Effect of drug-coated balloon angioplasty on in-stent restenotic coronary lesions analyzed with optical coherence tomography and serial coronary artery angioscopy

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ORIGINAL ARTICLE

Effect of drug-coated balloon angioplasty on in-stent restenotic coronary lesions analyzed with optical coherence tomography and serial coronary artery angioscopy

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Abstract
Drug-coated balloon angioplasty (DCBA) has been recognized for its utility in preventing in-stent re-restenosis (ISR); however, imaging of the neointima immediately after treatment and during follow-up has only been described in a few case reports. This study aimed to determine the efficacy and mechanism of the DCBA using imaging studies both immediately after the DCBA and during the follow-up period. We enrolled 15 consecutive patients who underwent DCBA for in-stent restenosis (ISR). The in-stent neointimal volume was evaluated using optical coherence tomography (OCT), and the in-stent yellow grade was assessed using coronary angioscopy (CAS) immediately after DCBA and during the median follow-up period of 9 (8–15) months. The neointimal volume was significantly reduced from 77.1 ± 36.2 mm^3 at baseline to 60.2 ± 23.9 mm^3 immediately after DCBA ($p = 0.0012$ vs. baseline) and to 46.7 ± 21.9 mm^3 during the follow-up ($p = 0.0002$ vs. post DCBA). The yellow grade of the residual plaques at the ISR lesion, which indicated plaque vulnerability, was significantly decreased in the follow-up CAG (from baseline: 1.79 ± 1.03, during the follow-up: 0.76 ± 0.82; $p < 0.0001$). These data suggest that DCBA may inhibit neointimal formation and provide angioscopic intimal stabilization for ISR lesions.

Keywords Drug-coated balloon · In-stent restenosis · Optical coherence tomography · Coronary angioscopy

Introduction

Percutaneous coronary intervention (PCI) with drug-eluting stent (DES) implantation is widely accepted as the standard revascularization treatment for severe coronary stenosis. The implantation of DESs reduces the incidence of in-stent restenosis (ISR), which is a major adverse effect of bare-metal stent implantation. However, ISR still occurs in approximately in 5–10% of patients after DES implantation [1]. Drug-coated balloon (DCB) angioplasty (DCBA) has been used in recent years to overcome the ISR after DES implantation and is recommended as a Class 1a therapeutic option in the current guidelines [2]. The system comprised of semi-compliant angioplasty balloons coated with an antiproliferative drug (paclitaxel) that is rapidly released upon contact with the vessel wall. Some advantages of DCBs include that they are stent platform- and polymer-free devices, they provide uniform drug delivery to the in-stent neointimal tissue, and the treatment can be provided repeatedly. The utility of DCBA for ISR has been demonstrated [3-6], but there are only a few reports of imaging studies of the neointima immediately after the treatment and during the follow-up [7, 8].

The aim of this study was to evaluate the changes in the tissue characteristics of the coronary ISR lesions that had been treated by DCBA with optical coherence tomography (OCT) and coronary angioscopy (CAS). The stent,

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lumen, and neointimal volumes, were evaluated, as well as the neointimal characteristics (neointimal grade and yellow grade), immediately after DCBA and at the time of the coronary angiography (CAG) follow-up.

Materials and methods

Study population

This study was a retrospective observational study and was carried out by the opt-out method on our hospital website. We enrolled 15 consecutive patients who underwent DCBA for ISR from January 2014 to April 2017. Patients after acute coronary syndrome (ACS), coronary artery bypass grafting (CABG), or with incomplete imaging studies (in terms of the imaging quality or timing) were excluded. Inclusion criteria were patients who underwent OCT and CAS of the ISR site at baseline and during the follow-up. ISR was defined as a stenosis diameter of ≥ 75% (American Heart Association classification) in the vessel segment, and a Mehran classification of class 1 or 2 was assumed [9].

Drug-coated balloon angioplasty procedure

All patients were pretreated with aspirin (100 mg daily) and clopidogrel (75 mg daily, $n=8$) or prasugrel (3.75 mg daily, $n=7$). All procedures were performed according to the standard clinical guidelines. After a diagnosis of stent restenosis by a CAG assessment, the coronary artery was initially imaged with OCT, and the vessel was pre-dilated with a non-compliant balloon, semi-compliant balloon, or scoring balloon. In all cases of stent restenotic lesions, DCBA (SeQuent Please® B.Braun, Melsungen AG, Vascular Systems, Berlin, Germany) was performed. The balloon diameter, length, inflation time, and inflation pressure were decided at the physician's discretion. The balloon size was the same as or larger than the previous stent for full coverage of the stent site, and the balloon was inflated to 7–11 atm, which was maintained for 30 s or more. Immediately following balloon dilatation, an additional 1.5 mg of intracoronary isosorbide dinitrate was administered and OCT was carried out.

Optical coherence tomography

The ILUMIEN™ OPTIS™ PCI optimization System (St. Jude Medical, St. Paul, MN, USA) was used in the present study. Following the Z-offset calibration, the OCT image catheter was advanced distally to the coronary culprit lesion or stented segment over a 0.014 inch conventional angioplasty guidewire [10]. After catheter placement, 10% low molecular weight dextran preheated to 37 °C (Otsuka Pharmaceutical CO., Ltd., Tokyo, Japan) was flushed through the 6 or 7Fr guiding catheter at a rate of 4–6 mL/s for approximately 3–6 s by manual injection. The entire target vessel was imaged with an auto-pullback during the blood removal. The OCT images were stored digitally for subsequent analysis. All OCT images were analyzed by an experienced investigator who was blinded to the clinical information, PCI procedure characteristics, and angiographic findings. An image analysis was performed using a dedicated off-line review system with semi-automated contour detection software (St. Jude Medical, MN, USA). This was performed prior to the predilatation of the DCB, immediately after the DCBA, and at the follow-up.

Coronary angioscopy

Coronary angioscopy was performed using the VISIBLE Fiber Imaging System FT-203F (FiberTech Co.Ltd., Tokyo, Japan) immediately after DCBA and during the follow-up. The outer section of a 4F probing catheter (Medikit, Tokyo, Japan) was used as a guide for the insertion of the optical fiber into the coronary artery. While the angioscopic observations were carried out, blood was removed from the view by an injection of 10% dextran through the probing catheter as previously reported [11, 12]. The angioscopy images were recorded on a digital recorder.

Angiographic assessment

Coronary angiography was performed in all patients at baseline during the 8–15 months follow-up. Coronary angiograms were obtained in multiple views and standard quantitative coronary angiography (CMS, MEDIS, Nuenen, The Netherlands) was used to measure the percent diameter stenosis and binary restenosis at the stented segment.

Optical coherence tomography

All cross-sectional images within the stent segment were initially screened for a quality assessment. Frames with an inadequate definition were excluded from the analysis. A qualitative OCT analysis was performed at 1-mm intervals to detect any intra-stent thrombus and neoatherosclerosis. The neointimal coverage was assessed on each individual strut and, where observed, the thickness from the lumen border to the center of the strut blooming was measured. The lumen and stent areas were traced automatically, and the neointimal area was then calculated (Fig. 1). These measurements were performed every 1 mm from the distal edge to the proximal edge of the stent. The neointimal area was defined as the stent area minus the lumen area, according to a previous report [13]. The neointimal volume was calculated using the following equation: Neointimal volume = Σ Neointimal area × stent length. The stent, lumen, and neointimal

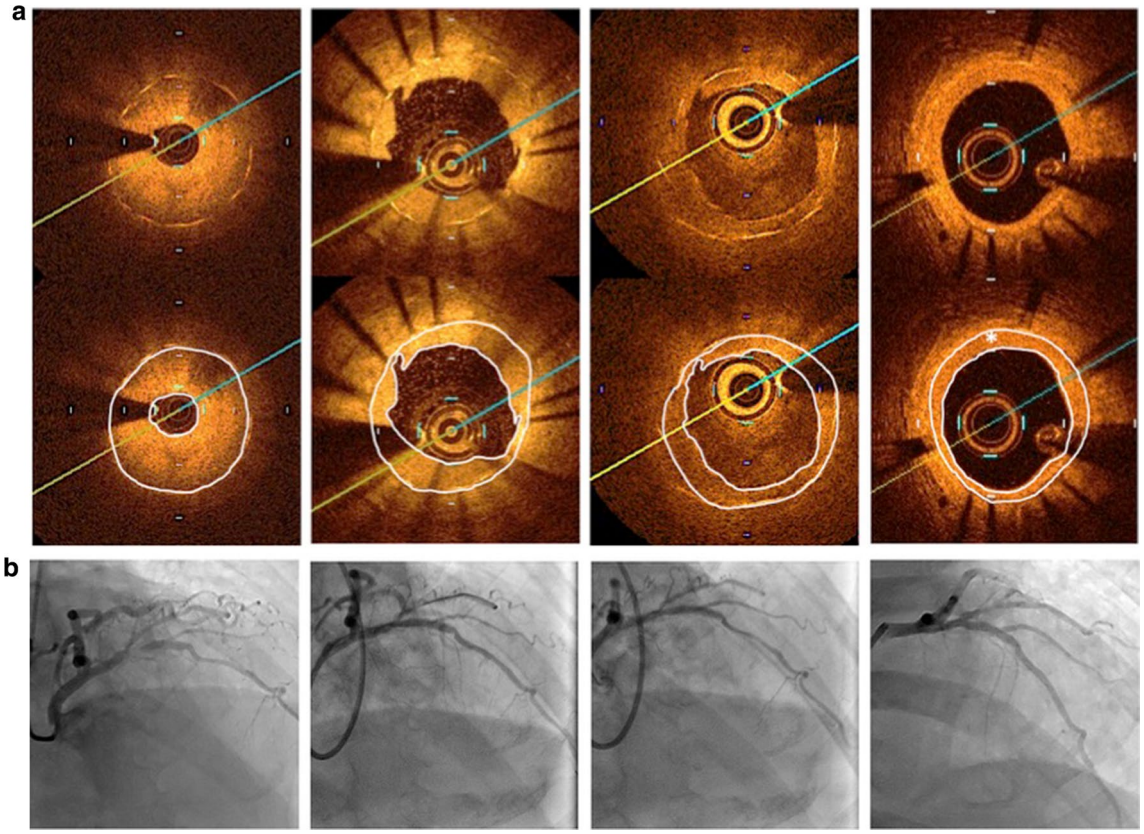

Fig. 1 Representative intravascular optical coherence tomography signal patterns and coronary angiography. The panels show the recordings (left to right): at baseline, postdilatation, post drug-coated balloon angioplasty (DCBA), and during the follow-up. The stent strut and lumen border (indicated by white outlines) were automatically detected. The neointimal area (*) was measured every 1 mm from the distal to the proximal stent distal edge. The neointimal volume = the number of slices × neointimal area. **a** Optical coherence tomography (OCT) images of coronary in-stent restenosis with DCBA. At baseline, a heterogeneous neointima was observed. The lumen area was seen to have increased after the dilatation with the plain balloon. After DCBA, a paclitaxel coating (high-intensity spotty coverage) was noted. **b** Coronary angiography showed in-stent restenosis (ISR) in the proximal left anterior descending artery at baseline. Follow-up coronary angiography revealed the absence of ISR after DCBA

volumes were compared between the baseline, post DCBA, and follow-up measurements.

For a qualitative analysis, the OCT signal patterns of the neointimal tissue were categorized into three patterns based on Gonzalo's classification [13]: homogeneous, layered, and heterogeneous patterns as shown in Fig. 2. An assessment of the tissue characteristics was carried out at the in-stent maximal lumen narrowing site, which was determined by the agreement of two observers who were blinded to the clinical and procedural characteristics [14].

Angioscopy

The neointimal grade on the stent struts and the yellow grade of plaque were assessed by a classification into four grades as previously described (Fig. 3) [15]. In brief, grade 0 described stent struts that were completely exposed (similar to immediately after implantation); grade 1, stent struts that were visible with dull light reflection; grade 2, no light reflection from the stent struts with slightly visible struts; and grade 3, stent struts that were completely covered, and not visible through the neointima (Fig. 3a). The yellow grade under the stent was classified as either: grade 0, white; grade 1, light yellow; grade 2, yellow; or grade 3, bright yellow (Fig. 3b) [16]. We evaluated the yellow grade and the neointimal grade at the proximal, mid, and distal sites of each stent. The maximum yellow grade and the minimum neointimal grade were evaluated immediately after the DCBA and during the follow-up. The angioscopic evaluations were made by two independent specialists in coronary intervention and angioscopy who were blinded to the patients' clinical status. In the case of disagreement, the plaque color was reevaluated. If the reevaluations remained discordant, the disagreement was resolved through discussion until a consensus was reached.

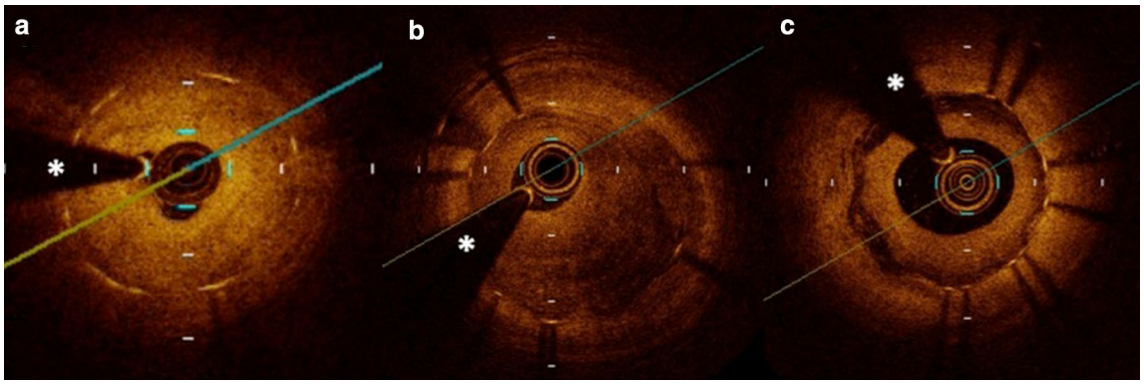

Fig. 2 Representative optical coherence tomography signal patterns of the neointimal tissue. The OCT signal patterns of the neointimal tissue. **a** A homogeneous pattern of the neointimal tissue was defined by uniform optical properties without a focal variation in the backscattering pattern. **b** A heterogeneous pattern was defined by focally changing neointimal optical properties and various backscattering patterns. **c** A layered pattern was defined by the presence of concentric layers with different optical properties: an abluminal high-scattered layer and the abluminal low-scattered layer. *Guide-wire artifact

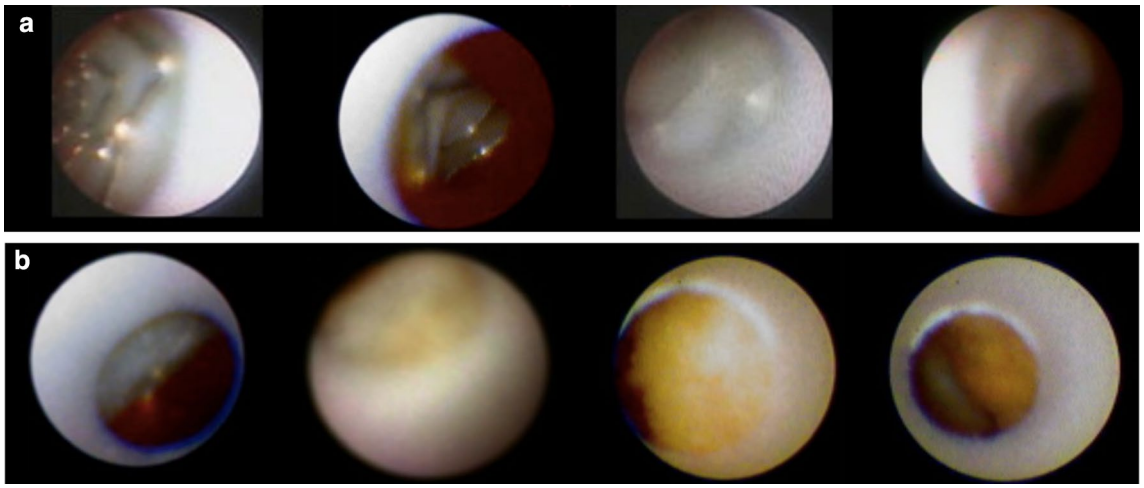

Fig. 3 Representative images from angioscopic assessments. **a** Representative images used for the classification of neointimal tissue. The panels show (left to right): Grade 0, complete exposure of the stent struts; grade 1, dull light reflection from the stent struts; grade 2, no light reflects but the stent struts are slightly visible; and grade 3, complete coverage. **b** Representative images of the yellow grade under the strut, classified into each grade. The panels show (left to right): Grade 0, white; grade1, light yellow; grade 2, normal yellow; and grade 3, bright yellow

Statistical analysis

Data are expressed as the means ± standard deviation or number (%). The mean values between the two groups were tested using the Student's *t* test. Comparison in the mean values or categorical variables at different time periods were analyzed by the paired *t* test or Chi-square test. We considered $p < 0.05$ to be statistically significant. All data were analyzed using IBM® SPSS® Statistics Desktop software (version 24.0, for Linux × 86–64, Mac OS X, Microsoft Windows, Ubuntu).

Results

Patient population

The patients and lesion characteristics at baseline are shown in Table 1. The mean age of the patients was 66.7 ± 11.5 years old, and the median term to follow-up was 9 (8–15) months. Regarding the previous stent sites, 6 (40%) patients were in the right coronary artery (RCA), 4 (27%) patients in the left anterior descending artery (LAD), and 5 (33%) patients in the left circumflex artery (LCX). The

Table 1 Baseline characteristics

	Total patients $n=15$
Age, median_(years)	66.7 ± 11.5
Sex_(male:female)	11:4
Follow-up CAG intervals_median (months)	9 (8–15)
Stented vessels	
LMT	0_(0)
LAD	4_(27)
LCX	5_(33)
RCA	6_(40)
Stent (BMS: DES)	6:9
Medication	
DAPT	15_(100)
ACEI/ARB	8_(53)
βblockers	8_(53)
Statins	13_(86)
Hypertension	14_(93)
Diabetes	11_(92)
Hemoglobin A1c_(NGSP) (%)	7.0 ± 0.9
Dyslipidemia	15_(100)
LDL-C_(mg/dL)	91.2 ± 30.4
HDL-C_(mg/dL)	47.4 ± 6.3
TC_(mg/dL)	166.0 ± 31.2
TG_(mg/dL)	145.0 ± 73.6
Hemoglobin_(g/dL)	12.4 ± 1.9
Baseline LV-EF_(%)	63.9 ± 15.5
eGFR_(mL/min/1.73mm^2)	54.8 ± 21.5
Hemodialysis	2_(13)
Angiographic data of ISR	
Pre DCBA MLD_(mm)	0.7 ± 0.5
Pre DCBA RD_(mm)	2.5 ± 0.6
Pre area stenosis_(%)	90.7 ± 7.9
Lesion length_(mm)	9.1 ± 3.4
Primary lesion type B2/C	3_(20)
Side branch involvement	3_(20)
Post DCBA MLD_(mm)	2.1 ± 0.5
Post area stenosis_(%)	27.4 ± 13.6
Follow-up MLD_(mm)	2.3 ± 0.5
Follow-up area stenosis_(%)	26.1 ± 17.4
Acute gain_(mm)	1.4 ± 0.7
Late loss_(mm)	− 0.2 ± 0.3
Loss index	− 0.5 ± 1.1
Recurrent-restenosis $n=15$	0_(0)
Median intervals from the stent implantation to the PCI for ISR with DCBs_(months)	13 (8–27)
Previous stent	
Diameter_(mm)	3.1 ± 0.4
Length_(mm)	22.4 ± 7.1
Predilatation balloon	
Semi-compliant balloon	2_(13)
Non-compliant balloon	3_(20)
Scoring balloon	10_(67)
Diameter_(mm)	3.1 ± 0.4
Length_(mm)	13.0 ± 1.4
DCBA procedure success	15_(100)
DCB	
Diameter_(mm)	3.1 ± 0.3
Length_(mm)	22.0 ± 6.1
Maximal inflation pressure_(atm)	8.2 ± 1.5
Inflation time_(sec)	60.0 ± 13.4

Categorical data are presented as *n*_(%), continuous data are presented as mean ± standard deviation

CAG coronary angiography, *LMT* left main trunk, *LAD* left anterior descending artery, *LCX* left circumflex artery, *RCA* right coronary artery, *BMS* bare metal stent, *DES* drug-eluting stent, *DAPT* double antiplatelet therapy, *ACEI* angiotensin-converting enzyme inhibitor, *ARB* angiotensin-receptor blocker, *NGSP* national glycohemoglobin standardization program, *LDL-C* low-density lipoprotein-cholesterol, *HDL-C* high-density lipoprotein-cholesterol, *TC* total cholesterol, *TG* triglycerides, *LV-EF* left ventricular-ejection fraction, *eGFR* estimated-glomerular filtration rate, *ISR* in-stent restenosis, *MLD* minimum lumen diameter, *RD* reference diameter, *DCBA* drug-coated balloon angioplasty

details of the stent type were 6 bare metal stents (BMSs) (2 with a Liberte®, 2 with a Multi-Link Penta®, 1 with a Duraflex™ and 1 with an Integrity™) and 9 DESs (4 with a PROMUS Element™, 3 with a PROMUS Premier™, and 2 with a TAXUS Element®). The mean stent diameter was 3.1 ± 0.4 mm and stent length was 22.4 ± 7.1 mm. The median duration from the stent implantation to PCI for ISR with DCBs was 13 (8–27) months.

Percutaneous coronary intervention procedure for in-stent restenosis

Predilatation was performed to scoring balloons in 10 (67%) patients, semi-compliant balloons in 2 (13%) patients, and non-compliant balloons in 3 (20%) patients. The mean balloon diameter and length for the predilatation were 3.1 ± 0.4 mm and 13.0 ± 1.4 mm, respectively. In all cases, DCBA was performed successfully. For DCBA, a length of the DCB was chosen that would overlap with the lesion by at least 2 mm at the proximal and distal margins. The mean balloon diameter and length for DCBA were 3.1 ± 0.3 mm and 22.0 ± 6.1 mm, respectively. The maximum dilated pressure was 8.2 ± 1.5 atm and the inflation duration was 60.0 ± 13.4 s. Each volume was examined in each case for scoring and non-scoring balloons (semi-compliant and non-compliant balloons) (10 and 5, respectively) (Table 2). For each neointimal volume at baseline, post DCBA, and during the follow-up, there was no significant difference between the scoring and non-scoring balloons: 76.4 ± 34.8 mm^3

Table 2 Evaluation of predilatation before and after drug-coated balloon angioplasty

Measurement	Pre-DCBA	Δpre/post-DCBA(%)	Post-DCBA	ΔPost/follow-up-DCBA(%)	Follow-up
Stent volume					
Scoring balloon	148.6 ± 65.4	16.2	169.6 ± 70.4	− 5.2	162.2 ± 73.6
Non-scoring balloon	200.6 ± 105.7	6.5	216.9 ± 122.6	2.4	212.9 ± 105.1
p value	0.4	0.21	0.5	0.21	0.42
Lumen volume					
Scoring balloon	71.9 ± 36.7	62.0	108.8 ± 51.5	7.6	115.6 ± 53.1
Non-scoring balloon	122.7 ± 72.8	25.9	157.8 ± 100.9	11.3	165.9 ± 93.8
p value	0.24	0.14	0.4	0.69	0.36
Neointimal volume					
Scoring balloon	76.4 ± 34.8	− 18.9	60.7 ± 23.7	− 25.3	46.6 ± 23.2
Non-scoring balloon	77.9 ± 38.6	− 20.5	59.1 ± 24.5	− 18.3	46.8 ± 19.1
p value	0.96	0.83	0.91	0.49	0.99

DCBA drug-coated balloon angioplasty

vs. 77.9 ± 38.6 mm^3, $p = 0.96$; 60.7 ± 23.7 mm^3 vs. 59.1 ± 24.5 mm^3, $p = 0.91$; and 46.6 ± 23.2 mm^3 vs. 46.8 ± 19.1 mm^3, $p = 0.99$. For each the lumen volume at baseline, post DCBA, and during the follow-up, there was no significant difference between the scoring and non-scoring balloons: 71.9 ± 36.7 mm^3 vs. 122.7 ± 72.8 mm^3, $p = 0.24$; 108.8 ± 51.5 mm^3 vs. 157.8 ± 100.9 mm^3, $p = 0.4$; and 115.6 ± 53.1 mm^3 vs. 165.9 ± 93.8 mm^3, $p = 0.36$. Further, for each stent volume at baseline, post DCBA, and during the follow-up, there was no significant difference between the scoring and non-scoring balloons: 148.6 ± 65.4 mm^3 vs. 200.6 ± 105.7 mm^3, $p = 0.4$; 169.6 ± 70.4 mm^3 vs. 216.9 ± 122.6 mm^3, $p = 0.5$; and 162.2 ± 73.6 mm^3 vs. 212.9 ± 105.1 mm^3, $p = 0.42$. For the rate of change of each volume no significant difference was identified between the scoring and non-scoring balloons; neointimal volume; Δ pre/post-DCBA (%): − 18.9% vs. − 20.5%, $p = 0.83$; and Δ post/follow-up (%): − 25.3% vs. − 18.3%, $p = 0.49$; lumen volume, Δ pre/post-DCBA (%): 62.0% vs. 25.9%, $p = 0.14$; Δ post/follow-up (%): 7.6% vs. 11.3%, $p = 0.69$; stent volume, Δ pre/post-DCBA (%): 16.2% vs. 6.5%, $p = 0.21$; Δ post/follow-up (%): − 5.2% vs. 2.4%, $p = 0.21$.

Angiographic assessment

The reference diameter at baseline was 2.5 ± 0.6 mm, and the lesion length was 9.1 ± 3.4 mm (Table1). The minimum lumen diameter (MLD) was significantly increased from 0.7 ± 0.5 mm at baseline to 2.1 ± 0.5 mm immediately after DCBA ($p < 0.0001$ vs. baseline), and to 2.3 ± 0.5 mm during the follow-up ($p = 0.04$ vs. immediately after DCBA). The area stenosis was significantly decreased immediately after DCBA as compared to that at baseline (90.7 ± 7.9% at baseline vs. 27.4 ± 13.6%, $p < 0.0001$). The area stenosis during the follow-up was numerically (but not significantly) decreased (27.4 ± 13.6% immediately after DCBA vs. 26.1 ± 17.4%, $p = 0.83$). The acute gain was 1.4 ± 0.7 mm, the late loss was − 0.2 ± 0.3 mm, and the loss index was − 0.5 ± 1.1. No cases had recurrent restenosis, target lesion revascularization (TLR), or composite major adverse cardiac events (MACE) during the median follow-up period of 9 (8–15) months.

Optical coherence tomography findings

Evaluation of the stent, lumen, and the neointimal volumes revealed that the neointimal volume was significantly reduced immediately after DCBA as compared to that at baseline (77.1 ± 36.2 mm^3 at baseline vs. 60.2 ± 23.9 mm^3, $p = 0.0012$), and the neointimal volume during the follow-up was also significantly reduced compared to that immediately after DCBA (60.2 ± 23.9 mm^3 post DCBA vs. 46.7 ± 21.9 mm^3, $p = 0.0002$) (Fig. 4a). The stent volume was significantly increased from 165.9 ± 84.7 mm^3 at baseline to 185.3 ± 93.9 mm^3 immediately after DCBA ($p = 0.0004$), and this increase was maintained during the follow-up (179.1 ± 88.7 mm^3; $p = 0.197$ vs. post DCBA) (Fig. 4b). The lumen volume was significantly increased immediately after DCBA as compared to that at baseline (88.8 ± 56.9 mm^3 vs. 125.2 ± 75.4 mm^3, $p = 0.0001$), and was also significantly increased during the follow-up as compared to that immediately after DCBA (125.1 ± 75.4 mm^3 vs. 132.4 ± 73.4 mm^3, $p = 0.03$) (Fig. 4c).

In terms of the tissue properties, the heterogeneous properties changed to homogeneous properties during the follow-up in two cases. However, the distribution of the neointimal properties did not significantly differ between the baseline and follow-up CAG values (Table 3) ($p = 0.64$). The neointimal volume reduction during the follow-up exhibited a similar trend regardless of the neointimal properties

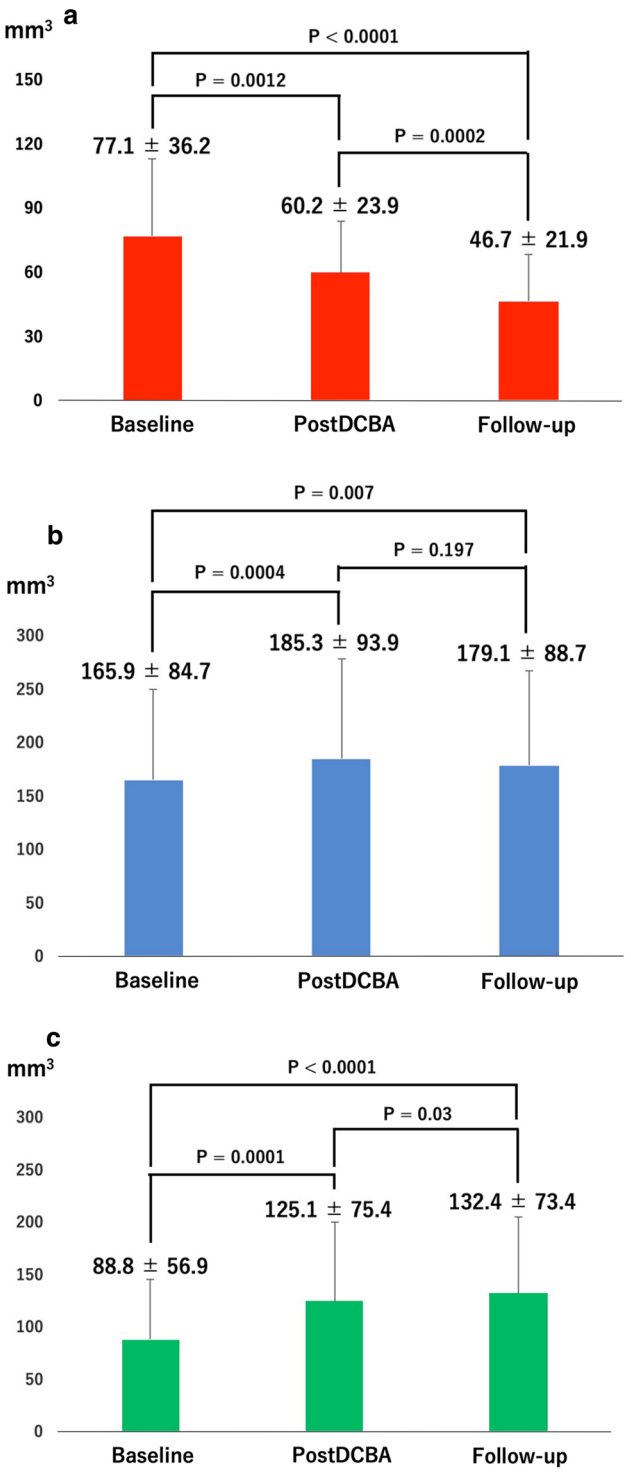

Fig. 4 Results of optical coherence tomography measurements. **a** The bar graph of the mean neointimal volumes at baseline, post drug-coated balloon angioplasty (DCBA), and during the follow-up. A significant decrease in the volume was observed post DCBA compared with baseline. The neointimal volume was also significantly decreased during the follow-up compared with post DCBA. **b** The stent volumes were significantly increased post DCBA compared to baseline, and this increase was maintained during the follow-up. **c** The lumen volumes were significantly increased post DCBA compared to baseline, and were also significantly increased during the follow-up compared to post DCBA

Table 3 Findings of optical coherence tomography

Neointimal tissue properties	Baseline (*n*)	Follow-up (*n*)
Homogeneous	8	10
Heterogeneous	4	2
Layered	3	3

Chi-square test

Degrees of freedom, 2; Chi-square value, 0.89; *p* value, 0.64

(Fig. 5a–c). In addition, the neoatherosclerosis was detected in four cases (PROMUS Element™, PROMUS Premier™, TAXUS Element®, and Multi-Link Penta® for each).

Coronary angioscopy findings

There was no significant difference in the neointimal grade between that immediately after DCBA and that during the follow-up (grade 1.69 ± 0.87 vs. grade 1.6 ± 0.88; $p = 0.08$) (Fig. 6a), and there was no major change in the distribution (degrees of freedom, 3; Chi-square value, 0.86; $p = 0.83$). (Fig. 6b) However, the yellow grade, which represented plaque vulnerability, was significantly decreased during the follow-up (grade 1.79 ± 1.03 vs. grade 0.76 ± 0.82; $p < 0.0001$). (Fig. 6c) In terms of distribution, there was a significant difference between the distribution observed immediately after DCBA and that during the follow-up (degrees of freedom, 3; Chi-square value, 21.77; $p < 0.0001$). During the follow-up, the prevalence of grade 0 was increased more than that was predicted (adjusted residual; 3.02), and that of grade 3 was decreased less than that was predicted (adjusted residual; − 2.89) (Fig. 6d).

Discussion

This study presents our evaluation of the changes in the in-stent neointima after DCBA by the OCT and CAS analysis. To the best of our knowledge, this study was the first report of the use of multiple modalities to assess the mechanism of DCBA for the prevention of restenosis at the site of the ISR in cases during clinical practice.

Mechanism of the efficacy after drug-coated balloon angioplasty

The usefulness of DCBA has been shown previously in the PACCOCATH ISR I, II, PEPCAD II, and PEPCAD DES trials [17-19]. In the PACCOCATH ISR I, II trial, the advantage of DCBA was shown in comparison to plain old balloon angioplasty (POBA) in terms of the late loss, the binary stenosis rate, and the MACE for BMS-ISR. In

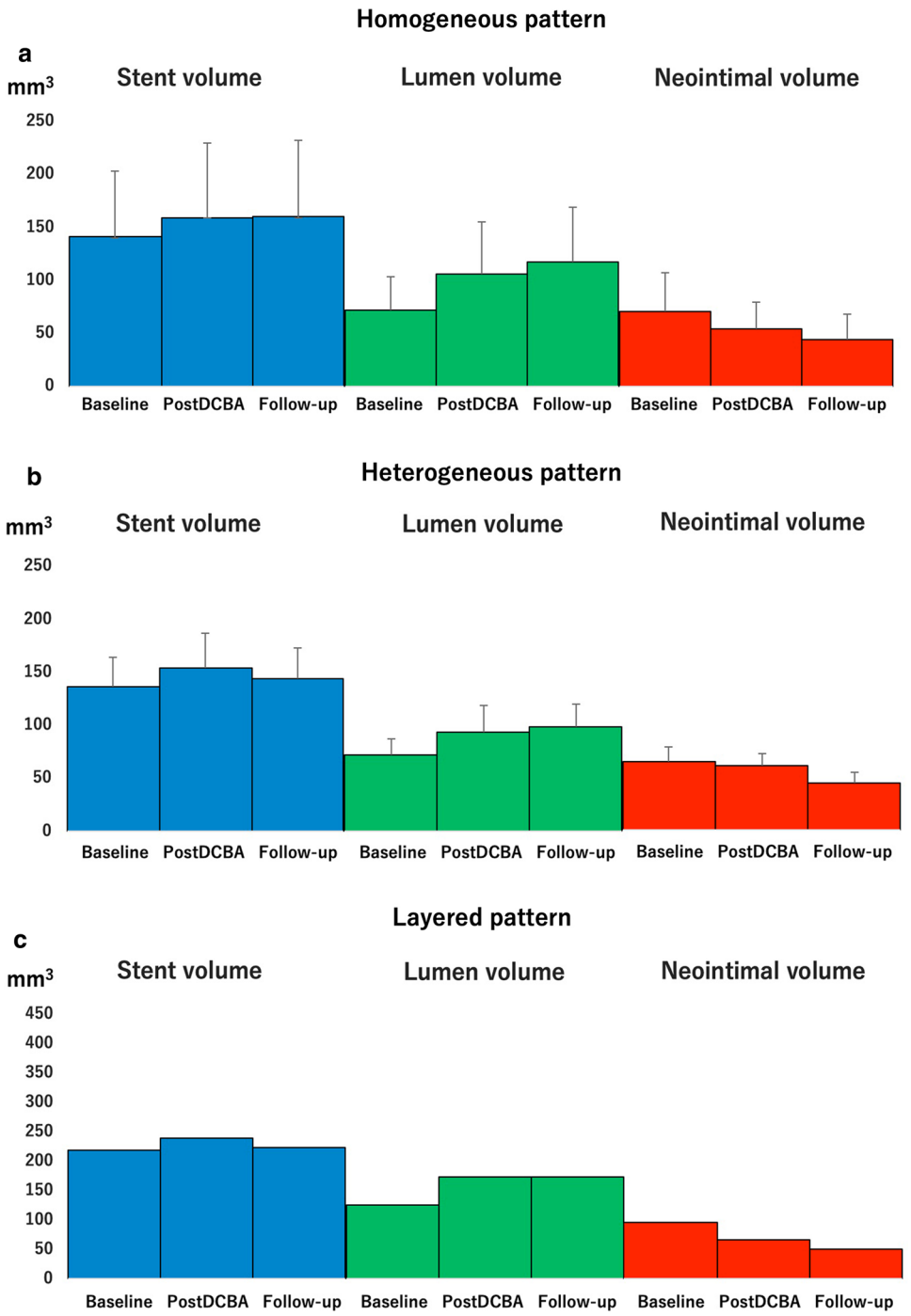

Fig. 5 Results of the analysis of the tissue properties by optical coherence tomography. The bar graphs show the mean stent, lumen, and neointimal volumes at baseline, post drug-coated balloon angioplasty (DCBA), and during the follow-up **a** homogeneous samples, **b** heterogeneous samples, and **c** layered samples. In each case, the neointimal volume was reduced during the follow-up compared to that at baseline and post DCBA

the PEPCAD II trial, the DCBA group was significantly superior in terms of in-segment late loss compared with DESs (paclitaxel-eluting). The PEPCAD DES trial showed that late loss, TLR, and MACE were significantly lower 6 months after DCBA than that following POBA for BMS-ISR. The present study revealed that the lumen and neointimal volumes changed significantly from the pre-DCBA volumes to those observed during the follow-up. In addition, the yellow grade of plaques was decreased during the follow-up, and the neointima appeared to have stabilized. Initially, the mechanical pressure exerted by the DCB led to a reduced neointimal volume. Later, paclitaxel, which binds to the microtube and controls the cell division by obstructing depolymerization [20-22], induced smooth muscle apoptosis and reduced the neointimal volume. In addition, the DCB is polymer-free and stent-free, which may suppress chronic inflammation, and the occurrence of neoatherosclerosis. As a result, paclitaxel may contribute

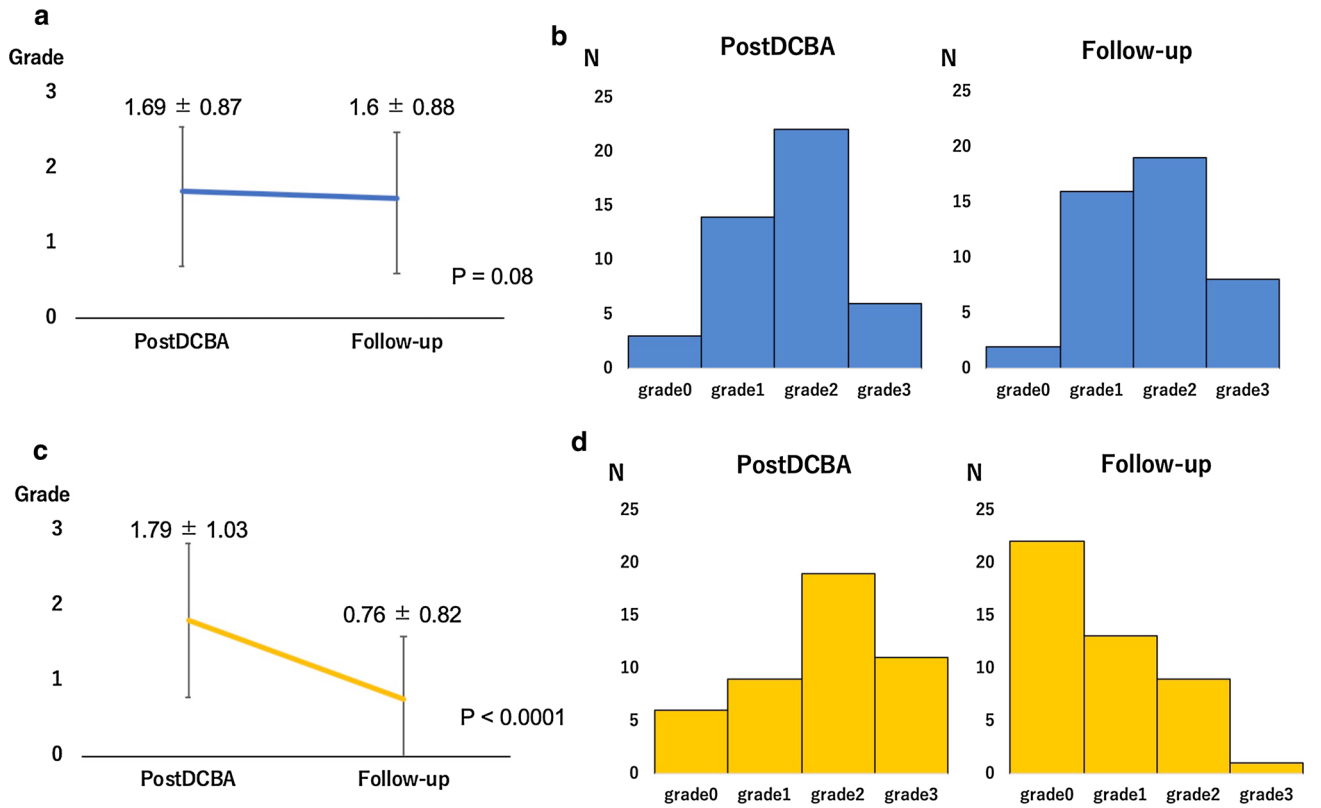

Fig. 6 Results of angioscopy assessments. **a** Graph showing the neointimal grade post drug-coated balloon angioplasty (DCBA) and during the follow-up. There was no significant change in the neointimal coverage between the two assessments. **b** Bar graph showing the distribution of the neointimal grade between post DCBA and during the follow-up. There was no significant change in the distribution (Chi-square test: degrees of freedom, 3; Chi-square value, 0.86; $p = 0.83$). **c** Graph of the results of the assessment of the yellow grade post DCBA and during the follow-up. The severity of the yellow grade decreased significantly during the follow-up. **d** Bar graph showing the distribution of the yellow grade ratings post DCBA and during the follow-up. There were significant differences between the two assessments. During the follow-up, a grade 0 was observed more frequently than predicted, and a grade 3 less frequently than predicted (Chi-square test: degrees of freedom, 3; Chi-square value, 21.77; $p < 0.0001$. Adjusted residual; grade 0: 3.02, grade 1: 0.85, grade 3: −1.89, grade 4: −2.89)

to the effects on the neointimal volume and the reduction in the yellow grade.

Tissue composition of in-stent restenosis by optical coherence tomography

Restenotic lesions were visualized after DES implantations using OCT and described according to their patterns of backscatter (which indicated the morphological characteristics) as homogeneous, heterogeneous or layered overlying the stent struts. The morphologic characteristics of the neointimal influence the onset of the recurrence of ISR after the DCBA [23]. Tada et al. compared the characteristics of ISR tissue, evaluated using OCT, between the DCBA and POBA treatments for ISR. The recurrence rates of ISR and TLR lesions with homogeneous patterns were significantly lower following the DCBA than after the POBA. On the other hand, the recurrence rates of ISR and TLR of lesions with heterogeneous patterns did not significantly differ between the two procedures [23]. That suggested that the heterogeneous pattern of ISR represented a vulnerable state, and indicated the risk of the recurrence ISR and TLR.

In the present study, OCT revealed that the prevalence of homogeneous patterns increased, while heterogeneous patterns decreased during the follow-up. This suggested the possibility of tissue stabilization during the chronic phase after DCBA, and also indicated that DCB may be an appropriate choice of treatment for ISR that involves heterogeneous properties. However, due to the small number of cases in this study, further investigations are required involving larger numbers of cases and evaluating the effectiveness of DCBA for each neointimal property.

The evaluation using coronary angioscopy

Coronary angioscopy is an intravascular imaging technique for the visual assessment of the plaque color. There have been numerous reports that have evaluated the vascular

response after stent implantations using CAS [24-27], and the usefulness of the technique for evaluating the neointimal characteristics and plaque characteristics has been proven. Previously, we published a case report evaluating the neointimal formation and plaque characteristics using CAS both immediately after DCBA and during the follow-up [7]. This case study found that neointimal healing—defined as regression (reduction in the neointimal volume on OCT) and stabilization (lower yellow grade on CAS) during the follow-up—occurred after DCBA because of the pharmacological effect of paclitaxel. These results guided the present study.

Evaluation of the predilatation before drug-coated balloon angioplasty

Drug-coated balloons are used following predilatation with scoring or non-scoring balloons (non-compliant and semi-compliant balloons). It has been reported that patients who are treated using scoring balloons exhibit a reduced intimal proliferation compared with treatment with non-scoring balloons [28]. Furthermore, significant reductions in the intima formation during the follow-up have been reported with the use of scoring balloons compared with non-scoring balloons [29]. We examined each volume in each case of scoring and non-scoring balloons (10 and 5, respectively) (Table 2), and did not identify a significant difference in the rate of change of each volume with regards to the type of balloon. Because this study was not randomized, we cannot draw firm conclusions; however, these results suggested that intima formation might be suppressed by both scoring and non-scoring balloons.

Clinical implication

The results of our study provided suggestive evidence that DCBA could reduce the neointimal volume and result in the lower yellow grade of plaques during the follow-up compared with that at baseline. These results strongly support the choice of DCBA as a first-line treatment of ISR.

Limitations

This study had some limitations that should be acknowledged. First, the retrospective design and small population meant that we could not unify the type of balloons. Second, we used only the SeQuent Please® in this study, and therefore, it might not be possible to generalize the results to other DCBs. Third, we found a discrepant result in the area stenosis remained significantly unchanged during the follow-up period despite a slightly greater increase in the OCT-derived lumen volume during the follow-up period than that after the DCBA. The area of stenosis was measured with a 2-dimensional assessment, but the OCT-derived lumen volume was measured with a 3-dimensional assessment, so we could not directly compare those measurements directly. The lumen volume increased significantly during the follow-up, and thus, the extent of the stenosis might have improved 3-dimensionally, but it was not reflected by 2-dimensional stenosis area.

Conclusion

The data presented here suggested that DCBA inhibits the proliferation of the neointima and provides angioscopic intimal stabilization for ISR lesions.

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Compliance with ethical standards

Conflict of interest Dr. Hirayama A and Hiro T are employed by the Department of Advanced Cardiovascular Imaging, Nihon University School of Medicine; which is endowed by Boston Scientific Corporation Japan, Abbott Medical Japan Co., Ltd and St. Jude Medical Japan Co., Ltd.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study and its protocols were approved by the Institutional Review Board of Nihon University Itabashi Hospital. This article does not contain any studies with animals performed by any of the authors.

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学位予備審査　補足資料

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本研究では冠動脈ステント留置後のステント内再狭窄(ISR: in-stent restenosis)部位に対して薬剤溶出性バルーン(DCB: drug-coated balloon)を用いて血行再建を行なった症例で、DCBによる治療時と慢性期に光干渉断層法（OCT: optical coherence tomography)と冠動脈血管内内視鏡(CAS: coronary angioscopy)を用いてステント内新生内膜の経時的変化を検討した。OCTでは急性期と比較し、慢性期に新生内膜体積が有意に減少し、それに伴い血管内腔体積が有意に増加した。また不安定新生内膜(Heterogeneous pattern)が、安定した新生内膜(Homogeneous patter)に変化する症例も認められた。CASでは不安定なプラークの存在を示唆する黄色度が治療直後より慢性期に有意に低下し、新生内膜の安定化が示唆された。本研究はオプトアウト方式で行なった後ろ向き観察研究であり、当院の臨床研究倫理審査委員会の許可を得て行なった(「冠動脈ステント留置後再狭窄病変への薬剤溶出性バルーンの有用性の検討」【RK-190514-6】)。

冠動脈狭窄症に対する経皮的冠動脈形成術(PCI: percutaneous coronary intervention)は近年目覚ましい発展を遂げてきた。PCI の黎明期に従来のバルーンのみを用いて行われた経皮的古典的バルーン血管形成術（POBA: plane old balloon angioplasty)後の冠動脈再狭窄率は 30-40%と高率であり、満足できる治療成績ではなかった。その後ステントの登場により再狭窄率は劇的に改善した。1990 年代に登場したベアメタルステント(BMS: bare-metal stent)により ISR は 20-30%に減少し、さらに新生内膜の増殖を抑制する薬剤が塗布された薬剤溶出性ステント(DES: drug-eluting stent)が 2004 年に本邦でも使用可能となり、再狭窄率は 5-10%まで減少した。

ISR の原因には各治療デバイスにより異なる病理学的要因が想定されている。POBA の場合、バルーンを拡張することで血管壁の脆弱な部分を中心にして血管内膜から中膜に解離を起こして血管を拡張することにより、血管内腔が拡大する。内膜から中膜の解離による損傷部位では、続いて修復・治癒の機構が働く。内弾性板の断裂部から血管平滑筋細胞が内膜亀裂部に遊出し、新生内膜として増殖し肥厚する。血管平滑筋細胞が過剰に増殖すると、冠動脈の再狭窄が惹起される。BMS の場合は、血管留置後のステントストラット(ステントの網状の部分)はプラーク表層に埋没する。ステントストラット周囲にはマクロファージや好中球などの炎症細胞が浸潤し、血小板やフィブリンの析出により小血栓が形成される。小血栓の形成部位に遊走した血管

平滑筋細胞が増殖して1ヶ月ほどでステントストラットを被覆する。さらに活性化した血管平滑筋細胞や細胞外マトリックスが増殖し、新生内膜が肥厚する。一方、DES では塗布された薬剤による血管平滑筋細胞の遊走・増殖の抑制により、新生内膜によるステントストラットの被覆や血管解離部に対する急性期の治癒機構の働きは遅延するため、新生内膜の生成は緩やかとなる。しかし、慢性期にはステントストラットやポリマー(薬剤を溶出させるための担体)により局所の炎症が発生し、マクロファージや多核巨細胞などの炎症細胞が出現する。炎症細胞からのサイトカインの分泌を介して、血管平滑筋細胞の遊走や増殖が促進され、ときに新生内膜の過剰な肥厚が起こる。

ISR に対して、従来は主に POBA や既存の冠動脈ステント内に新たなステントを追加する stent in stent 法が施行されていた。しかし、POBA のみでは再々狭窄を起こす可能性が高い。また、stent in stent 法のでは同じ狭窄部位にステントが重なるため血管内腔の狭小化をきたしやすいこと、2 剤の抗血小板薬の服用を長期に要すること、再々狭窄した場合の治療法の選択肢が限られることが問題であった。この ISR に対する治療成績を向上させるために DCB が登場し、本邦でも 2014 年より保健償還された。DCB の本邦での保険適応は、当初 ISR に限定されていたが、その後ステント留置が困難な小血管の狭窄に対する有用性も証明され、現在では 3 mm 以下の小血管の新規病変に対しても適応の幅を広げている。

DCB を用いて ISR を治療する際には、はじめに従来型の冠動脈拡張用バルーンで狭窄部を前拡張して十分な血管内腔を確保し、追加のステント留置を要する血管の解離の有無を確認する。前拡張に用いるバルーンにはスコアリングバルーンとノンスコアリングバルーンがあり、術者が病変に応じて使い分けている。スコアリングバルーンはバルーン表面にワイヤーが取り付けられており、拡張時にバルーンがスリップすることが少なく、前拡張の際に線維性プラークや石灰化病変に切れ込みが入るため良好な拡張が得られる。ISR に対する治療では、スコアリングバルーンが新生内膜の微小解離を増やして DCB に塗布された薬剤を標的組織に塗布・浸透させる体積を増やすことで、DCB 後の治療成績の向上をもたらすと考えられている。ノンスコアリングバルーンはバルーン表面にワイヤーのない標準型の血管拡張バルーンであるが、セミコンプライアントバルーンとノンコンプライアントバルーンがある。セミコンプライアントバルーンは拡張したバルーン径を調整できるのに対し、ノンコンプライアントバルーンでは一定以上の拡張圧ではバルーン径は規定以上には拡張しない。

DCB に使用されているパクリタキセルは主に肺癌や乳癌、頭頸部癌に用いられる抗癌剤である。パクリタキセルは細胞の微小管と結合し、蛋白重合を促進して微小管の構造を安定化させ、細胞分裂に必要な微小管の脱重合を阻害することで細胞分裂を抑制する。さらに細胞内の P53 や P21 を抑制して cyclin/CDK kinesis を阻害し、細胞周期を G 1 期で停止して細胞分裂を抑制する。パクリタキセルは脂溶性で数秒から数十秒の接触で容易に標的組織へ移行する。パクリタキセルは血管平滑筋細胞への感受性が高く、血管平滑筋細胞を死滅させることなく増殖を抑制することが可能である。DCB はバルーン表面に 3 μg/mm^2 のパクリタキセルが塗布されており、ISR 部位で拡張することでパクリタキセルが血管壁に塗布され浸透する。パクリタキセルの血管組織への残存は 28 日程度であり、DCB での治療後早期の活発な新生内膜生成を抑制する。新生内膜の生成過程が緩やかになるため、新生内膜の過度な肥厚による血管の狭窄を防ぐことが可能である。一方、パクリタキセルの血管内皮細胞に対する感受性は低く、増殖が抑制されないため、血管内皮細胞が適度に被覆され血栓形成を抑制する効果は維持される。

先に述べたように冠動脈ステントは ISR の軽減に一定の効果を発揮したが、一方でステント留置部には慢性的な炎症が持続することから、慢性期にステント内に脆弱なプラークを伴った新たな動脈硬化病変(neoatherosclerosis: 新生アテローム性動脈硬化)を誘発することがあり、ステント特有の ISR の原因として問題視されるようになった。さらにステントそのものによるアレルギー反応も ISR の機序として推察されている。すなわち、ステント留置後徐々にステントの金属イオンの融解溶出が生じ、この金属イオンが血管壁の構造蛋白と結合することでハプテンとして抗原性を獲得し、異物反応を含めた慢性炎症を惹起するとされている。ISR に対して、DCB はパクリタキセルにより過度の新生内膜の形成を抑制できる点とバルーンのみで治療を完遂できるためステントが残存することによる過剰な新生内膜の生成をきたさない点で理にかなった治療である。さらに DCB 後に ISR を繰り返した場合にも再度 DCB での治療を追加できる利点もある。現在も一次的な冠動脈狭窄に対する DES 留置は主流であるが、DCB でのステントレスストラテジーは今後新たな冠動脈カテーテル治療領域の治療戦略として注目されている。

DCB の臨床的な有用性は複数の大規模臨床試験で示されている。POBA との比較試験では、BMS で ISR において冠動脈造影での晩期内腔損失径[late luminal

loss(Late loss): 治療直後の血管内径−慢性期の血管内径]は有意に小さく(0.03±0.48 mm vs. 0.74±0.86 mm, p=0.002)、再々狭窄率は有意に低く(5% vs. 43%, p=0.002)、主要心血管イベント(MACE: major adverse cardiac events)発症率は抑制され(4% vs. 31%, p=0.01)、POBA に対する優位性が示された(N Engl J Med. 2006; 355: 2113−2124)。また、PEPCAD−DES 試験では DES での ISR における POBA との比較でも、Late loss (0.43±0.61 mm vs. 1.03±0.77 mm, p<0.001)、再々狭窄率(17.2% vs. 58.1%, p<0.001)、MACE 発症率(16.7% vs. 50.0%, p<0.005)において優位性が示され(J Am Coll Cardiol. 2012; 59: 1377−1382)、DCB がステントの種類によらず POBA よりも良好な臨床成績をもたらすことが証明された。一方、ISR に対する DCB と DES の比較では、BMS での ISR に対しては再血行再建術思考率(TLR: target lesion revascularization)(2% vs. 6%, p=0.17)、死亡(0%vs. 4%, p=0.31)において非劣性が確認された(J Am Coll Cardiol. 2014; 63: 1378−1386)。また DES での ISR に対しても ISAR−DESIRE 3 試験において TLR、MACE で DES に対する非劣性が示され(Lancet. 2013; 381: 461−467)、ISR を生じた既存のステントの種類によらず、DCB が DES と遜色ない臨床成績を示すことが示された。以上のように治療後の冠動脈造影所見のみならず生命予後においても DCB の良好な臨床成績のエビデンスを蓄積しており、 ISR に対する治療戦略の選択肢の一つとしての地位が確立を築いている。なお、本研究には含めていないが、研究期間内に当院で DCB を施行した 47 例中の再々狭窄率は僅か 4 例(9%)と従来の報告と遜色ない臨床成績が得られている。

OCT は冠動脈内に挿入したイメージワイヤーから近赤外線を照射して、対象から反射した近赤外線をもとに画像を構築し高速で撮影するデバイスである。本邦では 2000 年代後半から臨床応用され、急速に使用頻度が増加した。冠動脈内の評価には以前より血管超音波法(IVUS: intravascular ultrasound)が用いられており、その解像度は 100−200 μm であった。OCT の解像度は 10−15 μm と IVUS の約 10 倍の空間分解能を有することが特徴である。したがって、OCT は IVUS では描出困難な不安定プラークの薄い線維性被膜やステント留置後の新生内膜の性状を詳細に描出することができる。 OCT がもたらす狭窄病変の程度や長さ、病変や血管の性状などの情報は治療時のステントサイズや治療デバイスの選択を左右する。ステント留置後はステントストラットの圧着の程度、冠動脈解離や血栓の有無を評価することで追加治療の必要性を検討することもできる。慢性期においてはステント留置後の新生内膜の被覆や新生内膜性状を評価することが可能であり、臨床的な有用性が高い。日本循環

器学会の「冠動脈疾患の血行再建ガイドライン(2018 年改訂版)」では ISR に対する OCT の使用は推奨クラス IIa に位置づけられている。

OCT での新生内膜性状は、Homogeneous pattern・Heterogeneous pattern・Layered pattern の3パターンに分類される。Homogeneous pattern は繊維性成分や適度な血管平滑筋細胞などで形成され、内部が均一で成熟し、安定した新生内膜であるとされる。Heterogeneous pattern は増殖した血管平滑筋細胞・プロテオグリカンなどの粘液腫性細胞外基質・微小石灰化などで形成され、内部が不均一である。Layered pattern はマクロファージの浸潤に伴うフィブリン血栓などで形成される。Heterogeneous pattern、Layered pattern は共に未熟で不安定な新生内膜とされる。過去の報告では一般的には Homogeneous pattern は BMS 留置後によくみられ、Heterogeneous pattern と Layered pattern は DES 留置後によくみられるとされる。

一方 CAS は内視鏡イメージカテーテルとイメージモニター、レコーダーから構成されている。内視鏡イメージカテーテルは冠動脈血流を遮断せずに血管内の観察を行う血流維持型とカテーテルシャフト遠位端にある閉塞バルーンで冠動脈血流を遮断して観察を行う血流遮断型に分類される。CAS は冠動脈の血管内腔表面の画像を直接観察することが可能で、冠動脈に対するイメージングデバイスの中で唯一実際の血管内の色調をフルカラーで評価することができる。黄色プラークの色調や血栓の検出、ステント留置後の新生内膜被覆度や新生内膜内黄色度などを具体的に評価することで、肉眼的な病理診断が可能である。特に、黄色調の強いプラークほど不安定で破綻しやすく、不安定プラークの指標であるとされている。これを検出できる血管内イメージングデバイスは CAS のみであり、通常の冠動脈造影では到底得ることができない情報である。黄色調はプラークの構成成分や線維性被膜の厚さにより規定されるとされ、予後を反映すると報告されている(Circulation. 1996; 93: 2106-2113)。黄色調の強い黄色プラークが認められる症例では、急性冠症候群の発症率が高くなると報告されており(Am Heart J. 1995; 130: 195-203)、ステント留置時の合併症である急性冠閉塞を CAS で予見することで適切な追加治療を行うことが可能となる。また慢性期の CAS の所見において新生内膜の被覆が少なくステントストラットが露出している場合は、将来のステント血栓症のリスクが高まる可能性があるため2剤の抗血小板薬を継続するなど、内服薬の治療方針の決定にも重要な役割を担っている。一方、CAS の欠点としては冠動脈の内腔面のみの観察にとどまる点や、色調、面積・体積などを定量的に評価することが困難という点が挙げられる。黄色プラークや新生内膜の黄色度

は、肉眼的な黄色調をグレードで定性的に評価する。黄色調が強くなるほどグレードが上がる(黄色調分類; grade 0: 白色、grade 1: 淡黄色、grade 2: 黄色、grade 3: 濃黄色)。また新生内膜の被覆度もグレードが上がるほど新生内膜の被覆が強くなる(新生内膜被覆度分類; grade 0: 新生内膜の被覆なし、grade 1: 新生内膜に薄く覆われている、grade 2: 新生内膜によって被覆されているがステントが透見できる、grade 3: 新生内膜によって完全に被覆されステントは観察できない)。CAS は現在本邦でのみで保険償還されている血管内イメージングデバイスであり、当院を含め施行できる施設は全国でも 40 施設ほどに限られている。近年 CAS の有用性が徐々に明らかにされており、日本循環器学会の「安定冠動脈疾患の血行再建ガイドライン(2018 年改訂版)」においては推奨クラス IIb に位置づけられている。

現在、本邦では PCI の際は1種類のみの血管内イメージングデバイスを用い、また慢性期に施行する冠動脈造影の際にはイメージングデバイスを用いずに造影所見のみで冠動脈狭窄を評価することが多く、血管内デバイスを用いたとしても1種類のみであることが通常である。しかし、昨今の OCT や CAS のエビデンスを鑑みるに、より緻密な血管内画像の評価に基づく治療戦略の構築は ISR や再々狭窄を回避するためには不可欠である。本研究では DCB による治療時と慢性期で OCT(ILUMIEN™OPTIS™PCI optimization system; St. Jude Medical)と血流維持型の CAS(VISIBLE Fiber Imaging System FT-203F; FiberTech Co. Ltd.)の2種類の冠動脈に対するイメージングデバイスを使用し、複数の視点から経時的な画像評価を行なった。これまでに同様の先行研究はなく、PCI における臨床上の最大の問題である ISR 治療後の再々狭窄に対し、冠動脈の血管内画像評価に基づく新たな治療指針を示すことに貢献するものである。

本研究では OCT において慢性期の新生内膜体の積減少を示すことができた。新生内膜の減少は、DCB での治療時のバルーン自体による機械的圧迫と、パクリタキセルが塗布・浸透されることでの新生内膜の増殖の抑制が関与するものと考えられた。本研究で示した新生内膜体積の減少は血管内腔体積の有意な増大にも寄与しており、臨床的にも非常に意義のある変化であると考えられる。治療直後に比較して慢性期にさらに血管内腔が大きくなる現象は”Late lumen enlargement”と称される。本邦で後から DCB の保険適応となった 3 mm 以下の小血管の新規病変では Late lumen enlargement が DCB の使用根拠となることが報告されているものの、ISR 病変での

DCB による”Late lumen enlargement”を複数の血管イメージングデバイスを用いて報告したのは、本研究が初めてである。

症例数が限られていたため OCT での新生内膜性状の違いによる DCB の効果の違いについて十分な検討はできなかったが、本研究では新生内膜性状の種類によらず、慢性期に新生内膜体積が減少し血管内腔体積が増大する傾向が認められた。また有意差は認められなかったものの、不安定な新生内膜を示す Heterogeneous pattern から安定した新生内膜である Homogeneous pattern に変化した症例が 2 例存在した。冠動脈の再々狭窄をもたらす基礎疾患である脂質異常症や耐糖能異常に対する治療が功を奏した可能性も考えられるが、パクリタキセルの塗布・浸透により、成熟した新生内膜で治療部位が被覆され、新生内膜性状が変化した可能性も示唆された。新生内膜性状が DCB により変化することに関してはこれまでに報告がなく、今後の研究課題として症例数を増やして検討したい。

本研究では前拡張として用いるバルーン(スコアリングバルーン・ノンスコアリングバルーン)の違いによる DCB 治療後の各種体積の検討も行なったが、バルーンの種類によらず慢性期に新生内膜体積が減少し、血管内腔体積が増加する結果となった。ISAR-DESIRE 4 試験において、DES での ISR に対してスコアリングバルーンを前拡張に用いた場合の DCB 治療後 1 年の再々狭窄率は、その他の標準的バルーンを用いた場合よりも低かったと報告されている。同試験で使用された DCB が本研究で使用したものと異なることや、本研究では慢性期に再々狭窄を起こした症例は認めなかったことから単純に比較することはできないが、有意差はないものの本研究においてもスコアリングバルーンの方がノンスコアリングバルーンよりも慢性期の新生内膜体積の減少率は高かった。しかし、本研究で使用した DCB が前拡張のバルーンの種類によらず再々狭窄を防ぐことができる可能性も考えられ、今後症例数を増やして検討すべき課題である。

CAS では治療直後と慢性期の新生内膜の被覆度と被覆度 grade の分布に明らかな有意差は認めなかったが、被覆度は僅かながら低下していた。CAS は血管内膜表面のみを観察できるデバイスであり、評価は定性的で新生内膜の深部まで含めた詳細な評価には限界がある。一方、OCT では血管が断層面で表示され新生内膜の深部まで厚みを定量することができる。この新生内膜の検出能や評価法の違いが OCT と CAS での結果の相違に関与したと考える。

CAS での黄色度は治療直後と比較し慢性期に有意に低下する結果となった。DCB での治療後に黄色プラークを被覆するように適度な新生内膜での治癒機構が働くことや、TWINS 試験(CircJ. 2009; 73: 718-725)や JUPITOR 試験(N Engl J Med. 2008; 359: 2195-2207)でも示されたスタチンの抗炎症作用によるプラークの退縮が要因と考えられた。本研究において DCB 後の経時的な治療効果を肉眼病理学的に CAS で証明できたことは新規性があり、臨床的な意義は大きいと考える。

なお、本研究では CAS において慢性期のステント内血栓は一例も認めなかった。ステントストラットが露出すると血栓形成のリスクが高くなり急性冠症候群などの心血管イベントの温床となるため、血管内皮細胞による適度なステントの被覆が再々狭窄の回避には不可欠である。DCB に塗布されたパクリタキセルは血管平滑筋細胞の遊走・増殖を抑制することができる一方、血管内皮細胞による被覆は抑制しない。DCB では血管内皮障害が遷延せず、適度な新生内膜生成によりステント内血栓の抑制がなされている可能性が示唆された。

本研究の解析手法について、OCT での新生内膜体積・ステント体積・血管内腔体積の評価において治療前と治療直後、治療前と慢性期、治療直後と慢性期の各2群間で検討した。統計的な観点からは本来であれば Bonferroni 法などが好ましいが、症例数が少ないことや各々の観察時期を明確に分けて示した方が理解が容易なことから、t 検定で2群間の単純比較を行なった。

本研究の限界には症例数が少ないことが挙げられる。しかし、近年の冠動脈ステントでの治療成績の向上により ISR 発症率は 5-10%と非常に少ないため、希少な症例でのデータを 2 つの血管内イメージングデバイスで収集した点は本研究の価値を高める要素でもある。実際、本研究の研究期間内の当院における PCI 症例全 727 例中、DCB を使用したのは僅か 47 症例(6%)のみだった。さらに治療時と慢性期に OCT と CAS が共に施行できた症例を対象としたため症例数が限られた。DCB 後の慢性期に TLR の要否を検討した世界的な大規模レジストリー研究である SeQuent Please World Wide Registry(J Am Coll Cardiol. 2012; 60: 1733-1738)でも、症例数は 2095 例と循環器内科領域の大規模レジストリー研究の中では決して多くなく、症例集積の困難さを物語っている。また、症例数が限られたため ISR を起こした既存の冠動脈ステントの種類は BMS・DES を合わせた解析となった。限られた症例数ではあるが、BMS・DES

ともにDCBでの治療後の新生内膜の生成や経時的な性状の変化には差がない印象であった。

また本研究では慢性期の観察は中央値でDCB治療後9ヶ月となり最終転帰については言及できなかったが、少なくとも観察期間内には対象症例に再々狭窄は認めなかった。本研究の期間内に当院でDCBを施行した全47例でも、観察期間の中央値8.2ヶ月で再々狭窄は僅か4例(9%)であり、DCBはこれまでの報告と遜色ない治療成績を示している。DCBに関する大規模臨床試験での長期予後の報告では、DCBとPOBAの比較において3 年後のTLRやMACEの割合はDCB群で有意に低いことが示されている(JACC Cardiovasc Interv. 2015; 8:1695-1700)。また、DCBとDESとの比較においても3年後までのTLRやMACEの割合は同等であることが示されている(EuroIntervention. 2015; 11(8):926-934)。これらの報告におけるTLRやMACEの大部分は本研究での観察期間の中央値である9ヶ月より前に起きており、それ以降のイベント発症率は極めて少ない。DCB治療後9ヶ月では、新生内膜は十分に生成された後の観察になり、一度適正な新生内膜が形成されれば安定した新生内膜により再々狭窄は極めて少なくなる。したがって、観察期間9ヶ月でも再々狭窄の有無の評価は十分できており、その後の臨床的な治療成績も推察できる点では妥当な観察期間であったと考える。

DCB は治療後にステントなど異物が残存しないため、慢性炎症や血栓形成リスクを抑制することができ、現在の冠動脈カテーテル治療領域に残された課題の解決に適したステントレスストラテジーという治療戦略を可能にする治療デバイスである。本論文は新規治療デバイスに対する技術論文との印象を持たれる可能性があるが、DCBの有用性をOCTとCASの2種類の血管内イメージングデバイスで経時的に証明した点に臨床的な意義がある。冠動脈に対するステント治療が発展した現在でも、依然としてISRをきたす難治性の冠動脈狭窄症は存在する。難治性の冠動脈狭窄症に対するDCBの有用性は、これまで基礎的理論に基づく報告や臨床的な予後に関する報告のみで語られていた。DCBの有用性を臨床の現場での血管内画像所見から定量的に、また肉眼病理学的に証明した点で本研究には新規性があり臨床的な価値も高い。本邦では食生活の欧米化に加え、今後超高齢化がますます加速し、冠動脈疾患の有病者の全体数は増加していくと予想されている。難治性の冠動脈狭窄症の患者数もさらに増加すると考えられ、DCBの有用性を臨床の画像所見で証明した本研究の社会的な貢献度は高い。

本研究において、申請者は本研究の対象症例の急性期のカテーテル治療や慢性期の冠動脈造影検査を施行する際のご本人やご家族へのインフォームドコンセントや本研究の同意を得ることに直接携わり、実際カテーテル治療や冠動脈造影検査、各期での血管内イメージングデバイスの施行や評価を行った。また本研究の立案から、データ収集・統計処理、論文作成を申請者自身が行い、画像評価は冠動脈治療チームの複数の医師で確認し、統計処理や完成した論文については指導教員に助言をいただいた。本研究において申請者は論文作成の全ての行程に貢献し、学位に相応しい貢献であったと考える。