Usefulness of Functional Assessment in the Treatment of Patients With Moderate Angiographic Paclitaxel-Eluting Stent Restenosis

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Background: In recent years there has been a debate about the functional severity of restenosis of drug-eluting stents. The aim of the present study was to assess the functional severity of stenosis in patients with moderate angiographic restenosis after paclitaxel-eluting stents (PES) deployment.

Methods and Results: Forty-two patients with moderate angiographic restenosis at the in-stent segment and/or approximately 5 mm from the stent edge were enrolled. For comparison, furthermore, 42 patients with de novo stenosis lesions matched for angiographic severity were assigned to the control group. Quantitative coronary angiography and functional assessment using fractional flow reserve (FFR) were performed. Although percent diameter stenosis was not significantly different between the 2 groups (PES group, 40.6 ± 11.2%; de novo group, 40.6 ± 9.0%, P = 0.981), the functional severity of stenosis was significantly less in the PES group than in the de novo group (FFR: PES group, 0.86 ± 0.07; de novo group, 0.79 ± 0.10, P = 0.002).

Conclusions: FFR was preserved in patients with moderate angiographic restenosis after PES deployment, and the functional severity of restenosis is often limited. Therefore, revascularization should be performed with caution for patients with moderate angiographic restenosis after PES deployment. (Circ J 2013; 77: 1180–1185)

Key Words: Fractional flow reserve; Moderate angiographic restenosis; Paclitaxel-eluting stent

Ivory-stemmed stents (SES) and paclitaxel-eluting stents (PES) have been widely used as first-generation drug-eluting stents (DES), and various controlled trials and meta-analyses have raised some concerns about differences in the incidences of restenosis and target lesion revascularization (TLR).1-6 Many of these studies have shown that late lumen loss is significantly less with SES than with PES. In contrast, clinical follow-up alone tends to indicate that the incidences of death and myocardial infarction are similar to those determined on coronary angiography (CAG), although the incidence of TLR thus determined is lower.7 This suggests that the decision to conduct TLR based on CAG alone when assessing restenosis at the chronic stage after PES deployment probably leads to the overtreatment of PES-deployed patients.

Fractional flow reserve (FFR) is well known as a useful index for the physiological severity of coronary artery stenosis, and FFR=0.75 is also well recognized as the cut-off value for reversible myocardial ischemia. Therefore, FFR has been proposed as a useful variable to decide on the performance of percutaneous coronary intervention (PCI).8-10 In not only the bare metal stent (BMS) but also the DES eras, studies are available that have reported a good prognosis in patients who had angiographic restenosis if their FFR is preserved.11-14

The objective of the present study was to assess the functional severity of stenosis in patients with moderate angiographic restenosis after PES deployment and their counterparts with moderate de novo stenosis.

Methods

Subjects
The present study enrolled 42 Japanese patients who had moderate angiographic restenosis that was estimated as 75% on American Heart Association (AHA) classification (51–75% by
Functional Assessment of PES Restenosis

A 0.014-in pressure guidewire (Pressure Wire, St. Jude Medical, St. Paul, MN, USA) was advanced into the coronary artery and placed at the distal portion of the coronary artery as possible. Maximal hyperemia was induced by i.c. bolus injection of papaverine hydrochloride (12 mg for the left coronary artery and 8 mg for the right coronary artery) in 30 patients in the PES group and in all patients in the de novo group, and by the i.v. infusion of adenosine triphosphate disodium at a rate of 0.15 mg · kg⁻¹ · min⁻¹ in 12 patients in the PES group; furthermore, the simultaneous recording of aortic and distal coronary pressures was performed. FFR was calculated as the ratio of hyperemic mean distal coronary pressure to mean aortic pressure. After FFR measurement, the pressure sensor was pulled back slowly by hand from the most distal portion to the coronary ostium during maximum hyperemia, and pressure measurements were recorded along the entire coronary artery. The mean distal pressure (Pd)/mean aortic pressure (Pa) ratio was measured at portions just distal and proximal to the stent and at the coronary ostium of patients with PES restenosis. In de novo moderate stenosis lesions, in contrast, the Pd/Pa ratio was measured at portions just distal and proximal to the target lesion and at the coronary ostium (Figure 2). The subtraction of the Pd/Pa ratio at 2 different points was calculated as the estimated pressure gradient between the points.

Statistical Analysis
Data are given as mean±SD. Student’s t-test was performed to compare the means of continuous variables, and categorical variables were analyzed using the chi-square test. P<0.05 was
In the PES group, PCI was conducted at 9 months before follow-up CAG, and the procedural characteristics of the PES deployment are listed in Table 2. The single and double stent procedures were conducted in 67% and in 31% of patients, respectively. The average number of PES used was 1.4 ± 0.5.

At the time of follow-up CAG, 88% and 12% of patients were asymptomatic or presented chest pain, respectively. The severity of chest pain was evaluated using the Canadian Cardiovascular Society (CCS) classification. Non-invasive stress tests were conducted in 33% of patients before follow-up CAG. Although angiographic restenosis was detected in all patients, 3 (7%) and 1 (2%) underwent TLR and target vessel revascularization (TVR), respectively, based on FFR.

### Results

#### Patient Demographics and Lesion Characteristics

Patient demographics and lesion characteristics are summarized in Table 1. There was no significant difference in age, gender, coronary risk factors, past history of myocardial infarction, lesion location, or number of diseased vessels between the PES group (n=42) and the de novo group (n=42).

<table>
<thead>
<tr>
<th></th>
<th>PES</th>
<th>De novo</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. patients</td>
<td>42</td>
<td>42</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>69±8</td>
<td>66±10</td>
<td>0.153</td>
</tr>
<tr>
<td>Male (%)</td>
<td>30 (71)</td>
<td>35 (83)</td>
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<tr>
<td>Hypertension (%)</td>
<td>36 (86)</td>
<td>28 (67)</td>
<td>0.071</td>
</tr>
<tr>
<td>Dyslipidemia (%)</td>
<td>31 (74)</td>
<td>25 (60)</td>
<td>0.247</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>19 (45)</td>
<td>17 (40)</td>
<td>0.826</td>
</tr>
<tr>
<td>Current smoking (%)</td>
<td>10 (24)</td>
<td>15 (36)</td>
<td>0.340</td>
</tr>
<tr>
<td>Family history of CAD</td>
<td>7 (17)</td>
<td>9 (21)</td>
<td>0.782</td>
</tr>
<tr>
<td>Prior MI (%)</td>
<td>20 (48)</td>
<td>13 (31)</td>
<td>0.180</td>
</tr>
<tr>
<td>No. diseased vessels</td>
<td></td>
<td></td>
<td>0.746</td>
</tr>
<tr>
<td>1-vessel disease</td>
<td>20 (48)</td>
<td>19 (45)</td>
<td></td>
</tr>
<tr>
<td>2-vessel disease</td>
<td>13 (31)</td>
<td>16 (38)</td>
<td></td>
</tr>
<tr>
<td>3-vessel disease</td>
<td>9 (21)</td>
<td>7 (17)</td>
<td></td>
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<tr>
<td>Location</td>
<td></td>
<td></td>
<td>0.717</td>
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<tr>
<td>RCA</td>
<td>12 (29)</td>
<td>10 (24)</td>
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<tr>
<td>LAD</td>
<td>24 (57)</td>
<td>26 (62)</td>
<td></td>
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<tr>
<td>LCX</td>
<td>6 (14)</td>
<td>5 (12)</td>
<td></td>
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<tr>
<td>LMT</td>
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<td>1 (2)</td>
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</tr>
</tbody>
</table>

Data given as mean±SD or n (%). CAD, coronary artery disease; LAD, left anterior descending artery; LCX, left circumflex; LMT, left main trunk; MI, myocardial infarction; RCA, right coronary artery.

**PES Deployment and PES Patient Demographics at Follow-up CAG**

In the PES group, PCI was conducted at 9 months before follow-up CAG, and the procedural characteristics of the PES deployment are listed in Table 2. The single and double stent procedures were conducted in 67% and in 31% of patients, respectively. The average number of PES used was 1.4±0.5.

At the time of follow-up CAG, 88% and 12% of patients were asymptomatic or presented chest pain, respectively. The severity of chest pain was evaluated using the Canadian Cardiovascular Society (CCS) classification. Non-invasive stress tests were conducted in 33% of patients before follow-up CAG. Although angiographic restenosis was detected in all patients, 3 (7%) and 1 (2%) underwent TLR and target vessel revascularization (TVR), respectively, based on FFR.
Relationship Between %DS and FFR
The QCA results and the FFR are listed in Table 3. FFR was significantly higher in the PES group than in the de novo group (P=0.002), although %DS was not significantly different between the 2 groups and lesion length tended to be longer in the PES group than in the de novo group (P=0.054). The percentage of patients with FFR <0.75 was 10% in those with moderate restenosis after PES deployment, and 29% in patients with moderate de novo stenosis (P=0.054). Revascularization was performed for all patients of the PES group with FFR <0.75 and for 9 out of 12 in the de novo group with FFR <0.75. The FFR measurements for infarct-related artery were done for 24% in the PES group and for 19% in the de novo group, respectively (P=0.791).

The %DS and FFR are plotted in Figure 3. In the PES group, %DS had a significant inverse correlation with FFR (r=-0.509, P=0.0005). In the de novo group, however, there was no correlation between %DS and FFR (r=-0.296, P=0.0567). Although %DS was distributed almost identically, FFR was dispersed more widely in the de novo group than in the PES group. The %DS of 4 patients with FFR <0.75 in the PES group varied between approximately 30% and 70%, and 3 of them had %DS <50%.

Pressure Gradients
Estimated pressure gradients were calculated by the subtraction of the Pd/Pa ratio at different 2 points (Figure 4). No significant difference was found in pressure gradients distal and proximal to the stent and lesion between the 2 groups. In-stent and in-lesion pressure gradients, however, were significantly lower in the PES group than in the de novo group (P<0.0001).
Discussion

FFR was preserved in many patients with moderate angiographic restenosis after PES deployment, and the mean thereof was 0.86±0.07. By contrast, a study has reported a mean FFR of 0.9±0.05 in patients without angiographic restenosis at 6 months after DES deployment. A comparison of these data shows that FFR decreases minimally in many patients with angiographic moderate restenosis after PES deployment.

In general, FFR is estimated to decrease when lesion length is longer in patients with the equivalent %DS. In the present study, however, FFR was significantly higher (P<0.002) in the PES group than in the de novo group even when the %DS were almost identical. This indicates that the severity of restenosis lesions after PES deployment is possibly overestimated when assessed on CAG only, which leads us to consider that functional assessment is preferred.

Furthermore, it has been repeatedly reported that %DS had a significant inverse correlation with FFR in de novo stenosis, BMS and DES restenosis. FFR, however, was dispersed more widely in the moderate %DS range than in the mild and severe range. In the present study, we limited objective lesions to moderate de novo stenosis lesions and moderate PES restenosis. Thus the distribution of FFR varied widely. And in our assessment of %DS and FFR, the dispersion of FFR in the de novo group was wider than that in the PES group. This may be explained at least in part by qualitative differences in the pathogenesis of the lesions, that is, plaque – the cause for stenosis in the de novo group and neointimal proliferation – the cause for restenosis in the PES group. De novo plaque is formed during the progression of atherosclerosis. Therefore, we presume that the intimal surface could be more complex due to the morphology of the plaque itself that is affected by different pathologic events (eg, calcification and ulceration).

In contrast, studies in the BMS era have well demonstrated that neointimal proliferation after stent deployment is based on the formation of fibrous tissue mainly consisting of vascular smooth muscle, and angiography has shown that the neointimal surface is smooth.

A pressure gradient, as shown by Bernoulli’s principle, is formed by the sum of pressure loss caused by viscous friction of blood when blood passes through a stenosis, and pressure loss caused by normal arterial flow that is transformed first to high velocity in the stenosis and then to turbulent non-laminar distal flow that eddies at the exit from the stenosis. The latter effect is called flow separation. Therefore, according to this principle, the more complex morphology of the lesion causes (1) greater pressure loss by the turbulent flow; (2) greater pressure gradient; and eventually (3) a reduction in FFR. Following Bernoulli’s principle, the i.e. pullback pressure measurements in the present study indicated no difference in pressure gradient between the distal and proximal portions of the lesion. In-stent and in-lesion pressure gradients, however, were significantly lower in the PES group than in the de novo group (P<0.0001). But differences in the effects on blood flow by the neointima after PES deployment and by de novo plaque are impossible to specify when assessed based on angiographic findings only. Therefore, we deem it meaningful to measure FFR before deciding whether or not to perform TLR/TVR for the patients with moderate angiographic restenosis after stent implantation.

Only 33% of patients in the PES group underwent non-invasive stress tests before follow-up CAG. Furthermore, the implementation rates of the tests differed extensively among the participating medical institutions, ranging between 0% and 73%. No symptoms were found in 88% of patients, although they had moderate angiographic restenosis; their daily living activities were not impaired. Previous randomized clinical trials of SES and PES, in which follow-up CAG was performed at 6–8 months after stenting, reported that the TLR rates corresponded to nearly half to two-thirds of the restenosis rates on angiograms and that both the TLR rates and the restenosis rates were higher with PES than with SES. In contrast, another study reported no change in the TLR rates between SES and PES when patients were followed up clinically without undergoing follow-up CAG. The studies in which follow-up CAG was performed on a routine basis indicated that patients have angiographic restenosis lesions that are of no clinical concern. With regard to the present 42 patients with moderate angiographic restenosis after PES deployment, only 4 patients...
(10%) underwent TLR or TVR; furthermore, their %DS varied between approximately 30% and 70%, and 3 of them had %DS ≤50%. Therefore, it is impossible to determine the functional severity of stenosis based on angiographic findings only.

In patients with moderate angiographic restenosis after PES deployment, the functional severity of restenosis is often limited. Therefore, revascularization should be performed with caution for them.

**Study Limitations**

The present study had some limitations. First, there is the issue of selection bias. The majority of patients in the PES group were asymptomatic, in contrast to patients in the de novo group, who had symptoms. As noted, moderate angiographic stenosis in the de novo group was not a definite lesion responsible for chest symptoms. Therefore, we consider that the comparison of the de novo group with the PES group is reasonable. Second, sample size was relatively small despite being a multicenter study. Nevertheless, we believe that this study affords useful information on the functional severity of moderate angiographic restenosis after DES deployment. Third, the occurrence of vascular responses at the site of DES deployment, that is, delayed and impaired healing processes, suggests that there are risks for late thrombosis and very late thrombosis. Furthermore, a phenomenon called “late catch-up”, by which restenosis occurs several years after DES deployment, has been reported. Therefore, the adequacy of assessing patients at 9 months after PES deployment in the present study is debatable. We consider that the present patients need to be followed up continuously in the future.

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**Disclosures**

The sponsor was not involved in the study design; in the collection, analysis, and interpretation of data; in the writing of this report. All authors declare no conflict of interest.

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