Effect of Bare-Metal Nitinol Stent Implantation and Paclitaxel-Eluting Nitinol Stent Implantation on Vascular Response in the Superficial Femoral Artery Lesion Assessed on Intravascular Ultrasound

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Background: Although previous intravascular ultrasound (IVUS) studies reported that the drug-eluting stent (DES) has successfully decreased in-stent restenosis (ISR) by inhibiting neointimal hyperplasia (NIH) in the coronary artery lesion, no IVUS data for vascular response after DES implantation in the superficial femoral artery (SFA) have been published.

Methods and Results: We retrospectively analyzed 38 de novo SFA lesions from 32 patients who underwent endovascular therapy (EVT) with self-expanding bare-metal nitinol stent (25 lesions; BMS group) or self-expanding paclitaxel-eluting nitinol stents (13 lesions; PES group). At 6 months after EVT, follow-up IVUS was done to evaluate NIH. Serial IVUS volumetric analysis was done after stent deployment and at follow-up. Mean stent, lumen and neointimal areas were calculated as the volume divided by the stent length. The primary endpoint of this study was mean late lumen loss at 6-month follow-up. The mean follow-up period was 189 ± 39 days. Mean neointimal area was smaller in the PES group compared to the BMS group ($3.3 \pm 1.0 \text{ mm}^2$ vs. $10.2 \pm 4.1 \text{ mm}^2$, $P < 0.001$). Mean late lumen loss was significantly lower in the PES group compared to the BMS group ($-2.3 \pm 3.7 \text{ mm}^2$ vs. $2.1 \pm 4.7 \text{ mm}^2$, $P < 0.05$).

Conclusions: EVT with DES in SFA lesions might decrease NIH associated with ISR in short-term follow-up. (*Circ J* 2014; **78**: 1451–1458)

Key Words: Endovascular therapy; Intravascular ultrasound; Paclitaxel-eluting nitinol stent; Restenosis; Superficial femoral artery

Endovascular therapy (EVT) has been accepted widely as a minimally invasive treatment for patients with peripheral artery disease due to the effectiveness and the development of techniques and devices.^{1–3} In femoropopliteal artery lesions, EVT with self-expanding bare-metal nitinol stent (BMS) produces better clinical outcome compared to that with balloon angioplasty.⁴ A previous study reported that the primary patency rate of the superficial femoral artery (SFA) lesions treated with BMS is approximately 84% at 1 year.⁵ In contrast, the main limitation of the percutaneous revascularization with stent implantation remains the phenomenon of restenosis, which is an exaggerated healing response to the vessel

wall injury that occurs as a result of mechanical dilatation. Recent clinical study suggested that restenosis rate after stent implantation in the SFA lesions is approximately 45% at 2 years.⁶ Based on such a background, the self-expanding paclitaxel-eluting nitinol stent (PES; Zilver PTX; Cook Medical, Bloomington, IN, USA) has recently become available for the treatment of femoropopliteal lesions, and superior clinical outcomes after EVT with PES have been reported.^{7,8} The primary patency rate after PES implantation is reported as 90% at 1 year.⁷ The difference in the mechanisms underlying the vascular response after PES and BMS, however, is poorly understood. The purpose of the present study was to evaluate the

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chronic vascular response to the implantation of PES and BMS in SFA lesions using serial volumetric intravascular ultrasound (IVUS).

Methods

Patient and Lesions

All of the patients suffered from symptoms due to SFA lesions (Rutherford 2–5) that affected quality of life despite exercise and optimal medication. De novo SFA lesions treated with the SMARTControl™ stent (Cordis, Miami Lakes, FL, USA) or Zilver PTX stent at the Hyogo College of Medicine between September 2010 and January 2013 were retrospectively enrolled in this study. Patients with acute or subacute limb ischemia, a history of lower extremity bypass surgery, and untreated aorto-iliac artery disease were excluded from analysis. The study protocol was approved by the institutional review board of Hyogo College of Medicine. All patients signed specific written informed consent describing the follow-up angiography and IVUS.

Procedures

After the initial diagnostic angiography of the lower limb, indications for EVT were decided by more than 2 physicians. Approach for EVT was determined at the operator's discretion. After insertion of a 6-Fr sheath, unfractionated heparin (5,000 units) was given into the artery. The anticoagulation was accomplished by measurement of the activated clotting time within 250–300 s during EVT. After a 0.014/0.018-inch guidewire was advanced down to the lesion, pre-dilation was performed by the balloon with a diameter equal to the reference vessel diameter according to the visual estimation. When flow-limiting dissections or recoils caused a stenosis >30%, BMS or PES was implanted. Until June 2012, BMS have been used as a default strategy for every EVT at Hyogo College of Medicine. From July 2012, PES became commercially available, replacing BMS as the strategy of choice in every EVT because of effectiveness considerations. Therefore, BMS were implanted before July 2012 and PES were implanted after June 2012. Stent diameter that was 1–2 mm larger than the reference vessel diameter at proximal sites of the lesions on angiographic visual estimation was chosen. When multiple stents were required, the margin of the overlapping stent was <10 mm. Post-dilation was performed routinely in all lesions with a balloon of 5-mm diameter at a pressure of 14 atm (14.2×10^5 Pa). Dual anti-platelet therapy (DAPT; aspirin 100 mg/day and cilostazol 100 mg/day, or clopidogrel 75 mg/day) was started at least 1 week prior to EVT and continued during the follow-up period. Procedural success was defined as residual stenosis <30% and the absence of flow-limiting dissection on angiography.

Quantitative Vascular Angiography (QVA) and Stent Fracture

Angiography was obtained before EVT, immediately after EVT, and at 6-month follow-up with anteroposterior and/or oblique view. QVA analysis using commercially available software (CAAS 5.9; Pie Medical Imaging, Maastricht, The Netherlands) was done to determine lesion severity and to evaluate neointimal hyperplasia (NIH) at follow-up in a blinded fashion. The tip of the guiding catheter was not available as a calibration in QVA analysis because the movement of the catheterization table was required for angiographic evaluation for the entirety of the SFA lesions. It was, therefore, impossible to accurately measure the absolute values of reference vessel, minimum lumen, and in-stent minimum lumen diameters.

Only the percent diameter stenosis (%DS) was calculated as a ratio of the minimum lumen diameter or the in-stent minimum lumen diameter to the average [(proximal+distal) $\times 1/2$] reference vessel diameter.⁹ Angiographic restenosis was defined as recurrence of >50% DS as determined on QVA analysis within the stented segment or within the 5-mm segment proximal or distal to the stent edge. Stent fracture was assessed on X-ray at 6 months after stent implantation. Stent fracture was defined as clear interruption of stent struts identified on X-ray from multiple projections.

IVUS Imaging Protocol

IVUS was done in all cases with a commercially available IVUS console (s5™ Imaging System; Volcano, Rancho Cordova, CA, USA) and a phased-array 20-MHz IVUS catheter (Eagle Eye Gold; Volcano). At the end of the initial procedure and at 6-month follow-up, a slow pullback was performed from distal to proximal reference sites through the stented segment. A manual pullback at a constant speed of 10 mm/s was performed after initial deployment and at follow-up.

Serial 2-D IVUS

All IVUS images were reviewed and quantitative IVUS analysis was performed using computed planimetry (EchoPlaque; Indec Systems, Santa Clara, CA, USA) by an independent experienced observer who was blinded to the clinical and angiographic information. Image slices were obtained at 5-mm axial intervals throughout the entire segment including stented and proximal and distal reference sites, and stent and lumen borders were manually traced in all image slices. The image slices with the minimum lumen area (MLA), minimum stent area (MSA), and maximum stent area were selected from all image slices. The proximal and distal reference segments were selected as the most normal-looking cross-sections within the same arterial segment (typically, <10 mm proximal and distal to the stents), but before any large side branch. Proximal and distal reference segment external elastic membrane (EEM) area, lumen area, and plaque burden [(EEM area–lumen area)/EEM area] were measured. Stent expansion ratio was calculated as $MSA/[(\text{proximal reference lumen area} + \text{distal reference lumen area}) \times 1/2]$. Radial stent symmetry index was minimum/maximum stent diameter. Axial stent symmetry index was minimum/maximum stent area.¹⁰ The smallest radial stent symmetry index and axial stent symmetry index from all image slices within the stents were selected for analysis. In the follow-up IVUS analysis, neointimal (stent-lumen) area was also calculated within the stented segment. Percent neointimal area (%NIA) was defined as NIA divided by stent area. To assess reproducibility of volumetric IVUS measurements, intra- and inter-observer variability analysis was performed with quantitative measurements of stent area, lumen area, and NIA at follow-up from 50 randomly selected cross-sections in 10 patients. The images were re-measured by 1 observer for the intra-observer variability at 2 separate time points. The inter-observer variability was determined by the measurements conducted by 2 independent observers.

Qualitative parameters assessed in the study included: (1) stent edge dissection (defined as a disruption of the vessel luminal surface at the stent edges with visible flap¹¹); (2) tissue protrusion after stent deployment (defined as protrusion of tissue between stent struts extending inside a circular arc connecting adjacent struts on IVUS images¹⁰); and (3) thrombus at follow-up (defined as a low echoic mass, often mobile and extruding into the vessel lumen and sometimes becoming detached from the vessel wall¹²).

Table 1. Patient, Lesion, and Procedural Characteristics

	BMS (n=25)	PES (n=13)	P-value
Age (years)	74.9±9.4	75.1±7.4	0.96
Female	3 (12)	3 (23)	0.39
Body mass index	22.9±3.7	24.0±4.7	0.41
Hypertension	22 (88)	11 (85)	>0.99
Dyslipidemia	21 (84)	8 (62)	0.23
Diabetes mellitus	13 (52)	10 (77)	0.18
Smoker	8 (32)	1 (8)	0.13
Chronic renal disease	19 (76)	8 (62)	0.46
Coronary artery disease	11 (44)	7 (54)	0.73
Cerebral vascular disease	7 (28)	5 (38)	0.71
Ankle brachial index	0.67±0.12	0.68±0.18	0.88
Critical limb ischemia	4 (16)	1 (8)	0.64
Anti-platelet therapy			
Aspirin and clopidogrel	3 (12)	8 (62)	<0.01
Aspirin and cilostazol	21 (84)	4 (31)	<0.01
Lesion length (mm)	142.8±86.5	169.2±98.0	0.40
Chronic total occlusion	8 (32)	8 (62)	0.10
TASC II classification			
A/B	14 (56)	4 (31)	0.18
C/D	11 (44)	9 (69)	
Run off vessel			
0/1/2/3	3/8/9/5	1/3/8/1	0.48
Total stent length (mm)	164.0±80.6	215.4±95.3	0.09
No. stents used	1.8±0.9	2.0±0.8	0.58
Stent diameter (mm)	6.2±0.4	6.1±0.3	0.49
Post-dilatation balloon diameter (mm)	5.0±0.0	5.0±0.0	>0.99

Data given as mean±SD or n (%).

BMS, bare-metal nitinol stent; PES, paclitaxel-eluting nitinol stent; TASC, Trans-Atlantic Inter-society Consensus.

Serial Volumetric IVUS

To further investigate the in vivo mechanical behavior of the self-expanding stent and the vascular response in the entire lesion segment, serial volumetric analysis was performed immediately after stent deployment and at 6-month follow-up within the stent and in the persistent margins (10 mm proximal and distal to the stent edge). Measurements of vessel, lumen and stent areas were made at 5-mm axial intervals, and vessel, stent, lumen, plaque and neointimal volumes were calculated using Simpson's rule.¹³ For comparison between the 2 stent configurations, mean stent, lumen and NIA were computed as the volume divided by the stent length.¹⁴ Mean late lumen area loss was defined as mean lumen area immediately after initial deployment minus mean lumen area at follow-up. To evaluate the axial distribution of NIH, we divided each stent into 8 segments and aligned subsections to correct the difference of stent length. Average NIA for each segment was then obtained to analyze the axial distribution.

Endpoints

The primary endpoint of this study was IVUS findings including stent volume, neointimal volume, and late lumen loss at 6-month follow-up determined on quantitative IVUS analysis. The secondary endpoint of the study was the angiographic restenosis rate at 6-month follow-up.

Statistical Analysis

Statistical analysis was done using StatView version 5.0 (SAS Institute, Cary, NC, USA). Data are given as mean±SD. Con-

tinuous variables were examined using unpaired t-test or Mann-Whitney U-test. Categorical variables were compared using chi-squared test or Fisher exact test. The intra- and inter-observer variabilities were assessed on linear regression analysis. $P<0.05$ was considered statistically significant.

Results

Baseline Characteristics

A total of 38 de novo SFA lesions from 32 patients were analyzed in this study. BMS were implanted in 25 lesions of 21 patients (BMS group) and PES were deployed in 13 lesions of 11 patients (PES group). Initial procedural success was obtained in all cases and no procedure-related complications were reported both at baseline and at follow-up. The baseline characteristics are listed in Table 1. DAPT was continued during follow-up in almost all cases (96% in the BMS group and 93% in the PES group). DAPT with aspirin and clopidogrel was more frequent in the PES group compared to the BMS group (62% in the PES group vs. 12% in the BMS group). DAPT with aspirin and cilostazol was more frequent in the BMS group (84% in the BMS group vs. 31% in the PES group). Mean lesion length was 142.8±86.5 mm in the BMS group and 169.2±98.0 mm in the PES group ($P=0.40$). Average total stent length tended to be longer in the PES group compared to the BMS group (215.4±95.3 mm vs. 164.0±80.6 mm, $P=0.09$).

QVA and Stent Fracture

There was no difference in %DS of the target lesion before

Table 2. 2-D IVUS Analysis			
	BMS (n=25)	PES (n=13)	P-value
After initial stenting			
Minimum stent area (mm ²)	15.7±1.8	11.4±2.8	<0.001
Reference segment			
Proximal EEM area (mm ²)	44.9±16.4	47.0±20.3	0.75
Proximal lumen area (mm ²)	28.0±13.3	29.0±14.6	0.84
Distal EEM area (mm ²)	34.9±12.9	27.9±6.0	0.10
Distal lumen area (mm ²)	22.2±8.7	15.1±3.3	0.01
Stent expansion ratio	0.69±0.20	0.56±0.18	0.07
Radial stent symmetry index	0.71±0.13	0.71±0.15	0.93
Axial stent symmetry index	0.64±0.13	0.54±0.16	0.07
Stent edge dissection	14 (56)	6 (46)	0.73
Tissue protrusion	5 (20)	3 (23)	>0.99
6-month follow-up			
Minimum stent area (mm ²)	22.0±2.8	15.7±3.1	<0.001
Minimum lumen area (mm ²)	11.5±5.2	11.9±3.7	0.81
Maximum %NIH	57.2±18.1	39.0±18.9	<0.01
Stent expansion ratio	0.96±0.27	0.77±0.30	0.06
Radial stent symmetry index	0.82±0.09	0.79±0.13	0.32
Axial stent symmetry index	0.68±0.11	0.61±0.17	0.14
Stent edge dissection	8 (32)	4 (31)	>0.99
Thrombus	0 (0)	2 (15)	0.11

Data given as mean±SD or n (%).

EEM, external elastic membrane; IVUS, intravascular ultrasound; NIH, neointimal hyperplasia. Other abbreviations as in Table 1.

Table 3. Volumetric IVUS Analysis			
	BMS (n=25)	PES (n=13)	P-value
After initial stenting			
Stent volume (mm ³)	3,312±1,714	3,584±1,697	0.66
Mean stent area (mm ²)	20.0±2.0	16.3±1.7	<0.001
At 6-month follow-up			
Stent volume (mm ³)	4,816±2,829	4,768±2,278	0.96
Mean sent area (mm ²)	28.2±3.8	21.8±2.9	<0.001
Lumen volume (mm ³)	3,052±2,118	4,084±2,093	0.16
Mean lumen area (mm ²)	18.0±5.5	18.5±3.4	0.75
Neointimal volume (mm ³)	1,764±1,384	685±348	<0.01
Mean neointimal area (mm ²)	10.2±4.1	3.3±1.0	<0.001
Mean late lumen area loss (mm ²)	2.1±4.7	-2.3±3.7	<0.05

Data given as mean±SD or n (%).

Abbreviations as in Tables 1,2.

EVT between the 2 groups (80.1±19.6% in the BMS group and 87.6±18.1% in the PES group, $P=0.26$) on QVA analysis. Six months after stent implantation, follow-up angiography was performed in all lesions. On QVA analysis, in-stent %DS at follow-up tended to be lower in the PES group compared to the BMS group (23.2±10.7% vs. 37.2±10.5%, $P=0.06$). Angiographic restenosis was observed in 6 lesions (24%) in the BMS group and in 1 lesion (8%) in the PES group ($P=0.39$). Two stent fractures (15%; type 1 fracture and type 3 fracture) were detected in the PES group after 6 months after stent implantation. We detected no stent fracture in the BMS group.

Intra- and Inter-Observer Variability of IVUS Measurements
IVUS measurements of stent area, lumen area, and NIA had excellent intra- and inter-observer reproducibility. In the intra-

observer variability analysis, stent area ($r=0.997$, $P<0.0001$), lumen area ($r=0.952$, $P<0.0001$), and NIA ($r=0.932$, $P<0.0001$) measurements were highly correlated. In the inter-observer variability analysis, stent area ($r=0.994$, $P<0.0001$), lumen area ($r=0.938$, $P<0.0001$), and NIA ($r=0.933$, $P<0.0001$) measurements were also highly correlated.

Serial 2-D IVUS

Serial 2-D IVUS findings are summarized in **Table 2**. MSA was significantly smaller in the PES group than in the BMS group both at the initial procedure and at 6-month follow-up (11.4±2.8 mm² vs. 15.7±1.8 mm², $P<0.001$; and 15.7±3.1 mm² vs. 22.0±2.8 mm², $P<0.001$, respectively). There was no significant difference in MLA, however, at 6-month follow-up between the 2 groups because the PES group had significantly

Figure 1. Change in absolute stent volume between initial deployment and follow-up in the (A) self-expanding bare-metal nitinol stent and (B) self-expanding paclitaxel-eluting nitinol stent groups during 6 months.

smaller %NIA at 6-month follow-up compared to the BMS group ($39.0 \pm 18.9\%$ vs. $57.2 \pm 18.1\%$, $P < 0.01$). There were no significant differences in stent expansion ratio, radial stent symmetry indices, and axial stent symmetry indices between the 2 groups. During follow-up, MSA has become larger in both groups (from $15.7 \pm 1.8 \text{ mm}^2$ to $22.0 \pm 2.8 \text{ mm}^2$ in the BMS group, $P < 0.001$; and from $11.4 \pm 2.8 \text{ mm}^2$ to $15.7 \pm 3.1 \text{ mm}^2$ in the PES group, $P < 0.001$, respectively). Similarly, stent expansion ratio (from 0.69 ± 0.20 to 0.96 ± 0.27 in the BMS group, $P < 0.001$; and from 0.56 ± 0.18 to 0.77 ± 0.30 in the PES group, $P < 0.01$, respectively) and radial stent symmetry indices (from 0.71 ± 0.13 to 0.82 ± 0.09 in the BMS group, $P < 0.001$; and from 0.71 ± 0.15 to 0.79 ± 0.13 in the PES group, $P < 0.01$, respectively) became larger during the follow-up period in both groups.

Serial Volumetric IVUS

Serial volumetric IVUS findings are presented in Table 3. Mean stent area after initial procedure and at 6-month follow-up were significantly smaller in the PES group compared to the BMS group ($16.3 \pm 1.7 \text{ mm}^2$ vs. $20.0 \pm 2.0 \text{ mm}^2$, $P < 0.001$; and $21.8 \pm 2.9 \text{ mm}^2$ vs. $28.2 \pm 3.8 \text{ mm}^2$, $P < 0.001$, respectively). BMS increased 41.0% in mean stent area during the follow-up period (from $20.0 \pm 2.0 \text{ mm}^2$ to $28.2 \pm 3.8 \text{ mm}^2$, $P < 0.001$), and PES increased 35.6% in mean stent area (from $16.3 \pm 1.7 \text{ mm}^2$ to $21.8 \pm 2.9 \text{ mm}^2$, $P < 0.001$). The degree of increase in mean stent area during the follow-up period was similar between the BMS and PES groups (41.0% and 35.6%, $P = 0.41$). Stent volume also increased during the follow-up period in both groups (from $3,312 \pm 1,714 \text{ mm}^3$ to $4,816 \pm 2,829 \text{ mm}^3$ in the BMS group, $P < 0.001$, and from $3,584 \pm 1,697 \text{ mm}^3$ to $4,768 \pm 2,278 \text{ mm}^3$ in the PES group, $P < 0.01$; Figure 1). Mean NIA was significantly smaller in the PES group compared to the BMS group ($3.3 \pm 1.0 \text{ mm}^2$ vs. $10.2 \pm 4.1 \text{ mm}^2$, $P < 0.001$). As a result, mean late lumen area loss was smaller in the PES group compared to the BMS group ($-2.3 \pm 3.7 \text{ mm}^2$ vs. $2.1 \pm 4.7 \text{ mm}^2$, $P < 0.05$; Figure 2). The axial distribution pattern of NIH is shown in Figure 3. Although NIH was evenly distributed throughout the entire stented length in the BMS group, there was a trend to larger amount of NIH at the distal portion of the stented segment in the PES group. In the PES group, average NIA at the

Figure 2. Mean stent, neointimal and lumen area changes within the stented segment during the follow-up period. In the self-expanding paclitaxel-eluting nitinol stent (PES) group the stent area increased by 5.5 mm^2 in mean stent area and intimal area by 3.3 mm^2 during 6 months. As a result, the mean lumen area increased by 2.3 mm^2 during the follow-up period. In the self-expanding bare-metal nitinol stent (BMS) group, in contrast, the mean lumen area decreased due to large amounts of neointimal hyperplasia.

distal 4 segments tended to be larger than that at the proximal 4 segments ($3.6 \pm 2.5 \text{ mm}^2$ vs. $2.9 \pm 2.1 \text{ mm}^2$, $P = 0.09$).

Persistent Margins

Twenty margins for the BMS group and 9 margins for the PES group were acceptable for serial volumetric analysis. Mean

EEM, plaque, and lumen area at persistent margins were similar between the BMS group and the PES group both after initial stent deployment and at 6-month follow-up (Figure 4). Although mean EEM area at the proximal reference did not

change, mean EEM area at the distal reference slightly increased during the follow-up period (from $33.3 \pm 11.7 \text{ mm}^2$ to $35.7 \pm 12.5 \text{ mm}^2$, $P < 0.001$). The incidence of stent edge dissection after initial stent deployment and at follow-up was similar between the 2 groups (Table 2). Among 20 dissections identified on IVUS at the initial stent deployment, 8 dissections (40%) resolved and 12 dissections (60%) persisted during the follow-up period. No significant differences in the natural history of stent edge dissection existed between the 2 groups.

Discussion

To the best of our knowledge, this is the first study to report on chronic vascular response to the implantation of PES and BMS in SFA lesions using serial volumetric IVUS. The main findings of this study are as follows: (1) PES increased 35.6% in overall stent volume and BMS, 41.0%; (2) a significantly smaller amount of NIH at 6 months after stent implantation was identified in the PES group than in the BMS group; and (3) the vascular response at persistent margin was similar between the 2 groups.

Although BMS implantation in the SFA lesion has improved clinical outcome compared to balloon angioplasty, previous studies reported that the restenosis rate was still high: 32% in the FAST trial,¹⁵ 34% in the ASTRON trial,¹⁶ and 36% in the ABSOLUTE trial,⁴ respectively. In the coronary artery lesions, drug-eluting stents (DES) have successfully decreased the rate of in-stent restenosis (ISR) and target lesion revascularization (TLR) compared with BMS.^{17–19} In the lower extremity, however, sirolimus-eluting stent failed to demonstrate superiority on prevention of ISR compared to BMS.²⁰ In contrast, EVT with PES is associated with lower TLR rate and higher patency rate.⁷ Tepe et al reported that paclitaxel-coated balloon has a lower late lumen loss and TLR rate.²¹ In the SFA lesion, paclitaxel might be more effective compared to sirolimus for prevention of ISR.

Several studies have reported the safety and efficacy of EVT with PES for the SFA lesions.^{7,8} Dake et al reported that event-

free survival rate at 6 months after EVT with PES was 97%, and clinically driven TLR were performed in 10%.⁷ In that study, average lesion length was 66.4 mm, and 27% of the lesions were total occlusions in the PES group. In the current study, lesion length was longer (169.2 mm in the PES group) and the prevalence of chronic total occlusion (62% in the PES group) was higher than in previous studies. Despite a complicated lesion background, the present result is similar to that of previous studies.

A previous study reported that NIH is the arterial wall's healing response to mechanical injury.²² In an experimental study, Forrester et al proposed a paradigm for neointimal growth as a general wound-healing response.²³ Platelet aggregation, inflammatory cell infiltration, release of growth factors, medial smooth muscle cell (SMC) modulation and proliferation, proteoglycan deposition, and extracellular matrix remodeling were identified as the major indicators in the temporal sequence of this response. A previous human study of BMS noted that self-expanding stents had a 23.6% increase in stent volume between the procedure and 6-month follow-up.¹⁴ These reports suggest that chronic continuous mechanical injury by nitinol self-expanding stents to vessel walls might be associated with an increase in subsequent NIH. In the current study, BMS increased 41.0% in mean stent area during the follow-up period (from $20.0 \pm 2.0 \text{ mm}^2$ to $28.2 \pm 3.8 \text{ mm}^2$, $P < 0.001$), and PES increased 35.6% in mean stent area (from $16.3 \pm 1.7 \text{ mm}^2$ to $21.8 \pm 2.9 \text{ mm}^2$, $P < 0.001$). The degree of the increase in mean stent area during the follow-up period was similar between the 2 groups (41.0% and 35.6%, $P = 0.41$). The degree of increase in stent volume was also similar between the 2 groups. These results suggest that the radial force and the continuous mechanical injury from the stent were similar between BMS and PES. It was reported that paclitaxel induces arrest of the cell cycle in mitosis and inhibition of SMC migration.^{24,25} In the current study, paclitaxel may have attenuated NIH by arresting the cell cycle and inhibiting SMC migration, which would have led to a smaller amount of NIH in the PES group than in the BMS group.

In previous angioscopic assessment the prevalence of thrombus and yellow plaque was similar between the BMS group and the PES group.²⁶ In line with this, the prevalence of thrombus was similar between the 2 groups in the current study. Stent edge dissection could be induced by excessive vessel stretch during stent implantation and post-dilation. Previous IVUS study suggested that stent edge dissection without flow-limitation in the coronary artery is not associated with an increase in future adverse events, including ISR.²⁷ In addition, another IVUS study indicated that 75% of coronary stent edge dissections resolved without changes in vessel, lumen, and plaque area 6 months after the stent implantation.²⁸ In accordance with previous studies, in the present study approximately half of stent edge dissections resolved during the 6-month follow-up period both in the PES and BMS groups. Moreover, no edge restenosis at follow-up was detected for lesions in which edge dissection was identified at the baseline procedure. Thus, the clinical impact of minor edge dissections visible on IVUS seems to be minimal.

Study Limitations

This study was a retrospective analysis of data from a single-center, small-number, and non-randomized prospective study. Prospective randomized multi-center studies are required to reconfirm the results in a larger number of patients. Follow-up angiography and IVUS were performed at 6 months after EVT. Further long-term follow-up, however, might be neces-

sary to evaluate NIH after DES implantation.^{29–31} Because lesion length was too long (142.8 mm in the BMS group and 169.2 mm in the PES group), the IVUS pullback through the SFA lesion was performed manually. We recognize that the mechanisms leading to restenosis are different between BMS and DES. No qualitative comparison of neointima on IVUS findings between the BMS group and the PES group was attempted, however, due to the limited number of lesions with ISR in the PES group.

Conclusions

DES is safe and effective for treatment of SFA lesions in the short term. EVT with PES might decrease NIH associated with ISR.

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