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ORIGINAL ARTICLE

Plaque modification and stabilization after paclitaxel-coated balloon treatment for de novo coronary lesions

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Abstract

This study aimed to assess the healing response, as evidenced through temporal morphological and functional changes, following paclitaxel-coated balloon (PCB) treatment of de novo coronary lesions. This retrospective, observational study, included patients with significant de novo coronary lesions who were treated with PCB and had serial angiographic, intravascular ultrasound virtual histology (IVUS-VH), fractional flow reserve (FFR) measurements, and optical coherence tomography (OCT) performed before balloon angioplasty (BA), after BA, and at 9-month follow-up. A total of 20 patients (21 lesions) were included in this study. After PCB treatment, IVUS showed significant increases in the mean vessel area (12.0 ± 2.2 mm^2 to 13.8 ± 2.5 mm^2, $p = 0.023$), and mean lumen area (5.6 ± 1.2 mm^2 to 7.0 ± 1.5 mm^2, $p = 0.003$). Coronary flow was restored after BA with an FFR value of 0.87 ± 0.04 which was sustained at 9-month follow-up with no significant decrease (0.83 ± 0.08, $p = 0.329$). Serial OCT analysis showed that at 9-month follow-up dissections after BA sealed in 14 lesions (67%), whilst the macrophages decreased from 10 (50%) to 7 (35%) lesions, and the cap thickness of plaque increased from 0.12 ± 0.06 mm to 0.17 ± 0.09 mm ($p = 0.007$). PCB treatment for de novo coronary lesions showed persistent anatomical and functional patency at mid-term follow-up. Plaque modification, vascular remodeling, and plaque stabilization were also observed during follow-up.

Keywords Paclitaxel-coated balloon · De novo coronary lesions · Optical coherence tomography · Vessel remodeling · Fractional flow reserve

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Introduction

Although previous studies have shown promising angiographic and clinical outcomes of paclitaxel-coated balloon (PCB) treatment in some subsets of de novo coronary artery disease [1–3], there are limited data on the serial changes of plaque and the impact on the vessel after PCB treatment.

Recently published studies by our group suggested that de novo coronary lesions treated with PCB showed persistent anatomical and physiological patency with plaque modification and vessel remodeling [4–6]. In these studies, we concluded that following PCB treatment of de novo coronary lesions, coronary blood flow is maintained by means of luminal enlargement, and dissections after balloon angioplasty (BA) decrease or seal at follow-up. However, data on the serial changes of plaque healing after PCB treatment were not reported. Therefore, the aim of this study was to assess the temporal changes of plaque, and the overall healing processes in vessels following PCB treatment of de novo

coronary lesions. We performed serial angiographic, intravascular ultrasound virtual histology (IVUS-VH), fractional flow reserve (FFR) measurements, and optical coherence tomography (OCT) before BA, after BA, and at 9-month follow-up in de novo lesions treated with PCB.

Materials and methods

Population

This retrospective registry enrolled consecutive patients who met the inclusion criteria from a single center between June 2012 and January 2015. Patients with significant de novo epicardial coronary artery disease (≥ 50% diameter stenosis on angiography by visual estimation) due to stable or unstable angina with documented ischemia by treadmill test or FFR who were scheduled to undergo percutaneous coronary intervention (PCI) were considered eligible for this study. The angiographic inclusion criteria were the presence of de novo coronary lesion with a reference vessel diameter between 2.5 and 3.5 mm, a lesion length ≤ 24 mm and a thrombolysis in myocardial infarction (TIMI) flow of 3 following BAs in the target vessel. Exclusion criteria included patients with severe left ventricular dysfunction (ejection fraction < 35%), ST-segment elevation myocardial infarction requiring primary PCI, left main coronary artery disease, multivessel stenoses, ostial or heavily calcified or thrombotic lesions, bifurcation lesions treated with a 2-stent strategy, contraindication to adenosine and known chronic kidney disease (creatinine > 2 mg/dL). This study was carried out according to the Declaration of Helsinki guidelines and was approved by the Institutional Review Board ethics committee. All enrolled patients provided written informed consent.

Interventional procedure

All patients were treated with acetylsalicylic acid 200 mg and a loading dose of clopidogrel 300 or 600 mg before the procedure followed by maintenance clopidogrel 75 mg daily for 4 or 6 weeks. Cilostazol (100 mg, twice a day) was administered for 2 weeks to prevent vasospasm [7]. 100 U/kg of unfractionated heparin was injected intravenously to maintain an activated clotting time ≥ 250 s during the procedure. For PCB treatment, the patient underwent predilation with an optimal-sized balloon based on angiography (balloon-to-vessel ratio of 1.0), with the standard balloon shorter than the intended PCB size. The PCB (SeQuent Please®, paclitaxel-coated balloon catheter, B. Braun, Melsungen, Germany) was sized at 1:1 balloon-to-vessel ratio, delivered rapidly (median of 15 s) and inflated at nominal pressure for 60 s. Application of the PCB was decided by the interventional cardiologist performing the procedure based on the FFR measured after BA [4].

Quantitative coronary angiography (QCA) acquisition and analysis

Coronary angiographies before and after the procedure and at 9-month follow-up were analyzed using the Cardiovascular Angiography Analysis System (CAAS 5.10, Pie Medical Imaging B.V., Maastricht, The Netherlands) by an independent investigator (JH. L), who was blinded to clinical presentations before BA, after PCB treatment, and at 9-month follow-up.

IVUS-VH acquisition and analysis

200 µg intracoronary nitroglycerin was administered routinely before the image acquisition at baseline and at repeat assessment at 9-month follow-up. Baseline IVUS-VH assessments were performed before and after balloon angioplasty. Using the motorized transducer pullback system (0.5 mm/s), the 2.9-F IVUS imaging catheter (Eagle Eye, Volcano Corp., Rancho Cordova, California) was incorporated at 20-MHz phased-array transducer. Offline analyses were done with the computer VH software program (pcVH 2.2; Volcano Therapeutics, Rancho Cordova, California, USA) by an independent examiner (JN. N) who was unaware of the clinical characteristics of the patients. Geometric quantitative IVUS analyses were performed according to criteria from the IVUS clinical expert consensus document [8]. Compositional tissue characteristic areas were expressed in colors, as previously described (green for fibrous, yellow-green for fibrofatty, white for dense calcium and red for necrotic core) [9]. The IVUS-VH analyses were reported as mean area of each composition and as percentage change of volume. Plaque phenotype was identified based on plaque composition as pathologic intimal thickening (PIT), IVUS-VH-derived thin-cap fibroatheroma (TCFA), thick-cap fibroatheroma (ThCFA), fibrotic plaque and fibrocalcific plaque by one experienced, independent investigator (JN. N) [10, 11].

OCT acquisition and analysis

OCT was performed based at the operator's discretion before the procedure, after BA, and at 9-month follow-up. Fourier-domain OCT (C7XR, LightLab Imaging, Inc.; Westford, Massachusetts, United States) was used with the non-occlusive technique. The catheter was advanced distal to the lesion over a conventional 0.014-in. guidewire, and images were obtained by motorized pullback at 20 mm/s during continuous flushing of 20 mL of contrast media. Offline OCT analysis was performed by an independent investigator using proprietary software. The OCT images were analyzed using

the proprietary OCT console software (St. Jude Medical) by 2 independent experienced observers (JN. N and HH. K) who were blinded to clinical data. In case of discordance between the observers, a consensus reading was obtained. OCT analysis was performed on the 21 coronary lesions with the highest amount of plaque in the 20 patients who have pre-procedure, and 9-month follow-up OCT images. Follow-up OCT lesion was matched with a corresponding pre-procedure OCT lesion with proximal or distal reference. OCT images were analyzed using previously validated criteria for plaque characterization and classified into the following two plaque types: lipid plaque or fibrous plaque [12]. Briefly, lipid plaques were defined as diffusely bordered and signal-poor region, and fibrous plaques homogenous and signal-rich region. Macrophage images were defined as signal-rich, distinct or confluent punctuate regions with shadowing [13]. The quantitative measurements including minimum lumen area, reference lumen areas, and lesion length were performed by automated lumen contour detection followed by additional manual correction if needed [14].

FFR acquisition and analysis

FFR was measured before the procedure, after BA, and at 9-month follow-up but was not performed for subtotal occlusions without a clinical indication. After intracoronary nitroglycerine injection of 200 μg, FFR was measured using a 0.014-in. coronary pressure wire (PressureWire Certus, St. Jude Medical Systems; Uppsala, Sweden) placed distal to the lesion under hyperemic conditions induced by an intravenous adenosine infusion (140–180 μg/kg/min).

Follow-up and clinical outcomes

All patients were scheduled to undergo clinical and angiographic follow-up at 9 months. Serial angiographic data, IVUS-VH images, FFR measurements, and OCT images were analyzed. Clinical outcomes were defined according to the Academic Research Consortium criteria [15]. Binary restenosis was defined as a diameter stenosis ≥ 50% at angiographic follow-up. Late luminal loss was defined as the difference in minimal luminal diameter between post-procedure and follow-up images in the same segment (in-segment).

Statistical analysis

All statistical analyses were done using SPSS version 18.0 (SPSS, Inc., Chicago, Illinois, USA). Descriptive statistical methods were used to describe the data. Results are presented as mean ± standard deviation or median [interquartile range] for continuous variables and frequency (percentages) for categorical variables. The comparisons between the two groups were performed using the paired *t* test or Wilcoxon signed rank test for continuous variables and the Chi-square or Fischer exact test for categorical variables. All tests were two sided, and a p value < 0.05 was considered statistically significant.

Results

A total of 20 patients (21 lesions) were included in this study. Baseline clinical and procedural characteristics are shown in Table 1.

The angiographic QCA analysis data are presented in Table 2. The mean reference vessel diameter was 2.68 ± 0.35 mm. At 9-month follow-up after PCB treatment, there was a significant increase in the minimal lumen diameter (1.14 ± 0.53 mm vs. 2.14 ± 0.38 mm, $p < 0.001$) and a significant decrease in the diameter stenosis ($60.9 \pm 16.4\%$ vs. $23.7 \pm 8.5\%$, $p < 0.001$). Late luminal loss and net gain of the lesions were 0.03 ± 0.23 mm and 1.00 ± 0.55 mm, respectively. Dissections after BA disappeared at 9-month follow-up.

Serial geometric and compositional changes in lesion characteristics following IVUS-VH analysis are shown in Table 3. After PCB treatment, there were increases in mean vessel area from 12.0 ± 2.2 mm^2 to 13.8 ± 2.5 mm^2 ($p = 0.023$), and lumen area from 5.6 ± 1.2 mm^2 to 7.0 ± 1.5 mm^2 ($p = 0.003$). However, mean plaque area did not change significantly (6.4 ± 2.2 mm^2 to 6.8 ± 1.9 mm^2, $p = 0.828$). Although there were no significant changes in the percent atheroma volume or remodeling index, there was a significant increase in the minimal lumen area after BA which remained at 9-month follow-up (4.5 ± 1.0 mm^2 to 5.6 ± 1.4 mm^2, $p < 0.001$). No aneurysmal changes were detected on IVUS. On the other hand, all four IVUS-VH plaque compositions remained unchanged at 9-month follow-up. However, among the 10 TCFA detected at baseline, only 5 remained at follow-up, with 3TCFAs converting to ThCFA and 2 TCFA converting to PIT.

From FFR measurements, coronary flow was restored after BA with an FFR value of 0.87 ± 0.04 and this improvement was maintained at 9-month follow-up without any significant decrease in FFR (0.83 ± 0.08) (Table 2).

Serial OCT findings are shown in Table 4. Mean lumen area and lumen volume increased significantly from post-BA to 9-month follow-up (4.52 mm^2 vs. 5.18 mm^2, $p < 0.001$; and 72.8 μL vs. 93.8 μL, $p = 0.001$). Minimal lumen diameter and minimal lumen area also increased significantly after BA (1.50 mm vs. 1.96 mm, $p = 0.011$; and 1.77 mm^2 vs. 3.12 mm^2, $p = 0.011$), with a further increase at 9-month follow-up (1.96 mm vs. 2.22 mm, $p = 0.001$; and 3.12 mm^2 vs. 3.90 mm^2, p 0.001). Mean and minimal lumen symmetry changed from post-BA to 9-month follow-up (0.80 vs. 0.83, $p = 0.001$; and 0.58 vs. 0.68, $p = 0.010$), which is possibly because

Table 1 Baseline clinical and procedural characteristics

Variables	$n=20$
Age (years)	58.6 ± 6.6
Male	13 (65.0)
Cardiovascular risk factors	
Diabetes	4 (20.0)
Hypertension	11 (55.0)
Current smoker	7 (35.0)
Hypercholesterolemia	9 (45.0)
Family history of CAD	4 (20.0)
Clinical manifestation	
Stable angina	11 (55.0)
Unstable angina	9 (45.0)
Angiographic findings	$n=21$
Target vessel	
LAD	15 (71.4)
LCX	2 (9.5)
RCA	4 (19.0)
Lesion type (B2 and C)	14 (66.6)
Plain old balloon angioplasty	$n=21$
Balloon diameter (mm)	3.06 ± 0.29
Inflated balloon pressure (atm)	11.2 ± 2.2
Inflated balloon size (mm)	3.09 ± 0.23
Paclitaxel-coated balloon	$n=21$
Device diameter (mm)	3.11 ± 0.28
Device length (mm)	22.7 ± 4.4
Inflated device pressure (atm)	9.5 ± 2.0
Inflated device size (mm)	3.22 ± 0.29

CAD coronary artery disease, *LAD* left anterior descending artery, *LCX* left circumflex artery, *RCA* right coronary artery

Table 2 Serial quantitative coronary angiography analysis and functional measurements

	Pre-BA ($n=21$)	Post-BA ($n=21$)	Nine-month follow-up ($n=21$)	p value		
				Pre-BA vs. post-BA	Post-BA vs. 9 months	Pre-BA vs. 9 months
QCA						
Reference vessel diameter (mm)	2.68 ± 0.35	2.84 ± 0.32	2.75 ± 0.37	0.126	0.400	0.529
Minimal lumen diameter (mm)	1.14 ± 0.53	2.16 ± 0.30	2.14 ± 0.38	**< 0.001**	0.813	**< 0.001**
Diameter stenosis (%)	60.9 ± 16.4	23.7 ± 8.5	22.1 ± 10.6	**< 0.001**	0.590	**< 0.001**
Lesion length (mm)	21.6 ± 5.3	22.9 ± 5.3	21.6 ± 4.9	0.470	0.428	0.966
Acute gain (mm)	1.02 ± 0.54					
Late luminal loss (mm)			0.03 ± 0.23			
Net gain (mm)			1.0 ± 0.55			
Binary restenosis (n)			0			
Dissection (≥ type C) (n)		2	0			
FFR	0.71 ± 0.14	0.87 ± 0.04	0.83 ± 0.08	**< 0.001**	0.329	**< 0.001**

Bold indicates p value < 0.05 are statistically significant

BA plain old balloon angioplasty, *QCA* quantitative coronary angiography, *FFR* fractional flow reserve

Table 3 Serial gray-scale intravascular ultrasound (IVUS) and IVUS-virtual histology (IVUS-VH) analysis

Variable	Pre-BA ($n=21$)	Post-BA ($n=21$)	Nine-month follow-up ($n=21$)	p value		
				Pre-BA vs. post-BA	Post-BA vs. 9 months	Pre-BA vs. 9 months
Mean area, mm^2						
EEM	12.0 ± 2.2	13.3 ± 2.1	13.8 ± 2.5	0.085	0.457	**0.023**
Lumen	5.6 ± 1.2	6.9 ± 1.6	7.0 ± 1.5	**0.008**	0.866	**0.003**
Plaque	6.4 ± 2.2	6.4 ± 2.2	6.8 ± 1.9	0.641	0.608	0.828
Necrotic core	0.84 ± 0.61	0.84 ± 0.63	0.70 ± 0.48	0.997	0.450	0.438
Dense calcium	0.51 ± 0.44	0.51 ± 0.34	0.50 ± 0.41	0.983	0.939	0.961
Fibro-fatty	0.33 ± 0.17	0.29 ± 0.24	0.47 ± 0.33	0.569	0.054	0.093
Fibrous tissue	2.28 ± 1.21	1.98 ± 1.24	2.28 ± 1.15	0.457	0.438	0.999
Percent atheroma volume (%)	54.5 ± 7.3	49.3 ± 9.5	50.6 ± 6.0	0.066	0.614	0.074
Minimal lumen area (mm^2)	3.5 ± 0.5	4.5 ± 1.0	5.6 ± 1.4	**< 0.001**	**0.007**	**< 0.001**
Remodeling index	1.2 ± 0.3	1.3 ± 0.3	1.3 ± 0.3	0.288	0.474	0.676
Phenotype (n)						
TCFA	10	–	5			
ThCFA	11	–	14			
PIT	0	–	2			

Bold indicates p value < 0.05 are statistically significant

BA balloon angioplasty, *EEM* external elastic membrane, *TCFA* thin-cap fibroatheroma, *ThCFA* thick-cap fibroatheroma, *PIT* pathologic intima thickening

Table 4 Serial OCT analysis

Variable	Pre-BA (n = 21)	Post-BA (n = 21)	Nine-month follow-up (n = 21)	p value		
				Pre-BA vs. post-BA	Post-BA vs. 9 months	Pre-BA vs. 9 months
Analyzed length (mm)	13.0 [11.4–16.6]	15.5 [11.8–22.8]	15.5 [11.7–22.7]	0.592	0.672	0.833
Mean lumen area (mm^2)	4.59 [3.79–5.12]	4.52 [3.64–5.28]	5.18 [4.68–6.53]	0.123	**< 0.001**	**0.008**
Lumen volume (μL)	64.2 [45.7–93.4]	72.8 [59.3–95.3]	93.8 [69.1–112.5]	0.086	**0.001**	**0.011**
Minimal lumen diameter (mm)	1.50 [1.19–1.78]	1.96 [1.58–2.17]	2.22 [1.95–2.62]	**0.011**	**0.001**	**0.011**
Minimal lumen area (mm^2)	1.77 [1.13–2.59]	3.12 [2.10–3.75]	3.90 [3.01–5.52]	**0.011**	**0.001**	**0.011**
Mean lumen symmetry	0.84 [0.82–0.86]	0.80 [0.77–0.84]	0.83 [0.83–0.88]	0.138	**0.009**	0.593
Minimal lumen symmetry	0.72 [0.58–0.73]	0.58 [0.54–0.68]	0.68 [0.63–0.78]	0.441	**0.010**	0.476
Dissection flap						
Dissection flap [n(%)]	0	21 (100)	7 (33)		**< 0.001**	
Maximal thickness (mm)	0	0.67 ± 0.29	0.44 ± 0.21		**< 0.001**	
Maximal length (mm)	0	1.34 ± 0.71	0.68 ± 0.33		**< 0.001**	
Longitudinal length (mm)	0	11.9 ± 8.7	1.8 ± 1.5		**< 0.001**	
Plaque type [n(%)]						
Fibrous plaque	6 (30)	–	8 (40)			0.157
Fibrocalcific plaque	2 (10)		2 (10)			> 0.999
Lipid-rich plaque	12 (60)		10 (50)			0.157
Plaque characteristic						
TCFA [n(%)]	2 (10)		2 (10)			> 0.999
Macrophage [n(%)]	10 (50)		7 (35)			0.083
Cap thickness (mm)	0.12 ± 0.06		0.17 ± 0.09			**0.007**
Lipid arc (°)	158.9 ± 99.4		148.5 ± 106.4			**0.030**
Lipid long length (mm)	2.0 ± 1.8		3.1 ± 1.6			0.186
Calcium area (mm^2)	0.80 ± 0.91		0.95 ± 1.06			**0.021**

BA balloon angioplasty, *TCFA* thin-cap fibroatheroma

of healed dissections and vessel remodeling. At 9-month follow-up, dissections after BA were sealed in 14 lesions (67%), whilst the maximal thickness and length of residual dissected flaps on cross-sectional and longitudinal images decreased significantly (0.67 ± 0.29 mm vs. 0.44 ± 0.21 mm, $p < 0.001$; and 1.34 ± 0.71 mm vs. 0.68 ± 0.33 mm, $p < 0.001$; and 11.9 ± 8.7 mm vs. 1.8 ± 1.5 mm, $p < 0.001$). There were no significant changes in plaque compositions during follow-up. However, the number of macrophage decreased from 10 (50%) to 7 (35%) at 9-month follow-up, and the cap thickness of plaque increased from 0.12 ± 0.06 mm to 0.17 ± 0.09 mm ($p = 0.007$). The arc of lipid decreased significantly at 9-month follow-up (158.9 ± 99.4° vs. 148.5 ± 106.4°, $p = 0.030$), and calcium area significantly increased from 0.80 ± 0.91 mm^2 to 0.95 ± 1.06 mm^2 ($p = 0.021$).

The percentage changes in QCA, IVUS, FFR measurements, and OCT are presented in Table 5. In OCT analysis, the median percent changes of the minimal lumen areas between pre- and post-BA, and post-BA and 9-month follow-up were 75.2% [interquartile range (IR), 37.2–164.7%], and 50.5% [IR, 1.1–64.5%], respectively. The median percent increases in mean lumen areas between pre- and post-BA, and post-BA and 9-month follow-up were 6.0% [IR, 0.5–22.5%] and 22.8% [IR, 5.4–39.1%], respectively.

There were no angiographic binary restenosis or adverse clinical events except for one case of non-target lesion revascularization after PCB treatment (Table 2).

Discussion

The main findings of this retrospective observational study of de novo coronary lesions treated with PCB are (1) vessel and lumen area significantly increased after 9-month follow-up; (2) restored coronary blood flow after BA was sustained at 9-month follow-up without a significant decrease in FFR; (3) plaque modification and stabilization occurred after 9-month follow-up: the number and size of dissection flaps decreased, the number of TCFA decreased and cap thickness of plaque increased, the arc of lipid decreased significantly, and lumen symmetry changed from post-BA to 9-month follow-up. Therefore, PCB treatment for de novo coronary lesions maintained persistent anatomical patency and vascular healing, with plaque stabilization and vessel remodeling, and restored coronary blood flow during follow-up.

BA was originally developed as a revascularization therapy which restores coronary blood flow through intentional plaque modification [16]. Unfortunately, BA has important limitations, including poor vessel patency, high restenosis rates due to elastic recoil, and late negative remodeling [17]. Although coronary stents were developed in part to overcome the risk of elastic recoil and restenosis from BA, a caged vessel due to a permanent stent prevents late lumen enlargement and advantageous vascular remodeling [18].

PCB was developed to deliver a single dose of paclitaxel through 1 min of PCB inflation, which was proven in a preclinical trial [19]. Paclitaxel exerts potent anti-proliferative effects by binding to the subunit of tubulin, resulting in the arrest of microtubule function and thus promoting prolonged anti-proliferation [20]. As a result, paclitaxel can inhibit arterial smooth muscle cell proliferation and migration after being used locally [21]. The main pathophysiology of restenosis after BA is arterial remodeling and neointimal hyperplasia [22]. A previous study showed that PCB treatment of de novo coronary lesions after predilatation led to late lumen increase [23]. They suggested that this finding may be compensatory expansive remodeling opening up the possibility that PCB-only treatment results in direct modification of the atherosclerotic plaque. Recently, we showed that PCB treatment for de novo coronary lesions increased the vessel and

Table 5 Percent changes of QCA, IVUS, FFR measurements, and OCT

Variables	Pre-BA vs. post-BA ($n = 21$)	Post-BA vs. 9 months ($n = 21$)	Pre-BA vs. 9 months ($n = 21$)
QCA			
Minimal lumen diameter change (%)	75.0 [55.3 to 142.2]	1.3 [− 7.4 to 4.2]	79.6 [44.3 to 159.6]
Diameter stenosis change (%)	− 65.3 [− 70.2 to − 42.6]	− 2.9 [− 25.3 to 15.6]	− 62.0 [76.4 to − 37.1]
IVUS			
Minimal lumen area change (%)	28.7 [6.2 to 38.9]	6.4 [− 13.5 to 19.1]	19.8 [15.2 to 35.8]
Plaque volume change (%)	− 15.7 [− 21.3 to − 6.3]	18.6 [6.8 to 27.0]	6.0 [− 16.3 to 21.0]
FFR			
FFR change (%)	11.3 [5.5 to 21.7]	− 1.7 [− 10.3 to 2.1]	7.5 [− 0.6 to 22.3]
OCT			
Minimal lumen area change (%)	75.2 [37.2 to 164.7]	50.0 [1.1 to 64.5]	123.7 [56.5 to 276.9]
Mean lumen area change (%)	6.0 [0.5 to 22.5]	22.8 [5.4 to 39.1]	31.7 [18.7 to 41.0]

BA balloon angioplasty, *QCA* quantitative coronary analysis, *IVUS* intravascular ultrasound, *FFR* fractional flow reserve, *OCT* optical coherence tomography

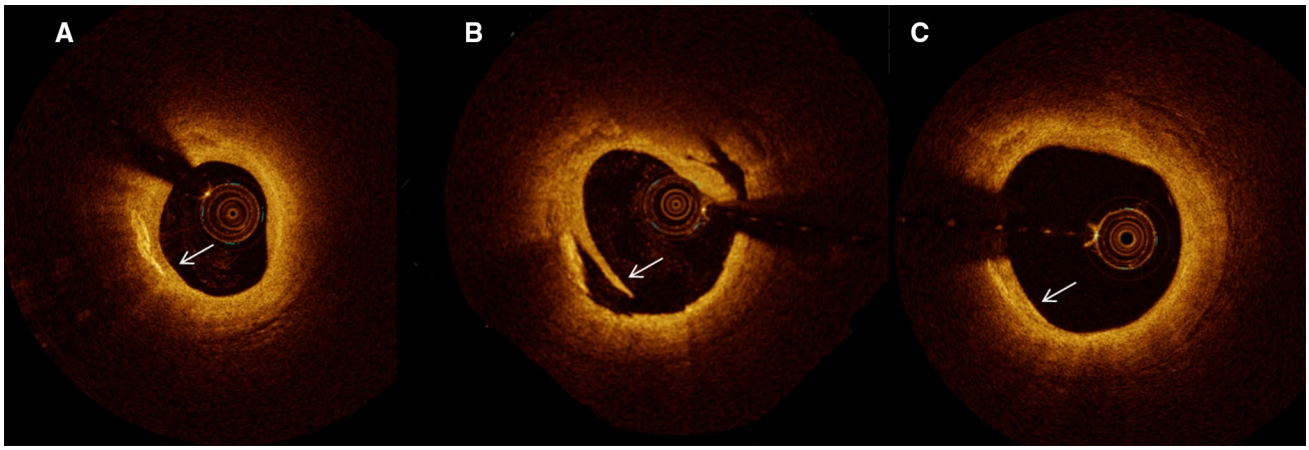

Fig. 1 Representative OCT images of healing process after DCB treatment. These 3 corresponding OCT images show the serial change of plaque characteristics after DCB treatment. **a** Baseline OCT image. The arrow indicates the active inflammatory lesion with macrophage signal. **B** The OCT image after balloon angioplasty. The arrow shows that the overlying fibrous cap was dissected by balloon angioplasty. **c** The OCT image at 9-month follow-up after DCB treatment. The previous dissection flap has disappeared and the arrow indicates that the cap thickness has increased, whilst the lipid and macrophage signal has decreased

lumen areas, suggesting that both intimal hyperplasia and arterial constriction were prevented by a coating of paclitaxel [5, 6]. Although the exact mechanism of this late lumen increase is not well understood, it is thought to be due to the local drug delivery effects of paclitaxel. Preceding laboratory results have shown that even short contact between taxane compounds and vascular smooth muscle cells can inhibit the proliferation of cells for a long period [21, 24]. Interestingly, PCB induce a much higher paclitaxel tissue concentration (~ 300 μg/g tissue) compared to paclitaxel-eluting stents (~ 3 μg/g tissue) [25], and dose-dependent positive vessel remodeling with reversible effects at long-term follow-up have been observed [26, 27].

In addition to previous results, this study showed that plaque modification and stabilization occurred after 9-month follow-up: the number and size of dissection flaps decreased, the number of TCFA decreased and cap thickness of plaque increased, the arc of lipid decreased significantly, and lumen symmetry changed from post-BA to 9-month follow-up. These results demonstrated that the healing process of the intimal dissections caused by BA can seal with shrinkage of the intimal tissue, without additional recurrent proliferation due to the cytostatic activity of paclitaxel (Fig. 1) [28]. As a result, paclitaxel can inhibit arterial smooth muscle cell proliferation and migration after being used locally, leading to favorable hemodynamics such as coronary patency with no significant change in FFR values (0.87 ± 0.04 vs. 0.83 ± 0.08, $p = 0.329$). In this context, this study is the first study investigating the course of vessel healing after PCB-only treatment using precise assessment such as OCT, and may be helpful to demonstrate the mechanism of vascular response after PCB treatment.

There are some limitations to our study that need consideration. First, this study was a single-center observational clinical study with small numbers. Second, because this study did not target all lesions of coronary artery disease, the results cannot be applied to patients beyond the inclusion criteria and study protocol. Third, although clinical and angiographic outcomes are promising, the nature of this registry that selectively applied PCB based on the FFR measured after BA does not allow for comparison with a reference technique. Finally, we could not identify if the definite cause of plaque stabilization was the healing process due to PCB treatment or the natural healing process due to BA. However, we can suggest that PCB treatment leads to the healing process with plaque stabilization because this study showed the vascular remodeling after PCB treatment compared to BA: the number and size of dissection flaps decreased, the number of TCFA decreased and cap thickness of plaque increased, the arc of lipid decreased significantly, and lumen symmetry changed from post-BA to 9-month follow-up.

In conclusion, PCB treatment for de novo coronary lesions showed persistent anatomical patency and vascular healing with plaque stabilization and vessel remodeling and restored coronary blood flow during follow-up. Therefore, PCB treatment may cause a change in either the structure, content or function of an atherosclerotic plaque, and it may achieve optimal prophylactic efficiency for vascular healing or plaque stabilization.

Compliance with ethical standards

Conflict of interest Authors have approved the final manuscript, which has not been published and is not under consideration for publication elsewhere. We declare that there is no conflict of interest for any author.

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