The Distal Protection During Primary Percutaneous Coronary Intervention Alleviates the Adverse Effects of Large Thrombus Burden on Myocardial Reperfusion

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Background The presence of intracoronary large thrombus burden (LTB) in the infarct-related artery increases the risk of distal embolization and no-reflow during percutaneous coronary intervention (PCI). Evaluation of whether the distal protection (DP) during primary PCI reduces adverse effects of LTB on myocardial reperfusion and infarct size was investigated.

Methods and Results A consecutive series of 88 patients with acute myocardial infarction undergoing primary PCI using DP were compared with 81 consecutive patients treated by primary PCI alone. The DP use showed similar post-procedural myocardial blush grade (MBG)-3 and infarct size, but improved corrected thrombolysis in myocardial infarction frame count (cTFC) (29±11 vs 35±20, p=0.011) and the incidence of ST-segment resolution (80.7% vs 66.7%, p=0.036) in patients with LTB present, however, the DP use reduced occurrences of no-reflow (0% vs 11.8%, p=0.036) and distal embolization (4.8% vs 17.6%, p=0.129), resulting in higher occurrences of MBG-3 (61.9% vs 35.3%, p=0.021) and ST-segment resolution (78.6% vs 50.0%, p=0.009), lower cTFC values (30±8 vs 40±22, p=0.012) and smaller infarct size (12.2±11.2 vs 18.7±11.1, p=0.015).

Conclusions With an improved myocardial reperfusion and smaller infarct size in patients with LTB, the DP during primary PCI might be a better strategy in this particular setting compared with conventional strategy. (Circ J 2006; 70: 232–238)

Key Words: Acute myocardial infarction; Distal protection; Myocardial reperfusion; Thrombus
group of 81 consecutive patients undergoing primary PCI without using the DP device for AMI during the preceding 1 year (control group). Inclusion criteria included continuous chest pain more than 30 min and associated with ST-segment elevation of at least 0.1 mV in 2 or more contiguous leads on the 12-lead electrocardiogram (ECG), and admission either within 6 h of symptom onset or between 6 and 24 h if there was evidence of continuing ischemia. Exclusion criteria were: presence of left bundle-branch block or pacemaker-induced rhythm at admission ECG; a small-sized vessel incapable of accepting DP device; significant left main coronary disease; severe proximal tortuosity; lesions situated in the distal portion of coronary artery; and previous myocardial infarction. Informed written consent was obtained from patients in accordance with the Declaration of Helsinki.

**Procedural Protocol**

The procedures were performed by means of femoral or radial approach, with arterial introducers of size 6 to 8-French. Before the procedure, 81–162 mg of aspirin was prescribed and 10,000 IU of heparin was given if not contraindicated. Thrombolytic agents were used according to the operator's discretion. Platelet glycoprotein IIb/IIIa receptor inhibitors were not used in the present study, as they were not available in Japan during the study period. During intervention, the activated clotting time was maintained at ≥250 s. All patients were treated with aspirin (81–162 mg daily). Ticlopidine (200 mg daily) was also administered for at least 3 months after a stent was implanted.

The GuardWire Plus (Medtronic Corp, Santa Rosa, CA, USA) consists of a 0.014-inch guidewire incorporating a central inflation lumen to which an elastomeric balloon (3.0–6.0 mm in diameter) is attached distally. Once distal to the lesion, injection of diluted contrast results in balloon inflation with subsequent cessation of antegrade flow. Intervention is then performed over the wire, after which liberated debris suspended within a stagnant blood column is aspirated through the aspiration catheter. The GuardWire balloon is then deflated and flow restored. Operators were instructed to position the elastomeric balloon as close to the lesion as possible to minimize exposure of unprotected side branches to embolic debris. In the case of GuardWire inability to cross the target lesion, a second attempt was made with a traditional guidewire as a ‘buddy’ wire and, if necessary, by predilation with a small sized balloon (1.5–2.0 mm in diameter). Aspiration prior to PCI was performed to decrease thrombus burden and improve distal visualization. The decision of whether to perform stent implantation was left to the discretion of the operator. All predilation and post-dilation balloon inflations, as well as stent placement, were to be protected if possible.

In the control group, primary PCI was performed according to standard methods without using a DP device. The use of thrombectomy device before balloon inflation, and coronary stents were at the discretion of the operator.

**Angiographic Analysis**

The angiograms were re-read as a single group by 2 experienced observers blinded to clinical data. Quantitative coronary analysis (QCA) was performed using the Cardiovascular Measurement System (CMS-MEDIS Medical Imaging Systems, Nuenen, The Netherlands).

Intracoronary thrombus was angiographically identified and scored in 5 degrees as previously described by Gibson et al. A patient was considered to have intracoronary LTB if Thrombolysis In Myocardial Infarction (TIMI) thrombus score 3 to 5 were present in the IRA with a diameter ≥3.0 mm. QCA parameters, TIMI flow grade, corrected TIMI frame count (cTFC), and myocardial blush grade (MBG) were measured as described previously. Follow-up coronary angiography and left ventriculography were performed at 6 months or earlier if they had recurrent symptoms. Left ventricular (LV) end-diastolic volume index (LVEDVI) and LV end-systolic volume index (LVESVI) were measured using Simpson's method, and the ejection fraction (EF) was calculated.

**ECG and Laboratory Data**

A serial ST-segment analysis on a 12-lead ECG recording just before and at the end of the coronary intervention was performed by 2 blinded observers. The sum of ST-segment elevation was calculated in each ECG from leads exploring the infarct area as described previously. A >50% reduction of the initial value was considered significant ST-segment elevation recovery.

Creatine kinase (CK) was measured every 8 h during the first day, then daily until discharge.

**SPECT Scintigraphic Analysis**

Before the patients were discharged, resting tailedium-201(T2) myocardial single-photon emission computed tomography (SPECT) was performed. After overnight fasting, an intravenous bolus injection of 201Tl (111 MBq) was performed at rest, and data acquisition was started 20 min after radionuclide injection using a one-headed SPECT system with low-energy, all-purpose, parallel-hole collimators (GCA-7100A, Toshiba, Tokyo, Japan). Tomographic slices (6-mm thick) were reconstructed for the vertical long-axis, horizontal long-axis, and short-axis. A defect score as a measurement of infarct size was calculated using a 17-segment 5-point scoring system (0, normal uptake; 1, mildly reduced; 2, moderately reduced; 3, severely reduced; 4, defective) in a blinded manner by the 2 experienced cardiologists. The sum of each score of the infarct-related segments was defined as the total defect score (TDS), indicating the severity of impaired myocardial perfusion.

**Definitions**

Angiographic procedural success was defined as a reduction in stenosis to <50% by QCA and a TIMI grade 3. Distal embolization was defined as the presence of filling defects or cut-off of the distal branch or vessel. No-reflow was defined as TIMI grade ≤1 flow in the distal IRA in the absence of a mechanical obstruction at the treatment site or evidence of distal embolization. Major adverse cardiac events (MACE) were defined as death, myocardial infarction, and target vessel revascularization during the hospital stay or at follow up. The angiographic restenosis was defined as a stenosis ≥50% measured with QCA on the follow-up angiography.

**Statistical Analysis**

Data were expressed as mean±SD for continuous variables and as percentages for discrete variables. Student's unpaired t-test or Mann–Whitney U-test was used to compare continuous variables between groups. Categorical variables were compared by χ² test or Fisher's exact test, as appropriate. Multivariate regression analysis was per-
formed to identify independent predictor of MBG-3 and ST-segment elevation resolution >50% after the procedure in patients with LTB present. This model included age, gender, infract location, diabetes, Killip class ≥2, thrombolytic therapy, multivessel disease, preinfarction angina, occluded IRA at baseline, the presence of collaterals, stent use, pain onset-to-PCI time, and the DP device use. A value of p<0.05 was considered statistically significant.

### Results

The baseline clinical and angiographic characteristics are shown in Table 1. There were no significant differences in the baseline characteristics of patients between the 2 groups.

#### Procedural and Clinical Outcomes in the DP Group and Controls

Table 2 summarizes the procedural outcomes and in-
Distal Protection for Large Thrombus Burden

Procedural and Clinical Outcomes in Patients With LTB

Before intervention, LTB was present in 42 of 88 (47.7%) patients in the DP group and 34 of 81 (42.0%) in the control group (p=0.43). Table 3 shows a comparison of the angiographic, procedural, and clinical outcomes of the 2 study groups in patients treated for large thrombus-containing lesions with and without DP. There were no significant differences in terms of baseline clinical and angiographic features between the 2 groups. After PCI, TIMI-3 flow, MBG-3 and ST-segment elevation resolution were obtained more frequently in the DP group, which also showed lower cTFC values. Furthermore, the incidence of no-reflow occurrence and TDS were significantly less in patients treated with DP. At 6 months, LVEF (53.7±14.1% vs 48.4±9.1%, p=0.052) tended to be higher and both LVEDVI (83.1±14.5 ml/m² vs 91.7±13.8 ml/m², p=0.044) and LVESVI (39.2±13.0 ml/m² vs 47.7±12.7 ml/m², p=0.029) were significantly lower in the DP group. The rate of occurrence of MACE was not significantly different (DP, 11.9%; controls, 20.6%, p=0.354).

In 76 patients who had LTB in the IRA, multivariate analysis indicated that the DP device use was an independent predictor of postprocedural MBG-3 (odds ratio, 2.70;
95% confidence interval, 1.03–7.08; p=0.043) and ST-segment elevation resolution >50% (odds ratio, 3.90; 95% confidence interval, 1.17–12.94; p=0.026).

Procedural and Clinical Outcomes in Patients Without LTB

However, 46 of 88 (52.3%) patients in DP and 47 of 81 (58.0%) patients in controls did not have LTB in the IRA (Table 4). At the baseline, clinical and angiographic characteristics were similar between the 2 treatment groups. After the procedure, there were no significant differences between the 2 groups in the frequencies of TIMI-3 flow, MBG-3, angiographically documented thromboembolic complications and ST-segment resolution >50%. Likewise, cTFC, peak CK values, and TDS were similar between the 2 groups. Similarly, no significant differences regarding LVEF (DP, 52.8±7.7%; controls, 52.0±8.6%, p=0.688), LVEDVI (DP, 86.7±13.2 ml/m²; controls, 85.4±18.6 ml/m², p=0.761) and LVESVI (DP, 41.4±12.1 ml/m²; controls, 41.5±12.6 ml/m², p=0.982) at 6 months were observed. In addition, cumulative MACE at 6 months were 15.2% in the DP group and 25.5% in the control group (p=0.217).

A Comparison of Myocardial Reperfusion and Infarct Size Between Patients With and Without LTB in Each Group

In controls, MBG-3 and ST-segment resolution >50 were significantly less frequent (35.3% vs 61.7%, p=0.019 and 50.0% vs 78.7%, p=0.007, respectively), and cTFC and TDS were significantly higher (40±22 frames vs 31±17 frames, p=0.047 and 18.7±11.1 vs 13.5±9.7, p=0.029, respectively) in patients with LTB. Conversely, no significant differences between patients with and without LTB were seen in terms of MBG-3 (61.9% vs 58.7%, p=0.776), ST-segment resolution (78.6% vs 82.6%, p=0.632), cTFC (30±8 vs 28±13, p=0.334), and TDS (12.2±11.2 vs 13.4±9.9, p=0.619) in the DP group. In addition, cTFC, ST-segment resolution and TDS were significantly correlated with TIMI thrombus score in controls (r=0.33, p=0.003; r=–0.43, p<0.001; r=0.37, p=0.001, respectively), whereas no significant correlations were seen between TIMI thrombus score and cTFC (r=0.04, p=0.738), ST-segment resolution (r=–0.18, p=0.094) and TDS (r=0.15, p=0.619) in the DP group.

Discussion

The major findings of the present study are as follows: (i) the use of the DP device during primary PCI showed similar microcirculatory filling and infarct size but improved postprocedural epicardial flow and ST-segment resolution; (ii) in patients with LTB present; however, the DP device use reduced thrombotic procedural complications, resulting in improvement of these surrogate markers of effective myocardial reperfusion and smaller infarct size; and (iii) in contrast, the use of DP did not improve epicardial flow or coronary microcirculatory function, or reduce infarct size in patients without LTB. Finally, the
presence of LTB significantly deteriorated markers of myocardial reperfusion and infarct size in patients treated with conventional PCI, a strategy of additional treatment using the DP device might alleviate adverse effects of LTB on myocardial damage because of reperfusion and the extent of infarct size in this population.

Adverse Effects of LTB on Myocardial Reperfusion

Improved perfusion of viable myocardium preserves cardiac function and conveys long-term survival benefits in patients with AMI. Mechanical reperfusion for AMI targets optimal revascularization of the epicardial coronary artery, but also aims at improved myocardial salvage. However, the presence of an intracoronary thrombus makes both of these goals difficult to achieve because balloon inflation or stent implantation might break down the organized thrombus into fragmented debris, which can lead to embolization of branch or distal vessels and occlusion of the microvasculature, culminating in microvascular dysfunction and no-reflow occurrence. Angiographic evidence of distal embolization during primary PCI has been reported to range from 6% to 15%, and is associated with more extensive myocardial damage and a subsequent poor prognosis. Fukuda et al revealed that an intracoronary mobile mass, which would be thrombus burden and/or plaque fragment, was a strong predictor of distal embolization. Likewise, the effective myocardial reperfusion after PCI is also limited by a 5% to 20% incidence of no-reflow, which has been shown to occur in proportion to the amount of thrombus in the IRA. Cura et al previously showed that the presence of a visible thrombus on a baseline angiogram was an independent predictor of the postprocedural suboptimal angiographic coronary flow, which is associated with increased mortality risk. Furthermore, other recent studies suggested that a large IRA, which mostly contained LTB and lipid pool-like plaque contents, played a crucial role in slow-flow or no-reflow during primary PCI. Thus, the presence of intracoronary thrombus, especially in cases with large amounts, has been identified as a risk factor of unfavorable outcomes because of increased risk of distal embolization and the subsequent no-reflow, and the prevention of these thromboembolic complications can be a critical issue in this setting.

The Efficacy of DP on Myocardial Reperfusion

Recently, the distal balloon occlusion and aspiration system became available and have been extensively used as an adjunct to primary PCI to reduce the thromboembolic complications in patients with AMI. A recent report using the intracoronary Doppler guidewire revealed that the use of the DP device effectively reduced the number of embolic particles detected as high-intensity transient signals. The analyses of several single-center trials have shown that primary PCI using DP device retrieves embolic debris in more than 50% of patients and might result in improved surrogate markers of effective reperfusion such as cTFC, MBG and ST-segment resolution, LV function, and clinical outcomes in comparison with either historical or concurrent controls. In the recently published randomized, multicenter EMERALD trial, however, the DP device use failed to show improved microvascular flow, greater reperfusion success, reduced infarct size, or enhanced event-free survival, as compared with primary PCI alone. Unfortunately, they did not analyze the relationship between the amount of thrombus and the efficacy of each reperfusion strategy in detail. In the present study, although the presence of LTB significantly deteriorated markers of myocardial reperfusion and extended infarct size in patients treated with conventional PCI, the DP use successfully diminished these adverse effects of larger thrombus. Importantly, the DP during primary PCI improved epicardial flow and microvascular integrity, and reduced infarct size in patients with LTB, whereas the DP use did not exert any salutary effects on these surrogate markers of myocardial reperfusion or infarct size in patients without LTB. This is the first report providing further information concerning the relationship between the size of thrombus and the efficacy of the DP compared with conventional reperfusion strategy. The findings of the present study are in agreement with those of the previous study in showing that the DP use improved myocardial reperfusion in large IRA ≥3.5 mm with high-burden thrombus formation. Additionally, comparable results were reported in patients treated with the X-Sizer thrombectomy system (EndiCOR, San Clemente, CA, USA), which was found to be particularly effective in larger IRA with a diameter >3.0 mm. These results strongly suggest that use of the DP device during primary PCI could alleviate the detrimental effects of thrombus on myocardial reperfusion, especially when LTB was present, which might therefore have contributed to smaller infarct size.

The major reason for the different outcomes between the present study and the EMERALD trial could be ascribed to differences in populations. The current study included a higher-risk population. Because patients with AMI presentation >6 h after the onset of symptom or cardiogenic shock were excluded in the EMERALD trial, our population was clearly different from that of this trial. Accordingly, times from symptom onset to hospital arrival in the present study was markedly longer than in the EMERALD trial (357 min vs 77 min). The risk of the distal embolization and, the slow-flow or no-reflow occurrence after primary PCI might increase in direct proportion to reperfusion time. Furthermore, the frequencies of Killip class ≥2 and diabetes in the present study were substantially more (19.5% vs 12.4%, and 32.0% vs 12.4%, respectively), and vessel size of the IRA in the current study was larger (DP, 3.32 mm vs 3.11 mm; control, 3.23 mm vs 3.06 mm). These conditions have been described to favor an abnormal myocardial perfusion. Indeed, in the control arm in the EMERALD trial, incidences of distal embolization (5.8% vs 9.9%) and no-reflow (2.5% vs 6.2%) were less frequent, resulting in more MBG-3 (52.9% vs 50.6%) and ST-segment resolution >70% (61.9% vs 40.7%), and lower cTFC values (20 frames vs 35 frames) than controls in the current study. Therefore, the different clinical and lesion characteristics might play a key role in the contradictory results.

Study Limitations

The current study has several potential limitations. First, the present study shows a retrospective single-center experience in a limited number of patients, requiring large confirmatory trials. Second, the current study was not structured and powered to show benefits in terms of clinical outcome. Instead, it assessed surrogate markers of effective myocardial reperfusion known to be associated with improved ventricular function and mortality. Third, ECG analysis was performed before and after PCI, and mean time intervals between ECG tracings obtained before and after PCI were similar in the 2 groups (DP, 184±60 min;
control, 193±78 min, p=0.403). Although continuous ECG recordings could have provided more accurate information, they are difficult to apply during PCI in such acutely ill patients. Finally, the results of the present study might not be applicable to the entire range of AMI because small-sized vessels, left main coronary disease, severe proximal tortuosity, lesions situated in the distal portion of coronary artery and previous myocardial infarction were excluded from the enrollment.

Conclusions

The use of the DP device during catheter-based treatment of AMI shows similar microcirculatory filling and infarct size, but improves coronary epicardial flow and ST-segment resolution, compared with conventional PCI alone. In patients with LTB present, however, the DP device use improves myocardial reperfusion and decreases infarct size by reducing thromboembolic procedural complications, indicating that the DP during primary PCI might alleviate the adverse effects of larger thrombus on myocardial reperfusion and infarct size in this particular population. Accordingly, an adjunctive treatment using the DP device should be particularly considered in cases with LTB present.

References