DELETERIOUS EFFECTS OF THE PACLITAXEL-COATED BALLOON ON CORONARY MICROCIRCULATION

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Abstract

Background: Therapeutic options for coronary in-stent restenosis include paclitaxel-coated balloon (PCB), as well as drug eluting stents (DES). A previous basic study has shown that 70% of paclitaxel flows out to the distal coronary artery and only 16% of paclitaxel is transferred to the vessel wall during PCB procedure. However, the effect of PCB on coronary microcirculation remains unknown. The aim of this study was to examine whether PCB impairs coronary microcirculation.

Methods and Results: Forty patients who underwent elective coronary revascularization for in-stent restenosis were randomly assigned to the DES group (n = 20) or the PCB group (n = 20). Coronary microcirculation was evaluated before and after angioplasty by measuring the microvascular resistance (MVR). The baseline characteristics were not different between the two groups. No significant changes were detected in MVR after DES (4.1 ± 0.8 vs. 4.3 ± 1.2, P = 0.17). However, the PCB group revealed a significant increase in MVR after revascularization (from 4.0 ± 0.9 to 6.7 ± 3.7, P < 0.001). Slow flow phenomena emerged in 2 patients who underwent PCB but none with DES. Moreover, relative changes of MVR after angioplasty correlated with the paclitaxel coated area (r = 0.69, P < 0.001).

Conclusions: These results suggest that PCB impairs the microcirculation. This deleterious effect might be caused in part by distal embolism with coated drug.

Key words: coronary microcirculation, microvascular resistance, paclitaxel coated balloon, percutaneous coronary intervention, coronary revascularization

Introduction

Percutaneous coronary intervention (PCI) is currently performed to treat ischemic heart disease; however, in-stent restenosis remains a limitation of this treatment. With regard to the methods to prevent restenosis, several large-scale randomized clinical trials have demonstrated that drug eluting stents (DES) lower the restenosis rate more effectively compared to bare metal stents (BMS)\textsuperscript{1-4}. However, the preventive effects are insufficient in some cases despite DES placement. Thus, restenosis continues to be a problem\textsuperscript{5-7}.

Recent study using animal models of restenosis have shown that the lipophilic character of paclitaxel enables rapid transfer and strong binding to the vascular wall tissue that allow drug absorption and intracellular retention to inhibit neointimal formation after balloon dilation\textsuperscript{8-12}. Favorable results have been reported after clinical use of paclitaxel-coated balloons (PCB) for in-stent restenosis treatment\textsuperscript{13,14}. The PCB surface is coated with a mixture of contrast agent and paclitaxel that prevents restenosis. According to previous studies, approximately 16% of the drug coating is effective in the vessel wall,
10-20% remains on the balloon, and 60-70% is lost during the procedure\textsuperscript{15-17}. However, the effect of paclitaxel lost in the blood stream in the distal coronary microcirculation remains unknown.

Coronary arteriography is an effective method of evaluating the presence of coronary artery lesions. However, it only allows evaluation of epicardial coronary arteries, which only accounts for 5% of that of the entire heart, whereas evaluating the remaining 95% comprising the coronary microcirculation is difficult. Microvascular resistance (MVR) can be measured today using a wire that enables simultaneous measurement of coronary artery pressure and blood flow. Therefore, this wire was placed in the coronary artery to take a direct measurement of MVR to evaluate the effect of paclitaxel that is released into the blood flow distal to the balloon on the coronary microcirculation.

### Methods

#### Patient Population

This study was a single center, prospective, randomized, clinical trial. Between April 2014 and March 2017, serial 57 patients with in-stent restenosis were underwent PCI in our hospital and were considered for enrollment in this study. Among them, 17 patients were excluded by the following the exclusion criteria. 40 patients who underwent coronary angioplasty with in-stent restenosis were enrolled. Eligible patients were assigned randomly to the DES group (n = 20) or the PCB group (n = 20). Exclusion criteria were as follows: acute coronary syndrome, heart failure, hypertrophic cardiomyopathy, pressure wire passage failure, severe aortic stenosis / regurgitation, atrial fibrillation, left ventricular ejection fraction < 30%, infarction, renal dysfunction > 2.0 mg/dL, total occlusion of culprit vessel, 3-vessel disease, left main stenosis, presence of definite thrombus or extreme tortuosity, and contraindication to adenosine. Patients were pre-treated with aspirin (100 mg) and clopidogrel (75 mg). Before PCI, patients received intravenous heparin with a target activated clotting time of > 300 sec. Blood samples were collected before and at six and 12 hours after PCI to measure creatine kinase-myocardial band (CK-MB), creatine kinase (CK), and high sensitive Troponin-T (hs-Trop T) levels. The objectives and protocol of this study were fully explained, and informed consent was obtained from all patients. This study was carried out with the approval of the regional ethics committee in accordance with the standards of the Declaration of Helsinki.

#### Percutaneous coronary intervention procedure and coronary physiology measurements

Cardiac catheterization was performed in patients in the fasting state following the oral administration of 5 mg of diazepam. All patients underwent PCI for the in-stent restenosis. All procedures were performed using standard techniques. The fractional flow reserve (FFR) was measured before and after PCI with plain old balloon angioplasty (POBA) and DES or PCB (Figure 1). FFR was calculated using the ratio of mean distal pressure to mean aortic pressure at maximal hyperemia\textsuperscript{18}. MVR was measured before and after PCI with DES or PCB (Figure 1) using a 0.014-inch intracoronary Doppler-tipped guide-wire (ComboWire, Volcano San Diego, CA, USA). MVR were determined as the ratio of mean distal pressure to average peak flow velocities during hyperemia\textsuperscript{19} (PMID : 11208673). Intravenous infusion of adenosine (150 μg/kg/min) was then administered via the femoral vein or large peripheral vein to induce steady

![Figure 1. Study design and flow](image-url)
state maximal hyperemia.

Statistical analysis
Data are presented as mean ± standard deviation (SD). Differences between means were compared using paired or unpaired Student’s t-tests, as appropriate. Correlations were evaluated using Pearson’s correlation coefficient. P < 0.05 was considered to indicate statistical significance. All statistical analysis was performed using SPSS for Windows version 19.0 (SPSS, Chicago, IL, USA).

Results
Baseline and procedural characteristics
As shown in Table 1, the DES and PCB groups did not differ significantly in age, sex, prevalence of cardiovascular risk factors, current medications, metabolic profiles, and left ventricular function. Angiographic and procedural characteristics were also comparable between the groups in terms of coronary anatomy, lesion type, procedural characteristics, and diameter and length of implanted stents or PCB (Table 2).

Physiological measurements
Fractional Flow Reserve
We successfully obtained the physiological parameters, such as pre- and post-POBA and post-DES or post-PCB FFR in all patients. No significant difference was found between the post-POBA FFR of the DES and PCB groups (FFR, post-POBA, 0.9 ± 0.03 vs. 0.89 ± 0.06, P=0.53). Likewise, no significant difference was detected between post-DES and post-PCB FFR of the DES and PCB groups (post-DES or PCB, 0.91 ± 0.03 vs. 0.90 ± 0.06, P = 0.67) (Figure 2).

Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>DES group (N = 20)</th>
<th>PCB group (N = 20)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>72.15±2.39</td>
<td>71.0±2.15</td>
<td>0.723</td>
</tr>
<tr>
<td>Male</td>
<td>16 (80)</td>
<td>16 (80)</td>
<td>0.478</td>
</tr>
<tr>
<td>Hypertension</td>
<td>12 (60)</td>
<td>11 (55)</td>
<td>0.999</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>12 (60)</td>
<td>11 (55)</td>
<td>0.765</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>12 (60)</td>
<td>13 (65)</td>
<td>0.751</td>
</tr>
<tr>
<td>Family history of CAD</td>
<td>5 (25)</td>
<td>6 (30)</td>
<td>0.731</td>
</tr>
<tr>
<td>Current smoking</td>
<td>5 (25)</td>
<td>10 (50)</td>
<td>0.107</td>
</tr>
<tr>
<td>Medications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>20 (100)</td>
<td>20 (100)</td>
<td>NS</td>
</tr>
<tr>
<td>ACE / ARB</td>
<td>17 (85)</td>
<td>17 (85)</td>
<td>0.686</td>
</tr>
<tr>
<td>CCB</td>
<td>5 (25)</td>
<td>6 (30)</td>
<td>0.731</td>
</tr>
<tr>
<td>Nitrates</td>
<td>15 (75)</td>
<td>16 (80)</td>
<td>0.713</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>6.83±0.19</td>
<td>6.76±0.12</td>
<td>0.749</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>146.4±4.43</td>
<td>148.4±4.82</td>
<td>0.761</td>
</tr>
<tr>
<td>Triglyceride (mg/dL)</td>
<td>126.4±14.0</td>
<td>103.9±11.6</td>
<td>0.226</td>
</tr>
<tr>
<td>LDL-cholesterol (mg/dL)</td>
<td>75.9±3.63</td>
<td>76.1±3.31</td>
<td>0.966</td>
</tr>
<tr>
<td>HDL-cholesterol (mg/dL)</td>
<td>52.3±2.99</td>
<td>55.6±3.37</td>
<td>0.465</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>57.3±2.71</td>
<td>54.8±2.57</td>
<td>0.508</td>
</tr>
</tbody>
</table>

Variables are presented as mean ± standard deviation or n (%) 
No significant differences were found between the two groups 
CAD: coronary artery disease, ACE: angiotensin converting enzyme, ARB: angiotensin receptor blocker, CCB: calcium channel blocker, HbA1c: Hemoglobin A1c, LDL: low-density lipoprotein, HDL: high-density lipoprotein, LVEF: left ventricular ejection fraction
Microvascular dysfunction of the PCB

Microvascular Resistance
MVR in the PCB group increased significantly from 4.0 ± 0.9 to 6.7 ± 3.7 mmHg/cm/s ($P < 0.001$), whereas that in the DES group did not change significantly (4.1 ± 0.8 vs. 4.3 ± 1.2 mmHg/cm/s, $P = 0.17$) (Figure 3).

Prevalence of slow flow phenomenon
Slow flow phenomenon developed in two patients overall: two in the PCB group and none in the DES group. The difference in the prevalence of slow flow phenomenon between the two groups was significant (10% vs. 0%, $P < 0.001$) (Table 3).

Table 2. Procedural features

<table>
<thead>
<tr>
<th>Variable</th>
<th>DES group ($N = 20$)</th>
<th>PCB group ($N = 20$)</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAD lesion</td>
<td>80%</td>
<td>80%</td>
<td>NS</td>
</tr>
<tr>
<td>Predilatation balloon diameter (mm)</td>
<td>3.25±0.05</td>
<td>3.15±0.05</td>
<td>0.20</td>
</tr>
<tr>
<td>Predilatation balloon pressure (atm)</td>
<td>8.1±3.3</td>
<td>7.9±3.6</td>
<td>0.48</td>
</tr>
<tr>
<td>DES / PCB diameter (mm)</td>
<td>3.25±0.08</td>
<td>3.15±0.05</td>
<td>0.21</td>
</tr>
<tr>
<td>DES / PCB length (mm)</td>
<td>26.8±0.77</td>
<td>24.5±1.41</td>
<td>0.171</td>
</tr>
<tr>
<td>Final dilatation pressure (atm)</td>
<td>13.9±0.06</td>
<td>13.5±0.05</td>
<td>0.049</td>
</tr>
</tbody>
</table>

Variables are presented as mean ± standard deviation or $n$ (%).
No significant differences were found between the two groups.
LAD: left anterior descending coronary artery, DES: drug eluting stent, PCB: paclitaxel coated balloon

Cardiac markers
To explore the myocardial injury on the procedure, we examined the CK, CK-MB, and hs-Trop T pre- and post-procedure. No significant change of CK and CK-MB was found pre- and post-procedure (data not shown). Furthermore, hs-Trop T in the PCB group did not differ significantly from 0.04 ± 0.03 to 0.06 ± 0.04 ng/mL ($P = 0.06$), similarly that in the DES group did not change significantly (0.03 ± 0.02 vs. 0.04 ± 0.03 ng/mL, $P = 0.09$) (Figure 4).
Correlation between balloon surface area and relative change in MVR

Figure 5 shows the correlations between balloon surface area and %change of MVR. Significant correlations were found between balloon surface area and the change of MVR in the PCB group ($r = 0.69, P < 0.01$), whereas that in the DES group were not found significantly ($r = 0.28, P = 0.07$).

Discussion

This is the first study to demonstrate that MVR increase following PCI with PCB in humans. The results further suggested that the drug on the balloon coating affects MVR in a dose-dependent manner, as the rate of MVR increase was correlated with the PCB balloon surface area. However, in the DES group, no significant change was detected in MVR or a correlation with stent size after implantation.

MVR is a value calculated from coronary artery pressure and coronary flow. FFR is calculated from the ratio of peripheral to proximal coronary pressure in the lesion, and indicates the severity of stenosis. As shown in Figure 2, we found no significant difference between pretreatment FFR ratios (post-POBA) in either the DES or PCB group (FFR, post-POBA, $0.9 \pm 0.03$ vs. $0.89 \pm 0.06$, $P=0.53$). Similarly, no significant difference was detected between post-DES and post-PCB FFR of the two groups (post-DES or PCB, $0.91 \pm 0.03$ vs. $0.90 \pm 0.06$, $P = 0.67$), indicating no differences in post-operative stenosis severity. As FFR is calculated from coronary artery pressures and MVR is calculated based on coronary artery pressure and coronary flow, the results suggested that the difference between post-DES and post-PCB MVR in our investigation may be attributed to coronary flow rather than to coronary pressure. Young et al. supports our findings, as they demonstrated that coronary flow reserve decreased after using PCB. In this study, slow flow phenomenon was observed in two patients in the PCB group and in 0 patients in the DES group, as shown in Table 3. Chung et al. have also reported one case of reduced post-PCB coronary flow. The PCB used in this patient was large with a surface area of the balloon (diameter 3.0 × length 30 mm), which was identical to the size of the PCB used for our patients. The pathogenesis of slow flow is heterogeneous, but distal embolization, ischemia-reperfusion injury, increased MVR to flow or microvascular spasm was suggested. As shown in Figure 5, the rate of MVR increase was positively correlated with PCB surface area in this study. Therefore, post-PCB MVR increase may be one of the mechanisms underlying the slow flow phenomenon.

Figure 4 shows changes in the values of troponin T, an indicator of myocardial injury. An abnormally high rate of troponin T increase was found in one case that exhibit-
ed slow flow. However, no statistically significant difference was found between baseline and post-treatment values in either the DES or PCB groups. Young et al. measured post-PCB coronary flow reserve and reported cases with reduced flow, which is consistent to our results; however, they also reported some cases with reduced flow in which flow reserve improved ten minutes later20). Therefore, we can speculate that myocardial injury occurred in some cases without MVR improvement.

The precise mechanism of post-PCB MVR increase is not clear. Neither acute occlusion, nor coronary artery dissection indicative of MVR increase was observed in either coronary arteriography or intravascular ultrasonography. No significant post-DES and post-PCB FFR differences were observed between the two groups (Figure 2), which suggests that differences of coronary artery pressure or of the extensibility of the lesion part are unlikely to affect MVR. Therefore, the factor underlying MVR increase can be attributed to coronary flow. Coronary microcirculation is a major contributor to coronary flow22), and microangiopathy is considered to be underlying cause of MVR increase20). Therefore, distal embolization is considered to be the primary underlying mechanism. The PCBs used in our study are coated with the free drug. To enhance the dissolution of the drug, a small amount of radiographic contrast agent is added to the coating13,16,23). Approximately 16% of the drug in the coating was reported to have an effect on the vessel wall, whereas 10-20% remains on the balloon, and 60-70% is lost during the procedure15-17). Furthermore, slow flow phenomenon was reported that just after the PCB deflation. Coronary angioscopy revealed white granular materials that might indicate undissolved drugs on the neointima, and undissolved drugs were floating and flowed distally24,25). Histopathological study reported that PCB angioplasty led to the possibility of distal embolization26). In contrast, there are no evidences of distal embolism of the drug in DES implantation, because the DES are coated with the drug combined polymer, not free drug. As shown in Figure 5, the balloon surface area calculated from balloon length and diameter showed a significant correlation with increase in %MVR, suggesting that the undissolved drug coated on the PCB was released into the distal circulation, occluding microvessels downstream.

Endothelium-dependent coronary vasomotion of PCB can be considered to be the second underlying mechanism. Nakamura et al. reported that PCB after dilation was associated with diminished endothelial-dependent vasomotor function in the distal coronary artery, compared with non-PCB dilation or native arteries in a porcine coronary stent model. Furthermore, it was reported that vascular inflammation in response to PCB may play a role in downstream endothelial dysfunction27). It is important to recognize that PCBs are designed to allow quick delivery of the microcrystals into the coronary artery. The effect of local and possibly distally embo-lized paclitaxel could potentially explain the acute effect observed in our study.

**Limitations**

First, this study was not a blinded study, with a small study population from a single center. Second, we only performed MVR measurement in acute phase. Further studies are warranted to clarify the pathophysiology and study the long-term effects of MVR after PCI with DCB.

**Conclusion**

Our results suggest that PCB impairs the microcirculation. This deleterious effect might be caused in part by distal embolism with coated drug.

**References**


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