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Serial Morphological and Functional Assessment of Drug-Eluting Balloon for In-Stent Restenotic Lesions

Mechanisms of Action Evaluated With Angiography, Optical Coherence Tomography, and Fractional Flow Reserve

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Objectives This study sought to elucidate the underlying mechanism through which drug-eluting balloons (DEB) restore coronary blood flow, by assessing the coronary vessel before, immediately after, and at 6-month follow-up with angiography, optical coherence tomography (OCT), and fractional flow reserve (FFR).

Background In-stent restenosis (ISR) treatment remains challenging. Drug-eluting balloons have been shown to be a valid treatment option in several studies. These studies focused on efficiency of the device, whereas the mechanisms of action of DEB in ISR treatment have not been investigated.

Methods In this prospective, single-center observational study, patients with ISR were treated with a second-generation DEB. Serial angiographic, OCT, and FFR measurements were performed before and after the procedure, as well as at 6-month follow-up.

Results Twenty-five patients were assigned to DEB treatment, with an angiographic and device success of 100% and 92%, respectively. Late luminal loss was 0.01 ± 0.43 mm. Median percent changes [interquartile range] between pre-and post-procedure, and post-procedure and follow-up were, respectively: lumen volume 75.1% increase [43.7 to 115.0], and 8% increase [−14.0 to 25.8]; stent volume 23.7% increase [15.5 to 40.0], and −1.2% decrease [−6.9 to 5.9]; and neointimal volume −14.4% decrease [−29.2 to −9.5], and −15.8% decrease [−38.1 to 28.3]. The FFR gradient along the treated stent (difference in FFR between the distal and the proximal stent edge) was 0.37 ± 0.18 pre-procedure, 0.06 ± 0.04 post-procedure, and 0.05 ± 0.05 at follow-up. In all post-procedural OCT images, intrastent dissections were seen, which were sealed at follow-up OCT.

Conclusions DEB restore coronary blood flow by means of a short-term mechanical effect, causing an increase in lumen and stent volumes and compression of neointimal hyperplasia (with intra-stent dissections). Due to the local drug effect, patency persists and may even improve at follow-up, with further increase in lumen volume, decrease in neointimal volume, and complete sealing of neointimal dissections. (J Am Coll Cardiol Intv 2013;6:569–76) © 2013 by the American College of Cardiology Foundation

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Long-term clinical outcomes of percutaneous coronary interventions (PCI) with stent implantation have improved during the last decades, but a subgroup of patients is still confronted with in-stent restenosis (ISR) (1,2). Initially, ISR was treated with conventional or cutting balloons, although with a high percentage of recurrent restenosis (3,4). Later, brachytherapy and drug-eluting stent (DES) strategies were explored. Although brachytherapy reduced recurrent restenosis as compared to conventional balloon, DES proved to be

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even superior, and they are currently the standard of care for this indication (5–7). Recently, drug-eluting balloons (DEB) have been considered as an alternative treatment strategy instead of DES (8). There is evidence that DEB achieve at least similar angiographic and clinical outcomes as DES, without the need for an additional layer of metal (9). Avoiding additional stent placement gives the operator more treatment flexibility in case of future reinterventions in the target lesion. Moreover, prolonged dual-antiplatelet therapy may not be necessary when using DEB technology (8,10,11).

Abbreviations and Acronyms

DEB = drug-eluting balloon(s)
DES = drug-eluting stent(s)
ISR = in-stent restenosis
FFR = fractional flow reserve
OCT = optical coherence tomography
PCI = percutaneous coronary intervention
QCA = quantitative coronary angiography
TLR = target lesion revascularization

Although the angiographic and clinical effectiveness of DEB in ISR has been demonstrated, its exact mechanism of action has not been fully exploited. No literature is available about the functional and intravascular morphological changes induced by DEB over time in ISR treatment. Even more, data on morphological ISR changes, even with other treatment strategies, are scarce (12–14).

In this light, the aim of our study was to get a better insight into the treatment of ISR lesions with DEB, focusing on their short-term and mid-term mechanisms. To achieve this, serial angiographic, fractional flow reserve (FFR), and optical coherence tomography (OCT) measurements have been performed before intervention, immediately after intervention, and at 6-month follow-up in a series of ISR lesions treated with DEB.

Methods

This study is a prospective, observational, single-arm study, aimed at assessing functional and intravascular morphological changes induced by the DEB in ISR lesions. The study, carried out according to the Declaration of Helsinki, was approved by the ethics committee of the University Medical Center Utrecht, and all included patients provided signed informed consent.

Patient selection. Patients with stable or unstable angina pectoris or silent ischemia, who were scheduled to undergo PCI because of ISR of a bare-metal stent or DES, were considered eligible. Documented ischemia had to be present. Exclusion criteria were left ventricular ejection fraction $\leq$30%, acute myocardial infarction, left main disease, ostial ISR (impossible to assess with OCT), life expectancy $<$1 year, known renal failure (creatinine $>$ 200 mg/dl), or recurrent ISR.

Interventional procedure, study device, and OCT, FFR, and angiographic data acquisition and analysis. All patients enrolled in the study were treated with acetylsalicylic acid (80 to 100 mg per day) and clopidogrel (300- to 600-mg loading dose before the procedure, if needed, and 75 mg per day maintenance). Heparin was administered intravenously in boluses (70 to 100 U/kg) to maintain an activated clotting time $\geq$250 s during the procedure. Administration of glycoprotein IIb/IIIa inhibitors was left to the physician's discretion.

After obtaining coronary angiograms, patients underwent sequential pre-dilation with standard balloons and dilation with the DEB. More specifically, the standard balloon diameter was sized with a 0.9:1 balloon-to-previous-stent ratio and shorter than the intended DEB, and inflated with high pressure (12 to 18 atm); the DEB diameter was sized with a 1.1:1 balloon-to-previous-stent ratio and inflated with low pressure (8 to 12 atm) during 60 s inflation. Post-dilation was left to the physician's discretion. Special care was taken to position each DEB in order to avoid potential geographic miss (i.e., DEB should extend a minimum of 5 mm proximal and distal to the pre-dilation balloon) and excessive DEB overlap (to avoid double dose) in case of multiple DEB use for long lesions (15). Additional bailout stenting was performed in case of stent-edge dissection or residual stenosis after balloon or DEB angioplasty. Acetylsalicylic acid was continued indefinitely after the procedure, and clopidogrel was continued for 3 months.

Methodological details on the study device used and the offline OCT, FFR, and quantitative coronary angiography (QCA) analysis can be found in the Online Appendix in the Additional Methods section.

Follow-up and endpoints. All patients were scheduled to undergo clinical and angiographic follow-up at 6 months. In case an event occurred, detailed review of the hospital files was performed. The main endpoints of this study were several OCT and FFR parameters. Secondary endpoints included: angiographic, device, and procedural success; angiographic measures; and clinical outcomes according to the Academic Research Consortium criteria (16). Angiographic success was defined as achievement of final residual stenosis $<$30% (by visual estimate) and Thrombolysis In Myocardial Infarction (TIMI) flow grade 3, using any

percutaneous method. Device success was defined as angiographic success using the DEB device. Procedural success was defined as angiographic success without the occurrence of in-hospital major adverse cardiac events. All outcomes were adjudicated by a clinical events committee.

Statistical analysis. Continuous variables are presented as mean ± SD or median [25th to 75th interquartile range]. Categorical variables are presented as counts and percentages. Continuous variables were compared between 2 groups using the paired Student *t* test or Wilcoxon signed rank test, as appropriate. Categorical variables were compared using the chi-square or Fischer exact test, as appropriate. A 2-tailed p value of 0.05 was considered statistically significant.

Results

Patient and procedural characteristics. Overall, 25 patients were included and underwent PCI for stable or unstable anginal complaints, according to the protocol, between August 2009 and May 2011. Baseline clinical and procedural characteristics are shown in Online Tables 1 and 2. Angiographic and procedural successes were achieved in all patients. Device success was achieved in 23 (92%) patients: in 1 patient, an additional stent was placed due to a dissection at the proximal edge of the old stent, and in another patient, an additional stent was implanted because of a residual significant stenosis before the proximal edge of the old stent. Both resulted in a good angiographic result.

Angiographic follow-up and adverse events at 6 months. The QCA and clinical data are presented in Table 1. Two patients refused to undergo angiographic control due to lack of symptoms. In-stent and in-segment late luminal loss were 0.01 ± 0.43 mm and −0.03 ± 0.43 mm, respectively. At follow-up, 4 patients (16%) had angiographic binary restenosis, of which 2 (8%) had target lesion revascularization (TLR). The 2 patients with a TLR were a 65-year-old woman and a 76-year-old man. The first patient had a diffuse DES restenosis as baseline lesion, which was treated successfully with DEB. At 6-month follow-up, a diffuse recurrent restenosis with a positive FFR was detected, and a clinically driven TLR was performed with 2-limus DES. The second patient was diabetic; his baseline lesion was a diffuse restenosis of a bare-metal stent, treated successfully with DEB. At 6-month follow-up, a recurrent diffuse restenosis with a positive FFR was detected, and the lesion was treated with implantation of a DES. Concerning the other 2 patients with binary restenosis and without TLR, 1 had a 60% focal in-stent diameter stenosis as measured by QCA, already present at baseline (at the distal end of the previously implanted stent), not treated with DEB and unchanged at follow-up. Both after treatment and at follow-up, the FFR over this lesion was negative. The other patient was diabetic and had a 53% in-stent diameter stenosis as measured by QCA, with negative FFR. Considering the patients had no complaints, with a negative FFR, no TLR was performed in either patient.

Table 1. QCA, Functional Measurements, and Clinical Events

QCA	Pre-Procedure (n = 25)	Post-Procedure (n = 25)	6-Month Follow-Up (n = 23)
Reference vessel diameter, mm	2.35 ± 0.46	—	—
Minimal luminal diameter, mm	0.58 ± 0.38	1.83 ± 0.47	1.83 ± 0.62
Diameter stenosis, %	75.3 ± 16.1	27.5 ± 15.9	26.0 ± 18.3
Lesion length, mm	26.4 ± 12.6	—	—
Acute gain, mm	—	1.26 ± 0.61	—
Residual binary restenosis	—	2 (8)	—
Late-luminal loss, mm			
In-stent	—	—	0.01 ± 0.43
In-segment	—	—	−0.03 ± 0.43
Binary restenosis	—	—	4 (16)
FFR	**(n = 22)**	**(n = 25)**	**(n = 23)**
Distal target vessel	0.54 ± 0.15	0.87 ± 0.08	0.86 ± 0.11
Distal of the stent	0.58 ± 0.17	0.92 ± 0.05	0.92 ± 0.07
Proximal of the stent	0.96 ± 0.07	0.97 ± 0.03	0.96 ± 0.05
In-stent gradient	0.37 ± 0.18	0.06 ± 0.04	0.05 ± 0.05
Clinical Events at 6-Month Follow-Up	—	—	**(n = 25)**
Cardiac death	—	—	0
Myocardial infarction	—	—	0
Target lesion revascularization	—	—	2
Stent thrombosis	—	—	0

Values are mean ± SD or n (%).
FFR = fractional flow reserve; QCA = quantitative coronary angiography.

OCT and FFR. In 4 patients, pre-procedure OCT images were not available due to an inability to cross the lesion with the OCT catheter. In 2 patients, both pre-procedure and post-procedure OCT data were not available, in 1 case because of poor image quality, and in the other due to technical issues with the OCT catheter (impossible acquisition of images). In 3 patients, OCT data at follow-up were not available. Two patients refused angiographic follow-up (see the preceding text), and in 1 patient the OCT images were of poor quality.

In 3 patients, pre-procedure FFR was not done due to impossible passage of the lesion with the FFR wire. Post-procedure FFR was performed in all patients. At follow-up, only the 2 patients without angiographic follow up had no FFR data. No complications occurred related to these procedures. A comprehensive overview of the OCT and FFR results are presented in Tables 1 to 3.

OCT-based lumen and stent volumes increased between pre- and post-procedure, and lumen volume tended to increase further at 6 months, meanwhile the stent volume stabilized. Neointimal volume decreased between pre- and post-procedure, and tended to further decrease at 6-month follow-up (further data are also available in Online Table 3).

Table 2. OCT Analysis in Coupled Patients

	Pre (n = 17)	Post (n = 17)	FU (n = 17)	p Value		
				Pre vs. Post	Pre vs. FU	Post vs. FU
Cross-section analyses						
Stent length analyzed	23.0 [19.1–35.9]	22.9 [19.1–35.7]	22.8 [19.4–35.7]	0.22	0.60	0.12
Minimal mean lumen diameter, mm	1.13 [1.04–1.33]	1.97 [1.69–2.21]	2.02 [1.71–2.32]	<0.001	<0.001	0.91
Minimal mean stent diameter, mm	2.49 [2.34–2.92]	2.75 [2.53–3.21]	2.92 [2.36–3.27]	<0.001	0.04	0.57
Minimal lumen area, mm^2	1.16 [0.93–1.72]	4.90 [2.71–5.57]	4.27 [3.02–6.28]	<0.001	<0.001	0.74
Minimal stent area, mm^2	5.42 [4.43–7.22]	8.00 [6.46–9.56]	7.95 [5.23–9.79]	<0.001	<0.01	0.80
Maximum neointimal area, mm^2	6.15 [5.01–7.75]	4.93 [3.94–5.35]	4.43 [3.61–3.72]	<0.001	<0.01	0.91
Neointimal area stenosis, %	53.4 [43.7–59.3]	32.2 [29.5–35.9]	31.3 [22.0–39.2]	<0.001	<0.01	0.65
Maximum neointimal area, %	83.4 [74.5–86.0]	48.3 [41.8–51.0]	42.4 [36.7–59.9]	<0.001	<0.001	0.69
Lumen volume, mm^3	78.5 [55.7–133]	152 [118–173]	178 [105–206]	<0.001	<0.001	0.49
Stent volume, mm^3	176 [132–237]	245 [180–261]	247 [176–273]	<0.01	<0.01	0.80
Neointimal volume, mm^3	87.5 [76.9–107]	76.2 [58.2–96.9]	57.3 [44.8–91.8]	<0.001	<0.01	0.23
Malapposition volume, mm^3	0 [0–0.36]	0.23 [0.06–0.58]	0.53 [0.11–1.54]	0.02	<0.01	0.19
Lumen symmetry*	0.75 [0.73–0.80]	0.69 [0.61–0.73]	0.73 [0.67–0.77]	<0.01	0.09	0.01
Stent symmetry	0.89 [0.85–0.91]	0.84 [0.81–0.87]	0.87 [0.82–0.89]	<0.01	0.03	0.52
Strut analyses						
Total no. struts analyzed	7,522	5,510	6,696			
Covered embedded struts, per lesion, %	100 [97.6–100]	97.2 [91.7–98.5]	97.3 [93.0–99.6]	<0.01	<0.01	0.61
Covered protruding struts per lesion, %	0 [0–1.23]	0.48 [0–1.13]	0.66 [0–1.76]	0.86	0.10	0.07
Uncovered struts per lesion, %	0 [0–0.48]	1.85 [1.15–7.04]	1.32 [0.08–3.35]	<0.01	<0.01	0.19
Malapposed struts per lesion, %	0 [0–0.21]	0 [0–0.17]	0 [0–1.72]	0.86	0.12	0.37
Covered struts overall (embedded and protruding) per lesion, %	100 [99.4–100]	98.1 [91.9–98.9]	97.3 [95.4–99.9]	<0.01	<0.01	0.43
Uncovered struts overall (uncovered and malapposed) per lesion, %	0 [0–0.56]	1.85 [1.15–8.11]	2.70 [0.11–4.55]	<0.01	<0.01	0.43

Values are median [interquartile range]. *Lumen symmetry lies between 0 and 1. A value of 1 means fully symmetric, with less symmetry with a decreasing value.
FU = follow-up at 6 months; OCT = optical coherence tomography; Post = post-procedure; Pre = pre-procedure.

Pre-procedure stent strut analysis showed minimal uncovered or malapposed struts mainly located at the edges of the stent, whereas there were few uncovered or malapposed stent struts visible directly after the procedure and at follow-up, without differences in the time points of acquisition.

Functionally, the in-stent FFR gradient decreased after the procedure, and tended to further decrease between post-procedure and follow-up.

In all post-procedure OCT images, dissections were seen through the DEB-dilated segment, mainly located where the baseline lesion was most severe. These dissections were

Table 3. Percentage Change in Coupled Patients

QCA	Pre-Post (n = 17)	Pre-FU (n = 17)	Post-FU (n = 17)
Minimal lumen diameter change, %	213 [90.0 to 604]	206 [124 to 509]	6.98 [−5.55 to 16.8]
Diameter stenosis change, %	−66.2 [−77.4 to −51.2]	−67.2 [−81.5 to −48.9]	−6.25 [−51.9 to 46.8]
OCT			
Minimal lumen area change, %	278 [140 to 360]	246 [99.7 to 391]	4.37 [−22.6 to 26.5]
Lumen volume change, %	75.1 [43.7 to 115]	71.8 [44.6 to 117]	8.0 [−14.0 to 25.8]
Stent volume change, %	23.7 [15.5 to 40.0]	21.3 [10.2 to 41.3]	−1.2 [−6.87 to 5.89]
Neointimal volume change, %	−14.4 [−29.2 to −9.46]	−27.8 [−49.1 to −2.69]	−15.8 [−38.1 to 28.3]
FFR	**(n = 20)**	**(n = 20)**	**(n = 20)**
FFR stent gradient change, %	−86.5 [−92.6 to −64.0]	−87.3 [−94.5 to −81.4]	−28.3 [−54.2 to 18.8]

Values are median [interquartile range].
Abbreviations as in Tables 1 and 2.

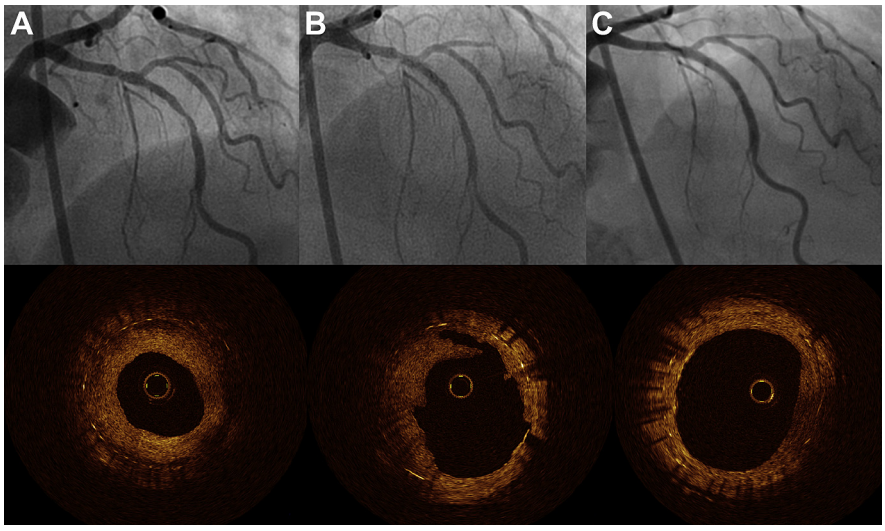

Figure 1. Pre-PCI, Post-PCI, and Follow-Up Angiographic Images Coupled to Corresponding OCT Images: Focal ISR

Optical coherence tomography (OCT) images were captured in corresponding segments (i.e., same OCT segment is depicted between pre-PCI, post-PCI, and follow-up) by means of a synchronization tool in the software. **(A)** Pre-PCI angiographic image shows a focal ISR, with the corresponding in-stent OCT image. **(B)** After the procedure, coronary flow is restored due to a mechanical effect. The OCT image demonstrates dissection of the neointimal plaque. **(C)** At follow-up, the coronary lumen increases further due to the drug effect. Dissections as seen with OCT have been restored, with a smooth endothelial coverage of stent struts, with minimal neointimal plaque. PCI = percutaneous coronary intervention. See Online Video 1.

not visible on angiographic images and were left untreated, because the angiographic result was satisfactory (Figs. 1, 2, and 3, Online Videos 1, 2, and 3). All these dissections were completely healed at follow-up with restoration of a "near-circular" lumen surface inside the stent. Lumen symmetry was used as surrogate measure for these dissections, in order to quantify them. Lumen symmetry was significantly lower directly after the procedure as compared

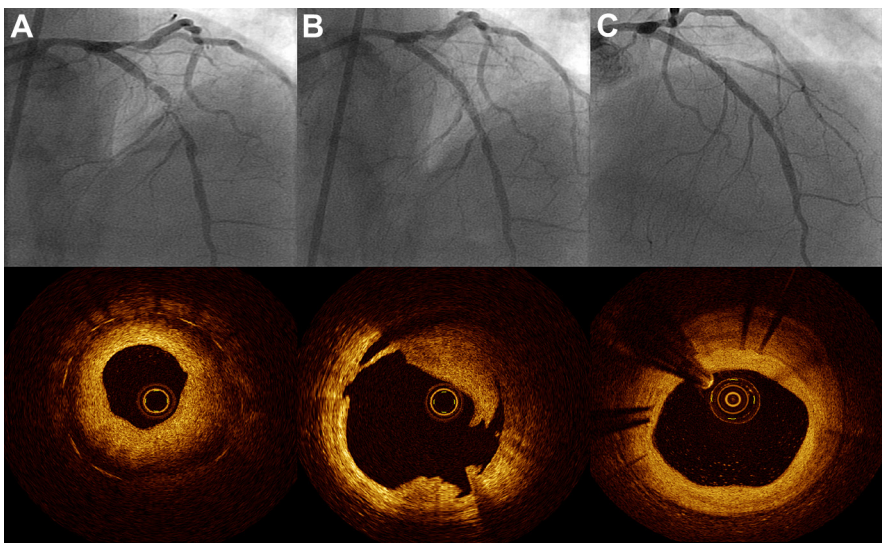

Figure 2. Angiographic Images Coupled to Corresponding OCT Images: Diffuse ISR With a Large Dissection

(A) Pre-PCI angiographic image shows a diffuse in-stent restenosis (ISR), with the corresponding in-stent OCT image. **(B)** After the procedure, coronary flow is restored due to a mechanical effect. The OCT image demonstrates a large stent-edge dissection of the neointimal plaque; remarkably, this is not seen on the angiographic images. **(C)** At follow-up, the coronary lumen stabilizes due to the drug effect. Dissections as seen with OCT have been restored, with minimal neointimal plaque. Abbreviations as in Figure 1. See Online Video 2.

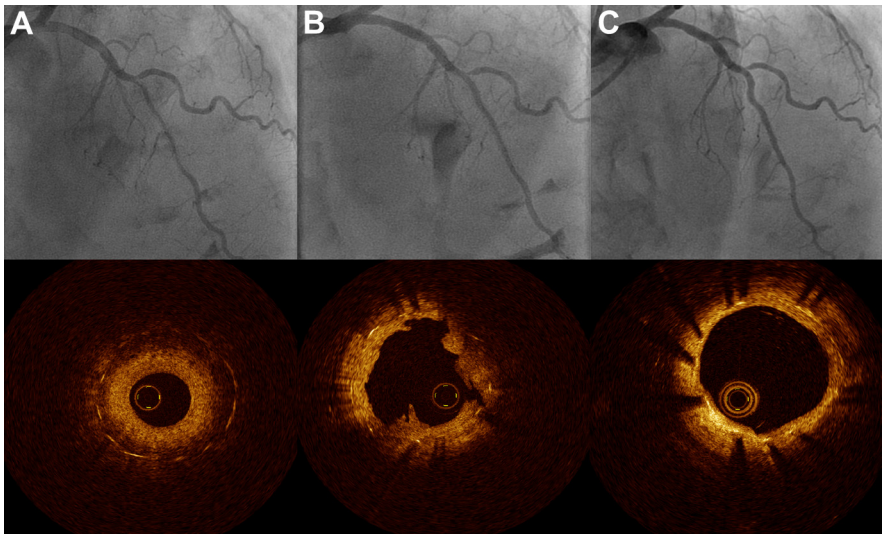

Figure 3. Angiographic Images Coupled to Corresponding OCT Images: Diffuse ISR With Microdissections

(A) Pre-PCI angiographic image shows a diffuse ISR, with the corresponding in-stent OCT image. **(B)** After the procedure, coronary flow is restored due to a mechanical effect. The OCT image demonstrates microdissections in the whole axial plane of the neointimal plaque. **(C)** At follow-up, the coronary lumen increases further due to the drug effect. Dissections as seen with OCT have been restored, with a smooth endothelial coverage of stent struts, with minimal neointimal plaque. Abbreviations as in Figure 1. See Online Video 3.

with pre-procedure and follow-up, whereas this was similar between pre-procedure and follow-up (Table 2).

Discussion

This prospective observational study shows that a strategy of balloon dilation and paclitaxel elution with DEB for in-stent restenotic lesions restores and maintains coronary blood flow by means of a short-term mechanical effect and a sustained pharmacological effect. Specifically, the mechanical balloon dilation causes an increase in the volume of the old stent, with concomitant compression and dissection of the neointimal tissue. These phenomena lead to an absolute increase in minimal lumen area to a value that does not generate ischemia anymore. The pharmacological effect of paclitaxel maintains coronary patency at follow-up, with a further trend toward a decrease in neointimal hyperplasia volume, leading to a nonsignificant increase in lumen volume. Despite this drug effect, no significant difference in uncovered or malapposed stent struts is noted, with overall satisfactory stent strut coverage at follow-up.

Interestingly, in the post-procedure OCT acquisitions, the in-stent restenotic segment treated with DEB showed extensive dissections of the neointimal tissue. These dissections were not treated because the angiographic result was satisfactory. All these dissections were completely healed at follow-up, with restoration of a near circular lumen surface inside the stent.

Considering the neointimal decrease between pre-, and post-procedure, this effect is attributable to a direct mechanical effect of the pre-dilation balloon and the DEB itself. This results in extra expansion of the restenotic stent and in compression of the neointimal volume (achieved also by means of several dissections as evident by OCT), causing stent and lumen increase. Interestingly, the neointimal volume tends to decrease beyond the intervention, as assessed at follow-up, and this is most likely caused by the drug effect. In experimental animal studies, it has been demonstrated that paclitaxel causes apoptosis and necrosis of endothelial and smooth muscle cells (17). Thus, it is possible that our findings (regression of neointimal volume with time) may be caused by similar cytotoxic mechanisms: apoptosis and necrosis of neointimal tissue. However, it is also possible that the healing process of the neointimal dissections caused by the short-term balloon trauma can lead with time to a cicatricial shrinkage of the neointimal tissue, without additional recurrent proliferation because of the cytostatic activity of paclitaxel (18). Although neointimal volume decreases, there is still a high percentage of strut coverage. This suggests a proper drug transfer deeper in the neointimal tissue, toward the smooth muscle cells. This may be due to the formula used on this DEB, paclitaxel in combination with a hydrophilic excipient. This excipient is added in order to increase the drug transfer over the vessel wall surface to the smooth muscle cells. Proper drug delivery to the smooth muscle cells is imperative in order to reduce restenosis, but as this study

suggests, this is also important to prevent endothelial toxicity. A previous study (19), by our group, assessed the effects of another DEB without a similar hydrophilic excipient. An important finding in that study is an insufficient reduction of neointimal hyperplasia, however, with a higher percentage of uncovered and malapposed struts than reported in the current study. Those findings suggest a superficial (toxic) effect of paclitaxel on the endothelial cells, instead of inhibiting the deeper-laid smooth muscle cell proliferation. In line with our current findings, this suggests the importance of adequate delivery of paclitaxel to the smooth muscle cells in order to reduce the restenotic process and at the same time preventing endothelial toxicity. A good endothelial coverage without excessive neointimal proliferation might well underscore a potential long-term beneficial effect in reducing late stent thrombosis without an increase in revascularization rates.

Study limitations. First, selection bias may have occurred in individual cases. Besides, patients with an ongoing acute coronary syndrome were not considered eligible for inclusion due to the complex nature of the study (i.e., pre- and post-procedural FFR and OCT). Hence, only elective patients were included in the study. Second, although clinical and angiographic outcomes are promising, the nature of this registry does not allow for comparison with a reference technique. Yet, this registry strengthens findings in other DEB studies. Finally, the number of patients included is relatively low. However, in this study, very sensitive techniques have been used that allow for accurate assessment of the short-term and mid-term mechanisms involved in restoring and maintaining coronary blood flow.

Conclusions

DEB restore coronary blood flow by means of a short-term mechanical effect, causing an increase in lumen and stent volumes and compression of neointimal hyperplasia (with intrastent dissections). Due to the local drug effect, patency persists and may even improve at follow-up, with a further increase in lumen volume, decrease in neointimal volume, and complete sealing of neointimal dissections. An early effective drug effect (in the therapeutic range for around 7 days) results in coronary patency up to 6 months, which seems to be caused by an appropriate distribution of paclitaxel into the vessel wall due to the formula combining the drug with a hydrophilic excipient.

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Key Words: drug-eluting balloon ■ fractional flow reserve ■ in-stent restenosis ■ optical coherence tomography.

APPENDIX

For an expanded Methods section, supplementary tables, and videos and their legends, please see the online version of this paper.