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Optical coherence tomographic analysis of drug-eluting in-stent restenosis at different times

A STROBE compliant study

Chunguang Feng, PhD[a], Peiying Zhang, PhD[a,*], Bing Han, PhD[a], Xianchi Li, MS[a], Yi Liu, MS[a], Dongdong Niu, BS[a], Yibing Shi, MS[b]

Abstract

The imaging characteristics of drug-eluting in-stent restenosis (ISR) at different times varied; however, the mechanism had not yet been elucidated.

To analyze the imaging characteristics of drug-eluting ISR at different time points by optical coherence tomography (OCT) and investigate the cause of the stent treatment failure.

A total of 70 patients with drug-eluting ISR undergoing OCT were enrolled (intimal hyperplasia ≥50% of stent area) and implanted with drug-eluting stents. According to stent implantation time, the patients were divided into 2 groups: early in-stent restenosis group (E-ISR group) (group A, n = 35, stent age ≤12 months) and late in-stent restenosis group (L-ISR group) (group B, n = 35, stent age ≥24 months). A qualitative analysis of the restenosis tissue included the nature of restenosis tissue (homogeneous and heterogeneous), neoatherosclerosis, thin-cap fibroatheroma (TCFA), and microvessels.

The ratio of ≥75% cross-sectional area stenosis between the L-ISR and E-ISR groups was (60.00% vs 34.28%, $P < .05$). The heterogeneous intima, neoatherosclerosis, TCFA, and microvessels were more prevalent in the L-ISR group as compared to the E-ISR group (71.43% vs 45.71%, $P < .05$; 48.57% vs 22.86%, $P < .05$; 25.71% vs 5.71%, $P < .05$; 22.86% vs 2.86%, $P < .05$, respectively).

The morphological characteristics of L-ISR were significantly different from those in the E-ISR; the former was closer to the atherosclerotic plaque, which provided a new approach for the treatment of drug-eluting ISR.

Abbreviations: BMS = bare metal stents, BVS = bioresorbable vascular scaffolds, DES = drug-eluting stents, E-ISR = early in-stent restenosis, ISR = in-stent restenosis, L-ISR = late in-stent restenosis, OCT = optical coherence tomography, PCI = percutaneous coronary intervention, TCFA = thin-cap fibroatheroma.

Keywords: bioresorbable vascular scaffolds, drug-eluting stents, in-stent restenosis, optical coherence tomography, percutaneous coronary intervention

1. Introduction

Percutaneous coronary intervention has been widely used in the treatment of coronary heart disease. As compared to the bare metal stents (BMS), drug-eluting stents (DES) significantly reduces the vascular intimal hyperplasia, late lumen loss, and repeat revascularization.[1,2] Several studies have shown that unlike BMS restenosis, whose manifestation is mostly homogeneous tissue with abundant smooth muscle cells, the manifestations of the drug-eluting in-stent restenosis (ISR) are increased in the presence of atherosclerotic changes in the neointima that occurs early and is widely distributed.[3–8] Therefore, the late catch-up phenomenon of DES restenosis is under intensive focus[9]; it leads to in-stent thrombosis, and the risk of acute coronary syndromes was significantly increased.[10–12] However, the mechanism of ISR of DES was yet unclear, and the manifestations of restenosis at different times were not identical.

Compared to the other imaging examinations, the optical coherence tomography (OCT) with a high axial resolution of approximately 10 to 20 μm has a unique value in the morphology and mechanism of DES restenosis.[13] Thus, the present study aimed to observe the pathological characteristics of coronary restenosis in patients with drug-eluting in-stent at different times by OCT to provide imaging evidence for understanding the pathological changes of ISR and explore the appropriate therapies.

2. Materials and methods

2.1. General data

A retrospective analysis was performed on 70 patients with ISR at the Xuzhou Central Hospital from February 2014 to December

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[a] Department of Cardiology, [b] Department of Imaging, Xuzhou Central Hospital in Jiangsu, Institute of Cardiovascular Disease, Xuzhou, China.

[*] Correspondence: Peiying Zhang, Department of Cardiology, Xuzhou Central Hospital in Jiangsu, Institute of Cardiovascular Disease, Xuzhou 221135, China (e-mail: fcg999@163.com).

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2016; these patients were implanted with DES. According to stent implantation time, the patients were divided into 2 groups: early in-stent restenosis group (E-ISR group) (group A, n = 35, stent age ≤12 months, 321–367 days) and late in-stent restenosis group (L-ISR group) (group B, n = 35, stent age ≥24 months, 741–1256 days). ISR is defined as a decrease in the luminal diameter by >50% in the stented area or the 5-mm borders adjacent to the stent,[14] and OCT imaging was performed. Exclusion criteria include patients with renal insufficiency (serum creatinine >120 μmol/L); patients with allergic reaction to contrast agent; patients with severe heart failure; patients who were not implanted with DES; patients with poor-quality OCT images.

Stent implantation was performed routinely. The operation began with heparin anticoagulation, followed by disposable intravenous injection (100 IU/kg). During surgery, according to the activated clotting time, heparin dosage was increased appropriately after 250 to 300 seconds. The dual antiplatelet drugs (aspirin + clopidogrel bisulfate or ticagrelor) were used for at least 12 months, and other medications were used optimally. The implantable stents included Firebird1 (MicroPort Scientific Corporation, Shanghai, China), Firebird2 (MicroPort Scientific Corporation), Excel (JW Medical Systems, Weihai, China), Partner (Lepu Medical Technology Co Ltd, Beijing, China), Buma (Sino Medical Sciences Technology Inc, Tianjin, China), Cypher (Cordis, Miami Lakes, FL), Resolute (Medtronic, Santa Rosa, CA), and Xience V, (Abbott Vascular, Abbott Park, IL).

This study was approved by the Ethics Committee of the hospital, and all patients signed the informed consent.

2.2. OCT examination method

The C7-XR OCT intravascular imaging system (Light Lab Image Inc, St. Paul, MN) was used for examination. The guiding catheter was seated into the coronary opening of the left and right targets under the guidance of the guiding wire. Then, along the guiding catheter, the guide wire was sent to the distal end of the culprit artery, and image catheter (Light Lab Image Inc) was sent to the distal end of the target lesion along the guiding wire. After accurate positioning, the contrast agent was injected into the coronary lumen at a speed of 4 mL/s through the guiding catheter, followed by the removal of the target intravascular blood. Concurrently, the OCT imaging system was activated generating images at 100 frames/s, and the image catheter was withdrawn at a speed of 15 mm/s. Subsequently, the image data were saved on a hard drive, and the C7XR OCT intravascular imaging system (Light Lab Image Inc) was used for OCT image analysis performed by 2 experienced physicians, blinded to the information about patients and surgical procedure.

Observation indicators of OCT: restenosis degree, nature of restenosis tissue, neoatherosclerosis, thin-cap fibroatheroma (TCFA), and microvessels.

The nature of restenosis tissue includes homogeneity and heterogeneity. Gonzalo et al defined heterogeneous intima as an uneven signal on OCT imaging. It might be a dark locally, or light area and the layered feature was obvious, irregular lumen, and exists in intimal microchannel.[14]

The manifestations of in-stent neoatherosclerosis in OCT images include an atherosclerotic change in the stent; after the high signal of intimal hyperplasia in the stent, a significant signal attenuation and blurring of boundary indicated lipid deposition.[15] *TCFA is defined as the location with the thinnest fibrous cap* (≤65 μm), and the angle with lipid tissue is ≥180.[16]

Microvessel is a pathway for the transmission of inflammatory cells and erythrocytes during the formation of lipid plaques, which is a vital mechanism for the transformation of stable plaques to unstable plaques; it is closely related to intraplaque hemorrhage and plaque rupture. The definition of neovascularization in OCT is nonsignal lumen structure images with ≥3 frames, and it does not interlink with a lumen that has a diameter ≤200 μm.[17]

2.3. Statistical analysis

SPSS 17.0 software was used for statistical analysis. Measurement data were expressed as mean ± standard deviation. Chi-square test of the 4-fold table was used for the comparison of enumeration data. Independent sample *t* test was used for the comparison of measurement data. $P < .05$ was considered as a statistically significant difference.

3. Results

3.1. Baseline data of 2 groups

No statistically significant difference was observed regarding the sex, age, risk factors for coronary heart disease, body mass index, family history, target blood vessel of stent implantation, stent length, and the number of stents. The patients were administered dual antiplatelet drugs for a minimum of 1 years and other optimal drug therapy for long-term treatment. The results are shown in Table 1 and the information about sent implantation in Table 2.

Table 1

Baseline data of 2 groups.

	Group A (n = 35)	Group B (n = 35)	*P*
Age, yr	63.47 ± 6.38	65.12 ± 7.67	.542
Male	25	23	.607
History of hypertension	10	13	.445
History of blood lipid metabolism abnormality	12	7	.179
History of type 2 diabetes mellitus	9	14	.203
History of smoking	18	15	.473
BMI	28.84 ± 3.16	29.18 ± 2.92	.847
Family history	14	10	.314
Stent site			
LAD	23	27	.290
LCX	6	8	.550
RCA	18	15	.473
Stent implantation time, days	321–367	741–1256	
Stent diameter, mm	3.08 ± 0.34	3.12 ± 0.29	.341
Stent length, mm	23.73 ± 5.17	24.61 ± 4.82	.617
No. implanted stents on average	1.34	1.43	.862
Medication			
Aspirin	35	35	
Ticagrelor	7	9	.569
Clopidogrel	28	26	.569
Nitrates	31	32	.690
Statins	34	35	1.0
ACEI	12	16	.329
ARB	7	4	.325
B-receptor blocker	34	32	.607

Blood lipid metabolism abnormality: L-LDL >70 mg/dL (1.8 mmol/L).

ACEI = angiotensin-converting enzyme inhibitors, ARB = angiotensin receptor blocker, BMI = body mass index, LAD = left anterior descending branch, LCX = left circumflex branch, RCA = right coronary artery.

Table 2

Information about different brands of stents.

	Firebird1	Firebird2	Excel	Partner	Buma	Cypher	Resolute	Xience V
Material	316L stainless steel	Cobalt-chromium alloy	316L stainless steel	316L stainless steel	316L stainless steel	316L stainless steel	Cobalt-chromium alloy	Cobalt-chromium alloy
Drugs	Rapamycin	Rapamycin	Rapamycin	Rapamycin	Rapamycin	Rapamycin	Zotarolimus	Everolimus
Polymer	Yes	Yes	Biodegradable polymer	Yes	Biodegradable polymer	Yes	Yes	Yes
Group A (47)	6	17	9	4	2	0	3	6
Group B (50)	11	6	10	6	6	2	5	4

The number of enrolled patients and implanted stents were limited, and hence, the first- and second-generation stents were not subdivided. In addition, several brands of stents were available (Table 2); however, detailed differences among the stents were unclear, which might have an impact on subsequent assessments.

The endothelial insufficiency of the stent and excessive intimal hyperplasia of patients with ISR in 2 groups existed simultaneously. A patient who was implanted with Cypher stent for 40 months did not show any neointima in the stent beam (Fig. 1A–C). The ≥75% cross-sectional area stenosis of patients in group A (stent age ≤12 months) was significantly less than that in group B (stent age ≥24 months), and restenosis was markedly increased over time. The comparison of morphological characteristics of restenosis between the 2 groups is shown in Table 3. The longer the stent age, the more significant the proportion of heterogeneity with more neoatherosclerosis and increased number of TCFA and microvessels.

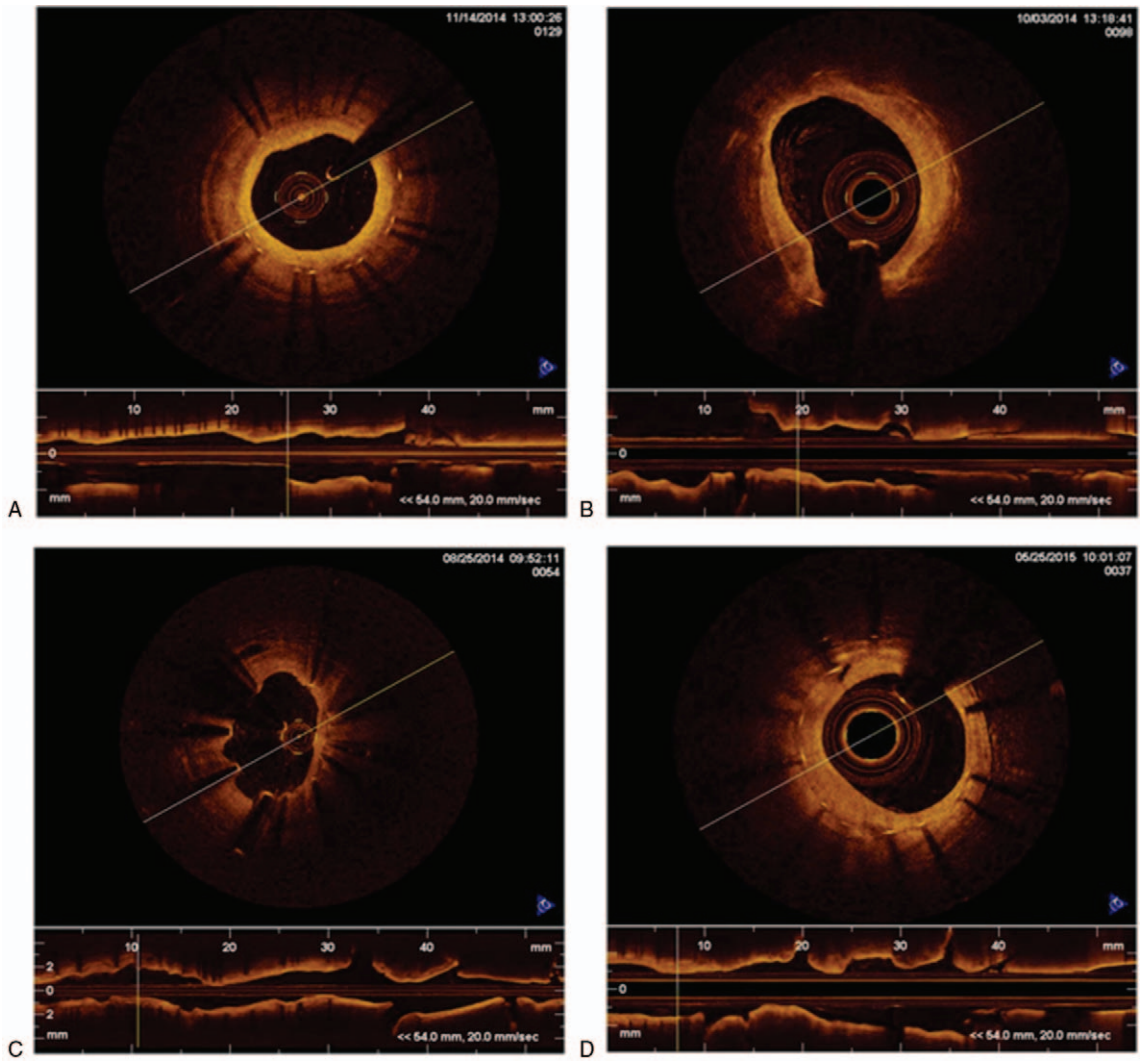

Figure 1. Representative optical coherence tomography (OCT) images of neointimal tissue. A, Homogeneous type. B, Heterogeneous type, thin-cap fibroatheroma (TCFA). C, Drug-eluting stents (DES) had been implanted for 40 months; intimal hyperplasia was accompanied with exposed stent girder steel and endothelial insufficiency. D, Neoatherosclerosis and microvessels.

Table 3

Optical coherence tomography manifestations in 2 groups.

OCT	Group A (n = 35)	Group B (n = 35)	*P*
Endothelial insufficiency and intimal hyperplasia existed simultaneously	6	4	.049
≥75% CSA stenosis	12 (34.28%)	21 (60.00%)	.031
Homogeneous	25 (71.43%)	16 (45.71%)	.029
Heterogeneous	10 (28.57%)	19 (54.29%)	.029
Neoatherosclerosis	8 (22.86%)	17 (48.57%)	.025
Thin-cap fibroatheroma	2 (5.71%)	9 (25.71%)	.049
Microvessels	1 (2.86%)	8 (22.86%)	.032

CSA = cross-sectional area, OCT = optical coherence tomography.

4. Discussion

In this study, OCT showed that endothelial insufficiency of the stent and excessive intimal hyperplasia of patients with ISR could exist simultaneously; the property of excessive neointimal hyperplasia was not unique, with a prolonged duration of DES implantation; thus, the morphology of ISR was obviously different. Among the patients with stent age ≤12 months, most of the neointima showed homogeneity, whereas most of the ISR (stent age ≥24 months) showed heterogeneity; the longer the stent age, the more the neoatherosclerosis and the number of TCFA and microvessels.

The shortcomings of this study include the sample size was small; the retrospective design of the study could not avoid the selection bias; the number of enrolled patients and implanted stents were limited, and hence, the first- and second-generation stents were not subdivided. Moreover, several brands of stents were available, and the matching between the 2 groups was not balanced that might have affected the subsequent assessment; the penetrating power of OCT was insufficient, thereby leading to diffused dark band with large boundary in the OCT image, rendering difficulty in distinguishing it from the image of the lipid core. Therefore, large clinical and experimental studies are essential to validate the current findings.

With the development of intracoronary imaging, OCT with a high axial resolution of approximately 10 to 20 μm has a unique value in the study of morphology and mechanism of ISR in comparison to the other imaging examinations.[13] Previous studies suggested that intimal hyperplasia after stent implantation is a stable event, and new entities are mainly fibrous tissues. However, this was not the case, and Gonzalo et al reported that the OCT manifestations of different ISR were varied. The restenosis tissue is not unique, including homogeneous intima, heterogeneous intima, microvessels, predominant backscatter manifestations, and uneven distribution of plaques.[14] TCFA leading to a marked increase in the possibility of plaque rupture is a major cause of the acute coronary syndrome, and the prognosis of the patients is poor.[18] Microvessel is the pathway for the transmission of inflammatory cells and erythrocytes during the formation of lipid plaques, which is a vital mechanism for the development of stable to unstable plaques; the more the number of microvessels, the thinner the fibrous cap and more the number of unstable plaques that are likely to rupture.[19,20]

The study by Kang et al[21] selected a total of 50 patients implanted with DES but presently had ISR. Among them, 30 patients presented stable angina pectoris and 20 presented unstable angina pectoris. The OCT manifestations in patients with unstable angina pectoris were thinner fibrous cap t (55 vs 100 μm $P = .006$), more TCFA (75% vs 37%, $P = .008$), intimal rupture (75% vs 47%, $P = .044$), and thrombus (80% vs 43%, $P = .010$). Compared to the patients with stent age <20 months, the incidence of neointimal formation in patients with TCFA and stent age >20 months was higher (69% vs 33%, $P = .012$) with commonly occurring erythrocyte-rich thrombosis (27% vs 0%, $P = .007$).

Proliferative intima transforms into neoatherosclerotic plaques in the stent, and the trend of plaque instability is obvious, which is closely related to the occurrence of very late stent thrombosis.[22,23]

In the study of Gonzalo et al,[14] the mean follow-up time was approximately 12 months, and the manifestations of TCFA and other neoatherosclerosis were not significant. However, in this study, the patients with ISR were divided into E-ISR group (stent age ≤12 months) and L-ISR group (stent age ≥24 months) according to stent implantation time, and it was found that with the passage of time, some stent girder steel was still exposed that was directly related to the in-stent thrombosis. In addition, in the cases of excessive intimal hyperplasia, the manifestations of heterogeneous intima were more pronounced; the specific manifestations including neoatherosclerosis, TCFA, and microvessels increased significantly. In this study, no significant difference was observed in the conventional risk factors of atherosclerosis including hypertension, diabetes mellitus, low-density lipoprotein cholesterol level, use of statins, smoking history, stent diameter, and stent length; however, a significant difference was observed in the stent time. The changes in neoatherosclerosis occurred primarily in the L-ISR group, indicating that the main mechanism of occurrence and development of neoatherosclerosis after stent implantation might be different as compared to general atherosclerosis.

Therefore, the detection of in-stent neoatherosclerosis by OCT could accurately observe the minutiae of the lipid plaques, including lipid core size, microvessels, and fibrous cap thickness. In addition, it determined the plaque vulnerability that not only predicted the occurrence of malignant events in clinical practice but also played a critical guiding role in the intervention of ISR and the occurrence of very late thrombosis. The previous studies on ISR usually focused on the reversal of intimal hyperplasia; however, the discovery of in-stent neoatherosclerosis would enable the physicians to intervene in in-stent atherosclerosis with respect to anti-inflammation and lipid regulation, thereby reducing the occurrence ISR or very late in-stent thrombosis. Thus, the purpose of reducing risk events and long-term mortality after stent implantation was achieved.[24]

Although DES reduces neointimal proliferation and the subsequent clinical restenosis compared with BMS, this benefit is paid back with an increased incidence of late stent thrombosis,[25] In addition, the presence of a permanent metallic cage within the arterial wall prevents a full restoration of normal vessel physiology.[26] The recently introduced bioresorbable vascular scaffolds (BVS) which disappears later on has the ability to restore vasomotion, normal physiology, avoid the jailing of side branches, and reduce chronic inflammatory stimulus and mechanical stress on the vessel. This was theoretically expected to translate into eradication of very-late device thrombosis, and a substantial reduction of restenosis, neoatherosclerosis, and late catch-up.[26,27] After initially encouraging results,[28,29] BVS resulted in much higher device thrombosis rates than DES.[30–32] Furthermore, the incidence of neoatherosclerosis has also been reported.[33,34] Indeed in most cases of scaffold thrombosis, a

mechanical cause can be identified in OCT. Suboptimal implantation with incomplete lesion coverage, underexpansion, and malapposition comprises the main pathomechanism for both early and late BVS thrombosis, similar to metallic stent thrombosis.[35] Optimization of preparation of lesions, confirming BVS size, expansion, and apposition of scaffolds is feasible by the OCT-guided BVS implantation. Consequently, it results in optimal angiographic manifestations and minimal chance of underexpansion, malapposition, and scaffold rupture or thrombosis.[36,37]

Author contributions

Conceptualization: Chunguang Feng.
Data curation: Chunguang Feng, Xianchi Li, Yi Liu, Dongdong Niu, Yibing Shi.
Formal analysis: Chunguang Feng, Peiying Zhang, Bing Han, Xianchi Li, Yi Liu.
Funding acquisition: Peiying Zhang.
Methodology: Chunguang Feng, Bing Han, Xianchi Li, Yibing Shi.
Project administration: Chunguang Feng.
Resources: Dongdong Niu.
Software: Yibing Shi.
Supervision: Peiying Zhang.
Validation: Peiying Zhang, Yi Liu.
Writing – original draft: Chunguang Feng, Bing Han.
Writing – review and editing: Chunguang Feng.

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