The Decrease of Plaque Volume During Percutaneous Coronary Intervention Has a Negative Impact on Coronary Flow in Acute Myocardial Infarction

A Major Role of Percutaneous Coronary Intervention-Induced Embolization

Hiroshi Sato, MD,* Hidetaka Iida, MD,* Atsushi Tanaka, MD,† Hidemasa Tanaka, MD,* Shinichii Shimodouzono, MD,* Eiji Uchida, MD,* Takahiko Kawarabayashi, MD,† Junichi Yoshikawa, MD‡ Himeji, Sakai, and Osaka, Japan

OBJECTIVES
The aim of this study was to evaluate how decreased plaque volume during percutaneous coronary intervention (PCI) affects coronary flow in patients with acute myocardial infarction (AMI).

BACKGROUND
Coronary flow after reperfusion therapy is a major determinant of clinical outcomes in patients with AMI. However, little is still known about the changes in coronary flow that appear after PCI in response to the decreased plaque during the procedure.

METHODS
The study group comprised 60 patients with AMI who underwent pre- and post-PCI intravascular ultrasound (IVUS). Qualitative and quantitative analyses were performed on all IVUS procedures. External elastic membrane volume (EEMV), lumen volume (LV), and plaque volume (PV) were measured every 1.0 mm to include the lesion and reference segments 3.0 mm proximal and distal to the lesion. The difference between pre- and post-PCI PV was defined as the index of the decrease in plaque volume (ΔPV). The corrected TIMI frame count (CTFC) was used to evaluate coronary flow after PCI.

RESULTS
Plaque volume was decreased at post-PCI IVUS in all 60 patients. Inadequate reflow (CTFC >40) was observed in 13 patients (21.7%). The decrease in PV was significantly larger in patients with inadequate reflow than in those with reflow (49.4 ± 18.9 vs. 31.7 ± 15.5 mm³, p = 0.0010). Also, ΔPV was significantly correlated with CTFC after PCI (r = 0.415, p = 0.0012).

CONCLUSIONS
The decrease in PV during PCI has a negative impact on coronary flow after PCI in patients with AMI. Embolization induced by PCI may occur in all patients with AMI. (J Am Coll Cardiol 2004;44:300–4) © 2004 by the American College of Cardiology Foundation

Percutaneous coronary intervention (PCI) is widely performed in patients with acute myocardial infarction (AMI) in order to restore the patency and adequate reflow in the infarct-related artery as early as possible. Unfortunately, PCI does not always guarantee a good clinical outcome. In fact, the procedure fails to achieve Thrombolysis In Myocardial Infarction (TIMI) flow grade 3 in 2% to 30% of cases, mainly due to the angiographic no-reflow phenomenon (1,2). Coronary flow after reperfusion therapy is a major determinant of clinical outcomes in patients with AMI (3–11). The TIMI flow grade classification (3) has been a valuable tool to compare angiographic and clinical outcomes after thrombolysis (4–9). Moreover, excellent epicardial blood flow, as assessed by the corrected TIMI frame count (CTFC), is reported to be associated with improved in-hospital and one-month clinical outcomes after thrombolytic administration (10,11).

Recent studies have indicated that PCI-induced plaque or thrombus release in patients with AMI might be attributable to angiographic no-reflow (12,13). Webb et al. (14) reported that particulate debris after saphenous vein graft intervention might contribute to distal embolization, no-reflow, and infarction. However, there have been few studies to clarify the effect of distal embolization on coronary flow after PCI in patients with AMI. The aim of this study was to investigate the effect of the decrease in plaque during PCI on coronary flow in patients with AMI.

METHODS
Study population. Of 70 consecutive patients with first AMI who underwent intravascular ultrasound (IVUS)-guided PCI in Tsukazaki Memorial Hospital between February 2000 and September 2002, a total of 60 who underwent pre- and post-PCI IVUS were enrolled in the present study. All patients were successfully recanalized with stenting within 12 h of the onset of symptoms. The diagnosis of AMI was determined from the presence of continuous chest pain for more than 30 min, ST-segment elevation above 0.2 mV on at least two contiguous electrocardiographic (ECG) leads, a threefold increase in serum creatine kinase (CK) levels, and TIMI flow grade 0, 1, or 2 at the time of initial emergent coronary angiography.

From the *Tsukazaki Memorial Hospital, Himeji; †Baba Memorial Hospital, Sakai; and ‡Department of Internal Medicine and Cardiology, Graduate School of Medicine, Osaka City University, Osaka, Japan.

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Nitroglycerin was the only agent used before and during the PCI procedure (no patients underwent thrombolysis or received glycoprotein IIb/IIIa inhibitors, adenosine, or verapamil). No patients with a previous myocardial infarction, subacute thrombosis, or cardiogenic shock were enrolled in the study.

Of the original 70 patients, 10 were excluded from the study for the following reasons: 5 patients with ostial and bifurcation lesions were excluded due to difficulty in analyzing the media-adventitia border and the possibility that the plaque would shift out of the range of the ultrasound image; 3 were excluded due to an inadequate IVUS image; and 2 were excluded due to the use of intra-aortic balloon pumping or percutaneous cardiopulmonary support during PCI.

The Ethics Committee of Tsukazaki Memorial Hospital approved the study protocol, and written, informed consent was obtained from all participants before coronary angiography.

**Study protocol.** All patients were treated by primary PCI with stenting, and all received heparin (100 U/kg) before the routine catheterization procedure. Immediately after diagnosis, the patients underwent coronary angiography and pre-PCI IVUS. Percutaneous coronary intervention was performed using a 7F-guiding catheter, 0.014-inch guidewire, monorail balloon catheter, and stent, according to conventional methods. Decision-making on the PCI strategy was left to the discretion of an individual PCI cardiologist.

Post-PCI IVUS and final angiography were performed after PCI, and the CTFC determined on angiography was used to assess post-PCI coronary flow. Inadequate reflow was defined as CTFC >40 in the absence of mechanical obstruction on the final angiograms after PCI. The IVUS catheter (3.2F Ultra cross, CVIS, Boston Scientific, Natick, Massachusetts) was carefully advanced distal to the lesion under fluoroscopic guidance, then pulled back automatically from the distal portion at 0.5 mm/s. As the catheter was pulled back, we manually infused a contrast medium for the IVUS image, carefully identifying the lumen area and lesion morphology. The IVUS images were recorded on S-VHS videotape for off-line analysis.

The angiographic criterion of <25% residual stenosis was used to determine the end point of PCI. Post-PCI IVUS was performed to exclude the possibility of mechanical vessel obstruction, including thrombus or dissection.

**Analysis of IVUS image.** Two independent observers who had no knowledge of the diagnoses and angiographic results performed off-line analysis of the recorded images after the procedure. Cross sections were analyzed for every 2 s of videotape, and each analyzed coronary segment was axially divided into several 1.0-mm segments. Quantitative measurements of the ultrasound images were performed at the diastolic phase every 2 s. When we encountered the systolic phase on the IVUS image, we shifted the image back and forth to the nearest diastolic phase. Identification of the side branches by IVUS and the presence of a calcified lesion were also helpful to locate the position of the IVUS transducer. On the basis of reproducible arterial landmarks, the same arterial segments were identified at the pre- and post-PCI assessments. The analyzed arterial segments encompassed the stented segments and reference segments 3.0 mm proximal and distal to the stented segments.

The morphologic features were classified according to a previous report (12). The methods for identifying the plaque composition and measuring the external elastic membrane cross-sectional area (EEM-CSA) by IVUS were also reported previously (15–17). The EEM-CSA was measured by tracing the outer border of the sonoluent zone, and an incidence of lesion EEM-CSA larger than proximal reference EEM-CSA was defined as positive remodeling. The lumen cross-sectional area (L-CSA) was measured by tracing the interface between the vessel lumen and the leading edge of the initial echogenic layer. When plaque and thrombus encompassed the catheter, L-CSA was assumed to be the size of the imaging catheter. The plaque area was calculated as EEM-CSA minus L-CSA. Each image slice was tabulated separately and used to calculate the external elastic membrane volume (EEMV), lumen volume (LV), and plaque volume (PV), according to Simpson’s rule.

**Angiographic analysis.** Coronary angiograms were reviewed separately by two independent observers who were unaware of the IVUS findings. To objectively evaluate an index of coronary flow as a continuous quantitative variable, the CTFC was measured with a frame counter on the ELK CAP-35B II cineviewer (ELMO, Nagoya, Japan). All angiograms were filmed at 30 frames/s. The CTFC after PCI in the infract-related artery was counted. Collateral flow was graded according to the Rentrop classification (18), with good collateral flow defined as grade 2 or 3.

**Statistical analysis.** All analyses were performed using StatView version 5.0 (Abacus Concepts). The results are expressed as the mean value ± SD for each measurement. Continuous variables were compared using both the paired and unpaired Student t test. Pearson’s correlation coefficient was used to measure associations between pairs of conti-
RESULTS

All 60 patients were treated by primary PCI with stenting, and eight of them had tandem stents without gaps. The patient characteristics are summarized in Table 1. Coronary artery lesions were observed with IVUS in all 60 patients and the analyzed arterial lengths encompassed reference segments 3.0 mm proximal and distal to the stented segments. The arterial segments analyzed in the present study encompassed reference segments 3.0 mm proximal and distal to the stented segments. The angiographic characteristics of the subjects are summarized in Table 4. Inadequate reflow (CTFC >40) on the final angiograms after PCI was observed in 13 patients (21.7%).

The decrease in plaque volume (ΔPV) was significantly larger in patients with inadequate reflow than in those with reflow (49.4 ± 18.9 vs. 31.7 ± 15.5 mm³, p = 0.0010) (Fig. 1). Three patients (5%) without mechanical vessel obstruction exhibited TIMI flow grade 1 after PCI. Fifty-seven patients (95%) with TIMI flow grade 2 or 3 exhibited a mean CTFC of 25.9 ± 16.7 after PCI. The post-PCI CTFC of these 57 patients significantly correlated with ΔPV (r = 0.415, p = 0.0012) (Fig. 2), but it did not show a significant correlation with either the onset-to-recanalization time or the peak CK-MB (onset-to-recanalization time: r = 0.060, p = 0.66; CK-MB: r = 0.221, p = 0.10).

DISCUSSION

The principal finding of the present study was a significant correlation between ΔPV during PCI and CTFC after PCI in patients with AMI. Moreover, the ΔPV was significantly larger in patients with inadequate reflow than in those with reflow. These findings suggest that ΔPV hindered coronary flow after the PCI procedure.

As the present study covered patients with AMI, the PV was thought to contain both plaque and thrombus volume. Given that IVUS is incapable of accurately assessing or quantifying the thrombotic material (19), we defined PV in this study as the sum of plaque and thrombus. Ahmed et al. (20) reported that the mechanisms of lumen enlargement after stenting involved significant axial redistribution of plaque from the lesion into the reference segments, vessel expansion, and either plaque embolization or compression. The ΔPV during PCI might be attributable to redistribution, compression, or embolization. The arterial segments analyzed in the present study encompassed reference segments 3.0 mm proximal and distal to the stented segments. As the change in PV was far less pronounced in the reference segments than in the stented segments (Fig. 3), the redistribution out of the 3.0-mm reference segments was not believed to have an important effect on ΔPV. Although the compression could not be clearly identified, neither the compression nor redistribution was thought to have an impact on coronary flow after PCI. Thus, the present study suggests that ΔPV was mainly the result of PCI-induced embolization.

The relationship between PCI-induced embolization and angiographic no-reflow has been reported earlier. Angio-

Table 1. Clinical Characteristics and Clinical Results of Study Group (n = 60)

| Age (yrs) | 62 ± 9.5 |
| Males | 54 (90%) |
| Coronary risk factors | | |
| Systemic hypertension | 26 (43%) |
| Diabetes mellitus | 20 (33%) |
| Current smoking | 38 (64%) |
| Hypercholesterolemia | 25 (42%) |
| Killip class | | |
| 1 | 53 (88%) |
| 2 | 6 (10%) |
| 3 | 0 |
| 4 | 1 (2%) |
| Pre-infarction angina | 37 (62%) |
| Onset to recanalization time (min) | 286 ± 275 |
| Peak CK-MB (IU/l) | 289 ± 170 |

Data are presented as the mean value ± SD or number (%) of patients. CK-MB = creatine kinase-MB fraction. Statistical significance in all comparisons was p < 0.05.

Table 2. Intravascular Ultrasound Volumetric Measurements in 60 Stented and Reference Segments

<table>
<thead>
<tr>
<th></th>
<th>Pre-PCI</th>
<th>Post-PCI</th>
<th>Difference</th>
<th>p Value (Paired)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EEMV (mm³)</td>
<td>379.7 ± 125.1</td>
<td>434.0 ± 132.8</td>
<td>54.4 ± 30.9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LV (mm³)</td>
<td>129.3 ± 51.2</td>
<td>219.1 ± 69.4</td>
<td>89.8 ± 36.0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PV (mm³)</td>
<td>250.4 ± 80.2</td>
<td>214.9 ± 74.7</td>
<td>35.5 ± 17.8</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Data are presented as the mean value ± SD. EEMV = external elastic membrane volume; LV = lumen volume; PCI = percutaneous coronary intervention; PV = plaque volume.

Table 3. Intravascular Ultrasound Morphologies in 60 Culprit Lesions

| | | |
|---|---|
| Positive remodeling | 30 (50%) |
| Eccentric | 30 (50%) |
| Fissure/dissection | 14 (23%) |
| Lipid pool-like image | 16 (27%) |
| Superficial calcium | 25 (42%) |
| Deep wall calcium | 16 (27%) |

Data are presented as the number (%).
graphic no-reflow is well known to occur after PCI in degenerated saphenous vein grafts. In these cases, distal embolization of plaque or thrombus from the lesion site is the likely mechanism (14). Prati et al. (21) found that a marked reduction of the plaque–media area was associated with postprocedural CK-MB release in patients who underwent coronary stenting for unstable angina, thereby implicating distal plaque embolization by stent deployment.

In a pre-PCI IVUS analysis of morphology at the culprit lesion in patients with AMI, Tanaka et al. (12) ascribed angiographic no-reflow to microvascular dysfunction resulting from the PCI-induced release of the lipid pool-like plaque contents. In a microscopic analysis of aspirate at the time of angiographic no-reflow, Kotani et al. (13) identified iatrogenic plaque disruption as one of the mechanisms for angiographic no-reflow during mechanical reperfusion therapy, and they witnessed an improvement in most of the angiographic no-reflow lesions when the intraluminal atherosclerotic debris was removed by the thrombectomy catheter. These reports suggest that PCI-induced embolization has an important effect on coronary flow after PCI.

In experimental settings, however, no-reflow has been attributed to causes as diverse as oxygen free radical production (22,23), cardiac sympathetic reflexes with resulting alpha-adrenergic macrovascular and microvascular constriction (24), local increases in angiotensin II receptor density (25,26), and interactions through selectins between activated polymorphonuclear leukocytes and the endothelium (27). Yet, the aforesaid findings have not been confirmed to apply to angiographic no-reflow after PCI in patients with AMI. Strategies successful in preventing or treating experimental models of no-reflow have not worked in human trials. Other factors besides the ischemic myocardial damage might have hindered the coronary flow after PCI. Given that the peak CK-MB did not show a significant correlation with CTFC after the PCI procedure in the present study, we conjectured that the myocardial damage was due not only to coronary flow, but also to other factors such as preconditioning, collateral flow grade, ischemic duration, and area of myocardium at risk.

In addition to being significantly larger in patients with inadequate reflow than in those with reflow, the ΔPV in the present study correlated well with CTFC after PCI. This pattern suggests that the amount of PCI-induced embolization is one of the important determinants of coronary flow in patients with AMI.
The PV decreased in all 60 of the patients investigated in the present study. Given the correlation between ΔPV and CTFC after PCI, we propose that PCI-induced embolization occurs and hinders coronary flow not only in patients with inadequate reflow, but also in those with reflow.

**Implications.** The coronary flow after reperfusion therapy is reported to be a major determinant of clinical outcomes in patients with AMI (3–11). As the ΔPV during PCI has negative impact on coronary flow after PCI, the prognosis in patients with AMI may be influenced by the degree of PCI-induced embolization. Thus, distal protection devices might be useful for patients with AMI to reduce PCI-induced embolization and to achieve better coronary flow after PCI.

**Study limitations.** The collapse of the culprit lesion due to total occlusions might have an effect on pre-PCI IVUS measurements in patients with AMI. Glycoprotein IIb/IIIa inhibitors were not used in the present study.

**Conclusions.** The ΔPV during PCI has a negative impact on coronary flow after PCI in patients with AMI. Our data suggest that PCI-induced embolization occurs and hinders coronary flow not only in patients with inadequate reflow, but also in those with reflow.

**REFERENCES**