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Possible mechanism of late lumen enlargement after treatment for de novo coronary lesions with drug-coated balloon

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ABSTRACT

Background: Drug-coated balloon (DCB) treatment for de novo coronary artery disease has demonstrated late lumen enlargement (LLE) in mid-term follow-up and it was considered as clinical benefit; however, its mechanism and the predictive factor remains unclear.
Methods: This study enrolled 46 consecutive patients (54 lesions) treated with DCB, using intravascular ultrasound (IVUS) at the index procedure and at the 9-month follow-up. We measured IVUS parameters at 1-mm intervals and calculated the mean volume of the external elastic membrane (EEM), lumen, and plaque. We calculated the dissection index (DI) defined as summation of the following points, 2: dissection over EEM, 1: intra-EEM dissection, 0: no dissection at every 1-mm interval, and divided by lesion length.
Results: IVUS showed that there was no flow limiting dissection just after DCB treatment, the mean EEM and lumen volume (LV) had significantly increased while mean plaque volume had significantly decreased at 9 months, and 74.1% lesions exhibited LLE. We divided the patients into three groups according to delta mean LV. Mean EEM volume significantly increased and mean plaque volume significantly decreased in the larger and smaller LLE groups, but not in the non-LLE group. The DI was higher in a descending order in the three groups. The multiple regression analysis demonstrated that the DI was the strongest predictor of the change in mean LV.
Conclusions: LLE after DCB treatment may be caused by vessel enlargement and plaque regression. The non-flow limiting larger dissection just after DCB treatment may strongly associate with the intending LLE.

1. Introduction

Percutaneous coronary intervention (PCI) is an effective treatment for patients with ischemic heart disease. Recent advances in drug-eluting stent (DES) technology have entirely succeeded in reducing the restenosis rate [1,2]. However, some concerns on PCI using DES persist. The treatment of small vessel coronary artery disease with DES is a challenging problem. It has been associated with an increased risk of adverse clinical events even with newer-generation DES implantation, because late lumen loss is relatively less well tolerated in such vessels [3–5].

Recent reports have shown that chronic late lumen enlargement (LLE) after drug-coated balloon (DCB) treatment for de novo coronary artery disease (CAD) has sometimes been observed to contribute to good results following DCB treatment [6,7]. Thus, DCB is now emerging as an effective and alternative treatment for de novo lesions especially in small coronary arteries [8,9].

However, the precise mechanism of LLE following DCB treatment remains unclear. This study aimed to uncover the possible mechanism of LLE following DCB treatment for de novo CAD using intravascular ultrasound (IVUS) and to elucidate the predictive factor of the intending LLE.

2. Materials and methods

2.1. Patient population

This was a prospective, observational, and single-arm study aimed at assessing intravascular geometric and compositional characteristic changes induced by DCB in de novo lesions. Our study was conducted between May 2017 and April 2019 at Hyogo Prefectural Himeji Cardiovascular Center and included 46 consecutive patients with 54 lesions, treated with DCB for de novo native CAD using IVUS guidance. Patients older than 18 years with stable or unstable angina, documented silent ischemia at their significant luminal narrowing de novo lesion, and defined as having ≥75% stenosis by visual estimation were considered eligible for this study. Exclusion criteria were presence of; 1) ST-segment elevated myocardial infarction within 48 h, 2) condition requiring hemodialysis, 3) restenosis lesion, 4) significant left main coronary artery

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disease, 5) ostial lesion and additionally, 6) life expectancy of <1 year and 7) contraindication or suspected intolerance to paclitaxel, aspirin, and prasugrel.

The Ethics Committee of Hyogo Prefectural Himeji Cardiovascular Center approved this study, which was carried out according to the guidelines of the 1975 Declaration of Helsinki. Before participation, informed consent was obtained from all eligible patients.

2.2. PCI procedures

The guidelines of the American College of Cardiology/American Heart Association, European Society of Cardiology, and Japanese Circulation Society recommend preprocedural dual antiplatelet therapy with aspirin and a thienopyridine as a class I indication [10–12] and we wanted to confirm the safety of dual antiplatelet therapy especially in patients with stable angina. Patients experiencing side effects from the dual antiplatelet therapy would have been excluded from enrollment in this study. Therefore, all patients were pre-treated with aspirin 200 mg and prasugrel 3.75 mg at least 14 days prior to the procedure or with a loading dose of prasugrel 20 mg just before the intervention; dosages approved for patients undergoing PCI in Japan [13]. Furthermore, 100 U/kg of unfractionated heparin was injected intravenously to maintain an activated clotting time > 250 s during the procedure.

In all procedures, scoring balloon, Lacrosse NSE™ (Goodman Co., Ltd., Nagoya, Japan) or cutting balloon (Boston Scientific, Marlborough, MA, USA) was used for pre-dilatation under IVUS guidance. This was because previous studies have shown significantly lower incidences of major dissection in target lesions treated with the scoring balloon than with other devices, and the optimal lesion preparation using a scoring balloon is essential for ensuring a low incidence of target lesion failure after DCB treatment [14,15]. Further, appropriate lesion preparation was performed, after which, the lesion was dilated once for at least 30 s with the paclitaxel- coated (3 μg/mm^2) balloon catheter based on Paccocath Technology (SeQuent Please™, B. Braun Melsungen AG, Berlin, Germany) for drug delivery. Balloon size and inflation pressure were selected at the operator's discretion.

2.3. Quantitative coronary angiographic measurements

Baseline post procedural and follow-up coronary angiograms were analyzed offline using a validated edge detection system (CMS-Medis Medical Imaging Systems, Leiden, Netherlands). The outer diameter of the contrast-filled catheter was used for calibration and the minimal lumen diameter (MLD) was obtained from the single worst view. Acute gain was defined as the difference between the MLD pre- and post- PCI. Late lumen loss was defined as the difference between the MLD immediately after the procedure and at the follow-up. The lesion type was also assessed according to the American Heart Association / American College of Cardiology classification [16]. Dissection type was assessed according to the National Heart, Lung and Blood Institute classification [17].

2.4. IVUS acquisition and analysis

Two hundred micrograms of intracoronary nitroglycerin were routinely administered before the image acquisition at the baseline and at repeat assessment at 9-month follow-up. Baseline IVUS assessments were performed before and after DCB dilatation. We obtained images of each lesion using the IVUS imaging catheter (AltaView Terumo Corp., Tokyo, Japan) with the motorized transducer pullback system (9 mm/s). Offline analyses were performed with the computer echo plaque (INDEC Medical Systems, Santa Clara, CA). Geometric characteristics of the DCB-treated lesions were analyzed according to the criteria of the IVUS clinical expert consensus document [18], and each lesion was confirmed with side by side angiography of distinguished branches.

The cross section was measured by IVUS at every 1-mm interval throughout the length of the treated lesion. The external elastic membrane (EEM), lumen, and plaque areas (EEM area - lumen area) were obtained by manual contour detection. Mean volume (sum of parameters at every 1-mm interval cross section / DCB treatment lesion length) and delta (Δ) values (9-month follow up value - post-procedure value of each parameter) were calculated. The remodeling and eccentricity indices were calculated as previously described [19,20].

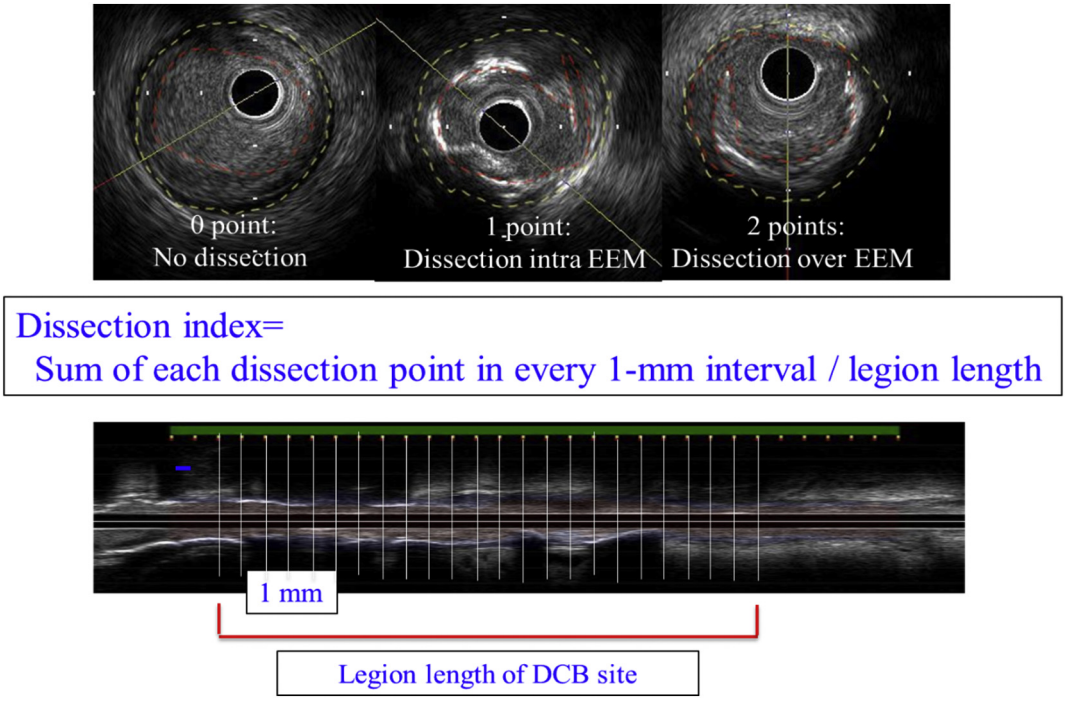

Fig. 1. Measuring method of the dissection index. Red-dot line indicates the lumen area, yellow-dot line indicates the EEM area. Dissection index was calculated as sum of each dissection point in every 1-mm interval cross section / lesion length. EEM: external elastic membrane. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

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Table 1
Baseline patients, lesion and procedural characteristics and clinical outcome.

Baseline patients characteristics ($n = 46$ patients)	
Age (y.o)	65.3 ± 11.4
Sex male, n (%)	37 (80.4)
Coronary risk factor, n (%)	
Hypertension	31 (67.4)
Dyslipidemia	37 (80.4)
Diabetes mellitus	24 (52.2)
Current smoker	10 (21.7)
Low density lipoprotein cholesterol level (mg/dL)	107.7 ± 38.7
High density lipoprotein cholesterol level (mg/dL)	44.2 ± 9.5
HbA1c (%)	6.6 ± 1.3
Stable angina pectoris, n (%)	31 (67.4)
Acute coronary syndrome, n (%)	15 (32.6)
Prior percutaneous coronary intervention, n (%)	15 (32.6)
Prior coronary artery bypass surgery, n (%)	0 (0.0%)
Chronic kidney disease, n (%)	13 (28.3)
Estimated GFR (ml/min/1.73m^2)	69.9 ± 16.3
Left ventricular ejection fraction (%)	53.4 ± 10.9
Medications at discharge	
Aspirin, n (%)	46 (100)
P2Y12 receptor antagonist, n (%)	46 (100)
ACEi/ARB, n (%)	31 (67.4)
B-blocker, n (%)	23 (50.0)
Statin, n (%)	43 (93.5)
Baseline lesion and procedural characteristics ($n = 54$ lesions)	
Target vessel, n (%)	
Left anterior descending artery	10 (21.3)
Left circumflex artery	19 (40.4)
Right coronary artery	18 (38.3)
Lesion type (B2/C), n (%)	35 (64.8)
Chronic total occlusion, n (%)	13 (24.1)
Use of rotablator, n (%)	4 (7.4)
Use of scoring balloon, n (%)	54 (100.0)
Scoring balloon diameter (mm)	2.51 ± 0.56
Scoring balloon maximum pressure (atm)	9.0 ± 3.7
DCB diameter (mm)	2.60 ± 0.53
DCB length (mm)	19.3 ± 5.0
DCB inflation pressure (atm)	7.9 ± 2.3
Clinical outcome at 9 months (n = 54 lesions)	
Major adverse cardiac events, n (%)	**2 (3.7)**
All cause death, n (%)	0 (0.0)
Cardiac death, n (%)	0 (0.0)
Myocardial infarction, n (%)	0 (0.0)
Thrombosis, n (%)	0 (0.0)
Target lesion revascularization	2 (3.7)

GFR; glomerular filtration rate, ACEi; angiotensin converting enzyme inhibitor, ARB; angiotensin receptor blocker, DCB; drug coated balloon. Bold values signifies the Dissection index.

A previous study demonstrated that circumferential deep vessel wall injury is correlated with late vessel size [21] and another study showed that medial dissection with intimal disruption is a possible mechanism of LLE [22]. Therefore, to assess the extent of dissection just after DCB treatment objectively, we calculated the dissection index (DI), which was defined as the summation of following points, 2) dissection over the EEM, 1) intra-EEM dissection, 0) no dissection in every 1-mm interval, and divided by lesion length (Fig. 1). All IVUS data were read by two independent observers (T.Y. and T.S). The first observer (T.Y.) repeated a blind analysis of all the data at two separate time points (at least a 1-week interval between the two analyses). If there was discordance between the two observers, a consensus diagnosis was obtained with repeated off-line readings.

2.5. Clinical outcomes and follow-up procedure

All patients were scheduled to undergo clinical, angiographic, and IVUS follow-up at 9 months. The primary endpoints of this study were serial changes in IVUS parameters, especially changes in mean lumen volume (LV).

2.6. Statistical analysis

All statistical analyses were performed using Medcalc (Medcalc, version 9.3; Medcalc Software, Mariakerke, Belgium).

Sample size was determined by power analysis using preliminary data in our laboratory with the following assumptions: type I error of 0.05 (two-tailed), power of 80%, difference of 0.6 and a standard deviation of 0.8 in mean LV just after DCB treatment and 9-months follow up. Therefore, a minimum of 21 patients would yield 80% power to detect a difference in the mean LV.

Continuous variables were presented as mean ± standard deviation or median (25th to 75th percentiles) and compared using Student's *t*-test for normally distributed data or the Mann–Whitney *U* test for non-normally distributed data. Data at different time points were analyzed with paired Student's t-test or Wilcoxon test, as appropriate. Categorical variables were presented as frequencies with percentage and were compared using the chi-square or Fisher's exact test, as appropriate. A two-sided *P*-value less than 0.05 indicated statistical significance. Multivariate regression analysis was used to determine significant factors indicating the changes in mean LV. Factors with univariate $P < .05$ were then entered into the multivariable models.

The relationships among the DI and Δ value of mean LV, EEM volume, and plaque volume were investigated using Spearman's rank correlation coefficient.

To assess the inter- and intra-observer variability of DI, the results were compared using the Bland-Altman plot.

3. Results

Table 1 shows the baseline and clinical characteristics of the participants. Mean age was 65.3 ± 11.4 years and 37 (80.4%) patients were male. Thirty-one patients (67.4%) had symptoms of stable angina. All the participants had received statins, but none of them received PCSK9 inhibitors. The size of the applied DCB catheter and inflation pressure are shown in Table 1. Four patients needed rotablator for lesion preparation. No cases used bailout stenting. And there was no in-hospital clinical event, including periprocedural myocardial infarction was observed, and the procedural success rate was 100%.

Two major adverse cardiovascular events (3.7%) were observed in the study population during the 9-month follow-up. Deaths, myocardial infarction, or thrombosis were not observed; however, two lesions required revascularization as a result of target lesion failures (Table 1).

Table 2 shows serial changes in quantitative coronary angiography data and IVUS findings immediately after DCB treatment and during the 9-month follow-up. Angiographic follow-up at 9 months showed similar results for MLD and % area stenosis, the mean late lumen loss was 0.04 ± 0.63 mm. Four lesions showed binary angiographic restenosis, and two occurred with target lesion revascularization. There were 28 angiographical dissections, however, they were not flow-limiting, and there was no need for bail-out stenting in this study population.

According to the IVUS findings, there were 43 lesions with IVUS-derived dissection immediately after DCB treatment. However, at follow-up, most (86.0%) IVUS-derived dissections had healed and only six lesions were found to have persisted, moreover, two cases (3.7%) resulted in target lesion revascularization. The mean DI was 0.44 and the estimated limit of agreement for the intra- and inter-observer variability in the DI was satisfactory based on the Bland-Altman plot. (intra-observer; mean difference: 0.008, upper two-standard deviation (2SD): 0.13 and lower 2SD: −0.14, inter-observer; mean difference: 0.012, upper 2SD; 0.13 and lower 2SD: −0.15).

During the 9-month follow-up, IVUS showed that the mean EEM volume and LV increased significantly while the mean plaque volume and percent plaque volume decreased significantly. In this study population, 74.0% (40/54) of lesions exhibited chronic LLE. To examine the characteristics linking chronic LLE in detail, we divided the patients into three (tertiles) groups according to Δ mean LV (non-LLE group; <

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Table 2
Quantitative coronary angiography data and intravascular ultrasound parameters in pre procedure, post DCB and 9 months follow-up.

	Pre procedure	Post DCB	9 months
Quantitative coronary angiographic data (n = 54 lesions)			
Reference diameter (mm)	2.12 ± 0.73	2.40 ± 0.66	2.37 ± 0.55
Minimal lumen diameter (mm)	0.44 ± 0.44	1.90 ± 0.71*	1.86 ± 0.55*
% area stenosis (%)	85.9 ± 25.8	36.2 ± 20.6*	34.8 ± 22.7*
Acute gain (mm)	NA	1.47 ± 0.53	NA
Late lumen loss (mm)	NA	NA	0.04 ± 0.63
Binary restenosis, n (%)	NA	NA	4 (7.4)
Angiographical dissection, n (%)	NA	28 (51.9)	6 (11.1)
NHLBI classification (A,B,C,D,E,F), n	NA	(10,7,11,0,0,0)	(6,0,0,0,0,0)
Balloon size to reference diameter ratio values	NA	1.08 ± 0.20	NA
Intravascular ultrasound parameter (n = 54 lesions)			
Mean EEM volume (mm^3/mm)	NA	8.72 (6.98,11.67)	8.92 (7.37,12.09) †
Mean lumen volume (mm^3/mm)	NA	4.04 (3.51,5.33)	4.75 (4.00,5.95) †
Mean plaque volume (mm^3/mm)	NA	4.89 (3.37,6.29)	4.30 (3.10,6.53) †
Mean %plaque volume (%)	NA	53.8 (46.5, 57.6)	47.8 (39.2, 54.5) †
Minimum lumen area (mm^2)	NA	3.00 (2.56, 3.63)	3.74 (2.99, 5.05) †
Late lumen enlargement, n (%)	NA	NA	40 (74.0)
Balloon / lumen ratio	NA	1.06 (0.97, 1.19)	NA
DCB / lumen ratio	NA	1.09 (0.99, 1.20)	NA
Dissection in IVUS image, n (%)	NA	43 (79.6)	NA
Dissection index	NA	0.44 (0.17, 0.8)	NA
Remodeling index	NA	1.05 (0.88, 1.15)	NA
Eccentricity index	NA	0.69 (0.34, 0.94)	NA

NHLBI; The National Heart, Lung and Blood Institute, EEM; extra elastic membrane, IVUS; intravascular ultrasound.
* P < .05 vs pre procedure.
† *P* < .05 vs post DCB.

0.29 mm^3/mm, smaller LLE group; ≥ 0.29 mm^3/mm, but <1.06 mm^3/mm, larger LLE group; ≥ 1.06 mm^3/mm) and compared the three groups. As shown in Tables 3 and 4, there were no clinically significant differences in baseline characteristic, lesion, and procedural characteristics among the three groups. Regarding the quantitative data, the MLD increased during the 9-month follow-up, and consequently, the percent area stenosis decreased in the larger and smaller LLE group, but not in the non-LLE group. Late lumen loss in the larger and smaller LLE groups was significantly lower than that in the non-LLE group. With regard to the IVUS data, Δ mean EEM volume was significantly higher, whereas Δ mean plaque volume and Δ mean percent plaque volume were significantly lower in a descending order in the three tertile groups.

The pre-dilation balloon diameter / distal reference lumen diameter ratio was larger in the larger and smaller LLE groups than in the non-LLE group, but the DCB / lumen ratio did not differ among the three groups. Although the prevalence rate of angiographically derived dissection was similar among the three groups, IVUS-derived dissection was more frequently observed in the larger and smaller LLE groups than in the non-LLE group. The DI was significantly higher in descending order in the three tertile groups. Meanwhile, the remodeling index was lower in descending order in the three tertile groups.

We investigated the relationship between chronic vascular reaction and the extent of dissection immediately after PCI. Fig. 2 shows the correlation between the DI and Δ mean LV, Δ mean EEM volume, and Δ mean plaque volume. The DI was positively associated with both lumen and vessel enlargement. Multivariate regression analysis showed that the strongest predictor of the intending LLE was the DI.

4. Discussion

To the best of our knowledge, this is the first study to assess the local mechanism of LLE after DCB treatment for de novo coronary lesions precisely. The main findings were as follows: 1) Significant vessel enlargement and plaque regression were observed during the 9-month follow-up after DCB, most prominently in the larger LLE group. 2) The DI was significantly associated with both lumen and vessel enlargement and it was the strongest predictor of future LLE.

In the plain old balloon angioplasty (POBA) era, recurrence of stenosis after intervention due to elastic recoil was a major limitation and was linked to poor clinical outcome compared with stent implantation [23]. Meanwhile, unlike the results reported for POBA, recent studies have found that DCB for de novo lesions involved low rates of target lesion revascularization and major adverse cardiac events, moreover, LLE has occasionally been observed [6,7]. Although LLE is considered a great advantage of DCB treatment for de novo CAD, its detailed mechanism has not been clarified. A previous IVUS series of de novo lesions successfully treated by POBA demonstrated that the most frequent reasons of lumen re-narrowing after POBA were decrement of the vessel area and increment of the plaque area [23]. The other trials revealed that the main mechanism of mean lumen loss was an increase in the plaque area [24,25]. Additionally, pioneer retrospective studies have described vessel shrinkage as causative of 50–70% of lumen loss [26,27]. Therefore, unfavorable remodeling is considered the major determinant of late lumen loss. Meanwhile, in case of DCB treatment, we observed on IVUS that both the mean EEM volume and mean LV significantly increased while mean plaque volume and mean percent plaque volume significantly decreased during the 9-month follow-up and these changes were most prominent in the larger LLE group. Similarly, the previous study based on serial IVUS-virtual histology analysis also showed that persistent anatomical and physiological patency after DCB treatment were due to plaque redistribution and vessel remodeling without chronic elastic recoil or plaque compositional change during the follow-up [28]. Therefore, we propose that the low rates of late lumen loss, target lesion revascularization and major cardiac events after DCB treatment were completely attributed to these different patterns of vascular response from POBA alone.

In a similar fashion with our present study, many studies exhibited chronic LLE after DCB treatment [22,28]. Previous studies indicated that non-occlusive residual coronary dissection was associated with favorable long-term outcome due to the positive influence of chronic vessel enlargement [29,30]. Funatsu et al. [22] demonstrated that lesions with type B dissection had a larger net gain than lesions with type A or no dissection, although type C-E dissection were an independent predictors of target lesion revascularization after DCB treatment. Furthermore, despite the data on the femoropopliteal arteries, another study

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Table 3
Comparison of patient, lesion and procedural characteristics, quantitative coronary angiography data and intravascular ultrasound parameters among three tertile groups of Δmean lumen volume.

Variable	non LLE group ($n = 18$)	smaller LLE group (n = 18)	larger LLE group (n = 18)	P value
Baseline clinical characteristics				
Age (y.o)	66.1 ± 12.0	65.8 ± 12.3	64.8 ± 10.0	0.94
Sex male, n (%)	15 (83.3)	12 (66.7)	16 (88.9)	0.24
Coronary risk factor, n (%)				
Hypertension	12 (66.7)	13 (72.2)	12 (66.7)	0.92
Dyslipidemia	14 (77.8)	16 (88.9)	13 (72.2)	0.47
Diabetes Mellitus	11 (61.1)	8 (44.4)	8 (44.4)	0.53
Current smoker	3 (16.7)	5 (27.8)	3 (16.7)	0.65
LDL level (mg/dl)	110.2 ± 45.9	105.5 ± 38.2	107.4 ± 35.4	0.94
HDL level (mg/dl)	44.7 ± 9.3	44.6 ± 9.6	43.4 ± 10.3	0.91
HbA1c (%)	6.8 ± 1.2	6.4 ± 1.1	6.7 ± 1.7	0.61
Acute coronary syndrome, n (%)	5 (27.8)	5 (27.8)	6 (33.3)	0.92
Prior PCI, n (%)	7 (38.9)	6 (33.3)	4 (22.2)	0.56
Chronic Kidney Disease, n (%)	9 (50.0)	2 (11.1)*	6 (33.3)	0.04
estimated GFR (ml/min/1.73m^2)	64.4 ± 19.7	74.4 ± 16.0	66.1 ± 15.0	0.18
LVEF (%)	54.9 ± 11.1	52.9 ± 9.2	50.2 ± 13.8	0.47
Lesion and procedural characteristics				
Target vessel, n (%)				
Left anterior descending artery	5 (27.8)	6 (33.3)	3 (16.6)	
Left circumflex artery	6 (33.3)	7 (38.9)	8 (44.4)	
Right coronary artery	7 (38.9)	5 (27.8)	7 (38.9)	0.79
Calcification, n (%)	9 (50.0)	8 (44.4)	4 (22.2)	0.20
Use of rotablator (%)	2 (11.1)	2 (11.1)	0 (0.0)	0.35
Use of Scoring balloon, n (%)	18 (100)	18 (100)	18 (100)	
Scoring balloon diameter (mm)	2.54 ± 0.58	2.39 ± 0.49	2.61 ± 0.63	0.49
Scoring balloon pressure (atm)	9.83 ± 5.00	9.00 ± 2.59	8.28 ± 3.25	0.47
DCB diameter (mm)	2.68 ± 0.51	2.53 ± 0.62	2.60 ± 0.49	0.70
DCB length mm)	18.7 ± 4.2	20.1 ± 5.5	19.2 ± 5.5	0.71
DCB pressure (atm)	7.89 ± 2.17	8.31 ± 3.05	7.61 ± 1.75	0.68
Quantitative coronary angiographic data				
Post PCI				
Minimal lumen diameter	2.06 ± 0.76	1.70 ± 0.65	1.95 ± 0.73	0.31
% area stenosis (%)	38.4 (21.1,48.8)	35.5 (25.2,61.9)	27.3 (15.7,40.7)	0.23
Acute gain (mm)	1.41 ± 0.54	1.47 ± 0.59	1.52 ± 0.50	0.83
Angiographic dissection, n (%)	6 (33.3)	11 (61.1)	11 (61.1)	0.16
NHLBI classification (A, B, C, D, E, F), n (%)	(3,1,2,0,0,0)	(4,2,5,0,0,0)	(3,4,4,0,0,0)	0.79
Follow up				
Minimal lumen diameter	1.54 ± 0.41	1.78 ± 0.39	2.25 ± 0.60*†	<0.001
% area stenosis (%)	41.8 (31.8,72.3)	29.3 (27.1,51.0)	17.1 (9.85,24.6) *†	0.0002
Late luminal loss (mm)	0.52 ± 0.65	−0.08 ± 0.60*	−0.31 ± 0.33*	<0.001
Intravascular ultrasonography parameters				
Post PCI				
Mean EEM volume (mm^3/mm)	9.82 (8.16, 12.56)	7.70 (6.81, 9.64)	8.98 (6.83, 11.75)	0.09
Mean lumen volume (mm^3/mm)	4.34 (3.70, 5.72)	3.60 (3.30, 4.32)	4.08 (3.08, 5.46)	0.09
Mean plaque volume (mm^3/mm)	5.36 (4.17, 7.34)	4.19 (3.00, 5.00)	4.97 (2.96, 6.29)	0.18
Minimum lumen area (mm^2)	2.98 (2.69, 4.48)	2.77 (2.62, 3.31)	3.31 (2.31, 4.87)	0.57
EEM area at MLA site (mm^2)	8.97 (8.35, 11.5)	7.67 (6.14, 9.20)	8.54 (6.14, 13.3)	0.10
Plaque area at MLA site (mm^2)	5.90 (4.93, 8.91)	5.03 (3.52, 6.73)	5.52 (3.97, 7.62)	0.12
Follow up				
Mean EEM volume (mm^3/mm)	9.71 (7.82, 12.48)	7.93 (6.99, 9.64)	9.47 (7.47, 14.08)	0.2
Mean lumen volume (mm^3/mm)	4.37 (3.51, 5.39)	4.43 (4.26, 4.91)	5.74 (4.64, 7.59) *†	0.03
Mean plaque volume (mm^3/mm)	5.13 (4.04, 7.33)	3.38 (2.61, 4.76)	4.30 (2.44, 5.95)	0.06
Minimum lumen area (mm^2)	3.22 (2.38, 3.52)	4.11 (2.97, 4.89)*	5.26 (3.65, 6.45) *†	0.0005
EEM area at MLA site (mm^2)	8.18 (7.62, 9.32)	8.33 (7.21, 9.95)	8.85 (8.17, 14.1)	0.49
Plaque area at MLA site (mm^2)	5.13 (4.78, 5.81)	4.33 (3.51, 6.21)	3.99 (3.61, 7.02)	0.36
Absolute Δ				
ΔMean EEM volume (mm^3/mm)	−0.24 (−0.63, −0.02)	0.38 (−0.0047, 0.62)*	0.99 (0.6, 1.5) *†	<0.0001
ΔMean lumen volume (mm^3/mm)	−0.21 (−0.28, −0.04)	0.75 (0.53, 0.84)*	1.45 (1.24, 2.18) *†	<0.0001
ΔMean plaque volume (mm^3/mm)	−0.038 (−0.28, 0.26)	−0.42 (−0.72, −0.08)*	−0.59 (−1.12, −0.007)*	0.04
ΔMinimum lumen area (mm^2)	−0.29 (−0.90, 0.37)	0.92 (0.44, 1.49)*	1.41 (1.00, 2.07) *†	<0.0001
ΔEEM area at MLA site (mm^2)	−0.66 (−2.16, 0.26)	0.35 (−0.42, 2.15)*	0.85 (0.57, 1.18)*	<0.0001
ΔPlaque area at MLA site (mm^2)	−0.93 (−2.57, 0.27)	−0.49 (−1.41, 0.84)	−0.46 (−1.38, 0.07)	0.52
Balloon / lumen ratio	0.99 (0.91, 1.06)	1.15 (1.00, 1.23)*	1.11 (0.98, 1.20)*	0.02
DCB / lumen ratio	1.05 (0.99, 1.16)	1.13 (1.02, 1.28)	1.11 (0.98, 1.21)	0.28
Dissection in IVUS image, n (%)	8 (44.4)	17 (94.4)*	18 (100)*	<0.0001
Dissection index	0.00 (0.00, 0.24)	0.46 (0.31, 0.80)*	0.81 (0.70, 0.93) *†	<0.0001
Remodeling index	1.08 (1.03, 1.17)	1.07 (0.84, 1.34)	0.90 (0.83, 1.04) *	0.04
Eccentricity index	0.56 (0.14, 0.85)	0.77 (0.49, 1.06)	0.69 (0.36, 0.93)	0.20

LLE; late lumen enlargement, PCI; percutaneous coronary intervention,
EEM; external elastic membrane, MLA; minimum lumen area.
DCB; drug coated balloon, NHLBI; The National Heart, Lung and Blood Institute.
* $P < .05$ vs non LLE group.
† $P < .05$ vs smaller LLE group.

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Table 4
Regression analysis for predicting changing Δ mean lumen volume.

Variable	Univariate		Multivariate	
	t	p-value	t	p-value
Minimal lumen diameter of post DCB	−1.504	0.14		
% area stenosis of post DCB	−0.099	0.92		
Acute gain	0.081	0.94		
NHBLI dissection classification	1.901	0.06		
Mean EEM volume of post DCB	−2.080	0.04	−0.342	0.73
Mean lumen volume of post DCB	−2.231	0.03	−0.571	0.57
Mean plaque volume of post DCB	−1.816	0.08		
Mean %plaque volume of post DCB	−0.131	0.90		
Minimum lumen area of post DCB	−1.794	0.09		
Balloon / lumen ratio	2.531	0.01	−0.295	0.77
DCB / lumen ratio	1.319	0.19		
Dissection in IVUS image	5.114	<0.0001	4.647	<0.0001
Dissection index	7.349	<0.0001	7.249	<0.0001
Remodeling index	−1.425	0.16		
Eccentricity index	0.921	0.36		

NHLBI; The National Heart, Lung and Blood Institute, EEM; external elastic membrane. DCB; drug coated balloon, IVUS; intravascular ultrasound.

showed that patients with dissection following DCB treatment had an acceptable outcome, and stent implantation is not necessary as long as the dissection does not result in acute restriction of blood flow [31]. The present study also showed that the DI, which indicated the extent of coronary dissection after DCB treatment, of the LLE group was significantly larger than that of the non-LLE group, and the DI was significantly correlated with both chronic lumen and vessel enlargement. Therefore, dissection after treatment might not be unfavorable, and non-flow-limiting larger dissection might be linked to low late lumen loss and favorable clinical outcomes after DCB treatment.

Since the National Heart, Lung and Blood Institute dissection classification system according to angiographic findings, which was established more than 20 years ago, we sometimes encountered a case that indicated slight discrepancy in the severity of dissection between angiographic and intravascular imaging. Hence, it is possible to both overestimate and underestimate the severity of dissection using angiographic findings alone [32,33]. Coronary dissection after balloon angioplasty may propagate to an intramural coronary hematoma, which may subsequently lead to restriction of the vessel lumen size and acute occlusion. However, up to 30% of intramural hematomas are not detected by angiography, but they are clearly observed by intravascular imaging such as IVUS and optical coherence tomography [34]. Conversely, spiral dissection is usually diagnosed as type D on angiography, but IVUS sometimes reveals less severe dissection [32]. Intravascular imaging devices guiding PCI is currently preferred, but there is no classification for evaluating dissection using intravascular imaging systems. Therefore, there is need for a new dissection grading system according to intravascular imaging findings, such as the DI, which we advocated in this study. Furthermore, we observed the pre-dilation balloon diameter /distal reference lumen diameter ratio was larger in the LLE group than in the non-LLE group. Additionally, pre-dilatation balloons, which we used in this study, were all scoring balloons, and it might be possible to make an intima incision with a lower inflation pressure compared to what was possible with the standard balloon [22]. This result might indicate that an appropriate size of predilatation using a scoring balloon was needed for sufficient preparation for therapeutic dissection without flow limitation and need for bail-out stent and is consequently linked to greater LLE.

In this study, we found not only vessel enlargement, but also plaque regression after DCB treatment. Plaque regression might be caused by paclitaxel delivered by balloon. Paclitaxel inhibits smooth muscle cell proliferation and migration in a dose-dependent manner and prevents neointima formation after balloon angioplasty [35]. Paclitaxel is a compound of much smaller size, with fewer effects specific to vascular biology; however, it is quite hydrophobic and insoluble and it binds tenaciously to tissue protein elements [36]. However, these compounds demonstrate more rapid planar than transmural diffusion [37]. The drug tissue binding capacity of paclitaxel was maximal in the intima and precipitously decreased within the most intimal area of the arterial media to less than half the intimal level. At the outer edge of the media, the paclitaxel binding capacity gradually increased and peaked within the adventitia [36]. This could be major limitation of the intracoronary drug delivery system, which led to poor localization efficiency and

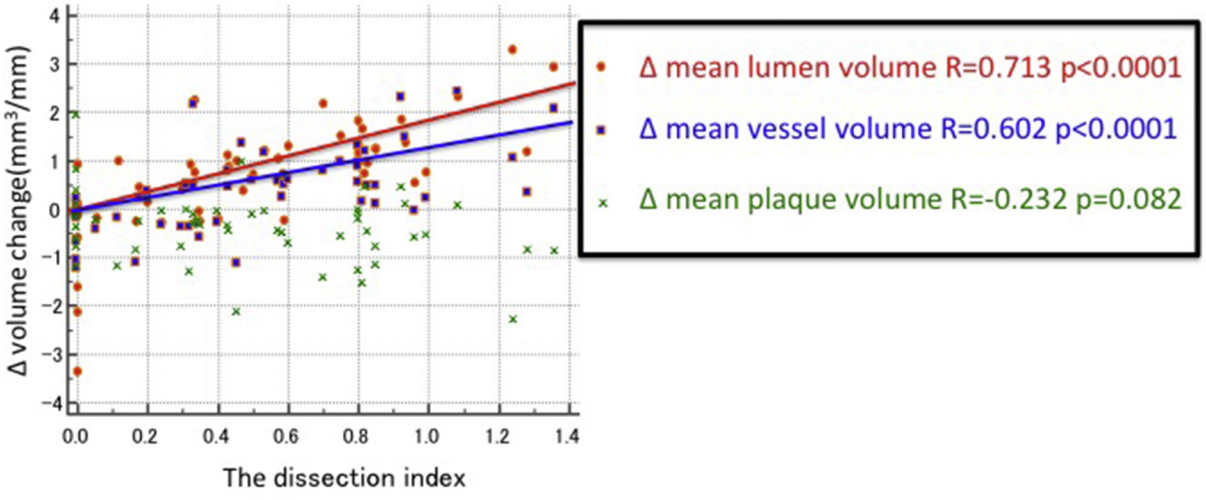

Fig. 2. Correlation of Δ mean lumen volume, Δ mean EEM volume, and Δ mean plaque volume with the dissection index. Red dots indicate Δ mean lumen volume, blue dots indicate Δ mean EEM volume, and green dots indicate Δ mean plaque volume. Δ: delta, EEM: external elastic membrane. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

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rapid washout of the agent from the target vascular wall after delivery [38]. Intriguingly, a previous study showed that intra-pericardial delivery of paclitaxel in large doses led to an increase in vessel enlargement and decrease in neointimal massed by apoptotic cells [39]. Similarly, favorable local pharmacokinetics and consistency of tissue loading have also been demonstrated after pericardial delivery compared with those after endoluminal delivery [40]. These results suggested that the effect of paclitaxel was more enhanced when it was filtrated and reached near the adventitia of the coronary arteries. Dissection can help transmural diffusion of the drug and additionally force paclitaxel to be delivered in high doses near the adventitia, such as in intra-pericardial paclitaxel delivery. This may be another reason why dissection adjunctive drugs are more conducive to vessel enlargement and plaque regression than POBA alone.

4.1. Limitations

Since this study was a single-center study with a small sample size, a prospective randomized multicenter trial with a large number of participants will be needed to confirm the mechanism of LLE. This study was not conducted comparing only the POBA arm because we wished to analyze just serial change of lesions and assess the mechanism of LLE after DCB treatment. In this study, we used IVUS for all PCI procedures and evaluated vessel dissection. However, dissections are more clearly detected by optical coherence tomography than by IVUS. Therefore, the results might be attenuated when IVUS is used. Nevertheless, we used IVUS in this study because we wished to examine the correlation between vessel change and dissection. Due to the complementary nature of IVUS and optical coherence tomography [41], future studies combining their will be warranted.

5. Conclusion

LLE after DCB treatment for de novo CAD was caused by both vessel enlargement and plaque regression. Dissection without flow limitation after the use of a pre-dilatation balloon of sufficient size may cause the intending LLE after DCB treatment.

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Author statement

All authors were involved in reporting the results of this study and all approved the final version of the submitted manuscript.

TY, TS, KU, TT, HK, and YY contributed in the conception, design and planning of the study.

All authors were involved in acquisition of data and critical revision of the manuscript for important intellectual content.

TY, TS, KU, TT and YY performed percutaneous coronary intervention with drug-coated balloon.

TY and TS did angiographic, IVUS and the statistical analysis.

Manuscript writing: TY and TS.

TS is responsible for the overall content and serves as guarantor.

Declaration of Competing Interest

The authors declare no conflicts of interest.

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