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Appearance of Lipid-Laden Intima and Neovascularization After Implantation of Bare-Metal Stents

Extended Late-Phase Observation by Intracoronary Optical Coherence Tomography

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Objectives We examined the neointimal characteristics of bare-metal stents (BMS) in extended late phase by the use of optical coherence tomography (OCT).

Background The long-term neointimal features after BMS implantation have not yet been fully characterized.

Methods Intracoronary OCT observation of BMS segments was performed during the early phase (<6 months, n = 20) and late phase (≥5 years, n = 21) after implantation. Internal tissue of the BMS was categorized into normal neointima, characterized by a signal-rich band without signal attenuation, or lipid-leaden intima, with marked signal attenuation and a diffuse border. In addition, the presence of disrupted intima and thrombus was evaluated. Neovascularization was defined as small vesicular or tubular structures, and the location of the microvessels was classified into peristent or intraintima.

Results Normal neointima proliferated homogeneously, and lipid-laden intima was not observed in the early phase. In the late phase, lipid-laden intima, intimal disruption, and thrombus frequently were found in comparison with the early phase (67% vs. 0%, 38% vs. 0%, and 52% vs. 5%, respectively; $p < 0.05$). Peristent neovascularization demonstrated a similar incidence between the 2 phases. The appearance of intraintima neovascularization was more prevalent in the late phase than the early phase (62% vs. 0%, respectively; $p < 0.01$) and in segments with lipid-laden intima than in nonlipidic segments (79% vs. 29%, respectively; $p = 0.026$).

Conclusions This OCT study suggests that neointima within the BMS often transforms into lipid-laden tissue during an extended period of time and that expansion of neovascularization from peristent to intraintima contributes to atherosclerotic progression of neointima. (J Am Coll Cardiol 2010;55:26–32) © 2010 by the American College of Cardiology Foundation

Bare-metal stents (BMS) implantation is a standard therapy in percutaneous coronary intervention. Histopathologically, neointima are mainly composed of vascular smooth muscle cells proliferating over stent struts associated with vascular healing response in the early phase (1). Although the authors of several clinical follow-up studies (2,3) have shown the long-term efficacy and safety of BMS, progressive lumen narrowing presenting with angiographic in-stent restenosis (ISR) is significantly associated with late adverse events such as thrombosis and myocardial infarction from 5 to 10 years after the struts are deployed (2,3). Therefore, a hypothesis has arisen that neointimal tissue inside the BMS changes during a 5-year period. Intracoronary optical coherence tomography (OCT) with high-resolution images (≈10 μm) provides visualization of microstructures on vessel walls and accurate tissue characterization in living patients (4–6). This OCT examination focusing on features inside the BMS was performed to validate neointimal changes during an extended period (≥5 years) after their implantation.

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Methods

Patient selection. Angiographic and OCT examinations after successful BMS implantation were performed in 20 patients <6 months (early-phase group) and 21 patients ≥5

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years (late-phase group). Patients of the late-phase group received plural examinations, one at <6 months (angiography alone as first follow-up) and one at ≥5 years (angiography and OCT as last follow-up). The reason for the last follow-up was: 1) evidence of myocardial ischemia such as silent myocardial ischemia, stable angina, or acute coronary syndrome (ACS) (7); or 2) planned follow-up angiography for other stent segments. Partial data of the early-phase group were reported previously (8), and patients who had undergone target lesion revascularization (TLR) due to ISR were excluded to estimate the natural process of the initial BMS. All patients provided their informed consent for the procedure, which was approved by the institutional review board.

Angiographic analysis. Coronary angiograms were analyzed by quantitative coronary angiography with a computer-assisted, automated edge detection algorithm (CMS, MEDIS, Nuenen, the Netherlands). The reference vessel diameter, minimum lumen diameter, and diameter stenosis (DS) were measured. We defined ISR as ≥50% of DS. Any angiographic abnormal findings (filling defect, haziness, or lumen irregularity) were qualitatively evaluated.

OCT imaging and analysis. The OCT procedure and anatomical exclusion criteria have been previously reported (8). The tissue inside the BMS was categorized as follows: 1) normal neointima, a signal-rich band without signal attenuation (9); 2) cholesterol crystals (i.e., oriented, linear, highly reflecting structures) (10); 3) calcification (i.e., well-delineated, signal-poor mass with sharp border) (4); and 4) lipid-leaden intima (i.e., diffuse border, signal-poor region due to marked signal attenuation) (4) (Fig. 1). Thrombus was defined as a mass protruding into the lumen (dimension ≥250 μm) (5), and disrupted intima were evaluated. Neovascularization differentiated from any side branches was defined as small vesicular or tubular structures (diameter ≤300 μm), and the location of the microvessels was divided into peristent (attaching to stent struts or exterior the center between the struts and lumen) or intraintima (interior the center between the struts and lumen) (Fig. 2). The minimum lumen area and maximum angle of lipid distribution were measured. When fibrous cap thickness at the thinnest part was ≤65 μm and angle of lipidic tissue was ≥180° (6), the intima was defined as a thin-cap fibroatheroma (TCFA)-like intima.

Abbreviations and Acronyms

ACS = acute coronary syndrome
BMS = bare-metal stent(s)
DS = diameter stenosis
ISR = in-stent restenosis
OCT = optical coherence tomography
TCFA = thin-cap fibroatheroma
TLR = target lesion revascularization

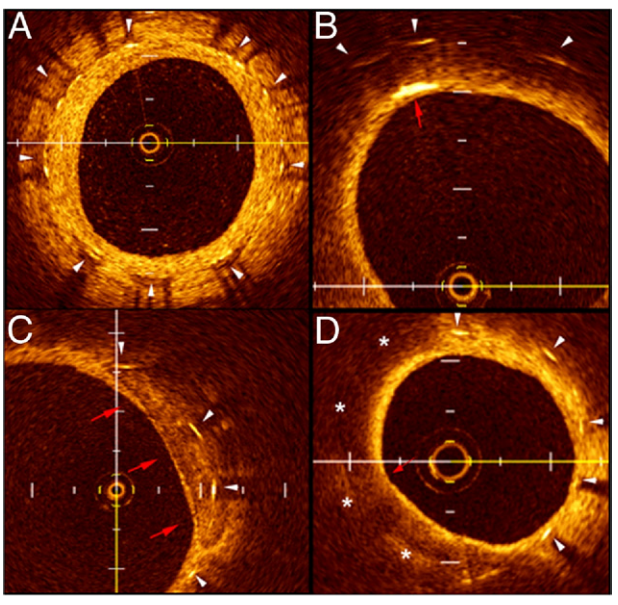

Figure 1 Normal Intima and Atherosclerotic Intima

Struts of a bare-metal stent (BMS) are clearly identified as high-signal spots with shadows **(white arrowheads)**. **(A)** Homogeneous high-signal band within the BMS shows proliferating normal neointima. **(B)** Cholesterol crystals **(red arrow)** are recognized as linear, marked high-signal structures within the BMS. **(C)** A well-delineated, signal-poor mass with sharp border shows a calcified nodule **(red arrows)**. **(D)** Lipid-laden intima is observed as a signal-poor area with diffuse border **(*)**. The stent struts in this area are invisible. This cross section shows thin-cap fibroatheroma-like intima (the thinnest fibrous cap = 30 μm; **arrow,** angle of lipidic tissue = 184.5°).

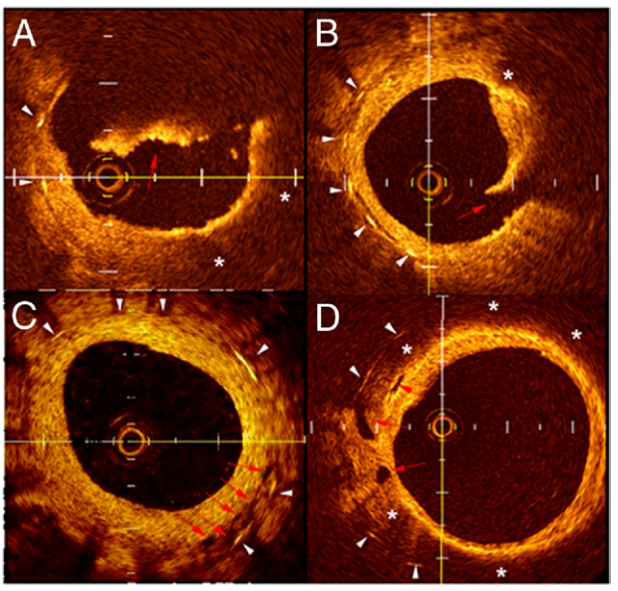

Figure 2 Thrombus, Intimal Disruption, and Neovascularization

White arrowheads indicate stent struts. **(A)** A massive thrombus protruding into the lumen **(red arrow)** and lipid-laden intima **(*)** are found in a patient with unstable angina. **(B)** Disrupted intima **(red arrow)** and lipidic tissue **(*)** are seen. **(C)** A cluster of small vesicular structures around stent struts, peristent neovascularization **(red arrows)** is observed in a patient of the early phase group. Normal neointima circumferentially covers the struts. **(D)** Intraintima neovascularization **(red arrows)** is seen as tubular and vesicular structures nearby the lumen. Neovascular beds are located at the margins of the lipidic area **(*)**. A microvessel at the 9-o'clock region is expanding from the peristent into the intima.

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Table 1 Patient Characteristics

	Early-Phase Group (n = 20)	Late-Phase Group (n = 21)	p Value
Age, yrs	65 ± 11	62 ± 11	0.55
Sex, male	16 (80)	21 (100)	0.10
Coronary risk factors			
Diabetes mellitus	7 (35)	8 (38)	0.84
Dyslipidemia	15 (75)	14 (67)	0.56
Hypertension	14 (70)	12 (57)	0.39
Current smoking	5 (25)	7 (33)	0.56
Obesity	8 (40)	6 (29)	0.44
Family history of coronary artery disease	3 (15)	3 (14)	0.95
Ejection fraction, %	60 ± 12	59 ± 10	0.80
Hemodialysis	0	2 (10)	0.26
Multivessel disease	5 (25)	8 (38)	0.37
Previous coronary artery bypass surgery	0	2 (10)	0.26
Reason for stenting			
Acute coronary syndrome	12 (60)	16 (76)	0.27
Silent myocardial ischemia or stable angina	8 (40)	5 (24)	
Medication			
Aspirin	20 (100)	18 (86)	0.08
Thienopyridines	18 (90)	11 (52)	0.007
Dual antiplatelet therapy	18 (90)	9 (43)	0.001
ACE inhibitor or ARB	12 (60)	11 (52)	0.62
Beta-blockers	7 (35)	6 (29)	0.66
Calcium-channel blockers	3 (15)	2 (10)	0.59
Statins	15 (75)	13 (62)	0.37
Insulin	0	1 (5)	0.32
Oral hypoglycemic agents	4 (20)	4 (19)	0.94

Values are mean ± SD or n (%).
ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blockers.

Statistical analysis. Data are presented as mean ± SD. Categorical variables are presented as frequencies, and they were analyzed by the Fisher exact test or chi-square test. Continuous data were tested by paired or unpaired Student *t* test. A p value <0.05 was considered to be statistically significant.

Results

Patient characteristics. Baseline characteristics, including coronary risk factors and the reason for BMS implantation, were similar between the early- and late-phase groups (Table 1).

Angiographic findings and clinical presentations. The early- and late-phase groups consisted of 22 stents in 20 segments and 24 stents in 21 segments, respectively. The quantitative coronary angiography parameters did not differ between the early-phase group and the first follow-up of the late-phase group. In the late-phase group, myocardial ischemia was documented in 2 patients with silent myocardial ischemia, 7 patients with stable angina, and 4 patients with ACS (3 unstable angina and 1 acute myocardial infarction). The minimum lumen diameter was smaller and DS was greater at the last follow-up in comparison with the early-phase group and the first follow-up, and angiographic abnormalities were observed in 3 ACS patients (1 haziness and 2 wall irregularities). New ISR occurred at the last follow-up in 13 patients, and they received clinical-driven TLR (Table 2). There were no differences in procedural and clinical characteristics between patients with and without ISR.

OCT findings. In the early-phase group, normal neointima was observed in all cross sections of the patients. There was 1 thrombus in 1 case (5%). In the late-phase group, calcification, cholesterol crystals, lipid-laden intima, disruption, and thrombus accounted for 10%, 14%, 67%, 38%, and 52% of patients, respectively. The angle of lipid-laden intima and thickness of fibrous cap was 213 ± 84° (range 86° to 360°) and 80 ± 59 μm (range 30 to 250 μm) in 14 patients who had lipid-laden intima, and TCFA-like intima was observed in 6 patients (29%). The frequencies of abnormal findings were greater in the late phase than in the early phase (Fig. 3). The minimum lumen area was smaller in the late phase in comparison with the early phase (3.4 ± 2.4 mm^2 vs. 5.2 ± 1.9 mm^2; p = 0.011). Overall, neovascularization was found at the ratio of 60% in the early-phase group and of 86% in the late-phase group (p = 0.06), and neovascularization of the early-phase group was localized in the peristent area. Although the incidence of peristent neovascularization was similar between the 2 groups (60% and 81%, respectively; p = 0.14), intraintima neovascular-

Table 2 Angiographic Findings and Clinical Presentation

	Early-Phase Group (n = 20)	Late-Phase Group (n = 21)	p Value*
Location of stent segment			
Right coronary artery	9 (45)	9 (43)	
Left anterior descending artery	8 (40)	7 (33)	0.76
Left circumflex artery	3 (15)	5 (24)	
Stent size, mm	3.3 ± 0.4 (n = 22)	3.4 ± 0.5 (n = 24)	0.46
Stent length, mm	18.1 ± 6.4 (n = 22)	17.7 ± 5.7 (n = 24)	0.82
Number of stents	1.1 ± 0.3	1.1 ± 0.4	0.72
Two overlapping stents	2 (10)	3 (14)	0.68

	CAG and OCT	First Follow-Up CAG Only	Last Follow-Up CAG and OCT	
Duration from stenting, months	4.6 ± 1.8	5.6 ± 2.1	91.5 ± 25.9†	<0.001
Clinical presentation				
Stent follow-up	20 (100)	21 (100)	8 (38)†	<0.001
Silent myocardial ischemia or stable angina	0	0	9 (43)†	<0.001
Acute coronary syndrome	0	0	4 (19)	0.06
Quantitative coronary angiography				
Reference vessel diameter, mm	2.94 ± 0.41	3.03 ± 0.48	2.98 ± 0.53	0.79
Length of stent segment, mm	18.8 ± 7.0	19.4 ± 6.8		0.78
Minimum lumen diameter, mm	2.20 ± 0.27	2.17 ± 0.32	1.64 ± 0.67†	0.001
Diameter stenosis, %	25.2 ± 10.8	28.4 ± 12.1	44.9 ± 21.9†	<0.001
In-stent restenosis	0	0	13 (62)†	<0.001
Qualitative abnormality	0	0	3 (14)	0.08
Target lesion revascularization	0	0	13 (62)†	<0.001

Values are n (%) or mean ± SD. *Early-phase group versus last follow-up of the late-phase group; †$p < 0.05$ between the first and last follow-ups. p = NS between early-phase group and the first follow-up of late-phase group.

CAG = coronary angiography; OCT = optical coherence tomography.

ization was more prevalent in the late phase than in the early phase (62% vs. 0%) (Fig. 4). The change in DS between the first and last follow-ups was greater, and ratios of ISR and TLR were greater in patients (or segments) with lipid-laden intima in comparison with those without lipid-laden intima (Table 3). Lipid-laden intima was more frequent in symptomatic than in asymptomatic patients ($p < 0.001$).

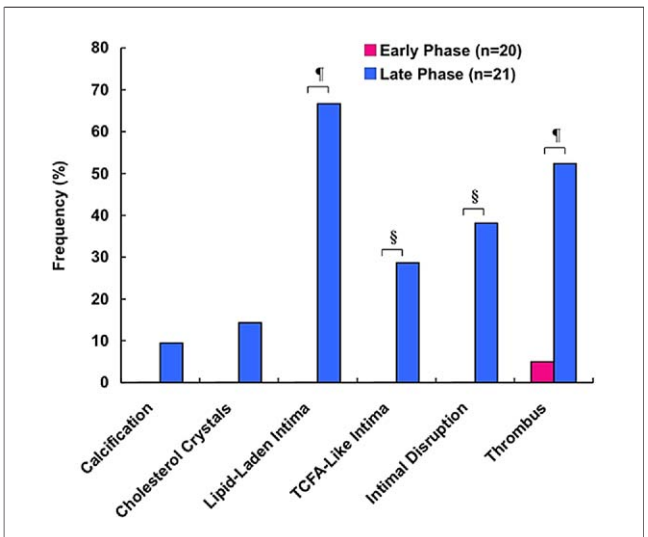

Figure 3 Frequencies of Atherosclerotic Findings

In the late phase, several kinds of atherosclerotic changes are found. The frequencies of lipid-laden intima, disruption, and thrombus are significantly greater in the late phase than in the early phase. §$p < 0.001$; ¶$p < 0.01$. TCFA = thin-cap fibroatheroma.

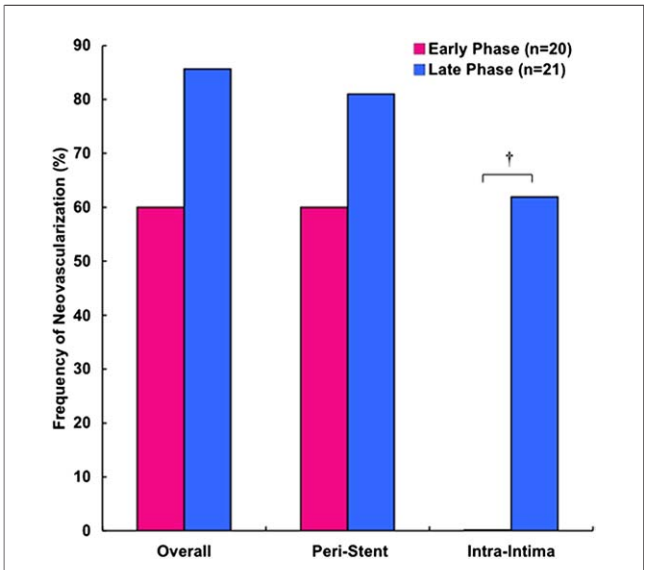

Figure 4 Prevalence of Neovascularization

The prevalence of overall and peristent neovascularization does not differ between the early and late phase. In contrast, the incidence of intraintima neovascularization is greater in the late phase than in the early phase. †$p < 0.001$.

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Table 3 Observations in the Group With Late Optical Coherence Tomography

	With Lipid-Laden Intima (n = 14)	Without Lipid-Laden Intima (n = 7)	p Value
Age, yrs	61 ± 13	65 ± 5	0.54
Coronary risk factors			
Diabetes mellitus	6 (43)	2 (29)	0.53
Dyslipidemia	10 (71)	4 (57)	0.51
Hypertension	8 (57)	4 (57)	>0.99
Current smoking	6 (43)	1 (14)	0.19
Reason for stenting			
Acute coronary syndrome	11 (79)	5 (71)	0.72
Silent myocardial ischemia or stable angina	3 (21)	2 (29)	
Medication			
ACE inhibitor or ARB	6 (43)	5 (71)	0.22
Statins	8 (57)	5 (71)	0.53
Oral hypoglycemic agents	3 (21)	1 (14)	0.69
Clinical presentation			
Silent myocardial ischemia or stable angina	8 (57)	1 (14)	0.06
Acute coronary syndrome	4 (29)	0	0.12
Angiographic findings			
Change in diameter stenosis, %	30.8 ± 16.3	5.9 ± 10.0	<0.001
In-stent restenosis	12 (86)	1 (14)	0.001
Qualitative abnormality	3 (21)	0	0.19
Target lesion revascularization	12 (86)	1 (14)	0.001

Values are mean ± SD or n (%).
Abbreviatons as in Table 1.

The frequencies of disruption, thrombus, and intraintima neovascularization were greater in segments with lipid-laden intima than in those without lipid-laden intima (Fig. 5). There was no relationship between intraintima neovascularization and thrombus formation (p = 0.39). In the late phase, 4 patients with ACS had both intimal disruption and thrombus and they showed angiographic ISR (Fig. 6).

Discussion

This extended late-phase (≥5 years) OCT observation after BMS implantation demonstrated that: 1) neointima often transforms into lipid-laden tissue with lumen narrowing; 2) neovascularization expanding from the peristent area into the intima may be responsible for atherosclerotic change; and 3) advanced atherosclerotic progression such as intimal disruption and thrombus formation may be associated with recurrence of myocardial ischemia, including ACS.

Proliferating tissue within the BMS segment in the early phase was recognized as homogeneous OCT signals. In contrast, various signal patterns of the late phase indicated growth of several sorts of tissues during an extended period of time. Notably, 67% of the patients had lipid-laden intima, and TCFA-like appearance accounted for 29%. The use of OCT enables one to detect lipidic elements of arterial wall with a high sensitivity and specificity (>90%) (4). Lipid-laden intima was correlated with intimal disruption and thrombus formation, and the rather complex morphology resembled a vulnerable plaque, typically observed at the culprit lesion of ACS (5). A post-mortem pathological study demonstrated that prominent infiltration by lipid-laden macrophages into neointima and adherent thrombus are found on disrupted lumen ≥4 years after BMS placement (11). Moreover, specimens obtained by directional

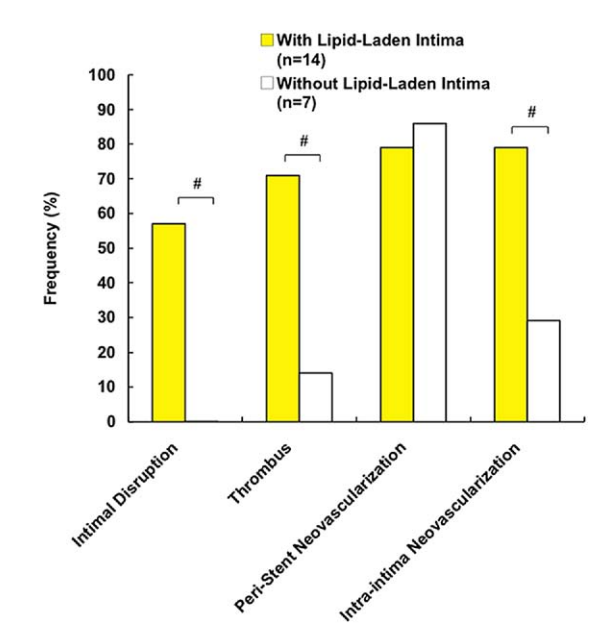

Figure 5 Comparison Between Lipidic and Nonlipidic Stent Segments at Late Phase

Stent segments with lipid-laden intima frequently have intimal disruption, thrombus, and intraintima neovascularization in comparison to the segments without lipid-laden intima. Peristent neovascularization is commonly found in both groups. #p < 0.05.

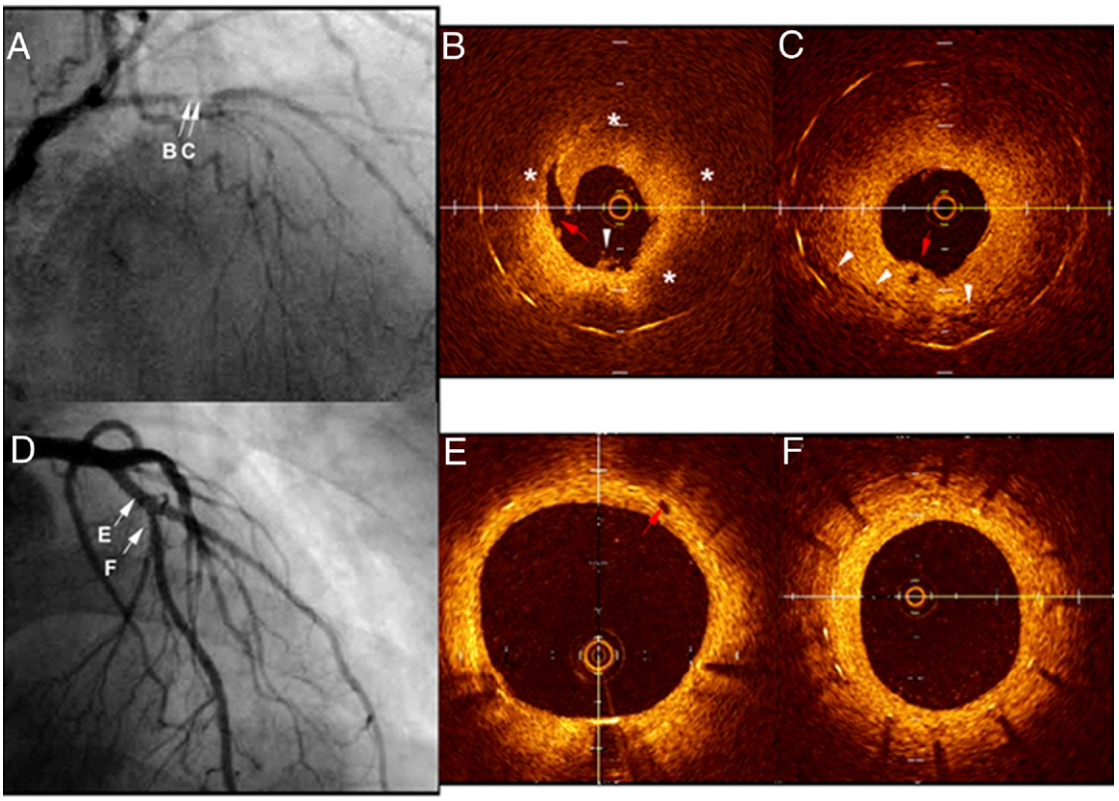

Figure 6 **Angiographic and Optical Coherence Tomographic Findings in the Late Phase**

(A) Coronary angiograms of a patient with unstable angina show new in-stent restenosis and haziness in the left anterior descending artery. This patient received stent implantation 131.8 months ago. **(B)** Optical coherence tomography shows the presence of lipid-laden intima **(*)**, intimal disruption **(red arrow)**, and small thrombus **(white arrowhead)** within the stent. **(C)** Another cross section shows intraintima **(red arrow)** and peristent **(white arrowheads)** neovascular beds. **(D)** In this case, coronary stent had been implanted in the left anterior descending artery 68.5 months previously. Angiograms show no in-stent restenosis. **(E and F)** Normal neointima within the stent and peristent microvessel **(red arrow)** are observed.

coronary atherectomy from new ISR lesions >5 years are composed of thrombus and atherosclerotic materials (cholesterol clefts, necrotizing foam cells, and inflammatory cells) facing on healed neointimal layer (12). These pathological findings are consistent with the current OCT findings.

A serial angiographic evaluation of the BMS segments revealed a triphasic luminal response characterized by an early narrowing phase during the course of 6 months, a medium-term regression phase from 6 months to 3 years, and a late narrowing phase beyond 4 years (2). It is understood that early lumen narrowing and medium-term regression are attributed to neointimal thickening by cell proliferation and thinning by neointimal remodeling, respectively (13). The present study showed that lumen narrowing during the late phase, including new appearance of ISR, remarkably increased in segments with lipid-laden intima than in nonlipidic segments. Therefore, activated atherosclerotic processes may promote subsequent neointimal remodeling and late lumen narrowing.

In atheroma of nonstent segments, neovascular networks expand from adventitia into plaque, and intraplaque microvessels bring recruitment of circulating macrophages and erythrocytes through the vasa vasorum. After phagocytosis of erythrocytes containing free cholesterol in their membranes by infiltrated macrophages, the deposition of foam cells and activated macrophages invite enlargement of necrotic core and plaque destabilization (14). Neovascular beds appear in peristent neointimal tissue at early phase after BMS implantation (15). Peristent microvessels probably advance toward the interior and build up intraintima neovascularization with time. The current results indicated that the expression of lipid-laden intima is closely associated with intimal disruption, thrombus formation, and intraintima neovascularization. Therefore, expanded intraintima neovascularization may play a key role in atherosclerotic progression and surrounding tissue instability, as well as intraplaque neovascularization of nonstent segments.

In the current series, ACS increased in 4 patients who showed angiographic ISR and OCT findings of intimal disruption and thrombus. A large-scale angiographic study revealed that ISR in the late phase is significantly associated with adverse cardiac events such as thrombosis and myocardial infarction (3). According to Hasegawa et al. (12), 43%

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of new ISR lesions that develop beyond 5 years are clinically represented as ACS. Our results propose the concept that thrombus formation originating from atherosclerotic intimal disruption of BMS segment can arise in the extended late phase, and the phenomenon may be one potential cause of very late thrombosis.

Study limitations. The study population was relatively small, and some selection bias might have influenced the results. Target BMS segments were not serially observed by the use of OCT because this imaging device has only recently been developed. Larger and serial studies are necessary for understanding the differences in intimal degeneration associated with clinical presentation. Although with the use of OCT there is the possibility of identifying neovascularization (6,16), the diagnostic accuracy is indistinct. Signal attenuation due to superficial thrombus (or lipid-laden intima) and limited penetration depth of OCT images (≈2 mm) interrupted the acquisition of information on the stent (or neointimal) area, vascular remodeling, and neovascularization in deep layers. Finally, intraintima hemorrhage could not be diagnosed because of the absence of OCT criteria.

Conclusions

This OCT study suggests that neointima within the BMS often transforms into atherosclerotic tissue in the extended late phase and that atherosclerotic progression of neointima may be attributed to neovascular expansion from peristent to intraintima.

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Key Words: neointima ■ stents ■ thrombus.