies, Palo Alto, California; carrier frequency of 3.5 MHz). The MCE images, including the parasternal short-axis view at the mid-papillary muscle level and the apical two-chamber view, were recorded on 1.25-cm VHS videotape.

**Analysis of echocardiographic data.** Two independent observers who had no knowledge of the patients’ data evaluated wall motion of 16 myocardial segments, as endorsed by the American Society of Echocardiography (14). The wall thickening of each myocardial segment was scored as follows: 4 = dyskinesia; 3 = akinesia; 2 = severe hypokinesia; 1 = hypokinesia; and 0 = normokinesia or hyperkinesia. The wall motion score (WMS) was calculated as the sum of the scores within the area at risk.

Two experienced echocardiographers who had no knowledge of the patients’ data analyzed the MCE image to identify the area of the no-reflow phenomenon, as described elsewhere (3,4). In brief, we defined the no-reflow zone on end-diastolic images as contrast perfusion defects after PTCA. We quantified the area of no-reflow as its ratio to the risk area at the baseline study. When the ratio exceeded 0.25, myocardial reperfusion in the corresponding segment was considered incomplete (MCE no-reflow). If this ratio was ≤0.25, we considered myocardial reperfusion was adequate (MCE reflow) (Fig. 1). Our previous study demonstrated the high reproducibility of measuring the size of the contrast defect (3).

**Analysis of ECG data.** On the 12-lead ECG recorded before PTCA, we measured the number of infarct-related Q-waves in the precordial leads. We also recorded the 12-lead ECG repeatedly during and after the angioplasty procedure. If the ST segments in the leads corresponding to the infarct-related lesion showed additional elevation (>2 mm) shortly after reperfusion, and this elevation

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**Figure 1.** Representative myocardial contrast echocardiography (MCE) images in patients with an anterior wall acute myocardial infarction (apical two–chamber view). **(Left)** Good contrast enhancement, with injection of sonicated contrast agent into the left coronary artery, was observed within the area at risk, and this patient had reflow on MCE. **(Right)** In contrast, a substantial amount of contrast defect was observed within the area at risk (area between arrows), even after successful opening of the culprit lesion, and this patient had no-reflow on MCE.
persisted at least 1 h after reperfusion, we designated it as ST segment re-elevation.

Analysis of clinical history. Physical examinations were precisely performed on hospital admission by at least one of the staff physicians, and the state of congestive heart failure was expressed as the Killip class. A detailed clinical history in each study patient was obtained by a staff physician. The onset of AMI was defined as the initiation of chest pain or chest discomfort persisting ≥30 min. Cardiac symptoms lasting <30 min were defined as a sign of angina pectoris, and angina occurring ≤48 h before the onset of infarction was defined as pre-infarction angina (10). A clinical history of risk factors, such as diabetes mellitus, hypertension, hyperlipidemia and smoking, was determined from a patient interview or medical records.

Statistics. All data are expressed as the mean value ± SD. We made comparisons by using one-way analysis of variance for continuous variables, and the significance of the difference was calculated by using the Scheffé F test for factor analysis. Categorical variables were compared by using the chi-square test. Univariate and multivariate logistic regression analyses were used to identify independent predictors for the development of the no-reflow phenomenon. Variables used for analysis included age, gender, coronary risk factors, Killip class, pre-infarction angina, distributions of the culprit lesion, elapsed time from symptom onset to reperfusion, number of Q-waves in the precordial leads, ST segment re-elevation after PTCA, WMS on the echocardiogram, presence of good collateral channels and occlusion status in the culprit lesion. Differences were considered significant at p < 0.05. Statistical analysis was performed using StatView, version 5.0 (SAS Institute, Cary, North Carolina).

RESULTS

Patient characteristics. There were 199 study patients (mean age 59 ± 10 years [range 25 to 86]; 158 men and 41 women). The culprit lesion was at the proximal portion of the left anterior descending coronary artery in 107 patients and at the middle portion in 92 patients. The mean time from symptom onset to coronary reperfusion was 6.1 ± 4.3 h. A stent was implanted in 10 patients. The peak CK level was 2,663 ± 1,961 IU/l.

Using MCE, a substantial amount of no-reflow was observed within the risk area in 79 patients (39.6%) (MCE no-reflow), and the remaining 120 patients were classified as having reflow (MCE reflow). The patients with MCE reflow showed lower peak CK value than those with MCE no-reflow (p < 0.0001). There were no significant differences in age, gender and coronary risk factors between the two subgroups (Table 1). The elapsed time from symptom onset to coronary reperfusion was also comparable between two subgroups.

Among the 120 patients with MCE reflow, 61 (50.8%) had one or more episodes of angina ≤48 h before symptom onset, whereas only 25 patients (31.6%) with MCE no-reflow had episodes of pre-infarction angina (p = 0.008). On hospital admission, the patients with MCE no-reflow had a significantly higher Killip class than those with MCE reflow.

Determinants of the no-reflow phenomenon. The WMS and number of infarct-related Q-waves in the ECG precordial leads before PTCA were significantly greater in patients with MCE no-reflow than in those with MCE reflow. The incidence of transient ST segment re-elevation shortly after coronary reperfusion was comparable between two subgroups. There was no difference in the distribution of culprit lesions between two subgroups. Complete occlusion (TIMI flow grade 0) of the left anterior descending coronary artery was more frequent in the patients with MCE no-reflow than in those with MCE reflow at the initial coronary angiographic study. There were no significant differences in the incidence of good collateral channels between two subgroups.

To determine the independent factors related to the development of the no-reflow phenomenon, we performed multiple logistic regression analysis. Univariate analysis revealed that the absence of pre-infarction angina, Killip class, complete occlusion of the culprit lesion, number of Q-
waves and WMS were independent predictors of the no-reflow phenomenon. Multivariate logistic regression analysis revealed that all of these factors, except for Killip class, are independent predictive factors of the no-reflow phenomenon (Table 2). The number of Q-waves has the highest Wald's chi-square value, followed by WMS, complete occlusion and absence of pre-infarction angina, suggesting that the number of Q-waves is the strongest factor to predict the no-reflow phenomenon.

**DISCUSSION**

In the present study, we investigated the factors related to the no-reflow phenomenon in 199 patients with a first anterior wall AMI. Univariate analysis indicated that the absence of pre-infarction angina, Killip class, number of Q-waves, WMS and TIMI flow grade 0 at the initial coronary angiographic study were the factors related to the no-reflow phenomenon. Multivariate analysis revealed that all of these factors, except for Killip class, are independent factors related to the no-reflow phenomenon. Thus, both greater size of the risk area and more severe myocardial damage at the moment of coronary reperfusion are closely related to the no-reflow phenomenon. In contrast, both residual coronary flow and preconditioning seem to suppress the progression of microvascular damage. To the best of our knowledge, this is the first report to reveal the factors relevant to the progression of microvascular dysfunction.

**Preconditioning angina.** Pre-infarction angina shortly before the onset of AMI limits infarct size and promotes cardiac functional recovery in reperfused patients with AMI (9,10), although its mechanism has not yet been fully understood. Our data demonstrate that pre-infarction angina may attenuate the development of the no-reflow phenomenon, and thus preserve both microvascular function and tissue perfusion after reperfusion. Komamura et al. (15) measured the temporal changes in coronary vein flow in patients with AMI and indicated that pre-infarction angina is a factor that prevents a progressive decrease in coronary flow, which implies the no-reflow phenomenon, after successful thrombolysis. Our study indicates that augmentation of myocardial perfusion is another mechanism of cardioprotection.

Several mechanisms are suggested for the protection of the coronary microvasculature by preconditioning. Experimental studies indicated that ischemic preconditioning prevents endothelial dysfunction after ischemia-reperfusion (16,17). Plugging of capillaries with leukocytes is one of the major mechanisms of microvascular dysfunction (18). Ischemic preconditioning reduces the adhesion of leukocytes after ischemia-reperfusion (19–21), probably through a decreased expression of endothelial adhesion molecules, such as intercellular adhesion molecule-1, on the cellular membrane surface (21). Inhibition of leukocyte adhesion might preserve endothelial function during ischemia (21), or vice versa (20).

**Severity of myocardial damage before coronary reperfusion.** Both the number of Q-waves and WMS on hospital admission were identified as factors related to the no-reflow phenomenon. This result indicates that both the size of the risk area and the severity of myocardial damages seem to be determinants of the no-reflow phenomenon. The WMS before reperfusion is mainly determined by the size of the risk area, because the risk area always shows dyskinesia or akinesia (22). Clinical and experimental studies have demonstrated that the size of the risk area is well correlated with the infarct size after reperfusion therapy (7,23). Myocardial necrosis extends from the center of the area at risk to the peripheral zone after coronary occlusion. The functional border zone is in the marginal zone of the risk area, and myocardial perfusion due to the diffusion from the normal

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**Table 2. Univariate and Multivariate Predictors of the No-Reflow Phenomenon**

<table>
<thead>
<tr>
<th></th>
<th>Univariate Analysis</th>
<th>Multivariate Analysis</th>
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<tbody>
<tr>
<td></td>
<td>Chi-Square*</td>
<td>p Value</td>
</tr>
<tr>
<td>Age</td>
<td>1.92</td>
<td>0.16</td>
</tr>
<tr>
<td>Gender</td>
<td>1.76</td>
<td>0.18</td>
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<tr>
<td>Diabetes mellitus</td>
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<td>Hypertension</td>
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<td>Hyperlipidemia</td>
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<td>Smoking</td>
<td>0.52</td>
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<tr>
<td>Symptom onset to reflow time</td>
<td>0.67</td>
<td>0.41</td>
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<tr>
<td>Absence of pre-infarction angina</td>
<td>7.03</td>
<td>0.008</td>
</tr>
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<td>Killip class</td>
<td>6.46</td>
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<tr>
<td>No. of Q-waves on ECG</td>
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<td>&lt;0.0001</td>
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<tr>
<td>Transient ST segment re-elevation</td>
<td>1.91</td>
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<tr>
<td>WMS</td>
<td>18.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>TIMI flow grade 0 at initial coronary angiography</td>
<td>14.2</td>
<td>0.0002</td>
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<td>Culprit lesion in proximal LAD</td>
<td>3.57</td>
<td>0.06</td>
</tr>
<tr>
<td>Good collateral channels</td>
<td>0.59</td>
<td>0.44</td>
</tr>
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*Denotes Wald's chi-square value. †Those graded as 2 or 3.

CI = confidence interval; OR = odds ratio; other abbreviations as in Table 1.
Peripheral myocardium plays an important role in preserving myocardial viability in this area. If the risk area is too large to be perfused with collateral or diffusive blood flow, the size of infarction would be greater. Because the no-reflow zone is correlated with the areas of necrosis (24), the greater the size of the area at risk could lead to the area of no-reflow, and thus the greater the size of the infarct zone.

The greater number of Q-waves implies the broader transmural damage in the anterior wall before coronary reperfusion. In canine studies, Kloner et al. (24,25) found that the no-reflow zone is located within the areas of necrosis and suggested that some kind of no-reflow phenomenon is already established before reperfusion. Our recent study using the Doppler guide wire demonstrated that the coronary flow velocity pattern specific to substantial no-reflow is found at the moment of reperfusion in some patients (26). These patients had a larger number of Q-waves before reperfusion, as compared with those who gradually developed a specific flow pattern. The present results also suggest that the no-reflow phenomenon has already been established before reperfusion, at least in some patients.

Residual coronary flow is a factor that attenuates the development of myocardial damage in patients with AMI (27,28). The present study showed that little residual coronary flow, such as TIMI flow grade 1, could prevent the development of the no-reflow after coronary reperfusion. A supply of coronary blood flow before reperfusion might protect the microvasculature, as well as the myocardium. In contrast, collateral channels on coronary angiography are not an independent determinant of the no-reflow phenomenon, possibly because the angiographic collateral flow grade does not always reflect myocardial perfusion through collateral channels (29).

**Study limitations.** The presence or absence of pre-infarction angina was assessed from a clinical history obtained by staff physicians, but ischemic episodes are not necessarily symptomatic. The significance of silent ischemia could not be evaluated in our study. We could not successfully analyze the effects of the drugs that patients had received before the onset of AMI. Drugs such as glyburide, which could affect drug metabolism and the effects of drugs themselves, were included in the study. Because a large number of patients with stent implants was too small, the number of patients with stent implants was too small.

**Clinical implications.** No-reflow after coronary reperfusion is associated with poor functional and clinical outcomes; thus, it would be useful, for risk stratification, to identify patients with a high risk of no-reflow. Recent reports have revealed that nicorandil (32) or adenosine (33) can prevent the development of the no-reflow phenomenon after a patient has had a reperfused AMI. Adenosine plays an important role in preconditioning by opening the K$_{ATP}$ channel through A$_1$ receptors (34,35), and nicorandil is also a potent opener of K$_{ATP}$ channels (34). Thus, either nicorandil or adenosine might prevent the development of no-reflow through the cellular mechanisms of ischemic preconditioning.

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