Coronary reperfusion therapy is widely performed in patients with acute myocardial infarction (AMI). However, patency of the infarct-related artery does not always guarantee salvage of myocardium at risk of ischemia. The phenomenon of microvascular no reflow is defined as inadequate myocardial perfusion through a given segment of the coronary circulation without angiographic evidence of mechanical vessel obstruction. Several investigators have documented that the no-reflow phenomenon is observed in >30% of patients after thrombolysis or catheter-based percutaneous coronary intervention (PCI) for AMI. Furthermore, it has also been reported that no reflow is associated with poor functional and clinical patient outcomes when compared with patients with adequate reflow after reperfusion. It might be important, therefore, to be able to predict which lesions are high risk for no reflow before beginning thrombolysis or PCI, but, to our knowledge, no study examining the relationship between lesion morphology and the no-reflow phenomenon has been performed. We have reported that preintervention intravascular ultrasound (IVUS) is able to identify lesion plaque morphology in the acute phase. The aim of the present study was to investigate the correlation between lesion morphology under preintervention IVUS and the no-reflow phenomenon.

Methods

Study Population

Our study population comprised 100 consecutive patients with AMI who underwent preintervention IVUS and were successfully recanalized with primary balloon angioplasty or stenting. IVUS was again performed to identify and exclude any mechanical vessel obstruction in cases of thrombolysis in myocardial infarction flow grade 0, 1, or 2 after intervention in the absence of angiographic stenosis. Angiographic no reflow was seen in 13 patients (13%). Univariate analysis indicated that hypercholesterolemia, fissure and dissection, lipid pool–like image, lesion, and reference external elastic membrane cross-sectional area correlate with the no-reflow phenomenon. Multivariate logistic regression analysis showed that lipid pool–like image (P<0.05; odds ratio 118; 95% CI 1.28 to 11 008) and lesion elastic membrane cross-sectional area (P<0.05; odds ratio 1.55; 95% CI 1.01 to 2.38) are independent predictive factors of no-reflow phenomenon after reperfusion for AMI.

Conclusions—Large vessels with lipid pool–like image are at high risk for no reflow after primary intervention for AMI. Also, plaque content may play a role in damage to the microcirculation after primary intervention for AMI. (Circulation. 2002;105:2148-2152.)

Key Words: microcirculation ■ reperfusion ■ plaque ■ angioplasty ■ myocardial infarction

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Circulation is available at http://www.circulationaha.org DOI: 10.1161/01.CIR.0000015697.59592.07
Study Protocol
Coronary angiography in all patients was performed using a 6F Judkins-type catheter via the femoral approach. All patients received an intravenous bolus injection of 10 000 IU of heparin and intracoronary isosorbide dinitrate (2 mg) before angiography. After completion of diagnostic coronary angiography and before any intervention, all patients were evaluated with IVUS. The IVUS catheter (3.2F Ultra cross, CVIS, Boston Scientific) was carefully advanced distal to the lesion under fluoroscopic guidance. It was then pulled back automatically from the distal portion at 0.5 mm/s, facilitating observation of the lesion. IVUS images were recorded on S-VHS video for offline analysis. While pulling back the catheter, we manually infused a contrast medium for IVUS imaging, carefully observing the lesion. After performing preintervention IVUS, PTCA or stenting was performed using a 7F guiding catheter, 0.014-inch guidewire, and a monorail balloon catheter, according to conventional methods. Decision-making on PCI strategy was left to the discretion of the individual PCI cardiologist.

Angiographic criteria of <25% residual stenosis and TIMI flow grade 3 were used to determine the end point of the interventional procedure. If TIMI flow grade after intervention (PTCA or stenting) was 0, 1, or 2 despite the absence of angiographic stenosis, repeat IVUS was performed to exclude the possibility of mechanical vessel obstruction. Additional PTCA or stenting was performed in the event of mechanical vessel obstruction, including dissection or thrombosis.

No reflow after reperfusion was defined as postprocedural TIMI grade 0, 1, or 2 flow in the absence of a mechanical obstructon on final postprocedural angiograms. On this basis, patients were divided into 2 groups, a reflow group and a no-reflow group.

A 12-lead ECG was recorded during and after PCI. Additional ST-segment elevation (>2 mm) immediately after balloonizing or stenting and in the absence of mechanical obstruction was defined as ST re-elevation.

Three thousand units of heparin were administered every hour during the procedure to maintain an activated clotting time >300 seconds. After PCI, intravenous infusion of heparin was continued for at least 24 hours to maintain an activated clotting time of 180 to 200 seconds. We also administered the following antiplatelet therapy: aspirin 80 mg per day after PTCA and aspirin 80 mg a day and ticlopidine 200 mg a day after stent implantation.

Analysis of IVUS Images
The morphological features revealed by our IVUS findings were interpreted by 2 independent experienced observers (D.F. and K.S.) unfamiliar with the angiographic and clinical data. A culprit lesion was considered eccentric if the ratio of lesion thickness on opposite sides of the lumen was <0.5 or if there was an arc of disease-free vessel wall. Fissure was defined as an abrupt, focal, superficial break in the linear continuity of the plaque and extending in a radial direction. Dissection was defined as rupture of the vessel wall creating one or more neolumina. A lipid pool–like image was defined as a pooling of low-echoic material or echolucent material covered with a high-echoic layer. Figure 1 shows a typical image.

Bright echoes at the surface of the lumen with an arc of >90 degrees of acoustic shadowing were defined as superficial calcium. Bright echoes deep in the vessel wall >90 degrees with acoustic shadowing were defined as deep wall calcium. Figure 2 shows the variety of preintervention IVUS images of AMI lesions.

Methods for the identification of plaque composition and measurement of external elastic membrane cross-sectional area by IVUS have been reported previously.7–9 Computer planimetry (TapeMeasure, Indec Systems) was used to measure lesion site and proximal and distal reference segment external elastic membrane cross-sectional area (EEM-CSA). We measured EEM-CSA (the area encompassed by the ultrasonic media-adventitia border) by tracing the leading edge of the adventitia and lumen cross-sectional area. Plaque area was calculated as EEM-CSA minus lumen CSA. Incidence of lesion EEM-CSA larger than proximal reference EEM-CSA was defined as positive remodeling.

Angiographic Analysis
Coronary angiograms were reviewed separately by 2 independent observers (Y.N. and T.S.) unaware of the IVUS findings. The degree of perfusion was evaluated according to TIMI criteria.6 Collaterals were graded according to the Rentrop classification,10 with good collateral flow defined as grade 2 or 3. Angiographic thrombus was defined as a filling defect seen in multiple projections surrounded by contrast in the absence of calcification and >10 mm in length.

Statistical Analysis
Results were expressed as mean value±SD for continuous variables. Qualitative data are presented as numbers (%). Continuous variables were compared using Student’s t test and categorical data with Fisher’s exact test. A multivariate logistic regression model was used.
TABLE 1. Clinical Characteristics and Clinical Results

<table>
<thead>
<tr>
<th></th>
<th>No-Reflow Group</th>
<th>Reflow Group</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n</td>
<td>13</td>
<td>87</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>62±8.0</td>
<td>64±11</td>
<td>0.51</td>
</tr>
<tr>
<td>Men</td>
<td>10 (77)</td>
<td>67 (77)</td>
<td>0.99</td>
</tr>
<tr>
<td>Coronary risk factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systemic hypertension</td>
<td>7 (53)</td>
<td>41 (47)</td>
<td>0.77</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>4 (31)</td>
<td>18 (25)</td>
<td>0.74</td>
</tr>
<tr>
<td>Smoking</td>
<td>11 (85)</td>
<td>48 (55)</td>
<td>0.07</td>
</tr>
<tr>
<td>Hypercholesterolemia (&gt;220 mg/dL)</td>
<td>9 (69)</td>
<td>33 (38)</td>
<td>0.04</td>
</tr>
<tr>
<td>Killip class</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>11 (85)</td>
<td>72 (83)</td>
<td>0.77</td>
</tr>
<tr>
<td>2</td>
<td>1 (8)</td>
<td>8 (9)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>1 (8)</td>
<td>3 (3)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>0</td>
<td>4 (5)</td>
<td></td>
</tr>
<tr>
<td>Preinfarction angina</td>
<td>3 (23)</td>
<td>35 (40)</td>
<td>0.36</td>
</tr>
<tr>
<td>Onset to recanalization time, min</td>
<td>239±183</td>
<td>228±214</td>
<td>0.87</td>
</tr>
<tr>
<td>ST-segment re-elevation</td>
<td>10 (77)</td>
<td>5 (6)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Number of patients with Q-wave myocardial infarction</td>
<td>12 (92)</td>
<td>60 (69)</td>
<td>0.1</td>
</tr>
<tr>
<td>Peak creatine kinase levels, IU/L</td>
<td>4346±2062</td>
<td>2016±1617</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Data presented are mean value±SD or number (%).

Results

Patient Characteristics and Clinical Results

Primary PTCA or stenting was successful in all patients. Stents were used in 73 of 100 (73%) patients. Angiographic no-reflow phenomenon was seen in 13 patients (13%). In 12 of these 13, there was TIMI 3 grade flow at some point before the no-reflow phenomenon. No ST re-elevation, however, was seen in these 12 cases at the same time as TIMI 3 grade flow was detected. In each case in the no-reflow group, ST re-elevation was only seen immediately after no reflow. Patient characteristics and clinical results for both groups are summarized in Table 1. Incidence of hypercholesterolemia (>220 mg/dL) was significantly higher in the no-reflow group than in the reflow group (92% versus 51%, P<0.01). The incidence of lipid pool–like image and fissure/dissection were significantly higher in the no-reflow group than in the reflow group (fissure/dissection, 92% versus 37%; lipid pool–like image, 92% versus 25%; P<0.01, respectively). Also, distal reference EEM-CSA, proximal reference EEM-CSA, and lesion EEM-CSA of the no-reflow group were larger than in the reflow group. There were no differences in positive remodeling rates between the 2 groups.

A multivariate logistic regression analysis showed that the presence of lipid pool–like images and lesion EEM-CSA are independent predictive factors of no reflow after reperfusion in patients with AMI (lipid pool–like image, odds ratio 118, 95% CI, 1.01 to 2.38; lesion EEM-CSA, odds ratio 1.55, 95% CI, 1.10 to 2.38).

IVUS Results

Coronary artery lesions were observed with IVUS in all patients without any serious procedural complications. Blood flow distal to the lesion was detectable in all cases, and the lumen was identified. The preintervention IVUS findings are summarized in Table 2. Eccentric plaque was observed significantly more frequently in the no-reflow group than in the reflow group (92% versus 51%, P<0.01). The incidence of lipid pool–like image and fissure/dissection, positive remodeling, and lesion EEM-CSA, and angiographic findings (preintervention TIMI grade, lesion site, good collateral channels, and thrombus). P<0.05 was considered statistically significant.

TABLE 2. Coronary Angiogram Findings

<table>
<thead>
<tr>
<th></th>
<th>No-Reflow Group (n=13)</th>
<th>Reflow Group (n=87)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infarct-related artery</td>
<td>Left descending artery</td>
<td>3 (23)</td>
<td>47 (54)</td>
</tr>
<tr>
<td>Left circumflex artery</td>
<td>1 (8)</td>
<td>4 (5)</td>
<td></td>
</tr>
<tr>
<td>Right coronary artery</td>
<td>9 (69)</td>
<td>36 (41)</td>
<td></td>
</tr>
<tr>
<td>TIMI flow grade 0 at initial angiogram</td>
<td>10 (77)</td>
<td>44 (51)</td>
<td>0.13</td>
</tr>
<tr>
<td>Good collateral flow</td>
<td>6 (46)</td>
<td>28 (32)</td>
<td>0.36</td>
</tr>
<tr>
<td>Large thrombus in angiogram</td>
<td>2 (15)</td>
<td>3 (3)</td>
<td>0.13</td>
</tr>
<tr>
<td>Stent use before no-reflow</td>
<td>9 (69)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Final stent use</td>
<td>13 (100)</td>
<td>60 (69)</td>
<td>0.02</td>
</tr>
<tr>
<td>Required intra-aortic balloon pumping</td>
<td>1 (8)</td>
<td>3 (3)</td>
<td>0.43</td>
</tr>
</tbody>
</table>

Data presented are number (%).

Discussion

It is well known that the angiographic no-reflow phenomenon occurs after intervention in degenerated saphenous vein grafts. In these cases, distal embolization of plaque or thrombus from the lesion site is the likely mechanism.11,12 Webb et al13 reported the presence of particulate material in 21 of 23 distal protection device procedures, in which pathological examination revealed the presence of particles with a necrotic core of cholesterol clefts, lipid-rich macrophages, and fibrins.

In patients with AMI, Sutsch et al14 have reported that plaque debris consisting of a necrotic core, inflammatory cells, cholesterol debris, and old and fresh thrombi are often retrieved from the distal portions of infarct-related arteries after direct angioplasty.

In the present study, we demonstrate that the angiographic no-reflow phenomenon after primary angioplasty or stenting in patients with AMI correlates with lesion IVUS morphology. The morphological features of the lipid pool–like image are similar to those of the lipid pool, observed in pathologically vulnerable plaques. Microembolization may occur when
artificial plaque rupture is induced during coronary intervention and the lipid pool with or without additional thrombus formation is washed out of the atheromatous plaque into the microcirculation. Our findings that lesions in large vessels constitute a high risk for no reflow would seem to be supported by the observation that large vessels are able to contain large amounts of plaque or thrombus. Impairment of autoregulation by plaque content or thrombus and accompanied by local release of vasoconstrictors has also been postulated as a potential mechanism. If vasoconstriction is one of the mechanisms, this would explain the favorable response seen with administration of a calcium antagonist.12,16,17

Recent studies have demonstrated that TIMI 2 grade flow after PCI, which we defined as angiographic no reflow, may be caused by microvascular dysfunction sustained in the ischemic region. Many mechanisms have been postulated for this microvascular dysfunction, including free radicals, cardiac sympathetic reflexes with resulting α-adrenergic macrovascular and microvascular constriction, regional changes in angiotensin II receptor density, and selectin-regulated interactions between activated polymorphonuclear leukocytes and the endothelium.23

In most of our no-reflow cases, however, there was TIMI 3 grade flow at some point before the no-reflow phenomenon, and subsequent ST segment re-elevation was observed immediately after angioplasty. Our data suggest that the no-reflow phenomenon is attributable to microvascular dysfunction resulting from the intervention-induced release of the lipid pool–like plaque contents rather than reperfusion injury.

Study Limitations
We did not use myocardial contrast echocardiography in this study. The interpretation of plaques in the present study was performed according to established IVUS criteria. However, the ultrasound classification of a lipid pool–like image is complex because of several factors, including instrument settings and visual interpretation.

Clinical Implications
No reflow after reperfusion in patients with AMI will be encountered in the catheterization laboratory. Preintervention IVUS for patients with AMI can be performed promptly and safely in the setting of the catheterization laboratory. The use of IVUS before intervention is therefore a useful tool for predicting the incidence of the no-reflow phenomenon after primary PCI in patients with AMI.

Preintervention IVUS may contribute to the development of new interventional strategies and techniques of distal protection for preventing the no-reflow phenomenon in the setting of acute myocardial infarction.

References
15. Deleted in proof.
No-Reflow Phenomenon and Lesion Morphology in Patients With Acute Myocardial Infarction
Atsushi Tanaka, Takahiko Kawarabayashi, Yoshiharu Nishibori, Toshihiko Sano, Yukio Nishida, Daiju Fukuda, Kenei Shimada and Junichi Yoshikawa

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