Distal Protection During Primary Coronary Intervention Can Preserve the Index of Microcirculatory Resistance in Patients With Acute Anterior ST-Segment Elevation Myocardial Infarction

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Background: The objective of this study was to investigate whether a distal protection (DP) device can preserve the index of microcirculatory resistance (IMR) after primary percutaneous coronary intervention (PCI) in patients with anterior ST-segment elevation myocardial infarction (STEMI).

Methods and Results: The study group of 36 consecutive patients with anterior STEMI were randomized into 2 groups of primary PCI with or without DP: stenting without DP (non-DP group, n=17) and with DP (DP group, n=19). The DP in all cases was Filtrap (Nipro, Japan). Following final coronary angiography after successful PCI, IMR was measured using PressureWire™ Certus (St Jude Medical, USA) at maximal hyperemia. The averaged IMR of the 36 patients with STEMI after primary PCI was 31.6. The IMR in the DP group was significantly lower than that in the non-DP group (26.6±25.8 U vs. 37.2±23.2 U, P=0.03242).

Conclusions: DP as an adjunctive therapy of PCI for acute anterior STEMI may have beneficial effects on myocardial microcirculation because of preservation of IMR. (Circ J 2011; 75: 94–98)

Key Words: Acute myocardial infarction; Distal protection; Index of microcirculatory resistance; Microcirculation

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Distal Protection and IMR in AMI

Methods

Patient Population
A total of 36 patients (age ≥18 years) admitted to Senri Critical Care Medical Center of Osaka Saiseikai Senri Hospital between February 2008 and August 2009 because of a first episode of anterior STEMI after successful primary PCI within 24 h of symptom onset were considered the study population. The diagnosis of STEMI was made on the basis of chest pain for more than 30 min and 0.1 mV ST-segment elevation in 2 contiguous ECG leads. Exclusion criteria were cardiac shock, history of old MI, severe liver and/or renal dysfunction, history of allergic reaction to drugs, and severe hypovolemia. The study was approved by Osaka Saiseikai Senri Hospital Ethics Committee, and every patient provided informed written consent.

Study Protocol
This study was a randomized, prospective, single-center study. In order to examine efficacy of DP in anterior STEMI the patients were divided into 2 groups: stenting without a DP device (non-DP group, n=17) or stenting with a DP device (DP group, n=19). The primary endpoint was the IMR and the secondary endpoints were Thrombolysis In Myocardial Infarction (TIMI) flow grade, ST resolution (STR), peak creatine kinase and CK-MB levels, and major adverse cardiac events (MACE) at 30 days after the procedure [MACE was defined as death, MI, or target lesion revascularization (TLR)].

Primary PCI
Following a diagnosis of STEMI, antiplatelet therapy was administered with a loading dose of 300 mg of clopidogrel or 200 mg of ticlopidine and 200 mg of aspirin before primary PCI, regardless of background therapy. Prior to coronary angiography (CAG) all patients received intravenous heparin (8,000 U before PCI) and intracoronary nitroglycerin (200 μg).

Following CAG, reperfusion was achieved by passing a guidewire through the IRA, and then all patients underwent aspiration thrombectomy with several repetitions of aspiration.10 Balloon predilatation was performed in patients in whom an extraction catheter could not be advanced into the lesion. The physicians, who were unaware of the treatment group assignment, determined whether the DP device (Filtrap, Nipro, Japan) would be used in the PCI, and stenting was performed according to routine practice.

Coronary Physiological Measurements
After successful stenting of the culprit lesion, a PressureWire™ Certus (St Jude Medical, USA) was advanced through the guiding catheter and positioned in the distal two-thirds of the IRA, beyond the stented region. This guidewire has a microsensor located 3 cm from the floppy tip, which enables simultaneous high-fidelity recording of coronary pressure and temperature with accuracies of 1 mmHg and 0.02°C. The shaft of the guidewire, acting as additional electric resistance, can be used as a second thermistor, recording the input signal at the coronary ostium of any fluid injection with a temperature different from that of blood. Proximal aortic and distal coronary pressures were recorded simultaneously. A single intracoronary bolus of 12 mg papaverine was used as a hyperemic agent. Mean hyperemic transit time was determined by averaging the transit times after 3 injections of 3 ml of room-temperature saline through the guiding catheter as previously described.12 IMR was defined as distal coronary pressure divided by the inverse of the mean hyperemic transit time, or more simply, distal coronary pressure multiplied by the mean hyperemic transit time [mmHg/s, or units (U)].3

Angiography
The initial and postprocedural blood flow in the IRA was graded according to the TIMI system.5,14 Collateral circulation was quantified according to the method of Rentrop et al.15 The images were independently analyzed offline by 2 experienced interventional cardiologists who were unaware of the IMR results.

Electrocardiography
For the analysis of STR, ECG was performed at admission to hospital and at 60 min after reperfusion. ST-segment elevation was summed from all the infarct-related leads on the baseline ECGs and from the same leads on the postprocedural ECGs.16 The percentage of STR from baseline to 60 min after the last contrast injection was calculated using Schroder’s classification: complete (>70%), partial (30–70%) or absent (<30%).17

Blood Samples
Blood samples for creatine kinase (CK) and CK-MB measurements were collected before reperfusion and at 1, 2, 6, 9, 12, 18, 24, 36, 48, and 72 h thereafter.18 Peak CK and CK-MB levels were defined as the highest CK and CK-MB values measured.

Coronary Risk Factors
Coronary risk factors were determined as follows: diabetes (history or presence of diabetes and/or a fasting plasma glucose concentration >126 mg/dl and/or a glycosylated hemoglobin level ≥6.5% detected during hospitalization); hypertension (history of hypertension and/or systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg); dyslipidemia (history of dyslipidemia and/or low-density lipoprotein cholesterol ≥140 mg/dl and/or high-density lipoprotein cholesterol <40 mg/dl and/or triglycerides 150 mg/dl).

Statistical Analysis
Values are mean±standard deviation and percentages. The Wilcoxon signed-rank test was used for paired comparisons. Spearman correlation analysis was used to assess correlations between IMR and measures of microvascular function or infarct size. A P value <0.05 was considered statistically significant. Statistical analysis was performed using JMP 7.0.1 (SAS Institute Inc, Cary, NC, USA).

Results

Patients’ Baseline Characteristics
Patient characteristics such as age, sex, risk factors and preinfarction angina were analyzed statistically and there were no significant differences between the 2 treatment groups (Table 1). Preinfarction angina was defined as 1 or more episodes of typical chest pain lasting less than 30 min during the week before infarction.

Angiographic Findings of the Culprit Lesion and the Recanalization Time
There were no significant differences between the 2 treatment groups for the following variables: collateral flow grade, ratio of multiple vessel disease, ratio of initial TIMI flow grade, symptom-onset to balloon time or door-to-balloon time.
time (Table 1).

Primary Endpoint
The mean IMR of all 36 patients with STEMI after primary PCI was 31.6 U. The IMR in the DP group was significantly lower than that in the non-DP group (26.6 ± 25.8 U vs. 37.2 ± 23.2 U, P=0.03242) (Figure).

Secondary Endpoints
There was no statistical significance between the 2 treatment groups for final restoration of TIMI flow grade 3, STR completion, peak CK, peak CK-MB and MACE at 30 days after procedure (Table 2). However, final restoration of TIMI 3 was 13/17 (78%) vs. 17/19 (89%) and STR completion was 4/17 (25%) vs. 9/19 (47%) for the non-DP and DP groups respectively. Peak CK was 3,281 ± 1,399 IU/L vs. 2,818 ± 1,555 IU/L for the non-DP and DP groups respectively. In terms of MACE at 30 days after procedure, 1 patient in the non-DP group died of severe pneumonia after deterioration in heart function.

Filter No-Reflow (FNR) Phenomenon
We also investigated the FNR phenomenon in the DP group, which revealed a high rate of 18/19 (95%). We confirmed that FNR is a transient impairment of epicardial flow and is reversible following removal of the filter.20,21

Discussion
In this study, the IMR in the DP group was significantly lower than that in the non-DP group, indicating that microvascular damage during primary PCI could be reduced by using a DP device in cases of acute anterior STEMI. This is the first study to report such an outcome.

IMR
STEMI patients frequently have impaired coronary microcirculation after primary PCI, which strongly influences prognosis.2 The IMR has been demonstrated to correlate very well with the true microvascular resistance, and it can distinguish normal and abnormal microcirculation function without being influenced by the presence of an epicardial stenosis.22 Fearon et al demonstrated that, compared with standard mea-

Table 1. Patients’ Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Non-DP (n=17)</th>
<th>DP (n=19)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>63.7 (8.4)</td>
<td>62.7 (12.2)</td>
<td>0.9494</td>
</tr>
<tr>
<td>Male</td>
<td>13 (76%)</td>
<td>15 (79%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Diabetes</td>
<td>5 (29%)</td>
<td>9 (47%)</td>
<td>0.2699</td>
</tr>
<tr>
<td>Hypertension</td>
<td>9 (53%)</td>
<td>11 (58%)</td>
<td>0.7652</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>10 (59%)</td>
<td>14 (74%)</td>
<td>0.345</td>
</tr>
<tr>
<td>Smoker</td>
<td>12 (71%)</td>
<td>13 (68%)</td>
<td>0.8879</td>
</tr>
<tr>
<td>Preinfarction angina</td>
<td>9 (50%)</td>
<td>9 (47%)</td>
<td>0.7385</td>
</tr>
<tr>
<td>Initial TIMI</td>
<td></td>
<td></td>
<td>1.000</td>
</tr>
<tr>
<td>0/1</td>
<td>16 (94%)</td>
<td>17 (89%)</td>
<td></td>
</tr>
<tr>
<td>2/3</td>
<td>2 (11%)</td>
<td>2 (11%)</td>
<td></td>
</tr>
<tr>
<td>Collateral grade ≥1</td>
<td>4 (24%)</td>
<td>2 (11%)</td>
<td>0.3911</td>
</tr>
<tr>
<td>Multivessel disease</td>
<td>9 (53%)</td>
<td>5 (26%)</td>
<td>0.1019</td>
</tr>
<tr>
<td>Onset-to-balloon time (min)</td>
<td>196 (223)</td>
<td>275 (223)</td>
<td>0.093</td>
</tr>
<tr>
<td>Door-to-balloon-time (min)</td>
<td>52 (30)</td>
<td>86 (140)</td>
<td>0.4757</td>
</tr>
</tbody>
</table>

Values are number (%), or mean (SD).

Table 2. Myocardial Damage and Outcome

<table>
<thead>
<tr>
<th></th>
<th>Non-DP (n=17)</th>
<th>DP (n=19)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Final TIMI flow grade 3</td>
<td>13 (78%)</td>
<td>17 (89%)</td>
<td>0.3911</td>
</tr>
<tr>
<td>STR complete</td>
<td>4 (25%)</td>
<td>9 (47%)</td>
<td>0.1787</td>
</tr>
<tr>
<td>Peak CK (IU/L)</td>
<td>3,281 (1,399)</td>
<td>2,818 (1,555)</td>
<td>0.7755</td>
</tr>
<tr>
<td>Peak CK-MB (IU/L)</td>
<td>279 (173)</td>
<td>296 (185)</td>
<td>0.8492</td>
</tr>
<tr>
<td>MACE</td>
<td>1 (6%)</td>
<td>0 (0%)</td>
<td>1.000</td>
</tr>
</tbody>
</table>

Values are number (%), or mean (SD).

CK, creatine kinase; MACE, major adverse cardiac events; STR, ST resolution. Other abbreviations see in Table 1.
measurements, IMR is a better predictor of microvascular damage and recovery of left ventricular function after STEMI. Lim et al also showed that IMR is a reliable, early, on-site determinant of myocardial viability and left ventricular recovery after primary stenting for AMI. Although the IMR may better predict the extent of microvascular damage after primary PCI, an effective therapy is not yet available. In this study, the STEMI patients in the DP group had significantly lower IMR values than those in the non-DP group, which indicates that microvascular damage after primary PCI can be reduced in cases of acute anterior STEMI by using a DP device.

Fearon et al reported that the mean IMR was 39 U in their study of patients with STEMI after primary PCI, although patients with stable coronary artery disease and no obvious microvascular dysfunction showed a much lower mean IMR of 21.9–23.0 U. Lim et al reported a mean IMR of 34 U in their patients with anterior AMI undergoing primary PCI with stenting. The STEMI patients in the non-DP group of our study had a similar mean IMR value (37.2 U), whereas the DP group had a lower mean IMR value of 26.6 U, which clearly suggests that impaired coronary microcirculation among the patients with STEMI was reduced when DP was provided.

According to previous studies, the optimal cut-off value of the IMR for left ventricular functional recovery may range from 32 U to 33 U. In the present study of STEMI patients, a higher mean IMR value than the optimal IMR cut-off value was recorded for the non-DP group, and a lower mean IMR value for the DP group. Although we did not confirm the significance of the secondary endpoints between the 2 groups, the lower IMR values in the DP group could possibly reflect real-time recovery of left ventricular function. We suggest that real-time quantitative measurement of the pressure-derived IMR immediately after PCI is a very important clinical technique for assessing microvascular dysfunction and indicating the need for adjunctive therapy. The recently developed novel dual-sensor (pressure and Doppler velocity) guidewire (PressureWire™ Certus, St Jude Medical) may provide more precise information about microvascular damage.

Effectiveness of DP
Reperfusion therapy is the established treatment for patients with STEMI and its success is evaluated by the TIMI flow grade on the final coronary angiogram. However, clinical studies using contrast echocardiography and Doppler flowmetry have revealed the existence of poor myocardial reperfusion, and those reports reemphasize the importance of restoring microvascular circulation, except for epicardial coronary flow. Accordingly, in both groups in the present study thrombus aspiration was performed, regardless of the amount of thrombi, because thrombus aspiration before primary angioplasty has been shown to improve myocardial reperfusion in AMI. The only difference between the present 2 groups was the use of a DP device and that was associated with lower IMR values. To our knowledge, our study is the first report of using a DP device to preserve IMR during primary PCI.

In the present DP group, FNR occurred at a high rate (95%) compared with the rate in elective PCI patients reported in a previous study. This finding suggests that STEMI patients are more susceptible to microvascular damage during PCI than elective PCI patients. Not only mechanical obstruction of the filter, but also other mechanisms, such as pharmacologically active debris and/or platelet aggregates, may play a role in FNR. The lower IMR values obtained in the DP group may have been obtained by using a DP device to reduce the microvascular damage from these factors.

Safety
In this study there was no case of delivery failure, vessel damage, or problems with device withdrawal in any of the 19 patients in whom the Filtrap was used.

Study Limitations
Firstly, 36 cases from a single center is a relatively small study group. Secondly, the clinical significance of a lowered IMR with use of DP has not been clarified, because significant differences between the 2 groups in the secondary endpoints were not analyzed. The length of time the microvascular disturbances persist and their prognostic significance are not known and further research is needed.

Conclusion
DP as an adjunctive therapy of PCI for acute anterior STEMI may have beneficial effects on myocardial microcirculation because of preservation of IMR.

Disclosures
There were no funding sources and there are no conflicts of interest.

References


